RADICAL CYCLIZATION APPROACH TO A CHEMOENZYMATIC SYNTHESIS OF MORPHINE

by

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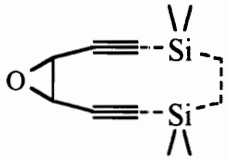
(ABSTRACT)

A three component, convergent synthesis of the isoquinoline alkaloid morphine was designed which incorporated the ten-membered silicon-containing epoxide **1**, the diene diol **2**, and the known oxazolone **3**.



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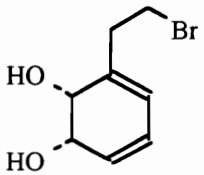

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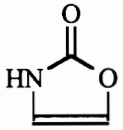

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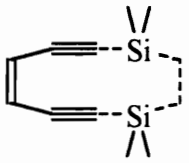
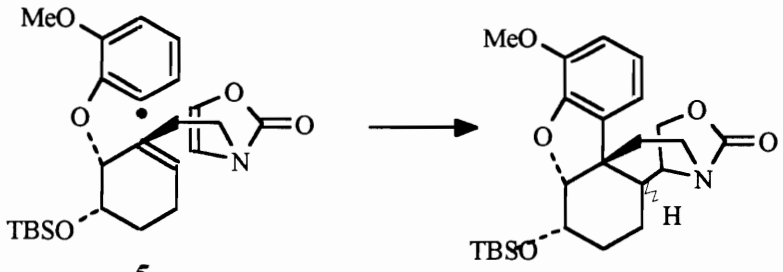
Diene diol **2** was isolated in the amount of 200 mg/L from the fermentation of (2-bromoethyl)benzene by *Pseudomonas putida* 39/D (*Pp* 39/D) and the absolute stereochemistry was proven by conversion to and comparison with a known compound.



4

The silicon-tethered enediyne **4** was prepared as a model for use in the well-known Bergman cyclization reaction as a "latent benzene reagent". Bergman cycloaromatization of similar enediynes has been demonstrated and the cyclization temperatures to form the benzenoid diradicals lies in the region 40-70°C. Cache molecular modeling of **4** did indeed predict a cyclization temperature around 65°C. Enediyne **4** did not undergo Bergman cyclization at such low temperatures and even survived heating for several days in a sealed tube at 150°C.

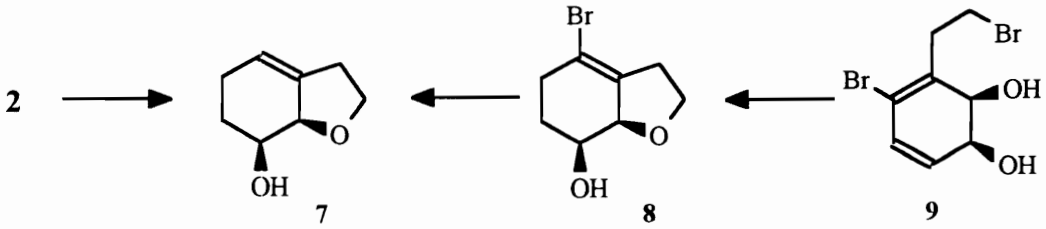
This approach was abandoned because it was shown in a related study that the tandem cyclization of **5** to **6** proceeded without stereocontrol and in poor yield. (Compound **6** resembled the intermediate radical that would have been obtained in the Bergman study). The aforementioned difficulties led to the revision of the approach to morphine to yield the second generation strategy in which the radical cyclization was carried out in separate steps.



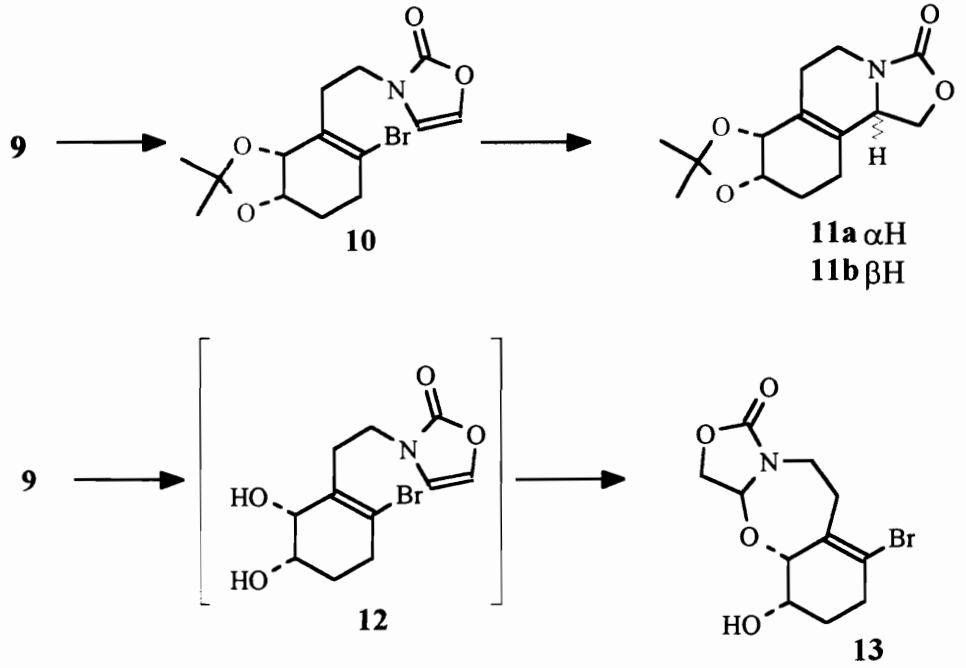
5 **6**

For the second generation approach, diene diol **7** was isolated in the yields of 2 mg/L and 440 mg/L from fermentation of *o*-bromo-(2-bromo)-1-ethylbenzene by *Pp*

39/D and JM109 respectively. Its absolute stereochemistry was proven by conversion to the benzofuran derivative **7** which was found identical to that obtained from **2**.



The new diol **9** was transformed to the protected derivative **10**. The radical cyclization of **10** gave the isoquinolines **11a** and **11b** in better yields (60% and 30% respectively) while attempted deprotection of **10** was surprisingly accompanied by an intramolecular cyclization and produced the interesting oxazapine **11**. The absolute stereochemistry of **11b** was proven by x-ray. Both isomers are being used through further conversion to both enantiomers of morphine.



To my Parents, Margie and Mike Stabile

Acknowledgments

Acquiring an advanced degree not only requires hard work, but several outside forces an persons to provide motivation and inspiration. Many people have contributed to my chemical knowledge and well-being during my stay at Virginia Tech; far too many to properly acknowledge here.

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Without the use of Dr. Karen Brewer's UV spectrophotometer, this and many diol projects would be incomplete. Thanks to her group for unlimited use.

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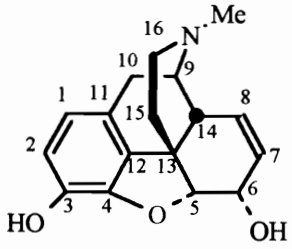
I. INTRODUCTION

As early as the 1st century A.D., opium has been used as a medication and as an illicit drug.[1a] Morphine, **14**, the major component of the opium poppy, produces the analgesic, euphoric and potentially addictive properties of the drug. To date, no other naturally occurring substance or synthetic drug has been isolated whose broad spectrum of analgesic properties can rival that of the compounds which make up the group of opium alkaloids.



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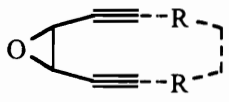
Unlike the anticancer agent, Taxol, isolated from the Yew tree which takes 100 years to mature, Morphine is isolated from the milky white or pink fluid that exudes from the unripened seed of the opium poppy, *Papaver somniferum*. Cultivation of the poppy plant and harvesting of the opium occurs yearly. Also, morphine does not have as intricate a structure as Taxol, but with sales increasing six fold over a period of ten years, (1984-1994),[1b] a practical synthesis may soon be deemed necessary due to the political and/or economic uncertainty of governments in the countries that currently produce it (Turkey, India, Thailand).

During the forty year span from the first total synthesis by Gates[2] to the most recent efforts by Overman[3] and Parker,[4] the subtle chemistry of the morphinan skeleton has been scrutinized and is well understood. Each portion of its biosynthesis has been documented with isolation and characterization of the enzymes which are involved in each step.[5] The main difficulties in the synthesis arise with the formation of the secondary ether linkage and the assembly of the C_{13} quaternary center. We envisioned the implementation of the Bergman[6,7] cyclization strategy in a brief, three component convergent synthesis of morphine, shown in Figure 1 and hoped to link components **1**, **2**, and **3** which would then react in a radical cascade fashion to give a morphinan



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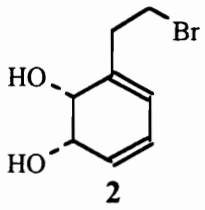

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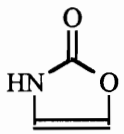


3

skeleton. Compound **1** was hoped to function as a "latent benzene reagent" by forming a benzene diradical upon heating and begin the cascade.

A second function of **1** involved the formation of the ether linkage, one of the main difficulties in building the morphine skeleton. Using the epoxide as a nucleophillic acceptor, the ether portion of the molecule would be joined without loss of stereocontrol or elimination problems. The most general and widely used method for the formation of ether linkages involves the well known Williamson ether synthesis. In this type of synthetic operation, the electronics are reversed with respect to the reaction

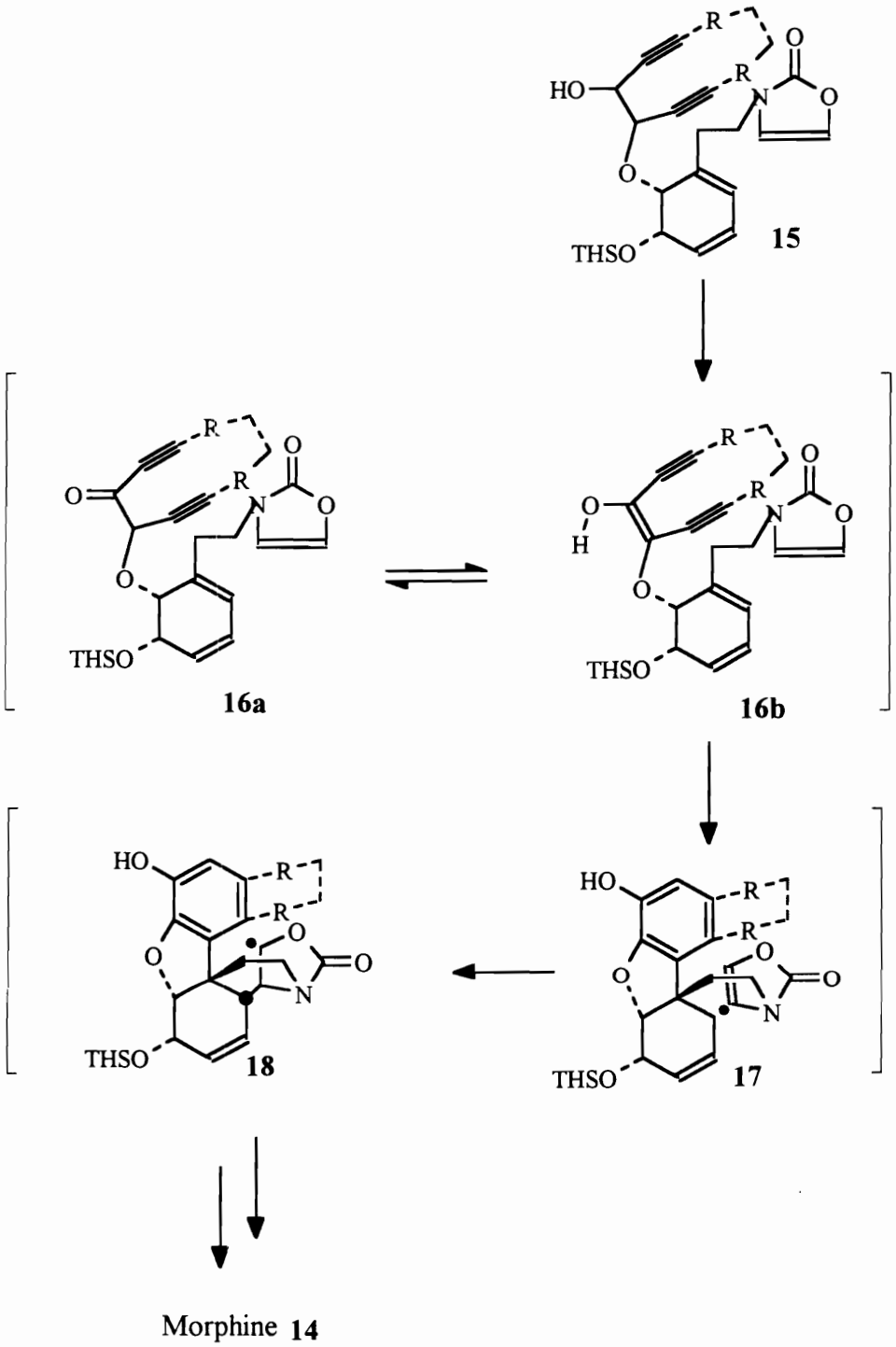


Figure 1. Proposed Radical Cascade Synthesis of Morphine

which was proposed to link **1** and **2**. The substrate acts as the electrophile and waits for attack of the oxygen nucleophile. A model for the investigation of this inital closure was envisioned in **4**.

Concurrent with the synthetic invesitigation of **4**, other members of our group investigated the radical cascade reaction by substituting a protected bromocatechol in place of the latent benzene precursor **5** and initiating the cascade with Bu_3SnH. After linking the three components and attempting the radical reaction, the results were disappointing. A pentacyclic compound corresponding to **6** was isolated from the reaction, but in low yield and lacking the correct stereochemistry for the synthesis of natural morphine.

This problem was alleviated by initiating a new strategy whereby a novel diol launched the synthesis. The preparation and isolation of diol **9** from an ortho substituted benzene and its role in the stepwise radical approach to morphine will be unveiled in the final chapters of this work.

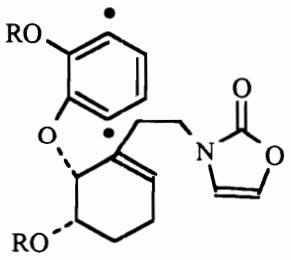
A review of the literature regarding aryl and vinyl radical cyclizations follows as well as a section outlining Bergman cycloaromatization and the combination of the two types of reactions. Since two of the crucial diol starting materials have been furnished from a biooxidation process, a table of the known diol metabolites has been included in the historical section.

II. HISTORICAL

1. Review of Aryl and Vinyl Radical Cyclizations

The field of radical cyclizations has been prolific as evidenced by the volume of literature and recent reviews.[8-12] Many of the reviews discuss free radical reactions by classes or reaction type which include: addition, fragmentation and cyclization. In light of the topic of this dissertation, only the relevant closures of phenyl radicals and vinyl radicals will be mentioned.

The possible radical precursors for this synthetic approach to morphine were envisioned to react either in an aryl or vinyl radical fashion. For the Bergman study, an aryl diradical **19** was apparent in the design, while in the second generation approach, vinyl radical formation in **20** was inherent in the key step.



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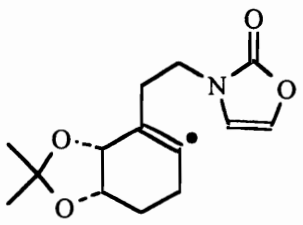

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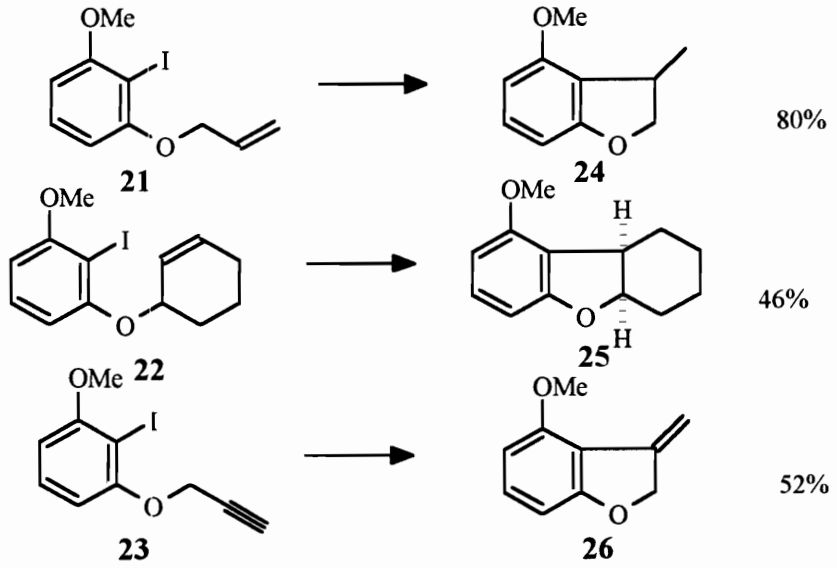
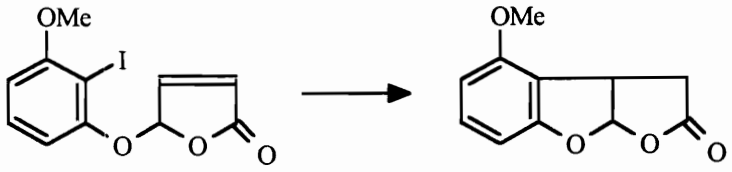
Methods of generating phenyl radicals involve application of the standard tin hydride with azobisisobutyronitrile (AIBN) as a convenient initiator,[8-12] photolysis of aryl halides,[13] samarium diiodide,[14] or the use of a cobalt 'salen' reagent.[15]

Snieckus has shown that reductive cyclization of iodophenyl ethers, **21**, **22**, and **23** with tin hydride produces the heterocyclic compounds **24**, **25**, and **26** in good to moderate yields, Scheme 1.



Scheme 1

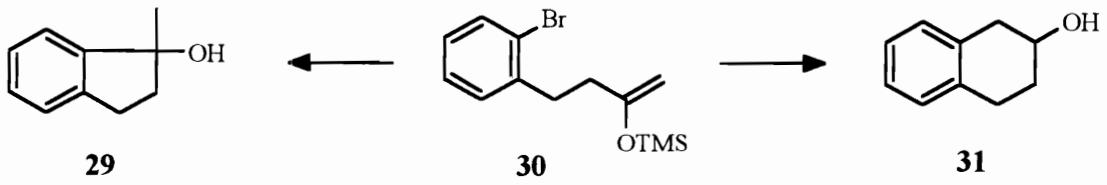
Moriya reported similar closures to dihyrofuran moieties when starting with allyloxylated bromobenzene.[17] The phenyl radical tin induced cyclization of ethers afforded the furobenzofuran ring system **28** as shown in Scheme 2.[18] The methodology for the formation of tricyclic systems from radical annelations was applied to the synthesis of aflatoxins B_1 and B_2.



27 **28**

Scheme 2

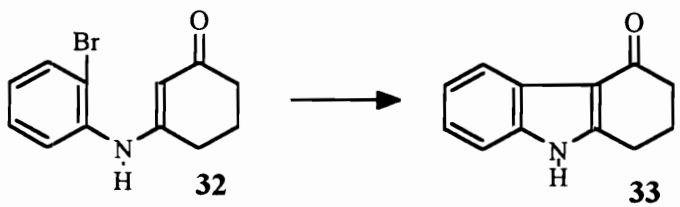
Allyl thioethers,[19] alkyl cuprates[20] and substituted enol ethers[21] also serve as radical acceptors to form the typical 6, 5 systems. Aryl radicals are extremely reactive towards 5-exo type cyclizations as evidenced by the rate constant of (5×10^8 s^{-1} at 50 °C).[22] An exception emerges in those transformations that use silyl enol ethers whose closures furnish a 6-endo trig cyclization, Scheme 3.[23]



29 **30** **31**

Scheme 3

Closures of the 5-exo type are found in examples of the use of photolysis for generation of aryl radicals. One notable example, apparent in Scheme 4, can be found in Kibayashi's work in which phenyl radical cyclizations were induced in the case of enamides.[24]



32 **33**

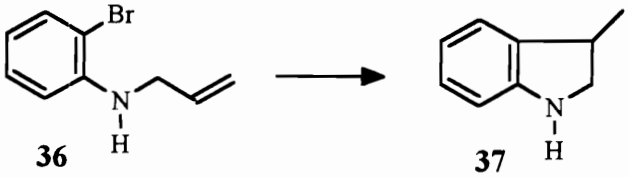
Scheme 4

Ultraviolet photostimulation was also used in conjunction with sodium borohydride and di-t-butyl peroxide[13] as radical initiators to effect a ring closure similar to the cyclizations reported by Snieckus which implemented tributyl tin hydride.

34 **35**

Scheme 4

With the emergence and exploitation of the vogue reagent, SmI_2,[25] phenyl radical cyclization involving bromoallyl anilines for the formation of simple indole systems was found to occur smoothly, Scheme 5.[14]



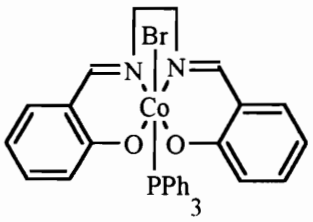
36 **37**

Scheme 5

Use of samarium diiodide simplified the purification of aryl cyclization products since isolation of such products from the reaction mixture did not involve troublesome removal of tin compounds.

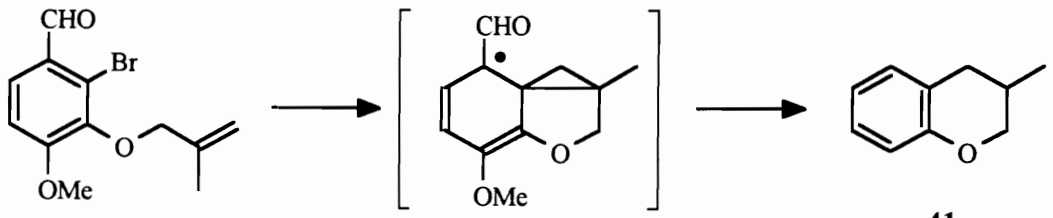
One final point of discussion is that of aryl cyclizations involving the cobalt 'salen' **38** or 'salophen' reagent.[15] Use of this compound was applied to the formation of both indoles and benzofurans. Reaction of (o-allyl)iodophenyl ethers with **38** in the

presence of sodium amalgam in tetrahydrofuran under argon resulted in immediate cyclization followed by trapping of the radical center with Co(II). This reagent was studied only in the case of non-substituted cyclic structures including benzofuran and indole type systems.



38

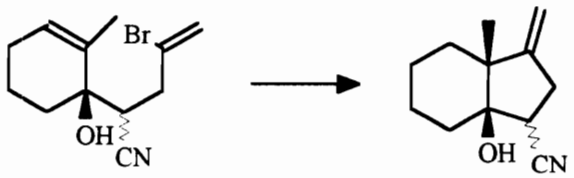
In the work of Beckwith[26] and Parker,[27] shown in Scheme 7, substitution at the olefin led to the creation of a quaternary center by cyclization and rearrangement to give the ring expanded product. Experimental conditions such as temperature and Bu_3SnH concentration were varied to study the rate of ring closure versus rearrangement. It was found that exo cyclization followed by rearrangement as well as direct endo cyclization were occurring.



39 **40** **41**

Scheme 7

Not only are aryl radicals useful tools for the synthetic organic chemist, but vinyl radicals also prove valuable in synthetic methods. Much of the research performed in the area of vinyl radical cyclization has been championed by Stork.[28,29] Stork and Mook have shown[30] the compatibility of vinyl radicals with unprotected functional groups and the insensitivity for steric hindrance in the reaction. (Scheme 8) An added feature of the reaction emerges when comparing vinyl with alkyl radical cyclizations. For instance, a simple alkyl radical reaction begins with two viable functional groups and all functionality is lost at the end of the reaction. Conversely, as a vinyl radical reaction is complete, a double bond remains in a clearly defined position, ready for further functionalization.

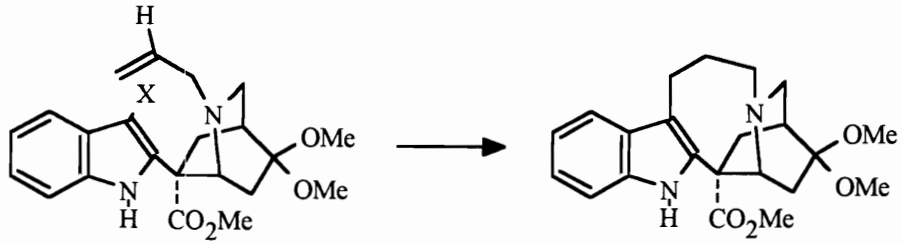


42 **43**

Scheme 8

Recent examples boast the utility of such reactions in natural product synthesis. Sundburg and Cherney[31] published their use of an intramolecular radical mediated synthesis of analogues of the iboga alkaloids. The preparation of the 5,6-homologues

in Scheme 9 posed the first synthetic application of intramolecular cyclization of 3-inolyl radicals.

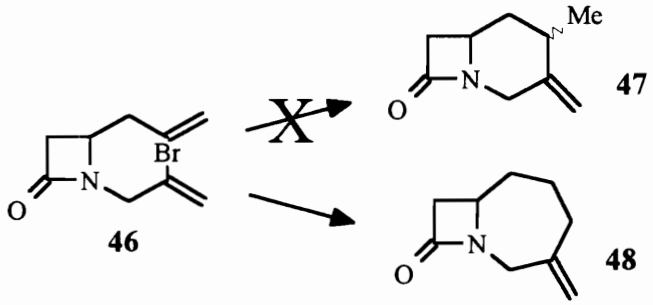


44 **45**

Scheme 9

The authors compared similar ring formation reactions via palladium catalyzed and electrophilic pathways. Although these pathways achieved the goal of formation of the desired alkaloid, the yields were modest. When compared to the radical counterparts, the electrophillic and palladium-type reactions were sensitive to derivitization of the starting compound.

In an effort to design a new synthesis for β-lactam antibiotics, Knight, Parsons and Southgate[32] used Stork's ring closure methodology. The initial findings depicted in Scheme 10 contrasted with the products expected. When treating the β-lactam **46**

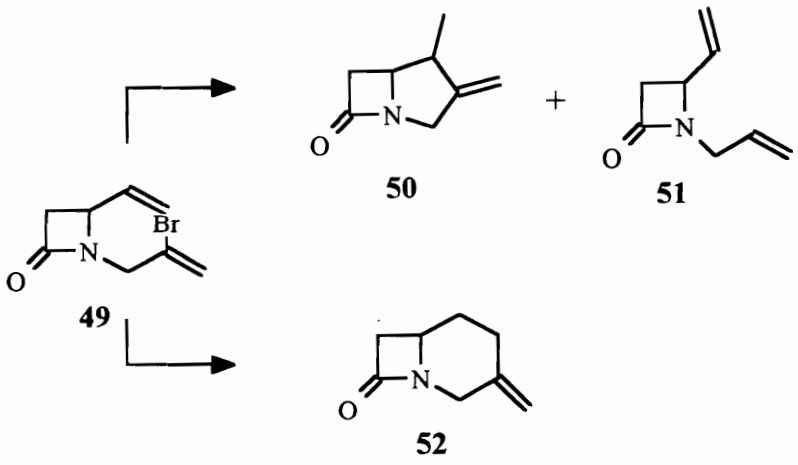


46 **47** **48**

Scheme 10

under photolytic tin mediated radical conditions, none of the carbacepham **47** was obtained, but instead, a 77% yield of the corresponding 4-7 system.

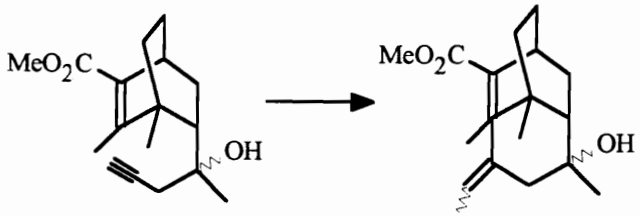
By simply freeing the starting substrate of one carbon unit and using **49** as the starting material, it was envisioned that the desired product **52** would be obtained via an analogous endo cyclization. Unfortunately, the findings of the reaction did not agree with the anticipated result: isolated was the methylcarbapenam **50** in 30% yield along with the reduction product **51** in a 70% yield. Simply reverting to thermal conditions and heating a 10 mM solution containing tributyltin hydride and the starting β-lactam **49** for four days, the only product obtained was the initially sought after carbacepham **52**.



Scheme 11

Thus, it was found for the synthesis of the β-lactam antibiotics that ring sizes could be designed depending on the reaction conditions, whether photolytic or thermal.

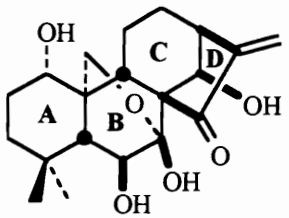
Another attractive feature of vinyl radicals appeared in the total synthesis of (±)seychellene.[33] In the key step (Scheme 12), a six membered ring formed intramolecularly to give **54** which emphasized the reactivity of the vinyl radical species relative to hydrogen abstraction.



53 **54**

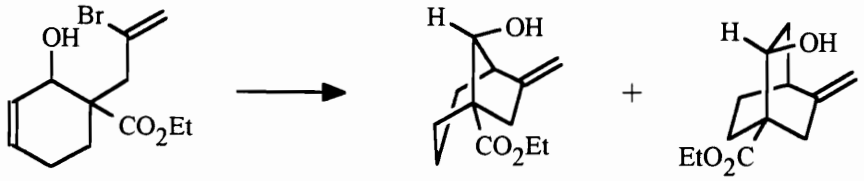
Scheme 12

A similar bicyclic ring closure was described in an approach toward the synthesis of the C/D subunit of Oridonin **55**, a diterpeoid with anti-tumor activity.[34]



55

The model study involved the radical cyclization of the allylic alcohol **56**. Under standard radical conditions, a 1:1 mixture of products, was obtained, Scheme 13.



56 **57a** **57b**

Scheme 13

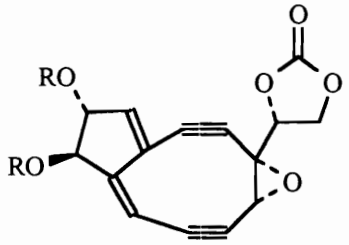
With this brief introduction to aryl radical cyclizations, the generation of free radicals under thermal conditions through Bergman cycloaromatization reactions will be discussed before entering the final section of this chapter which describes the harmony of the Bergman cyclization and aryl radical annulations.

II. HISTORICAL

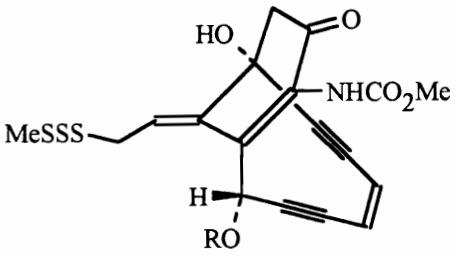
2. Overview of the Bergman Cyclization Reaction

The Bergman cyclization[6,7] has elicited much attention recently because of the research devoted to the synthesis and study of biological activity of several antibiotics containing the enediyne system. Some of the families of compounds possessing this unique molecular architecture and fascinating mode of action include: compounds

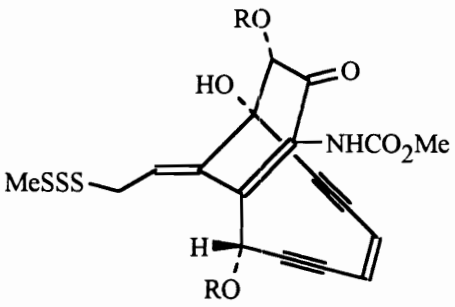
containing the Neocarzinostatin chromophore **58a**,[35] Calicheamicins **58b**,[36] Esperamicins **58c**,[37] Dynemicins **58d**[38] and Kedarcidin **58e**.[39]



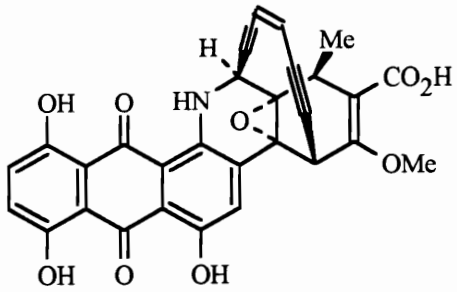
58a



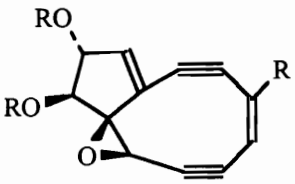
58b



58c



58d



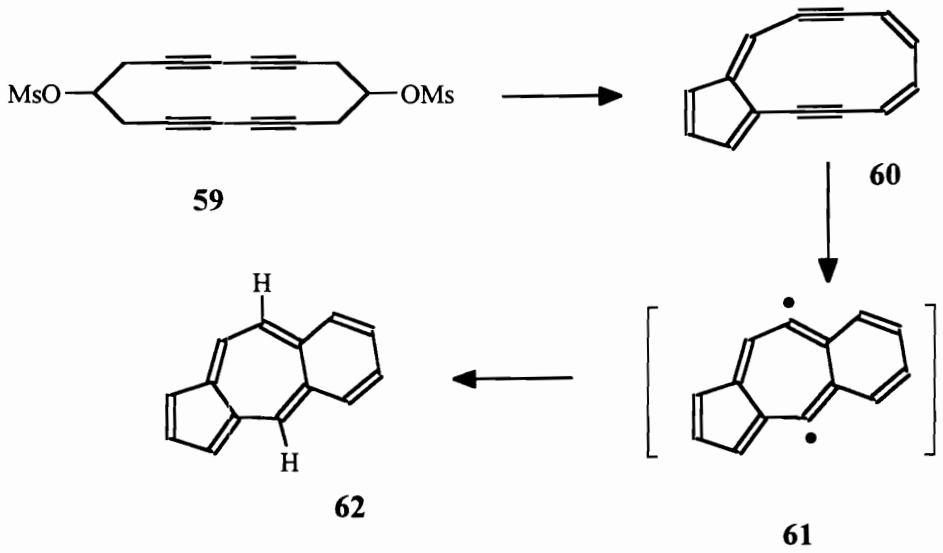
58e

Isolation of these anti-cancer substances has paved the way for the design of several synthetic strategies to probe and mimic their chemical and biological activity. These biologically active substances have the ability to sever a double strand of DNA under appropriate triggering conditions. Along with such triggering, two other design requirements are necessary for the enediyne antibiotics to function in the cell. A targeting system is necessary to direct the compound to the nucleic acid and the enediynyl system must be present in order for the compound to undergo the Bergman cyclization. All three of these design requirements have been succinctly documented for each of the general classes of enediyne natural products.[40]

In general, the triggering system activates the enediyne portion of the molecule which culminates in the formation of a diradical species and intercalates with the DNA which then leads to a double strand scission. Initially, the chemistry regarding the reactive intermediate was investigated without regard for the powerful biological aspects of the system.

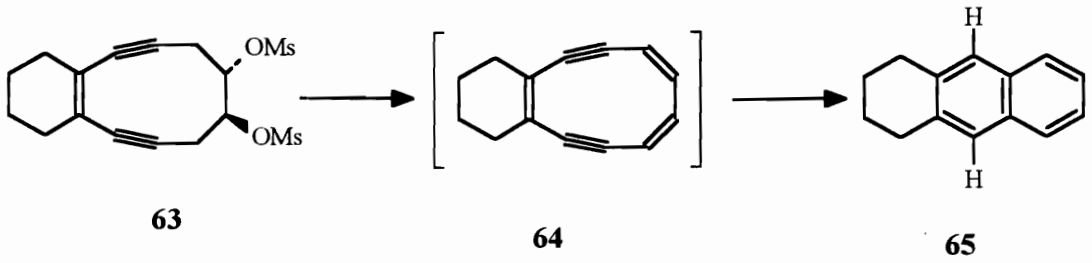
One of the first examples of cyclization via a diradical species, albeit unrecognized at the time, was disclosed by Sondheimer and Mayer in 1966.[41] The study involved the base-induced elimination of 3,5,11,12-cyclotetradeca- tetrayne-1,8-diol dimethanesulfoante **59** as a new route for the formation of dehydro [14] annulenes. As Mayer and Sondheimer pursued their research in the area of annulene

chemistry and aromaticity, they stumbled upon the compounds shown below in scheme 14.



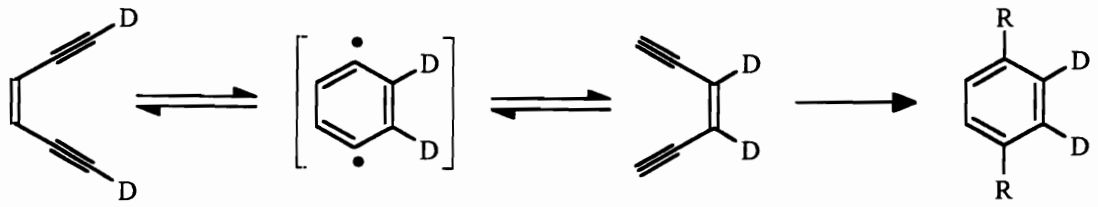
Scheme 14

A few years later, Masamune and his coworkers attempted the preparation of the [10]-annulene derivative **64**, but surprisingly isolated the naphthalene system **65**.[42]



Scheme 15

Both groups were not able to identify the intermediates as diradical species until a later example of a benzeniod diradical species appeared in the elegant work of Bergman in 1972.[7] In this study, cis-1,5-hexadiyne-3-ene, which was also prepared by Sondheimer in 1967,[43] was subjected to thermolysis conditions and was shown to undergo quantitative cyclization via 1,4-dehydrobenzene upon heating at 200°C. Bergman thus designed and demonstrated the cycloaromatization reaction of enediynes to earn the prestige of being identified with the reaction which now bears his name.

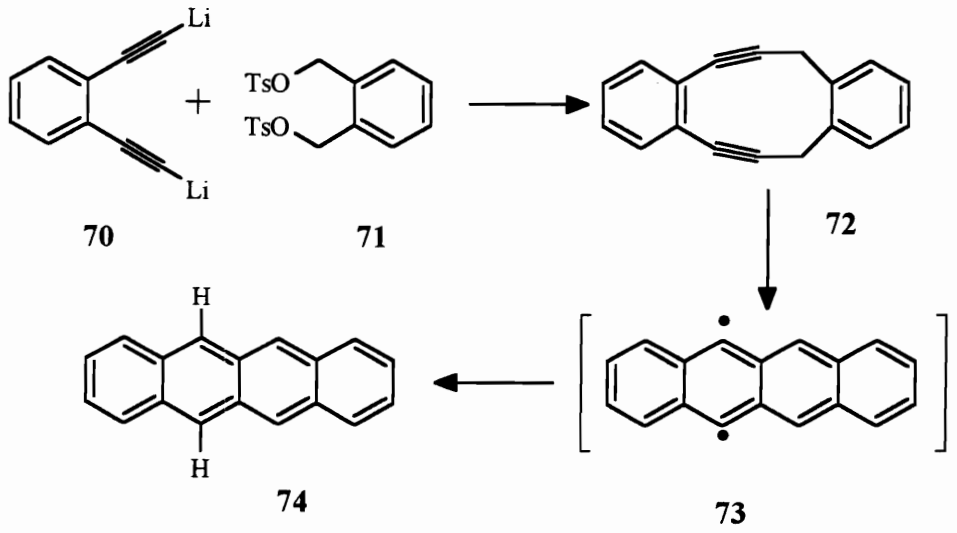


66 **67** **68** **69**

Scheme 16

Apparent from the above scheme is the radical nature of the reaction. Cyclization of the parent enediyne, **66** in hydrocarbon solvent led to benzene but in carbon tetrachloride, the parent system formed p-dichlorobenzene and thereby confirmed the presence of the diradical as a viable intermediate.

Much later, Wong and Sondheimer[44] published their results for the attempted formation of a ten-membered ring benzenediyne. Their desired compound, **72**, proved to be only a fleeting intermediate in the synthesis of a tetracyclic system, Scheme 17. However, in light of Bergman's results, they surmized that their isolated product was generated from a benzene diradical intermediate.

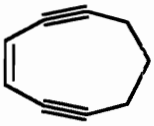
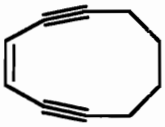
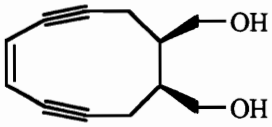
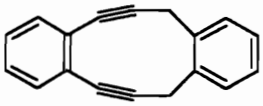
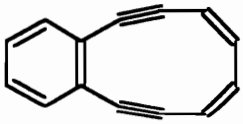
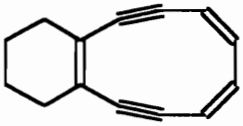
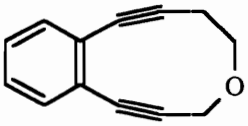
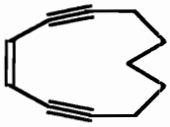


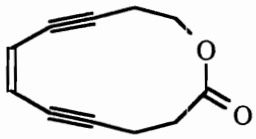
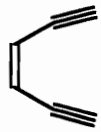
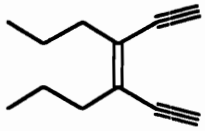
Scheme 17

The activation energy for the original Bergman process was estimated to be 32 kcal/mole at 200°C.[7] A useful guide for determining the ease of cyclization of an enediyne moiety was developed by Nicolaou in the late 1980's for simple cases. It was found that the distance between the remote acetylinic carbons, (c...d distance), could provide a method for predicting whether or not a certain compound would cyclize

spontaneously or require external heating to undergo cyclization. The rule appears to work well for simple monocyclic systems as shown in Table I.[45]

TABLE I. Stability and the c...d Rule

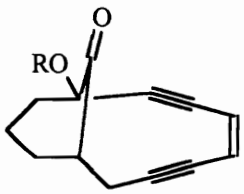
#	*Compound*	*Ring Size*	*c...d Distance [Å]*	*Stability*	*Ref.*
75		9	2.84	unknown compound	46
76		10	3.25	$t_{1/2}$ = 18 hr at 37°C	46,47, 48
77		10	3.20	$t_{1/2}$ = 11.8 hr at 37°C	49
78		10	3.03	cyclized at 25°C	44
79		10	3.01	cyclized < 25°C	42
80		10	2.99	cyclized < 25°C	42
81		10	3.40	$t_{1/2}$ = 52 hr at 37°C	50
82		11	3.61	stable at 25°C	46

#	*Compound*	*Ring Size*	*c...d Distance [Å]*	*Stability*	*Ref.*
83		12	3.77	stable at 25°C	51
84		-	4.12	stable at 25°C $t_{1/2}$ = 30 s at 200°C	7
85		-	3.94	stable at 25°C $t_{1/2} = 6.4 \times 10^{-4}$ s^{-1} at 156°C	7

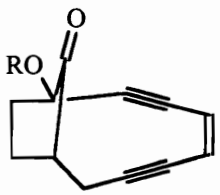
Compound **76** in Table I shows a carbocyclic enediyne with a ring size of 10. The c..d distance was calculated by MM2 to be 3.25Å. In general, a compound exhibiting a c...d distance greater than 3.31Å ought to be stable towards cyclization at ambient temperatures. However, compounds with calculated c...d distances less than 3.20Å should suffer spontaneous ring closure.[46]

It is interesting to note that the c...d distance of **76** falls in the middle of the critical range (3.31-3.20Å) but can be handled at ambient temperatures for purification. Slow decomposition of the compound occurs upon standing in solution or neat. Another interesting piece of data from the table arises in the case of cycloundecaenediyne **82**, which exists as a crystalline solid. An x-ray crystallographic analysis of **82** was undertaken to compare the experimentally derived c...d distance to the actual value. Surprisingly, the calculated value of 3.61Å falls quite close to the measured value of 3.66Å.[46]

There are however, several "exceptions" to this rule as there are to any tool devised as a guideline. One such exception was discovered by Magnus and his group during their studies of Esperamicin and Calicheamicin type antibiotics.[52] A general core enediyne structure **86** was synthesized and was compared to a similar structure **87** through cycloaromatization rate studies. Again, **86** , existing as crystalline solid was characterized by x-ray crystallography, and the measured c...d distance of 3.39Å proved to be in excellent agreement with the MM2 calculated value of 3.41Å. Following the general guidelines, this compound cyclized with an E_a of 24.6 kcal/mol. Its relative, **87**, with a c...d distance of 3.37Å was found to be remarkably resistant to ring closure and cyclized 650 times slower than **86**. Thus, the notion that distance between the remote acetylinic carbons in the ground state determines the rate of diyl formation does not provide an adequate prediction of the ease of cycloaromatization in some cases.



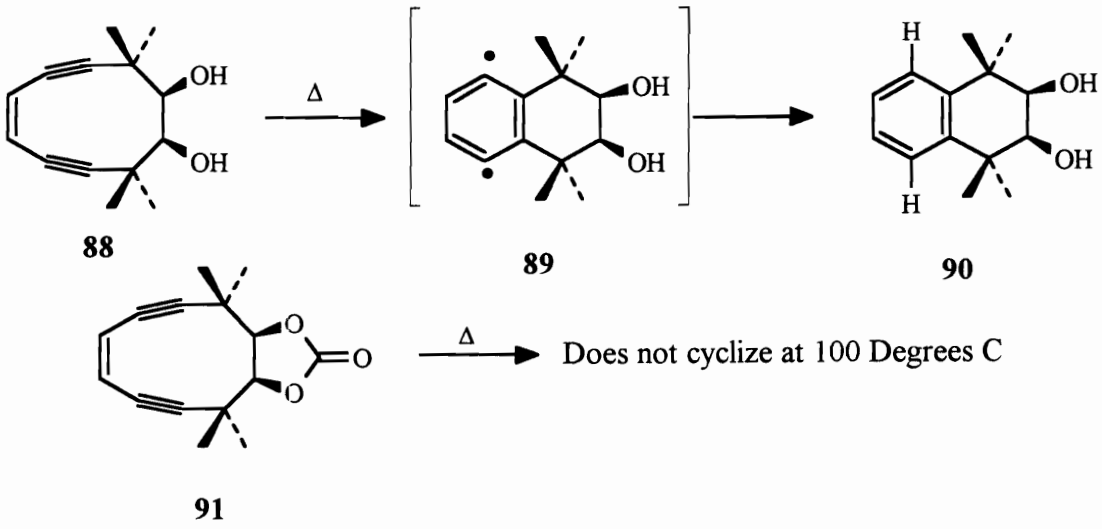
86



87

Another example of an exception is the closure of the ten-membered enediyne synthesized by Nicolaou and his group.[53] The carbonate, **91**, was prepared to act as a "locking device" that would prevent cycloaromatization. Indeed, the compound proved to be completely stable at 100°C for several hours although the calculated c...d distance of 3.424Å seemingly predicts a lower cyclization temperature. For example, a

similar structure, **88**, with the c...d distance of 3.422Å was synthesized by Nicolaou and cyclized smoothly with a half-life of four hours at 50°C.

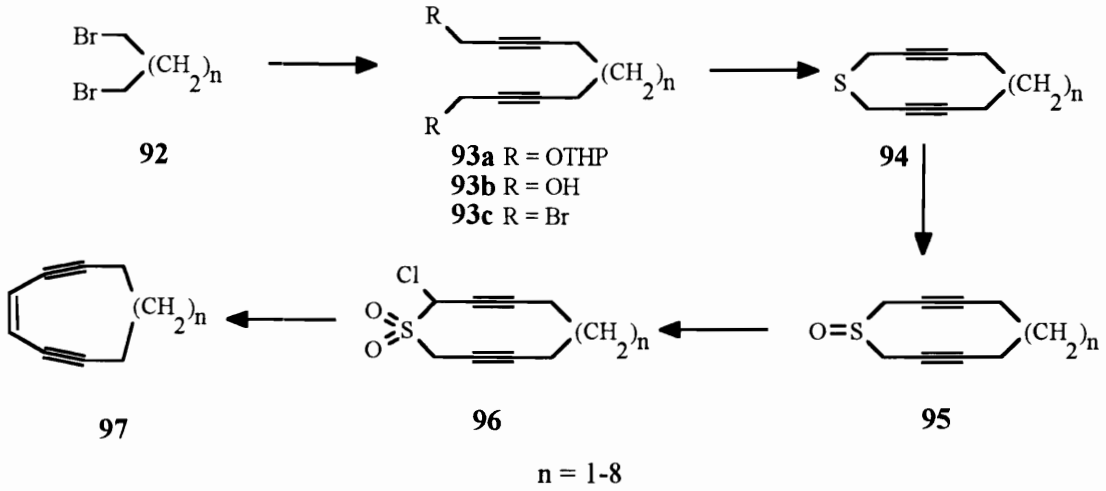


Scheme 18

With the knowledge of several perplexing results, investigations were directed towards the synthesis of simple monocyclic enediynyl systems in order to study the reactivity and stability of these novel chromophores. Nine and ten membered rings were of special interest since two biologically active compounds namely Neocarzinostatin and Dyneamicin incorporate a nine membered enediyne in their structure while Calicheamicin, Esperamicin and Kedarcicin embody a ten membered ring in their skeleton.

After several fruitless routes towards the synthesis of the parent monocyclic ten membered ring enediyne via palladium catalyzed coupling of acetylenes with vinyl halides, Nicolaou was the first to develop a viable synthetic pathway for its preparation.

In doing so, he also provided a general route for the synthesis of enediynyl rings ranging in sizes from eleven to sixteen, scheme 19. The key step involved a Ramberg-Backlund reaction for the formation of the ene portion of the ring.[47]

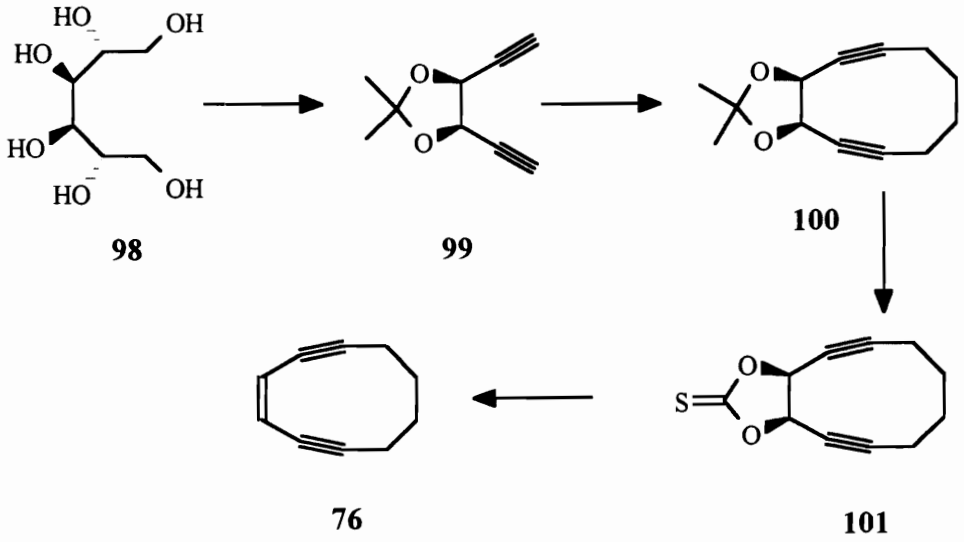


Scheme 19

The initial step of the synthesis involved reaction of the alkyl dibromides **92** with excess of the anion derived from tetrahydro-2-(2-propynloxy)-2H-pyran and n-BuLi to afford the acetylinic compounds **93a** which were subsequently deprotected with acidic methanol. The dibromides **93c** were then prepared using carbon tetrabromide and triphenylphosphine. Preparation of the sulfide **94** was accomplished *via* reaction of the dibromides with sodium sulfide under high dilution conditions. The sulfides were converted to the sulfoxides **95** using a stochiometric amount of m-chloroperbenzoic acid and then converted to the chlorosulfones **96** with sulfuryl chloride and oxidation to the sulfone **96** with an excess of mCPBA. Finally, treatment

of the chlorosulfones with potassium t-butoxide or methyl lithium afforded the desired monocyclic enediyne **97**.

