REACTIVITY OF SUBSTITUTED 4-PYRIDONES IN NORMAL AND INVERSE DEMAND DIELS-ALDER CYCLOADDITION

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ABSTRACT

The synthesis of the decahydroquinoline ring system has been explored extensively due to its appearance within many biologically active natural alkaloids. New compounds containing such a moiety are being discovered on an ongoing basis. The present work has sought to develop an alternative synthetic pathway to this system through the use of Diels-Alder [4 + 2] cycloaddition chemistry.

The initial focus of this research was on the development of an activated dienophile derived from 4-pyridone. Two such compounds were eventually synthesized, N-tosyl-3-formyl-5,6-dihydropyridin-4-one, and N-*t*-butoxycarbonyl-3-formyl-5,6-dihydropyridin-4-one. The reactivity of these compounds with several different dienes was then investigated in an effort to obtain the desired decahydroquinoline cycloadduct.

Under inverse electron demand Diels-Alder conditions, the synthesized compounds reacted with ethyl vinyl ether to consistently produce pyran containing bicyclic adducts under mild conditions. The products contained a mixture of isomers in varying ratio relative to the nitrogen substituent present.

Non-activated dienes did not react with the dienophiles under normal demand conditions even with the addition of lewis acid catalysts. However, cycloadducts were formed through reaction with the highly activated diene 1-dimethylamino-3-*tert*-butyldimethylsiloxy-1,3-butadiene. The products did not resemble the target decahydroquinoline system but instead appeared to be the result of reaction with the formyl group substituent, acting as a heterodienophile, to yield a dihydropyranone ring bridged to C-3 of the original pyridone derived dienophile.

ACKNOWLEDGMENTS

I would like to thank my committee members for their guidance along the course of this project. Also, my sincere appreciation goes to Dr. Shailesh Desai of Quality Chemical Laboratories. This research would not have been possible without his continuing input and direction. Finally, my thanks go to David Ray, also of Quality Chemical Laboratories, whose technical guidance contributed greatly towards the development of my own skills in the art of synthetic chemistry.

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INTRODUCTION

The present work has sought to develop upon currently available synthetic methods for the formation of the decahydroquinoline (**1**, Figure 1) ring system through the use of an intermolecular Diels-Alder reaction between a suitably activated diene and a 4-pyridone (**2**) derived dienophile. The general course of this research has involved the synthesis of a pyridone based activated dienophile, selection or synthesis of reactive dienes as necessary, and elucidation of the conditions under which the desired cycloaddition could take place.

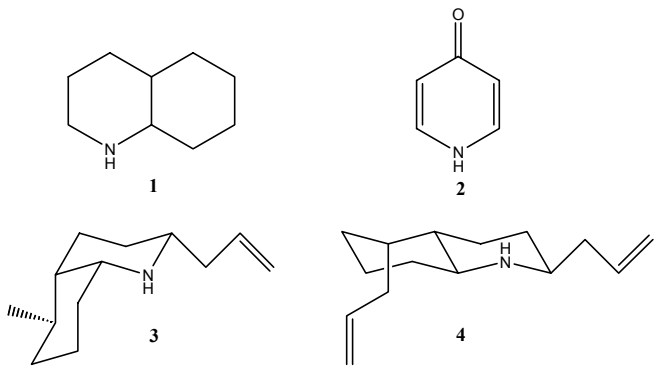
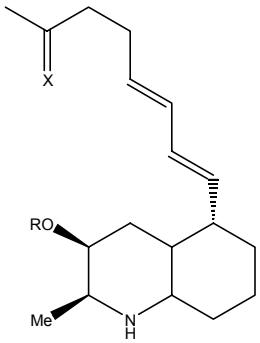


Figure 1: Decahydroquinoline (**1**), 4-pyridone (**2**), Pumiliotoxin C (**3**), and Alkaloid 219A (**4**).

Decahydroquinoline as it is found in nature is typically substituted in one or more positions and may exist as a subunit of a much larger compound. Pumiliotoxin C (**3**, Figure 1) and its related trans configuration, alkaloid 219A (**4**), were both isolated from the *Dendrobates* family of South American frogs. These are among several compounds from this source which have been shown to exhibit significant stimulus transduction and ion transport effects in the nervous system.[1]

[1] Daly, J.W.; Nishizawa, Y.; Padgett, W. L.; Tokuyama, T.; McCloskey, P.J.; Waykole, L.; Schultz, G. A.; Aronstam, R. S. *Neurochem. Res.* **1991**, *16*, 1207.

