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Choudhury, Anusuya, Ph.D.

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CHIRAL TETRALINS VIA ASYMMETRIC INVERSE ELECTRON DEMAND CYCLOADDITION OF HETEROAROMATIC SALTS WITH DIENOPHILES HAVING STEREOGENIC CENTERS

by

ANUSUYA CHOUDHURY

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

1991

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirements for the degree of Doctor of Philosophy.

July 16 1991
date

Richard V. Franck
Chairman of Examining Committee

July 16, 1991
date

Richard Pitzer
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The City University of New York

Abstract

CHIRAL TETRALINS VIA ASYMMETRIC INVERSE ELECTRON DEMAND CYCLOADDITION OF HETEROAROMATIC SALTS WITH DIENOPHILES HAVING STEREOGENIC CENTERS

by

Anusuya Choudhury

Advisor: Professor Richard W. Franck

The asymmetric cycloaddition reactions of isoquinolinium salts with a wide variety of chiral dienophiles (modified version of the Bradsher cycloaddition) to which the stereogenic center was attached in the form of ethers, orthoesters and acetals have been examined. Very high asymmetric induction (95+%) has been achieved for the case of chiral trans-2-phenyl cyclohexyl vinyl ether with excellent chemical yield. In order to avoid the difficulty of removing the chiral auxiliary which remains as a secondary ether in the cycloadduct in the case of chiral vinyl ethers, the chiral othoesters having a C2 axis were used, permitting the facile removal of the chiral auxiliary. But the face discrimination was not high. A sugar derived chiral vinyl acetal exhibits very high face control resulting in an enantiomerically pure compound.

Our configurational assignments are based on the comparison of the CD spectra of the products with CD's of tricyclic tetralins prepared from sugars of known configuration.

Cycloaddition of chiral ketene acetal dienophiles having complex substitution patterns, afford after work-up, highly functionalised tetralins with a masked hydroxy methylene substituent as a hemiacetal, a tertiary hydroxyl function at the position corresponding to 9-position of anthracyclines and a chemically manipulable 2,4 dinitrophenylamino group, matching the 7-position requirement of anthracyclines with a facile removal of the chiral auxiliary. The attempted effort to convert the cyclic acetal to lactone (which would give the required ester moiety at 10-position by regioselective opening) resulted in the rupture of C-C bond forming a tetralone derivative. Though the cycloaddition of these dienophiles and the subsequent manipulations were highly encouraging, we could not get an optically pure dienophile. A dienophile starting from optically active threonine was designed, the cycloaddition of which gave a mixture of diastereomers. The uniqueness and the beauty of this cycloaddition lies in the simultaneous creation of a tertiary hydroxyl group and the hydroxy alkyl side chain at 9-position during cycloaddition with the hydrolysis of the chiral director without additional effort.

In summary, we have achieved a practical synthetic route towards enantiomerically pure tetralins with absolute stereocontrol, which are building blocks for the AB ring synthon of anthracyclines.

Acknowledgements

I wish to express my deep sense of gratitude to Prof. R. W. Franck for his invaluable guidance, patience, inspiration and financial support throughout this work. I thank post docs Drs. V. Bhat, C. S. Subramanium, R. B. Gupta and S. Ramesh and my friends and coworkers R. Tripathy, Htwe Yin, Cliff Soll, Tony E. Nicholas, G.Grewal and Neelu Kaila for their helpful discussions. My heartfelt thanks go to my family members back in India, without their sacrifices I would not have been able to place myself in this position, which I doubt if I can pay back even little. I thank my husband Rabi, who always encourages me to study. I express my appreciation to my neighbour and a loving friend Vasanthini Balasanmugam for taking care of my little girl whenever I needed. Last but not the least I thank my little daughter Anannya who tilts my pen to move forward.

Table of Contents

List of Figures

List of Schemes

List of Tables

I. Asymmetric Cycloaddition Reaction of Isoquinolinium Salts

Introduction

A. Background

One of the important processes for the strategic placement of C-C bonds in organic chemistry is the Diels-Alder methodology. This reaction, discovered in 1928, features the annulation of an electron rich diene with an electron poor dienophile. The simultaneous and regioselective formation of two bonds with largely predictable stereochemistry with four chiral centers in one single synthetic operation highlights the importance of this reaction[1]. Bachman and Deno at first conceived the idea of the "inverse electron demand reaction" (IED)[2]. They suggested, in 1949, that the converse of the Alder rule[3] should hold, i. e., the preferential contribution of the electronic sequence of the reacting partners (dienes and dienophiles) should be exchanged compared to the classical Diels–Alder reaction. However, this proposition was first demonstrated in 1962 by Sauer and Wiest[4] through a kinetic study of the reaction of hexachloropentadiene with a series of dienophiles. An early example of an IED reaction with a charged diene was reported by both Bradsher[5] and Fields[6], where acridizinium ion **1** reacts with electron rich dienophiles such as vinyl ethers **2** to form adduct **3**.

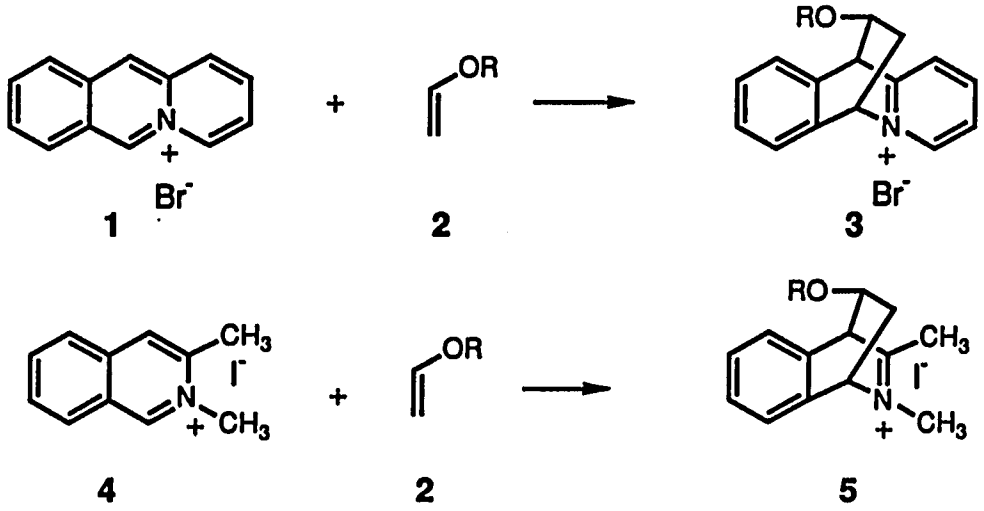
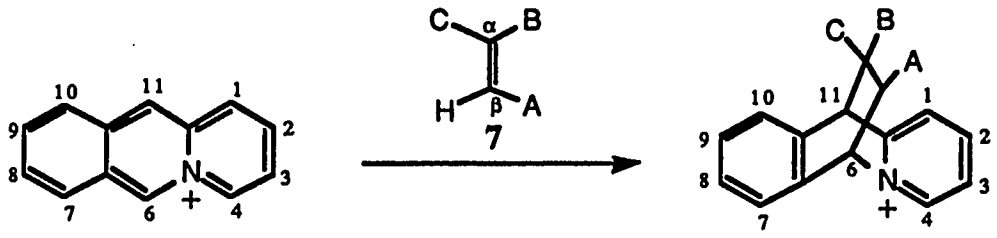


Fig.1 Polar cycloaddition reactions of acridizinium and isoquinolinium salts.

Bradsher and Day[7] demonstrated that isoquinolinium salt **4**, a system analogous to **1**, also undergoes IED reaction with vinyl ethers **2** to give cycloadduct **5**. The reaction of **4** was extended to other electron rich dienophiles such as cyclopentadienes[8,9] and styrenes[10]. There was not much synthetic application of this novel reaction for 20 years after the initial discoveries.

B. Regiochemistry

A spectacular feature is the observed regiospecificity of these reactions where, in the cycloadduct, the carbon 6 of the diene **6** (fig. 2) remains proximal to the β-carbon of the dienophile. The rationalization for such specificity, based upon the preferred orientation of a given positional isomer in the transition state has not been useful to explain the above regiochemical preferences[11-15].



6 **8**

Figure 2: Regiochemical preference of polar cycloaddition

It has been argued that the well-known Woodward-Hoffmann rules[16] have been unable to account properly for the observed regioselectivity. Other theoreticians[12,13] have concluded that the secondary interactions, originally proposed by Woodward, are insufficient to determine the regiochemistry and have emphasized the mutual importance of electrostatic effects and frontier orbital interactions. We believe, the failure of the famous Woodward-Hoffmann rule to rationalize the above regiochemistry is because the reaction does not follow a concerted and synchronous path as demanded by the rule. Salem has also reported[13] that in the dimerization of acrolein " the major contribution (60-70%) to the

favored regioisomer relative to other arises from electrostatic terms". The relative importance of these electrostatic effects appears to be predictable from frontier orbital considerations[17-19]. Bradsher proposed an electrophilic addition model to explain the inherent regiochemistry of these kind of cycloadditions, in which he suggested that the bonds created during the reaction are due to the electrostatic interaction between the most electropositive end of the diene with the polarizable electronegative end of the dienophile[20].

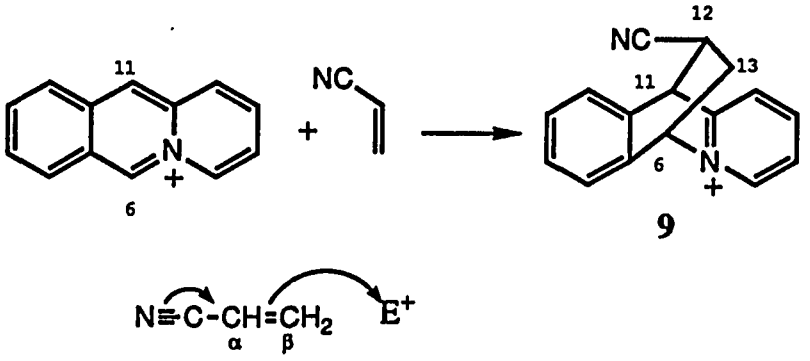


Figure: 3 Rationalisation of anomalous regiochemistry

This specificity has been found in the addition of many unsymmetrical alkenes to isoquinolinium salts[7,8] and as well as to other cations[21] including acridizinium cations. However, the reaction of acridizinium ion with acrylonitrile[22] afforded a single regioisomer **9** in which the nitrile group is at position 12 (Fig. 3), opposite to that predicted from ground state polarization alone. This "anomalous orientation " caused Fields et. al. and Schmidt (independently) to reject the electrophilic model. It was concluded "that the regioselectivity observed in polar cycloaddition always has a polar origin and is not only understandable in terms of ground state polarization and polarizability

understandable in terms of ground state polarization and polarizability but provides a new tool for the study of the electrophilic addition of large cations".

Houk[18] and Fleming[23] proposed that the largest HOMO coefficient of the donor acrylonitrile exists at the β-carbon atom, the position which will connect to 6 position of acridizinium ion at the site of the largest LUMO coefficients. A classical explanation of these FMO predictions is that, acrylonitrile (a less nucleophilic donor) is polarizable in the presence of a cation, its double bond has a charge distribution opposite to that predicted from ground state polarization alone. So the actual regiochemistry observed is influenced by the variable tendency of the unshared electrons of the electron withdrawing group to enter into complexes with the cationoid reagents as well as by the size of the cation.

Thus, the electrophilic addition model appears to rationalize the regioselectivity of most polar cycloadditions. The model fails in cases which have an electron withdrawing but polarizable group conjugated with the double or triple bond. In these cases the ground state polarization and polarizability exhibit opposite orientations, and prediction of regiochemistry can best be made by determining which atom has the largest HOMO coefficient of the system in reactions involving cation.

C. Stereochemistry

These kinds of polar cycloadditions show amazing stereoselectivity, in most instances 100%. Single crystal X-ray analysis of **11**, a single compound obtained by the addition of vinyl ethers to 2,3 dimethyl isoquinolinium ions[24] shows the cycloaddition occurs stereospecifically in a manner predictable from the repulsive forces which would be expected during the reaction. Again this structure would be predicted from the assumption that in the transition state the preferred orientation is that affording the maximum separation of like charges.

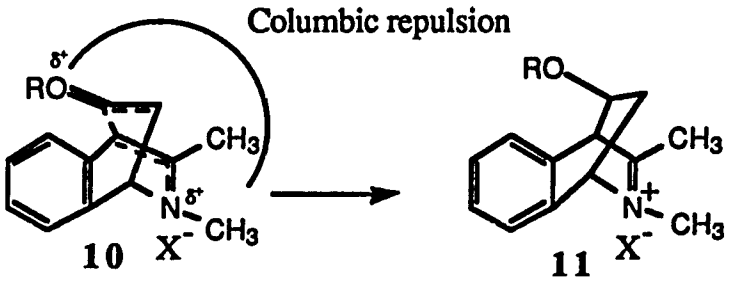
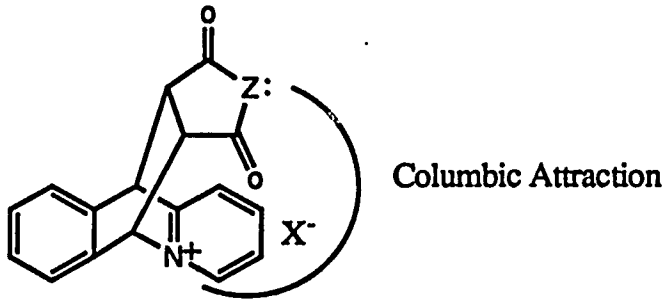


Fig. 4 Syn stereoselectivity of polar cycloaddition

The selectivity is consistent with the concept of a concerted and nonsynchronous nature of cycloaddition where electrostatic interactions develop early in the reaction. The topography of the process is seen to be syn (exo addition) with the alkoxy group oriented towards the phenylene ring. The same is true with acridizinium ions[25]. Based on this premise a stereoselectivity rule was proposed by Bradsher i.e. *If two geometrical isomers are possible in a polar cycloaddition and if the transition state leading to the establishment of second new sigma bond in these two isomers differ in the distance between the centers of the receding and developing positive charge, then the geometrical isomer formed in larger amount will be that with the greater distance between the charge centers in the transition state.*

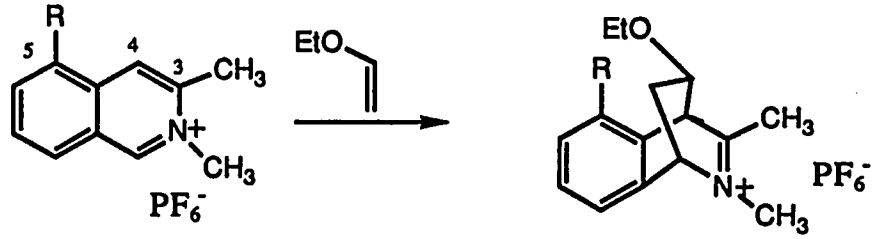


12 Z = O, NR

Fig.5 Anti stereoselectivity of polar cycloaddition

In contrast to the above topography, the addition of maleic anhydride[26] and aryl maleimide[27] to acridizinium ions was anti (endo selective addition) exclusively. Again this

has been explained by the preferential interaction of the unshared electron pair on the hetero atom in either maleic anhydride or maleimide with positively charged pyridinium ring **12** (Fig. 5). One of the implications of the electrostatic addition model for polar cycloaddition is that enhanced electrophilicity of the cation should result in an increased tendency toward cycloaddition. Installation of an electron withdrawing group e.g. NO_2 group in **13b** (Fig. 6) enhances the reaction rate by 120 times and an acetyl amino substituent at the same position shows a two fold increment compared to the parent system. The substituent at position 5 encumbers the adjacent peri hydrogen (H_4) of **13** which is again constrained by the neighboring substituent at position 3. The steric compression between the peri H at C-4 and the group at C-5 is relieved by addition, which moves it out of the plane. These results imply that in addition to electronic perturbation which is responsible for rate enhancement, steric factor has also a role to play. This combination of steric and electronic factors sometimes reduces the stereoselectivity (loses the uniqueness of stereoselection) giving a mixture of exo and endo products[28].



13 **14**

a. R = H
b. R = NO_2
c. R = NHCOMe

Fig.6 Effect of 5-substitution on the stereoselectivity of cycloaddition

D. Mechanism

The mechanistic details for this kind of polar cycloaddition had been studied by Bradsher where he proposed the existence of a charge transfer complex along the reaction

pathway[5(c-j)]. This proposition explained the high regio- and stereochemistry manifested in this cycloaddition. The comparable activation parameters of these reactions with those of classical Diels-Alder reactions made him propose a concerted pathway for these reactions[29]. Details of the inverse electron demand cycloaddition reaction of isoquinolinium salts have recently been studied by Franck[30]. The most important finding in Franck's scheme is the evidence for the mechanism of cycloaddition being a two step process. The conclusion was based on the isolation and characterization of one-bond products derived from the partitioning of the intermediate oxocarbonium **17** ion via solvent trapping and cycloaddition[30].

In every cycloaddition, when the reaction was worked up prior to acid treatment, there could be isolated a one bond product **19**. The proposal of an oxocarbonium ion which is the intermediate for both the observed one-bond and tricyclic adduct explained the observation. This, in fact, is the proof that the cycloaddition goes via two steps. Retention of configuration of dienophile is used as an evidence for a concerted cycloaddition pathway while the interception of intermediates is assumed to be a verification of a two step process. Gompper's review[31] uses the interception of intermediates as the determining factor in distinguishing between concerted and stepwise cycloaddition. During the study of acridizinium and isoquinolinium ions, Bradsher had observed that some of his results, in particular a kinetic study, could be explained by a two step process[32]. However the failure to detect the presence of an oxocarbonium ion seems to be one of the prime reasons for his revision of an earlier proposal for a stepwise mechanism in favor of a nonsynchronous concerted mechanism[32].

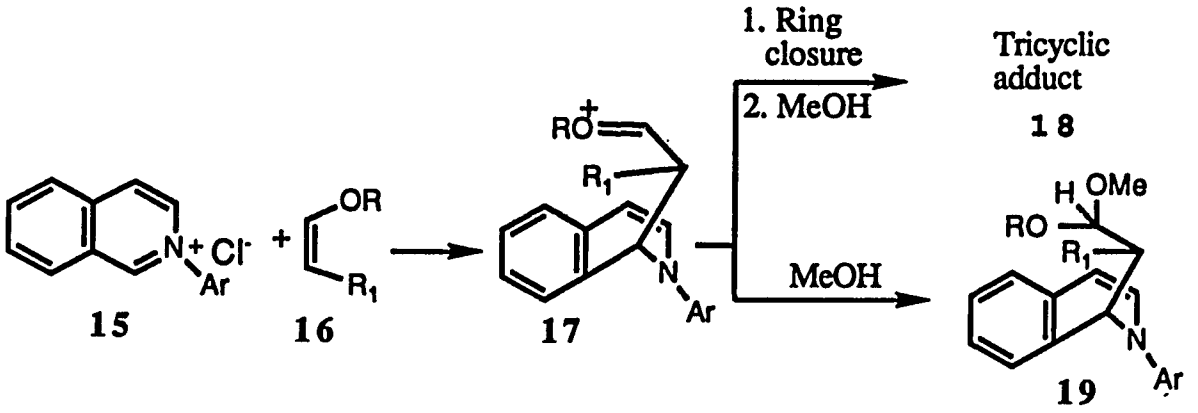
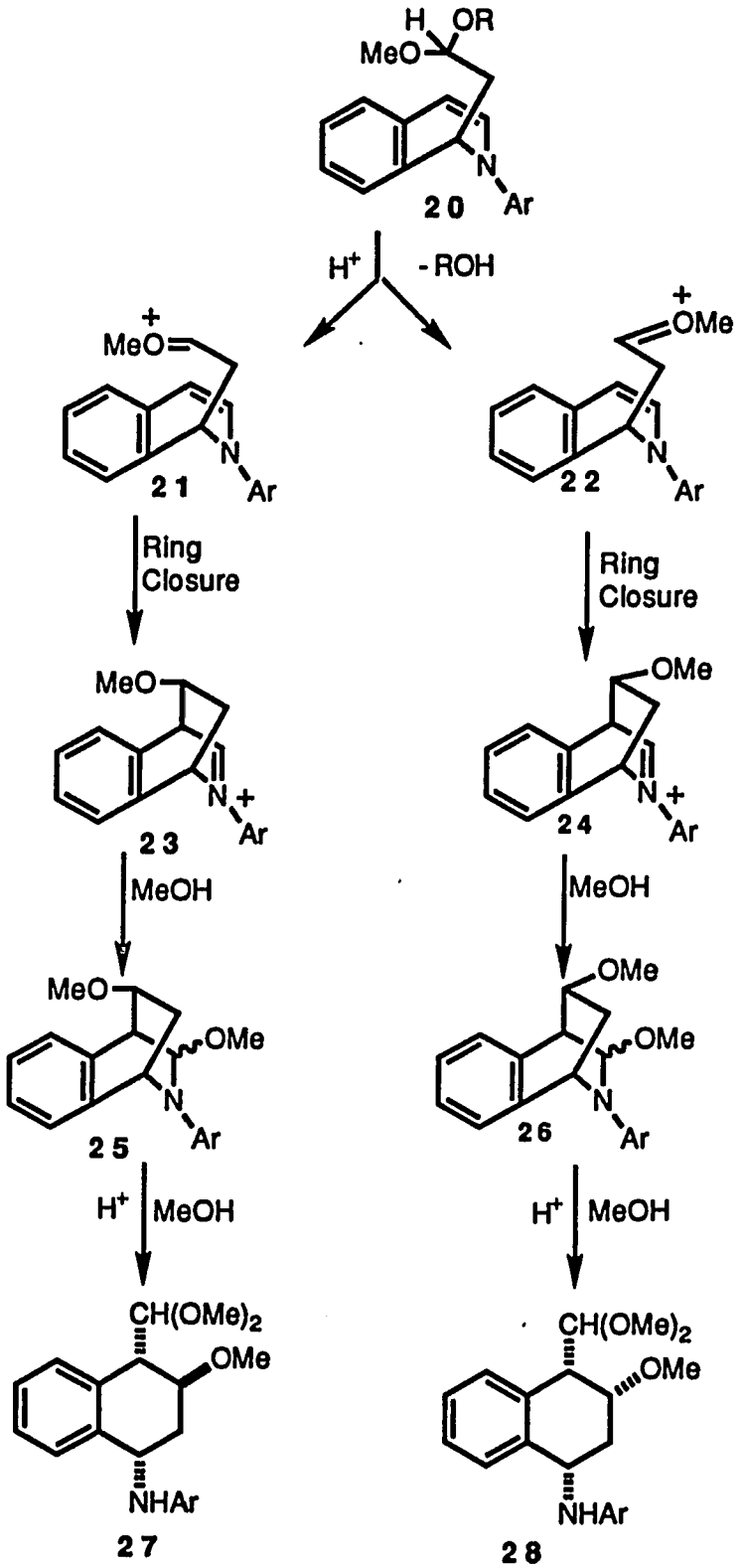


Fig. 7 Franck's proposed intermediacy of an oxocarbonium ion to form tricyclic and one bond roduct.

A two step process would be consistent with stereospecific retention if the ring closure step were faster than the loss of configuration of the stereochemical probe of the intermediate. Recycling experiments (Scheme 1) of the one-bond products **20** demonstrated that the rate of ring closure is indeed faster than the loss of configuration by C-C bond rotation in the oxocarbonium ion intermediates. For example, compound **27** with exo stereochemistry and its endo isomer **28** are formed from five different one bond products. However the ratio in none of these cases is same. The compounds **27** and **28** are formed from the oxocabonium ions **21** and **22** respectively. If the rate of rotation between **21** and **22** are faster than their rate of ring closure, then identical ratios of **27** and **28** would have been obtained regardless of the method of generation of **21** and **22**. It has also been shown that the ring closure of oxocarbonium ion intermediates is competitive with solvent trapping. The competition between ring closure and solvent trapping is influenced by the nucleophilicity of enamine intermediates. With an N-carboethoxy salt of isoquinoline the major product is one-bond adduct. But with N-methyl salt, the oxocarbonium ion intermediate can exclusively form a C-C bond in the second step because an N-methyl enamine is so much more reactive than the enamine in our standard system. The change



Scheme 1: Ring closure is faster than the C-C bond rotation in oxocarbonium ion intermediate.

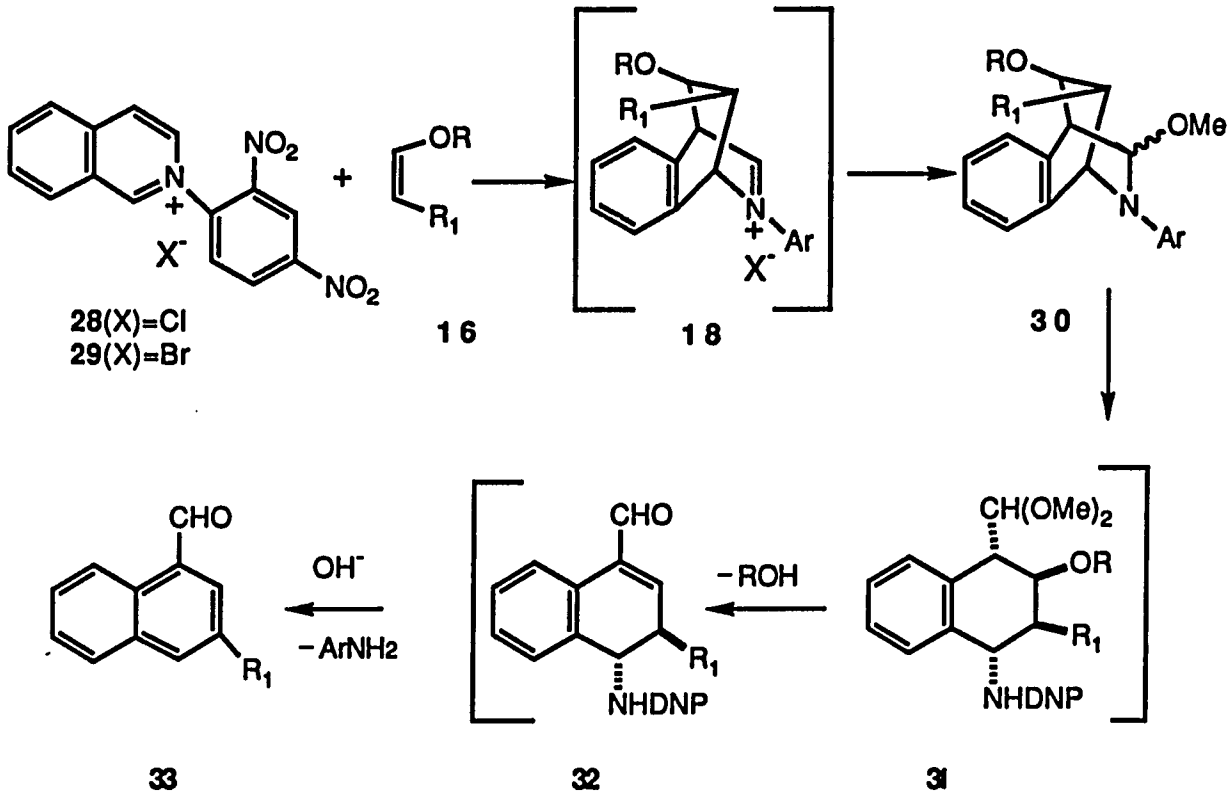
over from stepwise to concerted mechanism takes place by changing the N-carboethoxy to the N-methyl case. It has also been proved that the solvent trapping is a faster process than the rotation of oxocarbonium ion.

The changes in exo vs. endo addition is also consistent with two step process. The rationalization for exo is electronic in origin and the endo is based on steric grounds. One bond product could also originate from a stepwise reversal of the initial cycloadduct which in turn is formed by the concerted mechanism but control experiments which rule out the possibility in some cases have been carried out.

E. Development

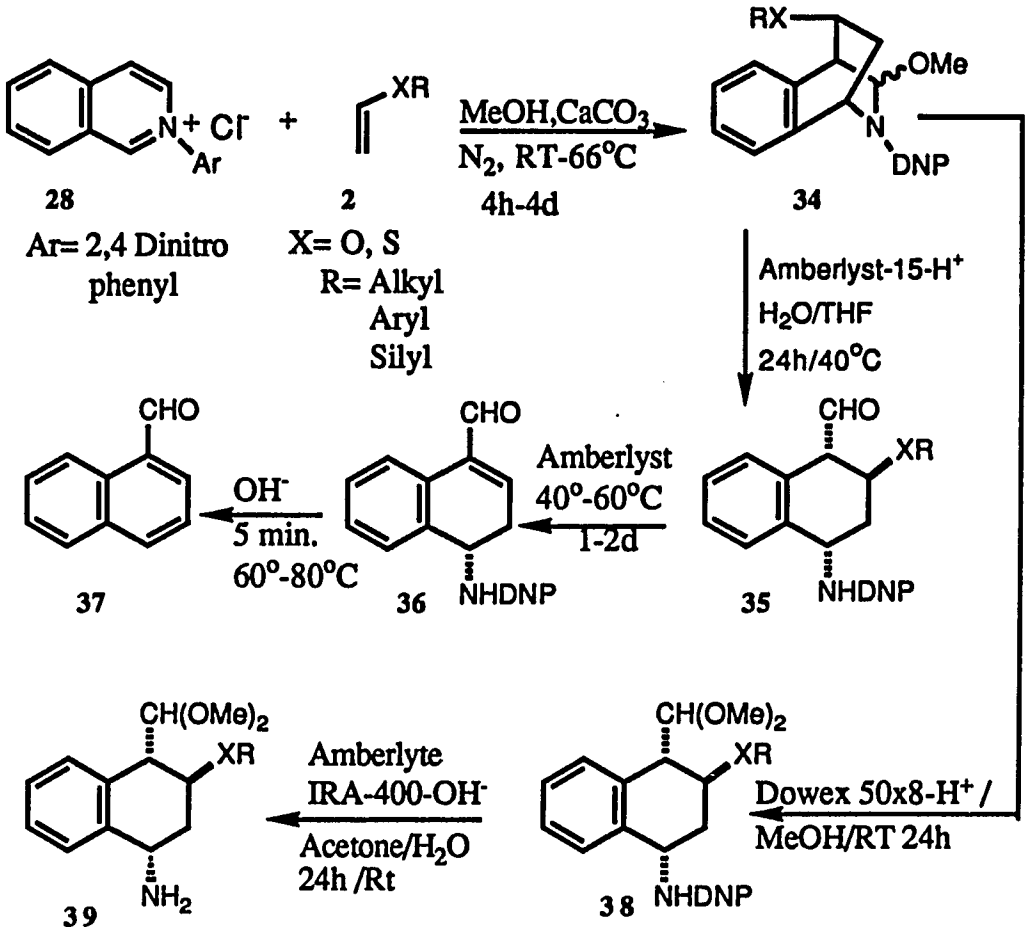
The introduction of inverse electron demand cycloaddition reactions of isoquinolinium salt developed by Bradsher had a limiting requirement of a substituent at position 3 of the salt. Falck[33] showed that by using 2,4 dinitro-chlorobenzene as the quaternizing agent, isoquinoline could itself be a useful diene. Powdered $CaCO_3$ was used as an acid scavenger and a compatible substrate for preventing the dienophile polymerization in this cycloaddition reaction. He applied this reaction in preparing aromatic aldehydes **33** (Scheme 2). Applying this methodology he synthesized racemic 14-epicorynoline and O-methylarnottianamide.

Among the achievements by Franck[30] (scheme3), the most spectacular is the stereospecific synthesis of chiral tetralins with up to four stereogenic centers[30]. The tricyclic adduct **30** in Falck's scheme translates to napthaldehyde **33** via the intermediacy of the very highly functionalised tetralin acetal **31**. Treatment of the tricyclic adduct **34** with Dowex (H^+) in dry methanol produces a highly functionalised tetralin with preservation of all the stereocenters. This scheme also features the preparation of saturated and α,β unsaturated aromatic aldehydes **36** and **37** respectively on treatment of the tricyclic adduct **34** with basic Amberlyst by single and double elimination from the tetralin acetal **35**.

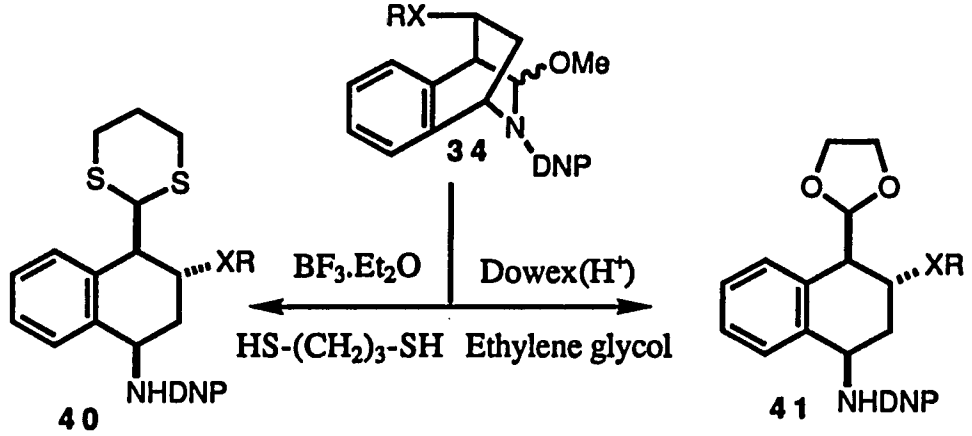


Scheme 2: Falck's use of 2,4 dinitrochlorobenzene as the quarternizing agent and preparation of naphthaldehyde.

Tetralin acetal on treatment with basic polymeric resin in acetone/water produces free amino compound by the elimination of 2,4-dinitrophenol[34]. The successful application of this methodology has been illustrated in the synthesis of Cryptosporin, a yellow fungal metabolite possessing a wide spectrum of biological activities, having a \ pyranonapthoquinone nucleus[35]. The tricyclic adduct **34** can be trapped as its dithiane derivative **40** using $BF_3.Et_2O$ as the Lewis acid and propane dithiol as the trapping agent. The versatility of the reaction is further proved by using ethylene glycol as the trapping agent forming a dioxolane derivative **41**[36]. These reactions are cleaner than their methanol counterpart giving a very high yield of the tetralin. When the adduct formation is 100% the tetralin formation is almost quantitative and does not need a chromatography for product purification. An additional advantage of the resulting system is its can tolerance of mild acidic condition.



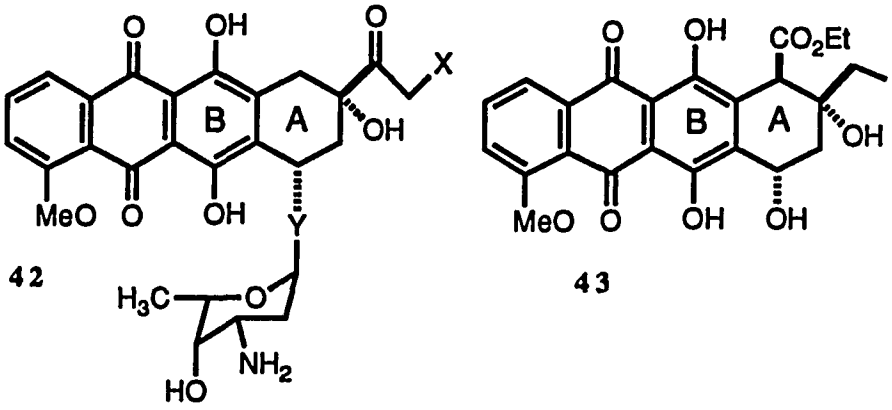
Scheme 3: Franck's scheme showing the trapping of the tricyclic adduct in the form of a substituted tetralin acetal



Scheme 4: Trapping of the tricyclic adduct as dithiane and dioxolane derivatives

The ready conversion of ethylene ketal to ester by applying Deslongchamps method[37] (ozonolysis) can furnish an ester functionality corresponding to the 10-position for anthracyclines **42** and **43**. This highly substituted derivative of tetralin corresponds to a

fundamental structure of A&B rings of the anthracycline antibiotics. The three stereocenters created during the cycloaddition have a predictable relative stereochemistry deduced from the mechanism of cycloaddition[30] and verified by exhaustive NMR decoupling and NOE experiments. The resulting functionalities can also be manipulated to the required ones for anthracyclines. This opened up a vast field for the construction of many important naturally occurring drugs possessing a tetralin skeleton e.g. aklacinomycins, adriamycins, nogalamycins, daunomycins etc. As the structure shows these drugs differ mainly on their A&B rings. As our modified version of the Bradsher Cycloaddition produces A&B rings corresponding to the anthracyclines, the reacting substrates can be modified to achieve an advanced synthon for this important framework.



(a) x=H, y=O daunomycin
(b) x=OH, y=O adriamycin
(c) x=H, Y=CH2 C-glycoside

Aklavinone

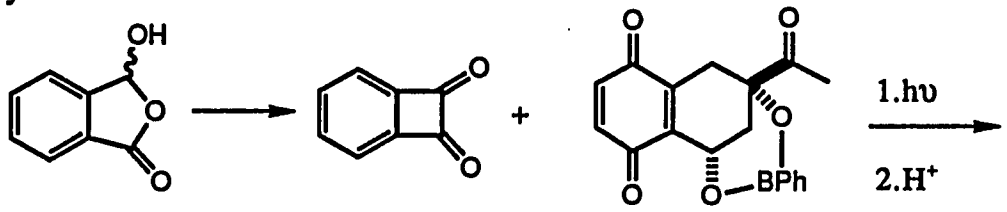
Fig.8 Antitumor anthracyclines

F. Research Goal

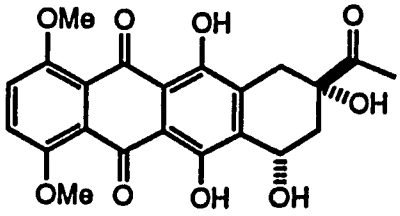
As only one of the antipodes of the drugs acts against the disease, the development of a method to synthesize homochiral tetralins was chosen as the subject of the research to be described below. Thus the Bradsher-Falck cycloaddition scheme was modified to induce optical activity in the final product. The use of chiral auxiliaries linked to either dienes or dienophiles in the Diels-Alder reaction has become a useful method for producing homochiral cyclohexenes[38-40]. The logical extension of techniques for chirality transfer to

the case of inverse-electron-demand cycloaddition has just begun to be developed[41-42]. Among the two theoretically possible ways to obtain one of the enantiomers in excess, i.e. chiral catalysis and attaching a chiral auxiliary to one of the components, the latter has met with real success so far. The chiral director biases the face discrimination during the cycloaddition giving diastereomeric product(s). Though this concept is common in classical Diels-Alder reactions; its introduction in to the IED reaction is still in its early stages. The pioneering work due to Posner[41] and Greene[42] will be presented in the discussion section.

Approaches to construct the anthracycline AB ring synthon, the real challenging portion of the anthracycline antibiotics are numerous [43]. An example is quinone (**46**) with all the right stereocenters and required functionality which can be merged to CD rings by Krohn›s photo cycloaddition[44] shown below.



44 45 46



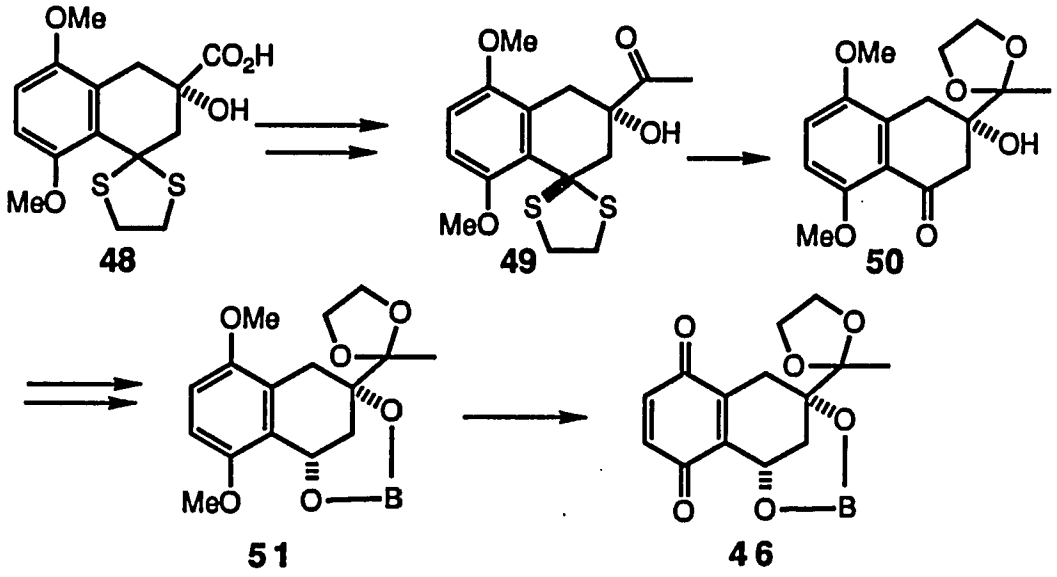
47

Scheme 5: Krohn's photocycloaddition

Flash vacuum pyrolysis of hydroxy phthalide yields the benzocyclobutanediones which can be coupled photochemically in high yield with the enantiomerically pure building block to afford (shown in scheme 5) 1-methoxy-daunomycinone in only two steps. The mild condition of the photochemically induced coupling reaction permits the use of fully

functionalized optically active building blocks. A limitation is the lack of regiocontrol with unsymmetrically substituted benzocyclobutanediones.

The quinone **46** can be obtained in 10 steps from the racemic bicyclic hydroxy acid **48**[45]. Resolution of racemic bicyclic hydroxy acid **48** was achieved using brucine. The acid functionality was reduced to alcohol, which was converted to ketone **49**. The ketone was converted to it's ethylene ketal and dethioacetalization was achieved using mercury. The ketone **50** was reduced with lithium borohydride and the resultant cis and trans alcohols were converted entirely to it's cis boronate **51** by the action of benzene boronic acid in the presence of tolune-4-sulphonic acid. Then it was oxidized to quinone **46** by oxidation with CAN.



Scheme 6: Synthesis of quinone **46**

Therefore, with Krohn's protocol and the synthon **46** as a guide our immediate concern was to develop suitable dienophiles bearing chiral auxiliaries for the cycloaddition experiment which would produce AB ring synthons of anthracyclines. The general reaction scheme (**Fig. 9**) is shown below.

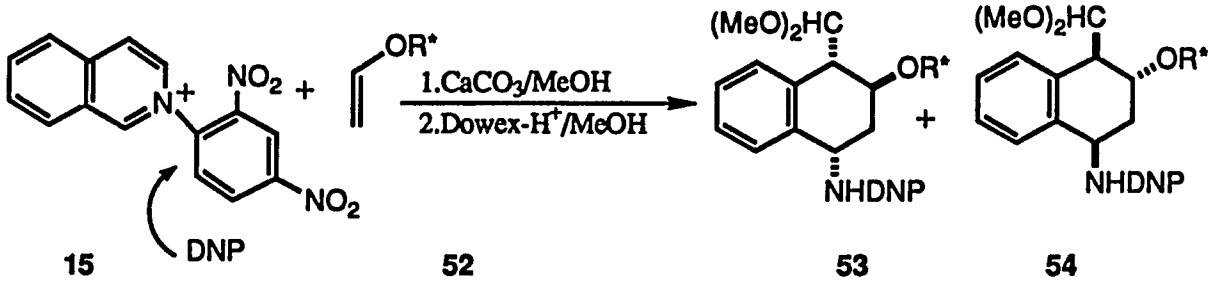


Fig.9: Cycloaddition reaction of isoquinolinium salt: dienophiles bearing chiral auxiliary

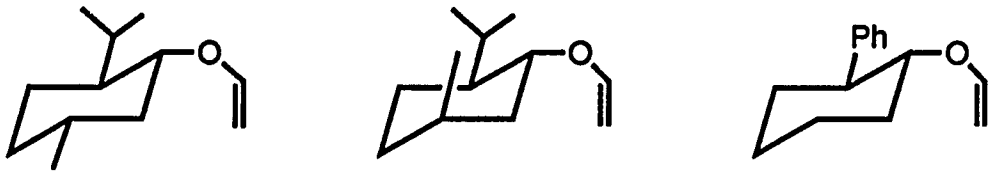
R* represents the chiral auxiliary attached to the dienophile. Structures **53** and **54** are two possible diastereomers resulting from the exo addition of the dienophile to the heteroaromatic salt. Hence a variety of dienophiles bearing chiral auxiliary were prepared and studied.

Results

A. Preparation of Dienophiles

Chiral Vinyl Ethers

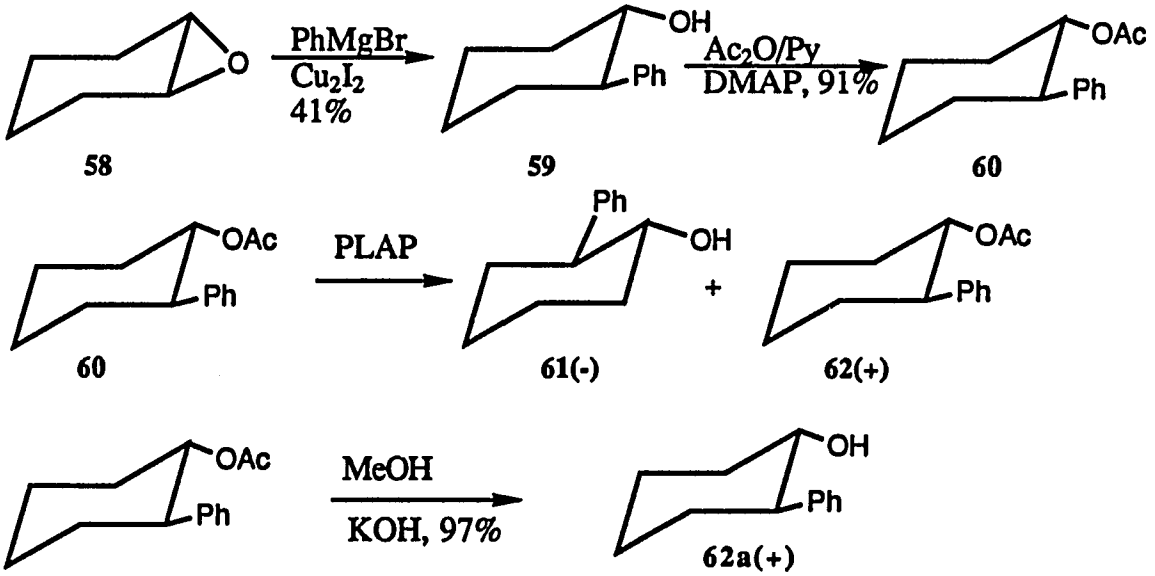
The following chiral vinyl ethers were prepared as shown, by trans-etherification with ethyl vinyl ether in the presence of mercuric acetate as the catalyst[46].



55 **56** **57**

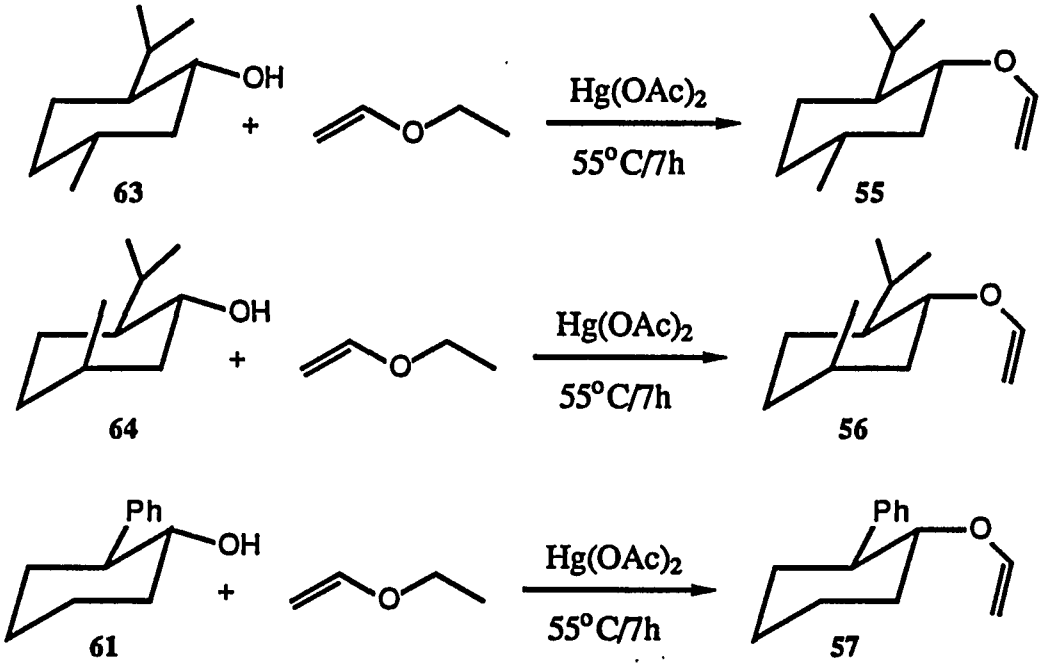
Fig.10: Chiral vinyl ethers for cycloaddition

Menthol and isomenthol were purchased from Aldrich. Trans phenyl cyclohexyl vinyl ether **57** was obtained from the corresponding alcohol which was obtained from the resolution of its racemic acetate by pig liver esterase[47] (Scheme 7).



Scheme 7: Enzymatic resolution by pig liver acetone powder of trans-2-phenylcyclohexyl acetate.

The opening of the cyclohexene epoxide with phenyl magnesium bromide produces the racemic trans phenyl cyclohexanol **59** which was acetylated with Ac_2O/Py. This racemic mixture of acetates was subjected to enzymatic hydrolysis with pig liver acetone powder which resolves the the racemic mixture to form alcohol **61** and acetate **62.** The silica gel chromatography separates the two isomers, affording **61** as a white crystalline solid and **62** a liquid. Base hydrolysis of the acetate releases the free alcohol. The purity of each compound was determined by converting each to its Mosher ester derivative[48].

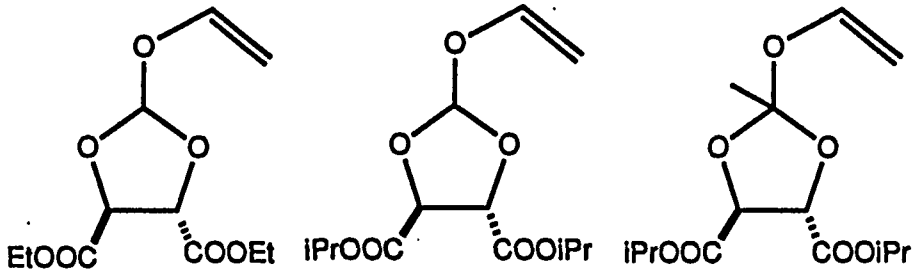


Scheme 8: Preparation of chiral vinyl ethers by trans-etherification with ethyl vinyl ether.

They were shown to be optically pure. Alcohol **61** was used for conversion to a vinyl ether. The chiral alcohols **61, 63** and **64** were treated with 10-fold excess of ethyl vinyl ether at 55°C for 7h. with mercuric acetate as the catalyst (Scheme 8). After the reaction was complete the mixture was cooled to room temperature and solid K_2CO_3 was added. Solvent was evaporated from the heterogeneous mixture. The solids were removed by filtration through a cotton plug and the resultant liquid filtrate was chromatographed on a florosil column to obtain the pure vinyl ether.