In early 1993, Semmelhack published his version of the synthesis of the parent ten- membered ring enediyne by utilizing the common sugar dulcitol **98** as the starting material.[48] After double acetonide protection of the sugar with dimethoxypropane,



98 **99** **100**

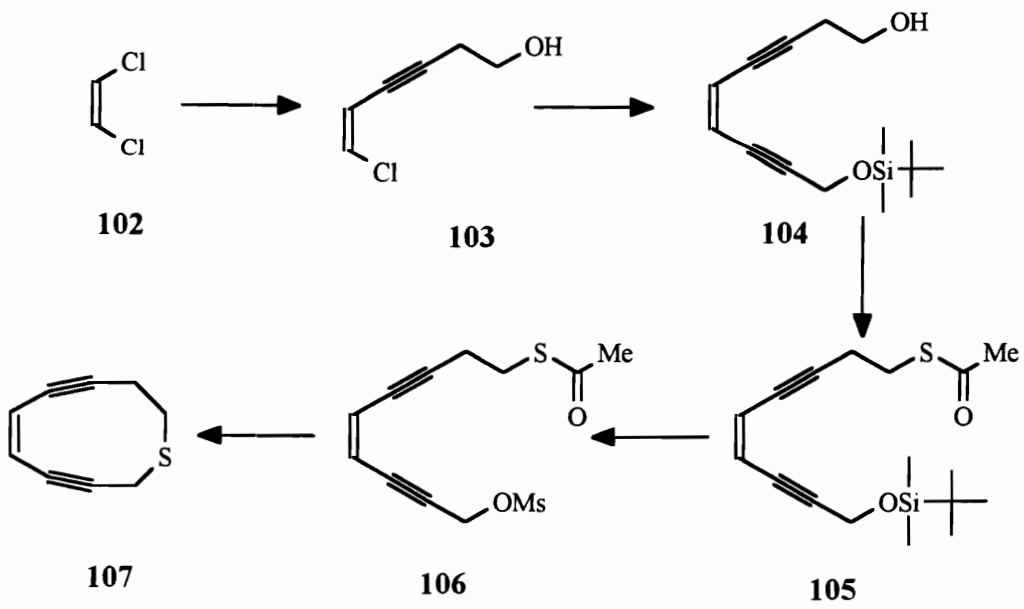
76 **101**

Scheme 20

substitution of the remaining terminal alcohols with chlorine by the reaction of carbon tetrachloride and triphenylphosphine, elimination with excess lithium diisopropyl amide to form the alkynes and reprotection of the resultant diol with dimethyoxy propane, 3,4-dioxy-dimethylmethylene-1,5-hexadyne **99** became available. This four step procedure was feasible on a scale of 100 grams. The remaining procedure involved alkylation of the acetylinic dianion with diiodobutane followed by conversion to the

diol under mildly acidic conditions. Subsequent conversion to the thionocarbonate with thiophosgene and fragmentation via the Corey-Winter reaction afforded the parent hydrocarbon **76**. The Bergman cyclization parameters for the parent compound **76** were identical for both Semmelhack and Nicolaou since the enediyne had a stability of 18 hours at 37 °C as discerned through half life studies.

Another member of the series of ten-membered enediyne model compounds, **107**, was synthesized in 1991.[54] This novel addition incorporated a sulfur atom in place of one of the carbons in the saturated portion of the ring. The synthesis produced a relatively stable, crystalline compound which cyclized smoothly when subjected to refluxing benzene containing 1,4-cyclohexadiene. The synthesis of the sulfur analogue began with cis-1,2-dichloroethylene **102**. Palladium coupling with 3-butyn-1-ol



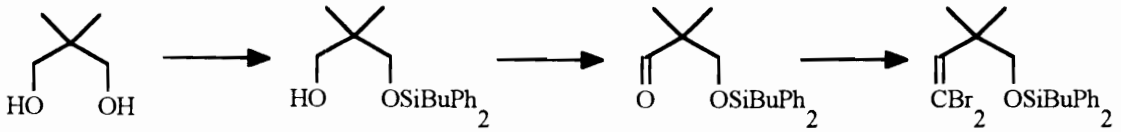
102 **103** **104** **105** **106** **107**

Scheme 21

produced the monocoupled product **103**, and a second palladium coupling with TBS protected propargyl alcohol added the rest of the necessary carbons to the compound. To complete the ring closure there remained simply the addition of a sulfur atom and cyclization. Addition of the sulfur took place by first formation of the mesylate and nucleophilic displacement with potassium thioacetate to provide **105**. Desilylation under acidic conditions and subsequent mesylation of the alcohol afforded the cyclization precursor **106** in 87% yield. The cyclic enediyne **107** was obtained through a careful addition of methanolic solutions of **106** and sodium methoxide to methanol over a period of 36 hours.

The final ten-membered cyclic enediyne to be discussed here was patented in late 1993.[55] An analogue of this compound was mentioned in this section, page 23, as an enediyne which deviated from the c...d distance correlation to predicted cyclization temperature.

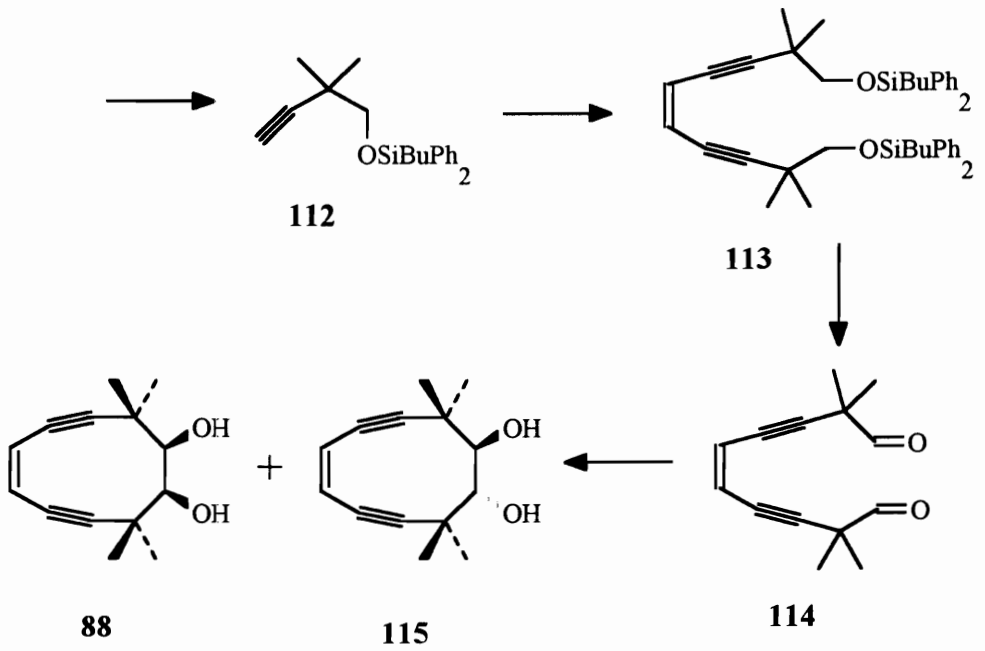
Starting with the readily available 2,2-dimethyl-1,3-propanediol **108**, monoprotection with t-butyldiphenylsilyl chloride followed by Swern oxidation formed



108 **109** **110** **111**

(continued)

(continued)



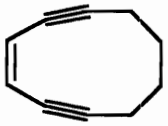
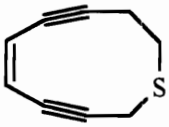
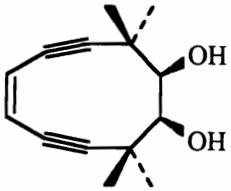
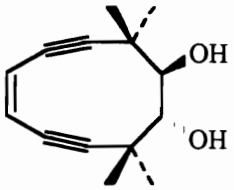
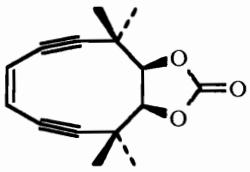
112 113 114 88 115

Scheme 22

aldehyde **110**. The acetylene portion of the compound was introduced first by reacting the aldehyde with carbon tetrabromide and triphenyl phosphine followed by methyl lithium. Next, a 2:1 ratio of **112** and cis-1,2-dichloroethylene were reacted via standard palladium coupling methods to afford **113** and desilylation was achieved using tetra-n-butylammonium fluoride in THF at room temperature. Swern oxidation afforded the dialdehyde **114** which was subsequently reacted with samarium diiodide in THF to give a mixture of cis and trans diols **88** and **115** in a 1:20 ratio.

A summary of Bergman reaction profiles including temperature required for cyclization and calculated or measured c...d distances for each of the above mentioned ten-membered cyclic enediynes are presented in Table II.

TABLE II

Entry #	*Compound*	*c...d (MM2)*	*c...d (measured)*	*Stability*	*Ref.*
76		3.25	-	$t_{1/2}$ = 18 h at 37°C	46,47,48
107		3.31	3.30	cyclized at 80°C	54
88			-	$t_{1/2}$ = 4 h at 50°C	55
115		-	3.422	$t_{1/2}$ = 22 h at 50°C	55
91		-	3.424	stable at 100°C	55

The information contained in Table II shows that insufficient examples exist to formulate a general set of rules. Several types of ten-membered ring enediyne compounds must still be investigated to discover their stability, cyclization potential and provide more information regarding cyclization tendencies. Also, the anomaly regarding compound **91** may explain why some compounds prefer to react via the Bergman cyclization and others resist the formation of the diradical species.

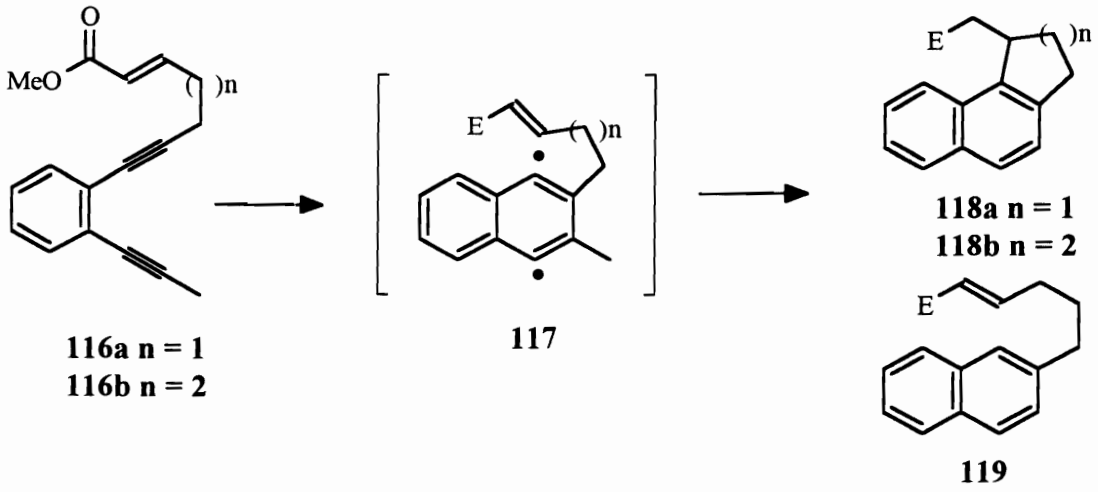
II. HISTORICAL

3. Review of Tandem Bergman-radical Cyclizations

With the renewed interest in the Bergman cyclization in the late 1980's, much of the research was focused towards the synthesis of enediyne natural products or their synthetic analogues. Several groups rushed to discover new enediyne natural products or attempt to prepare enediyne containing compounds with greater DNA cleaving ability. At that time, no research had been performed concerning the use of the extremely reactive Bergman diyl species in radical cyclizations.

In early 1990, Wisniewski-Grissom and Calkins reported the first tandem Bergman-radical cyclization.[56] Only four steps including two high yielding palladium

coupling reactions of 1,2-diiodobenzene were required to prepare the enediyne cyclization precursor. As shown in Scheme 23, compound **116a** provided indene **118a**



116a n = 1
116b n = 2

117

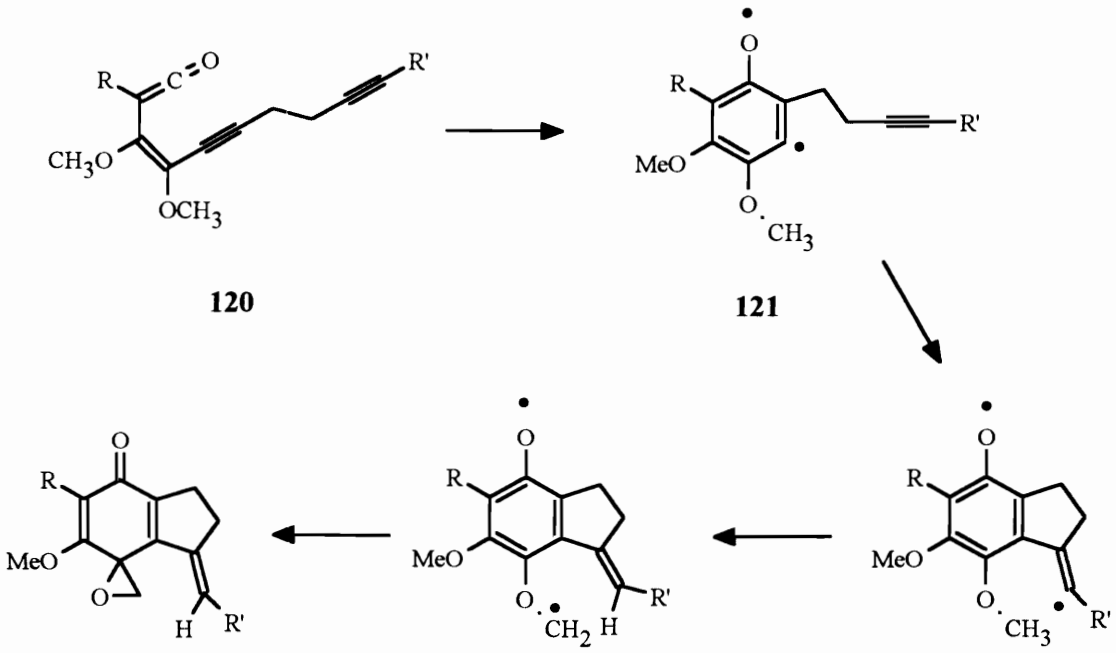
118a n = 1
118b n = 2

119

Scheme 23

in 72% yield on heating in chlorobenzene in the presence of hydrogen atom donor, 1,4 cyclohexadiene. When compound **116b** was subjected to identical conditions, product **118b** and **119** were formed in yields of 53% and 42% respectively.[56]

Shortly after the revelation of the first Bergman cyclization cascade, Moore and Wang disclosed similar results regarding the trapping of biradicals.[57-59] Using the biradical generated from an eneyne ketene **120**, Moore and Xia were able to form spiroepoxycyclohexadienones and quinones. The mechanism for this sequence is shown in Scheme 24.

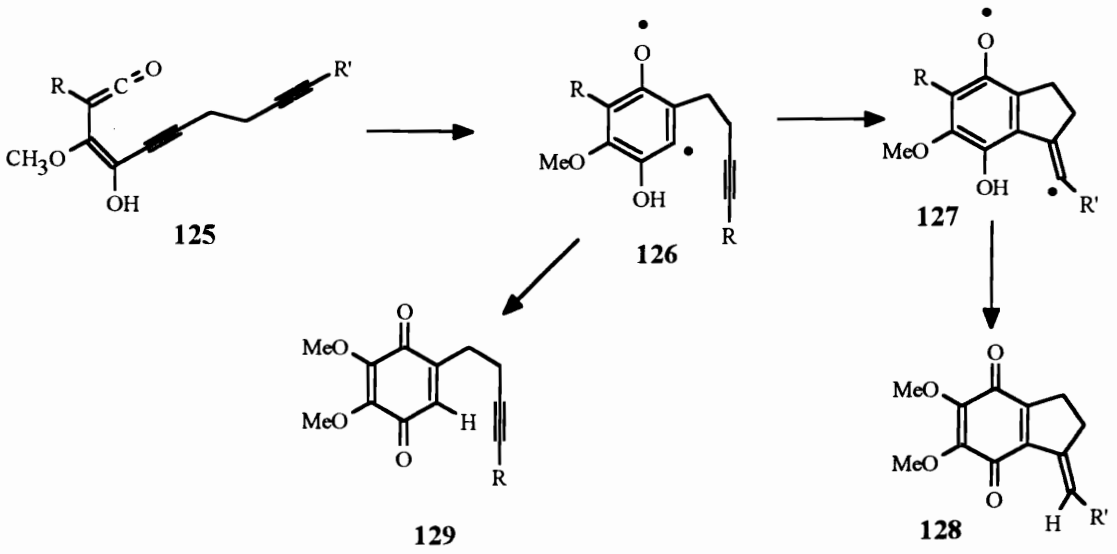


Scheme 24

The reaction depicted in scheme 24 was carried out in refluxing toluene. The initial mechanistic step was postulated to involve an exo addition to the more reactive ring based radical center of **121** by the proximal alkyne moiety. Subsequently, the resulting vinyl radical abstracted a hydrogen atom from the adjacent methoxy group which directly formed the spiroepoxycyclohexadienone.

In a related experiment, certain alkynyl ketenes were found to undergo thermolysis to form quinones rather than spiroepoxides. The results of the experiments were shown to depend on concentration. For example, thermolysis of **125** with high dilution conditions produced quinone **129** in a 63% yield while **128** was not detected.

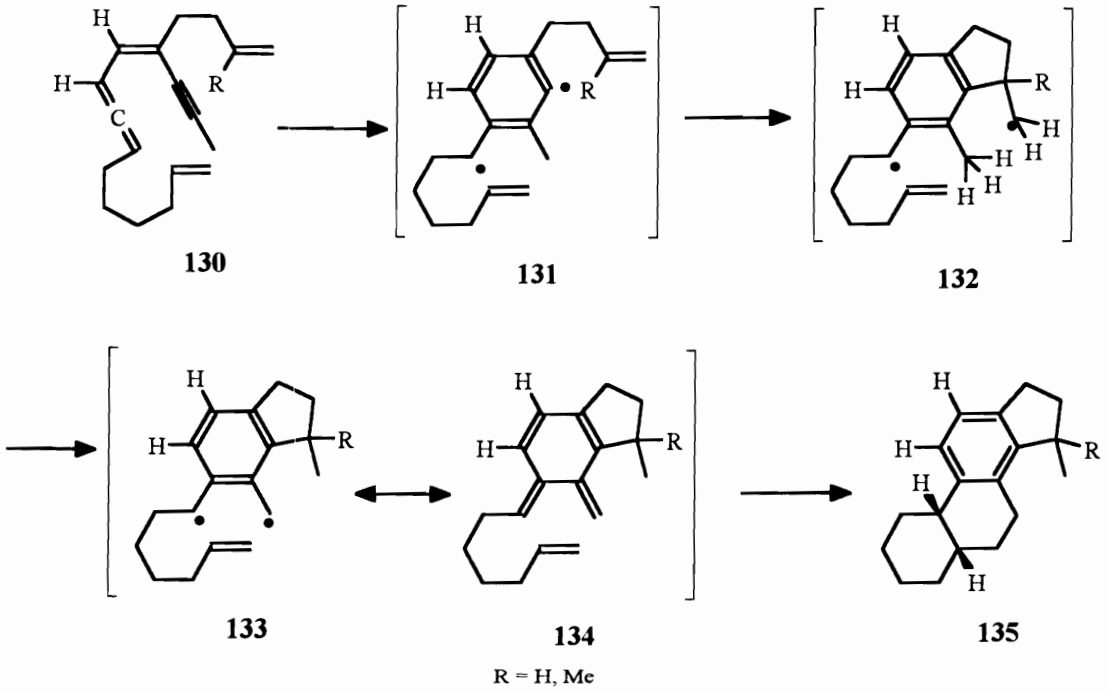
Correspondingly, under thermolytic conditions with a 0.7 M solution of **125**, a 12:1 ratio of **128** and **129** was found with yields of 4.2% and 66% respectively. Such a dilution study points to the fact that when given a choice, Bergman type diradicals react preferentially in an inter rather than intramolecular hydrogen atom transfer process.



Scheme 25

In 1993, Wang, Huang and Antemichael introduced an efficient and attractive strategy for the construction of polycyclic structures.[59] An acyclic enyne-allene served as the substrate for the formation of a tetracyclic steroidal skeleton in one step. Compound **130** was subjected to refluxing benzene resulting in the formation of a reactive biradical intermediate via Myers[60] cyclization followed by ring colsure. The 1,5 hydrogen transfer occured faster than the possible intramolecular traping of the

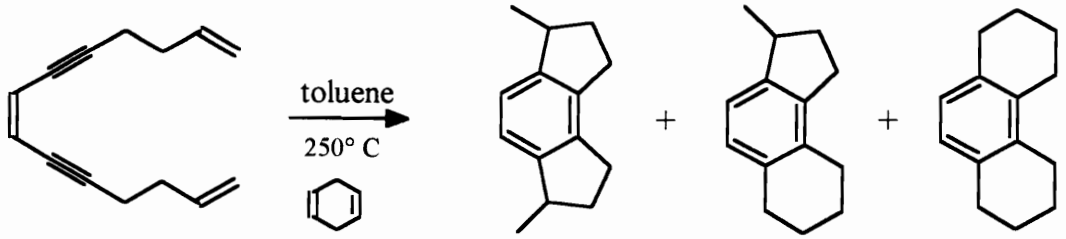
benzylic radical center by the carbon carbon double bond. The final step involved the intramolecular Diels-Alder cycloaddition to afford the steroid type skeleton in a 1: 1 mixture of diastereomers, Scheme 26.



Scheme 26

At the same time, Hudlicky and Boros[61] achieved the conversion of enediyne **136** to the indane system shown in Scheme 27 as a mixture of isomers **137**, **138**, and

139. This reaction once again demonstrated the viability of the reactive Bergman diyl as a center for the formation of new rings rather than simply a radical quenching site.



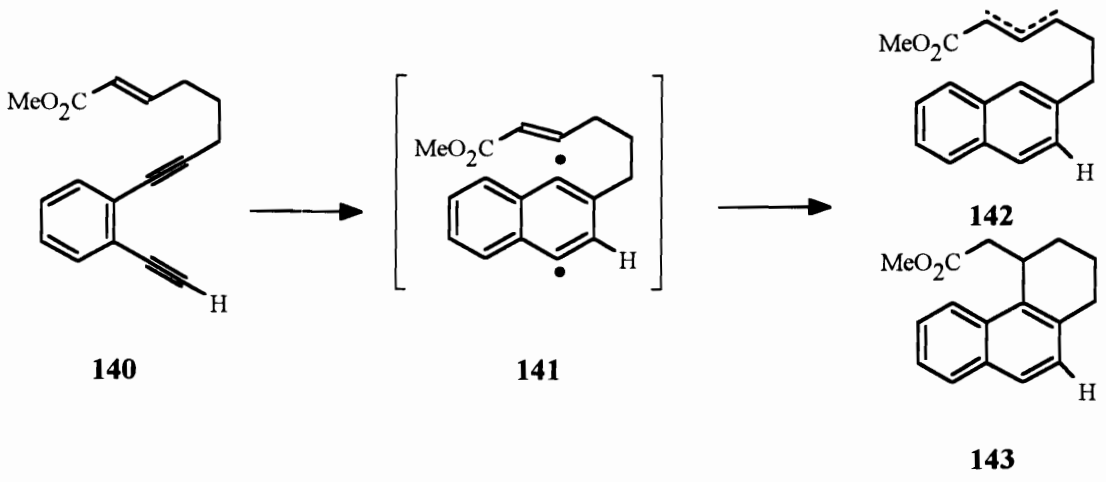
136 3 : 1 : 3

137 **138** **139**

Scheme 27

Most of the work performed in this area has been published by Wisniewski-Grissom and her group.[56,62-65] The enediyne **140** containing the tethered olefin radical acceptor was synthesized in five steps as shown in Scheme 27. The compound was then heated in chlorobenzene containing 1,4-cyclohexadiene at 240° for 8.5 hours. Not only was the method shown in Scheme 27 investigated for its synthetic utility, but also for the study of the mechanistic pathway of the enediyne-radical cyclization as well.

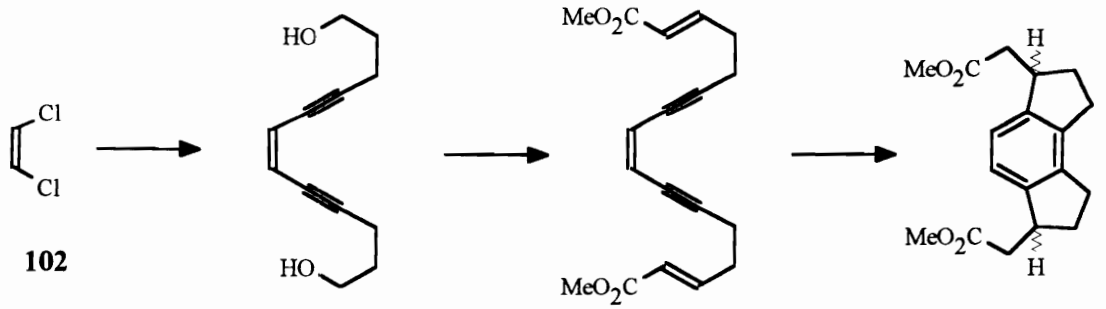
Substrate concentration, 1,4-cyclohexadiene concentration, olefin geometry and olefin electron content were varied in this study. The results suggested a first-order mechanism with the slow step being the inital 1,4 diracidal formation which is then followed by the rapid radical cyclization. The authors were not surprised by the result since it is known that a 6-exo aryl radical cyclization occurs quickly (2×10^7 at 80°).[T6]



140 **141** **142** **143**

Scheme 28

In later work, Wisniewski-Grissom expanded the tandem Bergman-radical cyclization methodology to include the formation of three rings in one step to produce structures resembling dihydrobenzindene **146**.[63] In other words, the reaction in Scheme 29 may be considered a *bis*-tandem enediyne-radical cyclization.



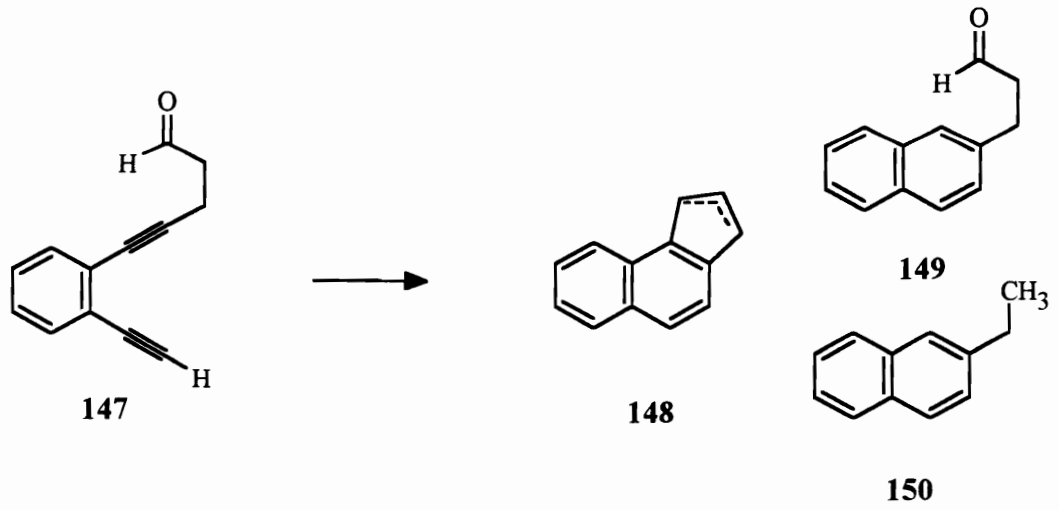
102 **144** **145** **146**

Scheme 29

The bis- tandem cylization was achieved *via* thermolysis of the radical precursor **145** at 245°for three hours in the presence of 1,4 cyclohexadiene to yield a 1:1 mixture

of diastereomers in 98% yield. To date this yield represents one of the best when compared to similar enediyne-radical cyclizations. Both tethers of the enediyne possess radical accepting centers which can immediately quench the aromatic radicals and thus the cyclization is more rapid, hence the higher yield. In turn, the resultant carbomethoxy radicals are quenched by 1,4 cyclohexadiene. In the cases where a rapid quenching site is not available to the aromatic biradical, polymerization has been observed which obviously reduced the yield.[63]

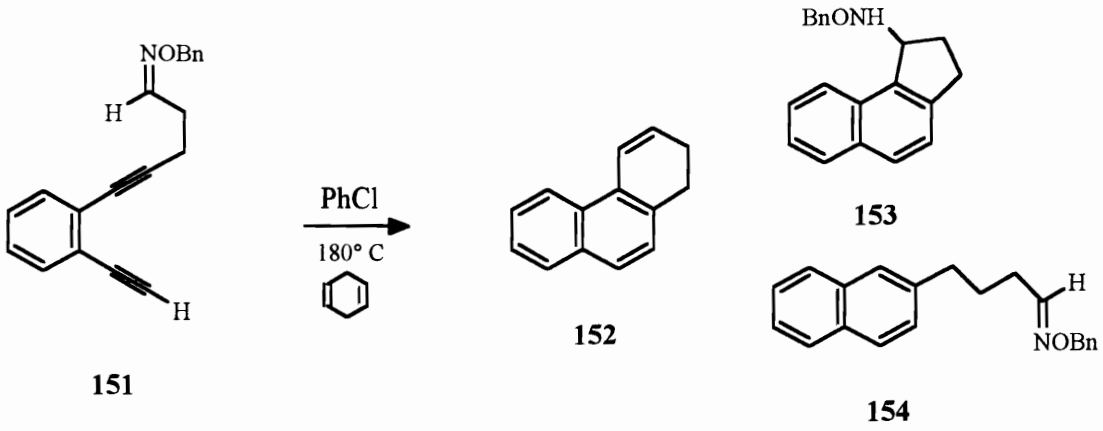
The concept of cyclization of an aryl radical onto aldehyde and oxime acceptors has been introcuded by Grissom, Scheme 30.[65] The results of this study appeared disappointing. A mixture of four products were formed in low yields. The desired compounds from the tandem cyclization were obtained as a mixture of diastereomers in a ratio of 1 : 2.5 and in low yield.



Scheme 30

Oxime ethers are known to be better radical acceptors than aldehydes. These ethers also appeared to be favorably involved in the reactive diyl quenching process. In

this case, the products resulting from tandem cyclization were indeed favored over the simple enediyne cyclization in a 6:1 ratio.[65]



151 152 153 154

Scheme 31

II. HISTORICAL

4. Compilation of Known Arene *cis*-Diols

Table III, a compilation of isolated *cis*-dihydrodiols, has been taken in part from the Ph.D. thesis of Austin S. McMordie from the School of Chemistry, Queen's University of Belfast, Belfast, U.K. Most of the published diols up to 1989 were compiled by McMordie. The table was first updated in 1993 and included in the Master's thesis of Michele Stabile. The table was later reviewed by Dr. S. Selifonov in July 1994 after an interesting meeting at the 1994 Gordon Research Conference on

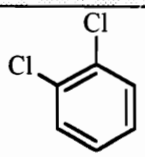
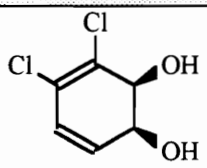
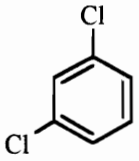
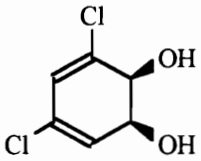
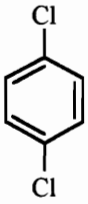
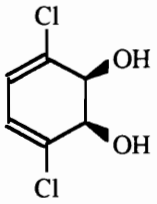
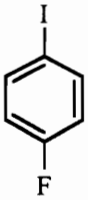
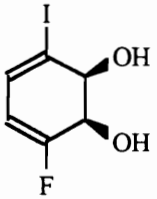
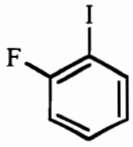
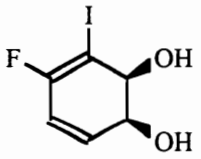
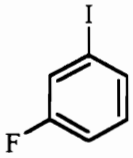
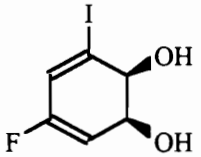
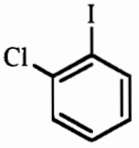
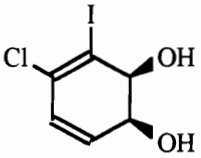
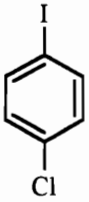
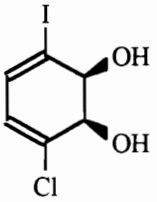
Biocatalysis. Newly reported structures that have been identified since 1992 have been added to update the table which now includes over one hundred entries.

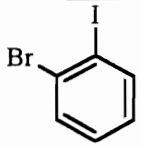
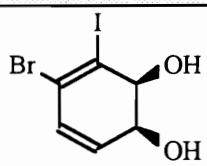
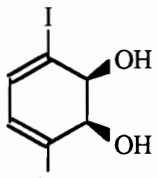
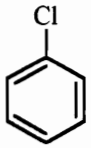
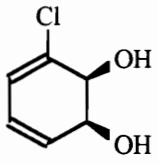
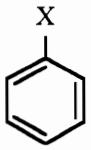
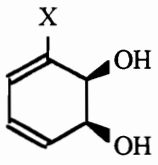
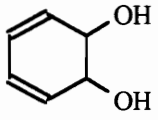
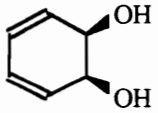
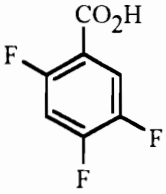
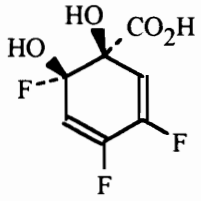
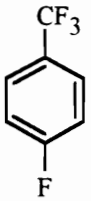
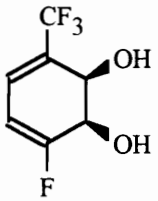
Isolation methods and the various strains of microorganisms along with the product(s) from the initial substrate have been listed. The key for the methods of identification of the various diols is shown below.

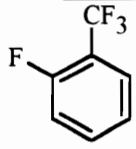
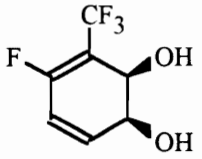
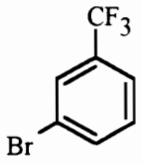
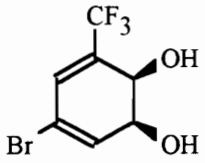
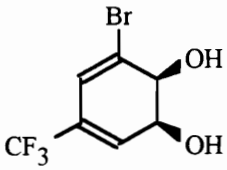
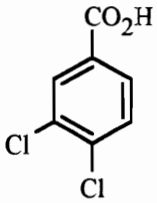
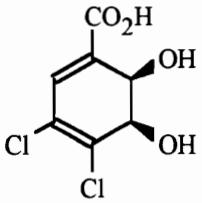
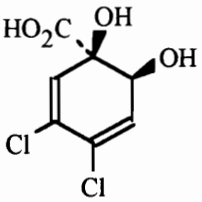
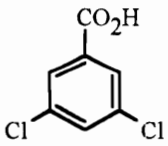
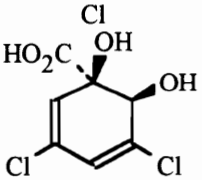
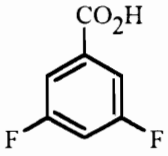
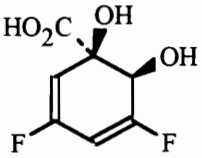
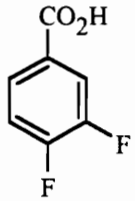
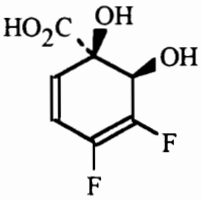
Product Identification Method

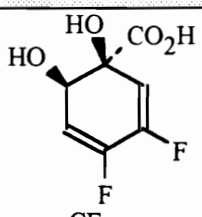
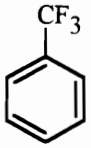
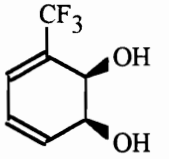
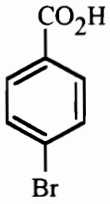
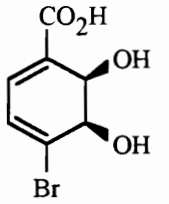
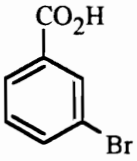
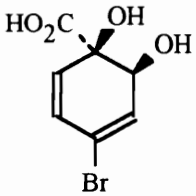
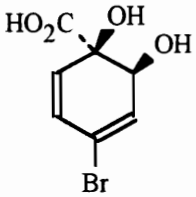
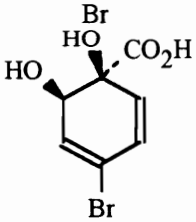
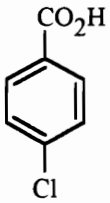
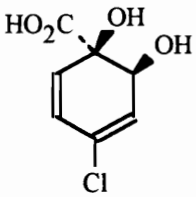
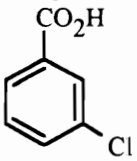
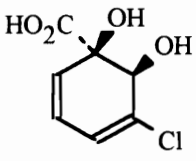
1. Product isolated - firm structural assignment by comparison with authentic samples or by ^{1}H NMR analysis.
2. Product isolated - structural assignment based on UV or MS spectral data or by identification of dehydration products
3. Product isolated - tenuous structural assignment
4. Product not isolated - structure of product proposed from nature of other degradation products
5. Product isolated - X-ray structure confirmation of diol or suitable derivative

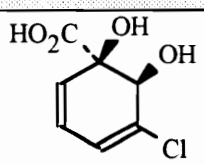
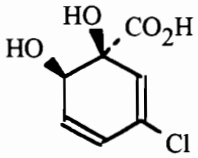
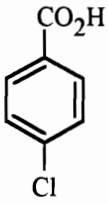
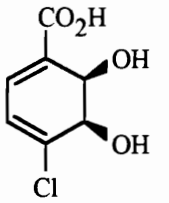
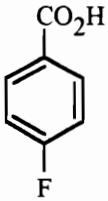
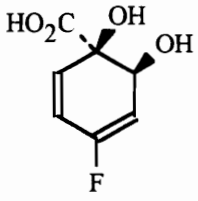
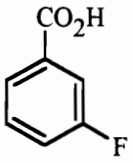
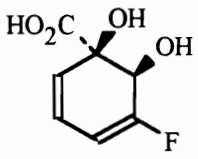
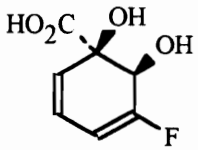
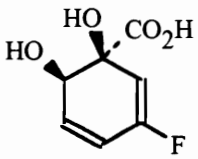
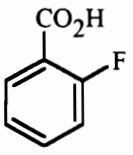
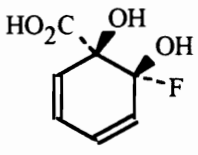
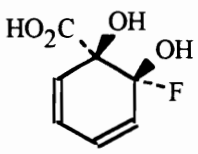
Table III
Products from the Biotransformations of Arenes and Cyclic Olefins

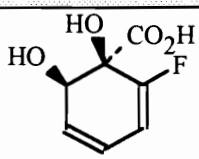
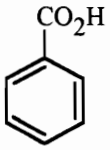
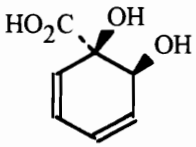
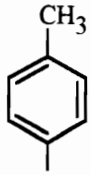
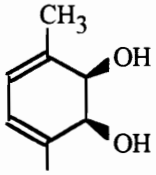
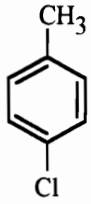
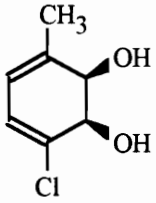
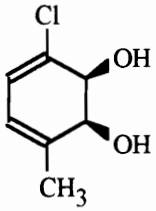
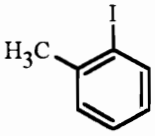
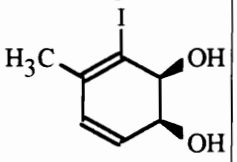
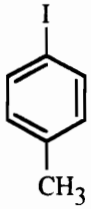
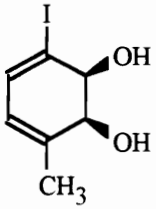
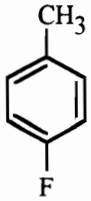
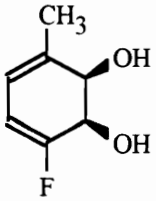
Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
1 $C_6H_4Cl_2$			*Pp* F1	1	66
2 $C_6H_4Cl_2$			*Pp* F1	1	66
3 $C_6H_4Cl_2$			*Pp* F1	1	66
4 C_6H_4FI			*Pp* UV4 *E. coli* JM109	1	67,68
5 C_6H_4FI			*Pp* UV4 *E. coli* JM109	1	68
6 C_6H_4FI			*Pp* UV4 *E. coli* JM109	1	68
7 C_6H_4ClI			*Pp* UV4 *E. coli* JM109	1	68
8 C_6H_4ClI			*Pp* UV4	1	67

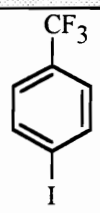
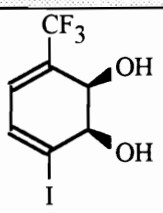
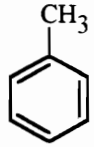
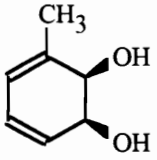
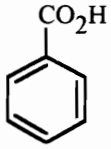
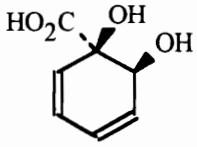
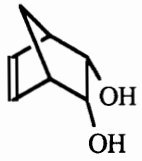
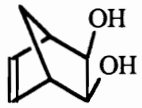
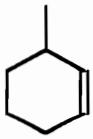
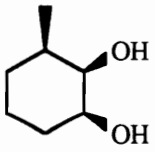
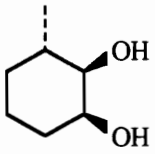
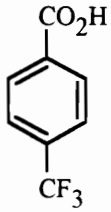
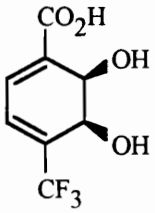
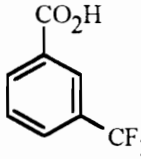
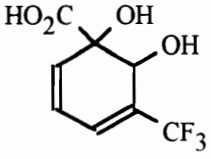
Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
9 C_6H_4BrI			*Pp* UV4 *E. coli* JM109	1	68
10 C_6H_4BrI			*Pp* UV4	1	67
11 C_6H_5Cl			strain WR 1306	1	69,70,71
12 C_6H_5X			*Pp* 39/D	1,5*	72,73*
	X = Br, Cl, I, F*				
13 C_6H_6			*Mycobacterium rhodochrous* *Pseudomonas aeruginosa*	4	74
			*P. putida* *Moraxella*	1	75,76,77
14 $C_7H_3F_3O_2$			*P. putida* JT103	4	78
15 $C_7H_4F_4$			*P. putida* NCIB 12190	1	79

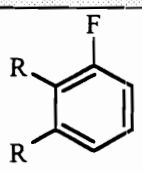
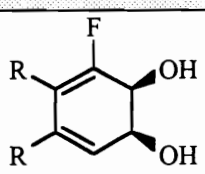
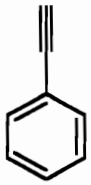
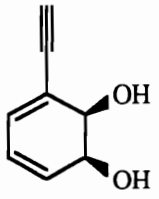
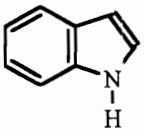
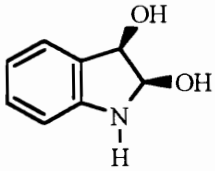
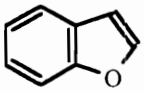
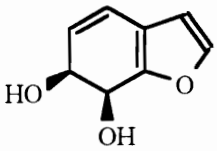
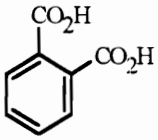
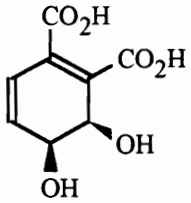
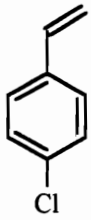
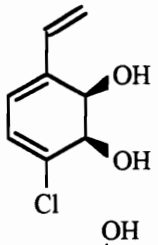
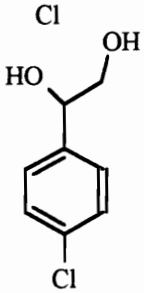
Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
16 $C_7H_4F_4$			*P. putida* NCIB12190	1	79
17 $C_7H_4BrF_3$			*Pp* 39/D	1	80
			*Pp* 39/D	1	80
18 $C_7H_4Cl_2O_2$			*P. putida* PL-pT-11/43	3	81
			*Pseudomonas sp.* B13	2	82
19 $C_7H_4Cl_2O_2$			*A. eutrophus* B9	1	82,83
20 $C_7H_4F_2O_2$			*P. putida* JT 103	1	78,84
21 $C_7H_4F_2O_2$			*P. putida* JT 103	1	84

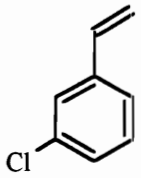
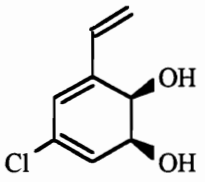
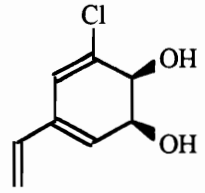
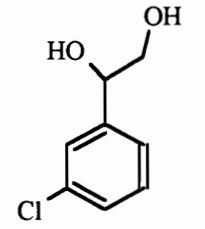
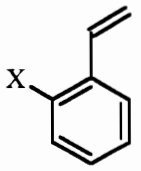
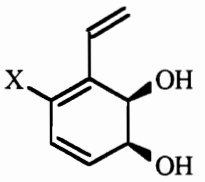
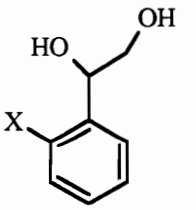
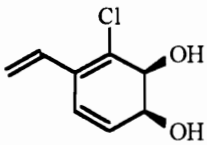
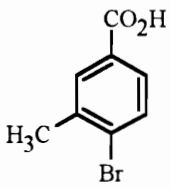
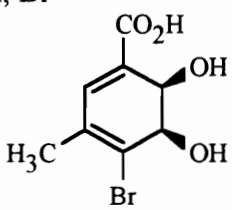
Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
			*P. putida* JT 103	1	84
22 $C_7H_5F_3$			*P. putida* UV4	1	73,79
23 $C_7H_5BrO_2$			*P. putida* JT 107	1,5	81,85
24 $C_7H_5BrO_2$			*A. europhus* B9	1	83
			*Pseudomonas sp.* B13	1	86
			*A. europhus* B9	1	83
25 $C_7H_5ClO_2$			*A. europhus* B9	1	82,83
26 $C_7H_5ClO_2$			*A. europus* B9 *P. putida*	1	82,83,87, 89

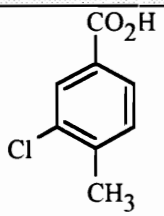
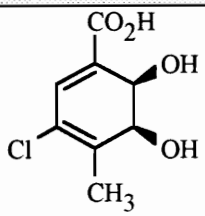
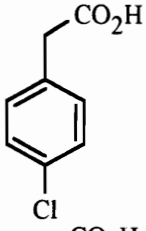
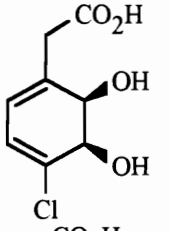
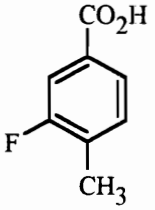
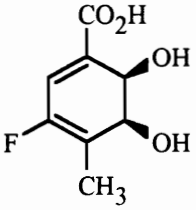
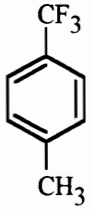
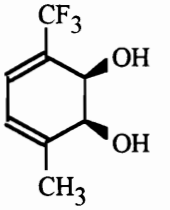
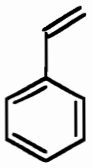
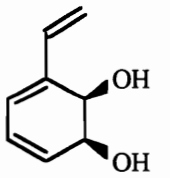
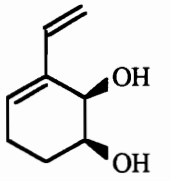
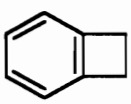
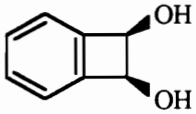
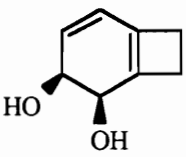
Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
			*A. europus* B9 *P. fluorescens*	2	82,83,89
			*Pseudomonas sp.* WR912	2	90
27 $C_7H_5ClO_2$			unidentified		91
28 $C_7H_5FO_2$			*Alicaligenes eutrophus* B9	1	83,87
29 $C_7H_5FO_2$			*A. eutrophus* B9	1	83,87
			*Pseudomonas*	2	86
			*A. eutrophus* B9	2	83
30 $C_7H_5FO_2$			*A. eutrophus* B9	1	83
			*A. eutrophus* B9	2	92