Lepadins A (**5**, Figure 2) and B (**6**), isolated from the tunicate *Clavelina lepadiformis* and the flatworm *Prostheceraeus villatus* respectively, have shown significant cytotoxicity against human cancer cell lines.[2]



A (**5**): X = H_2, R = $COCH_2OH$
B (**6**): X = H_2, R = H

Figure 2: Lepadins A (**5**) and B (**6**).

Decahydroquinoline systems have been synthesized through a variety of methods. These include an intramolecular Diels-Alder/retro-Mannich ring opening approach involving the addition of a Grignard reagent,[3] N-galactosyl imine mediated tandem Mannich-Michael condensation followed by conjugate cuprate addition to the bicyclic enone,[4] and the addition of carbon nucleophiles to substituted N-acyliminium ions derived from glutarimide, followed by ring closing metathesis.[5] These methods have all successfully produced the desired decahydroquinoline moiety, albeit with varying degrees of efficacy and product yield. The method currently under investigation for the production of decahydroquinoline would be a valuable addition to these studies as it involves the creation of the ring system through the straightforward [4 + 2] Diels-Alder cycloaddition of a suitably constructed dienophile to a diene.

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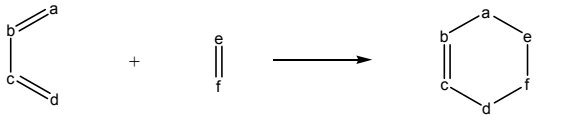
[2] Kubanek, J.; Williams, D. E.; de Silva, E. D.; Allen, T.; Andesen, R. J. *Tetrahedron Lett.* **1995**, *36*, 6189.
[3] Comins, D. L.; Al-awar, R. S. *J. Org. Chem.* **1992**, *57*, 4098.
[4] Weymann, M.; Schultz-Kukula, M.; Kunz, H. *Tetrahedron Lett.* **1998**, *39*, 7835.
[5] Maldaner, A. O., Pilli, R. A. *Tetrahedron Lett.* **2000**, *41*, 7843.

The Diels-Alder Reaction: Overview

Otto Diels and Kurt Alder first reported their observations regarding [4 + 2] cycloaddition chemistry in 1928.[6] In these types of reactions, 4 π electrons from a diene (**A,** Figure 3) and 2 π electrons from a dienophile (**B**) are involved in the loss of 2 π bonds and simultaneous gain of 2 σ bonds, the result being the formation of a six-membered ring (**C**).



A. Diene **B.** dienophile **C.** six-membered ring

Figure 3: Diels-Alder [4+2] cycloaddition.

In what is referred to as the *normal demand* condition, the electronic interaction is between the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital (LUMO) of the dienophile. According to frontier orbital theory,[7] the reactivity of any diene-dienophile pair will increase by decreasing the energy gap between HOMO and LUMO. In normal demand reactions, the LUMO energy of the dienophile can be lowered through the addition of an electron withdrawing group (EWG), such as CHO, COR, COOH, COOR, COCl, COAr, CN, NO_2, Ar, CH_2OH, CH_2Cl, CH_2NH_2, CH_2CN, CH_2COOH, $PO(OEt)_2$, or a halogen.[8] A dienophile becomes *activated* when it has been substituted with one or more EWGs. The diene is activated by a raise in its HOMO energy. This can be accomplished through the addition of an electron-donating group (EDG), such as CH_3, OH, OCH_3, NH_2, $NHCOCH_3$, CMe_3, or NMe_2.

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[6] Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460,* 98.
[7] For reviews, see: (a) Herndon, W. C. *Chem. Rev.* **1972,** *72*, 157. (b) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1975. (c) Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779.
[8] March, J.; Smith, M. B. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*; Wiley: New York, 2001.

In the *inverse demand* condition, the principal orbital interaction is between the HOMO of the dienophile and the LUMO of the diene. Therefore, activation of the reacting species would be done in the opposite manner, with the addition of EDGs to the dienophile and EWGs to the diene. The net result is the same as for normal demand reactions: reactivity is increased through the lowering of the energy gap between interacting HOMO and LUMO.

Mechanistic and Stereochemical Considerations

There are three principle mechanistic theories that have been proposed to explain the [4 + 2] cycloaddition. The first and perhaps best-supported theory is that of a multicentered, simultaneous formation of the two new σ bonds in which there is no intermediate and only one activation barrier (**A**, Figure 4). The other two theories derive from the possibility that the reaction occurs in a two-step process. They differ only in that one proposes the formation of a zwitterionic intermediate (**B**) following the initial σ bond formation, and the other postulates a biradical intermediate (**C**).