Preparation of Chiral Vinyl Orthoesters (65a and 65b)

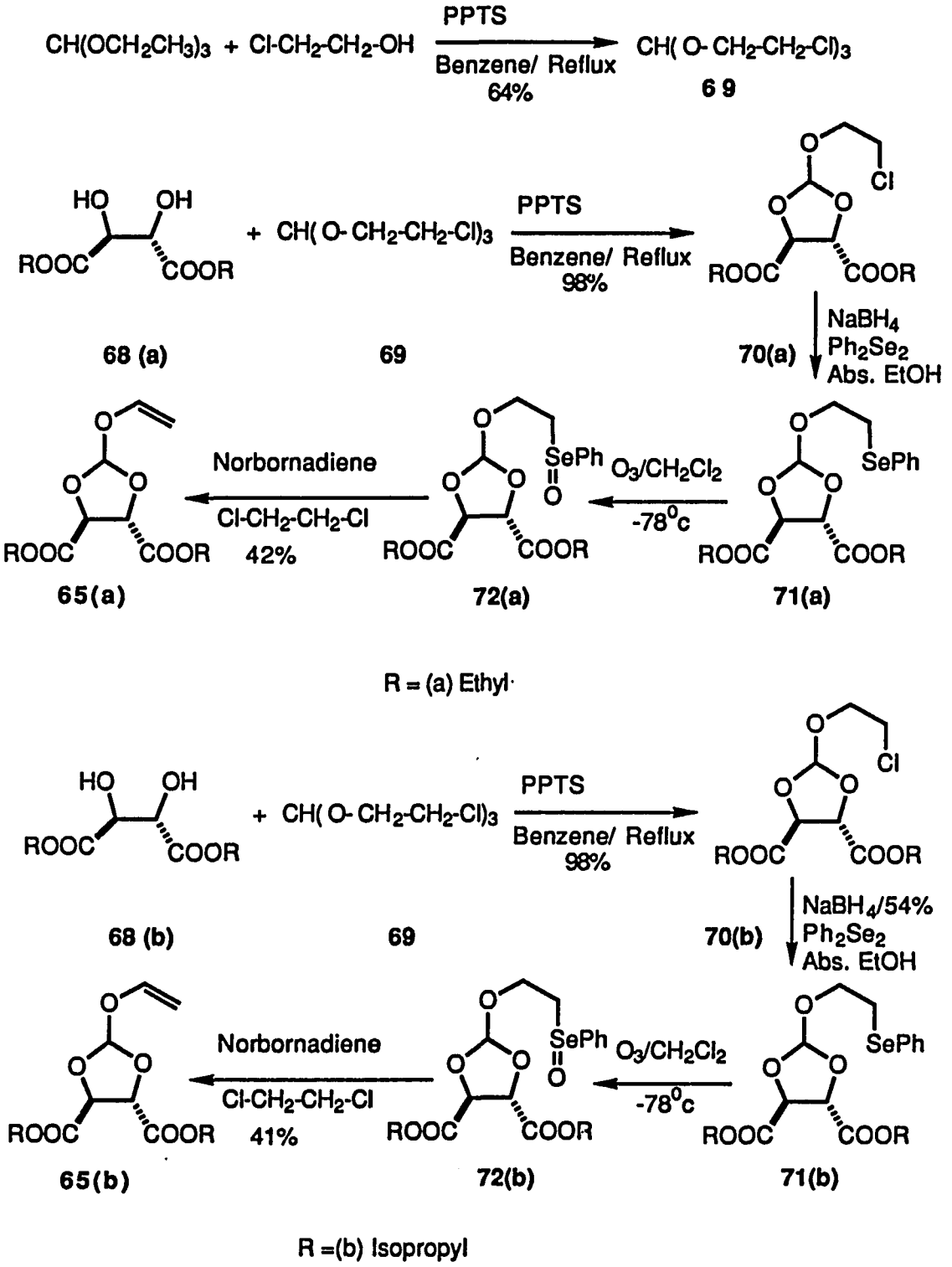
The selectivity shown by phenyl cyclohexyl vinyl ether **57** is phenomenal (see below in Table-1) but the chiral auxiliary after cycloaddition exists as a secondary ether which is not easy to cleave. Since the work-up step of our cycloaddition involves treatment with acid we searched for an acid-sensitive and base-stable dienophile bearing a chiral auxiliary which would be stable to cycloaddition (basic conditions) but would cleave during the work-up (acidic conditions) step removing the auxiliary. Chiral vinyl orthoesters fulfill these criteria. The following chiral vinyl orthoesters were prepared.



65a **65b** **67**

Fig.11: Chiral orthoester vinyl ethers for cycloaddition

This class of dienophiles possessing C2 symmetry have been prepared by the manipulation/combination of literature procedures[37]. Though the chiral part of the molecule is remote from the dienophilic double bond, we believed that the trans diaxial disposition of the ester moiety with a stereoelectronic bias will permit discrimination of the face of the double bond. Scheme 9 represents the method of preparation.

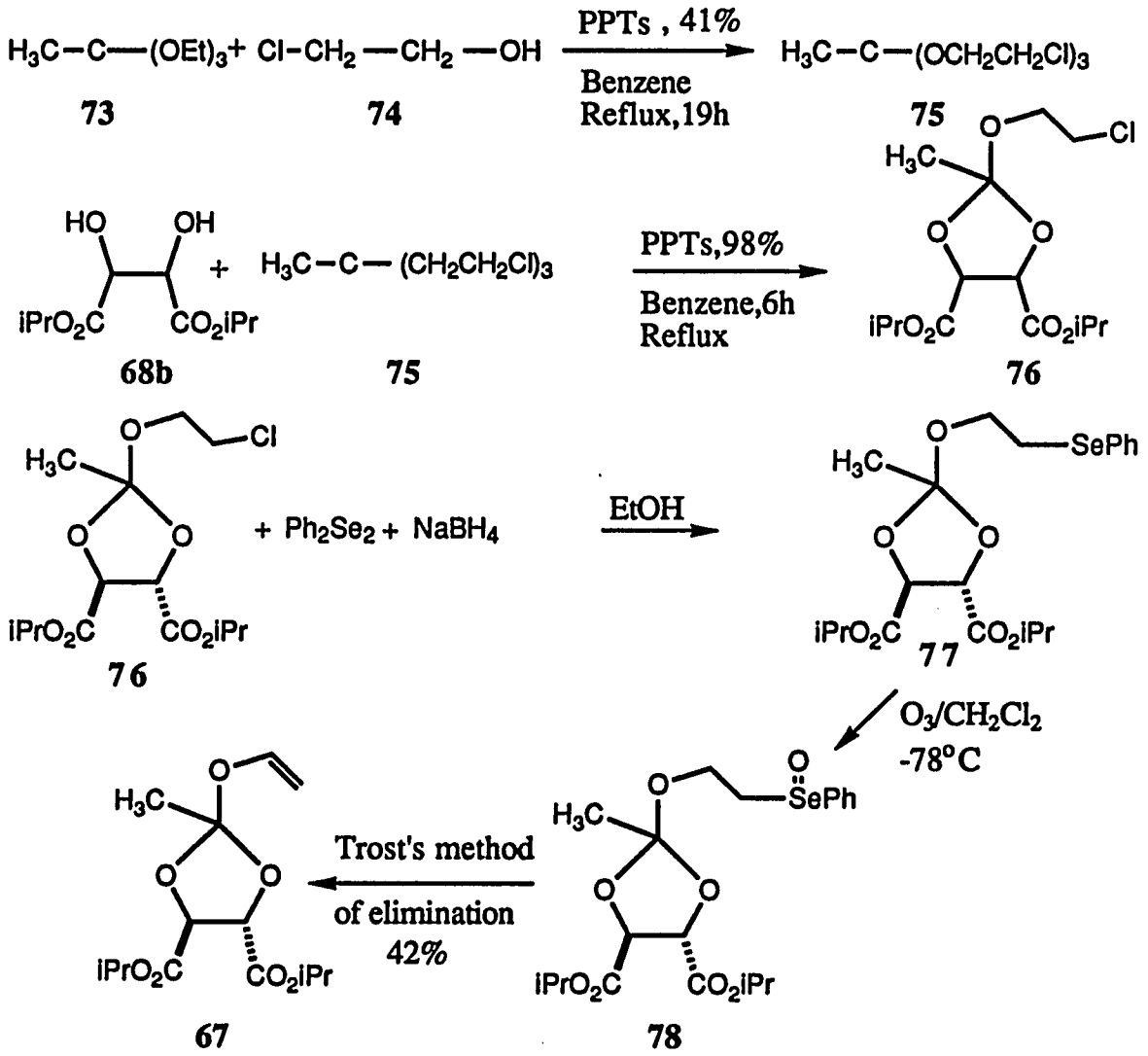


Scheme 9: Preparation of chiral orthoester vinyl ethers

The commercially available chiral dialkyl tartarate (diethyl and/or diisopropyl tartarate) **68(a/b)** was exchanged with tris-trichloro ethylorthoformate **69** with benzene as solvent

in the presence of pyridinium p-toluene sulfonate as the catalyst[37]. The resulting chloro orthoester **70(a/b)** formed in 98% yield and was converted to selenide **71(a/b)** by the reaction with diphenyl diselenide and sodium borohydride in ethanol. The selenide was converted to selenoxide **72(a/b)** by ozonolysis. Trost's method of elimination[49] followed by distillation gave the corresponding orthoester vinyl ethers **65a** in 42% and **65b** in 41% starting from the respective chloro compounds.

Preparation of Orthoacetate Vinyl Ether (67)



Scheme 10: Preparation of orthoacetate vinylether

Because the face selection from the above cycloadditons were highly disappointing, which we rationalize on basis of stereoelectronic grounds (described in the discussion section), the concept of designing a conformationally restricted orthoacetate vinyl ether **67** was developed. It was prepared as follows (Scheme 10). Triethyl orthoacetate **73** was exchanged with 2-chloroethanol **74** in the presence of PPTs (catalytic) and benzene as solvent. After 18h. the mixture was cooled to room temperature. The reaction mixture was washed with a cold aqueous solution of sodium bicarbonate and dried over sodium carbonate. The product was distilled off (87-90°C at 0.001mm/Hg) and identified as **75** by nmr. Trichloroethyl orthoacetate was exchanged with diisopropyl tartarate **68b**. The compound **76** was isolated in 98% yield. Chloro compound **76** was derivatised to its phenyl selenide derivative **77** by reacting it with diphenyl diselenide in the presence of sodium borohydride. Ozonolysis of **78** formed selenoxide **79** which was subjected to Trost's method of elimination[49] giving a 42% yield of the vinyl ether.

Chiral Vinyl Acetals

The poor facial discrimintion of the orthoester vinyl ethers but the elegance of their facile cleavage during the work-up step of cycloaddition stimulated us to develop other systems that could cleave with acid, with the hope that we could enhance the face selection. Vinyl acetals were seen to be viable alternatives. The following vinyl acetals were prepared (Fig 12)

(i) Preparation of trans 1-[2-(Vinyloxy)-methoxy-trans-2-phenyl] cyclo-hexanol (79):

Auxiliary **79**, a vinyl acetal was developed based on the above concept. We were also curious to know the effect of a phenyl group on face discrimination when it is two atoms removed from the dienophilic double bond compared to its vinyl ether counterpart. Scheme

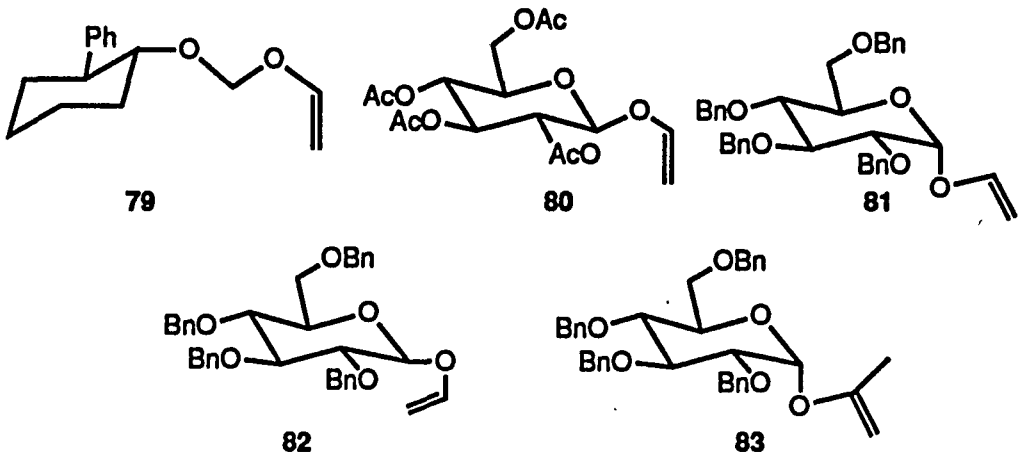
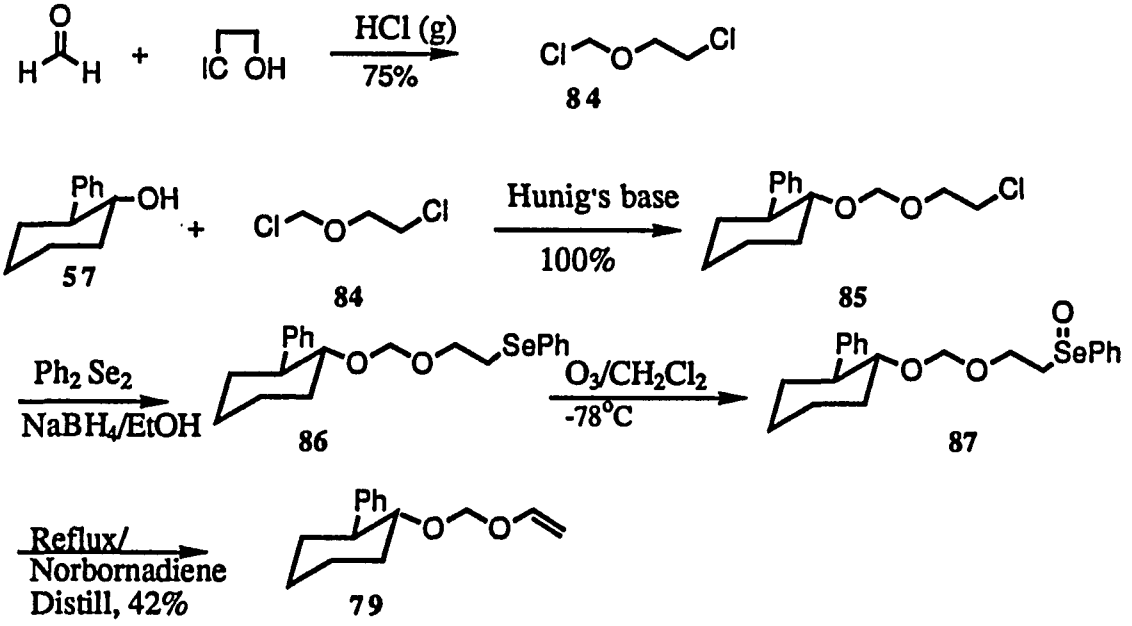


Fig.12: Chiral vinyl acetals for cycloaddition

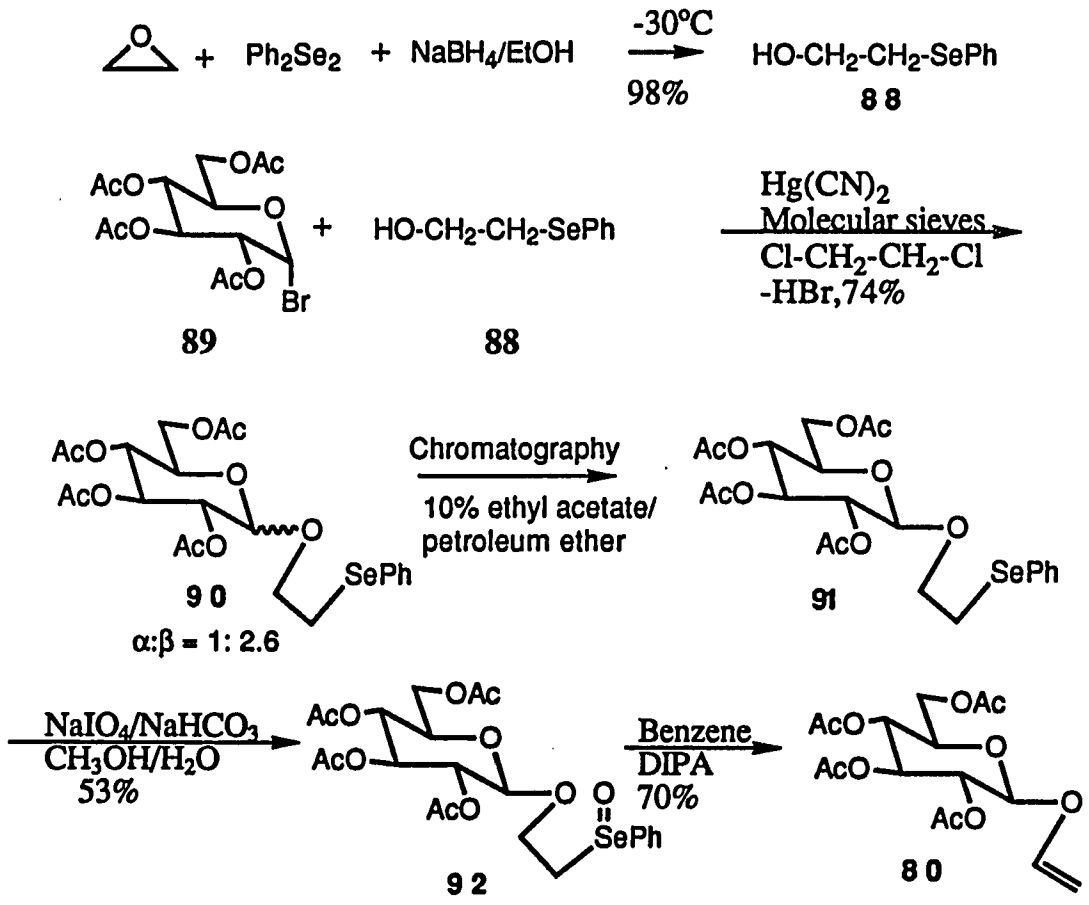
11, which describes the preparation of **79** is as follows. The reaction of formaldehyde with chloroethanol[44] in the presence of HCl produces chloroethoxymethoxymethane **84** which reacts with phenylcyclohexanol **57** in the presence of Hunig's base to give chloroacetal[51] **85**. The selenide **86** of the chloro compound was made by reducing diphenyl diselenide with sodium borohydride in the presence of ethanol. Ozonolysis of the selenide followed by Trost's method of elimination[49] gave the corresponding vinyl acetal **79**.



Scheme 11: Preparation of vinyl acetal (**79**)

(ii) Preparation of 2,3,4,6 Tetra-o-acetyl 1-vinyl glucupyranoside (80):

The use of dienylglycosides for cycloaddition reactions is not new [52-53]. But the use of vinyl glycosides in inverse electron demand reactions is not reported in literature. There were several concepts that could be tested using vinyl glycosides: 1. the fundamental interest of a sugar in biasing the face discrimination in an inverse electron demand cyclo addition. 2. The comparison of the induced selectivity of sugar attached to a diene (Stoodley's diene)[52] with the sugar attached to a dienophile (our case) where both species act as an electron-rich component in the cycloadditon reaction. 3. The selective cleavage of the carbohydrate chiral auxiliary from the cycloaddition product without affecting the

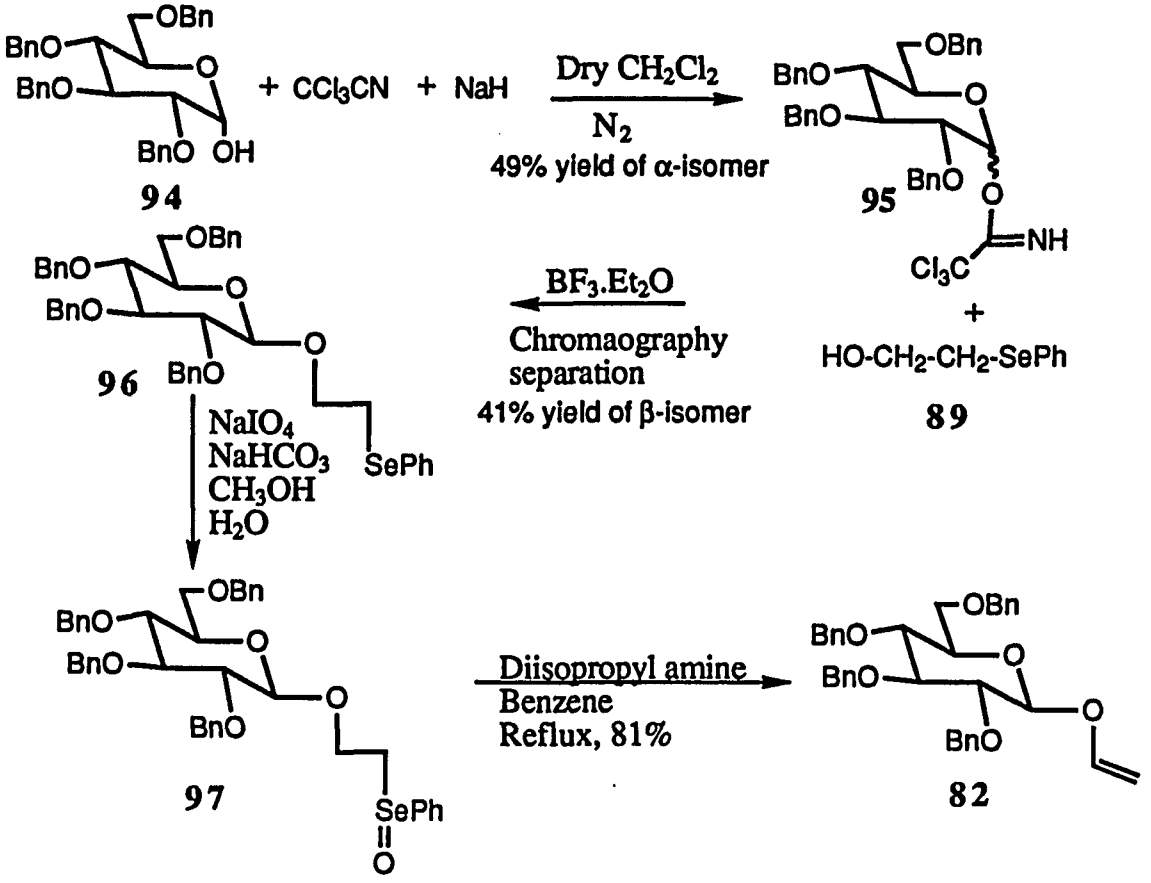


Scheme 12: Preparation of 2,3,4,6-tetra-O-acetyl -β-D-glucopyranoside (80)

tetralin functionality. Three different types of sugar dienophiles were prepared. Described (Scheme 12) is the preparation of 2,3,4,6-tetra-O-acetyl-1-vinyl-β-D-glucopyranoside **80**[54]. The nucleophilic opening of liquid oxirane[54] with phenyl selenide anion produces selenophenylethanol **88** which is then reacted with tetraacetyl bromosugar **89** in the presence of mercuric cyanide as the catalyst to produce the mixture of selenides **90** in 74% (α : β = 1 : 2.6). The β -selenide (characterised by the appearence of the anomeric proton at 4.68 ppm with a coupling constant of 8 Hz) **91** was separated chromatographically from its anomer (characterised by the appearence of the anomeric proton at 5.69 ppm with a coupling constant of 5.23 Hz) and oxidized with sodium periodate to yield (53%) the selenoxide **91**, which was refluxed with benzene as solvent in the presence of di-isopropyl amine to produce the vinyl ether **80**, which was characterized by the appearance of an anomeric proton at 4.84 ppm with a coupling constant of 7.84 Hz, and the melting point of 95°C (lit. mp. 97-98°C).

(iii) Preparation of 2,3,4,6 Tetra-O-benzyl-1-vinyl-β-D-glucopyranoside (82)

Tetra-O-benzyl-β-D-glucopyranoside **82** was prepared with some modification of the literature procedure[55]. Though this compound can be obtained from the trans etherification reaction (Scheme 14), the yield was quite poor (4.5%). Therefore Schmidt's glycosidation procedure was applied[55]. Scheme 13 presents the details. 2,3,4,6 Tetra-O-benzyl-α-D-glucopyranose **94** was treated with trichloroacetonitrile using sodium hydride as the base. This produces α-chloroimidate in 49% yield after chromatographic purification (characterised by the appearence of anomeric proton at δ 6.56 with a cis coupling constant of 3.5 Hz). The α-chloroimidate reacted with phenylselenoethanol **88** in the presence boron trifluoride etherate to form the corresponding β selenide as the major component. The pure isomer was obtained in 41% yield by radial chromatography. The

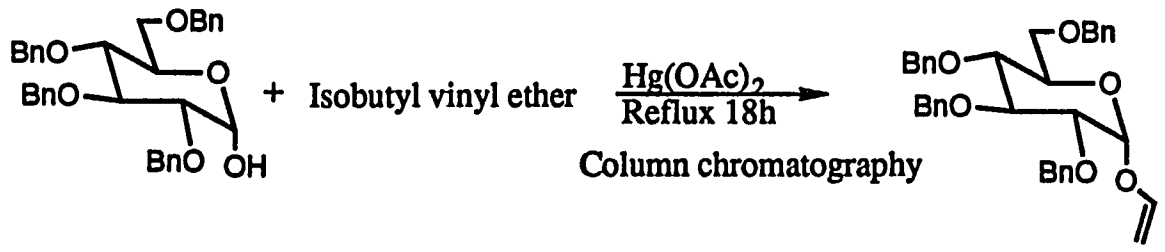


Scheme 13: Preparation of 2,3,4,6 tetra-O-benzyl-1-vinyl-β–D-glucopyranoside **(82)**

selenide **96** was oxidised with sodium meta periodate in the presence of methanol and water to give the corresponding selenoxide **97**. The selenoxide was subjected to elimination in refluxing benzene with diisopropyl amine as the base to give the required vinyl ether **82** in 81% yield.

(iv) Preparation of 2,3,4,6 Tetra-O-benzyl-1-vinyl-α- D-glucopyranoside (81)[56]:

Vinyl 2,3,4,6 -O- tetrabenzyl-α-D-glucopyranoside was prepared according to the literature procedure by refluxing the corresponding sugar **94** with isobutyl vinyl ether in the



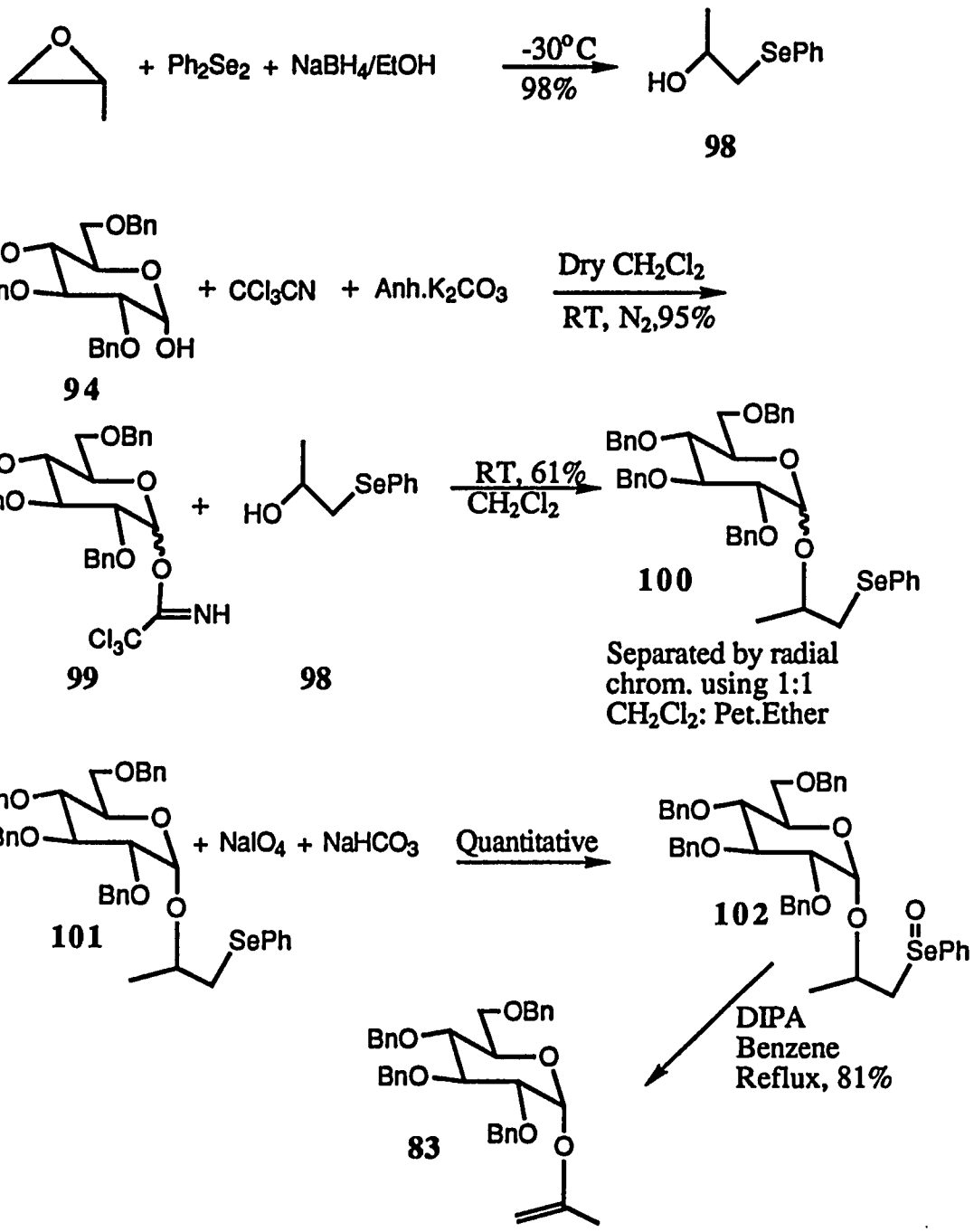
94 **81**

Scheme 14: Preparation of 2,3,4,6 tetra-O-benzyl-1-vinyl-α- D-glucopyranoside (**81**)

presence of mercuric acetate as the catalyst[46]. The resulting mixture of vinyl ethers were purified by column chromatography on silica using $CHCl_3$ as the solvent. The α-isomer of the mixture was eluted first in 30% yield from the column followed by the β isomer (4%). The α-isomer was a thick syrupy liquid whereas the β -isomer was a white crystalline solid of melting point 75-76°C. Again the α-isomer was characterised from the NMR form the coupling constant of the anomeric proton at 5.16 ppm (5.51Hz). As the result of the cycloaddition of the vinyl ether **81** in terms of yield and diastereoselectivity was highly encouraging, an isopropenyl ether that will generate a model anthracycline was our next target

(v) Preparation of 2,3,4,6 Tetra-O-benzyl-1-Isopropenyl-α-D-gluco-pyranoside (83):

Compound **83** was prepared as follows. The sugar chloroimidate was synthesised according to the Schmidt's method of glycosidation[55], (Scheme 15) by treatment of 2, 3, 4, 6 tetra-O-benzyl -α-D- glucopyranoside with trichloroacetonitrile in the presence of K_2CO_3 as the base. This produced the β-isomer of the resultant chloroimidate in 95% yield. This was treated with 1-methyl, 2-selenophenylethanol **98** obtained by nucleophilic opening of propylene oxide with pheny selenide anion) at room temperature with CH_2Cl_2 as the solvent giving 61% of the required selenide. The selenide **101** was oxidised with sodium meta periodate in the presence of



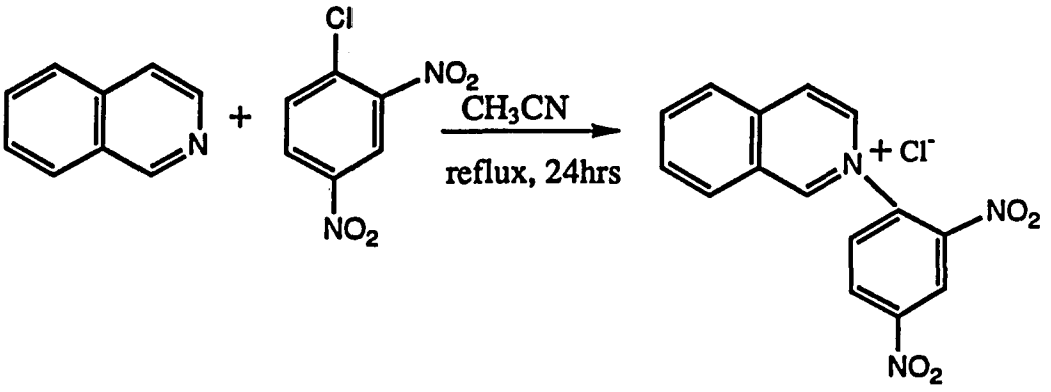
Scheme 15: Preparation of 2,3,4,6 tetra-O-benzyl-1-isopropenyl-α-D-glucopyranoside **(83)**

selenide anion at room temperature with CH_2Cl_2 as the solvent giving 61% of the required selenide. The selenide **101** was oxidised with sodium meta periodate in the presence of $NaHCO_3$. This procedure produced the selenoxide **102** in almost quantitative yield as a white solid. Refluxing the selenoxide in benzene in the presence of di-isopropyl amine

produced the required vinyl ether **83** in 81% yield. The pure compound was characterised from its coupling constant of 3.52 Hz of the anomeric proton at 5.36 ppm.

B. Preparation of the Diene

The diene was prepared by refluxing an equimolecular mixture of isoquinoline **103** and 2,4 dinitrochlorobenzene **104** in dry acetonitrile for 24 h (Scheme 16).



103 **104** **105**

Scheme 16: Preparation of 2,4 dinitro chlorobenzene salt of isoquinoline (**105**)

The salt **105** precipitated out from the mixture. It was filtered and washed with cold acetonitrile till the reddish color dissapeared and the yellow crystaline salt remains on the filter paper. It was dried under high vacuum till it became free flowing. This salt was used for all cycloaddition experiments.

C. Cycloaddition

A typical cycloaddition experiment is described below. The salt is dissolved in a minimum amount of dry methanol and to start with 1 to 3 equivalents of dienophile was added followed by the addition of anhydrous $CaCO_3$ (600 mg per each milimole of the substrate). The mixture is stirred at room temperature and if required, is subsequently heated to a maximum of 40°C. The completion of the reaction is checked by TLC. The mixture is then cooled to room temperature and the suspended $CaCO_3$ is filtered off through celite. The

cycloadduct-containing filtrate is concentrated using evaporation and then put under high vacuum for several hours.

Treatment of the adduct with acidic resin in the presence of dry methanol affords the tetralin acetal which is stable to base and also mild acid. The results of the cycloadditions are tabulated.

D. Stereochemical Characterisation of the Adducts

Previous work in this laboratories has unambiguously established the stereochemistry of the tetralin adducts from coupling constants of the products and noe experiments of the reaction of isoquinolinium salts with different dienophiles, having electron releasing heteroatoms such as oxygen, nitrogen and sulphur. Moreover the relative disposition of the functionalities of the tetralin adducts derived from the phenyl vinyl sulphides with isoquinolinium salts has been established by the single crystal X-ray analysis of the adduct[57], which proves our assumption of the exo fashion of cycloaddition in most cases with unsubstituted dienophiles. No deviation of this trend has been obtained so far. The nmrs of the cycloadducts discussed here in this text follows the regular predictable pattern, thus the relative stereochemistry is proved.

The heights / integrals of the methoxyl singlets of the isolated mixture of diastereomers were used to determine the diastereomeric excesses of the product.

% Diastereomeric excesses = [X-Y / X + Y] 100, where X and Y represent the individual heights of the methoxyl peaks.

The absolute stereochemistry of the major diastereomer is derived from the circular dichroism spectrum, which will be detailed in the following section. Fig.13 shows the diastereomers arising from the cycloaddition of isoquinolinium salts **105** with vinyl ethers **55**, producing **106** and**107**; with vinyl ether **56**, producing **108** and **109**; and vinyl ether **57**, producing **110**. Compound **111** was not detected by nmr.

The diastereomers **106** and **107**, and the diastereomers **108** and **109** were not separable under radial chromatographic conditions. The diastereomeric excesses, the yield and the absolute configuration of the major isomer have been tabulated in Table1.

The cycloaddition product from vinyl ether **57** was a single compound in 91% yield. The yields in case of the addition of **55** and **56** are moderate, i.e. 57% and 56% respectively,

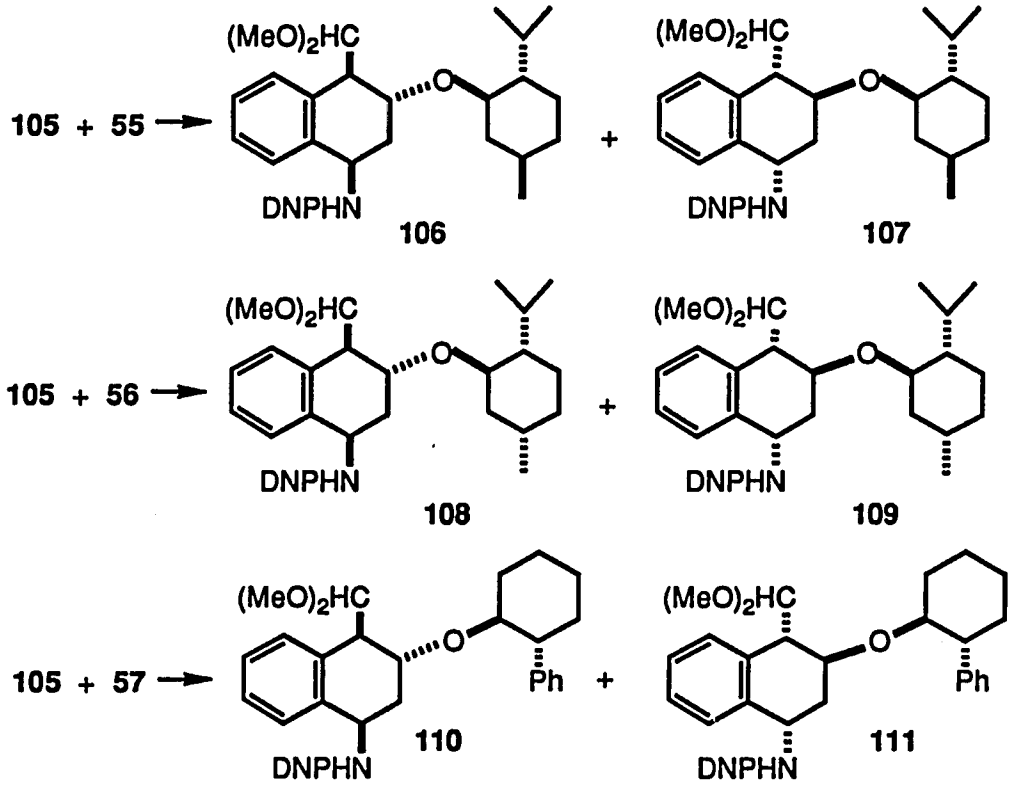


Fig. 13: Tetralins derived from the cycloaddition of chiral vinyl ethers

but the mass balance can be achieved by counting on napthaldehyde and 2,4 dinitroaniline resulting from the aromatisation of the cycloadduct. Table 1 shows the results of the addition of chiral vinyl ethers to isoquinolinium salts. The tetralin acetal produced in case of the cycloaddition of vinyl ethers has the chiral auxiliary attached to it.

TABLE 1

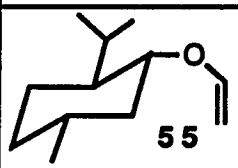
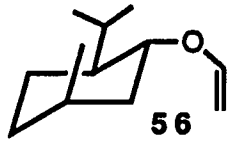
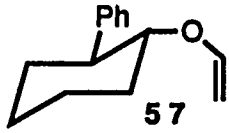
Entry	Dienophile	Major Diastereomer	Yield	de
a	 55	106	57%	36%
b	 56	108	56%	10%
c	 57	110	91%	95+%

Table 1: Cycloaddition of chiral vinyl ethers

entry a: reaction time 4 d, 2 equivalent of 62, 40°C entry b: reaction time 3 d, 2 equivalents of 63, 40°C entry c: reaction time 4 d, 1.1 equivalent of 64, room temperature.

The results of the cycloaddition of the chiral vinyl orthoesters is shown below. The tetralins have the hydroxyl group at 2-position produced from the hydrolysis of the chiral auxiliary. Whereas the addition of vinyl ether **65** and **66** to the isoquinolinium salt produced the mixture of enantiomeric alcohols produced from exo addition, the cycloaddition of **67** produced a mixture of exo and endo alcohols.

Table 2 shows the results of the cycloaddition reaction of chiral vinyl orthoesters. It is quite evident that the face discrimination is poor (in contrast to our great hope). The possible reason we have given is discussed in the following section. The chiral auxiliary was removed during the work-up step of the cycloaddition without requiring any extra effort. The crude alcohol was purified by radial chromatography.

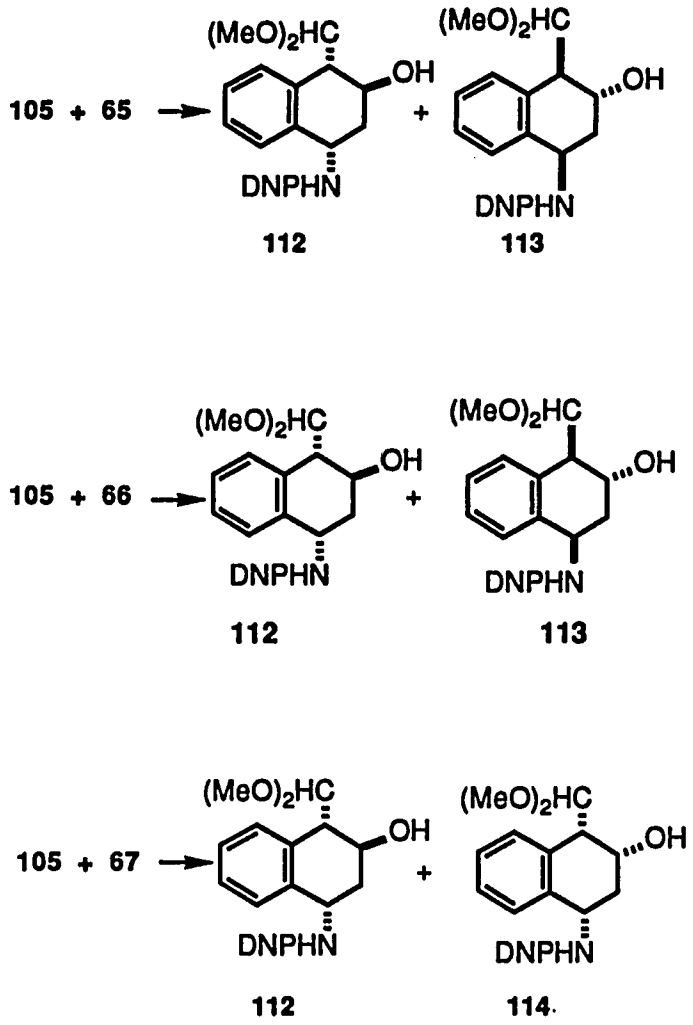


Fig 14: Tetralins derived form the cycloaddition of vinyl orthoesters

The Mosher ester of the resulting tetralin alcohol was made and compared with its racemic counterpart to determine the enantiomeric excesses of the product. The peak doubling of the acetal proton in nmr and the integral of the doubled peaks were used to determine the enantiomeric excesses of the reaction.

Cycloaddition of chiral vinyl acetals were tried. As is evident from Table-2, the cleavage of the chiral auxiliary in case of the cycloaddition of compound **79** (page 23, Fig 12) is facile but the other acetals remain inert to the work-up condition. Now the face discrimination

TABLE 2

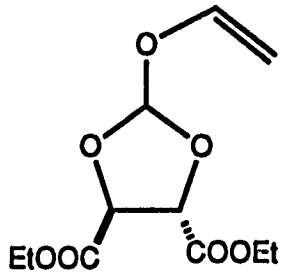
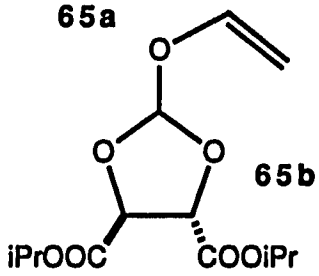
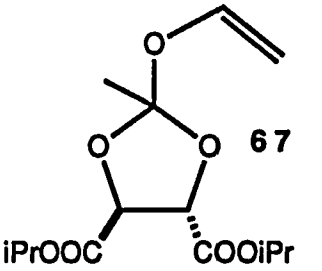
Entry	Dienophile	Major Enantiomer	Yield	ee
d	 65a	112	48%	16-20%
e	 65b	112	68%	5-11%
f	 67	112 exo: endo = 3.5 : 1	7%	

Table 2: Cycloaddition of chiral vinyl orthoesters

entry d: reaction time 7 d, 1.3 equivalents of 65 at room temperature entry e: reaction time 7 d, 1.1 equivalents of 66 at room temperature. f: reaction time 6 d, 1.3 equivalents of 67 at 42°C

in case of **112** (fig.15) is abruptly reduced compared to its vinyl ether counterpart. It may be beacause the face biasing element "phenyl" is further removed by two atoms away from the reactive site of the dienophile. The enantiomeric purity of the compound was

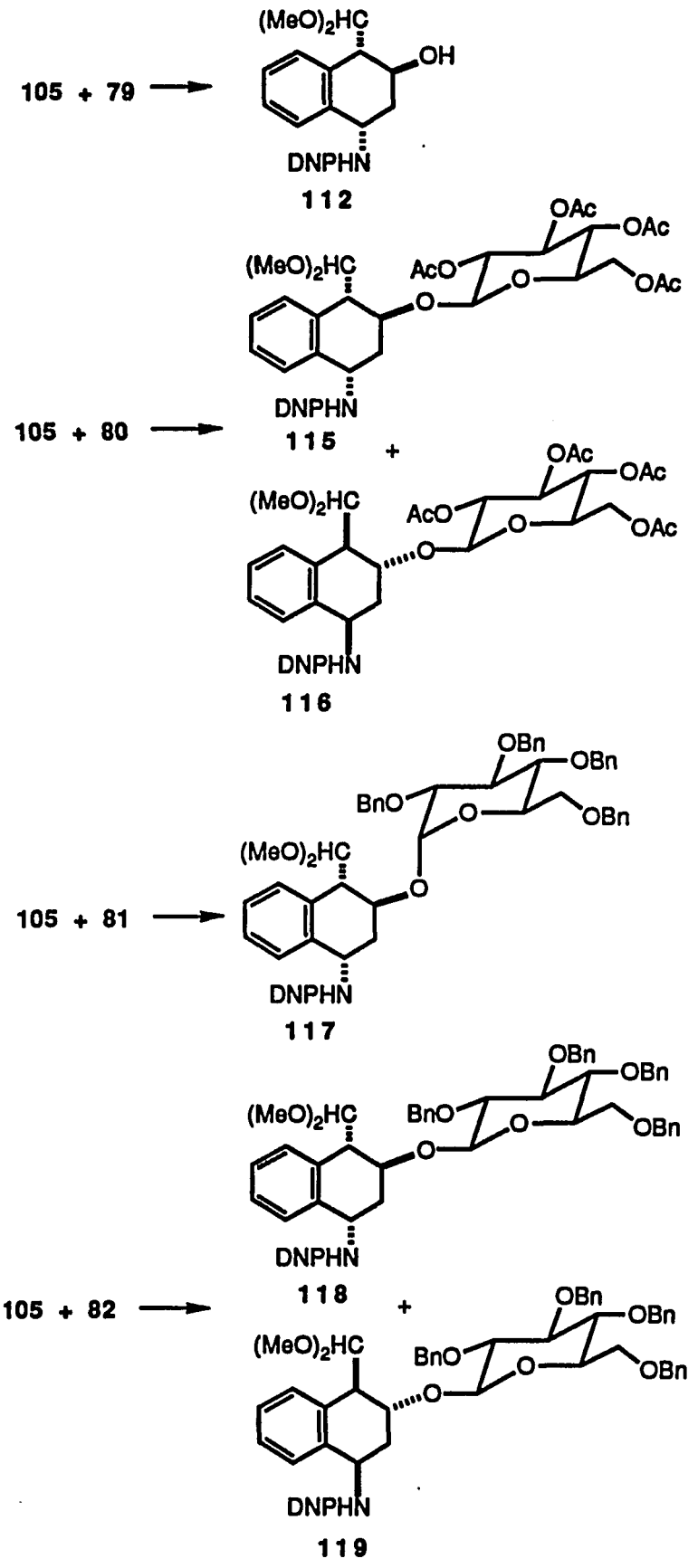


Fig 15: Tetralins from the cycloaddition of chiral vinyl acetals

TABLE 3

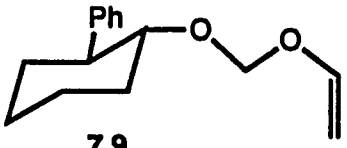
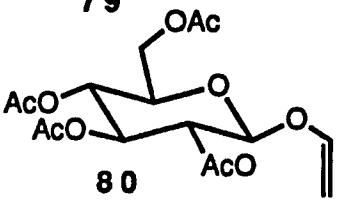
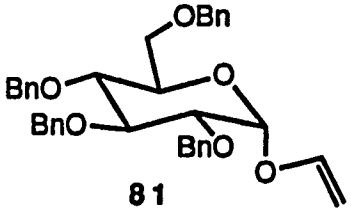
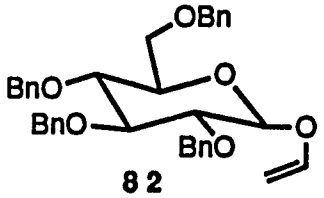
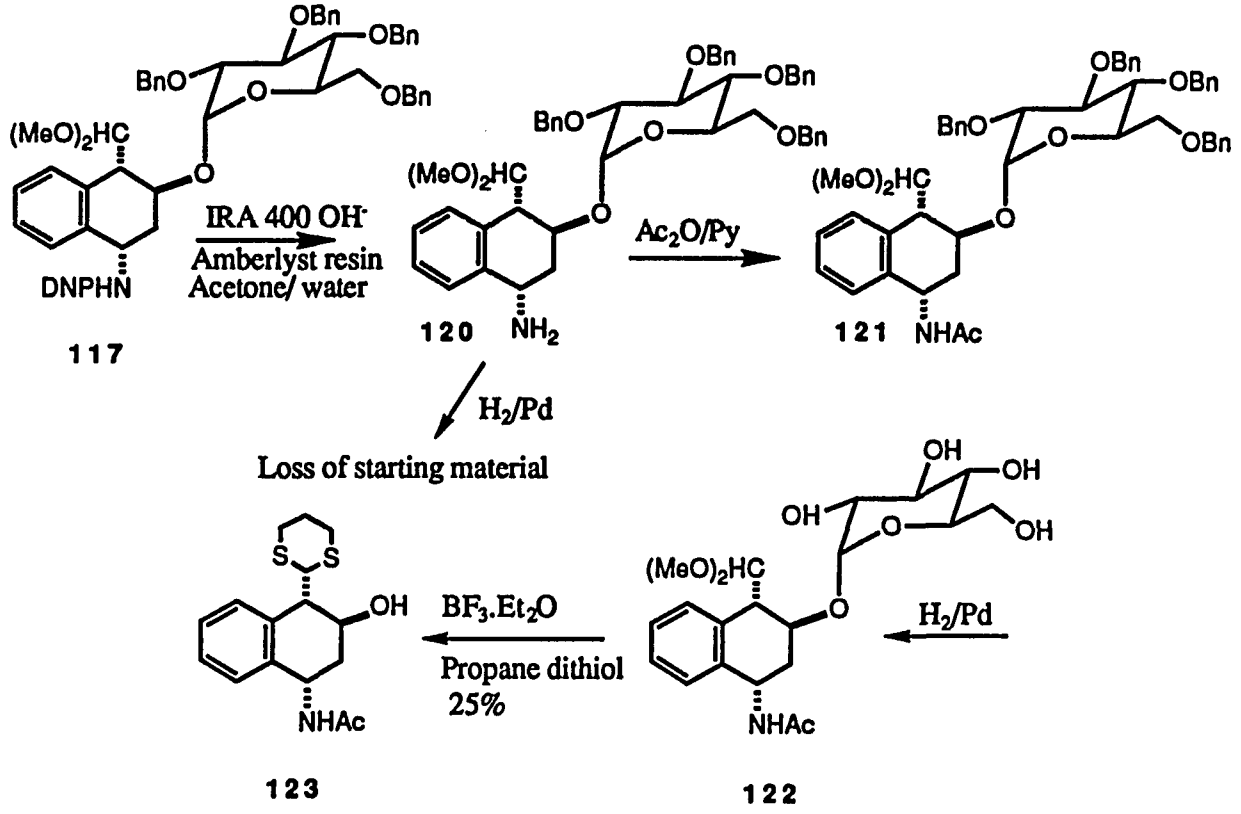
Entry	Dienophile	Major Diastereomer	Yield	de
g	 79	112	62%	55%
h	 80	115	31%	33%
i	 81	117	70%	95+%
j	 82	118	40%	50%

Table 3: Cycloaddition of chiral vinyl acetals

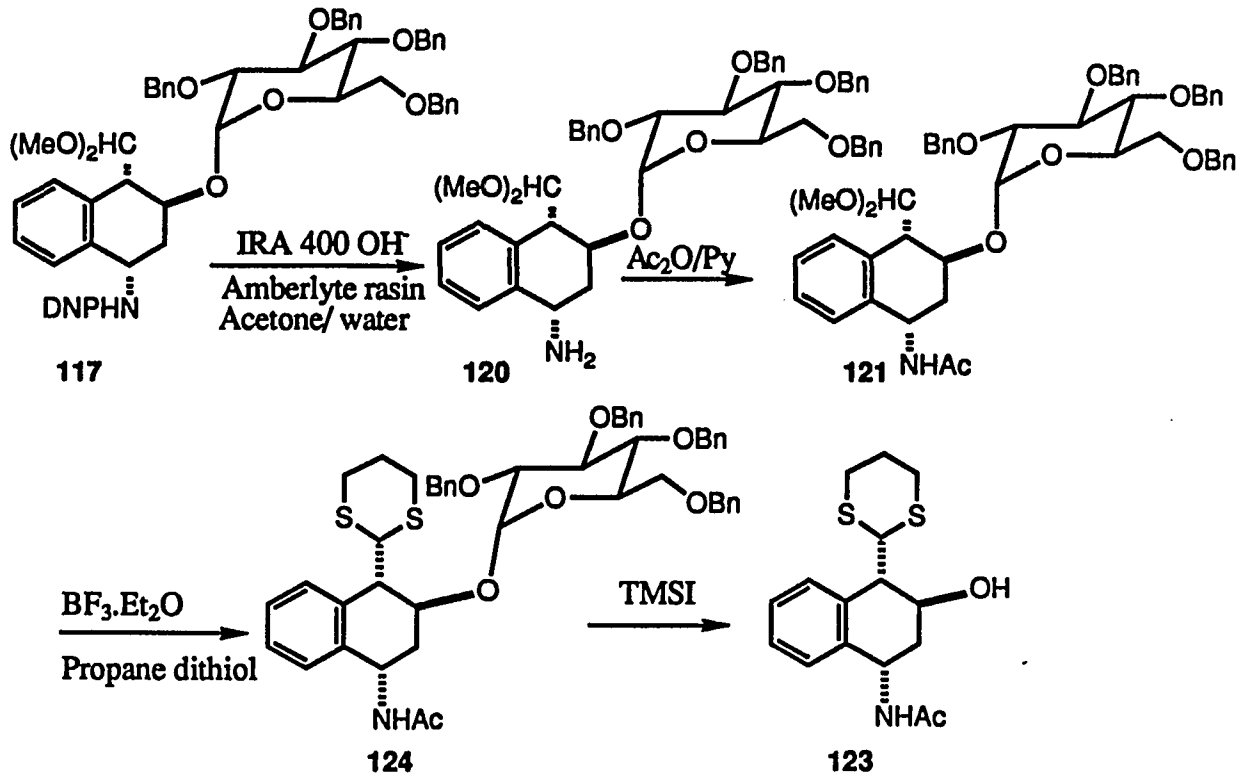
entry g: reaction time 6 d, 1 equivalent of 81 at room temperature; entry h: reaction time 7 d, 1 equivalent of 82 at 42°C; entry i: reaction time 7 d, 2.2 equivalent of 83 at 40°C; entry j: reaction time 11 d, 1 equivalent of 84 at 45°C.

detetrmined by converting the alcohol to its Mosher ester derivative. Compound **115** and **116** were not separable under the radial chromatographic condition, So the diastereomeric excesses could be determined by measuring the heights of the methoxyl peaks in the proton nmr spectrum.



