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**The Claisen rearrangement of 4-allyloxyisoquinolines, and
The Bradsher cycloaddition of 4-alkoxyisoquinolinium salts:
Synthesis of a model of the BC ring system of the angucyline**

Nicolas, Tony Eddy, Ph.D.

City University of New York, 1994

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**THE CLAISEN REARRANGEMENT OF 4-ALLYLOXYISOQUINOLINES
AND
THE BRADSHER CYCLOADDITION OF 4-ALKOXYISOQUINOLINIUM
SALTS: SYNTHESIS OF A MODEL OF THE BC RING SYSTEM OF
THE ANGUCYLINES**

b y

TONY E. NICOLAS

**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**

1994

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

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Tony E. Nicolas

Advisor: Professor Richard W. Franck

A general method for the functionalization of 4-hydroxyisoquinoline has been developed. This general procedure has been applied to the synthesis of 4-allyloxyisoquinolines possessing various substituents at C2 of the allylic moiety. These isoquinolinyl ethers have been found to readily undergo the Claisen rearrangement to provide 3-alkyl-4-hydroxyisoquinolines. The two-step sequence constitutes a convenient way of introducing alkyl substituents at C3. Attempts were made to further elaborate the Claisen products to enol ether **27**, a structure which embodies all the requisite functionalities for an intramolecular Bradsher cycloaddition. In a parallel study of the intermolecular Bradsher cycloaddition of 4-alkoxyisoquinolinium salts, the reaction was elaborated into a powerful methodology for the introduction of the cis-hydroxyls of the angucyclines 9a-12b ring junction with the concomitant placement of the C1 carbonyl. These studies have

culminated in a convenient synthesis of the BC ring **355** of the angucyclines.

•

AD MAJOREM DEI GLORIAM

TO THE GREATEST FAMILY ON EARTH

By the Sovereign grace of God, I was born into the perfect family. Even experts descriptions of the ideal family fall way short of the routine standards of the Nicolas family. The completion of this journey is simply the concretization of their ideals. This achievement, their achievement, is the culmination of love, patience, encouragement, and support which are unsurpassed among mortals. If the world were to catch a glimpse of the members of my family, society would enthrone them as icons of the highest virtues found in humanity.

To the greatest man: Gabriel Nicolas,

To the greatest woman: Costa Jean-Louis Nicolas,

To the greatest sisters: Carolle Nicolas Bolnet and Claude Nicolas Eliacin,

To the greatest little sister: Johanne Nicolas,

To the greatest brothers and my best friends: Adler "Dilo's" Nicolas and Paul Nicolas,

To the greatest nieces: Gina Bolnet, Johanne-Stephanie Bolnet, and Samantha Eliacin,

To the greatest nephews: David Bolnet, Samuel Eliacin Jr., and Paul Eliacin,

To Samuel Eliacin for a model of excellence,

To Guy-Marie Bolnet for his love and encouragements:

THANK YOU

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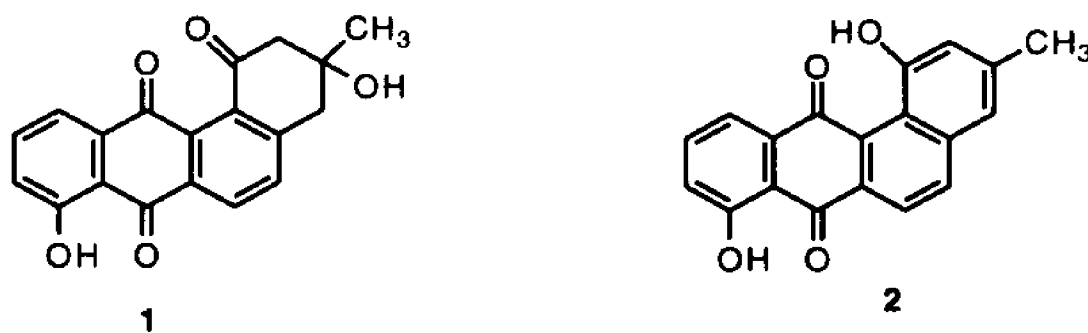
INTRODUCTION

1) The angucycline antibiotics

(i) Classification

The isolation and characterization of tetrangomycin **1** and tetrangulol **2** (scheme 1) in 1965 and 1966¹ ushered in a novel class of natural products characterized by their intriguing chemical structures and their varied biological activities.

Scheme 1: Tetrangomycin & tetrangulol

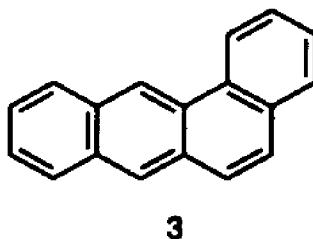


In reference to the angular disposition of their tetracyclic framework these compounds were named "angucycline group antibiotics".² An explosive growth of the angucycline field has been witnessed in the eighties, and at present, this class comprises more than one hundred representatives. Since biosynthetic studies³ have determined that the angucyclines arise from a decaketide chain processed through the polyketide biosynthetic pathway, the angucyclines now constitute, along with the tetracyclines and anthracyclines, the third group of tetracyclic decaketides.

Since all of the angucyclines reported thus far, were isolated as metabolites of Actinomycetes, isolated from soil samples or shallow sea mud, the production of such structures appears to be confined to these micro-organisms.⁴

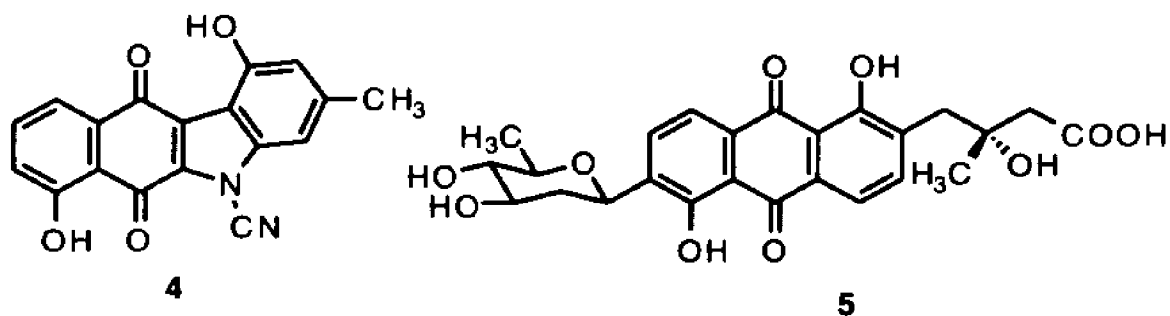
For classification purposes, the angucyclines are divided into two main groups.⁵ The first group comprises the natural products which exhibit the characteristic benz[a]anthracene **3** (scheme 2) motif present in tetrangomycin **1** and tetrangulol **2** (scheme 1). These are said to contain the "classical aglycone moiety".

Scheme 2: The benz[a]anthracene structure



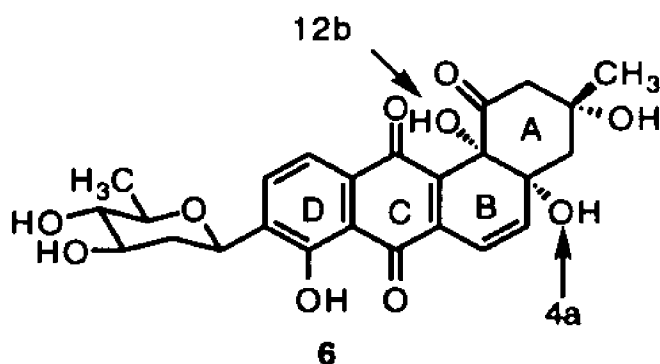
The second group, the angucyclines with a "non-classical aglycone moiety", encompasses all angucyclines in which the benz[a]anthracene substructure has been modified or rearranged. Prekynamycin⁶ **4** and vineomycinone-B₂⁷ **5** exemplify the second type (scheme 3).

Scheme 3: Prekynamycin and vineomycinone-B2



The classical angucyclines are further subdivided into those possessing a C-glycosidic moiety such as aquayamycin⁸ **6** (scheme 4) and those without the C-glycoside, exemplified by tetrangomycin **1**. The presence or absence of angular oxygens at the 4a and 12b positions of the classical angucyclines, provides a basis for a further subdivision of the group.

Scheme 4: Aquayamycin



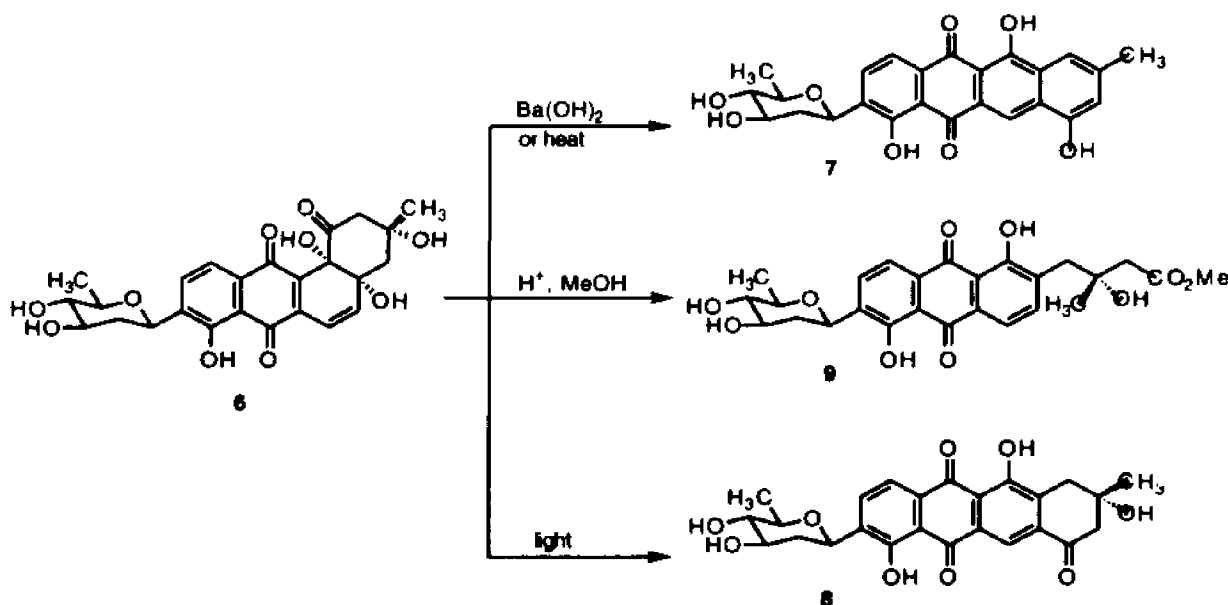
It is an interesting fact of the biogenesis of the 4a and 12b oxygenated classical angucyclines that the 4a hydroxyl is introduced via an acetate of the decaketide chain while the 12b hydroxyl originates from the air.⁹ The introduction of the latter oxygen has a stabilizing effect on the ring

system which is otherwise prone to dehydration.¹⁰ *This fact may prove quite important in synthetic designs to these natural products.*

(ii) The rearrangements of the angucyclines.

The most challenging aspect of a total synthesis of the more complex 4a and 12b oxygenated angucyclines is the construction of the AB ring system. This structural motif exhibits a marked propensity towards skeletal rearrangements under basic, acidic, and photochemical conditions. The rearrangement of aquayamycin 6 under basic and photochemical conditions, for example, gives rise to linear tetracyclic structures 7 and 8 which have no biological significance.¹¹

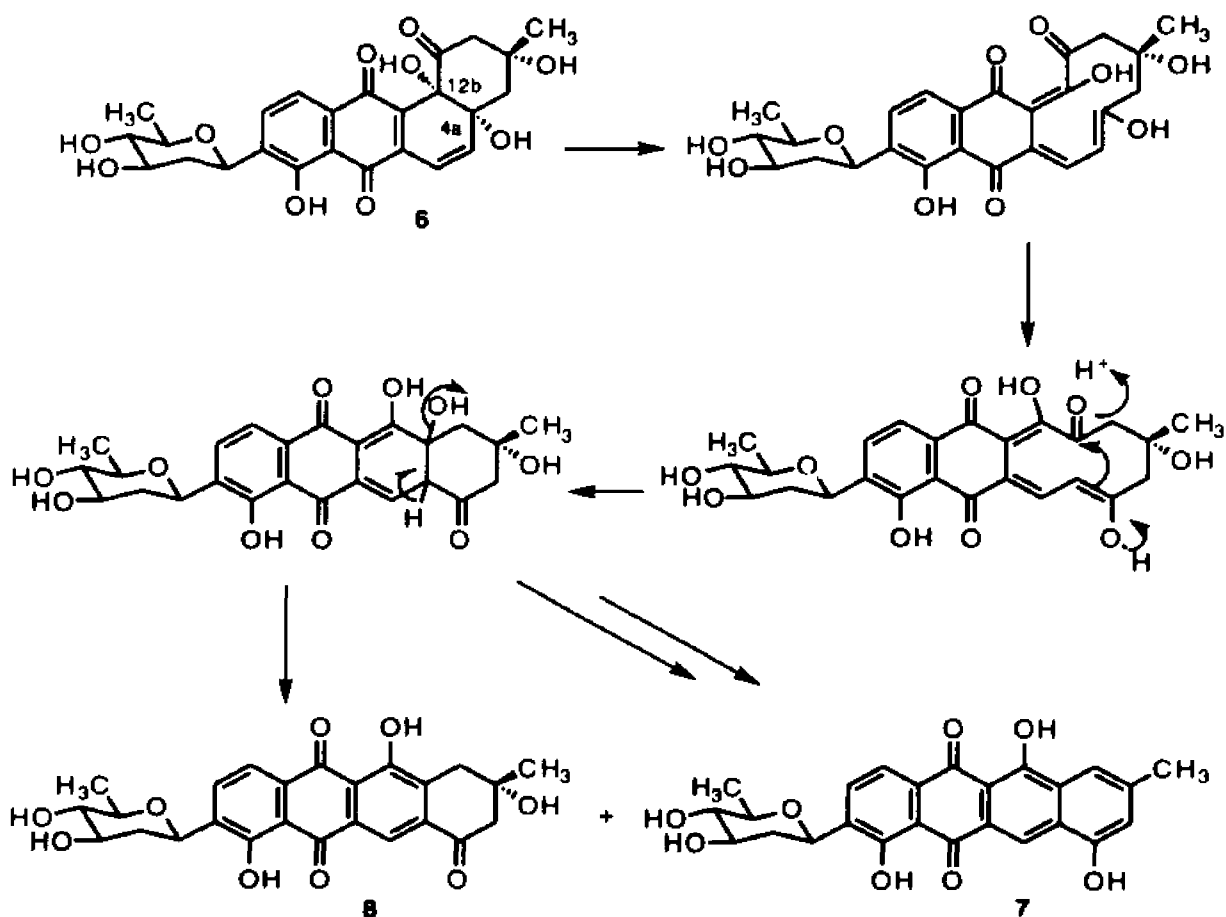
Scheme 5: The rearrangements of Aquayamycin



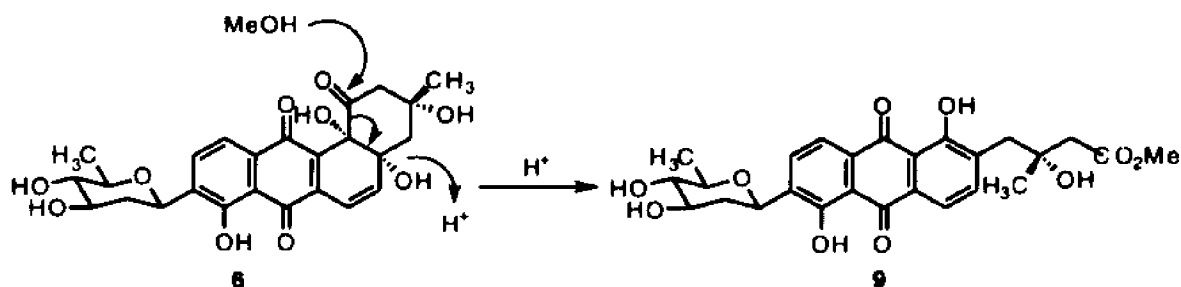
The rearrangement (scheme 6) proceeds through the cleavage of the 4a-12b bond, in a retro-Aldol or electrocyclic ring opening, followed by reannulation to the observed structures.¹²

Under acidic conditions, however, aquayamycin **6** is converted to vineomycinone-B2 methyl ester **9** via acid promoted attack of methanol at the C1 carbonyl (scheme 7).¹³ These transformations underscore the fragility of the AB ring structural array.

Scheme 6: Mechanism of the base or light induced rearrangement of Aquayamycin.



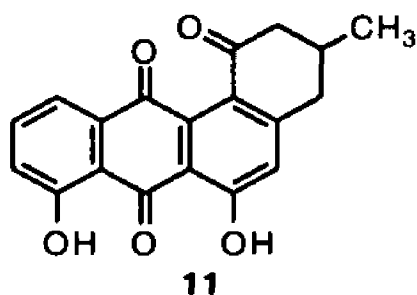
Scheme 7: The rearrangement of aquayamycin under acidic conditions.



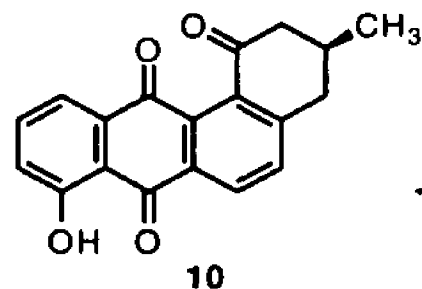
(iii) The synthesis of the angucyclines

Thus far, no total synthesis of the challenging oxygenated angucyclines has appeared in the literature. Most synthetic efforts have been concerned with the simple non-oxygenated congeners. The syntheses of tetrangulol¹⁴ **2** (scheme 1), ochromycinone¹⁵ **10**, 3-deoxyrabelomycin¹⁶ **11**, Vineomycinone B2 methyl ester¹⁷ **9**, SS-228R¹⁸ **12**, and urdamycinone B¹⁹ **13** have been reported (scheme 8).

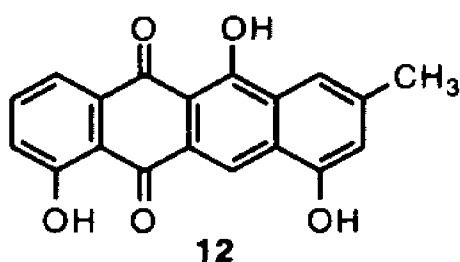
Scheme 8: Some Angucyclines that have been synthesized.



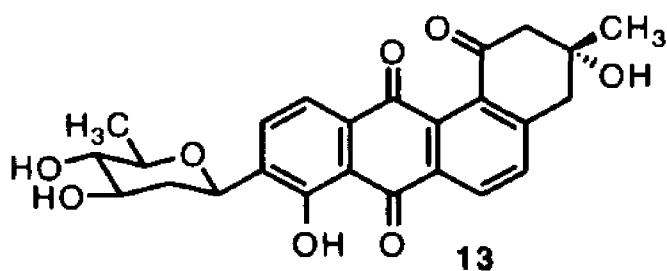
3-deoxyrabelomycin



Ochromycinone



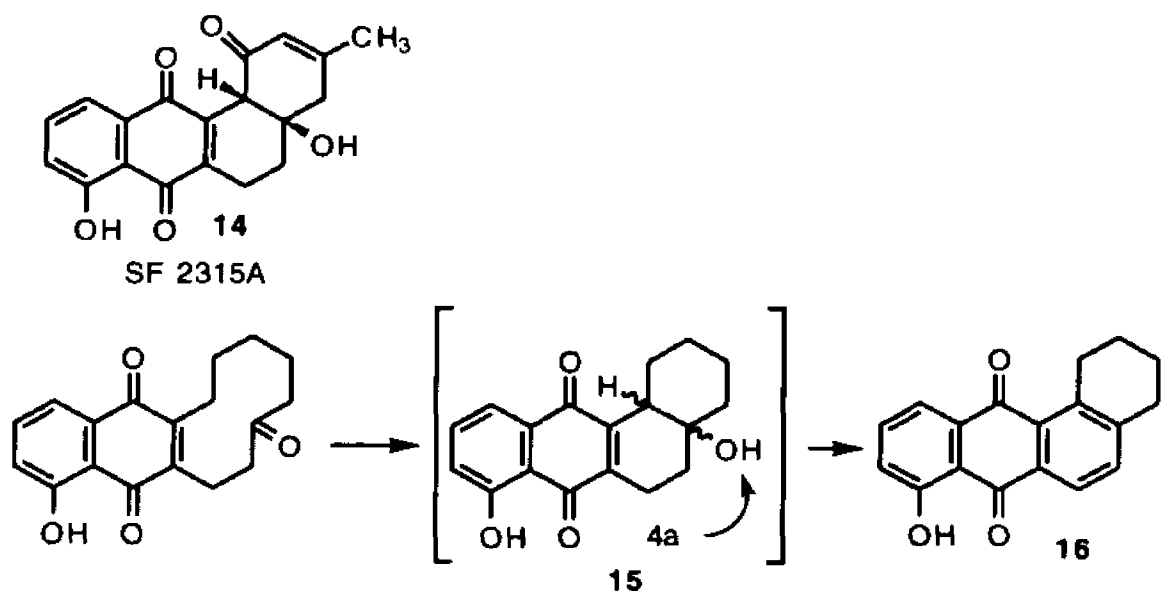
SS-228R



Urdamycinone B

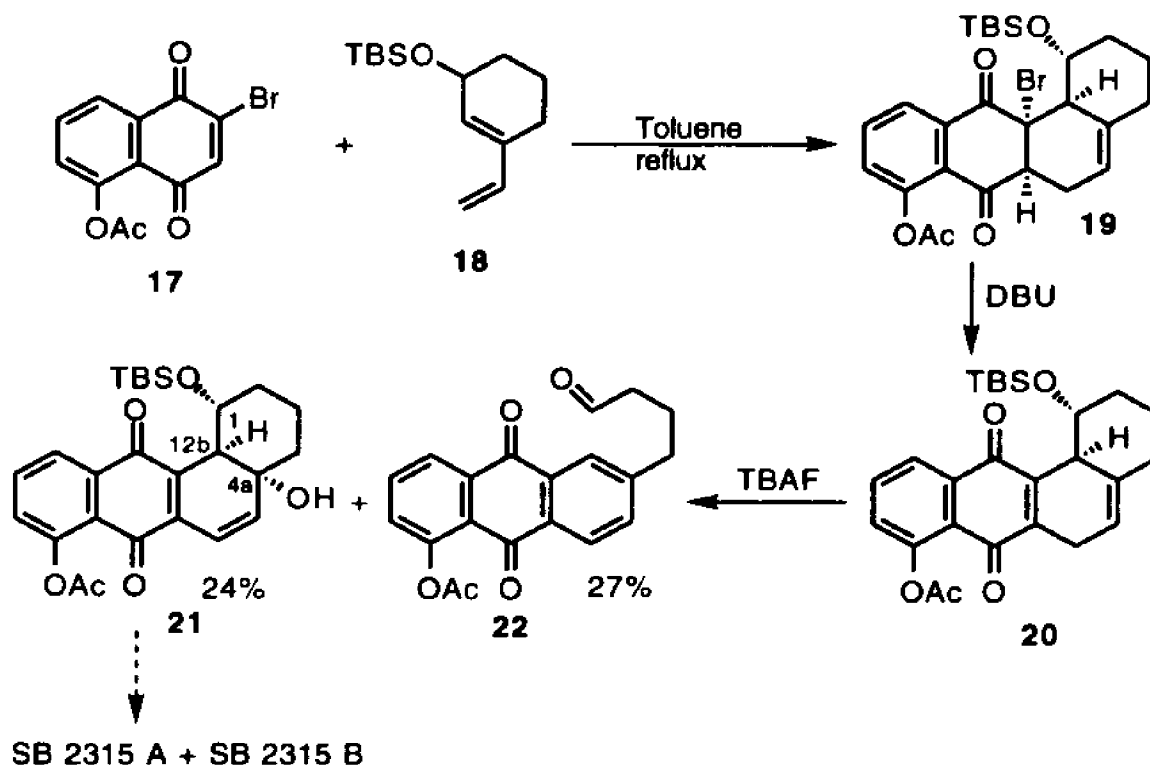
Recent synthetic efforts by Danishefsky²⁰ and Sulikowski²¹ on the more complex targets, only highlight the sensitivity of the AB ring system and the imperative of mild methodologies for its assembly. Danishefsky's model study to angucyclinone SF 2315A²² **14** (scheme 9), one of the simplest monooxygenated congeners, resulted in the elimination of the 4a hydroxyl of intermediate **15** to generate a benz[a]anthraquinone structure **16**.

Scheme 9: Danishefsky's model study to SF 2315A



Sulikowski, for his part, was able to quickly assemble the benz[a]anthracene tetracyclic framework via an elegant Diels-Alder reaction of bromo juglone derivative **17** and vinyl cyclohexene **18** followed by the dehydrobromination of the product **19** to quinone **20** (scheme 10).²³ Although admirably served by a serendipitous oxidation which resulted in the stereoselective introduction of the 4a hydroxyl, Sulikowski was unable to effect the final conversion of intermediate **21** to SF 2315 A **14**.

Scheme 10: Sulikowski's approach to the angucyclines.



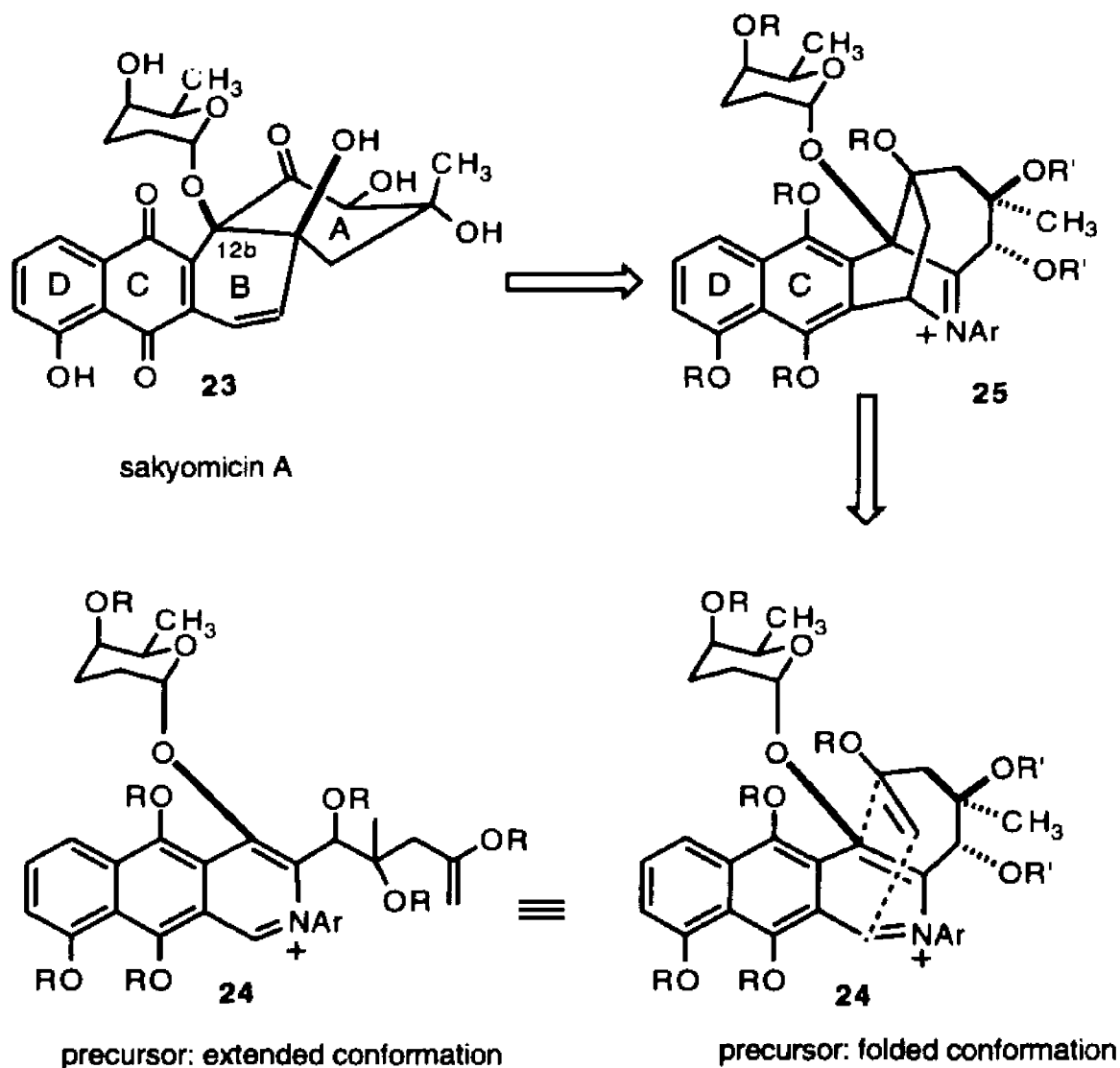
The sensitivity of the AB ring system proved to be at the heart of the problem. Fluoride induced removal of the silyl protecting group resulted in the fragmentation of the resulting alkoxide to anthraquinone **22** via cleavage of the C12b-C1 bond and δ -elimination of the 4a hydroxyl.

The magnitude of the challenge and the paucity of work on the more attractive oxygenated compounds has led to the cautious statement that "a synthesis of the more complex angucyclines may be a future goal for organic synthesis".²⁴

(iv) Our approach to the synthesis of Sakyomycin A.

We have set our sights on a total synthesis of sakyomycin A **23**²⁵ which has been reported to inhibit the proliferation of HIV in vitro.²⁶

Scheme 11: The retrosynthetic analysis of Sakyomicin A.



The formidable structural challenge that the natural product constitutes, makes it an attractive synthetic target. In addition, interest is heightened by the need to delineate a convenient route to synthetic analogues that may be of clinical benefit in the fight against AIDS. Our retrosynthetic approach to the target is outlined in scheme 11.

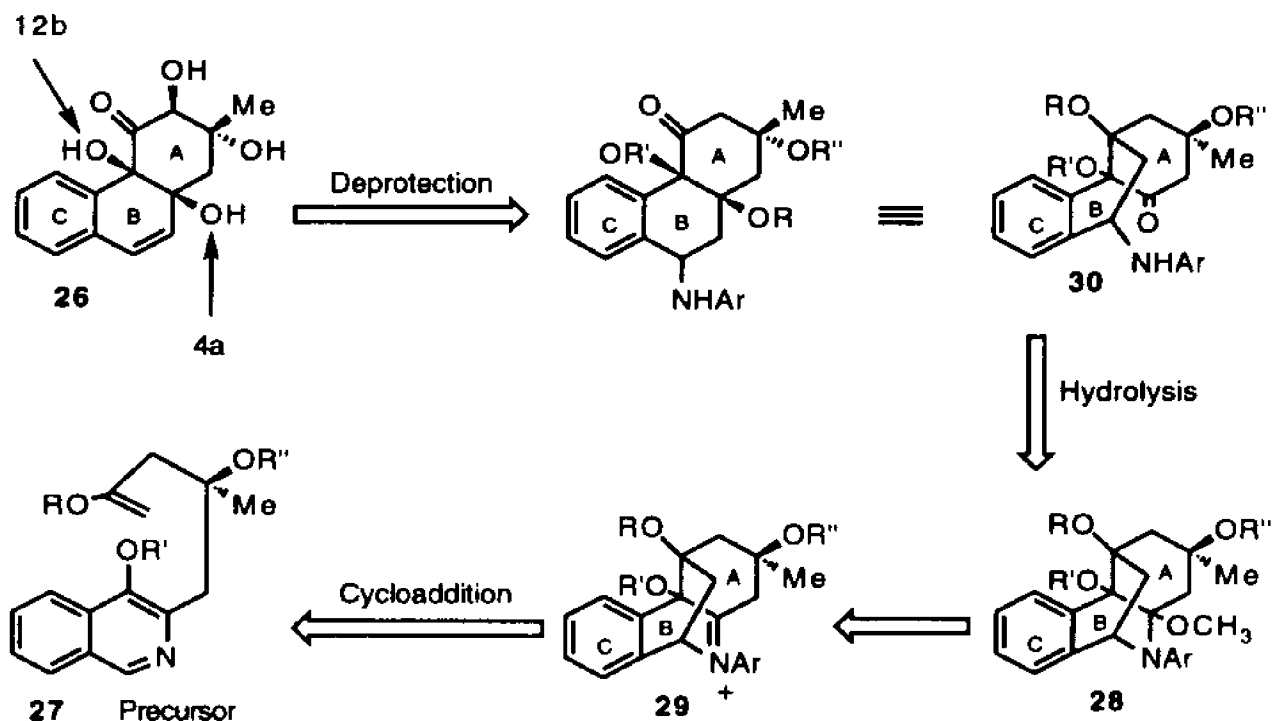
The key step in grafting the AB ring portion to the naphthoquinone, is the intramolecular Bradsher cycloaddition²⁷ of azanthracene **24**. The distinctive feature of this system is the presence of the enol ether moiety which is tethered to the aromatic system via a 3-carbon chain. The cycloaddition, in which the complete tetracyclic framework is assembled, is envisaged to proceed via intermediate **25**. In the process, the required functionalities of the AB ring system are concomittantly established.

However, in order to lay the foundation for this approach, the synthesis of an ABC ring model **26** was undertaken.

Our approach to the angucyclines ABC ring system **26**, illustrated for the Aquayamycin ABC segment (scheme 12), is based on an intramolecular version of the Bradsher²⁸ cycloaddition proceeding from precursor **27** via intermediate **28**. Our antithetic analysis comprises three major junctions:

- 1) The first stage consists in the synthesis of precursor **27** in which the enol ether moiety is appended to the isoquinoline nucleus at C3. The linker side chain carries a tertiary hydroxyl functionality as the precursor to the A-ring C3 tertiary alcohol. Upon quaternization, the precursor would be activated towards an intramolecular Bradsher cycloaddition.
- 2) The second stage is the cycloaddition itself. On the basis of the known preference for exo addition in the Bradsher cycloaddition, a cis outcome of the protected hydroxyls is predicted. The aminor **29** which is generated by the trapping of the iminium ion **28** by methanol can be subsequently hydrolyzed to unmask the keto group of the A-ring in aminoketone **30**.

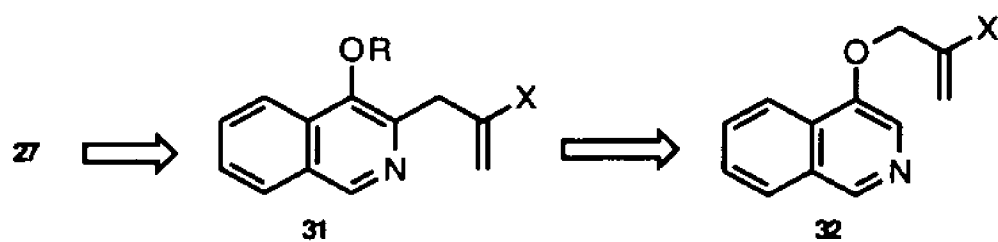
Scheme 12: Retrosynthetic analysis of the ABC ring system of aquayamycin



3) The third stage consists in functional group manipulations to unveil the free hydroxyl groups and to establish the B-ring double bond by Hoffman elimination of the amino group.

The antithetic analysis of precursor **27** suggested its elaboration from a 3-alkenyl-4-alkoxy substituted isoquinoline **31** which could be generated from the Claisen rearrangement of 4-allyloxy isoquinolinyl ether **32** (scheme 13).

SCHEME 13: Antithetic analysis of the Bradsher precursor

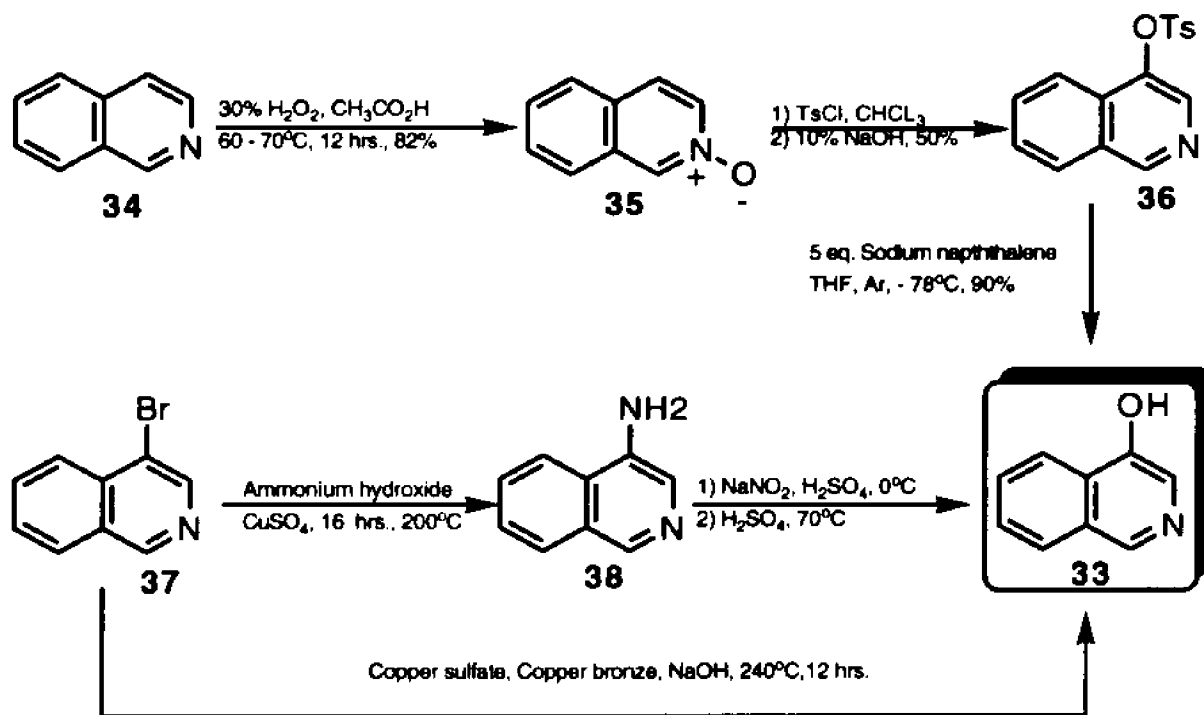


CHAPTER 1: THE SYNTHESIS OF OXYGENATED ISOQUINOLINES.

1) The synthesis of 4-hydroxyisoquinoline.

The synthetic route to 4-hydroxyisoquinoline **33** developed by Ochiai and Ikehara (scheme 14) involves the oxidation of isoquinoline **34** to its corresponding N-oxide **35** which yielded the 4-tosyloxyisoquinoline **36** upon treatment with toluene sulfonyl chloride.²⁹ Ochiai effected the hydrolysis of the tosylate to the desired 4-hydroxyisoquinoline **33** under reflux in the presence of sodium hydroxide.³⁰ We have found the use of sodium naphthalenide to be a more convenient and effective procedure for the removal of the tosylate.³¹ Via this procedure, the hydroxylated isoquinoline was obtained in 90% yields. 4-hydroxyisoquinoline could also be obtained via a two step sequence involving amination³² of the commercially available 4-bromo isoquinoline **37** to 4-aminoisoquinoline **38** followed by diazotization of the resulting amine (scheme 14).³³

Scheme 14: The synthesis of 4-hydroxy isoquinoline

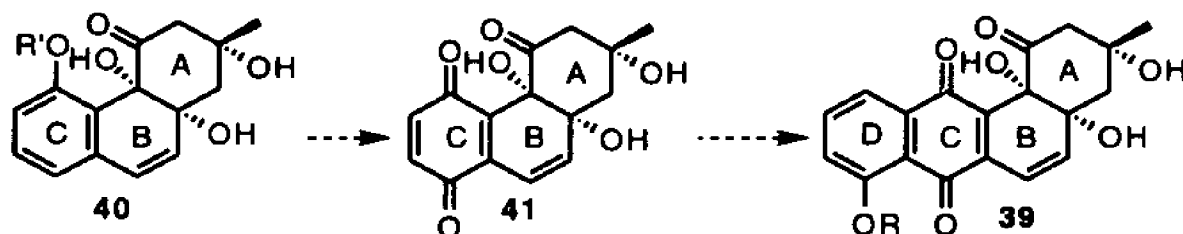


The two step sequence proved to be more tedious and much less reliable than the three-step sequence involving the isoquinoline N-oxide. The application of Gilman & Crainer's one-step synthesis however, proved to be the method of choice for the obtention of 4-hydroxyisoquinoline **33**.³⁴ The copper-catalyzed nucleophilic displacement of bromide from 4-bromoisoquinoline **37** generated the desired starting material **33** in very good yields (scheme 14).

2) The synthesis of 4,5-dioxygenated isoquinolines.

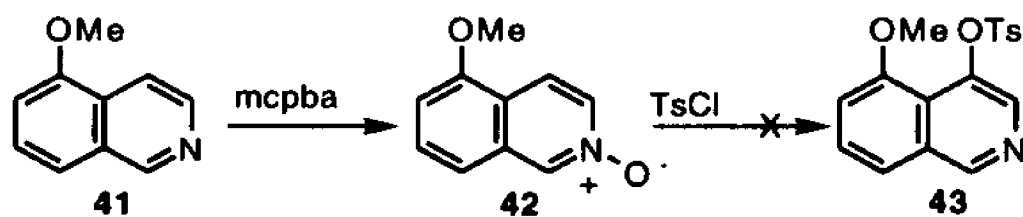
In one approach to the synthesis of the angucyclines **39**, we considered, in a first stage, the construction of the ABC ring portion with an oxygen functionality in the C ring **40** (scheme 15).

Scheme 15: The total synthesis of the angucyclines from dioxigenated isoquinolines



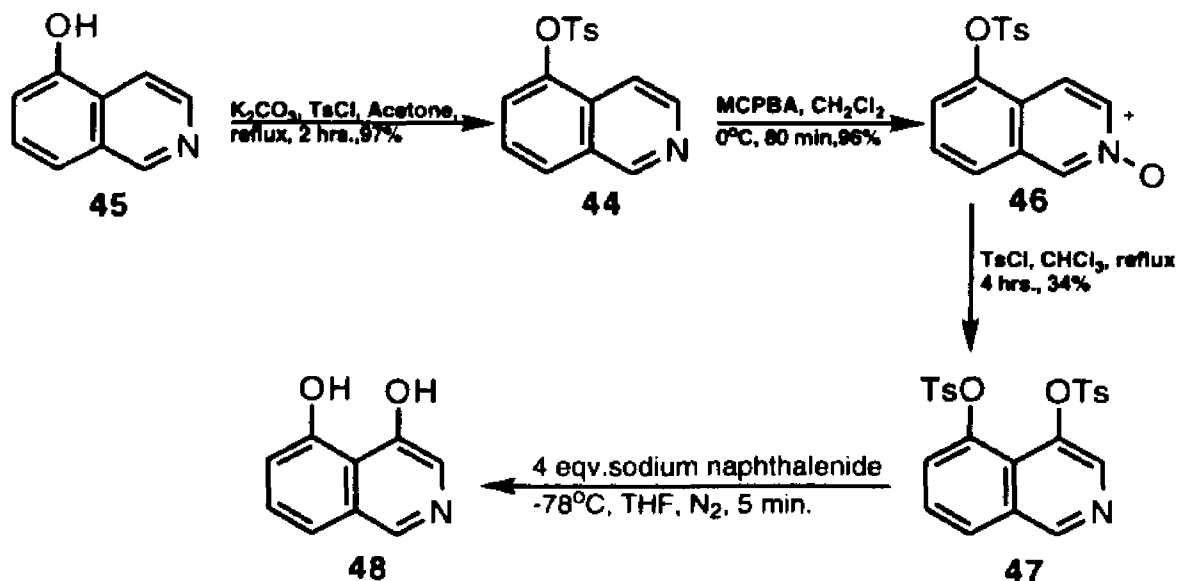
The design of the alkoxy group into the C ring would enable the conversion of the C ring into a quinone **41**. From the quinone, a Diels-Alder annulation would be the final step to complete the synthesis of the natural products. Such a sequence requires the synthesis of 4,5-dioxygenated isoquinolines. Of the three methods previously used to synthesize 4-hydroxyisoquinoline, only the N-oxide rearrangement lends itself to such a task. In a preliminary study in our lab, 5-methoxyisoquinoline **41** was treated with MCPBA and the resulting N-oxide **42** was refluxed in the presence of toluene sulfonyl chloride (scheme 16). The expected rearrangement of the N-oxide **42** to the desired 4-tosyloxy-5-methoxy isoquinoline **43** did not occur.

Scheme 16: The attempted synthesis of 5-methoxy-4-tosyloxyisoquinoline



The literature reports that in the presence of acetyl chloride, 5-nitro isoquinoline N-oxide led to 5-chloro isoquinoline N-oxide.³⁵ Although we find the authors structural assignment questionable (we believe the product to be the isocarbostyrl or 4-acetoxy derivative), it nevertheless pointed to the need of an electron withdrawing oxygen functionality at the 5-position of isoquinoline. Thus, we synthesized 5-tosyloxyisoquinoline **44** in 97% yield from the commercial 5-hydroxyisoquinoline **45**. Oxidation of **44** with MCPBA resulted in a 96% yield of the 5-tosyloxy-N-oxo-isoquinoline **46**. The formation of the N-oxide is easily ascertained by the characteristic upfield shift of H1 that oxidation of the nitrogen induces in such compounds. In sharp contrast to the 5-methoxy derivative **42**, the 5-tosyloxy isoquinoline N-oxide **46** did rearrange to the expected 4,5-ditosyloxy isoquinoline **47** albeit in disappointing yields (34%). The disappearance of the two doublets corresponding to H3 and H4 of the starting material and the appearance of the H3 singlet resonance in the product were taken as evidence of a successful rearrangement to the expected product.

Scheme 17: The synthesis of 4,5-dihydroxy isoquinoline



The low yields are attributed to the instability of the product under chromatographic and recrystallization conditions. The rearrangement of the corresponding acetates and benzoates, carried out by T. Maung in our lab, proceeded in lower yields. The ditosyloxy compound upon exposure to sodium naphthalenide was converted to the hitherto unreported 4,5-dihydroxy isoquinoline **48**. Considerable efforts were spent in attempts to differentiate the two hydroxyls. Maung's efforts towards that end have been, to date, unsuccessful. From a synthetic point of view, however, the proposed route, which does not require that the hydroxyl be differentiated, could be redesigned from a 4,5-dialkoxy isoquinoline.

CHAPTER 2: THE DERIVATIVES OF 4-HYDROXYISOQUINOLINE

In the context of the projected Claisen rearrangements as well as our study of the influence of 4-oxygenated substituents on the course of the Bradsher cycloaddition, various derivatives of 4-hydroxyisoquinoline **33** were synthesized. An added incentive to the derivatization of 4-hydroxyisoquinoline derived from the need to introduce from the outset of the synthetic venture the carbohydrate moiety present in a number of angucyclines, notably the 12b rhodinosyl moiety of sakyomycin A **23**.

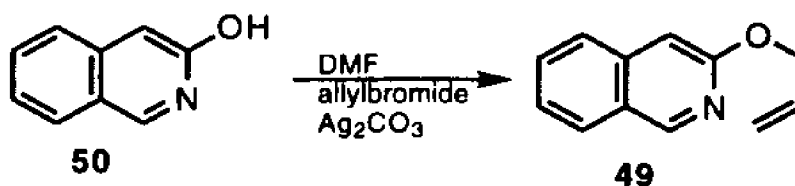
1) Literature results on the functionalization of hydroxyisoquinolines

In reactions directed towards O-alkylation, isoquinolines with hydroxyl substituents in the pyridine ring, unlike the analogously substituted benzene portion, display a peculiar behavior due to the existence of the tautomeric amide forms.³⁶ Since the hydroxyls of interest do not behave in a standard "phenolic" fashion, their functionalization requires special conditions.

Win and Tieckelmann's protocol for the synthesis of 3-allyloxy isoquinoline³⁷ **49** consisted in stirring a DMF solution of 3-isoquinolinol³⁸ **50** with allylbromide and silver carbonate (scheme18), since these conditions were known to lead to a preponderance of the O-alkylated product in the reaction of 2-pyridone with methyl iodide.³⁹ Although the yields for the desired 3-allyloxyisoquinoline **49** were not disclosed, the authors report that under these conditions, no isomeric

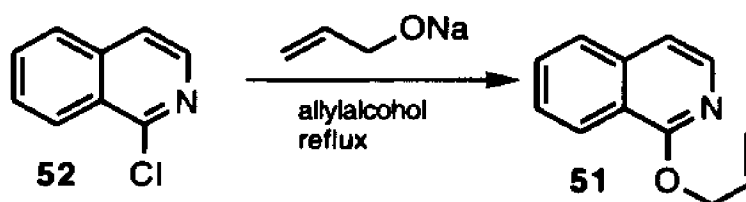
N-allyl-3-isoquinoline could be detected. Treatment of a methanolic solution of **50** with methyl iodide and sodium methoxide on the other hand resulted in N-alkylation.⁴⁰

SCHEME18: Win and Tieckelmann's synthesis of 3-allyloxyisoquinoline



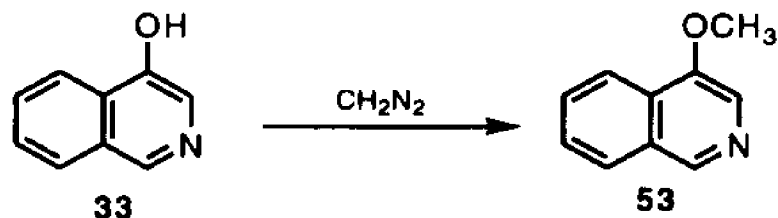
In an application of Fisher's methodology,⁴¹ Win and Tieckelmann effected the synthesis of 1-allyloxyisoquinoline **51** (scheme 19) by treatment of 1-chloroisoquinoline **52** with sodium allyloxide in allyl alcohol.⁴²

SCHEME 19: The synthesis of 1-allyloxyisoquinoline.



The synthesis of 4-methoxyisoquinoline **53** by treatment of 4-hydroxyisoquinoline **33** with excess diazomethane (scheme 20) has also been reported.⁴³ Unfortunately yields for the isolated product were not published.

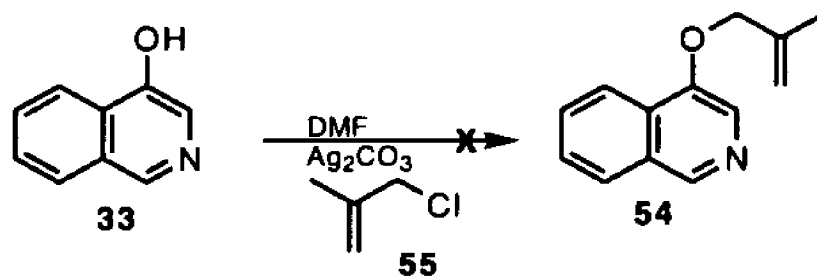
SCHEME 20: The synthesis of 4-Methoxyisoquinoline.



2) The functionalization of 4-hydroxyisoquinoline

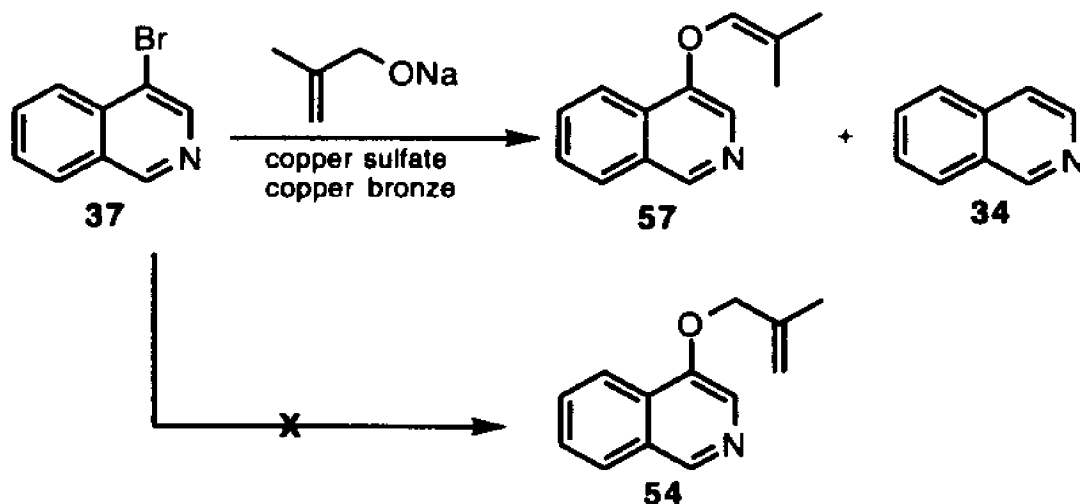
Our attempts (scheme 21) to extend Win and Tieckelmann's methodology⁴⁴ to the synthesis of 4-(2-methyl-2-propenyloxy)isoquinoline **54** using 4-hydroxyisoquinoline **33** and 3-chloro-2-methyl-propene **55** were disappointing. No organic material bearing the isoquinoline nucleus could be isolated. It appears that the weak base, silver carbonate, did not generate a high enough concentration of the alkoxide to induce preferential O-alkylation. Under these conditions N-alkylation was favored. The isoquinolinium salt product, unlike N-allyl-3-hydroxyisoquinolinium bromide is unable to tautomerize to a neutral amide form and consequently was lost during the aqueous work up.

SCHEME 21: Failure of the silver carbonate method to prevent N-alkylation.



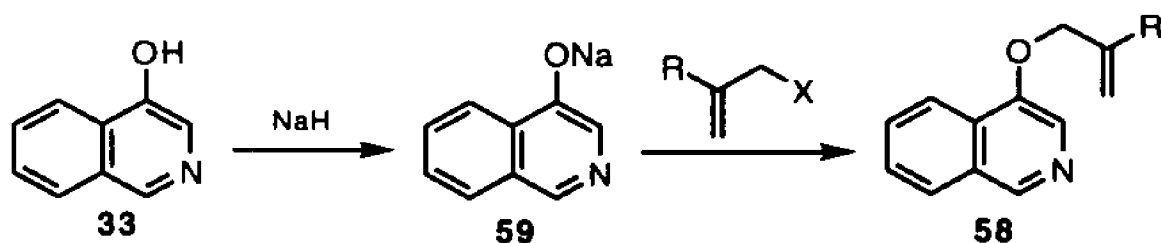
The reaction of 4-bromoisoquinoline **37** with the sodium salt of methallyl alcohol **56** (scheme 22) in the presence of copper bronze and copper sulfate, patterned after the published synthesis of 1-allyloxy isoquinoline **51** (scheme 19),⁴⁵ failed to generate the desired 4-(2-methyl-2-propenyloxy)isoquinoline **54**. The use of this protocol resulted mainly in the reduction of the starting bromide to isoquinoline **34** (scheme 22). A small amount of a product which on the basis of its ^1H NMR spectrum was characterized as enol ether **57** was also isolated.

SCHEME 22: Copper catalysis approach to 4-(2-methyl-2-propenyloxy)isoquinoline.



The failure of the published procedures led us to develop a general route to the required 4-allyloxy derivatives **58** of isoquinolines. Our approach, outlined in scheme 23, involves the generation of the 4-hydroxyisoquinoline salt **59** by treatment of 4-hydroxyisoquinoline **33** with sodium hydride followed by the addition of the required allyl halide. Under these conditions, the desired O-allylation process is predominant.

SCHEME 23: General synthesis of 4-allyloxyisoquinolinylethers.

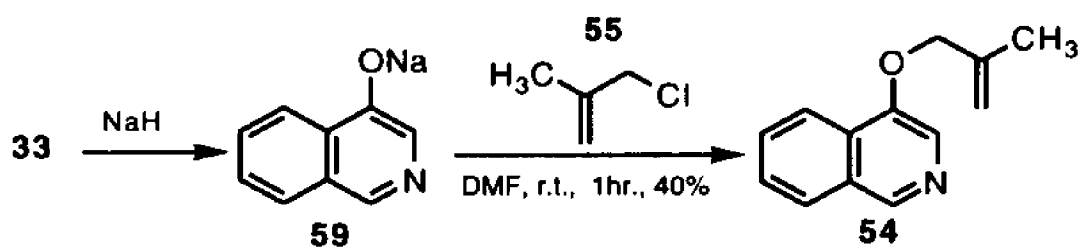


(i) The synthesis of 4-(2-methyl-2-propenyloxy)isoquinoline

The general procedure described above was applied to a synthesis of 4-(2-Methyl-2-propenyloxy)isoquinoline **54**. Thus, the propenyl isoquinolinyl ether was obtained in 63% yields via nucleophilic coupling of 3-chloro-2-methyl propene **55** with the sodium salt of 4-hydroxyisoquinoline **59** (scheme 24). The formation of the desired ether could be readily ascertained from the ^1H NMR spectrum. Evidence for the incorporation of the alkenyl side chain was provided by the appearance in the spectrum of a set of terminal vinyl protons.

The presence of the methylene and methyl protons at the expected chemical shifts served to confirm the structural assignment. The possibility of a C-3 alkylated product could readily be excluded due to the presence in the NMR spectrum of the singlet corresponding to the H3 proton.

Scheme 24: Synthesis of 4-(2-methyl-2-propenyloxy)isoquinoline.

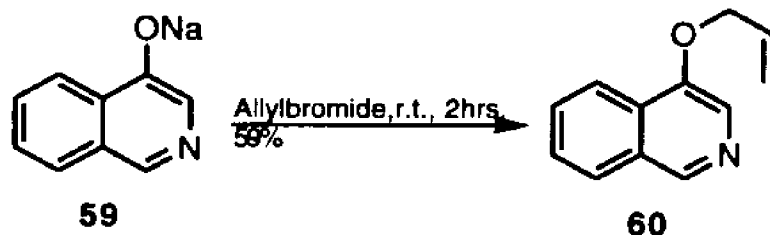


(ii) The synthesis of 3-(4-isoquinolinoxy)propene

The synthesis of 4-(2-propenyloxy)isoquinoline 60 was effected by treatment of the sodium isoquinolinoxy salt 59 with allyl bromide (scheme 25). The crude ether, of relatively high purity, as ascertained by NMR, could be obtained in 59% yields. Pure 4-(propenyloxy)isoquinoline 60 was isolated in 39% yields following column chromatography over florisil. The low yields of purified product are attributable to the decomposition of the product over silica gel and florisil. No other solid support was examined although the high material recovery in the purification of 4-(methoxymethyloxy)isoquinoline over basic alumina in our lab suggests that that this solid support could be standardized for the purification of

isoquinolinyl ethers. The identity of the isoquinolinyl ether was ascertained by the appearance in the ^1H NMR spectrum of the characteristic multiplet corresponding to the internal vinyl proton.

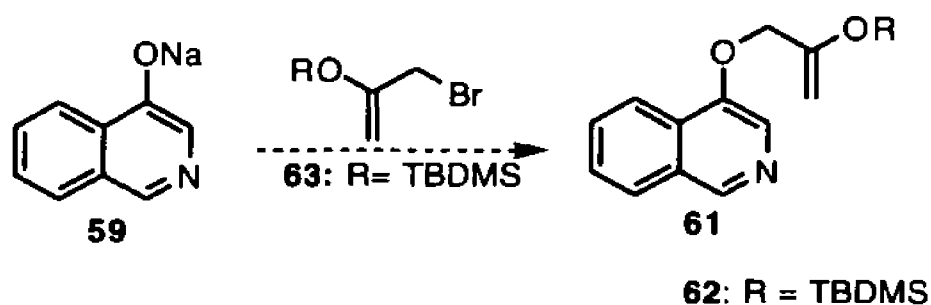
SCHEME 25: Synthesis of 4-allyloxyisoquinoline



(iii) The synthesis of 4-(2-methoxy-2-propenyloxy)isoquinoline

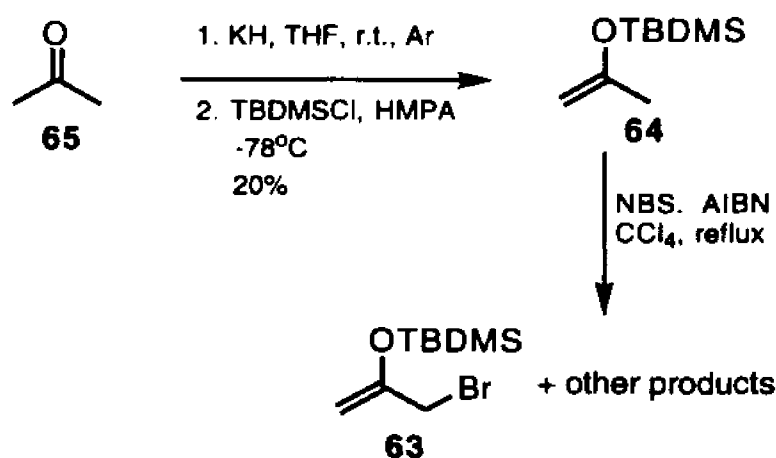
With a view towards the Bradsher precursor **27** (scheme 12) we were led to explore the possibility of introducing a keto group in the 3-appendage of the isoquinoline via the Claisen rearrangement of an isoquinolinyl ether bearing a masked carbonyl functionality. The Claisen rearrangement envisaged required access to 4-(2-alkoxy-2-propenyloxy)isoquinolines **61** (scheme 26). The synthesis of 4-(2-tert-butyldimethylsilyloxy-2-propenyloxy)isoquinoline **62** (scheme 26) for example necessitated in turn a simple route to 3-bromo-2-(tert-butyldimethylsilyloxy)propene **63** the required alkylating agent for 4-hydroxyisoquinoline.

SCHEME 26: An approach to 4-(2-Alkoxy)isoquinolines.



The starting material, 2-silyloxypropene **64** (scheme 27), required for the synthesis of **63** was obtained in 20 % yield (scheme 27) by the trapping of the acetone potassium enolate, generated by treatment of acetone **65** with potassium hydride, with tert-butyldimethylsilyl chloride (scheme 27).

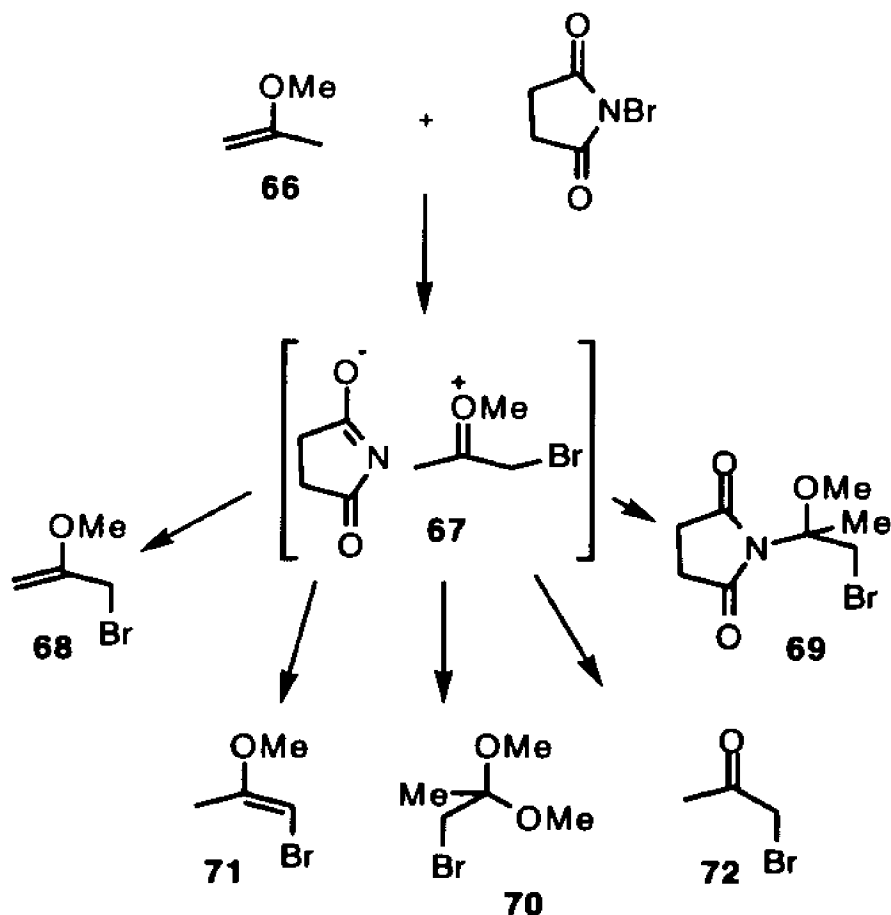
SCHEME 27: The synthesis of 2-tert-butyldimethylsilyloxypropene.



Our attempt to effect the allylic bromination of the product **64** with NBS (scheme 27), resulted in a grand mixture of products, as evidenced by the ^1H nmr spectrum. Our results parallels Hoffmann's⁴⁶ who observed a similar mixture in his attempted bromination of 2-methoxypropene

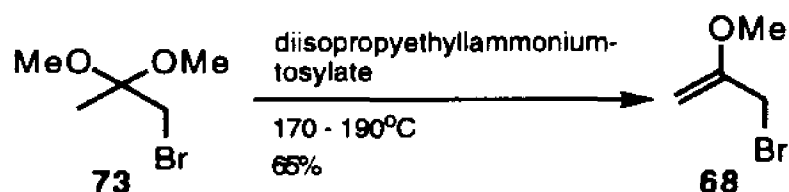
66. His explanation evokes the strong ionic character of the reaction which proceeds via **67** (scheme 28) to yield, in addition to the desired methoxyallylbromide **68**, products of nucleophilic attacks on the carbocation center of **67** by succinimide and methanol (products **69** and **70** respectively). Elimination products such as vinyl ether **71** and hydrolysis product **72** were also identified. The ionic nature of the process, according to Hoffmann's report, is reflected in the insensitivity of the reaction to free radical donors and inhibitors.

SCHEME 28: Hoffmann's bromination of 2-methoxypropene.



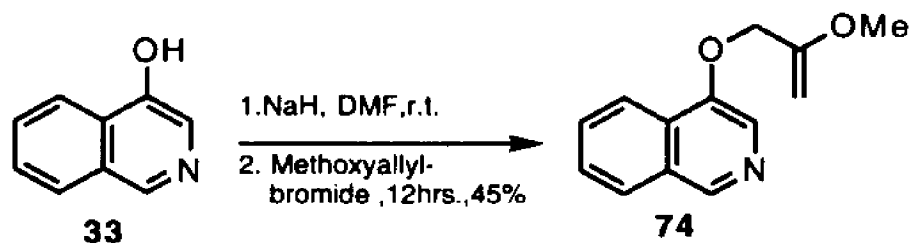
Although further experiments involving free radical donors and inhibitors to ascertain the ionic nature of the process were not carried out in the case of 2-(tert-butyldimethylsilyloxy)propene, it appears nonetheless that Hoffman's observations and explanation provide a reasonable account for the observed mixture of products. As the allylic bromination route proved unsuitable for the synthesis of the desired silyl vinyl ether **63**, we turned our attention to the synthesis of 3-bromo-2-methoxypropene **73** (scheme 29) as the means of introducing the masked carbonyl of the 3-appendage of 4-hydroxyisoquinoline. According to published procedures,⁴⁷ methoxy allyl bromide **68** was obtained (scheme 29) by cracking 3-bromo-2,2-dimethoxypropene **73** over diisopropylethylammonium tosylate.

Scheme 29: The synthesis of Methoxy allylbromide.



As per our general protocol, alkylation of 4-hydroxyisoquinoline **33** with methoxyallyl bromide **68** provided 4-(2-methoxy-2-propenyloxy)isoquinoline **74** in 79 % crude yield (scheme 30).

Scheme 30: The synthesis of 4-(2-Methoxy-2-propenyloxy)isoquinoline.



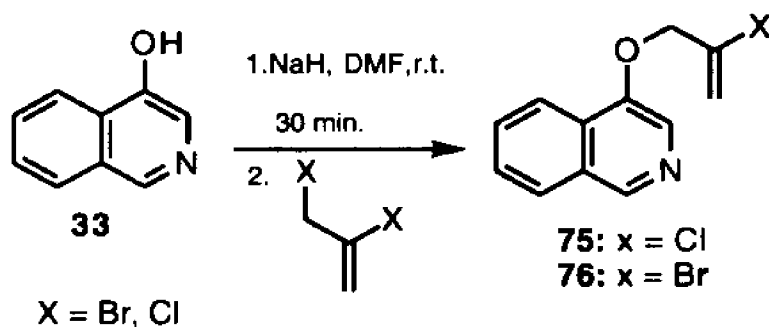
The 4-(2-Methoxy-2-propenyloxy)isoquinoline **74**, proved to be sensitive to silica gel as attempted purification by radial chromatography resulted in the isolation of only 23% of the pure product. Purification over a florisil column did not result in an improved yield of pure material. However, reasonable yields (60%) of **74** were finally obtained by column chromatography over basic alumina under a nitrogen atmosphere.

(iv) The synthesis of 4-(2-halo-2-propenyloxy)isoquinolines

Given the sensitivity of the enol ethers to the conditions of the Claisen rearrangement (vide infra) we decided to replace the vinylic methoxy group of **74** by a halide in the hope of obtaining a more stable isoquinolinyl ether. It was anticipated that the halide could be elaborated to the targeted Bradsher precursor following the Claisen rearrangement. Efforts to effect the coupling of 2,3-dichloropropene to 4-Hydroxyisoquinoline by means of Ando's KF-alumina method⁴⁸ were not successful due to the poor solubility of 4-hydroxyisoquinoline in the recommended solvents. Nevertheless, the desired halides could be

conveniently accessed by reacting the sodium or potassium salt of 4-hydroxyisoquinoline **33** with the appropriate 2,3-dihalopropene (scheme 31). Both the chloro **75e** and the bromo **76e** derivatives were thus synthesized.

Scheme 31: The synthesis of 4-(2-halo-2-propenyloxy)isoquinolines.



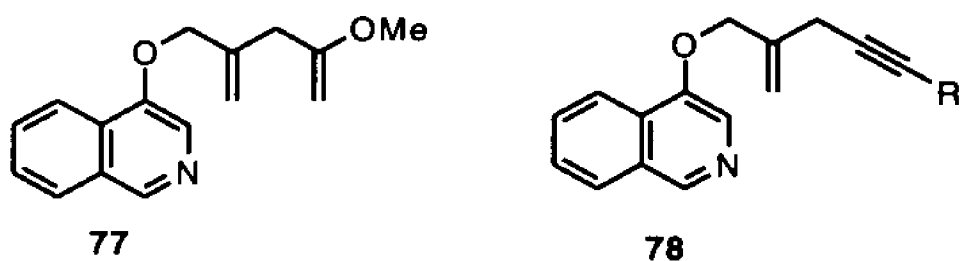
Although high yields of the reasonably pure (^1H NMR) crude chloro **75** and bromo **76** isoquinolinyl ethers (90 % and 78 % respectively) were obtained, purification proved again to be a problem as chromatography over florisil yielded only 39 % of pure 4-(2-chloro-2-propenyloxy)isoquinoline **75** while radial chromatography over silica gel furnished a mere 11 % of 4-(2-bromo-2-propenyloxy)isoquinoline **76**. Fortunately, in the context of our synthetic objectives, it was discovered that the crude ethers could suitably be rearranged to the Claisen products.

(v) The synthesis of 4-(2-methylene-5-trimethylsilyl-4-pentynyloxy)isoquinoline (106).

The premise for the synthesis of the isoquinolinyl ethers described thus far was the introduction of an extendable appendage at

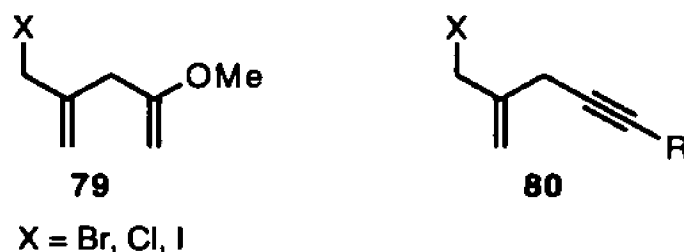
the 3-position of the isoquinoline nucleus via a Claisen rearrangement. Access to the Bradsher precursor would entail the attachment of a 3-carbon extension to the Claisen product. We have also investigated the ability of the Claisen rearrangement to position, at C-3, the complete 5-carbon appendage required in the Bradsher precursor. Such a Claisen rearrangement required isoquinolinyl ethers of type **77** or **78** (scheme 32) bearing either the required enol ether functionality or a masked precursor thereof.