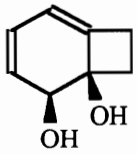
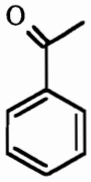
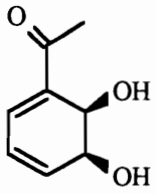
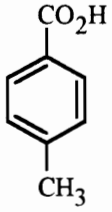
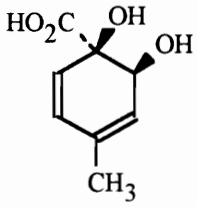
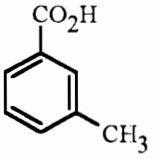
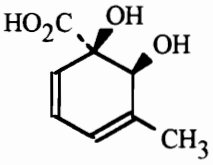
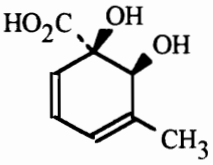
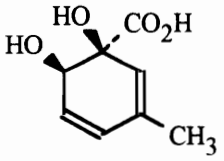
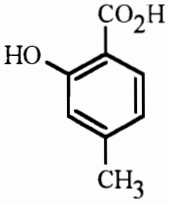
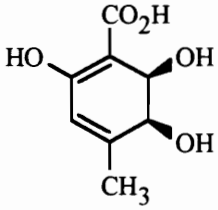
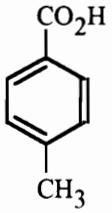
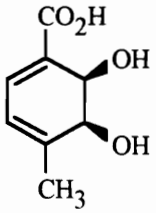
Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
			*Pseudomonas* sp. B39	2	93
31 $C_7H_6O_2$			*Alicaligenes eutrophus* B9	1	82,83,86, 87
32 C_7H_7Br			*P. putida*	1,5	69,94
33 C_7H_7Cl			*P. putida*	1	69,95
			*Pp* UV4	1	67
34 C_7H_7I			*Pp* UV4 *E. coli* JM109	1	68
35 C_7H_7I			*Pp* UV4 *E. coli* JM109	1	67,68
36 C_7H_7F			*P. putida*	1	69,76
			Pp UV4		67

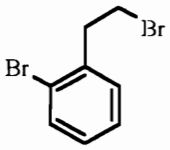
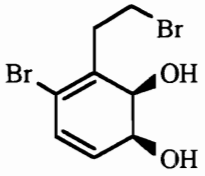
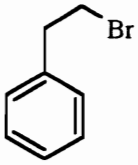
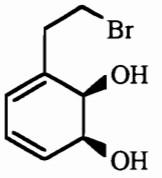
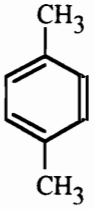
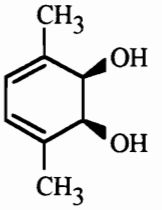
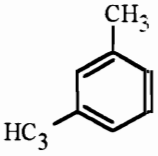
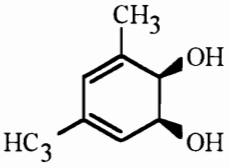
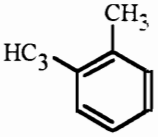
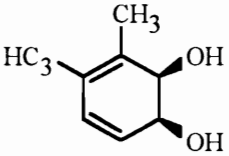
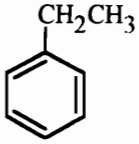
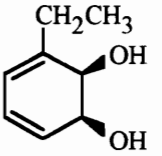
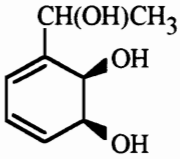
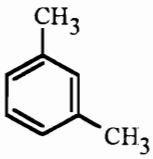
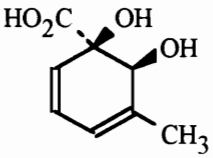
Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
37 $C_7H_4F_3I$			*Pp* UV4	1	67
38 C_7H_8			*P. putida*	1,5	69,70,73, 96,97,98, 99
39 $C_7H_7O_2$			*P. putida*	4,5	100
40 C_7H_8			*Pp* BM2	1	101
			*Pp* BM2	1	101
41 C_7H_{11}			*P. putida* 39/D	1	69,99, 102
			*P. putida* 39/D	1	69,99, 102
42 $C_8H_5F_3O_2$			*P. putida* PL-pT-11/43	1	85,103
43 $C_8H_5F_3O_2$			*P. putida* mt-1 *A. eutrophus* B9	1	104

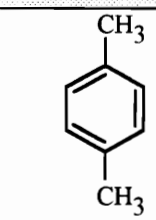
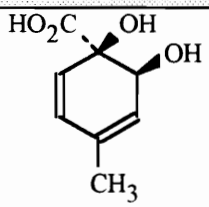
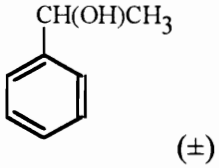
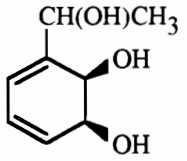
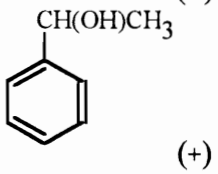
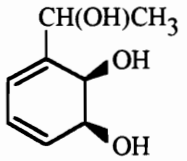
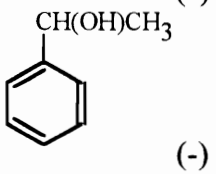
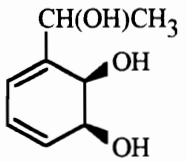
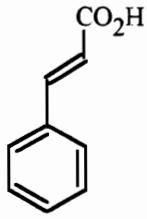
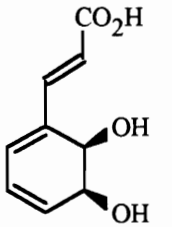
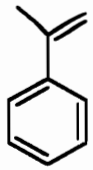
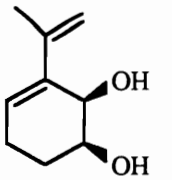
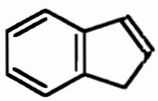
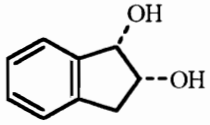
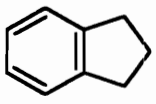
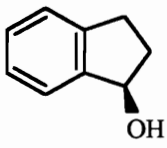
Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
44 $C_8H_5FO_4$			*P. testosteroni*	1	105
45 C_8H_6			*P. putida* 39/D	1	70
46 C_8H_6N			*P. putida* PPG7 in *E. coli*	1	106
47 C_8H_6O			*Pp* UV4	1	107
48 C_8H_6O4			*Micrococcus* sp. 12B	4	108
49 C_8H_7Cl			*P. putida* 39/D	1	109
			*P. putida* 39/D	1	109

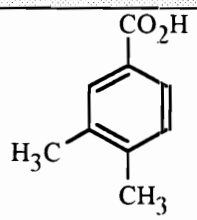
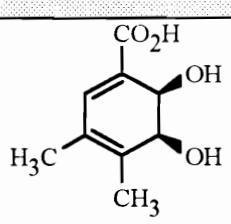
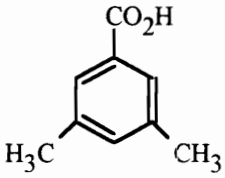
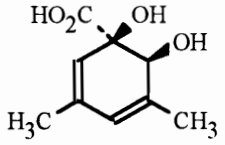
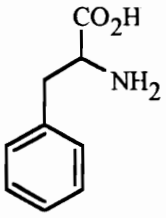
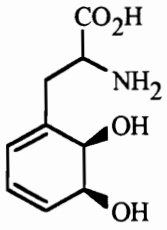
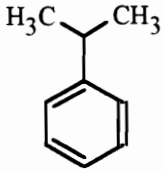
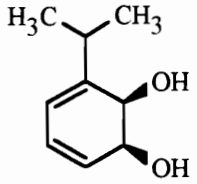
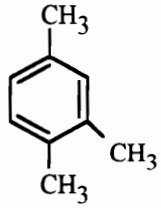
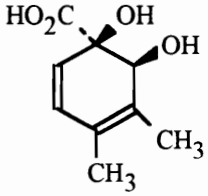
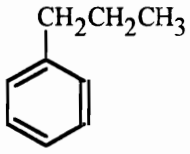
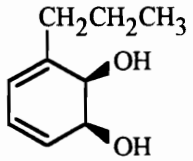
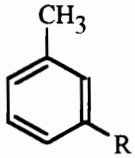
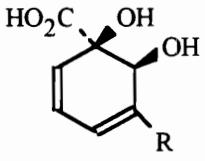
Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
50 C_8H_7Cl			*P. putida* 39/D	1	109
			*P. putida* 39/D	1	109
50 cont'd			*P. putida* 39/D	1	109
51 C_8H_7Cl			*P. putida* 39/D	1	110
			*P. putida* 39/D	1	110
			*P. putida* 39/D	1	110
	X = Cl, Br				
52 $C_8H_7BrO_2$			*P. putida* PL-pT-11/43	3	81

Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
53 $C_8H_7ClO_2$			*P. putida* PL-pT-11/43		81
54 $C_8H_7ClO_2$			*Pseudomonas* sp. CBS 3	4	111
55 $C_8H_7FO_2$			*P. putida* PL-pT-11/43	3	81
56 $C_8H_7F_3$			*Pp* UV4	1	67
57 C_8H_8			*P. putida* 39/D	1	70, 112
			*P. putida* 39/D	1	113
58 C_8H_8			*Pp* UV4	1	114
			*Pp* UV4	1	114

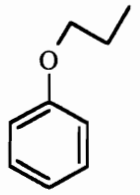
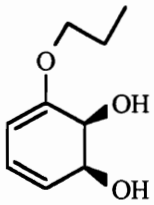
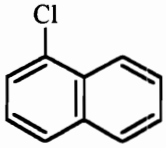
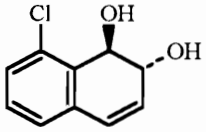
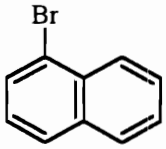
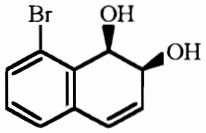
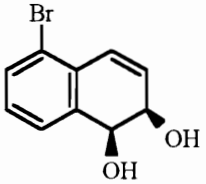
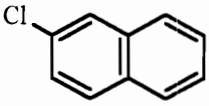
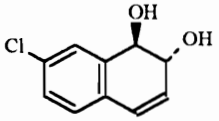
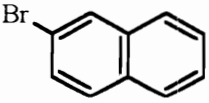
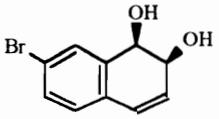
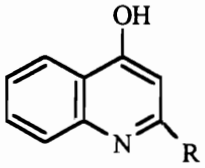
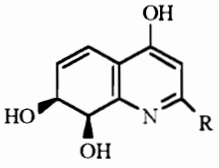
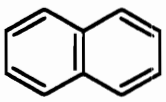
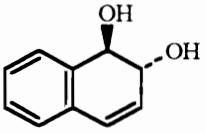
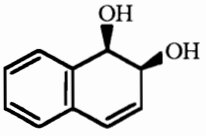
Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
			*Pp* UV4	1	114
59 C_8H_8O			*P. putida* 39/D	1	115
60 $C_8H_8O_2$			*A. europhus* B9	1	82,83
61 $C_8H_8O_2$			*A. europhus* B9	1	82,83,86
			*Pseudomonas* sp. B13	2	82,86
			*Pseudomonas* sp. B13	2	82,86
62 $C_8H_8O_3$			*P. putida* PL-pT-11/43	3	81
63 $C_8H_8O_2$			*P. putida* JT107	1	81

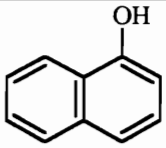
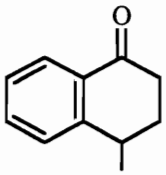
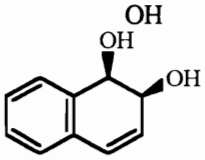
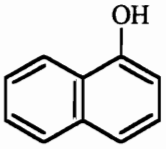
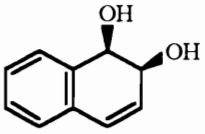
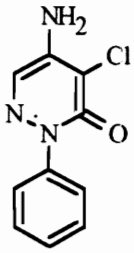
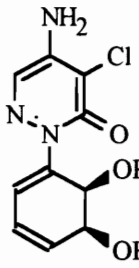
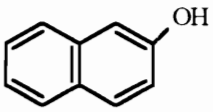
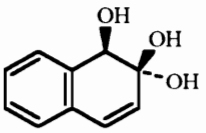
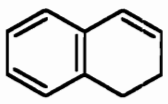
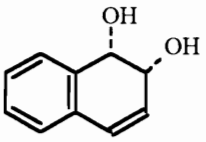
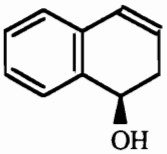
Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
64 $C_8H_8Br_2$			*P. putida* 39/D *E. coli* JM109	1	116
65 C_8H_9Br			*P. putida* 39/D *E. coli* JM109	1	117
66 C_8H_{10}			*P. putida* 39/D	1	118
67 C_8H_{10}			*P. putida* 39/D	1	118
68 C_8H_{10}			unknown	4	119
69 C_8H_{10}			*P. putida* 39/D	1	115
			*P. putida* 39/D	1	115
70 C_8H_{10}			*P. putida*	4	100,120

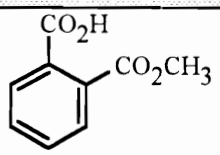
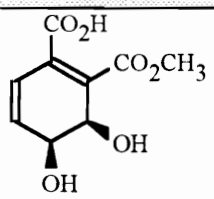
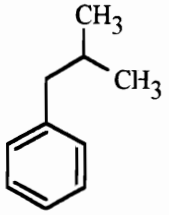
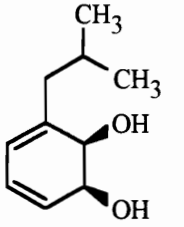
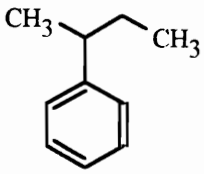
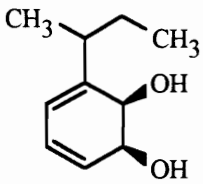
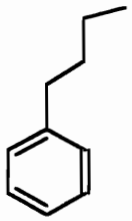
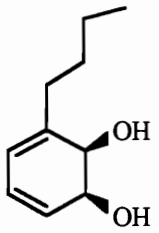
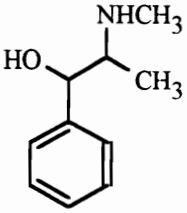
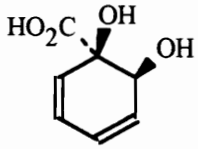
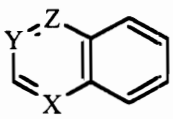
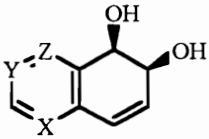
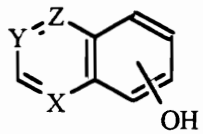
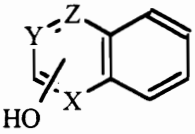
Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
71 C_8H_{10}			*P. putida*	4	100,120
72 $C_8H_{10}O$	 (±)		*P. putida* 39/D	1	115
73 $C_8H_{10}O$	 (+)		*P. putida* 39/D	1	115
74 $C_8H_{10}O$	 (-)		*P. putida* 39/D	1	115
75 $C_9H_8O_2$			unidentified	2	121,122
76 C_9H_{10}			*P. putida*	1	113, 123
77 C_9H_8			*P. putida*	1	113,123
78 C_9H_{10}			*P. putida* 39/D	1	124

Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
79 $C_9H_{10}O_2$			*P. putida* PT-pL-11/43	3	81
80 $C_9H_{10}O_2$			*Pseudomonas* sp. B13	2	82
81 $C_9H_{11}NO_2$			unidentified	4	122,125
82 C_9H_{12}			*P. desmolytica* *P. convexa*	2	126
83 C_9H_{12}			*P. putida*	4	100
84 C_9H_{12}			*Pp* F1	1	66
85 C_9H_{12}			*P. putida*	4	110

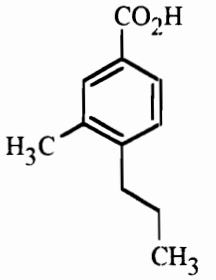
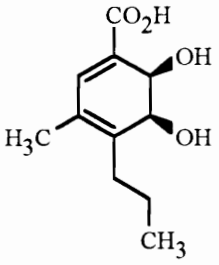
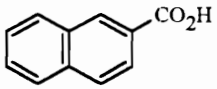
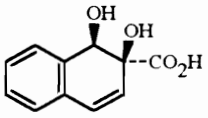
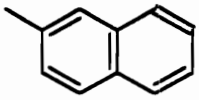
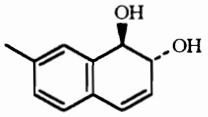
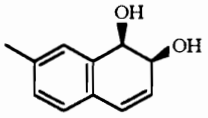
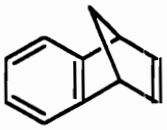
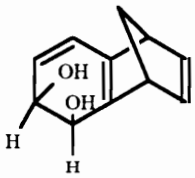
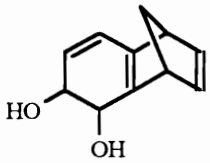
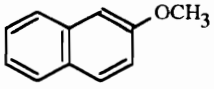
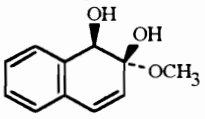
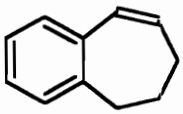
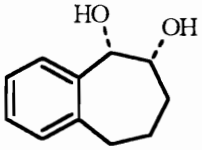
R = CH_2CH_3

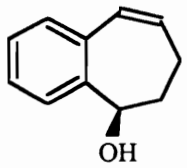
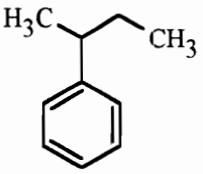
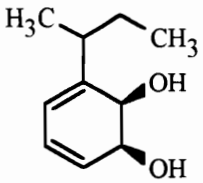
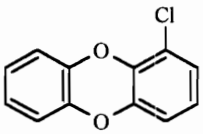
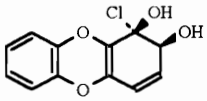
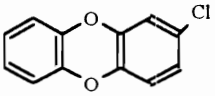
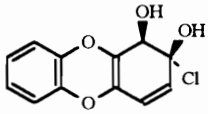
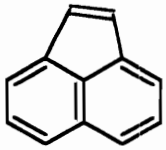
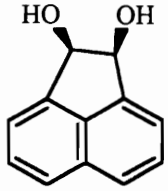
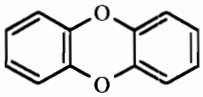
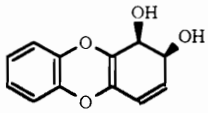
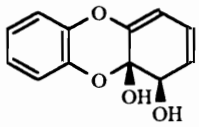
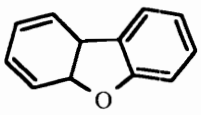
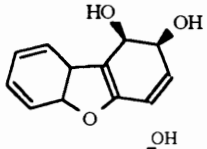
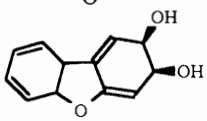
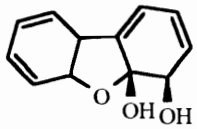
Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
86 $C_9H_{12}O$			*P. putida* 39/D	1	112
87 $C_{10}H_7Cl$			soil bacteria	3	127
88 $C_{10}H_7Br$			*P. putida* NCIB 98/11	1	128
			*P. putida* NCIB 98/11	1	128
89 $C_{10}H_7Cl$			*P. desmolyticum* *Pseudomonas* sp. A3;C22	3	129,130
90 $C_{10}H_7Br$			*P. putida* NCIB 98/11	1	128
91 $C_{10}H_7O_3$			partially purified enzyme from *P. fluorescens*	2	131
	R = CO_2H				
92 $C_{10}H_8$			soil pseudomonads	3	132,133,134
			*P. putida* 119 *Pseudomonas* sp. NCIB9816	1	135,136,137

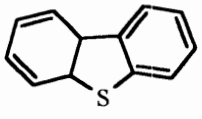
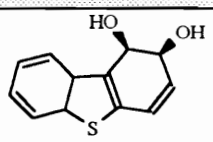
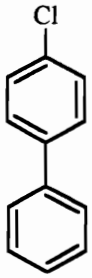
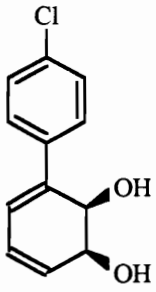
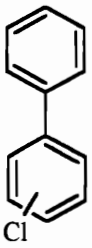
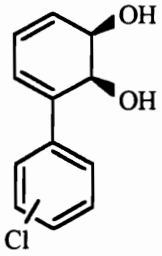
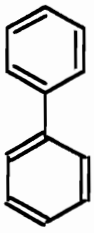
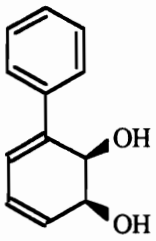
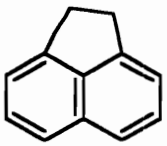
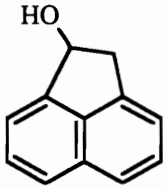
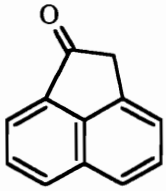
Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
			*Oscillatoria* sp. strain JCM	2	138,139
			*Oscillatoria* sp. strain JCM	2	138,139
			*Agmenellum quadruplaticum*	2	138,140
			*Agmenellum quadruplaticum*	2	138,140
			microbial populations from two Arkansas lake ecosystems	2	141
93 $C_{10}H_8ClN_3O$			unidentified	1	142
94 $C_{10}H_8O$			*P. testosteroni*	4	143
95 $C_{10}H_{10}$			*Pp* UV4		144
			*Pp* UV4		144

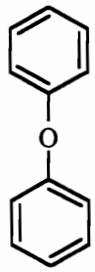
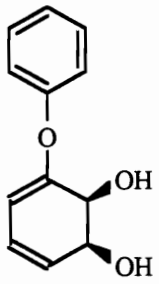
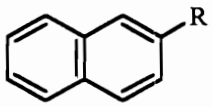
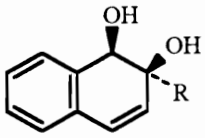
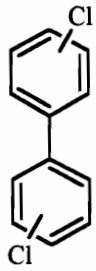
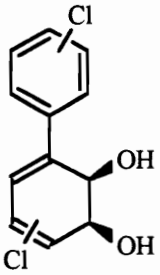
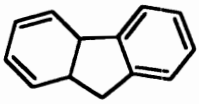
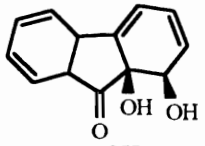
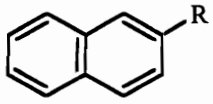
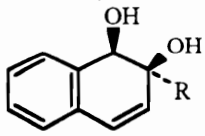
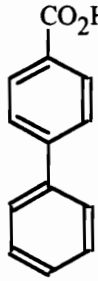
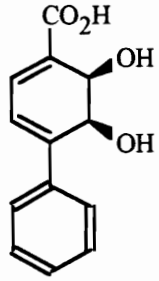
Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
96 $C_9H_8O_4$			*Micrococcus* sp. 12B *P. testosteroni*	4	108
97 $C_{10}H_{14}$			*P. desmolytica* *P. convexa*	2	126
98 $C_{10}H_{14}$			*P. putida* *P. acidovorans*	2	145
99 $C_{11}H_{16}$			*P. putida* PL-pT-11/43	3	81
100 $C_{10}H_{15}NO$			*P. putida* B1	4	145,146
101 $C_{10}H_8$			*Pp* 39/D	1	148
			*Pp* 39/D	1	148
			*Pp* 39/D	1	148

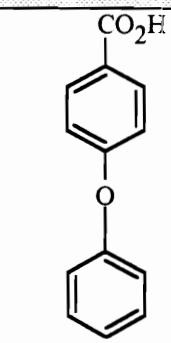
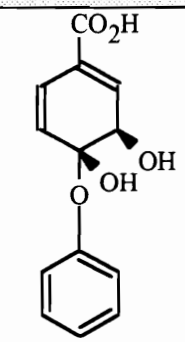
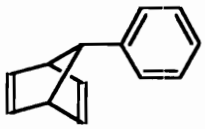
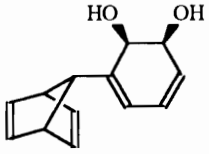
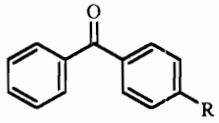
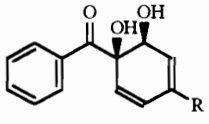
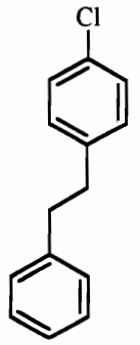
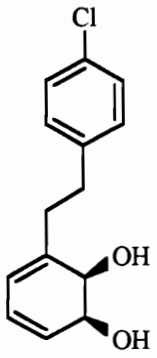
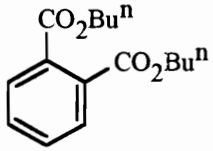
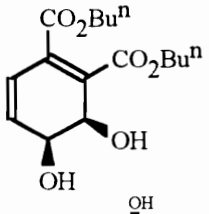
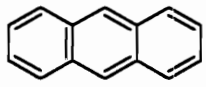
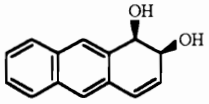
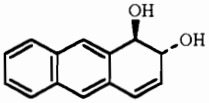
X = Y = Z = CH

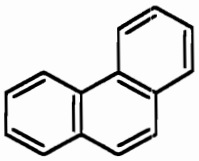
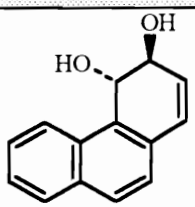
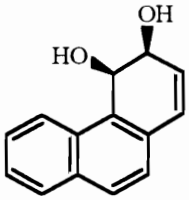
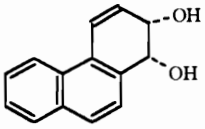
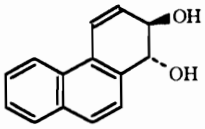
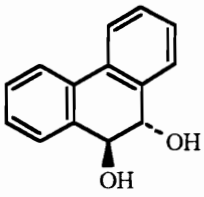
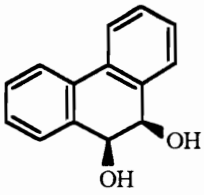
Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
	X = N; Y = Z = CH Y = N; X = Z = CH X = Y = N; Z = CH X = Z = N; Y = CH				
102 $C_{11}H_{14}O_2$			*P. putida* PL-pT-11/43	3	81
103 $C_{11}H_8O_2$			*P. testosteroni*	2	143
104 $C_{11}H_{10}$			soil bacteria	3	129
			*Pseudomonas* sp. A3;C22	4	130
105 $C_{11}H_{10}$			*Pp* BM2	1	101
			*Pp* BM2	1	101
106 $C_{11}H_{10}O$			*Pseudomonas* sp. A3;C22	4	130
107 $C_{11}H_{11}$			*Pp* UV4	1	144

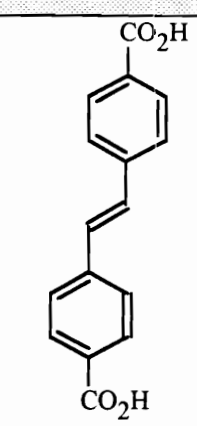
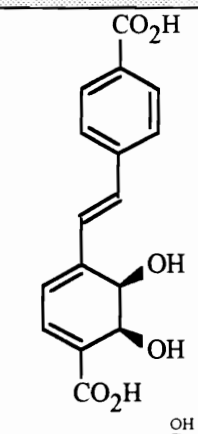
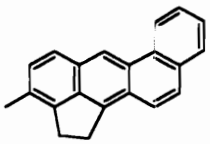
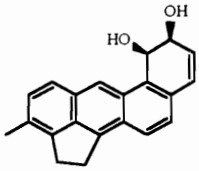
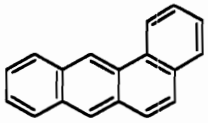
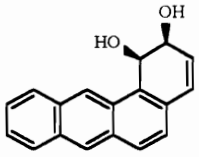
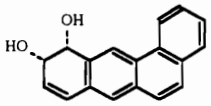
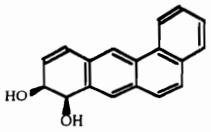
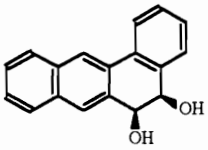
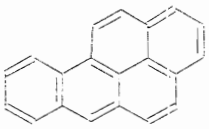
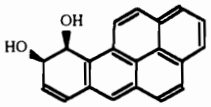
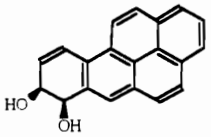
Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
			*Pp* UV4	1	144
108 $C_{11}H_{14}$			*P. putida* *P. acidovorans*	2	145
109 $C_{12}H_7ClO_2$			*Beijerinckia* B836	2	149
110 $C_{12}H_7ClO_2$			*Beijerinckia* B836	2	149
111 $C_{12}H_8$			*Beijerinckia* sp.	2	150
112 $C_{12}H_8O_2$			*Pseudomonas* NCIB 9816 *Beijerinckia* B836	1	149
112 cont'd			*Pseudomonas* sp. HH69	4	151
113 $C_{12}H_8O$			*Beijerinckia* B836	1	152
			*Beijerinckia* B836	2	152
			*Pseudomonas* sp. HH69	4	153

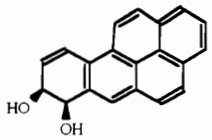
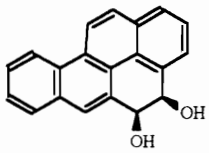
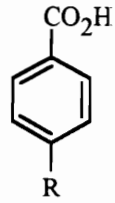
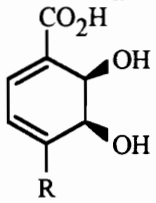
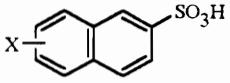
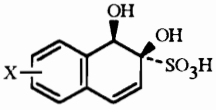
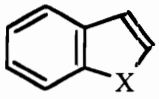
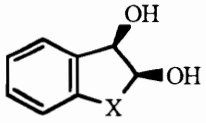
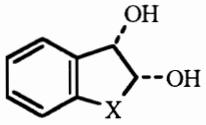
Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
114 $C_{12}H_8S$			*Beijerinckia* B836	1	154,155
115 $C_{12}H_9Cl$			*Pseudomonas* sp.	4	119
116 $C_{12}H_9Cl$			*Pp* F1		66
117 $C_{12}H_{10}$			*Beijerinckia* B836.	1	169,156,157
118 $C_{12}H_{10}$			*Beijerinckia* sp.	2	150
			*Beijerinckia* sp.	2	150

Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
119 $C_{12}H_{10}O$				1	158
120 $C_{12}H_{10}O$	 R = CO_2CH_3		*Pseudomonas* sp. A3; C22	1	105,130
121 $C_{12}H_xCl_n$			*Alicaligenes* sp. strain Y2	3	159
122 $C_{13}H_{10}$			*Brevibacterium* DPO 1361	1	160
123 $C_{13}H_{12}O$	 R = $CH_2CO_2CH_3$		*Pseudomonas* sp. A3; C22	1	130
124 $C_{13}H_{10}O_2$			unidentified		91

Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
125 $C_{13}H_{10}O_3$			*Pseudomonas* sp. POB 310	1	161
126 $C_{13}H_{12}$			*Pp* BM2	1	101
127 $C_{14}H_{10}O_3$	 R = CO_2H		*Pseudomonas* sp. HH69	2	162
128 $C_{14}H_{13}Cl$			*Pseudomonas* sp.	4	119
129 $C_{14}H_{22}O_4$			*Micrococcus* sp.	4	108
130 $C_{14}H_{10}$			*Flavobacterium*	3	131
			*P. putida* strain 119 *Beijerinckia* B8/36	1	163,164

Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
131 $C_{14}H_{10}$			*Flavobacterium*	3	165
			*P. putida* strain 119 *Beijerinckia* B8/36	1	163,166
			*P. putida* strain 119 *Beijerinckia* B8/36	1	163,166
			*Agamenellum quadruplicatum* PR-6	1	167
			*Agamenellum quadruplicatum* PR-6	1	167
			*Agamenellum quadruplicatum* PR-6	1	167

Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
132 $C_{16}H_{12}O_4$			*P. putida* PL-pT-11/43	3	81
133 $C_{21}H_{16}$			*Biejerinckia* sp.		119
134 $C_{18}H_{12}$			*Beijerinckia* B8/36	1	168,169
			*Beijerinckia* B8/36	1	168,169
			*Beijerinckia* B8/36	1	168,169
			*Beijerinckia* B8/36	1	168,169
135 $C_{21}H_{12}$			*Beijerinckia* B8/36	1	168
			*Beijerinckia* B8/36	1	168

Entry #	Substrate	Product(s)	Bacterium	Product Id. Method	Reference
135 cont'd			*Selenastrum capricornicum* (green algae)	2	170
			*Selenastrum capricornicum* (green algae)	2	170
136			*P. putida* PL-pT-11/43	3	81
	R = H; CH_3; C_2H_5; $^iC_3H_7$; $^tC_4H_9$; C_6H_5; $C_6H_5CH_2$; C_6H_5CO; C_2H_5O; C_3H_7O; $^nC_4H_9O$; Cl; Br; I; CH2Br; CF_3O				
137			*P. testosteroni*	4	130
			Pseudomonas sp. A3; C22; CN6; BN9		143
	X = 5-NH_2; 6-NH_2; 7-NH_2; 8-NH_2; 5-OH; 6-OH; 7-OH; 8-OH				
138			*Pp* UV4	1	171
			*Pp* UV4	1	171,172
	X = CH_2CH_2; OCH_2; SCH_2; CH_2; O; S; NH; CH=CH				

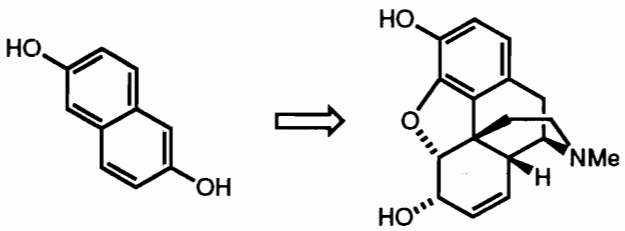
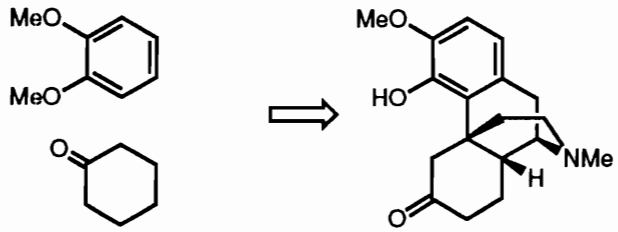
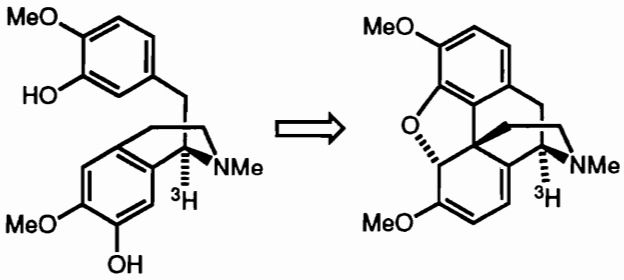
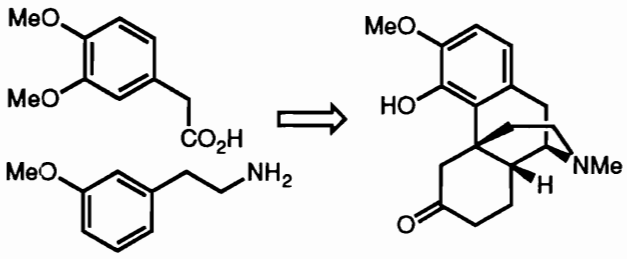
II. HISTORICAL

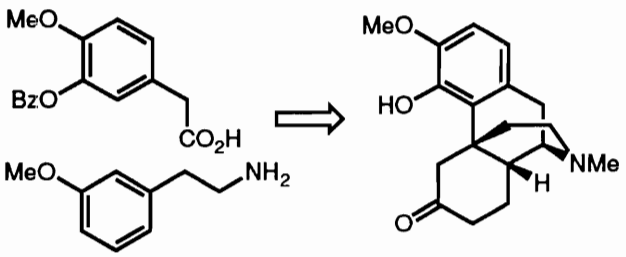
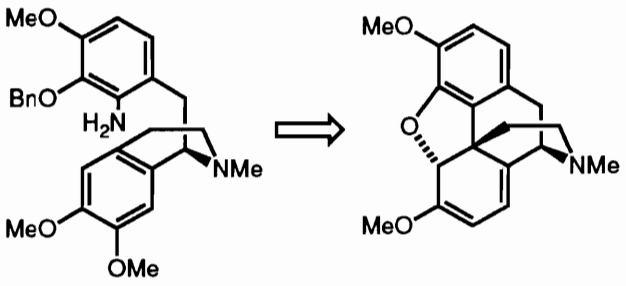
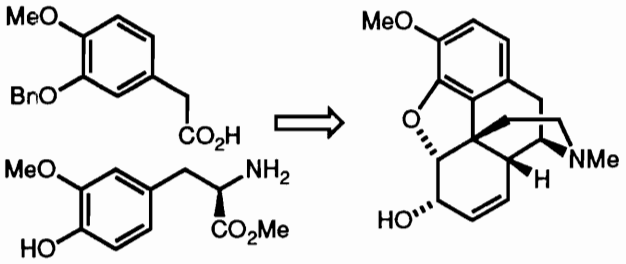
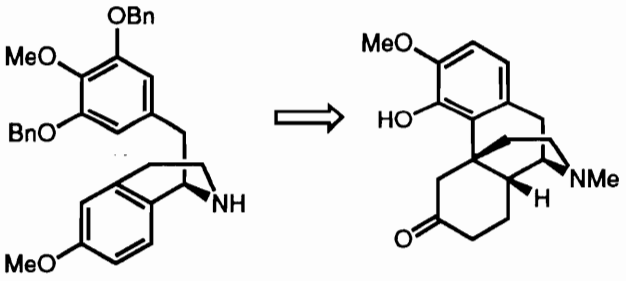
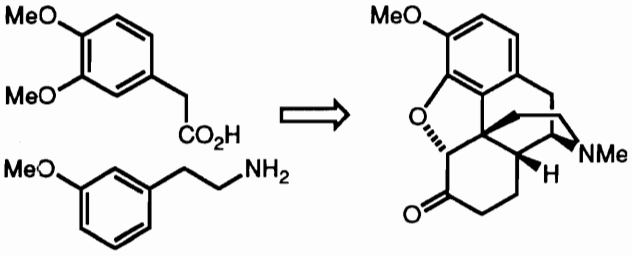
5. Review of Total and Formal Syntheses of Morphine

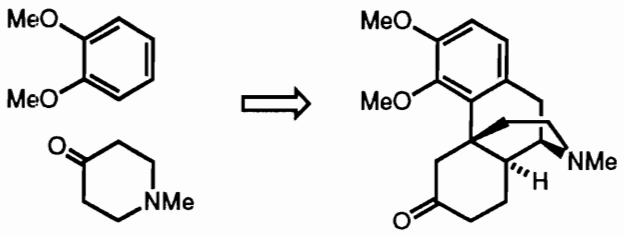
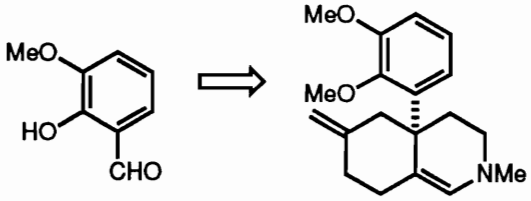
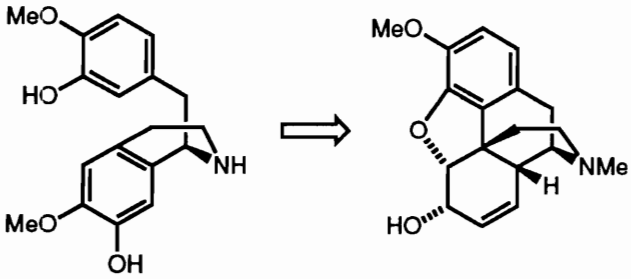
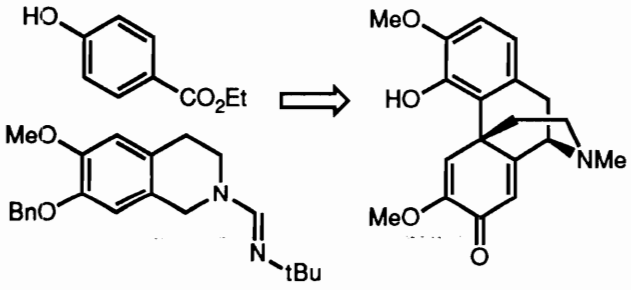
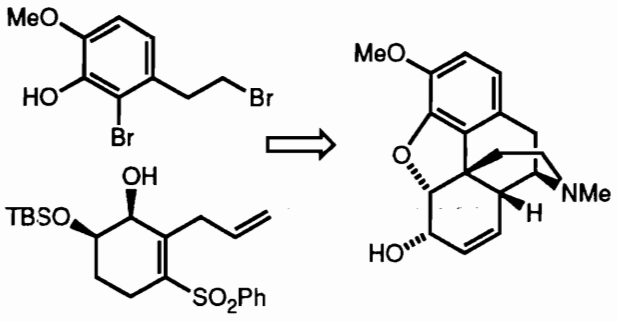
The following tables have been extracted from a forthcoming review in Studies in Natural Product Synthesis. Table IV presents a concise view of the total syntheses of morphine from the landmark synthesis of Gates[2] to the latest approach in 1993 by Overman.[3] For our purposes, a total synthesis included the synthesis of a naturally occuring alkaloid containing the complete stereochemically correct morphine azaskeleton - either morphine itself or another opiate which has been converted to morphine by well documented procedures, such as codeine, thebaine or neopinone. The synthesis of naturally occurring morphinans without the C_4-C_5 ether bridge were considered as well as compounds which intercepted an intermediate utilized in a previous total or formal synthesis.

The Table V in this section outlines the approaches to the ring systems of morphine. This synopsis is included so that one may understand the difficulties which have been encountered by several chemists in their quest for a synthesis of this desirable alkaloid.

Table IV. Summary of Reported "Total" Syntheses

Author Year	Starting Materials/Final Product	Steps; Yield(%)
Gates 1952 Ref 2		29; 0.00112%
Ginsburg 1954 Ref 173		22; 0.0137%
Barton 1963 Ref 174		3; < 0.012% by radio- dilution
Morrison, Waite & Shavel 1967 Ref 175		6; 3% (for cycliza- tion step)

Grewe 1967 Ref 176		6; 3% (for cycliza- tion step)
Kametani 1969 Ref 177		3; 2.8×10^{-5}
Schwartz 1975 Ref 178		4; 7.6%
Beyerman 1979 Ref 179		5; 28.3%
Rice **1980** **Ref 180**		**9;** **29%**

Evans 1982 Ref 181		11; 17.5%
Rapoport 1983 Ref 182		18; 1.13%
White 1983 Ref 183		6; 2%
Schäfer 1986 Ref 184		15; 3.0%
Fuchs 1987 Ref 185		16; 3.29%

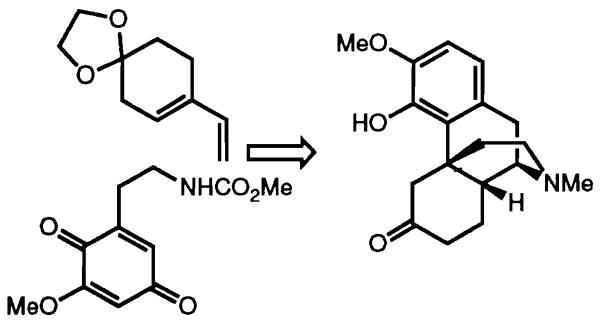
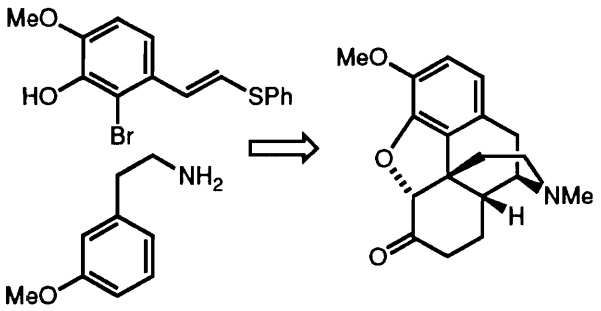
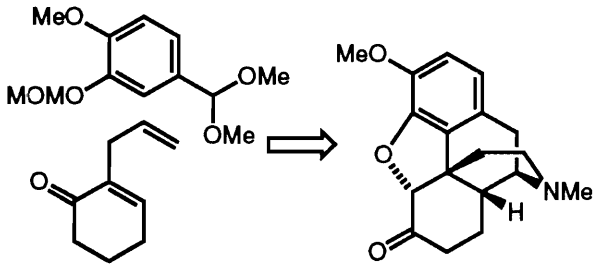
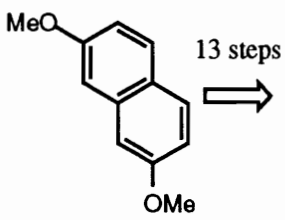
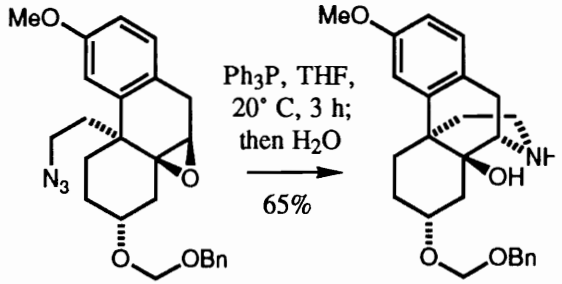
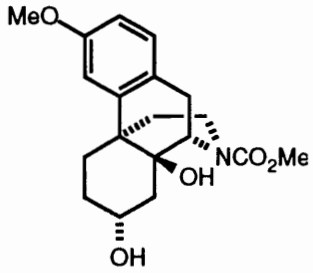
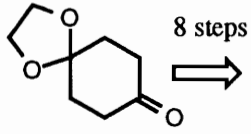
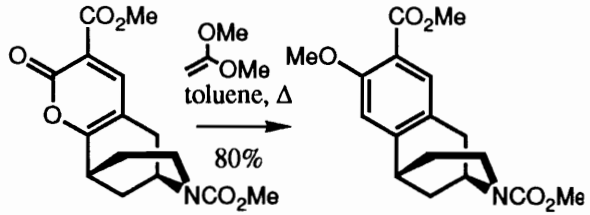
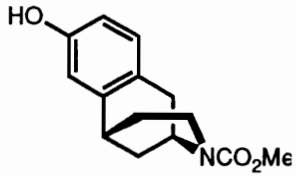
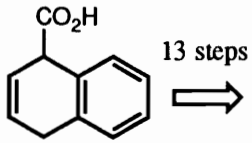
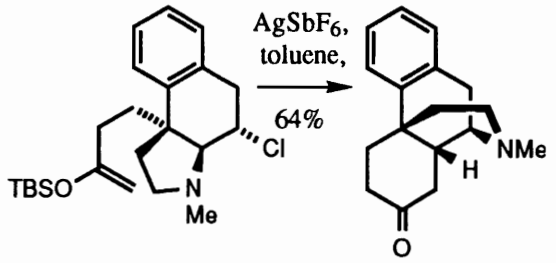
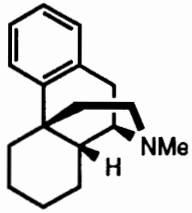
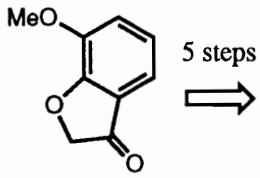
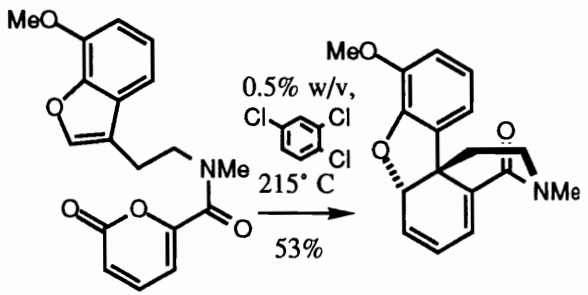
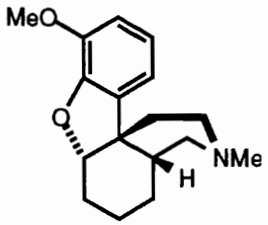
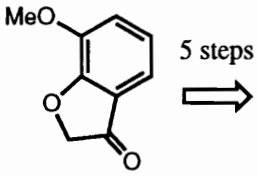
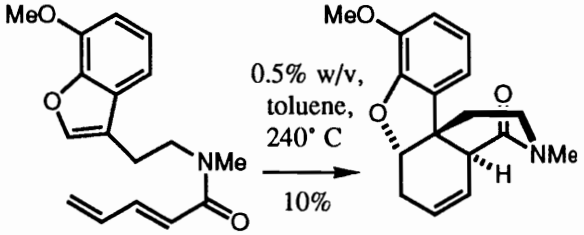
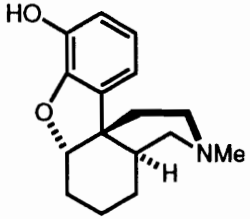
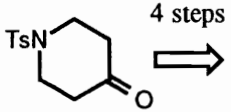
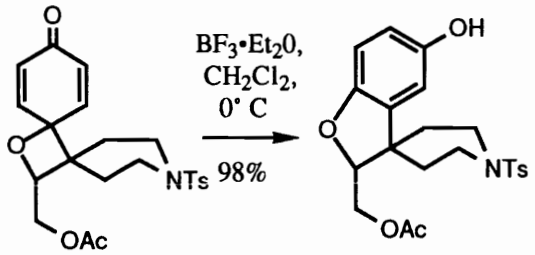
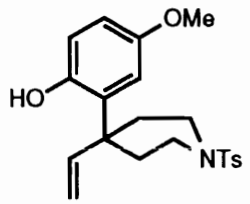
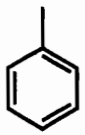
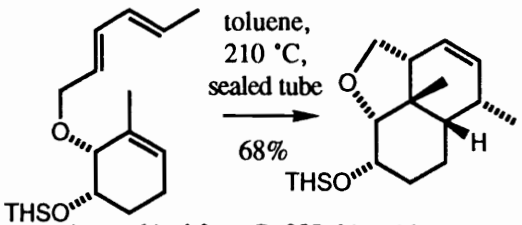
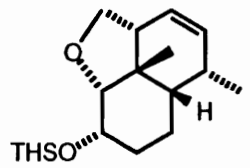
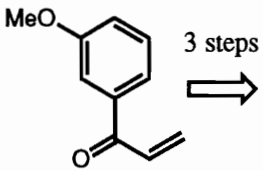
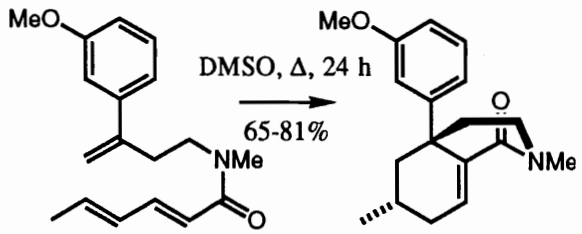
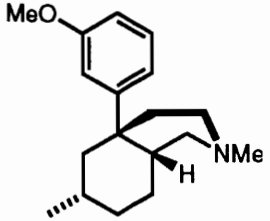
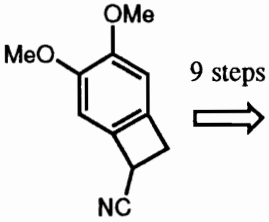
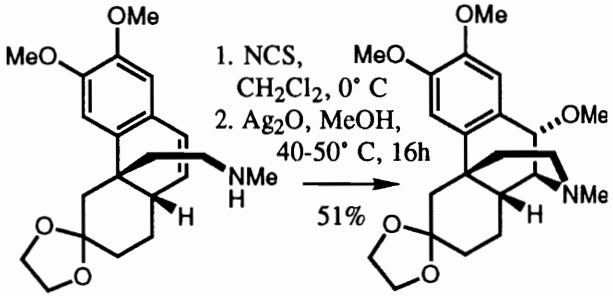
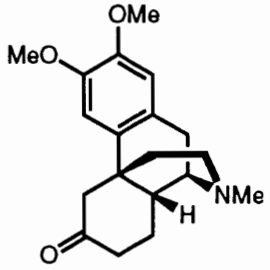
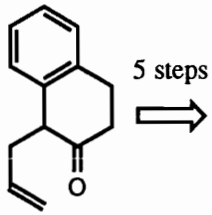
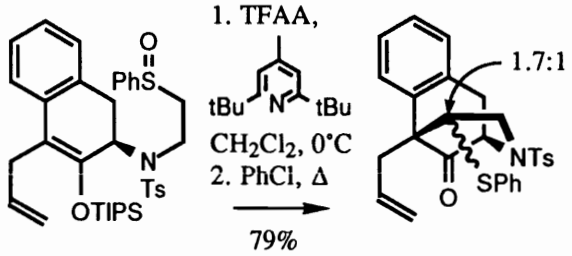
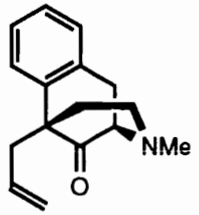
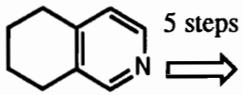
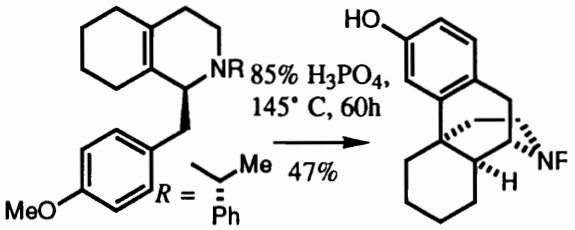
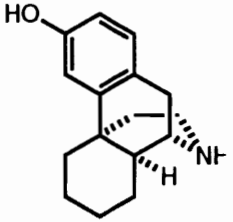
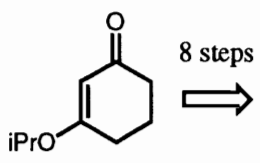
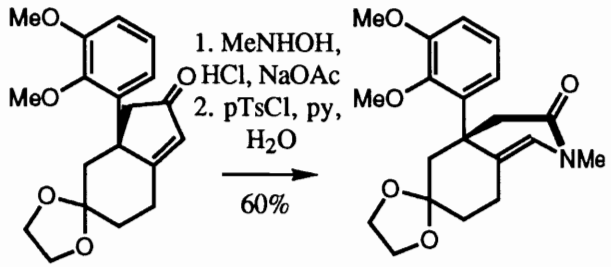
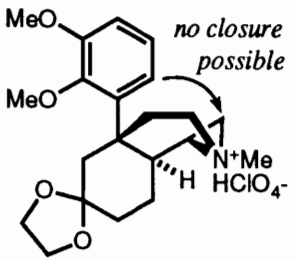
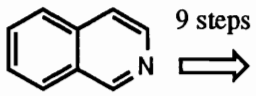
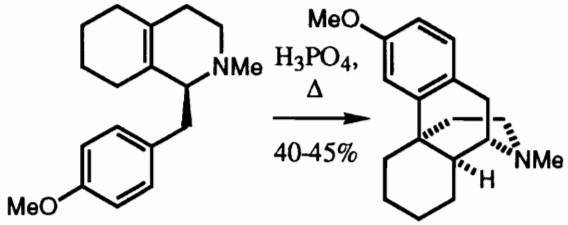
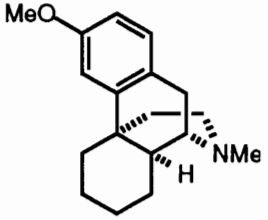
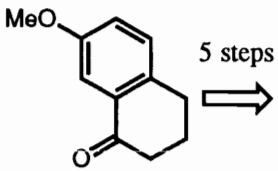
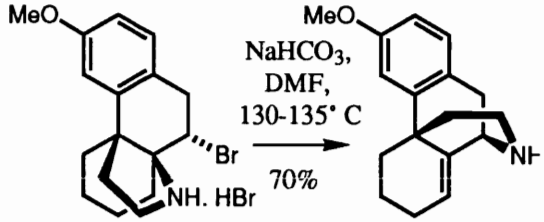
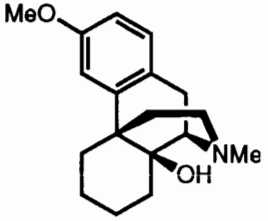
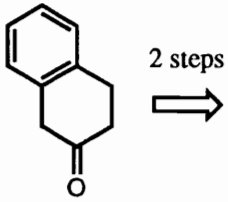
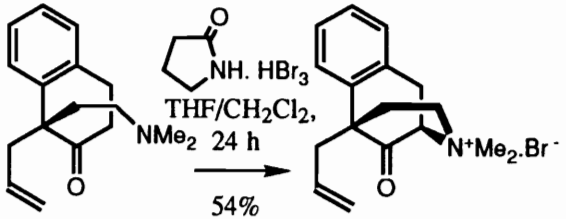
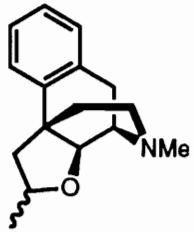
Tius 1992 Ref 186		18; 2.66%
Parker 1993 Ref 4		13; 9.42%
Overman 1993 Ref 3		14; 6.47%