Scheme 17: Hydrogenolysis-propane dithiol sequence

Compound **117** was produced as a single compound with the chiral auxillary intact. The results from vinyl ether **82** were two exo cycloaddition products, separable by radial chromatography. The diastereomeric excesses was determined from the amount of the individual isomer produced from the cycloaddition. The low isolated yield in case of entry h is due to the cleavage of acetates during the work-up step. The cleavage of the chiral auxilliary in case of entry i, which has a very good face discrimination and would provide a practical synthetic protocol for the anthracycline skeleton posed a great problem which will be discussed next. The high selectivity for case i is noteworthy for an -α- configured sugar. Stoodley[58] in his work with chiral dienes observed better selectivity with β-glycosides, which will be discussed in the following section.



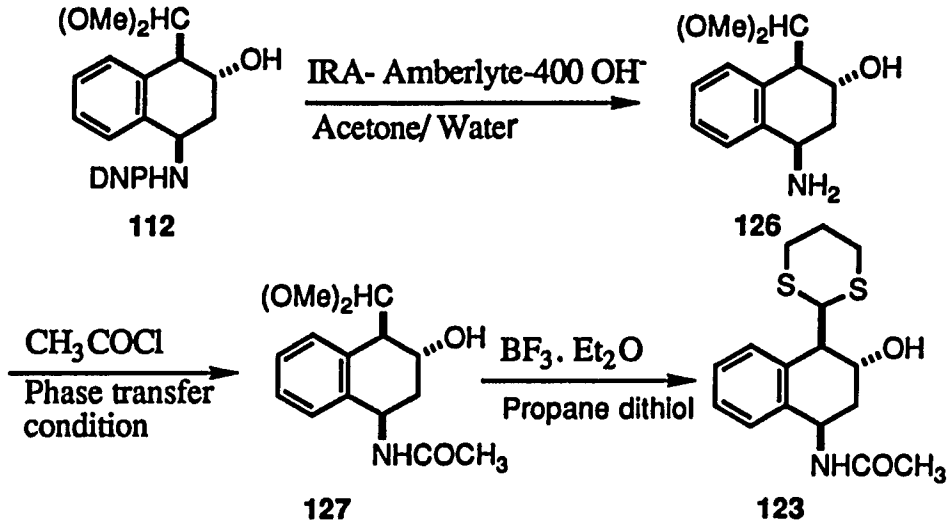
Scheme 18: Cleavage of chiral auxiliary from the cycloacetal **117**

The next immediate task was to remove the chiral auxiliary in our system so as to obtain a enantiomerically pure tetralin. Several methods were tried. Listed below is the summary of failures. One obvious approach is to hydrogenolyze the benzyls from **117** (scheme 18) and subsequently cleave the glycoside with acidic propane dithiol to form a sugar dithiane. Before the hydrogenolysis, the hydrogenation prone 2,4 DNP group must be removed.The tetralin acetal was subjected to basic resin treatment to remove the 2,4 dinitrophenyl group[34]. The attempted hydrogenation of the resulting free amino compound resulted in the loss of material. which was believed to be due to the presence of free amino group. So compound **120** was acetylated with acetic anhydride and pyridine. The acetylated dimethyl acetal **121** was hydrogenated at atmospheric pressure in the presence of a catalytic amount of palladium. The debenzylated compound **122** was cleaved with boron trifluoride etherate in the presence of propane dithiol to give the sugar cleaved dithiane **123**. Though this protocol worked, the yield (25%) of the last step leading to the product was not

respectable. The resulting white crystalline material which we thought as the boron complex was hard to break. Treatment of the white crystalline borate complex with mild acid to improve the yield of the process aromatised the product. Treatment with alkali had no substantial effect after many days. So the scheme was abandoned.

Finally the scheme which worked successfully is shown below. Treatment of the adduct **117** with polymeric basic rasin in the presence of water and acetone cleanly removed the dinitrophenyl group producing the amino compound[34]**120**. The amino compound was derivatised as its acetate **121** with acetic anhydride and pyridine. The dimethylacetal was converted to its dithio compound **124** by treatment with propane dithiol in the presence of boron trifluoride etherate. The resulting dithioacetate **124** reacted with trimethylsilyl iodide[59] which cleaved the chiral auxiliary giving the alcohol **123**. The difference between scheme 18 and scheme 19 is that compound **122** having free hydroxyl group reacts with boron trifluoride etherate forming a stable complex which does not cleave easily to release the product. However compound **121** having the benzyl groups is stable to the Lewis acid treatment. Though there are literature precedences for achieving a straight chain glucose dithiane from its cyclic counterpart using $BF_3.Et_2O$ and propane dithiol, an experiment carried out in our lab to do the same conversion in the case of tetra benzyl glucose was not successful giving a quantitative recovery of the starting material.

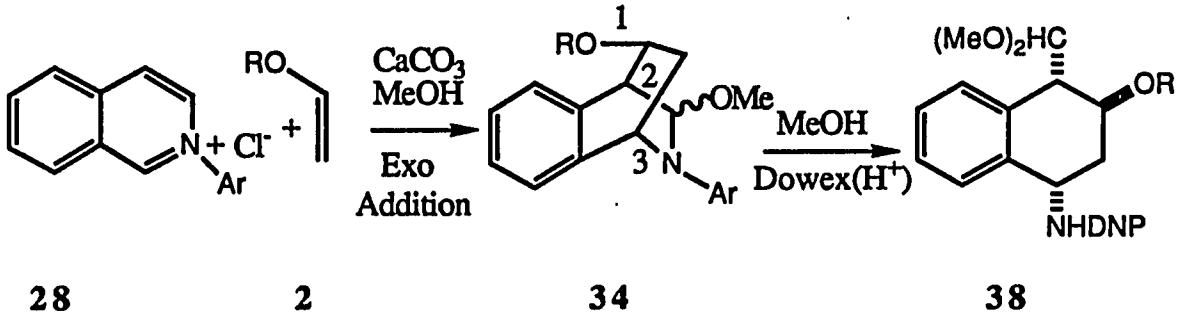
The chiral racemic counterpart of compound **123** was prepared (scheme 20) from the known precurser by the cycloaddition of isoquinolinium salt with O-TBDMS vinyl ether and the ^1H nmr spectrum was identical with **123**. A Mosher ester derivative[48] of the resultant alcohol **123** (optically active) was made to verify the optical purity of the product (and compared with the Mosher ester derivative prepared from the racemic dithaine) which showed the face discrimination is >95+% (have not racemised during the chemical transformations in scheme 19)



Scheme 19: synthesis of the racemic counterpart of **123**

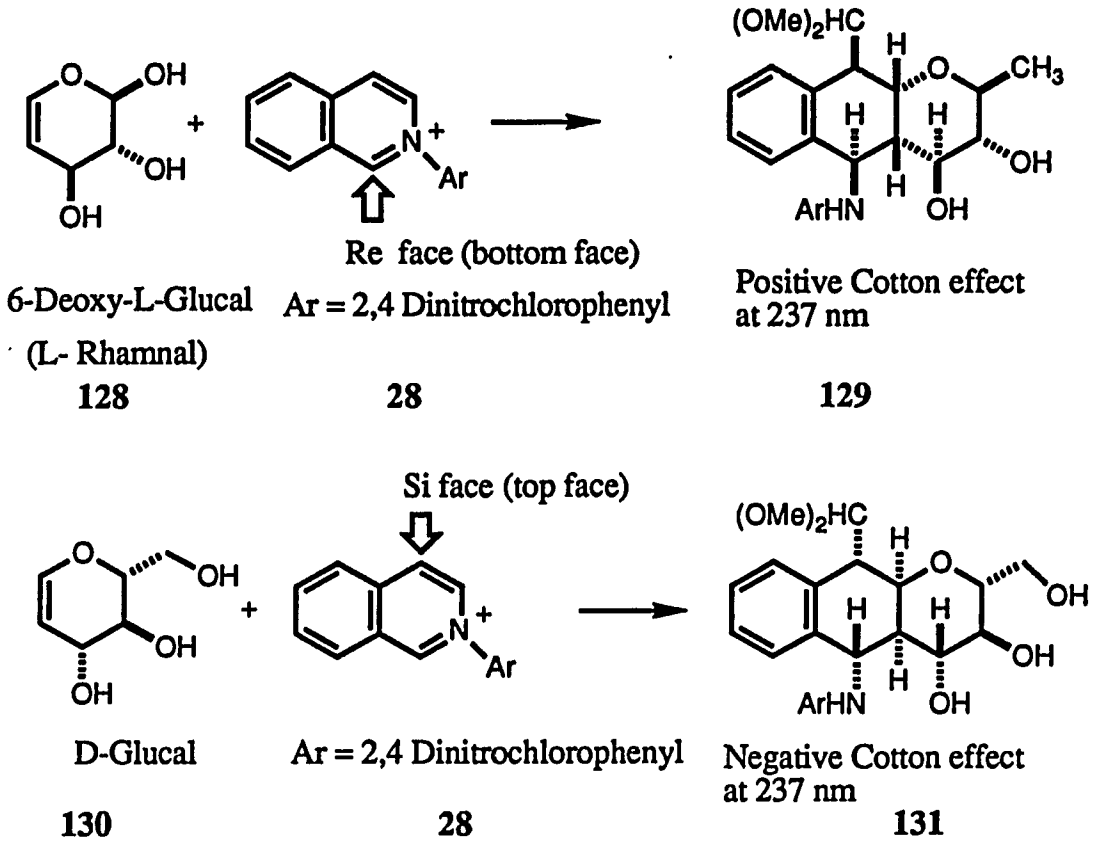
E. Configurational Assignment

Our assumption was that the cycloaddition goes via exo fashion i.e. the substituent on the dienophile and the double bonds on the diene orients trans to each other, the relative stereochemistry of the cycloaddition can be deduced from the mechanism of the



Scheme 20: Relative stereochemistry of cycloaddition of isoquinolinium salt

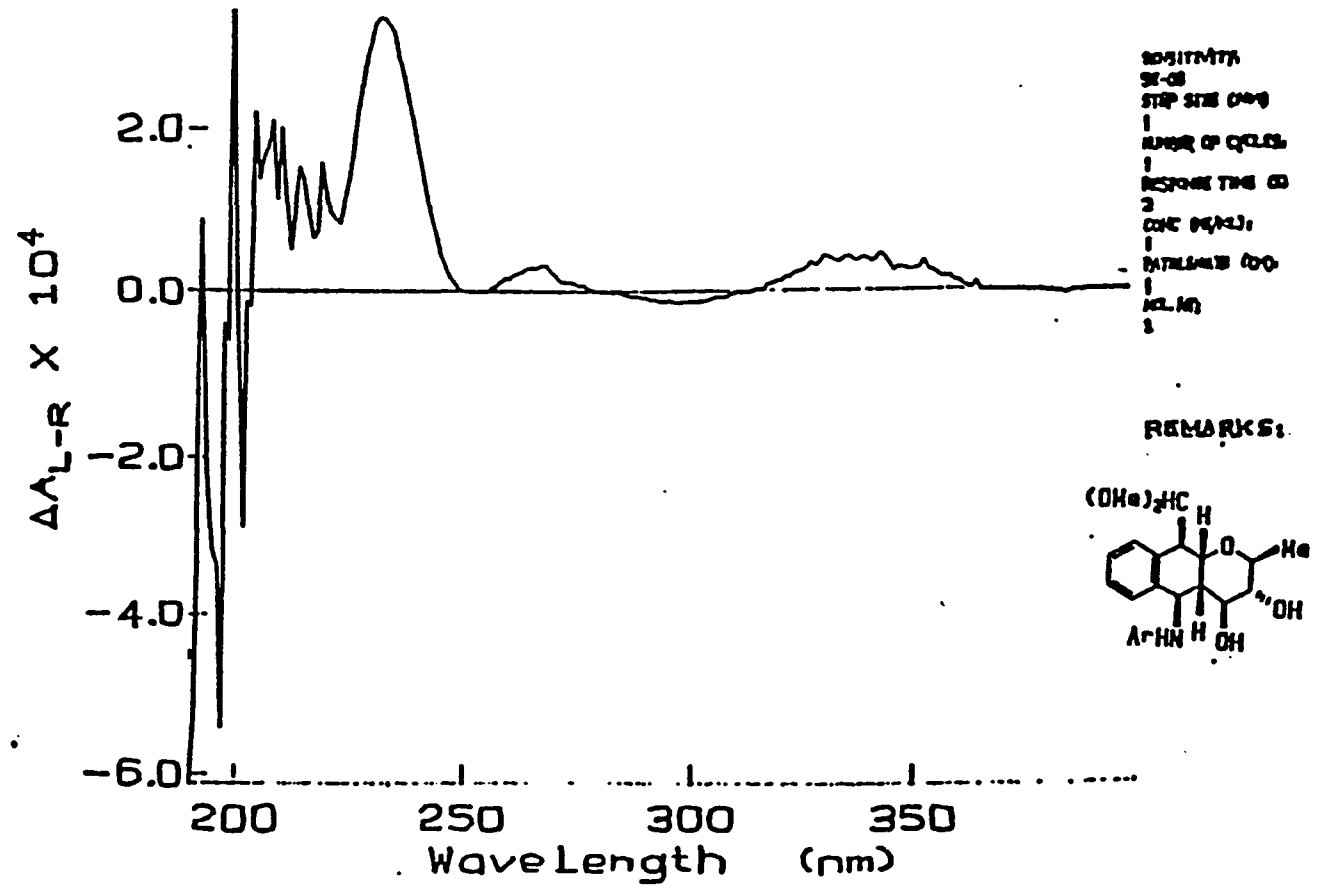
cycloaddition. Bonds 2 and 3 (Scheme 20) in the tricyclic adduct are cis to each other and again both of them are trans to bond 1.

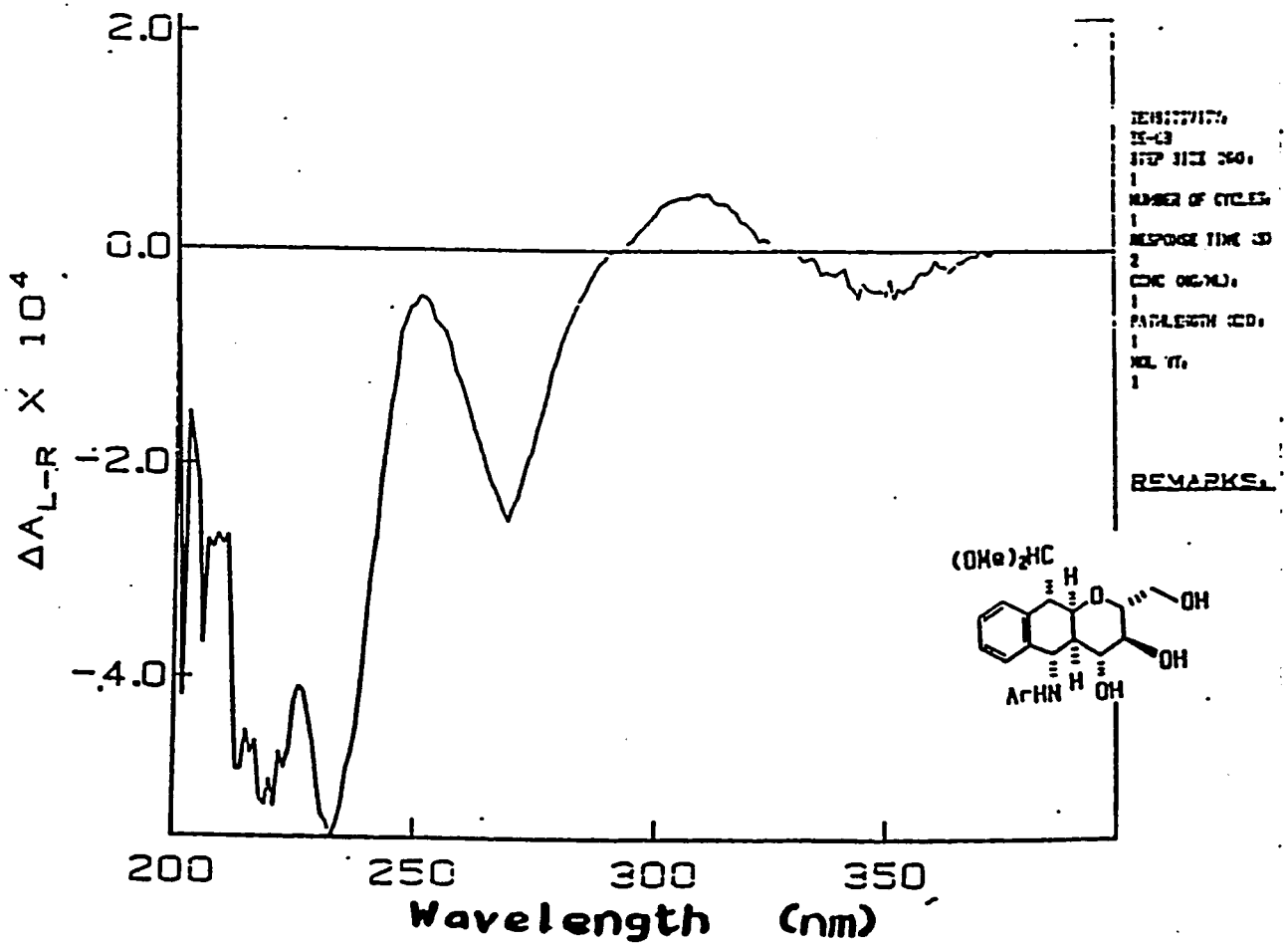


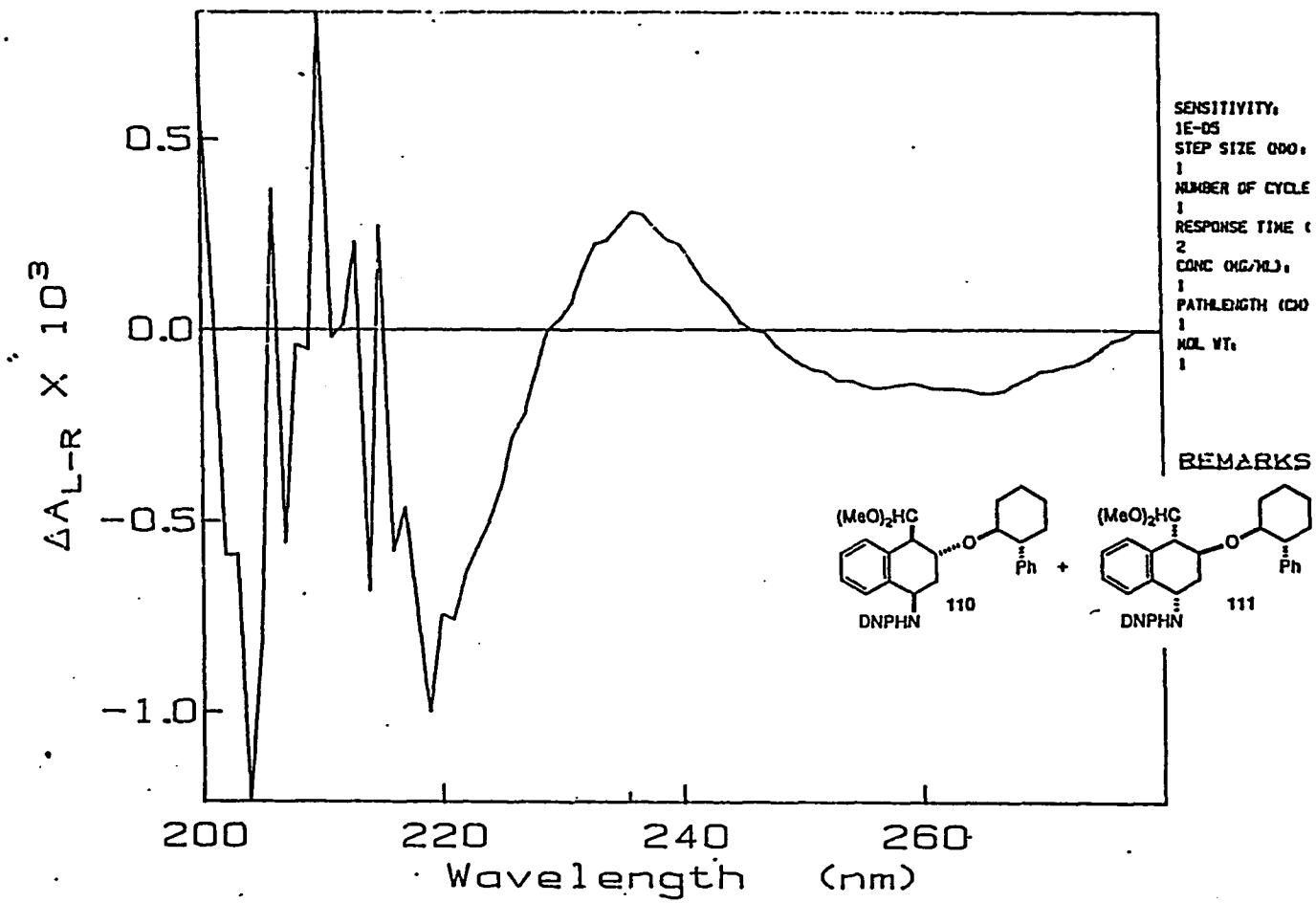
Scheme 21: Determination of absolute configuration

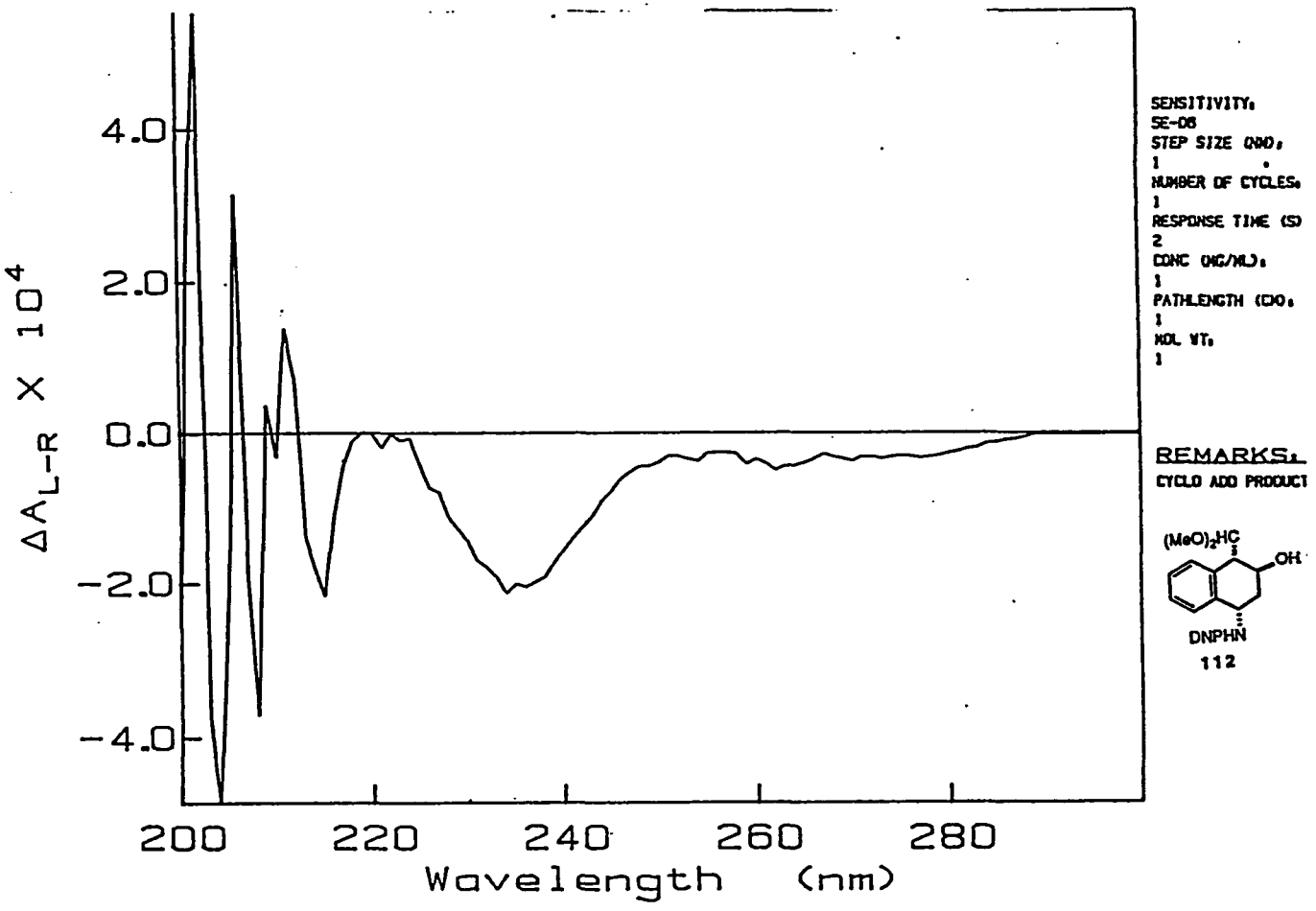
Our absolute configurational assignments are based on comparisons of CD spectra of the products with CDs of tricyclic tetralin adducts **129** and **131** prepared from sugars **128** and **130** respectively of known configuration.We observe equal and opposite cotton effects at 237 nm (-) for **129** and (+) for **131**, which we ascribe to an interaction between the 2,4-dinitrophenyl chromophore and the adjacent benzene ring[60]. A complete analysis of their nmr spectra leaves the assignment of relative, and hence absolute configurations unambiguous. Since all the tetralins have the same chromophoric pair, we assigned the configuration of the major product isomer of each cycloaddition by examining the sign of its Cotton effect at 237 nm. It appears that the remote aryl groups of the chiral auxiliaries do

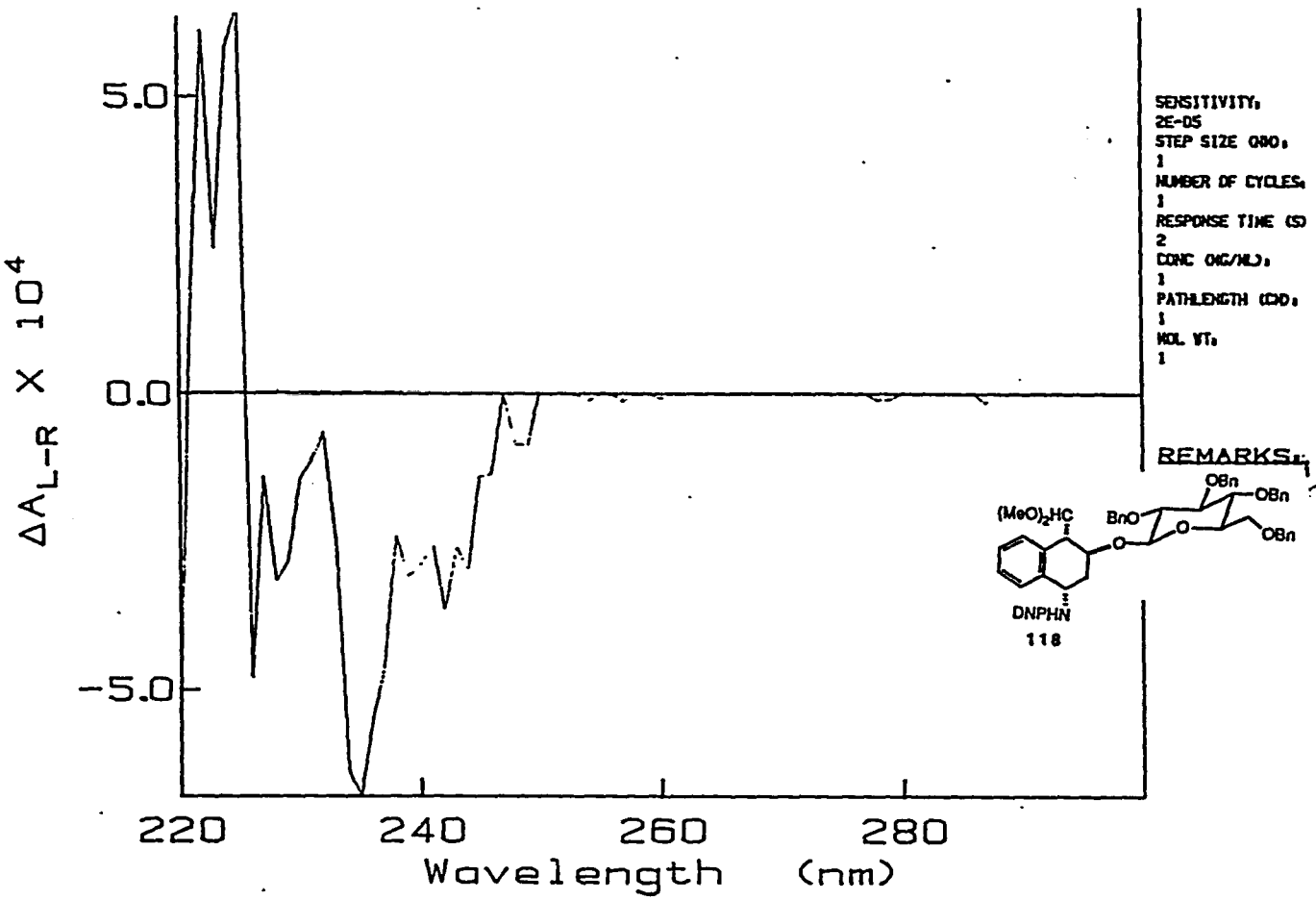
not interfere with the principal chromophore interaction. The separated diastereomers **118** and **119** from entry j (table 3) exhibited opposite Cotton effects at 237 nm, even though tetrabenzyl-D-glucose portion of the auxiliary is identical in both cases.Listed are some of the CD spectrums of the tetralin products.

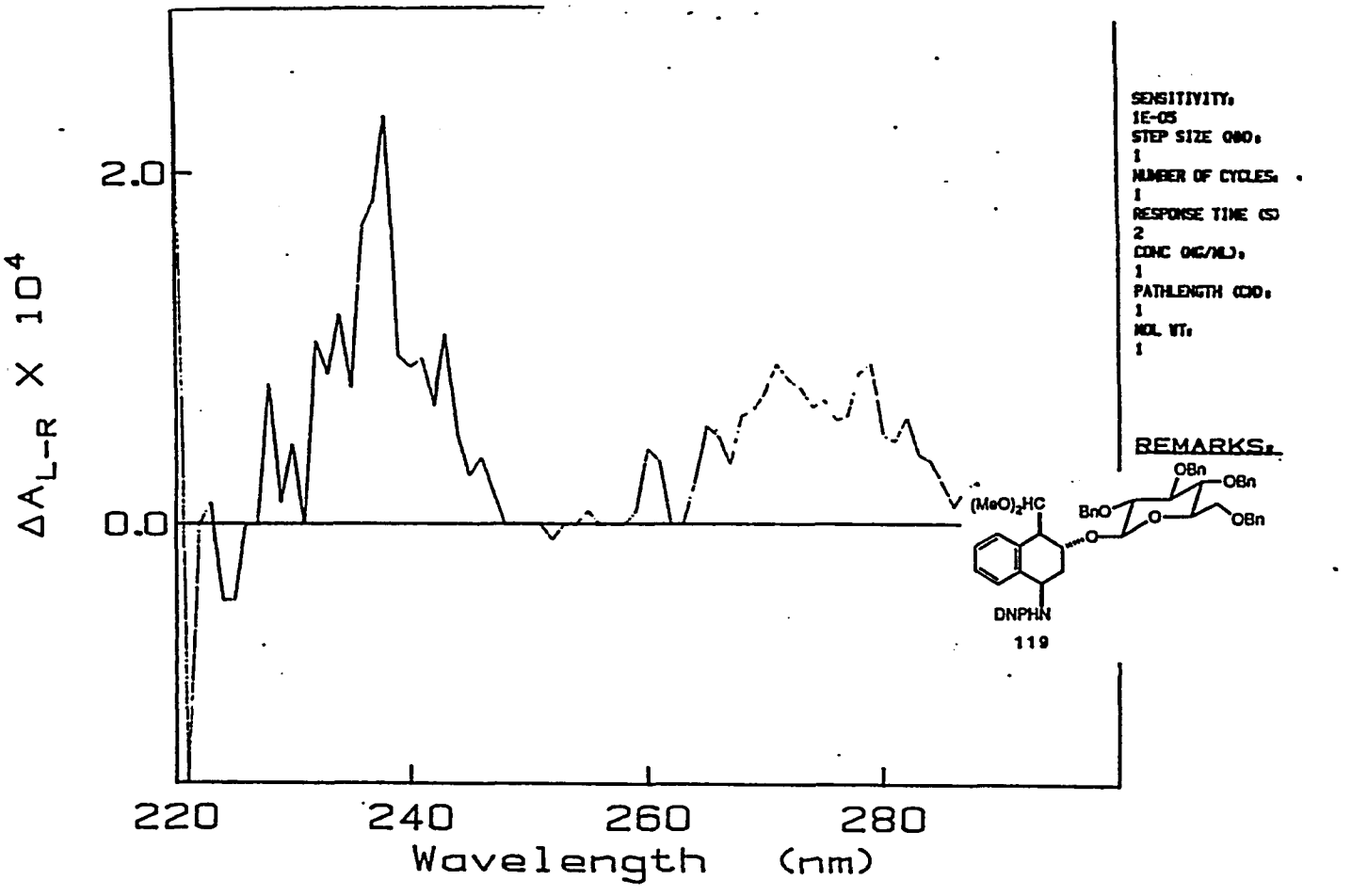

2.0
0.0
−2.0
−4.0
−6.0
ΔA L-R X 10⁴
200
250
300
350
Wavelength (nm)
REMARKS:
(OMe)2HC
H
O
OMe
OH
ArHN
H
OH


2.0
0.0
-2.0
-4.0
$\Delta A_{L-R} \times 10^4$
200
250
300
350
Wavelength (nm)
REMARKS:
(OHe)$_2$HC
H
O
OH
OH
ArHN
H
OH


0.5
0.0
−0.5
−1.0
ΔA L-R X 10 3
200
220
240
260
Wavelength (nm)
SENSITIVITY:
1E-05
STEP SIZE 000:
1
NUMBER OF CYCLE
1
RESPONSE TIME (
2
CONC (MG/ML):
1
PATHLENGTH (CM)
1
MOL WT:
1
REMARKS
(MeO)2HC
O
Ph
DNPHN
110
+
(MeO)2HC
O
Ph
DNPHN
111


4.0
2.0
0.0
−2.0
−4.0
$\Delta A_{L-R} \times 10^4$
200
220
240
260
280
Wavelength (nm)
SENSITIVITY:
SE-06
STEP SIZE (NM):
1
NUMBER OF CYCLES:
1
RESPONSE TIME (S)
2
CONC (MG/ML):
1
PATHLENGTH (CM):
1
MOL WT:
1
REMARKS:
CYCLO ADD PRODUCT
$(MeO)_2HC$
OH
DNPHN
112


5.0
0.0
-5.0
$\Delta A_{L-R} \times 10^4$
220
240
260
280
Wavelength (nm)
SENSITIVITY:
2E-05
STEP SIZE (NM):
1
NUMBER OF CYCLES:
1
RESPONSE TIME (S)
2
CONC (MG/ML):
1
PATHLENGTH (CM):
1
MOL WT:
1
REMARKS:
$(MeO)_2HC$
BnO
OBn
OBn
OBn
O
O
DNPHN
118

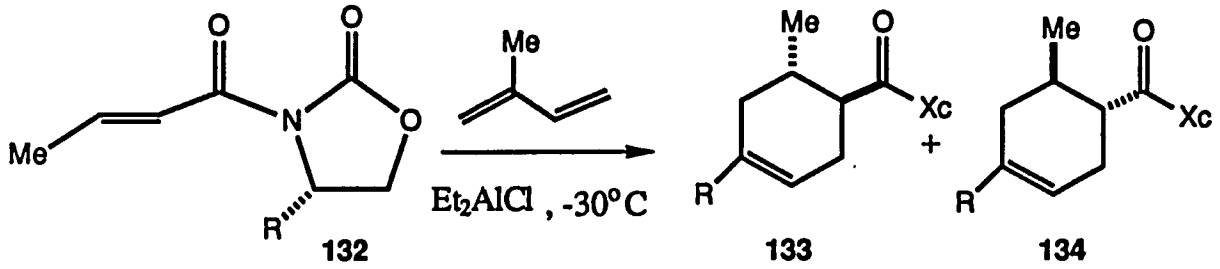

2.0
0.0
$\Delta A_{L-R} \times 10^4$
220
240
260
280
Wavelength (nm)
SENSITIVITY:
1E-05
STEP SIZE (NO:
1
NUMBER OF CYCLES:
1
RESPONSE TIME (S)
2
CONC (MG/ML):
1
PATHLENGTH (CM):
1
MOL WT:
1
REMARKS:
$(MeO)_2HC$
DNPHN
119
OBn
OBn
OBn
BnO
O
O

Discussion

Chiral control in asymmetric synthesis is one of the most challenging current problems of organic chemistry. Experimental investigation and understanding of the interactions responsible for high selectivity is essential to achieve compounds of interest. Challenging aspects include the ability to fix several chiral centers simultaneously, ease of transformation of initial products in to desirable intermediates, high selectivities making diastereomer separation unnecessary, and synthetic usefulness in terms of costs and yields. New developments in this area have impacted strongly the synthesis of natural and unnatural products, including classes with important physiological activities. Moreover, highly stereocontrolled processes of wide scope and usefulness merit mechanistic studies to pinpoint the factors responsible for their high selectivity. Specific identification of these interactions is greatly preferable to the reasonable guesses commonly developed to explain new phenomena. It is quite common in our experience and others, to find that the actual explanation is different from expectation. Inverse electron-demand Diels Alder reactions are in principle well-suited to the challenges of developing chiral control in the synthesis of a carbon skeleton. This is a developing area and there are not many reports in this area.

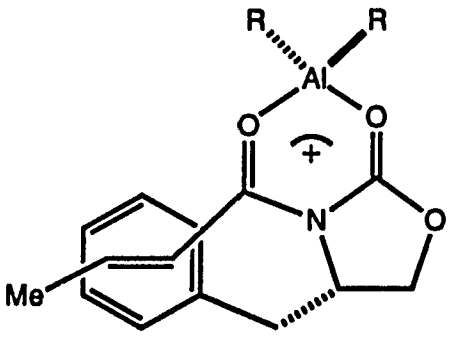
The results presented in our version of IED cycloaddition reveal in the case of trans phenyl cyclohexyl vinyl ether **57** and the vinyl ether from 2,3,4,6-O-tetrabenzyl-α-D-glucopyranose (entry i, table 3) show a spectacular diastereoface selection. Aromatic rings have been suggested to shield selectively one of the diastereofaces in Diels-Alder reactions, ene reactions, photochemical [2+2] cycloadditions, Michael reactions, nickel promoted [3+2} cycloadditions, Claisen rearrangements, nucleophilic carbonyl addition, and diastereoselective glyoxylate ene reactions[61]. These studies suggest that some property of the phenyl ring, either shape, size, or electronic character is absolutely required although these results do not demand the presence of an electronic effect. A thorough study of asymmetric Diels-Alder reactions with α,β-unsaturated N-oxazolidinones by Evans[40] highlights some property of the aromatic ring responsible for diastereoface discrimination.

As the spatial bulk of isopropyl is considered to be greater than the benzyl, some kind of electronic effect is responsible for this increased diastereoface selectivity. If this is the case, this π-stacking interaction is expected to decrease the electron-withdrawing nature of the dienophile, thus decreasing the rate of the cycloaddition along with increased diastereoface selectivity.



132 133 134

Substrate	Ratio
R=$CHMe_2$	5.3:1
R=CH_2Ph	20.7:1
R=CH_2 cyclohexyl	9.7:1



Model for Pi-stacking interaction

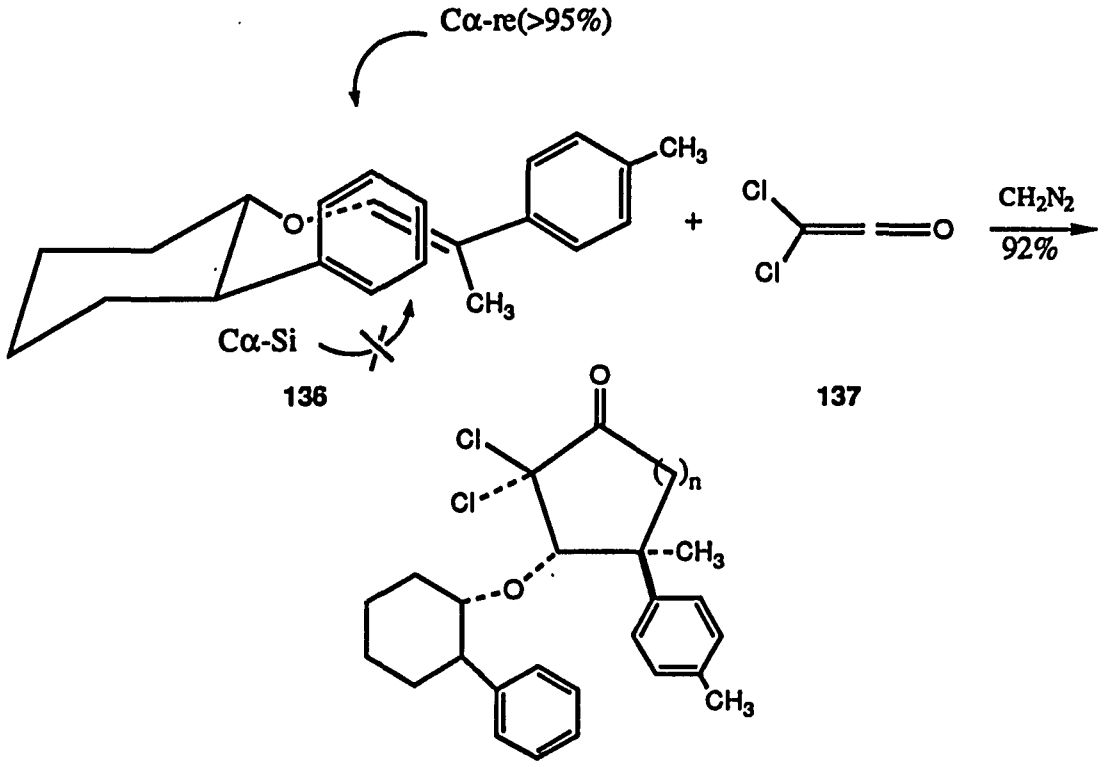
135

Scheme 22: Evan's pi-stacking model

A comparative study between benzyl and cyclohexylmethyl shows phenyl -substituted dienophile reacting 1.3 times faster than its fully saturated analogue. So the conclusion is derived as follows: there is little if any electronic reorganisation. The substituents on the

phenyl do not have much effect on the reaction. Finally comparing the alkylation of oxazolidinone and Diels-Alder reaction at a common reaction temperature, Evans proved that π-facial differentiation, which is basically controlled by steric effects, is enhanced by the electronic contributions documented in the Diels-Alder transition states.

He says, "We believe the "enhanced steric effect", promoted by electronic contributions, observed in these reactions results largely from dipole-dipole and van-der Waals attractions and not from charge transfer interactions."



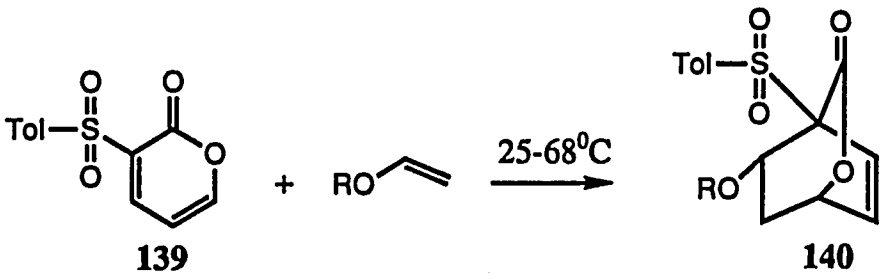
138

Scheme 23: Greene's scheme

Again the enantiocontrolled approach towards the synthesis of (-)-α-Cuparenone and (+)-β-Cuparenone by Greene[42] via asymmetric olefin ketene cycloaddition (scheme 23) shows a very high diastereoface control with phenyl as the chiral biasing group. The expectation and the experimental result was that, the enol ether **136** would react with dichloroketene in a favourable π-face discriminating transition state. This discriminaion is due to an S-trans

or a nearly S-trans conformation of the enol ether, where steric effects are minimized. This would effectively expose the Cα-re face of the enol ether to dichloroketene attack, while positioning the Cα-Si face so as to be sterically shielded by the adjacent phenyl group. Greene ascribed the interaction to both steric effects and π–π interactions. But he did not report comparative data for cyclohexyl and isopropyl substituents.

Posner's[41] inverse electron demand asymmetric Diels Alder reaction of 3-arenesulfonyl-2-pyrone with chiral vinyl ethers produce bicyclic bridged lactone adducts as shown in Scheme 24.



139 140

R	%de
8-phenylmenthyl	~5
Ph(i-pr)CH	84
Ph(t-Bu)CH	90

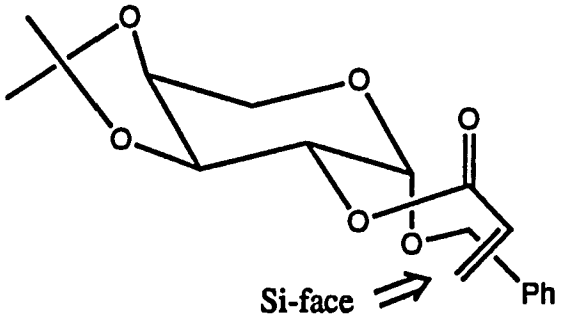
Scheme 24: Posner's scheme

The best cases in this cycloaddition are when the control element is phenyl isopropyl carbinyl and phenyl t-butyl carbinyl with diastereomeric excesses of 84% and 90% respectively. The surprising case is Corey's famous auxiliary 8-phenylmenthyl which gives a poor face discrimination of 5%. No mechanistic explanation has been put forward. According to Posner *"this high level of stereocontrol was especially gratifying and somewhat surprising because the stereogenic center in the reactant alkyl vinyl ether is insulated from the reacting vinyl moiety by a freely rotating ether linkage"*. Actually the

unsaturated ether linkage is not freely rotating as claimed by Posner, but there is a conjugation between the ether oxygen and unsaturated double bond, which has been shown by theoretical calculations and experiments discussed later in this section.

Posner and Wettlaufer proposed no mechanism for the asymmetric induction observed in their work since the relative configuration of all the chiral centers of the product and the face at which the chiral vinyl ether reacted was unknown.

In a Lewis acid catalysed Diels-Alder reaction of a sugar derived dienophile Shing[62] has achieved a heightened level of stereocontrol with benzyl compared to methyl as the substituent.

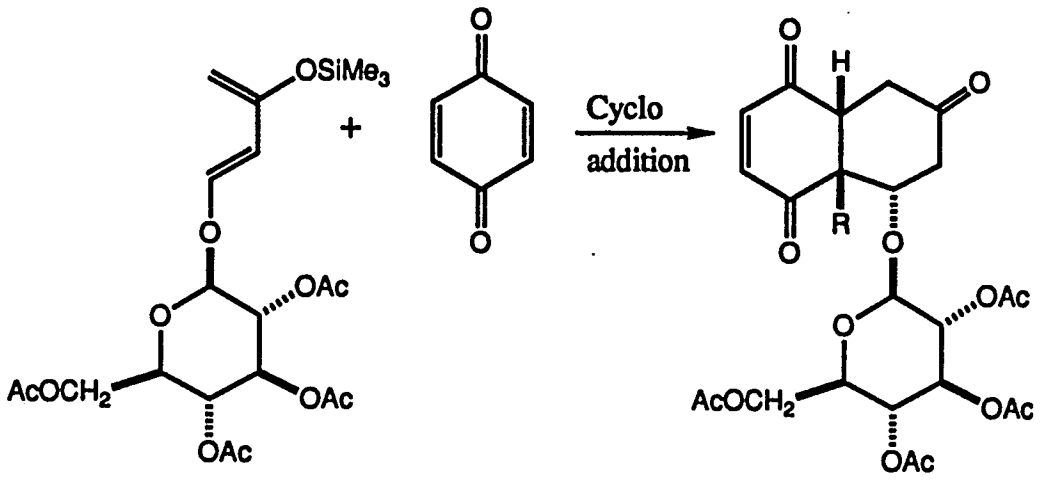


141

Fig.16 Shing's priposal of π–stacking

He has rationalised it in terms of the Oppolzer postulate, that the antiperiplanar orientation of carbonyl group and double bond causes the phenyl ring to shield the re-face more effectively, there by causing the diene addition to the si-face (fig. 16).