Scheme 32: Isoquinolinyl ethers bearing a 5-carbon extension.



The synthesis of such isoquinolinyl ethers in turn requires access to allylhalides **79** or **80** (scheme 33).

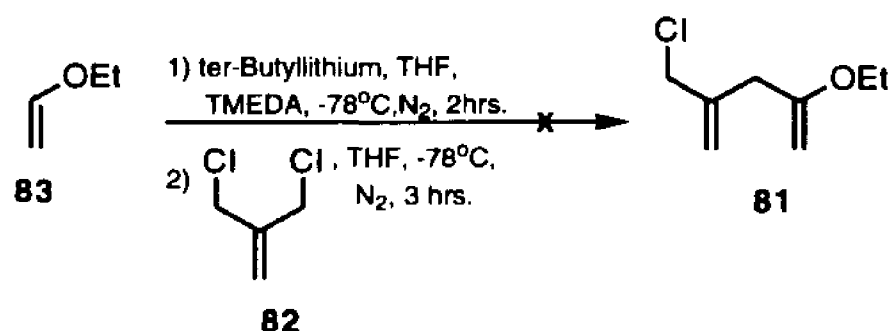
Scheme 33: Unconjugated 1,4-pentadienyl and pentaenynyl halides.



a) The synthesis of 2-alkoxy-4-(halomethyl) penta-1,4-diene.

Since the enol ether moiety tethered to the isoquinolinium nucleus by a 3-carbon chain is the main feature of the Bradsher precursor, we first considered the possibility of synthesizing 2-ethoxy-4-(chloromethyl) penta-1,4-diene **81** by coupling 3-chloro-2-(chloromethyl)-2-propene **82** to α -ethoxy vinyl lithium (from the deprotonation of ethyl vinyl ether **83**) (scheme 34).

Scheme 34: The coupling of α -ethoxyvinyl lithium to methallyl dichloride.



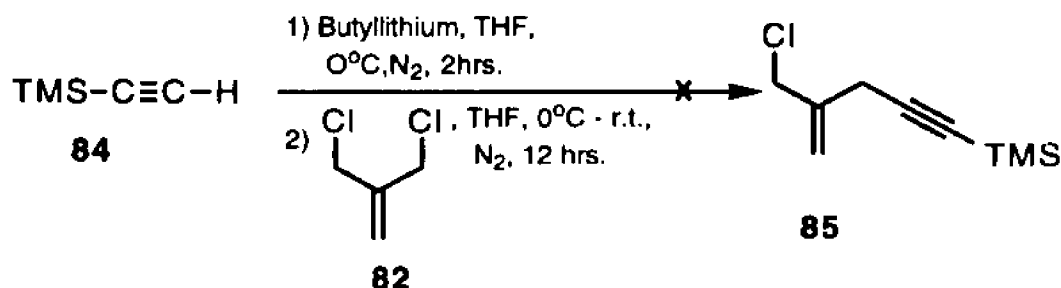
Boeckman's procedure was used as a guide and we generated⁴⁹ α -ethoxyvinyl lithium by treatment of ethyl vinyl ether **83** in THF with *tert*-butyllithium at -78°C . To the resulting solution was added a solution of 3-chloro-2-(chloromethyl)-2-propene **82** in THF. Stirring at -78°C did not result in the expected coupling nor did stirring from -78°C to room temperature achieve the desired aim. The cuprate⁵⁰ derivative obtained from the treatment of α -ethoxyvinyl lithium with cuprous iodide also failed to deliver the desired enol ether. The failure of these reactions is attributable to the low reactivity of 3-chloro-2-(chloromethyl)-2-propene **82** coupled with the instability of α -

ethoxyvinyl lithium and its cuprate derivative at temperatures above 0 °C. In fact, Boeckman estimates the decomposition temperature of the cuprate to be between -35 and -25 °C.⁵¹

b) The synthesis of the acetylenic precursor via coupling of methallyl dihalo derivatives

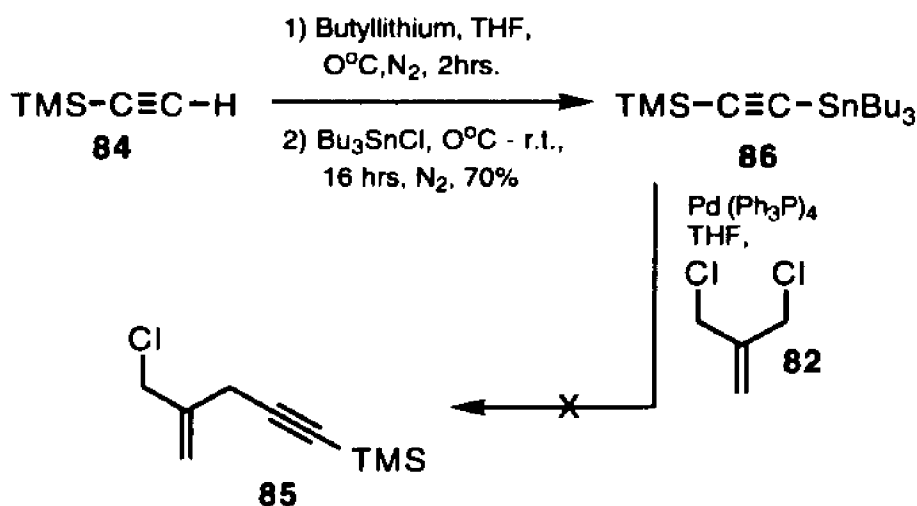
In order to circumvent the problem posed by the instability of α -ethoxyvinyl lithium at high temperatures, an alternative to the direct introduction of the enol ether was considered. In the event, the 2-carbon piece bearing the enol ether was replaced by an acetylenic precursor which could be converted to an enol ether at a later stage. In that hope, the coupling of lithio-2-trimethylsilyl acetylene (generated by the treatment of trimethylsilyl acetylene **84** with tert-butyl lithium) with 3-chloro-2-(chloromethyl)-2-propene **82** was attempted (scheme 35). The expected 1-(tert-butyldimethylsilyl)-4-(chloromethyl)-pent-4-ene-1-yne **85** could not be isolated. The very formation of the desired product under these conditions seems doubtful. It appears that even with a reagent that is stable at room temperature, 3-chloro-2-(chloromethyl)-2-propene proves too unreactive to undergo the desired coupling.

Scheme 35: The coupling of trimethylsilyl acetylide with methallyl dichloride.



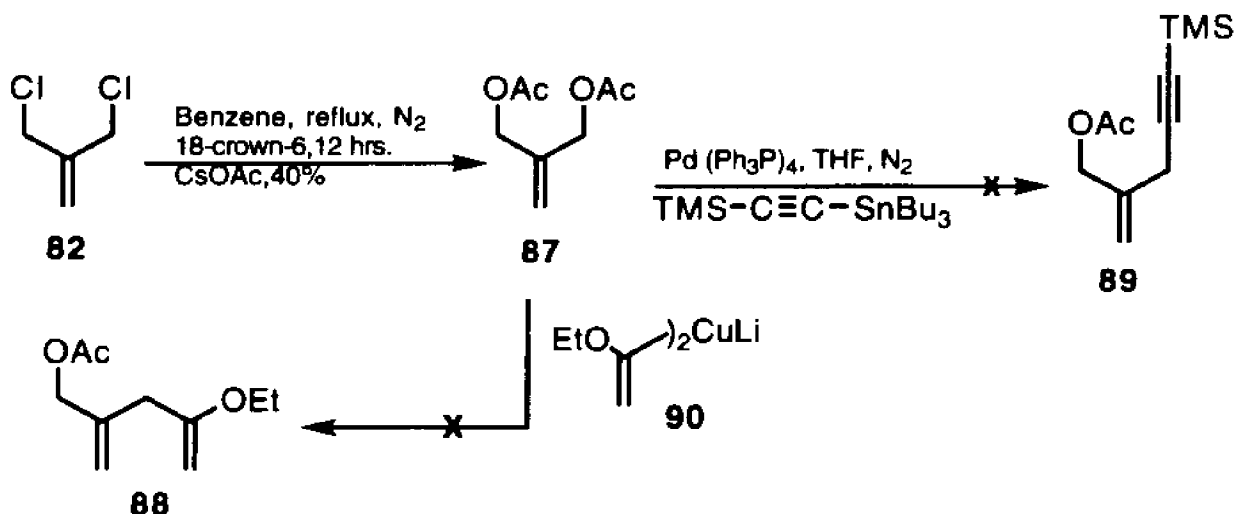
The failure of alternate routes to 1-(tert-butyldimethylsilyl)-4-(chloromethyl)-pent-4-ene-1-yne **85** also attests to the lack of reactivity of 3-chloro-2-(chloromethyl)-2-propene **82**. The tin derivative of trimethylsilylacetylene **84**, 1-trimethylsilyl-2-tributylstannyl acetylene **86**, was synthesized according to Logue's⁵² procedure (scheme 36) by treating 1-lithio-2-trimethylsilyl acetylene with tributyltinchloride. The successful course of this reaction supports our contention that it was the lack of reactivity of methallyl dichloride rather than a failure to generate the trimethylsilyl lithium acetylide which was responsible for the failure of the previously attempted coupling to 3-chloro-2-(chloromethyl)-2-propene **82**. The palladium mediated coupling of the stannyl derivative **86** to 3-chloro-2-(chloromethyl)-2-propene **82** using PdPh_4 was unsuccessful (scheme 36).⁵³ Here again, we believe that the lack of reactivity of the halide precluded the formation of the desired product.

Scheme 36: The coupling of trimethyl silyl tributyl stannyl acetylene with methallyl dichloride.



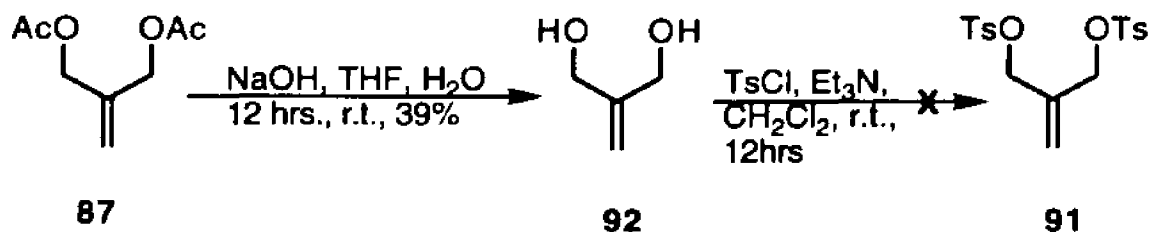
In search of a more reactive electrophile so as to facilitate the desired coupling, the diacetox derivative of 3-chloro-2-(chloromethyl)-2-propene **82**, 3-acetoxy-2-(acetoxymethyl)-2-propene **87** was synthesized by treating 3-chloro-2-(chloromethyl)-2-propene with two equivalents of cesium acetate in refluxing benzene (scheme 37). The diacetox compound was obtained in 40 % yield.

Scheme 37: Methallyl diacetate and its coupling reactions.



As with the dichloro compound, attempted coupling of diacetoxymethallyl derivative **87** to the cuprate of α -ethoxyvinyl lithium **90** failed to deliver the desired enol ether **88**. Efforts to effect the palladium mediated displacement of the allylic acetate by our acetylenic tin derivative **86** also met with failure as no compound corresponding to enyne **89** could be isolated. In the hope that the ditosyloxy derivative **91** might prove a valuable electrophile in the coupling schemes that were being investigated, its synthesis was attempted. For this purpose, the diacetoxymethallyl compound was hydrolyzed to the diol **92** (scheme 38). Unfortunately, the ditosylate could not be obtained by treatment of the diol with tosyl chloride.

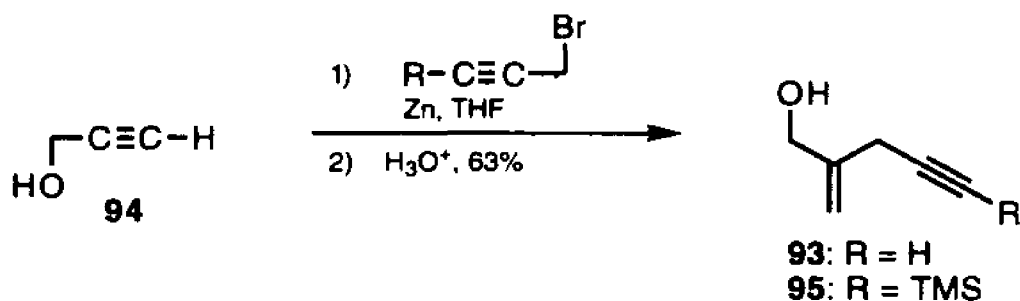
Scheme 38: The synthesis of the ditosyloxy derivative of methallyl dichloride.



c) The synthesis of the acetylenic precursor via addition of propargylic bromides to propargyl alcohol.

The synthesis of β -enynes of type **93** has been realized in a French laboratory by the addition of propargylic zinc species to propargyl alcohol **94** (scheme 39).⁵⁴ We were attracted to these structures since an anticipated uneventful conversion of the allylic alcohol into a leaving group would provide a suitable electrophile for coupling to 4-hydroxyisoquinoline.

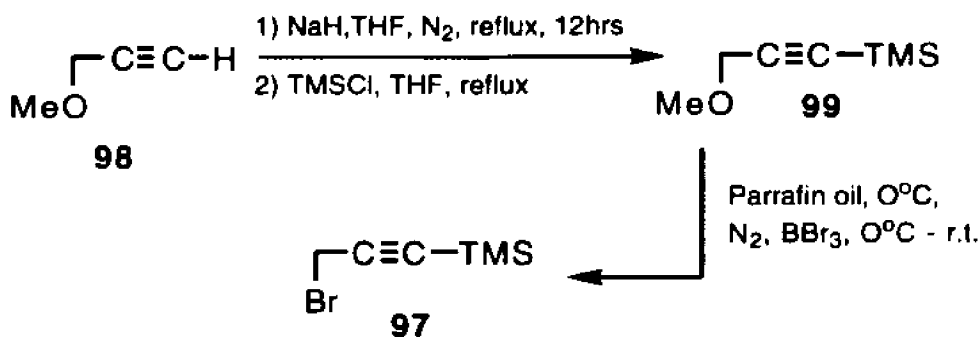
Scheme 39: The synthesis of unconjugated enynes from propargyl alcohol.



We therefore considered the extension of the French methodology to the synthesis of the novel 1-(trimethylsilyl)-4-(hydroxymethyl)-pent-4-ene-1-yne **95** (scheme 40). The proposed transformation involved

the addition of the zinc anion from 1-trimethylsilylpropargyl bromide to propargyl alcohol. The synthesis of 1-trimethylsilylpropargyl bromide **97** can be accomplished in two ways. The first approach (scheme 41) involves the protection of methyl propargyl ether **98** as the trimethylsilyl derivative **99** by treatment with potassium hydride followed by the capture of the anion generated with trimethylsilylchloride.

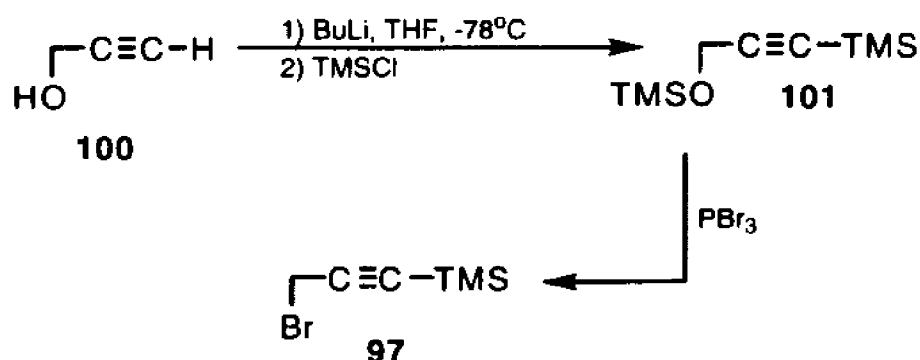
Scheme 41: The synthesis of trimethylsilylpropargyl bromide.



According to the published procedure the conversion of 1-trimethylsilyl propargyl ether **99** to 1-trimethylsilyl propargyl bromide **97** is carried out by exposing the ether to BBr₃ in mineral oil followed by the distillation of the product from the reaction mixture.⁵⁵ Although the yields reported are in the order of 70 % we never succeeded in isolating above 40 % yields of the desired 1-trimethylsilylpropargylbromide in a process that shows quite a propensity towards polymerization. Even the tedious process of insuring complete saturation of the mineral oil prior to its use as the reaction medium did not result in an improvement of the yield of isolated product.

A more convenient approach to the desired 1-trimethylsilylpropargylbromide **97** (scheme 42) consists in the bis-silylation of propargyl alcohol **100** followed by treatment of the silyl derivative **101** with phosphorus tribromide.

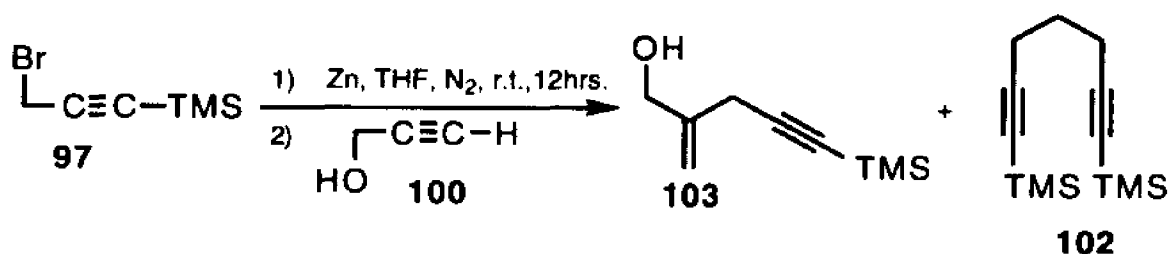
Scheme 42: The synthesis of trimethylsilyl propargyl bromide.



With the 1-trimethylsilyl propargyl bromide **97** in hand, we studied the coupling of the zinc derivative thereof to propargyl alcohol. The French procedure⁵⁶ calls for the formation of the zinc derivative by treating the propargyl bromide with zinc metal followed by the addition of propargyl alcohol. In our hands (scheme 43), such conditions resulted in the formation of diyne **102** arising from self coupling of the propargylbromide. The crude reaction mixture consisted of three fractions that could not be separated by distillation. Nevertheless a tedious separation on florisil eluted with petroleum ether proceeding with extensive decomposition of material allowed us to isolate a small amount of the desired enyne alcohol **103** in addition to the unwanted dimer. Fast and complete conversion of the bromide to the zinc anion could not be achieved so as to prevent dimerization from occurring. The

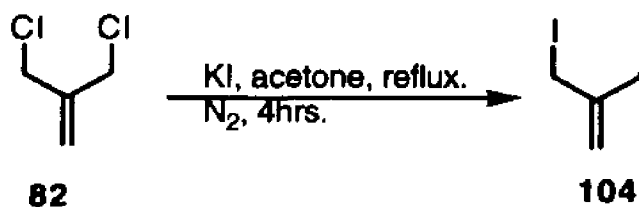
dismal yield of the desired allyl alcohol did not permit us to carry out the anticipated conversion of the hydroxyl to a leaving group followed by the coupling of the resulting electrophile to 4-hydroxyisoquinoline.

Scheme 43: The Zinc mediated addition of trimethylsilylpropargyl bromide to propargyl alcohol.



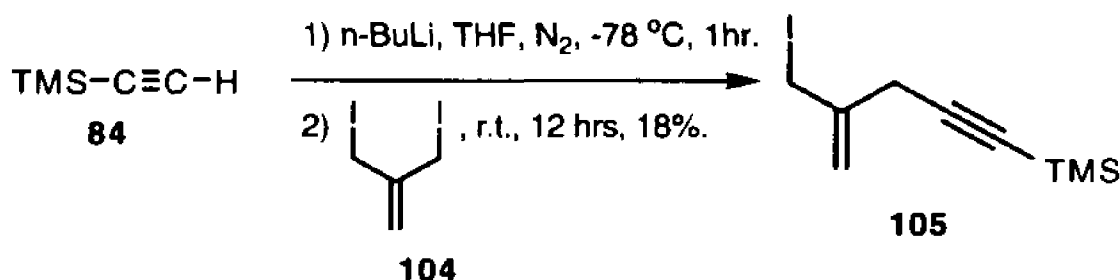
Access to the desired acetylenes **80** (scheme 33) required that the problem posed by the low reactivity of 3-chloro-2-(chloromethyl)-2-propene **82** be circumvented. In the event, 3-chloro-2-(chloromethyl)-2-propene was converted to 3-iodo-2-(iodomethyl)-2-propene **104** according to Doerr's⁵⁷ procedure by refluxing it with potassium iodide (scheme 44).

Scheme 44: The synthesis of methallyl diiodide.

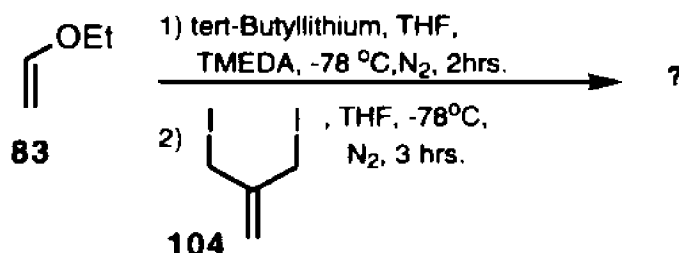


The reaction of 3-iodo-2-(iodomethyl)-2-propene **104** with 0.5 equivalent of 1-lithio-2-trimethylsilyl acetylene (scheme 45) gave the required 2-iodomethyl-5-trimethylsilyl-penten-1-yne-4. **105** in 18 % yield. The iodide could be purified from excess 3-iodo-2-(iodomethyl)-2-propene **104** by column chromatography (silica gel eluted with petroleum ether).

Scheme 45: The synthesis of the acetylenic side chain.



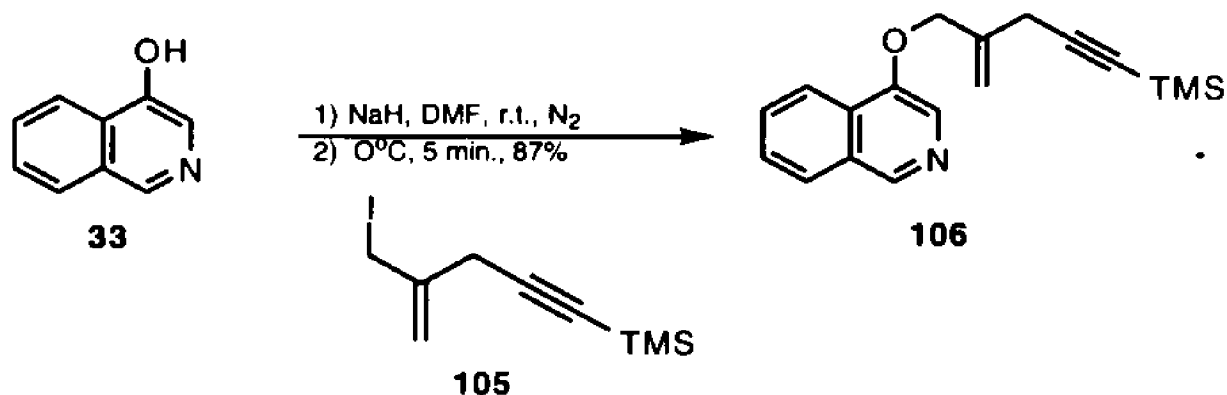
The reactivity of 3-iodo-2-(iodomethyl)-2-propene **104** in the successful coupling to 1-lithio-2-trimethylsilyl acetylene renewed our hope that the enol ether moiety required in the Bradsher precursor could be introduced directly. Unfortunately, the product obtained in the coupling of α -ethoxyvinyl lithium to the diiodo propene **104** (scheme 46) proved to be too unstable for characterization.

Scheme 46: The reaction of α -ethoxyvinyl lithium with methallyl diiodide.

d) The succesful synthesis of 4-(2-methylene-5-trimethylsilyl-4-propenyloxy)isoquinoline

Addition of 2-iodomethyl-5-trimethylsilyl-penten-1-yne-4 **105** to a DMF solution of the 4-hydroxyisoquinoline salt **59** at 0°C resulted in its instantaneous conversion to the desired 4-(2-methylene-5-trimethylsilyl-4-pentynyloxy)isoquinoline **106** in 56% yield (scheme 47). As expected, the coupling of the allyl iodide occurs much more readily than that of the chlorides and bromides previously studied. The iodo couplings took place at room temperature over a period of 30 minutes to an hour. Overnight stirring was required to effect the coupling of methoxyallyl bromide.

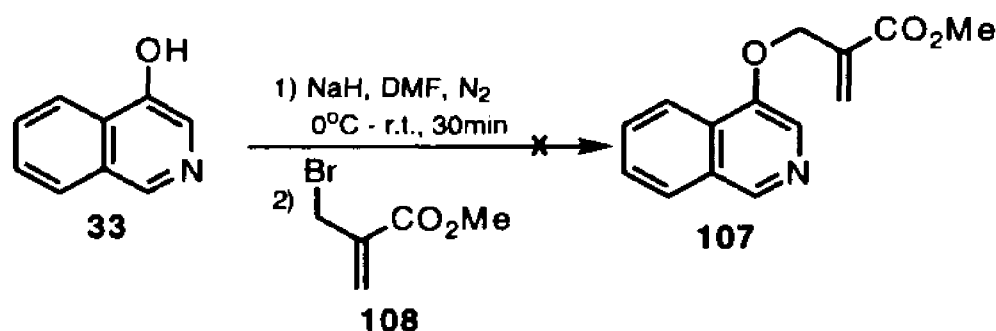
Scheme 47: The synthesis of 4-(2-methylene-5-trimethylsilyl-4-pentynyloxy)-isoquinoline.



(vi) The attempted synthesis of the 4-(2-carbomethoxy-2-propenyloxy)-isoquinoline.

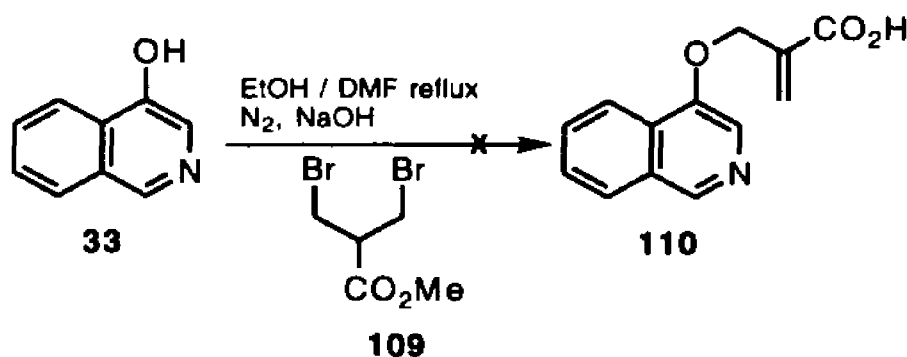
The synthesis of 4-(2-Carbomethoxy-2-propenyloxy)isoquinoline **107** was envisaged as an alternate option to the Bradsher precursor which could arise by elaboration of the carbomethoxy appendage present in the side chain. Reliance on our sodium hydride methodology (scheme 48) followed by the addition of methyl-(2-bromomethyl)acrylate **108** proved unsuccessful as we failed to isolate the desired isoquinolinyl ether **107** from the complex reaction mixture obtained.

Scheme 48: The attempted synthesis of 4-(2-carboethoxy-2-propenyloxy)-isoquinoline.



A circuitous route (scheme 49) to the desired ester required the coupling of 4-hydroxyisoquinoline **33** to Methyl-β,β'-dibromoisobutyrate **109** in a tandem alkylation dehydrobromination with attendant ester hydrolysis to generate the acid **110**.⁵⁸ No reaction was observed under these conditions.

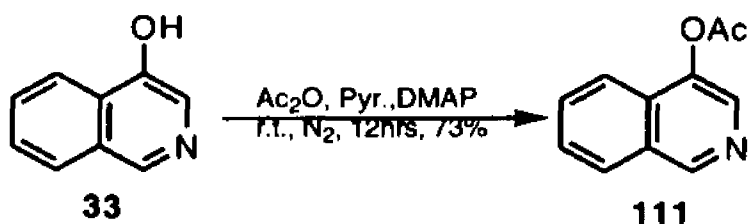
Scheme 49: The attempted synthesis of 4-(2-propenyloxy-2-carboxylic acid)-isoquinoline.



(vii) The synthesis of 4-acetoxyisoquinoline.

The conversion of 4-hydroxyisoquinoline **33** to the 4-acetoxy derivative **111** was effected under the normal acetylation conditions by stirring a pyridine solution of the starting material with acetic anhydride and DMAP for 12 hours (scheme 50). The pure acetate **111** was obtained in 73 % yield following radial chromatography.

Scheme 50: The synthesis of 4-acetoxyisoquinoline.

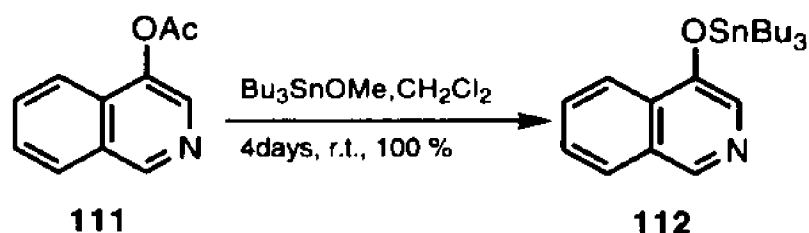


(viii) The synthesis of 4-(tributylstannyloxy)isoquinoline.

In an effort to increase the nucleophilicity of the 4-hydroxyl group without recourse to the sodium hydride treatment we decided to synthesize the stannyl derivative of 4-hydroxyisoquinoline. The desired 4-(tributylstannyloxy)isoquinoline **112** is most conveniently synthesized by treatment of 4-acetoxyisoquinoline **111** with exactly one equivalent of tributyl tin methoxide in dichloromethane (scheme 51). The reaction mixture was stirred at room temperature for 24 hours. In addition to the TLC evidence which indicates the disappearance of the starting material and the formation of a slower moving spot which decomposes on silica gel the ^1H NMR spectrum proved quite diagnostic in ascertaining the formation of the stannyl product. The spectrum clearly reveals the disappearance of the methoxy

and acetoxy peaks of the starting material and the presence of a tributyl stannyl group with an integration matching that of the isoquinolinyl protons. The product obtained in quantitative yield was of very high purity, indicating that the reaction probably proceeds so as to generate the volatile methyl acetate which is removed *in vacuo*. along with the solvent

Scheme 51: The synthesis of 4-tributylstannyloxyisoquinoline.



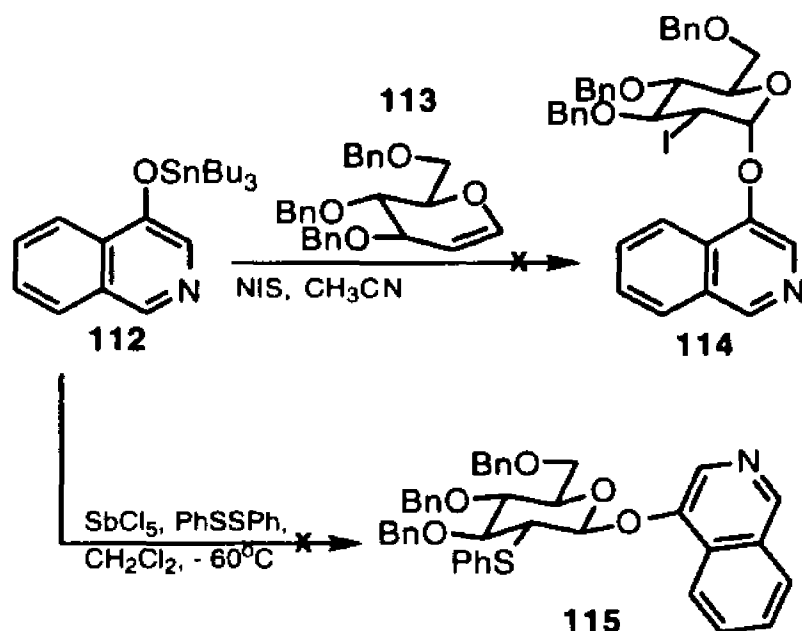
(ix) The synthesis of 4-Isoquinolinylglycosides.

a) Attempted synthesis by the addition of 4-(tributylstannyloxy)isoquinoline to glycals.

Thiem's⁵⁹ NIS method for the addition of nucleophiles to glycal was applied in the attempted coupling of 4-(tributylstannyloxy)isoquinoline 112 to 3,4,6-tetra-O-benzyl-glucal 113 (scheme 52). The reaction was not successful as tedious chromatography failed to yield any compound corresponding to the desired α -isoquinolinyl glycoside 114. Recourse to Franck's phenylbis(phenylthio)sulfonium salt methodology⁶⁰ (scheme 52) equally failed to effect the desired coupling leading to β -glycoside 115.

The failure of these two proven glycosidation methods is attributable to the poor solubility of the isoquinoline species.

Scheme 52: Glycosidation reactions with 4-tributylstannyloxy isoquinoline.

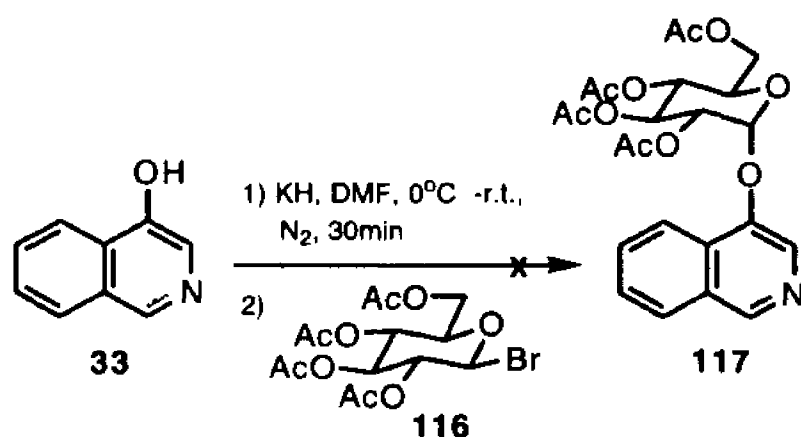


b) attempted synthesis by our general protocol.

Basing our approach on literature precedents for the synthesis of phenyl glycosides⁶¹ and following our well established procedure for the derivatization of 4-hydroxyisoquinoline, we attempted its coupling to bromo-2-3-4-6-tetraacetyl-D-glucoside **116** (scheme 53). The starting isoquinoline **33** was treated with potassium hydride in DMF followed by the addition of the glucosyl bromide **116**. No reaction was

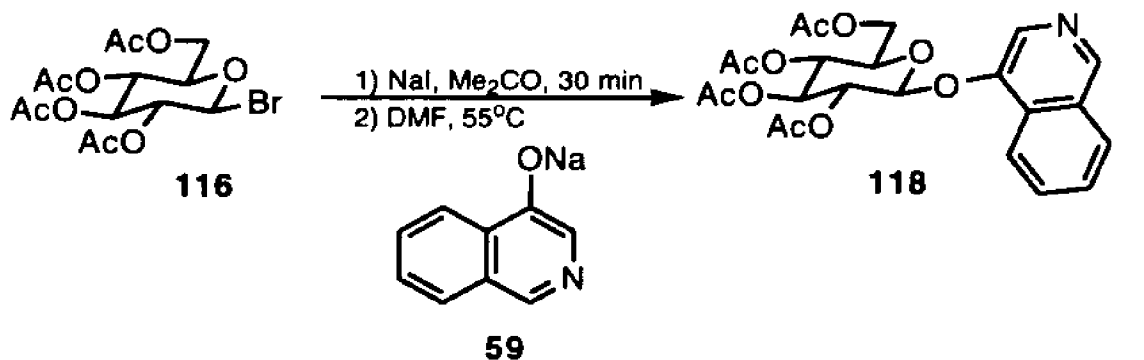
observed under these conditions. Refluxing the reaction mixture in DMF and increasing the reaction time failed to generate the desired isoquinolinyl glycoside **117**.

Scheme 53: Nucleophilic displacement on glycosyl bromides.



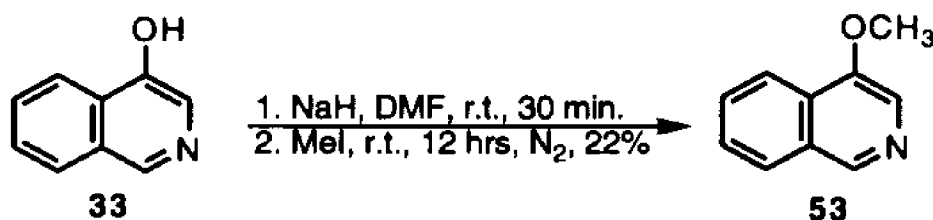
In his synthesis of 2-acetoxy-3,4,6-tri-O-acetylglucal Ferrier⁶² had effected the conversion of tetra-O-acetylglucosyl bromide to the iodo derivative prior to the dehydrohalogenation step to the glucal. Thus, 2,3,4,6-tetraacetylglucosyl bromide **116** was converted to the iodo derivative (scheme 54) by treatment with sodium iodide in acetone. Without isolation of the glucosyl iodide the acetone solution was added to a DMF solution of the sodium salt of 4-hydroxyisoquinoline and the reaction was heated at 55°C for three days. Upon work up and purification quite dismal yields of the desired 4-isoquinolinyl- 2,3,4,6-tetraacetyl-glucoside **118** could be isolated.

Scheme 54: The synthesis of 4-isoquinoliny glycosides.

**(x) The synthesis of 4-methoxyisoquinoline**

The conversion of 4-hydroxyisoquinoline to its methyl ether **53** proceeds in rather poor yields. The literature report⁶³ which describes the use of diazomethane for such functionalization failed to report the yield of the isolated material (see scheme 20). Application of our standard protocol with methyl iodide as the electrophile (scheme 55) resulted in the isolation of only 28 % of the expected ether. Competing nitrogen alkylation and the instability of the product to silica gel can be evoked to account for the low yields observed.

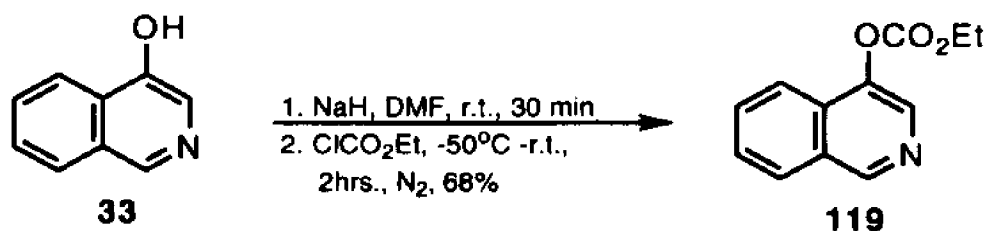
Scheme 55: The synthesis of 4-methoxyisoquinoline.



(xi) The synthesis of ethyl 4-isoquinolinyl carbonate

A slight modification of our protocol proved necessary in order to obtain reasonable yields of the desired ethoxycarbonyl derivative **119** of 4-hydroxyisoquinoline (scheme 56). The addition of ethyl chloroformate to a solution of 4-hydroxyisoquinoline at 0 °C followed by stirring at room temperature resulted in only 7 to 20 % yield of the carbonate. Better results (68 % yields) were obtained by adding the electrophile at - 50 °C. In general the yields varied from 30 to 68 %. The appearance of the ethyl triplet and quartet in the ¹H nmr spectrum was used to characterize the product.

Scheme 56: The synthesis of 4-ethoxycarbonyloxy isoquinoline.

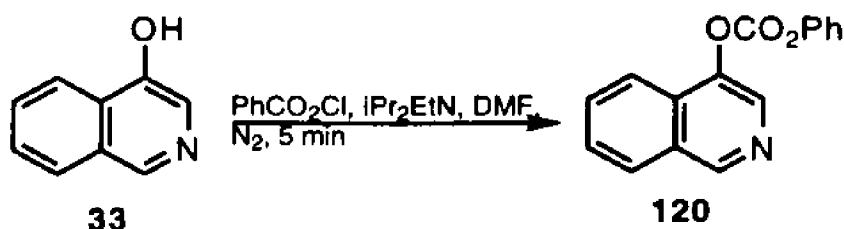


(xii) The synthesis of phenyl 4-isoquinolinyl carbonate

In a departure from the procedure employed for the synthesis of the ethylcarbonate derivative **119** (scheme 56) which proved unsuccessful in this instance, our approach to the phenyl derivative **120** involved the addition of phenyl chloroformate to a DMF solution of 4-

hydroxyisoquinoline containing 1 equivalent of Hunig's base (scheme 57). The desired phenylcarbonate **120** was obtained in 22 % yield.

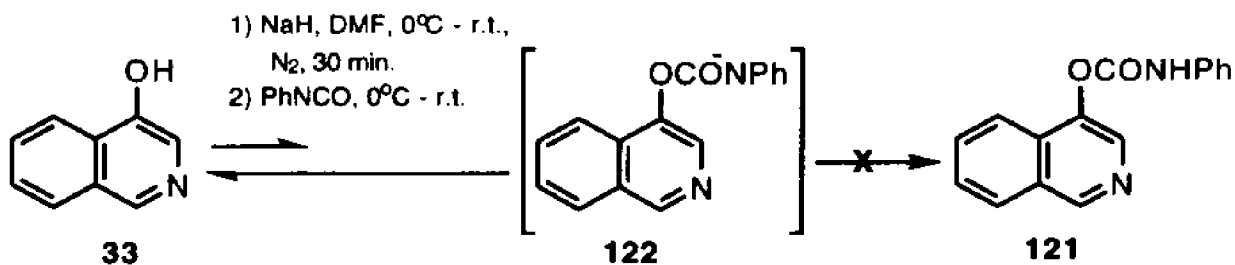
Scheme 57: The synthesis of 4-(PhenylCarbonate)isoquinoline



(xiii) The attempted synthesis of the 4-(Phenylcarbamoyl)-isoquinoline.

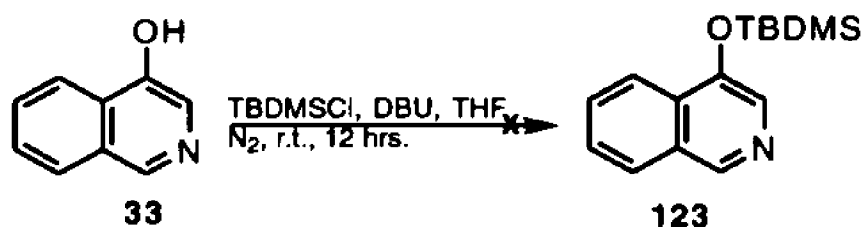
In an effort to accomplish the synthesis of 4-(Phenylcarbamoyl)-isoquinoline **121** various reaction conditions were examined. The initial attempt, run according to our general procedure, yielded only diphenyl urea upon workup (scheme 58). All efforts, including prolonged reaction time, temperature variations, and the use of a catalyst (DMAP), failed to generate the desired carbanilide **121**. Our failure to isolate any product of coupling may be due to a thermodynamically favorable reversal of the adduct **122** resulting from attack of the isoquinolinyl nucleophile on phenylisocyanate (scheme 58).

Scheme 58: The synthesis of 4-(phenylcarbamate)isoquinoline.



(xiv) The attempted synthesis of 4-tert-butyl-
dimethyldimethylsilyloxyisoquinoline.

In the context of the silylation of 3-(2-methyl-2-propenyl)-4-hydroxyisoquinoline **143** (vide infra), which could only be achieved after much experimentation, it became of interest to ascertain whether the difficulties associated with such a derivatization were due principally to steric hindrance induced by the 3-substituent. For this purpose the silylation of 4-hydroxyisoquinoline itself was attempted. It was discovered that under the standard silylation conditions ⁶⁴ the silylation of 4-hydroxyisoquinoline itself could not be achieved. Variations of reaction parameters were unsuccessful in generating 4-(tert-butyl-*dimethylsilyloxy*)isoquinoline **123** (scheme 59).

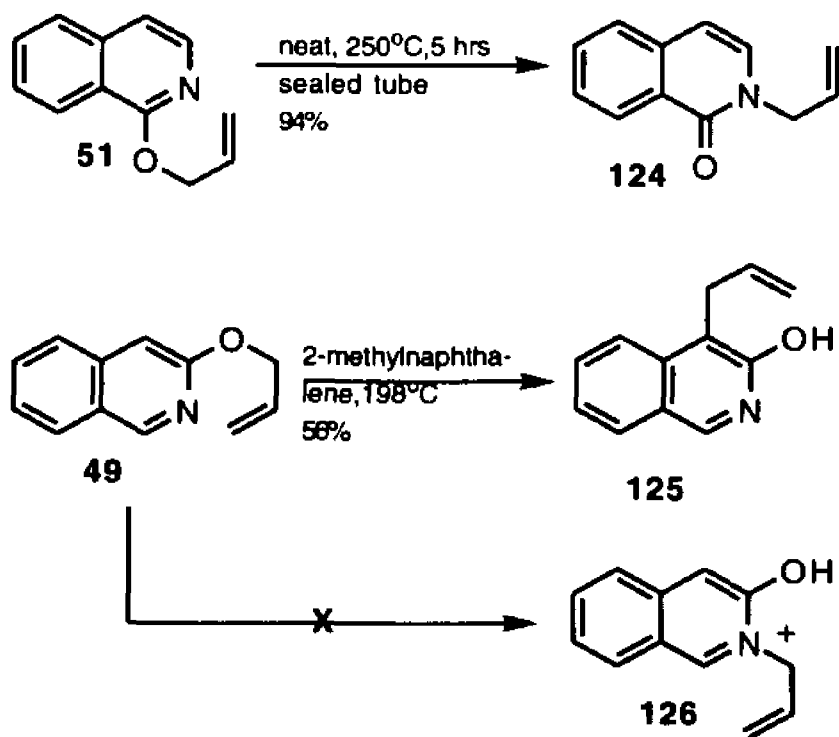
Scheme 59: The synthesis of 4-(tert-butyl-*dimethylsilyloxy*)isoquinoline.

CHAPTER 3: THE CLAISEN REARRANGEMENT OF ALLYLOXYISOQUINOLINES

1) The Claisen rearrangement of 1- and 3-allyloxyisoquinolines.

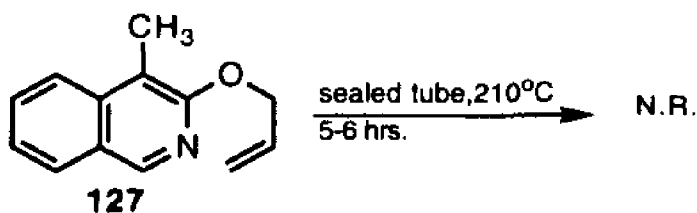
Previous work on the Claisen rearrangement of isoquinolines involved the 1- and 3- allyloxyisoquinoline derivatives **51** and **49** (scheme 60).⁶⁵

Scheme 60: The Claisen rearrangement of 1 and 3- allyloxyisoquinolines.



Win and Tieckelmann observed that when neat 1-allyloxyisoquinoline **51** was heated in a sealed tube for 5 hours at 250 °C it rearranged to the N-allyl-1-isoquinolinol **123** in 94 % yield (scheme 60).⁶⁶ Under sealed tube conditions, the Claisen rearrangement of 3-allyloxyisoquinoline **49** (scheme 9) in 2-methylnaphthalene took place at 190 °C.⁶⁷ The product, 4-allyl-3-isoquinolinol **125** was isolated in 56% yields along with 34% of unrearranged starting material. The competing migration to the nitrogen terminus did not occur since the 3-hydroxy-N-allyl-isoquinolinium salt **126** was not observed. These results, are in accordance with the observations in the naphthalene series in which the thermal rearrangement is regioselective and exhibits a preference for one migration terminus.⁶⁸ In fact, when the preferred migration terminus in the isoquinoline is blocked, as in the case of 4-methyl-3-allyloxyisoquinoline **127** (scheme 61), heating at 210 °C in a sealed tube for 5 to 6 hours resulted only in the recovery of the starting material (scheme 61).⁶⁹

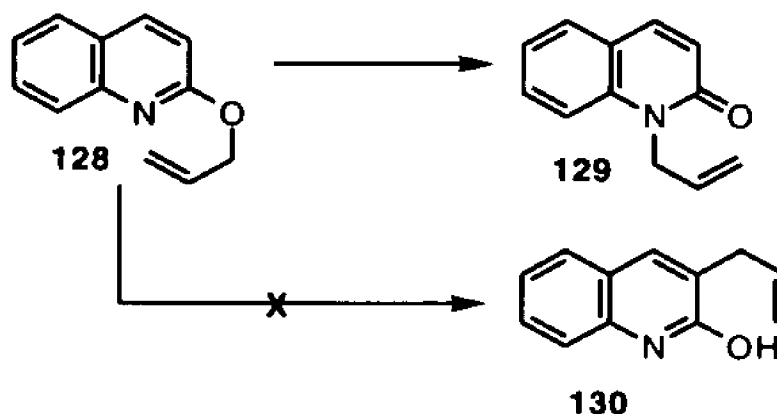
Scheme 61: Interfering with the preferred migration terminus in isoquinoline Claisen rearrangements.



The regioselective course of the migration is also exhibited in the quinoline series (scheme 62) in which 2-allyloxyquinoline **128** rearranges exclusively to the N-allyl-2-quinoline **129**.⁷⁰ Competing

rearrangement to C3 leading to 2-hydroxy-3-allylisoquinoline **130** was not observed.

Scheme 62: The Claisen rearrangement of quinoline ethers.



Similarly, under Claisen conditions, the rearrangement of 7-allyloxyquinoline **131** resulted in the exclusive formation of 8-allyl-7-quinolinol **132** (scheme 63).⁷¹

Scheme 63: The Claisen rearrangement of 7-allyloxyquinoline.

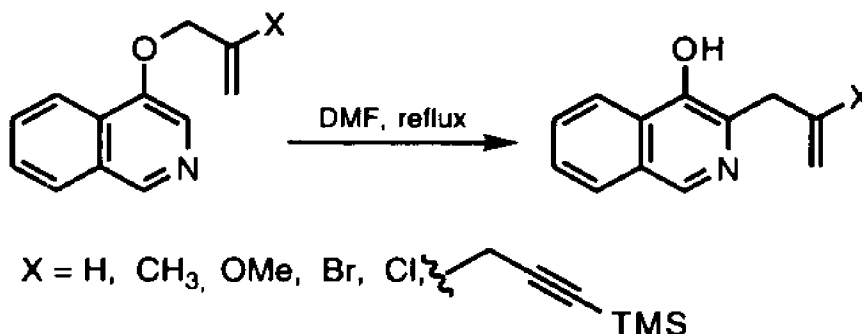


2) the Claisen rearrangement of 4-allyloxy isoquinolines

The various Claisen rearrangements that have been explored were chosen so as to introduce functionalities amenable to chemistry leading

to the Bradsher precursor **27**. These Claisen rearrangements are summarized in scheme 64.

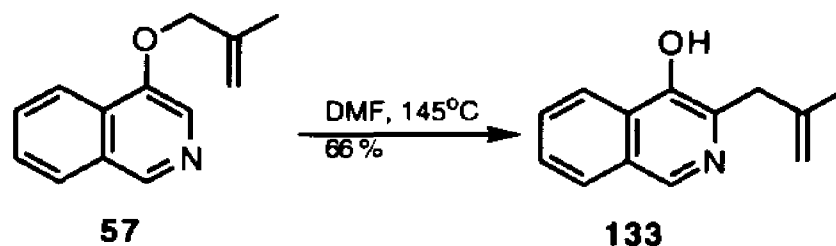
Scheme 64: Summary of the Claisen rearrangements of 4-allyloxyisoquinolines.



(i) The Claisen rearrangement of 4-(2-propenyloxy) isoquinoline

As per the protocol employed by Win and Tieckelman,⁷² when neat 4-(2-methyl-2-propenyloxy) **57** was heated directly at 200 °C in a flask under a nitrogen atmosphere, tlc analysis revealed a streak of products. Under more careful conditions, however, with the heating carried out progressively from 175 to 200 °C over a 1 hour period, a small amount of the desired Claisen product, 4-(2-Methyl-2-propenyloxy)isoquinoline **133** (scheme 65) could be isolated following radial chromatography.

Scheme 65: The Claisen rearrangement of 4-(2-methyl-2-propenyloxy)-isoquinoline

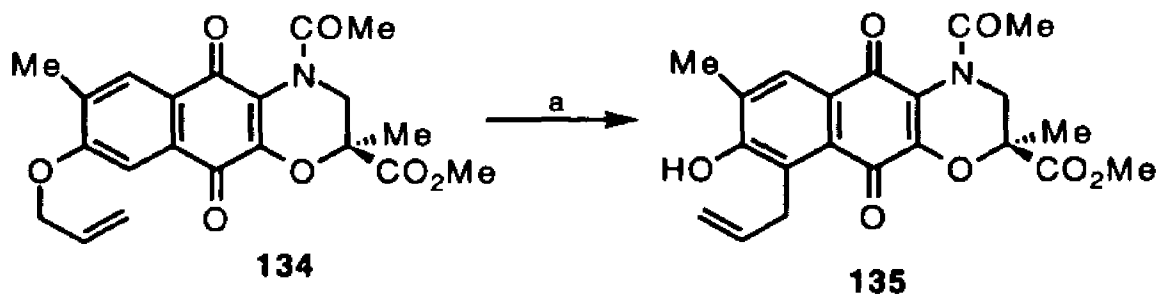


We have found that the Claisen rearrangement of 4-(2-methyl-2-propenyloxy)isoquinoline does not require the sealed tube conditions prescribed by Win and Tieckelmann.⁷³ The rearrangement is most cleanly effected by carrying out the reaction in the presence of a solvent (scheme 65). Although both decalin and DMF were found to be suitable, DMF became the solvent of choice since it allowed for a more expedient work up and afforded slightly higher yields than decalin. The average yields were 68% in decalin and 74% in DMF. The disappearance, in the product nmr spectrum, of the singlet corresponding to H3 of the starting material provided unmistakable evidence for the successful course of the Claisen rearrangement.

It is known that under conditions of Lewis acid catalysis, the high temperatures normally required for the Claisen of allyl aryl ethers can be substantially lowered.⁷⁴ Kosikowski,⁷⁵ for example, reports that the high temperatures required for the aromatic Claisen rearrangement of **134** (scheme 67) resulted in extensive decomposition of the allyl aryl ether. On the other hand, subjecting the corresponding hydroquinone to six equivalents of boron trichloride resulted in a clean and efficient (94% yield) rearrangement to quinone **135** - where reoxidation of the

initial hydroquinone product to the quinone occurred during work up. The reaction took place between -23°C and room temperature.

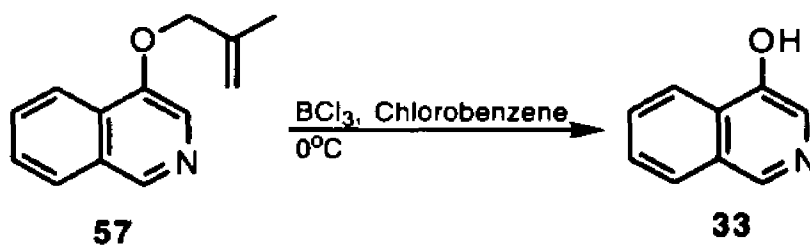
Scheme 67: Kozikowski's Lewis acid catalyzed Claisen rearrangement.



a = 1. Na_2SO_3
 2. BCl_3 , Chlorobenzene
 CH_2Cl_2 , -23°C -r.t.

Unfortunately, attempts to carry out the BCl_3 -catalyzed rearrangement of 4-propenyl ether **57** (scheme 68) resulted in the cleavage of the propenyl ether.⁷⁶

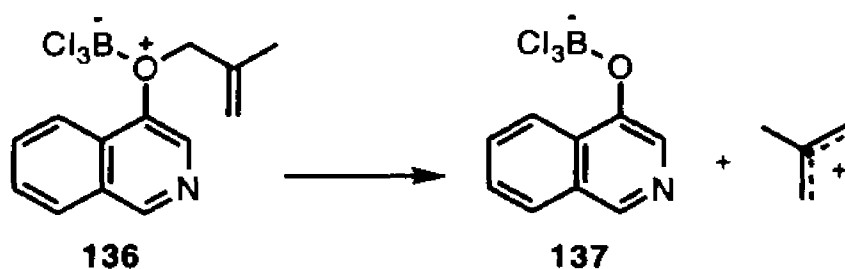
Scheme 68: The cleavage of the isoquinolinylnyl ethers under Lewis acid conditions



The cleavage of the alkenyl moiety can be explained by evoking the prior complexation of a mole of boron trichloride to the ether oxygen,

followed by the extrusion of the stabilized allyl cation from complex **136** generate the boronate ester **137** (scheme 69).

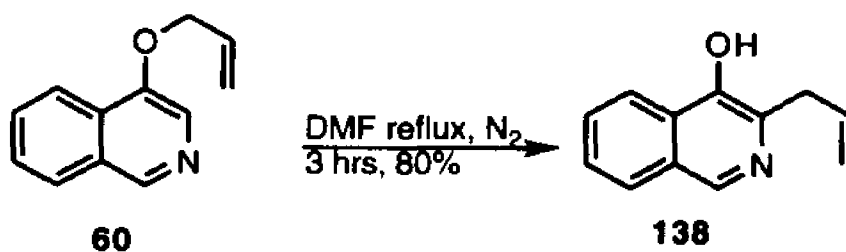
Scheme 69: Mechanism for the Lewis acid cleavage of 4-(2-methyl-2-propenyloxy)isoquinoline.



(ii) The Claisen rearrangement of 4-(2-propenyloxy)isoquinoline

The Claisen rearrangement of 4-(2-propenyloxy)isoquinoline **60** (scheme 70) proceeded smoothly in refluxing DMF (192 °C bath temperature) and the 3-(2-propenyl)-4-hydroxyisoquinoline product **138** was obtained in 90% crude yield (scheme 70).

Scheme 70: The Claisen rearrangement of 4-(2-propenyloxy)-isoquinoline.

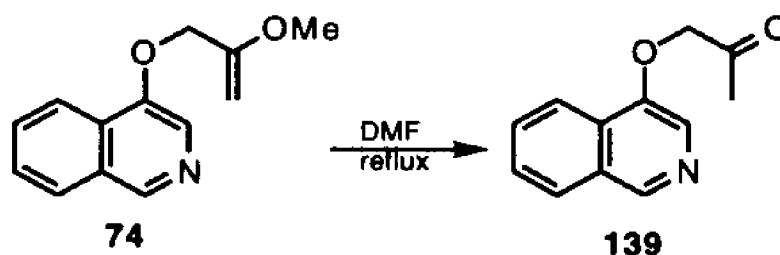


(iii) The Claisen rearrangement of 4-(2-methoxy-2-propenyloxy)isoquinoline

The crude enol ether, 4-(2-methoxy-2-propenyloxy)isoquinoline **74**, obtained by the coupling of 4-hydroxyisoquinoline with 2-methoxy-3-bromopropene **68** (scheme 29), displayed a very clean nmr. Yet, subjecting it to the Claisen rearrangement, after the fashion of the vinylhalide Claisen reactions (*vide infra*), resulted only in the isolation of the ketone resulting from the thermolysis of the enol ether moiety (scheme 71).

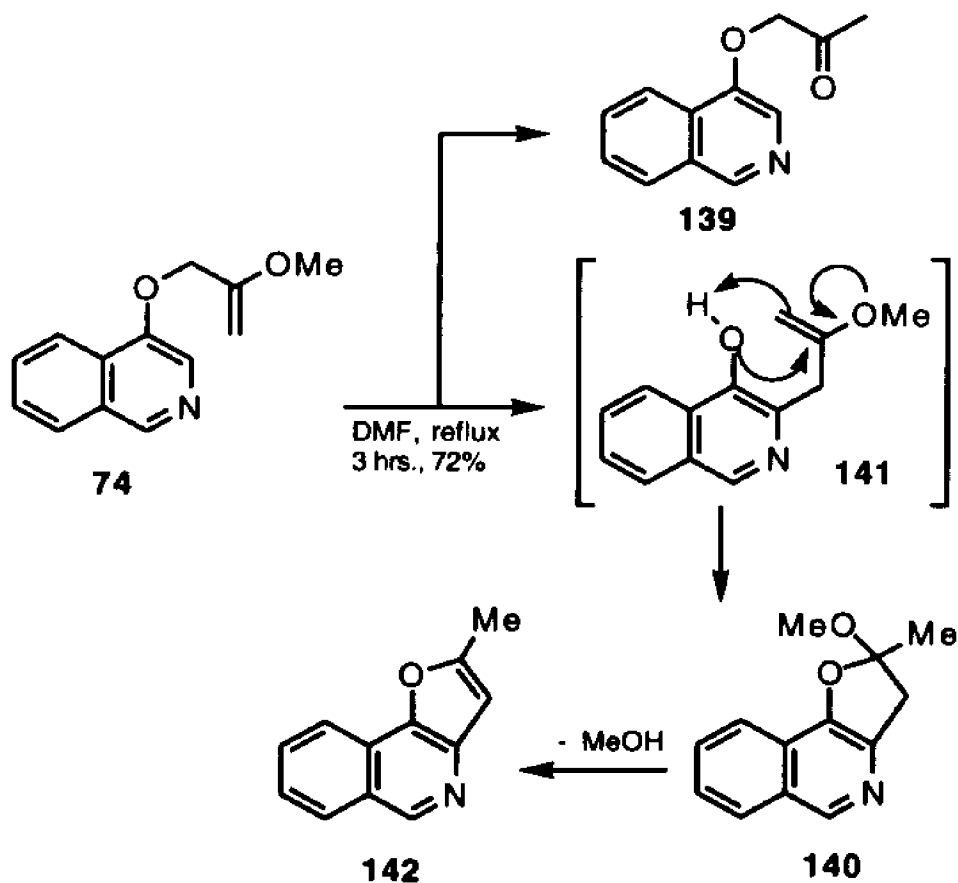
In the hope of promoting an anionic "oxy-Claisen", the hydrolysis product, ketone **139** was treated with LDA at - 78 °C and the reaction mixture allowed to come to room temperature. The nmr of the reaction mixture did not display the signals corresponding to the 3-(2-oxo-propyl)-4-hydroxyisoquinoline **143** (scheme 73) expected from the Claisen rearrangement.

Scheme 71: The Claisen rearrangement of the crude 4-(2-methoxy-2-propenyloxy)-isoquinoline.



We have found that material of very high purity is required for the Claisen rearrangement of 4-(2-methoxy-2-propenyloxy)isoquinoline **74** and that catalytic amounts of acidic impurities are sufficient to effect its thermolysis to ketone **139**. The Claisen rearrangement of pure 4-(2-methoxy-2-propenyloxy)isoquinoline **74**, when carried out in DMF, at 150 °C for 3 hours, proceeded to a 72% combined yield of a 3:1 mixture of starting material and ketal **140** (scheme 72). The ketal resulted from the cyclization of the Claisen product **141** initially formed. A small amount of the hydrolyzed product **139** was also identified.

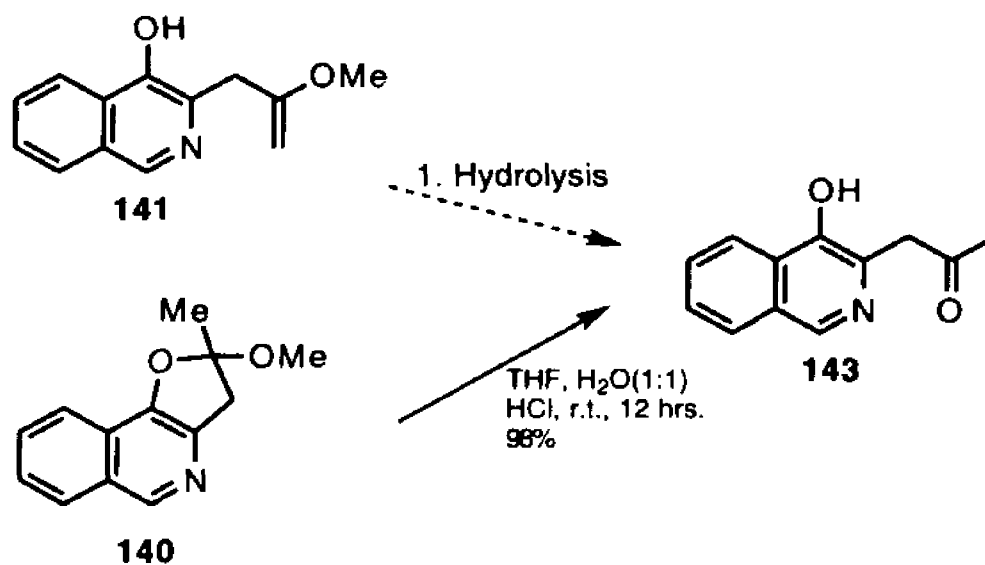
Scheme 72: The Claisen rearrangement of the pure 4-(2-methoxy-2-propenyloxy)isoquinoline.



The starting 4-(2-methoxy-2-propenyloxy)isoquinoline **74** and ketal **140** have the same R_f on tlc and a variety of solvent mixtures did not succeed in separating them. This fact made it difficult to follow the progress of the reaction so that insufficient reaction times and lower temperatures resulted in the isolation of inseparable mixtures of ketal and starting material. Our attempts to push the reaction to completion by increasing reaction times and temperatures resulted in the complete disappearance of the starting material. Unfortunately, these reaction conditions introduced the additional problem of the conversion of the ketal to the furano[3,2-c]isoquinoline **142** so that a mixture of both products was obtained (scheme 72).

Purification by radial chromatography resulted in substantial decomposition of the ketal. Extensive experimentation failed to produce conditions that would reliably generate the ketal uncontaminated by either starting material or the furano[3,2-c]isoquinoline. Our approach to the Bradsher precursor called for the hydrolysis of the Claisen product **141** to the hydroxyketone **143** (scheme 73). The ketal obtained proved to be an equally valid intermediate as hydrolysis proceeded cleanly to give the hydroxyketone **143** in 98% yield. It also came as a surprise that under the conditions of acidic hydrolysis concomitant elimination to the furano[3,2-c]isoquinoline **142** did not occur.

Scheme 73: Hydrolysis of the ketal to the hydroxy ketone.

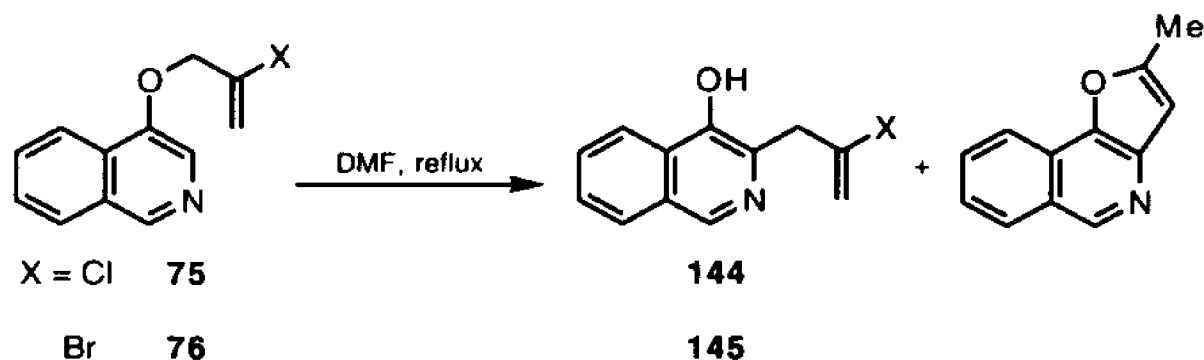


The hydroxyketone **143** proved to be a very sensitive compound and could not be easily handled. It decomposed on standing at -5°C . The compound turned out to be sensitive to base. Exposure to sodium hydride, in an effort to generate the allyl ether via our standard method, resulted in the complete decomposition of the material. In another example of the base sensitivity of **143**, our efforts to utilize base (sodium hydroxide) extraction to separate a mixture of the hydroxyketone **143** and ketone **139** (from the hydrolysis of the mixture of **74** and **140** resulting from the incomplete rearrangement of isoquinolinylenoether **74**) were successful, but extensive decomposition of the hydroxyketone ensued.

(iv) The Claisen rearrangement of vinylhalides

Given the sensitivity of 4-(2-methoxy-2-propenyloxy)isoquinoline **74** to the conditions of the Claisen rearrangement, we decided to replace the vinylic methoxy group with a halogen in the hope that the vinylic halide would confer increased stability to the ether while at the same time providing a handle to elaborate the Claisen products to the Bradsher precursor.

Scheme 74: The Claisen rearrangement of the vinyl halides

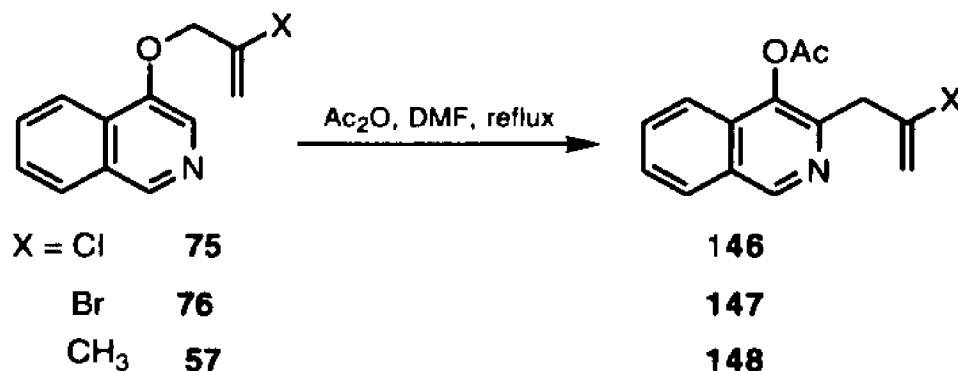


The 4-(2-chloro-2-propenyloxy)isoquinoline derivative **75** undergoes the Claisen rearrangement to yield 3-(2-chloro-2-propenyl)-4-hydroxyisoquinoline **144** in 60% yield accompanied by 12% of the furano[3,2-c]isoquinoline (scheme 74). Similarly, the Claisen rearrangement of the bromo derivative, 4-(2-bromo-2-propenyloxy)isoquinoline **76**, lead to 3-(2-bromo-3-propenyl)-4-hydroxyisoquinoline **145** and the furanoisoquinoline in yields of 66% and 23% respectively (scheme 74).

Elaboration of the Claisen products to the Bradsher precursor **27** requires the eventual protection of the 4-hydroxyl group. We have found that a one pot Claisen with concomitant acetyl protection could

be achieved by carrying out the Claisen rearrangements in the presence of 2-3 equivalents of acetic anhydride. Under these conditions, 3-(2-chloro-2-propenyl)4-acetoxyisoquinoline **146** and 3-(2-bromo-2-propenyl)4-acetoxyisoquinoline **147** were obtained in 13 and 60 % yield respectively. The higher yield of **147** is attributable to the fact that acetic anhydride was used as a cosolvent in the reaction whereas only 2-3 equivalents were used in the synthesis of **146**. Under these conditions and in the presence of catalytic amounts of DMAP, the rearrangement of 4-(2-methyl-2-propenyloxy)isoquinoline **57** proceeded cleanly to the acetoxy derivative **148**.

Scheme 75: Claisen rearrangement with concomittant protection as the acetoxy derivative.