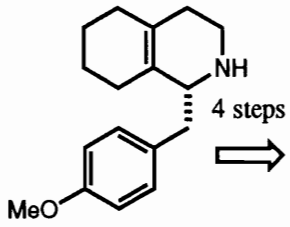
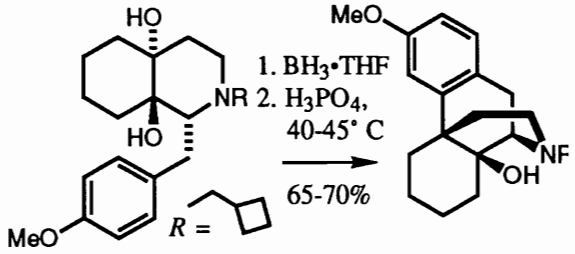
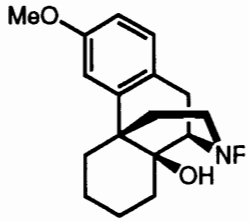
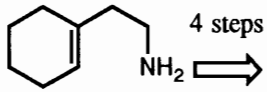
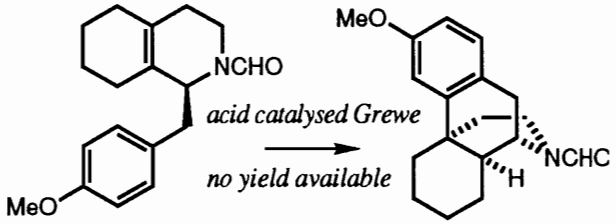
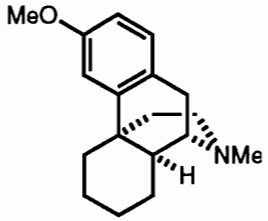
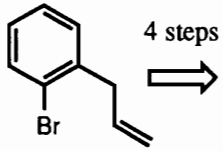
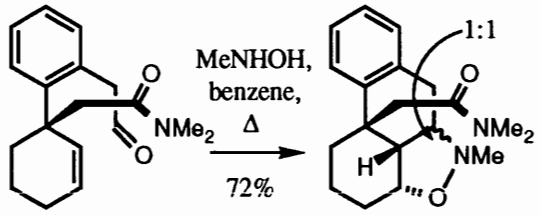
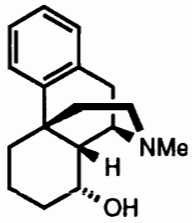
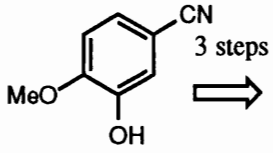
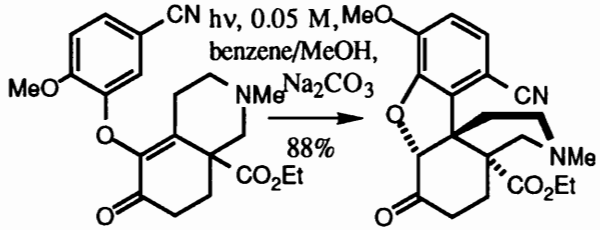
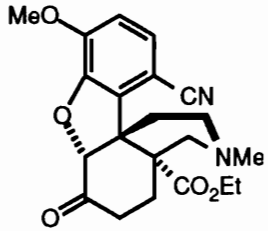
Table V. Synopsis of Approaches to the Ring Systems of Morphine

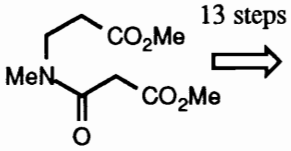
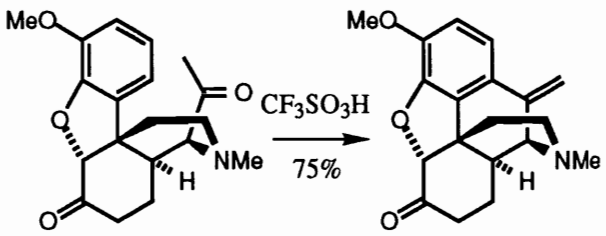
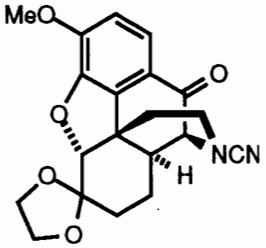
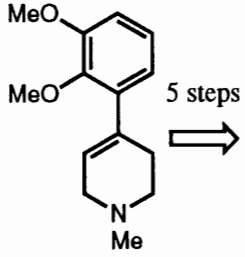
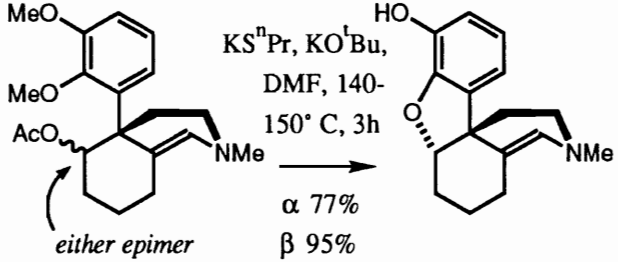
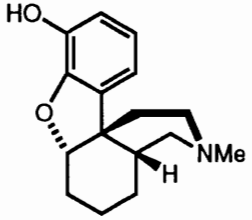
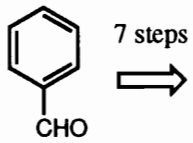
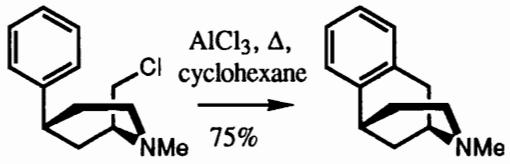
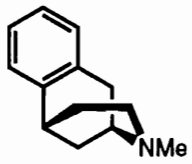
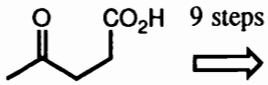
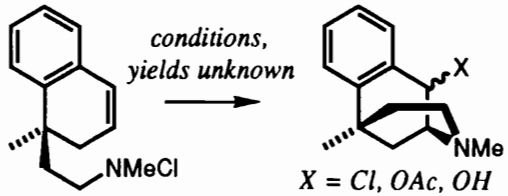
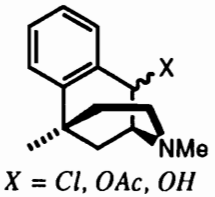
Author/Date	Starting Material	Key Step	Final Product
d'Angelo, 1990 Ref 187		 *>95% e.e. from chiral Robinson*	
Boger, 1982 Ref 188			
Broka, 1988 Ref 189			

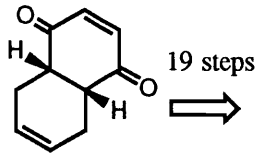
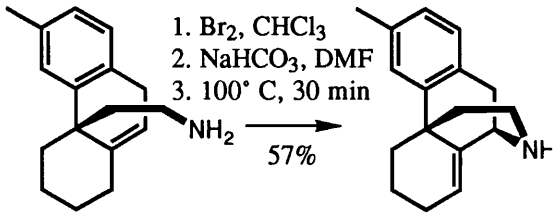
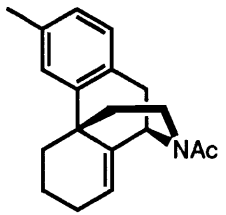
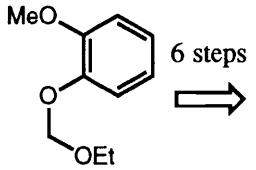
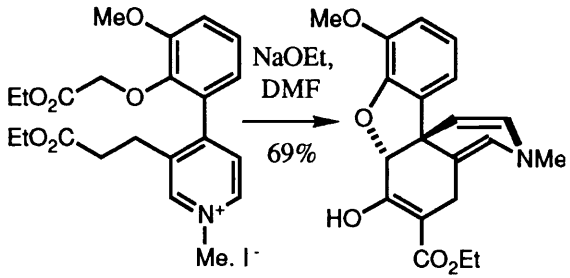
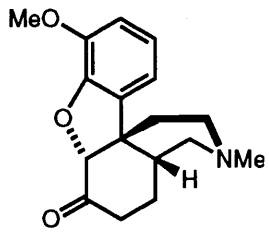
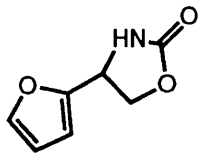
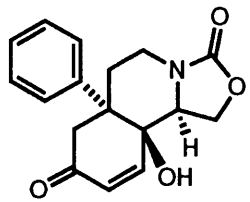
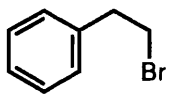
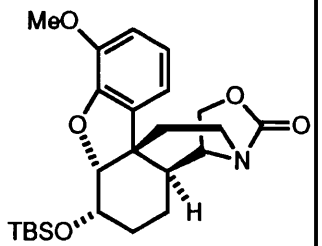
Ciganek, 1981 Ref 190,191	 5 steps	 0.5% w/v, 215° C 53%	
Ciganek, 1981 Ref 190,191	 5 steps	 0.5% w/v, toluene, 240° C 10%	
Ciufolini, 1993 Ref 192	 4 steps	 $BF_3 \cdot Et_2O$, CH_2Cl_2, 0° C 98%	
Hudlicky, 1992 Ref 193	 4 steps	 toluene, 210 °C, sealed tube 68% *homochiral from Pp39D biooxidation*	

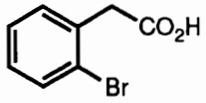
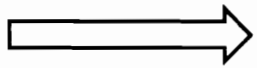
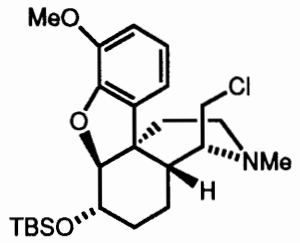
Jones, 1985 Ref 194			
Kametani, 1986 Ref 195			
Magnus, 1991 Ref 196			
Marazano, 1993 Ref 197			

McMurry, 1984 Ref 198			
Meyers, 1986 Ref 199		 *99% e.e. from chiral formamidine*	
Monkovi´c, 1973 Ref 200			
Monkovi´c, 1975 Ref 201			

Monkovi´c, 1978 Ref 202			
Noyori, 1987 Ref 203		 97% e.e. *(from chiral hydrogenation)*	
Parsons, 1984 Ref 204			
Schultz, 1976 Ref 205			

Schultz, 1985 Ref 206			
Shenvi, 1984 Ref 207			
Stella, 1977 Ref 208			
Stella, 1983 Ref 209			

Tius, 1986 Ref 210			
Weller, 1983 Ref 211			
Hudlicky 1992 Ref 212		Several steps	
Hudlicky 1993 Ref 212		Several steps	

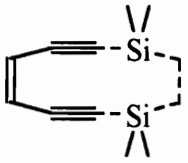
Hudlicky 1994 Ref 212		Several steps 	

III. DISCUSSION

1. Introduction

The intriguing nature of the Bergman cyclization prompted the application of this cycloaromatization reaction in the present work towards a synthesis of morphine. In recent years, with the exception of the work of Grissom, focus in this area has been on the synthesis of enediyne containing compounds such as dyneamicin, espearamicin and calicheamicin rather than in the use of this diradical reaction as a instrument for the formation of compounds containing aromatic rings.

In general, the majority of the bis-alkyne portions of a typical enediyne antibiotic are linked in a stepwise fashion rather than through the connection of the strained nine or ten membered ring in one step. Described in the following sections is the synthesis and cyclization studies of the key macrocycle **4** which was prepared after modification of Nicolaou's pathway for the formation of a similar carbocyclic compound, cyclodeca-3-ene-1,5-diyne **76**.



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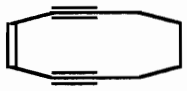
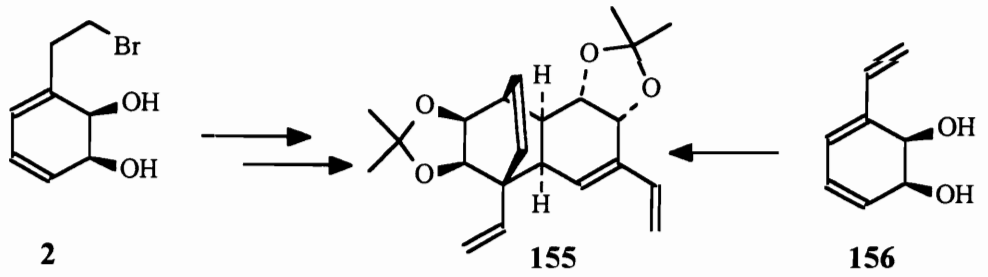


76

Concurrent with the synthetic studies towards silicon containing macrocyclic enediyne **4**, a well known procedure for the biooxidation of aromatic compounds was carried out to obtain compound **2**, required for the envisioned convergent synthesis of

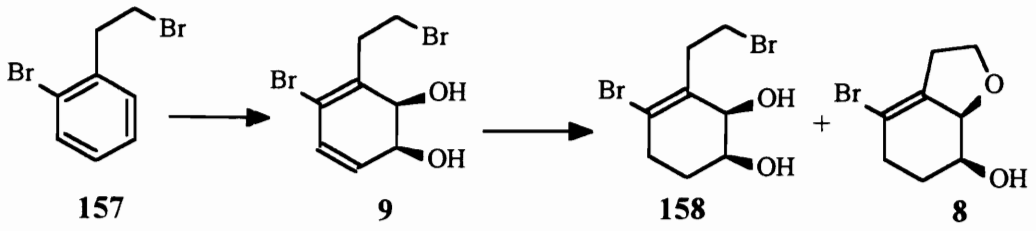
morphine. Conversion of the readily available (2-bromoethyl)benzene produced the expected cis-diene diol **2** which was isolated as a rather unstable white solid. A transformation of **2** to **155** proved the absolute configuration as shown.



2 **155** **156**

Figure 2. Convergent Synthesis for Proof of Absolute Stereochemistry

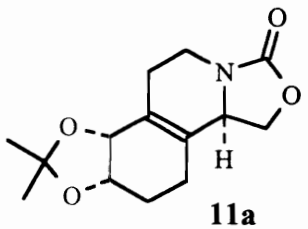
When it became clear that the Bergman radical cyclization approach to morphine proved unsuccessful, a second-generation pathway was pursued. For the second-generation attempt, a new substrate, **157**, prepared from 2-bromophenylacetic acid was exposed to *Pseudomonas putida*. Since di-substituted compounds are generally poor substrates for the microorganism, low yields of product were expected. Indeed, the yield using *Pp* 39/D was poor, but use of Gibson's genetically engineered strain of *E. coli* (JM109) fashioned a workable yield of the desired chiral synthon **9**.



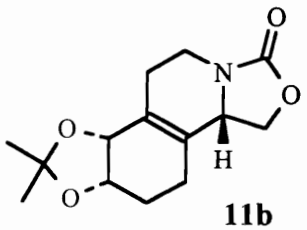
157 **9** **158** **8**

Scheme 32

This second generation synthesis involved the conversion of the new diol in four steps to a separable mixture of isomeric isoquinolines **11a** and **11b**. The key step in



11a



11b

this pathway necessitated a stepwise vinyl radical cyclization rather than the initial aryl radical cascade as was originally envisioned. The major isoquinoline product has been used in our group towards the synthesis of unnatural morphine, while the minor product could be converted, using the same methodology from the isomeric series, to natural morphine.

After the discussion of the synthesis of the key starting compounds for the first generation synthesis of morphine, the remarkable and stereocontrolled synthesis of the key isoquinoline for use in the second generation morphine synthesis will be presented.

III. DISCUSSION

2. Isolation, Structure and Absolute Stereochemical Determination of (1*S*,2*R*)-3-(2-bromoethyl)cyclohexa-3,5-diene-1,2-diol

For the preparation of **2**, the first component necessary for the radical cascade, the powerful technology using enzymes was employed. In recent years, use of enzymes in organic synthesis has exploded as evidenced by several reviews on applications of

enzymes in synthesis.[213] Within the past few years, the use of microorganisms producing a dioxygenase enzyme has been exploited to provide for the preparation of multigram quantities of chiral starting material, now commercially available.[214]

In general, the microbial oxidation process consists of two phases: induction and production. The induction process causes the microorganism, *Pseudomonas putida* 39/D (*Pp* 39/D), to produce the operant enzyme, toluene dioxygenase, when exposed to a small amount of an aromatic compound. Several known inducers include: toluene, chlorobenzene, bromobenzene, indole, and styrene. Whether or not a new substrate will induce toluene dioxygenase production can be determined by use of a color test in which indigo is produced.[215] Figure 3 details the reaction pathway by which the dye is formed when the bacteria grows in the presence of indole or another inducer of the enzyme.

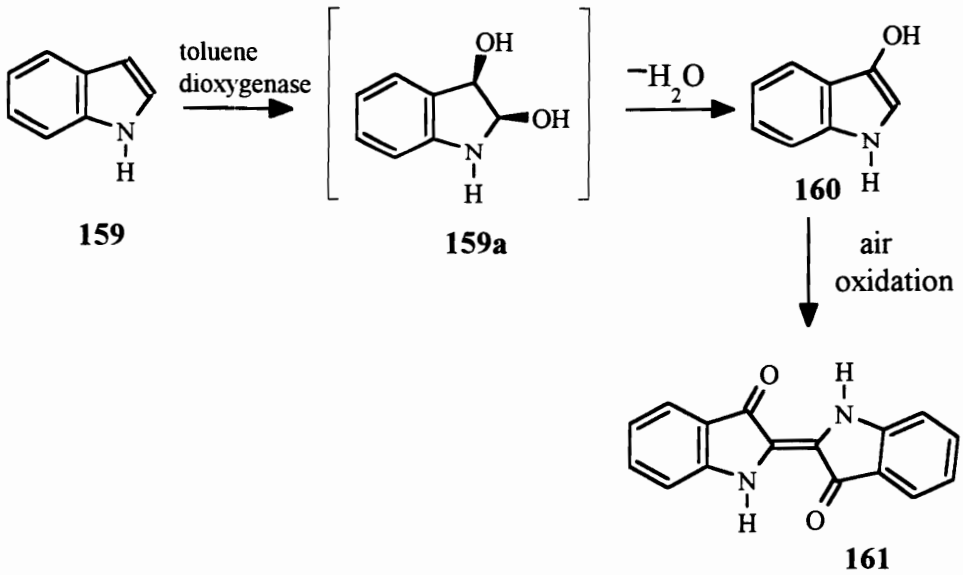
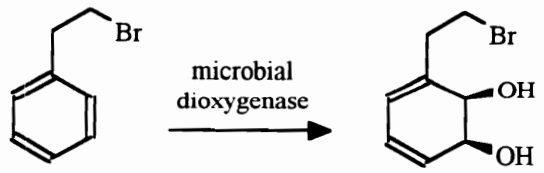


Figure 3. Formation of Indigo from Indole

To determine whether or not (2-bromoethyl)benzene would induce the operant enzyme, the substrate was analyzed by an indigo test. For the indigo test, a plate of agar was streaked with *Pseudomonas putida* 39/D and incubated in the presence of a small vial containing the bromoethyl benzene to allow the vapors of the compound to saturate the plate. After twenty four hours, single colonies of cells had grown and the plate was removed from the incubator. The vial of substrate was replaced with several crystals of indole. Within thirty minutes, the cells appeared blue in color, indicative of indigo formation and affirmed that (2-bromoethyl) benzene was an inducer of the dioxygenase enzyme.

The toluene dioxygenase mediated dihydroxylation of (2-bromoethyl)benzene accomplished with *Pp* 39/D in a 2 L scale reactor according to a previously established protocol,[216] afforded the bromoethyl benzene cis-dihydrodiol **2** as the sole product in a



2

yield of 200 mg/L of culture. The isolated crystalline diol was dried under vacuum at ambient temperature to obtain an accurate yield. Five hours later, a black oil appeared in place of the white crystals in the flask. Analysis of the oil showed the presence of phenolic decomposition products. It was quickly noted that the diene diol could be handled as a solid for only short periods of time at ambient temperature.

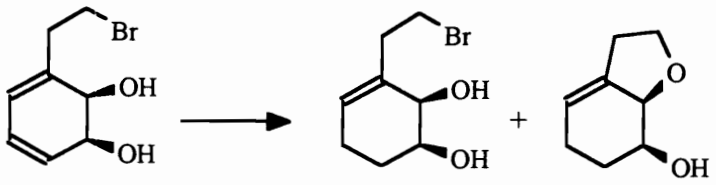
When the biotransformation was run again, Gibson's genetically engineered organism, *E. coli* JM109 p(DTG601)[217] was used and the yield increased drastically to 5 g/L, thereby providing approximately 30g of product. The high yield occurs since the experimental conditions of growth, induction and substrate addition for JM109 differ from those used for *Pp* 39/D. Typical growth conditions for the *Pp* 39/D do not require external feeding after the initial sugar supply has been depleted. With *the E. coli* system, once the microorganisms have consumed the initial supply of the carbon source, the cells are then grown under "glucose limited feeding conditions." (These conditions were developed at the laboratories of Genencor International Inc.) In other words, the culture is provided with a predetermined amount of glucose to force the colonies to continue dividing without arriving at a resting state. Such continued growth allows for a greater number of colonies in the medium. In general, the number of colonies can be measured by the optical density of the cells $(O.D.)_{660}$. Cultures of JM109 grown in this manner give typical O.D. values of 70, while Pp 39/D cultures only have a maximum cell density of 5. Thus, a greater number of cells corresponds to a higher production capacity and increased yield.

The induction process for the *Pseudomonas* occurs continuously, as a stream of the aromatic substrate vapors are bubbled into the media from six hours after the start of the reaction until the cells die. The sugar, isopropyl-β-thio-D-galactoside (IPTG) induces the production of the toluene dioxygenase enzyme and this induction occurs at one time, when the absorbance of the culture has reached approximately 20.

Again, with the *Pp* 39/D the substrate is continuously introduced into the fermentor over the typical 30 hour reaction time. Substrate is only introduced to the reaction within the last 2-3 hours of the fermentation in the case where the genetically engineered microorganism is employed. All of these conditions influence the JM109 to afford higher yields of diene diols.

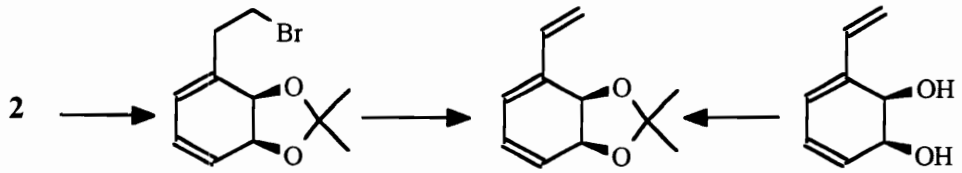
The crude 30g of diene diol from the JM109 fermentation was recrystallized from methylene chloride/hexanes even though it had a fleeting stability at ambient temperature. Drying of the product for only twenty minutes after purification and immediate storage thereafter at -78 °C may account for a slight deviation in the actual yield. To ensure its stability, the diol in pure form can be stored for long periods of time at -78 °C. In slightly acidic solution, the diol survives for a short period of time considering that the half-life of the diene diol in deuterated chloroform was 5 days.

For characterization purposes, the diene diol was reduced with diimide, which afforded in a 10:1 ratio the desired cyclohexenediol **162** and the benzofuran derivative 7, resulting from an intramolecular S_N2 alkylation during the diimide reduction. The reduced diol **162**, after two recrystallizations from methylene chloride/hexanes was stable as a white solid for an indefinite time at ambient temperature.



2 **162** **7**

We hoped to prove the stereochemistry of **2** by conversion to **164**, the metabolite from styrene, whose absolute stereochemistry was proven in the total synthesis of Zeylena.[70b] Protection of **2** as an acetonide gave **163** which was dehydrohalogenated to afford the known styrene diol derivative **164**.



163 **164** **156**

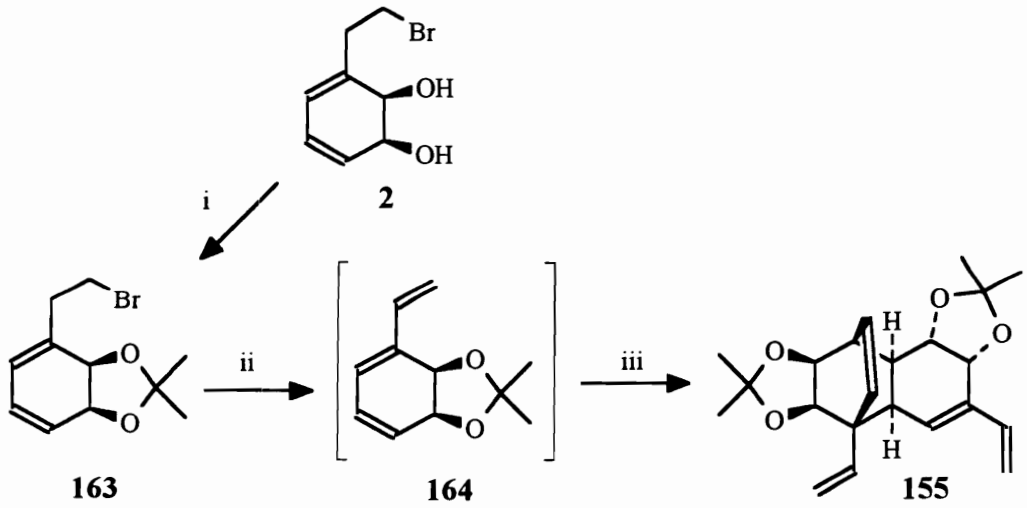
Scheme 33

Analysis of the acetonide **164** gave a rotation value of -78.0. In order to determine the absolute stereochemistry of **2**, comparison of the observed rotation value with a literature value or comparison with an authentic sample was necessary. Since the diol derived from styrene (**156**) was readily available, a sample was quickly protected with 2,2-dimethoxypropane in methylene chloride with a catalytic amount of *p*-toluene sulfonic acid. Isolation of the acetonide **164** followed by purification and analysis revealed a vast difference in the magnitude of the rotation values.

Curiously, although the sample of **164** had appeared pure by ^{1}H NMR, analysis of the compound by thin layer chromatography (TLC) after obtaining the puzzling rotation value, showed that the compound was contaminated by dimerization products such as **155**. Such dimerization products had been previously described by C.H. Boros.[218]

For additional evidence of this phenomenon, Dr. Seoane's notebook was perused as he had worked with compound **164** in question. Reading the notebook page concerning characterization of **164**, the clarification was scrawled in small print. "Unable to obtain accurate $[\alpha]_D$ because of polymerization of sample."

Thus, although **164** could be isolated, correlation of absolute stereochemistry and establishment of optical purity proved difficult because of the commencement of dimerization and contamination of the sample with the known dimer **155**. As the absolute stereochemical configuration of **155** is known, we then decided to fully convert the styrene derivative to the dimer for evaluation of optical purity as well as correlation of absolute stereochemistry.



i. 2,2-dimethoxypropane, acetone, pTsOH, ii. DBU, benzene, reflux 5 hr., iii. neat, RT, 2-3 weeks

Scheme 34

After elimination of the bromide from **163** with DBU in benzene at reflux, the crude product was allowed to stand neat at room temperature for 5 days to fully dimerize.

Although traces of dimer **155** were present as soon as styrene acetonide **164** was isolated, additional reaction time was necessary to afford a 40% conversion of the starting material to the desired product. The dimer, isolated according to the published method, had an $[\alpha]_D^{25}$ of +71 (c = 0.41, $CHCl_3$). When compared to the literature value ($[\alpha]_D^{25}$ = +73.8, c = 0.81, $CHCl_3$) the optical purity of the diol corresponds to 96%.

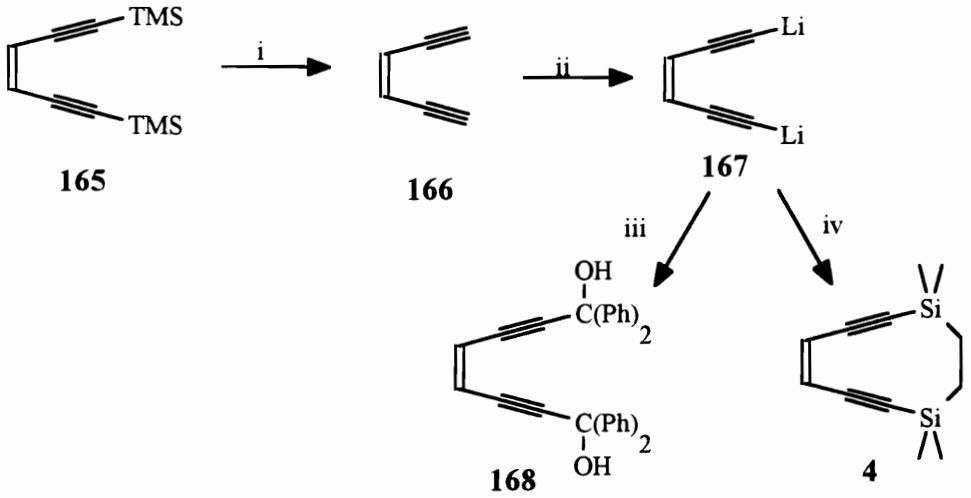
Now that the chiral component for the morphine synthesis had been prepared, investigation regarding the synthesis of the key enediyne moiety began. The synthetic trials are presented in the next section.

III. DISCUSSION

3. Synthesis of 1,1,8,8-tetramethyl-1,8-disilacyclodec-2,6-diyne-4-ene

After the successful preparation and characterization of the cis-diene diol, the synthesis of **4** was approached with eagerness. The initial idea for the synthesis of 1,1,8,8-tetramethyl-1,8-disilacyclodec-2,6-diyne-4-ene involved the use of Vollhardt's method of stereospecific coupling[219] to form the bis acetylinic portion of the

compound. Indeed, reaction of trimethylsilyl acetylene and cis-dichloroethylene in benzene with a catalytic amount of tetrakis triphenylphosphine palladium(0), copper iodide and n-butyl amine afforded the TMS protected enediyne **165**. Desilylation was



i. LiOH, THF/H_2O; ii. BuLi; iii. benzophenone; iv. bis(chlorodimethylsilyl)ethane

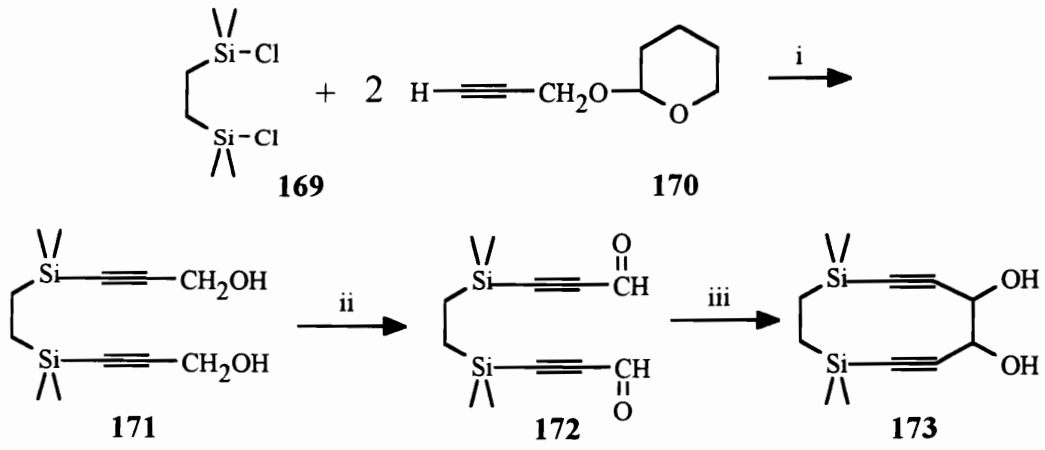
Scheme 35

achieved according to Danishefsky's protocol[220] via lithium hydroxide in a tetrahydrofuran (THF)/water mixture. The resulting enediyne **166** was difficult to handle and only stable in solution at -30°C. Generation of the alkynyl dianion **167** with butyl lithium followed by alkylation with bis(chlorodimethylsilyl)ethane did not appear to work upon the first and second attempt at the reaction. Thus, in order to prove that

the dianion had indeed formed upon addition of base, a literature compound[220] **168** was prepared.

Addition of benzophenone to the dilithioenediyne with standard work up procedures afforded **168**. Once again, the reaction was attempted with addition of the silyl substrate and a tantalizing 1 mg of product was obtained. However, at that point in time, this synthetic pathway was abandoned due to the poor yield of the reaction as well as the instability of enediyne **166**.

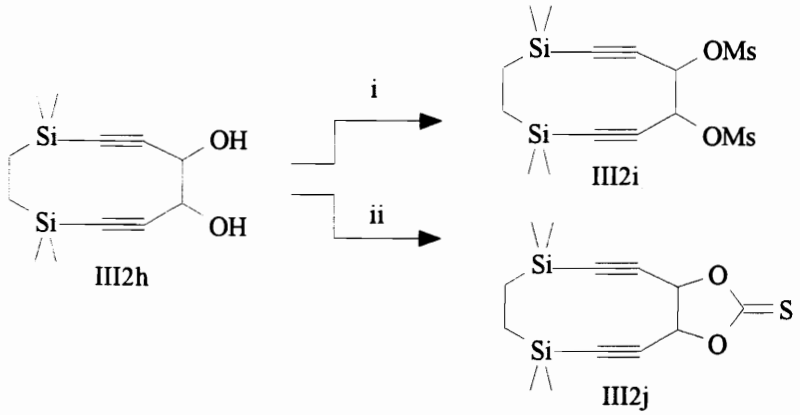
The second pathway involved a different method for the formation of the ten membered ring. Beginning with the known dialdehyde **172**,[221] a samarium diiodide pinnacol type coupling[222] was employed to obtain the closed skeletal ring of the macrocycle and form **173**.



i. EtBr, Mg; ii. Jones; iii. SmI_2

Scheme 36

The next step involved elimination of the diol **171** to form the alkene. One of the elimination sequences involved protection **173** as mesylate **174** and elimination induced with sodium naphthalenide.[223] The second sequence shown in scheme 37



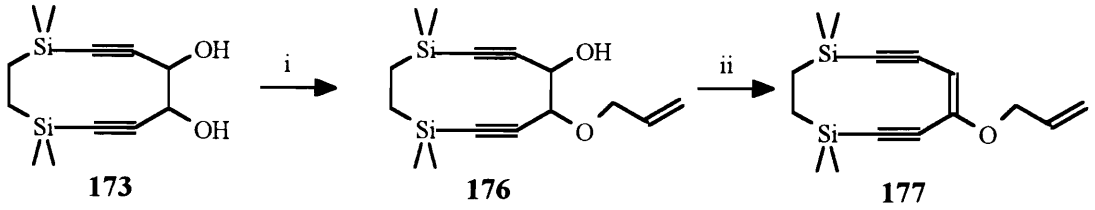
i. MsCl, DMAP; ii. thiophosgene, DMAP

Scheme 37

relied on a Corey-Winter elimination which had shown some success to Semmelhack[48] in his synthesis of an analogue of the carbocyclic form of the enediyne **76**. After protection of diol **173** as the thionocarbonate **175**, elimination was attempted with 1,3-dimethyl-2-phenyl-1,3-diaza-2-phospholidine as this reagent was commercially available. Upon failure of this reaction, a more reactive phosphine, 1,2,3-trimethyl-1,3-diaza-2-phospholidine was synthesized,[224] and applied to thionocarbonate **175** in the

same manner. Again, none of these methods furnished a workable synthetic yield of the target enediyne **4**.

At this point, any form of an enediyne was desired. It was postulated that monoprotection of diol **173** followed by elimination of the free alcohol would yield a tethered type of enediyne. For this approach, the diol was protected using dibutyltin oxide[225] in refluxing benzene followed by refluxing of the "tin" acetonide in allyl bromide to afford **176**.



173 **176** **177**

i. Bu_2SnO, allyl bromide; ii. Tf_2O, CH_2Cl_2 then DBU, benzene

Scheme 38

Initial attempts at elimination were not fruitful when the remaining alcohol was converted to a mesylate. With the more reactive triflate, the elimination occurred smoothly to give **177** albeit in low yield. At last, an enediyne resembling the desired target had been prepared! Compound **177** was subjected to standard cyclization conditions (10 eq. 1,4-cyclohexadiene, deuterated benzene, heat) and monitored by ^1H NMR. After heating compound **177** for 15 minutes at 65 °C, no change was apparent. The temperature was increased by 15 degrees and new signals began to slowly appear in the spectrum. The starting material took 65 hours to react completely, but the

desired cyclization product(s) **179** and **180**, shown in Figure 4 were not apparent after first glance at the spectral data.

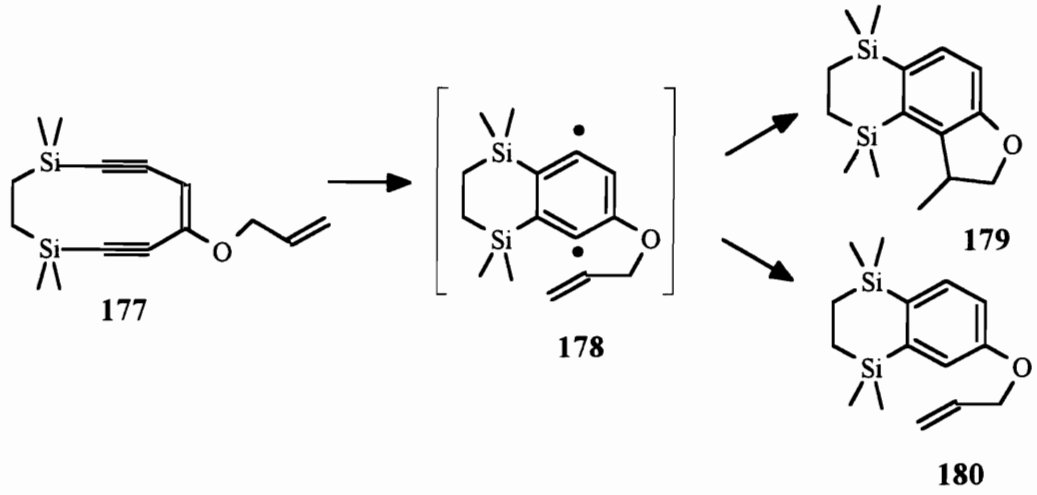
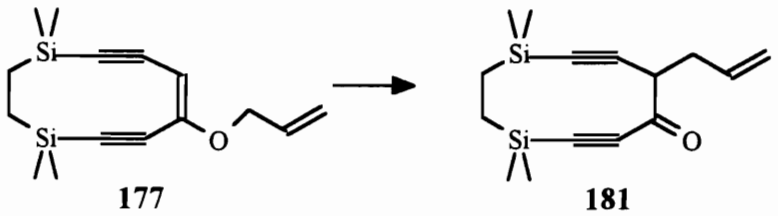


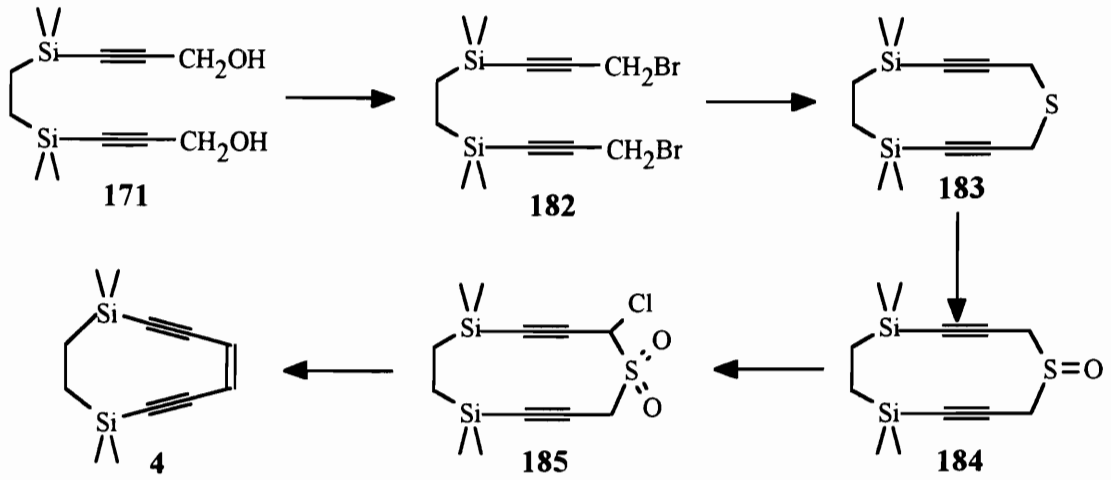
Figure 4. Expected Bergman Cyclization Products

Inspection of the spectral data showed a disappointing lack of proton signals in the aromatic region, and it was apparent the compound had not undergone Bergman cyclization. Instead, as discerned from further analysis, **177** had simply rearranged in a Claisen-type manner. The predicted cyclization temperature occurred in the range of 60-75 °C, where such rearrangements should not be a competing process. Now, synthesis of the target enediyne and its cyclization profile increased in importance.



Scheme 39

A final pathway which did allow isolation of a tangible amount of the desired compound was related to the glamorous pathway of Nicolaou.[46,47] To start, the known diol[221] **171** was brominated with carbon tetrabromide and triphenyl phosphine in methylene chloride to produce a colorless oil in excellent yield. Next, the dibromide



Scheme 40

182 was reacted under phase transfer catalyst conditions to produce the cyclic sulfide **183** in low yield. Oxidation of this rather unstable sulfide with m-chloroperoxybenzoic acid at -30°C followed by subsequent chlorination with sulfuryl chloride and oxidation again with mCPBA yielded the chlorosulfone **185** in a modest yield.

The crystalline sulfone **185** was subjected to methyl lithium at -78°C to effect a Ramberg-Backlund rearrangement. Analysis of the product by ^{1}H NMR was

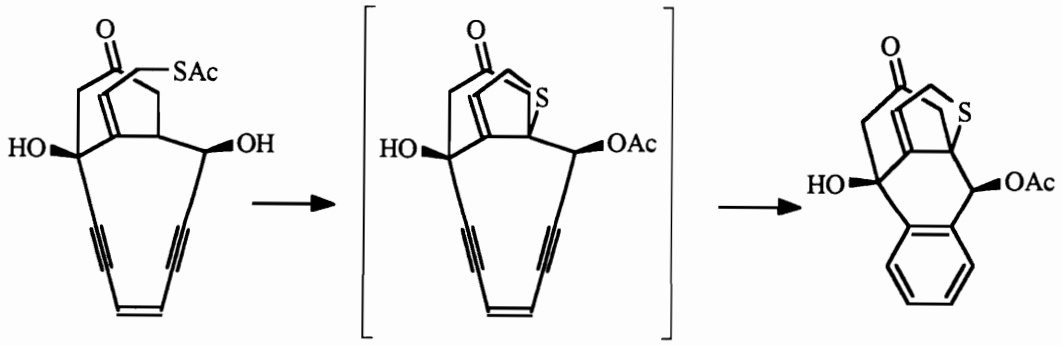
encouraging after noting the signals present at δ 6.01, 0.65 and 0.16. Each signal appeared as a singlet and the integration for 2, 4, and 12 protons respectively concurred with the number of protons in enediyne **o**. The typical shift for a vinyl proton in several enediyne compounds falls in the range from 5.6-6.2. In retrospect, the ^{1}H NMR spectrum matched that observed after isolation of enediyne **4** from the pathway outlined in Scheme 35. This evidence, and other spectral data showed that the enediyne **4** was obtained in an 18% yield and provided enough material to investigate the Bergman cyclization profile.

III. DISCUSSION

4. Cyclization Studies of 1,1,8,8-tetramethyl-1,8-disila-2,6-diyne-4-ene **4**

With the achieved synthesis of **4**, we were ready to test the viability of the compound for use as a "latent benzene reagent". Reaction conditions were chosen after screening several articles pertaining to Bergman cycloaromatization reactions.[226] The majority of enediyne model systems had been subjected to heat in the presence of the hydrogen atom donor, 1,4-cyclohexadiene (CHD), to effect formation of an aromatic adduct.

Some of the previously reported enediyne type compounds were functionalized with groups which could trigger a change in either hybridization or strain of the enediyne containing ring. For example, during the mechanistic studies of Calicheamicin and Esperamicin antibiotics, the enediyne **186**, in a solution of THF was treated with triethylamine in the presence of CHD. The compound was left at room temperature in the THF solution to cyclize. After fifteen hours, complete conversion of **186** to **188** occurred. It was proposed that the transformation involved acetyl migration from the sulfur to the neighboring hydroxyl group.[226a] The free thiolate anion could then undergo an intramolecular Michael type addition to the double bond and the strained ring would suffer spontaneous cycloaromatization.