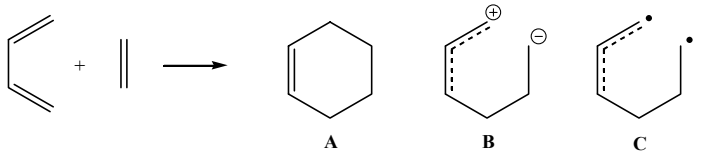


Figure 4: Multicenter (**A**), zwitterionic (**B**), and diradical (**C**) mechanisms.

One of the more significant points in support of the multicentered mechanism is the universal, stereospecific *cis* addition of dienophile to diene known as the "*cis*" principle. The steric arrangement of substituents on both reactants is preserved within the adduct. If the substituents are *trans* on the dienophile for example, they will remain *trans* in the product. This observation is commonly interpreted to imply a synchronous formation of

bonds. Sauer points out that this does not however completely rule out the possibility of a two-step reaction.[9] If the ring closure step is very fast, the opportunity for rotation about the C-C bond axis during an intermediate transition step would not exist and the *cis* principle would still be maintained.

In a comparative kinetic study, the rate of ion formation from *p*-substituted α,α-dimethylbenzyl chlorides is increased by 10^9 when the *para* substituent is changed from a methoxy to a nitro group. A similar change in substituent in the Diels-Alder reaction of *p*-substituted 1-phenylbutadienes with maleic anhydride produces an increase in rate of only tenfold (10^1). This difference implies that the cycloaddition is not proceeding through a zwitterionic mechanism. Also, [4 +2] reaction rates in the gas phase are comparable to those in solution, which leads to the conclusion that any intermediate could only be slightly more polar than the ground state as solvation is not necessary. The possibility of a biradical singlet intermediate has been implied by some studies and may be dependent on the type of substrates involved in the reaction.[10]

It is worth noting several other rules that have been applied to Diels-Alder cycloaddition stereochemistry and mechanism. The first of these is the "*endo*" rule, which describes the addition of unsymmetrical dienophiles to dienes. In the reaction of cyclopentadiene with maleic anhydride for example, maleic anhydride in the transition state will be oriented face to face with its carbonyl groups either underneath the conjugated double bonds of cyclopentadiene or turned 180° away. The *endo* rule states that the former orientation will be favored because this maximizes the "secondary orbital overlap [that] can occur between the π system of the diene and a π system in conjugation

[9] Sauer, J. *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 16.
[10] Li, Y.; Padias, A. B.; Hall Jr., H. K. *J. Org. Chem.* **1993***, 58*, 7049.

with the dienophilic double bond."[11] The conformation of the cycloadduct is generally *endo* (**a**, Figure 5) when the reaction is under kinetic control. However, an *endo* adduct can redissociate to form the more stable *exo* (**b**) adduct if the reaction becomes thermodynamically controlled.

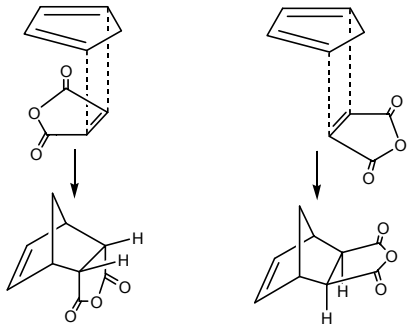


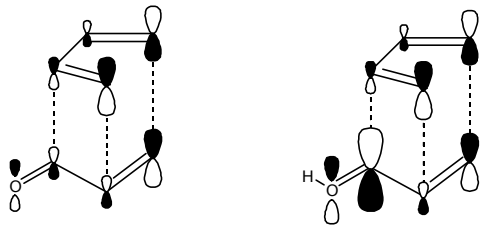
Figure 5: *Endo* (**a**) and *exo* (**b**) addition pathways.

The *ortho*, *para*, and *meta* rules are useful for predicting regiochemistry in unsymmetrical diene and dienophile addition reactions. When there is a substituent at C-1 of the diene, the addition will most likely result in an *ortho* positioning of the substituent with respect to a substituent on the dienophile if the reaction is of the normal demand type (EDGs on the diene and EWGs on the dienophile). If the diene is 2-substituted, the *para* rule predicts that, under normal demand conditions, the cycloadduct will form with diene and dienophile substituents *para* relative to each other. The *meta* rule applies when both diene and dienophile bear electron donating substituents and predicts *meta* orientation of substituents in the adduct.[12] These rules are derived from frontier molecular orbital theory and in general agree very well with experimental results.[13]

[11] Woodward, R. B.; Hoffmann, R. *Angew. Chem. Int. Ed. Engl.* **1967**, *8*, 781.
[12] Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092.
[13] Eisenstein, O.; Lefour, J. M.; Anh, N. T.; Hudson, R. F. *Tetrahedron.* **1977**, *33*, 523.