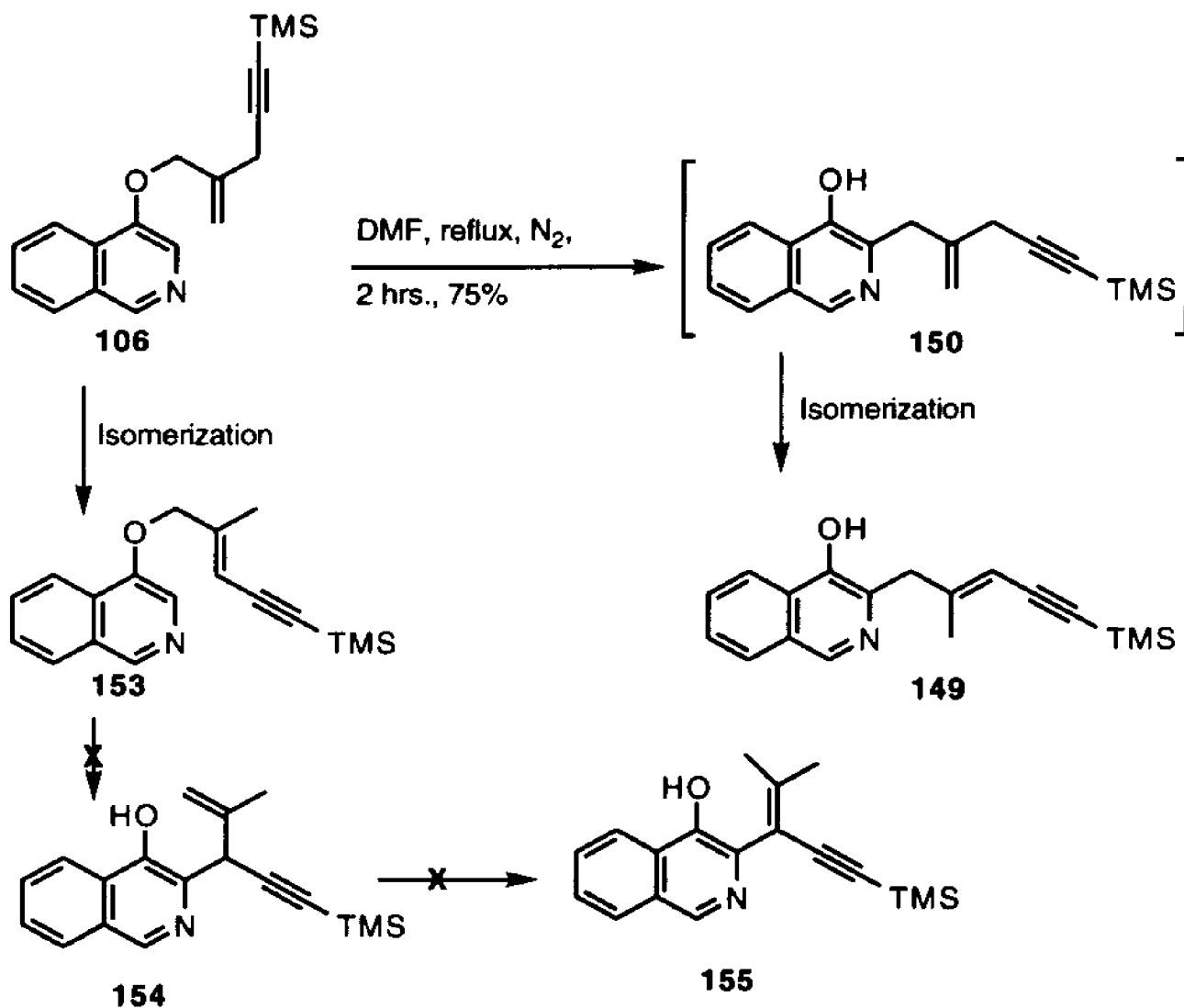
The identity of the acetoxy derivative **148** was confirmed by its synthesis from the 4-hydroxy compounds. Refluxing the 4-hydroxy derivatives **133** in the presence of 2-3 equivalents of acetic anhydride gave rise to **148**.

(v) The Claisen rearrangement of 4-(2-methylene-5-trimethylsilyl-4-pentynyloxy) isoquinoline

The Claisen rearrangements described thus far, were based on the introduction of an extendable appendage at the 3-position of the isoquinoline nucleus followed by the attachment of a 3-carbon extension. We have also investigated the ability of the Claisen rearrangement to introduce at C3 the complete 5-carbon appendage required for the Bradsher precursor.

Upon heating at 160 °C in DMF over 90 minutes, 4-(2-methylene-5-trimethylsilyl-4-propynyloxy) isoquinoline **106** undergoes a Claisen rearrangement to enyne **149**. Unfortunately, the original Claisen product **150** could not be isolated as it isomerized to conjugated enyne **149**.

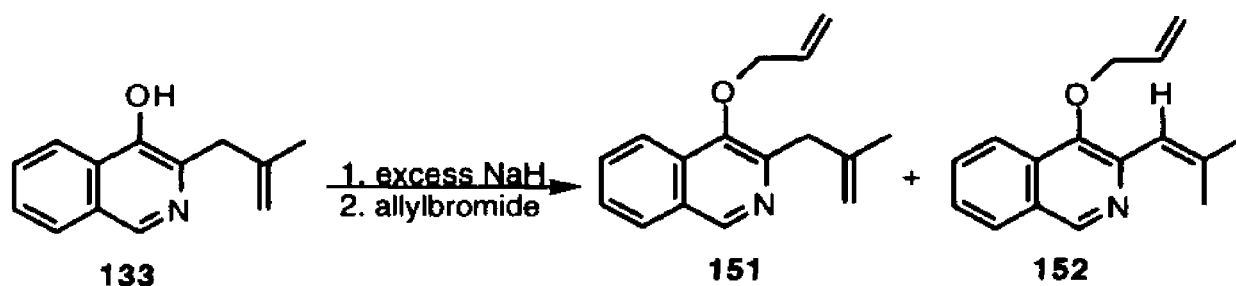
Scheme 76: The Claisen rearrangement of 4-(2-methylene-5-trimethylsilylpropynyloxy)isoquinoline.



The fact that the double bond was conjugated with the triple bond and not with the aromatic system was determined by comparison of the chemical shift of the vinyl proton in **149** with the vinyl proton in 3-(2-methyl-1-propenyl)-4-allyloxyisoquinoline **152**. The vinyl isoquinoline **152** had been previously obtained as a side product during our

conversion of 3-(2-methyl-2-propenyl)-4-hydroxyisoquinoline to its allyloxy derivative **151**. The use of an excess of sodium hydride resulted in the isomerization of the double bond into conjugation with the heterocyclic system. The vinyl proton in **152** appears at 6.63 ppm. The corresponding methylene protons in **151** are upfield at 3.79 ppm. In conjugated enyne **149** the vinyl proton appears at 5.51 ppm, which is consistent with a shielding effect of the acetylene moiety. One, on the other hand, would expect conjugation with the aromatic system to bring the vinyl proton into the range observed in **152**.

Scheme 77: The protection of 3-(2-methyl-2-propenyl)-4-hydroxyisoquinoline as the allyl ether.



The precise geometry of the double bond could not be determined on the basis of coupling constants of the vinyl proton which appears as a singlet in the nmr spectrum. It is quite striking that the double bond isomerized into conjugation with the acetylenic moiety rather than with the aromatic system. The direction of the isomerization points to the enyne as thermodynamically more stable. If so, one wonders why this isomerization was not observed in a conversion of **106** to **153**. Such an isomerization preceding the Claisen rearrangement itself can be excluded since no products such as **154** and **155** (scheme 76) were observed.

On the assumption that the isomerization was base catalyzed, we switched from DMF to the non basic solvent chlorobenzene. Lowering the temperature and varying reaction times in chlorobenzene did not succeed in suppressing the undesired isomerization.

3) The protection of the Claisen products:

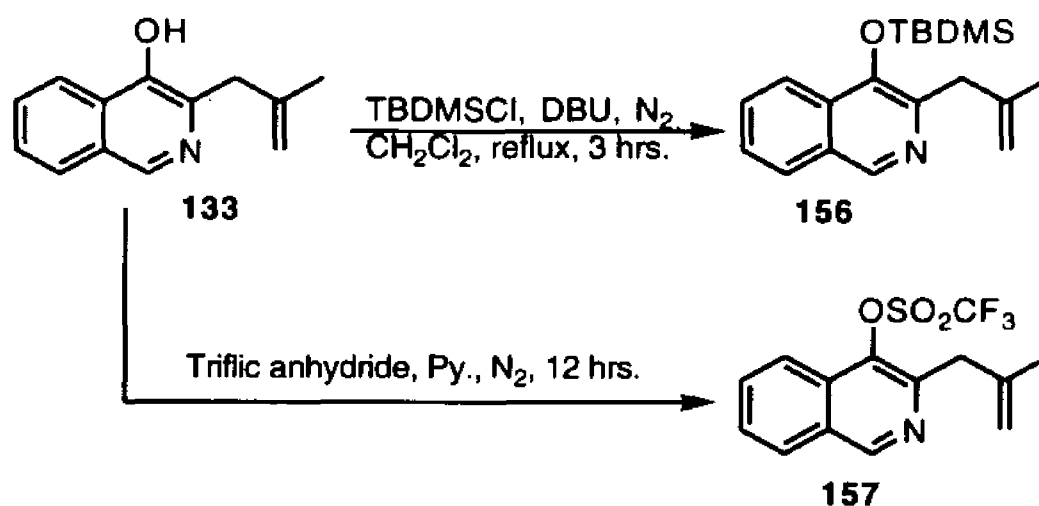
In the preceding section, the protection of the hydroxyl group of the Claisen products has been described for specific compounds in the appropriate context (schemes 75 and 77). In this section, we wish to provide more details on the functionalization of the C4-hydroxyl.

In view of the final deprotection steps required to unmask the ring junction hydroxyls (scheme 12) and mindful of the sensitivity of the ring system it seemed prudent to install a silyl ether at C4 of the Claisen products. It was anticipated that the silyl group could be removed under conditions that would not adversely affect the AB ring construction.

Subjecting 3-(2-methyl-2-propenyl)-4-hydroxyisoquinoline **133** to standard silylation conditions (TBDMSCl, DBU, CH₂Cl₂, r.t.) failed to furnish the desired ether **156**. Resorting to a more powerful silylating agent (TBDMS triflate) and/or to the activation of the nucleophile as its alkoxide was not successful. The starting material was recovered unchanged even after prolonged treatments under the reaction conditions. However, the conversion of the hydroxyl to the alkoxide followed by the addition of TBDMS triflate resulted in the formation of a new product which was not identified. The fact that no alkylsilyl peaks appeared in the nmr spectrum discounted the formation of the desired

ether **156**. In the eventuality that an alkoxide exchange might have produced the triflate ester **157**, the Claisen product **133** was treated with triflic anhydride and pyridine. The nmr spectra revealed that the two products were different. The desired ether was finally synthesized by refluxing the reaction mixture (TBDMSCl, DBU, CH₂Cl₂) for three hours.

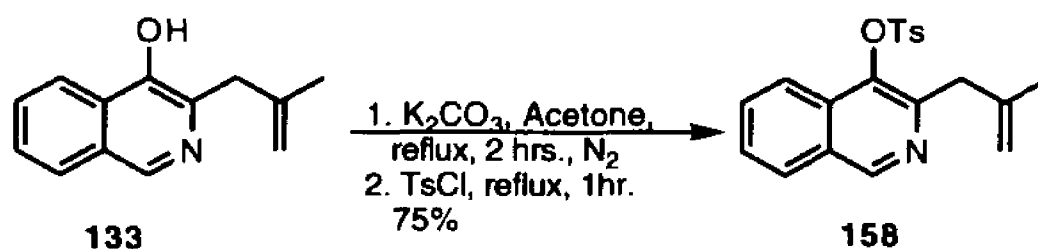
Scheme 78: The synthesis of 3-(2-methyl-2-propenyl)-4-silyloxyisoquinoline.



The silyl group was quite labile and easily cleaved under the conditions employed to functionalize the double bond.

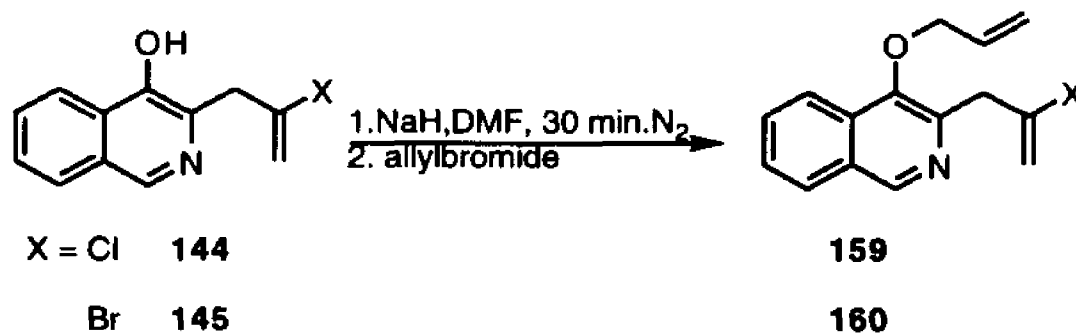
The synthesis of 3-(2-methyl-2-propenyl)-4-tosyloxyisoquinoline **158** was also effected under refluxing conditions. A 75% yield of the ester was obtained by refluxing **133** in acetone in the presence of potassium carbonate and tosyl chloride.

Scheme 79: The synthesis of 3-(2-methyl-2-propenyl)-4-tosyloxyisoquinoline.



The protection of the 3-(2-halo-3-propenyl)-4-hydroxyisoquinoline was achieved by treatment of the respective halide with sodium hydride followed by the addition of allyl bromide. Thus, 3-(2-chloro-3-propenyl)-4-hydroxyisoquinoline **144** and 3-(2-bromo-3-propenyl)-4-hydroxyisoquinoline **145** gave rise to 3-(2-chloro-3-propenyl)-4-allyloxyisoquinoline **159** and 3-(2-bromo-3-propenyl)-4-allyloxyisoquinoline **160** respectively.

Scheme 80: The synthesis of 3-(2-halo-2-propenyl)-4-allyloxyisoquinoline.



CHAPTER 4: THE ELABORATION OF THE CLAISEN PRODUCTS

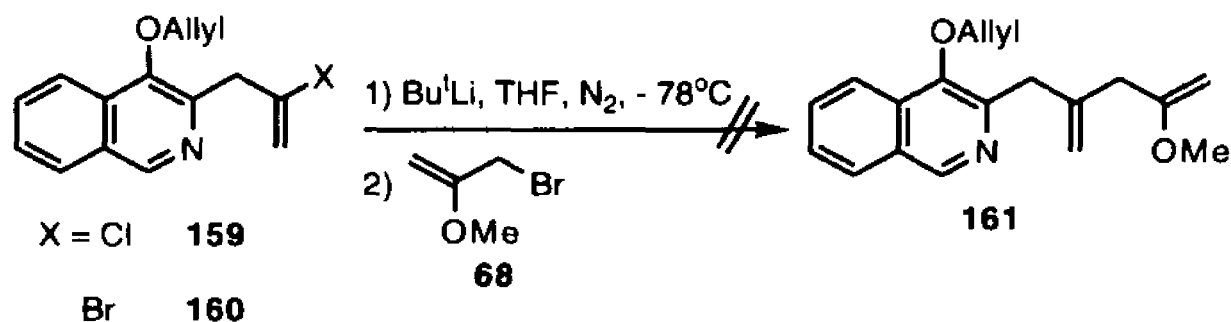
As previously stated, the Claisen rearrangements that we investigated were designed to introduce, at C3 of the 4-alkoxy isoquinoline ring, an extendable appendage that could be further elaborated into the fully functionalized side chain of the Bradsher precursor **27**. This section chronicles our efforts to achieve that aim.

1) Elaboration of the vinyl halides

(i) anionic coupling

3-(2-Chloro-2-propenyl)-4-allyloxy isoquinoline **159** (scheme 81) was treated with tert-butyl lithium in an attempt to generate the vinyl anion. It was anticipated that the anion could be reacted with 3-bromo-2-methoxy propene **68** to yield the 1,4-diene **161** a useful analogue of our targeted Bradsher precursor **27**.

Scheme 81: The coupling of the vinyl halides



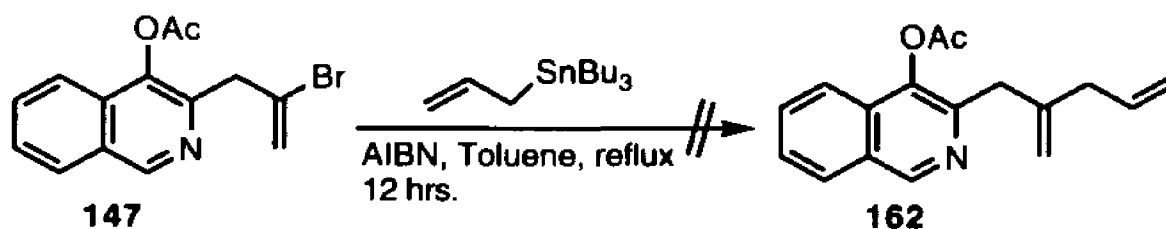
Upon addition of tert-butyl lithium to a THF solution of **159** at $-78\text{ }^{\circ}\text{C}$ the reaction mixture turned immediately dark. The subsequent addition of methoxyallyl bromide **68** to the reaction mixture failed to induce the desired C-C bond formation and resulted in the isolation of the starting material. Since the lithium halogen exchange could be facilitated by replacing the vinyl chloride with the corresponding bromide we investigated the coupling of methoxyallyl bromide to 3-(2-bromo-2-propenyl)-4-allyloxy isoquinoline **160** via the corresponding vinyl anion. The darkening of the vinyl halide solution upon the addition of tert-butyl lithium was again observed. As in the case of the vinyl chloride, work up of the reaction mixture resulted in the recovery of the starting halide. In the hope of suppressing the suspicious darkening of the reaction mixture, which occurs upon the addition of tert-butyl lithium at $-78\text{ }^{\circ}\text{C}$, the temperature was lowered to $-90\text{ }^{\circ}\text{C}$. The lowering of the reaction temperature did not prove helpful in promoting the desired coupling. At this lower temperature however the instantaneous darkening of the reaction mixture which occurred upon the addition of tert-butyl lithium at $-78\text{ }^{\circ}\text{C}$ did not occur. A greenish

taint was imparted to the reaction mixture upon addition of the alkyl lithium reagent.

(ii) free radical coupling

Given the disappointing results of the anionic coupling, a free radical route to the desired precursor was sought. To assess the feasibility of this process we investigated the coupling of 3-(2-bromo-2-propene)-4-acetoxy isoquinoline **147** to allyl tributyl tin. Exposure of the starting material to allyl tributyl tin under free radical conditions failed to generate the expected diene **162** and resulted in the recovery of the starting isoquinoline.

Scheme 82: Free radical coupling of the vinyl bromide

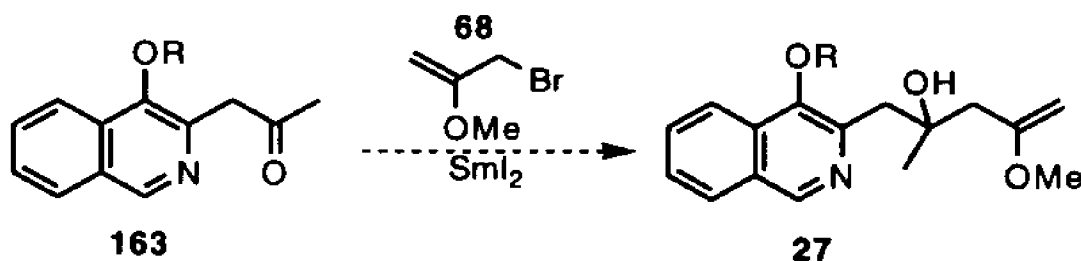


Prolonged reaction times led to the isolation of isoquinolines in which the C3 side chain, which had been introduced by the Claisen rearrangement, was cleaved.

2) Elaboration of the hydroxy ketone

Our troubles with hydroxy ketone **143** have been discussed earlier. This synthetic route was pursued with the hope of adding, to the protected derivative **163**, a three-carbon fragment derived from methoxylallyl bromide **68** so as to complete the synthesis of the precursor (scheme 83). Since we viewed the instability of the hydroxy ketone **143** as arising from the acidity of the α -hydrogens this precluded the use of the basic lithium or magnesium allyl anion derived from methoxyallyl bromide. We reasoned therefore that a samarium or cerium based reagent was required.

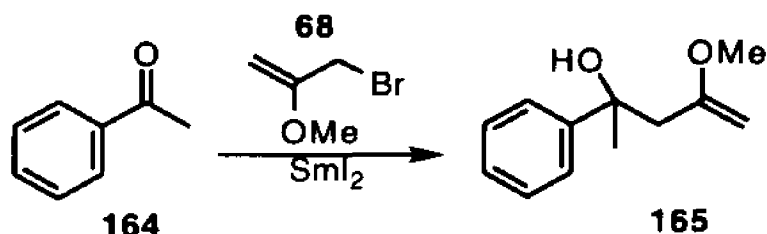
Scheme 83: Samarium mediated coupling of methoxy allyl bromide



In view of the anticipated coupling, we had previously demonstrated, in a parallel study, that the samarium reagent derived from methoxyallyl bromide added successfully to acetophenone **164** to generate the tertiary alcohol **165**. The crude nmr revealed that the reaction had proceeded quite cleanly. The product was easily identified by the appearance of an AB quartet corresponding to the methylene group. Furthermore, the incorporation of the 2-methoxy propenyl moiety was ascertained by the presence of the methoxy and vinylic

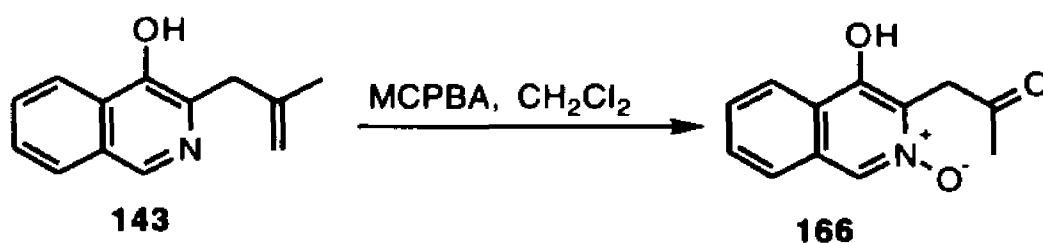
resonances. Unfortunately, efforts to further purify the enol ether **165** by radial chromatography resulted in the decomposition of the material.

Scheme 84: Samarium mediated addition of methoxyallyl bromide to acetophenone.



However the difficulties associated with the synthesis of **143** via the Claisen rearrangement led us to abandon this route to the Bradsher precursor. An alternative approach to the hydroxy ketone **143** is via the ozonolysis of 3-(2-methyl-2-propene)-4-hydroxy isoquinoline **133**. Under ozonolysis conditions however concomittant oxidation of the nitrogen resulted in the formation of N-oxide **166**.

Scheme 85: The ozonolysis route to the hydroxy ketone.

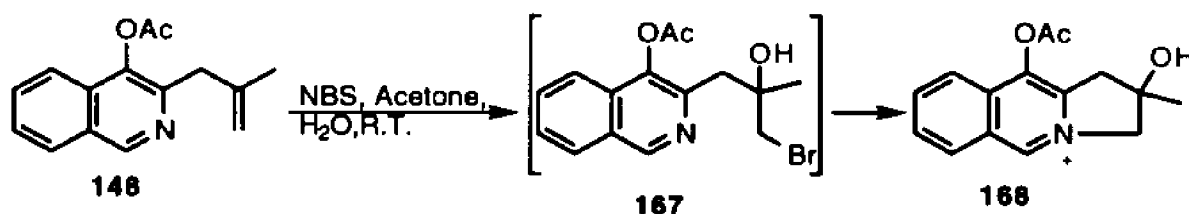


3) elaboration of 3-(2-methyl-2-propenyl)-4-alkoxyisoquinoline

(i) via the bromohydrin

With a view towards a primary halide suitable for coupling to α -methoxy vinyl lithium, 3-(2-methyl-2-propene)-4-acetoxy isoquinoline **148** was treated with NBS in acetone and water so as to generate the corresponding bromohydrin **167**. Alternatively, the bromohydrin formation was attempted in DMSO and water. Careful monitoring of the reaction by tlc revealed the gradual disappearance of the starting material and the formation of a slower moving product. Unfortunately the product formed also fades away with time giving rise to a polar material which remains on the base line. Aqueous work up yielded no organic material. It appears then, on the basis of the tlc data, that the desired bromohydrin **167**, as it is generated, reacts rapidly in an intramolecular alkylation of the aromatic nitrogen. The resulting 1 salt **168** is subsequently lost during the aqueous work up.

Scheme 86: The synthesis of the bromohydrin.

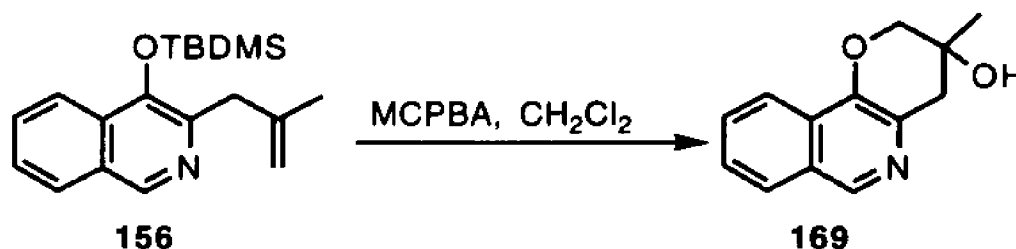


(ii) via the epoxide

The intramolecular nucleophilic attack of the isoquinoline nitrogen on the primary bromide of bromohydrin **167** occurs unimpeded by any geometric restrictions. We surmised that the alternative conversion of the double bond of the 3-(2-methyl-2-propenyl)-4-alkoxy isoquinolines to an epoxide might present severe geometric constraints to the unwanted alkylation.

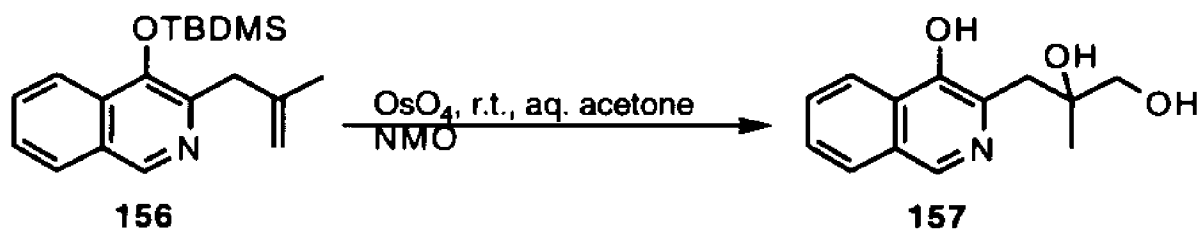
The oxidation of the silyloxy derivative **156** proved to be troublesome due to the lability of the silyl group. Attempted conversion of the double bond to the epoxide using mCPBA led to the isolation of the dihydropyranyl derivative **169** following radial chromatography.

Scheme 87: The oxidation of the silyloxy derivative.



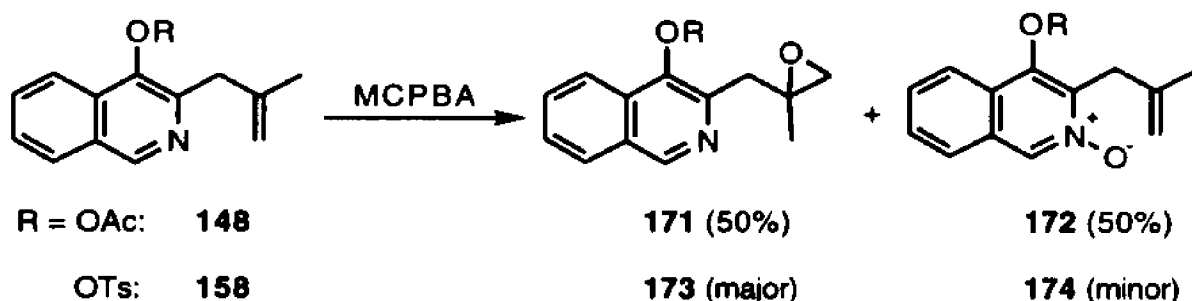
The formation of pyranyl ether **169** can be envisaged to occur through the opening of the generated epoxide by the alkoxy group resulting from the loss of the silyl group. An alternate route to the desired epoxide involved the dihydroxylation of the double bond followed by the tosylation of the primary hydroxyl group. Unfortunately, dihydroxylation of **156** under osmium tetroxide conditions resulted in the isolation of diol **157** in which the silyl group had again been cleaved.

Scheme 88: The dihydroxylation of the silyloxy derivative.



Examination of the diol reveals that it does not lend itself to the selective formation of the epoxide without complicating concurrent production of the dihydropyranyl **169** derivative previously observed. We turned then our attention to the epoxidation of 3-alkenyl isoquinolines bearing a sturdier 4-alkoxy functionality. Upon exposure to mCPBA in dichloromethane, 3-(2-methyl-2-propenyl)-4-acetoxy isoquinoline **148** gave rise to the desired oxirane **171**. Unfortunately, the nucleophilicity of the nitrogen led to the concurrent formation of the N-oxide **172**.

Scheme 89: The epoxidation of the acetoxy and tosyloxy derivatives.

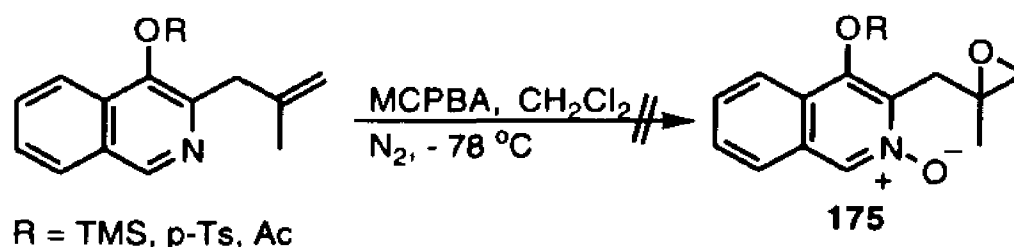


Attempted separation of the 1:1 mixture of epoxide/N-oxide resulted in the complete decomposition of the material. No chromatographic solid phase tried was successful in preventing this decomposition. Efforts to circumvent this problem involved using an excess of peracid to convert the starting alkene to N-oxide/epoxide **175** followed by reduction of the N-O bond in the hope of generating the desired epoxide in good yields. In the event excess peracid failed to alter the observed 1:1 ratio of products.

On the characterization of the epoxides and N-oxides:

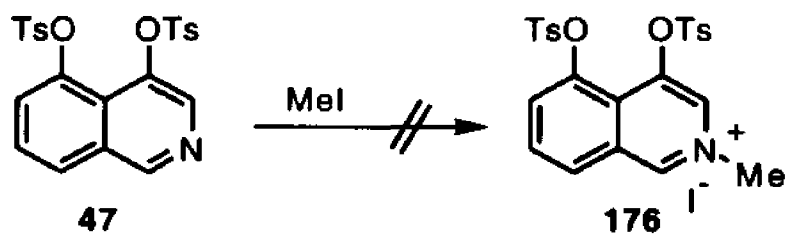
The conversion of the isoquinoline derivatives to their corresponding N-oxides results in a 0.5 ppm upfield shift of the ^1H nmr resonances of H1 and H3. Both the N-oxides of 5-tosyloxy and 5-methoxyisoquinoline display this upfield shift which is observed in the parent isoquinoline. This observation has been quite useful in ascertaining the oxidation level of the isoquinoline nitrogen in our oxidation products. In 3-(2-methyl-2-propenyl)-4-tosyloxyisoquinoline **158** the H1 resonance appears at 9.15 ppm. The fact that the chemical shift remains the same in going to epoxide **173** indicates that the nitrogen had not been concomitantly oxidized. In the 4-acetoxy series **148** H1 resonates at 9.1 ppm. The crude nmr of the oxidation products of **148** displays two lowfield singlets. The resonance at 9.1 ppm was assigned to epoxide **171** while the upfield signal at 8.8 ppm was assigned to N-oxide **172**. The identification of ozonolysis product **166** was based on a similar argument. In 3-(2-methyl-2-propenyl)-4-hydroxyisoquinoline **143** H1 appears at 8.8 ppm. The crude nmr of the ozonolysis product displays no resonances between 9 ppm and 8.1 ppm indicating that concurrent oxidation of the nitrogen had also occurred.

Scheme 90: The N-oxide / epoxide.



It had become clear that the instability of the epoxide to chromatography required a method that would generate the compound free of the contaminating N-oxide. This requirement necessitated in turn a complete deactivation of the aromatic amine towards nucleophilic reactions. Our earlier struggles to generate the salts of 4-tosyloxyisoquinoline **36** as well as our failure to obtain 4,5-ditosyloxy-N-methylisoquinolinium salt **176** from 4,5-ditosyloxyisoquinoline **47** had shown that the tosyloxy group at C4 drastically deactivated the nitrogen.

Scheme 91: Quaternization of 4,5-ditosyloxyisoquinoline.



These results led us to study the oxidation of 3-(2-methyl-2-propenyl)-4-tosyloxyisoquinoline **158**. Upon treatment with mCPBA, **158** gave rise to epoxide **173** as the major product of the reaction mixture (scheme 89).

Although the epoxide was contaminated by minor amounts of the N-oxide **174** (scheme 89), as ascertained by an analysis of the crude ^1H nmr, these results constituted a decisive improvement over the 1:1 mixture obtained in the epoxidation of the acetoxy counterpart. It came as a pleasant surprise that complete suppression of the N-oxide could be achieved by using magnesium monoperoxy phthalate as the oxidant. Under these conditions the desired epoxide could be obtained in a crude yield of 98% . The purity of the material, as ascertained by ^1H nmr obviated the need for any chromatographic treatment.

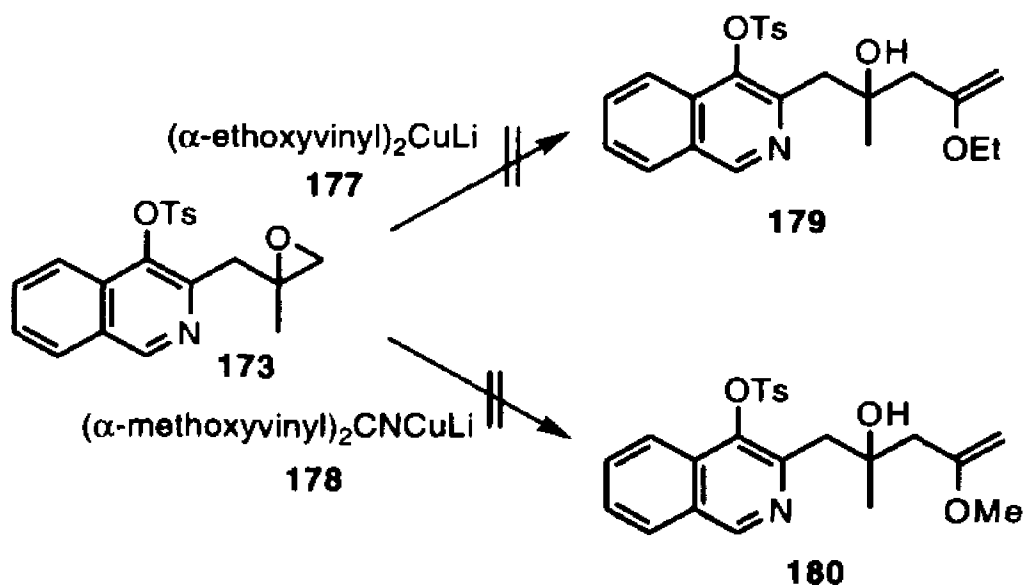
4) elaboration of the epoxide

The four step synthetic sequence from 4-hydroxy isoquinoline to the required epoxide proved to be quite efficient and straightforward. With the exception of the synthesis of ether **57**, every step in the sequence is amenable to satisfactory scale ups. With epoxide **173** in hand, we investigated its conversion to the Bradsher precursor **27**. The synthesis of the precursor from the epoxide requires only the attachment of a two-carbon piece bearing the enol ether moiety or a precursor thereof.

(i) Reactions of the epoxide with α -alkoxy vinyl metals:

α -ethoxy vinyl lithium was generated following Boeckman's procedure and converted to the divinyl cuprate by treatment with cuprous halide. We were not successful in our attempt to generate the Bradsher precursor **179** by reacting epoxide **173** with the Boeckman reagent **177**. The failure of the cuprate to form the desired C-C bond can be attributed, as per Boeckman's explanation, to the decomposition of the reagent at temperatures above $-30\text{ }^{\circ}\text{C}$. The use of the more reactive and more stable Lipshutz reagent, mixed higher order cuprate **178** was equally disappointing. The Bradsher precursor **180** was not formed.

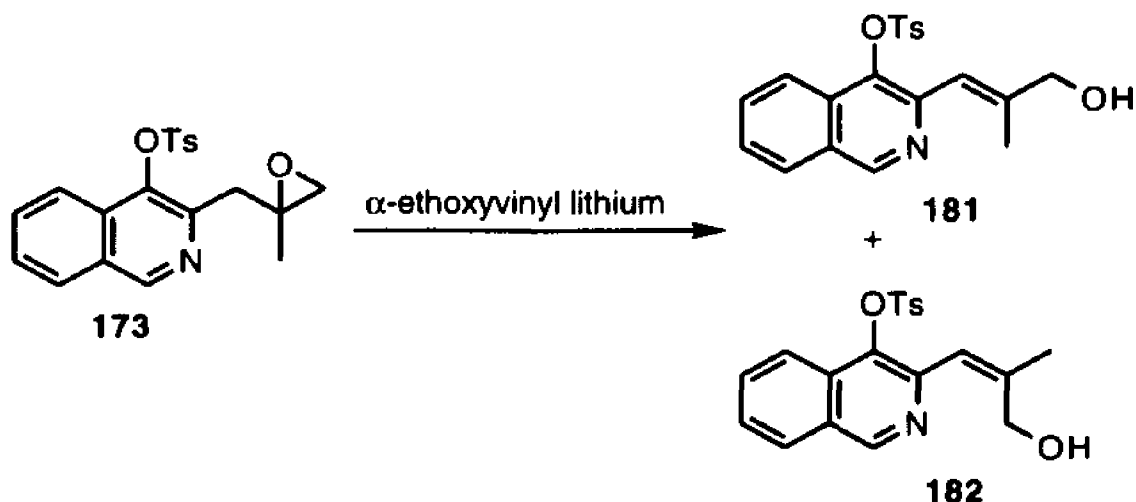
Scheme 92: Vinyl copper reagents in the opening of the epoxide.



Ganem's adaptation of the α -ethoxy vinyl lithium methodology to the opening of epoxides requires simply the addition of $\text{BF}_3\cdot\text{OEt}_2$. These conditions however resulted in the decomposition of the starting

epoxide. Since exposure to chromatographic solid phases had clearly shown the sensitivity of the epoxide to acidic and basic conditions we attributed the failure of the Ganem procedure to the decomposition of the starting material in the presence of $\text{BF}_3 \cdot \text{OEt}_2$. Treatment of the epoxide **173** with α -methoxy vinyl lithium in the absence of $\text{BF}_3 \cdot \text{OEt}_2$ (scheme 93) allowed the isolation and characterization of two allylic alcohols **181** and **182** differing in the stereochemistry of the double bond. On the basis of NOE studies the E stereochemistry was assigned to the faster moving spot while the double bond stereochemistry of the slower moving alcohol was confirmed as Z.

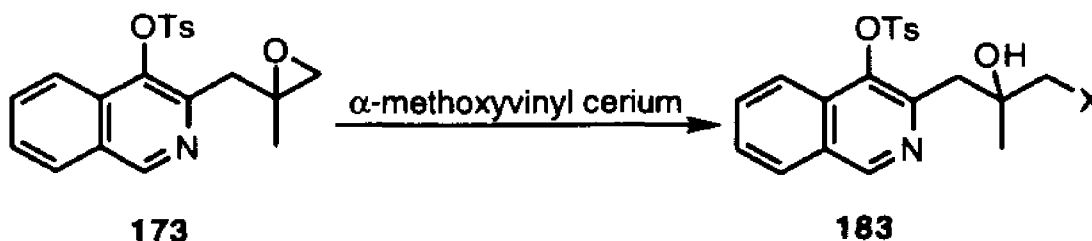
Scheme 93: α -ethoxyvinyl lithium in the opening of the epoxide.



The formation of the allylic alcohols attests to the acidity of the "benzylic" protons which are abstracted by α -ethoxy vinyl lithium leading to the observed alcohols through the fragmentation of the epoxide. In the hope that complexation of the oxirane oxygen with the

metal of the vinyl anion might lead to a facile opening of the ring the epoxide was reacted with vinyl magnesium bromide. Under these conditions decomposition of the starting material was observed. The use of α -methoxy vinyl magnesium bromide made by transmetalation of α -methoxy vinyl lithium with the epoxide led to the same results. The addition of cerium reagents to carbonyls have been shown to be quite useful. The lower basicity of these reagents coupled with the ability of the metal to complex with the carbonyl oxygen suggested that a cerium based reagent might be successful in opening the epoxide while suppressing the formation of the allylic alcohols **181** and **182** which arise as a consequence of the acidity of the C1' protons. The cerium reagent obtained from a transmetalation of α -methoxy vinyl lithium with cerium chloride was reacted with epoxide **173** at -78°C .

Scheme 94: α -methoxyvinyl cerium in the opening of the epoxide.



In contrast to the behavior of the corresponding lithium and magnesium reactions, in which the disappearance of the starting material is almost instantaneous, the cerium reaction proved to be very slow. The temperature was gradually raised by ten degree increments and maintained at the given temperature for about 1/2 hour. Even at room temperature the reaction was very slow and proceeded over 24 hours

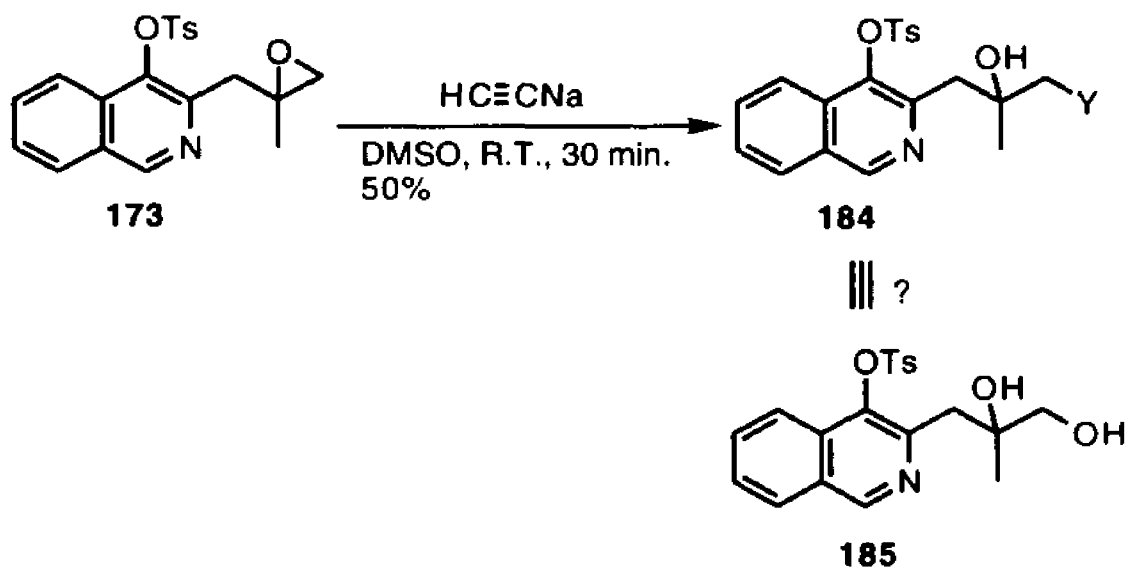
before the complete disappearance of the starting material. The ^1H nmr of the isolated product **183**, displayed two AB quartets as would be expected from the opening of the epoxide but the failure to observe the methoxy and vinyl protons from the expected attachment of the α -methoxy vinyl moiety indicated that the desired C-C bond formation had not taken place.

(ii) Reaction of the epoxide with acetylenic anions:

Given our inability to directly couple the two-carbon enol ether piece to the epoxide we turned our attention to acetylenic species which could be converted to the enol ether in a subsequent step.

The addition of sodium acetylide to a DMSO solution of the epoxide (scheme 95) resulted in an immediate change in the color of the solution which became immediately black. This observation was reminiscent of the behavior of the vinyl halide compounds in the presence of tert-butyl lithium. After work up and radial chromatographic purification of the reaction crude a product **184** which displays two AB quartets in its NMR spectrum was obtained. Although the evidence indicated an opening of the oxirane moiety the absence of an acetylenic proton pointed to the addition of a different nucleophile than the expected sodium acetylide.

Scheme 95: Sodium acetylide in the opening of the epoxide.



In an interesting twist, when the sodium acetylide was added at $-78\text{ }^{\circ}\text{C}$ and the reaction mixture was allowed to rise to room temperature the darkening of the solution was not observed and the starting epoxide was left untouched. Of further interest is the fact that the isolated product 184 in which the oxirane was opened differed from the structure 183 previously observed in the attempted addition of the α -methoxy vinyl cerium reagent. It is quite probable that one of the structures corresponds to the diol 185 (scheme 95) resulting from addition of hydroxide ion to the secondary carbon of the epoxide but further work to elucidate the structure of the two products was not carried out. In an effort to weaken the C-O bond of the oxirane by metal complexation the sodium acetylide reaction was carried out in the presence of added lithium chloride. Warming the reaction mixture from $-78\text{ }^{\circ}\text{C}$ to room temperature and stirring for 12 hours failed to effect any changes in the starting epoxide. Turning our attention to lithium

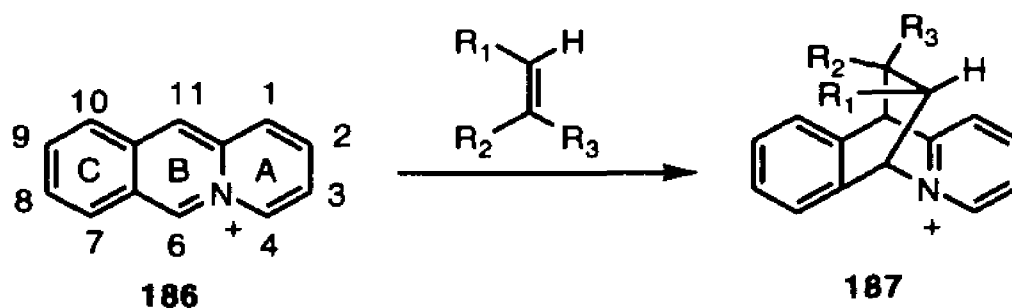
acetylides which are known to open epoxides, we reasoned that the decreased basicity of the lithium acetylides compared to that of the vinyl anions used earlier would not lead to the unwanted formation of the allylic alcohols 181 and 182. Reaction of the epoxide 173 with trimethyl silyl lithium acetylide at -78°C for 4 hours resulted in the recovery of the starting material. Prolonged reaction with the same reagent at room temperature resulted in the decomposition of the epoxide. The reaction of the epoxide with trimethyl silyl boron acetylide led to the decomposition of the starting material as observed earlier when the Ganem procedure was employed.

CHAPTER 5: THE BRADSHER CYCLOADDITION OF NON-OXYGENATED ISOQUINOLINES.

1) The cycloaddition of aromatic salts

In 1958, Bradsher who pioneered the extension of polar cycloadditions to azaaromatic systems, reported the first example of a polar cycloaddition reaction of a quaternary salt.⁷⁷ In his studies on the acridizinium ion **186**, he discovered that alkenes, even poorly nucleophilic ones, add to the aromatic system to generate adducts of type **187** (scheme 96).

Scheme 96: The cycloaddition of the acridizinium cation.

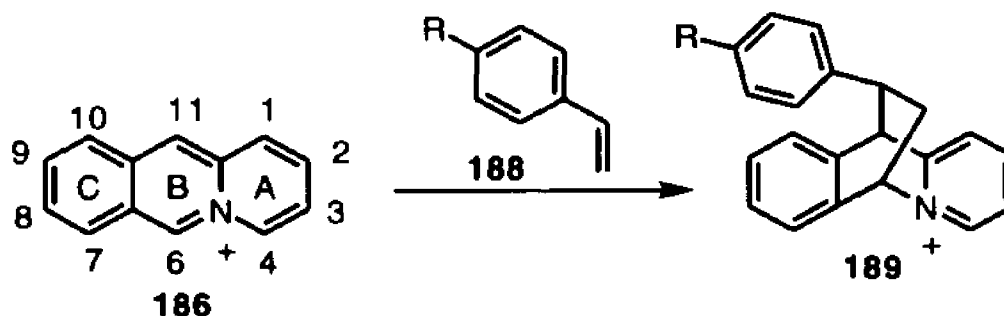


In a subsequent extension of the studies on the acridizinium ion, Fields⁷⁸ concluded from a thorough investigation involving variation of temperatures and solvents that the reaction was a clear example of an inverse electron demand Diels-Alder.⁷⁹ In support of this conclusion it was found

that electron rich ketene dimethyl acetal reacted readily whereas tetracyanoethylene failed to add to the electron deficient heterocyclic salt.⁸⁰

As the addition of substituted styrenes **188** to the acridizinium salt **186** was investigated⁸¹ (scheme 97), the fastest relative rate (4.3) to product **189** was observed in the addition of p-methoxy styrene. The p-nitro derivative was the slowest (0.34). Methyl substitution at the para position resulted in a faster rate (1.7) than that observed for the nitro case. The fact that the more nucleophilic para-methoxy styrene reacted faster than its methyl and nitro congeners lent further credence to the inverse electron demand Diels-Alder nature of the cycloaddition.

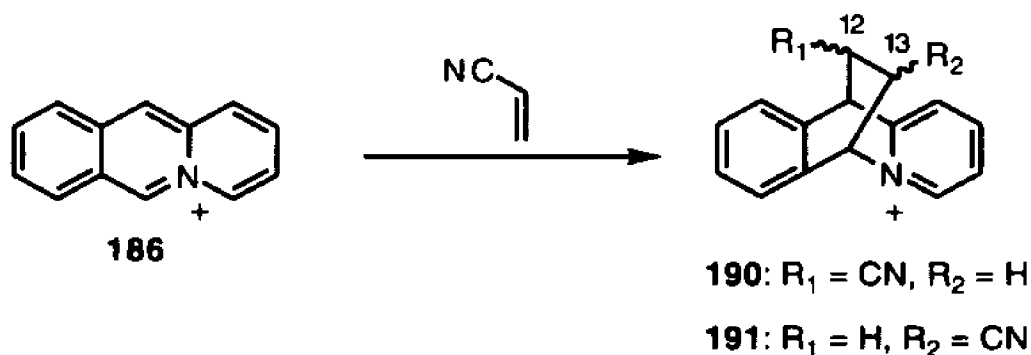
Scheme 97: The cycloaddition of styrenes to the acridizinium cation.



R	rate
CH ₃ O	4.3
CH ₃	1.7
NO ₂	0.34

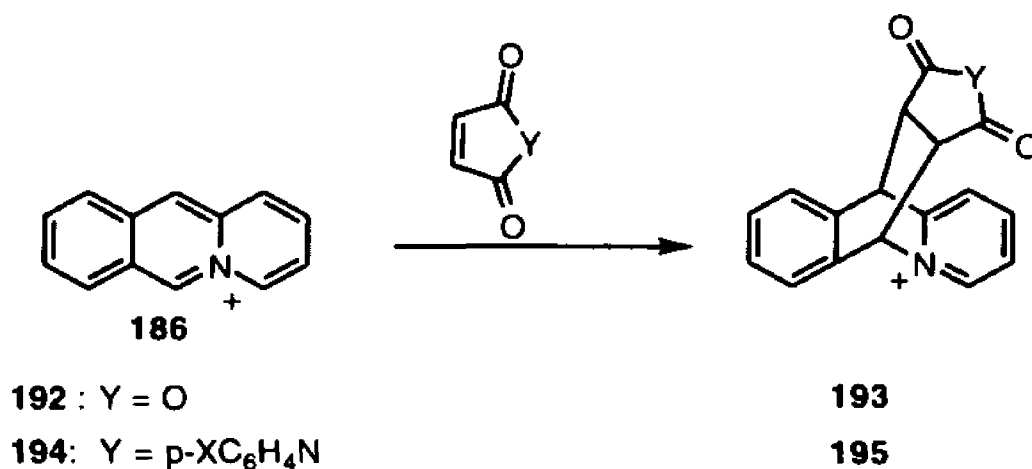
The cycloaddition elicited further interest when it was discovered that the addition of unsymmetrical alkenes to the aromatic nucleus was regiospecific.⁸² The regioselectivity was explained on the basis of the respective polarities of the attacking alkenes and the acridizinium salt. The more nucleophilic carbon of the alkene was observed to attack C6 which had been previously shown to be the most electrophilic center of the acridizinium system.⁸³ In an interesting twist, when the polarity of the alkene was reversed as in the case of acrylonitrile (scheme 98), the 12- **190** rather than the 13-cyano **191** adduct was observed.⁸⁴ As the polarity of acrylonitrile would have led to the prediction that the 13-cyano compound would be the product, a concerted mechanism was thought to be operative in this particular case..⁸⁵

Scheme 98: Regioselectivity in the cycloaddition of the acridizinium cation.



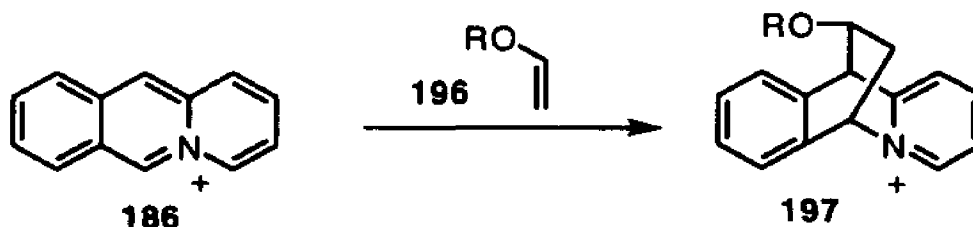
The addition of maleic anhydride **192** (scheme 99),⁸⁶ carried out by Bradsher, revealed yet another facet of the cycloaddition: its stereoselectivity. The cycloaddition gave rise to only one stereoisomer **193**.

Scheme 99: Stereoselective addition of maleic anhydride and maleimides to the acridizinium cation



The stereochemistry was elucidated and shown to be the syn adduct in which the anhydride moiety lies above the pyridinoid ring.⁸⁷ Similar stereoselectivity in the case of the N-arylmaleimide **194** adducts⁸⁸ **195** (scheme 99) led Bradsher to postulate that the stereochemistry was controlled by the formation of charge transfer complexes between the positively charged nitrogen and the unshared pairs of electron on the heteroatoms of the alkene addend.⁸⁹ The observed stereoselectivity was reversed when enol ethers **196** rather than maleic anhydride or maleimides were added to the acridizinium ion (scheme 100).⁹⁰

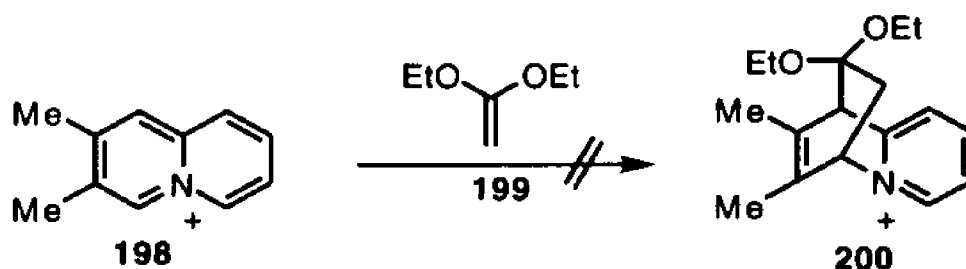
Scheme 100: Stereoselective addition of vinyl ethers to the acridizinium cation.



The addition of enol ethers **196** resulted in adducts **197**, in which the alkoxy group lies anti to the pyridinoid ring.⁹¹ The stereochemistry of the cycloadduct was derived as much from nmr evidence as from analogy with the x-ray proven stereochemistry of the isoquinoline series.⁹²

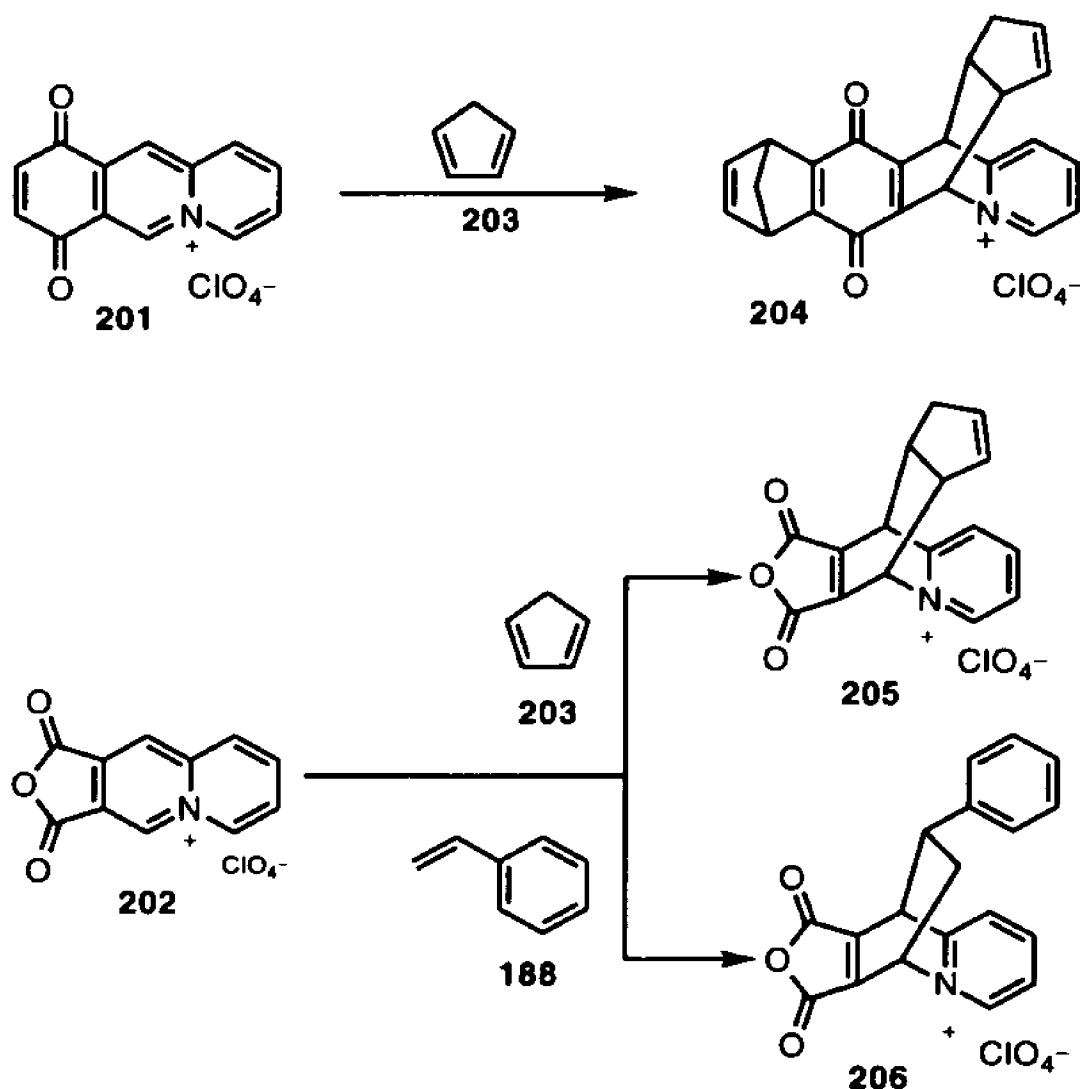
In an attempt to determine the minimum structural requirements for the cycloaddition, Fields⁹³ sought to induce the cyclization of alkenes with an acridizinium analogue **198** in which the C ring had been reduced to a pair of methyl substituents at C6a and C10a (scheme 101).

Scheme 101: The cycloaddition of 2,3-dimethyl-4a-azonianaphthalene.



As the attempted cycloaddition of 2,3-dimethyl-4a-azonianaphthalene **198** with ketene diethyl acetal **199** failed to generate adduct **200**, further research revealed that in the presence of electron withdrawing substituents such as quinones **201** and anhydrides **202** as the C ring replacement, the cycloaddition proceeded as expected and satisfactory yields of cycloadducts were obtained (scheme 7).^{94,95}

Scheme 102: The cycloaddition of acridizinium quinones and anhydrides.

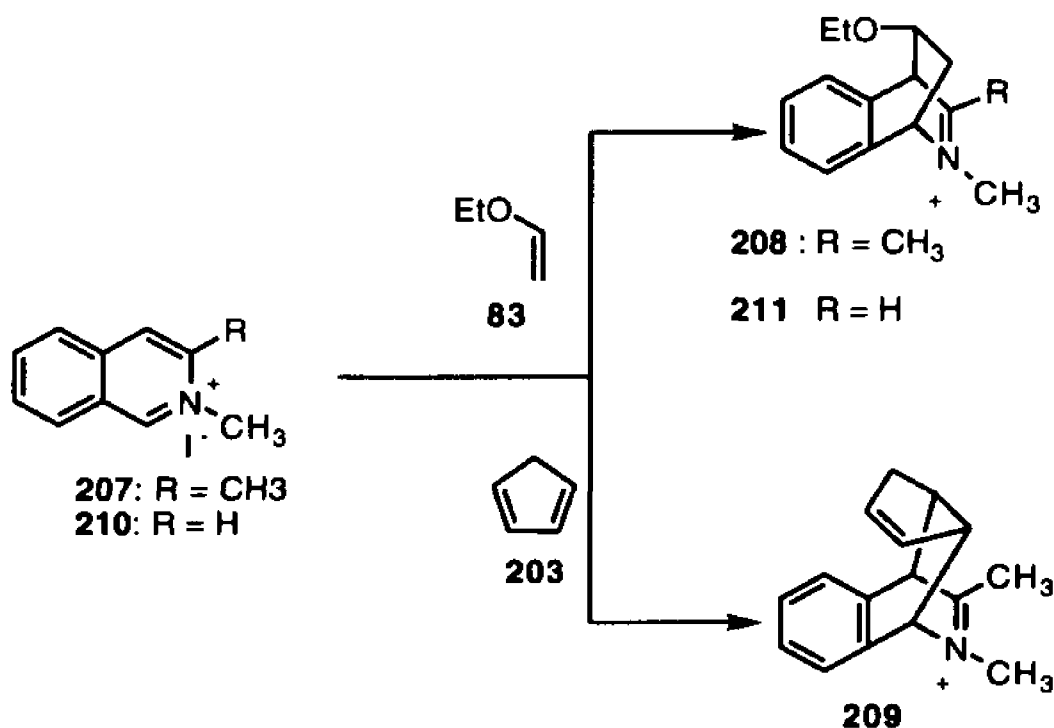


Cycloaddition of cyclopentadiene **203** to the quinone analogue **201** resulted in the addition of two moles of cyclopentadiene to yield adduct **204**.⁹⁶ In a conventional Diels-Alder fashion, addition of one mole of cyclopentadiene to the quinone occurred with concomitant inverse electron demand Diels-Alder addition of a second mole across the C6 - C11 carbons. In its reaction with the anhydride **202**, cyclopentadiene

yielded the 1:1 adduct **205**. The addition of styrene **188** to the anhydride afforded cycloadduct **206**.

Bradsher's own modification of the acridizinium system consisted in the replacement of the A ring with a pair of methyl substituents at the 2 and 6 positions. He thus discovered that ethyl vinyl ether (as well as a large variety of enol ethers) added successfully across the C1-C4 positions of the 2,3-dimethylisoquinolinium iodide cation **207** to yield the tricyclic imminium ion **208** (scheme 103). The cycloaddition of cyclopentadiene to **207** on the other hand led to the tetracyclic structure **209**.

scheme 103: The cycloaddition of ethyl vinyl ether and CPD to isoquinolinium salts.

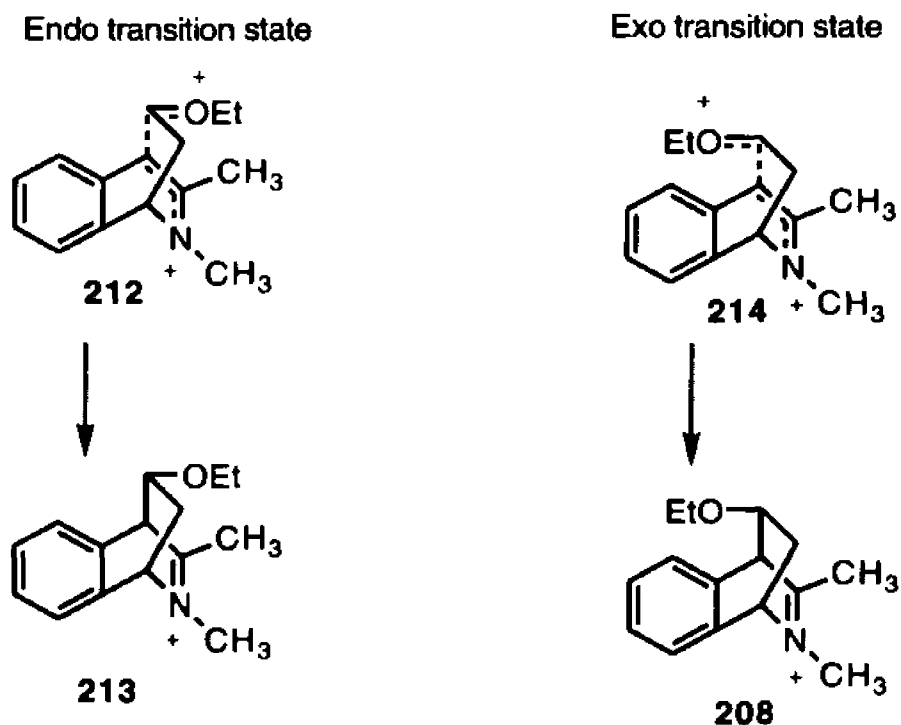


The stereochemistry of adducts **208**⁹⁷ and **209**⁹⁸ was determined by X-ray crystallography. Thus, the alkoxy group of the

enol ether was found to lie above the plane of the phenylene ring in an anti arrangement to the positively charged nitrogen.

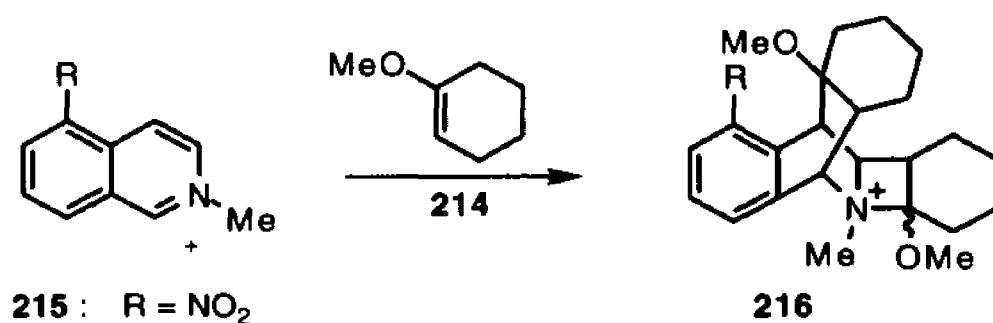
In terms of the concerted non-synchronous mechanism proposed by Bradsher,⁹⁹ the stereoselective formation of the adduct resulting from exo addition of the dienophile can be accounted for by evoking the principle of maximum separation of like charges in the transition state leading to the exo product. The endo transition state **212** in which the charge repulsion is maximized by the proximity of the oxonium and iminium ions is higher in energy and does not lead to the formation of the endo isomer **213**. The exo transition state **214** in which the charges are maximally separated is favored and leads to **208**.

Scheme 104: The maximum separation of charge principle.



Further attempts at removing the vestiges of the A ring of the acridizinium ion in order to obtain simpler analogues capable of undergoing cycloaddition led to the N-methyl isoquinolinium cation **210** (scheme 103). Unfortunately, efforts to isolate pure adducts **211** from the reaction with vinyl ethers proved unfruitful. According to the Bradsher rationale, the failure of the N-methylisoquinolinium cation to generate pure products is attributable to the higher reactivity of the unsubstituted imminium ion **211** (scheme 103) compared to its 3-substituted homologue **208**. In **211** the now unhindered electrophilic C3 position of the imminium salt is capable of adding another mole of enol ether to yield a 2:1 adduct.¹⁰⁰ In the addition of methoxycyclohexene **214** to the 5-Nitro-N-methylisoquinolinium cation **215** (scheme 105) nmr evidence strongly supports the 2:1 structure **216** as the product of the reaction.¹⁰¹

Scheme 105: C3 unsubstituted isoquinolinium salts 2:1 adduct.

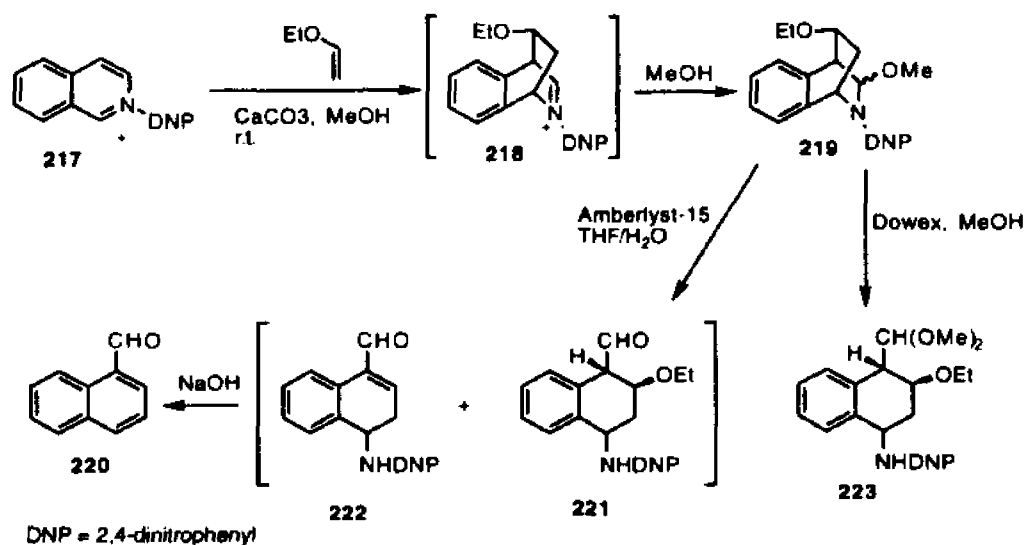


According to Bradsher, "early experiments ... directed towards the cycloaddition of alkenes with isoquinolinium salts having no substituent at position 3, ... were frustrated almost certainly by the great reactivity

of the cycloadduct first obtained, resulting in complicating nucleophilic attacks by the solvent or excess alkene".¹⁰²

The increased reactivity of the unsubstituted isoquinolinium salt was cleverly exploited by Falck (scheme 11) who carried out the cycloaddition of ethyl vinyl ether to 2,4-dinitrophenyl isoquinolinium salt **217** in methanol.¹⁰³ Under these conditions, the reactive imminium ion **218** which is generated is immediately trapped by the solvent to yield a pair of tricyclic amins **219** epimeric at C2.

Scheme 106: Falck and Franck's modification of the Bradshe cycloaddition.



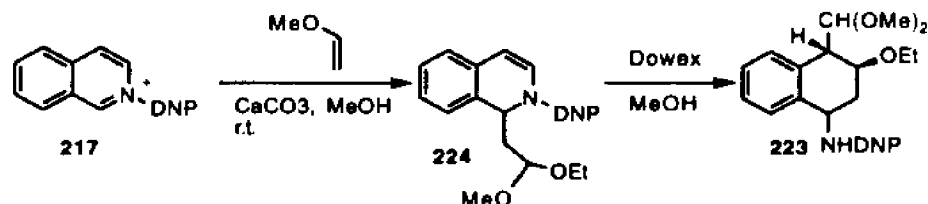
The mixture was hydrolyzed with Amberlyst-15-resin in THF/H₂O and treated with sodium hydroxide to effect its conversion to naphthaldehyde **220**. Falck's recommendation that the hydrolysis product be converted to the naphthaldehyde without purification is probably due to the fact that it proved impossible to isolate the aminoaldehyde **221** free of the contamination product **222** resulting from β -elimination of the alkoxy group in **221**.

The acidity of the α hydrogen results in a facile elimination to α,β -unsaturated aldehyde **222** setting up the stage for the elimination of the aromatic amino group. In the aromatization process, however, the cleverly disposed stereogenic centers of the tetralin are destroyed. In a significant improvement of the Bradsher cycloaddition, Franck¹⁰⁴ effected the cleavage of the aминаl moiety under anhydrous conditions (Dowex resin/Methanol) with the overall effect of trapping the sensitive aminoaldehyde **221** as its stable dimethyl acetal derivative **223**.