186 **187** **188**

Figure 5. Bergman Cyclization Induction by Geometry Alteration

In a similar experiment,[226b] bicyclic compound **190** underwent reductive cycloaromatization at room temperature by reaction with sodium borohydride in methanol with CHD present to produce **191**. The enedione counterpart to **189** cyclized

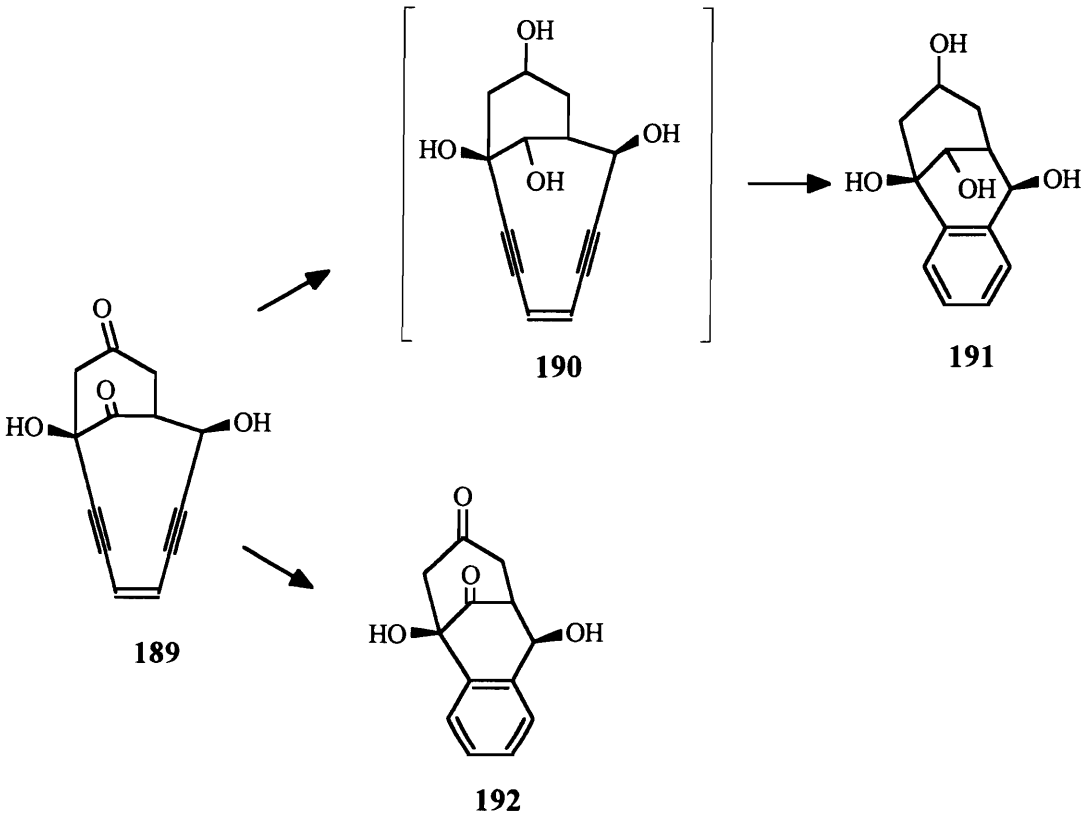


Figure 6. Bergman Cyclization Induced by Hybridization Change

under harsher conditions. Possibly, changing the geometry from trigonal to tetrahedral reduced the energy barrier necessary for the transformation.

Armed with this knowledge, the conditions to determine the cycloaromatization conditions for "latent benzene reagent" **4** were selected. Monitoring the reaction was simplified by using deuterated benzene as the solvent. Cycloaromatization reactions can be run in almost any solvent, but the boiling point of benzene was in the "predicted" cyclization range and allowed for easy evaporation at the end of the reaction. Also, since the "silicon" enediyne **4** did not posses any functionality which could aid the cyclization by way of ring strain or hybridization change, addition of triggering agents was deemed unnecessary.

After dissolving the silicon containing macrocyclic enediyne in deuterated benzene, adding ten equivalents of CHD, and degassing the sample for 15 minutes, a ^{1}H NMR was obtained for use as a standard. Since the Claisen rearrangement (discussed in section 3) occurred at 80 °C in the tethered case without competing cycloaromatization observed at that temperature, the starting temperature selected for the reaction was 80 °C. Also, since the carbocyclic enediyne **76** prepared by Nicolaou[46,47] and Semmelhack[48] had a half life of fifteen minutes at 60 degrees, the mixture was only heated for 15 minutes.

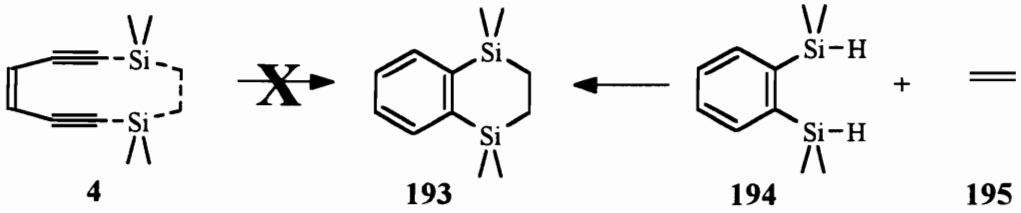
Analysis of the reaction by ^{1}H NMR after heating for fifteen minutes showed no obvious change in composition of the reaction contents when comparing the original

spectra with the second set of proton data. Table VI shows that even heating the enediyne at higher temperatures and for longer times proved unrewarding.

Table VI. Cyclization Conditions for 4		
Temperature	**Time**	**Result**
80 °C	15 minutes	S.M.
100 °C	1 hour	S.M.
135 °C	1 hour	S.M.
170 °C	8 hours	S.M.
225 °C	8 hours	S.M.

S.M. = staring material

Expected cyclization product **193** is a known compound and had been prepared via palladium catalysis.[227] The characteristic proton signals for **193** were not apparent

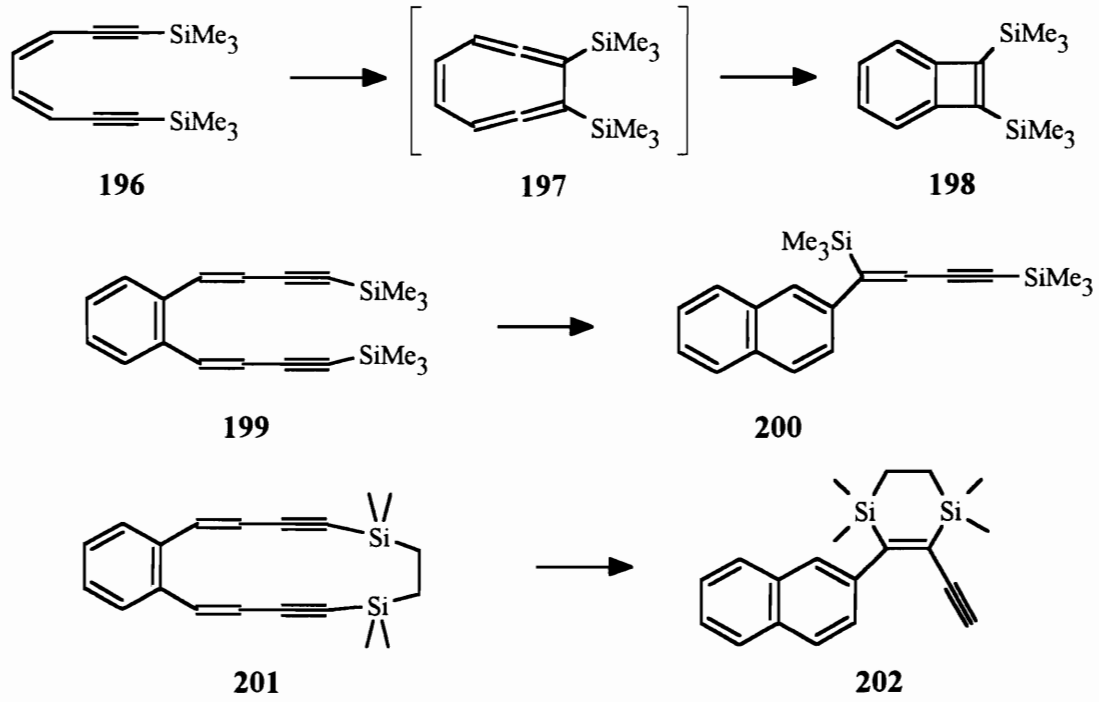


4 **193** **194** **195**

in the ^{1}H NMR spectrum observed after analysis of the reaction mixture from heating enediyne **4** to 225 °C.

Unsaturated silicon containing moieties similar to **4** had been prepared by Vollhardt and Berris in 1982[221] during a study to synthesize and analyze

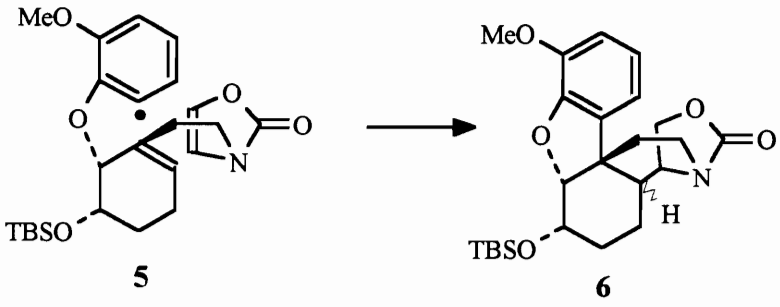
benzocyclobutacylooctatetraene aromatic type comounds. When subjected to flash vacuum pyrolysis conditions, dienediynes **196**, **199** and **201** cycloaromatized at temperatures of 650, 560 and 750 °C respectively.



The Bergman cyclization did not occur at the predicted temperature. In fact, compound **4** did not cyclize to any extent and thus would not serve as a viable synthon for the preparation of morphine. Perhaps if enediyne **4** had been subjected to temperatures greater than 225 °C, a Bergman cyclization may have occurred. At any rate, deficiencies were apparent in the overall radical cascade concept as shown in the work of Parker[4] and our group.[227a]

The two examples of radical cascade approaches towards morphine showed uncontrollable stereoselectivity and low yields for the key reaction. The first

cyclization had been performed by other members of this group with a compound **5** that incorporated the diene diol **2** mentioned in part 2 of this discussion. A substituted catechol ring linked to the diol moiety served as a model for the enediyne. Cyclization occurred with the use of tributyltin hydride and high temperatures.

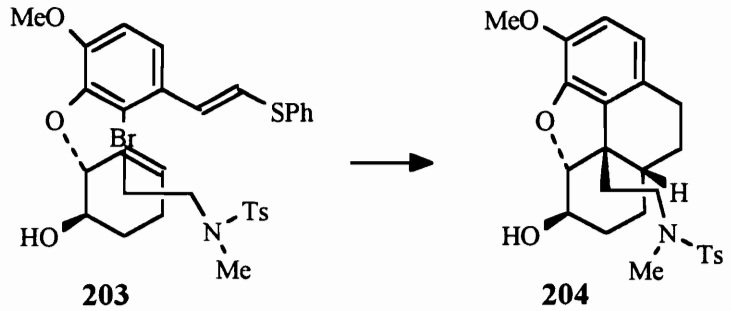


5 **6**

Figure 7. Hudlicky Radical Cascade

After several trials, the desired product **6** was isolated in differing amounts, most likely a result of the high temperature necessary to achieve the reaction. The yields of the reaction ranged from 2%-12%.

A similar phenomenon arose in Parker's[4] radical cascade reaction, Figure 8.



203 **204**

Figure 8. Parker's Radical Cascade Approach to Morphine

Homolytic cleavage was induced by tributyltin hydride to form an aryl radical which was closed to form the furan ring. The subsequent radical was trapped by the β-carbon of the styrene intermediate to afford the tetracyclic carbon skeleton of morphine in a 32% yield. Although the yield for the cascade was shown to be slightly higher in this case, we abandoned the radical cascade approach in favor of a stepwise reaction.

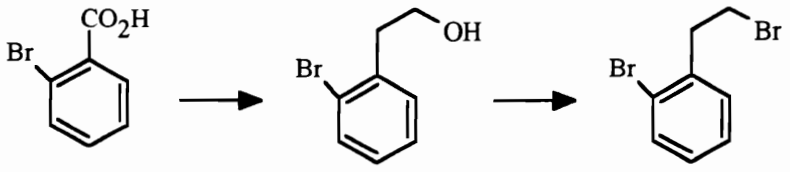
The same general synthesis from the first-generation pathway was used for the second-generation synthesis, but with adjustments of the methodology to simply form one radical closure at a time. The stepwise approach required production, isolation and characterization of another chiral diene diol which would replace **2** in the overall synthesis. Preparation and characterization of the cyclohexadiene diol is presented in the next section.

III. DISCUSSION

5. Structure and Absolute Stereochemical Determination of (3R,4S)-1-Bromo-2-(2-bromoethyl)-cyclohexa-1,5-diene-3,4-diol

With literature precedent[66,110] concerning the preparation of ortho substituted cyclohexadiene cis-diols, the approach to **9** commenced. Since 1-bromo-2-(2-

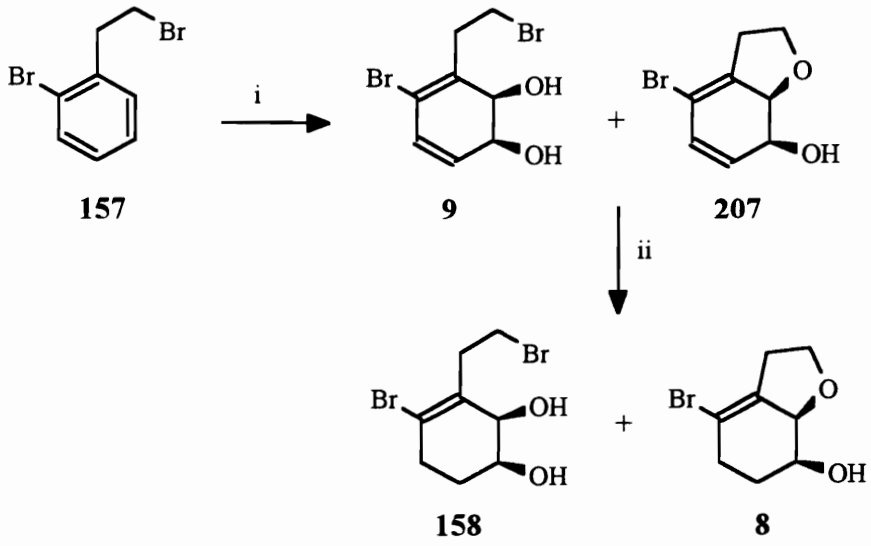
bromoethyl) benzene was not commercially available, it was prepared from the rather expensive 2-bromophenylacetic acid **205** in two steps.[228b]



205 **206** **157**

Figure 9. Synthesis of Biooxidation Substrate

An indigo test with the purified dibromo substrate proved negative, indicating that the compound did not induce production of the dioxygenase enzyme. Biooxidation of **157** with *Pp* 39/D under toluene induction conditions afforded 2.3 mg/L of the desired diol **9**, 3.1 mg/L of the furan **207** and 16 mg/L of toluene diol from



157 **9** **207** **158** **8**

i. *Pp* 39/D or JM109; ii. potassium azodicarboxylate, MeOH, AcOH

Scheme 41

the induction period. The low yields were not surprising since the diols derived from *ortho*-bromo and *ortho*-chloro styrene were isolated in the amounts of 20 mg/L and 350 mg/L respectively. When the transformation of 1-bromo-2-(2-bromoethyl)benzene **157** was run using JM109, the yield was 190 mg/L and 84 mg/L for **9** and **207** respectively.

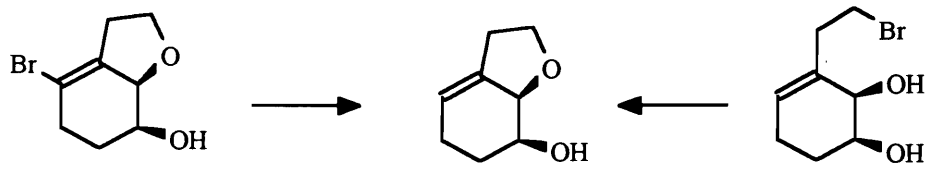
Though the diol was a white solid which survived only a few hours at ambient temperature, its stability was enhanced when in solution. A half life of **9** in deuterated chloroform showed $t_{1/2}$ equal to seven days as determined by ^{1}H NMR studies. To obtain a compound with enhanced stability, the less hindered double bond was reduced with diimide to result in a white crystalline compound **158** which had an indefinite stability at room temperature. The furan by-product **8** was also isolated at this point, but contributed to a greater portion of the yield than it had in the case of the mono-bromo cyclohexadiene diol reduction.

For additional proof of the regiochemistry of the diol as well as an interest in the ease of formation of **8**, the dihydrodiol was cyclized to the furan under basic conditions. The reaction was quantitative, but slow. Since the cyclization appeared slow, the isolation producer for the diol was modified in an attempt to avoid formation of the furan by-product. In general, for a typical work-up, before the cells of either *Pp* 39/D or JM109 are removed by high speed refrigerated centrifugation, the pH of the media/culture was increased to 8 or 8.5. Knowing that formation of furan **8** occurred presumably from an intramolecular S_N2 reaction in basic solution, keeping the pH as

close to neutral as possible was thought to eliminate the problem. One danger of keeping the pH low emerges in the acid sensitive nature of the diols. Performing the extraction procedure quickly and immediately after centrifugation appears to eliminate the majority of furan formation.

Even under the most cautious work up conditions, inevitably some furan will be formed in the reduction step. In view of the costly nature of **158**, the furan has been converted back to the diol using tetraethylammonium bromide and boron trifluoride etherate by other members of our group.[229]

After isolation of the diene diol, determination of the absolute stereochemistry ensued. Although the furan was viewed initially as an annoying by-product it now appeared in a different light. Simple dehalogenation of the bromofuranol derivative from the second biotransformation would afford furanol **7** isolated from the first biooxidation study for the morphine project (discussed in section III.2). Indeed, reaction of the cyclized-by-product with sodium in refluxing ethanol afforded the known furanol **7**, and provided the absolute stereochemical proof. ($[\alpha]_D^{26}$ of **7** = +50.6, c = 0.88 $CHCl_3$; lit = +46.4, c = 0.45 $CHCl_3$)



8 **7** **162**

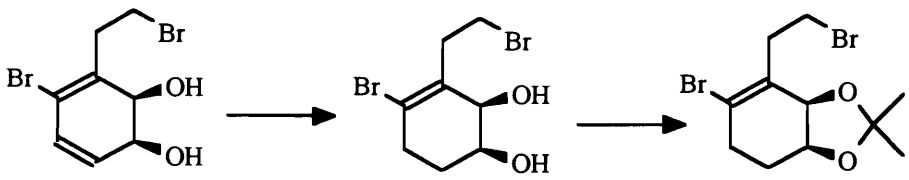
Figure 10. Pathway for Absolute Stereochemical Proof

With the desired component for the stepwise radical approach to morphine in hand, we initiated the synthesis for the first radical precursor.

III. DISCUSSION

6. Synthesis of an Isoquinoline Precursor to Morphine

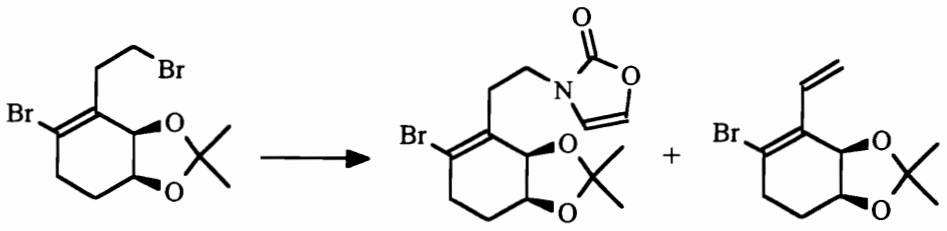
A typical fermentation process would yield on average 3 g of a crude diol mixture which was directly reduced with potassium azodicarboxylate and subsequently protected as an acetonide with 2,2-dimethoxypropane in methylene chloride solution containing a catalytic amount of *p*- toluene sulfonic acid. The yield over the two steps was 50%, not including the amount of diene diol recovered from the furan by-product recycling procedure.



9 **158** **208**

Scheme 42

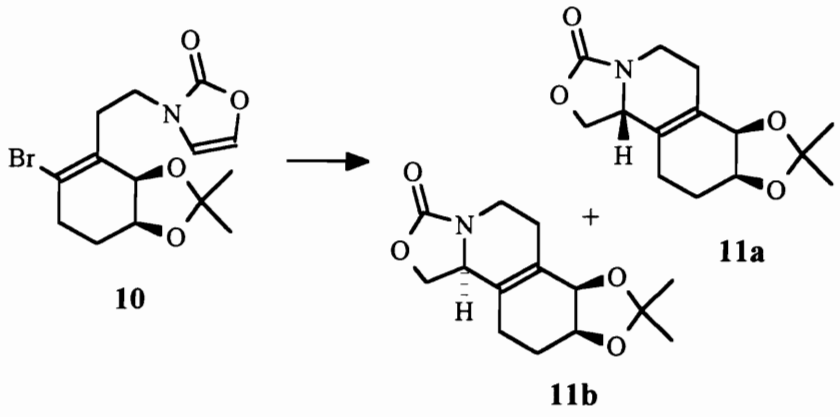
After acetonide formation, alkylation of the substrate **208** with sodium hydride and the known oxazolone moiety in DMSO at 0 °C gave **10** in a low yield of 20%. Even after attempts to increase the yield of this step by changing reaction times, temperatures or conditions, the eliminated compound **209** still predominated as the major product.



Scheme 43

Thus, the synthesis continued despite the encumbrance of the alkylation step. With the desired radical cyclization precursor in hand, excitement built as the first reaction was attempted. The initial trial reaction was performed on a scale of 10 mg and by Andrew Gum as production of the diol continued. His findings showed that the cyclization reaction afforded the desired tricyclic products, as a mixture of two

compounds (**11a** and **11b**) but neither the ratio of the two compounds nor the structure of the major product was evident at the time.



Scheme 44

After a workable quantity of the alkylated product had been amassed, the cyclization reaction was performed on a larger scale. It was then discovered that the reaction occurred in an gratifying yield of 80% and with a 2:1 ratio of products. The reaction products were easily separated using flash column chromatography to yield one compound which immediately solidified and another which solidified after storage at 0 °C overnight.

In order to distinguish between the two isomers, proton NMR spectra were run of each isomer in different solvents in order to see the individual signals without overlap. The solvent which achieved the best separation of the proton signals for both compounds was deuterated benzene. It was envisioned that the proton at C_9 of only

one isomer should be able to interact through space with one of the methyl groups of the acetonide. Observation of nÖe studies of each compound however, proved inconclusive.

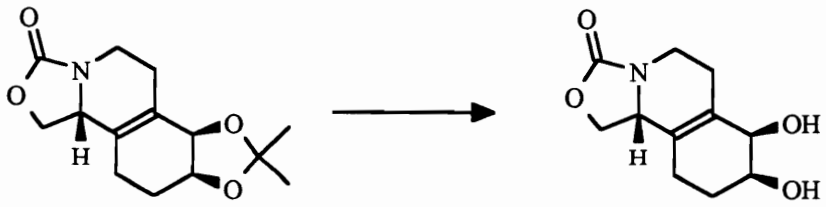
The next task involved analysis of the coupling constants and decoupling experiments in an attempt to determine the relative confomation of the tricyclic compounds. The proton data is shown in table VII..

Table VII : "Top R_f isomer" in d_6 benzene

Shift in ppm	Coupling Constant(s)	Proton Assignment
3.87	t, J = 6.5	16*eq*
3.82	m	6
3.67	d, J = 5.8	5
3.56	m	10*ax*
3.22	m	10*eq*,9
2.44	ddd, J = 13, 11.7, 4.6	16*ax*
2.01	d, J = 16	15
1.85	brs	15

Although analysis of the NMR data relying on coupling constants, pointed tentatively to the major compound, concrete evidence was necessary before continuing the synthesis with this precious material. Since the acetonide of the major product was isolated as a solid, an attempt was made to grow crystals suitable for x-ray analysis. After experimenting with numerous solvents, solvent combination, and temperatures, we sought to deprotect the acetonide, for surely, the resultant diol would form superior crystals.

Deprotection of the acetonide group was achieved with Amberlyst acidic resin in methanol/water solution. Purification of diol **210a** delivered the most beautiful white crystals that were sparingly soluble in most solvents except for methanol or water.



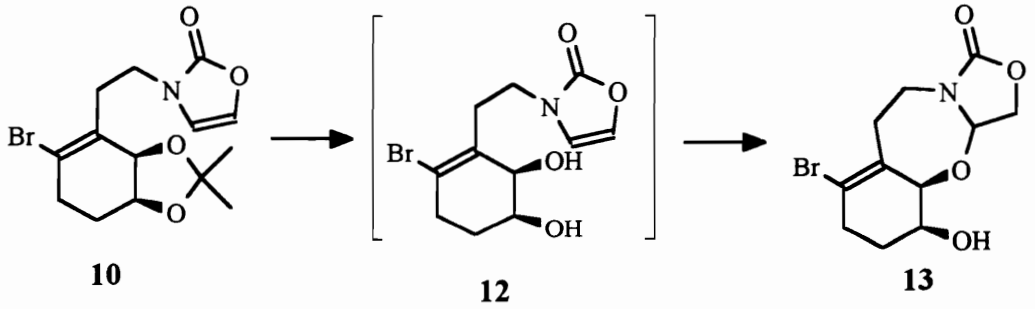
11a **201a**

Scheme 45

The solid was persuaded to dissolve in hot ethyl acetate and was then left to stand at room temperature. After waiting patiently for one week, small cubes almost identical to coarse granules of salt were present in the bottom of the vial. Luckily, the

crystals were suitable for x-ray analysis[230] and the results from the diffraction analysis disclosed the arrangement of the stereocenters in question. Inspection of the solved crystal structure revealed that attachment of the hydrogen occurred on the same face relative to the hydroxyl groups. This information proved that the major product **11a** could be related to the enantiomer of morphine for our purposes, while the minor product **11b** could serve as a precursor for the synthesis of morphine.

In hopes to reverse the product ratio of the two isomers, it was postulated that the acetonide portion of the compound may have some directing effects during the radical cyclization. Thus, the alkylated cyclization precursor **10** was subjected to the same deprotection conditions used for the isoquinoline.

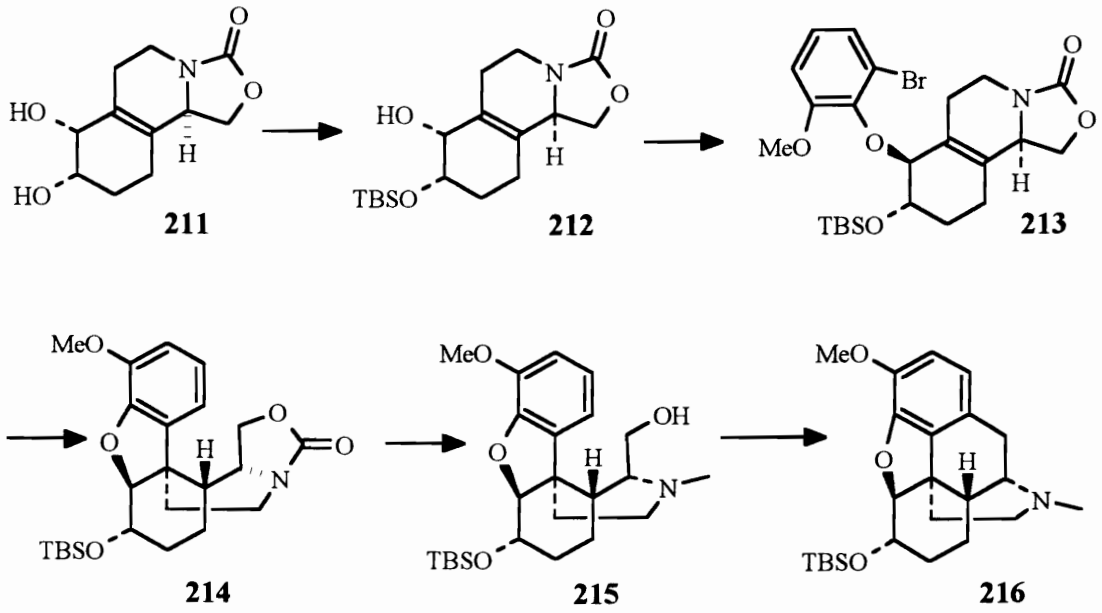


10 **12** **13**

Scheme 46

Unfortunately, during the deprotection of the precursor, the newly formed diol cyclized upon itself in situ to form an interesting oxazepine ring system **13** and the original procedure for the formation of **11a** was retained.

More of the major isoquinoline was prepared in an assembly line fashion and was handed to Dr. G. Butora who completed the remaining portion of the synthesis, outlined below.

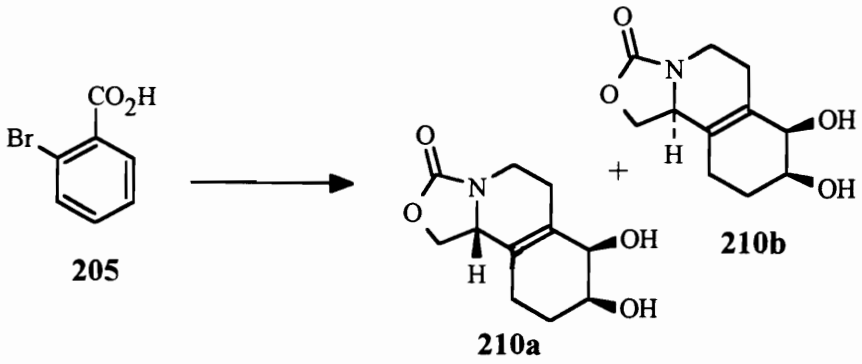


Scheme 47

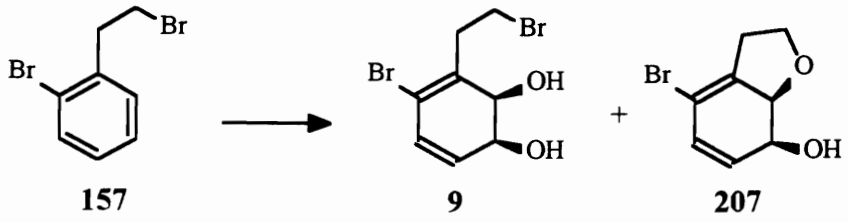
Thus, the preparation of "ent"-morphine involved mono-TBS protection of the "lower" diol to afford **212** and Mitsunobu inversion at the remaining alcohol functionality. The second radical precursor **213** was then formed and underwent cyclization. The pentacyclic compound **214** was isolated after induction of the aryl radical reaction with tributyltin hydride and AIBN. Unfortunately, closure occurred with quenching of the radical at C_{14} from the wrong face of the molecule. The isoquinoline has thus proven to be a key intermediate in this synthesis of morpine.

IV. CONCLUSION

The isoquinoline alkaloid, morphine, remains a sought after target. Isoquinoline precursors, **11a** and **11b** have been prepared in seven steps from 2-bromophenylacetic acid.

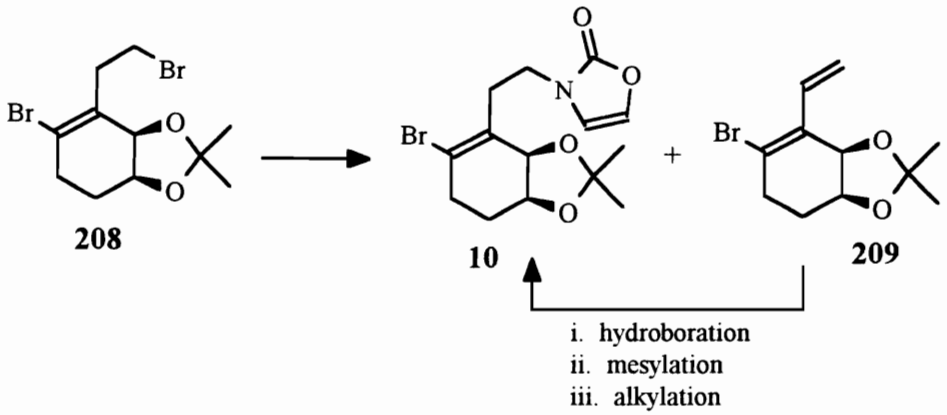


The biotransformation remains the lowest yielding step, but the highest yield obtained in this case was reported by a chemist. With the aid of a well-trained microbiologist or adaptation of the toluene dioxygenase producing microorganisms to better tolerate the toxic 1-bromo-1-(2-bromoethyl) benzene, production of muligram quantities of the coveted diol should be possible.



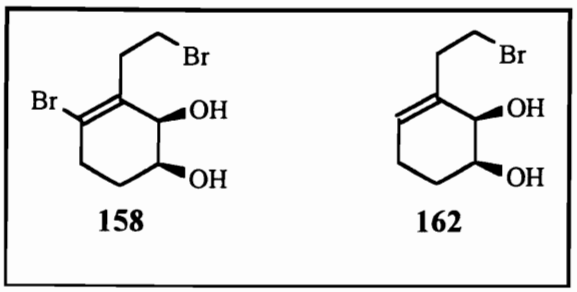
The problematic alkylation step has been analyzed by members of the "morphine group" and the eliminated product **209** can now be recycled to give the

radical precursor **10** in an 80% yield over two steps. Progress has also been made by



the "morphine group" towards the preparation of the morphinan skeleton in the enantiomeric series. Current studies are focused on preparation of the isoquinoline precursor in one step from an aromatic isoquinoline moiety.

Not only are the two isoquinoline compounds highly useful for the stereoselective synthesis of both isomers of morphine, but the newly isolated diol metabolites may offer chemists in natural product synthesis some useful chiral starting materials. The two *cis*-dihydrodiols are the first isolated which would allow, through nucleophilic substitution, the preparation of functionalized derivatives.



V. EXPERIMENTAL SECTION

Unless otherwise noted, all starting materials were obtained from commercial supplers and used without further purification. Tetrahydrofuran (THF), benzene and diethyl ether (Et_2O) were distilled from sodium/benzophenone ketyl under argon immediately prior to use. Methylene chloride (CH_2Cl_2) was distilled from CaH_2 under argon immediately prior to use. Pyridine and triethylamine (Et_3N) were distilled from CaH_2 and stored over KOH pellets in a dessicator until use. Reactions involving air and/or moisture sensitive reagents were executed under an inert atmosphere of dry argon and the glassware was flame dried under vacuum. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh). Infrared (IR) spectra were reported in wavenumbers (cm^{-1}). The ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were obtained as solutions in deuterio-chloroform ($CDCl_3$) unless otherwise indicated. Chemical shifts were reported in parts per million (ppm, δ) and were referenced to $CHCl_3$ at δ 7.24 for ^1H NMR or to the center line of the $CDCl_3$ triplet at δ 77.0 for ^{13}C NMR. Coupling constants were reported in hertz (Hz). Splitting patterns were designated as s, singlet; d, doublet; t, triplet; q, quartet;, m, multiplet; br, broad.

Melting points were determined on a Thomas Hoover capillary apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 FTIR or Perkin-Elmer 283B. NMR spectra were recorded on a Bruker WP-270 or Varian Unity 400. Optical rotations were measured on Perkin-Elmer 241 digital polarimeter. Mass

spectra were determined on Varian MAT-112 instrument (low resolution) or VG-7070 E-HF (exact mass). Elemental Analyses were performed by Atlantic Microlabs Inc.

Microbial oxidation of (2-bromoethyl)benzene by *Pseudomonas putida* 39/D. Fermentations were carried out as described earlier[216] in a 2L fermentor without toluene induction since (2-bromoethyl)benzene induces the production of toluene dioxygenase. From 5g of (2-bromoethyl)benzene delivered into the fermentation broth, 500 mg of crude extract was purified on deactivated silica (1:1 hexane/ethyl acetate) to afford 300 mg of pure **2**.

(1*S*,2*R*)-3-(2-bromoethyl)cyclohexa-3,5-diene-1,2-diol (2).

R_f = 0.33 (1:1 hexane/ethyl acetate), mp = 49-50 °C (hexane/methylene chloride)

$[\alpha]_D^{25}$ = +89.8 (c = 1.1, $CHCl_3$)

^{1}H NMR δ 5.94 (1H, m), 5.84 (1H, d, J = 4.5), 5.79 (1H, d, J = 4.5), 4.27 (1H, br s), 4.06 (1H, d, J = 6), 3.53 (2H, t, J = 6), 3.15 (2H, br s), 2.77 (2H, m)

^{13}C NMR δ 137.7 (C), 128.1 (CH), 124.3 (CH), 121.9 (CH), 69.3 (CH), 68.6 (CH), 37.1 (CH_2), 31.3 (CH_2)

MS *m/z* (rel. int.) (EI+) 219 (M, 2), 202 (12), 107 (60), 79 (100).

(1*S*,2*R*)-3-(2-bromoethyl)cyclohex-5-ene-1,2-diol (162) To an ice cooled solution of diol **2** (440 mg, 2.01 mmol), in 2 mL methanol was added potassium azodicarboxylate (975 mg, 5.02 mmol). A solution of acetic acid (0.69 mL, 12.06 mmol) in 2 mL methanol was added dropwise over 1 hour. The solution was gradually warmed to room temperature and stirred overnight. After slow addition of saturated aqueous $NaHCO_3$ (3 mL), the solvent was concentrated under reduced pressure. The remaining residue was dissolved in water (3 mL) and brine (8 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over Na_2SO_4, and

evaporated to yield 186 mg of **162** (42%) and 18 mg of **7** (6%) after purification by flash column chromatography (1:1 hexane/ethyl acetate).

R_f = 0.35 (1:1 hexane/ethyl acetate)

mp = 95-96 °C (hexane/methylene chloride)

$[\alpha]_D^{25}$ = -63.6 (c = 1.02, $CHCl_3$)

IR (KBr) 3260, 2810, 980

^{1}H NMR δ 5.66 (1H, s), 4.01 (1H, d, J = 4), 3.77 (1H, ddd, J = 14, 7, 4), 3.52 (2H, t, J = 7), 2.94 (2H, brs), 2.74 (1H, m), 2.62 (1H, m), 2.20, (1H, m), 2.09 (1H, m), 1.71 (2H, m)

^{13}C NMR δ 134.5 (C), 128.4 (CH), 69.5 (CH), 68.5 (CH), 37.9 (CH_2), 32 (CH_2), 25.2 (CH_2), 23.8 (CH_2)

MS *m/z* (rel. int.) (EI+) 220 (M, 2), 176 (100), 97 (80), 83 (95)

Anal. Calcd. for $C_8H_{13}O_2Br$: C, 43.46; H, 5.89. Found: C, 43.23, H 5.89.

(7*S*,7a*R*)-2,3,5,6,7,7a-hexahydrobenzofuran-7-ol (7). The bromofuranol 8 (100 mg, 0.4566 mmol) was reacted with freshly cut and cleaned sodium in refluxing ethanol (3 mL) for 2 hours. The reaction was carefully quenched with ice water (5 mL) and concentrated in vacuo. Extraction with ethyl acetate (3 x 8 mL) followed by drying over Na_2SO_4 and purification on a flash column (1:1 hexane/ethyl acetate) yielded 30 mg of the furan **7**.

R_f = 0.32 (1:1 hexane/ethyl acetate)

$[\alpha]_D^{23}$ = +46.4 (c = 0.45, CHCl3)

IR (neat) 3490 (br), 2920

^{1}H NMR δ 5.61 (1H, s), 4.22 (1H, s), 4.02 (1H, s), 3.92 (2H, m), 2.55 (2H, m), 2.21 (2H, m), 2.02 (2H, m), 1.61 (2H, m)

^{13}C NMR δ 133.6 (C), 119.4 (CH), 76.9 (CH), 66.9 (CH_2), 64.4 (CH), 30.7 (CH_2), 25.1 (CH_2), 20.7 (CH_2).

MS *m/z* (rel. int.) (EI+) 140 (M, 15), 96 (98), 83 (70), 76 (100)

HRMS calcd for $C_8H_{12}O_2$ 140.0837 found 140.083.

(1*S*,2*R*)-1,2-isopropylidene-dioxy-3-(2-bromoethyl)-cyclohexa-3,5-diene (163). The diol **2** (1.0 g, 4.5 mmol) was dissolved in acetone (30 mL) with stirring. 2,2-Dimethoxypropane (1 mL, 5.5 mmol) was added followed by a catalytic amount of *p*-toluenesulfonic acid. Stirring continued at room temperature until no starting material was observed by TLC monitoring (approximately 15 min.). The reaction was quenched with 10% aq. NaOH solution (8 mL) and extracted with ether (3 x 10 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and evaporated to yield 0.92 g of a colorless oil, 78% yield.

R_f = 0.46 (7:3 hexane/ethyl acetate)

$[\alpha]_D^{25}$ = +101.5 (c = 1.2, $CHCl_3$)

IR (neat) 2980, 2880, 1370, 1040

^{1}H NMR δ 5.97 (1H, dd, J = 9.5, 5.5), 5.83 (1H, dd, J = 9.5, 4), 5.77 (1H, d, J = 5.5), 4.63 (1H, dd, J = 8.5, 4), 4.54 (1H, d, J = 8.5), 3.53 (2H, m), 2.82 (1H, m), 2.69 (1H, m), 1.37 (3H, s), 1.35 (1H, s)

^{13}C NMR δ 134.9 (C), 124.4 (CH), 123.5 (CH), 120.8 (CH), 105.4 (C), 72.8 (CH), 70.9 (CH), 37.2 (CH_2), 30.6 (CH_2), 26.8 (CH_3), 25 (CH_3)

MS *m/z* (rel. int.) (CI+) 259 (M, 3), 201, (50), 121 (100)

HRMS calcd for $C_{11}H_{15}O_2Br_2$ 59.0334 found 259.0346

(1*S*,2*R*)-1.2-isopropylidene-dioxy-3-ethenylcyclohexa-3,5-diene (164). The bromoethyl acetonide **163** (57 mg, 0.22 mmol) was dissolved in benzene (10 mL). DBU (0.05 mL, 0.33 mmol) was added and the mixture was brought to relux for 6 hours. After cooling the solution to room temperature it was poured into 8 mL of water. The aqueous layer was separated and extracted with methylene chloride (2 x 5 mL). Combination of the organic fractions followed by drying over Na_2SO_4 and evaporation yielded 62 mg of a crude oil. Flash column chromatography of the residue

(7:3 hexane/ethyl acetate) gave the styrene acetonide **164** (21 mg, 53%) as a colorless oil.

(1*S*,2*S*,5*S*,6*S*,7*R*,8*S*,9*S*,10*S*)-1,4-diethyenyl-5,6,9,10-bis(isoproplyidenedioxy)-tricyclo-[6.2.2.0]-dodeca-3,11-diene (155). The acetonide **164** was left at room temperature for 2 weeks. Purification by flash column chromatorgaphy, 8:2 hexane/ethyl acetate yielded 8 mg of the major dimer whose ^{1}H NMR spectrum and $[\alpha]_D$ corresponded to the literature values.[218]

1,1,8,8-tetramethyl-1,8-disilacyclodeca-2,6-diyne-4,5-diol (173).

Procedure A: With stirring, the dialdehyde (2.4 g, 9.6 mmol) was added neat to a room temperature solution of SmI_2 (320 ml, 31.6 mmol, (0.1M solution in THF)). The initial deep blue color of the samarium solution changed to a dark orange within thirty seconds following the addition of the dialdehyde. After stirring for 15 minutes, a precipitate appeared. The lanthanide species was then dissolved with 4 ml of 0.1 N aq HCl solution. One third of the resulting solution was evaporated and extracted with Et_2O. Evaporation of the combined organic layers afforded a brown foam, 2.12 g, 87% crude yield.

Procedure B: To a stirred and cooled (-10°) solution of the dialdehyde (125 mg, 0.498 mmol) in degassed THF (30 ml) was added the titanium tetrachloride (0.24 ml, 2.24 mmol) and the zinc powder (292 mg, 4.48 mmol) in small portions. The mixture was stirred for one hour at 0° and was subsequently quenched with 10% aq K_2CO_3 solution. Methylene chloride (50 ml) was added, the mixture was filtered through celite and the solvent was evaporated.. Purification using a flash silica column (2:1 hexane/ethyl acetate) afforded 12 mg of white crystals, a mixture of cis and trans diols.

Procedure C: To the Mg (0.195 g, 8.0 mmol) in 3 ml of THF under argon was added mercuric chloride (60 mg, 0.22 mmol). The mixture was stirred for 15 minutes at room temperature before cooling to -10° and addition of $TiCl_4$ (0.33 ml, 3.0 mmol). A solution of the dialdehyde (250 mg, 1.0 mmol) in 4 ml THF was added and the mixture was stirred at 0° for one hour and 15 minutes. The reaction was quenched with 2 ml sat. Na_2CO_3 solution and filtered through celite. The organic layer was washed with brine, dried and evaporated. Purification of the product on a flash silica column (2:1 hexane/ethyl acetate) yielded 30 mg of a mixture of cis/trans diols, 12 % yield.

R_f = 0.31 (2:1 hexane/ethyl acetate); mp = 113-114 °C (benzene/hexanes)

IR (CCl_4) 3375 (br), 3005, 2961, 2359, 1407

^{1}H NMR ($CDCl_3$ 400 MHz) δ 4.40 (d, J = 4, 2H), 2.25 (d, J = 4, 2H), 0.74 (s, 4H), 0.17, (s, 12H);

^{13}C NMR δ104.5 (C), 93.6 (C), 68.9 (CH), 7.9 (CH_2), -2.5 (CH_3), -3.0 (CH_3)

MS (*m/z* (rel. int.)) 252 (10, M+), 235 (100), 145 (45)

1,1,8,8-tetramethyl-1,8-disilacyclodeca-2,6-diyne-4,5-methylsulfonate (174). Diol **173** (67 mg, 0.266 mmol) was dissolved in methylene chloride (12 mL) under argon at 0 °C. Freshly distilled pyridine (0.05 mL, 0.6115 mmol) was added followed by methanesulfonyl chloride (0.05 mL, 0.6115 mmol). After stirring at room temperature for 2 hours, 1% HCl solution was added and the mixture was extracted with methylene chloride, washed with brine, dried over Na_2SO_4, filtered and evaporated to yield 115 mg of a brown solid. Purification of the crude compound on a flash silica gel column (7:3 hexane/ethyl acetate) yielded 44 mg, 41% of **174**.

R_f = 0.43 (7;3 hexane/ethyl acetate)

mp = 97-100 °C

IR ($CHCl_3$) 2960, 2360, 1414

^{1}H NMR 5.34 (2H,s), 3.16 (6H,s), 0.74 (4H,s), 0.18 (12H, s)

^{13}C) NMR 99.4 (C), 96.5 (C), 72.2 (CH), 39.5 (CH_3), 7.58 (CH_2), -2.46 (CH_3), -3.6 (CH_3)

MS *m/z* (rel. int.) CI+ 409 (M,2), 313 (100), 219 (51)

1,1,8,8-tetramethyl-1,8-disilacyclodeca-2,6-diyne-4,5-dioxythionocarbonate (175).

To a stirred solution of the diol **173** (77 mg, 0.306 mmol) and DMAP (90 mg, 0.734 mmol) in 2 ml dry methylene chloride at 0° under argon was added thiophosgene (0.03 ml, 0.367 mmol). The solution was stirred at 0° for 1 hour. Silica gel (0.6 g) was added and the mixture was warmed to room temperature. After evaporation of the solvents, the silica was applied directly to a flash column with 1:1 hexane/ethyl acetate as the eluant. A viscous, yellowish oil which later solidified was obtained in the amount of 30 mg. 34% yield

R_f = 0.84 (2:1 hexane/ethyl acetate)

IR (CCl_4) 2970 (w), 1320, 1270

^{1}H NMR ($CDCl_3$, 400 MHz) 5.32 (s, 2H), 7.94 (s, 4H), 0.23(s, 12H)

^{13}C NMR ($CDCl_3$ 400 MHz) 190.4 (C), 105.2 (CH_3, 96.1 (C), 76.0 (CH), 8.4 (CH_2), -2.4 (CH_3), -4.5 (CH_3)

MS (*m/z* (rel. int.)) 294 (35, M), 206 (35), 191 (100)

1,1,8,8-tetramethyl-1,8-disilacyclodeca-2,6-diyne-5-(2-propenyloxy)-4-ol (176).

A 250 ml flask containing the diol **173** (1.78 g, 7.06 mmol) was charged with benzene and dibutyl tin oxide (2.10 g, 8.48 mmol). The mixture was refluxed overnight with azeotropic removal of water with the use of a Dean-Stark trap. Initially, the tin compound did not dissolve. However, after refluxing overnight, the dibutyl tin oxide was completely solubilized, indicating the end of the reaction.

After evaporation of the solvent, 4 g of compound was obtained which, without further purification, was dissolved in an excess of allyl bromide. With careful monitoring, the reaction was found to be incomplete after the solution was brought to reflux for one day. After two days of refluxing, the starting material was consumed and silica gel was added to the mixture. The solvents were removed on a rotory evaporator and the compounds which had adsorbed onto the silica were directly chromatographed using a flash silica column and eluting with 8:2 hexane/ethyl acetate. The mono allyl ether was obtained as a yellow oil, 740 mg, 36% yield.

R_f = 0.45 (10:1 hexane/ethyl acetate)

IR (neat) 3400 (br), 2945, 2900, 2160, 1250

^{1}H NMR δ 5.91 (m, 1H), 5.33 (d, J = 16, 1H), 5.23 (d, J = 12, 1H), 4.53, (dd, J = 7, 4, 1H), 4.29 (dd, J = 12.5, 6, 1H), 4.21 (d, J = 7, 1H), 4.03 (dd, J = 12.5, 6, 1H), 2.45 (d, J = 4, 1H), 0.74 (s, 2H), 0.72 (s, 2H), 0.16 (s, 6H), 0.15 (s, 6H)

^{13}C NMR δ 133.7 (CH), 118.2 (CH_2), 102.1 (C), 103.5 (C), 94.3 (C), 92.8 (C), 75.1 (CH), 70.6 (CH_2), 67.2 (CH), 7.7(CH_2), -2.3 (CH_3), -3.1 (CH_3)

MS (*m/z* (rel. int.)) 292 (2, M), 251 (18), 145 (100)

1,1,8,8-tetramethyl-1,8-disilacyclodeca-2,6-diyne-5-(2-propenyloxy)-4-ene. (177). To the allylether **176** (190 mg, 0.651 mmol) in methylene chloride at 0 °C was added pyridine (0.13 mL, 1.627 mmol) followed by dropwise addition of triflic anhydride (0.16 mL, 0.976 mmol). After stirring at 0 °C for 15 minutes, the reaction was poured into 1% HCl (10 mL), extracted with methylene chloride. The combined organic portions were dried over Na_2SO_4, filtered and evaporated. The triflate was quickly passed through a plug of silica (25:1 hexane/ethyl acetate) to give 89.6 mg (32%) of a colorless oil which was used immediately in the next reaction.

The triflate (89.6 mg) was dissolved in benzene, 6 mL. DBU (0.035 mL, 0.212 mmol) was added dropwise at room temperature. After stirring for 15 minutes, the solution had turned aquamarine in color. Silica (100 mg) was added and the solvent was evaporated. The mixture was applied directly to a flash silica column (98:2 hexane/ethyl acetate) to yield 28 mg of a colorless oil, 48%.

R_f = 0.29 (98:2 hexane/ethyl acetate)

IR (neat) 2817, 2120

^{1}H NMR ($CDCl_3$) d 5.91 (1H, m), 5.31 (1H, s), 5.33 (1H, d, J = 16), 5.26 (1H, d, J = 16), 4.39 (2H, d, J = 5.6), 0.39 (4H, s), 0.04 (12H, s)

^{13}C NMR ($CDCl_3$) d 148.1 (C), 132.2 (CH), 118.5 (CH), 101.2 (C), 98.8 (C), 95.2 (CH_2), 84.1 (CH_2), overlapping signals 70.2 (C), 9.69 (CH_2), 7.89 (CH_2), -0.28 (CH_3), -2.27 (CH_3).