In the sugar series, we don't have a good hypothesis as to why β–benzylated sugar gave a poorer face discrimination than the α–case. Since our examination of models where the exo and endo anomeric effects have been used to fix ground state conformations does not show

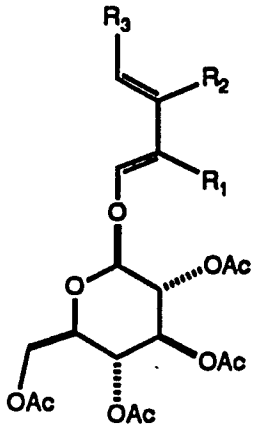


Scheme 25: Stoodley's cycloaddition of diene bearing sugar as the chiral auxilliary

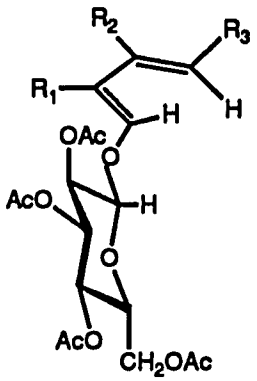
cycloadduct in most cases could be crystallised. Thus an operationally simple route to functionalized homochiral cis-decalins and cyclohexenes could be achieved.

an obvious face discrimination. Stoodley's synthesis of (+)-4 -demethoxydaunomycinone[52] using a diene attached to 2, 3, 4, 6-tetra-O-acetyl-β-D-glucopyranose exhibits a high diastereocontrol. With p-benzoquinone **143** as the dienophile, the diene **142** showed a quite respectable degree of selectivity of 8:1[52]. A similar selectivity was observed with 2-methoxy carbonyl p-benzoquinone. The major

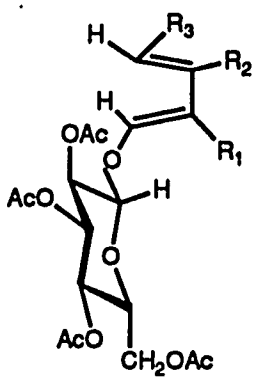
The polarization in Stoodley's work is comparable with ours because the cycloaddition components i.e. his diene **142** and our dienophile **80** are both electron rich. But the induction level is low with β sugar linked to the dienophile in our system (entry h in table 3). However 2,3,4,6-O-tetrabenzyl-α-D-glucopyranoside **81** shows excellent diastereoface selection with a respectable chemical yield in contrast to the α-cases of Stoodley where his observed selection for diene **148** with N-phenyl Maleimide was 36 : 64. Stoodley has tried to evaluate the effect of anomeric configuration on the face selectivity[58].



145



146

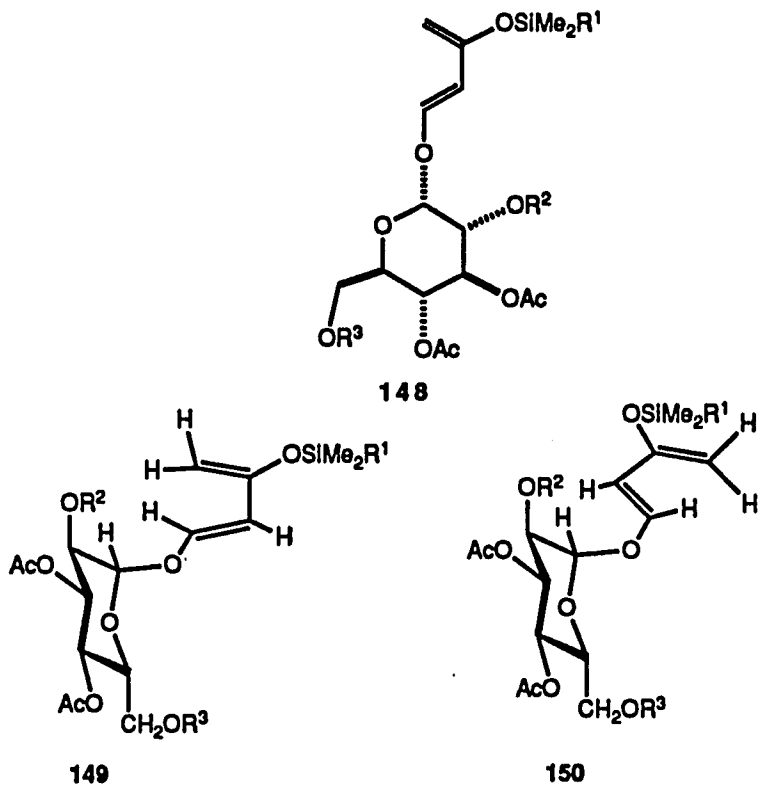


147

R_1 = H, R_2= $OSiMe_2Bu^t$, R_3 =H

Fig: 17: Stoodley's conformers for β-configured sugar

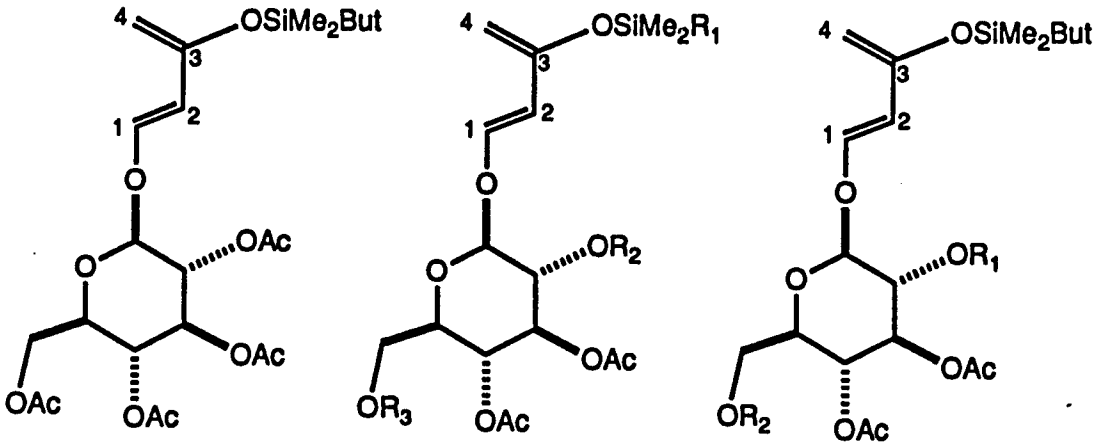
In the case of β-dienes **145**, the ratio (of the cycloaddition of his diene with N-phenyl maleimide) of the cycloadducts was 85 : 15, whereas the α-diene having similar substituents ended up giving 55: 45 mixture of adducts. The ratio in both α and β cases increase in both cases when the 6'-O- acetyl group is replaced by 6'-O- benzyl group and declines when the 2'- O-acetyl is replaced by 2'-O-benzyl group. In terms of his model the results are consistent with the notion that with β-dienes the reaction goes via the conformer **146** and a-conformer goes via **149.**



$R_1 = Bu^t$, $R_2 = Ac$, $R_3 = Ac$

Fig. 18: Stoodley's conformers for α-configured sugar

He has assumed that the benzyl group acts as a more effective shield than an acetyl group, so the face selectivity can be explained. But he does not have any explanation for this shielding wheather it is due to π-stacking or steric interaction. Because the chemical shifts of the 1-, 2-, and 4-hydrogen atoms of compounds **151, 152** and **153** (Fig.19) were remarkably constant, he has established that there is no evidence for interactions between the diene moiety and the phenyl groups. The experiment by Stoodley throws some light as to why our α-configured benzylated sugar shows a high face discrimination. The bulk of the benzyl group either at 6-position or at 2-position may be responsible for the facial discrimination.



151 **152** **153**

a. $R_1 = Bu^t$, R_2= Ac, R_3 = Ac

b. $R_1 = Bu^t$, R_2= Ac, $R_3 = CH_2Ph$

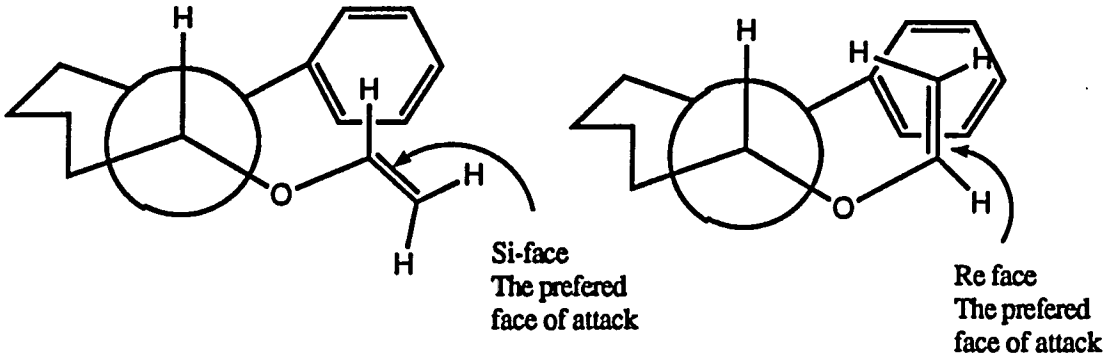
c. $R_1 = Bu^t$, R_2=CH_2Ph, R_3 = Ac

a. R_1 = Ac, R_2= CH_2Ph

b. $R_1 = CH_2Ph$, R_2= Ac

Fig. 19: Stoodley's rationalisation for π-stacking

In our case[63] (Fig. 20) of the vinyl ether derived from trans 2-phenyl cyclohexanol, we can not say for sure what are the factor/factors responsible for this high level of face discrimination. The ground state conformation of vinyl ethers has been the subject of intense study[64a,b,c]. There is now general agreement between experimental and computational studies that unsubstituted vinyl ethers prefer a cisoid conformation[65]. A second minimum, 1.2 Kcal/mole higher in energy and separated by a small



154 (si attack) **155** (re attack)

Fig.20 Our rationalisation of phenyl group as face discriminating element

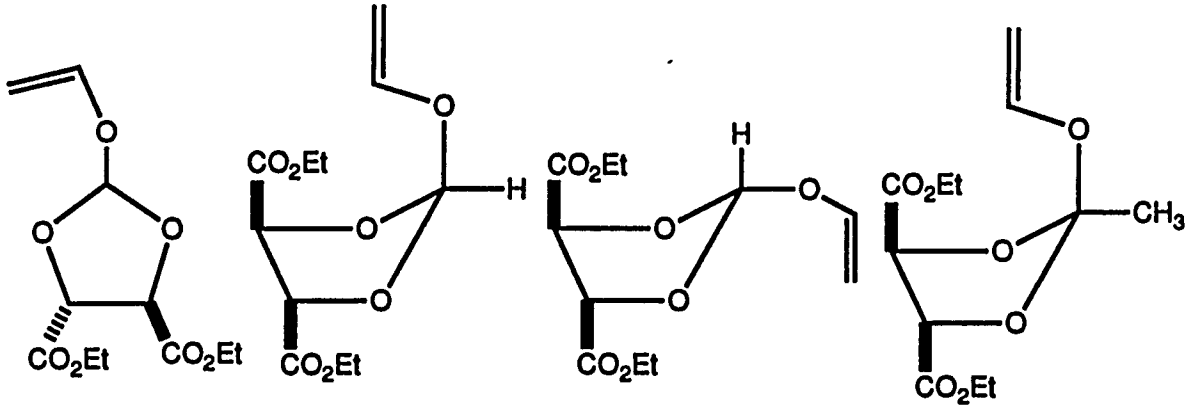
(4.5 Kcal/mole) barrier is the transoid-staggered form. So any small steric or electronic preference in the ground state can be overcome when the lower energy requires a change in conformation. We believe certainly that the π-stacking does not operate to fix a ground state conformation. Both the faces in models **154** and **155** (Fig. 20) seem to be equally exposed or shielded. From the knowledge of the absolute configuration of the product **110** the attack occurs from the si-face of the vinyl ether **57.** But this argument is only on the basis of ground state conformation of vinyl ether and moreover does not take in to account the orientation of vinyl ether with respect to isoquinolinium salt. Also the interpretation of this experiment is complicated by our lack of knowledge concerning the steric bulk of phenyl and isopropyl (Prof.D. Evans[40] has pointed out the steric bulk of an isopropyl group is normally considered to be greater than that of a benzyl substituent) and more over we do not have a comparable case of cyclohexyl in the place of phenyl to visualise the type of interaction responsible. But we can probably exploit the structural homology between menthyl and phenyl cyclohexyl (assuming similar size) to suggest that the interaction responsible is steric in nature. In the case of vinyl acetal **74,** as the reacting center is removed from the phenyl substituent the diastereoface selectivity drops drastically compared to **57.** The major diastereomer produced is in opposite sense to the vinyl ether case **57.**

57 **74**

Fig.21 Comparision between vinyl ether **57** and vinyl acetal **74**

In the vinyl orthoester series, we believe that the reason that the ee's are low is that the dienophile can exist in two cyclic conformations **65a** and **65b.** We can think about the

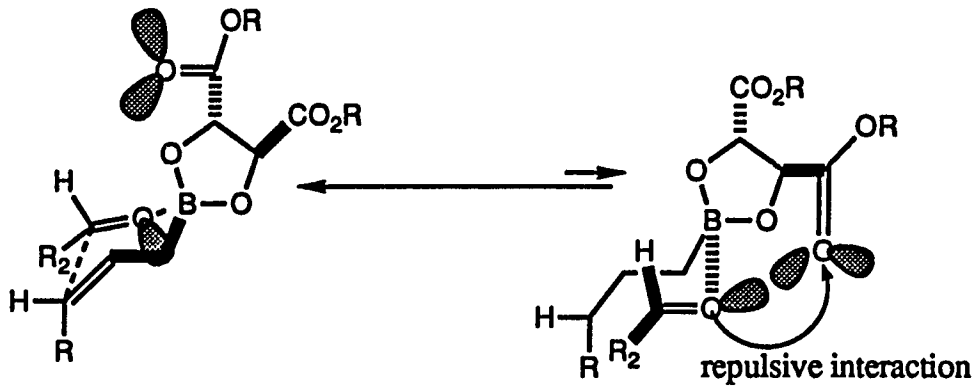
steric effects in **65b** which would reinforce face selectivity of the quasi-axial vinyl ether; and we can think about anomeric effect which might favour **65a**. However, the very steric effect that might enhance face selectivity in the reaction of **65a** would probably also favour the population of conformer **65b** where it is hard to visualise any face selectivity for the cycloaddition of vinyl ether. Hence we undertook the preparation of **67** where there should be no steric advantage of conformer of type **65b**. But this dienophile lost the stereoselection upon cycloaddition and ended up producing a mixture of exo and endo product.



65 **65a** **65b** **67**

Fig 22: Orthoester discussion

But in an analogous case of Roush's metallo-aldol reaction[66] he has observed a very high asymmetric induction with chiral allyl boronates which he ascribed as n/n electronic repulsive interaction involving the aldehydic oxygen atom and the β-face ester group (**157**) that destabilises one of the transition states with respect to other (fig. 23). These electronic interactions are possible since a favored conformation of the α-heteroatom substituted carbonyl system is one in which the hetero atom and the carbonyl are syn coplanar[67,68]. The origin of asymmetry is not realised by simple steric interaction since the aldehydic R_2 substituent is too far removed to interact strongly with the tartarate ester functionality and



Disfavored

156 **157**

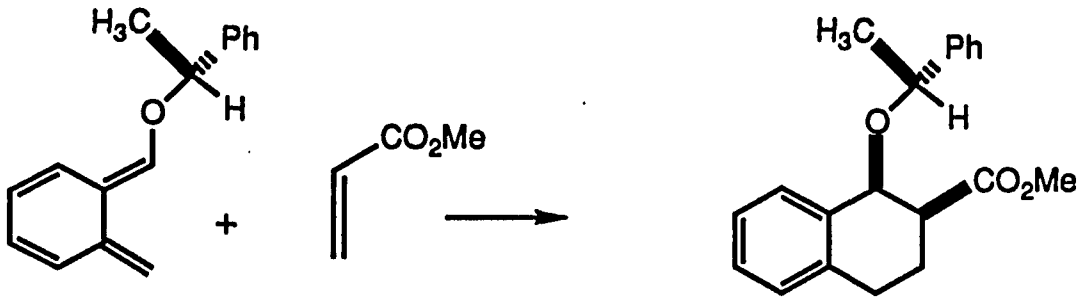
Fig 23: Roush's explanation of diastereofacial discrimination in mettalo aldol reaction

also the alkyl group present in the tartarate ligand seems to have a relatively minor effect on the overall reaction stereoselectivity.Though our orthoester vinyl ether system is structurally analogous to the allyl boronates, the system failed to give even a fair level of induction because of the reason that the face discriminating element is too remote from the reaction site in the transition state.

The asymmetric induction in Diels-Alder reactions of α-alkoxyorthoquinodimethanes with achiral dienophiles by Charlton shows excellent diastereoface selectivity. He has tried to put forward a rationalisation though the exact mechanism of induction is still unknown. As an example, in the conversion of **158** to**159** it was found that an (R) -1-phenylethoxy group directed addition of methyl acrylate to the upper face of **158** (si face at the α center) such that the major product had the (1'R,1S, 2S) configuration (R center blocking the re-face).

A mechanism to explain the face selectivity, based on π-stacking of the chiral auxiliary to the o-QDM[69], has been shown to be inconsistent with the product stereochemistry and it was proposed that reaction from conformation shown in Scheme 25 (**158**) might explain

the face selectivity due to the different size of the phenyl and methyl groups. Results by Posner and Wettlaufer seemed to be inconsistent with the above proposal[41].



158 **159**

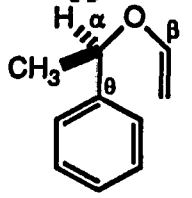
Scheme 26: Charlton's cycloaddition

Their observation was that the face selectivity of the reaction increases as the bulk of the alkyl group in the chiral auxiliary increases. To test the hypothesis in the system above, the methyl in **158** should be changed to iso-propyl or tert-butyl. An increase in selectivity would be inconsistent with the hypothesis that the face selectivity is due to the conformation of the o-QDM as shown in **158** whereas a decrease would suggest that **158** plays a role in the reaction. It is also necessary to determine the attacked face of o-QDM by determining the configuration of the cycloadduct relative to that of the chiral auxiliary.

Molecular Orbital calculations[70] were carried out for **160** which serves as a model for **158** to reduce the computational requirement. Ab initio calculations were carried out at STO-3G set with optimization of bond lengths and bond angles. Charlton et.al. performed the calculations on an Amdahl 470/V8 using the programme MONSTERGAUSS.

The first general observation results from the calculation is that the dihedral angle β in **155** (Fig.24) always optimizes to a value of 180° or 0°. This is presumably due to the conjugation of double bond with lone pair electrons on the ether oxygen.

Since these calculations represent the models for o-QDM conformation with β near 0°, they are not of interest because this conformation is sterically impossible for **158**. Finally the most stable conformer of **158** is approximately is that shown below **163** (Fig. 26).



160

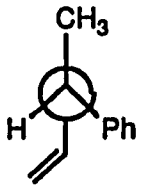
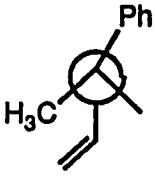
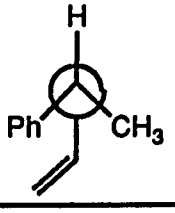
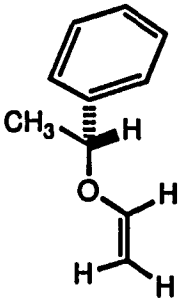
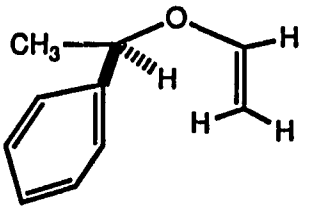
Conformation	Angles (°) α	β	θ	Energy (relative) kJ/mol
	70	184	37	0.0
	164	161	35	2.78
	300	187	119	2.30

Fig. 24 Abinitio calculation of **160**

The two structures **161** and **162** below (fig. 25) represents the two extremes.

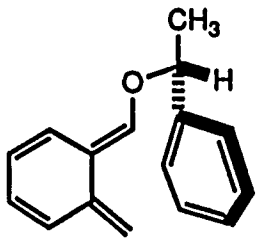




161 (180°) **162** (0°)

Fig.25 Possible conformers of **160**

Therefore Charlton et. al. proposed that the face selectivity in cycloaddition of **163** arises due to the difference in steric bulk of the phenyl and the hydrogen substituents. This differs slightly from the conformation previously proposed (in **158**) to account for the diastereoface selectivity, where face selectivity depended on the relative size of the phenyl and methyl substituents. They proposed that the reaction occurs from the conformer **163** is more consistent with the experimental data since exchanging the methyl for an isopropyl or tert-butyl would improve the diastereoselectivity (as observed) by increasing the preference of conformer **163**, which conformation provides the most room for the alkyl substituent.



163

Fig. 26 Stable conformer of Charlton's diene

Posner and Wettlaufer proposed no mechanism for the asymmetric induction observed in their work since the relative configuration of all the chiral centers of the product and the face and the face at which chiral vinyl ether reacted is unknown.

Conclusion

In conclusion we can say there is no simple explanation for the observation that why the phenyl substitution (**57**) in entry c (Table 1) results in a high diastereo face discrimination in our case. More experiments e.g. substituting cyclohexyl with phenyl in the case of **57** and substitution of a dihydrobenzene in stead of phenyl in **57** would give us some idea if

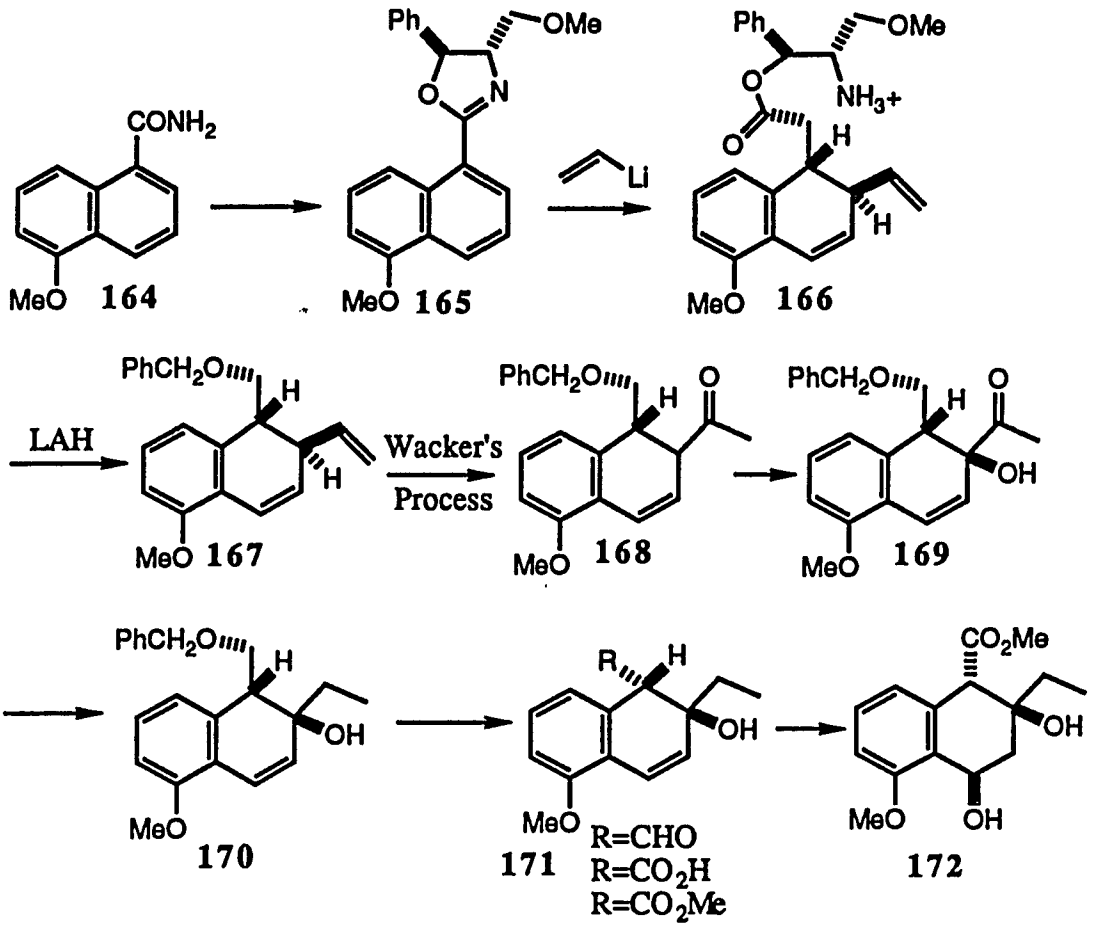
the aromatic sextet is responsible for the observed results. Molecular Orbital calculations might give some insight to this problem also. Nevertheless the above described inverse electron demand cycloaddition of isoquinolinium salts with electron-rich dienophiles opens up a new route to optically pure tetralins which are building blocks of several anthracycline antibiotics.

II. Model Study for the AB Ring Synthon of Anthracycline Antibiotics

Introduction

Anthracyclines are an important class of compounds. They are one of the most important chemotherapeutic agents available for the treatment of some cancers. The molecular biologists have evaluated the mechanism of their cardiotoxicity and their interaction with DNA. It has been found that the biological activity of these antitumour anthracyclines is related to their ability to complex with DNA with the consequent inhibition of replication and transcription[71]. For the synthetic organic chemist this important class of compounds pose a challenge for the development of chemo-, regio-, and stereoselective methods for introduction of functionality[72,43]. A review in Tetrahedron[43] reflects the numerous approaches from different laboratories throughout the world towards the construction of this class. The parent compounds daunomycin and adriamycin have been synthesized many times over the years. Aclacinomycin A is a clinically important antitumour agent belonging to the anthracycline group isolated by Oki et al.from the culture of Streptomyces galilaeus MA144-M1 in 1975. It consists of the tetracyclic quinoid aglycone aklavinone linked at C-7 to a trisaccharide composed of the amino sugar L-rhodosamine and two other deoxy sugars, 2-deoxy-L-fucose and L-cinerulose A. The absolute configuration of the aglycone is 7S, 9R and 10R.

The ability of aclacinomycin A to bind to DNA is similar to that of doxorubicin, however, aclacinomycin A is classified as one of the class II anthracyclines which mainly inhibits RNA synthesis, in contrast to class I anthracyclines which show similar inhibition of DNA and RNA synthesis. The drug shows antitumor activity superior to that of doxorubicin in some experimental models such as human xenografts of gastric cancer, CD mouse mammary carcinoma and colon 38. It is also active against Ehrlich tumors, Lewis lung carcinoma and B 16 melanoma, while it is less active against L1210 and P388 leukemias.



Scheme 27: Meyers' approach towards the AB ring synthon of anthracyclines

Toxicological studies performed in hamsters indicate that aclacinomycin A produces a milder cardiac toxicity than does doxorubicin. In patients, it is active against leukemias but its response rate in solid tumours is much lower than that of doxorubicin. Gastrointestinal symptoms such as nausea and vomiting occur in the majority of the patients but they are generally milder than with doxorubicin.

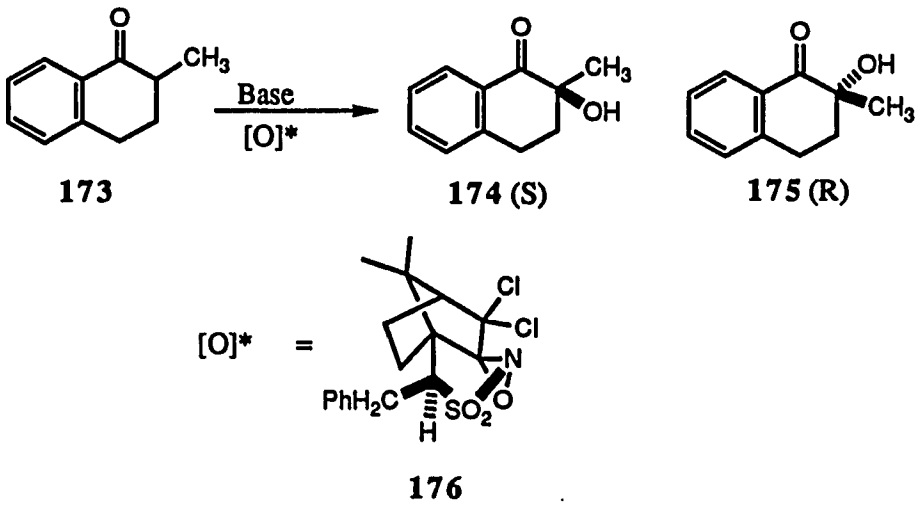
This class of compounds possessing a tetracyclic skeleton and three stereochemical centers in the A ring stimulated the scientific community to achieve a practical synthetic protocol for AB ring synthons. The following are some of the achievements during the recent years.

Meyers' Approach

In recent years Meyers' group[73] has synthesised AB ring synthons of anthracyclines by asymmentric addition to chiral naphthalenes. The chiral oxazoline **165** was formed from

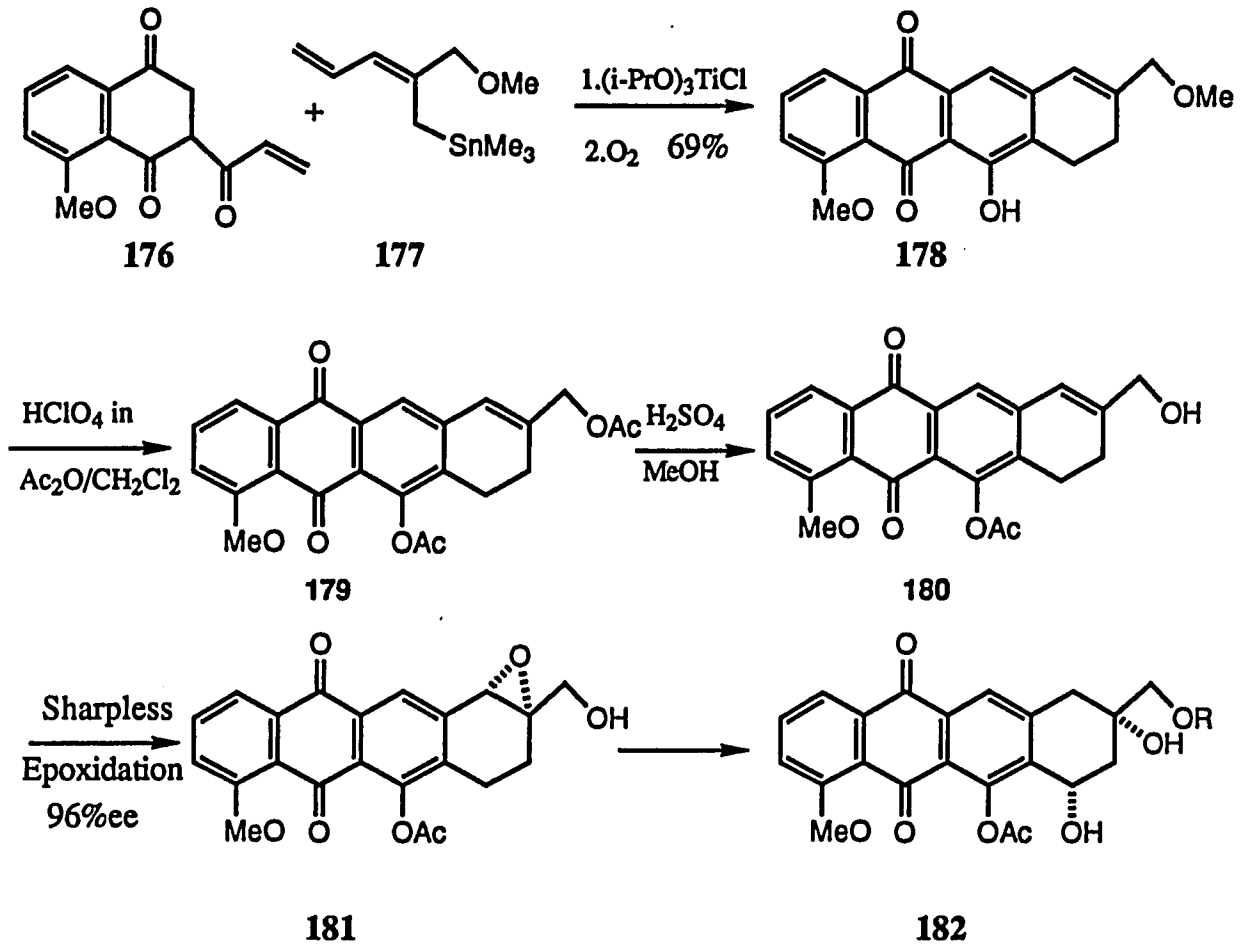
the amide **164** by first converting it to imidate, followed by the addition of (S,S)-(+)-1-methoxy-2-amino-3-phenyl-3-hydroxypropane. The crucial asymmetric addition was performed by using vinyl lithium and quenching the reaction with TFA. Compound **166** was reduced with LAH to crystalline alcohol **167** with an enantiomeric purity of 87%. The alcohol was converted to the benzyl ether and then subjected to Wacker's process to form the methyl ketone **168**. The tertiary hydroxyl group was introduced by Davis's procedure[74]. Then the reduction of the methyl ketone to an ethyl group and debenzylation affored the diol. The Sharpless procedure[75] converted the primary hydroxyl group to the carbomethoxy derivative. The introduction of the final functionality i.e.the 7-hydroxyl group[76] was achieved by treatment with NBS. The enantiomeric purity of the final product was 88%.

A recent development by Davis's group[77] towards the enantioselective synthesis of tertiary -α- hydroxy carbonyl compounds **174** employing ((8,8-Dichlorocamphoryl) sulphonyl) oxaziridine) as the oxidising agent **176** for the enolates ended up in giving very high stereoinduction of about 90-95% (Scheme 28).



Scheme 28: Davis's asymmetric epoxidation of enolates

The Japanese group[78] reported an efficient asymmetric synthesis of 11-deoxy anthracyclinone by the Sharpless asymmetric epoxidation of the tetracyclic alcohol **180** which is readily prepared by the tandem Michael / Diels-Alder reaction[78] (Scheme 29).



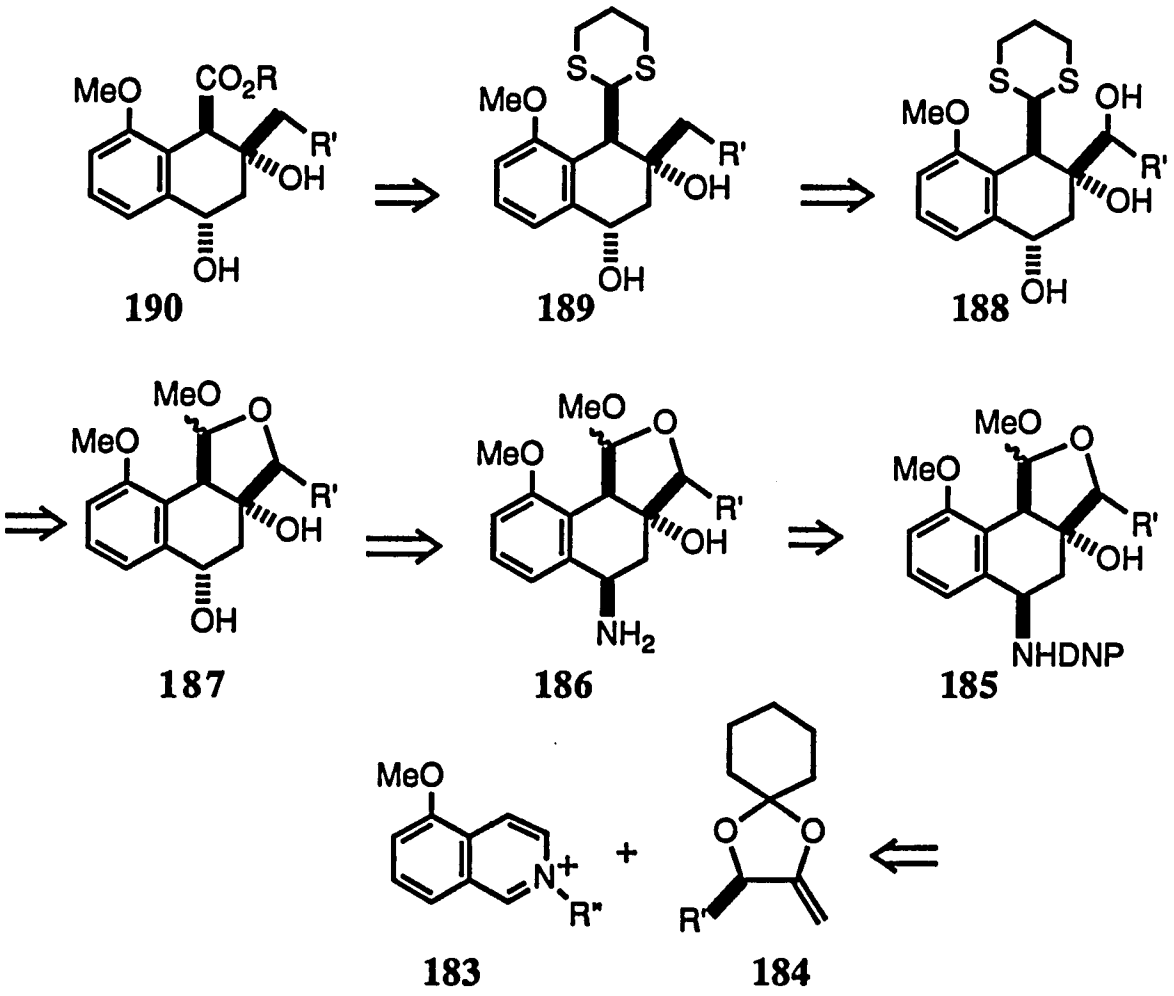
Scheme 29: Japanese approach to anthracyclines

Results and Discussion:

In the past few years our group at Hunter has been exploring routes towards the anthracyclines [30,35,36,62]. As described in the previous section, our modified version of the inverse electron demand cycloaddition reaction of isoquinolinium salts, results in a highly functionalised tetralin which corresponds to AB ring synthon of the anthracycline

antibiotics. Two basic questions have to be addressed. The first and the most important one is the control of diastereo / enantio selectivity which has been addressed in the first chapter. The second problem is the compatibility of the system during the manipulation of functional groups to the desired ones. The retrosynthetic scheme shown in Scheme 30, describes our plan to obtain the precise functionality required for the natural antibiotic.

The design concept of the dienophile has a hydroxy alkyl side chain at the 9-position with the concomitant generation of the required tertiary hydroxyl center at the same position. The advantage of this kind of dienophile is that R* induces the chirality, and the extra step to cleave the chiral auxiliary is not required. The work-up step of the cycloaddition which

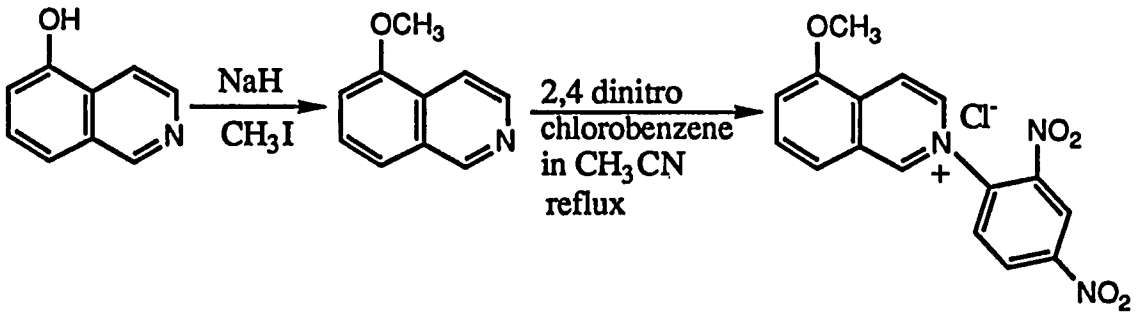


Scheme 30: Retrosynthetic scheme based on our approach of cycloaddition of of isoquinolinium salts

involves the treatment with acids will do the job.

A. Synthesis of the Diene:

5-Methoxy isoquinoline **169** was prepared from commercially available 5-hydroxy isoquinoline **168** by alkylation with methyl iodide in the presence of sodium hydride as the base (Scheme 31). .



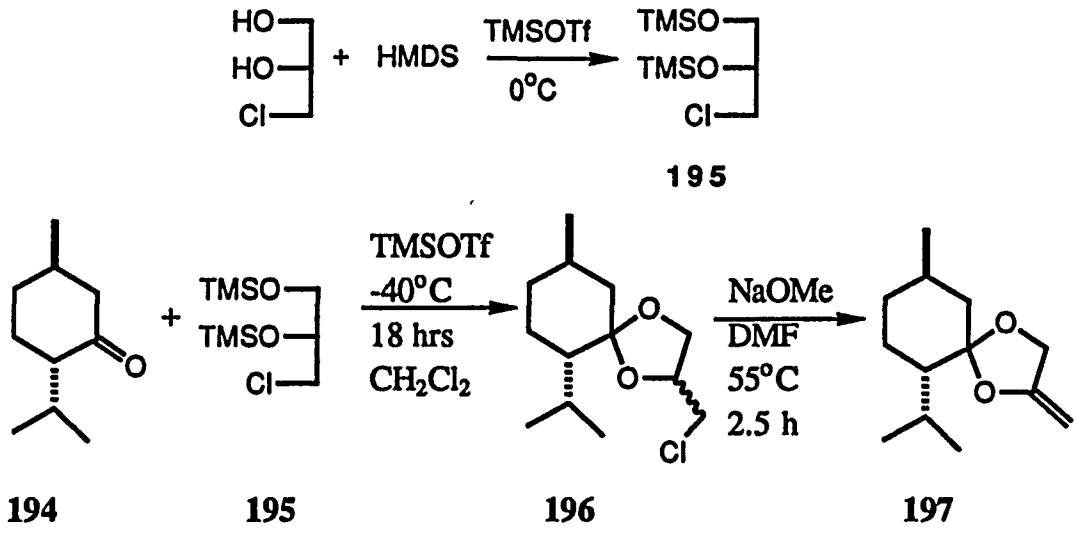
191 **192** **193**

Scheme 31: Synthesis of 5-methoxy -2,4-dinitro isoquinolinium chloride

This was quaternised with 2,4 dinitrochlorobenzene by refluxing in acetonitrile as the solvent for 24 h. The precipitated salt **193** was filtered and washed with cold acetonitrile to give yellow crystals. A radial chromatography was done to get the pure compound.

B. Synthesis of the Dienophile:

Readily available l-menthone was subjected to ketalisation with the bis-TMS derivative of 1-chloro 2,3 propane diol at -40°C for 18 h in the presence anhydrous CH_2Cl_2 as the solvent with a catalytic amount of trimethylsilyl trifluromethanesulfonte[79] (Scheme 32).

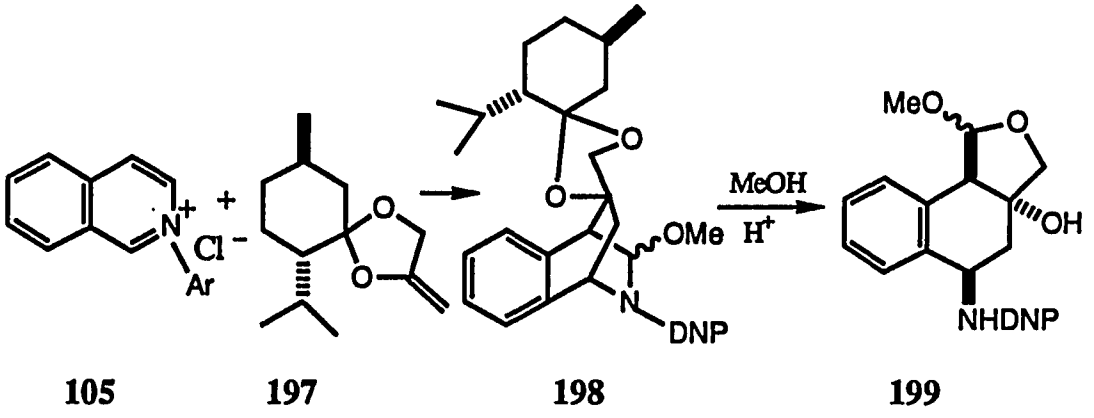


Scheme 32: Synthesis of dienophile **197**

The resulting chloromethylene ketal **196** was dehydrochlorinated using freshly prepared sodium methoxide in DMF at 50°C for 2 h. giving the required vinyl ether **197** which is an unseparable mixture of two diastereomers.

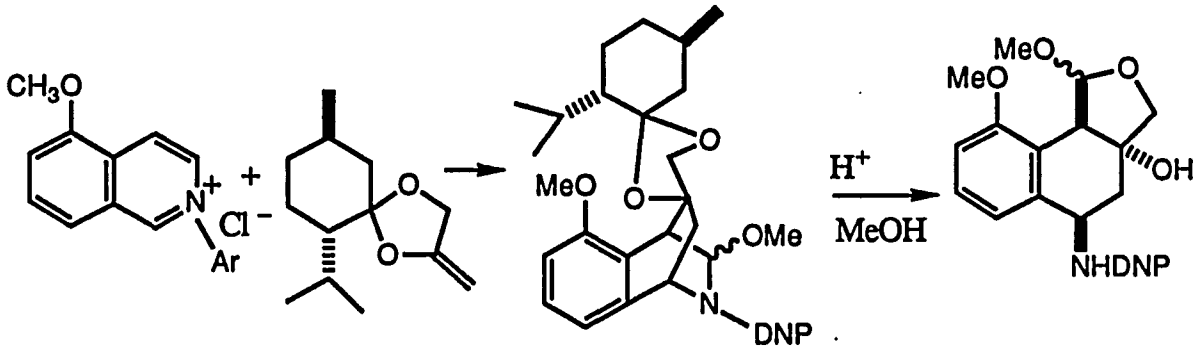
C. Cycloaddition

Cycloaddition of isoquinolinium salt **105** with **197** in the presence of $CaCO_3$ in dry methanol produces the cycloadduct 198 which on treatment with acid and methanol (dry) produces the tetralin cyclic hemiacetal **199** (Scheme 33).



Scheme 33: Cycloaddition of isoquinolinium salt **105** with **197**

The corresponding 5-methoxy substituted isoquinolinium salt **193** cycloadds to vinyl ether **197** in the presence of suspended $CaCO_3$ and dry methanol gives **200** as the cycloadduct which on treatment with acid and dry methanol produces **201** as the corresponding hemiacetal.



193 **197** **200** **201**

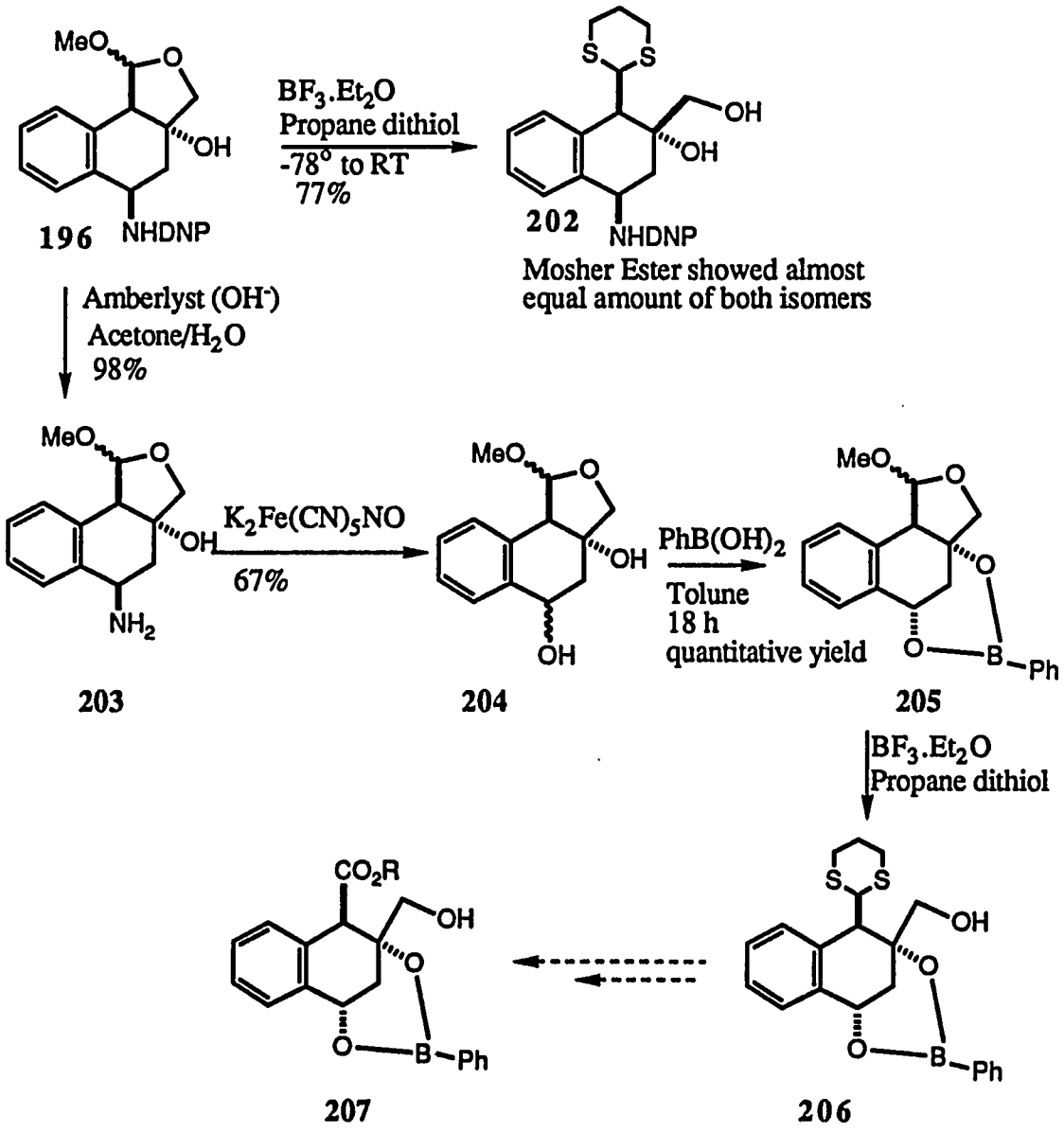
Scheme 34: Cycloaddition of isoquinolinium salt **193** and **197**

For the next set of manipulations acetal **196** was chosen. The product **196** has a tertiary hydroxyl group at 9-position corresponding to anthracyclines. The hydroxy methylene group generated at the same position is masked in the form of a cyclic hemiacetal which can be unravelled as shown in Scheme 34. At this stage the enantiomeric purity of the product was estimated by converting the primary hydroxyl of **202** to a Mosher ester derivative[48]. It was a 1:1 mixture of two enantiomers.

D. Generation of Hydroxyl Group at 7-Position

The transformation of the 2,4 dinitrophenyl-amino group to the required hydroxyl group can be achieved in two steps. Treatment of compound **196** with basic Amberlyst in acetone

/water removes the 2,4 dinitrophenyl group giving **203** as the free amino compound[34]. Subsequent treatment of amino **203** with sodium nitroprusside in basic medium resulted in the formation of the hydroxyl group[80] at the position which corresponds to 7-position of the anthracycline aglycone. This hydroxyl group in **204** is not stereospecifically generated but was epimerised to the required one by equilibrating it with phenylboronic acid[45].