2) The mechanism of the Bradsher cycloaddition

In his earlier studies on the addition of ethylene derivatives to the acridizinium ion, Bradsher had made a convincing case for the operation of a two-step mechanism in the addition of substituted styrene derivatives.¹⁰⁵ In the case of the isoquinolinium salt however, the stereospecific exo addition coupled with the failure to isolate reaction intermediates leading to cycloadduct led Bradsher postulate a concerted non-synchronous mechanism.¹⁰⁶ However, in his own investigation of the reaction, Franck¹⁰⁷ reported the isolation of acetal **224** (scheme 107) in which only one bond had formed between the enol ether and the isoquinolinium salt. Accordingly this acetal was referred to as the "one-bond product".

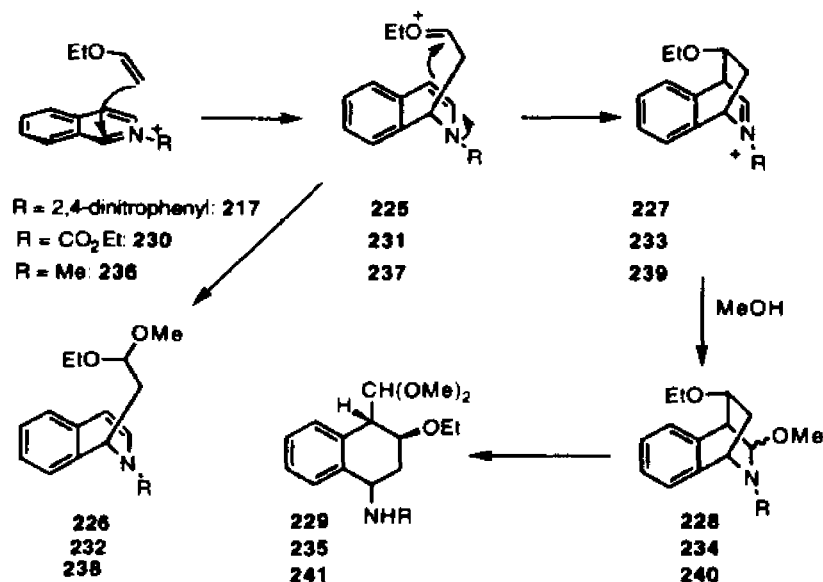
Scheme 107: Franck's isolation of the one-bond product.



As the second bond between the alpha carbon of the enol ether and C4 of the isoquinolinium nucleus had not formed in the one-bond product, this raised the possibility that the reaction might proceed through a two-step mechanism. In fact, when a methanolic solution of the one-bond product was treated with Dowex (scheme 107) acetal **223**, resulting from the cyclization of the one-bond product **224**, could be isolated.¹⁰⁸ This result pointed to the existence of a one-bond intermediate. Although the isolation and the recycling of the one-bond products did not constitute an unequivocal proof of a two step mechanism for the cycloaddition, this finding led Franck into a more detailed study of the reaction.

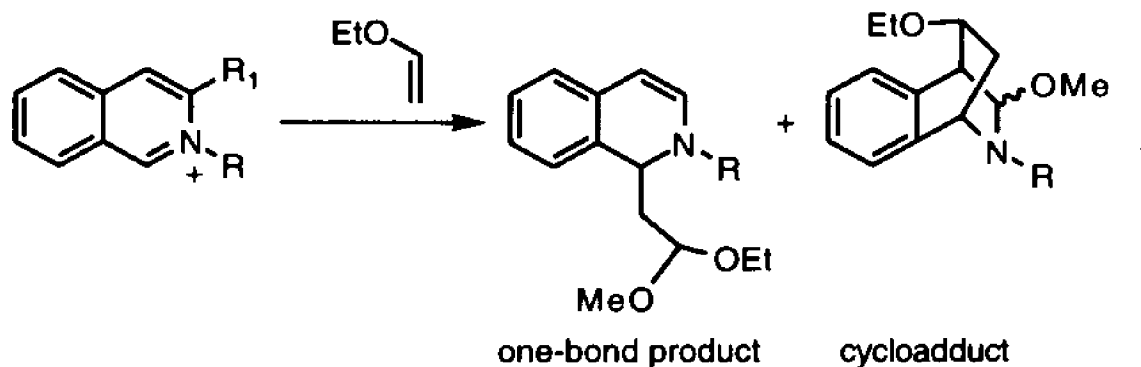
As a result of an insightful and thorough investigation, Franck proposed (scheme 108) that the first step in the reaction is the attack of the nucleophilic beta carbon of the enol ether at C1 of the isoquinolinium salt.

Scheme 108. Franck's mechanism for the cycloaddition.



Following a minor pathway, the resulting oxocarbenium ion **225** can be trapped by methanol to give the one-bond acetal **226**. In the major pathway, oxocarbenium ion **225** undergoes intramolecular attack by the enamine giving rise to the iminium ion **227**. Capture of **225** by methanol generates the tricyclic amina **228** which can be converted to acetal **229**. On the basis of this hypothesis, it was anticipated that varying the nucleophilicity of the enamine would affect the formation of the second bond between the alpha carbon of the enol ether and C4 of the isoquinolinium salt. Franck has demonstrated (scheme 109) that when the usual 2,4-dinitrophenyl substituent on the nitrogen is replaced by a carboethoxy group **230** (schemes 108 and 109), this results in a substantial increase (schemes 108 and 109) in the amount (usually less than 5%) of one bond product **232** isolated.¹⁰⁹

Scheme 109: Modulating enamine nucleophilicity in isoquinolinium salts cycloadditions.



R	R1	% one-bond	% cyclo adduct
CO ₂ Me	H (230*)	82 (232)	14 (234)
DNP**	H (217)	8.5 (226)	90 (228)
Me	Me (207)	0	

* The numbers in parenthesis refer to the structures in previous schemes. In particular, scheme 108.

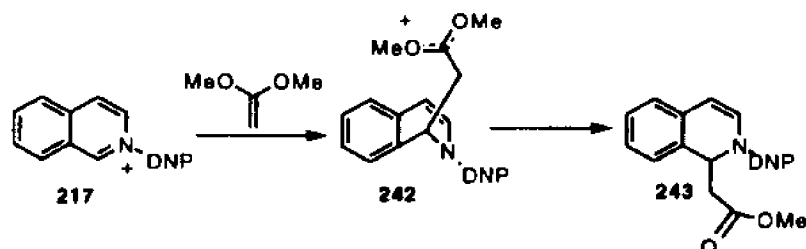
** DNP = 2,4-dinitrophenyl

In fact it becomes the major product (82% yield) with only 14% of the 1,4-cycloadduct observed. This increase in the observed yield of one bond product is attributed to the decreased nucleophilicity of the intermediate enamine **231** (scheme 108) thereby resulting in a higher probability of solvent (MeOH) capture of the intermediate oxocarbenium ion. On the other hand, increasing the nucleophilicity of the intermediate enamine **237** by using the methyl salt **236** resulted in the complete suppression of the one bond pathway (scheme 109).

" A corollary electronic effect which changes the ratio of C-C bond formation to solvent trapping"¹¹⁰ was displayed in the addition of

ketene dimethyl acetal **199** to the 2,4-dinitrophenyl isoquinolinium salt **217** (scheme 110).

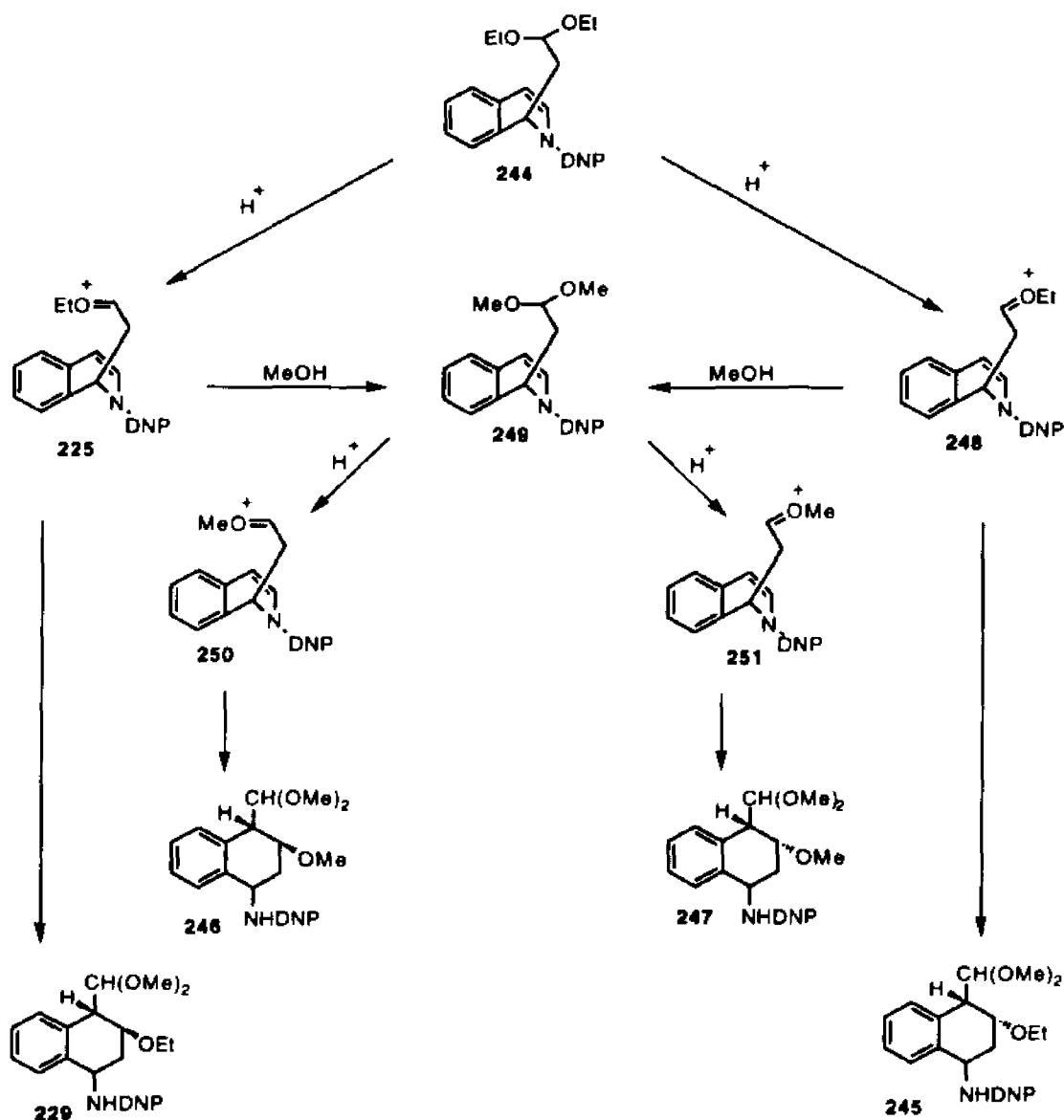
Scheme 110: The cycloaddition of ketene dimethyl acetal to 2,4-dinitrophenyl-isoquinolinium salts.



In this case, it is the reactivity of the intermediate oxocarbenium ion **242** which was decreased. As previously demonstrated by modulating enamine reactivity, adversely affecting the rate of ring closure by generating a more stable carbocation resulted in a predominance of the product **243** resulting from solvent capture.

The two step mechanism proposed by Franck had to address the question of the stereospecificity as well as the stereoselective course of the reaction. The stereochemical outcome of the reaction can be supported by a two step mechanism only by postulating that the ring closure step (the enamine capture of the oxocarbenium ion) to be faster than solvent capture (leading to one bond product) and C-C bond rotation (which leads to a mixture of *exo* and *endo* isomers).

Scheme 111: Rate of ring closure vs. solvent capture.

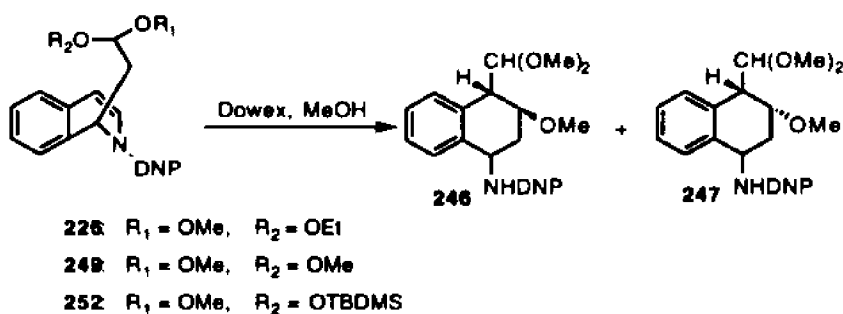


The diethyl acetal **244** isolated from the reaction of ethyl vinyl ether **83** and 2,4-dinitrophenylisoquinolinium salt **217** carried out in ethanol, was "recycled" (scheme 111). Upon exposure to acidic methanol, the major products, acetals **229** and **245** were isolated in 94% yield while the C2 methoxy analogues **246** and **247** were obtained in a combined yield of only 6% yields. Clearly, the major products arise from a fast internal capture of the acid-generated ethoxycarbonium ions **225** and

248. The scenario for the generation of the minor products involves solvent capture and exchange in **225** and **248** to generate acetal **249**. Acid catalyzed elimination of methanol from acetal **249** leads to the minor products via oxocarbenium ions **250** and **251**. Had the rate of solvent capture been comparable or faster than the ring closure step a higher proportion of the C2-methoxy products would be observed. One is forced therefore to conclude that the rate of ring closure is faster than solvent trapping.

The fact that the rate of ring closure is faster than rotation about the C-C bond in the oxocarbenium ion was cleverly demonstrated by generating compounds **229** and **245** from different mixed acetals one bond precursors (scheme 112).

Scheme 112: Rate of ring closure vs. C-C bond rotation.



One-bond product	% 22	% 37	% 35	% 36
226	31	19	47	3
249	•	•	86	14
252	•	•	40	60

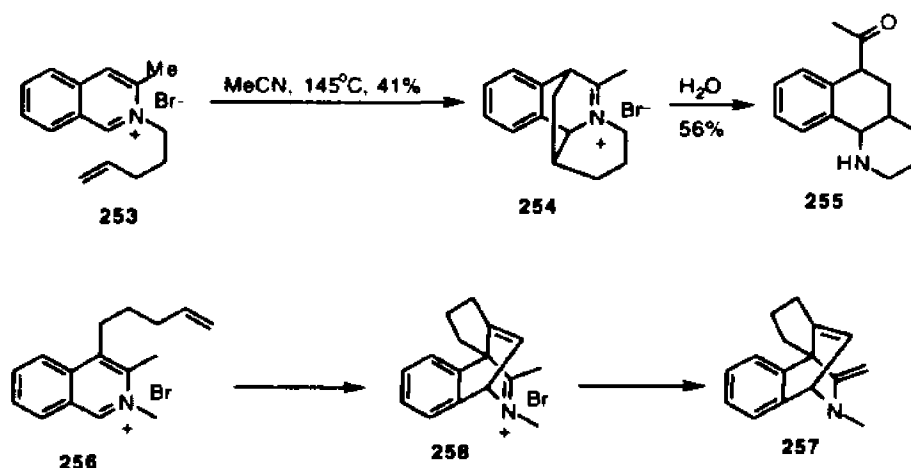
Each recycling experiment gave rise to a different ratio of **246** and **247**. Therefore, one can exclude a fast C-C bond rotation in the

generated oxocarbenium ions so as to achieve equilibrium mixtures of exo **250** and endo **251** oriented ions. In the event of such equilibration, the observed ratio of products would be identical in each recycling experiment. Franck concluded therefore that the rate of ring closure is faster than C-C bond rotation in the intermediate carbocations generated.

3) The intramolecular Bradsher cycloaddition

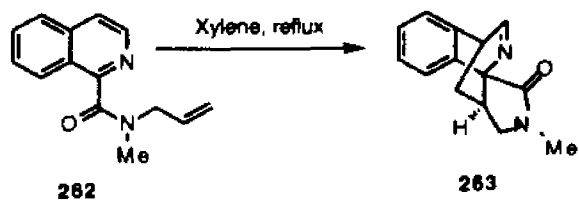
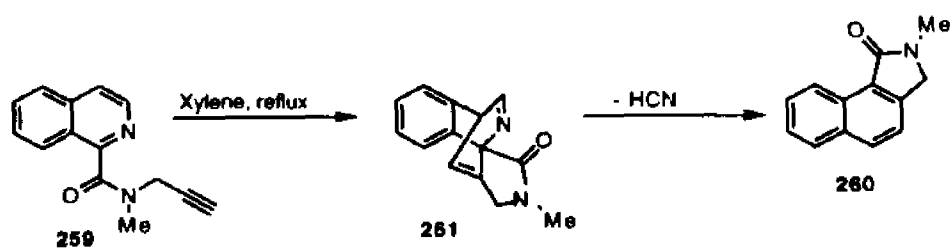
The intramolecular version of the Bradsher cycloaddition has been studied by Sammes (scheme 18).¹¹¹ He observed that the tethering of a pentenyl side chain to the isoquinolinium framework resulted in a thermally promoted addition of the alkenyl moiety across the 1,4 positions. Two examples where the linkage to the unsaturation is at the 2 and 4 positions of the isoquinoline have been documented (scheme 113). Thus, N-pentenyl-2-methyl isoquinolinium bromide **253** cyclized to the imminium ion **254** which could be hydrolyzed to amino ketone **255**. The cycloaddition of N-methyl-3-methyl-4-pentenyl isoquinolinium bromide **256** provided enamine **257** via imminium ion **258**.

Scheme 113: Sammes intramolecular versions.



In a recent report, Wuonola¹¹² has unveiled a novel intramolecular example where an acetylene or an alkene is appended to C1 via an amide linkage (scheme 19). The cycloadditions were found to proceed well under refluxing conditions without prior activation of the heterocycle in the form of its ammonium salt. Cycloaddition of acetylenic amide **259** gave rise to N-methyl pyrrolidone **260** from the extrusion of HCN from the intermediate imine **261**. The addition of allyl amide **262** yielded cycloadduct **263**.

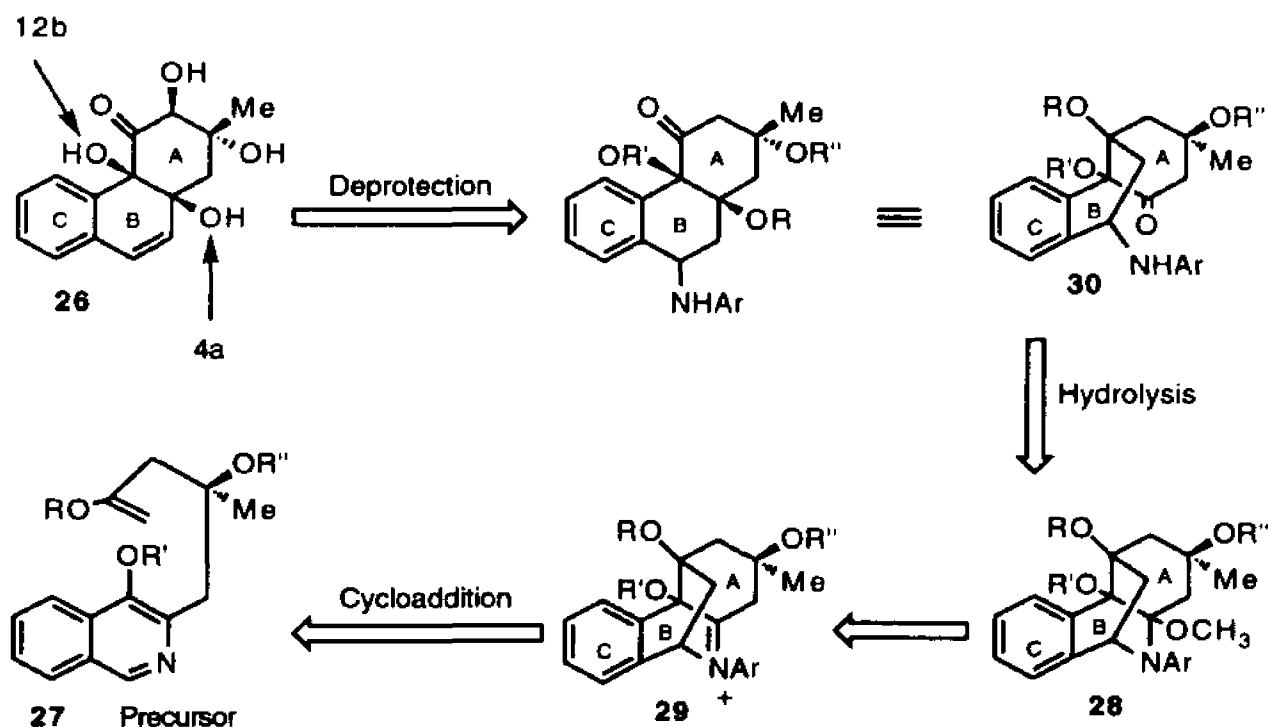
Scheme 114: Wuonola's intramolecular versions



CHAPTER 6: OUR STUDY OF THE BRADSHER CYCLOADDITION OF 4-ALKOXYISOQUINOLINIUM SALTS.

As the retrosynthetic scheme shows (see scheme12, reproduced below), our approach to the AB ring system of the angucyclines is predicated on the ability of the Bradsher reaction to position the hydroxyl groups of the ring junction, in particular, the 12b hydroxyl.

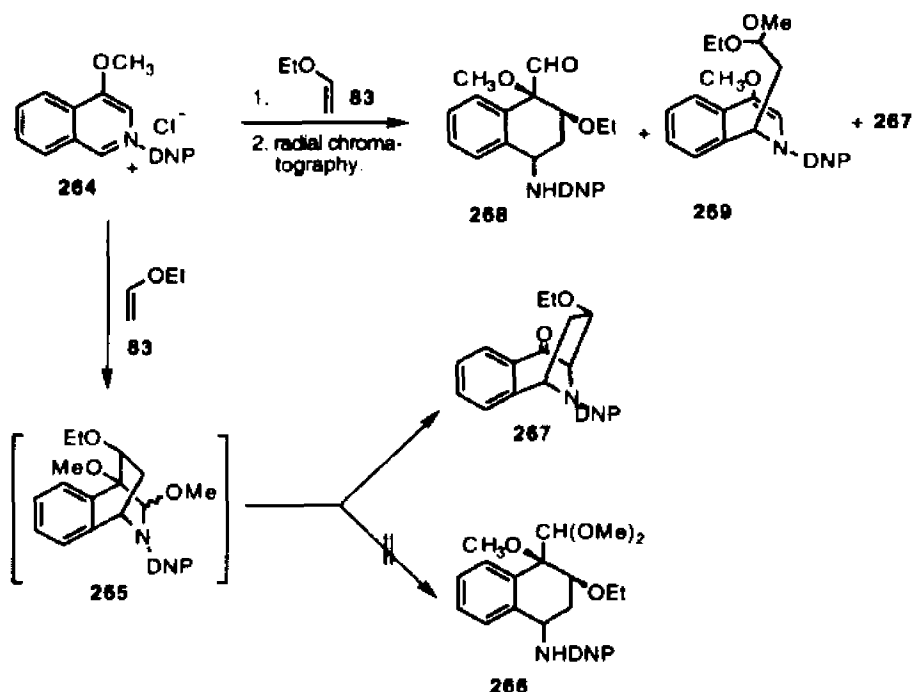
Scheme 12: Retrosynthetic analysis of the ABC ring system of Aquayamycin



Such an approach in turn, requires 4-alkoxy substituted isoquinolines since the oxygen functionality at the 4 position is destined to become the 12b hydroxyl of the angucycline BC-ring junction while the 4a hydroxyl of the natural products would be furnished by the enol ether. At the outset of our investigation there had been no report in the literature of the cycloaddition of 4-alkoxy isoquinolinium salts. The

first order of business therefore was to determine the feasibility of such a process. In the event, 4-methoxyisoquinolinium salt **264** was reacted with ethyl vinyl ether **83** in methanol with suspended calcium carbonate as an HCl scavenger.¹¹³

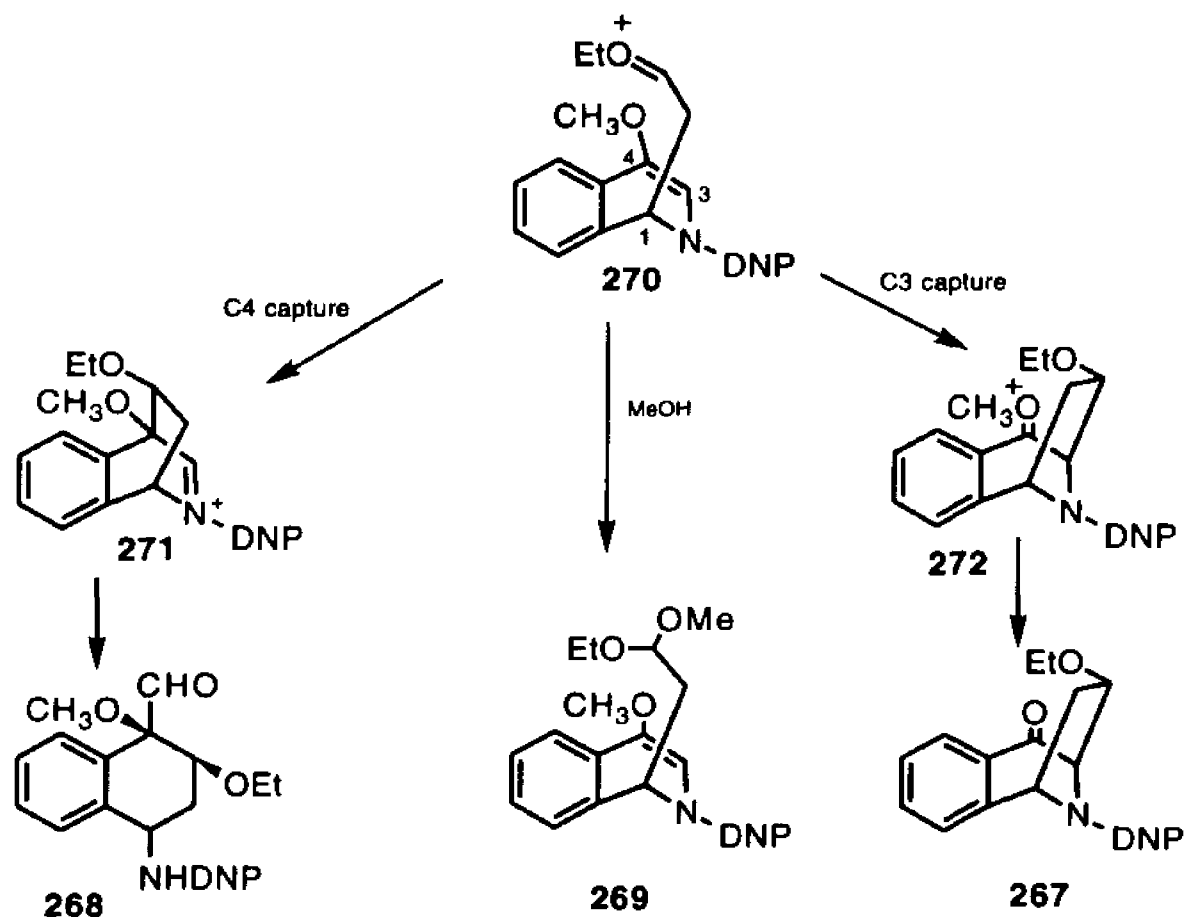
Scheme 115: The cycloaddition of 4-methoxy isoquinolinium salt



In accord with the standard protocol of our laboratory,¹¹⁴ the crude reaction product, expected to be the tricyclic aminal **265**, was not characterized, but treated directly with an acidic resin (Dowex H⁺) in anhydrous methanol so as to effect the conversion of the putative intermediate **265** to acetal **266**. The major product isolated was ketone **267**. In contrast to the structure of the desired adduct, acetal **266** in which ring closure took place by the addition of the enol ether across the 1,4 positions of the isoquinoline nucleus, in cycloheptanone **267**, the addition was established across the 1,3 positions. Henceforth

aldehyde **268** (or its dimethyl acetal derivative **266**) will be referred to as the 1,4-adduct whereas endo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-ethoxy (ketone **267**) will be referred to as the 1,3-adduct. In very careful work in our laboratory, the experiment was repeated.¹¹⁵ In a break from the established procedure, the crude reaction mixture was chromatographed rather than subjected to the acid/methanol treatment. In addition to the the 1,4- **268** and 1,3- **267** adducts, a mixed acetal **269** was isolated in which only one bond had formed between the enol ether and the isoquinolinium salt. Although the Bradsher cycloaddition had been considered a case of inverse electron demand Diels-Alder,¹¹⁶ it is unlikely that three separate pathways would be operative in this reaction so as to generate the three products in equal amounts. A concerted 1,4 addition and 1,3 dipolar mechanism may account for the aldehyde and ketone formation but the presence of the one-bond product suggested rather the existence of a common intermediate partitioning along three different paths. This result further corroborated previous evidence for the operation of a stepwise mechanism in the Bradsher cycloaddition.

Scheme 116: Mechanism for the addition of 4-methoxy isoquinolinium salt.

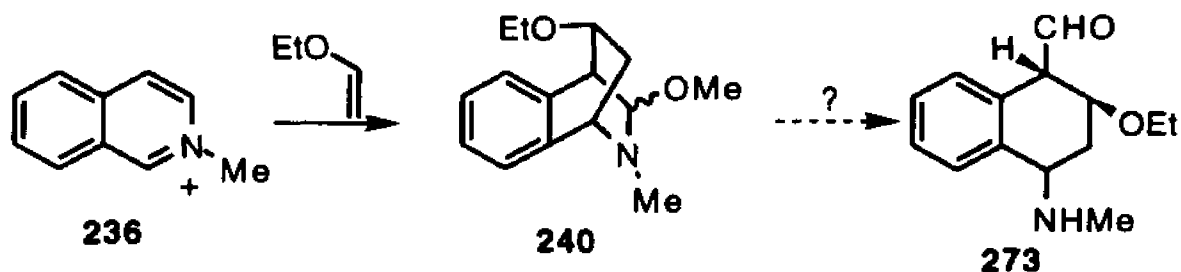


Franck¹¹⁷ proposed that the first step is the attack of the nucleophilic β -carbon of the enol ether at C1 of the isoquinolinium salt giving rise to oxocarbenium ion intermediate **270**. The one bond product **269** arises from capture of the oxocarbenium ion by the solvent methanol. As observed in the unsubstituted case, the normal course of the reaction is the capture of the oxocarbenium ion by the enamine functionality. Such a process led to the 1,4-adduct **268** via iminium ion **271**. In previous cases, C4 of the heterocycle being unsubstituted presented neither steric nor electronic complications for the enamine trapping of

the oxocarbenium ion. In the present situation however, the methoxy substituent at C4 renders C3 part of an enol ether which competes with C4 for the nucleophilic capture of the oxocarbenium ion. Trapping then by the enol ether led to the 1,3-adduct **267** through the intermediacy of oxocarbenium ion **272**.

In order to successfully apply the Bradsher strategy to the synthesis of the angucyclines, the pathway leading to the 1,3-adduct had to be suppressed. As an inspection of the intermediate oxocarbenium ion **270** will suggest, decreasing the nucleophilicity of the enol ether by placing electron withdrawing groups at the C4-hydroxyl of the isoquinolinium salt and/or increasing the nucleophilicity of the enamine by replacing the 2,4-dinitrophenyl group with electron donating substituents would greatly favor the 1, 4-pathway over the 1,3. Previous experiments with the 2- methyl isoquinolinium salts **236** had shown that while the cycloaddition proceeded in a normal fashion to aminal **240** there was to date no procedures to effect its transformation to the aldehyde **273**.¹¹⁸

Scheme 117: Cycloaddition of the methyl isoquinolinium salt.



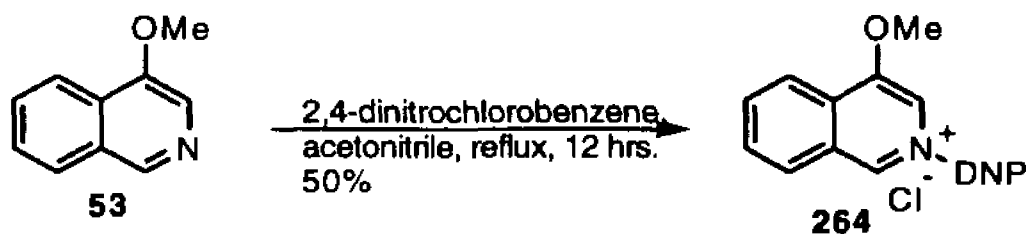
Therefore, in practice, we sought to eliminate the enol ether trapping leading to the 1,3-adduct **267** by placing electron withdrawing

substituents at the C4-hydroxyl of isoquinolinium salt. For the purpose of studying this novel variation in the Bradsher cycloaddition various 2-(2,4-dinitrophenyl)-4-oxygenated isoquinolinium salts as well as various enol ethers were synthesized.

1) The synthesis of 4-oxygenated-n-arylisoquinolinium salts.

The 2-(2,4-dinitrophenyl)-4-methoxy isoquinolinium chloride **264** was synthesized, in an application of literature protocols, by refluxing 4-methoxy isoquinoline **53** and dinitrochlorobenzene in acetonitrile for twelve hours.¹¹⁹

Scheme 118: 2-(2,4-DNP)-4-methoxy isoquinolinium salt.

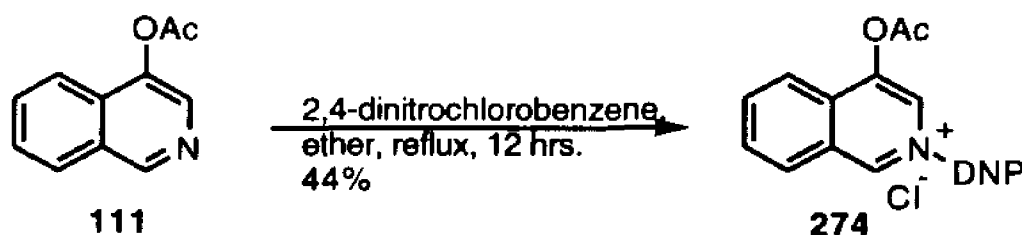


The product which was isolated as a brown solid precipitating out of the solution was obtained in 50% yields (unoptimized). The structure of the salt was ascertained from its proton nmr spectrum which exhibited, in addition to the 2,4-dinitrophenyl group resonances, a characteristic deshielding of all the aromatic protons from their counterparts in the starting material.

Our original attempts at synthesizing 2-(2,4-dinitrophenyl)-4-acetoxy isoquinolinium chloride **274** of 4-acetoxyisoquinoline **111**

involved refluxing the isoquinolinyl ether and 2,4-dinitrochlorobenzene in acetonitrile.

Scheme 119: 2-(2,4-DNP)-4-acetoxy isoquinolinium salt.

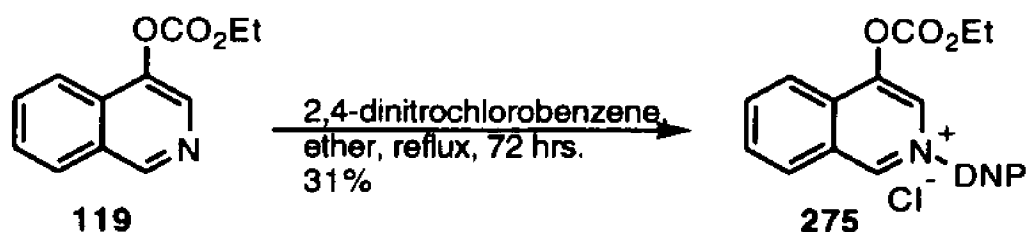


The reaction proceeded at a much slower rate than observed for the conversion of 4-methoxyisoquinoline to its DNP salt. This observation is consistent with reduced electron density at the nitrogen due to the deactivating effect of the 4-acetoxy substituent. Tlc monitoring revealed the complete disappearance of the starting material after five days while a yellow precipitate begins to form after twelve hours. Unfortunately only 25% yields of the desired salt **274** could be isolated. The salt appears to be unstable and prolonged heating to effect the complete conversion of the starting material resulted in substantial decomposition of the product formed. The yield of the desired salt was increased to 44% by refluxing in ether for twelve hours. Unreacted starting material and 2,4-dinitrochlorobenzene were removed by repeated ether washing of the yellow solid that precipitated from the reaction mixture.

The ethoxycarbonyl group of 4-(ethoxycarbonyloxy)isoquinoline **119**, like the acetoxy group of **111**, deactivates the isoquinoline nitrogen toward the desired nucleophilic aromatic substitution reaction

with 2,4-dinitrochlorobenzene to yield 2-(2,4-dinitrophenyl)-4-(carboethoxy) isoquinolinium chloride **275**.

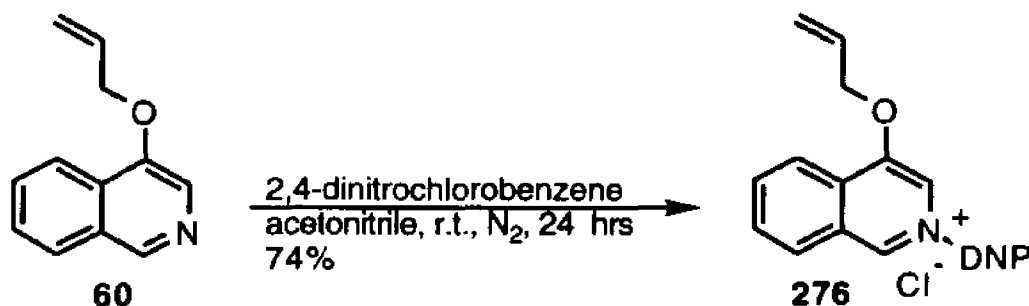
Scheme120: 2-(2,4-DNP)-4-carboethoxy isoquinolinium salt.



The problem encountered in the synthesis of the acetoxy salt surfaced again in this context: slow conversion of the starting material, carbonate **119**, to product and decomposition of the salt **275** formed under prolonged treatment under the reaction conditions. Under reflux conditions in acetonitrile over 48 hours only 11% of the salt could be isolated. The yield was increased to 31% by carrying out the reaction in ether over a three day period. Prolonged heating in ether (five days) resulted in a slight decrease in the yield (28%) of the product. This decrease in yield is attributed to the relative instability of the salt under the reaction conditions.

The conditions that proved adequate for the synthesis of the 4-methoxy, acetoxy and ethoxycarbonyl salts delivered only a brown gum in the case of the 4-allyloxy derivative, 2-(2,4-dinitrophenyl)-4-allyloxy isoquinolinium chloride **276**.

Scheme 121: The synthesis of 2(2,4-dinitrophenyl)-4-allyloxyisoquinolinium chloride.

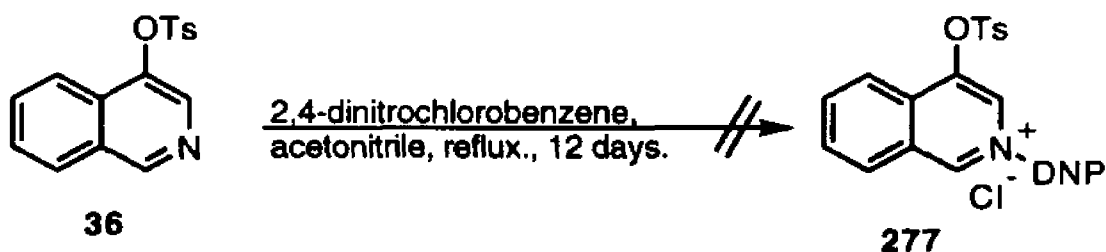


Surprisingly the ¹H nmr was consistent with the structure expected for the desired salt. In fact the "gum" could even be used in the Bradsher cycloaddition to yield the anticipated tetralins. Nevertheless we still sought conditions that would yield a crystalline salt for ease of handling and storage purposes. Refluxing the starting material, 4-allyloxy isoquinoline **60** (scheme 164), in either acetonitrile or ether as well as carrying the reaction in THF under pressure resulted in the obtention of the same non-crystalline material which could not be recrystallized. It was observed that 2,4-dinitrochlorobenzene "dissolved" in the viscous 4-allyloxy isoquinoline to yield a homogeneous mixture. The mixture was stirred at room temperature for twelve hours and upon addition of small amounts of ether a yellow solid precipitated out. A 74% yield of the salt could be obtained following repeated washings with diethyl ether. Crystalline material could also be obtained by stirring the 4-allyloxyisoquinoline with 2-4-dinitrochlorobenzene in acetonitrile at room temperature for four days. The desired salt precipitates out of acetonitrile as well. Nevertheless the salt displays an appreciable solubility in acetonitrile so that repeated washing resulted in slightly lower yields. We speculate that better results could be obtained by

stirring the two components in ether at room temperature. It is clear therefore that the problem encountered earlier was due to the fact that the reaction mixture was heated.

The problems encountered in the synthesis of 4-acetoxy and 4-ethoxycarbonyl isoquinolinium salts **274** and **275** also plagued our efforts to obtain 2-(2,4-dinitrophenyl)-4-tosyloxy isoquinolinium chloride **277**. The presence at C4 of a stronger electron withdrawing group than previously studied resulted in almost complete deactivation of the nitrogen. Upon stirring ester **36** with 2,4-dinitrochloro benzene for four days, inspection of the tlc trace revealed the formation of a slow-moving material presumed to be the desired salt **277**. Nevertheless, the starting starting 4-tosyloxy isoquinoline **36**, was still present in the reaction mixture after refluxing in acetonitrile for twelve days. No attempt was made to elucidate the structure of the "product" formed since it became obvious that the tosyloxy salt would be of little practical value with regard to our synthetic aims. The 4-tosyloxy group deactivation of the isoquinoline nitrogen towards electrophilic reagents has been advantageously exploited in our elaboration of the Claisen products.

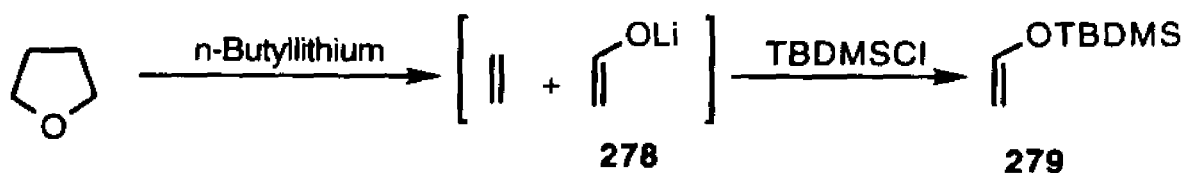
Scheme 122: 2-(2,4-DNP)-4-tosyloxy isoquinolinium salt.



2) The synthesis of the vinyl ethers

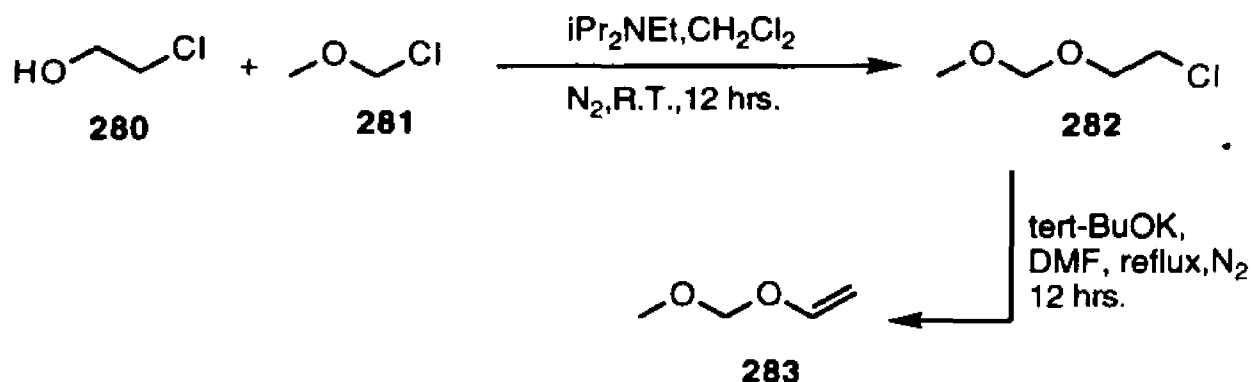
The fragmentation of tetrahydrofuran in the presence of alkyllithium reagents results in the extrusion of ethylene and the generation of the acetaldehyde enolate **278**.¹²⁰ Capture of the enolate with tert-butyldimethylsilyl chloride effected the overall transformation of tetrahydrofuran to tert-butyldimethylsilyl vinyl ether **279**.

Scheme 123: The synthesis of TBDMS vinyl ether.



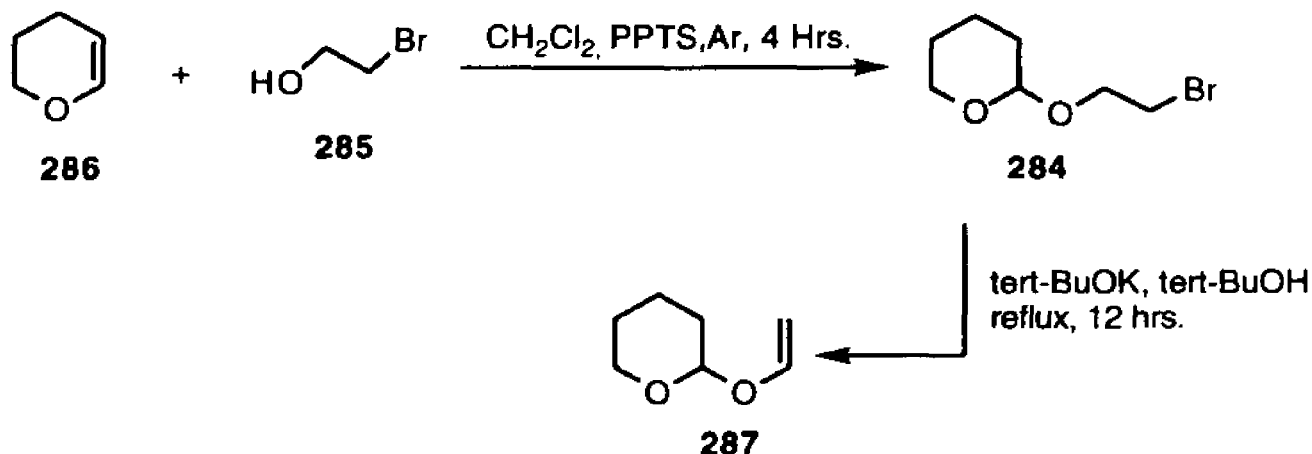
The protection of 2-chloroethanol **280** as the methoxymethyl ether derivative **282** was accomplished by treating it with chloromethyl methyl ether **281** in the presence of diisopropyl ethyl amine. Our attempts to effect the dehydrochlorination of **282** by using DBU or potassium hydroxide were not successful. The synthesis of the desired vinyl ether **283** from 2-chloroethyl chloromethyl ether **282** was accomplished by refluxing it over potassium tert-butoxide.

Scheme 124: The synthesis of methoxy methyl vinyl ether.



The tetrahydropyranyl derivative **284** of 2-bromoethanol **285** was obtained by treatment of the alcohol with dihydropyran **286** in the presence of pyridinium para-toluene sulfonate. The mixture of conformers could subsequently be dehydrochlorinated to the desired tetrahydropyranyl vinyl ether **287**.

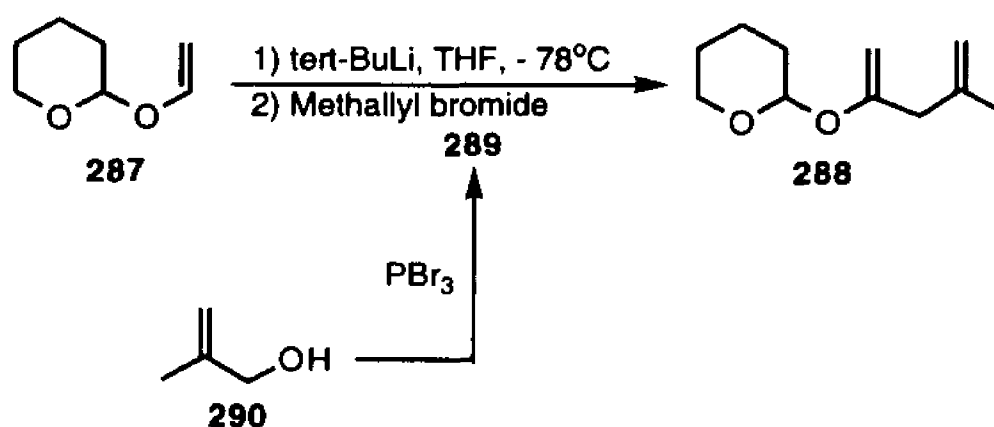
Scheme 125: The synthesis of tetrahydropyranyloxy vinyl ether.



The one-pot procedure of D'Angelo¹²¹ proved to be more convenient. Accordingly, a mixture of 2-chloroethanol and dihydropyran was stirred overnight in the presence of catalytic amounts of HCl. Potassium *tert*-butoxide was then added and the mixture was brought to reflux. The desired vinyl ether **287** was obtained following aqueous work up.

As part of an intermolecular Bradsher cycloaddition approach to the AB ring system of the angucyclines, the branched vinyl ether **288** was needed. The tetrahydropyranyl vinyl ether **287** was deprotonated with *tert*-butyl lithium¹²² and the α -lithio derivative was condensed with 2-methyl-3-bromopropene **289** obtained from treatment of 2-methyl-2-propenol **290** with phosphorus tribromide.¹²³ Thus enol ether **288** was obtained in 16 % unoptimized yields.

Scheme 126: The synthesis of 1-(2-methylpropenyl)tetrahydropyranyl vinyl ether.

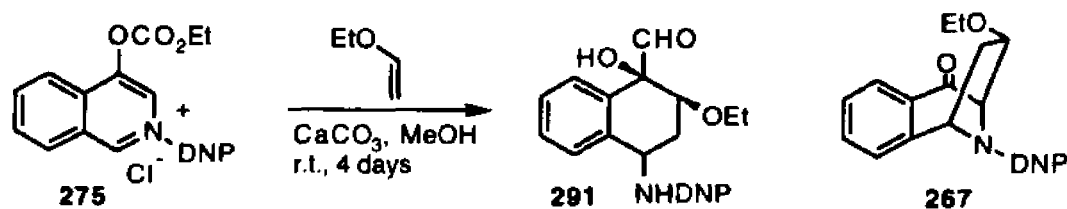


The unsatisfactory yields of the product is attributed to the protonation of the α -tetrahydropyranyloxyvinyl lithium by phosphoric acid impurities in the 2-methyl-3-bromopropene used in the coupling.

3) Our study of the Bradsher cycloaddition of 4-alkoxyisoquinolinium salts:

The cycloaddition of 2-(2,4-dinitrophenyl)-4-(ethoxycarbonyl)-isoquinolinium chloride 275 with ethyl vinyl ether 83 led to a 44% yield of aldehyde 291 and 21% of endo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-ethoxy (1,3 adduct 267) previously described by Franck.¹²⁴ Amino aldehyde 291 was easily identified by the characteristic singlet resonance of the aldehyde proton at 9.82 ppm in the ¹H nmr spectrum. Furthermore, the broad doublet for the NH proton at 8.88 ppm proved to be diagnostic of the opening of the isoquinoline ring.

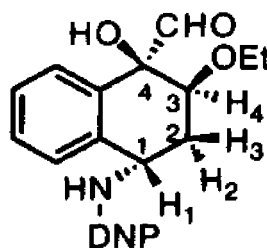
Scheme 127: The cycloaddition of 4-carboethoxy isoquinolinium salt.



The isolation of hydroxy aldehyde **291** suggests that the ethoxycarbonyl group is unstable under the reaction conditions.

Characterization of the Bradsher adducts: Confirmation of the cis-disposition of the oxygen functionalities.

The structure of **291** was assigned on the basis of its ¹H nmr spectrum which displays, at 9.82 ppm, a sharp singlet resonance corresponding to the aldehyde proton.

**291**

The appearance at 8.88 ppm of a broad doublet assigned to the NH proton proved to be quite diagnostic in the characterization of the

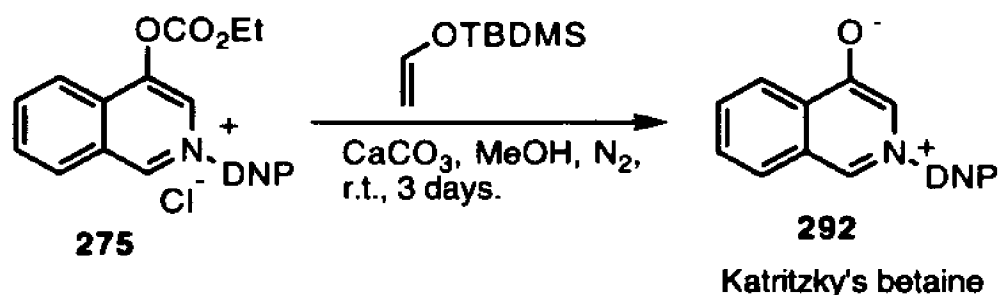
amino aldehydes synthesized in this study. By comparison, the NH resonance is conspicuously absent in the structures assigned to the one-bond and 1,3 products. Inspection of the coupling constants in the tetralin allowed us to assign the relative stereochemistry of the cyclohexane ring. The doublet of a doublet at 4.09 ppm corresponding to H4 exhibits two small coupling constants (2.1 Hz and 7.6 Hz) to the methylene group protons (H2 and H3). The magnitude of the "J" values points to an equatorial arrangement of H4. The ethoxy group is therefore assigned to the axial position. The benzylic proton, H1, which appears as a doublet of a doublet exhibits a large coupling (12.9 Hz) of the order of an axial-axial coupling and was therefore assigned an axial position leaving the amino group in the equatorial position. Since the aldehyde and amino groups arise from the cleavage of the C-N bond in the intermediate aminal, the relative cis stereochemistry of the two groups, established in the cycloaddition, is retained. A consideration of the mechanism of the Bradsher cycloaddition reveals that the two groups per force are cis. On the basis therefore of the mechanism and the axial orientation of the benzylic proton H1, the aldehyde group was assigned an axial orientation. The hydroxyl group at C4 must therefore be positioned equatorially. With the axial orientation of the ethoxy group, *the cis positioning of the alkoxy functionalities by the Bradsher reaction, the basic tenet of our approach to the angucyclines, was thus clearly established.* The diastereotopic methylene protons, H2 and H3, were distinguished on the basis of their chemical shifts. The more shielded resonance was assigned to the axial proton. This distinction was further supported by the two small coupling constants (5.1 Hz and 7.5 Hz) exhibited by the downfield signal. The chemical shifts and

coupling constants arguments that led to the structural and stereochemical characterization of the hydroxy product proved to be remarkably consistent in the tetralin series synthesized in this study. In addition to the ^1H nmr data, the infrared spectral analysis was, of course, unequivocal in determining the presence and absence of the NH stretching frequency. The band at 3300 cm^{-1} which appears in the spectra of the 1,4-adducts was absent in the spectra of the 1,3-adducts. The 1,4-adducts displayed an aldehyde band at 1730 cm^{-1} . On the other hand, the carbonyl of the 1,3-adducts appears at 1700 cm^{-1} , as would be expected for conjugated ketones.

As far as our objective to suppress the 1,3 pathway is concerned, the ethoxycarbonyl group, notwithstanding the cleavage, was successful in deactivating C3 thus disfavoring the 1,3 pathway.

The addition of tert-butyldimethylsilyl vinyl ether to salt **275** resulted in no identifiable products. In this case, apparently, the cycloaddition proceeds at a much slower pace than the decomposition of the salt as it loses the ethoxycarbonyloxy group.

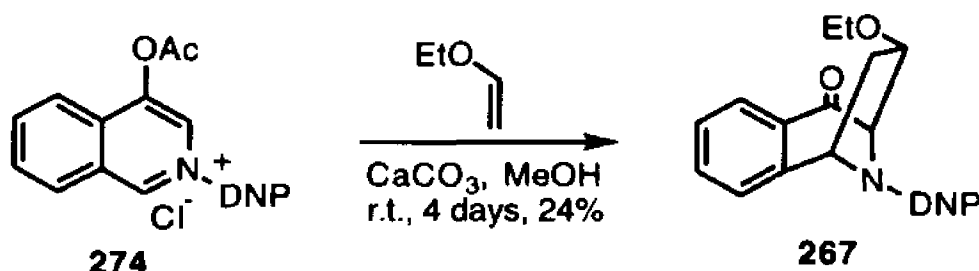
Scheme 128: TBDMS vinyl ether reaction with 4-carboethoxy isoquinolinium salt.



The removal of the protecting group led to the betaine **292** analogous to the N-methyl derivative **337** (scheme 150) previously reported by Katritzky.¹²⁵ The Katritzky betaine is known to undergo cycloaddition reactions, albeit with electron deficient alkenes. However, the unfavorable electronic pairing of the reactants in our case does not lead to a vinyl ether adduct.

The cycloaddition of 2-(2,4-dinitrophenyl)-4-(acetoxy)-isoquinolinium chloride **274** with ethyl vinyl ether **83** led to the isolation of the 1,3 adduct endo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-ethoxy **267** in 24% yields. No other products were observed (scheme 139).

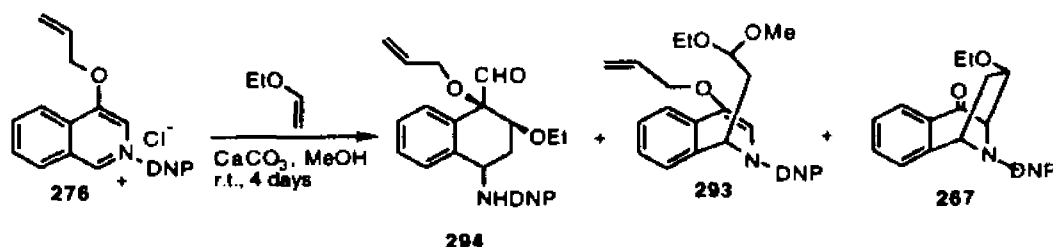
Scheme 129: The cycloaddition of 4-acetoxy isoquinolinium salt.



It comes as no surprise that the reaction being carried out under the standard conditions for the removal of the acetoxy group results in extensive decomposition to the Katritzky betaine **292**. No products could be isolated in the reaction of tert-butyldimethylsilyl vinyl ether with the acetoxy salt. Apparently, the slower addition of a less reactive enol ether does not compete effectively with the removal of the acetyl group.

The cycloaddition of ethyl vinyl ether to the 4-allyloxyisoquinolinium salt **276** gave rise to one-bond product **293** and the desired aldehyde **294**, expected from the 1,4-addition of the enol ether, in 9% and 18% yields respectively. In addition, an 11% yield of 1,3 adduct **267** was also obtained. The aldehyde **294** displayed the characteristic aldehyde and NH protons as well as the resonances corresponding to the allyl group (particularly the multiplet corresponding to the internal vinyl proton). An analysis of the coupling constants, which led to the assignment of an equatorial position for the CHOEt proton and an axial orientation of the benzylic proton, established the relative cis arrangements of the alkoxy functionalities of the cyclohexyl fragment. One-bond product **293** was identified by the presence of the vinyl singlet at 5.1 ppm. The presence of the dihydro pyridine ring was ascertained by the absence of an NH resonance as well as a characteristic upfield shift of the H2 proton of the 2,4-dinitrophenyl group. This upfield shift is also observed in the 1,3 adduct and is evidence that no C-N bond breaking has taken place. Furthermore, the diastereotopic protons alpha to the acetal carbons appear at nearly the same chemical shift. This is indicative of free rotation about the C-C bond since the chemical shift difference between the two protons is significant when they are constrained into the 1,4 or 1,3 rings.

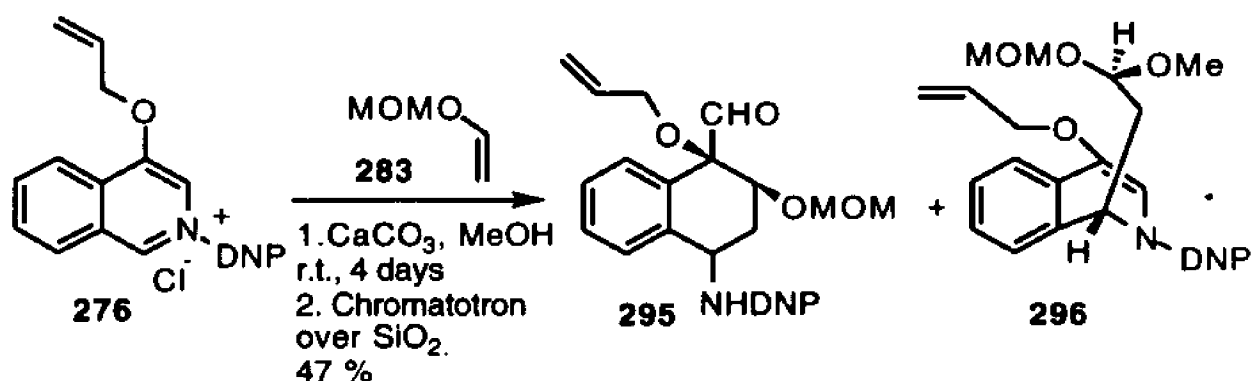
Scheme 130. The cycloaddition of 4-allyloxy isoquinolinium salt with ethyl vinyl ether.



The separation of the products by radial chromatography proved to be very tedious as silica gel induces further transformations of the products. It is believed for example that the 1,3 adduct **267** isolated arises from such a transformation since an examination of the ^1H nmr of the crude reaction mixture prior to chromatography reveals that it is absent. The isolation of analytically pure samples required repeated chromatography of the various fractions. The rest of the reaction mixture consisted mainly of a mixture of aldehyde **294** and one-bond **293** products.

Treatment of 2-(2,4-dinitrophenyl)-4-allyloxyisoquinolinium chloride **276** with methoxymethyl vinyl ether **283** under the conditions of the Bradsher reaction led to the isolation of aldehyde **295** in 46% yield following radial chromatography (scheme 141). The structure of the adduct was assigned by comparison of its ^1H nmr spectrum with the previously identified adducts. In addition to the aldehyde and NH resonances, the incorporation of the methoxymethyl group was ascertained by the presence of an AB quartet at 4.83 due to the acetal protons.

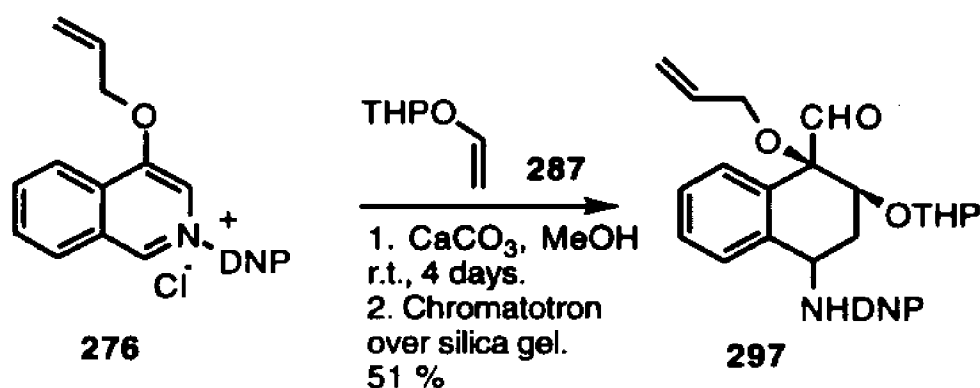
Scheme 131: The cycloaddition of 4-allyloxy isoquinolinium salt with methoxy methyl vinyl ether.



A minor chromatographic fraction was identified as a mixture of diastereomeric one-bond products **296** on the basis of the ^1H nmr spectrum. Surprisingly, no fraction corresponding to the 1,3 adduct **267** was isolated.

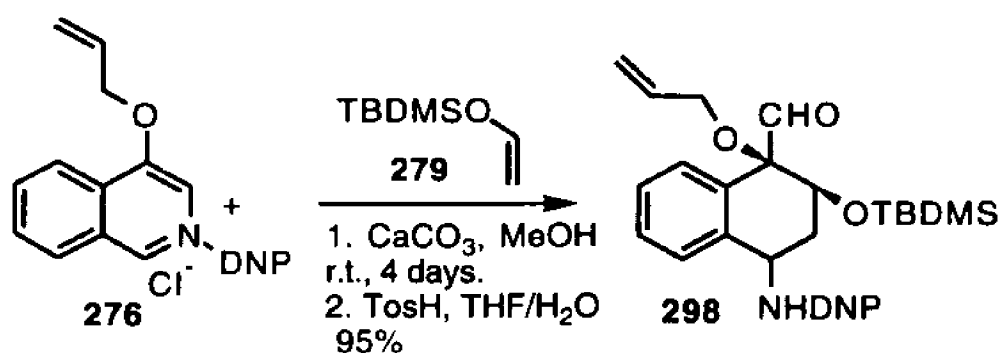
Tetrahydropyranyl vinyl ether **287** reacted with allyloxy salt **276** uneventfully to produce aldehyde **297** in 51% yield accompanied by various side products which although not fully identified seem to correspond to one-bond structures on the basis of their ^1H nmr spectra.

Scheme 132: The cycloaddition of 4-allyloxy isoquinolinium salt with tetrahydropyranyloxy vinyl ether.



The cycloaddition of the tert-butyldimethylsilyl vinyl ether **279** to salt **276** proved ideal for our synthetic purposes.

Scheme 133: The cycloaddition of 4-allyloxy isoquinolinium salt with terbutyldimethylsilyl vinyl ether.



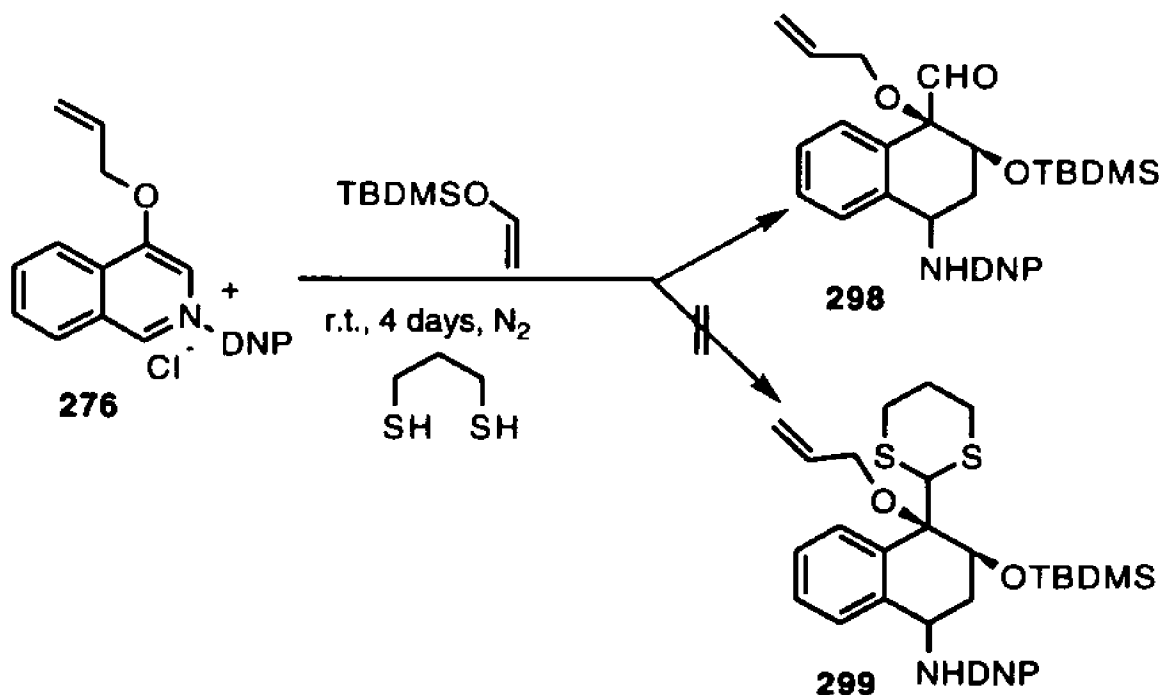
Upon stirring at room temperature for three days in methanol with suspended calcium carbonate, the crude reaction mixture was filtered in order to remove the base. Rather than immediate chromatographic treatment as was done in previous cases, the crude mixture was treated with p-toluene sulfonic acid in THF/H₂O for 12 hours. This procedure allowed for the obtention of a quantitative yield of the desired aldehyde **298** with an exceptional degree of purity as ascertained by ¹H nmr.

Although it came as a pleasant surprise that the 4-allyloxy group proved quite successful in steering the reaction exclusively down the 1,4-pathway the mechanism by which it exerts its influence is not obvious in the context of a two-step mechanism.

Franck¹²⁶ and Falck¹²⁷ had shown earlier that a one pot cycloaddition with concurrent protection of the ensuing aldehyde could be effected by carrying out the cycloaddition in the presence of propane

dithiol. The usual acid scavenger, calcium carbonate, was omitted so as to allow the acid generated to catalyze the dithio acetal formation. In an attempt to extend the methodology to the 4-alkoxy isoquinolinium series, the cycloaddition of 4-allyloxy isoquinolinium salt **276** and TBDMS vinyl ether **279** was carried out in methylene chloride in the presence of one equivalent of propane dithiol (scheme 134). Under these conditions however polymerization of the enol ether occurred much faster than the cycloaddition and although a small amount of aldehyde **298** was obtained, none of the expected dithiane derivative **299** could be isolated.

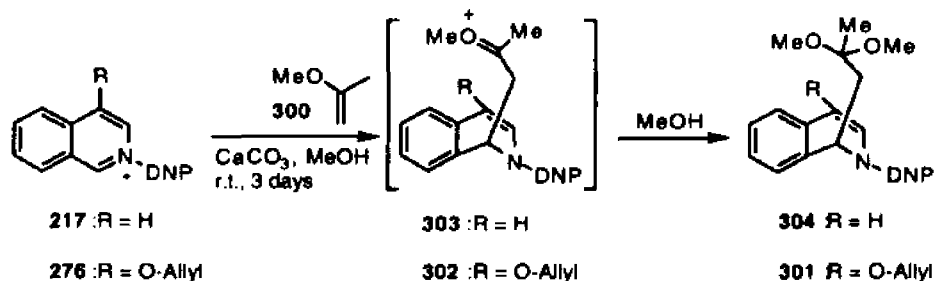
Scheme 134: The cycloaddition of 4-allyloxy isoquinolinium salt with tertbutyldimethylsilyl vinyl ether in the presence of propane dithiol.



The cycloaddition of the allyloxy salt described thus far were carried out with unsubstituted vinyl ethers. Our interest in the stereochemical outcome of the addition branched vinyl ethers and the prospect of an intermolecular Bradher route to the angucyclines led us to study the reaction of 2-methoxy propene **300** and tetrahydropyranyl vinyl ether **288** with salt **276**.

The crude ^1H nmr revealed that the cycloaddition of salt **276** with 2-methoxypropene had led quantitatively to ketal **301**, the one-bond product resulting from preferential solvent capture of oxocarbenium ion **302**.

Scheme 135: The cycloaddition of 4-allyloxy isoquinolinium salt with methoxy propene.