MS *m/z* (rel. int.) EI+ 274 (35), 145 (41), 73 (100).

1,1,8,8-tetramethyl-1,8-disilacyclodeca-2,6-diyne-5-propenyl-4-one. (181).

Enediyne **177** (3 mg, 0.01 mmol) was dissolved in d_6 benzene (0.8 mL) and transferred to a thick walled NMR tube. 1,3-Cyclohexadiene (0.08 mL, 0.8 mmol) was added to the mixture and the sample was degassed for 30 minutes with a stream of argon. After heating the sample at 55 °C for 8 hours, the starting material remained, unchanged. The reaction temperature was increased to 80 °C and after 60 hours, the starting material had been consumed. Evaporation of the solvents yielded 1.3 mg of a yellow oil, 43%.

R_f = 0.5 10:1 (hexane/ethyl acetate)

IR (neat) 2810, 2100, 1725

^{1}H NMR ($CDCl_3$) 5.84 (1H, m), 5.12 (2H, m), 3.27 (1H, m), 2.50 (2H, m), 0.23 (4H, s), 0.17 (12H, s)

^{13}C NMR ($CDCl_3$) 185.4 (C), 133.6 (CH), 117.9 (CH_2), 106.7 (C), 104.0 (C), 100.1 (C), 91.7 (C), 48.1 (CH), 35.4 (CH_2), 7.89 (CH_2), -2.61 (CH_3), -3.33 (CH_3)

Bis[1,2-dimethylsiliyl-2-(propynylbromo)]-ethane (182).

To a stirred solution of the diol **171** (11.0 g, 43.3 mmol) and carbon tetrabromide (27 g, 86.6 mmol) in 200 ml methylene chloride at 0° was added dropwise a solution of triphenyl phosphine (34 g, 130 mmol) in 100 ml methylene chloride. The mixture was stirred overnight. The resultant orange solution was filtered and the methylene chloride was evaporated. Filtration of the remaining residue and trituration with ether yielded 18 g of crude compound. The compound was purified on a flash silica column, 4:1 hexane/methylene chloride to afford 11.1 g of a colorless oil, 68% yield.

R_f = 0.40 (hexane/methylene chloride, 4:1)

IR (neat) 2960, 2170, 1245, 1200

^1H NMR δ 3.92 (4H, s), 0.58 (4H, s), 0.16 (12H, s)

^{13}C NMR ($CDCl_3$, 270 MHz) δ 100.5 (C), 91.4 (C), 14.6 (CH_2), 8.1 (CH_2), -2.6 (CH_3)

MS (EI, 70 eV) *m/z* (rel. int.) 380 (M, 2), 223 (60), 175 (60), 147 (80)

Anal calcd for $C_{12}H_{20}Br_2Si_2$ C 37.90, H 5.31; found C 38.00, H 5.36.

5-thia-1,1,8,8-tetramethyl-1,8-disilacyclodeca-2,6-diyne (183).

The dibromide **182** (1.0 g, 2.64 mmol) was dissolved in methylene chloride (26 mL) and water (35 mL). After dissolving tetrabutyl ammonium bromide (0.27 g, 0.789 mmol), $Na_2S•9H_2O$ (0.76 g, 3.16 mmol) was added with vigorous stirring. After two hours, the layers were separated, the organic layer was washed with water, dried and evaporated to afford a cream colored solid. Purification of the product via flash column chromatography (4:1 hexane/methylene chloride) yielded 120 mg, 18%.

R_f = 0.43 (hexane/methylene chloride, 2:1);

mp = 118-121 °C

IR (CCl_4) 2910, 2360, 2343, 1186

^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.39 (4H, s), 0.57 (4H, s), 0.12 (12H, s)

^{13}C NMR ($CDCl_3$, 270 MHz) δ 101.1 (C), 87.4 (C), 19.9 (CH_2), 8.6 (CH_2), -2.3 (CH_3)

MS (EI, 70 eV) *m/z* (rel. int.) 252 (M, 1), 224 (100), 209 (90), 147 (35)

5-thia-1,1,8,8-tetramethyl-1,8-disilacyclodeca-2,6-diyne-5,-oxide (184)

To a cooled (-30°) solution of the sulfide **183** (1.4 g, 5.56 mmol) in 85 ml methylene chloride was added mCPBA (1.6 g, 5.67 mmol). After 30 min, dimethyl sulfide, 4 ml, was added and stirring continued for an additional 15 min. The reaction was then concentrated in vacuo. The residue was dissolved in ether (100 ml) extracted with sat. aq $NaHCO_3$, (2 x 60 ml), and brine (1 x 30 ml).Drying of the etherial layer with $MgSO_4$ and evaporation gave 1.3 g of a light yellow semi-solid Purification by flash column chromatography gave 940 mg of a white solid, 63%.

R_f = 0.52 (ether);

mp = 177-178 °C

IR (CCl_4) 2960, 2910, 2170, 1240

^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.84 (2H, d, J = 12), 3.71 (2H, d, J = 12), 0.59 (4H, s). 0.16 (12H, s)

^{13}C NMR ($CDCl_3$, 270 MHz) δ 193.6 (C), 93.2 (C), 42.2 (CH_2), 8.4 (CH_2), -2.5 (CH_3)

MS (EI, 70 eV) *m/z* (rel. int.) 268 (M, 1), 225 (12), 145 (50), 96 (100)

Anal calcd for $C_{12}H_{20}OSSi_2$ C 53.66, H 7.52; found C 53.67, H 7.58.

5-thia-1,1,8,8-tetramethyl-1,8-disilacyclodeca-2,6-diyne-5,5-dioxide (185).

To a -78 °C solution of the sulfoxide **184** (248 mg, 0.9253 mmol) in methylene chloride was added pyridine (0.26 mL, 3.238 mmol) followed by addition of sulfuryl chloride (1.9 ml of a 1M solution in methylene chloride, 1.943 mmol). After 1 hour and 40 min, the solution was quenched with water (4 mL) and warmed to room temperature. The mixture was extracted with sat. aq. $NaHCO_3$ solution (5 mL), water (5 mL), sat. $CuSO_4$ solution (2 x 5 mL), and brine (10 mL). After drying over $MgSO_4$, filtration and evaporation, the residue was dissolved in dry methylene chloride (15 mL), cooled to 0 °C and mCPBA (495 mg, 2.868 mmol) was added. After stirring the mixture overnight, 2 drops Me2S were added. The mixture was extracted with $NaHCO_3$ solution (10 mL), water (10 mL), dried over $MgSO_4$ and evaporated to give 427 mg of a brown foam. Purification of the crude product on a flash silica column (10:1 methylene chloride/hexane) yielded 263 mg of a cream-colored solid, 90%.

R_f = 0.51 (10:1 methylene chloride/hexane)

IR ($CHCl_3$) 2980, 2910, 2190, 1800

^{1}H NMR ($CDCl_3$) 5.74 (1H, dd, J = 12, 2.6), 4.32 (1H, m), 4.15 (1H, m), 0.66 (4H, s), 0.18 (12H, s)

^{13}C NMR 99.8 (C), 94.4 (C), 59.7 (CH), 42.9 (CH_2), 8.2 (CH_2), -2.8 (CH_3)

MS *m/z* (rel. int.) CI+ 319 (2), 157 (28), 139 (100)

1,1,8,8-tetramethyl-1,8-disilacyclodeca-2,6-diyne-4-ene (4). To a cooled -78 °C solution of MeLi (0.47 mL of a 1.6 M soln in Et_2O, 0.7547 mmol) in ether (8 mL), was added the sulfone **185** (200 mg, 0.6289 mmol) in ether (15 mL). Immediately after the addition was complete, saturated aq. NH_4Cl solution (4 mL) was added and the reaction was diluted with pentane and water. The layers were separated, the organic was dried over Na_2SO_4, filtered and evaporated to give 140 mg of an orange oil. Purification of the crude compound on a flash silica column (98:2 pentane/ether) yielded 20 mg of a colorless semi-solid 15%.

R_f = 0.27 (98:2 pentane/ether)

IR (neat) 2900, 2110

UV (CH_3CN) λ_{max} 274, 290

^1H NMR δ 6.0 (2H, s), 0.66 (4H, s), 0.16 (12H, s)

^{13}C NMR δ 121.8 (CH), 103.0 (C), 100.2 (C), 8.7 (CH_2), -2.5 (CH_3).

(3*R*,4*S*)-1-Bromo-2-(2-bromoethyl)-cyclohexa-1,5-diene-3,4-diol (9).

Fermentations using *Pp* 39/D were carried out as described earlier using toluene as the inducer.[216] From 5 g of 1-bromo-2-(2-bromoethyl)benzene, 174 mg of crude extract was obtained. After HPLC purification of the mixture using a Microsorb C18 prep. column, 70/30 methanol/water, and a flow rate of 10 ml/min, the pure compounds eluted as follows: 87 mg of toluene diol as a result of the induction, 25 mg (3 mg/L) of the furan **197** and 18 mg (2 mg/L) of the desired diene diol **9**.

R_f = 0.37 (1:1 hexane/ethyl acetate)

mp = 59-63 °C

$[\alpha]_D^{26}$ = +72.1 (c = 0.64, MeOH)

^1H NMR δ 6.08 ((1H, dd, J = 9.9, 2.5), 5.86 (1H, dd, J = 9.9, 2.5) 4.37 (1H, m), 4.21 (1H, m), 3.57 (2H, m), 3.05 (1H, m), 2.95 (1H, p), 2.43 (1H, d, J = 8.9),
2.27 (1H, d, J = 8.4)

^{13}C NMR ($CDCl_3$) δ 135.7 (C), 130.0 (CH), 129.9 (CH), 119.0 (C), 71.1 (CH), 67.9 (CH), 36.5 (CH2), 29.9 (CH2).

MS *m/z* (rel. int.) EI+ 300 (M+2, 1), 298 (M, 2), 280 (28), 199 (37), 185 (65), 91 (100)

(7*S*, 7a*R*)-4-Bromo-2,3,7,7a-tetrahydrobenzofuran-7-ol (197).

^1H NMR δ 6.16 (1H, d, J = 9), 5.97 (1H, ddd, J = 1, 5.7, 9), 4.30 (2H, m), 4.22 (1H, t, J = 5.7), 4.00 (1H, m), 2.67 (2H, m), 2.19 (1H, s)

^{13}C NMR δ 140.1, (C), 131.9 (CH), 125.4 (CH), 106.6 (C), 81.7 (CH), 68.2 (CH_2), 61.9 (CH), 32.1 (CH_2)

(3*R*,4*S*)-1-Bromo-2-(2-bromoethyl)-cyclohexa-1-ene-3,4-diol (198). To an ice cooled solution of diol **9** (1.19 g, 3.69 mmol) in methanol (10 mL) was added potassium azodicarboxylate (1.43 g, 7.38 mmol). A solution of acetic acid (4.2 mL, 73.8 mmol) in methanol (10 mL) was added dropwise over 1 hour. The solution was allowed to gradually warm to room temperature and stirred overnight. After slow addition of saturated aq. $NaHCO_3$ solution (10 mL), the solvent was concentrated under reduced pressure. The remaining residue was dissolved in water (10 mL) and brine (15 mL) and extracted with ethyl acetate (3 x 15 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and evaporated. Purification by flash column chromatography (1:1 hexane/ethyl acetate) yielded 553 mg of a white solid **198**, 50% and 258 mg, 32% of a yellow oil, **8.**

R_f = 0.42 (1:1 hexane/ethylacetate)

mp = 119-120 °C

$[\alpha]_D^{26}$ = -69.0 (c = 0.93, $CHCl_3$)

IR (KBr) 3250 (br), 2980, 1490

^1H NMR δ 4.18 (1H, d, J = 3.2), 3.86 (1H, m), 3.54 (2H, m), 2.90 (2H, m)2.63 (3H, m), 1.93 (1H, m), 1.77 (2H, m)

^{13}C NMR δ 133.4 (C), 127.4 (C), 70.2 (CH), 68.2 (CH), 37.7 (CH_2), 34.7 (CH_2), 29.8 (CH_2), 27.1 (CH_2)

MS *m/z* (rel. int.) EI+ 302 (M+2, 5), 300 (m, 11), 283 (64), 175 (58), 67 (100)

HRMS calcd for $C_8H_{12}O_2Br_2$ (M-OH) 280.9177, found 280.9184.

(7*S*,7a*R*)-4-Bromo-2,3,5,6,7,7a-hexahydrobenzofuran-7-ol (8). The diol **9** (126 mg, 0.57 mmol) was dissolved in acetone (8 mL). K_2CO_3 (629 mg, 4.56 mmol) was added and the mixture was stirred at room temperature overnight. After filtration through

celiet and purification on a flash silica gel column (1:1 hexane/ethyl acetate), 48 mg of **8** as a colorless oil was obtained in a 61% yield.

R_f = 0.32 (1:1 hexane/ethyl acetate)

$[\alpha]_D^{26}$ = +50.6 (c = 0.8, $CHCl_3$)

IR (neat) 3450, 2950, 1310

^1H NMR ($CDCl_3$) d 4.27 (1H, s), 4.06 (2H, m), 3.93 (1H, m), 2.63 (3H, m), 2.40 (1H, m), 2.25 (1H, s), 2.07 (1H, m), 1.73 (1H, m)

^{13}C NMR δ 133.7 (C), 115.9 (C), 79.2 (CH), 66.3 (CH_2), 63.7 (CH), 32.4 (CH_2), 30.6 (CH_2), 27.2 (CH_2)

MS *m/z* (rel. int.) EI+ 221 (M+2, 8), 219 (M, 9), 139 (76), 95 (100)

(3*R*,4*S*)-3,4-isopropylidenedioxy-1-bromo-2-(2-bromoethyl)-cyclohe-1-ene-3,4-diol (199). The diol **198** (776 mg, 2.59 mmol) was dissolved in acetone. 2,2-Dimethyoxy propane (6 ml) and a catalytic amount of *p*-tolune sulfonic acid were added. after stirring the mixture at room temperature fo three hours, the contents were concentrated to afford 843 mg of a brown oil. Purification of the mixture using a flash column (10% deactivated silica, 9:1 hexane/ethyl acetate), yielded 790 mg of a pale yellow oil, 90%.

R_f = 0.21 (20:1 hexane/ethyl acetate)

$[\alpha]_D^{25}$ = +93.7 (c = 1.2 CHCl3)

IR (neat) 3100, 2900,1100

^1H NMR δ 4.52 (1H, d, J = 4), 4.38 (1H, m), 3.54 (2H, m), 2.83 (3H, m), 2.42 (1H, ddd, J = 17.5, 4, 3.4), 2.03 (1H, m), 1.87 (1H, m), 1.37 (3H, s), 1.35 (3H, s)

^{13}C NMR ($CDCl_3$) d 132.0 (C), 126.2 (C), 109.1 (C), 75.7 (CH), 72.4 (CH), 37.2 (CH_2), 31.7 (CH_2), 27.8 (CH_3), 26.5 (CH_3), 26.2 (CH_2)

MS *m/z* (rel. int.) 342 (M+2, 5), 340 (10), 259 (31), 183 (62), 55 (100)

HRMS calcd for $C_{11}H_{16}O_2Br_2$ 337.9517 found 337.9515.

(3*R*,4*S*)-3,4-isopropylidenedioxy-1-bromo-2-(2-oxazoloethyl)-cyclohexa-1-ene-3,4-diol (10). An argon filled, flame dried flask was charged with the oxazolone (185 mg, 2.16 mmol) and NaH (75 mg, 1.87 mmol). The mixture was dissolved in 5 mL dry DMSO at 0 °C which immediately induced foaming of the solution. After stirring for 15 minutes, the mixture began to solidify. To the semi-solid mixture was added the acetonide 199 (490 mg, 1.44 mmol) in 3 mL DMSO, dropwise. An additional 2 mL DMSO was used to rinse the flask containing the acetonide and was subsequently added dropwise to the mixture. After allowing the solution to gradually warm to room temperature over 5 hours, 10 mL of water was added to quench the reaction. After washing with brine (10 mL), extraction with ethyl acetate (3 x 15 mL) and drying over $MgSO_4$, the combined organics were filtered and evaporated to give 1.3 g of a crude oil. Purification on a flash column (7:3 hexane/ethyl acetate), yielded 153 mg of the N-alkylated compound **10** (30%) and 238 mg of the product resulting from elimination **200** (64%).

R_f = 0.43 (1:1 hexane/ethyl acetate)

$[\alpha]_D^{27}$ = +42.4 (c = 0.83, $CHCl_3$)

IR (neat) 3486, 3207, 1523, 1347

^{1}H NMR δ 6.77 (1H, d, J = 2.1), 6.57 (1H, d, J = 2.1), 4.54 (1H, d, J = 5), 4.36 (1H, ddd, J = 5, 5, 3), 3.87 (1H, m), 3.63 (1H, m), 2.69 (3H, m), 2.38 (1H, ddd, J = 17.2, 4.6, 4.6), 1.97 (1H, m), 1.86, (1H, m)

^{13}C NMR δ 155.6 (C=O), 130.4 (C), 127.4 (CH), 126.6 (CH), 115.8 (CH), 109.0 (C), 75.2 (CH), 72.5 (CH), 41.4 (CH_2), 33.4 (CH_2), 31.9 (CH_2), 27.7 (CH_3), 26.4 (CH_2), 26.3 (CH_3)

Anal calcd for $C_{14}H_{18}O_4NBr$ C 48.84, H 5.28; found C 48.78, H 5.27.

11a and 11b: In a flame dried flask charged with argon, the acetonide 199 (150 mg, 0.436 mmol) was dissolved in freshly distilled benzene (25 mL). After the solution was degassed with a stream of argon, tributyltin hydride (0.12 mL, 0.479 mmol) was quickly added via glass pipette. A catalytic amount of AIBN was added and the solution was brought to reflux for 1 hour and 30 minutes. The solvent was then evaporated and the residue was applied to a flash silica column (6:4 hexane/ethyl acetate) to give 46 mg of a viscous oil (**11a**) and 30 mg of a solid (**11b**), 66% overall.

(5R,10R,11S) 10,11,12,13-tetrahydrobenzo-10,11-dimethylmethylenedioxy-1-aza-3oxabicyclo[4.3.0]non-4-en-2-one (11b).

R_f = 0.16 (7:3 hexane/ethyl acetate)

mp = 102-105 °C

$[\alpha]_D^{26}$ = +201.2 (c = 0.89 $CHCl_3$)

IR (neat) 2980, 1720

^1H NMR δ 4.47 (1H, t, J = 8.5), 4.35 (1H, m), 4.26 (1H, m), 3.98 (1H, q, J = 6.6), 3.91 (1H, t, J = 7.9), 3.01 (1H, ddd, J = 13.3, 11.9, 4.7), 2.55 (1H, m), 2.12 (2H, m), 1.87 (1H, d, J = 16), 1.71, 2H, m), 1.36 (2H, s), 1.31 (3H, s)

^{13}C NMR 129.4 (C), 128.3 (C), 108.9 (C), 75.7 (CH), 72.4 (CH), 66.8 (CH_2), 55.0 (CH), 37.8 (CH_2), 27.9 (CH_3), 26.5 (CH_3), 25.5 (CH_2), 24.3 (CH_2), 19.7 (CH_2)

MS *m/z* (rel. int.) EI+ 265 (2), 250 (28), 190 (51), 105 (100)

HRMS cacld for $C_{14}H_{20}NO_4$ 266.1392 found 266.1394

(5S,10R,11S) 10,11,12,13-tetrahydrobenzo-10,11-dimethylmethylenedioxy-1-aza-3oxabicyclo[4.3.0]non-4-en-2-one (11a).

R_f = 0.09 (7:3 hexane/ethyl acetate)

$[\alpha]_D^{25}$ = -100.8 (c = 0.66 $CHCl_3$)

IR (neat) 2982, 1756

^{1}H NMR δ 4.49 (1H, t, J = 8.8), 4.24 (3H, m), 3.97 (2H, m), 3.01 (1H, ddd, J = 13.6, 12, 4.8), 2.32 (1H, d, J = 12), 2.21 (1H, m), 2.01 (1H, m), 1.83 (3H, m), 1.37 (6H, s)

^{13}C NMR 157.4 (C), 130.2 (C), 128.4 (C), 108.5 (C), 73.6 (CH), 72.7 (CH), 66.7 (CH_2), 54.9 (CH), 38.3 (CH_2), 28.0 (CH_3), 26.2 (CH_3), 25.4 (CH_2), 24.1 (CH_2), 21.0 (CH_2)

MS m/z (rel. int.) EI+ 265 (8), 190 (100), 151 (39), 105 (48)

HRMS cacld for C $_{14}H_{19}NO_4$ 265.1314 found 265.1313

210a and 210b General procedure: A suspension of the acetonide **10a** (288 mg, 1.70 mmol) and Amberlyst® strongly acidic resin (300 mg) in methanol/water (9 mL/1 mL) was stirred at room temperature overnight. The mixture was filtered through a plug of celite and evaporated. The residue was adsorbed onto silica and purified on a flash silica column (8:1 ethyl acetate/ethanol) to afford 200 mg of diol **210a**.

(5R,10R,11S)-10,11,12,13-tetrahydrobenzo-10,11-dioxy-1-aza-3-oxabicyclo[4.3.0]non-4-en-2-one (210a).

Rf = 0.43 (4:1 ethyl acetate/methanol)

mp = 150-153 °C

IR (KBr) 2872, 1740

^{1}H NMR δ 4.47 (1H, t, J =8.7), 4.25 (1H, t, J = 6.7), 3.97 (2H, m), 3.89 (1H, s), 3.75 (1H, s), 3.06 (1H, ddd, J = 13, 11.7, 4.7), 2.61 (1H, d, J = 4.7), 2.40 (1H, m), 2.25 (1H, m), 1.97 (2H, s), 1.80 (2H, m), 1.70 (1H, s)

^{13}C NMR δ 130.4 (C), 130.1 (C), 124.9 (C), 69.0 (CH), 68.3 (CH), 66.6 (CH_2), 55.3 (CH), 38.1 (CH_2), 25.3 (CH_2), 24.9 (CH_2), 24.3 (CH_2)

M/Z (rel. int.)

HRMS calcd for $C_{11}H_{16}NO_4$ 226.1079 found 266.1064

(5S,10R,11S)-10,11,12,13-tetrahydrobenzo-10,11-dioxy-1-aza-3-oxabicyclo[4.3.0]non-4-en-2-one (210b).

R_f = 0.38 (2:1 acetone/ethyl acetate)

$[\alpha]_D^{26}$ = +108.4 (c = 0.5 MeOH)

IR (neat) 3480, 2970, 1720

^{1}H NMR δ 4.46 (1H, t, J = 8), 4.22 (1H, t, J = 7.5), 4.01 (1H, t, J = 8), 3.93 (2H, m), 3.85 (1H, brs), 3.39 (1H, d, J= 7), 3.19 (1H, d, J = 5.6), 2.98 (1H, d, J = 12, 4), 2.54 (1H, brs), 2.03 (1H, s), 1.88 (2H, m), 1.75 (2H, m)

^{13}C NMR δ 157.5 (C), 129.8 (C), 129.4 (C), 70.7 (CH), 68.1 (CH), 67.1 (CH_2), 54.8 (CH) 38.0 (CH_2), 26.1 (CH_2), 25.8 (CH_2), 22.2 (CH_2)

HRMS calcd for $C_{11}H_{15}NO_4$ 225.1001 found 225.0967.

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naphthalenediol; 4,5-dihydroxy-3-oxo-1-cyclohexene-1-carboxylic acid; furo[3.4-d]-1,3-dioxol-4(3aH)-1-dihydro-6-hydroxy-2,2-dimethyl-[3aR-(3aα,6aα)

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229. Unpublished results by T. Hudlicky, G. Butora, and A. Gum.

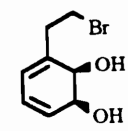
230. Khalil Abboud, Department of Chemistry, University of Florida, Gainesville, FL 32611.

VII. APPENDIX

Selected Spectra

1. (1S.2R)-3-(2-bromoethyl)cyclohexa-3,5-diene-1,2-diol (**2**)
   ^{1}H NMR (270 MHz), ^{13}C NMR (400 MHz)
2. (1S,2R)-3-(2-bromoethyl)cyclohex-5-ene-1,2-diol (**162**)
   ^{1}H NMR (400 MHz), ^{13}C NMR (400 MHz)
3. (7S,7aR)-2,3,5,6,7,7a-hexahydrobenzofuran-7-ol (7)
   ^{1}H NMR (400 MHz), ^{13}C NMR (400 MHz)
4. (1S,2R)-1,2-isopropylidenedioxy-3-(2-bromoethyl)cyclohexa-3,5-diene (**163**)
   ^{1}H NMR (400 MHz), ^{13}C NMR (400 MHz)
5. 1,1,8,8-tetramethyl-1,8-disilacyclodeca-2,6-diyne-4,5-diol (**173**)
   ^{1}H NMR (400 MHz), ^{13}C NMR (400 MHz)
6. 1,1,8,8-tetramethyl-1,8-disilacyclodeca-2,6-diyne-5-(2-propenyloxy)-4-ol (**176**)
   ^{1}H NMR (400 MHz), ^{13}C NMR (400 MHz)
7. 1,1,8,8-tetramethyl-1,8-disilacyclodeca-2,6-diyne-5-(2-propenyloxy)-4-ene (**177**)
   ^{1}H NMR (400 MHz), ^{13}C NMR (400 MHz)
8. 1,1,8,8-tetramethyl-1,8-disilacyclodeca-2,6-diyne-propenyl-4-one (**181**)
   ^{1}H NMR (400 MHz), ^{13}C NMR (400 MHz)
9. Bis[1,2-dimethylsilyl-2-(bromopropynyl)]ethane (**182**)
   ^{1}H NMR (270 MHz), ^{13}C NMR (270 MHz)
10. 5-thia-1,1,8,8-tetramethyl-1,8-disilacyclodeca-2,6-diyne (**183**)
    ^{1}H NMR (270 MHz), ^{13}C NMR (270 MHz)
11. 5-thia-1,1,8,8-tetramethyl-1,8-disilacyclodeca-2,6-diyne-5-oxide (**184**)
    ^{1}H NMR (270 MHz), ^{13}C NMR (270 MHz)
12. 5-thia-1,1,8,8-tetramethyl-1,8-disilacyclodeca-2,6-diyne-5,5-dioxide (**185**)
    ^{1}H NMR (270 MHz), ^{13}C NMR (270 Mhz)

13. 1,1,8,8-tetramethyl-1,8-disilacyclodeca-2,6-diyne-4-ene (**4**)
    ^{1}H NMR (400 MHz), ^{13}C NMR (400 MHz)
14. (3R,4S)-1bromo-2-(2-bromoethyl)cyclohexa-1-ene-3,4-diol (**158**)
    ^{1}H NMR (400 MHz), ^{13}C NMR (400 MHz)
15. (7S,7aR)-4-Bromo-2,3,5,6,7,7a-hexahydrobenzofuran-7-ol (**8**)
    ^{1}H NMR (MHz), ^{13}C NMR (MHz)
16. (3R,4S)-3,4-isopropylidenedioxy-1-bromo-2-(2-bromoethyl)cyclohex-1-ene-3,4-diol (**199**) ^{1}H NMR (400 MHz), ^{13}C NMR (400 MHz)
17. (3R,4S)-3,4-isopropylidenedioxy-1-bromo-2-(2-oxazoloethyl)cyclohexa-1-ene-3,4-diol (**10**) ^{1}H NMR (400 MHz), ^{13}C NMR (400 MHz)
18. (5R,10R,11S)-10,11,12,13-tetrahydrobenzo-10,11-dimethylmethylenedioxy-1-aza-3-oxabicyclo[4.3.0]non-4-en-2-one (**11b**)
    ^{1}H NMR (400 MHz), ^{13}C NMR (400 MHz)
19. (5S,10R,11S)-10,11,12,13-tetrahydrobenzo-10,11-dimethylmethylenedioxy-1-aza-3-oxabicyclo[4.3.0]non-4-en-2-one (**11a**)
    ^{1}H NMR (400 MHz), ^{13}C NMR (400 MHz)
20. (5R,10R,11S)-10,11,12,13-tetrahydrobenzo-10,11-dioxy-1-aza-3-oxabicyclo-[4.3.0]non-4-en-2-one (**210a**)
    ^{1}H NMR (400 MHz), ^{13}C NMR (400 MHz)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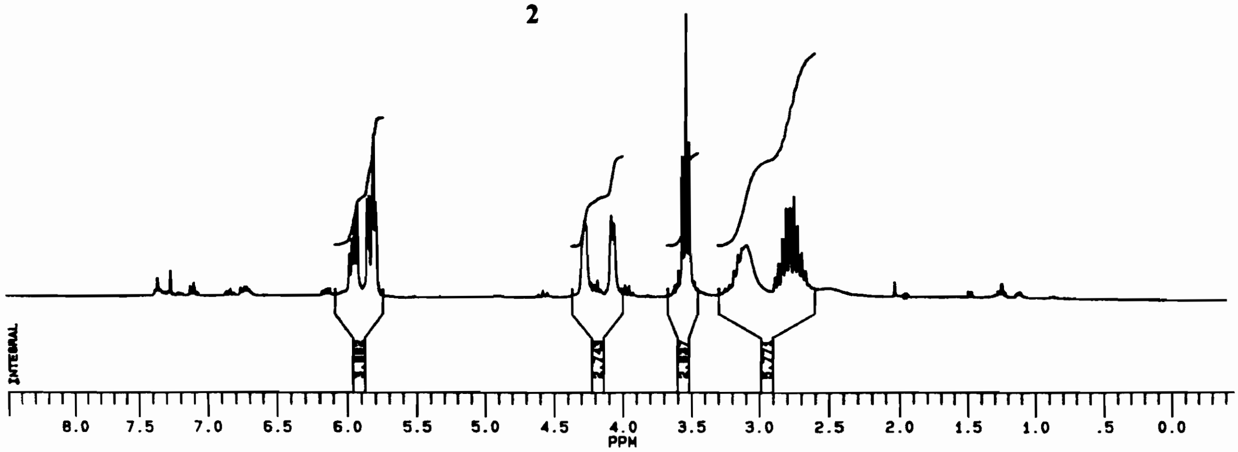
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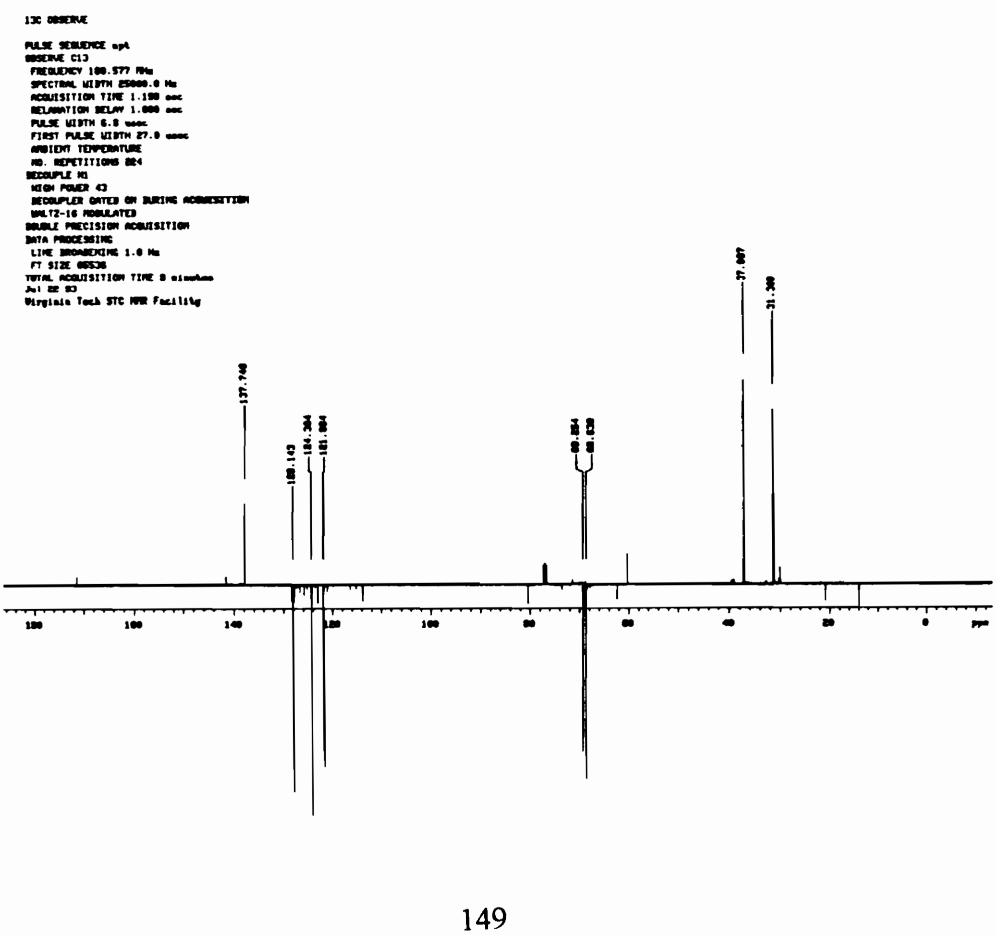
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DECOUPLER GATED ON DURING ACQUISITION
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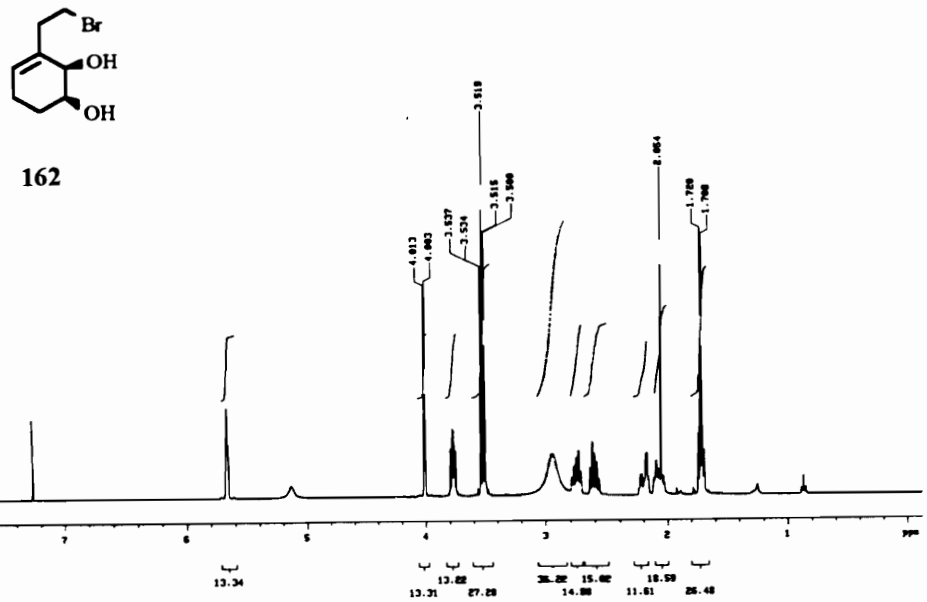

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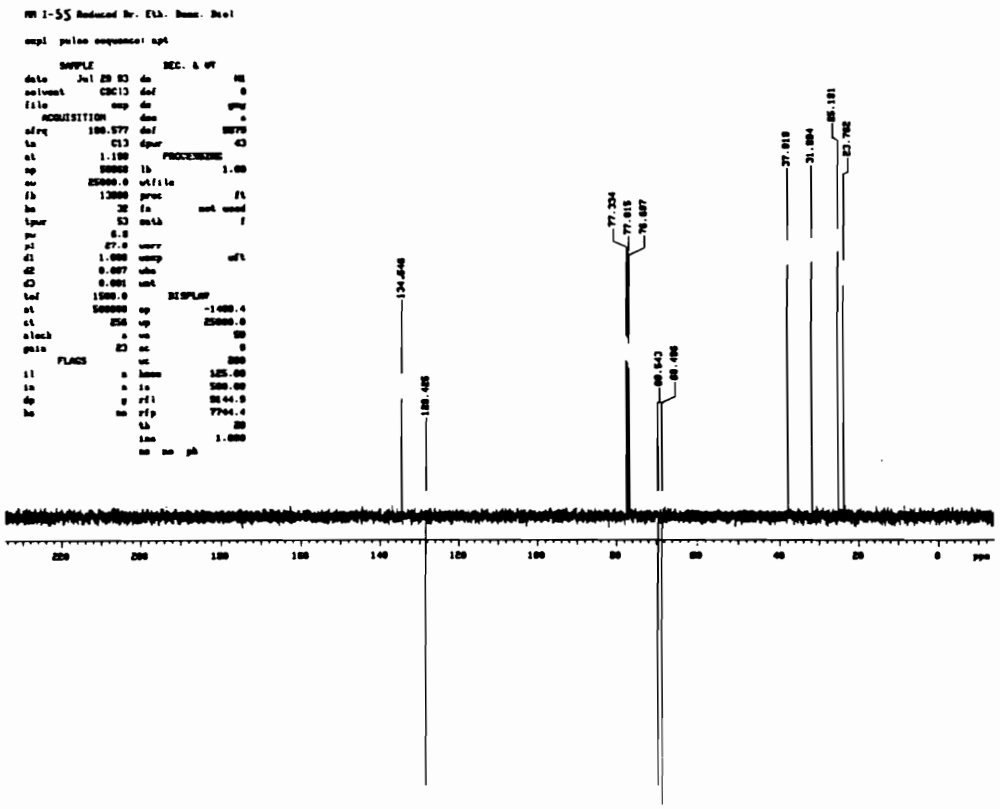

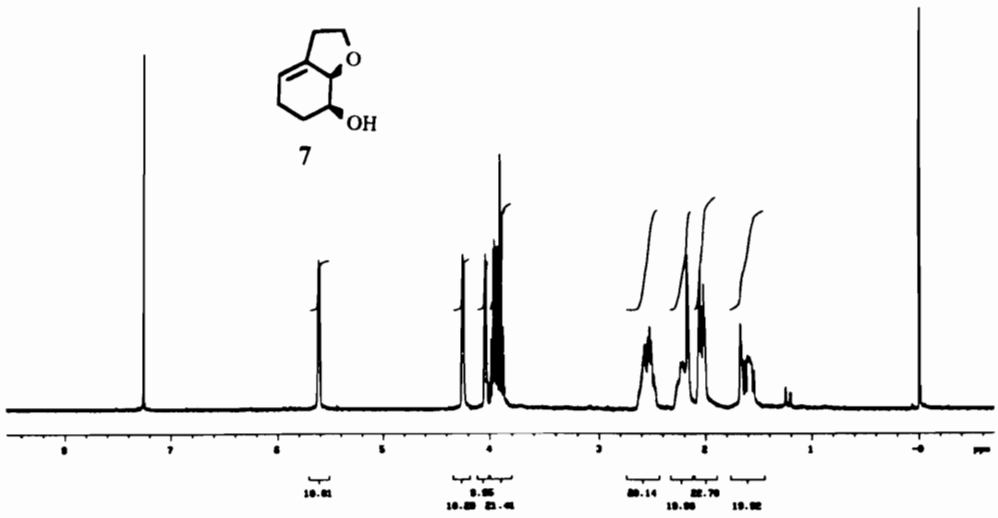
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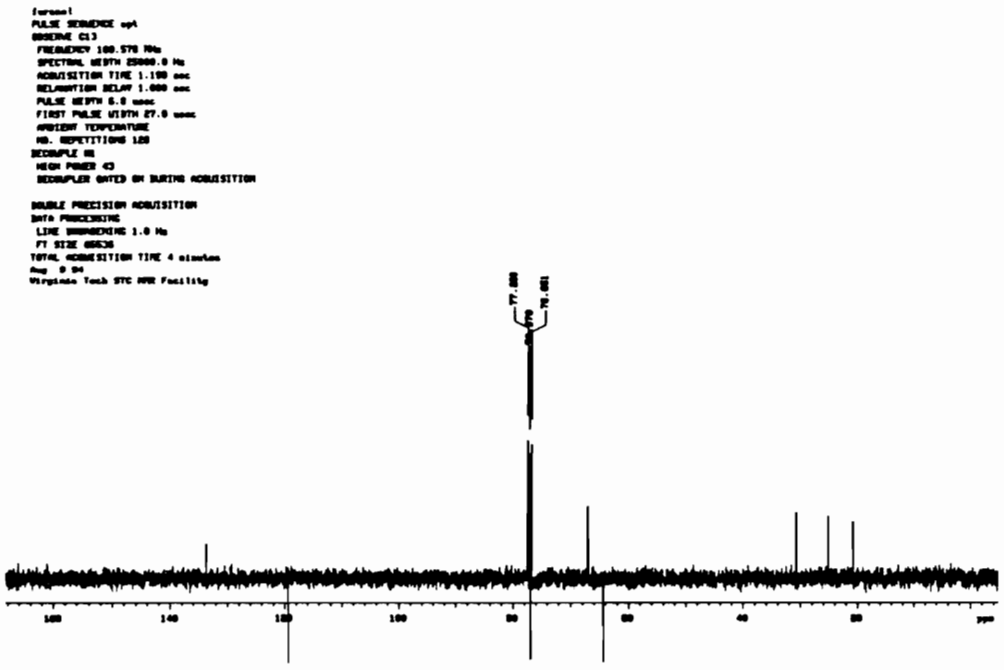
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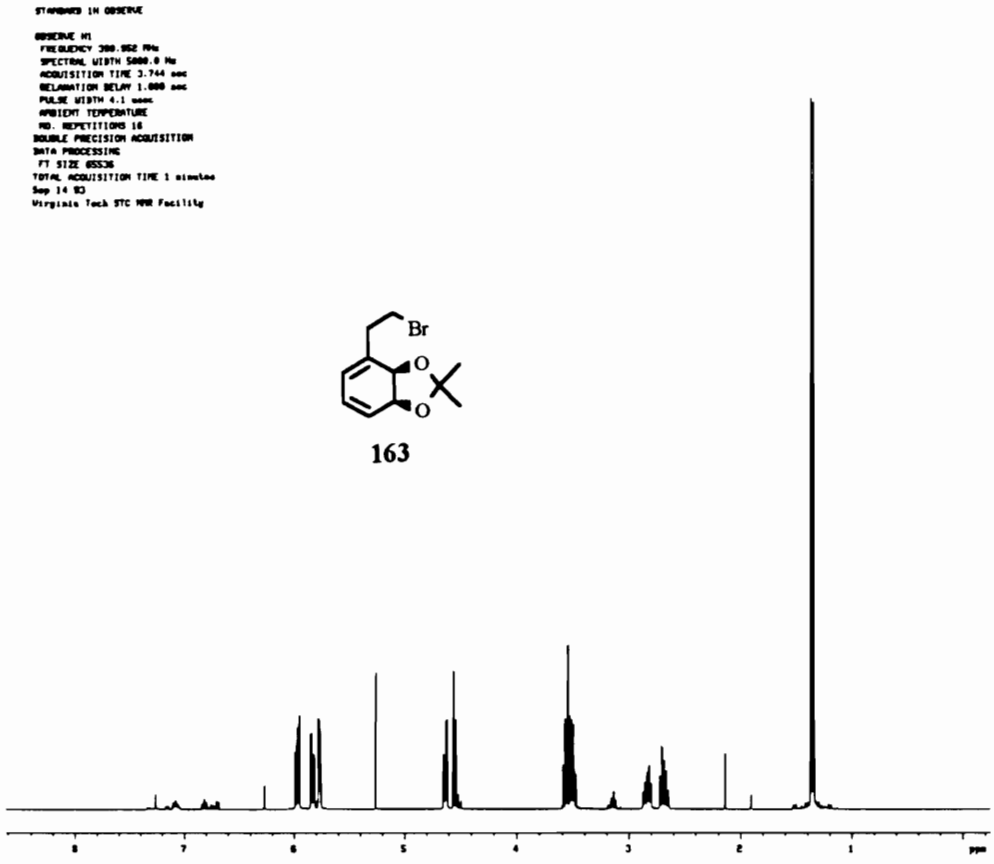
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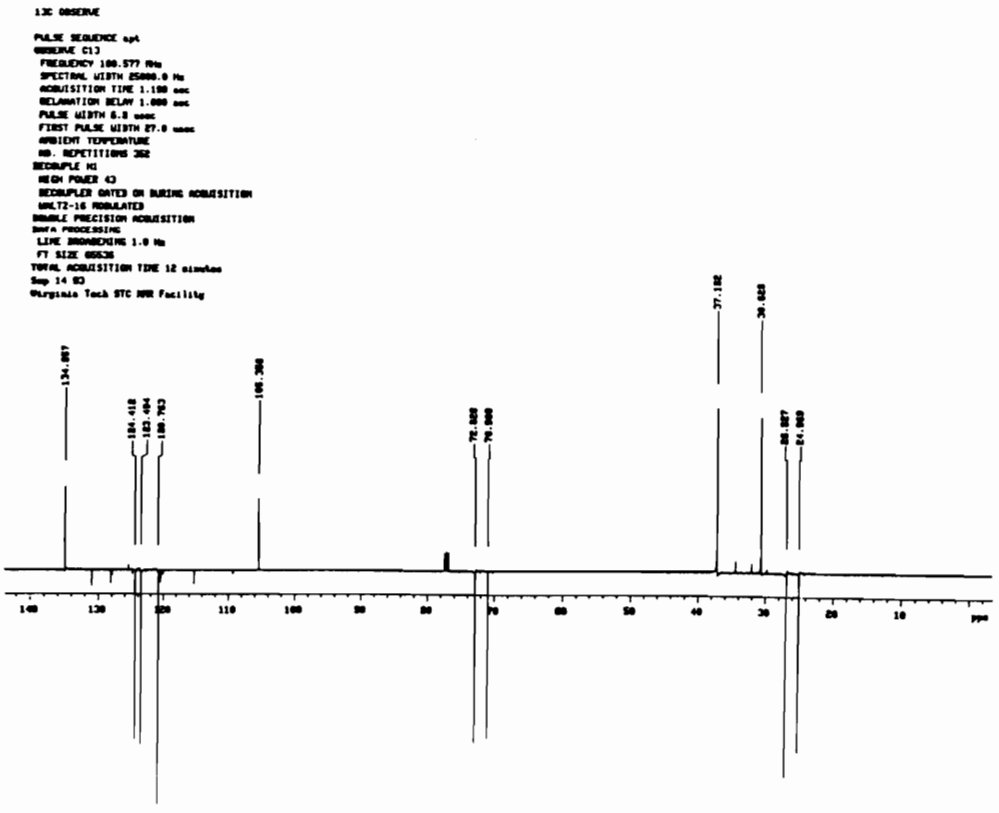
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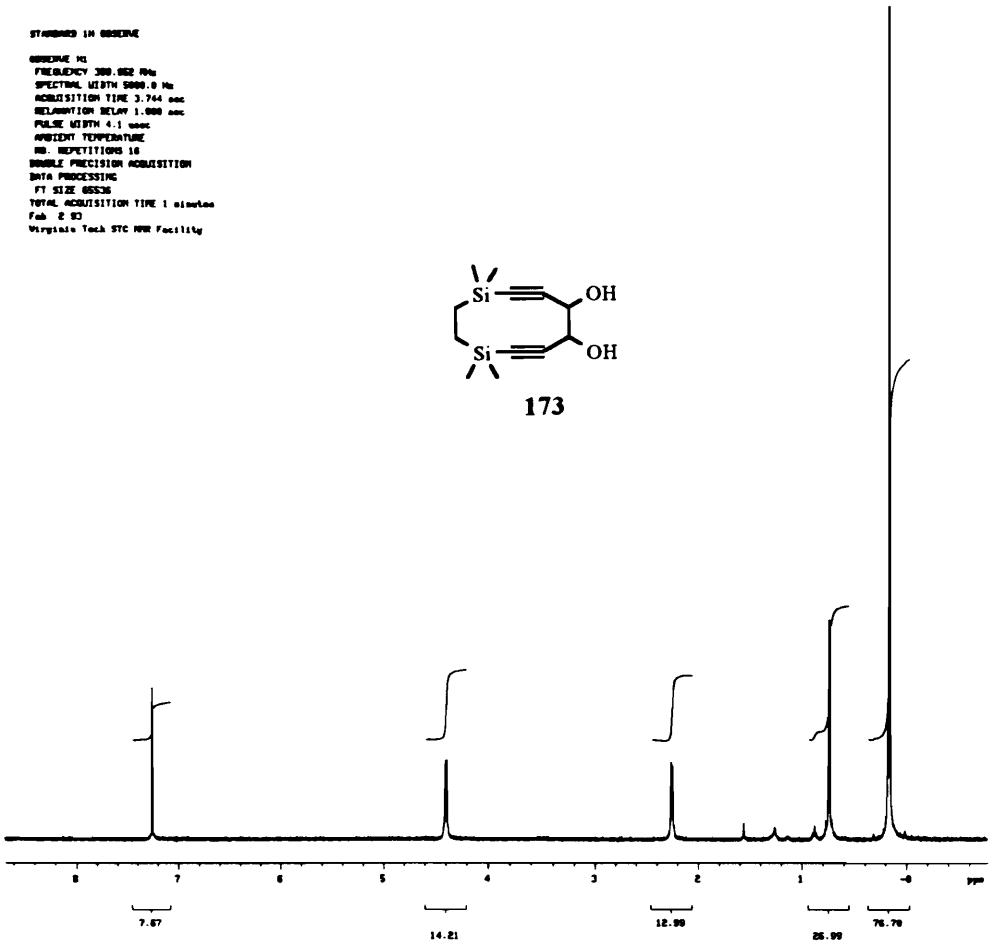
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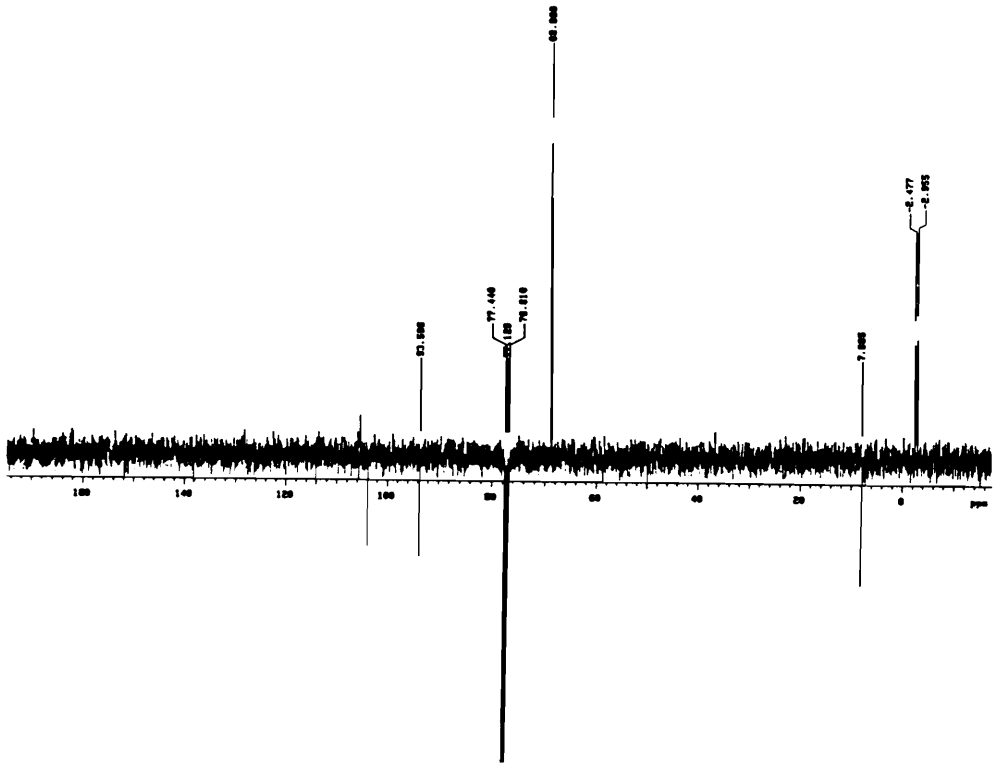