Scheme 35: Manipulation of the cycloadduct **196**

E. Manipulation at Position 10 and Synthesis of Tetralone:

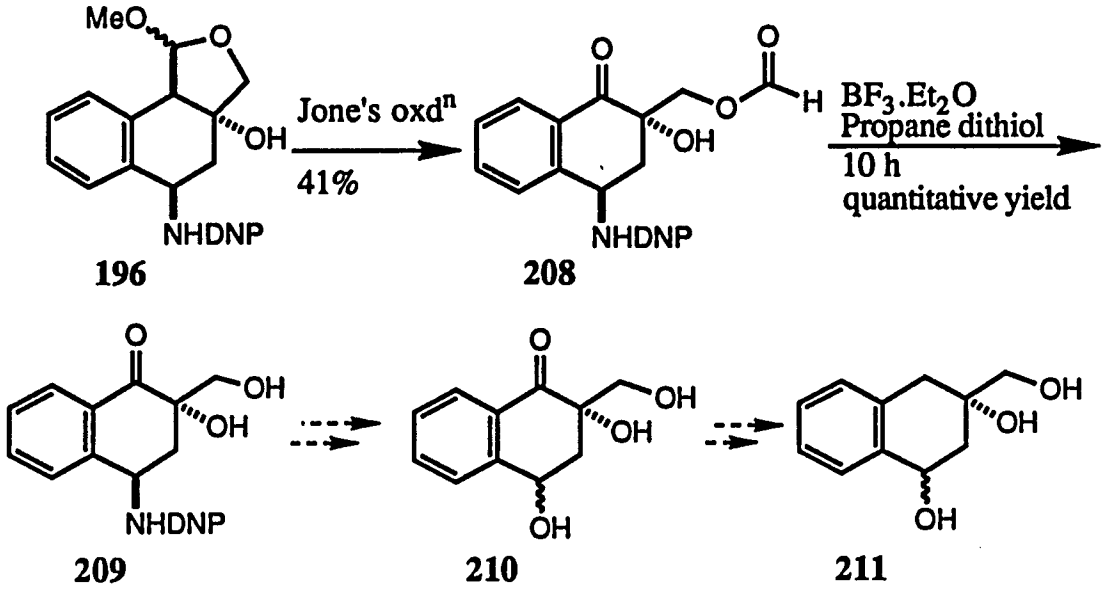
Now the hemiacetal moeity **205** was treated with boron trifluoride etherate in the presence of propane dithiol which forms the dithiane. This process generated the hydroxymethylene group at 9-position simultaneously. So to complete the AB ring synthon, all one has to do is to tranform the substituent at 10-position to the required acid or ester.

Attempts were made to convert directly the hemiacetal linkage to the required ester functionality needed at C-10 for anthracyclines of the aklavinone type. A literature search stimulated us to try chromium oxidants[81]. Jones oxidation of the acetal converted one of the epimers to a tetralone function (Scheme 36) while the other epimer remained intact. Though the reaction did not take the expected course it became a blessing in disguise as it led us to a route towards the decarbomethoxy derivative of the anthracyclines which are more potent than the parent.

For the other epimer a longer reaction time resulted in aromatisation of the starting material. This process suffers from the limitation of the fact that the vinyl ether **197** derived from the racemic propane diol is diastereomerically impure. Attempted separation of the diastereomers through chromatography or distillation was unsuccessful. The worthwhile result is the fact that the cycloaddition works very well with these kinds of dienophiles.

In order to bypass the problem of obtaining an optically homogeneous dienophile several modifications were included in our next design.

1. Dihydroxy butyric acid derivative, being optically pure can be a viable alternative to these kinds of dienophiles. So the problem of separation can be avoided.



Scheme 36: Synthesis of tetralone

2. The auxiliary was readily available and also the dienophile i.e. the vinyl ketene acetal will be ruptured during the work-up step of the cycloaddition saving us one extra step of the removal of chiral auxiliary.

3. The resultant cycloadduct will end up as a secondary hydroxy ethyl component which after deoxygenation will give ethyl substituent at 9-position which is the required functionality for aklavinone.

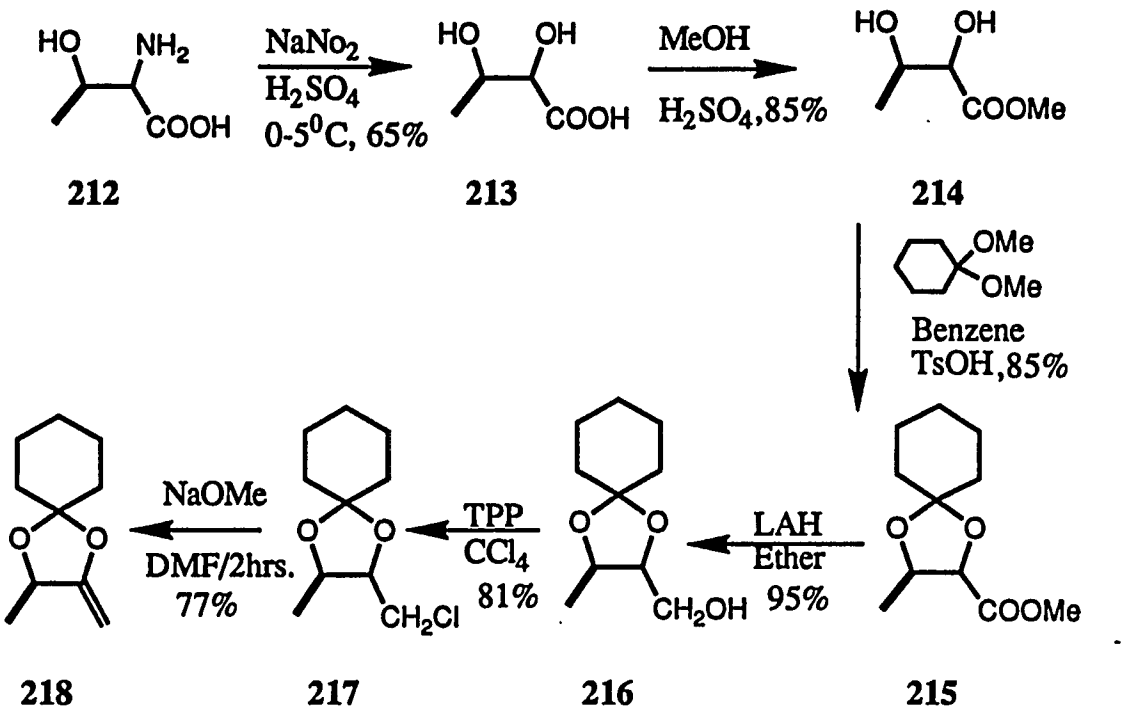
4. As procedures have been worked out for the conversion of 2,4 dinitrophenylamino group to hydroxyl group, it will become the required 7-hydroxy group for anthracyclines.

5. The only new functional group manipulation will be the conversion of the dithiane to ester[82] which has not been realised in these systems.

F. Synthesis of Threonine Derived Dienophile:

The dienophile came from optically active threonine and was prepared as follows. Optically

active l-threonine **212** was diazotised[83] with sodium nitrite in the presence of sulfuric acid. The resulting dihydroxy acid **213** was esterified to it's methyl ester derivative **214** in 85% yield using methanol with sulfuric acid as the catalyst. The next step i.e.the protection of

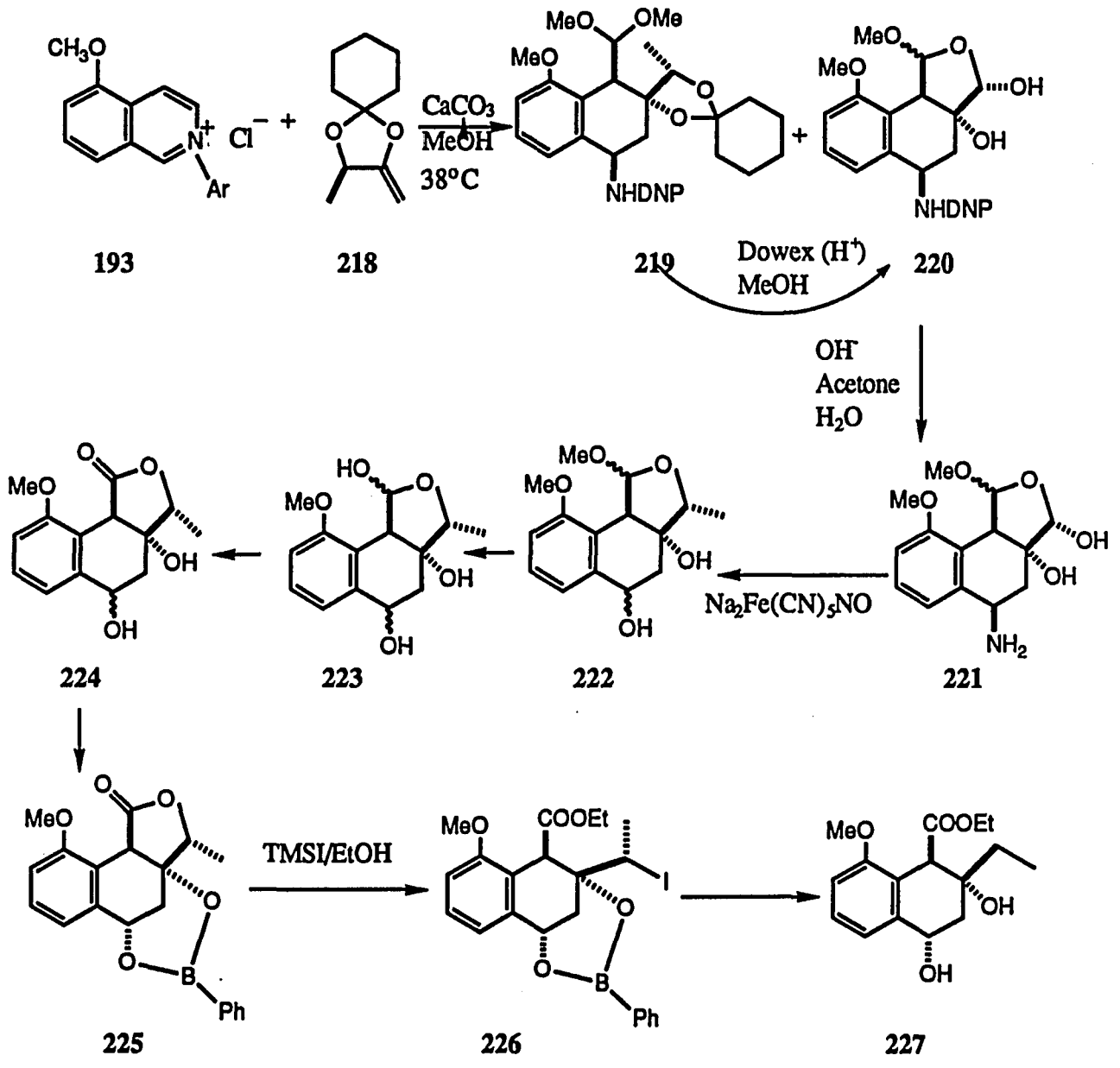


Scheme 37: Synthesis of threonine derived dienophile

the dihydroxy group in the form of cyclohexylidine ketal was achieved in 85% yield with 1,1 dimethoxycyclohexane with TsOH as the catalyst, in the presence of 4A° molecular sieves at room temperature with benzene as the solvent. The cyclohexylidine methyl ester was reduced with LAH in ether giving the corresponding alcohol **216** in 95% yield. The conversion of the alcohol to chloro compound **217** was achieved using TPP/CCl_4 in 81% yield. Dehydrohalogenation of the chloro compound in the presence of NaOMe/DMF at 50°C for 2h. afforded the required vinyl ether **218** in 77% yield.

Cycloaddition of vinyl ether **218** to 5-methoxy salt of isoquinoline **193** produced the open chain acetal **219** along with the cyclic hemiacetal **220**. The open chain acetal **219** undergoes the hydrolysis of cyclohexylidinee ketal on treatment with dowex (H^+)/MeOH and slowly forms **220** . Treatment of **220** with basic amberlyst in acetone/water gives the

free amino compound **221** which on treatment with sodium nitroprusside converts the amino group to hydroxyl group **222.** The rest of the conversions have not been reduced to practice.



Scheme 38: Cycloaddition of vinyl ether **218**

Conclusion:

In chapter I, we have shown that chiral tetralins with very high optical purity can be achieved by employing dienophiles bearing chiral auxiliaries (**57**) and (**81**). This protocol led us towards a model synthon of AB ring synthon of anthracyclines. Subsequent attempts in chapter II, to arrive at the actual system, e.g. for the synthesis of AB ring of aklavinone, as already discussed, requires the employment of a more substituted diene and dienophile. While the substitution on the isoquinolinium salt probably alters the electronic balance, which affects the rate of the reaction, the complex substitution pattern on the dienophile, as required for the natural product, or a combination of the both, drops the face selectivity. A plausible solution to this major problem might be to use additional chiral control elements for attainment of a respectable degree of diastereoface selection. Masamune's concept of double diastereoselection[84] by installing a matched pair of chiral auxiliaries on both the reacting partners in a wide variety of reactions like aldol, Diels-Alder, hydroboration, allylboration etc. is found to be useful in the synthesis of complex natural products. In our system the additional chiral directing group can be used as a quaternising agent on nitrogen, which has the added advantage of facile removal after the cycloaddition. Of course some experimentation will be required to find a suitable chiral auxiliary to act as a complementary matched pair with the chiral directing group on the dienophile. Once this is achieved a full spectrum of chiral tetralin frameworks with any substitution pattern will be easily accecible through our method. So the following sets of experiments will have to be done.

1. The diastereoselectivity of the isoquinolinium salt quaternised with chiral quaternising agent will have to be determined. Let the diastereo selectivity of the process=X.

2. The inherent diastereoselectivity of the dienophile bearing chiral auxiliary has to be determined by reacting with isoquinolinium salt quaternised with 2,4 dinitrochlorobenzene or other quaternising agent. Let the diastereo selectivity of the process=Y.

3.The third experiment will constitute the reaction of the chiral salt with chiral dienophile. If the diastereo- selectivity is less than either x or y then the two chiral auxiliary constitute a

mismatched pair. So by using either of the antipodes a greater selectivity will result, which might be very practical towards the synthesis of optically pure compounds.

III. Experimental

General Experimental

NMR spectra were recorded on GE QE 300 and JEOL FX 400 instruments with tetramethyl silane as the internal standard and $CDCl_3$ as the solvent. Infrared spectra were recorded on a Perkin -Elmer 1310 spectrophotometer. The high resolution mass spectra were obtained by the mass spectral facilities at Rockefeller University, New York and the Pennsylvania State University, University Park, PA. The Circular Dichroism spectra were recorded in a Jobin-Yvon Mark circular Dicrograph and scanned in Apple IIe computer (ISA Software). High pressure experiments were performed with a LECO TEM-PRES Pressure Generator (Model PG-100 HPC). Melting points were uncorrected and were determined on a Fisher-Johns melting point apparatus. Thin layer chromatograms were done on a precoated TLC sheets of silica gel 60 F_{254} (E. Merck) and visualised with potassium permanganate spray, phosphomolybdic acid and/or short- and long wave ultraviolet light. PLC plates were prepared by using Kieselgel 60 PF_{254} (E. Merck), and chromatotron (radial chromatography) plates were prepared by using Kieselgel 60 PF_{254} gipshaltig (E. Merck). Flash chromatography was performed with silica gel (230-400 mesh) purchased from Aldrich Chemical Co. Dry tetrahydrofuran (THF) was obtained by distillation, under nitrogen, from sodium-benzophenone ketyl. Other solvents were purified and dried by using standard procedures.

General Procedure for Determining the Diastereomeric Ratios of the Cycloadducts.

The diastereomeric ratios of the Diels-Alder Adducts were determined from the ^1H NMR spectra of the products. Although diastereomeric excesses could be determined by comparison of the integrated intensities of separate peaks in the ^1H NMR spectra of the crude reaction mixture, the reported ratios are those of the isolated mixtures of the diastereomers. In case of hydrolysed products, the enantiomeric excesses could be

determined by preparing a Mosher ester derivative and comparing the peaks with the corresponding racemic counterpart.

Determination of the Absolute Configuration of the Product:

The configurational assignments are made by comparision of the CD spectra of the product with the CD's of tricyclic tetralin adducts derived from the cycloaddition of the sugar dienophiles of known absolute configuration to isoquinolinium salts.

Preparation of Menthyl Vinyl Ether (55): A two-necked flask was charged with menthol (6.1 mole, 1 g) and a catalytic amount of mercuric acetate (38.46 mg), 10 molar equivalents (4.61 g, 6.12 ml) of ethyl vinyl ether was added and the reaction mixture was kept at 40°C for 7h. The completion of the reaction was checked by tlc. Then the reaction mixture was allowed to cool to room temperature and 0.25 g of K_2CO_3 was added. The mixture was put on a rotary evaporator to remove excess ethyl vinyl ether and the volatile byproducts of the reaction. Distillation of the residue directly out of the potassium carbonate at water pressure at 63°C-70°C gave pure menthyl vinyl ether to give 0.75 g (49%) yield which was stored over dry K_2CO_3 for subsequent use. IR ($CHCl_3$) 3180, 2910, 2860, 1630, 1445, 1380, 1365, 1010 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.28 (dd, 1H, J=6.51 Hz, 14.08 Hz), 4.24 (dd, 1H, J=1.21 Hz, 14.05 Hz), 3.90 (dd, 1H, J= 6.51 Hz, 1.19 Hz), 3.54-3.45 (m, 1H), 2.11-2.00 (m, 2H), 1.67 -1.60 (m, 2H), 1.40 - 1.26 (m, 2H), 1.04 - 0.72 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.17, 87.43, 79.65, 47.73, 40.83, 34.37, 31.45, 25.78, 23.46, 22.10, 20.71, 16.31.

Preparation of Isomenthyl Vinyl Ether (56): A two necked flask was charged with isomenthol (1g, 0.0061 mole) and a catalytic amount of mercuric acetate (38.46 mg), 10 molar equivalents (4.61 g, 6.12 ml) of ethyl vinyl ether was added and the reaction mixture was refluxed at 40°C for 7h. The completion of the reaction was checked by tlc. Then the reaction mixture was allowed to cool to room temperature and 0.25 g of K_2CO_3 was added. The mixture was put on a rotary evaporator to remove excess ethyl vinyl ether and the volatile byproducts of the reaction. The residue was chromatographed on a florosil

column using 10% ethyl acetate / petroleum ether to yield 0.755 g (50%) as a colorless oil. IR ($CHCl_3$) 2920, 2880, 1630, 1460, 1370, 1320 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.33 (dd, 1H, terminal vinylic, J_{trans} = 14.66 Hz, J_{cis} = 6.59 Hz), 4.31(dd, 1H, J_{trans}=14.12 Hz, J_{gem}=1.37 Hz), 4.01-3.96 (m, 2H), 1.96 -1.1.85 (m, 2H), 1.69 -1.63 (m, 2H), 1.60 -1.41 (m, 3H), 1.39 -1.00 (m, 1H), 0.98 - 0.88 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) 151.00, 87.61, 76.56, 45.73, 35.75, 29.92, 27.22, 26.02, 20.98, 20.70, 20.61, 19.19.

Preparation of trans (-)-2-Phenylcyclohexyl Vinyl Ether (57)

A. Preparation of Racemic trans-2-Phenylcyclohexanol (59): Grignard reagent (PhMgBr, 18.995 ml, 3M solution in ether) was syringed into a flame dried, two-necked flask fitted with a condensor and adapter. The flask was cooled to -30°C and Cu_2I_2 (90.0082 mol, 1.57 g) was added. The mixture was stirred for 10 minutes then dry THF was added to solubilize the precipitate. Then a solution of cyclohexene epoxide (0.125 mol, 12.625 ml in 12 ml THF) was added dropwise. The mixture was stirred at 0°C for 2h. Then it was quenched with 50 ml of a saturated solution of $(NH_4)_2SO_4$. The organic layer was washed with saturated portions of $(NH_4)_2SO_4$ till the aqueous layer was no longer blue. The combined aqueous layers were extracted with ether, the organic layers combined, dried ($MgSO_4$), and concentrated to afford 8.65 g (41%) of the racemic alcohol which was recrystallized from pentane giving a white solid mp 56.5-57°C (Lit. 57-58°C). IR ($CHCl_3$) 3592, 3461, 2941, 2863, 1604, 1497, 1451 cm^{-1}; ^1H NMR ($CDCl_3$) 7.35-7.15 (m, 5H), 3.64 (ddd, 1H, J= 5.4, 10.8, 10.8 Hz), 2.42 (ddd, 1H, J = 5.4, 10.8, 16.5 Hz), 2.11 (m, 1H) , 1.84 (m, 2H), 1.76 (m, 1H), 1.62 (S, 1H), 1.53-1.25 (bm, 4H).

B. Preparation of Racemic trans-2-Phenylcyclohexyl Acetate (60): To a solution of 0.0363 g of 4-dimethylaminopyridine and 8.387 ml (0.103mole) of pyridine in 30 ml of CH_2Cl_2 was added dropwise with stirring a solution of 8.65 g (0.0491 mole) of alcohol (59) in 15 ml of CH_2Cl_2. After 10 min 9.2 ml (0.0982 mole) of acetic anhydride was added dropwise over 1.5 h.. After 2 h the reaction was poured into a mixture of

24.55 ml of 6N HCl, 36.82 ml of ice and 75 ml of Et_2O. The organic layer was washed with 60 ml of 2N HCl. The combined aqueous layers were extracted with Et_2O, the combined organics were washed with saturated $NaHCO_3$ and dried over $MgSO_4$. Concentration afforded 9.65 g (91%) of the racemic acetate (**60**) as a slightly viscous liquid. IR ($CHCl_3$): 3070, 2940, 2860, 1730, 1604, 1497 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30 -7.15 (m, 5 H), 4.97 (ddd, 1 H, J = 5.4 , 11.0, 11.0 Hz), 2.65 (ddd, 1H, J = 5.4, 11.0, 16.5 Hz), 2.13 (m, 1 H), 1.93 (m, 1 H), 1.84 (m, 1 H), 1.78 (m, 1 H), 1.74 (s,, 3 H), 1.56 (m, 1 H), 1.46 (m, 1 H), 1.41 (m, 1 H), 1.35 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 169.9, 143.1, 128.2, 127.5 , 126.4 , 75.7, 49.8 , 33.9 , 32.4 , 25.9, 24.8, 20.7 .

C. Enzymatic Hydrolysis: Preparation of (-) trans -2-Phenylcyclohexanol (61): To 350 ml of 0.5 M, pH 8.0 KH_2PO_4 / K_2HPO_4 aqueous buffer at 31°C was added with rapid stirring, a solution of 9.65 g (0.0045 mole) of racemic acetate **60** in 48.69 ml (0.0688 mole) of acetone. The heterogeneous mixture was stirred for 1 h before adding 1.46 g of Pig Liver Acetone Powder (PLAP). The reaction was monitored by quenching aliquots with 2 N HCl and extracting with CH_2Cl_2. After 140 h, 0.4426 g of additional PLAP was added and after 240 h, the reaction was quenched by acidification to pH 4.0 with 2 N HCL. To the acidic solution 44.26 g of sodium chloride and 22.13 ml of CH_2Cl_2 were added and the mixture was stirred for 1h before allowing to stand until all the PLAP residue had settled. The aqueous supernatant was carefully removed and filtered through cotton leaving the PLAP residue behind. The aqueous layers were then, extracted twice with 22 ml portions of CH_2Cl_2. The residue was poured into large centrifuge tubes, shaken with CH_2Cl_2 and centrifuged to break the emulsion. The organic layer was removed, filtered through cotton and concentrated. This extraction process was repeated until no additional product was obtained. A total of 2.6733 g of a yellow liquid was obtained. Preparative chromatography with 30% EtOAc/Petroleum Ether afforded 0.2966

g (-)- alcohol and 1.887 g of the (+) -acetate. The (-)-alcohol was recrystallized from pentane. mp 63-64°C, (lit. mp 64-65°C) .

D. Preparation of (+)-trans-2-Phenylcyclohexanol (62a): To a solution 15 g (0.0683 mol) of the acetate (**60**) in 70 mL of MeOH was added 9.587 g (0.1709 mol) and 85% KOH. The resulting solution was heated to 50°C for 3 h, cooled to ambient temperature and concentrated to afford 11.74 g (97%) of **62a**. The product was used after recrystallization from pentane.

E. Preparation of trans (-)-2-Phenylcyclohexyl Vinyl Ether (57): A solution of 1.68 mmole (0.2966 g) of trans (-) 2- phenyl cyclohexanol (**61**) and 16.8 mmol (1.2096 g=1.604 ml) of ethyl vinyl ether was refluxed with a catalytic amount of mercuric acetate. The reaction course was followed by tlc. After 18 h the reaction mixture was cooled to room temperature and solid K_2CO_3 was added. The mixture was concentrated on a rotary evaporater to remove excess ethyl vinyl ether and ethanol. Then the K_2CO_3 was filtered off. A radial chromatography using 20% ethyl acetate/ petroleum ether separated the vinyl ether **57** as the fastest moving band on radial chromatography. Yield = 163 mg (48%). IR ($CHCl_3$) 3010, 2930, 2850, 2395, 1645, 1445, 1210, 1060, 765 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.18-7.40, (5H, m, aromatic), 6.11 (1H, dd, J =6.57 Hz and 14.17 Hz), 4.18 (1H, dd, terminal vinylic, J=1.42 Hz, and Jtrans=14.07 Hz, 3.86-3.95 (1H, m), 3.83 (1H, dd, terminal vinylic, Jgem = 1.46Hz, Jcis = 6.55 Hz), 2.27- 2.33 (1H, m) 2.67-2.76 (1H, m), 1.80-2.00 (2H, m, aliphatic), 1.4-1.65 (5H, m, aliphatic); ^{13}C NMR ($CDCl_3$, 75 MHz) 151.1, 128.27, 127.63, 126.27, 87.43, 81.83, 50.37, 34.11, 32.19, 29.72, 25.92, 24.86.

Preparation of 2-Vinyloxy-4,5-dicarboethoxy -1,3-dioxolane (65a)

A. Preparation of tris-Trichloroethyl Orthoformate (69): Triethyl orthoformate (3.7 g, 25 mmol, 5.15 ml) and 2-chloro ethanol (12.07 g, 150 mmol, 14.84 ml) were refluxed overnight in benzene (100 ml) with a catalytic amount of p-tolune sulfonic acid (100 mg) as the catalyst. The reaction mixture was cooled to room temperature and washed

with a saturated solution of $NaHCO_3$ and the mixture was dried over anhydrous Na_2CO_3. The mixture was filtered and evaporated to dryness on rotary evaporation. The mixture was distilled and 2.511 g (64%) of tris chloroethyl orthoformate was collected at 71-73°C / 0.5 mm / Hg. ^1H NMR ($CDCl_3$, 400 MHz) δ 5.22 (s, 1H), 3.73 (t, 6H), 3.54 (t, 6H).

B. Preparation of 2-(β-Chloroethoxy)-methyl-4,5-trans-dicarboethoxy-1,3-dioxolane (70a): Commercial optically active l-diethyl tartarate **68a** (3.6416 g, 17.6 mmol) and tris chloro ethyl orthoformate **69** (4.4457 g, 17.6 mmol) were refluxed with benzene (80 ml) and PPTS (25 mg) as catalyst. The reaction course was followed by tlc (phosphomolybdic acid as the spraying agent). After 10h the reaction was complete. The mixture was cooled to room temperature. It was washed with a saturated solution of $NaHCO_3$ and dried over Na_2CO_3. It was concentrated on a rotary evaporator and then put under high vacuum. The crude product without purification was used in the next step. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.13 (s, 1H), 5.01 (d, 1H, J = 3.5 Hz), 4.71 (d, 1H, J = 3.8 Hz), 4.32-4.23 (m, 4H, overlapping quartets), 3.90-3.85 (m, 2H), 3.65-3.60 (m, 2H), 1.38-1.33 (m, 6H).

C. Preparation of 2-(β-Phenylselenoethoxy)-methyl-4,5-trans-di-carboethoxy-1,3 dioxolane (71a): Diphenyl diselenide (176 mg, 0.564 mmol) was stirred in 8 ml of absolute ethanol until a clear yellow solution was obtained. Then $NaBH_4$ (45 mg, 1.18 mmol) was added to it batch-wise. The mixture became colorless. This colorless solution was added to a chloroethyl orthoester (**70a**) (296 mg, 1 mmol) solution in 7 ml of absolute ethanol. The

resultant mixture was refluxed for 24 h at which time tlc showed the completion of the reaction. During the reaction a NaCl precipitate appeared. The reaction mixture was cooled to room temperature. The precipitated NaCl was filtered off through a sintered funnel. Excess ethanol was evaporated with a rotary evaporater. The residue was partitioned between ethyl acetate and saturated $NaHCO_3$ solution. The aqueous layer was extracted

twice with ethyl acetate.The organics were washed with brine and dried over Na_2CO_3 and concentrated and finally dried under vacuum to give the crude selenide product.

D. Formation of Selenoxide (72a): Ozone was bubbled through the selenide **71a** dissolved in 15 ml of CH_2Cl_2 at -78°C until the blue color of ozone persisted. After being purged with N_2 the reaction mixture was allowed to warm to room temperature. The solvent was removed by a rotary evaporater to give the corresponding selenoxide as a white solid.

E. Preparation of 2-vinyloxy-4,5-trans-dicarboethoxy-1,3 dioxolane(65a): The selenoxide (**72a**) was dissolved in 10 ml of 1,2-dichloroethane and added drop wise at a rate of 15ml/hr via a syringe pump to a refluxing solution (pot temperature 110-115°C) of 15 ml of 1, 2 dichloroethane with 10 ml of 2,5-norbornadiene. After the addition, the reflux was continued for 10 minutes and the volatile components were removed by distillation. The orange residue was distilled bulb to bulb to give the required vinyl ether **65a** (68-70°C at .004 mm/Hg). Yield = 109 mg (42%) starting from the chloro orthoester (**70a**).

This compound was not pure enough for analysis even after being distilled. An analytical sample was prepared by eluting the compound on a preparative plate (predeveloped with 3% triethyl amine in petroleum ether). IR ($CHCl_3$) 3000, 2990, 1770, 1670, 1650, 1400, 880 cm^{-1}; ^1H NMR ($CDCl_3$,300 MHz) δ 6.43 (dd, 1H, J = 6.55 Hz , 14.10 Hz), 6.29 (s, 1H), 5.13 (d, 1H, J = 4.24 Hz), 4.80 (d, 1H, J = 4.24 Hz), 4.58 (dd, 1H, J =10.24 Hz, 10.24 Hz), 4.31 - 4.28 (m, 5H), 1.35 -1.30 (m, 6H). LRMS (Isobutane) 217 (M-43). ($C_{11}H_{16}O_7$ requires 260)

Preparation of 2-Vinyloxy-4,5-dicarbisopropoxy-1,3-dioxolane (65b)

A. Preparation of 2-(β-Chloroethoxy)methyl-4,5-trans-dicarboisopropoxy-1,3-dioxolane (70b): Commercial optically active l-diisopropyl tartarate **68b** (498.5 mg, 2.128 mmol) and tris chloroethyl orthoformate **69** (560.5 mg, 2.228 mmol) were refluxed with benzene (40 ml) and PPTS (25 mg) as catalyst. After one day when the

reaction was complete as shown by tlc, the mixture was cooled to room temperature. It was washed with a saturated solution of $NaHCO_3$ and dried over Na_2CO_3. It was concentrated on a rotary evaporator and put under high vacuum. The crude product **70b** without purification was used in the next step.

B. Preparation of 2-β-Phenylselenoethoxy-4,5-trans-dicarboisopropoxy-1,3-dioxolane (71b): Diphenyl diselenide (365 mg, 1.17 mmol) was stirred with absolute ethanol to get a clear solution. Then $NaBH_4$ (142 mg, 3.78 mmol) was added to it batch-wise. The mixture became colorless. This colorless solution was added to the solution of chloroorthoester **70b** (0.705 mg, 2.17 mmol) in absolute ethanol. The resultant mixture was refluxed for 24 h at which time tlc showed the completion of the reaction. During the reaction a precipitate of NaCl was observed. The reaction mixture was cooled to room temperature. The precipitated NaCl was filtered off through a sintered funnel. Excess ethanol was evaporated with a rotary evaporator. The residue was partitioned between ethyl acetate and

saturated $NaHCO_3$ solution. The aqueous layer was extracted twice with ethyl acetate.The organics were washed with brine and dried over Na_2CO_3 and concentrated and finally dried under vacuum to give the crude selenide **71b** product (yield=0.5151 g i.e. 54%).

C. Formation of Selenoxide (72b): Ozone was bubbled through the selenide **71b** dissolved in 15 ml of CH_2Cl_2 at -78°C until the blue color of ozone persisted. After being purged with N_2 the reaction mixture was allowed to warm to room temperature. The solvent was removed by a rotary evaporator to give the corresponding selenoxide **72b** as a white foamy solid.

D. Preparation of 2-Vinyloxy-4,5-trans-dicarboisopropoxy-1,3-dioxolane (65b): Compound **72b** was dissolved in 10 ml of 1,2- dichloroethane and added drop wise at a rate of 15 ml/hr via a syringe pump to a refluxing solution (pot temperature 110-115°C) of 15 ml of 1,2 dichloroethane with 10 ml of 2,5 norbornadiene. After the addition, the reflux was continued for 10 minutes and the volatile components were removed by

distillation. The orange residue was distilled bulb to bulb to give the required vinyl ether (61-64°C at .075 mm/Hg). Yield = 243 mg (41%) starting from the chloro orthoester. This compound was not pure enough for analysis even after being distilled. An analytical sample was prepared by eluting the compound on a preparative plate (pre developed with 3% triethyl amine in petroleum ether. IR ($CHCl_3$) 3540, 2980, 2950, 1750, 1735, 1725, 1650, 1640, 1470, 1380 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.35 (dd, 1H, J = 14.1, 6.55 Hz), 6.21 (s, 1H), 4.72 (d, 1H, J = 4.26 Hz), 4.54 (d, 1H, J = 1.82 Hz), 4.49 (d, 1H, J = 1.79 Hz), 4.3-4.16 (m, 2H), 1.36-1.16 (m, 12H). LRMS (Isobutane) 217 (M-71) ($C_{11}H_{16}O_7$ requires 260).

Preparation of 2-Vinyloxy-2-methyl-4,5-trans-dicarboisopropoxy-1,3-dioxolane (67)

A. Preparation of tris-Trichloroethyl Orthoacetate (75): To a solution of triethyl orthoacetate (4.055 g, 25 mmol) and 2-chloro ethanol (12.075 g, 150 mmol) in 100 ml of dry benzene was added a catalytic amount of PPTs. The mixture was refluxed for 19 h, when the tlc showed the completion of the reaction. The mixture was cooled to room temperature and washed with saturated solution of $NaHCO_3$. It was dried over anhydrous Na_2CO_3. Then the mixture was concentrated and put under high vacuum. Distillation (87-90° at 0.001mm/Hg) of the residue out of the Na_2CO_3 furnished the right compound in 45% (3 g) yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.83 (t, 6H), 3.66 (t, 6H), 1.55 (s, 3H).

B. Preparation of 2-(β-Chloroethoxy)-2-methyl-4,5-trans-dicarbo-isopropoxy-1,3-dioxolane (76): To a solution of l-diisopropyl tartarate (468.5 mg, 2 mmol) in 40ml of dry benzene was added tris trichloroethyl orthoacetate (530 mg, 2 mmol). A catalytic amount of PPTs (45 mg) was added. Then the mixture was refluxed with occasional checking of tlc. The rection was complete after 5.5 h. The mixture was cooled to room temperature, washed with a saturated solution of $NaHCO_3$, dried over Na_2CO_3 and concentrated. The crude product (0.6787 g) was good enough to be used in the next step.

^1H NMR ($CDCl_3$, 300 MHz) δ 5.13-5.04 (m, 2H), 4.81 (d, 1H, J = 5.9 Hz), 4.61 (d, 1H, J = 5.88 Hz), 3.82 (t, 2H), 3.56 (t, 2H), 1.64 (s, 3H), 1.27-1.24 (m, 12 H).

C. Preparation of 2-(β-Phenylselenyl ethoxy)-2-methyl-4,5-trans-dicarbo-isopropoxy-1,3-dioxolane(77): To a solution of diphenyl diselenide (678 mg, 2.02 mmol) in ethanol (20 ml)was added $NaBH_4$ (114 mg, 3 mmol) batch-wise till a colorless solution is obtained. This colorless solution was added to the stirred solution of chloro compound **76** in benzene. The resultant mixture was refluxed for 24 h at which time tlc showed the completion of the reaction. During the reaction a precipitate of NaCl was observed. The reaction mixture was cooled to room temperature. The precipitated NaCl was filtered off through a sintered funnel. Excess ethanol was evaporated with a rotary evaporator. The residue was partitioned between ethyl acetate and saturated $NaHCO_3$ solution. The aqueous layer was extracted twice with ethyl acetate.The organics were washed with brine and dried over Na_2CO_3 and concentrated and finally dried under vacuum to give the crude selenide **77** (yield=0.5374 g).

D. Preparation of 2-(β–Phenylselenoxyethoxy)-2-methyl-4,5-trans-dicarbo-isopropoxy-1,3-dioxolane (78): Ozone was bubbled through the selenide **77** dissolved in 15 ml of CH_2Cl_2 at -78°C until the blue color of ozone persisted. After being purged with N_2 the reaction mixture was allowed to warm to room temperature. The solvent was removed by a rotary evaporator to give the corresponding selenoxide **78** as a white foamy solid.

E. Preparation of 2-Vinyloxy-2-methyl-4,5-trans-dicarboisopropoxy-1,3-dioxolane (67): Compound **78** was dissolved in 10 ml of 1, 2-dichloroethane and added drop wise at a rate of 15ml/hr via a syringe pump to a refluxing solution (pot temperature 110-115°C) of 15 ml of 1, 2 dichloroethane with 10 ml of 2,5 norbornadiene. After the addition, the reflux was continued for 10 minutes and the volatile components were removed by distillation. The orange residue was distilled bulb to bulb to give the required vinyl ether (65-67°C at 0.075 mm/Hg). Yield = 253 mg (42% starting from the chloro

compound). This compound decomposed during the distillation and was not pure enough for analysis. It was used for the cycloaddition experiment as such. An analytical sample could not be prepared, as the compound was too sensitive and decomposed, but the crude material was used for cycloaddition experiment.

1-[2-(Vinyloxy)methoxyl]-trans-2-phenylcyclohexane (79)

A. Preparation of 1-(β-Chloroethoxy)-chloromethane (84): 2-Chloroethanol (10 g, 12 ml, 0.125 mmol) was vigorously stirred in a flask over an ice bath and formaldehyde (3.75 g, 0.125 mmol) was added. Then dry HCl gas was passed through the reaction mixture for 6 h. The stirred mixture separated into two layers. The mixture was poured into a separatory funnel and the lower layer was taken and stored over calcium chloride. The compound was distilled [56°C at 20 mm/Hg] from $CaCl_2$ prior to its use. Yield = 97 mg (75%). ^1H NMR ($CDCl_3$, 300 MHz) δ 5.59 (s, 2H), 3.98 (t, 2H), 3.75 (t, 2H).

B. Preparation of 1-[β-(Chloroethoxy)]-methoxy-trans-2-phenylcyclohexanol (85): Trans-2-phenylcyclohexanol (142 mg, 0.8068 mmol) and bis chloro compound (93 mg, 1.2102 mmol) from the previous step were placed in a dry flask with a magnetic stirrer. Hunig's base (156.11 mg, 1.2102 mmol) was added followed by dry CH_2Cl_2 (6 ml) as solvent. The reaction mixture was stirred at room temperature for 16 h. After the reaction was complete (by tlc) the solvent was evaporated. The residue was passed through a florisil column eluting with dichloromethane to remove the color. The eluent from the column was concentrated to give the desired compound in 100% yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35-7.20 (m, 5H), 4.67 (d, 1H, J = 7.30 Hz), 4.33 (d, 1H, J = 7.30 Hz), 2.98-2.92 (m, 1H), 2.61-2.52 (m, 1H), 1.96-1.33 (m, 6H).

C. Preparation of 1-[β-(Phenylselenoethoxy)]-methoxy-trans-2-phenylcyclohexanol (86): Diphenyl diselenide (75 mg, 0.481 mmol) was dissolved in 3 ml of absolute ethanol and $NaBH_4$ (36.53 mg, 1.135 mmol) was added batch-wise. The resulting mixture was added to a stirred solution of compound **85** in ethanol and refluxed for 50 h.

Then it was cooled to room temperature. The reaction mixture was filtered through a sintered funnel to remove precipitated NaCl. The bulk of ethanol was removed by rotary evaporation and the residue was partitioned between ethyl acetate and saturated $NaHCO_3$. The aqueous phase was extracted three times (5 ml each) with ethyl acetate. The combined organic layer was washed with a saturated aqueous $NaHCO_3$ followed by brine and then dried over anhydrous K_2CO_3. Removal of the solvent gave an orange oil as crude selenide **86**.

D. Preparation of 1-[β–(Etheleno)methoxy]-trans-2-phenylcyclohexanol (79): Ozone was bubbled into a solution of the above selenide **86** in CH_2Cl_2 at -78°C until the blue color of ozone persisted. After being purged with N_2 the reaction mixture was allowed to warm up to room temperature. The solvent was removed with a rotary evaporator. The resultant white slurry was dissolved in 1,2 dichloroethane and added drop-wise at a rate of 15 ml/ hr. via a syringe pump to a refluxing solution (pot temperature 110°C) of norbornadiene in 1,2 dichloroethane. After the addition was complete, the reflux was continued for another 10 minutes and the volatile components were removed by distillation. The orange residue was distilled bulb to bulb and the distillate collected at 59°C-60°C at 0.1mm/Hg was identified as the required vinyl acetal **79**. Yield = 0.441 mg (42%, from the starting chloro compound). IR ($CHCl_3$) 2920, 2880, 1720, 1630, 1610, 1445, 1120, 1025 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36-7.02 (m, 5H), 6.15 (dd, 1H, J = 6.52 Hz, 14.08 Hz), 4.73 (d, 1H, J = 6.79 Hz), 4.39 (d, 1H, J = 6.80 Hz), 4.32 (dd, 1H, J = 14.08 Hz, 1.49 Hz), 3.99 (dd, 1H, J = 1.48 Hz, 6.55 Hz), 3.73-3.66 (m, 1H), 2.59-2.53 (m, 1H), 2.3-0.88 (m, 8H).^{13}C NMR ($CDCl_3$, 75 MHz) 149.46, 128.28, 127.95, 127.83, 126.24, 93.15, 90.62, 80.74, 51.17, 33.82, 33.28, 25.92, 25.09. LREIMS 189 (M-43), 159 (M-73), 91 (M-141) ($C_{15}H_{20}O_2$ requires 232) .

Preparation of 2,3,4,6-O-Tetraacetyl-1-vinyl-β-D-glucopyranoside (80).

A. Preparation of 2-Phenylseleno-ethan-1-ol (88): To the yellow solution of diphenyl diselenide (2.6 g, 8.33 mmol) in absolute ethanol (30ml), $NaBH_4$ (0.63 g, 16.66

mmol) is added in small portions while stirring under N_2. The colorless solution was then cooled to -30°C and liquid oxirane (1ml, 20 mmol, 1.2 equivalent) was added. After 30 minutes of stirring at -20°C, the mixture was concentrated under vacuum, and the residue was extracted with CH_2Cl_2 (2x20 ml). The organic phase was washed with water, dried with $MgSO_4$ and evaporated to give nearly pure compound **88** (392 mg = 98%) as a slightly yellow oil. ^1H NMR (CCl_4) δ 7.40 (m, $2H_{arom}$) 7.15 (m, $3H_{arom}$), 3.65 (t, 2H, J = 9 Hz), 2.95 (t, 3H, J = 9Hz).

B. Preparation of [β–(Phenylselenyl)ethyl]-2,3,4,6-tetra-O-acetyl-β-D-glycopyranoside (90): A mixture of the phenylselenyl compound **88** (201 mg, 1 mmol), $Hg(CN)_2$, and powdered 4A° molecular sieves in 1,2 dichloroethane (20 ml) was stirred under argon for 2h. 2, 3, 4, 6-tetra-O-acetyl-β-D-glucopyranosyl bromide **89** (493 mg, 1.2 mmol) was then added. After 20 h of stirring the mixture was filtered, washed with 10% aqueous KI solution (2x10 ml), dried with Na_2SO_4 and evaporated. The residual oil was chromatographed over silica gel; eluent hexane/ethyl acetate (6/4) yielding the pure β-isomer **90** in 0.5355 g (53.55%) and α-isomer in 0.2338 g (20.55%). ^1H NMR β -isomer ($CDCl_3$, 300 MHz), δ 7.40 (m, $2H_{arom}$), 7.27 (m, $3H_{arom}$), 4.68 (d, $1H_{anom}$, J = 8 Hz), 3.09 (t, 2H, J = 9Hz), 2.18-2.00 (4s, 12 H). ^1H NMR α -isomer ($CDCl_3$, 300 MHz), δ 7.55-7.49 (m, 2H), 7.31-7.24 (m, 3H), 5.69 (d, 1H, J = 5.23 Hz), 5.20-5.17 (m, 1H), 4.93-4.89 (m, 1H), 4.36-4.32 (m, 1H), 4.21-4.13 (m, 2H), 3.96-3.90 (m, 1H), 3.79-3.72 (m, 2H), 3.07- 3.03 (m, 1H), 2.14-2.02 (m, 12H).

(c) Oxidation of the [β-(Phenylselenyl)ethyl]glucosides (90) and the Formation of the Selenoxide (91): To a solution of the glucoside **90** (100 mg, 0.189 mmol) in methanol : water (6 : 1, 7 ml) was added $NaIO_4$ (60.7 mg, 0.283 mmol) followed by $NaHCO_3$ at room temperature. The reaction mixture was stirred at room temperature for 1.5 h. The suspension was filtered and the filtrate was put on a rotary evaporator to be concentrated. The remaining residue was extracted with dichloromethane (3 x 25 ml). The combined extract was washed with water (10 ml) followed by brine solution (20 ml). The

extract was dried over $MgSO_4$ and the excess solvent was removed to furnished the selenoxide **91** as a white crystalline solid (55 mg, 40%) which was used for the next step without further purification.

D. Elimination of the Selenoxide 91 to Form the Vinyl Glycoside 80: To a solution of the selenoxide **91** (55 mg, 0.1 mmol) in benzene (20 ml) at reflux was added diisopropyl amine (0.07 ml, 0.5 mmol) neat . After 45 minutes, the reaction mixture was cooled to room temperature. The excess of benzene was removed to furnish the crude vinyl ether which was purified by preparative tlc (methanol : dichloro methane = 1 : 19). The pure vinyl glucoside **80** was obtained as a white crystalline solid mp. 95°C (lit. mp. 97-98°C) (25 mg, 60%). IR ($CHCl_3$) 3010, 2295, 1745, 1365, 1210, 1040, 920 cm^{-1} ; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.31 (dd, 1H, J =), 5.07-5.01 (m, 2H), 5.19-5.14 (m, 1H), 4.85 (d, 1H, J = 7.84 Hz, Anomeric H), 4.60 (dd, 1H, J = 1.93 Hz & 14.02 Hz), 4.18-4.33 (m, 3H), 3.78-3.84 (m, 1H), 2.05-2.11 (4s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) 170.61, 169.22, 148.65, 98.94, 93.11, 72.63, 72.13, 70.84, 69.89, 68.11, 61.96, 61.90, 61.84, 20.7, 20.65.

Preparation of 2,3,4,6 Tetra-O-benzyl-1-vinyl-α-D-glucopyranoside (81): 2,3,4,6 Tetrabenzyl-α-D-glucopyranose (1 g) and mercuric acetate (0.4 g) were added to the redistilled isobutyl vinyl ether (5 ml) and the mixture was refluxed for 18 h. The solution was cooled and concentrated to a syrup which was dissolved in ethyl acetate-cyclohexane (1: 2) and chromatographed using the same solvent mixture on 15 g of neutral Woelm alumina. The fractions containing vinyl glycosides were concentrated and dissolved in CCl_4. A silica column chromatography with $CHCl_3$ as the eluent separated α from β vinyl glycoside. The α anomer of the vinyl glycoside which is a thick syrapy like liquid came first followed by it's β anomer, which is a solid of melting point 74-76°C. IR ($CHCl_3$) 3000, 2940, 2880, 1960, 1880, 1815, 1645, 1630, 1497, 1455, 1360, 1325, 910, 850 cm^{-1} ; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.50-7.30 (m, 20H), 7.28-7.20 (m, 2H), 6.46 (dd, 1H, J = 6.54 Hz, 14.09 Hz), 5.16 (d, 1H, J = 5.51 Hz), 5.11-5.08 (m, 1H),

4.96-4.86 (m, 3H), 4.77-4.50 (m, 3H), 4.31 (dd, 1H, J = 1.62 Hz, 6.56 Hz), 4.11-4.11 (m, 1H), 3.88-1.67 (m, 5H).^{13}C ($CDCl_3$) 148.54, 138.77, 138.22, 137.98, 137.85, 128.55, 128.45, 128.41, 128.32, 128.15, 128.00, 127.91, 127.77, 127.67, 96.31, 92.67, 82.06, 79.37, 76.71, 75.87, 75.19, 73.49, 70.78, 68.17.

Preparation of 2, 3, 4, 6-tetra-O-Benzyl-1-vinyl-β-D-glucopyranoside (82).

A. Preparation of 2, 3, 4, 6-Tetra-O-benzyl-α-D-glucopyranosyl trichloro-acetimidate (95): A solution of the 2, 3, 4, 6 tetra-O-benzyl -α-D-glucopyranoside (1.2 g, 2.22 mmol) was made with 10 ml of dry CH_2Cl_2. Trichloroacetonitrile (1 ml) was syringed into the flask. Then 5 mg of NaH (50% dispersion in mineral oil washed 3 times with petroleum ether) was taken in a pipet with dichloromethane and added to the reaction mixture. The mixture was stirred vigorously for 15 minutes. Then another batch of NaH (70 mg) was added and the mixture was kept stirring for another 2.5 h to effect anomerisation. The product was separated by chromatography using 3:2 petroleum ether and ether to give 780 mg (48%) of pure α-isomer as white crystalline solid. m.p.= 75°C (lit. m.p. = 77°C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.60 (s, 1H, NH), 7.55-7.05 (m, 20H, 4 C_6H_5), 6.56 (d, 1H, $J_{1,2}$ = 3.5 Hz), 5.1-3.7 (m, 14H).

B. Preparation of 2'-Phenylseleno-ethyl-2, 3, 4, 6-tetra-O-benzyl-β-D-glucopyranoside (96): The trichloroimidate **95** (590 mg, 0.861 mmol) was dissolved in dry dichloromethane (30 ml) and 2-phenylseleno ethanol (173.7 mg, 0.065 mmol) was added to it. The stirring mixture was cooled to -18°C and boron trifluoride etherate (426 mg, 150 μl) in 10 ml ether was added drop wise via a syringe pump for 30 min. After 2 h at -18°C the reaction mixture was treated with solid Na_2CO_3 and then with dichloromethane/ aqueous $NaHCO_3$ solution. The dichloromethane extract was washed with water and dried over Na_2SO_4. It was concentrated by rotary evaporation to give a white oil (crude). A silica gel chromatography using 3-7% Ethyl acetate / petroleum ether gave the pure compound as a thick oil. Yield = 251 mg (41%). ^{1}H NMR ($CDCl_3$, 300

MHz) δ 7.67-7.23 (m, 25H), 5.08-4.60 (m, 8H), 4.49 (d, 1H, J = 7.74 Hz), 4.2-4.4 (m, 1H), 3.92-3.70 (m, 5H), 3.68-3.52 (m, 2H), 3.25-3.20 (m, 2H).

C. Preparation of 2'-Phenylseleno-oxido ethyl-2, 3, 4, 6-tetra-O-benzyl-α-D-glucopyranoside (97): The phenylseleno glycoside (251 mg, 0.347 mmol) was dissolved in 7 ml of methanol/water (6/1) mixture. The solid did not seem to go to solution. So 3 ml of methanol was added followed by a few drops of THF and the mixture was agitated ultrasonically. To the almost homogeneous solution was added $NaIO_4$ (82 mg, 0.38 mmol) followed by $NaHCO_3$ (44 mg, 0.52 mmol). The reaction mixture was stirred at room temperature for 2 h. A thick cloudy suspension appeared. The reaction mixture was filtered through a sintered funnel. The solids were washed with dichloromethane and the filtrate concentrated to give a white residue which was used in the next step without further purification.