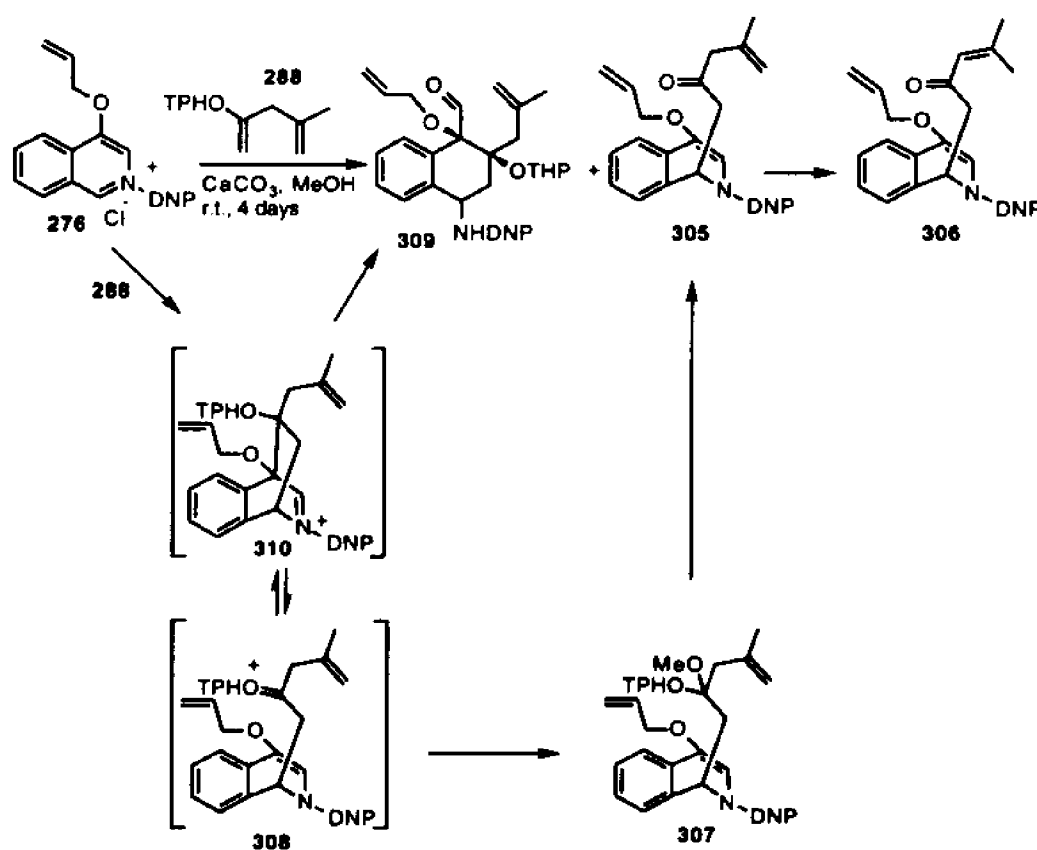


These results are in agreement with the observation that in the parent unsubstituted isoquinolinium salt **217**, the reaction with 2-methoxy propene led to a substantial increase in the amount of one-bond product **304** formed. This outcome was explained on the basis of the decreased reactivity of the very stable oxocarbenium ion **303**, formed from initial attack of the enol ether at C1, towards nucleophilic capture by the enamine. Steric retardation of the ring closure step is appreciable since the second bond formation now brings into play an electrophilic carbon center which is tertiary. In the case of the 4-allyloxy system **302**, this

steric hindrance is further amplified by the presence of the allyloxy group at C4. It is not therefore surprising that solvent capture occurs faster than the C-C bond formation involving the two tertiary centers.

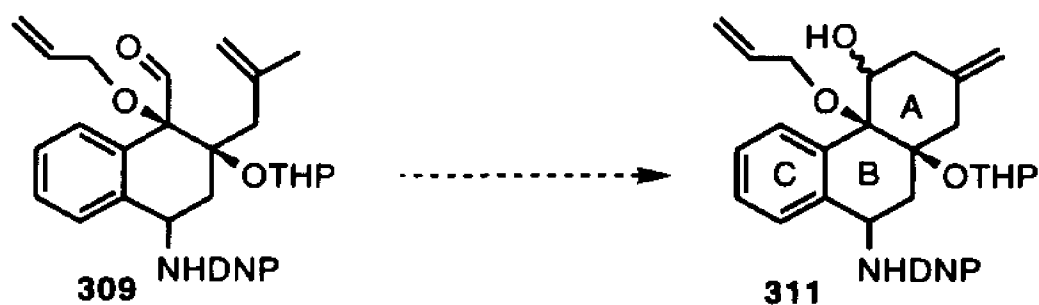
The cycloaddition of 1-(2-methylpropenyl)tetrahydropyranyl vinyl ether **288** confirmed the above result that the reaction of branched vinyl ethers with isoquinolinium salts result mainly in the formation of one-bond products (scheme 136). The unconjugated enone **305** was obtained in 25% yields accompanied by 10% of the α,β unsaturated isomer **306**.

Scheme 136: The cycloaddition of 4-allyloxy isoquinolinium salt with 1-(2-methylpropenyl) tetrahydropyranyl vinyl ether.



The one-bond ketones observed arise undoubtedly from hydrolysis of ketal **307** which is the product of solvent capture of oxocarbonium ion **308**. The α,β unsaturated ketone **306** is produced by facile isomerisation of the terminal double bond of **305** into conjugation with the carbonyl. This reaction differed significantly from the 2-methoxy propene case in that the presence of aldehyde **309** (ca. 7% yield) could be ascertained by ^1H nmr of one of the fractions obtained by radial chromatography. It seems that in spite of the steric hindrance associated with the second bond formation oxocarbonium **308** is more reactive than its counterpart **302** so that a small amount of the product **310** resulting from enamine trapping can be observed. Given the low yields of aldehyde **309**, it was not possible to pursue the plan of generating the tricyclic frame **311** ring of the ABC model from the cyclization of such an intermediate (scheme 137).

Scheme 137: The proposed closure of the A ring.

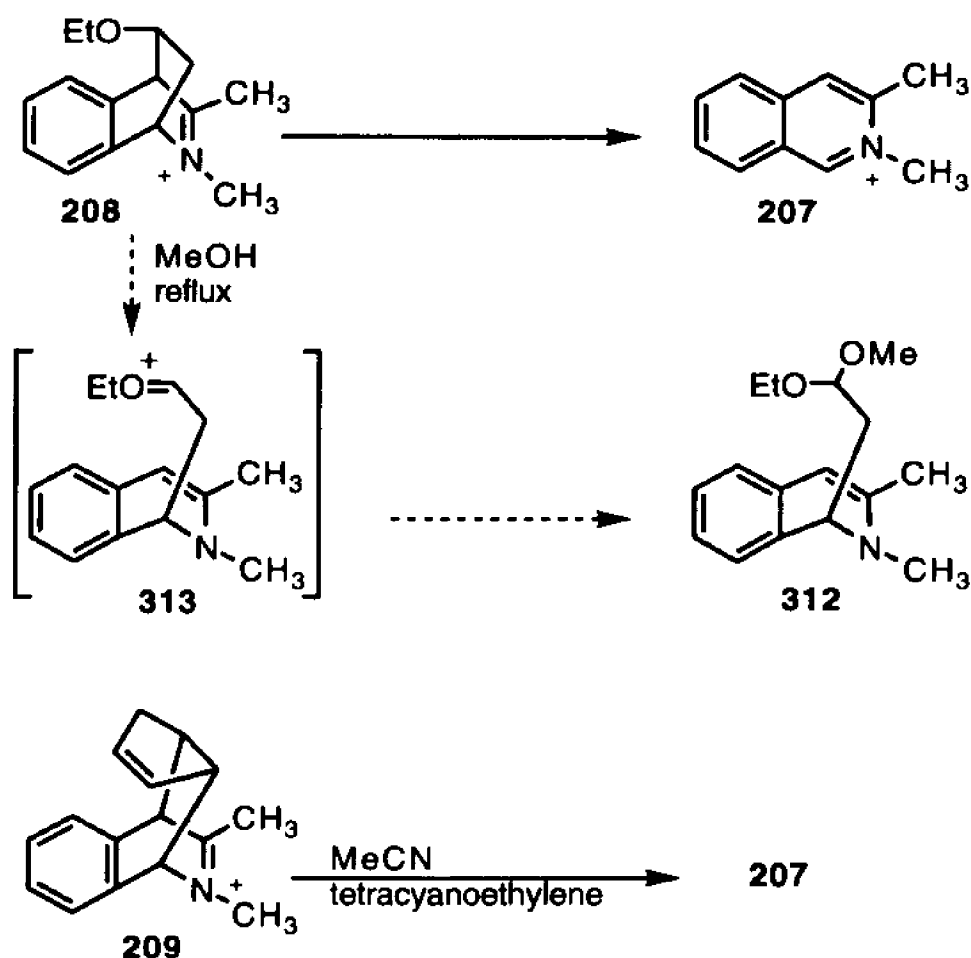


CHAPTER 7: THE REVERSAL OF THE BRADSHER CYCLOADDITION

1) The early cases of reversal of the Bradsher adducts.

Although the Bradsher cycloaddition has been extensively studied by Bradsher,¹²⁸ Franck,¹²⁹ and Falck¹³⁰ with regard to both its mechanistic implications and synthetic potential, yet only two cases of observed reversal of the original cycloadducts have appeared in the literature (scheme 138).

Scheme 138: The early cases of reversal of the Bradsher adducts.



Bradsher reports that refluxing the imminium adduct **208** of ethyl vinyl ether **83** and 2,3-dimethyl isoquinolinium iodide **207** in acetonitrile for three hours led to the recovery of the original salt **207**.¹³¹ Further proof of the "ease of dissociation" of the 2,3-dimethyl isoquinolinium adducts was provided in the cyclopentadiene series.¹³² Under the reaction conditions (acetonitrile, room temperature), the cyclopentadiene adduct **209** in the presence of tetracyanoethylene, a

cyclopentadiene scavenger, dissociated to the extent of 17% to the isoquinolinium salt **207** over a two-week period. The question of the concertedness or stepwise nature of the retro-Bradsher reactions observed has been addressed by Bradsher.¹³³ The dissociation of adduct **208** at 62.5 and 104 °C was found to follow first order kinetics.¹³⁴ From measurements of the enthalpy and entropy of activation which were found to lie within the range reported for retro-Diel-Alder reactions, Bradsher concluded that the reaction proceeds via a cyclic transition state. He did not, however, rule out the possibility of a two-step process.¹³⁵ We believe that the concertedness of the retro-Bradsher process could also be studied by carrying out the reversal experiment in refluxing methanol rather than acetonitrile. The isolation of the one bond product **312** which could only arise by methanol capture of intermediate **313** would be proof that the reaction followed a stepwise course where bond breaking in the adduct occurs sequentially. In the absence of such an experiment one can only postulate, on the basis of Franck's studies involving ethyl vinyl ether, that a stepwise mechanism might also be operative. It is difficult to make predictions on the concertedness of the reversal in the cyclopentadiene case. Bradsher has postulated a concerted non synchronous mechanism for the forward reaction. Considering the conditions under which the adduct reverses, the cyclopentadiene case appears to be an example where both the Bradsher and the retro-Bradsher reactions are concerted.

We have discovered that the adducts resulting from the addition of enol ethers to 2-(2,4-dinitrophenyl)-4-oxygenated isoquinolinium salts undergo a facile stepwise reversal in the presence of acids.

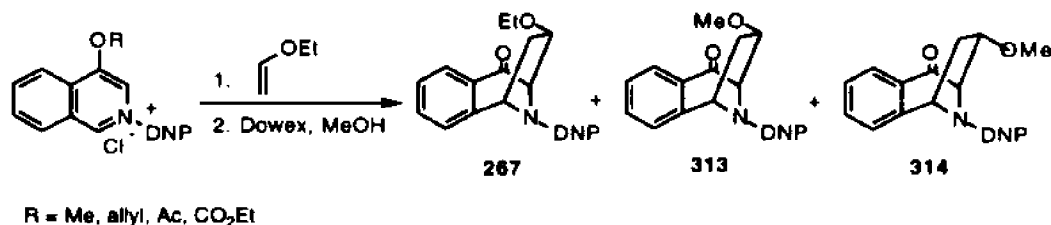
The reversal appears to be quite general as the reaction is tolerant of variations of both the substituents introduced by the enol ethers and the modified alkoxy groups at the 4 position (isoquinoline numbering) of the adducts.

Since two parameters, the vinyl ether substituent and the C4 hydroxyl protecting groups, were varied both in the cycloaddition and the reversal studies the various cases of reversal of the Bradsher adducts will be discussed in the context of the vinyl ether used.

2) The reversal of the ethyl vinyl ether adducts.

As previously discussed, the cycloaddition of ethyl vinyl ether to 2-(2,4-dinitrophenyl)-4-methoxy isoquinolinium chloride **264** gave rise to 1,4- and 1,3- adducts **268** and **267** in addition to the one-bond product **269** (scheme 115). These products were obtained after exposure of the crude material to radial chromatography over silica gel. On the other hand, when the reaction crude was treated with Dowex and methanol (as per Franck's protocol to generate the 1,4 adduct in the protected form of its dimethyl acetal **266**)¹³⁶ the 1,3 adduct **267** was the major product isolated (scheme 139). The same material was characterized from the Dowex/methanol treatment of the crude mixture resulting from the addition of ethyl vinyl ether to the 4-carbonate, acetoxo, and allyloxy salts (scheme 139).

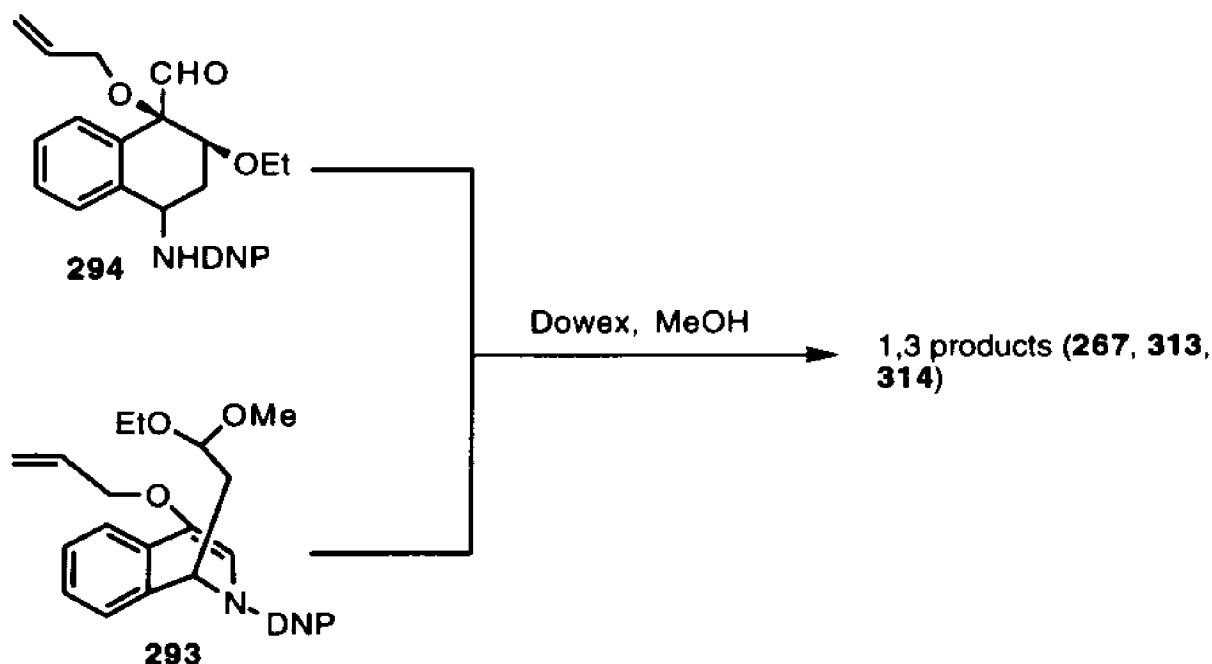
Scheme 139: The reversal of the ethyl vinyl ether adduct of the 4-methoxy isoquinolinium salt.



In all these experiments, minor components identified as 1,3 adducts endo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-methoxy **313** and exo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-methoxy **314** were also isolated. It may be recalled that the cycloaddition of the 4-acetoxy salt produced the ethoxy-1,3 adduct **267** exclusively due to the removal of the acetyl group under the reaction conditions. Therefore no meaningful conclusions can be drawn from the results of the Dowex/methanol reaction. The outcome of the reaction was not affected by the acid treatment since in all likelihood the product was already formed. On the other hand, 1,4 and one-bond products had been previously characterized from chromatographic purification of the crude ethyl vinyl ether adducts to the 4-carbonate and 4-allyloxy, and 4-methoxy salts. Therefore, the only possible interpretation of the results in the treatment the 4-carbonate and allyloxy, and 4-methoxy crude with acid is that the previously identified components of the crude (aldehyde and one-bond products) are being converted to the 1,3 adduct. The conversion of the presumed components of the reaction crude to 1,3 adduct **267** was confirmed by

the control experiments in which aldehyde **294** and one-bond product **293** were separately subjected to the Dowex/methanol treatment. Both compounds gave rise to the 1,3 adducts previously identified (scheme 140).

Scheme 140: The reversal of the 1,4 and one-bond ethyl vinyl ether-allyl salt products.

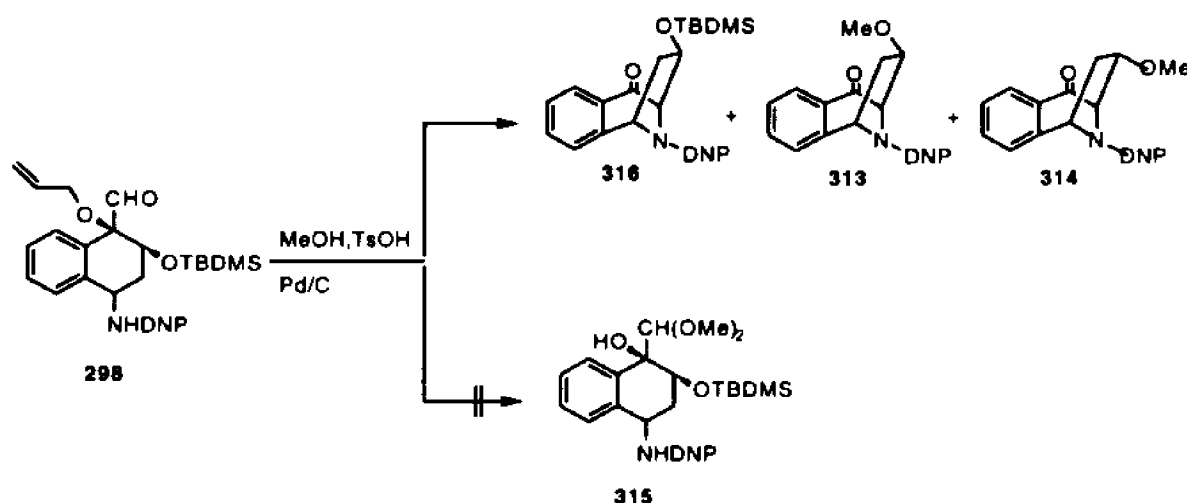


3) The reversal of the tert-butyldimethyl silyl vinyl ether adducts.

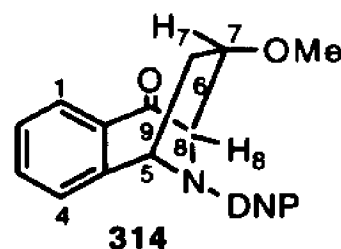
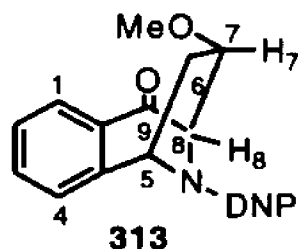
Our encounter with the reversal process in the tert-butyldimethyl silyl adducts occurred as we attempted to remove the allyl protecting group from aldehyde **298** in order to generate hydroxy tetralin **315**. Following Scheffod's procedure, the aldehyde was treated with p-toluene sulfonic acid and Pd/C in methanol (scheme 141).¹³⁷ Three products were isolated. On the basis of their nmr spectra they were assigned structures corresponding to a 1,3 adduct bearing a silyloxy

group at C7 endo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-tert-butyldimethylsilyloxy **316** and the two diastereomeric methoxy 1,3 adducts **313** and **314**.

Scheme 141: The reversal of the silyl vinyl ether adduct of the 4-allyloxy salt.

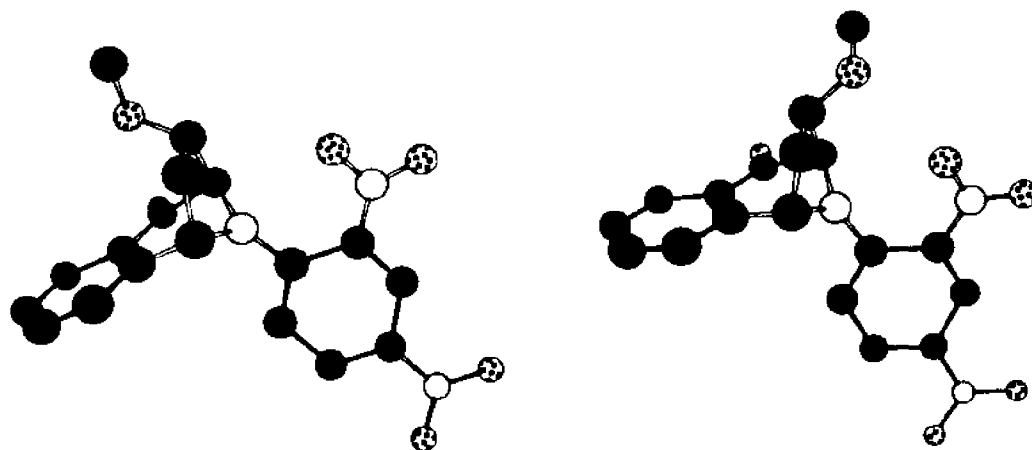


We took advantage of the presence of the methoxy epimers **313** and **314** to assign the stereochemistry of all the 1,3 adducts isolated in this work. H7 in the nmr spectrum of the faster moving methoxy diastereomer **313** appears at 4.63 ppm. The corresponding H7 resonance of the slower moving isomer **314** is shifted upfield, appearing at 4.08 ppm.



The upfield shift is indicative of a stereochemical arrangement which positions H7 in the shielding cone of the carbonyl. Therefore the faster moving methoxy-1,3 adduct endo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-methoxy **313** has the methoxy group oriented towards the phenyl ring in a trans arrangement with the C8-N bond. The stereochemical assignment was confirmed by comparing the coupling constants obtained by molecular mechanics calculations on the two structures (scheme 142) with the experimentally derived values. Of particular significance is the coupling constant between H7 and H8. The experimentally observed value is 11.7 Hz for the endo isomer with a calculated value of 8.1 Hz. On the other hand the corresponding values in the exo series are 0.0 Hz (experimental) and 1.5 Hz (calculated). The relative trend corroborates the stereochemical arrangement which was assigned on the basis of the chemical shift of H7 in the two series.

Scheme 142: MM2 structures of the 1,3 methoxy adducts

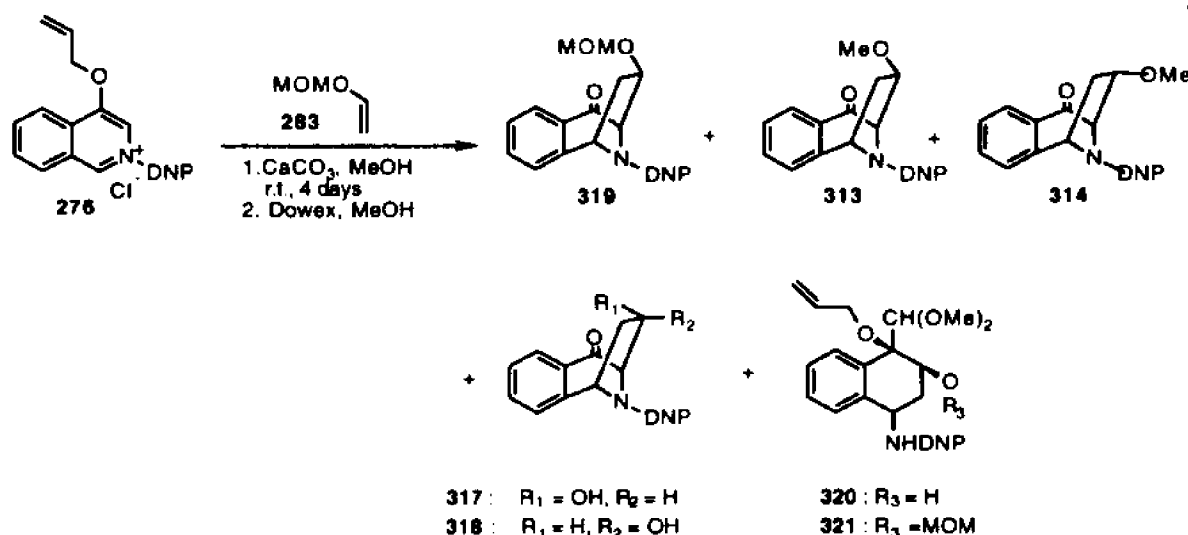


Although in the parent system the reversals reported by Bradsher¹³⁸ occurred upon heating the cycloadducts, it must not be inferred in this case that the refluxing conditions are responsible for the observed retro-Bradsher fragmentation of the silyl adduct. When tert-butyl dimethylsilyl vinyl ether is allowed to undergo the cycloaddition and the crude reaction mixture is treated directly with p-toluene sulfonic acid and methanol at room temperature for 12 hours, the three 1,3 adducts previously observed were isolated. The reversal of silyloxy tetralin **298** could also be triggered by exposure to TsOH in trimethyl orthoformate. It is evident therefore that the acidic conditions were responsible for the case of reversal observed earlier in the silyl series.

4) The reversal of the methoxymethyl vinyl ether adducts.

The crude mixture obtained from reacting methoxymethyl vinyl ether **283** with 2-(2,4-dinitrophenyl)-4-allyloxy isoquinolinium salt **276** was subjected to the Dowex/methanol treatment (scheme 143).

Scheme 143: The reversal of the methoxy methyl vinyl ether adduct of the 4-allyloxy salt.



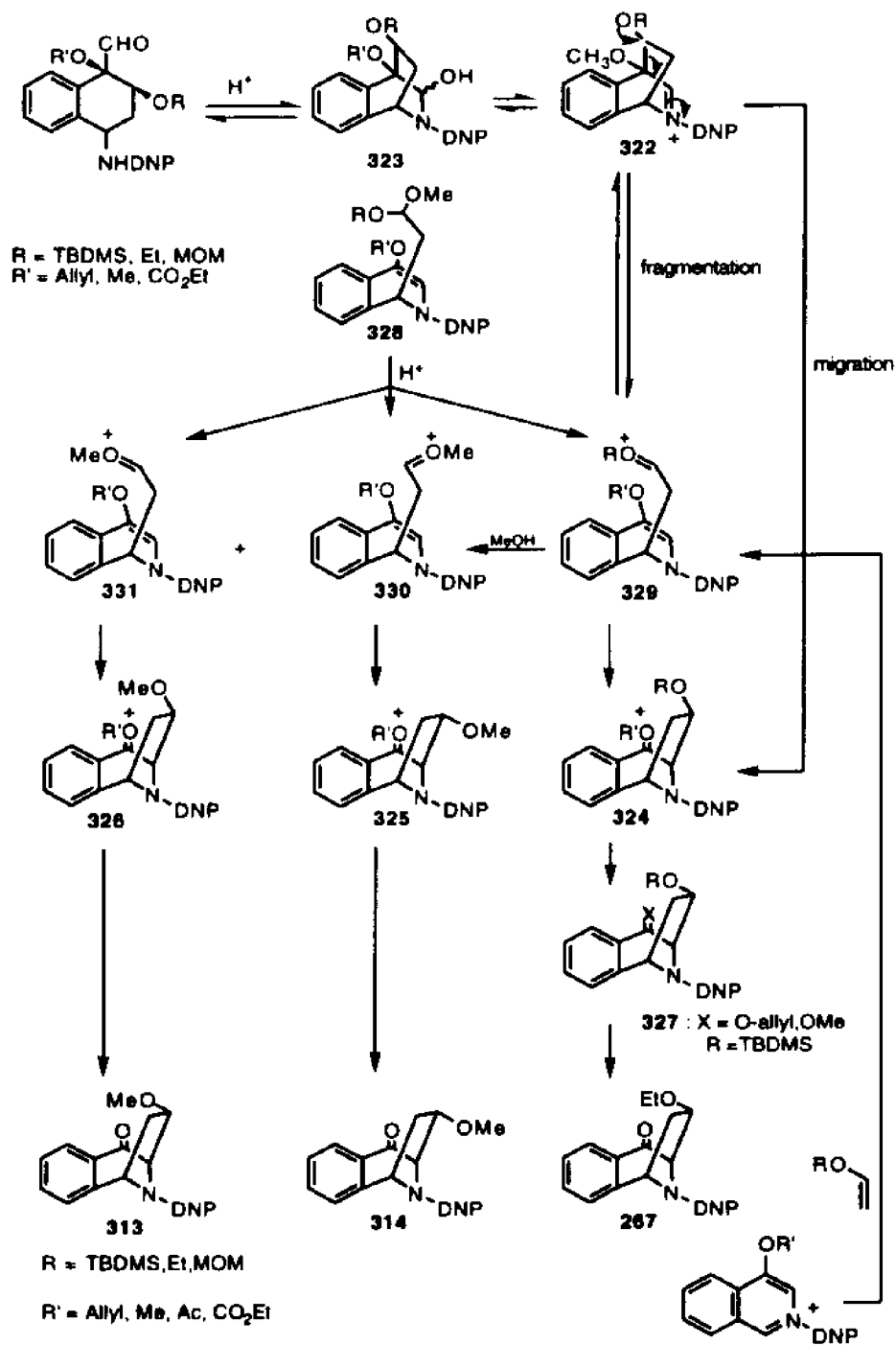
This resulted in a grand mixture which consisted mainly of deprotected 1,3 adducts endo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-hydroxy **317** and exo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-hydroxy **318** (43% yield) which could not be separated by radial chromatography. The two methoxy diastereomers **313** and **314** were obtained in 11% and 3.4% yields respectively while the MOM protected 1,3 adduct endo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-methoxymethyl **319** was isolated in 9% yields. Quite surprisingly, a small amount of acetal **320** survived the reaction conditions and was isolated in 1% yield. When exposed to p-toluene sulfonic acid in trimethylorthoformate the 1,4

adduct **295** undergoes the same reversal as occurs in methanol although a 34% yield of acetal **321** where the methoxymethyl group had been retained could also be obtained.

5) The mechanism of the retro-Bradsher fragmentation.

The examples reported above provide a clear evidence for the reversal of the Bradsher adducts of the 4-alkoxyisoquinolinium salt series.

Scheme 144: The mechanism of the retro-Bradsher



The proposed mechanism for the reversal proceeds through the same intermediates invoked by Franck¹³⁹ to account for the course of the forward reaction (scheme 108). Yet, a more complex picture emerges for the acid catalyzed retro-Bradsher which displays a dependence on very subtle electronic differences between the various adducts studied. The formation of the 1,3-adducts from the respective aldehydes can be adequately explained by postulating an acid catalyzed reversal to tricyclic iminium ion **322**, the putative intermediate in the forward reaction, via hemiaminal **323**. However, the conversion of the iminium ion to the 1,3 adducts, as will be discussed later, is substrate dependent. Nevertheless, all the 1,3 products arise, of necessity, from the fragmentation or rearrangement of the iminium ion to oxocarbenium ions **324**, **325** and **326**. The benzylic cations subsequently add methanol to yield the respective ketals (the intermediate ketal **327** has been isolated from the reaction of the silyl adduct with *p*-toluenesulfonic acid in trimethylorthoformate) which upon hydrolysis during the chromatographic process gave rise to the 1,3 adducts observed. The one-bond product **328** entry into the pathway leading to the 1,3 adducts is effected by an acid catalyzed conversion to oxocarbenium ions **329**, **330**, and **331**.

(i) Dependence on the structure of the enol ether.

The fastest rates of rearrangement observed in our study of the Bradsher reversal were displayed by the ethyl vinyl ether adduct **294** followed by the silyl adduct **298**. The methoxymethyl adduct appears to be the slowest one undergoing the retro-Bradsher. The observed

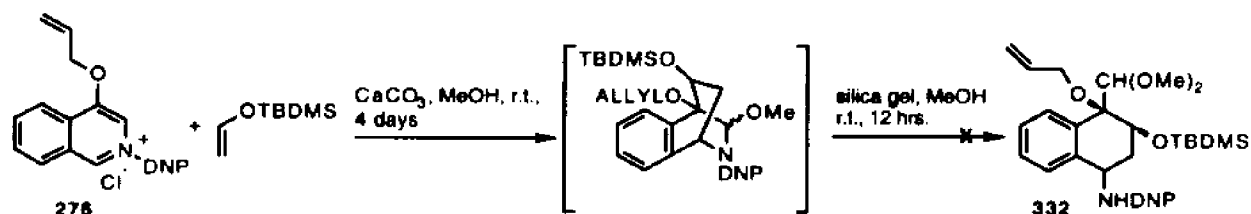
rates are consistent with qualitative estimates of the electron donating ability of the three groups examined. The greater the electron donating ability of the substituents, the faster the C4-C10 fragmentation to one-bond oxocarbenium ion **329** or migration to the cyclic oxocarbenium ion **324**, and the faster the reversal. On that basis it becomes clear why the ethyl vinyl ether adduct, the crude nmr spectrum of which is striking for the conspicuous absence of resonances corresponding to the 1,3 adduct, exhibits the greatest propensity to undergo the retro-Bradsher. The adduct is not stable to silica gel chromatography. It undergoes a Bradsher reversal during the process and gives rise, in addition to the one-bond product **293**, the familiar ethoxy 1,3 adduct **267**. It has also been observed that when the pure 1,4 ethyl vinyl ether adduct **294** was allowed to stand in CDCl₃ (nmr sample) for a week at room temperature it evolved into a mixture containing the possible products of reversal of the 1,4 adduct and of conversion of the one-bond to 1,3 structures. A similar behavior was observed in the case of the one-bond product.

(ii) Dependence of the reversal on the strength of the acid.

The Bradsher reversal exhibits an interesting correlation with the strength of the acid used to catalyze the reaction. It is thought for example that all the 1,4 aldehydes isolated are products of the conversion of the respective intermediate tricyclic amins on silica gel. Attempts to effect this conversion under more convenient conditions by stirring the crude with silica gel in moist dichloromethane failed to effect the desired transformation. Even the crude ethyl vinyl ether

failed to generate the aldehyde under these conditions (scheme 145). Similar efforts employing silica gel in methanol to transform the crude silyl adduct directly to acetal **332** were unsuccessful.

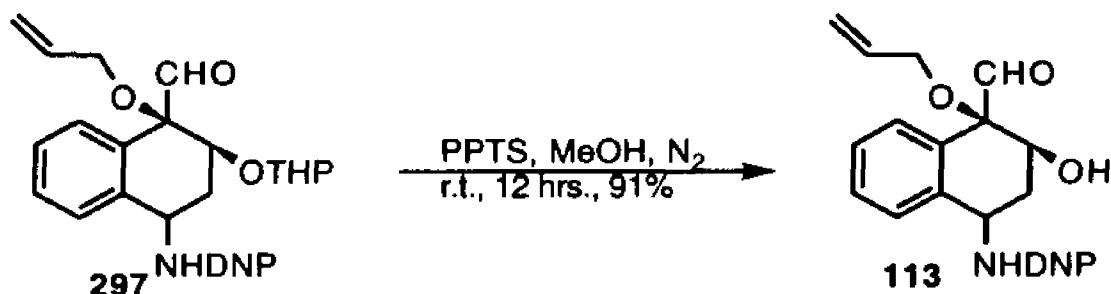
Scheme 145: The cycloaddition of 4-allyloxy isoquinolinium salt with ethyl vinyl ether. Silica gel conversion to the acetal.



Evidently, a particular threshold ratio of silica gel to product must be achieved in order to effect the hydrolysis of the aminal.

In the hope of effecting the conversion of the aldehydes to their dimethyl acetal without the drawback of the reversal, PPTS was chosen as the catalyst. The silyloxy aldehyde **298** on which these conditions were tested remained unchanged whether the reaction was carried out in MeOH or $\text{HC}(\text{OMe})_3$. In an interesting twist, the same conditions (PPTS/MeOH) applied to the tetrahydropyranyloxy aldehyde **297** resulted in the clean removal of the THP group to afford hydroxy aldehyde **333** in 91% yield.

Scheme 146: The cleavage of the THP group from the Bradsher adduct.



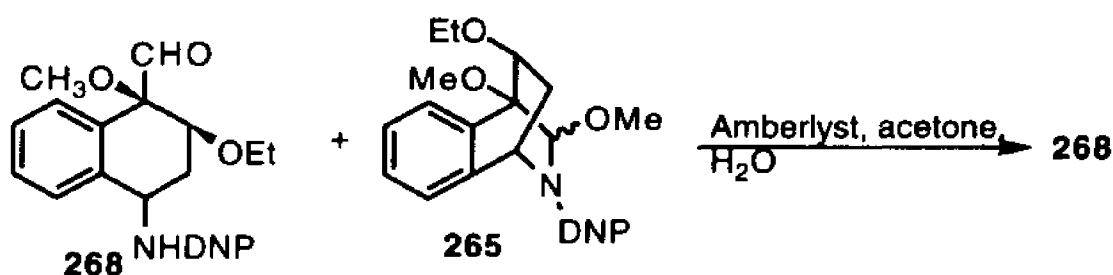
No reversal products were observed. These results indicate that PPTS is not strong enough to protonate the carbonyl so as to induce the reversal cascade. On the other hand, Dowex resin and p-toluenesulfonic acid have been found to be quite efficient in promoting the reversal.

(iii) Dependence on the solvent system.

A striking and, initially, quite puzzling solvent dependence of the reversals has been observed in the course of these studies. The solvent effect is most evident in the sharp contrast between MeOH and water. It may be noted that the highest yields (95%) of cycloadducts in the 4-alkoxyisoquinolinium series were obtained by treatment of the crude tert-butyldimethylsilylvinyl reaction crude with TsOH in THF/H₂O. In sharp contrast, treating the crude with TsOH in MeOH resulted in an acid induced conversion of the crude to the reversal products. In his classic mechanistic study of the Bradsher cycloaddition, Franck¹⁴⁰ reports, in the 4-methoxyisoquinolinium series, an interesting case of water assisted suppression of the reversal pathway - although at this stage the reversal path may not have been envisaged - in favor of hydrolysis

to the aldehyde. As the original chromatographic separation had failed to yield aldehyde **268** in pure form, the mixture of aldehyde and aminoral **265** was treated with amberlyst resin in moist acetone resulting in an efficient conversion of the mixture to the sole aldehyde (scheme 147).

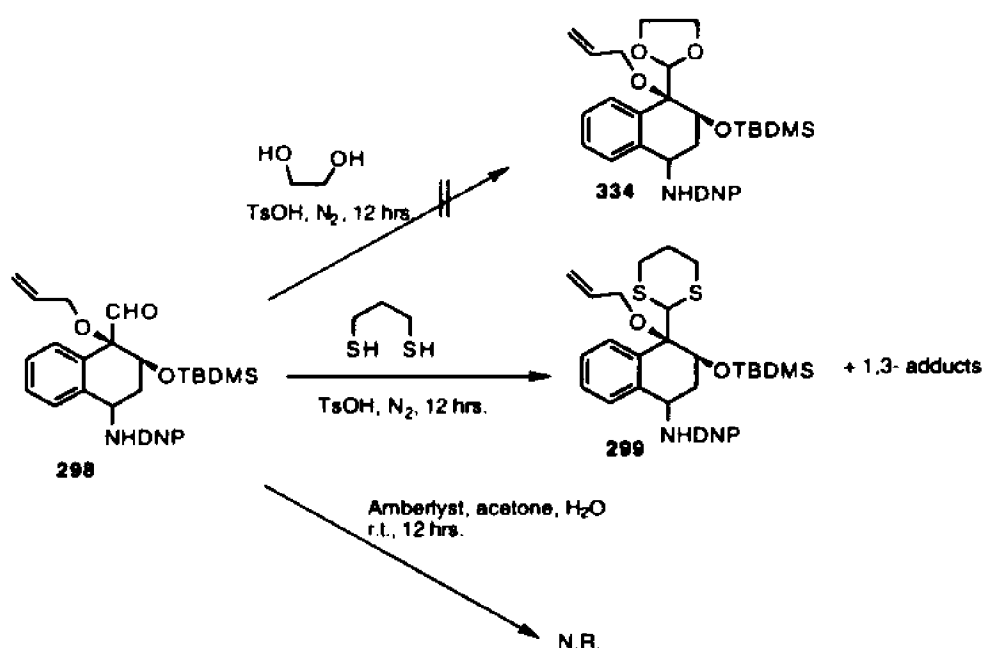
Scheme 147: Franck's suppression of the Bradsher reversal.



Interestingly, the acid catalyzes the hydrolysis of the aminoral and yet does not induce the retro-Bradsher reaction of the component aldehyde. This observation is even more surprising considering the fact that the ethyl adducts in these series are the most prone to the retro-Bradsher reaction. In this study, we have found that when the silyloxy aldehyde **298** was subjected to the same conditions (Amberlyst/Acetone/H₂O treatment) in an attempt to cleave the silyl group, the starting material was recovered unchanged. It is not clear at this stage whether one should ascribe the absence of reversal products to the solvent or to the acid employed. Nevertheless our own experience with these adducts leads us to believe that the solvent played quite an important role in these two examples. Another interesting case of the impact of the solvent on the reaction path was discovered in our attempts to effectively compete with the retro-Bradsher by making the cyclic acetal

derivative **334** of the 1,4 adducts (scheme 148). To that effect silyloxy aldehyde **298** was treated with TsOH in ethylene glycol. Upon stirring at room temperature for twelve hours the starting material was recovered unchanged. Yet, upon treatment with TsOH in THF/MeOH the recovered aldehyde was smoothly converted into the familiar 1,3 adducts mixture.

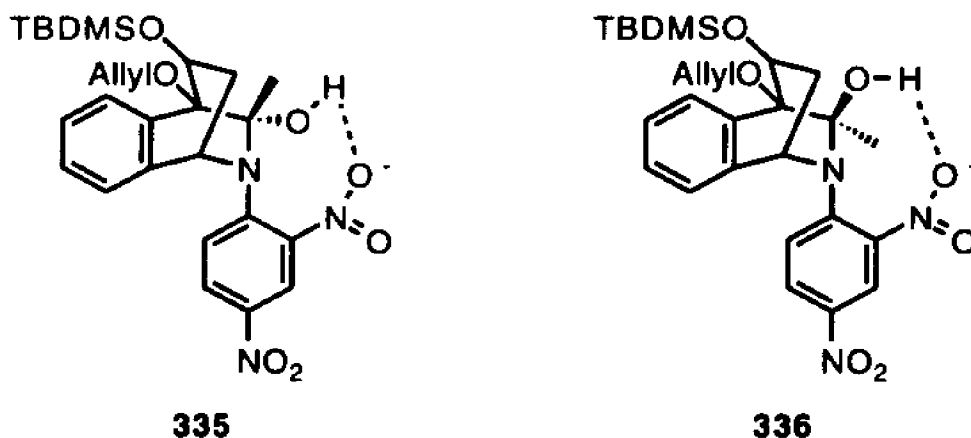
Scheme 148: The cyclic acetals of the silyl vinyl ether adduct of the 4-allyloxy salt.



The enigmatic role of the solvent is further shrouded by the fact that TsOH /propane dithiol treatment of the silyloxy aldehyde generates both the reversal products and dithianyl tetralin **299**. At this juncture the role of the solvent in determining the reaction course in the dioxygenated tetralins under reversal conditions is not fully understood. To explain the preferential formation of the aldehyde in aqueous acid, we surmise that the rate of capture of tricyclic iminium ion **322** by water to regenerate hemiaminal **323** (scheme 144) must be much faster than the reversal (fragmentation or migration of the C4-C10

bond). We believe that in addition, the equilibrium constant for the hemiaminal **323** to iminium ion **322** is small. The hemiaminal hydroxyl proton may be engaged in H-bonding to the o-nitro group of the 2,4-dinitrophenyl group a situation that would severely retard C3-O bond cleavage (leading to reversal) by the elimination of water from the hemiaminal and favor C3-N bond cleavage (leading to the aldehyde). MM2 calculations show that in both diastereomers **335** and **336** (scheme 149), the hemiaminal hydroxyl proton is engaged in H-bonding to the o-nitro group. In methanol on the other hand the generation of the iminium ion from the aminal is not impeded by any competing processes and acid catalyzed equilibration is facile. Therefore the major pathway is C-O bond cleavage and the ensuing retro-Bradsher process.

Scheme 149: Hydrogen bonding in the hemiaminal.



(iv) **Reversal through bond migration. vs. a one-bond oxocarbenium ion intermediate**

The fact that in the retro-Bradsher reaction the 1,3 adduct in which the alkoxy group (originally introduced by the enol ether) of the tetralin is retained leads to interesting mechanistic implications. The adduct **267** was the major product isolated in the reversal of the ethoxy aldehyde **294** while the 1,3 methoxy diastereomers **313** and **314** constituted the minor components of the reaction mixture. It was further observed that the major adduct **267** was produced as a single stereoisomer in which the stereochemistry (assigned by comparison with the ^1H nmr spectra of the diastereomeric methoxy derivatives) around the carbon bearing the alkoxy group was retained. These results lead us to postulate the existence in the reversal process of two different pathways which diverge from a common intermediate: tricyclic iminium ion **322**. It is unlikely that the 1,3 ethoxy adduct arises from one-bond oxocarbenium ion **329** since the diastereomeric 1,3 ethoxy adduct, which would arise through a C-C bond rotation in that intermediate, was not observed. For the one-bond oxocarbenium ion pathway to be a viable one the assumption must be made therefore that the retention of the tetralin alkoxy group consonant with the stereoselectivity observed arises as a consequence of a very fast ring closure step involving capture of the oxocarbenium ion by C3. In the parent system studied earlier Franck had demonstrated that a very fast ring closure step accounts well for the retention of stereochemistry in a stepwise cyclization process. Invoking a similarly very fast ring closure step to explain the retention of stereochemistry in the formation of the 1,3 adduct would entail specious extrapolations from enamine trapping in a six-membered transition state (Franck's system) to enol ether trapping

in a seven-membered case. It seems much simpler to envision the 1,3 adduct as arising from a migration of the C4-C10 bond in **322** leading to the more stable benzylic and heteroatom-stabilized carbocation **324**. The presence of the two 1,3 methoxy products, **313** and **314**, points to the existence of a parallel pathway involving C4-C10 bond breaking in the iminium ion **322** to produce oxocarbenium ion **329**. The fragmentation of intermediate **322** is then followed by exchange with the solvent leading to the methoxy products via the oxocarbenium ion precursors **331** and **330**. In the reversal of the ethyl adduct the bond migration pathway is predominant as evidenced by the ratio of 1,3 ethoxy to 1,3 methoxy adducts. In the silyl case however, the ratio is not drastically skewed towards the 1,3 silyloxy adduct indicating that the bond breaking pathway is now competitive with bond migration. These results may be an indication that the migration proceeds through a bridged intermediate which is better stabilized by the ethyl group than by the silyl. Interestingly, in the reversal of the methoxy methyl adduct **295**, in Dowex and methanol, the bond breaking pathway is favored as the major products identified are secondary alcohols **317** and **318** (scheme 143). It is not known at this stage whether the secondary alcohols arise in a final deprotection step or whether the deprotection precedes the reversal to generate a free hydroxyl.

(v) The stability of the 1,3 adducts.

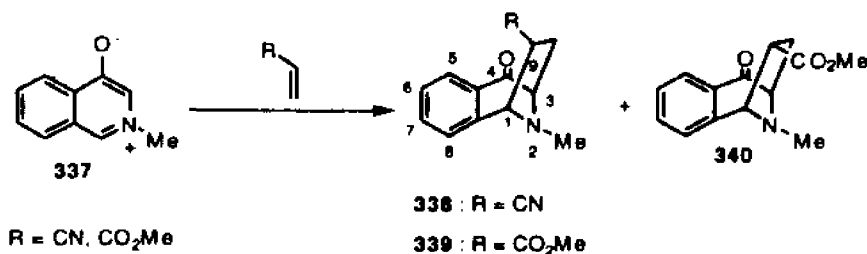
As discussed earlier, one-bond products and 1,4 adducts can be converted to 1,3 adducts upon treatment with acid. Our studies reveal however that the 1,3 adducts themselves undergo no further

transformations nor do they interconvert when subjected again to the reaction conditions. In experiments involving treatment of 1,3 ethoxy **267**, silyloxy **316**, and methoxy adducts **313** and **314** with acid, the starting materials were recovered unchanged. The ethoxy derivative was found to be quite stable under basic conditions as well. Given the influence of the solvent on the retro-Bradsher rearrangement, we entertained the thought that there could exist a solvent dependent 1,4 to 1,3 equilibrium such that water would favor the 1,4 while methanol would shift the equilibrium towards the 1,3 adduct. This equilibrium would imply a conversion of the 1,3 adduct to the 1,4. In order to test this idea, the 1,3 silyloxy adduct **316** was stirred with TsOH in a THF/H₂O mixture for 24 hrs. The starting material was recovered unchanged.

6) Katritzky's synthesis of the 1,3 adduct

The dipolar cycloaddition of nitrogen heterocycles has been shown to be a valuable synthetic tool. The 1,3 dipolar cycloaddition of dipolarophiles such as N-phenylmaleimide, acrylonitrile, methyl acrylate, and methyl methacrylate to aromatic betaines 1-methyl-3-oxidopyridinium and 1-phenyl-3-oxidopyridinium had been previously studied.¹⁴¹ Katritzky further extended the range of the heterocyclic dipoles to include 2-methyl-4-oxidoisoquinolinium **337**.¹⁴² Thus, the betaine **337** was found to react with acrylonitrile to yield three products. Of the three products detected, the authors report the isolation and characterization of only heptanone **338**.

Scheme 150: Katritzky's 1,3 dipolar cycloadditions.



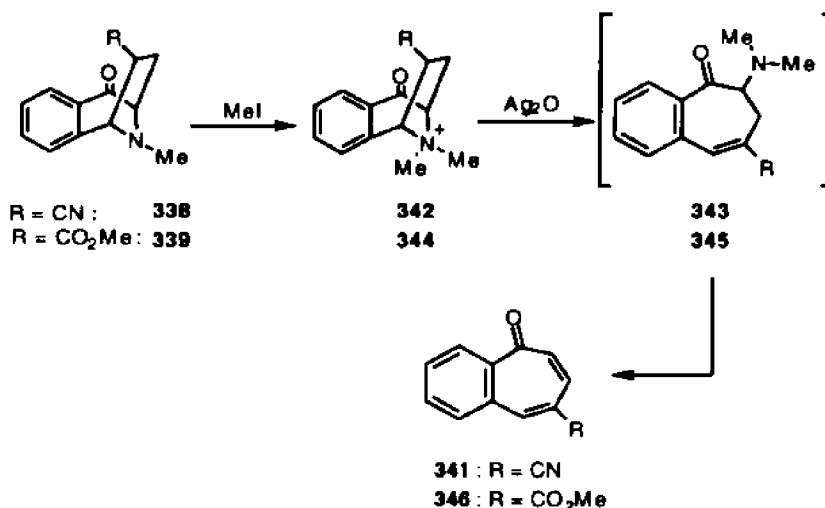
The assignment of endo stereochemistry to the nitrile group was based on the coupling constant between H1 and H9 ($J_{1,9} = 6.9$ Hz). In a similar manner 2-methyl-4-oxopyridinium **337** reacted with methyl acrylate to yield two diastereomeric adducts which were identified as the endo and exo heptanones **339** and **340**. The stereochemical assignments in this series was based as in the acrylonitrile case on the H1-H9 coupling constants (Endo: $J_{1,9} = 6.4$ Hz; Exo: $J_{1,9} = < 0.5$ Hz).

The work described herein and Katritzky's methodology which both lead to the substituted benzocycloheptanone framework display some interesting contrasts and similarities. Of note are the different mechanisms of the two cycloadditions. The different mechanism for each process is based on a reversal of the electronic roles of the two components in each instance. Whereas the benzocycloheptanone obtained via the Bradsher route involves cycloaddition of electron deficient 2-(dinitrophenyl)-4-allyloxyisoquinolinium chloride to enol ethers (in a case of inverse electron Diels-Alder demand followed by acid induced reversal) Katritzky's example showcases the addition of an electron-rich heterocycle to electron deficient alkenes. It comes therefore as no surprise that the regiochemical outcomes of the two processes are different. The electron donating group of our olefinic

addend is introduced at C10 of the benzocycloheptanone while the Katritzky adducts are functionalized at C9 with electron withdrawing substituents. The Bradsher-retro-Bradsher route to the 1,3 adducts exhibits a higher level of stereoselectivity than the Katritzky route. Via the Bradsher process, the 1,3 ethoxy adduct **267** was obtained as a single stereoisomer whereas the 1,3 dipolar cycloaddition gave rise to 1:1 endo/exo mixture. Although the Katritzky group did not characterize the other two products detected in the addition to acrylonitrile one may suspect that the exo isomer was present in the reaction mixture. The comparably higher level of stereoselectivity observed in the Bradsher-retro-Bradsher sequence is quite remarkable considering the fact that it is the outcome of a sequence of two-reactions involving multistep mechanisms. The stereochemical preference for the endo ethoxy 1,3 adduct **267** is anchored in two crucial steps. The first one is the electronically controlled "exo" (with respect to the azadiene portion of the heterocycle) mode of addition of the enol ether to the isoquinolium salt, which establishes the eventual configuration at C10. The second step is the bond migration in intermediate **322** (scheme 144) proceeding with retention of configuration at that center.

Katritzky demonstrated the usefulness of the cycloaddition by converting the acrylonitrile adduct **338** to 2-dimethylamino-4-cyano-6,7-benzotropone **341** (scheme 151).¹⁴³

Scheme 151: Katritzky's benzotropone synthesis.



The synthetic sequence involved the formation of the methyl iodide salt **342** followed by a one-pot Hoffman elimination to the benzocycloheptadienone **343** which spontaneously aromatizes to the benzotropone **341** when the elimination is carried out using silver oxide. A similar conversion of the methyl acrylate adducts (illustrated in scheme 151 for the endo isomer **339**) to 4-(methoxycarbonyl)-6,7-benzotropone **346** was also effected. The synthesis of **346** proceeded via salt **344** and heptadione **345**. In reference to the tedious methods previously employed to synthesize 6,7-benzotropones,¹⁴⁴ Katritzky¹⁴⁵ concluded that his 1,3-dipolar cycloaddition of 2-methyl-4-oxoisoquinolinium to dipolarophiles was of "preparative significance". Further comparison of the dipolar cycloaddition route to the Bradsher-retro-Bradsher sequence reveals the superiority of the latter in terms of convenience and yields. The Katritzky betaines were obtained by a tedious procedure which involved the conversion of 4-hydroxy-2-methylisoquinolinium iodide to 2-methyl-4-oxoisoquinolinium by ion

exchange chromatography. The highest yield of dipolar adduct reported is 18%. The Bradsher sequence on the other hand furnishes **267** in 81% yields. It appears therefore that the 1,3 Bradsher adducts may prove to be more useful synthons for the synthesis of benzotropones.

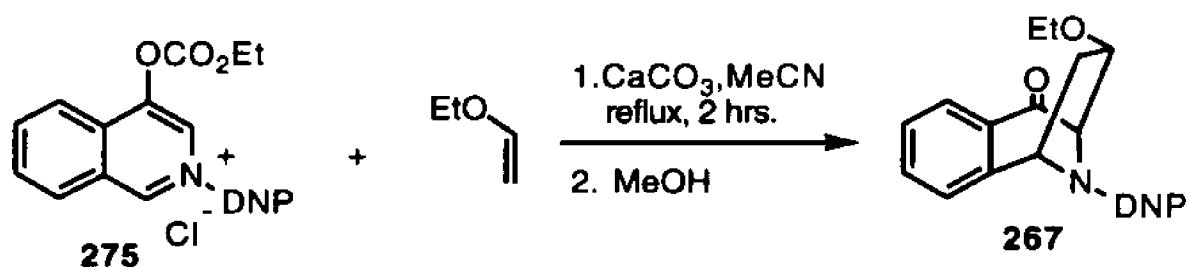
7) On the general mechanism of the Bradsher cycloaddition.

The demonstration of the existence in the 4-alkoxyisoquinolinium series of a reversal pathway for the Bradsher cycloaddition leads to interesting retrospective considerations on the general mechanism proposed earlier.

Given the fact that the previous two-step mechanism¹⁴⁶ includes two key intermediates, one-bond oxocarbonium ion **329** and tricyclic iminium ion **322** (schemes 108, 116, and 153) which are also postulated to lie in the retro-Bradsher path it is a wonder that the forward reaction does not yield the same product mixture observed upon acid triggering of the reversal process. Taking for example the fastest and most facile case of retro-Bradsher studied, the reversal of the ethyl vinyl ether adducts, it is surprising that in the ¹H nmr of the reaction crude the quite characteristic resonances of 1,3 adducts are conspicuously absent although the presence of the one-bond product may be ascertained. If a two step mechanism is to be considered for the Bradsher cycloaddition in the 4-oxygenated isoquinolinium series a very fast ring closure argument must be invoked by analogy to cyclization in the parent isoquinoline system. In our opinion, it appears highly improbable in the 4-alkoxyisoquinolinium series that the sterically hindered trisubstituted enamine terminus of **270** [= **329** (R=

Et; scheme 144)] for example (scheme 116) would undergo ring closure to the 1,4 adduct **271** [= **322** (R= Et; scheme 144)] (scheme 116) faster than 1,3 ring closure by the less hindered enol ether terminus C3 to yield **272** (scheme 116). We believe therefore that *the Bradsher cycloaddition of 4-alkoxyisoquinolinium salts proceeds via a concerted mechanism*, followed by a fast solvent capture of the iminium⁺ ion generated. Since the reaction is carried out in suspended CaCO₃ as an acid scavenger the reversal pathway which is acid catalyzed is effectively suppressed. We have also demonstrated that when the cycloaddition of ethyl vinyl ether **83** to 2-(2,4-dinitrophenyl)-4-(carboethoxy) isoquinolinium chloride **275** is carried out in refluxing acetonitrile followed by the addition of methanol two hours later, only the 1,3 adduct **267** was observed (scheme 152).

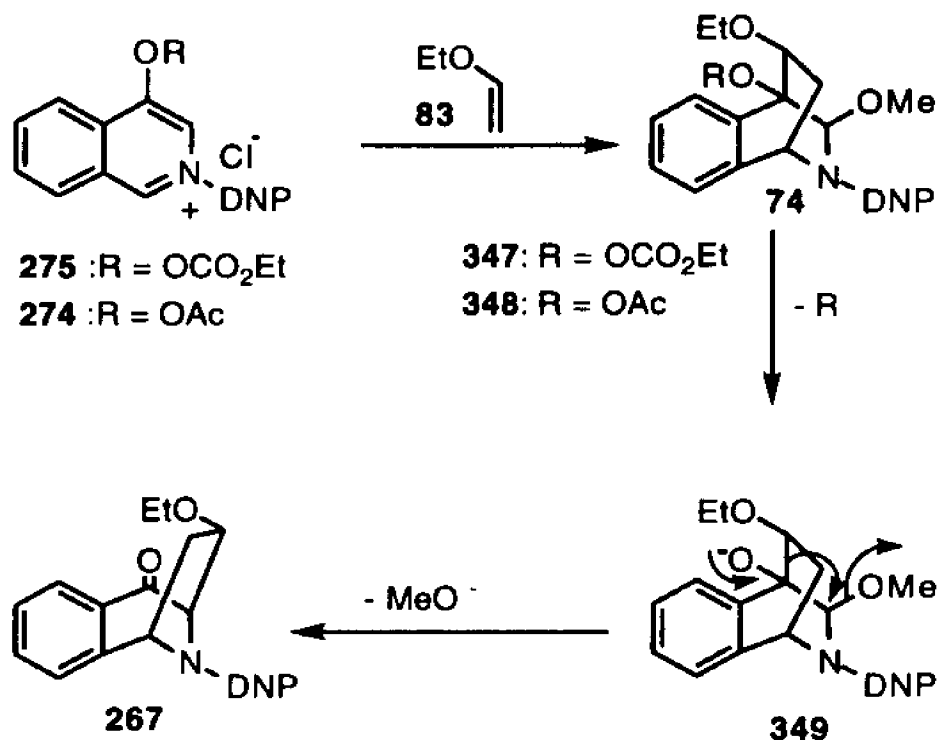
Scheme 152: The cycloaddition in acetonitrile.



In the absence of methanol to quickly trap it, the putative iminium ion intermediate **322** (scheme 144) rearranges through a fast reversal path to the 1,3 adduct. Therefore, the nucleophilic methanol later injected into the reaction mixture added to the oxocarbenium ion **324** (scheme 144) of the 1,3 structure. The concerted view of the cycloaddition accounts for the hitherto puzzling role of the 4-allyloxy substituent. It had been

introduced into the isoquinoline nucleus as part of our efforts to deactivate C3 of the iminium ion **329** towards nucleophilic capture of the oxocarbonium ion. Although quite successful in steering the reaction course down the 1,4 pathway the electronic influence of the allyl group in the context of a two-step mechanism for the cycloaddition was not understood. However, from the present perspective of a concerted process for the reaction, we believe that the allyl group proved to be simply a sturdier group than the acetoxy and ethylcarbonyloxy substituents which had been found earlier to give high yields of the 1,3 adduct. The 1,3 adduct generated in the case of the 4-acetoxy and carbonate derivatives is thought to arise from the respective 1,4 adducts **347** and **348** (scheme 153). The cleavage of the protecting groups under the reaction conditions generates the tertiary alkoxide **349** which collapses to the carbonyl with concomitant migration of the C4-C10 bond and the extrusion of methoxide to generate the 1,3-adduct **267**. The allyl group, on the other hand, does not cleave and therefore intermediate **74** (scheme 153) does not rearrange.

Scheme 153: 1,3-adduct from 4-acetoxy-, ethoxycarbonyl isoquinolinium salts.



The earlier experiment (scheme 115) reported by Franck¹⁴⁷ in which ethyl vinyl ether **83** adds to 2-(2,4-dinitrophenyl)-4-methoxy isoquinolinium salt **264** to yield equal amounts of 1,4, 1,3, and one-bond products warrants another look. It may very well be that the products isolated arose (during chromatography over silica gel.) from a reversal of the original cycloadduct **271** (scheme 116) generated in a concerted process. A fast capture of iminium ion **271** (scheme 116) to generate aminal **265** (scheme 115) does not allow for a retro-Bradsher. As previously noted, the crude nmr of the ethyl vinyl ether adduct to 2-(2,4-dinitrophenyl)-4-allyloxy isoquinolinium chloride does not show resonances corresponding to the 1,3-adduct. Since the nmr spectrum of Franck's crude reaction mixture is not available it is not possible to

ascertain whether the 1,3-adduct was generated during the chromatographic process from the rearrangement of an intermediate produced in a concerted process.

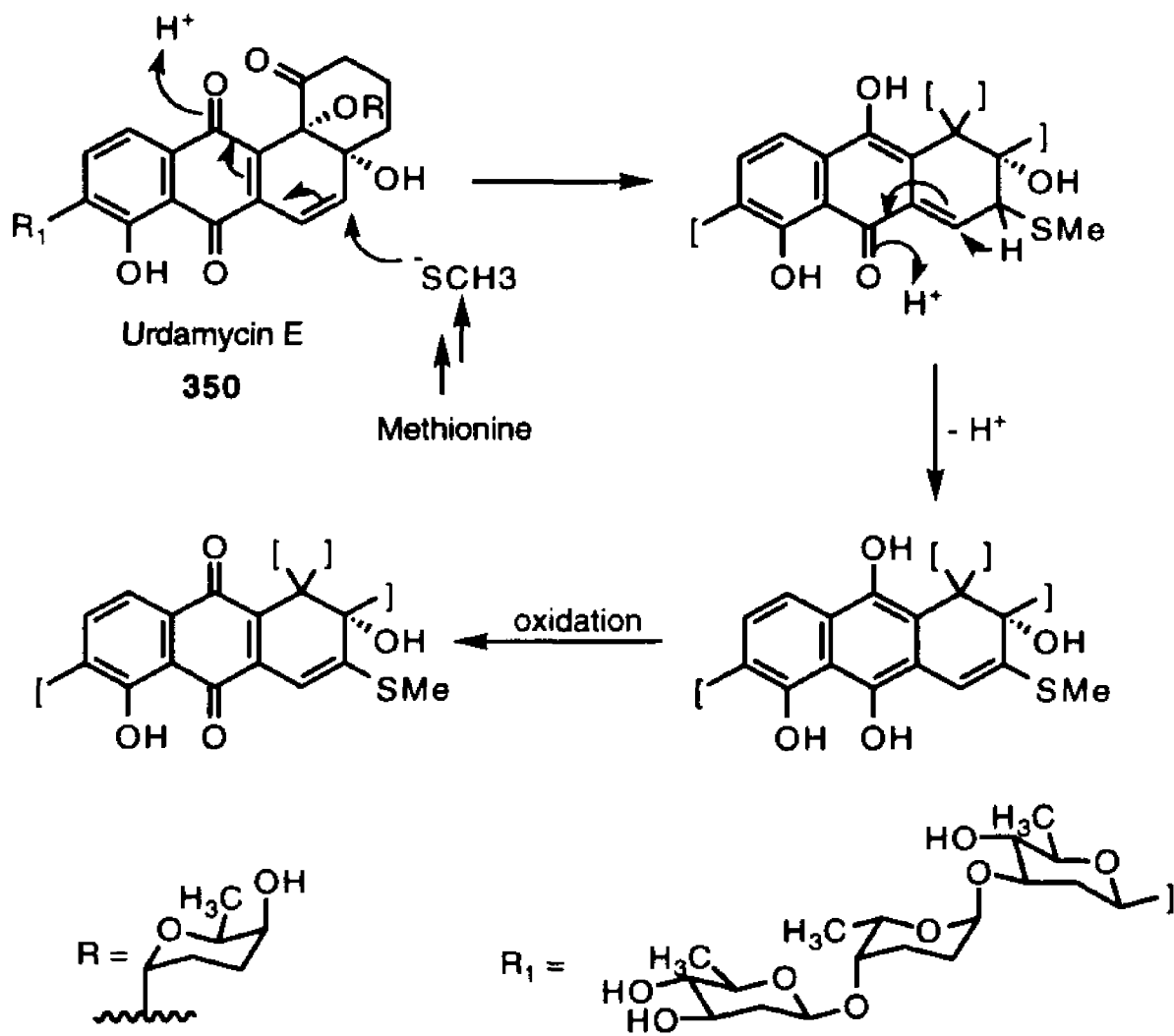
An explanation for the predominant formation of one-bond products in the cycloaddition of branched vinyl ethers:

A two-step mechanism explains quite well the observation that the cycloaddition of branched vinyl ethers results mainly in the isolation of one-bond products (schemes 135 and 136). Attributing the preferential formation of the one-bond products to a steric retardation in the formation of the second bond leading to the 1,4 adducts is quite an attractive argument. Nevertheless, an explanation based on a concerted view of the cycloaddition is equally sound. As the cycloaddition proceeds in a concerted fashion, the tricyclic iminium ions generated exhibit a higher propensity towards Bradsher fragmentation since this process leads to even more stable carbocations, **302** (scheme 135) and **308** (scheme 136), than observed in the fragmentation of adducts of unsubstituted vinyl ethers. We can therefore adequately account for the presence of a small amount of aldehyde **309**, in the cyclization of branched vinyl ether **288** (scheme 136) by evoking a concerted addition to the isoquinolinium salt **276**. The sterically congested iminium ion generated **310** (scheme 136) simply undergoes a retro-Bradsher reaction (with concomittant relief of strain) faster than its capture by methanol to give the 1,4 adduct **309**.

CHAPTER 8: THE ELABORATION OF THE BC RING OF THE ANGUCYCLINES

As an inspection of the angucyclines¹⁴⁸ architectural features quickly reveals, the construction of the AB ring with its attendant sensitivity to harsh conditions¹⁴⁹ is arguably the most challenging aspect of a total synthesis of these natural products. From the perspective of their biological activity on the other hand one may question the necessity of a fully functionalized A ring. Professor Franck has postulated that enzyme inhibition occurs by nucleophilic attack of RTase's cysteine sulfhydryl group on the angucyclines' Michael acceptor double bond resulting in an irreversible inhibition of the enzyme. His hypothesis is supported by experiments on the biosynthetic origins of the urdamycins.¹⁵⁰ These studies have revealed that the S-methyl group of urdamycin E is introduced by nucleophilic attack of a methyl thiolate (derived from methionine) on the Michael site of ring B.

Scheme 154: The introduction of the S-methyl group of urdamycin E.



The biosynthetic process could be mimicked in the laboratory by the nucleophilic attack of various thio compounds on the Michael acceptor of urdamycin E.¹⁵¹

For the purpose of identifying the essential features responsible for the biological activity of angucyclines, the synthesis of simpler derivatives of the natural product is important. In sakyomycin A **23**, for example, the biological activity may depend simply on the presence of the B-ring

Michael acceptor, the ring junction hydroxyl, and the rhodinosyl glycoside.

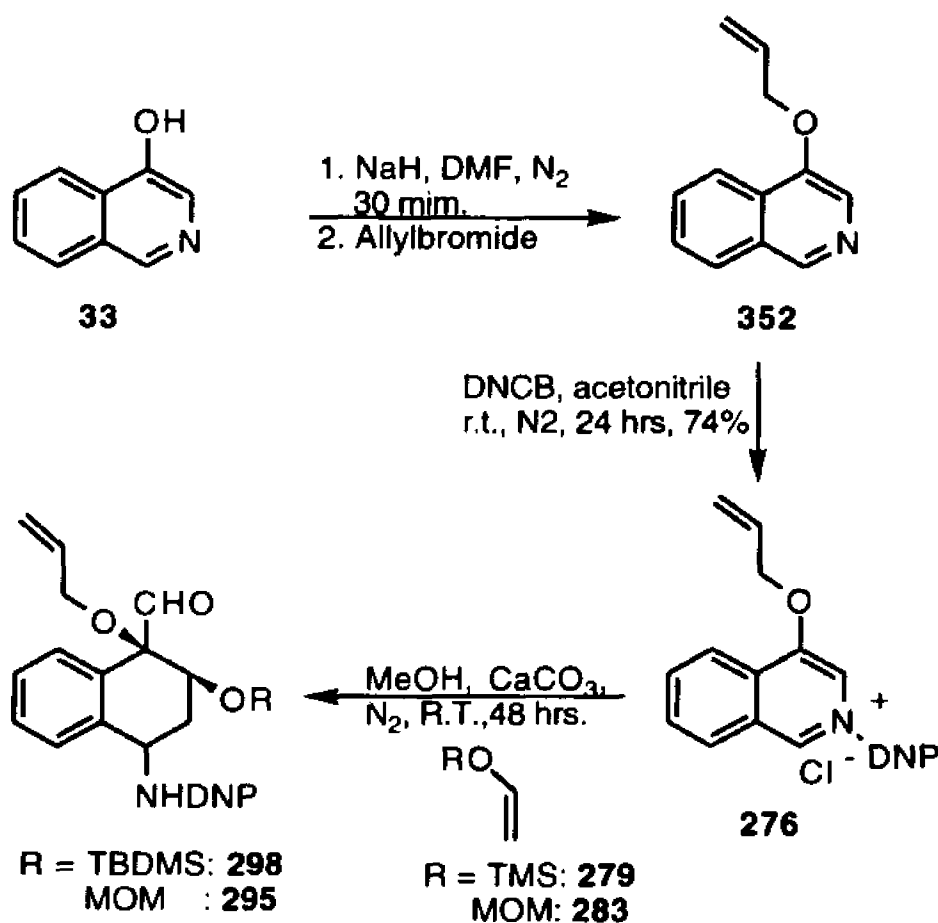
If in fact the AB ring system is the most difficult part of the synthesis of the angucyclines it may be further argued that the most difficult sub-goals of the AB-ring construction are:

- (i) The positioning of the hydroxyl groups of the ring junction in the *cis* relative stereochemistry of the natural product.
- (ii) The construction of the glycosidic linkage.

We have synthesized a model **355** (scheme 156) of the BC ring system of the angucyclines which demonstrates the power of the Bradsher cycloaddition in meeting these challenges.

The silyloxy aldehyde **298**, obtained from the cycloaddition of *tert*-butyldimethylsilyl vinyl ether in quantitative yields, embodies the essential features of the BC ring system of the angucyclines. The *cis* hydroxyl groups in protected form are in place along with the carbonyl functionality of the A ring. The vestigial amino group from the isoquinoline remains appended to the tetralin and provides a handle for introducing the double bond of the B-ring.