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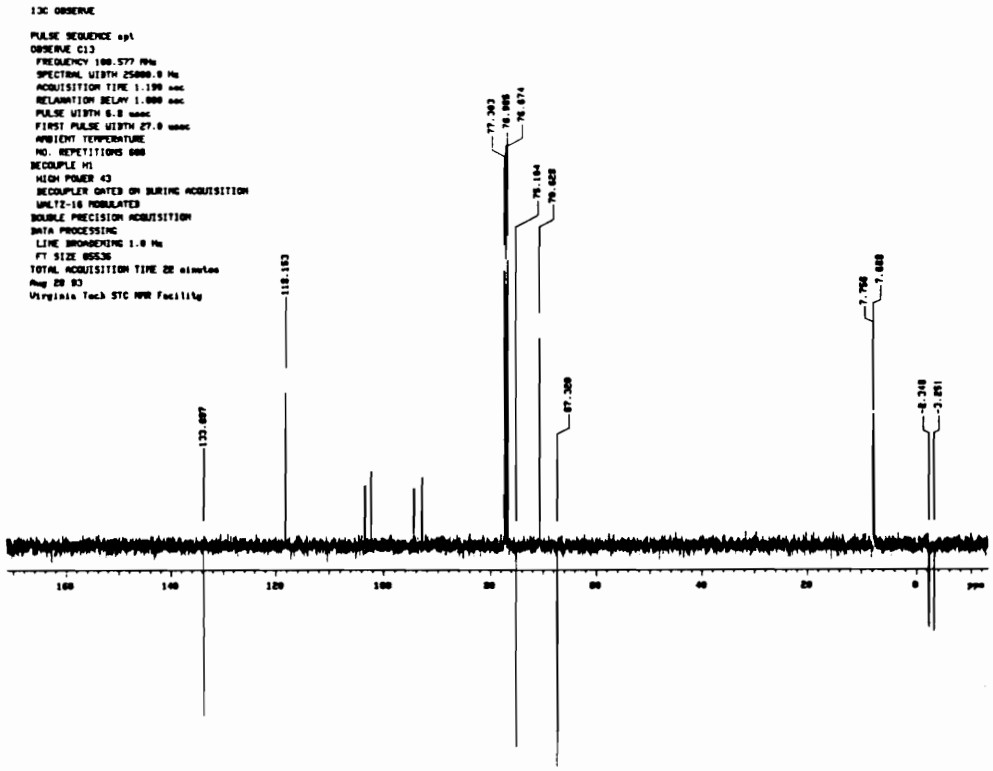
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Aug 29 03
Virginia Tech STC NMR Facility
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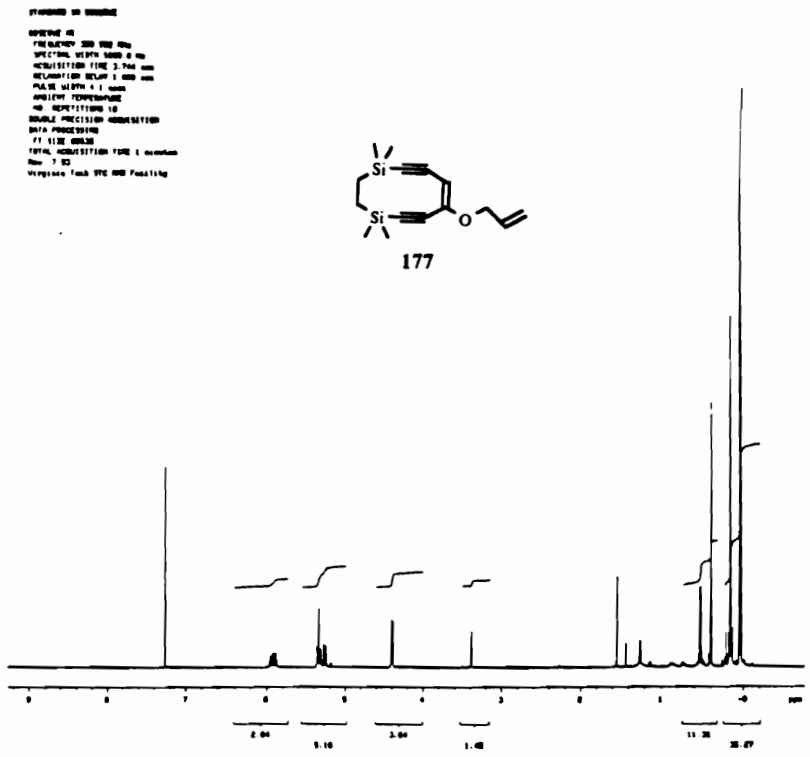

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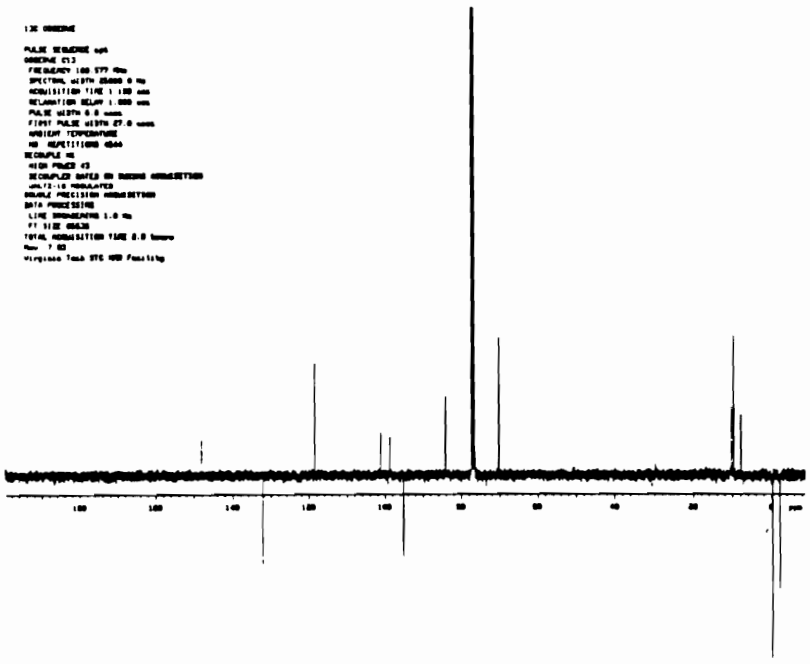

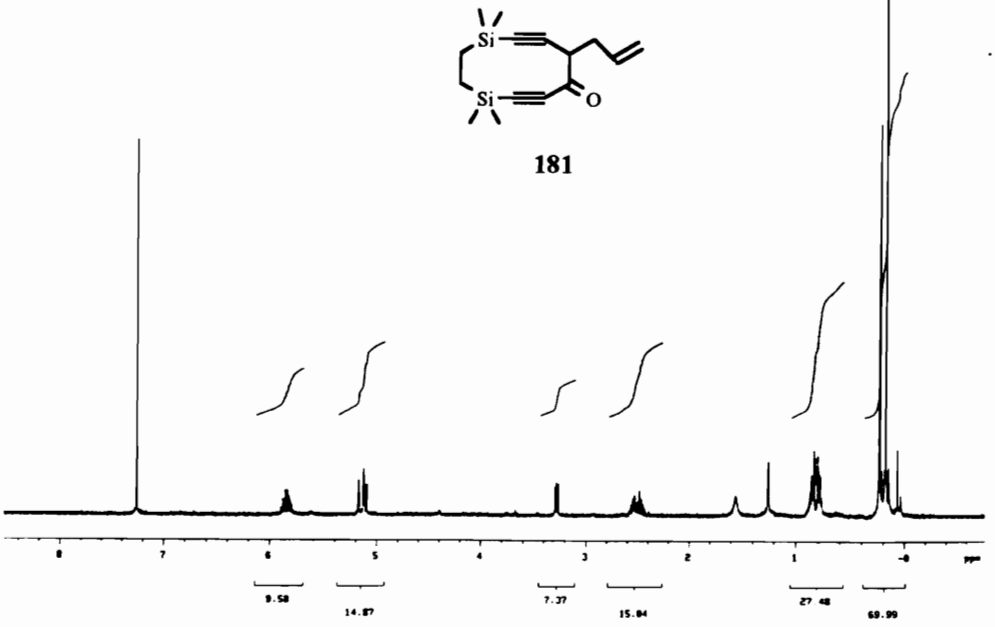
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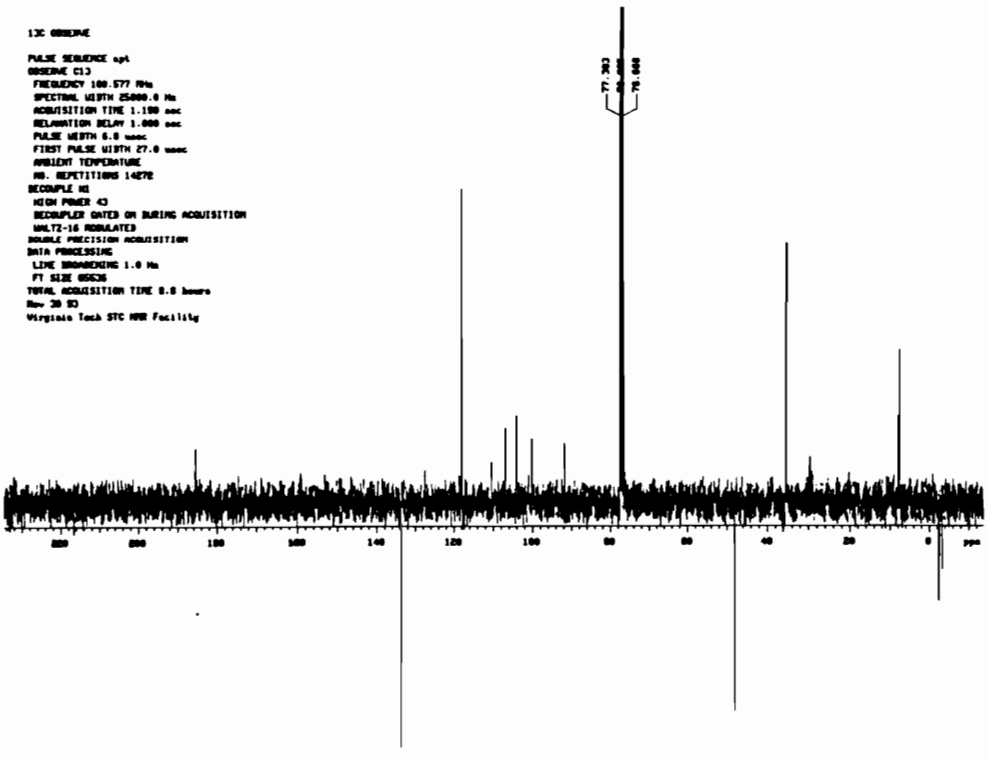
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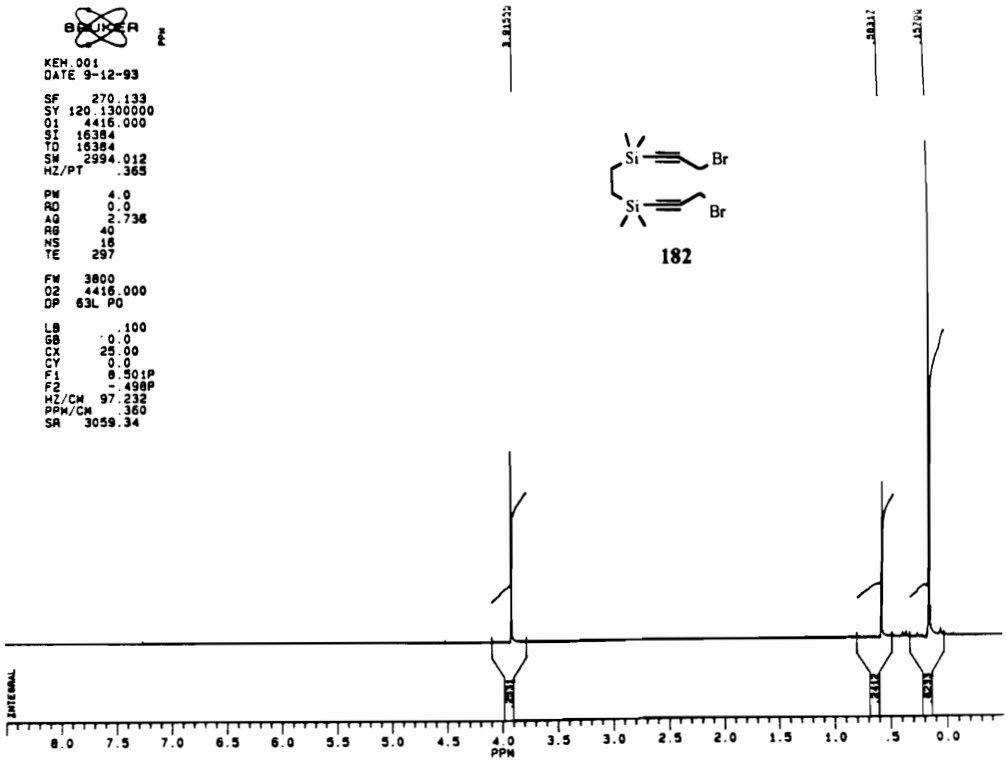
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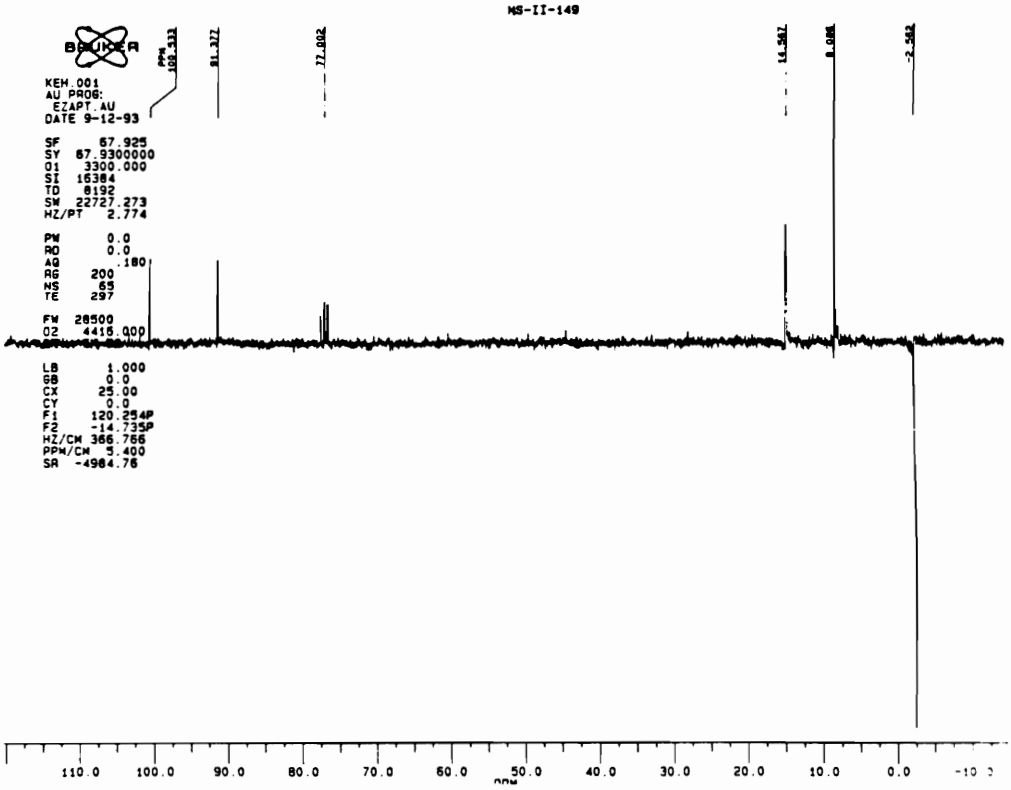
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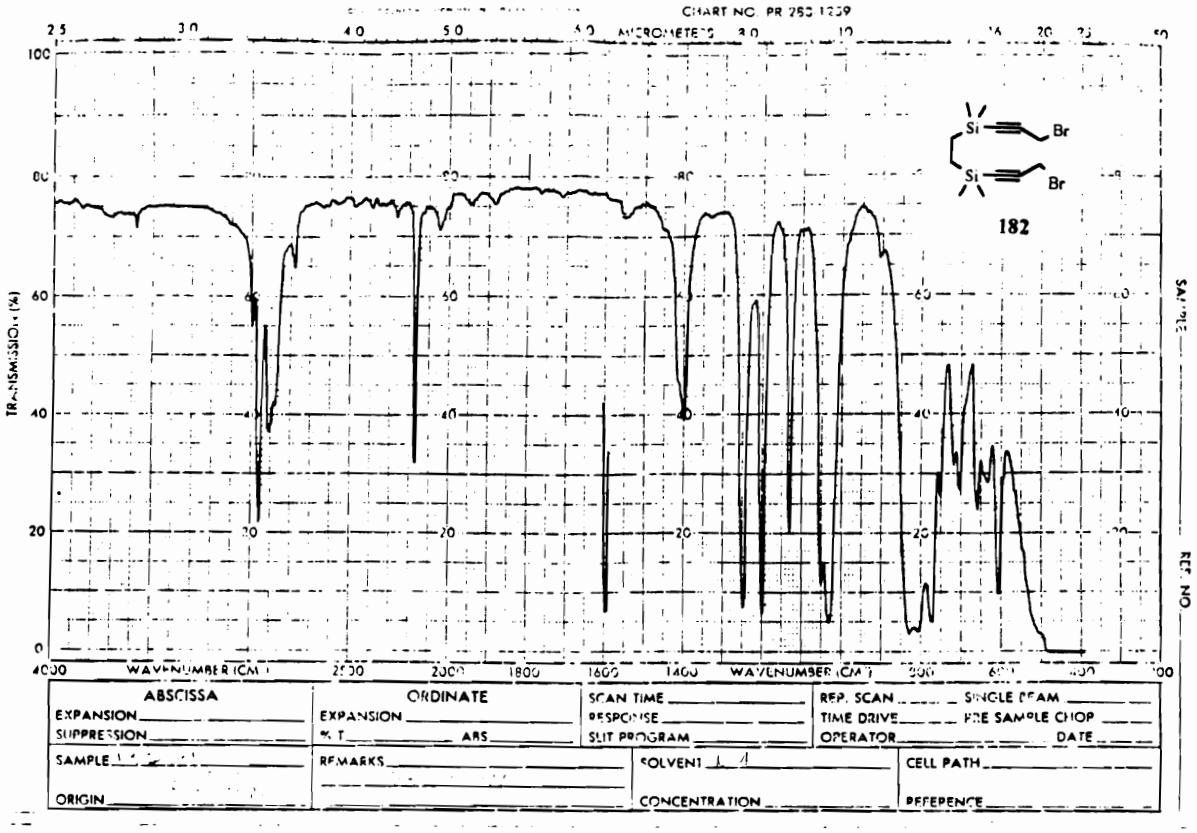
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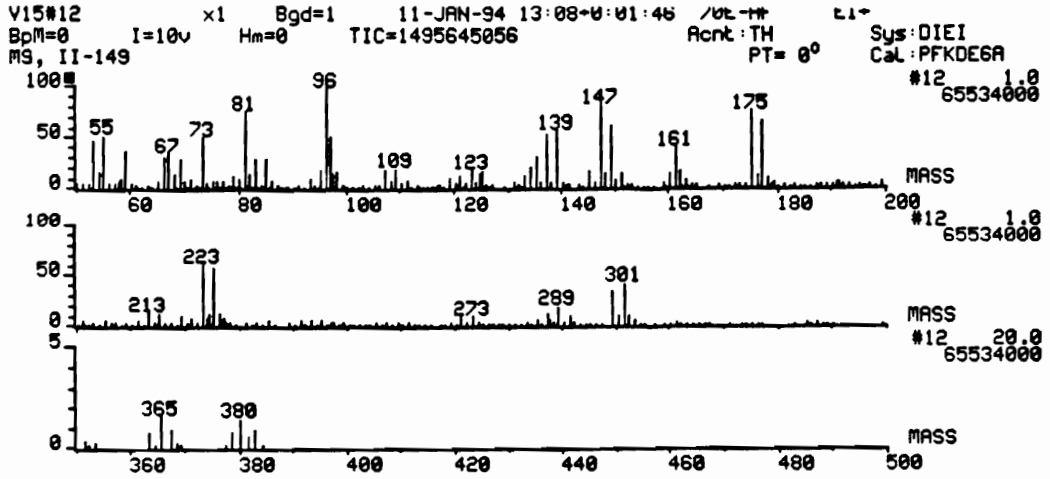
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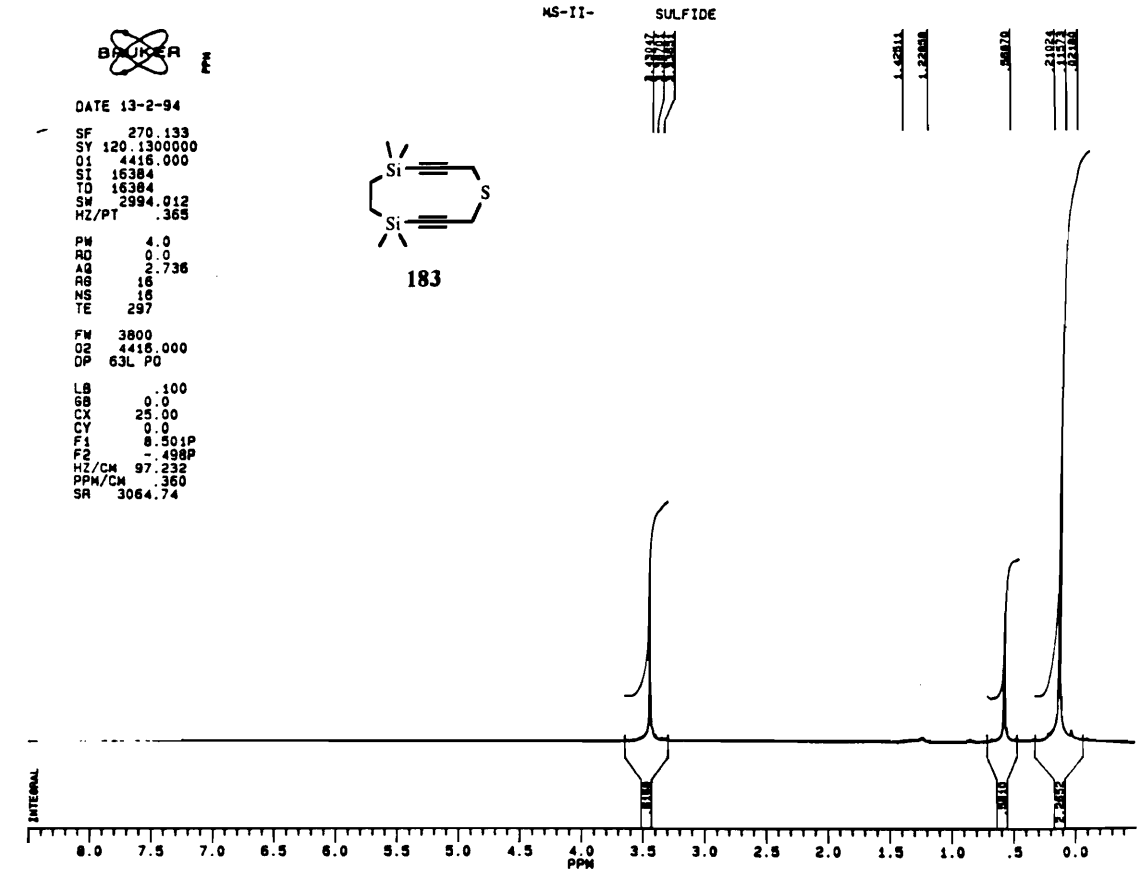
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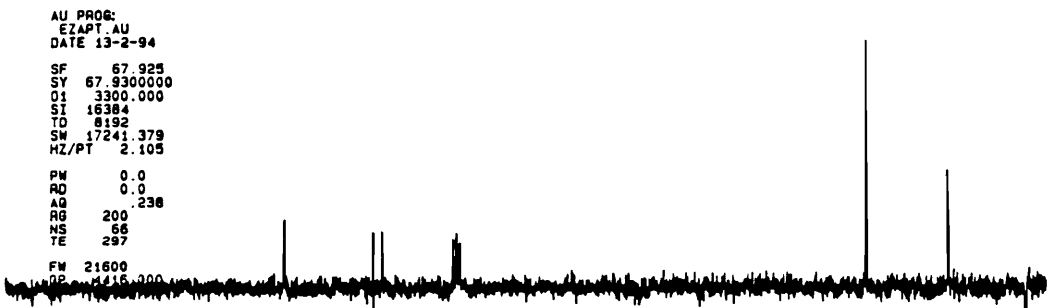
Si
S
Si

183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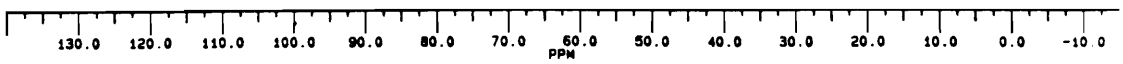
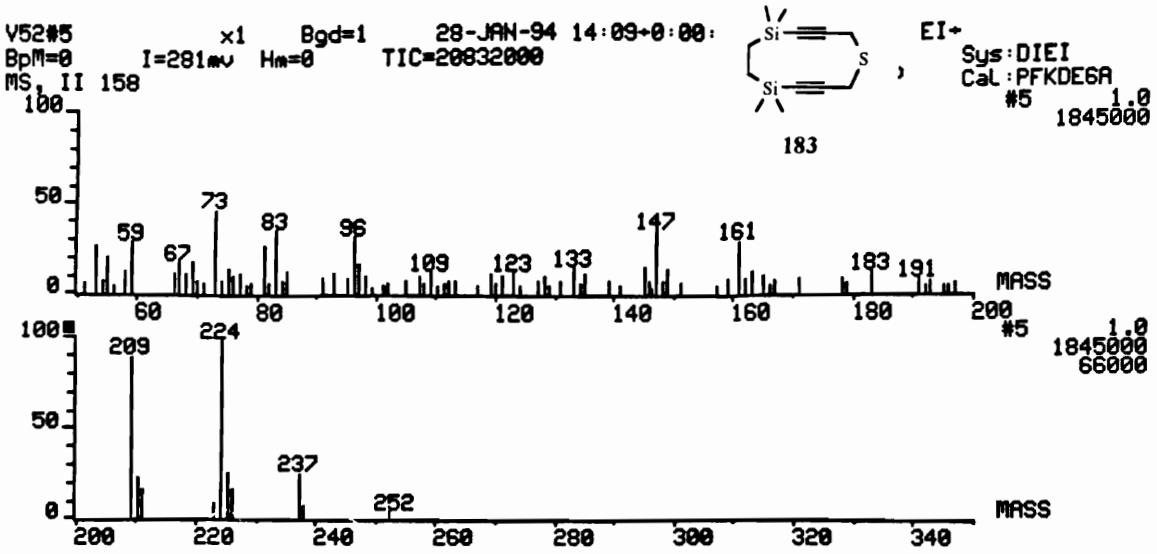
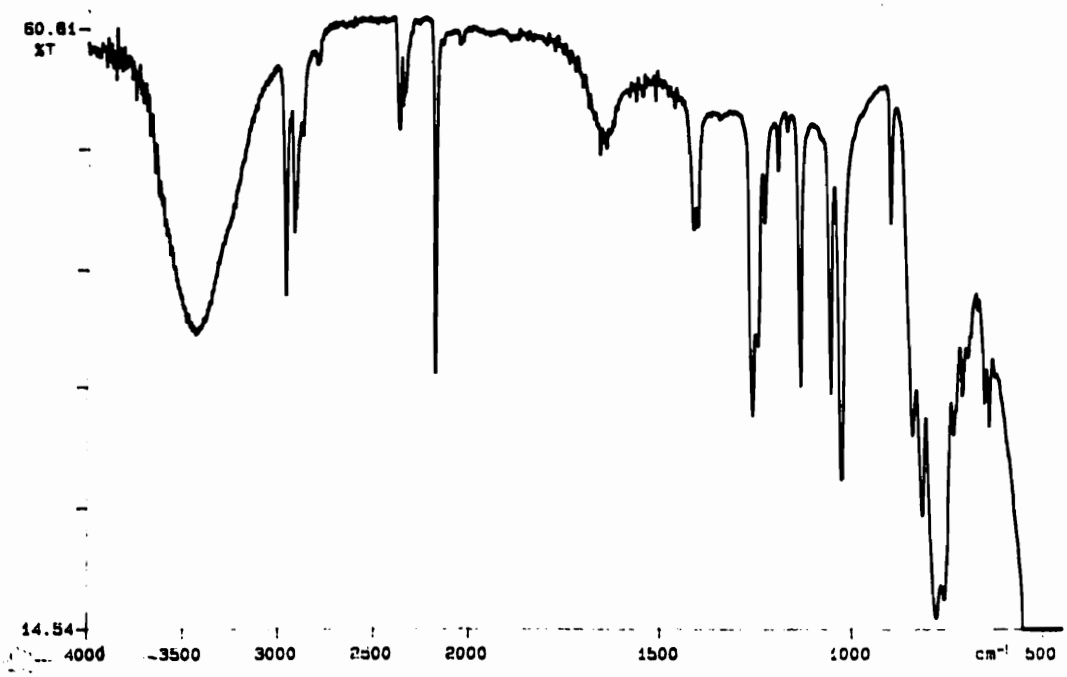
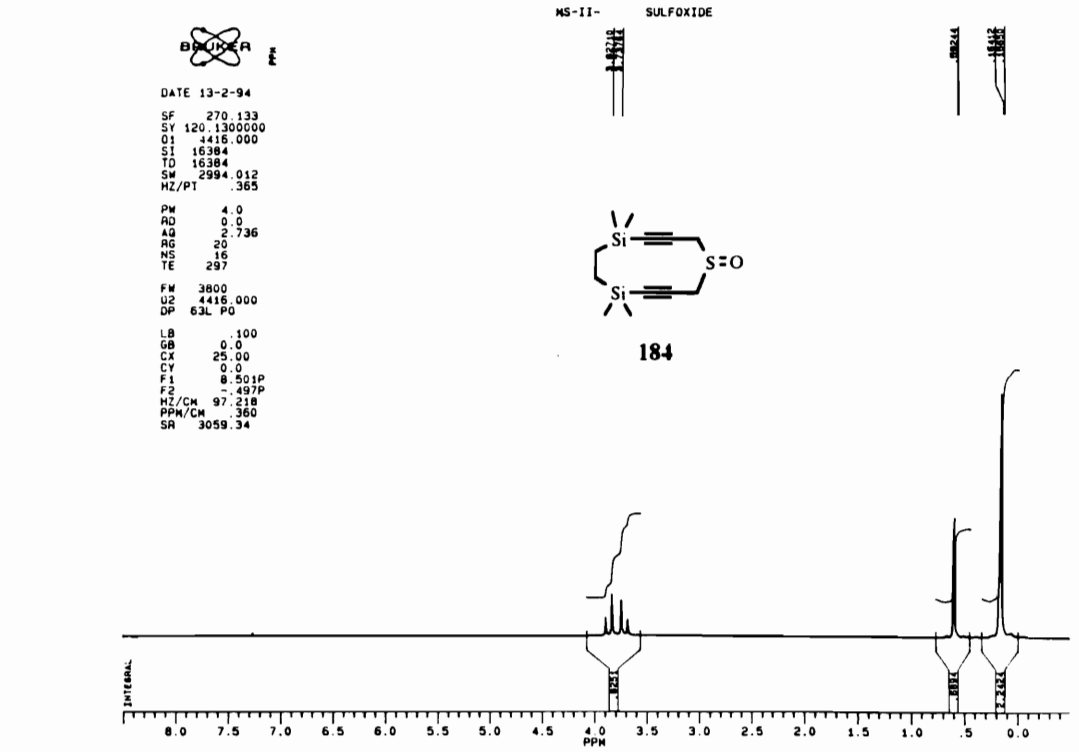
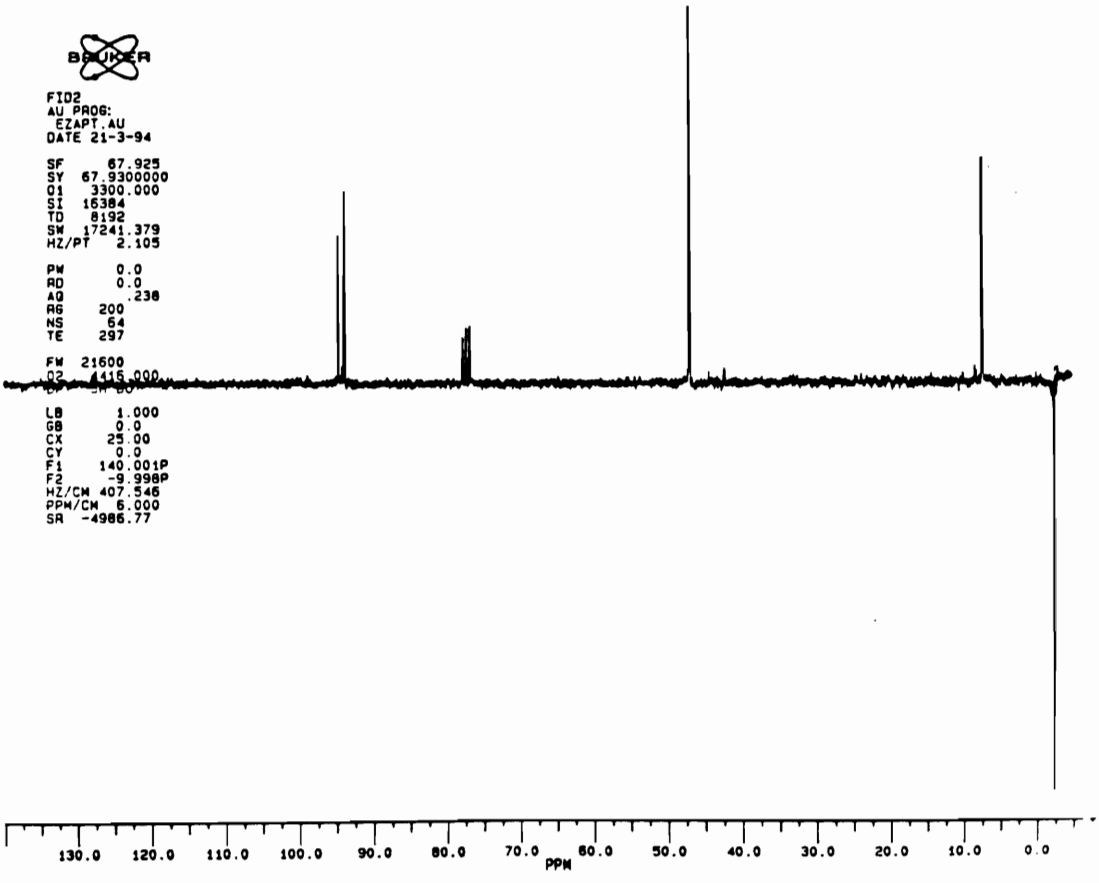

130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0.0 -10.0
PPM


V52#5 x1 Bgd=1 28-JAN-94 14:09+0:00:
BpM=0 I=281mV Hm=0 TIC=20832000
MS, II 158
EI+
Sys:DIEI
Cal:PFKDEGA
#5 1.0
1845000
Si
S
Si
183
MASS
#5 1.0
1845000
66000
MASS


60.81
%T
14.54
4000
3500
3000
2500
2000
1500
1000
cm-1
500


MS-II- SULFOXIDE
DATE 13-2-94
SF 270.133
SY 120.1300000
O1 4416.000
SI 16384
TD 16384
SW 2994.012
HZ/PT .365
PW 4.0
RD 0.0
AQ 2.736
RG 20
NS 16
TE 297
FW 3800
O2 4416.000
DP D3L P0
LB .100
GB 0.0
CX 25.00
CY 0.0
F1 8.501P
F2 -.497P
HZ/CM 97.218
PPM/CM .360
SR 3059.34
Si
S=O
Si
184
INTEGRAL
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5 0.0
PPM


FID2
AU PROG:
EZAPT.AU
DATE 21-3-94
SF 67.925
SY 67.9300000
O1 3300.000
SI 16384
TD 8192
SW 17241.379
HZ/PT 2.105
PW 0.0
RD 0.0
AQ .238
RG 200
NS 64
TE 297
FW 21600
O2 4415.000
LB 1.000
GB 0.0
CX 25.00
CY 0.0
F1 140.001P
F2 -9.998P
HZ/CM 407.546
PPM/CM 6.000
SR -4986.77
130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0.0
PPM

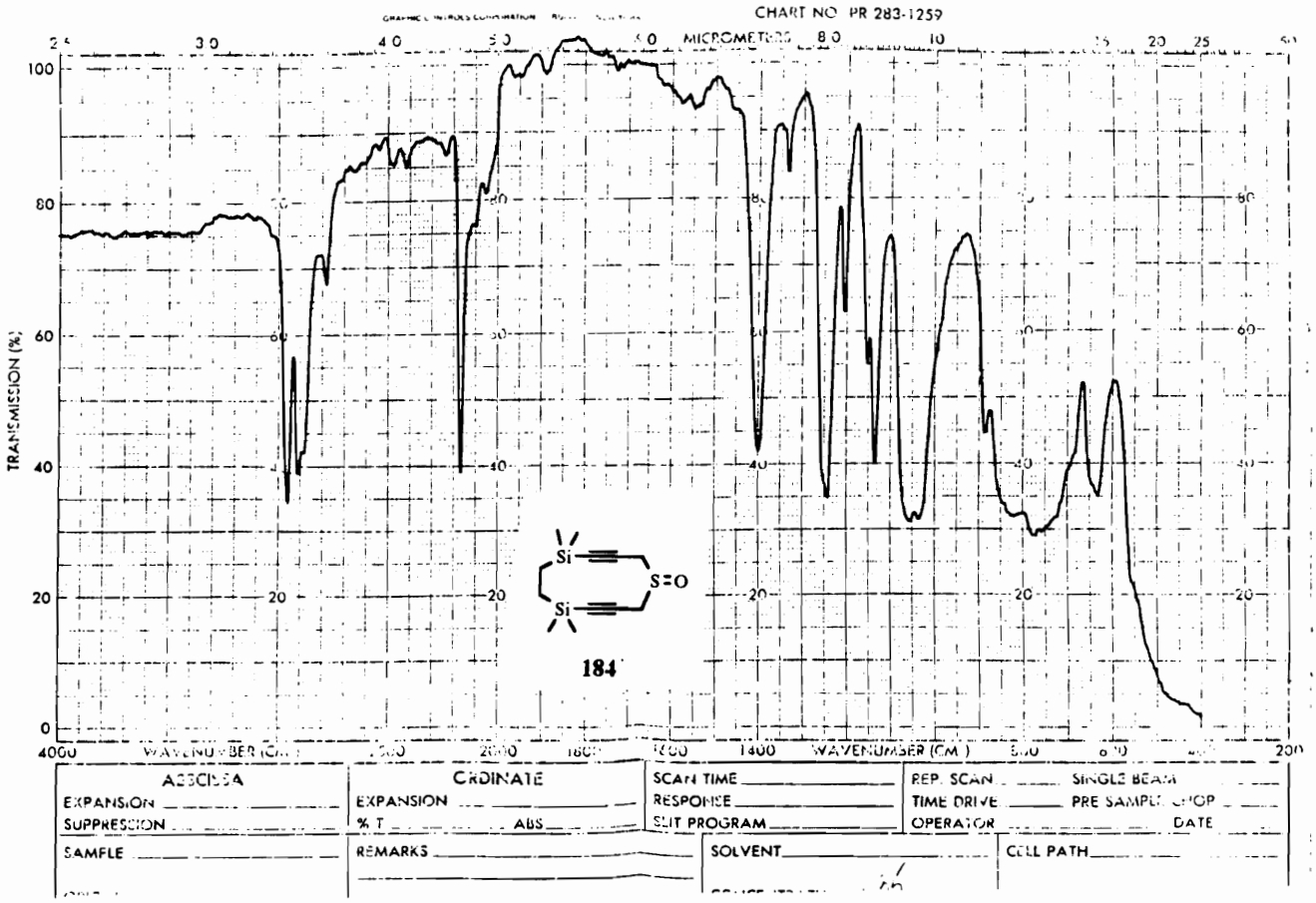
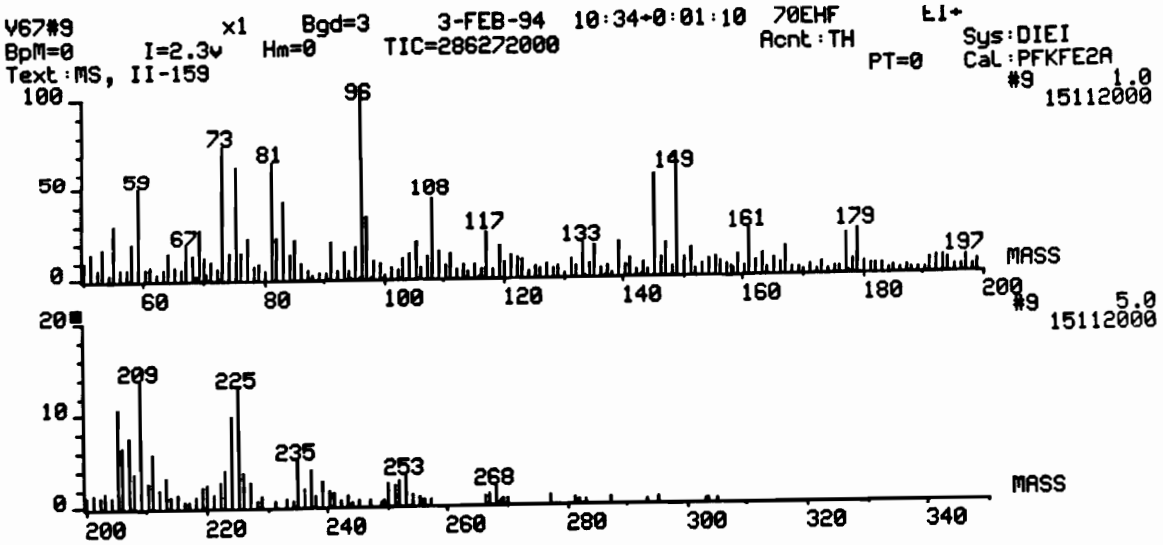
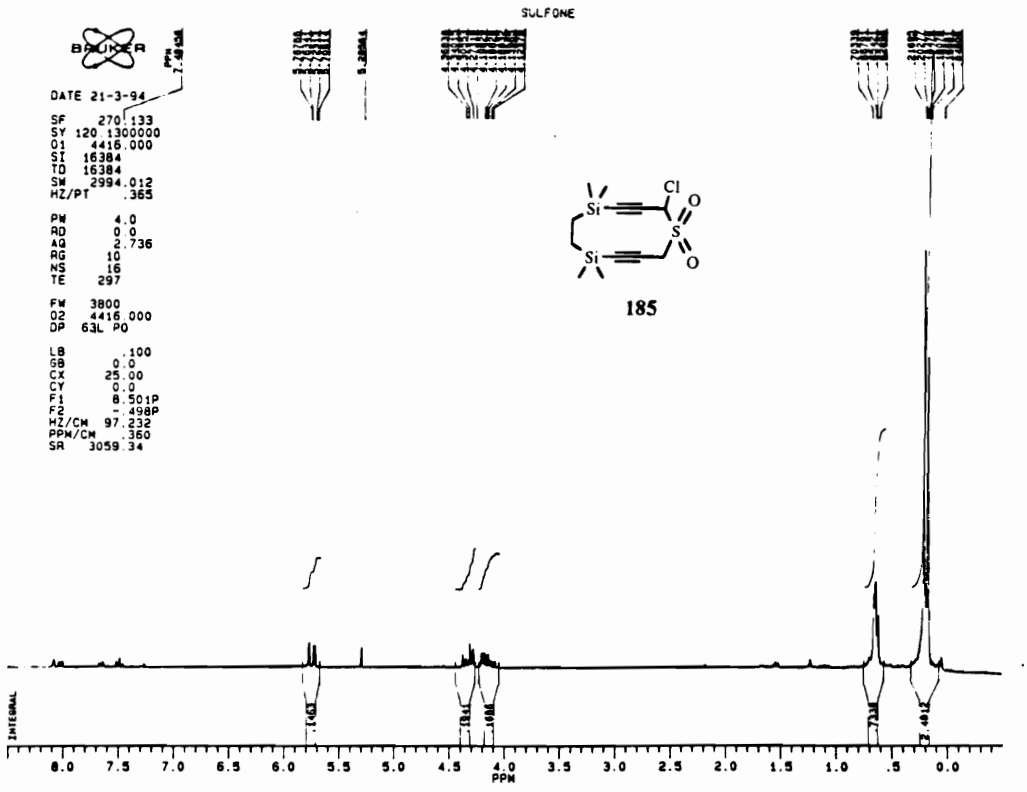
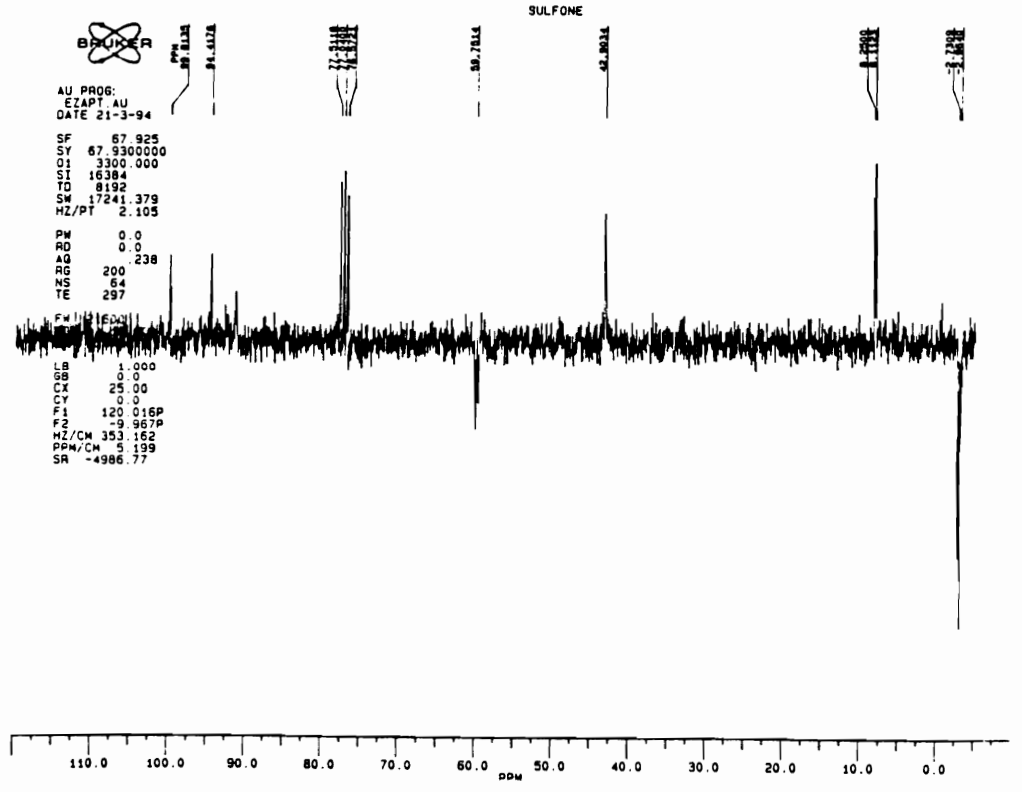
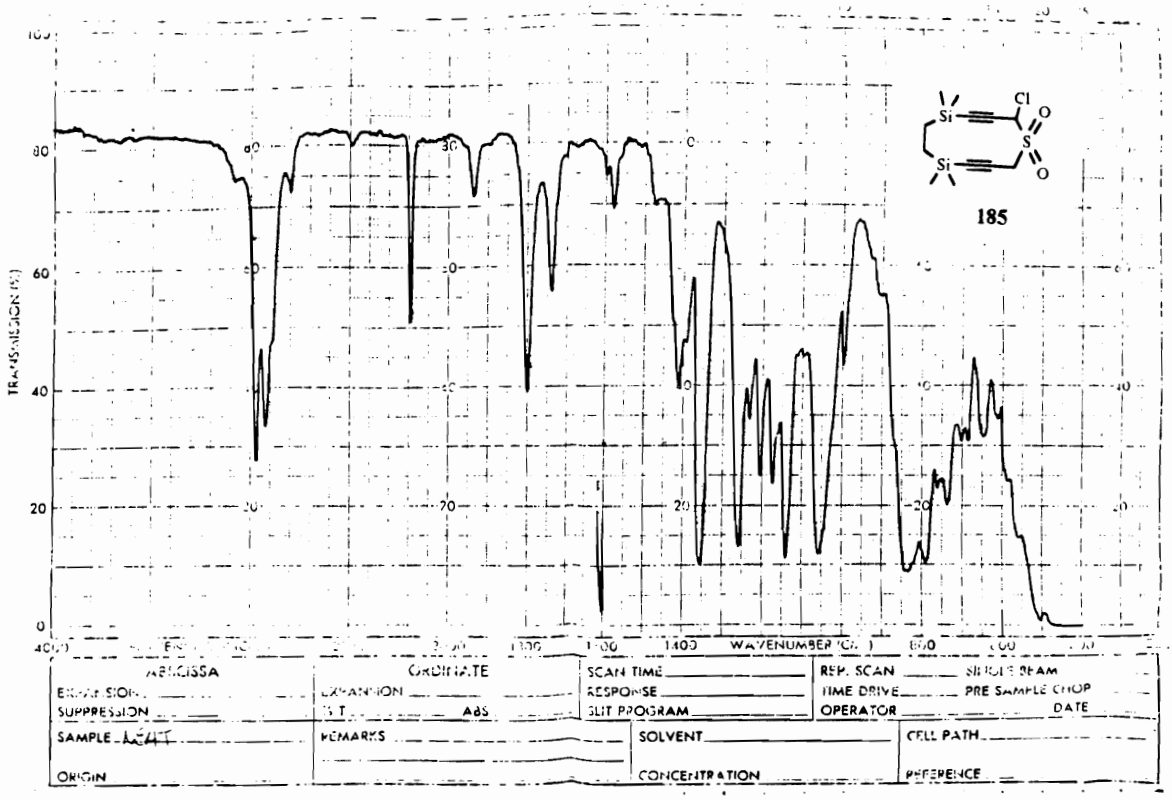