D. Preparation of 2, 3, 4, 6 Tetra-O-benzyl-1-vinyl-β-D-glucopyranoside (82): The white residue of the selenoxide (156 mg, 0.21 mmol) was refluxed in benzene (30 ml) with diisopropylamine (0.09 ml) as the catalyst for 1 h. The course of the reaction was followed by tlc. The reaction mixture was cooled to room temperature after the completion of the reaction. Excess benzene was evaporated in rotary evaporator. The crude compound was subjected to preparative layer chromatography using dichloromethane as the solvent. Yield = 156 mg (81%). IR ($CHCl_3$) 2880,1700, 1460, 1370 cm^{-1} ; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.48-7.34 (m, 18H), 7.30-7.27 (m, 2H), 6.60 (dd, 1H, J = 6.41 Hz, 13.92 Hz), 5.08-4.63 (m, 11H), 4.38 (dd,1H, J = 6.50 Hz, 1.62 Hz), 3.90-3.63 (m, 5H).

~~(v).~~ Preparation of 2, 3, 4, 6-Tetra-O-benzyl-1-isopropenyl-α-D-glucopyranoside (83):

A. Preparation of 3-Selenophenyl Propan-2-ol (98): A clear solution of diphenyl diselenide (1.56 g, 5 mol) in ethanol (20 ml) was made. Then $NaBH_4$ was added batch-wise till a colorless solution was obtained. It was cooled to CCl_4/ dry ice bath temperature

and was kept stirring for 10 min. Then the propylene oxide was added drop-wise and the mixture was led stirring for another 30 min. at that temperature. The tlc showed the completion of the reaction. The reaction vessel was warmed up to room temperature and put on rotary evbaporation to remove ethanol. The resultant slurry was dissolved in dichloromethane and dried over anhydrous $MgSO_4$ and evaporated to give 2.022 g (95%) of the pure compound as a clear oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.60-7.55 (m, 2H), 7.35-7.29 (m, 3H), 3.92-3.87 (m, 1H), 3.18-3.12 (m, 1H), 2.95-2.88 (m, 1H), 2.45 (d, 1H, J = 3.46 Hz), 1.32 (d, 1H, J = 6.20 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.07, 129.22, 127.31, 66.06, 38.57, 22.42.

B. Preparation of 2, 3, 4, 6-Tetra-O-benzyl-β-D-glucopyranosyl trichloro-acetiimidate (99): Trichloroacetonitrile (1 ml) and anhydrous K_2CO_3 (1 g, freshly ignited). The mixture was stirred vigorously under nitrogen for five hrs. The reaction mixture was filtered through a pad of silicagel which was washed repeatedly with dichloromethane. The combined filtrate was concentrated and was put under high vacuum to remove the excess of trichloroacetonitrile. The crude product (1.04 g, 82%) was obtained, which is a mixture of α and β isomers, with β as the major isomer.

C. Preparation of 2, 3, 4, 6-Tetra-O-benzyl-1-[2'-(phenylseleno)-isopropyl]-α-D-glucopyranoside (101): To a solution of O-(2, 3, 4, 6-Tetra-O-benzyl-β--D-glucopyranosyl)trichloro acetimidate (**99**) (760 mg, 1.1 mmol) in dry dichloromethane (5 ml) was added **98** (472 mg, 2.2 mmol) and TsOH (34 mg). The reaction mixture was stirred at room temperature under nitrogen for 4.5 h. Solid $NaHCO_3$ (100 mg) was added to the reaction mixture and stirring was continued for 20 minutes. The mixture was diluted with dichloromethane (30 ml) and filtered. The filtrate was washed with water (15 ml) and with brine (20 ml). The dried solvent (magnesium sulfate) was evaporated to give the crude product which was purified by radial chromatography (petroleum ether : dichloromethane 1 : 1) to furnish the purified product as liquid (488 mg, 61%).

D. Preparation of 2, 3, 4, 6-Tetra-O-benzyl-1-[2'-(phenylselenoxido) isopropyl]-α-D-glucopyranoside (102): The solution of glycoside (117 mg, 0.161 mmol) was made using methanol:water (6:1) with ultrasonic agitation. The insoluble material was dissolved by the drop-wise addition of methanol followed by THF. To the glycoside solution was added $NaIO_4$ (51.65 mg, 0.241 mmol) and $NaHCO_3$ (14.8 mg, 0.177 mmol). The mixture was stirred at room temperature for 2 h. The thick white precipitate was filtered off through a sintered funnel. The white solid on the funnel was washed with dichloromethane (5x15 ml). The filtrate was concentrated to give a white mass. The white mass was taken up in dichloromethane and washed with water. The water layer was extracted with dichloromethane (5x20 ml). The combined organics were concentrated and put under high vacuum to give crude selenoxide as a white solid (126 mg).

E. Preparation of 2, 3, 4, 6-Tetra-O-benzyl-1- isopropenyl-α-D-gluco-pyranoside (83): The selenoxide was dissolved in 10ml of dry benzene and 3 drops of di-isopropyl amine was added. Then the mixture was refluxed for 45 minutes. After the reaction was complete, it was cooled to room temperature and the solvent evaporated under rotary evaporation. Then it was put under high vacuum. A silica gel column chromatography using dichloromethane : petroleum ether (1:1) separated the pure vinyl ether. Yield 83 mg (81%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.46-7.16 (m, 20 H), 5.36 (d, 1H, J = 3.52 Hz), 5.07-4.46 (Series of multiplets, 8H), 4.32 (d, 1H, J = 1.38 Hz), 4.09-3.80 (m, 1H), 3.78-3.66 (m, 6H), 1.91 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 128.45, 128.37, 127.91, 127.84, 127.68, 127.55, 93.91, 87.02, 82.07, 79.73, 77.46, 76.60, 75.67, 75.13, 73.48, 73.02, 70.67, 68.39, 20.56.

Preparation of 1-Dimethoxymethyl-2-menthoxyl-4-[1'-(2',4'-dinitro-phenylamino)] -1, 2, 3, 4-tetrahydronapthalene (106 & 107) by Cyclo-addition of Isoquinolinium Salt (105) with Menthyl Vinyl Ether (55): A two neck flame-dried flask with stirring bar was charged with isoquinolinium salt (33 mg, 0.1

mmol) and 60 mg of anhydrous $CaCO_3$. The mixture was dissolved in a minimum amount of dry methanol. Menthyl vinyl ether (36 mg, 0.2 mmol) was added to the reaction mixture. The mixture was stirred at 40°C for 4d. at which time tlc showed the completion of the reaction. The mixture was passed through celite containing CH_2Cl_2 to filter off $CaCO_3$. The solution was concentrated and put under vacuum for 2 h. The dry cycloadduct was stirred with 33 mg of dowex (H^+) and 1 ml of dry methanol for 24 hrs. The mixture was passed through a cotton plug to filter off the resin. The cotton was washed with CH_2Cl_2 till the cotton became colorless. The filtrate was poured into 20 ml of distilled water. It was extracted with CH_2Cl_2 till the aqueous layer was colorless. The combined organics were washed with a saturated solution of $NaHCO_3$ followed by brine and dried over Na_2SO_4 to give the crude cycloadduct. Radial chromatography using 2-20% ethyl acetate/petroleum ether produced 31mg (58%) of the acetal which was a mixture of two diastereomers which could not be separated. IR ($CHCl_3$) 3610, 3360, 2940, 2885, 1690, 1620, 1600, 1500, 1460, 1380, 1340, 1090 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.13 (d, 1H, J = 2.93 Hz), 8.87 (dd, 1H, J = 13.19 Hz, 8.79 Hz), 8.15 (dd, 1H, J = 2.93 Hz, 2.20 Hz), 7.28-7.00 (m, 3H), 5.14-5.13 (m, 1H), 4.36-4.20 (m, 1H), 3.41 (d, 1H, J = 4.40 Hz), 3.25 (s, 3H), 3.19-3.11 (m, 2H), 2.28-0.52 (m, 20H). CIHRMS $(M+H)^+$ 542.2866, ($C_{29}H_{39}O_7N_3$ requires $(M+H)^+$ 542.2866).

Preparation of 1-Dimethoxymethyl-2-isomenthoxyl -4-[1'-(2',4'-dinitrophenylamino)] -1,2,3,4-tetrahydronapthalene (108 & 109) by Cycloaddition of Isoquinolinium Salt (105) with Isomenthyl Vinyl Ether (56): A two-neck flame-dried flask with stirring bar was charged with isoquinolinium salt (33 mg, 0.1 mmol) and 60 mg of anhydrous $CaCO_3$. The mixture was dissolved in a minimum amount of dry methanol. Isomenthyl vinyl ether (36 mg, 0.2 mmol) was added to the reaction mixture. The mixture was stirred at room temperature for 2d. Tlc showed the completion of the reaction. The mixture was passed through celite containing CH_2Cl_2 to filter off $CaCO_3$. The solution was concentrated and put under vacuum for 2 h. The dry cycloadduct was stirred

with 33 mg of dowex (H^+) and 1 ml of dry methanol for 24 h. The mixture was passed through a cotton plug to filter off the resin. The cotton was washed with CH_2Cl_2 till the cotton became colorless. The filtrate was poured in to 20 ml of distilled water. It was extracted with CH_2Cl_2 till the aqueous layer was colorless. The combined organics were washed with a saturated solution of $NaHCO_3$ followed by brine and dried over Na_2SO_4 to give the crude cycloadduct. Radial chromatography using 2-20% ethyl acetate/petroleum ether produced 29 mg (56%) of the acetal. ^1H NMR (400 MHz, $CDCl_3$) δ 9.19 (m, 1H), 8.96-8.94 (m, 1H), 8.25-8.21 (m, 1H), 7.37-7.20 (m, 3H), 7.08 (d, 1H, J = 9.52 Hz), 5.25-5.19 (m, 1H), 4.45-4.43 (m, 1H), 4.225-4.221 (bm, 1H), 3.79-3.57 (m, 1H), 3.48 and 3.47 (two closely lying singlets for two methoxyl protons, 3H), 3.328 and 3.321 (two closely lying singlets for two methoxyl protons, 3H), 3.20-3.18 (m, 1H), 2.34-2.16 (m, 1H), 1.99 -0.74 (series of multiplets, 20H). CIHRMS $(M+H)^+$ 542.2866, ($C_{29}H_{39}O_7N_3$ requires $(M+H)^+$ 542.2866).

Preparation of 1-Dimethoxymethyl-2-trans-β-Phenylcyclohexyl-4-[1'-(2',4'-dinitro-phenylamino)]-1,2,3,4-tetrahydronapthalene (110) by Cyclo-addition of Isoquinolinium Salt (105) with trans-2-Phenylcyclohexyl Vinyl Ether (57): A sample of the 2,4 dinitrophenyl salt of isoquinoline (250 mg, 0.74 mmole) was added to a two necked flame dried flask equipped with a stirring bar and 1ml of methanol was added. The above vinyl ether was added (150 mg, 0.75 mmole) followed by $CaCO_3$ (444 mg).The mixture was stirred at room temperature for 4 days under an atmosphere of nitrogen. The reaction was followed by tlc. After the disappearance of the starting material the mixture was passed through a pad of celite slurried with CH_2Cl_2. Celite layer was washed with CH_2Cl_2 till the celite became colorless. The filtrate was concentrated and put under high vacuum for 2 h. The resulting orange residue was treated with 250 mg of Dowex (H^+) with 1 ml of methanol and stirred at room temperature for 24 h. The resin was filtered through a cotton plug and the filtrate was poured in 30 ml of distilled water. It was extracted with CH_2Cl_2 till the aqueous layer was colorless. The

organic layer was washed with a saturated solution of $NaHCO_3$ and washed with brine. It was dried over anhydrous Na_2SO_4 and concentrated. Radial chromatography of the oil (eluting with 5-80% Ethyl acetate-/Petroleum ether), afforded 380mg (90%) of the pure acetal. ^1H NMR (300 MHz, $CDCl_3$) δ 9.508 (d, 1H, J = 2.44Hz), 8.5630 (d, 1H, J = 7.994 Hz), 7.336-7.063 (m, 9H, Aromatic), 6.968 (d, 1H, C<u>H</u>NH, J = 7.32 Hz), 4.364 (d, 1H, C<u>H</u>$(OMe)_2$, J = 4.27 Hz), 3.644 (ddd, 1H, J = 4.28 Hz, 10.07 Hz, 12.51 Hz), 3.462 (s, 3H, OC<u>H</u>$_3$), 3.282 (s, 3H, OC<u>H</u>$_3$), 3.108 (bd, 1H), 2.471-1.274 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 130.283, 129.336, 128.78, 128.655, 128.451, 128.282, 128.236, 128.036, 127.909, 127.564, 127.403, 127, 330, 127.018, 126.849, 126.389, 125.851, 124.338, 118.447, 109.149; CIHRMS m/e (relative intensity) 561.2475, ($C_{29}H_{39}O_7N_3$ requires 561.2481).

Preparation of 1-Dimethoxymethyl-2-hydroxyl -4-[1'-2'4'-dinitro-phenylamino)]-1, 2, 3, 4 -tetrahydronapthalene (112) by Cycloaddition of Isoquinolinium Salt (105) with the Orthoester Vinyl Ether(65a): A two-neck flame-dried flask with stirring bar was charged with isoquinolinium salt (35 mg, 0.105 mmol), 60 mg of anhydrous $CaCO_3$ and the above vinyl ether **65a** (44 mg, 0.143 mmol) and 0.2 ml of methanol. The mixture was stirred at room temperature. After 7 days tlc showed the completion of the reaction. The mixture was passed through celite containing CH_2Cl_2 to filter off $CaCO_3$. The solution was concentrated and put under vacuum for 2 hrs. The dry cycloadduct was stirred with 35 mg of Dowex (H^+) and 2 ml of dry methanol for 24 h. The mixture was passed through a cotton plug to filter off the resin. The cotton was washed with CH_2Cl_2 till it became colorless. The filtrate was poured into 20 ml of distilled water. It was extracted with CH_2Cl_2 till the aqueous layer was colorless. The combined organics were washed with saturated $NaHCO_3$ followed by brine and dried over Na_2SO_4 to give the crude cycloadduct. Radial chromatography using 15% ethyl acetate/petroleum ether produced 11 mg (33%) of the acetal. ^1H NMR ($CDCl_3$, 300 MHz) δ 9.22 (d, 1H, J =2.68 Hz), 8.75 (d, 1H, J = 7.51 Hz), 8.35 (dd, 1H, J = 2.53 Hz, 9.85

Hz), 7.45-7.24 (m, 3H), 7.18 (d, 1H, J = 9.62 Hz), 5.08-5.06 (m, 1H), 4.78 (d, 1H, J = 6.38 Hz), 4.66-4.61 (m, 1H), 3.59 (s, 3H), 3.53 (d,1H, J = 4.76 Hz), 3.414 (s, 3H), 3.28-3.25 (m, 1H), 2.46 (m, 1H), 2.12 (m, 1H), 1.62 (bs, 1H).

Preparation of 1-Dimethoxymethyl-2-hydroxyl-4-[1'-(2',4'-dinitro-phenylamino)]-1, 2, 3, 4 -tetrahydronapthalene (112) by Cycloaddition of Isoquinolinium Salt (105) with the Orthoester Vinyl Ether (65b): A two-neck flask with a stirring bar was charged with isoquinolinium salt (49.45 mg, 0.149 mmol), 90 mg of anhydrous $CaCO_3$ and the above vinyl ether **65b** (43 mg, 0.149 mmol) and 0.2 ml of methanol. The mixture was stirred at room temperature. After 4 d tlc showed the completion of the reaction. The mixture was passed through celite containing CH_2Cl_2 to filter off $CaCO_3$. The solution was concentrated and put under vacuum for 2 h. The dry cycloadduct was stirred with 90 mg of Dowex (H^+) and 3 ml of dry methanol for 24 h. The mixture was passed through a cotton plug to filter off the resin. The cotton was washed with CH_2Cl_2 till it became colorless. The filtrate was poured into 20 ml of distilled water. It was extracted with CH_2Cl_2 till the aqueous layer was colorless. The combined organics were washed with saturated $NaHCO_3$ followed by brine and dried over Na_2SO_4 to give the crude cycloadduct. Radial chromatography using 15% ethyl acetate/petroleum ether produced 40.6 mg (67.5%) of the acetal. ^1H NMR ($CDCl_3$, 300 MHz) δ 9.22 (d, 1H, J =2.68 Hz), 8.75 (d, 1H, J = 7.51 Hz), 8.35 (dd, 1H, J = 2.53 Hz, 9.85 Hz), 7.45-7.24 (m, 3H), 7.18 (d, 1H, J = 9.62 Hz), 5.08-5.06 (m, 1H), 4.78 (d, 1H, J = 6.38 Hz), 4.66-4.61 (m, 1H), 3.59 (s, 3H), 3.53 (d,1H, J = 4.76 Hz), 3.414 (s, 3H), 3.28-3.25 (m, 1H), 2.46 (m, 1H), 2.12 (m, 1H), 1.62 (bs, 1H).

Preparation of 1-Dimethoxymethyl-2-hydroxyl-4-[1'-(2',4'-dinitro-phenyl-amino)]-1,2,3,4 -tetrahydronapthalene (112&114) by Cycloaddition of Isoquinolinium Salt (105) with the Orthoester Vinyl Ether (67): A solution of the salt (50 mg, 0.15 mmol) was made in 1 ml of dry methanol and the dienophile (61 mg, 0.202 mmol) was added to it. dry $CaCO_3$ (121 mg) was added to it. The reaction mixture

was heated to 42°C and stirred for 6d. Some decomposition of the salt was shown on tlc. The mixture was cooled to room temperature and filtered through celite containing dichloromethane as the solvent. The filtrate was concentrated and put under high vacuum for 2h. The dry cycloadduct was treated with 66 mg of the Dowex (H)+ and 3 ml of the dry methanol. The mixture was stirred for 24h at room temperature. The reaction mixture was passed through a cotton plug and poured into 30 ml of distilled water. The organics were extracted out from the water layer with dichloromethane till the aqueous layer was colorless. The combined organics were washed with a saturated solution of $NaHCO_3$, dried over Na_2SO_4 and concentrated. The crude NMR shows it was a mixture of two compounds. A pplc was done (1:1 ethyl acetate /hexane) to separate the two isomeric exo and endo alcohols (exo:endo 3.5 :1). **exo alcohol 112** ^1H NMR ($CDCl_3$, 300 MHz) δ 9.22 (d, 1H, J =2.68 Hz), 8.75 (d, 1H, J = 7.51 Hz), 8.35 (dd, 1H, J = 2.53 Hz, 9.85 Hz), 7.45-7.24 (m, 3H), 7.18 (d, 1H, J = 9.62 Hz), 5.08-5.06 (m, 1H), 4.78 (d, 1H, J = 6.38 Hz), 4.66-4.61 (m, 1H), 3.59 (s, 3H), 3.53 (d,1H, J = 4.76 Hz), 3.414 (s, 3H), 3.28-3.25 (m, 1H), 2.46 (m, 1H), 2.12 (m, 1H), 1.62 (bs, 1H). **endo alcohol 114** ^1H NMR ($CDCl_3$, 300 MHz) δ 9.54 (d, 1H, J = 8.64 Hz), 9.21 (d, 1H, J = 2.67 Hz), 8.31 (dd, 1H, J = 9.55 Hz and 2.66 Hz), 7.50-7.28 (m, 3H), 7.25 (d, 1H, J = 9.65 Hz), 5.18-5.14 (m, 1H), 4.97 (d, 1H, J = 4.42 Hz), 4.62-4.54 (m, 1H), 3.58 (s, 3H), 3.54 (s, 3H), 3.26-3.20 (m, 1H), 2.44-2.39 (m, 2H).

Preparation of 1-Dimethoxymethyl-2-hydroxyl -4-[1'-(2' 4'-dinitrophenyl)-amino]-1, 2, 3, 4- tetrahydronapthalene (112) by Cycloaddition of Isoquinolinium Salt (105) with Vinyl Acetal (79): A two-neck, flame-dried flask with stirring bar was charged with isoquinolinium salt (42 mg, 0.1266 mmol) and 92 mg of anhydrous $CaCO_3$. The mixture was dissolved in minimum amount of dry methanol. Compound **79** (38 mg, 0.163 mmol) was added to the reaction mixture. The mixture was stirred at 40°C for 6d. Tlc showed the completion of the reaction. The mixture was passed

Compound **79** (38 mg, 0.163 mmol) was added to the reaction mixture. The mixture was stirred at 40°C for 6d. Tlc showed the completion of the reaction. The mixture was passed through celite containing CH_2Cl_2 (dried over $MgSO_4$) to filter off $CaCO_3$. The solution was concentrated and put under vacuum for 2 h. The dry cycloadduct was stirred with 60 mg of Dowex (H^+) and 3 ml of dry methanol at room temperature till as lower moving spot (the acetal where the chiral auxiliary is hydrolysed) appeared at the expense of farther moving spot. The mixture was passed through a cotton plug to filter off the resin. The cotton was washed with CH_2Cl_2 till it became colorless. The filtrate was poured in to 20 ml of distilled water. It was extracted with CH_2Cl_2 till the aqueous layer was colorless. The combined organics were washed with a saturated solution of $NaHCO_3$ followed by brine and dried over Na_2SO_4 to give the crude cycloadduct. Radial chromatography using 2-25% ethyl acetate/petroleum ether yielded 20 mg (62%) of the alcohol. ^1H NMR ($CDCl_3$, 300 MHz) δ 9.22 (d, 1H, J =2.68 Hz), 8.75 (d, 1H, J = 7.51 Hz), 8.35 (dd, 1H, J = 2.53 Hz, 9.85 Hz), 7.45-7.24 (m, 3H), 7.18 (d, 1H, J = 9.62 Hz), 5.08-5.06 (m, 1H), 4.78 (d, 1H, J = 6.38 Hz), 4.66-4.61 (m, 1H), 3.59 (s, 3H), 3.53 (d,1H, J = 4.76 Hz), 3.414 (s, 3H), 3.28-3.25 (m, 1H), 2.46 (m, 1H), 2.12 (m, 1H), 1.62 (bs, 1H).

Preparation of 1-Dimethoxymethyl-2-(2', 3' 4' 6' Tetra-O-acetyl -β-D-glucopyranosyloxy)-4-(2",4"-dinitro,1"-amino)-1, 2, 3, 4-tetrahydro-napthalene (115&116) by the Cycloaddition of Isoquinolinium Salt (105) with 2.3,4,6 Tetra-O-acetyl-1-vinyl-β-D-glucopyranoside (81): A two-neck, flame-dried flask with stirring bar was charged with isoquinolinium salt (42.8 mg, 0.129 mmol) and 77.4 mg of anhydrous $CaCO_3$. The mixture was dissolved in minimum amount of dry methanol to which 2,3,4,6, tetra-O-acetyl-1-vinyl -β-D-glucopyranoside (48 mg, 0.129 mmol) was added. The reaction was complete by tlc in 7 d. The mixture was passed through celite containing CH_2Cl_2 to filter off $CaCO_3$. The solution was concentrated and put under vacuum for 2 h. The dry cycloadduct was stirred with 39 mg of Dowex (H^+) and 1 ml of dry methanol for 24 h. The completion of the reaction was monitered by tlc.The

water. It was extracted with CH_2Cl_2 till the aqueous layer was colorless. The combined organics were washed with a saturated solution of $NaHCO_3$ followed by brine and dried over Na_2SO_4 to give the crude cycloadduct. Radial chromatography using 2-20% ethyl acetate/petroleum ether yielded 31.2 mg (33%) of the acetal. IR ($CHCl_3$) 2940, 1750, 1620, 1600, 1370, 1340 cm^{-1}; CILRMS (methane) m/e 733 ($C_{33}H_{39}O_{16}N_3$ requires 733).

Preparation of 1-Dimethoxymethyl -2-(2', 3' 4' 6' tetra-O-benzyl -α-D-glucopyranosyloxy) -4-(2", 4"-dinitro, 1"-amino)-1, 2, 3, 4- tetrahydro-napthalene (117) by the Cycloaddition of Isoquinolinium Salt (105) with 2.3,4,6 Tetra-O-benzyl-1-vinyl-α-D-glucopyranoside (81): A two-neck, flame-dried flask with stirring bar was charged with isoquinolinium salt (33.1 mg, 0.1 mmol) and 60 mg of anhydrous $CaCO_3$. The mixture was dissolved in minimum amount of dry methanol to which 2,3,4,6, tetra-O-benzyl-1-vinyl -α-D-glucopyranoside (58.27 mg, 0.1 mmol) was added. After 4d another 80 mg of vinyl ether was added.The mixture was stirred at 40°C for 7d. Tlc showed the completion of the reaction. The mixture was passed through celite containing CH_2Cl_2 to filter off $CaCO_3$. The solution was concentrated and put under vacuum for 2 h. The dry cycloadduct was stirred with 33 mg of Dowex (H^+) and 2 ml of dry methanol (with 1ml of dry dichloromethane as the cosolvent to dissolve the adduct) for 24 h. The completion of the reaction was monitered by tlc.The mixture was passed through a cotton plug to filter off the resin. The cotton was washed with CH_2Cl_2 till the cotton became colorless. The filtrate was poured into 20 ml of distilled water. It was extracted with CH_2Cl_2 till the aqueous layer was colorless. The combined organics were washed with a saturated solution of $NaHCO_3$ followed by brine and dried over Na_2SO_4 to give the crude cycloadduct. Radial chromatography using 5-30% ethyl acetate/petroleum ether yielded 65 mg (70%) of the acetal. IR ($CHCl_3$) 3350, 2940, 1700, 1625, 1600, 1500, 1450, 1430, 1340, 1075 cm^{-1}; ^1H NMR ($CDCl_3$,300 MHz) δ 9.173 (d, 1H, J = 2.65 Hz), 8.934 (d, 1H, J = 8.59 Hz), 7.811 (dd, 1H, J = 2.59 Hz, 2.59 Hz), 7.496-7.201 (m, 20H), 7.197-7.105 (m, 2H), 6.951 (d, 1H, J = 9.62 Hz), 5.346-5.257 (m,

1H), 5.117 (d, 1H, J = 4.65 Hz), 5.103-3.5 (m, 19H), 3.457 (s, 3H), 3.317 (s, 3H), 2.450-2.412 (m, 1H), 2.268-2.263 (m, 1H). CIHRMS m/e (relative intensity) 925.37875 ($C_{53}H_{55}O_{12}N_3$ requires 925.3786).

Preparation of 1-Dimethoxymethyl-2-(2', 3' 4' 6' tetra-O-benzyl -β-D-glucopyranosyloxy)-4-(2",4"-dinitro,1"-amino)-1, 2, 3, 4-tetrahydro-napthalene (118 & 119) by the Cycloaddition of Isoquinolinium Salt with 2, 3, 4, 6 Tetra-O-benzyl-1-vinyl-β-D-glucopyranoside (82): A two-neck flame-dried flask with stirring bar was charged with isoquinolinium salt (49.7 mg, 0.15 mmol) and 90 mg of anhydrous $CaCO_3$. The mixture was dissolved in a minimum amount of dry methanol (0.5 ml) and 2,3,4,6, tetra-O-benzyl-1-vinyl -β-D-glucopyranoside (85 mg, 0.15 mmol) was added to the reaction mixture. After 5d another 14 mg of vinyl ether was added to allow the unreacted salt to go the product. The mixture was stirred at 45°C for another 8d. Tlc showed the completion of the reaction. The mixture was passed through celite containing CH_2Cl_2 to filter off $CaCO_3$. The solution was concentrated and put under vacuum for 2 h. The dry cycloadduct was stirred with 50 mg of Dowex (H^+) and 3 ml of dry methanol (with 1ml of dry dichloromethane as the cosolvent to dissolve the adduct) for 24 h. The completion of the reaction was monitored by tlc.The mixture was passed through a cotton plug to filter off the resin. The cotton was washed with CH_2Cl_2 till the cotton became colorless. The filtrate was poured into 30 ml of distilled water. It was extracted with CH_2Cl_2 till the aqueous layer was colorless. The combined organics were washed with a saturated solution of $NaHCO_3$ followed by brine and dried over Na_2SO_4 to give the crude cycloadduct. Radial chromatography using 8-20% ethyl acetate/petroleum ether afforded two acetals in 2.3 : 1 ratio (total yield = 56 mg (40%). **Isomer i (118):** ^1H NMR ($CDCl_3$, 300 MHz) δ 9.03 (d, 1H, J = 1.6 Hz), 8.71 (d, 1H, J = 8.53 Hz), 7.21 (dd, 1H, J = 2.67 & 2.64 Hz), 7.31- 7.04 (m, 23H), 6.53 (d, 1H, J = 9.69 Hz), 5.19-5.00 (m, 1H), 4.99 - 4.48 (m, 7H), 4.37 (d, 1H, J = 4.82 Hz), 3.68-3.41 (m, 5H), 3.36 (s, 3H), 3.35-3.30 (m, 1H), 3.24 (s, 3H), 2.41-2.34 (m, 1H), 2.16 -2.11 (m, 1H);

Isomer ii (119): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.15 (d, 1H, J = 2.67 Hz), 8.97 (d, 1H, J = 8.45 Hz), 8.15 (dd, 1H, J = 9.56 & 2.54 Hz), 7.43 -7.03 (m, 24H), 5.34-5.33 (m, 1H), 4.96-4.45 (m, 8H), 3.78-3.49 (m, 5H), 3.47 (s,3H), 3.45-3.34 (m, 1H), 3.33 (s, 3H), 2.7-2.6 (m, 1H), 2.44-2.21 (m, 1H).

Preparation of 1-Dimethoxymethyl-2-(2', 3' 4' 6' Tetra-O-benzyl-α-D-glucopyranosyloxy)-4-amino-1, 2, 3, 4-tetrahydronaphthalene (120) : To a solution of the compound **119** (172 mg) in 10 ml acetone, 1 ml of water was added. A turbidity appeared. The cloudy suspension was broken using a few drops of acetone. Then 1.72 g of Amberlyst IRA-400-OH^- (basic resin) was added. The reaction mixture was stirred efficiently at room temperature for 4 days. The completion of the reaction was checked by TLC. The resin was filtered through a sintered funnel. The solvent was evaporated and the resultant pink solid was dried under high vacuum. A radial chromatography was done using 5% CH_3OH/CH_2Cl_2 mixture affording 111.9 mg (79%) of the pure amino compound. IR ($CHCl_3$) 2980, 1720, 1550, 1520, 1480, 1380, 1100. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.51-7.11 (m, 243 H, arom), 5.08 (d, 1H, J = 4.52 Hz), 4.95-4.37 (m, 16H), 3.83-3.51 (m, 4H), 3.37 (s, 3H), 3.2 (s, 3H), 2.34-2.08 (m, 2H).

Preparation of 1-Dimethoxymethyl -2-(2', 3' 4' 6' tetra-O-benzyl -α-D-glucopyranosyloxy)-4-acetylamino-1, 2, 3, 4-tetrahydronapthalene (121) : The glycoside acetal **120** (111 mg, 0.143 mmol) was dissolved in a minimum volume of pyridine and acetic anhydride (29.17 mg, 0.286 mmol, 0.031 ml) was added followed by dimethylaminopyridine (3.5 mg, 0.0286 mmol). The reaction mixture was stirred under N_2 for 2 h. tlc (1:1 ethyl acetate/petroleum ether) showed the completion of the reaction. The mixture was concentrated on a rotary evaporator followed by high vacuum. Then a radial chromatography was done using (1:1 ethyl acetate/petroleum ether). The second band (UV visible) was shown to be the acetate by NMR. Yield = 94 mg (81.8%). IR ($CHCl_3$) 2940, 2880, 1670, 1610, 1500, 1460, 1380, 1080; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25-7.16 (m, 24H), 6.17 (d, 1H, J = 9.04 Hz), 5.29- 5.19 (m, 1H), 4.97 (d, 1H, J = 3.67 Hz),

4.89-4.39 (series of multiplets, 11H), 3.88-3.47 (m, 6H), 3.31 (s, 3H), 3.21 (s, 3H), 2.57-2.16 (m, 1H), 1.95 (s, 3H), 1.99-1.92 (m, 1H). CIHRMS (m/e) 801.38785 ($C_{49}H_{55}O_9N$ requires 801.111).

1-(1',3' Dithianyl)-2-(2', 3' 4' 6' tetra-O-benzyl -α-D-glucopyranosyloxy) -4-acetylamino -1, 2, 3, 4- tetrahydronapthalene (124): To a stirred solution of the compound **121** in dry CH_2Cl_2 (63.2 mg, 0.0772 mmol in 3 ml) under nitrogen was added propane dithiol (36.89 mg, 35ml, 0.3416 mmol). The stirred solution was cooled to -10°C and after 15 minutes, then $BF_3.Et_2O$ (35.07 mg, 27 ml, 0.247 mmol) was added drop wise and stirring was continued for another 10 minutes at -10°C. Then the solution was warmed up to 0°C-5°C and stirred for 30 minutes. Tlc showed the completion of the reaction (1:1 Ethyl acetate:petroleum ether). The reaction was quenched by the drop-wise addition of a saturated solution of $NaHCO_3$ at ice bath temperature and stirred at ambient temperature for 30 min. Then it was poured into a separatory funnel, washed with a saturated $NaHCO_3$ solution, water and extracted with CH_2Cl_2 three times, dried over Na_2SO_4 and concentrated. It was purified by radial chromatography (1:1 / Ethyl acetate:petroleum ether) to yield 110 mg (72%) of **124**. IR ($CHCl_3$) 2920, 1670, 1500, 1460, 1370 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.52-7.49 (m, 1H), 7.37-7.29 (m, 21H), 7.18-7.16 (m, 2H), 5.81 (d, 1H, J = 7.38 Hz), 5.43-5.36 (m, 1H), 5.10 (d, 1H, J = 2.59 Hz), 4.98-4.39 (m, 10H), 3.44-3.91 (m, 7H), 2.89 -2.78 (m, 3H), 2.45 -2.18 (m, 2H), 2.07 (bs, 4H).

Preparation of 1-[2'-(1' 3')-Dithianyl]-2-hydroxy-4-acetylamino-1, 2, 3, 4 tetrahydronapthalene (123): A two-neck flask with N_2 adapter was washed with hexamethyl disilazane and dried in an oven at 100°C. The starting material **124** (19 mg, 0.022 mmol) was dried at high vacuum for two hours. The μl syringes and the ordinary syringes and needdles were dried under high vacuum. Freshly distilled and dry CH_2Cl_2 was added to the compound and TMSI (69 ml, 0.485 mmol) was added drop- wise.The solution became brown and the mixture was stirred for 2.25 h. Then the mixture was

poured into 0.5 ml of CH_3OH and stirred for 1 hr. Then it was concentrated with a rotary evaporator to remove the volatile impurities. The crude residue was taken up in ethyl acetate, washed with aqueous $NaHCO_3$, followed by brine, dried over Na_2SO_4 and evaporated to give a white solid. A PLC on silica was done using 70:30 ethyl acetate/petroleum ether which gave 3.8 mg (83%) of the pure compound as a white foamy mass. IR ($CHCl_3$) 3425, 2900, 1665, 1500, 1120 cm^{-1}; ^1H NMR ($CDCl_3$,300 MHz) δ 7.54 (d,1H, J = 7.62 Hz), 7.42 (m,3H), 5.88-5.80 (bm, 1H), 5.32-5.26 (m,1H), 4.74 (d,1H, J = 3.2Hz), 4.54-4.47 (m, 1H), 3.28-3.25 (m,1H), 2.99-2.82 (m, 6H), 2.41-2.34 (m,1H), 2.05 (s, 3H), 2.07-2.01 (m, 1H). EIHRMS (m/e) relative intensity 323.0983 ($C_{16}H_{21}O_2NS_2$ requires 323.10153).

Preparation of Bis -1, 2-trimethyl silyloxy-3-chloro propanediol (195): To a solution of 3-chloro-1,2 propanediol (1.10 g, 10 mmol) in 10 ml of dry THF at 0°C was added trifloromethanesulfonate (0.05 ml, 1 mol%) followed by addition of hexamethyl disilazane (4.035 g, 5.27 ml, 25 mmol). The mixture was stirred for 15 min. at that temperature while soft solids came out. The solution was warmed to room temperature and poured into 100 ml of water. The water layer was extracted with dichloromethane (3x75 ml). The combined organics were dried over anhydrous Na_2CO_3 and concentrated to give a colorless liquid, yield = 1.85 g (75%). ^1H NMR ($CDCl_3$, 300 MHz) δ 3.91-3.68 (m, 1H), 3.65-3.61 (m, 3H), 3.54-3.49 (m, 1H), 0.208 (s, 9H), 0.174 (s, 9H).

Preparation of -1,4-Dioxa-3-chloromethyl-7-methyl-10-isopropyl spiro -(4,5)-decane (196): The bis-TMS protected alcohol **195** (1.78 g, 7 mmol) was charged into a flame-dried flask with a magnetic stirring bar. Then l-(+)-menthone (1.295 ml, 1.156 g, 7.5 mmol) was added followed by the addition of 10ml of dry dichloromethane. The reaction mixture was cooled to -40°C. Then 0.13 ml of TMSOTf was added. The reaction mixture was allowed to stir at -40°C for 18 h. The reaction was quenched by the addition of 10 ml of a 2% solution of NaOH at the same temperature. The mixture was warmed to room temperature and stirred for 30 min. The resulting white cloudy solution

was added into a separatory funnel containing aqueous $NaHCO_3$ solution. The aqueous layer was extracted with petroleum ether (4x50 ml). The organics were combined and dried over anhydrous Na_2CO_3 and then concentrated by rotary evaporation to give the crude product as a colorless oil. It was distilled bulb to bulb. The fraction distilling at 75-85°C at 20mm/Hg was the required compound as shown by NMR. But it exists as a mixture of diastereomers which could not be purified. ^1H NMR ($CDCl_3$, 300MHz) δ 4.34 -4.09 (m, 2H), 4.05 -3.35 (series of multiplets, 3H), 2.45-1.05 (series of multiplets, 7H), 1.05 -0.78 (series of multiplets, 9H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 113.92, 113.55, 113.41, 113.38, 75.85, 75.70, 74.82, 74.45, 68.22, 68.19, 67.67, 67.27, 49.82, 49.46, 48.55, 48.31, 46.71, 45.85, 44.78, 44.70, 44.43, 43.78, 43.70, 34.50, 34.35, 30.79, 30.35, 30.27, 24.90, 24.54, 24.41, 24.23, 23.63, 23.48, 23.40, 23.30, 23.19, 23.12, 22.14, 22.01, 18.88, 18.47, 18.14, 18.07; LREI (m/e) 246 ($C_{13}H_{23}O_2Cl$ requires 246).

Preparation of -1,4-Dioxa-3-vinyl-7-methyl-10-isopropyl spiro -(4,5)-decane 197: To a flask containing freshly prepared sodium methoxide (75 mg, 1.365 mmol), 1 ml of dry DMF was added followed by the addition of the chloro compound **196**. The mixture was stirred at 50°C for 2h. The mixture was cooled to room temperature and taken up in dichloromethane. It was washed with water (7x50 ml) to remove the DMF. The combined organics were dried over anhydrous Na_2CO_3 and concentrated by rotary evaporation to give the crude vinyl ether. Then a rapid flash chromatography was done using 3% ether / hexane to give the vinyl ether **197** (a mixture of two diastereomers, which could not be purified) as a colorless oil. ^1H NMR ($CDCl_3$, 300MHz) δ 4.58 - 4.5 (m, 2H), 4.32 -4.25 (m, 1H), 3.86 -3.82 (m, 1H), 2.2 - 0.8 (series of multiplets, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.38, 115.44, 66.44, 66.35, 48.96, 48.82, 44.76, 43.91, 34.43, 34.35, 30.35, 30.21, 24.77, 24.67, 23.51, 23.39, 23.28, 21.95, 21.89, 18.75, 18.21.CIHRMS (m/e) 211.16980, ($C_{13}H_{22}O_2$ requires 211.1699).

Preparation of 1-Methoxy-3a-hydroxy-5[1'-(2',4'-dinitrophenylamino)]-1, 2, 3, 4 tetrahydronaphtho -[1,2-c]-tetrahydrofuran (199) by Cycloaddition

of Vinyl Ether 197 to Salt 105): To a solution of salt **105** (115 mg, 0.4524 mmol) in 0.4 ml of methanol was added 330 mg of anhydrous $CaCO_3$ followed by the addition of vinyl ether **197** (150 mg, 0.452 mmol). The reaction mixture was stirred at room temperature for 2d. Another 100µl of the vinyl ether was added. The completion of the reaction was checked by tlc. The crude reaction mixture was passed through celite containing a dichloromethane slurry. The celite was washed with dichloromethane till it (celite) became colorless. The filtrate was concentrated by rotary evaporation then put under high vacuum for 2 h. The adduct was then treated with 4 ml of methanol and 150 mg of Dowex(H^+). After 15h tlc showed the complete formation of the acetal. Then the resin was filtered off through a cotton plug to 50 ml of water. The filtrate was extracted with of dichloromethane (3x50 ml). The combined organics were washed with a saturated solution of $NaHCO_3$ and then with brine. The organic layer was dried over anhydrous Na_2SO_4. The crude product was purified by radial chromatography using 5-30% ethyl acetate /petroleum ether to give two epimeric acetals. Combined Yield=146 mg (70%) [acetal **199a** = 69mg, acetal **199b** =77mg]. Compound**199a** IR ($CHCl_3$) 3340, 1620, 1590, 1340, 1130 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.22 (d, 1H, J = 2.65 Hz), 8.88 (bd, 1H), 8.31 (dd, 1H, J = 2.52 Hz and 9.56 Hz), 7.37 - 7.11 (m, 5H), 5.30-5.20 (m, 1H), 4.97 (d, 1H,J = 3.4 Hz), 4.04 (d, 1H, J = 8.99 Hz), 3.82 (d, 1H, J = 8.96 Hz), 3.50 (s, 3H), 3.28 (d, 1H, J = 3.53 Hz), 2.41 (dd, 1H, J = 13.17 Hz, 4.72 Hz), 2.05 (dd, 1H, J = 13.05 Hz, 11.27 Hz). CIHRMS (m/e) relative intensity 401.12230, ($C_{19}H_{19}O_7N_3$ requires 401.12237).

Compound 199b: IR ($CHCl_3$) 3320, 1610, 1590, 1500, 1415, 1330 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 9.25 (d, 1H, J = 2.63 Hz), 8.93 (bd, 1H,J = 9.38 Hz), 8.35 (dd, 1H, J = 2.79 Hz), 2.26 Hz), 7.40-7.30 (m, 3H), 5.31-5.23 (m, 1H), 5.00 (d, 1H, J = 3.43 Hz), 4.08 (d, 1H J = 9.01 Hz), 3.85 (d, 1H J = 8.94 Hz), 3.54 (s, 3H), 3.32 (bd, 1H, J = 2.91 Hz), 2.47 (dd, 1H, J = 4.59 Hz, 0.73Hz), 2.38- 2.08 (m, 2H).

Preparation of 1-Methoxy-3a-hydroxy-5-amino 1, 2, 3, 4 tetrahydro naptho [1,2-c]-tetrahydrofuran (203): A solution of **199-a** (32 mg, 0.074 mmol) in 10

ml of acetone was treated with 1 ml of water . The cloudy suspension was broken by adding a few drops of water. Then 410 mg of Amberlyst (IRA-400-OH^-) was added to the mixture. It was stirred vigorously for 20 h. Tlc showed the completion of the reaction. The resin was filtered off and the residue was washed with few ml of acetone. The filtrate was evaporated and the crude residue was put under high vacuum for 5h. The crude product was purified by preparative plate chromatography using 5% methanol / dichloromethane. Yield = 21 mg (98%). ^1H NMR ($CDCl_3$, 300 MHz) 7.57-7.53 (1H, m), 7.37-7.26 (3H, m), 4.88 (1H, d, J =3.56Hz), 4.27-4.23 (1H, m), 4.00 (1H, d, J = 8.66Hz), 3.80 (1H, d, J = 8.64Hz), 3.47 (3H, s), 3.22 (1H, d, J = 3.22Hz), 2.24 (1H, dd, J = 4.18Hz,13.03 Hz), 1.85-1.81 (1H, m).

Preparation of 2,4-Dihydroxy 6-methoxy- 1, 2, 3, 4 tetrahydro naptho[1,2-c]-2'-methoxy-2', 3', 4', 5' tetrahydrofuran 204 (major): A solution of $Na_2Fe(CN)_5NO$ (171.32 mg, 0.575 mmol) in 0.668 ml of water was added dropwise to a solution of amine (22 mg, 0.0936 mmol) and Na_2CO_3 (10.02 mg) in 0.3 ml of water. The solution was stirred for 24 h and 133 mg of K_2CO_3 was added. The mixture was stirred for 30 min. Then the mixture was extracted with ether (3x25 ml). The ether extracts were dried over $MgSO_4$ and evaporated. A preparative plate layer chromatography was done using 3.5-5% methanol-dichloromethane mixture. Two isomers were separated (combined yield = 67%), the major isomer was isolated as a foamy solid and the minor isomer as a liuid.

Major isomer: ^1H NMR ($CDCl_3$) δ 7.36-7.22 (m, 4H), 5.01-4.99 (m, 1H), 4.73 (d, 1H, J = 4.10 Hz), 4.19 (bs, 1H), 4.01 (d, 1H, J = 8.70 Hz), 3.78 (d, 1H, J = 8.71 Hz), 3.44 (bs, 4H), 2.33 (dd, 1H, J =3.35 Hz, 14.40 Hz), 2.12 (dd, 1H, J = 3.31 Hz, 14.44 Hz).

Preparation of -6-Methoxy- 1, 2, 3, 4 tetrahydro naptho-[1,2-c]-2'-methoxy-2', 3', 4', 5' tetrahydrofuran 2,4-dihydroxy phenyl boronate (205): The diol (10 mg, 0.0427 mmol) was charged in a two-neck flask with a magnetic stirring bar in it. Phenyl boronic acid (9 mg, 0.854 mmol) was added followed by the

addition of 0.2 mg of TSOH. The mixture was stirred for 18h with 0.3 ml of dry tolune in it. Tlc showed the completion of the reaction. The reaction mixture was transfered into a separatory funnel. It was washed with 10% $KHCO_3$ solution and dried over Na_2SO_4 and concentrated. A PPLC was done using 2 : 1 petroleum ether and ethyl acetate to collect the product which was partially decomposed on tlc plate. ^1H NMR ($CDCl_3$) δ 7.73-7.15 (m, 9H), 5.28-5.22 (bt, 1H), 4.82 (d, 1H, J = 5.02 Hz), 4.34 (d, 1H, J = 8.44), 3.95 (d, 1H, J = 8.46), 3.54 (d, 1H, J = 4.93 Hz), 3.5 (s, 3H), 2.34-2.29 (bd, 2H).

Preparation of compound 208: A solution of **196a** (10 mg, 0.024 mmol) in 3 ml of acetone was titrated with Jones reagent by dropwise addition and stirred vigorously at room temperature. The course of the reaction was followed by tlc. It was complete after 1h. Then 1 ml of isopropanol was added to the reaction mixture and stirred. The mixture was poured into water and extracted with ethylacetate, dried over sodium sulfate and concentrated. A plc using 35%ethyl acetate/ petroleum ether gives the pure product as a yellow amorphous powder. Yield = 7mg (70%). IR ($CHCl_3$) 3400, 2980, 1750, 1620, 1360 cm^{-1} ; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.27 (d, 1H, J = 2.65 Hz), 8.97 (bd, 1H, J = 9.63 Hz), 8.41 (dd, 1H, J = 9.48 Hz, 2.57 Hz), 8.09 (s, 1H), 7.76-7.47 (m, 3H), 7.19 (d, 1H, J = 9.56 Hz), 5.58-5.50 (m, 1H), 4.64 (d, 1H,J = 11.47 Hz), 4.46 (d,1H, J = 11.48 Hz), 3.01 (bd, 1H), 2.78 -2.72 (m, 1H), 2.54-2.46 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) 194.20, 160.19, 147.65, 141.51, 135.36, 130.97, 130.90, 129.36, 129.28, 129.19, 125.89, 125.83, 124.48, 113.95, 72.98, 66.15, 47.93, 38.13. Mass Calcd.for C_{18} H_{15} O_8 N_3 401.0859, found 401

Preparation of 2,3 Dihydroxybutyric acid (213): To a suspension of l-threonine (0.978 g, 8.22 mmol) in 3.22 ml of water was added 1.7 ml of aqueous concentrated HCl. The mixture was cooled to -5°C and a solution of $NaNO_2$ (850 mg, 12.33 mmol) in 1.82 ml of water was added drop-wise through a dropping funnel during 1h. Brown fumes evolved. The resulting clear solution was allowed to stand over night at room temperature. The reaction mixture was put on a rotary evaporater at 48°C. Evaporation of the reaction

mixture gave a white solid which was suspended in ethyl acetate. The suspension was stirred for 15 minutes and filtered. The solid was washed with ethyl acetate repeatedly until it was no longer sticky. The resultant organics were dried over Na_2SO_4 and evaporated to give a pale yellow oil. Yield = 626 mg (63.5%). IR ($CHCl_3$) 3580, 2920, 2860, 1730, 1120 cm^{-1}; ^{1}NMR ($CDCl_3$, 300 MHz) δ 4.44-4.39 (m, 2H) 1.43 (d, 3H).

Preparation of Methyl 2,3 dihydroxy butyrate (214): A solution of the 2,3 dihydroxy butyric acid (626 mg, 5.21 mmol) was made in 6 ml of methanol and 15 drops of concentrated H_2SO_4 were added slowly. The mixture was heated to 65-70°C for 2h. Then it was cooled to room temperature and put on a rotary evaporator to remove methanol. The concentrate was taken up in dichloromethane and washed with water (2x50ml). The water layer again was extracted with 50 ml of dichloromethane. The combined organics were washed with aqueous $NaHCO_3$, dried over Na_2SO_4 and evaporated to give a colorless oil. This was distilled with a aspirator (94°C/20mm Hg) to give the pure compound. Yield = 635 mg (90.8%). IR ($CHCl_3$) 3640, 3560, 2960, 2460, 1720, 1660,1430, 1000, 940, 900, 850 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.30-4.25 (m,2H), 3.83 (s, 3H) 1.32 (d, 3H, J= 6.10Hz).

Preparation of 1,4 Dioxa 2-carbomethoxy 3-methyl spiro [4,5] decane (215): A two-necked flask was charged with 4A° molecular sieves. The dihydroxy methyl ester **213** (204 mg, 1.522 mmol), dimethoxy cyclohexanone (1.5 ml) and p-toluene sulphonic acid (30 mg) were added to the flask followed by 15 ml of dry benzene. The reaction mixture was stirred at room temperature for 2.5 d. The course of the reaction was followed by tlc. The molecular sieves were filtered off. The filtrate was added in to an ice cold solution of aqueous $NaHCO_3$ and the organic layer was extracted. The extract was again washed with water (2x50ml). The organic layer was washed with anhydrous Na_2CO_3 and concentrated to give a red oil which was distilled at (101-104°C /30mm Hg) to give the pure compound. The distillation was done from solid anhydrous Na_2CO_3 otherwise the cyclohexylidine ester decomposed to diol. Yield = 276.9 mg (85%). IR

($CHCl_3$) 3460, 2840, 2680, 2460, 1720, 1430 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.41-4.35 (m, 2H), 3.83 (s, 3H), 1.69-1.43 (m, 10H), 1.38 (d, 3H, J=6.10 Hz).