Scheme 155: The synthesis of the BC ring model. Part A

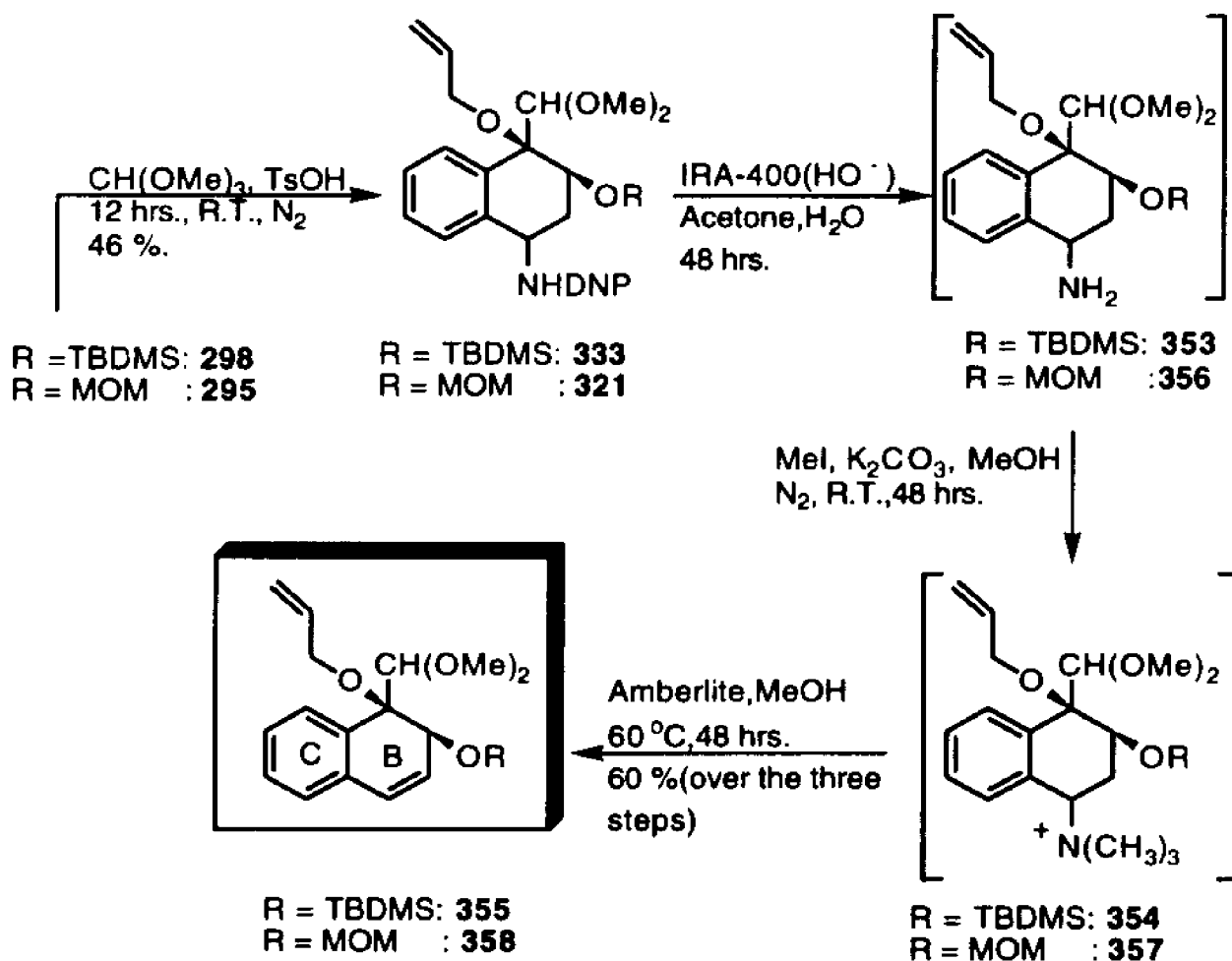


The sequence (scheme 155) commenced with 4-hydroxyisoquinoline **33** which was converted, according to the general procedure previously described, to the allyl ether **60**. The conversion of **60** to the DNP salt **276** and the cycloaddition of vinyl ethers **279** and **283** have been discussed earlier. The generation of the double bond required the removal of the 2,4-dinitrophenyl group, a requirement which in turns necessitated the protection of the aldehyde.

The dimethyl acetal **353** was obtained in yields of 25 to 33% by treatment with *p*-toluenesulfonic acid in trimethylorthoformate

(scheme 156). The low yields are due to the competing retro-Bradsher process. The disappearance of the aldehyde peak and the presence of the singlet resonance for the acetal proton provided evidence for the formation of dimethyl acetal **333**.

Scheme 156: The synthesis of the BC ring model. Part B



The 2,4-dinitrophenyl group was removed by treatment of the acetal with amberlite resin in moist acetone to yield benzylic amine **353**. In an attempt to avoid what was assumed to be products of acetone self-condensation, the reaction was carried out in methylene chloride. Only

starting material could be detected by tlc after prolonged stirring under these conditions. The amine obtained could not be purified by chromatography over silica gel as it decomposed during the process. The crude amino acetal **353** which displays no 2,4-dinitrophenyl protons in the ^1H nmr spectrum was exhaustively methylated (methyl iodide, potassium carbonate, methanol, room temperature, 48 hrs) and the resulting ammonium salt **354** was deaminated (Amberlite, MeOH, 3 days) to generate alkene **355** in 60 % yield over the three steps. The elimination product was easily identified by the presence of the vinylic protons in the ^1H nmr spectrum. The overall sequence which resulted in the synthesis of the BC ring system of the angucyclines could be duplicated for the methoxyl methyl derivative **295**. Thus, the removal of the 2,4-dinitrophenyl group from acetal **321** gave amine **356**. The Hoffman elimination of the ammonium group of **357** to give the MOM protected BC ring model **358** is under investigation.

The BC ring model presents some interesting characteristics. Of great importance is the presence of the allyloxy group. The retention, on the benzylic alcohol, of the protecting group which had been positioned at the outset of the synthetic sequence (the protection of the hydroxyl group of 4-hydroxyisoquinoline) demonstrates the possibility that a glycosidic moiety might also be retained. It is clearly the best way of avoiding the non trivial task of introducing the rhodinosyl group after constructing the tetracyclic aglycone. A measure of the difficulty of introducing the glycosyl moiety of the tertiary hydroxyl of the angucyclines may be grasped in the failure of a peracetylation of aquayamycin to acetylate any of the aglycone hydroxyls.¹⁵² The presence of the protecting groups on the non benzylic hydroxyl groups

of **128** and **134** is also significant. These two hydroxyls with their protecting groups can be directly traced to the starting enol ethers used in the cycloaddition. Therefore our synthesis of the BC ring system provides an encouraging precedent for the introduction of the glycosidic moiety of angucyclines such as Sakyomycin A.

EXPERIMENTAL

General experimental: NMR spectra were recorded on GE QE 300 (300 MHz), JEOL FX 400 (400 MHz) instruments with CDCl_3 or CD_3OD as solvent. Infrared Spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. High resolution Mass spectra were obtained from the Pennsylvania State University Mass spectrometry Facility. Thin-layer chromatography was done on precoated TLC sheets of silica gel 60 F254 (E. Merck) and short/long-wave ultraviolet light was used to visualize the spots. Chromatotron (radial chromatography) plates were prepared by using Kieselgel 60 PF254 gipshaltig (E. Merk). Solvents were purified and dried by using standard procedures. All experiments were done under an inert atmosphere of nitrogen or argon.

1) The synthesis of the isoquinolinyl ethers

4-(2-Methyl-2-propenyloxy) isoquinoline (57).

To a flame-dried flask equipped with a nitrogen inlet was added 440 mg of a 60% sodium hydride (NaH)-mineral oil dispersion (264 mg effective weight of sodium hydride, 11 mmol). The dispersion was washed twice with 2 mL of petroleum ether which had previously been dried over sodium sulfate and the remaining solid was suspended in 1 mL of dry DMF. Upon cooling to 0 °C (ice water bath), a solution of 4-hydroxyisoquinoline³⁴ (145 mg, 1 mmol) in 4 mL of DMF was added dropwise and the formation of the isoquinolinoxy salt was allowed to proceed at room temperature for a 10 minute period. The formation

of the salt is monitored by the disappearance of the insoluble sodium hydride resulting in a homogeneous solution of the isoquinolinoxy salt. The reaction vessel was cooled to 0 °C and commercially available 3-chloro-2-methyl propene (**55**) (0.146 mL, 1.5 mmol) was added dropwise at that temperature. The mixture was stirred at room temperature for 1 hour. The stirring was discontinued when Tlc analysis (4% MeOH/ CH₂Cl₂) revealed the disappearance of the starting material. The reaction crude was pipetted into an Erlenmeyer flask containing crushed ice and the aqueous mixture was washed with three portions of ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The crude was purified by column chromatography (Silica gel, 2% MeOH/ CH₂Cl₂) to give 79 mg (40%) of the isoquinolinyl ether.

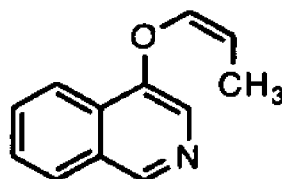
¹HNMR (300 MHz, CDCl₃) δ 8.84(s, 1H, H-1), δ 8.18(d, 1H, J=8.4 Hz, H-8), δ 8.03(s, 1H, H-3), δ 7.83(d, 1H, J=8.2 Hz, H-5), δ 7.58(t, 1H, J= 8.2 Hz, H-7), δ 7.51(t, 1H, J=7.9, H-6), δ 5.16(s, 1H, vinyl), δ 5.01(s, 1H, vinyl), δ 4.60(s, 2H, methylene), δ 1.85(s, 3H, methyl). ¹³CNMR (75 MHz, CDCl₃) δ 149.5, 144.9, 140.0, 129.4, 129.0, 128.8, 128.1, 127.4, 126.7, 120.9, 112.9, 72.0, 19.2.

4-(2-propenoxy)isoquinoline (**60**).

To a flame-dried 50-mL two-neck round-bottom flask under nitrogen was added a 50% suspension of sodium hydride (NaH) (1.1 eq, 364.1 mg, 7.6 mmol). The sodium hydride was washed with two successive portions of petroleum ether dried over magnesium sulfate. The "oil-free" sodium hydride was suspended in 2 mL of dry DMF and the

reaction flask was cooled to 0 °C. Following the dropwise addition of a solution of 4-hydroxyisoquinoline³⁴ (1 g, 1eq., 6.90 mmol) in 24 mL of dry DMF the cooling bath was removed and the reaction mixture was allowed to stir at room temperature until homogeneous mixture (15 - 30 min) was obtained. The electrophile, allylbromide (1.1 eq., 126.28 mg, 0.1051 mL, 1.14 mmol), in 1 mL of dry DMF was added at room temperature. The reaction was stirred at room temperature for 2 hr. as The disappearance of the starting material was followed by Tlc (2:1 ethyl acetate/petroleum ether). The crude reaction mixture was pipetted into a separatory funnel containing crushed ice (200 mL) and extracted with three 200 mL portions of ethyl acetate. The combined ethyl acetate extracts were further washed with three 50-mL portions of water, and dried over sodium sulfate. After removal of the solvent *in vacuo*, 755 mg (59%) of the crude 4-(propenyloxy)isoquinoline (**60**) was obtained. Following column chromatography (florisil/20 % ethyl acetate/methylene chloride) 94.4 mg (39%) of the pure product 4 (propenyloxy)isoquinoline (**60**) was isolated. ¹HNMR (300 MHz, CDCl₃): δ 8.89 (s, 1H, H1), δ 8.24 (d, 1H, J_{ortho}=8.3 Hz, J_{meta}=0.99 Hz, H8), δ 8.07 (s, 1H, H-3), δ 7.93 (d, 1H, J_{meta} = 0.83 Hz, J_{ortho} = 8.11 Hz), δ 7.70 (t, 1H, J = 8.22 Hz, H-7), δ 7.62 (t, 1H, J = 8.10 Hz, H-6), δ 6.13 (m, 1H, vinyl), δ 5.53 (dd, 1H, J_{trans} = 17.3 Hz, J_{gem} = 1.5 Hz), δ 5.36 (dd, 1H, J_{cis} = 10.6 Hz, J_{gem} = 1.4 Hz), δ 4.78 (dd, 2H, J = 5.2 Hz, J = 1.34 Hz). ¹³CNMR (75 MHz, CDCl₃) δ 69.32, δ 117.86, δ 121.09, δ 124.07, δ 126.75, δ 127.50, δ 128.30, δ 129.09, δ 129.44, δ 132.61, δ 145.16. HRMS calcd for C₁₂H₁₁NO 185.0841, found 185.0837.

The use of an excess of sodium hydride (1.4 eq.) resulted in the isolation of the enol ether resulting from the isomerization of the double bond of 4-allyloxyisoquinoline product.



^1H NMR (300 MHz, CDCl_3): δ 8.96 (s, 1H, H1), 8.26 (d, 1H, $J=8.4$ Hz, H8), 8.17 (s, 1H, H3), 7.97 (d, 1H, $J=8.0$ Hz, H5), 7.73 (dt, 1H, $J=1.3$ Hz, $J=8.3$ Hz, H7), 7.66 (dt, 1H, $J=1.3$ Hz, $J=8.2$ Hz, H6), 6.60 (dd, 1H, $J=1.7$ Hz, $J_{\text{cis}}=6$ Hz, OCHCHMe), 5.07 (q, 1H, OCHCHMe), 1.84 (dd, 3H, $J=1.7$ Hz, $J=6.9$ Hz, Me). LRMS calcd for $\text{C}_{12}\text{H}_{11}\text{NO}$ 185.08, found 184.95.

4-(2-Methoxy-2-propenyloxy) isoquinoline (74).

To a flame-dried 50-mL two-neck round-bottom flask under nitrogen was added a 35 % suspension of potassium hydride (KH) (1.1 eq, 434.6 mg, 3.79 mmol). The potassium hydride was washed with two successive portions of petroleum ether which had been previously dried over magnesium sulfate. The "oil-free" potassium hydride was suspended in 2 mL of dry DMF and the reaction flask was cooled to 0°C . Following the dropwise addition of a solution of 4-hydroxyisoquinoline (500 mg, 1 eq., 3.45 mmol) in 10 mL of dry DMF the cooling bath was removed and the reaction mixture was stirred at room temperature until a homogeneous mixture was obtained (15 - 30

min). After addition of 3-bromo-2-methoxy propene (65/35 mixture of 3-bromo-2-methoxy propene and 2,2-dimethoxy-1-bromopropene) (1 eq., 3.5 mmol, 881 mg) the reaction mixture was stirred at room temperature for 12 hrs. The reaction mixture was pipetted into a separatory funnel containing crushed ice (20 mL) and extracted with three 20 mL portions of ethyl acetate. The combined ethyl acetate extracts were further washed with three 20-mL portions of water, and dried over sodium sulfate. After removal of the solvent *in vacuo*, 583.1 mg (79%) of the crude 4-(2-methoxy-2-propenyloxy) isoquinoline (**74**) was obtained. Chromatography over basic alumina (Brockman activity 1), eluting with ethyl acetate, gave 337 mg (45%) of the pure product. ^1H NMR (300 MHz, CDCl_3) δ 8.90 (s, 1H, H-1), δ 8.26 (d, 1H, $J=8.04$ Hz, H-8), δ 8.10 (s, 1H, H-3), δ 7.93 (d, 1H, $J=7.9$ Hz, H-5), δ 7.69 (t, 1H, $J=8.08$, H-7), δ 7.61 (t, 1H, $J=7.52$, H-6), δ 4.69 (s, 2H, methylene), δ 4.42 (d, 1H, $J=2.5$ Hz, vinylic), δ 4.24 (d, 1H, $J=2.6$ Hz, vinylic), δ 3.65 (s, 3H, methoxy).

4-(2-Chloro-2-propenyloxy) isoquinoline (**75**).

To a flame-dried 25-mL two-neck round-bottom flask under nitrogen was added an 80% suspension of sodium hydride (NaH) (1.1 eq, 34.14 mg, 1.14 mmol). The sodium hydride was washed free of its accompanying mineral oil by two successive treatments with petroleum ether dried over magnesium sulfate. The oil-free sodium hydride was suspended in 1 mL of dry DMF and the reaction flask cooled to 0 °C. Following the dropwise addition of a solution of 4-hydroxyisoquinoline (150 mg, 1eq., 1.03 mmol) in 5 mL of dry DMF the cooling bath was removed and the reaction mixture allowed to stir at room temperature

until obtention of a homogeneous mixture (15 - 30 min). The electrophile 2,3-dichloropropene (1.1 eq., 126.28 mg, 0.1051 mL, 1.14 mmol) in 1 mL of dry DMF was added at room temperature. The reaction was allowed to stir at room temperature for 12 hrs. The reaction crude was pipetted into a separatory funnel containing crushed ice (30 mL) and extracted with three 50 mL portions of ethyl acetate. The combined ethyl acetate extracts was further washed with three 20-mL portions of water, and dried over sodium sulfate. After the removal of the solvent *in vacuo*, the crude 4-(2-chloro-2-propenyloxy)isoquinoline was obtained in 90% yield (219 mg). Following column chromatography (florisil/ethylacetate) the pure product 4-(2-chloro-2-propenyloxy)isoquinoline was isolated in 39 % yield (94.4 mg). ^{13}C NMR (75 MHz, CDCl_3) δ 147.33, 144.54, 134.50, 128.21, 127.69, 126.58, 126.22, 125.35, 123.05, 119.48, 112.98, 69.11. LRMS calcd for $\text{C}_{12}\text{H}_{10}\text{ClNO}$ 219.95, found 219.10.

4-(2-Bromo-2-propenyloxy) isoquinoline (76).

A 114 mg (3.79 mmol, 1.1 eq.) sample of an 80% sodium hydride (NaH)-mineral oil dispersion was introduced into a flame-dried two-neck round-bottom flask under nitrogen. After washing twice with 2 mL portions of petroleum ether dried over magnesium sulfate, the sodium hydride was suspended in 5 mL of dry DMF. The flask was cooled to 0 $^{\circ}\text{C}$ and a solution of 4-hydroxyisoquinoline (500 mg, 3.45 mmol, 1 eq.) in 15 mL of DMF was added dropwise at that temperature. After the removal of the cooling bath, the formation of the sodium isoquinolinoxy salt (monitored by the disappearance of the sodium hydride and the

obtention of a homogeneous solution) was allowed to proceed at room temperature for 30 minutes. Upon addition of 2,3-dibromopropene (758.14 mg, 392 μ L, 3.79 mmol, 1 eq.) at 0 °C. Upon stirring at room temperature for 20 min. the reaction was stopped after Tlc analysis (1:1 hexane/Ethyl acetate) revealed the disappearance of the starting material. The reaction crude was pipetted into a separatory funnel containing crushed ice (100 mL volume) and washed with three 100 ml portions of ethyl acetate. The combined organic layer was washed with water and brine and dried over sodium sulfate. After removal of the solvent *in vacuo* the crude 4-(2-bromo-2-propenenyloxy)isoquinoline was obtained in 78 % yields (711.1 mg). Attempted purification by radial chromatography (Silica gel, 2mm chromatotron plate, 5% ethylacetate/hexane) furnished only 96 mg (11% yield) of the desired 4-(2-bromo-2-propenenyloxy)isoquinoline. ¹HNMR (300 MHz, CDCl₃) δ 8.92 (s, 1H, H-1), δ 8.24 (d, 1H, J = 8.4 Hz, H-8), δ 8.05 (s, 1H, H-3), δ 7.93 (d, 1H, J = 8.2 Hz, H-5), δ 7.73 (t, 1H, J = 8.2 Hz, H-7), δ 7.62 (t, 1H, J = 8.0 Hz, H-6), δ 6.10 (d, 1H, J_{vic} = 1.9 Hz, vinylic), δ 5.76 (d, 1H, J_{vic} = 2.0 Hz, vinylic), δ 4.87 (s, 2H, methylene).

4-Isoquinolinyl(2-methyl-5-trimethylsilyl-2-penten-4-yne) ether (106).

To a flame-dried 25-mL two-neck round-bottom flask under nitrogen was added a 50% suspension of sodium hydride (NaH)-mineral oil dispersion (1.1 eq, 54.65 mg, 1.14 mmol). The sodium hydride was washed free of its accompanying mineral oil by two successive treatments with petroleum ether dried over magnesium sulfate. The

oil-free sodium hydride was suspended in 1 mL of dry DMF and the reaction flask cooled to 0 °C. Following the dropwise addition of a solution of 4-hydroxyisoquinoline (165.1 mg, 1eq., 1.14 mmol) in 5 mL of dry DMF the cooling bath was removed and the reaction mixture allowed to stir at room temperature until obtention of a homogeneous mixture (15 - 30 min). Cooling of the reaction mixture to -50 °C was followed by the dropwise addition of a solution of 2-(iodomethyl)-5-trimethylsilyl-pent-2-ene-4-yne (1 eq., 316.5 mg, 1.14 mmol) in 1 mL of dry DMF. The reaction was allowed to proceed over a period of 2 hrs while allowing for a gradual increase of the bath temperature to 10 °C. The reaction crude was pipetted into a separatory funnel containing crushed ice (10 mL) and extracted with three 50 mL portions of ethyl acetate. The addition of 20 mL of brine solution was required in order to facilitate product extraction. The combined ethyl acetate extracts were further washed with three 20-mL portions of water, and dried over sodium sulfate. After the removal of the solvent *in vacuo*, the crude was subjected to radial chromatography (1 mm silica gel plate eluted with dichloromethane). The pure product, 3-(2-methyl-5-trimethylsilyl-2-penten-4-yne)-4-hydroxyisoquinoline **106** was isolated in 56 % yield (56.8 mg). ¹HNMR (300 MHz, CDCl₃) δ 8.90 (s, 1H, H-1), δ 8.22 (d, 1H, J=8.2 Hz, H-8), δ 8.08 (s, 1H, H-3), δ 7.43 (d, 1H, J=7.8 Hz, H-5), δ 7.69 (t, 1H, J=8.1 Hz), δ 7.62 (t, 1H, J=8.1 Hz, H-6), δ 5.44 (s, 1H, vinyl), δ 5.38 (s, 1H, vinyl), δ 4.78 (s, 2H, OCH₂-), δ 3.22 (s, 2H, propargylic).

4-acetoxyisoquinoline (III).

To a pyridine (5 mL) solution of 4-hydroxyisoquinoline (503 mg, 3.4 mmol) and DMAP (42.4 mg) was added 0.7 mL of acetic anhydride. The mixture was stirred at room temperature for 2 hrs and taken into 100 mL of water. The aqueous solution was extracted with ethyl acetate (2x 100 mL) and the organic extract was further washed with water. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. The crude was purified by radial chromatography (4 mm chromatotron plate; the sample was loaded using acetone; the elution was carried out with a 20 % ethyl acetate-petroleum ether mixture). The pure 4-acetoxyisoquinoline was obtained in 52 % yield. ^1H NMR (300 MHz, CDCl_3) δ 9.18 (s, 1H, H1), 8.43 (s, 1H, H3), 8.03 (d, 1H, $J=8.2$ Hz, H8), 7.88 (d, 1H, $J=9.1$ Hz, H5), 7.76 (dt, 1H, $J_{\text{meta}}=1.2$ Hz, $J_{\text{ortho}}=8.3$ Hz, H7), 7.66 (dt, 1H, $J_{\text{meta}}=1.2$ Hz, $J_{\text{ortho}}=8.1$ Hz, H6), 2.51 (s, 3H, acetoxy). ^{13}C NMR (75 MHz, CDCl_3) δ 168.94, 150.23, 142.40, 135.69, 130.81, 130.72, 130.67, 127.71, 127.64, 120.26, 20.69. HRMS calcd for $\text{C}_{11}\text{H}_9\text{NO}_2$ 187.0634, found 187.0638.

4-tributylstannyloxyisoquinoline (112)

To a solution of 4-acetoxyisoquinoline 111 (1 eq., 480 mg, 2.57 mmol) in 10 mL of methylene chloride was added 739 μL (1eq., 824.14 mg, 2.47 mmol) of tributyl tin methoxide. The reaction mixture was stirred at room temperature for 5 days. Tlc analysis (SiO_2 , EtOAc) of the reaction mixture revealed the complete disappearance of the starting material. The solvent was evaporated under reduced pressure. The desired 4-tributylstannyloxyisoquinoline was obtained as a yellow solid in quantitative yields. ^1H NMR (300 MHz, CDCl_3) δ 8.62 (s, 1H, H1), 8.21

(d, 1H, $j=8.0$ Hz), 7.97 (d, 1H, $j=7.8$ Hz, H5), 7.84 (s, 1H, H3), 7.72-7.60 (m, 2H, H6 and H7), 1.29-0.81 (m, 27H, n-butyl₃)

Ethyl 4-isoquinolinylcarbonate (119).

A 116 mg (5 mmol, 1.4 eq.) sample of a 50% sodium hydride (NaH)-mineral oil-mineral oil dispersion was introduced into a flame-dried two-neck round-bottom flask under nitrogen. After washing twice with 5 mL portions of petroleum ether which had been previously dried over magnesium sulfate, the sodium hydride was suspended in 5 mL of dry DMF. The flask was cooled to 0 °C and a solution of 4-hydroxyisoquinoline (500 mg, 3.45 mmol, 1 eq.) in 15 mL of DMF was added dropwise at that temperature. After the removal of the cooling bath, the formation of the sodium isoquinolinoxy salt (monitored by the disappearance of the sodium hydride and the obtention of a homogeneous solution) was allowed to proceed at room temperature for 30 minutes. The reaction mixture was cooled to -50 °C and 0.4 mL of ethyl chloroformate (1.1 eq., 413 mg, 4 mmol) was added at that temperature. The reaction was allowed to warm up to room temperature and stirred for 2 hrs. The reaction crude was carefully pipetted into a separatory funnel containing crushed ice and extracted with ethyl acetate. The ethyl acetate extract was washed copiously with water and dried over magnesium sulfate. After the removal of the solvent *in vacuo* and radial chromatography (2mm chromatotron plate; 10-30 % EtOAc-petroleum ether) of the residue, the carbonate was obtained in 68 % yield (509 mg). ¹HNMR (300 MHz, CDCl₃) δ 9.16 (s, 1H, H1), 8.50 (s, 1H, H3), 8.01 (d, 1H, $J=8.2$ Hz, H8), 7.95 (d, 1H, $J=7.6$ Hz, H5),

7.75 (dt, $J=1.3$ Hz, $J=7.0$ Hz, H7), 7.65 (t, 1H, H6), 4.38 (q, 2H, CH_2Me), 1.43 (t, 3H, CH_2CH_3). $^{13}\text{CNMR}$ (75 MHz, CDCl_3) δ 153.24, 150.40, 150.25, 142.80, 135.34, 130.86, 129.44, 127.82, 127.39, 120.07, 65.41, 14.14.

Phenyl 4-isoquinolinylcarbonate (120)

A DMF (2 mL) solution of 4-hydroxyisoquinoline (100 mg, 0.7 mmol, 1 eq.) and Hünig's base (2 eq., 178.3 mg, 1.4 mmol, 240 μl) was stirred at 0 °C over a 10 minute period. Upon addition of 87 μl of phenyl chloroformate (1 eq., 108 mg, 0.7 mmol) the stirring was continued at that temperature for an additional 5 minutes as Tlc (ethyl acetate) monitoring revealed the disappearance of the starting material. The crude reaction mixture was taken into 100 mL of water and extracted with two 100 mL portions of ethyl acetate. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. Attempted purification by radial chromatography led to the isolation of 47 mg of impure carbonate. Further purification by preparative thin layer chromatography (silica gel; 30 % ethyl acetate-petroleum ether) resulted in the isolation of 40.3 mg of the pure material (22 % yield). $^1\text{HNMR}$ (300 MHz, CDCl_3) δ 9.24 (s, 1H, H1), 8.67 (s, 1H, H3), 8.10 (t, 2H, $J=7.6$ Hz), 7.85 (t, 1H, $J=8.3$ Hz), 7.74 (t, 1H, $J=7.9$ Hz), 7.51-7.32 (m, 5H).

2) The Claisen rearrangements

3-(2-methyl-2-propenyl)-4-hydroxyisoquinoline (133).

A solution of 4-(2-methyl-2-propenyloxy)isoquinoline (393.7 mg) in DMF (10 mL) was refluxed (bath temperature: 170 °C) under nitrogen for 3.5 hrs. The analysis of the reaction mixture by Tlc, was done in a 2:1 petroleum ether/EtOAc solvent mixture. The solid support was eluted twice so as to achieve adequate separation of the various spots. The reaction mixture was allowed to cool to room temperature and taken into 100 mL of water. The aqueous solution was washed with two 75 mL portions of ethyl acetate. The ethyl acetate extract was further washed with water (6x100 mL). The organic extract was dried over sodium sulfate and the solvent was removed under reduced pressure to yield 316.8 mg of the crude 3-(2-methyl-2-propenyl)-4-hydroxyisoquinoline. The product was obtained in 66% yield (259.7 mg) following column chromatography over florisil (eluted with a 1:1 petroleum ether/ethyl acetate mixture). ¹H NMR (300 MHz, CDCl₃) δ 8.81 (s, 1H, H1), 8.25 (d, 1H, J=7.9 Hz, H8), 7.90 (d, 1H, J=8.2 Hz, H5), 7.67 (broad s, 1H, OH), 7.64 (t, 1H, J=8.4, H-7), 7.54 (t, 1H, J=8.0 Hz, H-6), 4.85 (s, 1H, vinyl), 4.91 (s, 1H, vinyl), 3.82 (s, 2H, methylene), 1.71 (s, 3H, methyl). ¹³C NMR (75 MHz, CDCl₃) δ 146.67, 143.93, 142.91, 135.80, 129.52, 128.70, 128.60, 126.96, 126.89, 121.24, 112.62, 41.68, 22.16. HRMS calcd for C₁₃H₁₃NO 199.0998, found 199.0988.

3-(2-methyl-2-propenyl)-4-acetoxyisoquinoline (148).

a) via a one-pot Claisen with concomittant acetylation.

To a DMF solution (5 mL) of 4-(2-methyl-2-propenyloxy)isoquinoline (162.5 mg, 0.82 mmol, 1 eq.) was added 4.4 mg of DMAP followed by 231 μ L of acetic anhydride (3 eq., 250.1 mg, 2.45 mmol). The mixture was refluxed under nitrogen for 2.3 hrs at which point tlc analysis (2:1 petroleum ether/ethyl acetate) revealed the disappearance of the starting material. The reaction crude was taken into 50 mL of water and washed with two 50 mL portions of ethyl acetate. The ethyl acetate extract was washed with water (5x 50 mL). The organic phase was dried over sodium sulfate and following the removal of the solvent *in vacuo*, 241 mg (90% yield) of pure 3-(2-methyl-2-propenyl)-4-acetoxyisoquinoline was obtained. ^1H NMR (300 MHz, CDCl_3) δ 9.14 (s, 1H, H1), 7.96 (d, 1H, $J=8.2$ Hz, H8), 7.68 (d, 2H), 4.88 (s, 1H, vinyl), 4.78 (s, 1H, vinyl), 3.64 (s, 2H, methylene), 2.45 (s, 3H, OAc), 1.72 (s, 3H, methyl). ^{13}C NMR (75 MHz, CDCl_3) δ 168.7, 149.9, 144.6, 143.0, 140.5, 130.7, 130.4, 128.7, 127.6, 127.0, 120.3, 112.5, 41.6, 22.2, 20.6.

b) via acetylation of 3-(2-methyl-2-propenyl)-4-hydroxyisoquinoline **133**.

To a solution of 3-(2-methyl-2-propenyl)-4-hydroxyisoquinoline **133** (1 eq., 21.3 mg, 0.11 mmol) and DMAP (0.1 eq., 1.3 mg, 0.01 mmol) in 1 mL of pyridine was added acetic anhydride (2 eq., 21.9 mg, 0.21 mmol). The reaction was allowed to proceed at room temperature for 1 hr. Following the removal of the solvent under reduced pressure (high vac and 45 $^{\circ}\text{C}$ oil bath) the residue was taken into EtOAc and washed with water. The organic extract was dried over sodium sulfate and the solvent was removed under reduced pressure (rotary evaporator). The

crude 3-(2-methyl-2-propenyl)-4-acetoxyisoquinoline **148** was thus obtained in 57 % yields (15.2 mg).

3-(2-methyl-2-propenyl)-4-allyloxyisoquinoline (151).

To a flame-dried two-neck flask equipped with a nitrogen inlet was added 25.32 mg of a 50% sodium hydride (NaH)-mineral oil dispersion (12.66 mg effective weight of sodium hydride, 0.53 mmol, 1.4 eq.). The dispersion was washed twice with 1 mL portions of petroleum ether (which had previously been dried over sodium sulfate) and the remaining solid was suspended in 1 mL of dry DMF. Upon cooling to 0 °C, a solution of 3-(2-methyl-2-propenyl)-4-hydroxyisoquinoline (75 mg, 0.38 mmol) in 1.5 mL of DMF was added dropwise and the formation of the isoquinolinoxy salt was allowed to proceed at room temperature for 30 min. The formation of the salt is monitored by the disappearance of the insoluble sodium hydride resulting in a homogeneous solution of the isoquinolinoxy salt. The reaction vessel was cooled to 0 °C and allylbromide (1.1 eq., 50.1 mg, 35.8 µl, 0.41 mmol) was added dropwise at that temperature. The mixture was stirred at room temperature for 6 hrs. The reaction crude was pipetted into a Erlenmeyer flask containing crushed ice and the aqueous mixture was washed with three 50 mL portions of ethyl acetate. The combined organic extracts were further washed with water and with brine. The EtOAc solution was dried over sodium sulfate and concentrated *in vacuo*. The crude was purified by radial chromatography (1mm chromatotron plate eluted with 10 % EtOAc/petroleum ether). The expected 3-(2-methyl-2-propenyl)-4-allyloxyisoquinoline (**151**) was

obtained in 59% yield (53 mg) along with 1 mg of isomer **152**. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 9.06 (s, 1H, H1), 8.00 (d, $j=9.8$ Hz, $j=8.4$ Hz, H8), 7.97 (d, $j=8.2$ Hz, H5), 7.70 (dt, $j=1.2$ Hz, $j=8.4$ Hz, H7), 7.57 (dt, $j=1.1$ Hz, $j=8.2$ Hz, H6), 6.26-6.13 (m, 1H, allyl internal vinyl), 5.50 (ddd, 1H, $j=1.6$ Hz, $j=3.2$ Hz, $j=15.6$ Hz, trans vinyl), 5.34 (ddd, 1H, $j=1.2$ Hz, $j=2.3$ Hz, $j=9.2$ Hz, cis vinyl), 4.89 (s, 1H, $\text{ArCH}_2\text{CHCH}_3\text{CH}_2$), 4.67 (s, 1H, $\text{ArCH}_2\text{CHCH}_3\text{CH}_2$), 4.54 (ddd, 2H, $j=1.3$ Hz, $j=2.8$ Hz, OCH_2), 3.75 (s, 2H, ArCH_2), 1.81 (s, 3H, Me).

3-(2-propenyl)-4-hydroxyisoquinoline (138).

A solution of 4-(2-propenyloxy)isoquinoline (86.5 mg) in 4 mL of DMF (4 mL) was refluxed under nitrogen for 3 hrs. The reaction mixture was allowed to cool to room temperature and taken into 100 mL of water. The solution was washed with three 50 mL portion of ethyl acetate. The ethyl acetate extract was washed with three 50 mL portions of water. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure to yield 79.3 mg (90% yield) of 3-(2-propenyl)-4-hydroxyisoquinoline. Extensive decomposition of the material occurs upon exposure to silica gel or florisil. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.85 (s, 1H, H1), 8.16 (s, 1H, $J=8.4$ Hz, H8), 7.92 (d, 1H, $J=8.1$ Hz, H5), 7.69 (t, 1H, $J=7.1$ Hz, H7), 7.56 (t, 1H, $J=6.9$ Hz, H7), 6.18-6.10 (m, 1H, internal vinyl), 5.37-5.27 (m, 2H, terminal vinyl), 3.85 (d, 2H, $J=6.4$ Hz, allylic). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 149.47, 145.16, 132.61, 129.44, 129.09, 128.30, 127.50, 126.76, 124.07, 121.09, 117.86, 69.32.

3-(2-methyl-2-propenyl)-4-(tert-butyldimethylsilyloxy)isoquinoline (156).

A solution of 3-(2-methyl-2-propenyl)-4-hydroxyisoquinoline **148** (1 eq., 152 mg, 0.8 mmol) and DBU (1.5 eq., 174.4 mg, 1.1 mmol) in 20 mL of dichloromethane, was refluxed for 3 hrs. under nitrogen. Tlc analysis (4 % MeOH/CH₂Cl₂) of the reaction mixture revealed the complete disappearance of the starting silyl ether. The reaction mixture, upon cooling to room temperature, was poured into a separatory funnel containing crushed ice. The mixture was washed with water and the organic phase was dried over magnesium sulfate and concentrated *in vacuo*. Purification by radial chromatography (1mm chromatotron plate, eluted with dichloromethane) allowed the isolation of 201 mg (84 % yield) of 3-(2-methyl-2-propenyl)-4-(tert-butyldimethylsilyloxy)isoquinoline **156**. ¹HNMR (300 MHz, CDCl₃) δ 8.91 (s, 1H, H1), 8.01 (d, 1H, J=8.6 Hz, H8), 7.88 (d, 1H, J=7.9 Hz, H5), 7.61 (dt, 1H, J_{meta}=1.2 Hz, J_{ortho}=8.6 Hz, H7), 7.49 (t, 1H, J=7.3 Hz, H6), 4.84 (s, 1H, vinyl), 4.67 (s, 1H, vinyl), 3.68 (s, 2H, methylene), 1.68 (s, 3H, methyl), 1.12 (s, 9H, tert-butyl), 0.17 (s, 6H, SiMe₂).

3-(2-methyl-2-propenyl)-4-tosyloxyisoquinoline (158).

An acetone (10 mL) of 3-(2-methyl-2-propenyl)-4-hydroxyisoquinoline **148** (1 eq., 265 mg, 1.3 mmol) was refluxed for 1 hr. in the presence of suspended potassium carbonate (5 eq., 920 mg, 6.7 mmol). Following the addition of tosyl chloride (1.2 eq., 305 mg, 1.6 mmol) the refluxing was continued for another hour. Upon cooling, the mixture was filtered and

the solvent was removed under reduced pressure. The residue was purified by radial chromatography (2mm silica gel chromatotron plate; CH₂Cl₂). The tosylate ester **158** was obtained in 85 % yield (388 mg). ¹HNMR (300 MHz, CDCl₃) δ 9.15 (s, 1H, H1), 7.96 (d, 1H, J_{ortho}=7.9 Hz, H8), 7.91 (d, 1H, J_{ortho}=8.0 Hz, H5), 7.86 (d, 2H, J=8.3 Hz, tosylate ortho H's), 7.65 (dt, 1H, J_{meta}=1.2 Hz, J_{ortho}=8.1 Hz, H7), 7.60 (t, 1H, J=8.1 Hz, H6), 7.37 (d, 2H, J=8.1 Hz, tosylate meta H's), 4.82 (s, 1H, vinyl), 4.60 (s, 1H, vinyl), 3.50 (s, 2H, methylene), 2.48 (s, 3H, tosylate methyl), 1.60 (s, 3H, methyl). ¹³CNMR (75 MHz, CDCl₃) δ 150.64, 146.20, 145.75, 142.70, 140.03, 133.33, 131.31, 130.88, 129.99, 128.80, 128.22, 127.28, 127.10, 121.80, 112.78, 40.54, 22.36, 21.67. HRMS calcd for C₂₀H₁₉NO₃S 353.1087, found 353.1087.

3-(2-methyl-2,3-epoxy)-4-tosyloxyisoquinoline (173).

A solution of 3-(2-methyl-2-propenyl)-4-tosyloxyisoquinoline (1 eq., 388 mg, 1.1 mmol) and magnesium monoperoxy phthalate (MMPP) (1.5 eq., 815.2 mg, 1.6 mmol) in 10 mL of a 1:1 THF/H₂O mixture was stirred at room temperature over a 16 hr. period (Tlc in 2:1 petroleum ether/ethyl acetate; 2x elution). The reaction crude was washed with 50 mL of saturated sodium bicarbonate solution and the basic solution was extracted with two 50 mL of ethyl acetate. The ethyl acetate extract were further washed with 50 mL of a saturated sodium bisulfite solution. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure to yield 304 mg (97 % yield) of the relatively pure crude epoxide. The epoxide proved to be very sensitive under chromatographic conditions. **173**: ¹HNMR (300

MHz, CDCl₃) δ 9.14 (s, 1H, H1), 7.97 (d, 1H, J=7.5 Hz, H8), 7.90-7.84 (3H, two merging doublets, H5 and the tosylate ortho H's), 7.67-7.56 (2H, two merging dt, H6 and H7), 7.39 (d, 2H, J=8.1 Hz, tosylate meta H's), 3.22-2.94 (AB quartet, 2H, J=14.4 Hz, OCH₂), 2.71-2.56 (AB quartet, 2H, J=4.8 Hz, H1'). ¹³CNMR (75 MHz, CDCl₃) δ 150.6, 145.9, 144.7, 140.4, 133.5, 131.3, 130.9, 130.1(2 carbons), 128.3 (2 carbons), 127.5, 127.1, 122.0, 56.6, 53.7, 39.5, 21.7, 21.4. HRMS calcd for C₂₀H₁₉NO₄S 369.1036, found 369.1047.

The mcpba oxidation of 3-(2-methyl-2-propenyl)-4-acetoxyisoquinoline 148 3-(2-methyl-2,3-oxo)-4-acetoxyisoquinoline (171) and 3-(2-methyl-2-propenyl)-2-oxo-4-acetoxyisoquinoline (172).

Mcpba (2.2 eq., 1.24 mmol, 310 mg) was added to a methylene chloride (5 mL) solution of 3-(2-methyl-2-propenyl)-4-acetoxyisoquinoline **148** (1 eq., 135.6 mg, 0.56 mmol). The reaction mixture was stirred at room temperature for 12 hrs. Following successive washings with saturated solutions of sodium bisulfite and sodium bicarbonate, the methylene chloride extract was dried over sodium sulfate. Removal of the solvent under reduced pressure gave rise to 137.2 mg (95 % yield) of a mixture of **171** and **172**. Analysis of the ¹H nmr of the mixture resulted in the following assignments. **171**: ¹HNMR (300 MHz, CDCl₃) δ 9.13 (s, 1H, H1), 8.1-7.4 (m, Ar), 3.21 (AB quartet, J_{gem}=14.2 Hz, OCH₂), 2.72 (AB quartet, J_{gem}=5 Hz, ArCH₂), 2.51 (s, 3H, OAc), 2.25 (s, 6H, merging of the methyl protons of **171** and **172**). **172**: ¹HNMR (300 MHz, CDCl₃) δ 8.85 (s, 1H, H1), 8.1-7.4 (m, Ar), 4.81 (s, 1H, trans terminal vinyl), 4.63 (s, 1H,

$j=0.5$ Hz, cis terminal vinyl), 3.79 (s, 2H, ArCH₂), 2.46 (s, 3H, Ac), 2.25 (s, 6H, merging of the methyl protons of **171** and **172**).

3-(2-bromo-2-propenyl)-4-hydroxyisoquinoline (145).

A solution of 4-(2-bromo-2-propenyloxy)isoquinoline **76** (90 mg) in DMF (2 mL) was refluxed (bath temperature: 150 °C) under nitrogen for 1.5 hrs. The reaction mixture was allowed to cool to room temperature and taken into 50 mL of water. The aqueous solution was washed with ethyl acetate (x3 50 mL). The ethyl acetate extract was further washed with water (3x 20 mL) and dried over sodium sulfate. Upon removal of the solvent *in vacuo* 74.6 mg of a 5:1 mixture of 3-(2-bromo-2-propenyl)-4-hydroxyisoquinoline and furano[3,2-*c*]isoquinoline **142** were obtained. Attempted purification by radial chromatography over silica gel resulted in extensive decomposition of the material. **145**: ¹HNMR (300 MHz, CDCl₃) δ 8.82 (s, 1H, H-1), 8.23 (d, 1H, $J = 8.3$ Hz, H-8), 7.88 (d, 1H, $J = 8.1$ Hz, H-5), 7.64 (t, 1H, $J = 7.84$ Hz, H-7), 7.54 (t, 1H, $J = 7.25$ Hz, H-6), 5.58 (s, 1H, vinylic), 5.46 (s, 1H, vinylic), 4.19 (s, 2H, methylene). **142**: ¹HNMR (300 MHz, CDCl₃) δ 9.10 (s, 1H, H1), 8.20 (d, 1H, $J_{ortho}=8.5$ Hz, H8), 8.07 (d, 1H, $J_{ortho}=8.3$ Hz, H5), 7.79 (t, 1H, H6), 7.56 (t, 1H, H6), 6.80 (s, 1H, furan), 2.61 (s, 3H, CH₃). ¹³CNMR (75 MHz, CDCl₃) δ 156.7, 148.8, 141.7, 130.6, 128.3, 125.3, 123.4, 118.8, 105.1, 14.5. HRMS calcd for C₁₂H₉NO 183.0684, found 183.0695.

3-(2-bromo-2-propenyl)-4-Acetoxyisoquinoline (147).

a) via Acetylation of 3-(2-bromo-2-propenyl)-4-hydroxyisoquinoline.

To a suspension of 3-(2-bromo-2-propenyl)-4-hydroxyisoquinoline (219 mg, 0.83 mmol, 1 eq.) and DMAP (0.1 eq., 10.14 mg, 0.08 mmol) in pyridine (1 mL) was added 160 μ l of acetic anhydride (2 eq., 1.66 mmol). The mixture, kept under a nitrogen atmosphere, was stirred at room temperature overnight (tlc: methylene chloride; double elution). The reaction mixture was taken into 50 mL of water and washed with three 60 mL of ethyl acetate followed by brine. The organic extract was dried over sodium sulfate. Following the removal of the solvent under reduced pressure, 241 mg of reasonably pure product was obtained. Attempt to further purify the product by column chromatography (florisil; CH₂Cl₂ to 9:1 CH₂Cl₂/EtOAc) resulted in decomposition of the product and the isolation of only 140 mg (55% yield) of the product. ¹HNMR (300 MHz, CDCl₃) δ 9.17 (s, 1H, H1), 8.02 (d, 1H, J=8.2 Hz, H8), 7.23 (uneven d, 2H, H5), 7.64 (m, 1H, H6), 5.65 (d, 1H, J=1.1 Hz, vinylic), 5.59 (d, 1H, J=0.85 Hz, vinylic), 4.05 (s, 2H, methylene), 2.50 (s, 3H, acetoxy). LRMS calcd for C₁₄H₁₂BrNO₂ 305.01, found 305.10, M+2 307.10.

b) via a one-pot Claisen with concomitant acetylation.

To a solution of 4-(2-bromo-2-propenyloxy)isoquinoline (1 eq., 59.4 mg, 0.23 mmol) in 1 mL of DMF was added acetic anhydride (3 eq., 68.9 mg, 0.68 mmol). The mixture was refluxed for 50 min. The reaction mixture was allowed to cool to room temperature and was poured over crushed ice. The aqueous solution was extracted with EtOAc and further washed with water. Upon drying (Na₂SO₄) and the removal of the solvent *in vacuo*, the residue was subjected to radial chromatography (SiO₂; elution with 10-20 % EtOAc/petroleum ether). The desired 3-(2-

bromo-2-propenyl)-4-acetoxyisoquinoline **147** was isolated in 13% yields (7.6 mg).

3-(2-bromo-2-propenyl)-4-allyloxyisoquinoline (160).

To a flame-dried flask equipped with a nitrogen inlet was added 10.3 mg of an 80% sodium hydride (NaH)-mineral oil dispersion (8.2 mg effective weight of sodium hydride, 1.2 mmol). The dispersion was washed twice with 2 mL of petroleum ether which had previously been dried over sodium sulfate and the remaining solid was suspended in 1 mL of dry DMF. Upon cooling to 0 °C, a solution of crude (a 5:1 mixture of **145** and **142** from the Claisen rearrangement of **76**) 3-(2-bromo-2-propenyl)-4-hydroxyisoquinoline (75 mg, 0.28 mmol) in 3 mL of DMF was added dropwise and the formation of the isoquinolinoxy salt was allowed to proceed at room temperature for 40 min. The formation of the salt is monitored by the disappearance of the insoluble sodium hydride resulting in a homogeneous solution of the isoquinolinoxy salt. The reaction vessel was cooled to 0 °C and allylbromide (1.2 eq., 29.5 µl, 0.34 mmol) was added dropwise at that temperature. The mixture was stirred at room temperature for 20 min. The stirring was discontinued since TLC analysis (2:1 Hexane/EtOAc) revealed the disappearance of the starting material. The reaction crude was pipetted into a Erlenmeyer flask containing crushed ice and the aqueous mixture was washed with three 50 mL portions of ethyl acetate. The combined organic extracts were washed with water (8x 50 mL) and brine. The EtOAc solution was dried over sodium sulfate and concentrated *in vacuo*. The crude was purified by radial chromatography (1mm

chromatotron plate eluted with 5% EtOAc/Petroleum ether). The expected 3-(2-bromo-2-propenyl)-4-allyloxyisoquinoline (**160**) was obtained in 51% yield (44 mg) accompanied by 10% of furano[3,2-*c*]isoquinoline **142**. **160**: ^1H NMR (300 MHz, CDCl_3) δ 9.09 (s, 1H, H1), 8.09 (s, 1H, $j_{\text{ortho}}=8.6$ Hz, H8), 8.01 (d, 1H, $j_{\text{ortho}}=8.2$ Hz, H5), 7.75 (dt, 1H, $j_{\text{meta}}=1.2$ Hz, $j_{\text{ortho}}=8.3$ Hz, H7), 7.62 (dt, 1H, $j_{\text{meta}}=0.9$ Hz, $j_{\text{ortho}}=8.0$ Hz, H6), 6.29-6.16 (m, 1H, allyl internal vinyl), 5.67 (s, 1H, $j=1.3$ Hz, $\text{ArCH}_2\text{CHBrCHH}_{\text{trans}}$), 5.63 (s, 1H, $j=1.3$ Hz, $\text{ArCH}_2\text{CHBrCHH}_{\text{cis}}$), 5.54 (dd, 1H, $j=1.5$ Hz, $j_{\text{trans}}=17.2$ Hz, allyl trans vinyl), 5.37 (dd, 1H, $j=1.3$ Hz, $j_{\text{cis}}=11.8$ Hz, allyl cis terminal vinyl), 4.61 (d, 2H, $j=5.5$ Hz, OCH_2), 4.20 (s, 2H, ArCH_2). ^{13}C NMR (75 MHz, CDCl_3) δ 148.23, 148.03, 142.56, 133.19, 131.32, 130.98, 130.24, 127.60, 127.14, 121.27, 118.48, 75.72, 43.56.

3-(2-chloro-2-propenyl)-4-hydroxyisoquinoline (**144**).

A solution of 4-(2-chloro-2-propenyloxy)isoquinoline (48.5 mg) in DMF (1mL) was refluxed under nitrogen for 1.4 hrs. The reaction mixture was allowed to cool to room temperature and taken into 20 mL of water. The solution was extracted with ethyl acetate (3x 50 mL). The ethyl acetate extract was washed repeatedly with water and dried over sodium sulfate. Following the removal of the solvent *in vacuo*, the crude was purified by radial chromatography (1mm silica gel plate; the material was loaded with acetone and eluted with 10-20 % ethyl acetate/petroleum ether). The expected 3-(2-chloro-2-propenyl)-4-hydroxyisoquinoline **144** was obtained in 52 % yield. The furano[3,2-*c*]isoquinoline **142** was isolated in 11 % yields. **144**: ^1H NMR (300 MHz,

CDCl_3) δ 8.88 (s, 1H, H1), 8.34 (d, 1H, $J=8.3$ Hz, H8), 7.96 (d, 1H, $J=8.1$ Hz, H5), 7.72 (t, 1H, $J=7.8$ Hz, H7), 7.62 (t, 1H, $J=7.4$ Hz, H6), 5.28 (s, 1H, vinyl), 5.21 (s, 1H, vinyl), 4.16 (s, 2H, methylene). $^{13}\text{CNMR}$ (75 MHz, CDCl_3) δ 144.3, 134.0, 129.9, 129.1, 128.5, 127.3, 127.2, 121.0, 42.3. HRMS calcd for $\text{C}_{12}\text{H}_{10}\text{ClNO}$ 219.0451, found 219.0445.

142: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 9.10 (s, 1H, H1), 8.20 (d, 1H, $J_{\text{ortho}}=8.5$ Hz, H8), 8.07 (d, 1H, $J_{\text{ortho}}=8.3$ Hz, H5), 7.79 (t, 1H, H6), 7.56 (t, 1H, H6), 6.80 (s, 1H, furan), 2.61 (s, 3H, CH_3). $^{13}\text{CNMR}$ (75 MHz, CDCl_3) δ 156.7, 148.8, 141.7, 130.6, 128.3, 125.3, 123.4, 118.8, 105.1, 14.5. HRMS calcd for $\text{C}_{12}\text{H}_9\text{NO}$ 183.0684, found 183.0695.

3-(2-chloro-2-propenyl)-4-allyloxyisoquinoline (159).

To a flame-dried flask equipped with a nitrogen inlet was added 14.4 mg (1 eq.) of an 50% sodium hydride (NaH)-mineral oil dispersion (7.2 mg effective weight of sodium hydride, 0.3 mmol). The dispersion was washed twice with 2 mL of petroleum ether which had previously been dried over sodium sulfate and the remaining solid was suspended in 1 mL of dry DMF. Upon cooling to 0 °C, a solution of 3-(2-chloro-2-propenyl)-4-hydroxyisoquinoline **144** (75 mg, 0.28 mmol) in 2 mL of DMF was added dropwise and the formation of the isoquinolinoxy salt was allowed to proceed at room temperature for 20 min. The formation of the salt is monitored by the disappearance of the insoluble sodium hydride resulting thereby in a homogeneous solution of the isoquinolinoxy salt. The reaction vessel was cooled to 0 °C and

allylbromide (1 eq., 26.5 μ l, 0.3 mmol) was added dropwise at that temperature. The mixture was stirred at room temperature for 60 min. The stirring was discontinued since TLC analysis (2:1 Hexane/EtOAc) revealed the disappearance of the starting material. The reaction crude was pipetted into a Erlenmeyer flask containing crushed ice and the aqueous mixture was washed with three 50 mL portions of ethyl acetate. The combined organic extracts were washed with water (8x 50 mL) and brine. The EtOAc solution was dried over sodium sulfate and concentrated *in vacuo*. The crude was purified by radial chromatography (1mm chromatotron plate eluted with 20% EtOAc/Petroleum ether). The expected 3-(2-chloro-2-propenyl)-4-allyloxyisoquinoline (**159**) was obtained in 39 % yield (32 mg). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 9.03 (s, 1H, H1), 8.03 (d, 1H, $J_{\text{ortho}}=8.4$ Hz, H8), 7.93 (d, 1H, $J_{\text{ortho}}=8.3$ Hz, H5), 7.68 (dt, 1H, $J_{\text{meta}}=0.8$ Hz, $J_{\text{ortho}}=7.8$ Hz, H7), 7.55 (t, 1H, $J=7.9$ Hz, H6), 6.23-6.10 (m, 1H, allyl internal vinyl), 5.49 (dd, 1H, $J_{\text{gem}}=1.4$ Hz, $J_{\text{trans}}=17.2$ Hz, allyl trans vinyl), 5.34-5.30 (s & dd, 2H, allyl cis vinyl + $\text{ArCHCHClCHH}_{\text{trans}}$), 5.18 (s, 1H, $J=10$ Hz, $\text{ArCHCHClCHH}_{\text{cis}}$), 4.56 (d, 2H, $J=5.5$ Hz, OCH_2), 4.03 (s, ArCH_2). $^{13}\text{CNMR}$ (75 MHz, CDCl_3) δ 148.4, 148.1, 142.3, 140.2, 133.3, 131.4, 130.3, 129.4, 127.7, 127.2, 121.3, 118.1, 114.1, 75.8, 41.5. HRMS calcd for $\text{C}_{15}\text{H}_{14}\text{ClNO}$ 259.0764, found 259.0781.

The Claisen rearrangement of 4-(2-methoxy-2-propenyloxy)isoquinoline. The synthesis of 4-methoxy-4-methyldihydrofurano[3,2-c]isoquinoline (**140**).

A solution of 4-(2-methoxy-2-propenyloxy)isoquinoline (87 mg) in DMF (2mL) was refluxed (bath temperature: 160 °C) under nitrogen for 12 hrs. Upon cooling, the reaction mixture was taken into water and washed with ethyl acetate. The ethyl acetate extract was washed copiously with water and dried over sodium sulfate. The solvent was removed under reduced pressure. Following column chromatography under nitrogen (Basic alumina Brockman activity I, 80-200 mesh; ethyl acetate) the 4-methoxy-4-methyldihydrofurano[3,2-c]isoquinoline **140** was obtained in 60 % yield. ¹HNMR (300 MHz, CDCl₃) δ 8.77 (s, 1H, H-1), 7.92 (two d, 2H, H-5 & H-8), 7.64 (t, 1H, J=8.17 Hz, H-7), 7.52 (t, 1H, J=8.06 Hz, H-6), 3.48 (2H, J=17 Hz, methylene), 3.34 (s, overlapping the AB quartet, 3H, methoxy), 1.79 (s, 3H, methyl).

The acid-catalyzed opening of the dihydrofuranylisquinoline. The synthesis of 2-(2-oxo-propyl)-4-hydroxyisoquinoline (143).

The ketal (28 mg) was dissolved in 2 mL of a 1:1 mixture of water and THF. After the addition of 6 drops of concentrated HCl the mixture was allowed to stir at room temperature overnight. The reaction crude was rendered slightly basic by means of a saturated solution of sodium bicarbonate and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure to yield 28 mg (98 % yield) of exceptionally pure 2-(2-oxo-propyl)-4-hydroxyisoquinoline. ¹HNMR (300 MHz, CDCl₃) δ 8.80 (s, 1H, H1), 8.30 (d, 1H, J=8.35 Hz, H8), 7.92 (d, 1H, J=8.14 Hz, H5), 7.70 (t, 1H, J=7.93 Hz, H7), 7.60 (t, 1H, J=7.94 Hz, H6), 4.23 (s, 2H, methylene), 2.40 (s, 3H, methyl). IR: 1700 cm⁻¹

3-(2-methyl-5-trimethylsilyl-2-propene-4-yne)-4-hydroxyisoquinoline (149).

A solution of 30 mg of 3-(2-Methyl-5-trimethylsilyl-2-penten-4-yne)-4-hydroxyisoquinoline **106** in 5 mL of DMF was refluxed for 1.5 hours. Upon cooling, the reaction crude was taken into 100 mL of water. The aqueous solution was washed with acetate (3x 50 mL portions). The combined ethyl acetate extract was further washed with water (5x 50 mL) and dried over sodium sulfate. The crude product, 3-(2-methyl-5-trimethylsilyl-2-propene-4-yne)-4-hydroxyisoquinoline **149**, was obtained in 80 % yields. Efforts to obtain an analytical sample by radial chromatography over silica gel (CH₂Cl₂ then 5 % EtOAc/CH₂Cl₂) resulted in extensive decomposition of the material. **149**: ¹HNMR (300 MHz, CDCl₃) δ 8.94 (s, 1H, H-1), 8.12 (d, 1H, J=8.5 Hz, H8), 7.92 (d, 1H, J=8.1 Hz, H5), 7.68 (t, 1H, J=7.7Hz, H7), 7.60 (t, 1H, J= 7.9 Hz, H6), 5.48 (s, 1H, vinylic), 3.85 (s, 2H, methylene), 1.95 (s, 3H, methyl), 0.16 (s, 9H, TMS).

3) *The isoquinolinium salts*

1) 2-(2,4-dinitrophenyl)-4-methoxyisoquinolinium chloride. (264).

A mixture of 4-methoxyisoquinoline **54** (92,4 mg, 0.57 mmol, 1eq.) and 1-chloro-2,4-dinitrobenzene (117.2 mg, 0.57 mmol, 1 eq.) in 1 mL of acetonitrile was refluxed under nitrogen for 10 hours. The solvent was removed in vacuo and the residue was washed repeatedly with Et₂O

in order to remove unreacted starting material. Upon drying *in vacuo*, 2-(2,4-dinitrophenyl)-4-methoxy isoquinolinium chloride **42** was obtained as a brown solid in 50% yields (105 mg).

2) 2-(2,4-dinitrophenyl)-4-acetoxy-isoquinolinium chloride (274).

A mixture of 4-Acetoxyisoquinoline **55** (160 mg, 0.9 mmol, 1eq.) and 1-chloro-2,4-dinitrobenzene (289 mg, 1.4 mmol, 1.6 eq.) in 10 mL of diethylether was refluxed under nitrogen for 5 days. Increasing amounts of a yellow precipitate appeared during the course of the reaction. The reaction crude was allowed to cool to room temperature as the solid settled to the bottom of the flask. The supernatant was carefully removed using a pasteur pipette. The same procedure was employed in order to remove the ether layer from the subsequent washes. Upon drying *in vacuo*, the desired 2-(2,4-dinitrophenyl)-4-acetoxy-isoquinolinium chloride **56**. was obtained in 25% yield (86.7 mg) as a yellow solid which turns brown upon standing.

3) 2-(2,4-dinitrophenyl)-4-(ethoxycarbonyloxy)-isoquinolinium chloride (275).

A mixture of 4-(ethoxycarbonyloxy)isoquinoline **57** (254.2 mg, 1.2 mmol, 1eq.) and 1-chloro-2,4-dinitrobenzene (56 mg, 1.8 mmol, 1.5 eq.) in 10 mL of diethyl ether was refluxed under nitrogen for 4 days. A yellow precipitate began to form after 12 hours. The reaction was allowed to proceed for 4 days. Tlc (ethyl acetate/petroleum ether 1:1) still showed the presence of unreacted starting material. Upon cooling

the product settled to the bottom. The solvent was pipetted out and the salt was washed repeatedly with ether in order to remove unreacted starting materials. The salt was dried *in vacuo* and 137.6 mg (28% yield) of 2-(2,4-dinitrophenyl)-4-(ethoxycarbonyloxy) isoquinolinium chloride **58** was obtained.

4) 2-(2,4-dinitrophenyl)-4-allyloxyisoquinolinium chloride (276).

1-chloro-2,4-dinitrobenzene (57.2 mg, 0.28 mmol, 1 eq.) was allowed to form a homogeneous mixture with 4-allyloxyisoquinoline (55 mg, 0.30 mmol, 1.1 eq.) by stirring the two components at room temperature under nitrogen for 10 minutes. Freshly distilled (over P₂O₅) acetonitrile (0.7 mL) was added. The stirring was continued for an additional 12 hours resulting in the formation of a yellow precipitate. The solvent was removed after sedimentation of the product and the salt was washed repeatedly with diethyl ether. The solid was dried *in vacuo* and the expected 2-(2,4-dinitrophenyl)-4-(allyloxy)-isoquinolinium chloride **276** was obtained in 63% yield (73 mg). ¹HNMR (300 MHz, CDCl₃) δ 9.83 (s, 1H, H1), 9.26 (d, 1H, J_{meta}=2.4 Hz, DNP), 8.90 (dd, 1H, J_{meta}=2.5 Hz, J_{ortho}=8.7 Hz, DNP), 8.63 -8.61 (dd which merges with a singlet, H8 and H3), 8.48 (d, 1H, J_{ortho}=8.1 Hz, H5), 8.36 (dt, 1H, J_{meta}=1.1 Hz, J_{ortho}=7.1 Hz, H7), 8.31 (d, 1H, J_{ortho}=8.7 Hz, DNP), 8.16 (dt, 1H, J_{meta}=1.0 Hz, J_{ortho}=7.1 Hz), 6.17 (m, 1H, internal vinyl), 5.56 (dd, 1H, J_{vic}=1.5 Hz, J_{trans}=17.3 Hz, trans vinyl), 5.42 (dd, 1H, J_{gem}=1.3 Hz, J_{cis}=19.5 Hz, cis vinyl), 4.88 (m, 2H, OCH₂-vinyl).

4) The Bradsher cycloaddition

The cycloaddition of ethyl vinyl ether to 2-(2,4-dinitrophenyl)-4-methoxy isoquinolinium chloride. Immediate treatment with Dowex.

Ethyl vinyl ether (93 mg, 120 mL, 1.3 mmol, 4 eq.) was added at room temperature to a mixture of 2-(2,4-dinitrophenyl)-4-methoxy isoquinolinium chloride (105 mg, 0.32 mmol, 1 eq.) and CaCO₃ (193.4 mg, 2 mmol, 6 eq.) in 2 mL of dry MeOH. The mixture was stirred at room temperature for 2 days. The crude was filtered over Celite using methylene chloride to give a reddish material (222 mg) following the removal of the solvent *in vacuo*. The crude adduct was dissolved in 3 mL of dry MeOH and after the addition of 444 mg of acidic Dowex resin the mixture was allowed to stir overnight at room temperature. The resin was removed by filtration (over Celite) and the solvent was removed *in vacuo*. Upon radial chromatography (1mm chromatotron plate; 5% EtOAc/Petroleum ether as the eluent) the 1,3 adduct endo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-ethoxy **267** was isolated in 71% yield (87.5 mg).¹H, IR, and HRMS have been reported.¹⁵³ ¹³CNMR (75 MHz, CDCl₃) δ 192.5, 144.9, 144.1, 139.6, 138.4, 134.8, 129.8, 128.6, 128.3, 127.3, 125.1, 123.0, 119.8, 76.9, 71.0, 66.6, 62.2, 39.1, 14.8.

The cycloaddition of ethyl vinyl ether to 2-(2,4-dinitrophenyl)-4-acetoxy-isoquinolinium chloride.

Ethyl vinyl ether (1 mL, 10.5 mmol) was added at room temperature to a mixture of 2-(2,4-dinitrophenyl)-4-acetoxy-isoquinolinium chloride(

50 mg, 0.1 mmol, 1 eq.) and CaCO_3 (51 mg, 0.5 mmol, 5 eq.) in 1 mL of dry MeOH. The mixture was stirred at room temperature for 4 days. The crude was filtered over Celite using methylene chloride to give a reddish material following the removal of the solvent *in vacuo*. The crude material was purified by radial chromatography to give the 1,3 adduct **endo-6.7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-ethoxy 267** as the only characterizable product in 24% yield (12 mg). ^1H , IR, and HRMS have been reported.¹⁵⁴ ^{13}C NMR (75 MHz, CDCl_3) δ 192.5, 144.9, 144.1, 139.6, 138.4, 134.8, 129.8, 128.6, 128.3, 127.3, 125.1, 123.0, 119.8, 76.9, 71.0, 66.6, 62.2, 39.1, 14.8.

The cycloaddition of ethyl vinyl ether to 2-(2,4-dinitrophenyl)-4-(ethoxycarbonyloxy)isoquinolinium chloride.

Ethyl vinyl ether (82 μL , 0.9 mmol, 4 eq) was added at room temperature to a mixture of 2-(2,4-dinitrophenyl)-4-(ethoxycarbonyloxy) isoquinolinium chloride (90 mg, 0.2 mmol, 1 eq.) and CaCO_3 (86 mg, 4 eq.) in 1 mL of dry MeOH. The mixture was stirred at room temperature for 2 days. The crude was filtered over Celite, using methylene chloride. A reddish material (124.9 mg) was obtained following the removal of the solvent *in vacuo*. The crude product was subjected to radial chromatography (2 mm chromatotron plate. The sample was loaded with CH_2Cl_2 and eluted with 10 % EtoAc/petroleum ether). The first fraction consisted of 50.4 mg (66 % yield) of the 1,3 adduct **endo-6.7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-ethoxy 267**. The second band (17.2 mg)

was identified as hydroxy aldehyde **291** (19% yield). **291**: ^1H NMR (300 MHz, CDCl_3) δ 9.77 (s, 1H, CHO), 9.19 (d, $J=2.6$ Hz, 1H, 2,4-DNP), 8.83 (broad d, $J=7.8$ Hz, 1H, NH), 8.33 (dd, $J=2.4$ Hz, $J=9.5$ Hz, 2,4-DNP), 7.43 - 7.31 (m, 4H, phenyl), 7.08 (d, $J=9.5$ Hz, 1H, 2,4-DNP), 5.19 (dd, $J=7.6$ Hz, $J=12.9$ Hz, 1H, CH-NHAr), 4.04 (dd, $J=2.12$ Hz, $J=7.6$ Hz, 1H, CH-OEt), 3.79 - 3.72 (m, 1H, OCH_2Me), 3.60 - 3.53 (m, 1H, OCH_2Me), 2.59 (ddd, $J=5.1$ Hz, $J=7.5$ Hz, $J=13.4$ Hz, 1H), 2.59 (m, 1H), 1.57 (broad s, 1H, OH), 1.23 (t, 3H, Me). ^{13}C NMR (75 MHz, CDCl_3) δ 199.1, 147.5, 136.7, 135.1, 134.3, 131.0, 130.6, 129.7, 129.5, 127.6, 124.9, 124.5, 114.0, 78.2, 73.8, 66.0, 49.6, 29.7, 15.4. LRMS calcd for $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_7$ 401.01, found M-29 (-CHO) 372.25, M-74 (OEt + CHO) 327.10

The cycloaddition of ethyl vinyl ether to 2-(2,4-dinitrophenyl)-4-allyloxy isoquinolinium chloride. Immediate treatment with Dowex.

Ethyl vinyl ether (61.8 mg, 81 mL, 0.86 mmol, 4 eq.) was added at room temperature to a mixture of 2-(2,4-dinitrophenyl)-4-allyloxy-isoquinolinium chloride (83 mg, 0.21 mmol, 1 eq.) and CaCO_3 (85.7 mg, 0.86 mmol, 4 eq.) in 2 mL of dry MeOH. The mixture was stirred at room temperature for 2 days. The crude was filtered over Celite using methylene chloride to give a reddish material following the removal of the solvent *in vacuo*. The crude adduct was dissolved in 7 mL of dry MeOH and after the addition of 109 mg of acidic Dowex resin the mixture was allowed to stir at room temperature for 12 hours. The resin was removed by filtration over a Celite pad and the solvent was removed *in vacuo*. The crude was dissolved in EtOAc and washed with a saturated sodium bicarbonate solution. The EtOAc extract was washed

with brine, dried over Na_2SO_4 and the solvent was removed *in vacuo* to yield 88.3 mg of a mixture consisting of the 1,3 adduct endo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-ethoxy **267** (71%) and the two methoxy 1,3 diastereomers. The endo methoxy isomer **313** endo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-methoxy constituted 15% of the mixture while the epimer **314** exo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-methoxy was present in 11%. **313**: ^1H NMR (300 MHz, CDCl_3), δ 8.62 (d, $J=2.6$ Hz, 1H, 2,4-DNP), 8.13 (dd, $J=9.2$ Hz, $J=2.7$ Hz, 1H, 2,4-DNP), 7.99 (d, $J=7.7$ Hz, 1H, Phenyl), 7.55 (dt, $J=1.3$ Hz, $J=7.5$ Hz, 1H, Phenyl), 7.38 (dt, $J=1$ Hz, $J=7.7$ Hz, 1H, Phenyl), 7.25 (d, $J=7.7$ Hz, 1H, Phenyl), 6.94 (d, $J=9.2$ Hz, 1H, 2,4-DNP), 4.82 (two doublet merging into a triplet, 2H), 4.63 (ddd, $J=2.7$ Hz, $J=7.0$ Hz, $J=11.7$ Hz, 1H), 3.38 (s, 3H, OMe), 3.06 (ddd, $J=7.2$ Hz, $J=9.4$ Hz, $J=13.0$ Hz, 1H), 1.92 (dd, $J=2.7$ Hz, $J=13.3$ Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 192.5, 144.8, 144.1, 139.8, 138.5, 135.0, 129.7, 128.7, 128.4, 127.4, 125.1, 123.0, 119.9, 78.8, 70.8, 62.3, 58.7, 38.9. IR (CCl_4): 2960, 2920, 1700, 1600, 1520, 1330, 1250, 1100 cm^{-1} . HRMS calcd for $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}_6$ 369.0962, found 369.0971. **314**: ^1H NMR (300 MHz, CDCl_3), δ 8.64 (d, $J=2.7$ Hz, 1H, 2,4-DNP), 8.16 (dd, $J=2.7$ Hz, $J=9.3$ Hz, 1H, 2,4-DNP), 7.94 (d, $J=7.2$ Hz, 1H, Phenyl), 7.56 (dt, $J=1.35$ Hz, $J=7.5$ Hz, 1H, Phenyl), 7.39 (dt, $J=1.1$ Hz, 7.6 Hz, 1H, Phenyl), 7.18 (d, $J=7.3$ Hz, 1H, Phenyl), 6.96 (d, $J=9.3$ Hz, 1H, 3,4-DNP), 5.02 (d, $J=6.7$ Hz, 1H), 4.66 (s, 1H), 4.08 (dd, $J=3.8$ Hz, $J=7.5$ Hz, 1H), 3.47 (s, 3H, OMe), 2.58 (ddd, $J=3.7$ Hz, $J=7.0$ Hz, $J=13.2$ Hz, 1H), 2.46 (dd, $J=7.4$ Hz, $J=13.2$ Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 193.3, 144.6, 144.5, 139.6, 138.5, 135.6, 129.0, 128.4, 128.1, 127.8, 125.3, 123.2, 119.7, 81.3, 73.5, 62.8, 57.8,

39.8. IR (CCl₄): 2960, 2920, 1700, 1600 , 1520, 1330, 1300, 1250, 1100, 1000 cm⁻¹. HRMS calcd for C₁₈H₁₅N₃O₆ 369.0962, found 369.0969.