CHART NO. PR 283-1259
MICROMETERS
TRANSMISSION (%)
WAVENUMBER (CM)
Si
S=O
Si
184
ABSCISSA
EXPANSION
SUPPRESSION
ORDINATE
EXPANSION
% T
ABS
SCAN TIME
RESPONSE
SLIT PROGRAM
REP. SCAN
TIME DRIVE
OPERATOR
SINGLE BEAM
PRE SAMPLE CHOP
DATE
SAMPLE
REMARKS
SOLVENT
CELL PATH

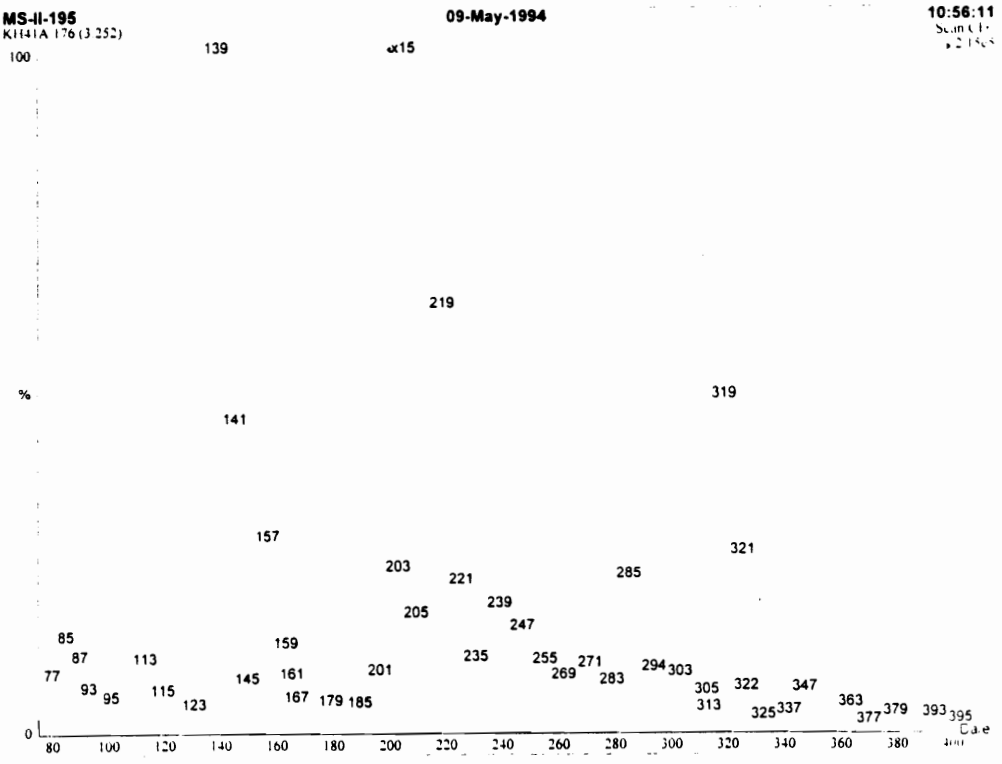

V67#9 x1 Bgd=3 3-FEB-94 10:34+0:01:10 70EHF EI+
BpM=0 I=2.3v Hm=0 TIC=286272000 Acnt:TH PT=0 Sys:DIEI
Text:MS, II-159 CaL:PFKFE2A
#9 1.0
15112000
MASS
#9 5.0
15112000
MASS


SULFONE
DATE 21-3-94
SF 270.133
SY 120.1300000
O1 4416.000
SI 16384
TD 16384
SW 2994.012
HZ/PT .365
PW 4.0
RD 0.0
AQ 2.736
RG 10
NS 16
TE 297
FW 3800
O2 4416.000
DP 63L PO
LB .100
GB 0.0
CX 25.00
CY 0.0
F1 8.501P
F2 -.498P
HZ/CM 97.232
PPM/CM .360
SR 3059.34
Cl
O
Si
S
Si
O
O
185
INTEGRAL
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5 0.0
PPM


SULFONE
AU PROG:
EZAPT.AU
DATE 21-3-94
SF 67.925
SY 67.9300000
O1 3300.000
SI 16384
TD 8192
SW 17241.379
HZ/PT 2.105
PW 0.0
RD 0.0
AQ .238
RG 200
NS 64
TE 297
LB 1.000
GB 0.0
CX 25.00
CY 0.0
F1 120.016P
F2 -9.967P
HZ/CM 353.162
PPM/CM 5.199
SR -4986.77
110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0.0
PPM


TRANSMISSION (%)
WAVENUMBER (CM⁻¹)
ABSCISSA
ORDINATE
SCAN TIME
REP. SCAN
SINGLE BEAM
ERASE STOP
EXPANSION
RESPONSE
TIME DRIVE
PRE SAMPLE CHOP
SUPPRESSION
%T
A&S
SLIT PROGRAM
OPERATOR
DATE
SAMPLE NEAT
REMARKS
SOLVENT
CELL PATH
ORIGIN
CONCENTRATION
REFERENCE

185


MS-II-195
KH41A 176 (3.252)
09-May-1994
10:56:11
100
%
0
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
139
x15
219
141
319
157
321
203
221
285
205
239
247
85
159
235
87
113
255
271
294
303
77
145
161
201
269
283
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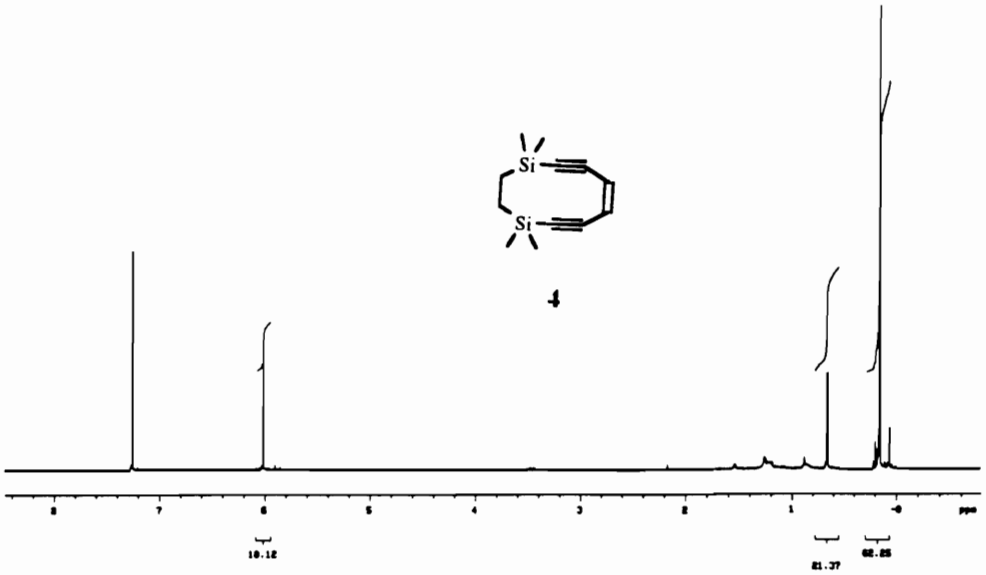
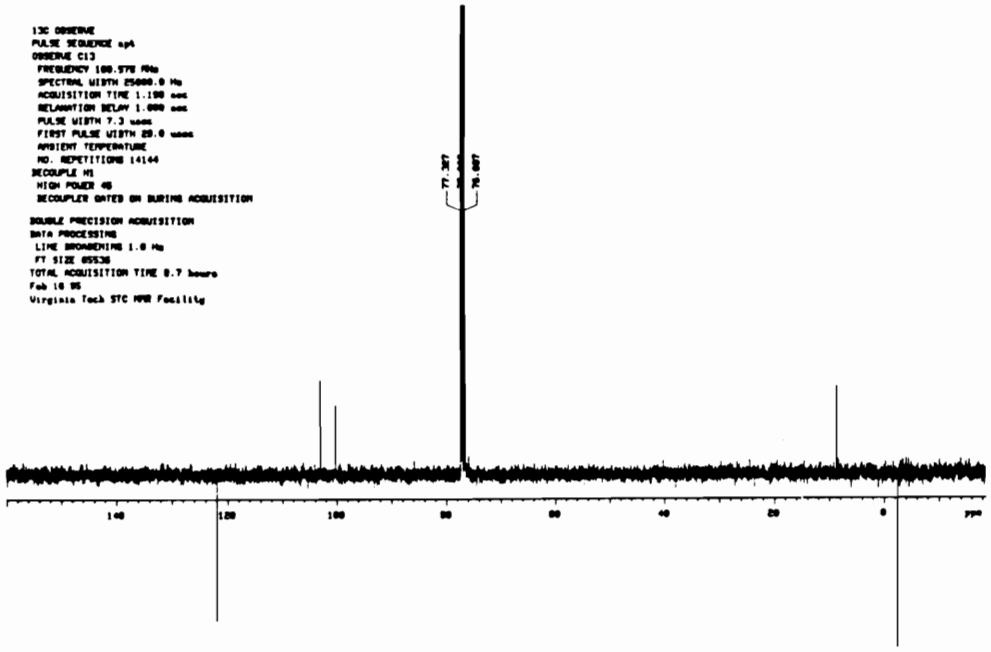
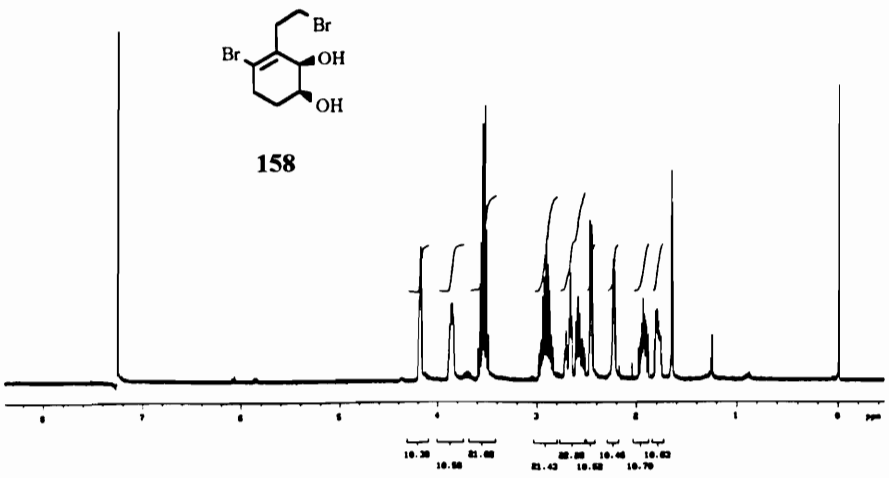
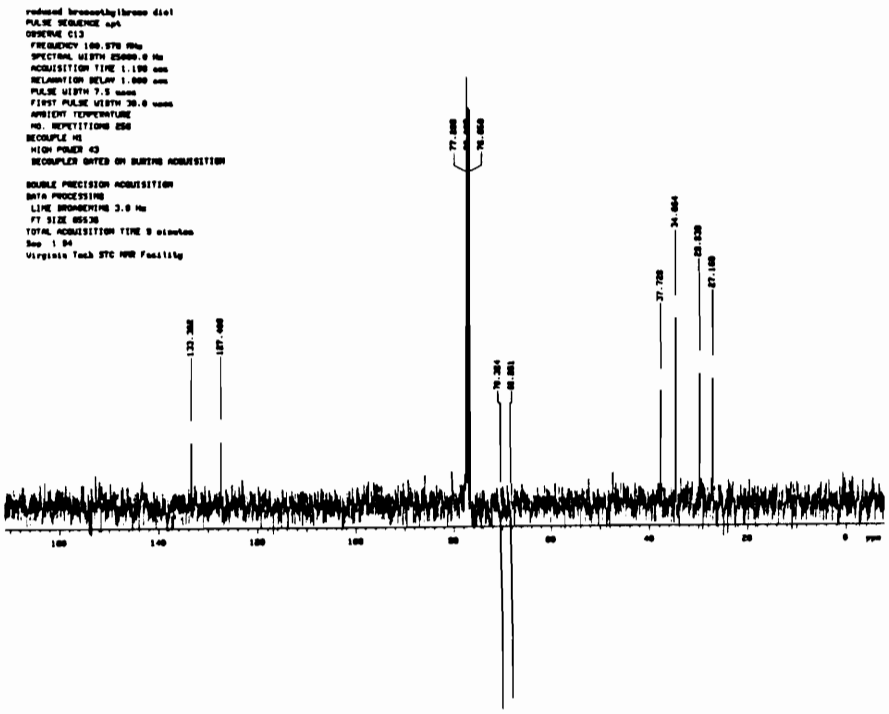
95
115
167
179
185
305
322
347
313
325
337
363
377
379
393
395

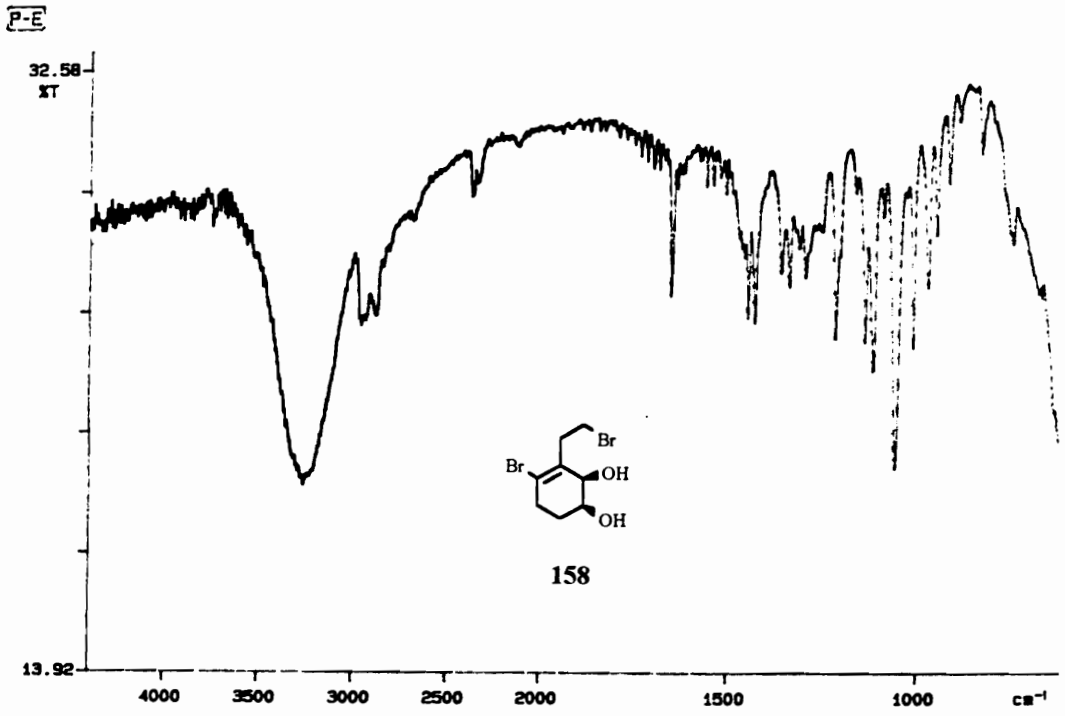

Si
Si
4
8
7
6
5
4
3
2
1
0
ppm
10.12
81.37
82.85


13C OBSERVE
PULSE SEQUENCE opA
OBSERVE C13
FREQUENCY 100.576 MHz
SPECTRAL WIDTH 25000.0 Hz
ACQUISITION TIME 1.100 sec
RELAXATION DELAY 1.000 sec
PULSE WIDTH 7.3 usec
FIRST PULSE WIDTH 20.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 14144
DECOUPLE H1
HIGH POWER 48
DECOUPLER GATED ON DURING ACQUISITION
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 65536
TOTAL ACQUISITION TIME 8.7 hours
Feb 10 95
Virginia Tech STC NMR Facility
77.307
76.887
140
120
100
80
60
40
20
0
ppm

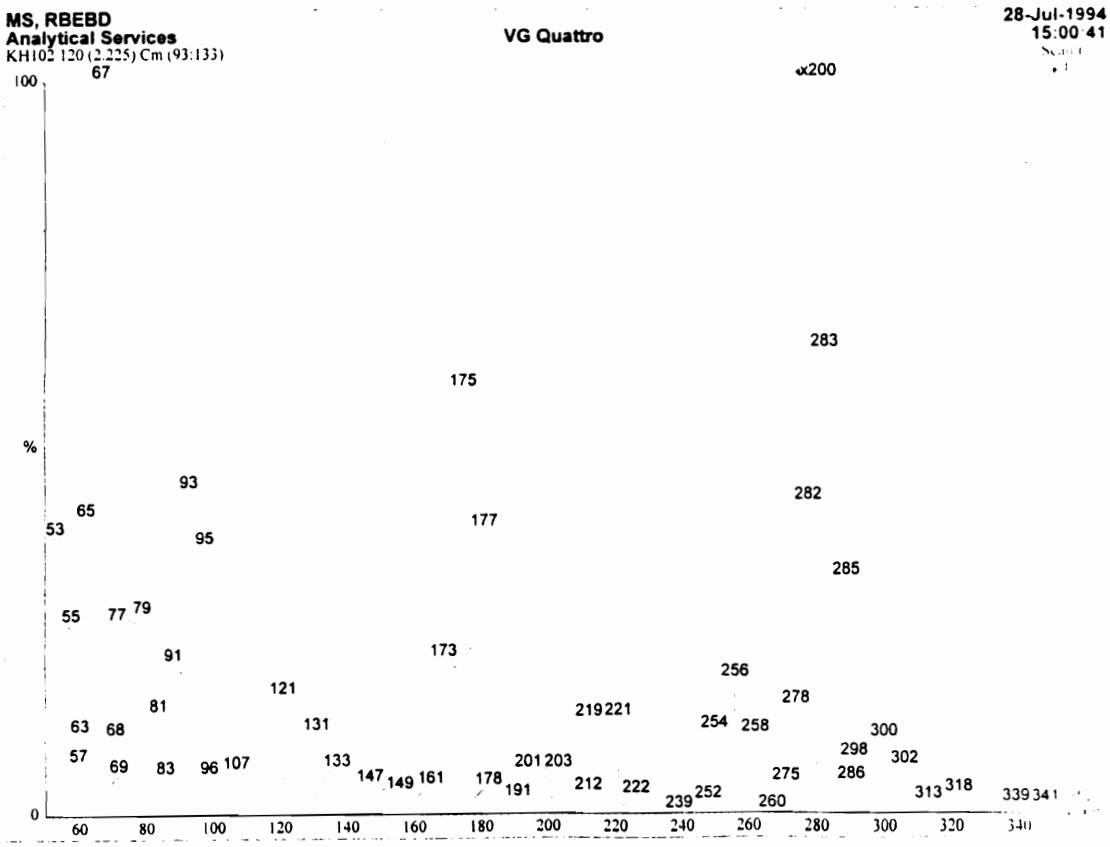


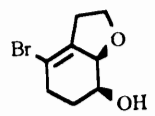
158




P-E
32.58
%T
13.92
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
Br
Br
OH
OH

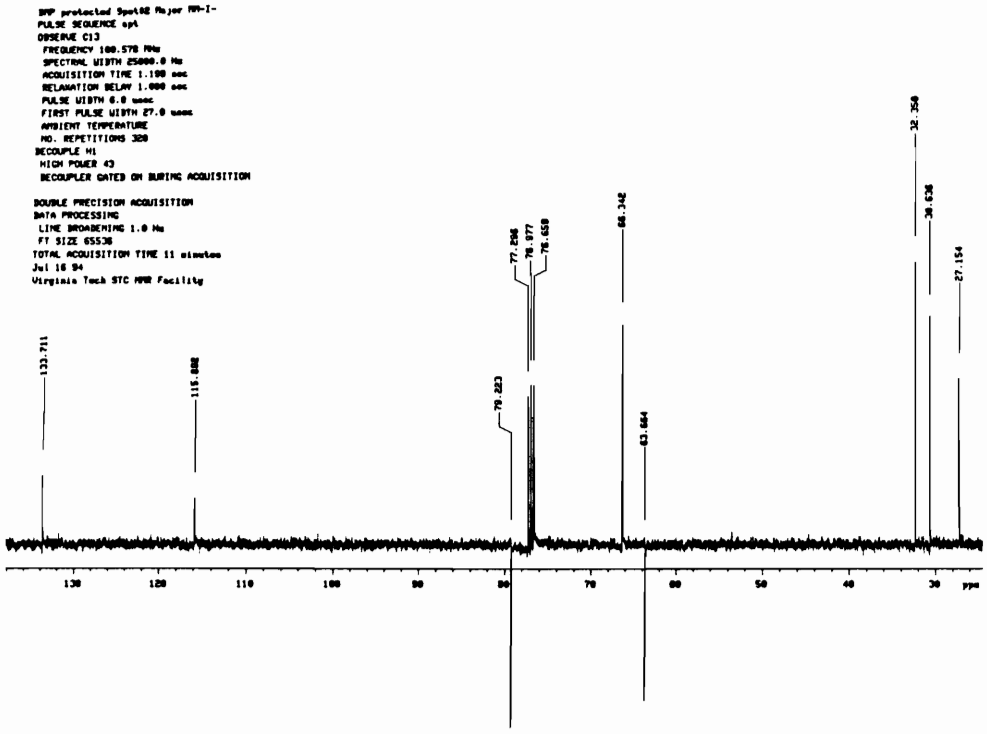
158

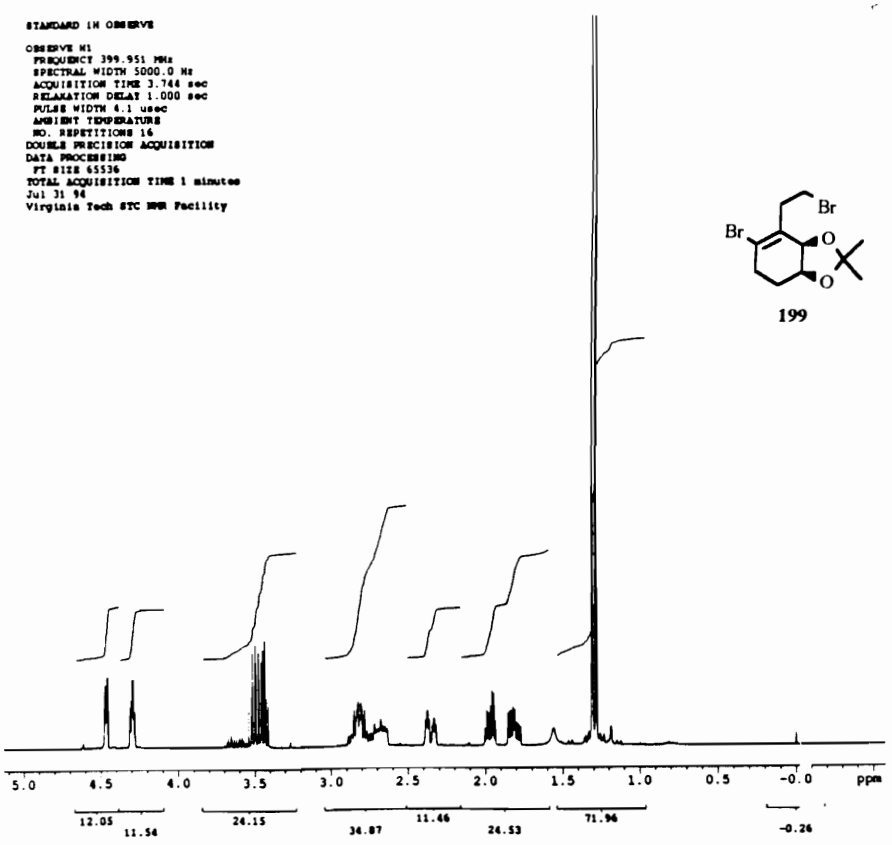

MS, RBEBD
Analytical Services
KH102 120 (2.225) Cm (93:133)
VG Quattro
28-Jul-1994
15:00:41
x200
100
%
0
67
65
53
93
95
55
77
79
91
81
63
68
57
69
83
96
107
121
131
133
147
149
161
175
177
173
178
191
201
203
212
219
221
222
239
252
254
256
258
260
275
278
282
283
285
286
298
300
302
313
318
339
341
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340

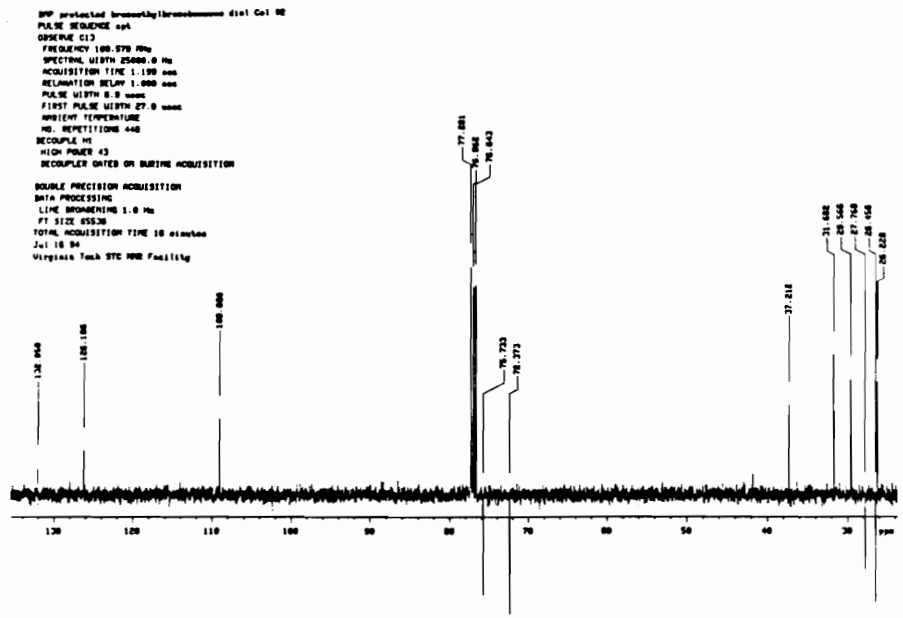

Br
O
OH

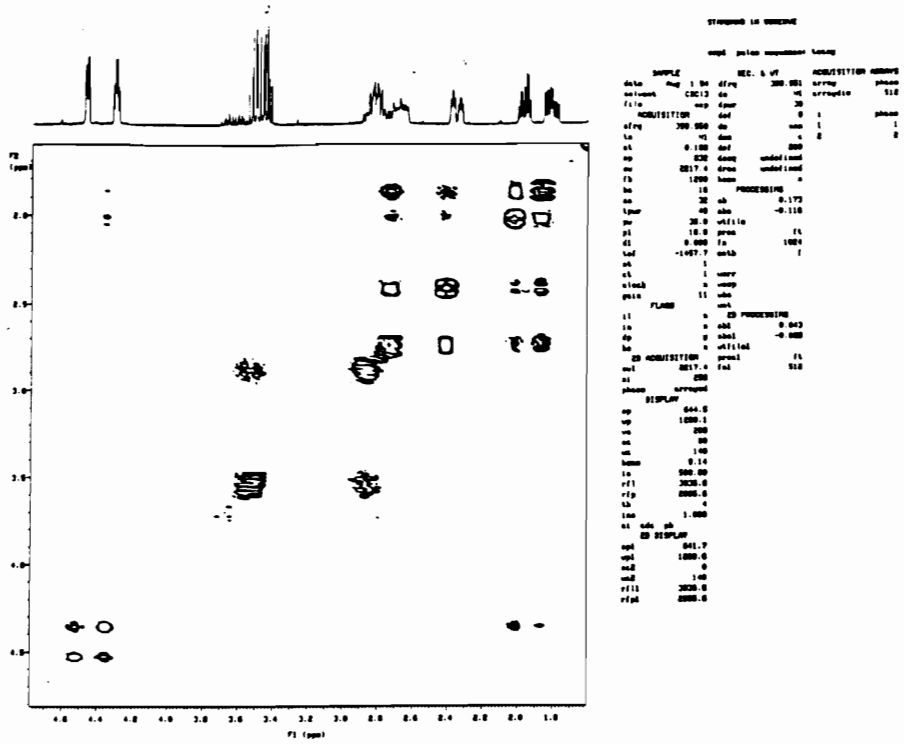
8

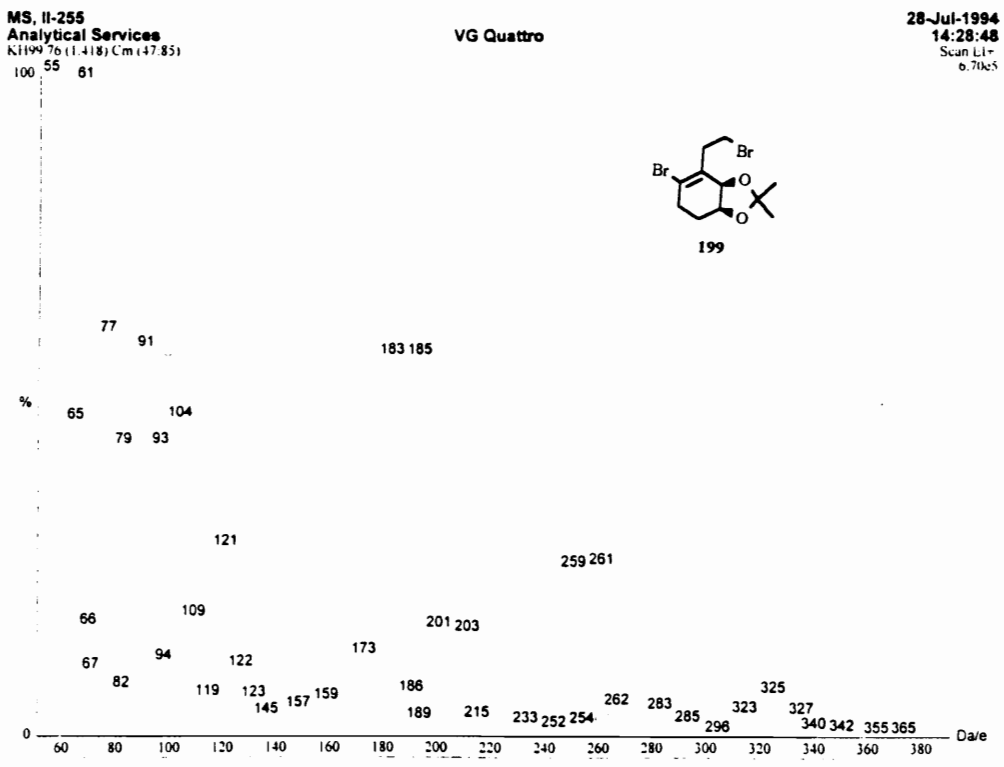
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.05
22.06
11.0811.30
33.8410.31
10.98
10.08
8.88

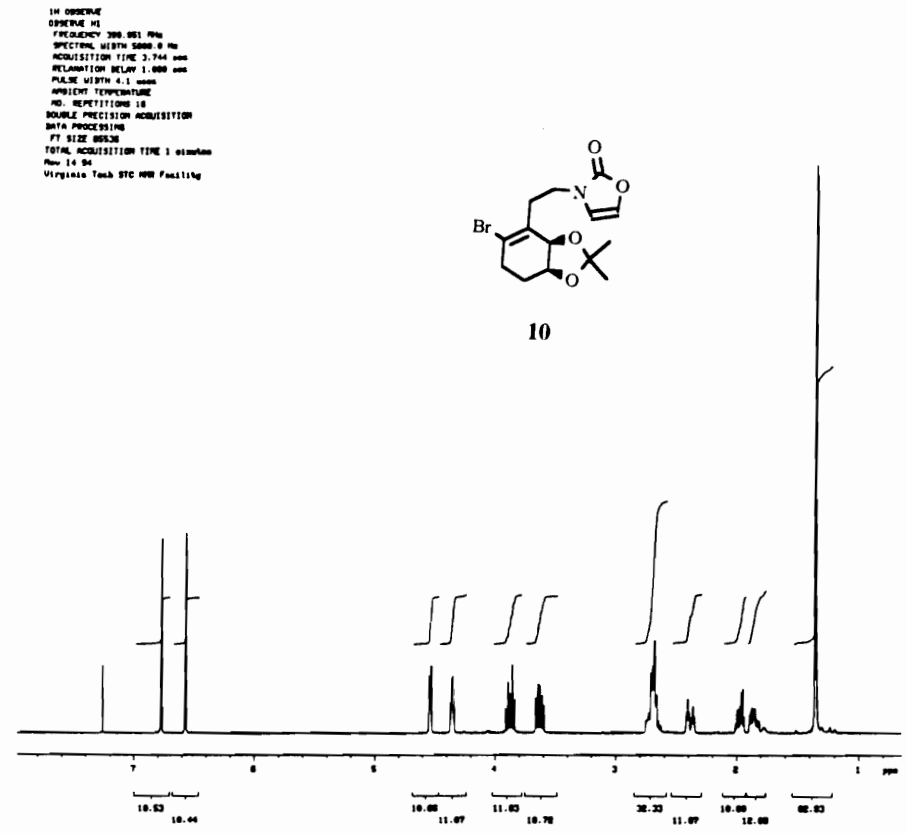

DMP protected Spot8E Major RM-I-
PULSE SEQUENCE opt
OBSERVE C13
FREQUENCY 100.578 MHz
SPECTRAL WIDTH 25000.0 Hz
ACQUISITION TIME 1.198 sec
RELAXATION DELAY 1.000 sec
PULSE WIDTH 6.0 usec
FIRST PULSE WIDTH 27.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 320
DECOUPLE H1
HIGH POWER 43
DECOUPLER GATED ON DURING ACQUISITION
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 65536
TOTAL ACQUISITION TIME 11 minutes
Jul 18 94
Virginia Tech STC NMR Facility
133.711
115.888
79.223
77.256
76.977
76.659
68.342
63.664
32.359
30.636
27.154
130
120
110
100
90
80
70
60
50
40
30
ppm


STANDARD 1H OBSERVE
OBSERVE H1
FREQUENCY 399.951 MHz
SPECTRAL WIDTH 5000.0 Hz
ACQUISITION TIME 3.744 sec
RELAXATION DELAY 1.000 sec
PULSE WIDTH 4.1 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 65536
TOTAL ACQUISITION TIME 1 minutes
Jul 31 94
Virginia Tech STC NMR Facility
Br
Br
O
O
199
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
-0.0
ppm
12.05
11.54
24.15
34.87
11.46
24.53
71.96
-0.26

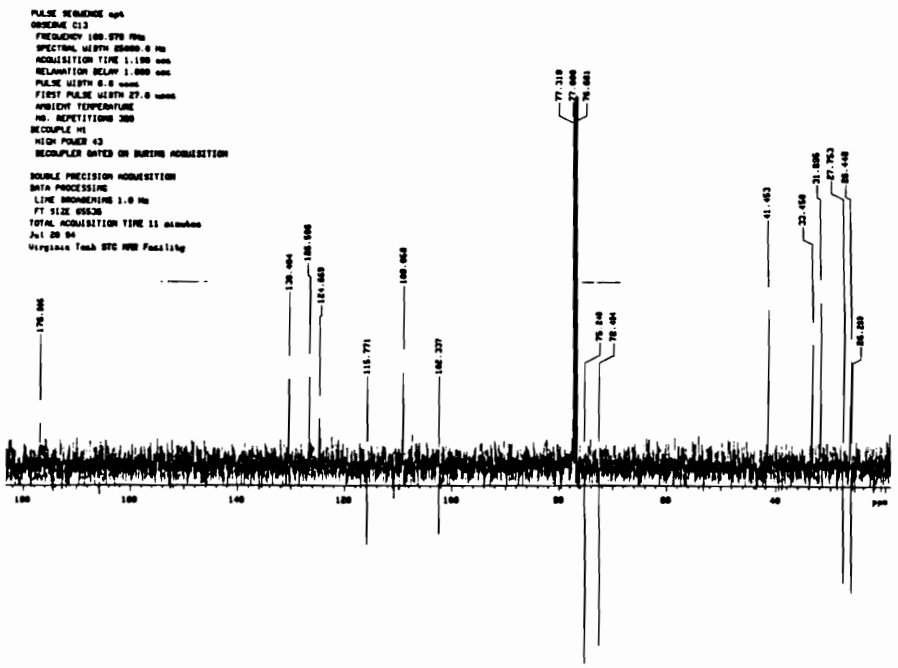

PULSE SEQUENCE apt
OBSERVE C13
FREQUENCY 100.579 MHz
SPECTRAL WIDTH 25000.0 Hz
ACQUISITION TIME 1.199 sec
RELAXATION DELAY 1.000 sec
PULSE WIDTH 8.9 usec
FIRST PULSE WIDTH 27.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 448
DECOUPLE H1
HIGH POWER 43
DECOUPLER GATED ON DURING ACQUISITION
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 65536
TOTAL ACQUISITION TIME 10 minutes
Jul 16 94
Virginia Tech STC NMR Facility
77.081
76.842
76.643
130.950
128.186
100.000
79.733
79.373
37.218
31.682
29.566
27.749
26.454
26.228
130
120
110
100
90
80
70
60
50
40
30
ppm

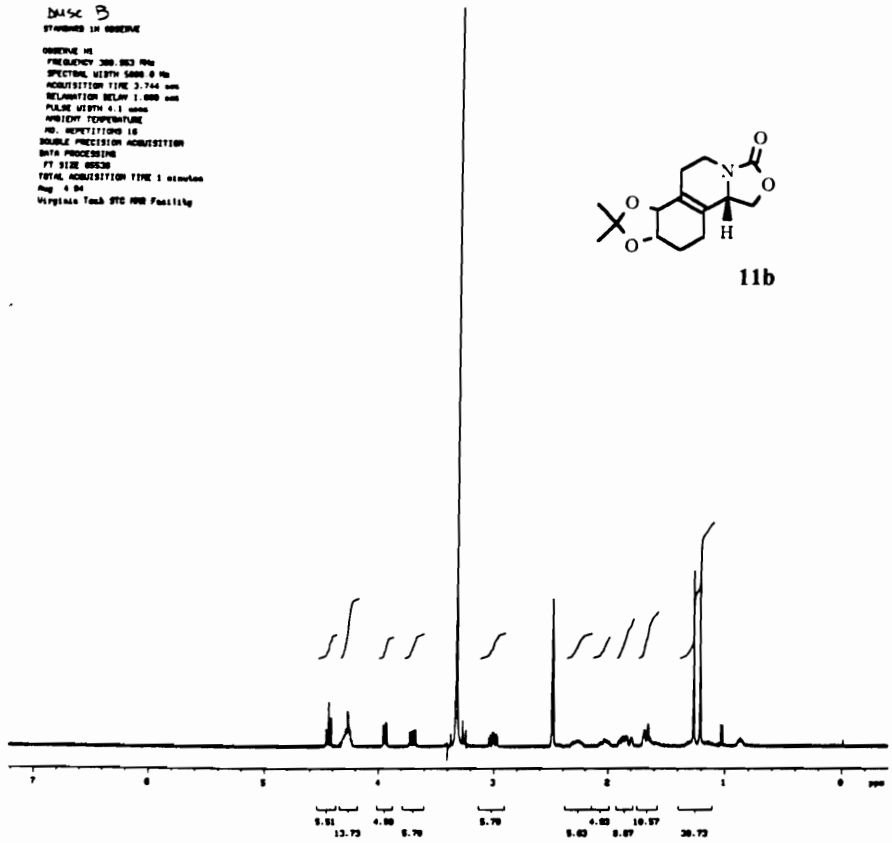



MS, II-255
Analytical Services
KH99 76 (1.418) Cm (47:85)
VG Quattro
28-Jul-1994
14:28:48
Scan EI+
6.70e5
Br
Br
O
O
199
%
Da/e

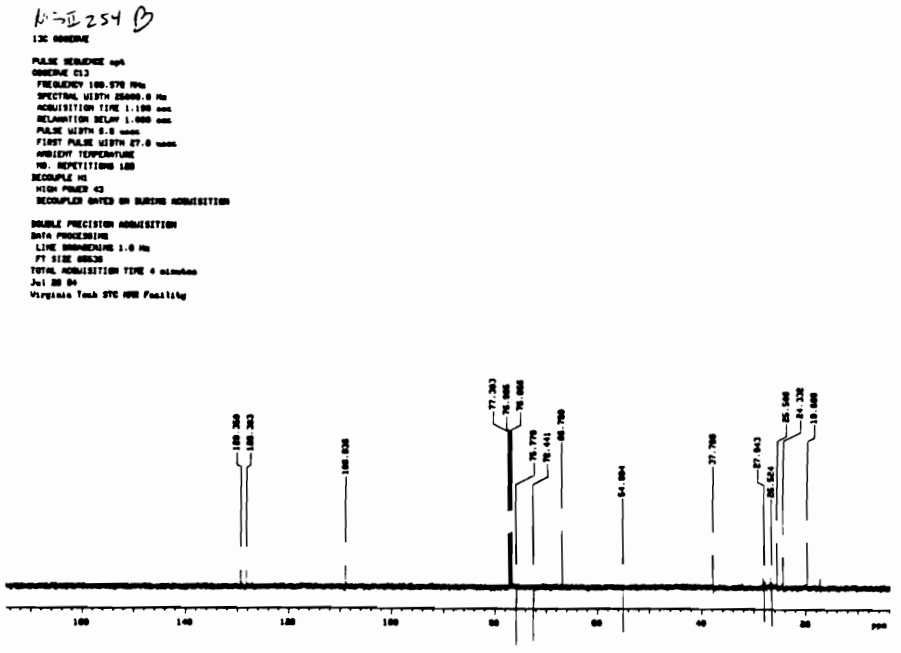


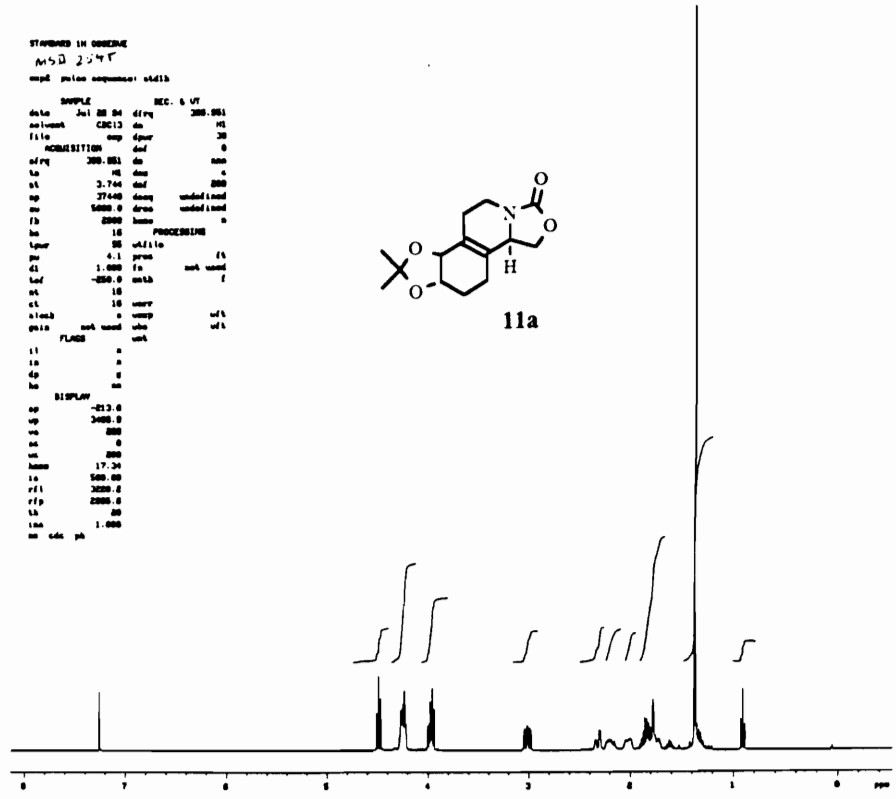
10



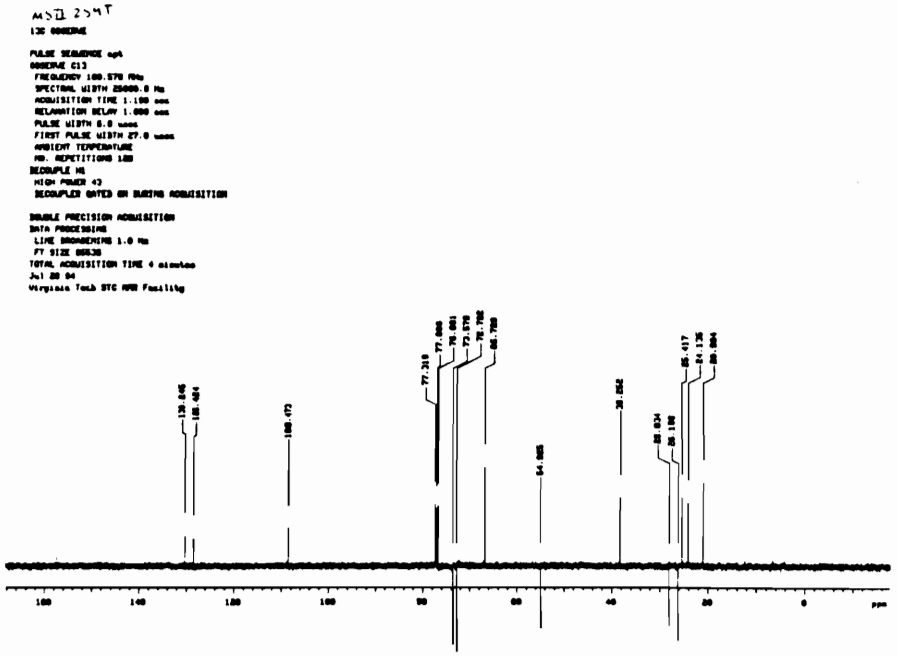


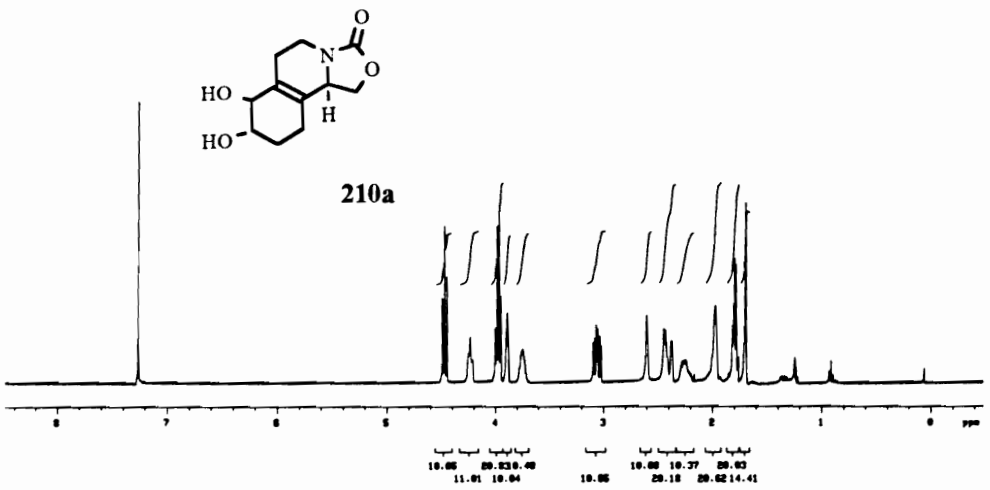
11b



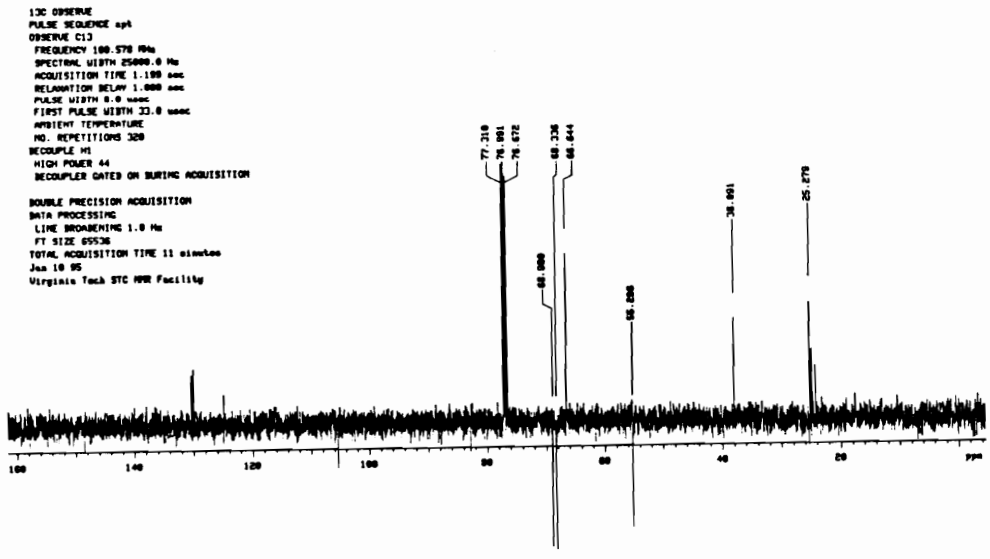


11a




O
N
O
HO
H
HO

210a


13C OBSERVE
PULSE SEQUENCE apt
OBSERVE C13
FREQUENCY 100.578 MHz
SPECTRAL WIDTH 25000.0 Hz
ACQUISITION TIME 1.199 sec
RELAXATION DELAY 1.000 sec
PULSE WIDTH 8.0 usec
FIRST PULSE WIDTH 33.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 320
DECOUPLE H1
HIGH POWER 44
DECOUPLER GATED ON DURING ACQUISITION
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 65536
TOTAL ACQUISITION TIME 11 minutes
Jan 10 95
Virginia Tech STC NMR Facility
77.310
76.991
76.672
68.336
68.044
68.000
55.888
38.991
25.879

VIII. VITA

Michele Stabile was born in Pittsburgh, Pennsylvania on August 14, 1968. She graduated from Canevin High School in 1986 and entered Loyola College in Baltimore, Maryland that same year. In the spring of 1990, she earned her Bachelor of Science in Chemistry and continued her education at Virginia Polytechnic Institute and State University.

After being instructed in the art of Biotransformation, Michele presented some of her early work entitled "New Metabolites form the Microbial Oxidation of 3-Bromotrifluoro Toluene" at the 43rd SE Regional ACS Meeting in Richmond, Virginia in November 1991. In early 1993, she was granted a Masters of Science at VPI under the direction of Dr. Tomas Hudlicky and she remained in his group to pursue her Doctorate. Shortly thereafter, she received an award for Excellence in Teaching in the Organic Laboratories.

She accepted the privilege of another presentation at the 45th SE Regional ACS Meeting in Johnson City, Tennessee in September 1993. The talk was entitled "Efficient Synthesis of Functionalized Aromatic Systems."

In March of 1994, Michele aided in the 1st US "Biotransformations in Action" short course at Tech. After presenting a poster at the July 1994 Gordon Conference in Biocatalysis, she accepted a post-doctoral position in the laboratories of Professor J. Bryan Jones at the University of Toronto.

Michele R Stabile