Preparation of 1,4 Dioxa 2-hydroxymethyl 3-methyl spiro-[4,5]- decane (216): A suspension of lithium aluminium hydride (1.291 g, 33.98 mmol) was made in 20 ml of anhydrous ether and stirred for 30 minutes. A solution of cyclohexylidine ester **215** (2.424 g, 11.327 mmol) in 30 ml of anhydrous ether was added to the ice cold solution of LAH in ether via a syringe pump (0.5 ml/minute). After the addition the mixture was warmed up to room temperature and stirred for 3d. The completion of the reaction was checked by tlc. Then the reaction flask was cooled to ice-bath temperature and 6ml of ethyl acetate was added. Then 0.57 ml of water was added followed by the addition of 0.57 ml of 4N NaOH. The heterogeneous mixture was stirred for 30 minutes and allowed to settle. The ether layer was taken out. The white solid was washed with ether (4x75 ml). The combined organics were dried over $MgSO_4$ and concentrated which was dried under high vacuum to give the pure compound **216** as a pink oil. Yield = 1.953 g (98%). IR ($CHCl_3$) 3600, 3500, 2930, 2880, 1710, 1460, 1380, 1370, 1270, 1100, 1040, 1000, 930 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.34-4.29 (m, 1H) 4.13-3.98 (m, 2H), 3.84-3.77 (m, 1H), 2.63 (t, 1H), 1.61-1.52 (m, 10H), 1.33 (d, 3H, J=6.49 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 101.73, 67.92, 63.72, 63.56, 33.60, 34.04, 25.34, 22.29, 23.08, 16.27.

Preparation of 1,4 Dioxa 2-chloromethyl 3-methyl spiro -[4,5]- decane (217): Triphenyl phosphine (394 mg, 1.068 mmol) was stirred in CCl_4 (1 ml) till it goes to the solution. Then the starting alcohol **191** (188 mg, 1.068 mmol) was added. The mixture was heated at 55-60°C. A violent reaction occurred showing the condensasion of the solvent at the bottom part of the condenser. When the reaction was subsided, the bath was heated to 80-85°C and heated for 20 min. at that temperature. Then it was cooled to room temperature and stirred for 9h. Triphenylphosphine oxide precipitated out. The mixture was stirred with 30ml of 1:1 ether / pentane for 15 min. It was allowed to settle

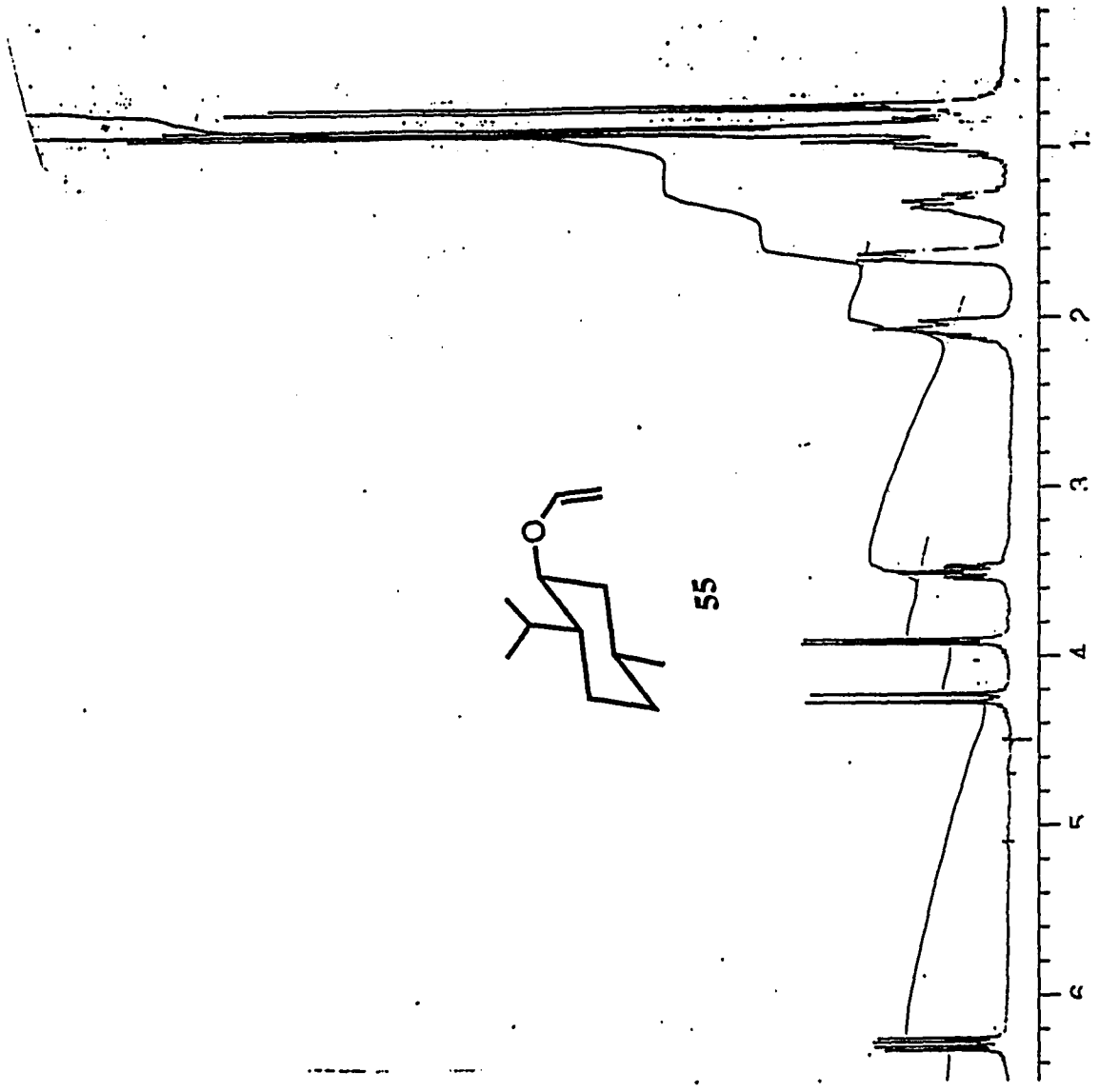
and extracted 4 times (4x30ml) with 1:1 ether / pentane . The combined ogranics were dried over Na_2CO_3 and concentrated. A column chromatography using 10%ether / petroleum ether was done on florosil and the pure compound **217** was separated as a colorless oil. Yield = 176.93 mg (81%). IR ($CHCl_3$) 2980, 2900, 1450, 1400,1360, 1310, 1285,1260, 1200, 1160, 1120, 1090, 1070,970, 940, 880 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.28 (dq, 1H, J=1.69 Hz, 6.17 Hz) 4.28 (dd, 1H, J=12.91Hz, 1.80 Hz) 3.92 (dd,1H, J=12.92 Hz, 1.80 Hz) 3.79 (bm, 1H), 1.89-1.28 (m, 10H) 1.28 (d, 3H, J=6.19 Hz). ^{13}C NMR $CDCl_3$ 99.21, 65.75, 65.16, 59.00, 38.010, 27.80, 25.65, 22.57, 22.47, 19.36. Low resolution Mass Calcd. for $C_{10}H_{17}O_2Cl$ 204 Found 204.

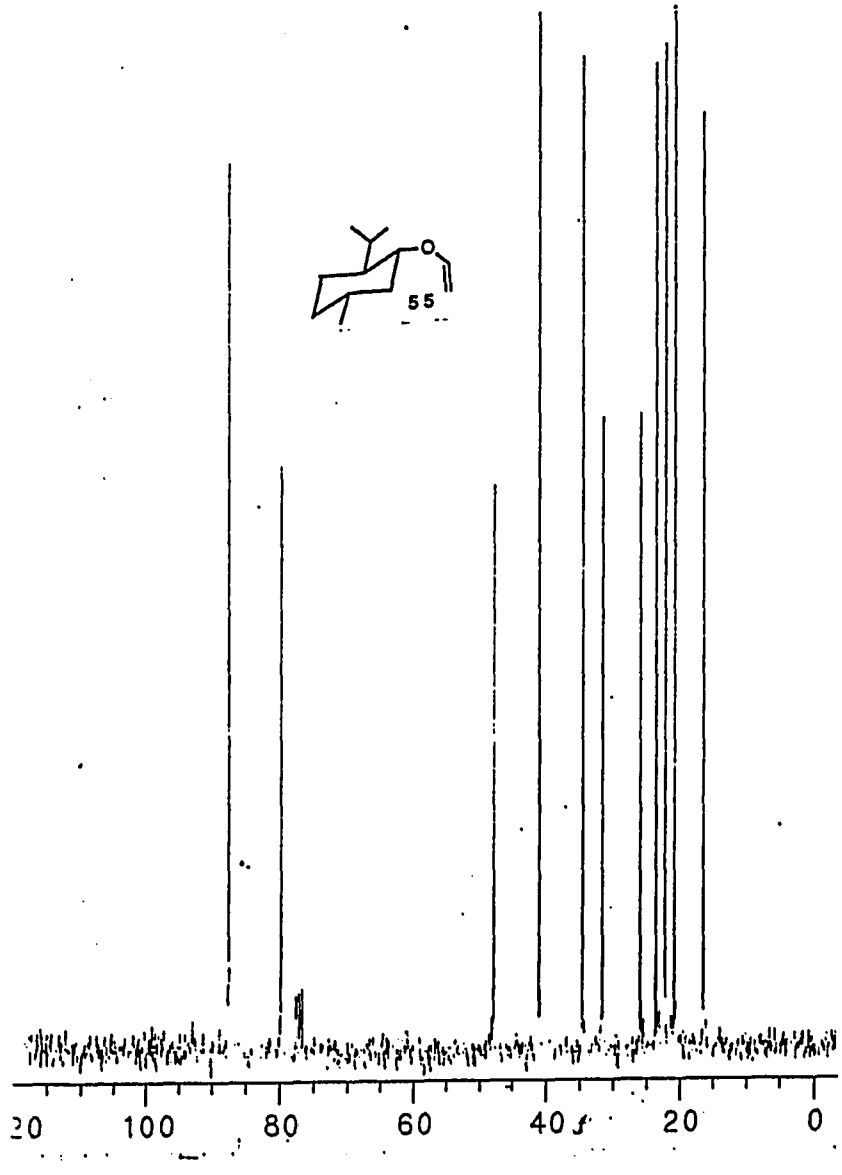
Preparation of -1,4- Dioxa 2-vinyl 3-methyl 3-methyl spiro-[4,5]- decane (218): To a solution of freshly prepared NaOMe (927 mg, 17.17 mmol) in 5 ml of DMF was added the chloro compound **217** (1.4056 g, 6.87 mmol). The mixture was heated at 52°C (bath temperature) for 2.5h. It was cooled to room temperature and the mixture was added to water. The aqueous mixture was extracted with pentane (3x25 ml). The organics were dried over Na_2CO_3 and evaporated to give a colorless oil. Yield = 895 mg (77%). ^1H NMR ($CDCl_3$, 300 MHz) δ 4.491- 4.495 (bs, 1H), 4.1-4.07 9m, 2H), 1.70-1.19 (m, 13H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.66, 139.99, 105.17, 98.92, 94.06, 58.47, 33.09, 25.53, 22.52, 20.06.Mass Calcd.for $C_{10}H_{16}O_2$ 168 Found 169.0 $(M+H)^+$.

Preparation of 1-Methoxy-3-methyl-3a-hydroxy-5[1'-(2',4'-dinitro phenyl-amino)] 1, 2, 3, 4 tetrahydro naptho [1,2-c]-tetrahydrofuran (220) by Cycloaddition of 193 with 218: To a solution of the salt (33 mg, 0.083 mmol) in 0. 1 ml of methanol was added 66 mg of anhydrous $CaCO_3$ followed by the addition of vinyl ether (28μl, 0.166 mmol) **218**. The heterogeneous mixture was stirred under the atmosphere of nitrogen. After the reaction is complete the mixture was passed through a celite containing dichloromethane slurry. The filtrate was concentrated and put under vacuum for 3h. It was treated with 66 mg of Dowex (H^+) in dry methanol and stirred for 3d. Then the reaction mixture was poured into water and washed with a saturated solution

of $NaHCO_3$, then extracted with dichloromethane till the aqueous layer is colorless. Then the organics were combined, dried over anhydrous Na_2SO_4 and concentrated to afford the crude adduct acetal which was purified under radial chromatographic condition (2-10% of ethyl acetate / petroleum ether) to give a yellow foamy mass. Four compounds were isolated. Total yield of the cycloaddition is 67%. The reported NMR is for the major compund ^1H NMR ($CDCl_3$, 300 MHz) δ 9.23 (d, 1H, J = 2Hz), 9.02 (d, 1H, J = 9.02Hz), 8.25 (m, 1H), 7.12(d, 1H, J = 9 Hz), 6.96(d, 1H, J = 9 Hz), 6.9 (d, 1H, J = 9 Hz), 5.48 (d, 1H, J = 4.5 Hz), 5.3-5.18 (m, 1H), 4.08 (q, 1H), 3.92 (s, 3H), 3.4 (d, 1H, J = 4.5 Hz), 3.3 (s, 3H), 2.46-2.24 (m, 2H), 1.36 (d, 3H, J = 6.8 Hz); CIHRMS (m/e) relative intensity 445.1458 ($C_{21}H_{23}N_3O_8$ requires 445. 1425).

IV. Appendix

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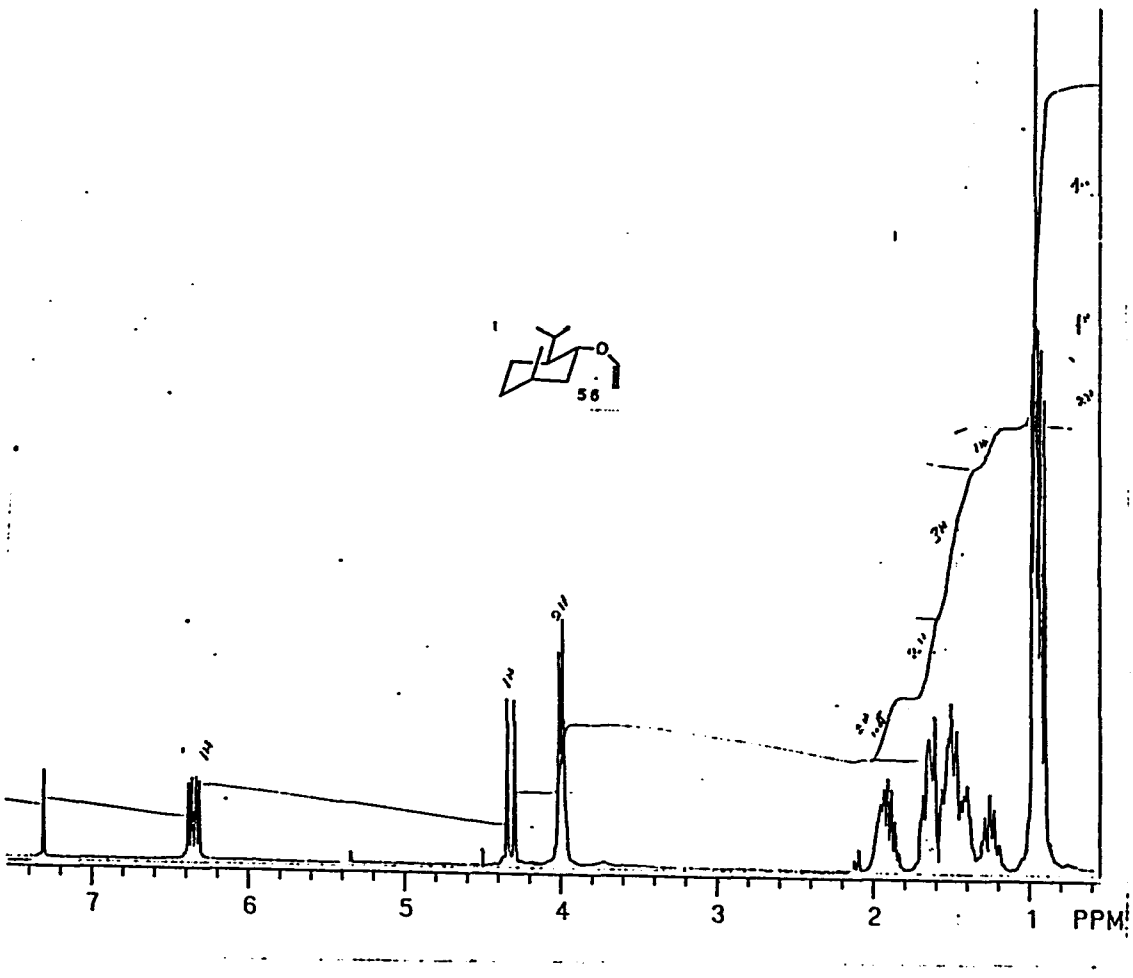
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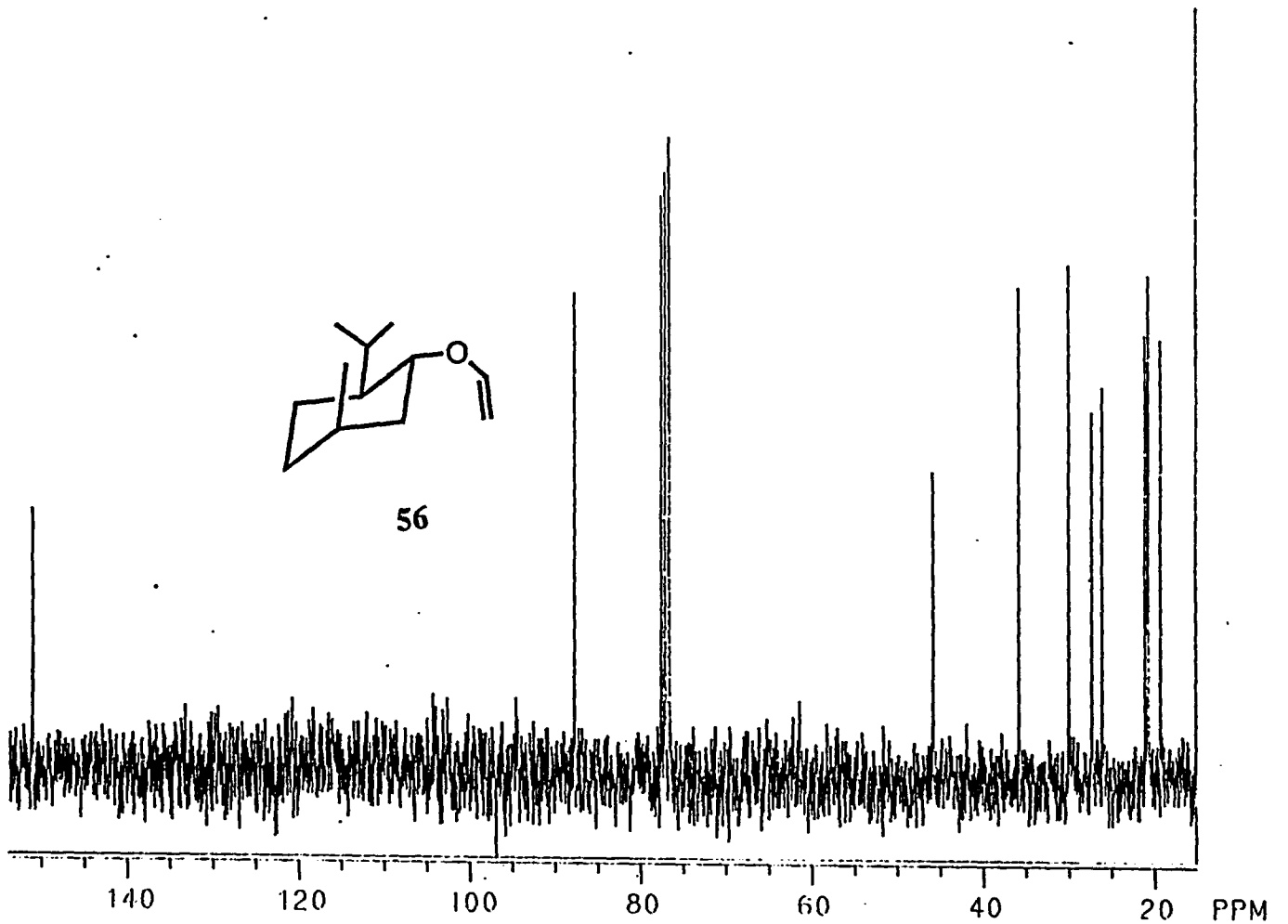

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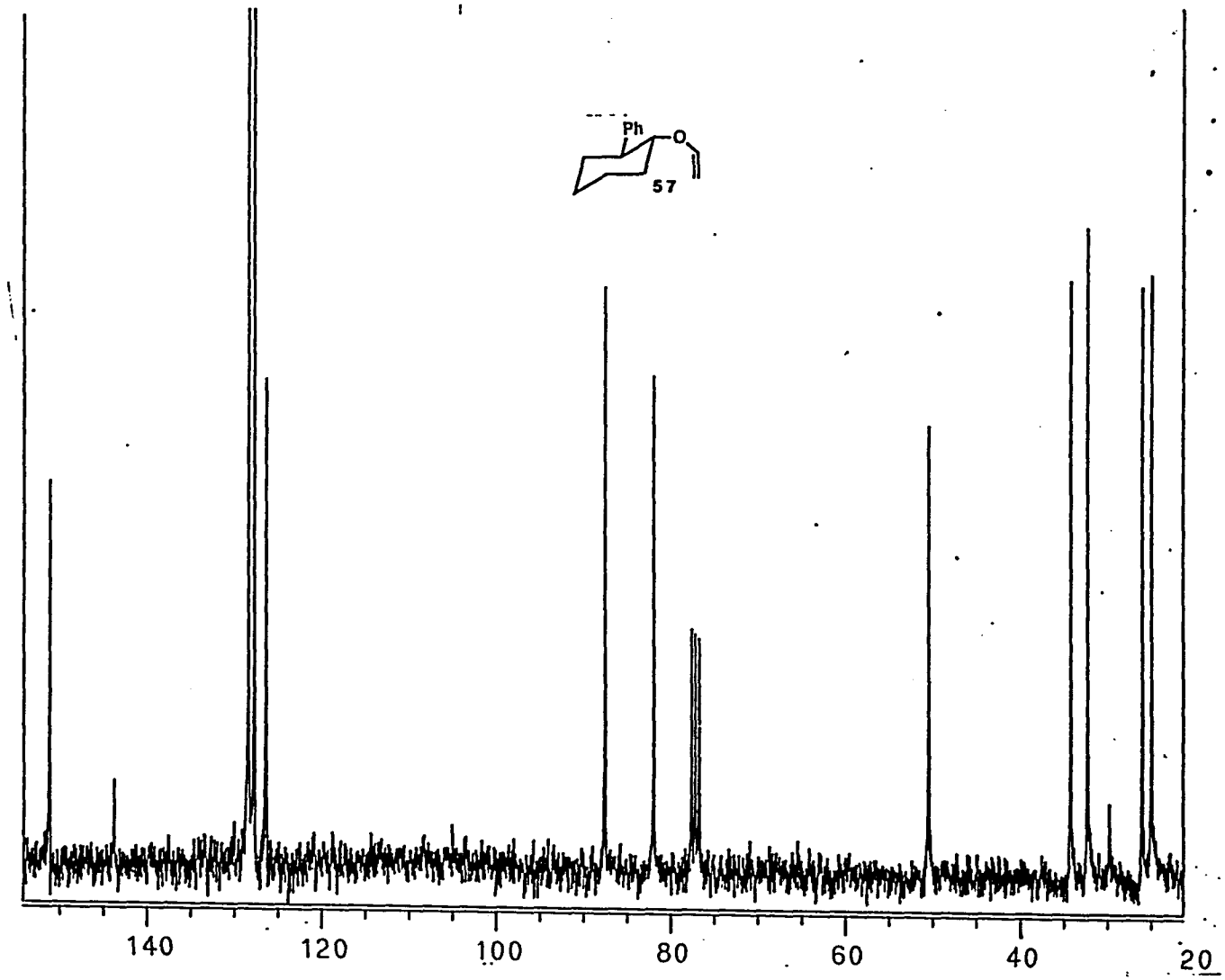
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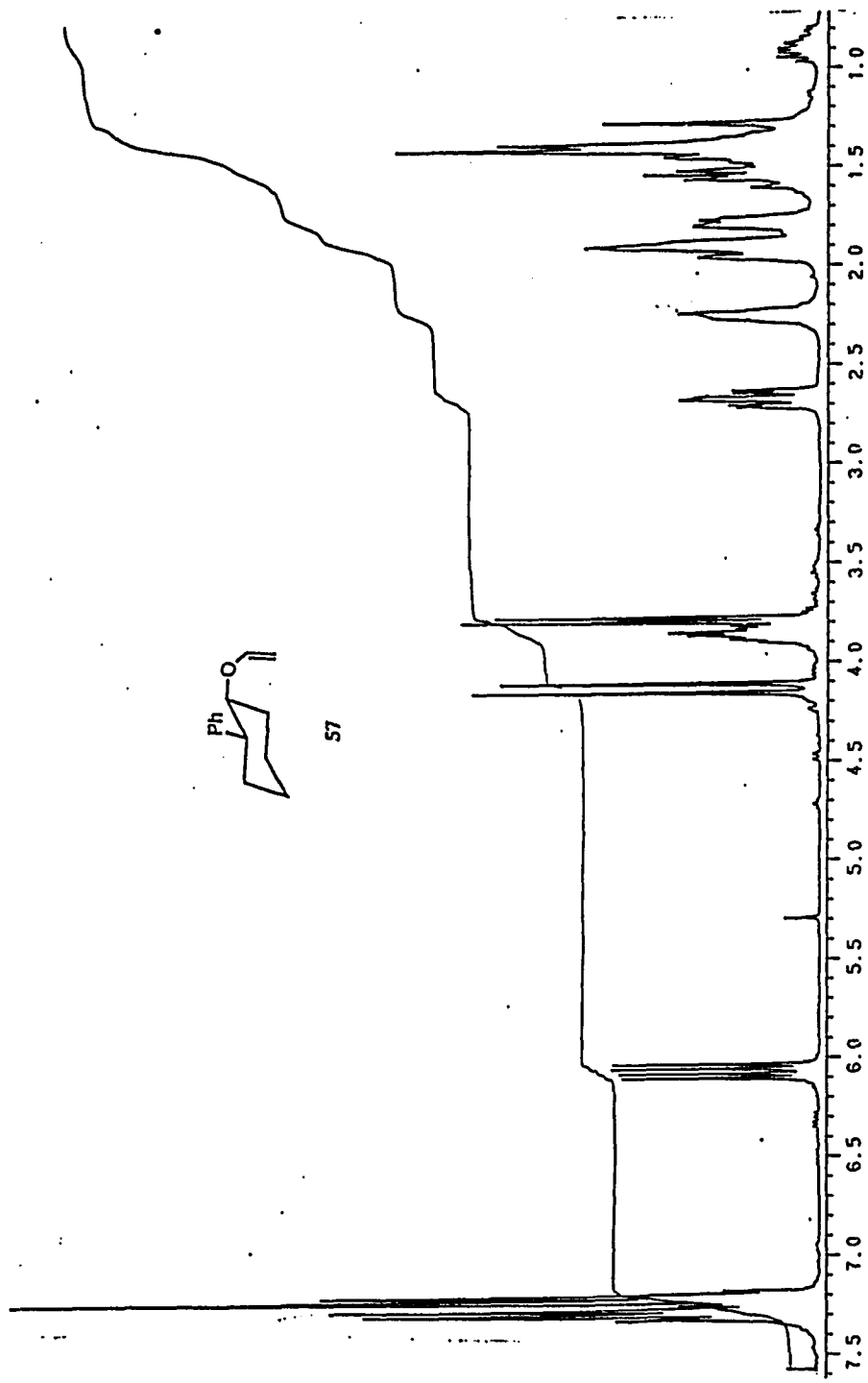
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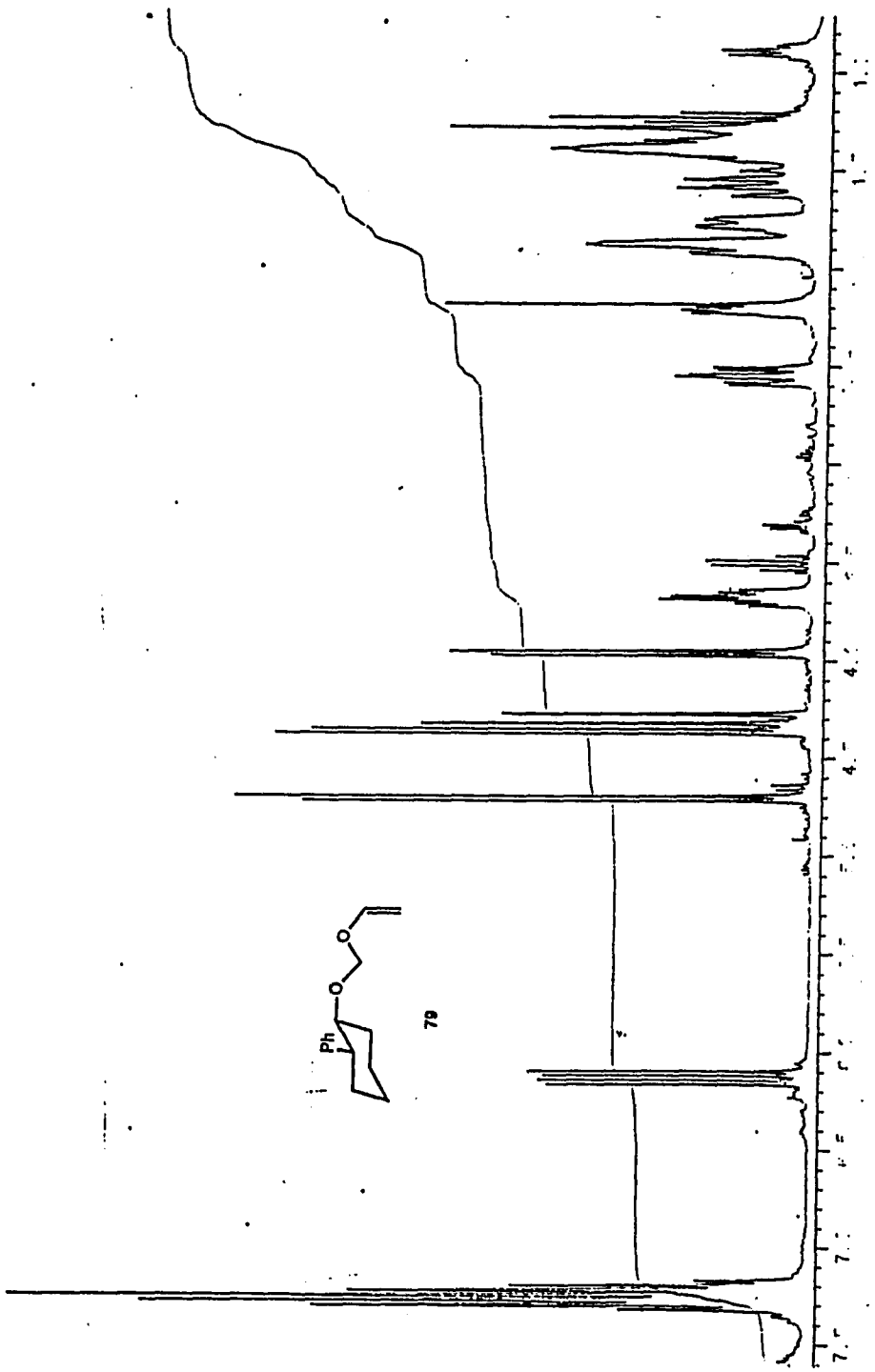
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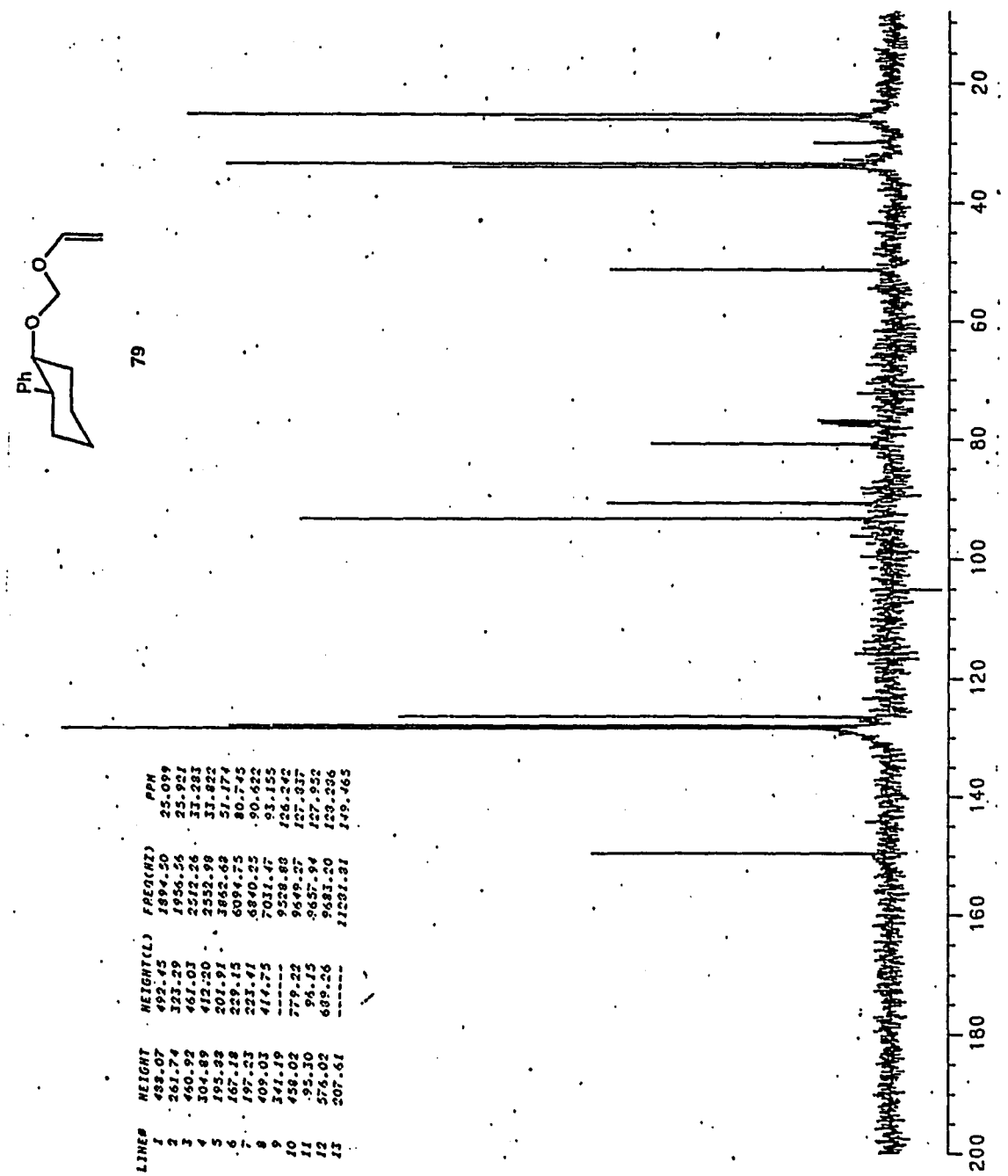
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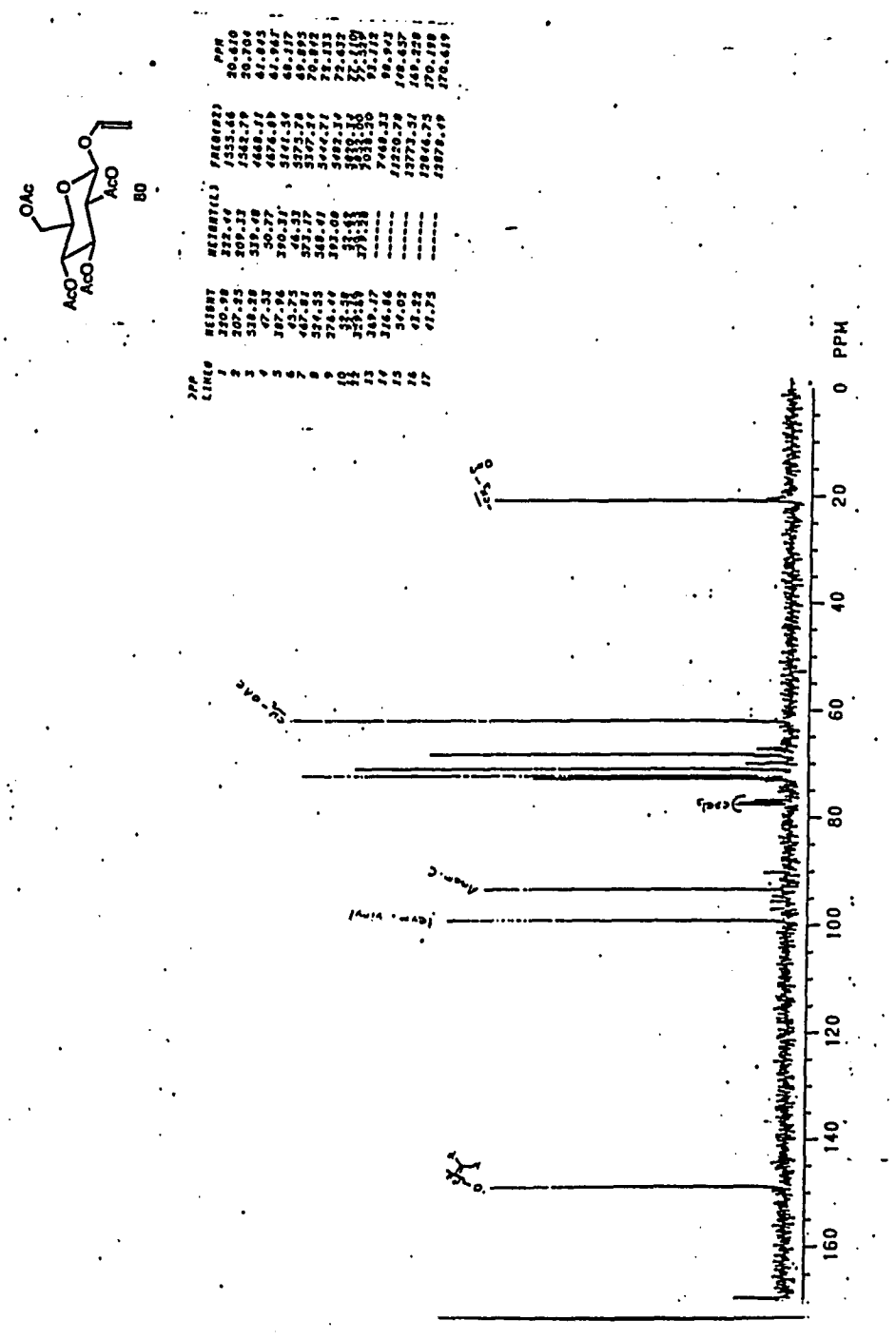
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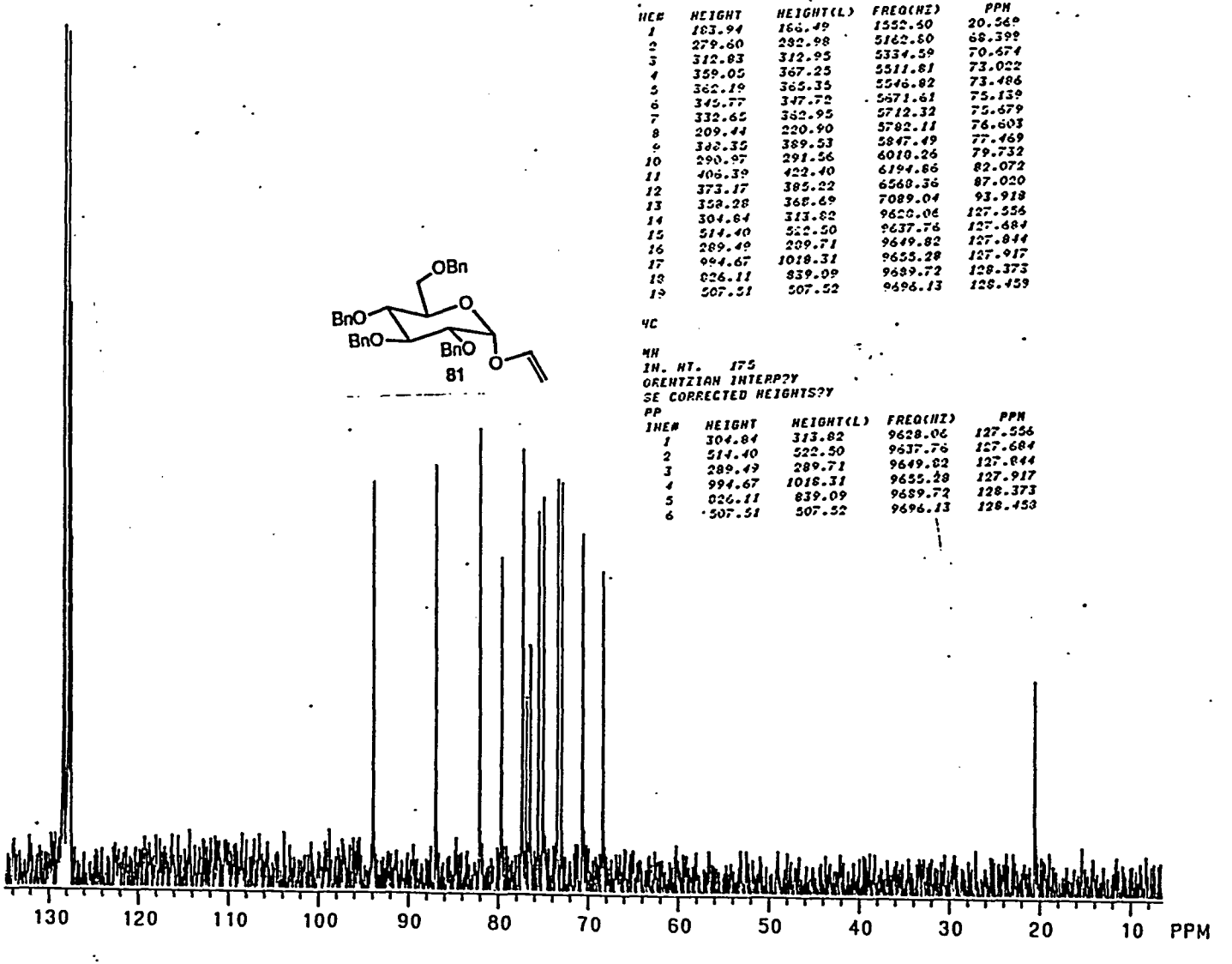

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6	345.77	347.72	5671.61	75.139
7	332.65	362.95	5712.32	75.679
8	209.44	220.90	5702.11	76.603
9	388.35	389.53	5847.49	77.469
10	290.97	291.56	6010.26	79.732
11	406.39	422.40	6194.86	82.072
12	373.17	385.22	6560.36	87.020
13	358.28	368.69	7089.04	93.918
14	304.84	313.82	9628.06	127.556
15	514.40	522.50	9637.76	127.684
16	289.49	289.71	9649.82	127.844
17	994.67	1018.31	9655.28	127.917
18	826.11	839.09	9689.72	128.373
19	507.51	507.52	9696.13	128.459