The cycloaddition of ethyl vinyl ether to 2-(2,4-dinitrophenyl)-4-allyloxyisoquinolinium chloride.

Ethyl vinyl ether (37.22 mg, 49 mL, 0.5 mmol, 4 eq.) was added at room temperature to a mixture of 2-(2,4-dinitrophenyl)-4-allyloxyisoquinolinium chloride **276** (50 mg, 0.13 mmol, 1 eq.) and CaCO₃ (52 mg, 0.5 mmol, 4 eq.) in 2 mL of dry MeOH. The mixture was stirred at room temperature for 2 days. The crude was filtered over Celite using methylene chloride to give a reddish material (69.8 mg) following the removal of the solvent *in vacuo*. A portion of the crude (32 mg) was subjected to radial chromatography (1mm chromatotrom plate; eluent: 25% CH₂Cl₂/Petroleum ether). The isolated fractions required further purification. The expected aldehyde **294** was isolated in a combined yield of 40%. The 1,3 adduct endo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-ethoxy **267** and the one-bond product **293** were obtained in 24% and 19% yields respectively. The yields are adjusted for the total weight of the crude reaction mixture. **294**: ¹HNMR (300 MHz, CDCl₃) δ 9.65 (s, 1H, CHO), 9.21 (d, J=2.6 Hz, 1H, 2,4-DNP), 8.83 (d, J=8.5 Hz, 1H, NHDNP), 8.31 (dd, J=9.5 Hz, J=2.6 Hz, 1H, 2,4-DNP), 7.63 (d, J=7.6 Hz, 1H, phenyl), 7.63 (d, J=7.6 Hz, 1H, phenyl), 7.47 - 7.31 (m, 3H, phenyl), 7.02 (d, J=9.6 Hz, 1H, 2,4-DNP), 6.05 - 5.92 (m, 1H, internal vinyl), 5.36 (dd, J=17.2 Hz, J=1.5 Hz, 1H, trans terminal vinyl), 5.22 (dd, J=10.52 Hz, J=1.4 Hz, 1H, cis terminal vinyl), 5.32 - 5.27 (ddd, overlapping the cis terminal vinyl

proton, 1H, CH-NHAr), 4.29 (dd, J=6.1 Hz, J=2.1 Hz, 1H, CH-OEt), 4.17 - 4.14 (ddd, 2H, allylic methylene), 3.84 - 3.74 (m, 1H, OCH₂Me), 3.65 - 3.55 (m, 1H, OCH₂Me), 2.68 (dt, J=4.5 Hz, J=10.4 Hz, 1H), 2.29 (ddd, J=2.1 Hz, J=10.0 Hz, J=13.8 Hz, 1H). ¹³CNMR (75 MHz, CDCl₃) δ 198.7, 147.9, 136.9, 134.6 (two peaks), 131.8, 131.0, 130.6, 129.6, 129.5, 129.0, 126.8, 124.6, 116.8, 113.9, 82.5, 74.3, 66.6, 65.8, 49.0, 31.7, 15.4. IR (CCl₄): 3340, 3100, 2960, 2920, 1730, 1600, 1580, 1420, 1330, 1250 cm⁻¹.

293: ¹HNMR (300 MHz, CDCl₃) δ 8.67 (d, J=2.6 Hz, 1H, 2,4-DNP), 8.30 (dd, J=2.7 Hz, J=9.5 Hz, 1H, 2,4-DNP), 7.66 (J=1.1 Hz, J=7.7 Hz, 1H, Phenyl), 7.60 (d, J=9.6 Hz, 1H, 2,4-DNP), 7.37 (dt, J=1.1 Hz, J=7.7 Hz, 1H, Phenyl), 7.30 (dt, J=1.4 Hz, J=7.7 Hz, 1H, Phenyl), 7.04 (d, J=7.6 Hz, 1H, Phenyl), 6.14 - 6.01 (m, 1H, internal vinyl), 5.46 (dd, J=1.4 Hz, J=17 Hz, trans terminal vinyl), 5.33 (dd, J=1.3 Hz, J=10.6 Hz, 1H, cis terminal vinyl), 5.17 (t, 1H), 5.11 (s, J=1.0 Hz, 1H), 4.45 - 4.30 (m: AB quartet + dd, 3H), 3.80 - 3.72 (m, 1H, CH₂Me), 3.59 - 3.48 (m, 1H, CH₂Me), 3.29 (s, 3H, OMe), 2.26 - 2.15 (m, 2H), 1.32 (t, J=7 Hz, 3H, Me). HRMS calcd for C₂₃H₂₅N₃O₇ 455.1662, found 455.1703.

The cycloaddition of tert-butyldimethylsilyl vinyl ether to 2-(2,4-dinitrophenyl)-4-allyloxy isoquinolinium chloride.

Tert-butyldimethylsilyl vinyl ether (122.3 mg, 155 mL, 0.77 mmol, 4 eq.) was added at room temperature to a mixture of 2-(2,4-dinitrophenyl)-4-allyloxy-isoquinolinium chloride **276** (75 mg, 0.19 mmol, 1 eq.) and CaCO₃ (77.4 mg, 0.77 mmol, 4 eq.) in 2 mL of dry MeOH. The mixture was stirred at room temperature for 2 days. The

crude was filtered over Celite using methylene chloride to give a reddish material. The crude was dissolved in 4 mL of THF/H₂O (1:1) and was stirred at room temperature for two days in the presence of 5 mg of TsOH. The crude was diluted with EtOAc and washed with a saturated sodium bicarbonate solution. The combined EtOAc extracts was dried over Na₂SO₄ and the solvent was removed under reduced pressure. Upon drying *in vacuo*, 100 mg (quantitative yield) of pure aldehyde **298** (purity ascertained by ¹H nmr) was obtained. **298**: ¹HNMR (300 MHz, CDCl₃) δ 9.70 (s, 1H, CHO), 9.21 (d, J=2.7 Hz, 1H, 2,4-DNP), 8.78 (d, J=8.3 Hz, 1H, NH), 8.32 (dd, J=9.5 Hz, J=2.6 Hz, 1H, 2,4-DNP), 7.52 - 7.26 (m, 4H, Phenyl), 7.06 (d, J=9.6 Hz, 1H, 2,4-DNP), 6.00 - 5.91 (m, 1H, internal vinyl), 5.30 (dd, J=17.3 Hz, J=1.6 Hz, 1H, trans terminal vinyl), 5.20 (dd, J=10.5 Hz, J=1.5 Hz, 1H, cis terminal vinyl), 5.32 (ddd overlapping the resonance of the trans vinyl proton, 1H, CHNHAr), 4.67 (dd, J=7.3 Hz, J=2.6 Hz, 1H, CHOTBDMS), 4.16 (d, J=5.2 Hz, 2H, allylic CH₂), 2.54 (ddd, J=5.3 Hz, J=7.3 Hz, J=13.6 Hz, 1H), 2.29 (ddd, J=2.7 Hz, J=8.4 Hz, J=13.6 Hz, 1H), 0.89 (s, 9H, tert-Butyl), 0.11 (s, 6H, SiMe₂). ¹³CNMR (75 MHz, CDCl₃) δ 199.98, 147.68, 136.41, 134.72, 131.94, 130.75, 130.64, 130.53, 129.67, 128.89, 127.49, 124.66, 124.44, 116.46, 113.86, 83.24, 68.72, 66.78, 49.40, 35.07, 25.79, 18.01. IR (CCl₄): 3330, 3110, 2930, 2830, 1730, 1620, 1590, 1510, 1430 cm⁻¹, 1340, 1030 cm⁻¹. HRMS calcd for C₂₆H₃₃N₃O₇Si 527.2089, found M-29 (- CHO) 498.2038.

The cycloaddition of methoxymethylvinyl ether to 2-(2,4-dinitrophenyl)-4-allyloxy isoquinolinium chloride.

Methoxymethyl vinyl ether (113. mg, 1.28 mmol, 8.5 eq.) was added at room temperature to a mixture of 2-(2,4-dinitrophenyl)-4-allyloxy isoquinolinium chloride (59 mg, 0.15 mmol, 1 eq.) and CaCO_3 (128 mg, 1.28 mmol, 8.5 eq.) in 1 mL of dry MeOH. The mixture was stirred at room temperature for 3 days. The crude was filtered over Celite using methylene chloride to give a reddish material which was subjected to radial chromatography (2mm silica gel chromatotrom plate; the crude was loaded using acetone and eluted with a 35 to 100 % CH_2Cl_2 /Petroleum ether mixture). The fastest moving band , eluting with 80% CH_2Cl_2 /Petroleum ether, (8.5 mg) was identified as a mixture of one-bond products. The desired aldehyde **295** (32 mg) was eluted off the plate with pure CH_2Cl_2 in 47% yields. ^1H NMR (300 MHz, CDCl_3), δ 9.63 (s, 1H, CHO), 9.19 (d, $J=2.7$ Hz, 1H, 2,4-DNP), 8.81 (d, $J=8.3$ Hz, 1H, NH-Ar), 8.31 (dd, $J=9.5$ Hz, $J=2.6$ Hz, 1H, 2,4-DNP), 7.65 (d, $J=7.3$ Hz, 1H, Phenyl), 7.51 - 7.36 (m, 3H, Phenyl), 7.13 (d, $J=9.6$ Hz, 1H, 2,4-DNP), 6.02 - 5.91 (m, 1H, internal vinyl), 5.35 (dd, $J=17.2$ Hz, $J=1.6$ Hz, trans terminal vinyl), 5.22 (dd, $J=10.5$ Hz, $J=1.4$ Hz, 1H, cis terminal vinyl), 5.35 - 5.29 (ddd, overlapping the trans vinyl resonance, 1H), 4.83 (AB quartet, $J=6.9$ Hz, 2H, acetal), 4.56 (dd, $J=6.3$ Hz, $J=2.2$ Hz, 1H, CH-OMOM) , 4.14 (ddt, $J=1.4$ Hz, $J=5.3$ Hz, $J=12.3$ Hz, 2H, allylic CH_2), 3.45 (s, 3H, OCH_3), 2.80 (dt, $J=6.1$ Hz, $J=13.9$ Hz, 1H), 2.29 (ddd, $J=2.3$ Hz, $J=9.7$ Hz, $J=13.8$ Hz, 1H).

The cycloaddition of methoxymethylvinyl ether to 2-(2,4-dinitrophenyl)-4-allyloxy isoquinolinium chloride. Dowex treatment.

Methoxymethyl vinyl ether (76.8 mg, 2 mmol, 2 eq.) was added at room temperature to a mixture of 2-(2,4-dinitrophenyl)-4-allyloxy isoquinolinium chloride **276** (389.3 mg, 1 mmol, 1 eq.) and CaCO₃ (402 mg, 0.4 mmol, 4 eq.) in 3 mL of dry MeOH. The mixture was stirred at room temperature for 3 days. The crude was filtered over Celite using methylene chloride to give a reddish material upon removal of the solvent under reduced pressure. The crude was dissolved in 10 mL of methanol and 450 mg of Dowex were added. The mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered over a Celite bed and the solvent was removed under reduced pressure. The crude product was subjected to radial chromatography (2 mm silica gel chromatotron plate). Elution with a 40% EtOAc/Petroleum ether mixture gave rise to two bands. The slower moving band (153 mg) was identified as a mixture of hydroxy ketones **317** and **318**. Of the faster moving band (172 mg), 50 mg were further purified by preparative Tlc (silica gel; 50-50 EtOAc/Petroleum ether as the eluent). The first fraction (11.9 mg) corresponded to endo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-methoxy **313**. The epimer exo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-methoxy **314** (3.7 mg) eluted next. The next fraction (10 mg) was identified as the methoxymethyl 1,3 adduct endo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-methoxymethyl **319**. Acetal **320** (0.1 mg) constituted the last fraction. **319**: ¹H NMR (300 MHz, CDCl₃) δ 8.54 (d, J=2.6 Hz, 1H, 2,4-DNP), 8.05 (dd, J=2.7 Hz, J=9.2 Hz, 1H, 2,4-DNP), 7.91 (d, J=7.7 Hz, 1H, Phenyl), 7.47 (dt, J=1.3 Hz, J=7.5 Hz, 1H, Phenyl), 7.26 (dt, J=1.0 Hz, J=7.7 Hz, 1H, Phenyl), 7.17 (d, J=7.6 Hz, 1H, Phenyl), 6.86

(d, $J=9.2$ Hz, 1H, 2,4-DNP), 4.93 (ddd, $J=2.6$ Hz, $J=7.3$ Hz, $J=9.3$ Hz, 1H), 4.75 (d, $J=6.9$ Hz, 1H), 4.68 (d, $J=7.2$ Hz, 1H), 4.52 (AB quartet, $J=6.9$ Hz, 2H), 3.21 (s, 3H, Me), 3.00 (ddd, $J=7.0$, $J=9.3$, $J=13.2$ Hz, 1H), 1.89 (dd, $J=2.5$, $J=13.2$, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 192.7, 144.9, 144.0, 139.8, 138.5, 135.1, 129.7, 128.8, 128.4, 127.5, 125.2, 123.1, 119.9, 96.3, 73.6, 70.9, 62.4, 56.0, 39.1. IR (CCl_4): 2940, 1690, 1600, 1470, 1340 cm^{-1} . LRMS calcd for $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_7$ 399.11 found 398.95.

The cycloaddition of tetrahydropyranyl vinyl ether to 2-(2,4-dinitrophenyl)-4-allyloxy isoquinolinium chloride.

Tetrahydropyranyl vinyl ether **287** (21.5 mg, 0.17 mmol, 1 eq.) was added at room temperature to a mixture of 2-(2,4-dinitrophenyl)-4-allyloxy isoquinolinium chloride **276** (65 mg, 1 mmol, 1 eq.) and CaCO_3 (61 mg, 0.34 mmol, 2 eq.) in 2 mL of dry MeOH. The mixture was stirred at room temperature for 2 days. The crude was diluted with ethyl acetate and filtered over Celite to give a reddish material (224 mg) upon removal of the solvent under reduced pressure. The resulting mixture was subjected to radial chromatography (1 mm silica gel chromatotron plate). Elution with a 10% EtOAc/Petroleum ether mixture resulted in the isolation of aldehyde **297** (42.5 mg) in 51% yield. ^1H NMR (300 MHz, CDCl_3), δ 9.56(s, 1H, CHO), 9.19 (d, $J=2.7$ Hz, 1H, 2,4-DNP), 8.82 (d, $J=8.5$ Hz, 1H, NH), 8.27 (dd, $J=2.7$ Hz, $J=9.6$ Hz, 1H, 2,4-DNP), 7.69 (d, $J=7.2$ Hz, 1H, Phenyl), 7.53 - 7.41 (m, 3H, Phenyl), 7.37 (d, $J=9.7$ Hz, 1H, 2,4-DNP), 6.04 - 5.91 (m, 1H, internal vinyl), 5.44 (m, 1H, CH-NHAr), 5.41 (dd, $J=1.6$ Hz, $J=17.2$ Hz, 1H, trans terminal vinyl), 5.23 (dd, $J=1.3$ Hz, $J=10.4$ Hz, 1H, cis terminal vinyl), 4.69 (d, $J=6.7$ Hz, 1H),

4.57 (d, $J=5.2$ Hz, 1H, CH-OTHP), 4.12 (d, $J=5.3$ Hz, 2H), 4.06 - 4.02 (m, 2H), 3.64 - 3.57 (m, 2H), 2.93 (dt, $J=5.3$ Hz, $J=13.7$ Hz, 1H), 2.14 (t, 1H, $J=13.1$ Hz), 1.88 - 1.58 (m 4H). ^{13}C NMR (75 MHz, CDCl_3) δ 197.5, 148.1, 137.6, 136.4, 134.4, 131.6, 130.8, 130.4, 129.6, 129.4, 128.8, 126.4, 124.4, 116.8, 114.7, 103.5, 82.2, 75.0, 66.3, 65.5, 49.0, 32.2, 31.8, 25.2, 21.4. IR (CCl_4): 3330, 3110, 2930, 2830, 1730, 1620, 1590, 1510, 1430, 1340, 1030 cm^{-1} . LRMS calcd for $\text{C}_{25}\text{H}_{27}\text{N}_3\text{O}_8$ 497.18, found M-29 (-CHO) 468.25.

The cycloaddition 2-tetrahydropyranyloxy-4-methyl-1,4-pentadiene to 2-(2,4-dinitrophenyl)-4-allyloxy isoquinolinium chloride.

2-Tetrahydropyranyloxy-4-methyl-1,4-pentadiene **288** (47.3 mg, 0.26 mmol, 2 eq.) was added at room temperature to a mixture of 2-(2,4-dinitrophenyl)-4-allyloxy-isoquinolinium chloride **276** (50 mg, 0.13 mmol, 1 eq.) and CaCO_3 (52 mg, 0.5 mmol, 4 eq.) in 1 mL of dry MeOH. The mixture was stirred at room temperature for 3 days. The crude was filtered over Celite (using methylene chloride). The material obtained upon removal of the solvent under reduced pressure was subjected to radial chromatography. Various fractions were obtained. One fraction, which was a mixture of products, clearly displayed the signals (CHO, NH-DNP) expected from aldehyde **309**. The amount of the aldehyde was estimated at ca. 7% yield. One-bond ketone **305** and enone **306** were isolated in 25% and 10% yield respectively. **306**: ^1H NMR (300 MHz, CDCl_3) δ 8.65 (d, 1H, DNP), 8.30 (dd, 1H, DNP), 7.55 (d, 1H, Ph), 7.35 (t, 1H, Ph), 7.26 (t, 1H, Ph), 6.90 (d, 1H, DNP), 6.20-6.00 (m, 1H, allyl internal vinyl), 5.60 (s, 1H, vinylic α -proton), 5.49 (dd, 1H,

allyl trans vinyl), 5.35 (dd, 1H, allyl cis vinyl), 5.25 (s, 1H, ring vinyl), 4.97 (dd, 1H, ArCHNDNP), 4.42 (d AB quartet, allyl CH₂), 2.57 (m, 2H, α-CH₂) 2.19 (s, 3H, Me), 2.01 (s, 3H, Me).

The cycloaddition 2-methoxypropene to 2-(2,4-dinitrophenyl)-4-allyloxy isoquinolinium chloride.

2-Methoxypropene (0.4 mL) was added at room temperature to a mixture of 2-(2,4-dinitrophenyl)-4-allyloxy-isoquinolinium chloride **276** (20 mg, 0.05 mmol, 1 eq.) and CaCO₃ (21 mg, 0.2 mmol, 4 eq.) in 1 mL of dry MeOH. The mixture was stirred at room temperature for 3 days. The crude was diluted with methylene chloride and filtered over Celite. Upon the removal of the solvent under reduced pressure a reddish material (20 mg) which was identified as one-bond product **301** was obtained. ¹HNMR (300 MHz, CDCl₃) δ 8.63 (d, 1H, DNP), 8.31 (dd, 1H, DNP), 7.80 (d, 1H, Ph), 7.69 (d, 1H, Ph), 7.50-7.30 (m, 2H, Ph), 7.21 (d, 1H, DNP), 6.20-6.10 (m, 1H, allyl internal vinyl), 5.50 (dd, 1H, allyl trans vinyl), 5.39 (dd, 1H, allyl cis vinyl), 5.29 (t, 1H, AcCHCH₂N), 5.19 (s, 1H, ring vinyl), 4.45 (d AB quartet, allyl CH₂), 3.29 (s, 6H, OMe₂), 1.25 (s, 3H, Me).

5) The BC ring

Making the dimethyl acetal (333) of the silyloxyaldehyde.

Silyloxy aldehyde **298** (140 mg, 0.3 mmol) was dissolved in 3 mL of trimethyl orthoformate. Following the addition of 5 mg of TsOH (0.03

mmol) the mixture was stirred at room temperature. After 5 min. the initially yellow reaction mixture turned red. The reaction was stopped after 15 minutes as Tlc analysis (6:1 Petroleum ether/ethyl acetate) revealed the disappearance of the starting material. The reaction crude was diluted with EtOAc and washed with a saturated sodium bicarbonate solution. The organic extract was dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude was purified by radial chromatography (2mm silica gel chromatotrom plate; the compound was loaded using methylene chloride and eluted with a 5% ethyl acetate/petroleum ether mixture). The mixed ketal **327** of the 1,3 adduct, endo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-allyloxy-9-methoxy-5H-benzocyclohepten-5,8-imine-7-tert-

butyldimethylsilyloxy (66.4 mg, 46% yield) eluted first followed by the dimethyl acetal **333** (56 mg, 33% yield). The 1,3 adduct endo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-tert-butyldimethylsilyloxy **316** which was eluted using a 10% ethyl acetate/petroleum ether mixture was obtained in 10% yields (12 mg). **316**: ¹HNMR (300 MHz, CDCl₃), δ 8.62 (d, J=2.6 Hz, 1H, 2,4-DNP), 8.13 (dd, J=2.6 Hz, J=9.2 Hz, 1H, 2,4-DNP), 7.95 (d, J=7.8 Hz, 1H, Phenyl), 7.53 (dt, J=0.9 Hz, J=7.4 Hz, 1H, Phenyl), 7.38 (t, J=7.6 Hz, 1H, Phenyl), 6.95 (d, J=9.2 Hz, 1H, 2,4-DNP), 5.06 (ddd, J=1.9 Hz, 1H), 4.80 (d, J=6.8 Hz, 1H), 4.63 (d, J=7.3 Hz, 1H), 3.01 (ddd, J=6.9 Hz, J=8.6 Hz, J=13.0 Hz, 1H), 1.83 (dd, J=1.9 Hz, J=12.8 Hz, 1H), 0.73 (s, 9H, tert-butyl), 0.08 (s, 3H, Me), 0.03 (s, 3H, Me). ¹³CNMR (75 MHz, CDCl₃) δ 192.5, 144.7, 144.1, 139.6, 138.4, 134.6, 130.3, 128.5, 128.4, 127.1, 124.0, 123.1, 119.9, 72.3, 70.3, 62.8, 41.9, 25.5, 17.8, - 5.08, - 5.1. LRMS calcd for C₂₃H₂₇N₃O₆Si

469.17 found M-57 (-tert-butyl) 411.85, M-282 (-TBDMS and 2,4-DNP) 187.00.

333: ^1H NMR (300 MHz, CDCl_3), δ 9.18 (d, $J=2.7$ Hz, 1H, DNP), 8.78 (broad d, $J=8.2$ Hz, 1H, NH-DNP), 8.28 (dd, $J=2.6$ Hz, $J=9.6$ Hz, 1H, DNP), 7.65 (d, $J=7.8$ Hz, 1H, Phenyl), 7.39 (t, $J=1.5$ Hz, $J=7.5$ Hz, 1H, Phenyl), 7.30 (t, $J=1.3$ Hz, $J=7.6$ Hz, 1H, Phenyl), 7.25 (d, $J=7.5$ Hz, 1H, Phenyl), 7.10 (d, $J=9.6$ Hz, 1H, DNP), 5.92 - 5.81 (m, 1H, internal vinyl), 5.25 (dd, $J=1.8$ Hz, $J=17.3$ Hz, 1H, trans terminal vinyl), 5.21 - 5.12 (m, 1H, CH-NHAr), 5.09 (dd, $J=1.8$ Hz, $J=10.5$ Hz, 1H, cis terminal vinyl), 4.71 (dd, $J=3.1$ Hz, $J=8.2$ Hz, 1H, CH-OTBDMS), 4.38 (s, 1H, -MeO-CH-OMe-), 3.99 (dq, $J=5.0$ Hz, $J=12.9$ Hz, 2H, OCH_2 -vinyl), 3.59 (s, 3H, MeO), 3.25 (s, 3H, MeO), 2.49 (ddd, $J=3.4$ Hz, $J=7.4$ Hz, $J=13.4$ Hz, 1H), 2.15 (septet, $J=4.7$ Hz, $J=8.3$ Hz, $J=13$ Hz, 1H), 0.90 (s, 9H, tert-butyl), 0.14 (s, 3H, - $\text{Si}(\text{CH}_3)_2$), 0.09 (s, 3H, - $\text{Si}(\text{CH}_3)_2$). ^{13}C NMR (75 MHz, CDCl_3) δ 147.6, 136.8, 136.1, 136.0, 130.8, 130.2, 128.5, 128.3, 128.1, 127.0, 124.6, 114.7, 113.9, 111.9, 81.0, 68.0, 66.3, 58.1, 50.6, 36.2, 25.9, 18.1, - 4.4, - 4.7. HRMS calcd for $\text{C}_{28}\text{H}_{39}\text{N}_3\text{O}_8\text{Si}$ 573.2508, found M-57 (-tert-butyl) 516.1816.

The synthesis of the BC ring model (355).

The dimethyl acetal **333** (30 mg, 0.05 mmol) was dissolved in 9 mL of an acetone/water mixture (8:1) and 485 mg of Amberlite basic resin was suspended in the solution. The mixture was stirred at room temperature under nitrogen for 3 days. The disappearance of the starting material was followed by Tlc (silica gel; 8:1 ethyl acetate/petroleum ether). The reaction mixture was filtered over a Celite pad and the acetone was removed under reduced pressure. The

residue was taken into ethyl acetate, washed with water and brine solution and dried over sodium sulfate. The solvent was removed under reduced pressure and the viscous residue was placed *in vacuo* while heating (45°C) with a water bath. The crude ^1H NMR unequivocally confirmed the cleavage of the 2,4-dinitrophenyl group. Attempts to purify the amine by radial chromatography over silica gel resulted in the decomposition of the product. Therefore, the crude amine acetal **353** (32.5 mg) was treated with 1 mL of methyl iodide and 150 mg of potassium carbonate in 1 mL of methanol. The mixture was stirred under nitrogen at room temperature for 2 days. The reaction was monitored by Tlc (silica gel/ethyl acetate). The disappearance of the starting material on Tlc was followed by the 2,4-dinitrophenyl hydrazone test. The product does not give a positive test under these conditions but its presence was ascertained by treating the plates with ammonium molybdate. The ammonium salt gives rise to a brown spot which turns to blue upon standing. The reaction mixture was filtered over a Celite pad and the solvent was removed under reduced pressure. To the crude ammonium salt **354** in 15 mL of MeOH was added 700 mg of Amberlite and the mixture was refluxed for 48 hours. The reaction mixture was filtered over Celite and the solvent was removed under reduced pressure. Purification by preparative Tlc (Basic Alumina; 4:1 Hexane/Ethyl acetate) afforded the alkene in 60 % yields from the acetal. ^1H NMR (300 MHz, CDCl_3), δ 7.98 (m, 1H, $J=1.6\text{ Hz}$, H5), 7.29 (m, 2H, H5 and H7), 7.09 (m, 1H), 6.39 (dd, 1H, $J=1.7\text{ Hz}$, $J=9.8\text{ Hz}$, H1), 5.99 (dd, 1H, $J=3.2\text{ Hz}$, $J=9.7\text{ Hz}$, H2), 5.87 (m, 1H, allyl internal vinyl), 5.24 (ddd, 1H, $J=1.9\text{ Hz}$, $J=17.3\text{ Hz}$, $J=3.8\text{ Hz}$, allyl trans vinyl), 5.05 (ddd, 1H, $J=1.6\text{ Hz}$, $J=3.5\text{ Hz}$, $J=10.5\text{ Hz}$, ally cis vinyl), 4.88 (dd, 1H, $J=1.8\text{ Hz}$, $J=3.1\text{ Hz}$,

H3), 4.59 (s, 1H, acetal), 4.00 (m, 2H, allyl methylene), 3.57 (s, 3H, OMe), 3.45 (s, 3H, OMe), 0.97 (s, 9H, tert-butyl), 0.18 (s, 6H, SiMe₂). ¹³C NMR (75 MHz, CDCl₃) δ 134.0, 131.2, 130.4 (another peak at 133.3 could also be assigned to one of the quaternary aromatic carbons), 129.4, 128.0, 127.2, 126.7, 126.3, 114.4, 110.1, 80.6, 69.1, 66.3, 59.1, 57.1, 25.9, 18.1, - 4.5, - 3.8. HRMS calcd for C₂₂H₃₄O₄Si 390.2227, found 390.2226.

Making the dimethyl acetal of the methoxymethyl aldehyde 295

To the methoxymethyloxy aldehyde **295** (22.5 mg, 0.05 mmol) in 1 mL of MeOH was added 11 mL of trimethyl orthoformate. Following the addition of 1 mg of TsOH (0.005 mmol) the mixture was stirred at room temperature for 12 hours. The reaction crude was diluted with EtOAc and washed with a saturated sodium bicarbonate solution. The organic extract was dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude was purified by radial chromatography (1 mm silica gel chromatotrom plate; the compound was loaded using methylene chloride and eluted with a 20% methylene chloride/petroleum ether mixture). The desired acetal **321** was obtained in 34% yields (9 mg). A slower fraction (11mg) which was not characterized was also isolated. **321**: ¹H NMR (CDCl₃), d 9.19 (d, J=2.7 Hz, 1H, DNP), 8.81 (broad d, J=8.1 Hz, 1H, NH), 8.29 (dd, J=2.7 Hz, J=9.5 Hz, 1H, DNP), 7.67 (d, J=7.7 Hz, 1H, Phenyl), 7.43 - 7.27 (m, 3H, Phenyl), 7.15 (d, J=9.7 Hz, 1H, DNP), 7.15 (d, J=9.7 Hz, 1H, DNP), 5.96 - 5.87 (m, 1H, internal vinyl), 5.29 (dd, J=1.8 Hz, J=17.2 Hz, 1H, trans terminal vinyl), 5.22 - 5.15 (m, 1H, CH-NHAr), 5.12 (dd, J=1.7 Hz, J=12.3 Hz, 1H, cis terminal vinyl), 4.85 (AB quartet, J=6.7 Hz, 2H, -O-CH₂-O-), 4.55 (dd, J=3.3 Hz,

$J=7.6$ Hz, 1H, CH-OMOM), 4.36 (s, 1H, MeO-CH-OMe), 4.19 (AB quartet, 2H, OCH₂-vinyl), 3.57 (s, 3H, OMe), 3.42 (s, 3H, OMe), 3.15 (s, 3H, OMe), 2.59 - 2.52 (m, 1H), 2.46 - 2.22 (m, 1H).

*The removal of the 2,4-dinitrophenyl group from the dimethyl acetal***321.**

The dimethyl acetal (9 mg, 0.02 mmol) was dissolved in 1 mL of an acetone. After the addition of 5 drops of water, 40 mg of Amberlite basic resin was suspended in the solution. The mixture was stirred at room temperature under nitrogen for 3 days. The workup, which was identical to the procedure followed in the case of **353**, led to the isolation of 7mg of the deprotected amine **356**.

*The cleavage of the THP group from the tetrahydropyranyloxy aldehyde***297**

To a solution of tetrahydropyranyloxy aldehyde **297** (8.6 mg, 0.02 mmol) in methanol was added 0.6 mg (0.002 mmol) of PPTS. The mixture was stirred at room temperature for 12 hours. The solvent was removed under reduced pressure and the residue taken into ethyl acetate. The ethyl acetate layer was washed with water and dried over sodium sulfate. Following the removal of the solvent *in vacuo* the product mixture was purified by radial chromatography (1mm silica gel chromatotron plate; the compound was loaded using chloroform and eluted with a 10% ethyl acetate/Petroleum ether mixture). The hydroxy aldehyde **113** was obtained in 91% yield (6.5mg). ¹H NMR

(300 MHz, CDCl_3), d 9.71 (s, 1H, CHO), 9.20 (d, $J=2.7$ Hz, 1H, 2,4-DNP), 8.78 (d, $J=8.1$ Hz, 1H, NH), 8.31 (dd, $J=2.7$ Hz, $J=9.5$ Hz, 1H, 2,4-DNP), 7.64 (d, $J=7.2$ Hz, 1H, Phenyl), 7.38 - 7.51 (m, 3H, Phenyl), 7.10 (d, $J=9.6$ Hz, 1H, 2,4-DNP), 6.06 - 5.94 (m, 1H, internal vinyl), 5.86 (m, 1H, CH-NHAr), 5.40 (dd, $J=1.4$ Hz, $J=17.2$ Hz, 1H, trans terminal vinyl), 5.28 (dd, $J=1.3$ Hz, $J=10.5$ Hz, cis terminal vinyl), 4.64 (d, $J=5.2$ Hz, 1H, CH-OH), 4.11 (dq, $J=5.5$ Hz, $J=12.4$ Hz, 2H, allylic CH_2), 2.72 (dt, $J=5.8$ Hz, $J=13.7$ Hz, 1H), 2.50 (broad s, 1H, OH), 2.33 (ddd, $J=2.3$ Hz, $J=8.9$ Hz, $J=13.8$ Hz, 1H). Low resolution mass spectrum calcd for $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_7$ 413.12 found 412.85.

The retro-Bradsher reaction of the one-bond products 293.

One-bond mixed acetal **293** (1mg) in 1mL of methanol was treated with 1 mg of TsOH. The mixture was stirred under nitrogen at room temperature for 3 hours. The solvent was removed under reduced pressure and the residue taken into ethyl acetate was washed with water and brine. The ethyl acetate layer was dried over sodium sulfate and concentrated under reduced pressure. The crude ^1H nmr revealed a 3:1 mixture of endo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-ethoxy **267** and endo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-methoxy **313**. The ratio of exo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-methoxy **314** in the mixture could not be accurately determined from the integration trace.

The Bradsher reversal of the ethyl vinyl ether adduct 294.

To aldehyde **294** (5 mg) in 1 mL of methanol was added 1 mg of TsOH. The mixture was stirred at room temperature for 3 hours at which point the complete disappearance of the starting material was ascertained by Tlc. The solvent was removed under reduced pressure and the residue taken into ethyl acetate. The ethyl acetate solution was washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The crude ^1H nmr revealed a 4:2:1 mixture of endo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-ethoxy **267**, endo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-methoxy **313** and exo-6,7,8,9-tetrahydro-10-(2,4-dinitrophenyl)-9-oxo-5H-benzocyclohepten-5,8-imine-7-methoxy **314** respectively. The ratios were determined by comparison of the methoxy peaks in **313** and **314** with the methyl peak in **267**.

5-Tosyloxyisoquinoline (44).

Potassium carbonate (4.76 gm, 34.4 mmol 5 eq.) was added to a solution of 5-Hydroxy isoquinoline (1g, 6.8 mmol, 1 eq.) in acetone (200 mL) and the mixture was refluxed for two hours. After the addition of an acetone (10 mL) solution of tosyl chloride (1.57 gm, 8.26 mmol, 1.2 eq.) the refluxing was continued for another hour. The reaction mixture was allowed to cool to room temperature and the potassium carbonate was filtered off. After the removal of the solvent *in vacuo* the residue was dissolved in ethyl acetate (100 mL) and washed with water (50 mL). The ethyl acetate extract was dried over sodium sulfate and the solvent

was removed *in vacuo*. The desired 5-tosyloxy isoquinoline was obtained in 97% yields. ^1H NMR (300 MHz, CDCl_3) δ 9.17 (s, 1H, H1), 8.39 (d, 1H, $J=6.0$ Hz, H3), 7.84 (d, 1H, $J=8.1$ Hz, H3), 7.71 (d, 2H, $J=8.3$ Hz, tosylate H_{ortho}), 7.59 (d, 1H, $J=6.0$ Hz, H8), 7.47-7.39 (m, 2H), 7.24 (d, 2H, $J=7.9$ Hz, tosylate H_{meta}), 2.35 (s, 3H, methyl).

5-Tosyloxy-N-oxido isoquinoline (46).

To a solution of 5-tosyloxyisoquinoline (1 eq., 346.7 mg, 1.16 mmol) in 5 mL of methylene chloride at 0 $^{\circ}\text{C}$ was added a 300 mg portion of MCPBA (1.5 eq., 1.73 mmol) as a dichloromethane (5 mL) solution. The reaction mixture was allowed to stir at room temperature for 80 minutes. After successive washes with saturated sodium bicarbonate and sodium bisulfite solutions, the dichloromethane extract was washed with water and dried over sodium sulfate. Following the removal of the solvent *in vacuo* the N-oxide was obtained in 97 % yield. ^1H NMR (300 MHz, CDCl_3) δ 8.83 (s, 1H, H1), 8.08 (d, 1H, $J=7.5$ Hz, H3), 7.75 (d, 2H, $J=8.1$ Hz, tosylate H_{ortho}), 7.69-7.28 (m, 8H), 2.45 (s, 3H, methyl).

4,5-ditosyloxyisoquinoline (47).

To a chloroform (10 mL) solution of 5-tosyloxy-N-oxido isoquinoline (1.5 gm, 4.76 mmol) was added 2.5 gm of tosyl chloride (2.7 eq., 13 mmol) and the mixture was heated at 85 $^{\circ}\text{C}$ for 12 hours. The solvent was removed *in vacuo* and the crude was subjected to radial chromatography. The rearrangement product, 4,5-ditosyloxyisoquinoline was isolated in 27 % yield (0.6 gm). ^1H NMR (300

MHz, CDCl_3) δ 9.10 (s, 1H, H1), 8.12 (s, 1H, H3), 7.90-7.19 (m, 11H), 2.41 (s, 3H, methyl), 2.38 (s, 3H, methyl).

4-Isoquinolinyl-2,3,4,6-tetraacetoxy- β -glucopyranoside (118).

a) The preparation of 4-sodium isoquinolinate **59**.

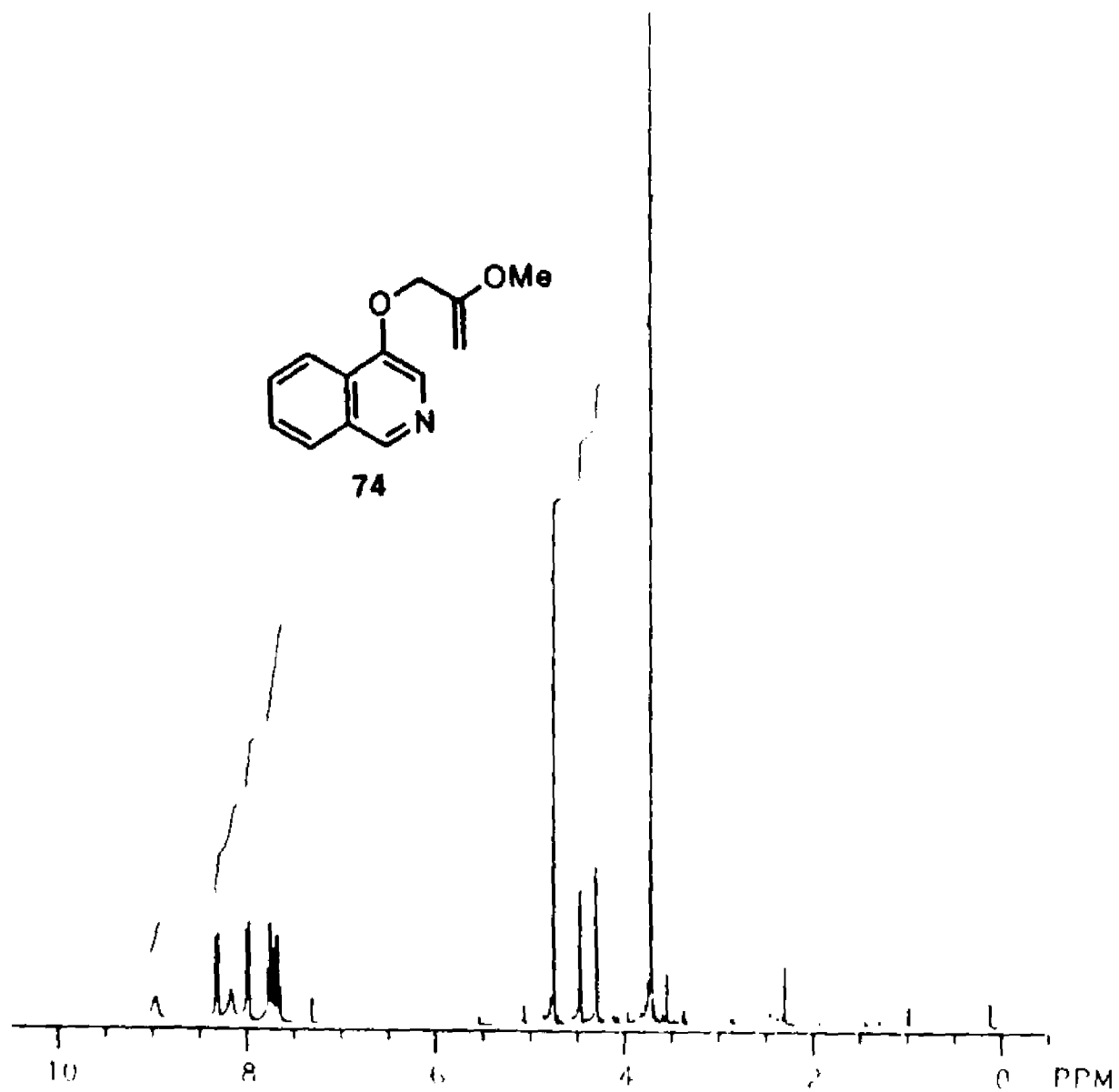
To a flame-dried flask equipped with a nitrogen inlet was added 23 mg of a 80% sodium hydride (NaH)-mineral oil dispersion (1.4 eq., 18.4 mg effective weight of sodium hydride, 0.76 mmol). The dispersion was washed twice with 2 mL of petroleum ether which had previously been dried over sodium sulfate and the remaining solid was suspended in 2 mL of dry DMF. A solution of 4-hydroxyisoquinoline (100 mg, 0.69 mmol) in 10 mL of DMF was added dropwise and the formation of the isoquinolinoxy salt was allowed to proceed at room temperature for a 10 minute period.

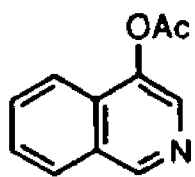
b) The synthesis of Iodo-2,3,4,6-tetraacetyl- α -glucopyranoside.

A solution of bromo-2,3,4,6-tetraacetyl- α -glucopyranoside **116** (286.5 mg, 0.70 mmol) in 10 mL of acetone was stirred for 1/2 hr. at room temperature in the presence of sodium iodide (103.4 mg, 0.69 mmol). Upon the removal of the solvent the above solution of 4-sodium isoquinolinate was added to the crude iodo glycoside. The flask was fitted with a condenser and the mixture, kept under nitrogen, was heated at 55 °C for 72 hrs. The crude was poured over crushed ice and extracted with EtOAc. The organic extract was washed copiously with water and dried over sodium sulfate. Following the removal of the solvent under reduced pressure, the product was subjected to radial chromatography (1mm chromatotrom plate; elution: 10 % EtOAc/petroleum ether). The desired 4-Isoquinolinyl-2,3,4,6-

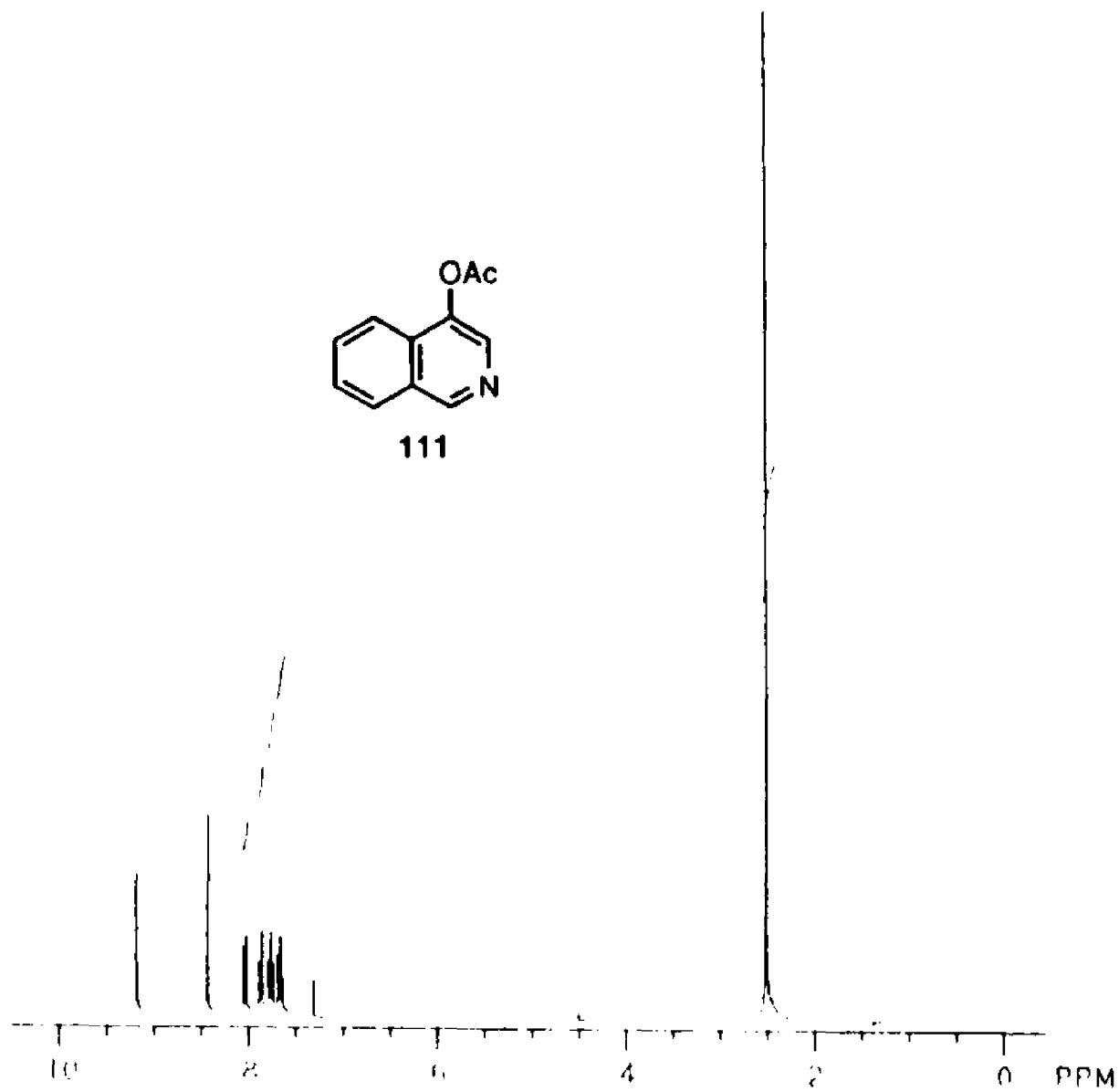
tetraacetoxy- β -glucopyranoside **118** was obtained in 3 % yields (10 mg). **118**: ^1H NMR (300 MHz, CDCl_3) δ 9.01 (s, 1H, H1), 8.27 (s, 1H, H3), 8.06 (d, 1H, $J_{\text{ortho}}=8.2$ Hz, H8), 7.97 (d, 1H, $J_{\text{ortho}}=7.9$ Hz, H5), 7.73 (dt, 1H, $j_{\text{meta}}=1.1$ Hz, $J_{\text{ortho}}=8.3$ Hz, H6), 7.63 (dt, 1H, $J_{\text{meta}}=1.1$ Hz, $J_{\text{ortho}}=8.1$ Hz, H7), 5.51 (dd, 1H, $J_{1,2}=7.9$ Hz, $J=9.5$ Hz, H2'), 5.38 (t, 1H, $J=9.3$ Hz, H3'), 5.29 (d, 1H, $J=7.8$ Hz, H1'), 5.22 (t, 1H, $J=9.8$ Hz, H4'), 4.35 (dd, 1H, $J=5.6$ Hz, $J=12.3$ Hz, CH_2), 4.21 (dd, 1H, $J=2.1$ Hz, $J=12.3$ Hz, CH_2), 3.99 (ddd, $j=2.2$, $j=5.6$ Hz, $j=10.0$ Hz, H5'), 2.09-2.00 (3 singlets, 12H, OAc's). ^{13}C NMR (75 MHz, CDCl_3) δ 170.62, 170.10, 169.45 (two peaks), 146.29, 146.23, 131.47, 129.06, 128.93, 128.66, 127.50, 125.40, 120.99, 99.37, 79.69, 75.92, 72.54, 72.43, 71.05, 68.22, 61.82, 20.68, 20.61. HRMS calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_{10}$ 475.1478, found 475.1467.

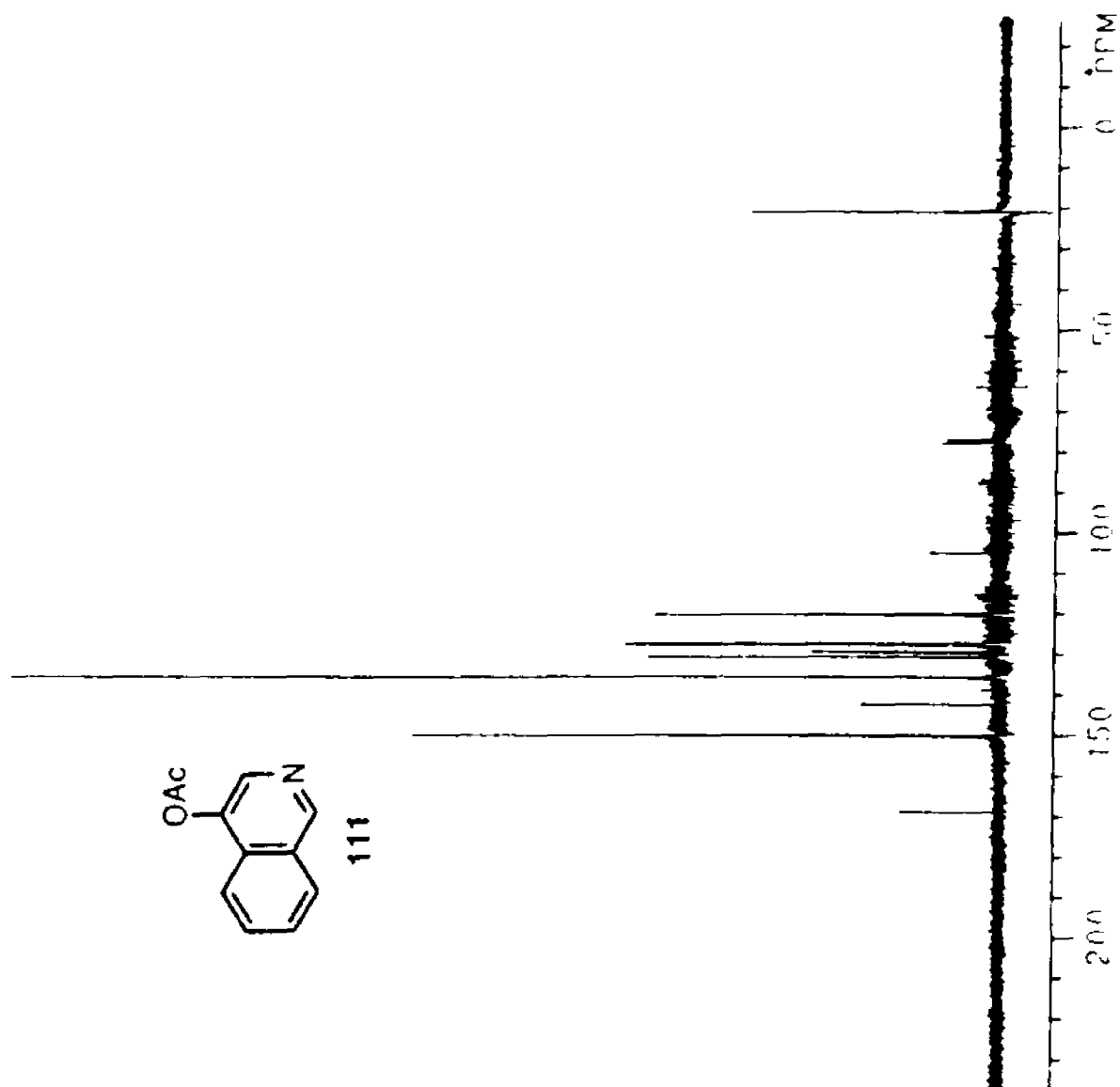
APPENDIX

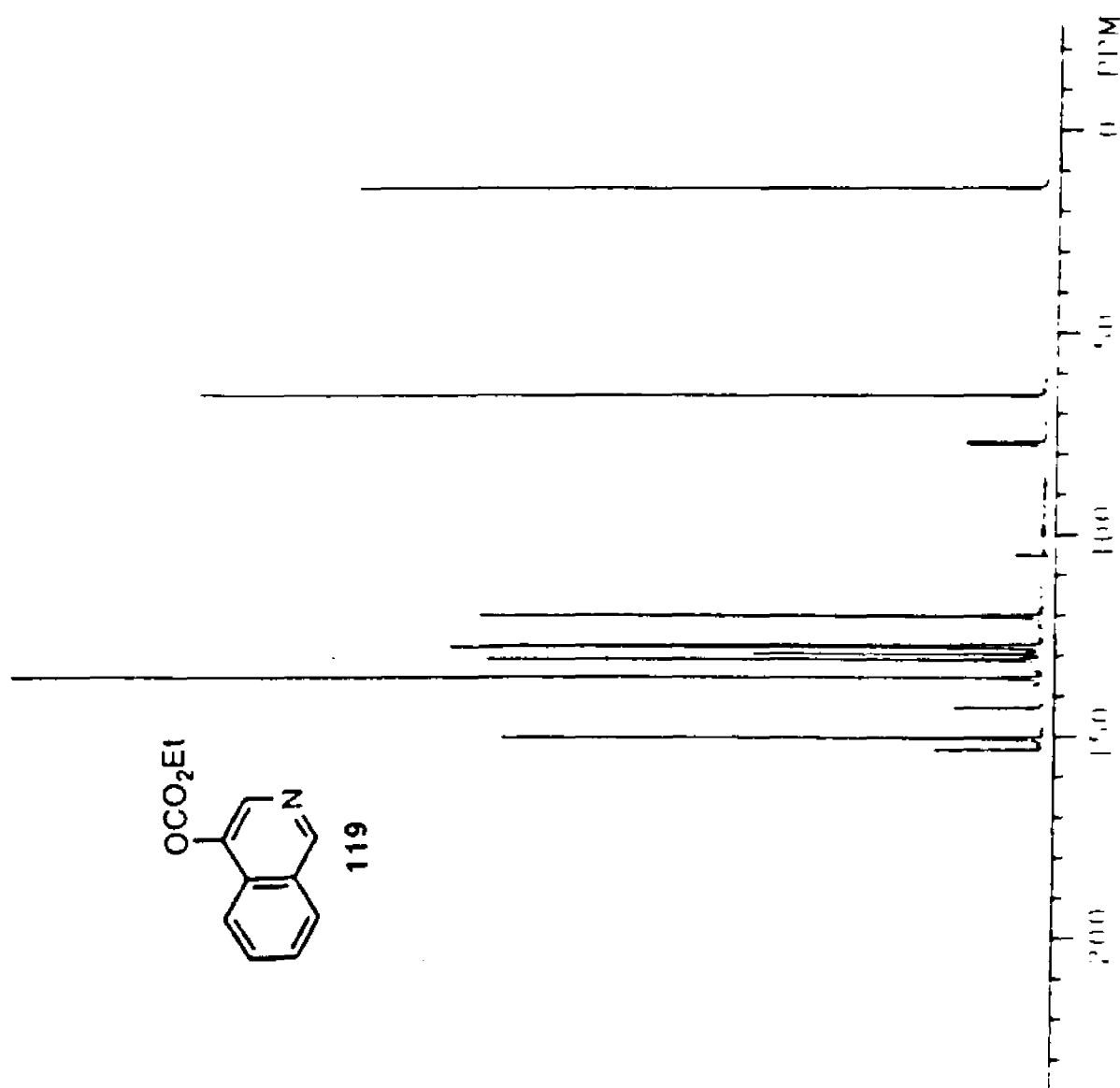


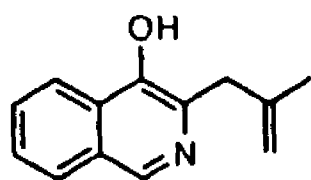


111

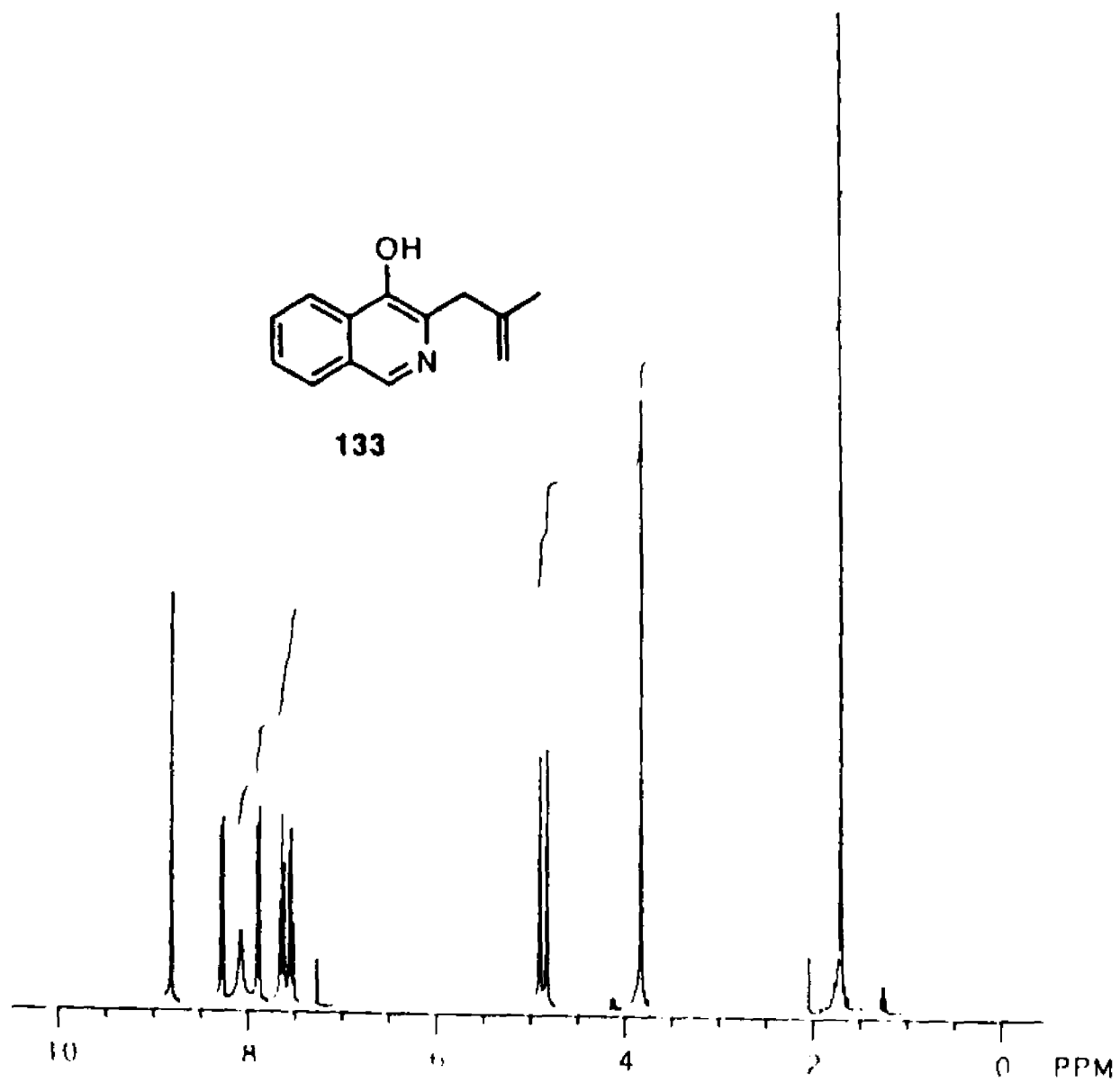


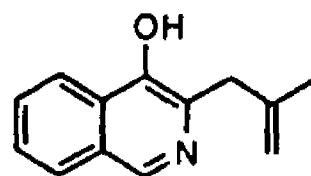




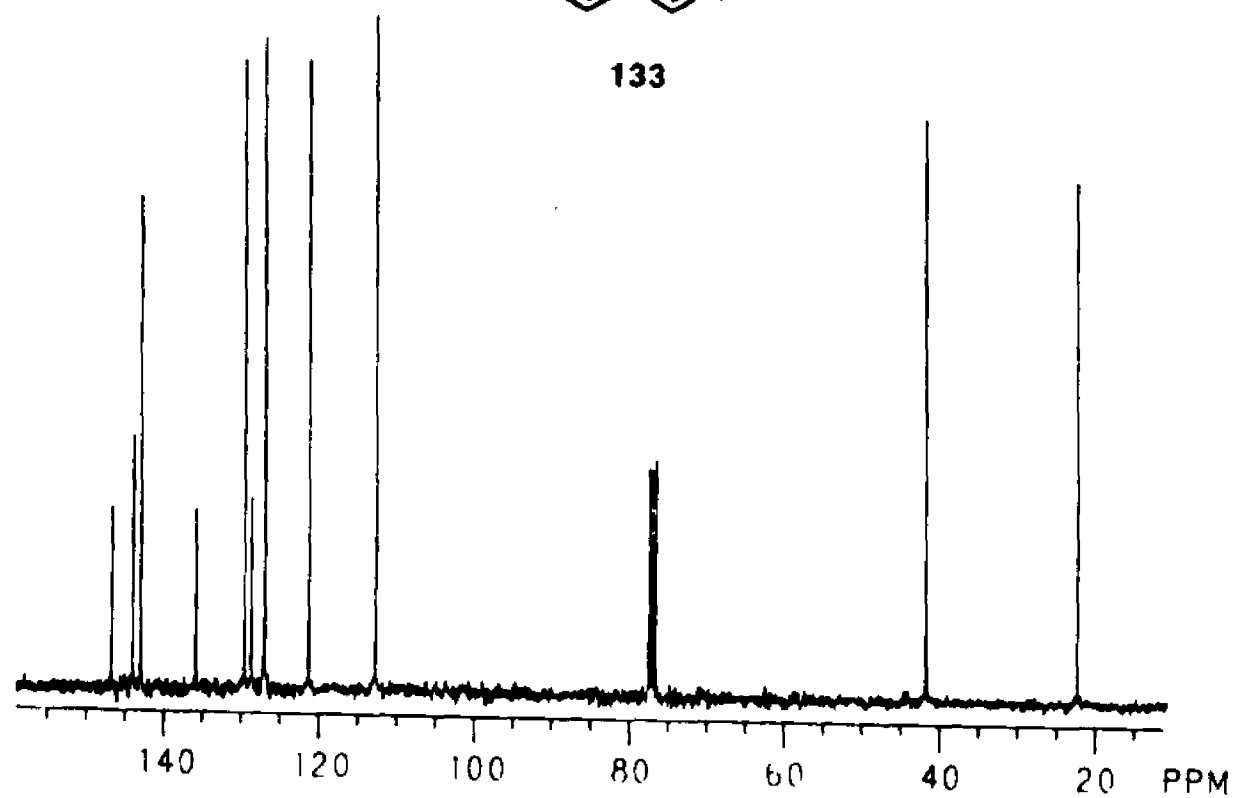


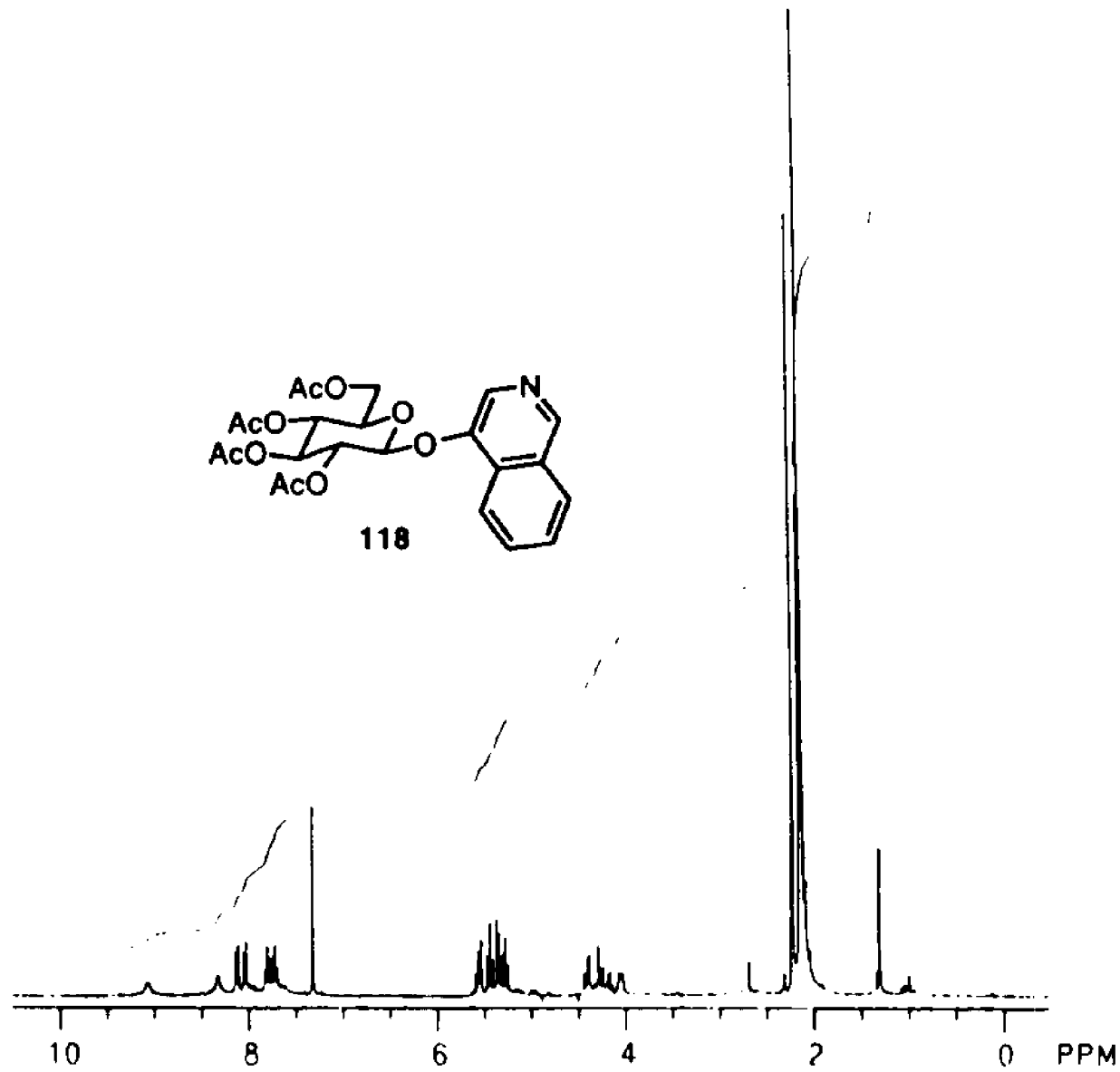
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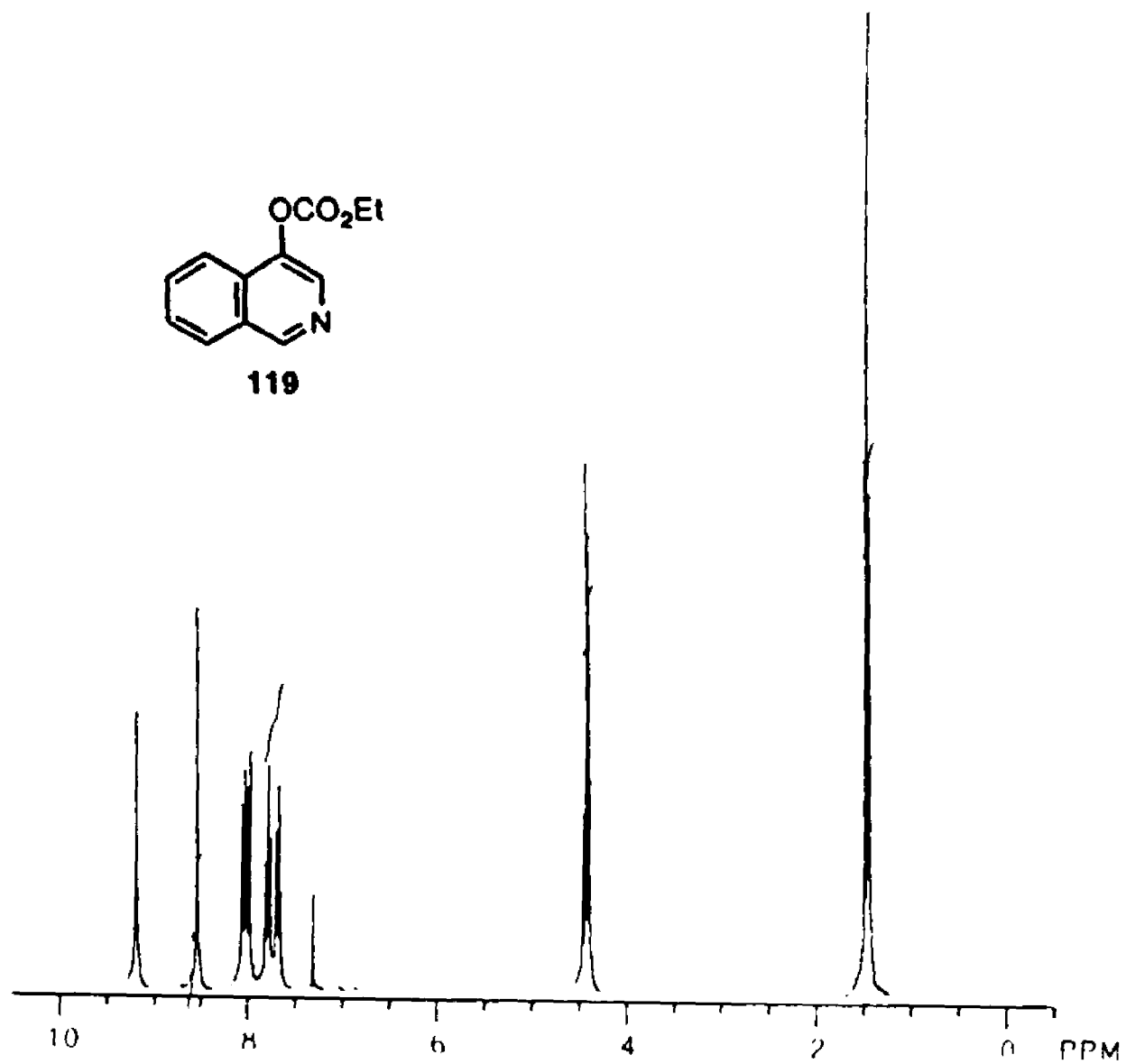
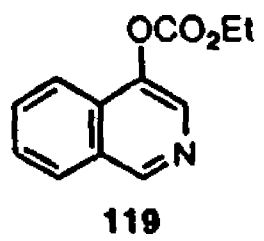


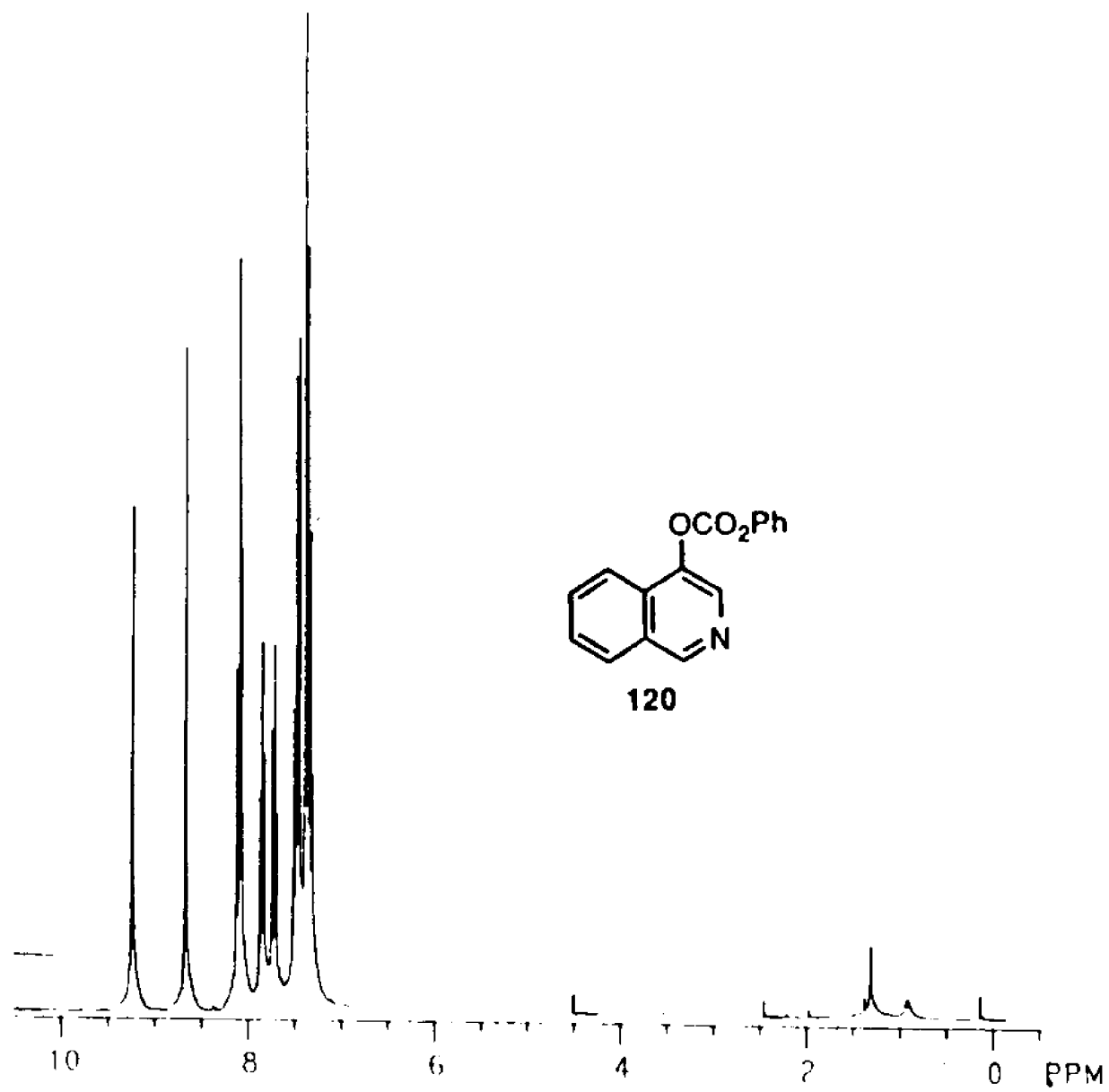


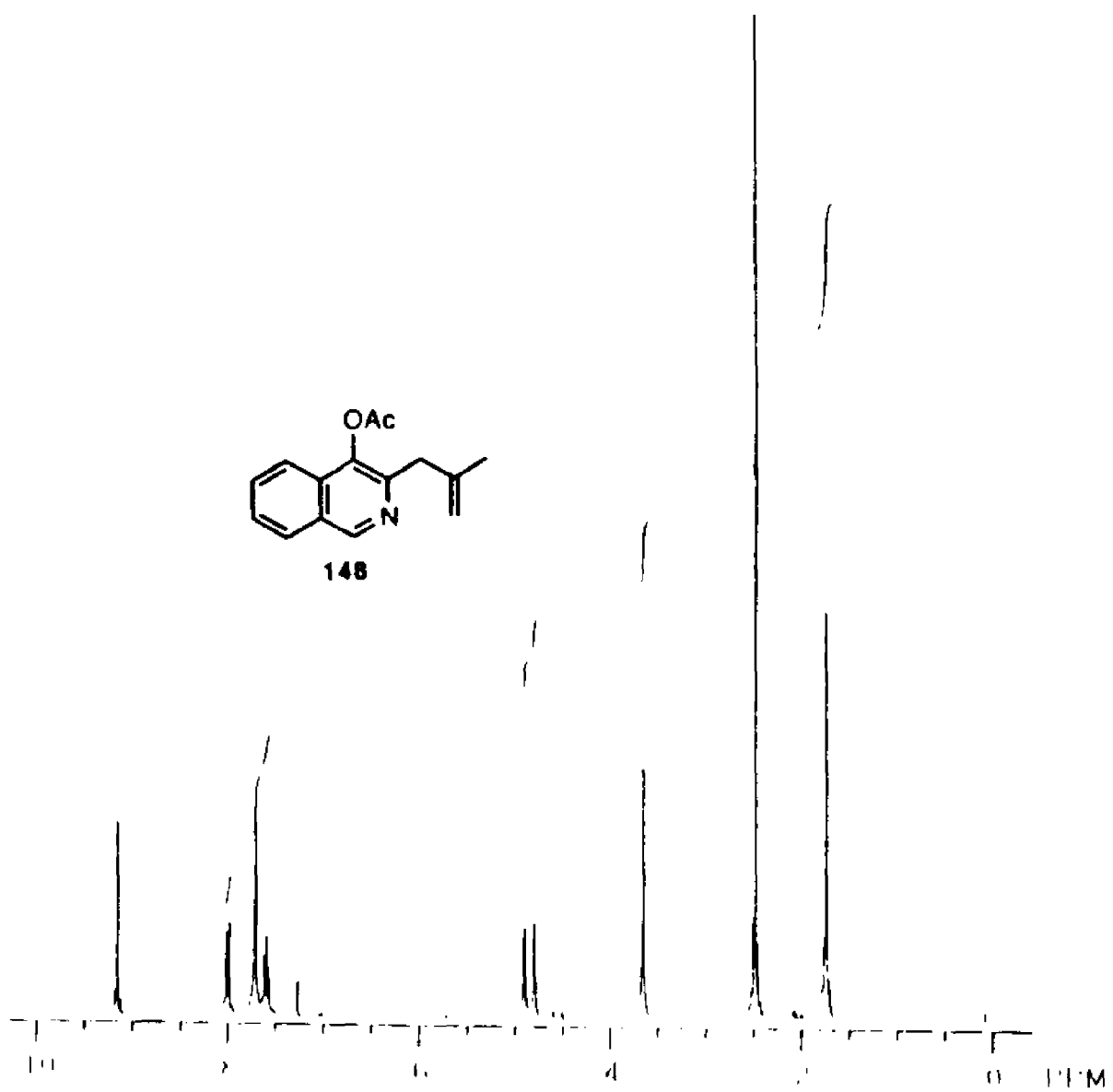
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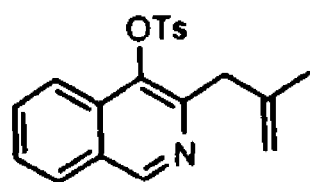




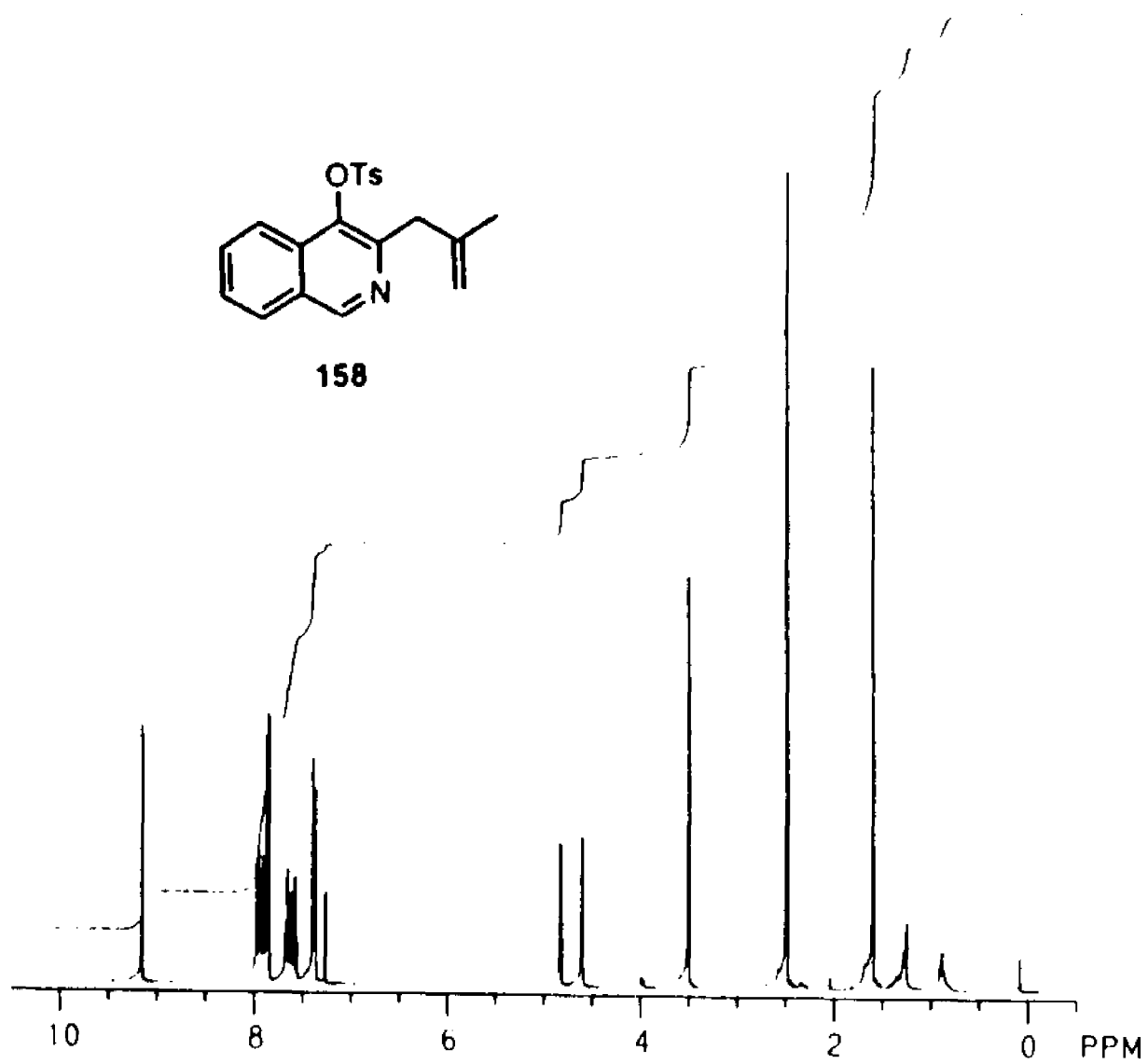


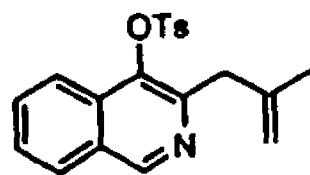




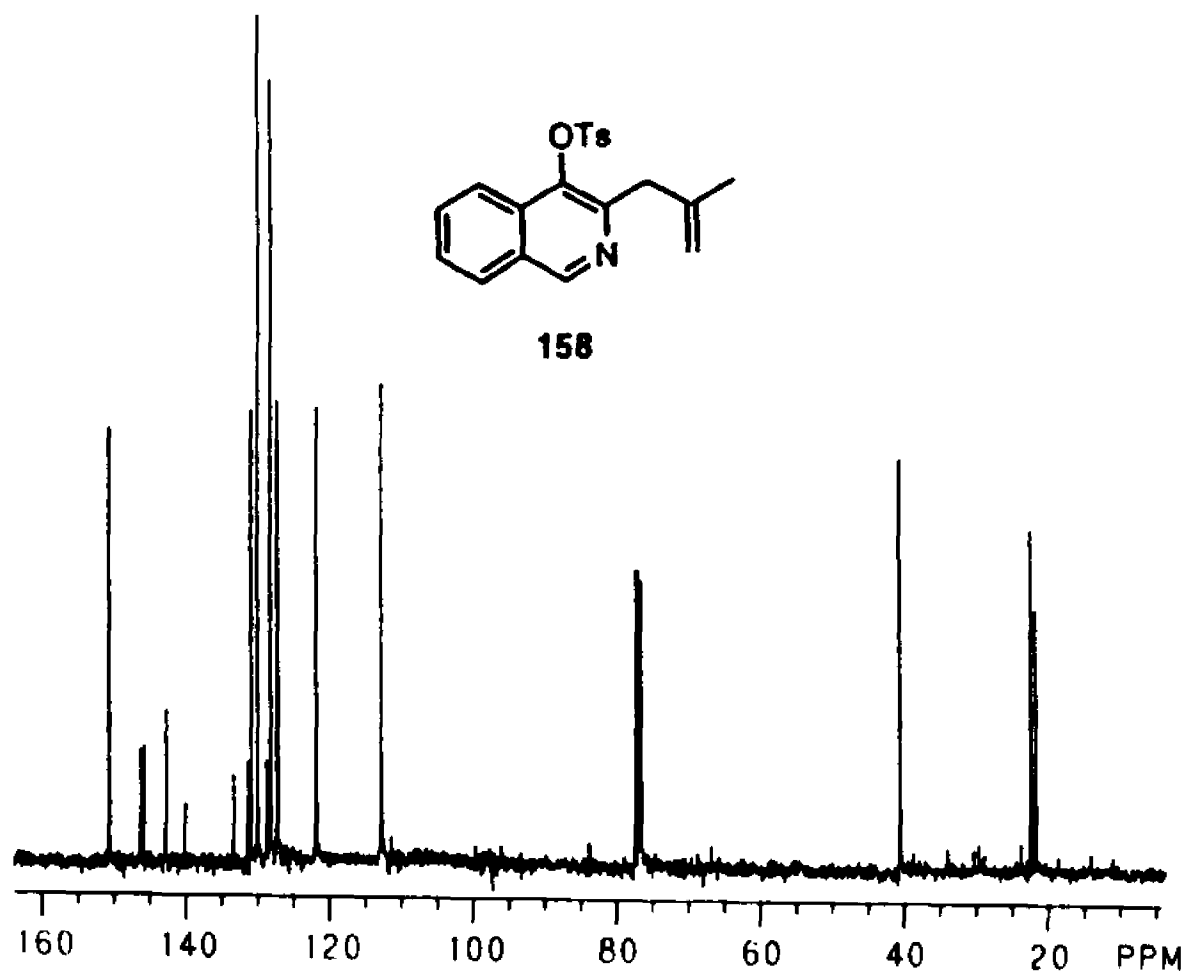


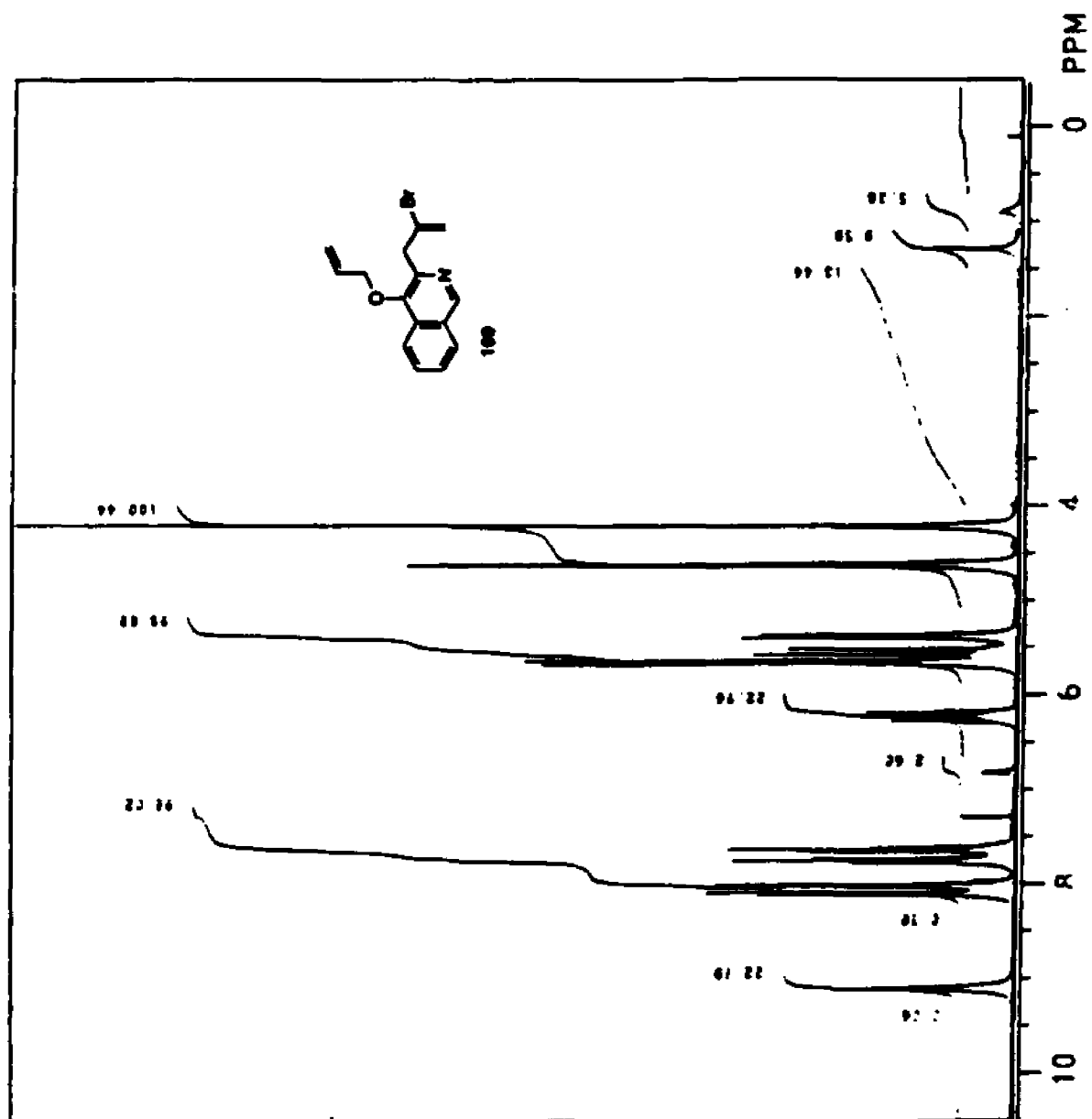
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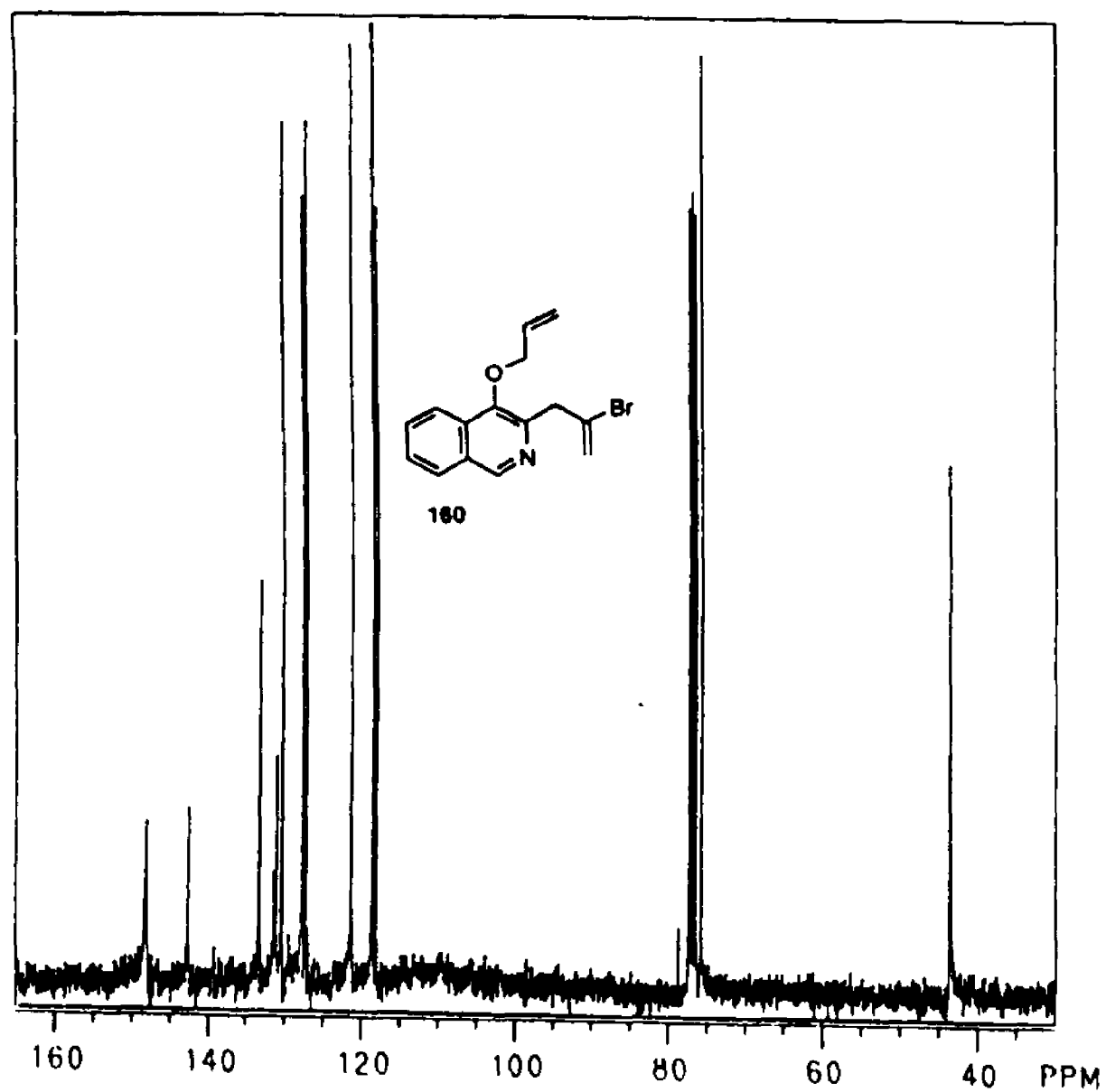


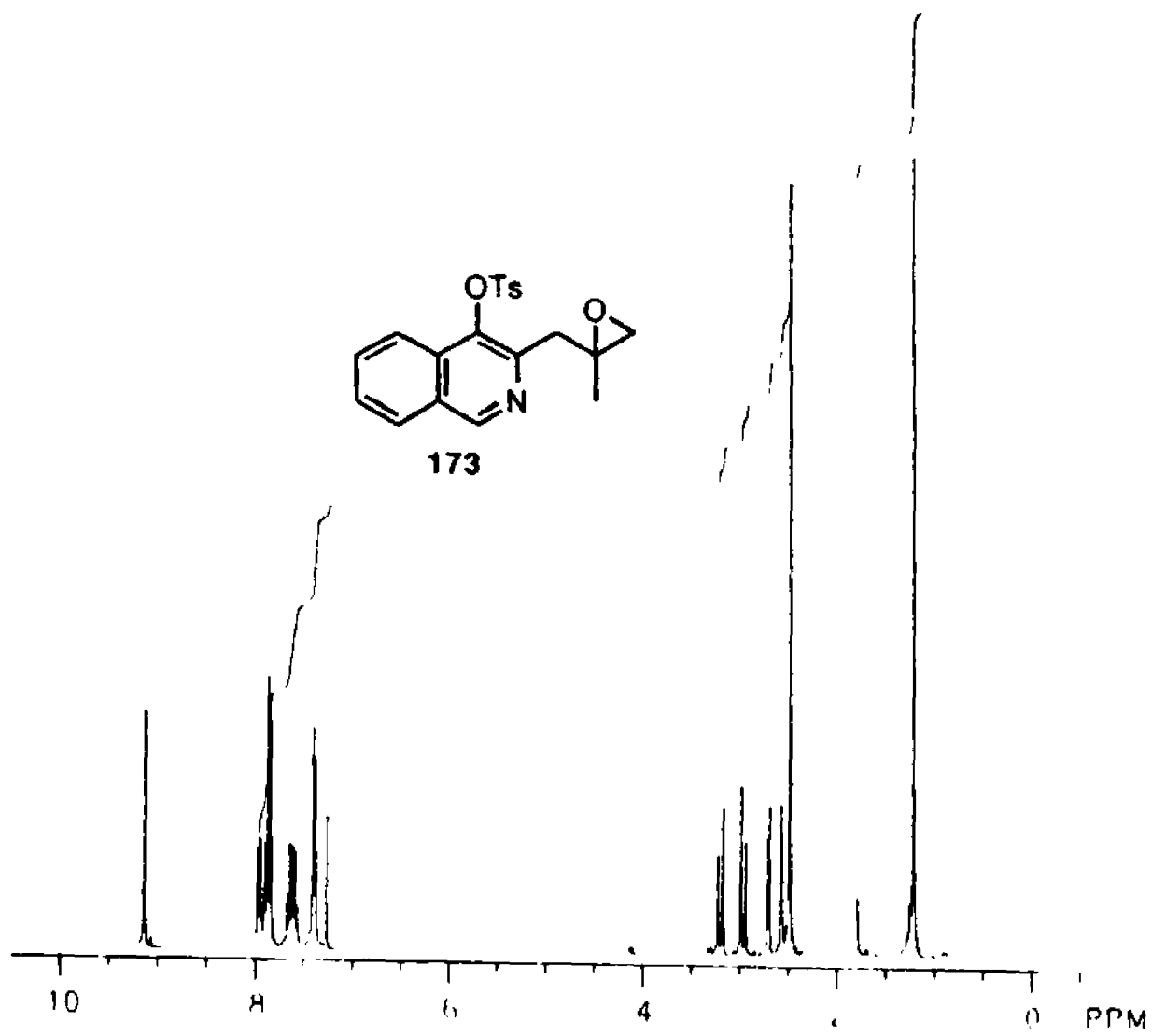


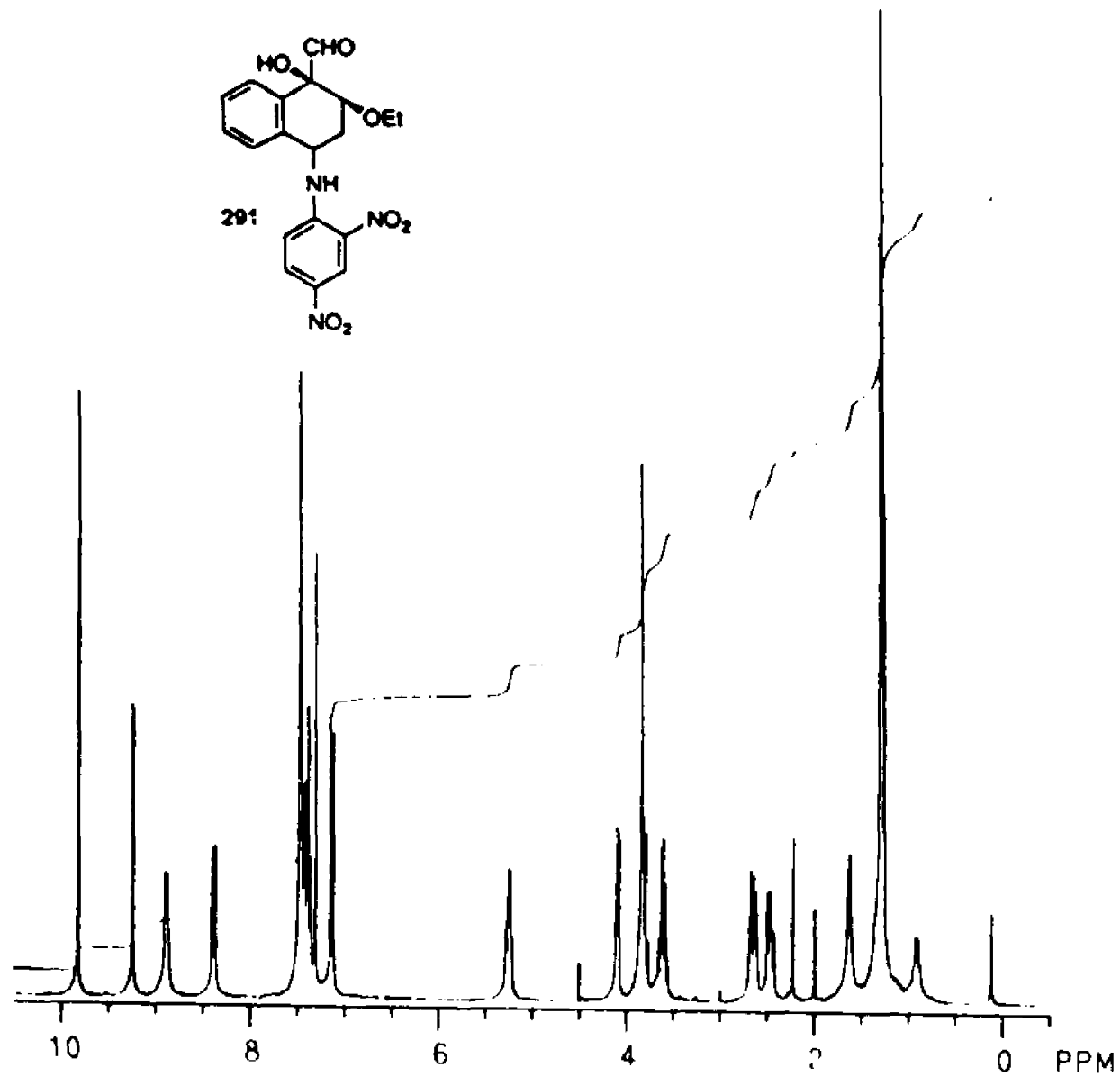
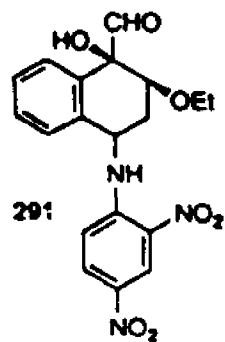
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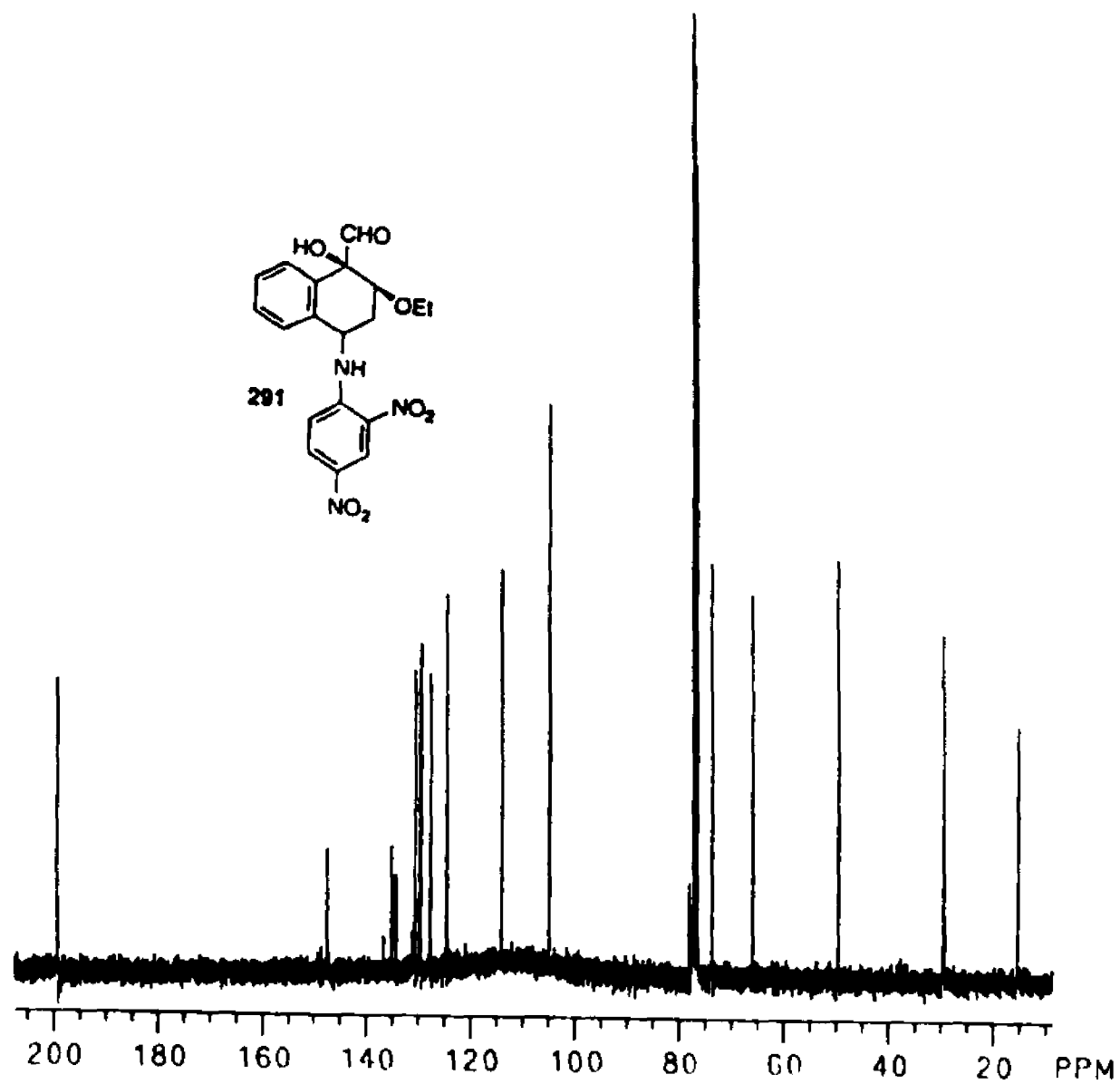


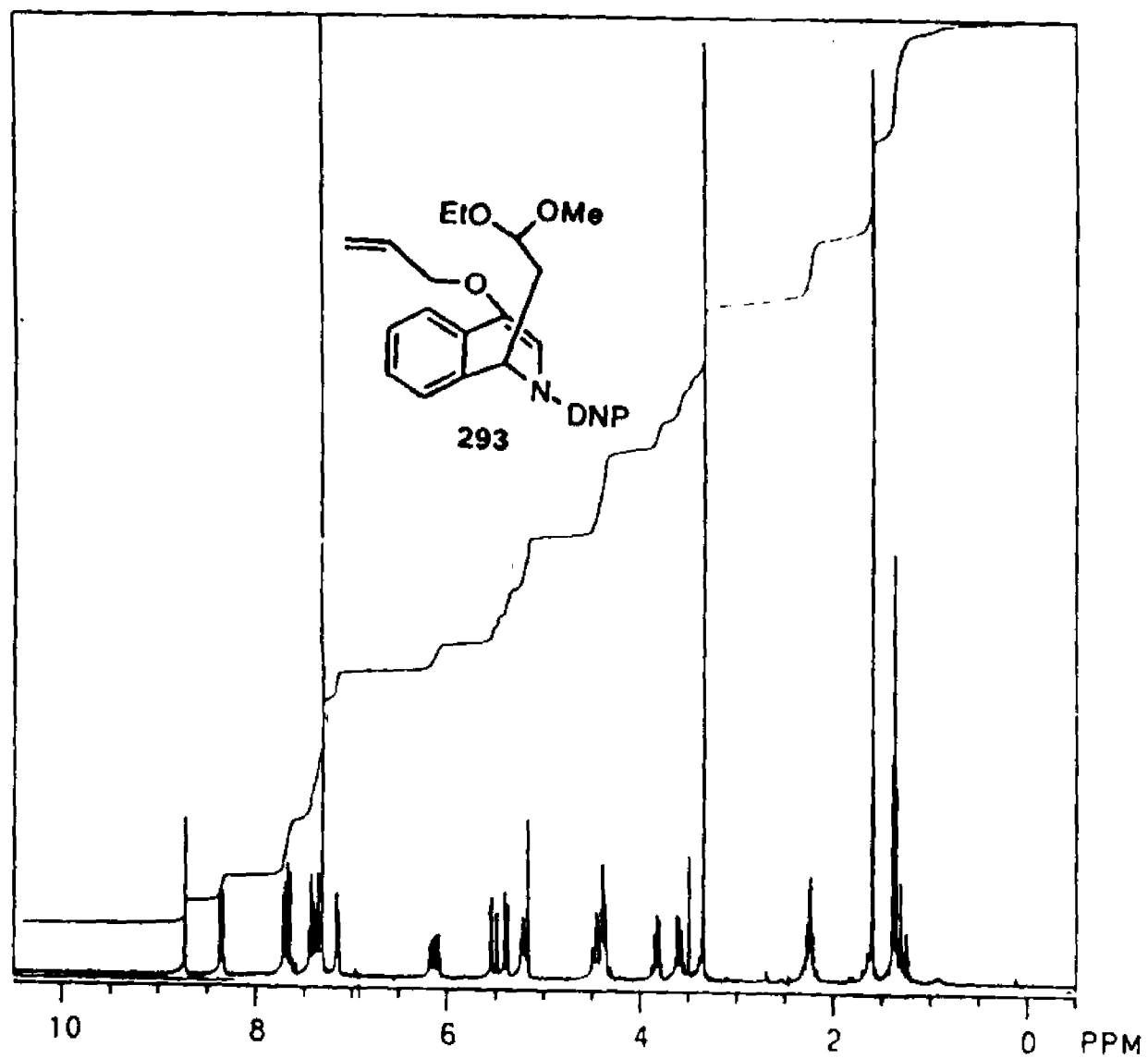


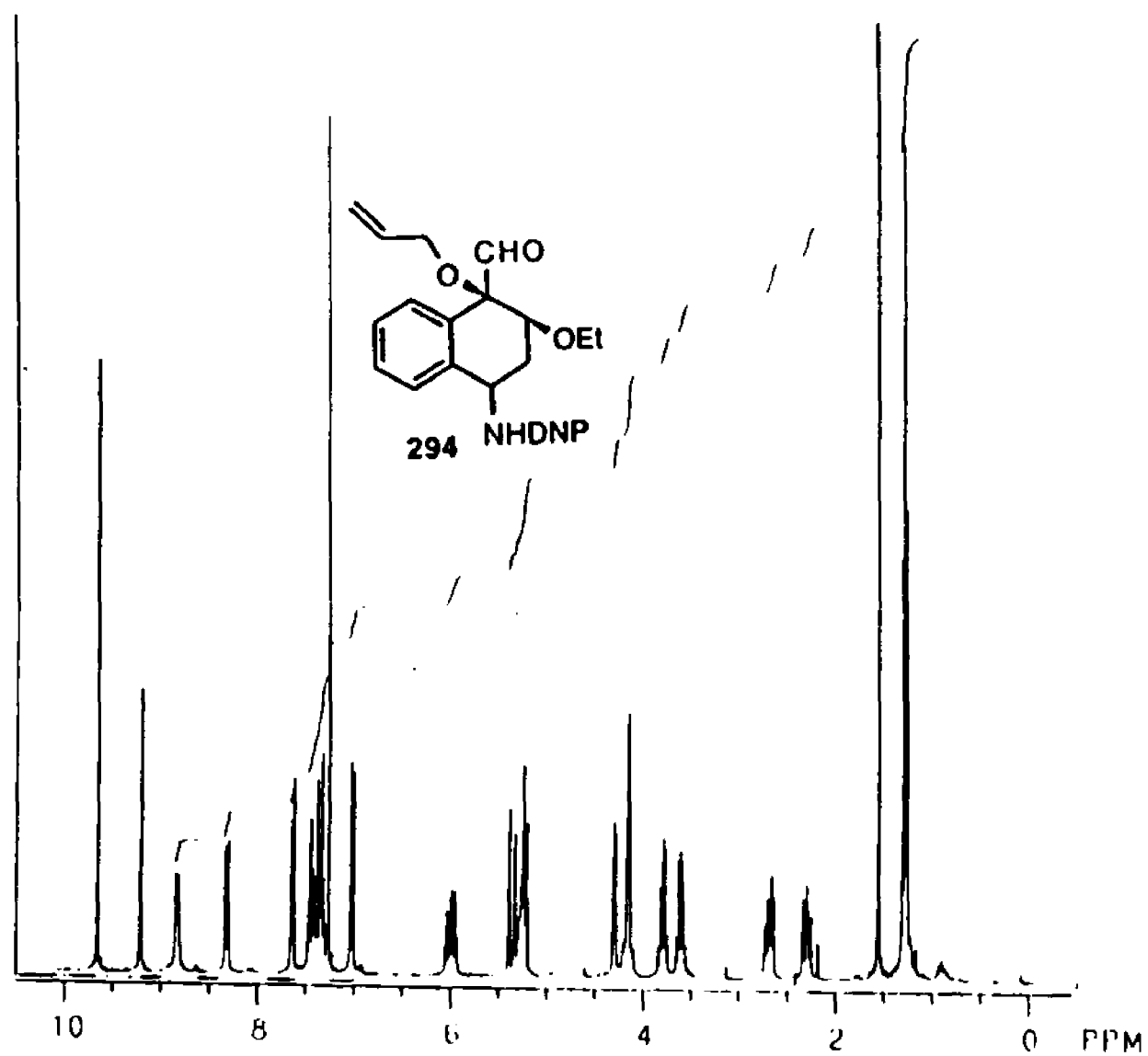


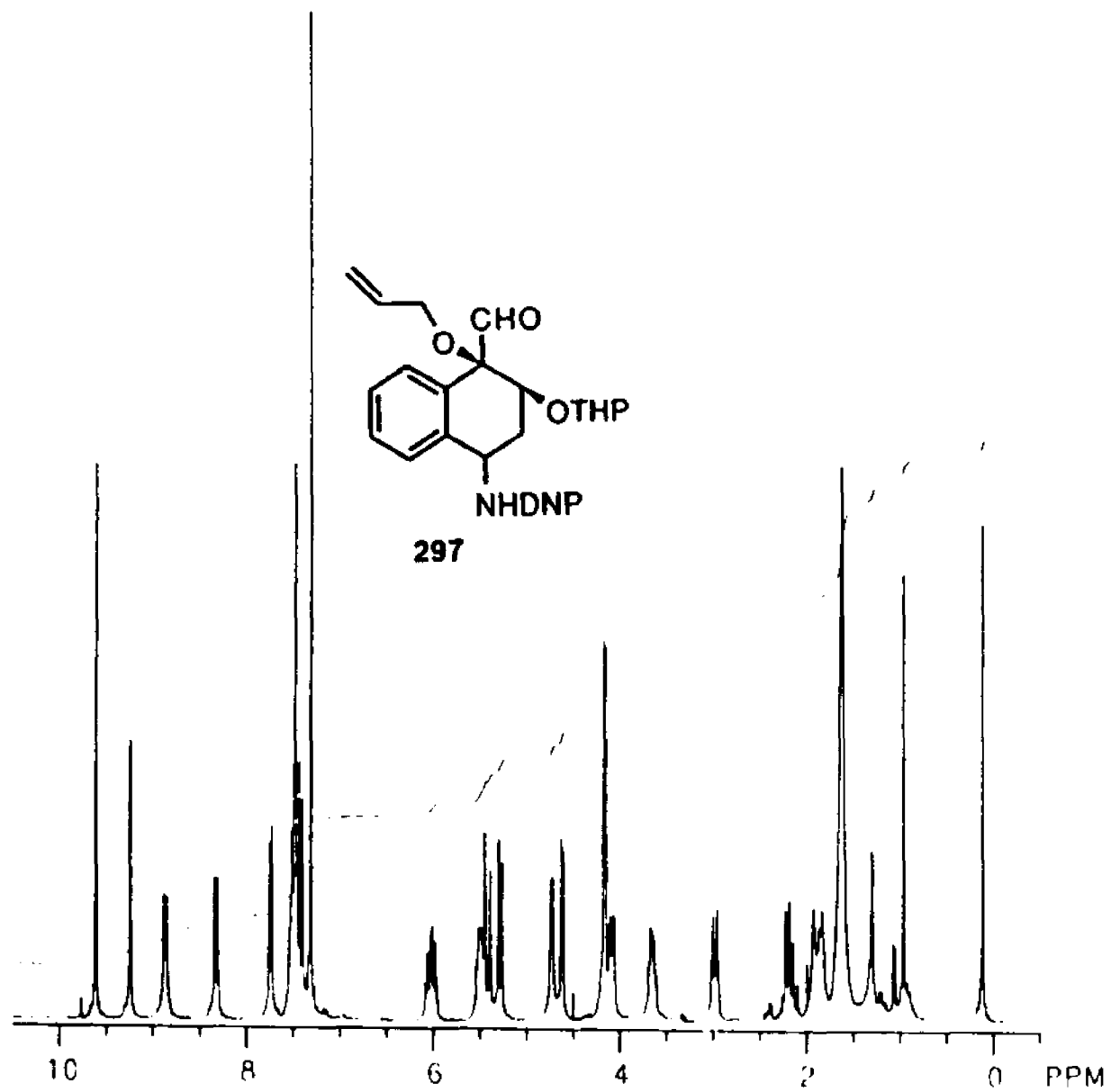


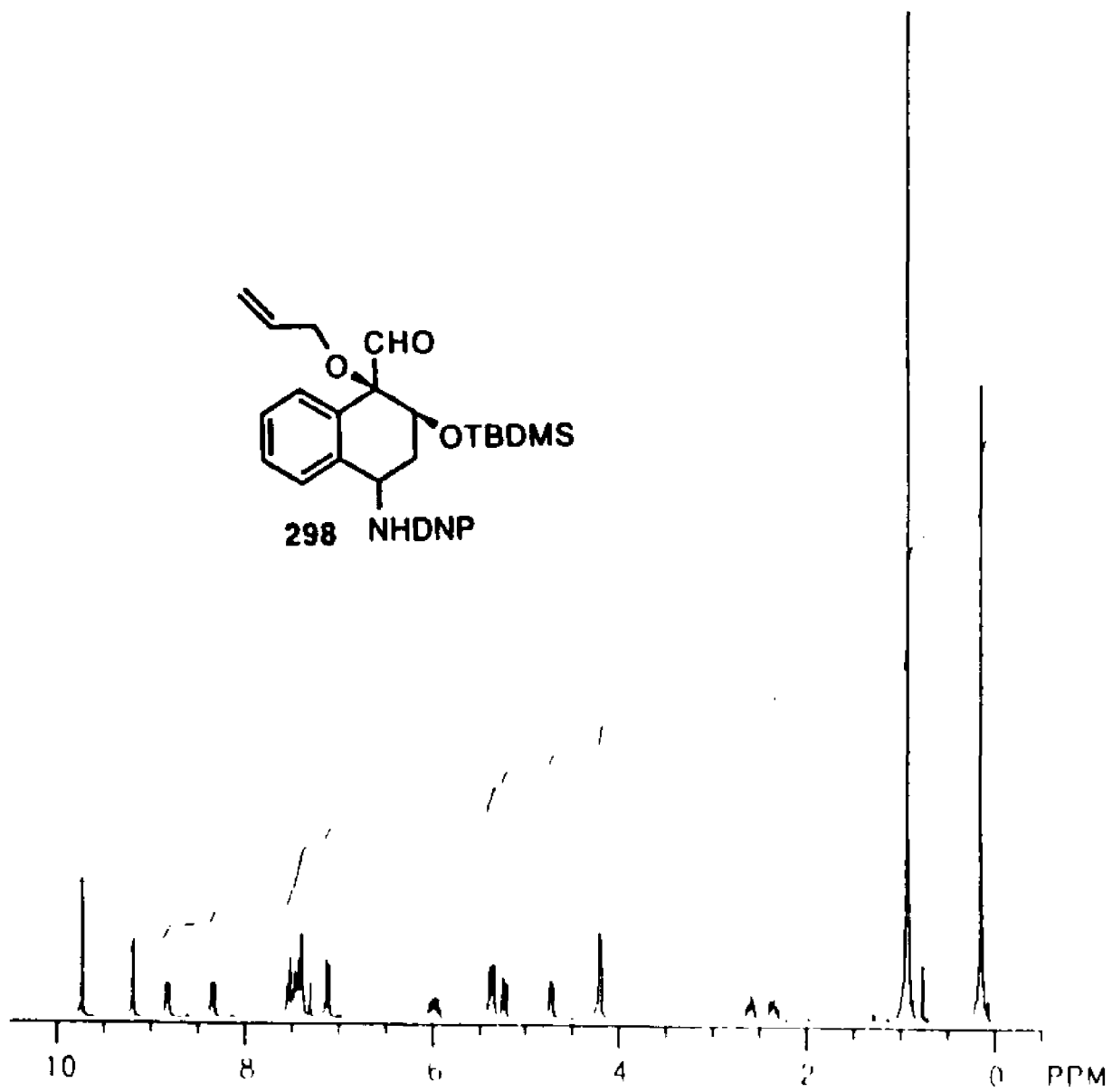
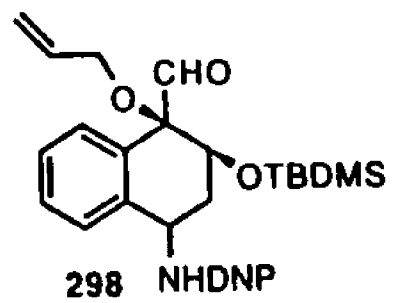


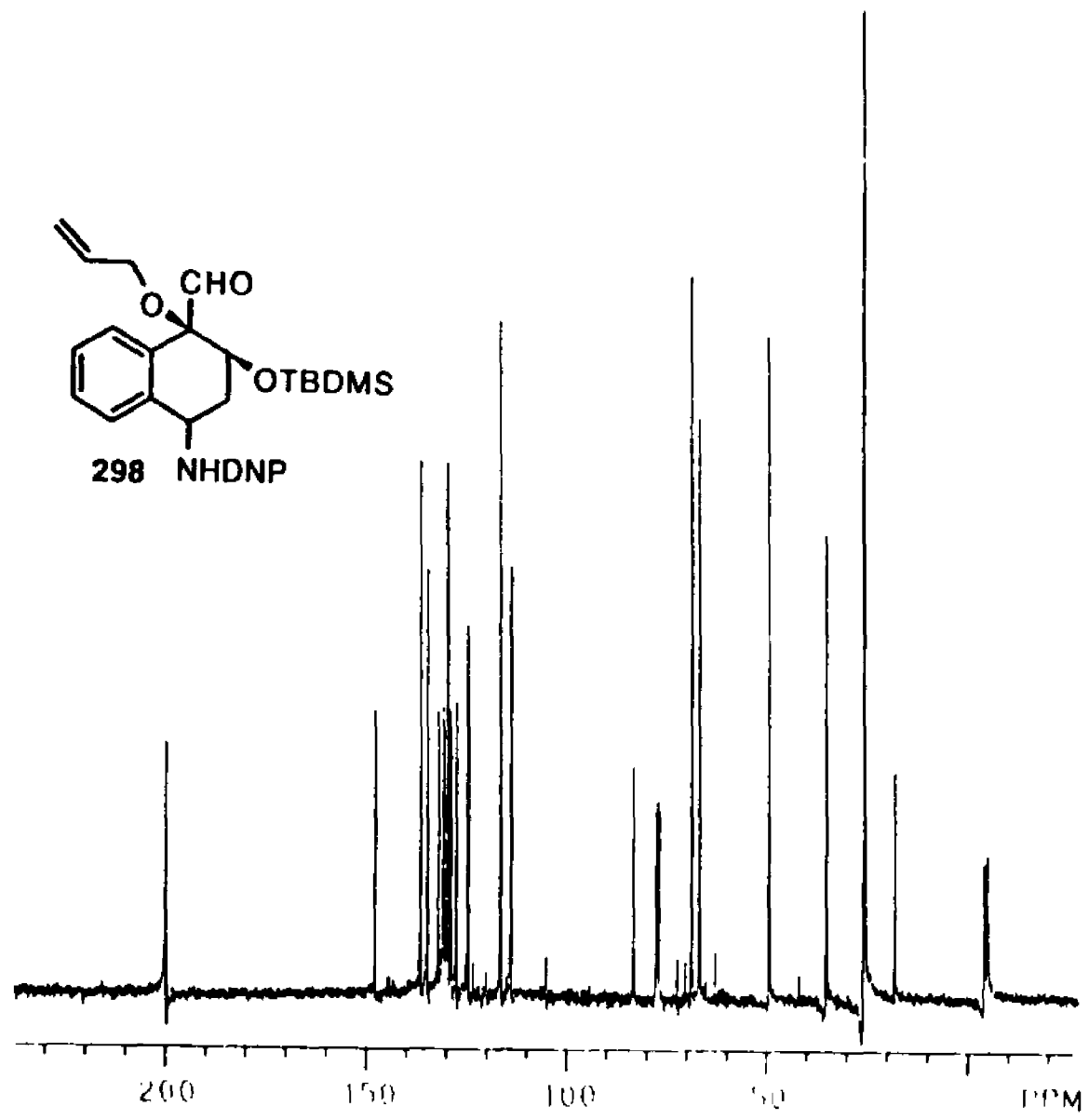


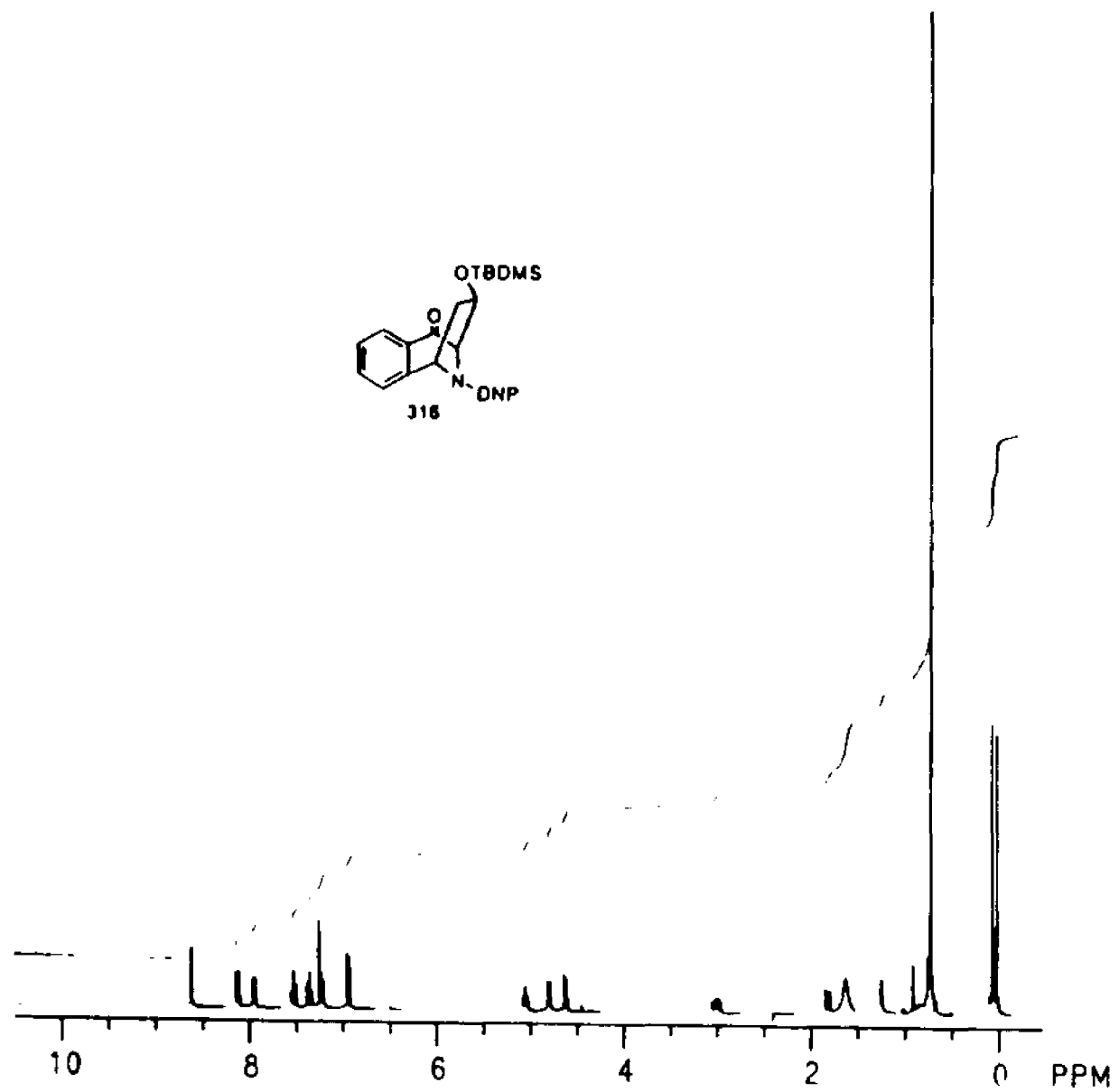


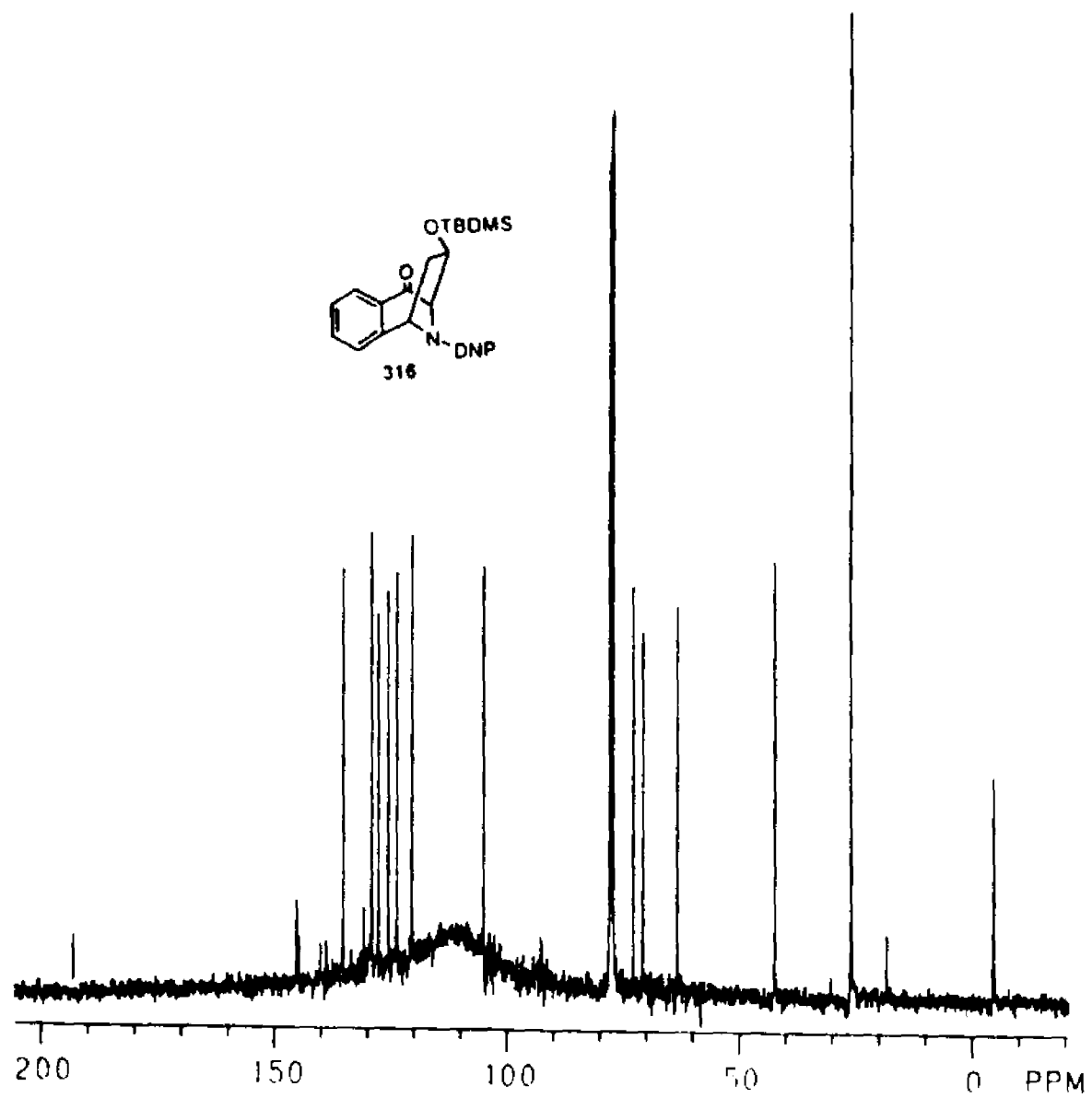


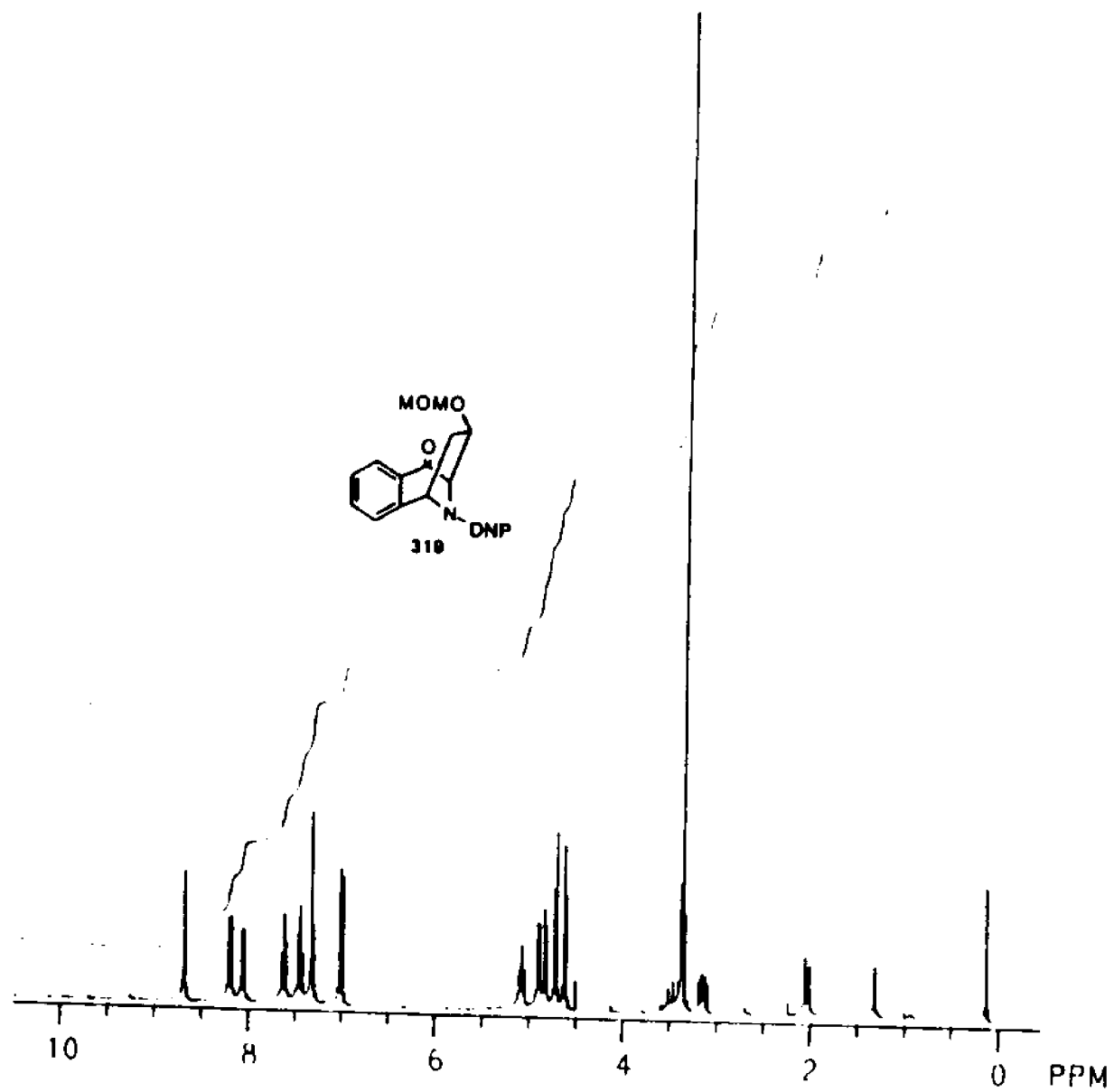


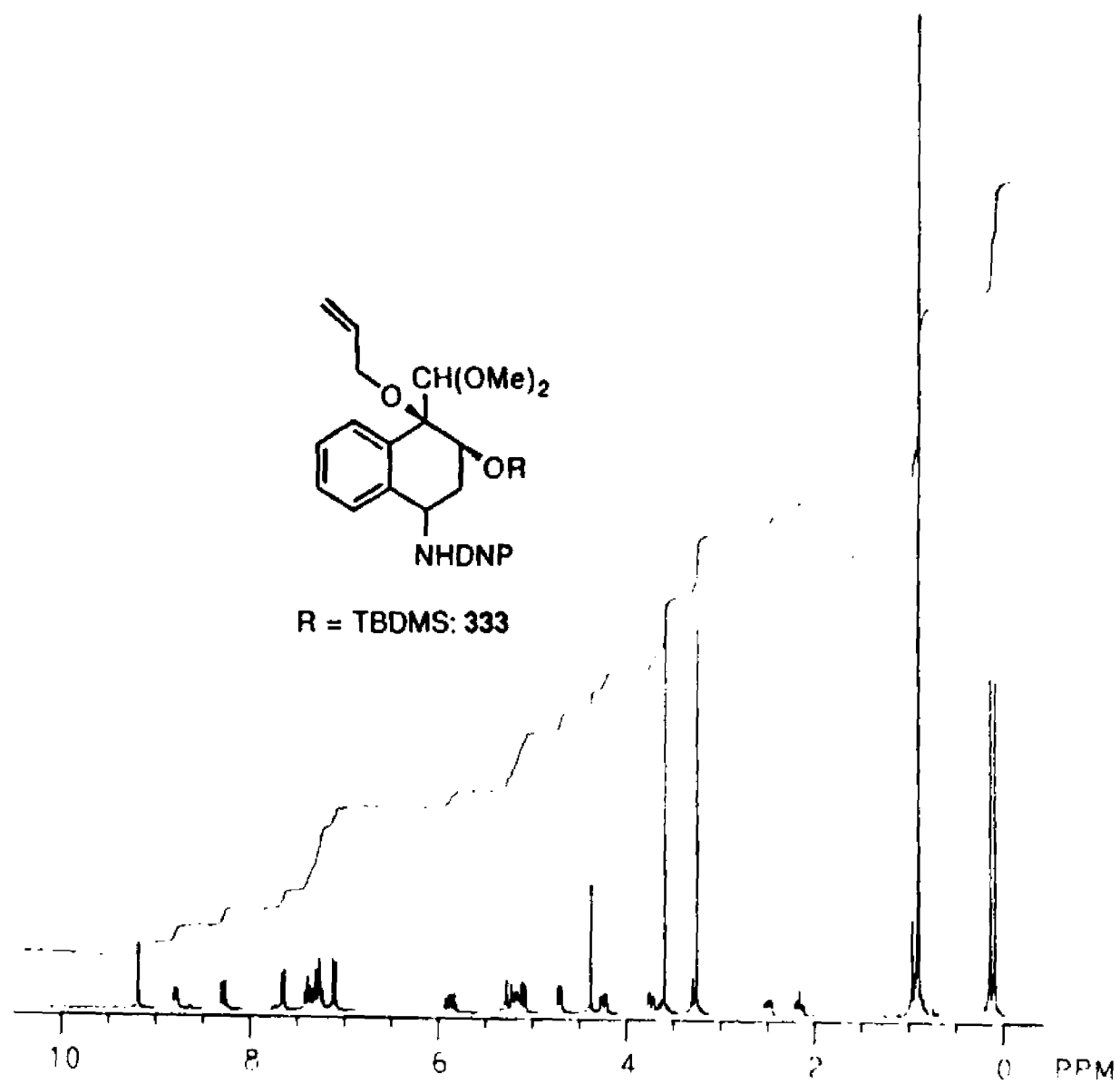


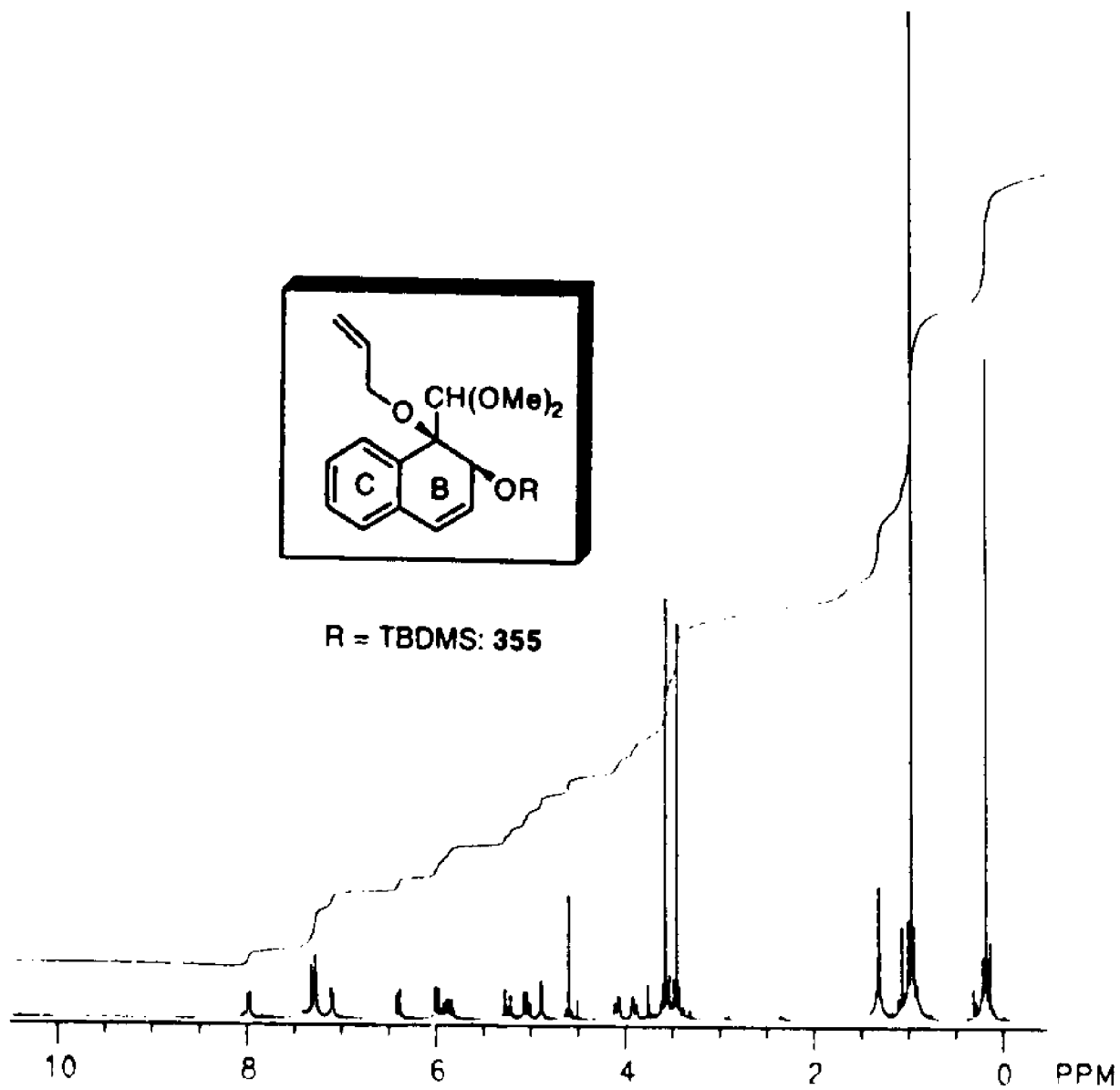












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