YC

MH
IN. HT. 175
ORENTZIAN INTERP?Y
SE CORRECTED HEIGHTS?Y
PP

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4	994.67	1018.31	9655.28	127.917
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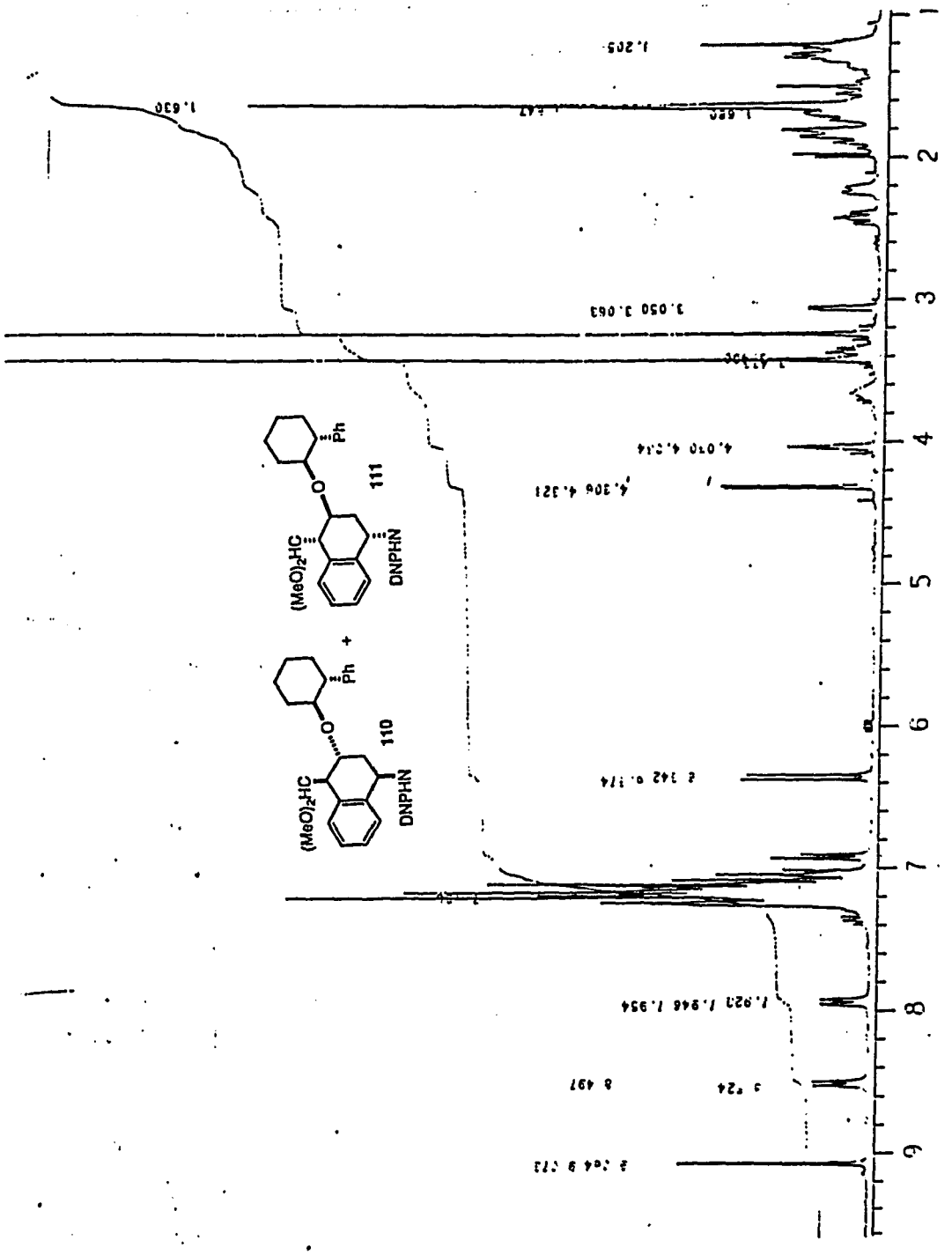
6	507.51	507.52	9696.13	128.453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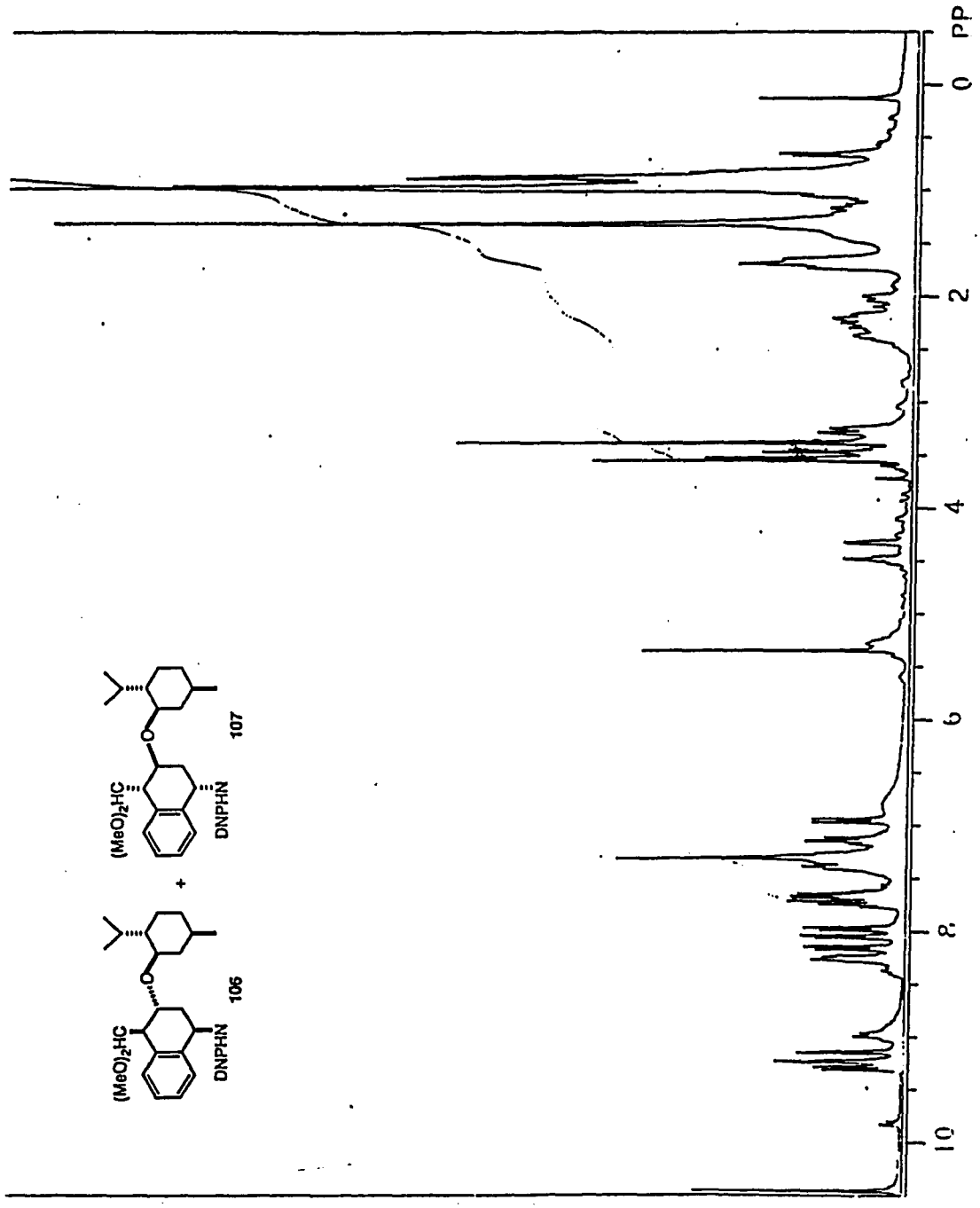
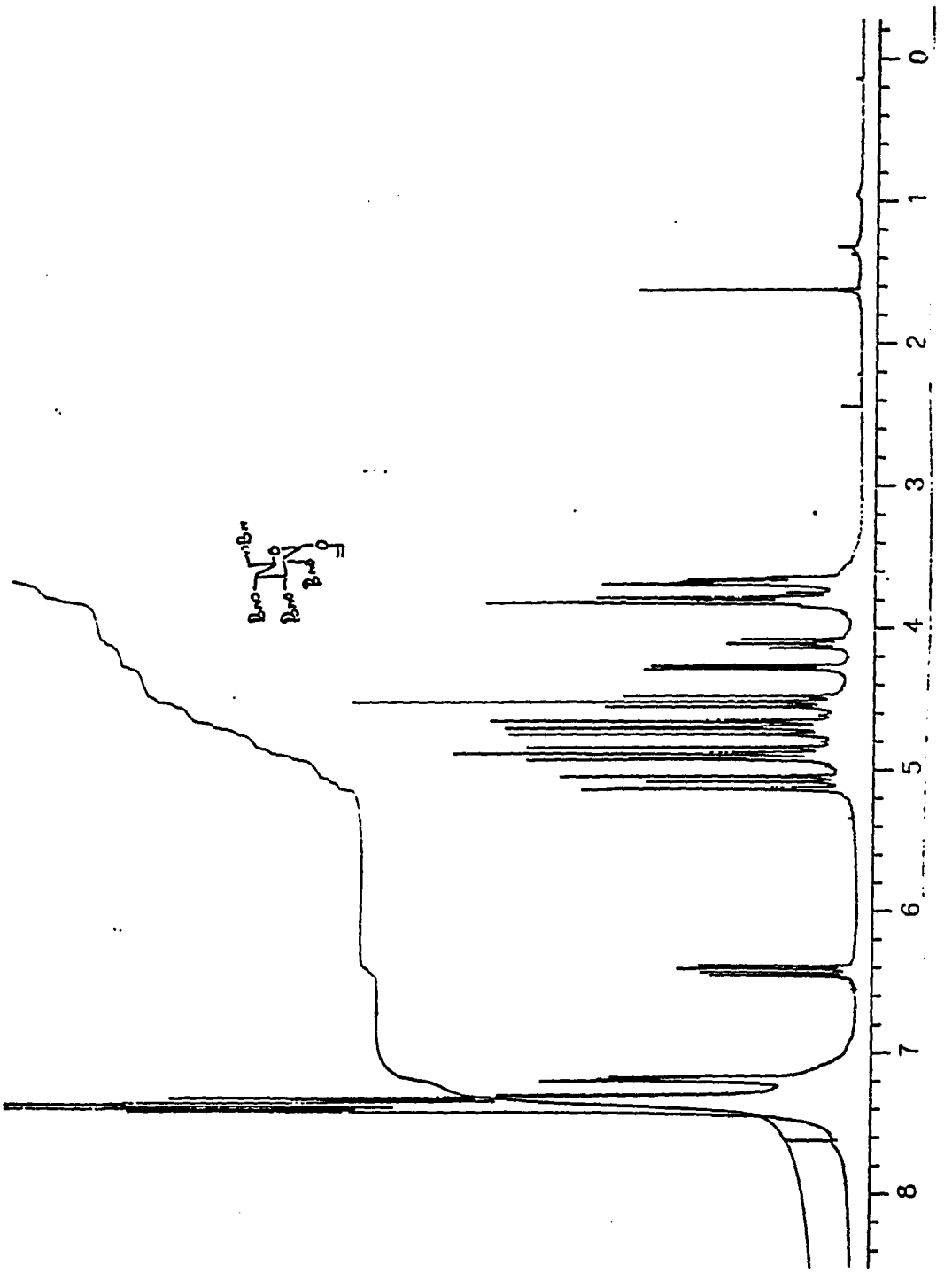
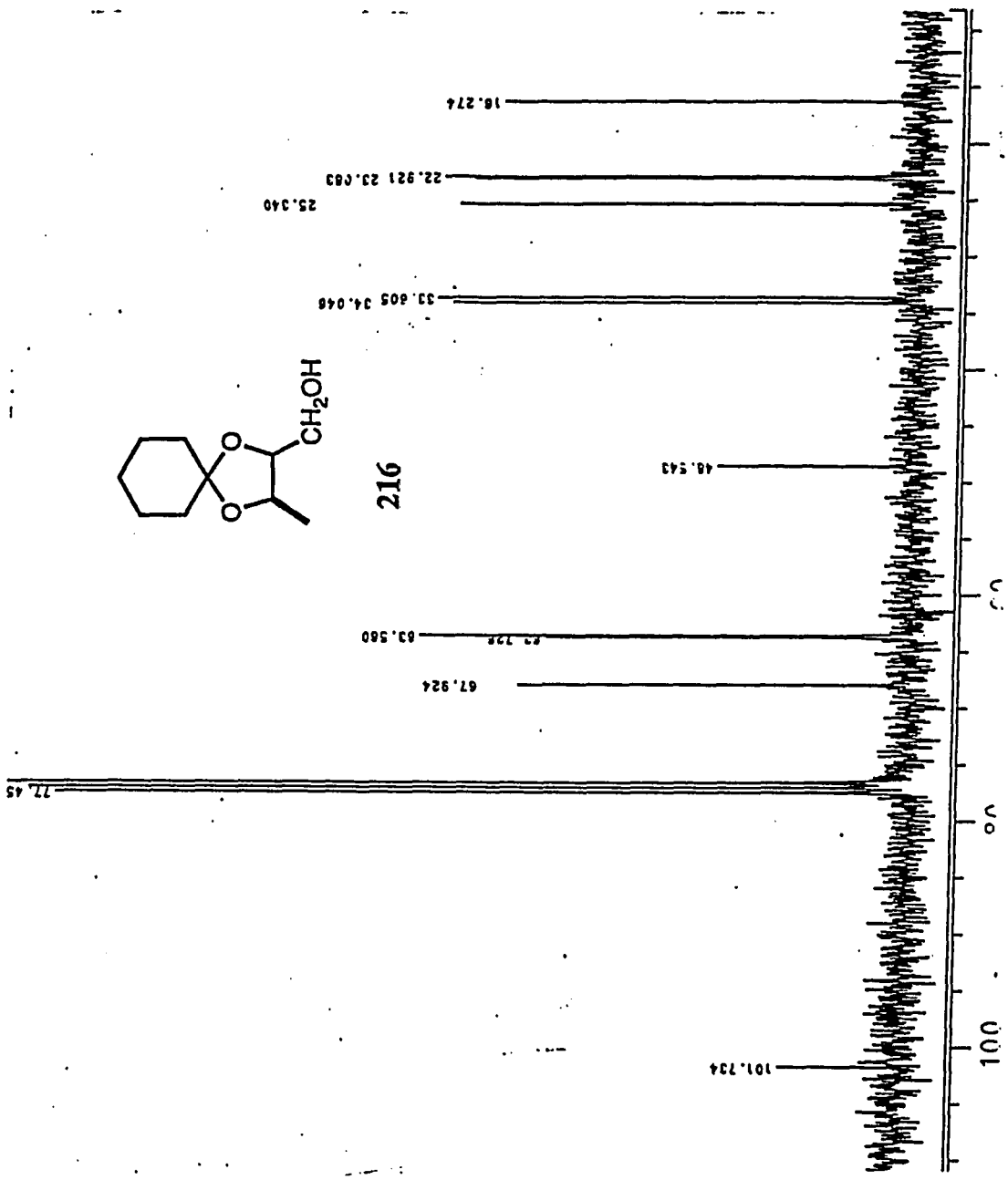
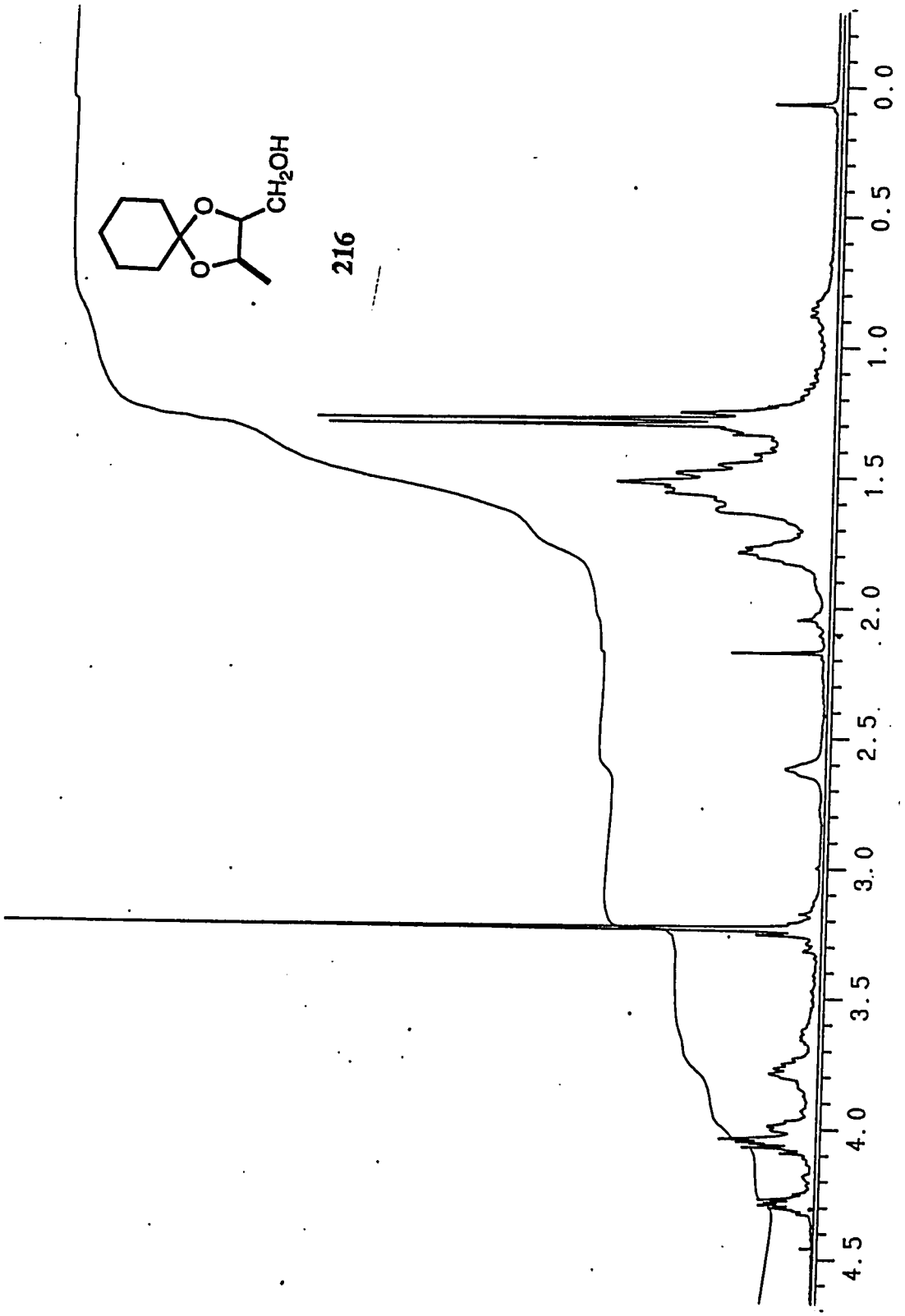
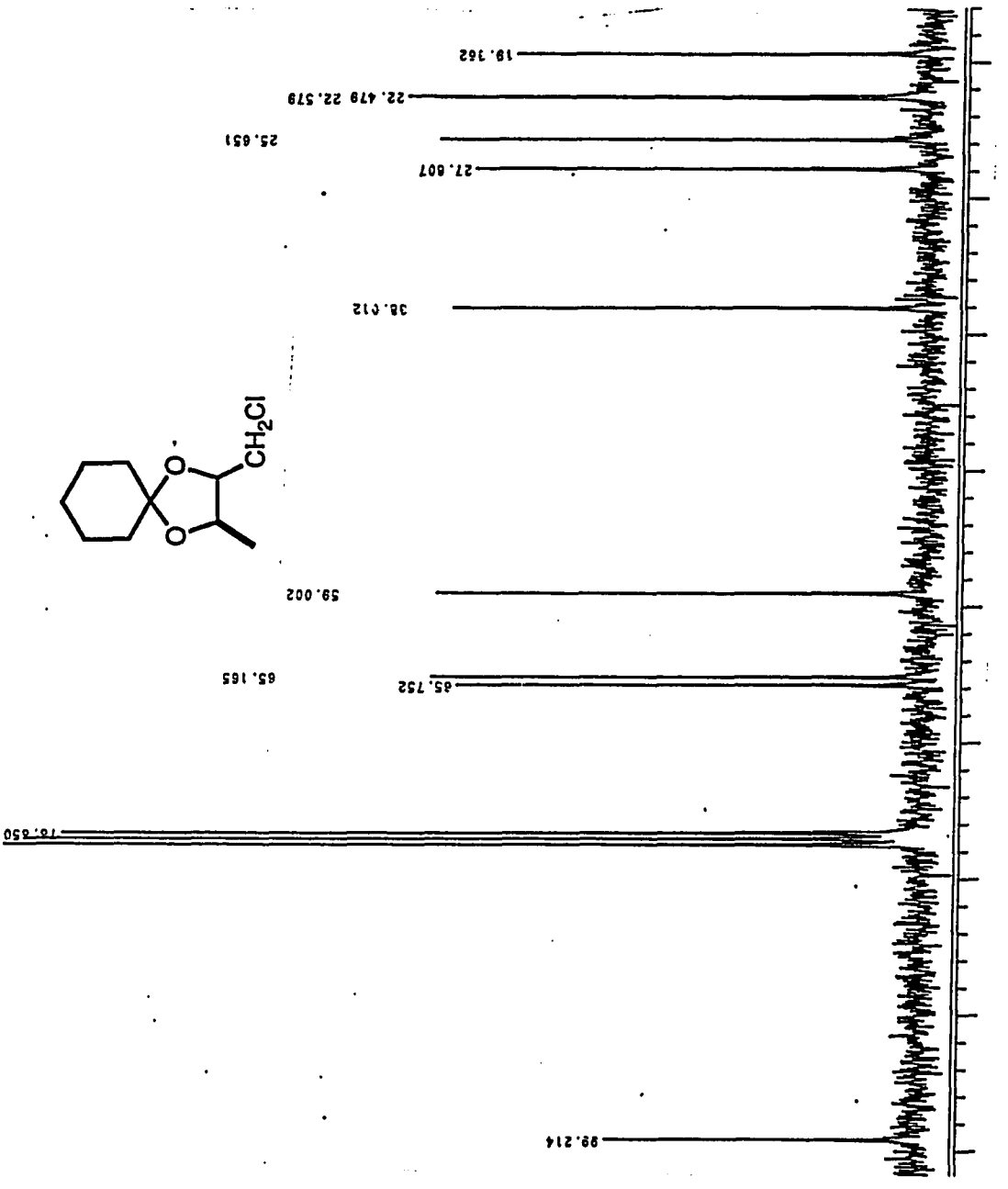
DNPHN

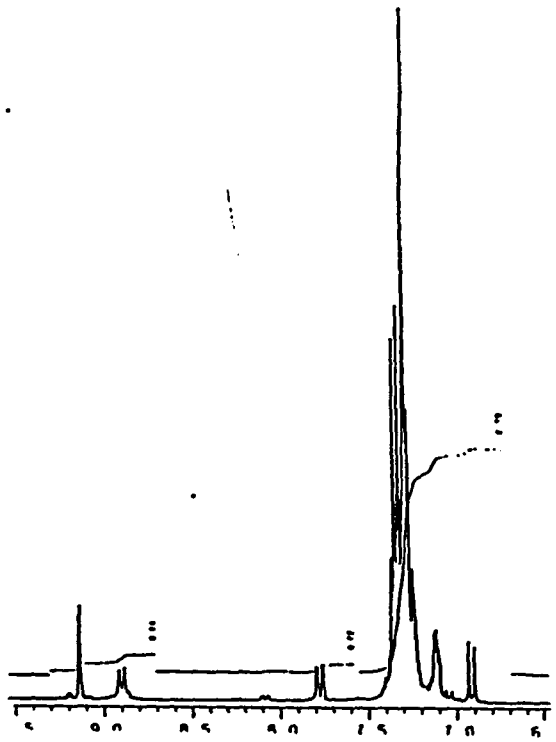

PP
0
2
4
6
8
10
(MeO)2HC
DNPHN
107
+
(MeO)2HC
DNPHN
106

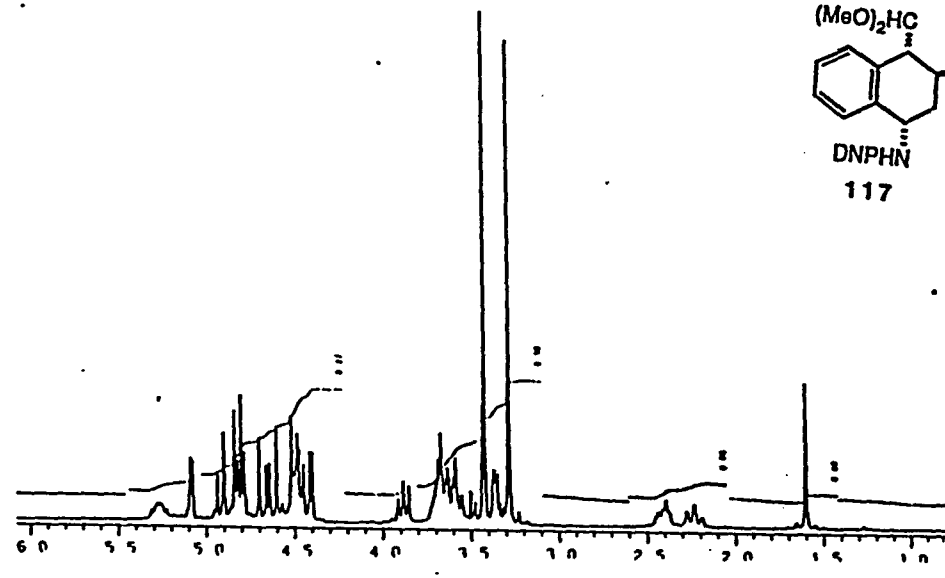

0
1
2
3
4
5
6
7
8

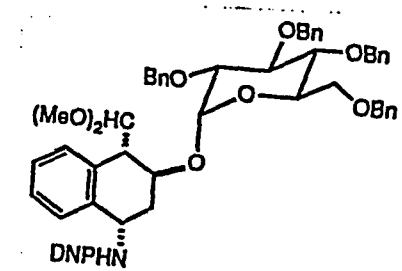

216
CH2OH
O
O
101.734
67.924
63.560
48.543
33.805
34.048
25.340
22.921
23.083
18.274
77.45
100
50


CH2OH
O
O
216
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

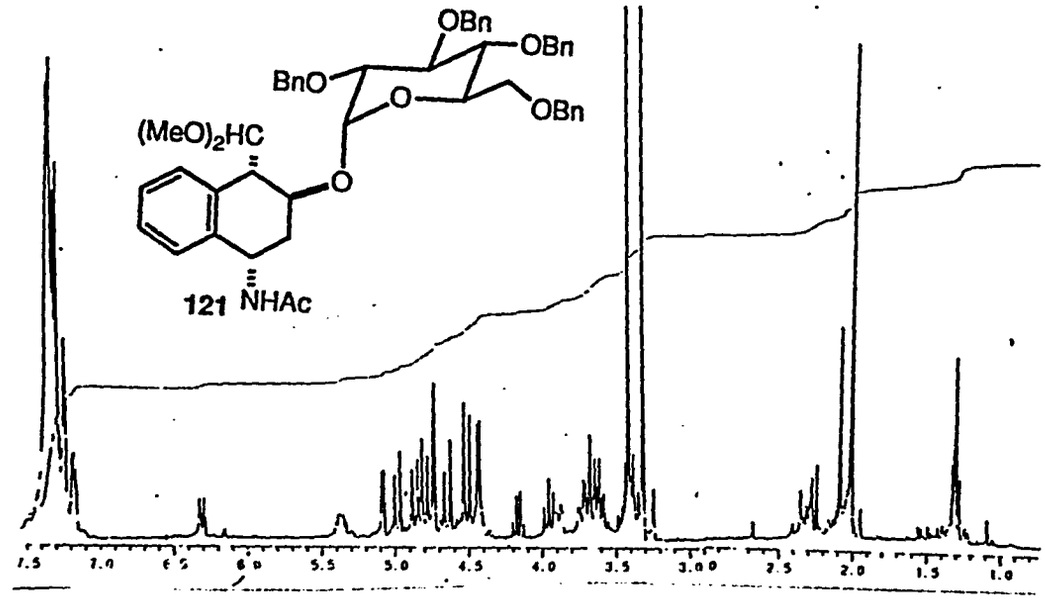

19.362
22.479 22.579
25.651
27.807
38.012
59.002
65.752
65.165
76.650
99.214
CH2Cl
O
O

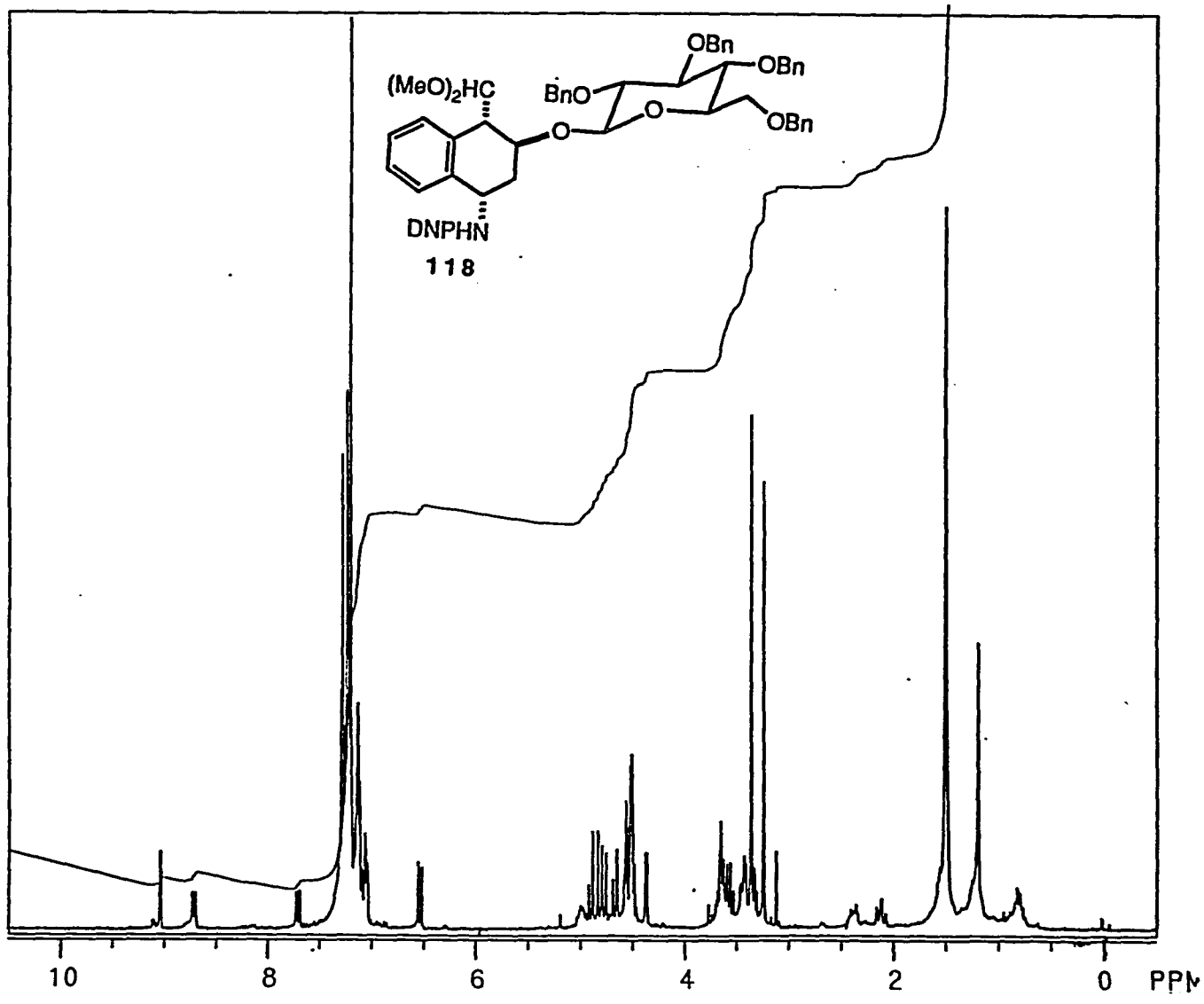


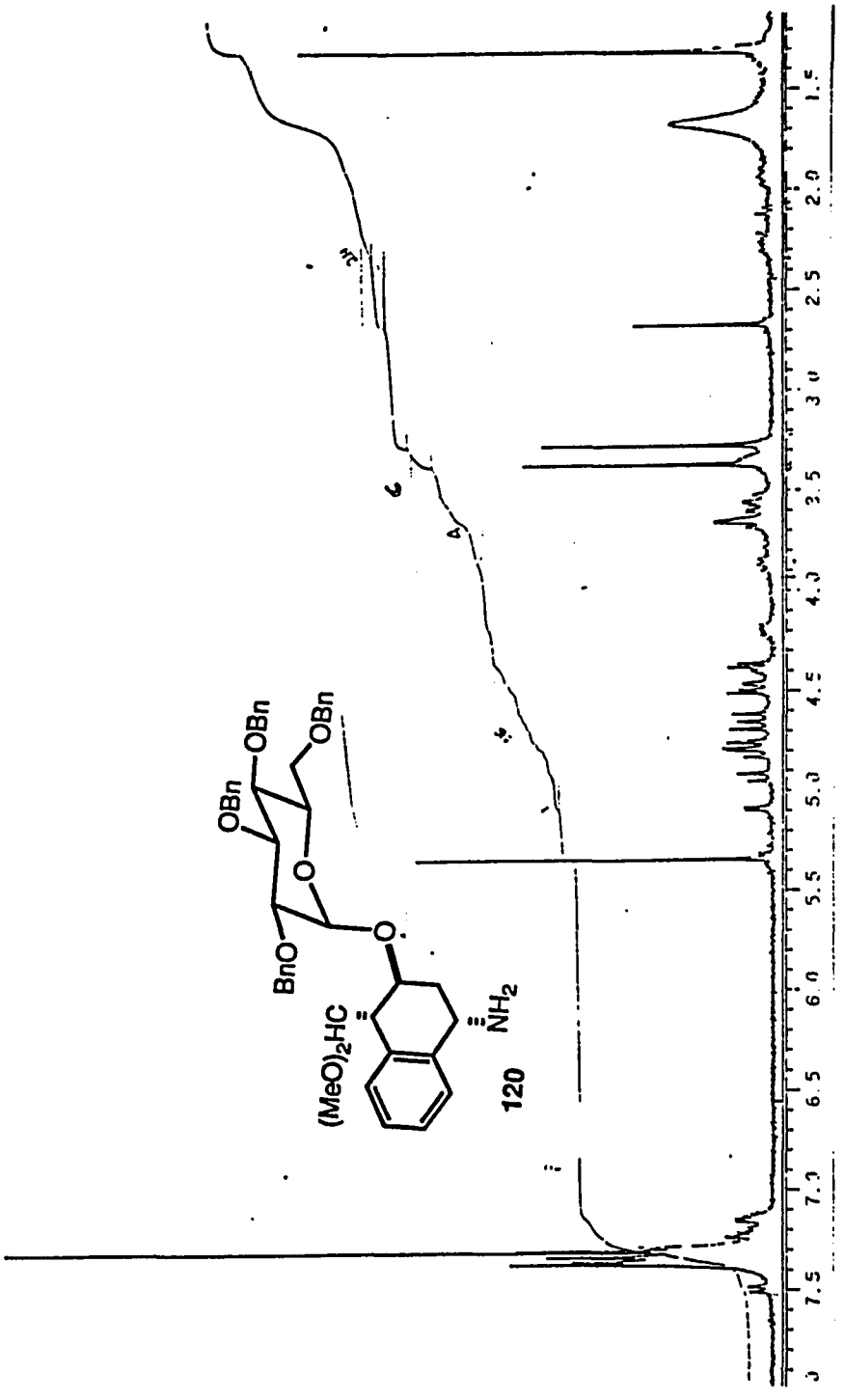


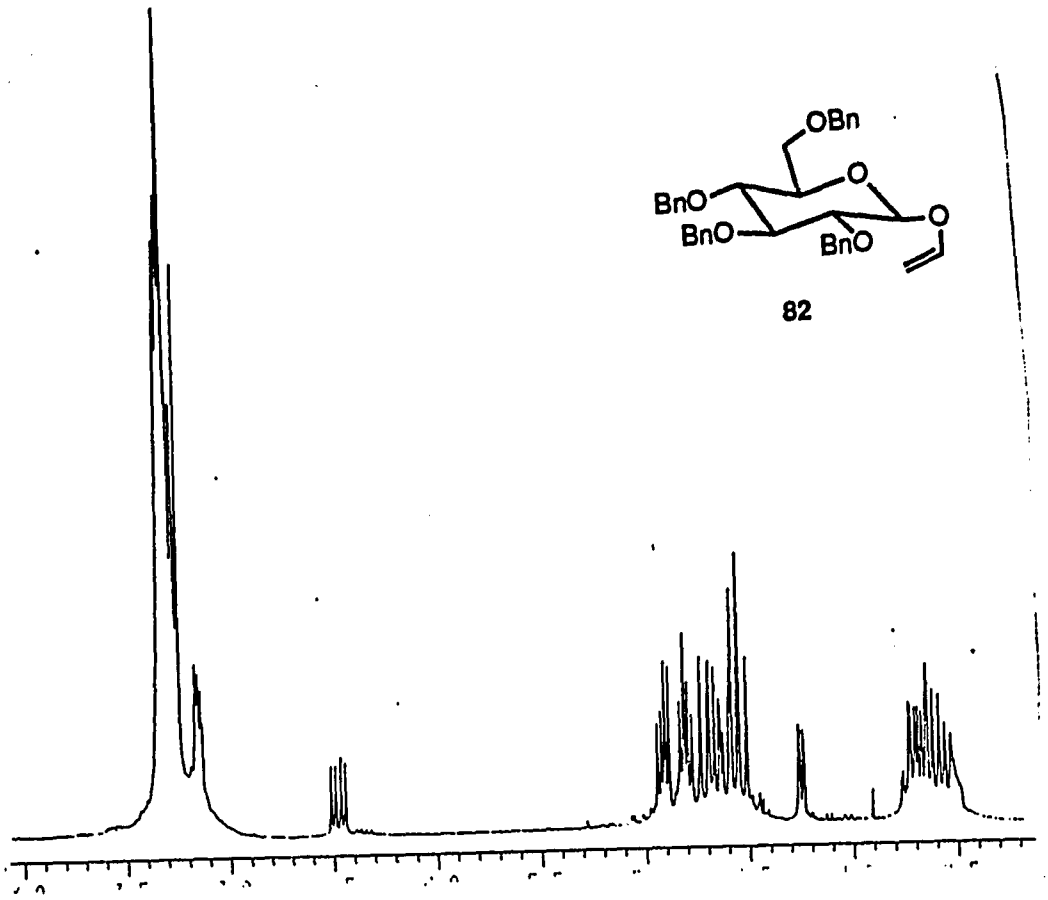


117

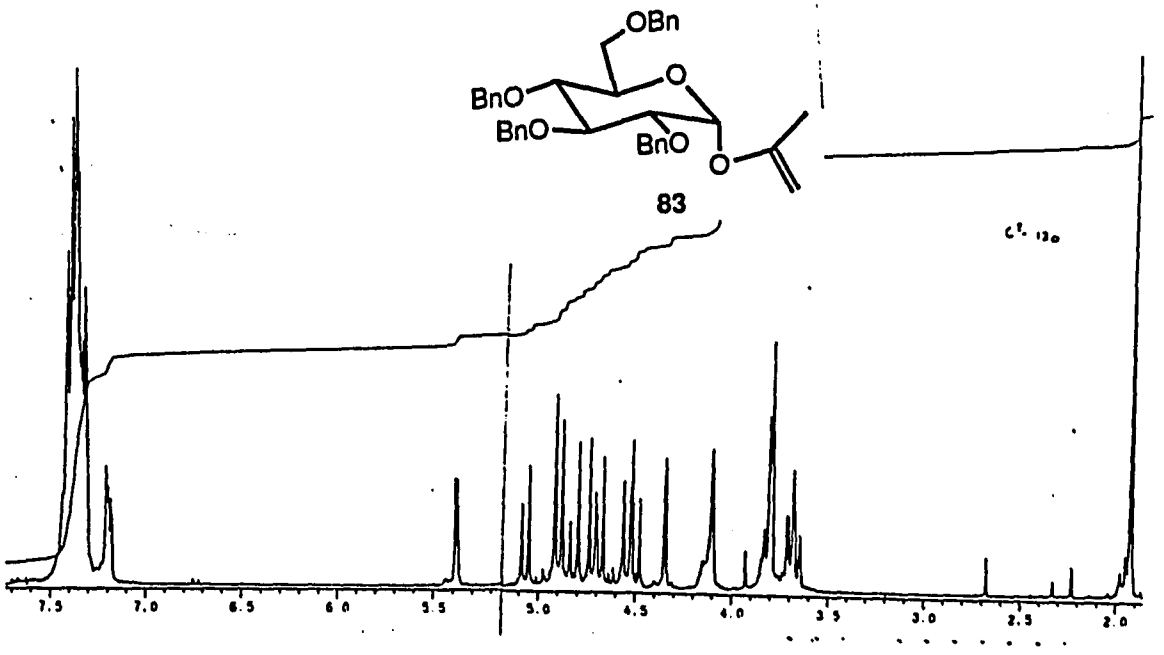

OBn
OBn
BnO
O
OBn
(MeO)2HC
O
NHAc
121


OBn
OBn
(MeO)2HC
BnO
O
O
OBn
DNPHN
118
10
8
6
4
2
0
PPM

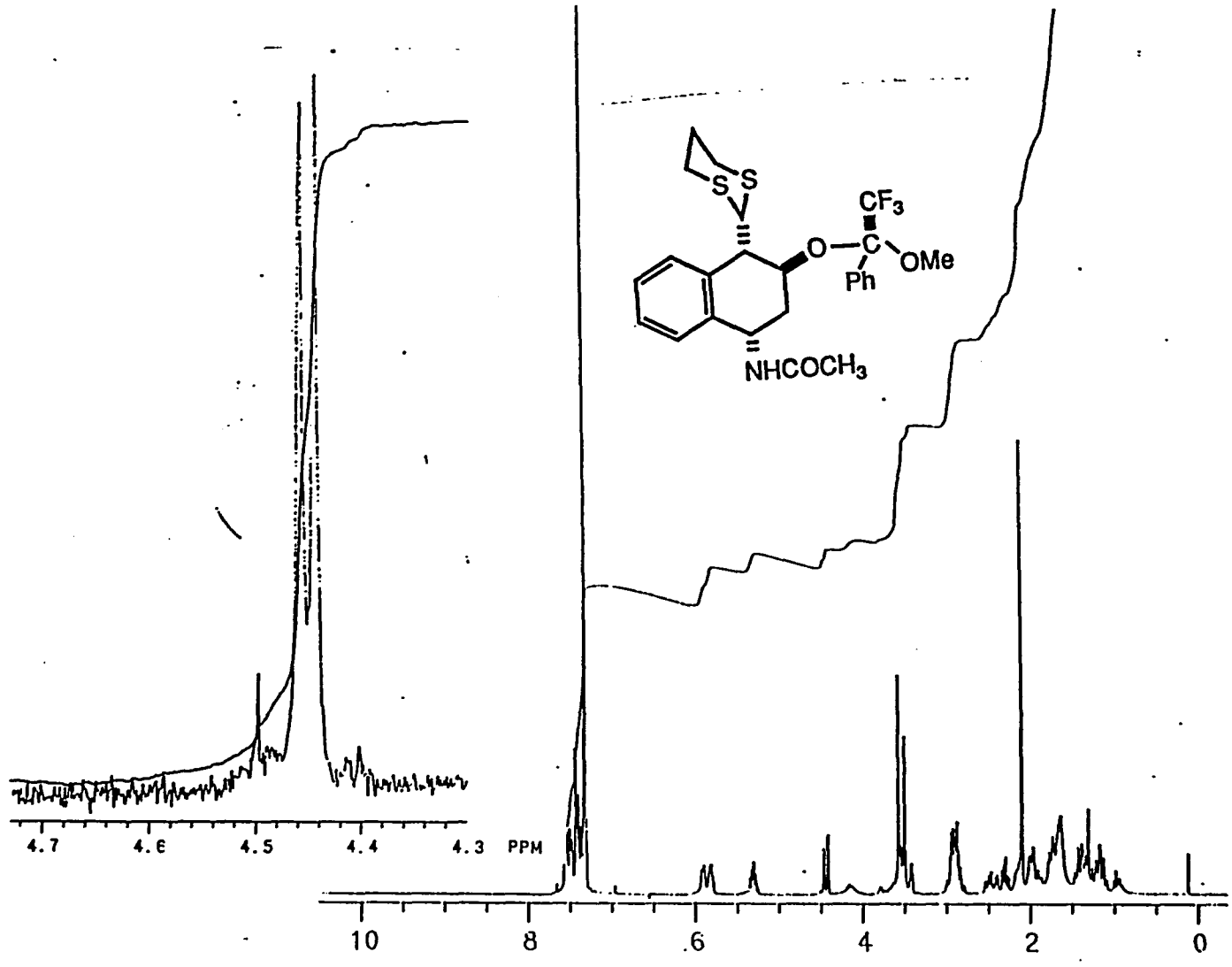

OBn
OBn
OBn
BnO
O
O
(MeO)2HC
NH2
120

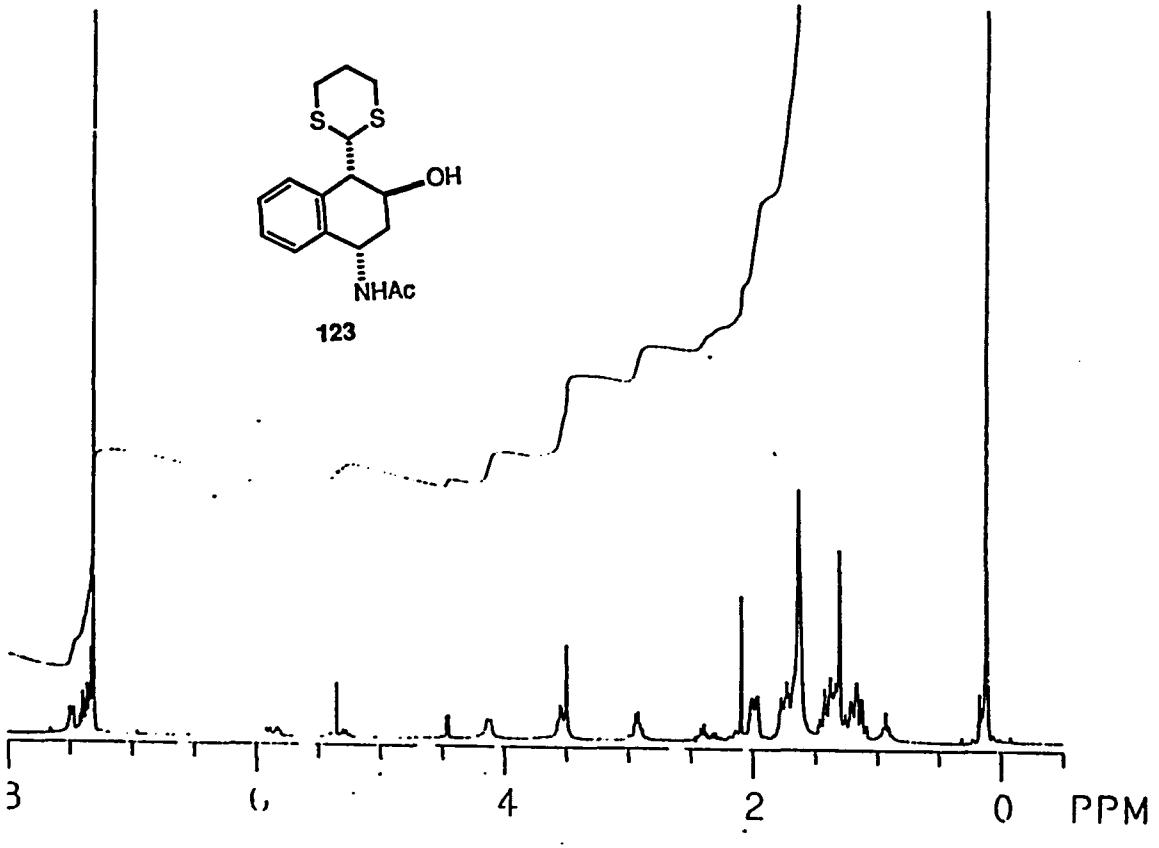

OBn
BnO
BnO
BnO
O
O

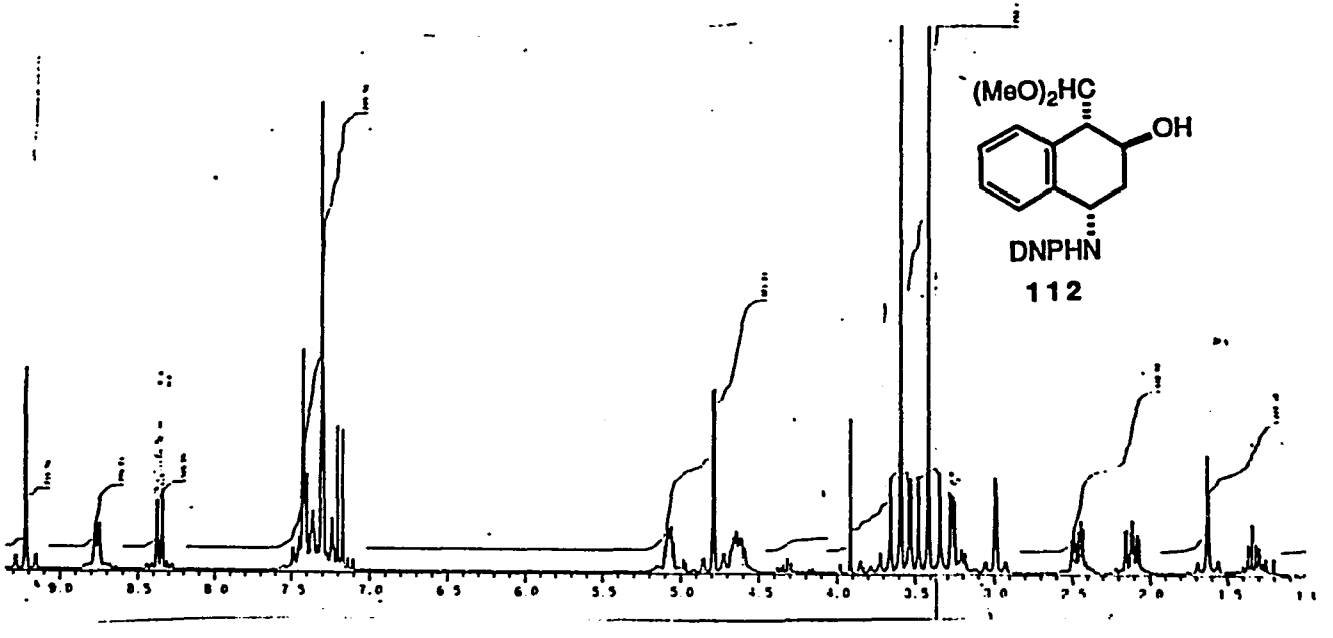
82

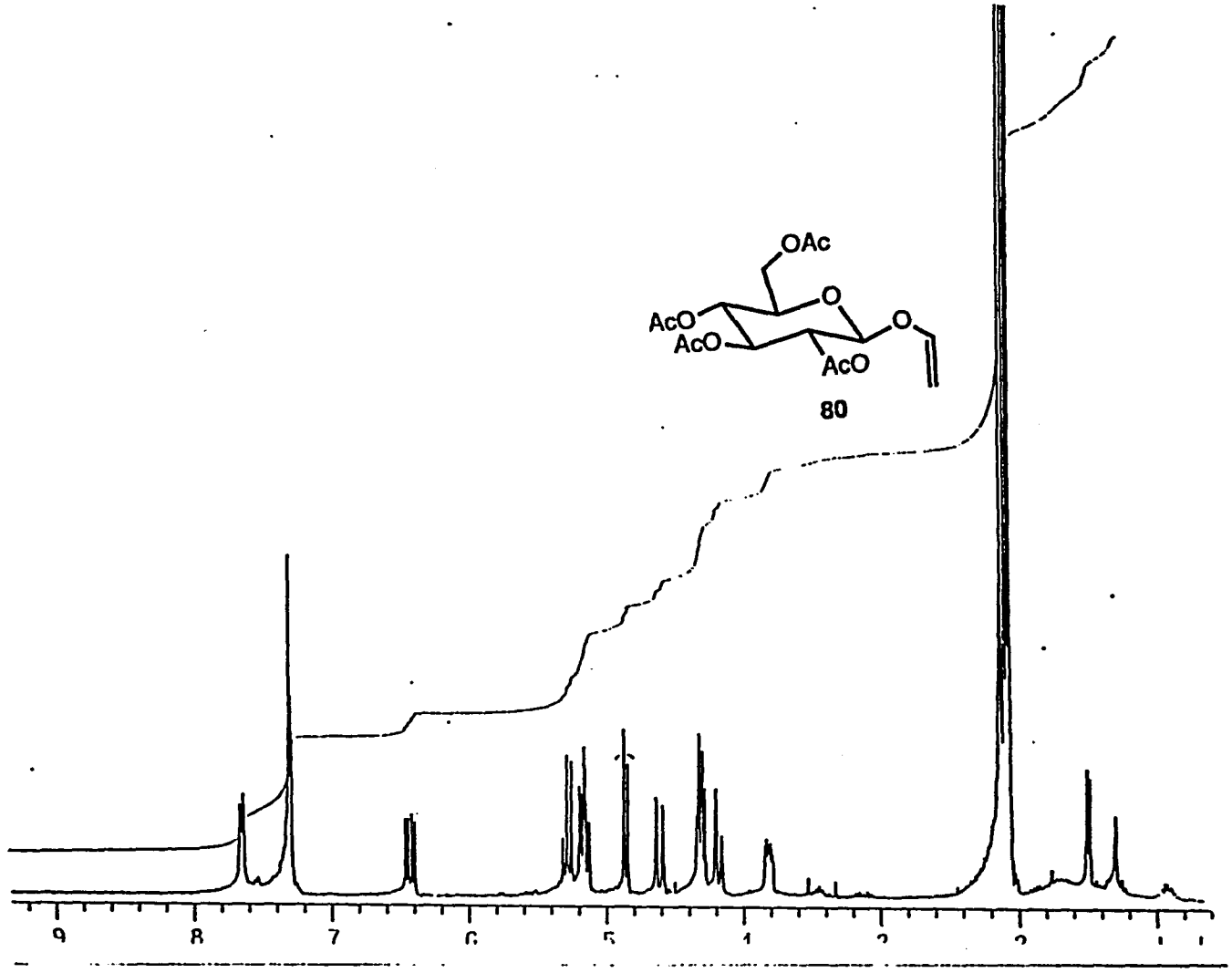

OBn
BnO
BnO
BnO
O
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0

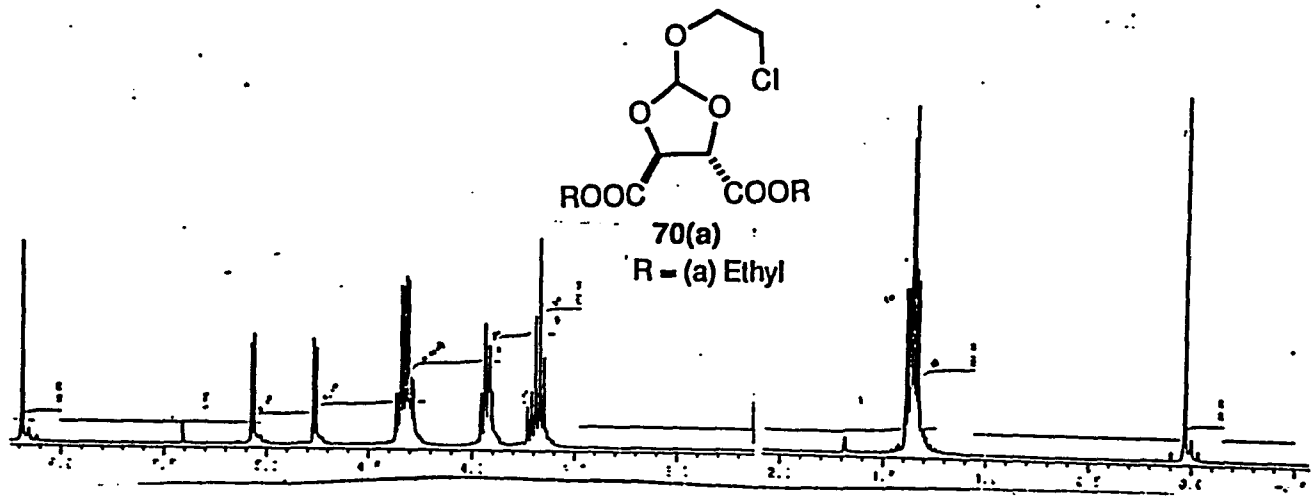
83


S
S
CF3
O
C
OMe
Ph
NHCOCH3
4.7
4.6
4.5
4.4
4.3
PPM
10
8
6
4
2
0


S
S
OH
NHAc
123
3
4
2
0
PPM

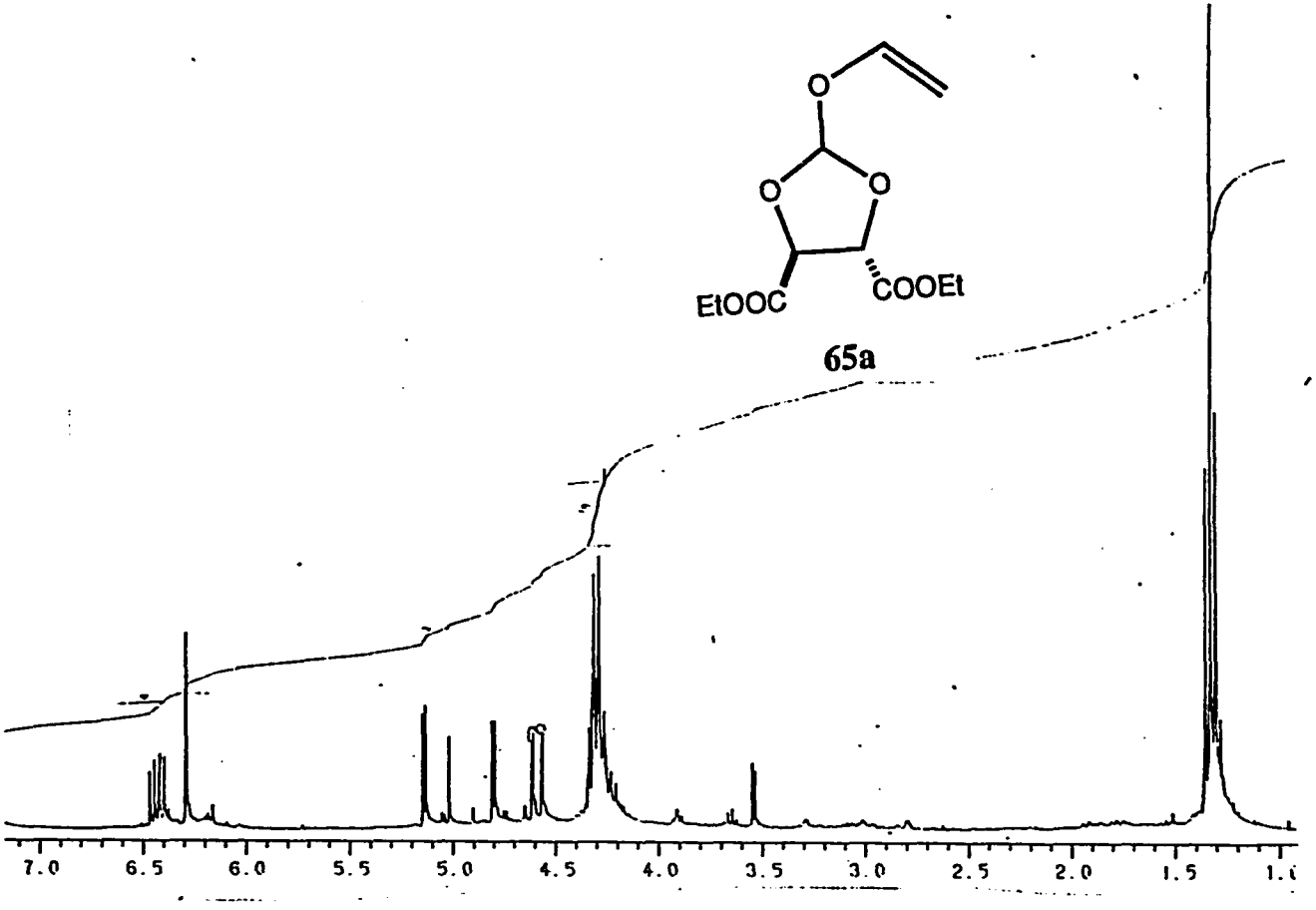

(MeO)2HC
OH
DNPHN
112


OAc
O
AcO
AcO
AcO
O
80
9
8
7
6
5
4
3
2
1



70(a)

R = (a) Ethyl



65a

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