Lewis Acid Catalysis

Yates and Eaton are credited with first reporting remarkable rate acceleration of the Diels-Alder reaction through the use of a Lewis Acid, which in their case was aluminum chloride.[14] Soon thereafter, Inukai and Kasai extended this work using aluminum chloride, methyl acrylate, and butadiene derivatives.[15] They attributed the observed rate acceleration of the cycloadditions to the exaggerated electron withdrawal caused by the complex formed between the carbonyl oxygen of the methyl acrylate dienophile and the aluminum chloride Lewis Acid. Houk and Strozier corroborated these findings and reported increases in reaction rate, regioselectivity (*ortho: meta: para* outcomes), and stereoselectivity (*endo: exo* ratios).[16] They proposed the formation of a tighter transition state between diene and dienophile in Lewis Acid catalyzed reactions due to the greatly increased secondary orbital interactions. This idea was supported in molecular orbital studies of acrolein compared with protonated acrolein (their choice of Lewis Acid coordinated analogue). Their results showed a significant increase in the orbital coefficient on the carbonyl carbon, which translates to an increase in secondary orbital interaction between the reacting species (Figure 6).



a. Diene with acrolein **b.** Diene with protonated acrolein

Figure 6: Orbital interactions of diene HOMO with (**a**) acroleine LUMO, and (**b**) protonated acrolein LUMO**.**

[14] Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, *82*, 4436.
[15] (a) Inukai, T.; Kojima, T. *J. Org. Chem.* **1966**, *31*, 1121. (b) Inukai, T.; Kojima, T. *J. Org. Chem.* **1967**, *32*, 869.
[16] Houk, K. N.; Strozier, R. W. *J. Am. Chem. Soc.* **1973**, *95*, 4094.

Many different Lewis Acids have been employed in Diels-Alder reactions. Some of the more common are boron trifluoride (BF_3), ferric chloride ($FeCl_3$), stannic chloride ($SnCl_4$), and zinc chloride ($ZnCl_2$).[17] The effect of a Lewis Acid on reaction outcome however is not always beneficial and is highly substrate specific.[18] Most studies show that the correct Lewis Acid to use with a given set of substrates is usually best decided by experimentation.[19]

Related Syntheses: Carbon and Oxygen Systems

Dienophiles containing the α,β-unsaturated ketone moiety have been used extensively in Diels-Alder reactions. Acrolein (**7**, Figure 7) is perhaps the simplest of these, consisting of a single carbon-carbon double bond substituted with a formyl (CHO) EWG. Computational studies have shown that the formyl group of acrolein lowers LUMO energy to roughly half that of unsubstituted ethylene, thus implying that it can provide significant activation to a dienophile under normal demand conditions.[20] Formyl dienone **8** (Figure 7) contains an acrolein moiety within a six-membered ring and reacts with the simple diene piperylene (**9**) to form bicyclic adducts under mild conditions.[21]

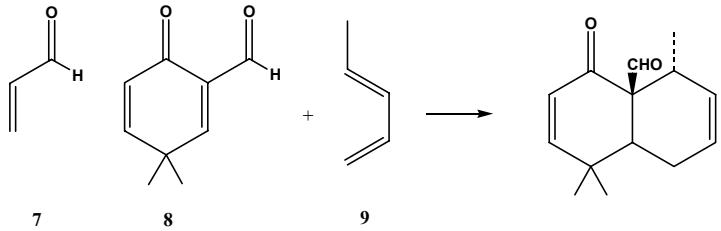
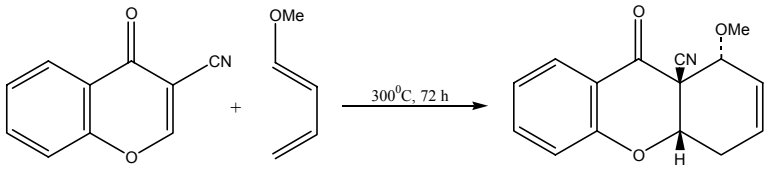


Figure 7: Acrolein (**7**), formyl dienone (**8**) and piperylene (**9**).

[17] For an example of a correlative study between Lewis Acid and reactivity, see: Liu, H.; Browne, E. N. C. *Can. J. Chem.* **1987**, *65*, 1262.
[18] Seth, P. P.; Totah, N. I. *Org. Lett.* **1999**, *1*, 1411.
[19] Fringuelli, F.; Pizzo, F.; Taticchi, A.; Halls, T. D. J.; Wenkert, E. *J. Org. Chem.* **1982**, *47*, 5056.
[20] Hehre, W. J.; Overman, L. E.; Kahn, S. D.; Pau, C. F. *J. Am. Chem. Soc.* **1986**, *108*, 7381.
[21] Liotta, D.; Saindane, M.; Barnum, C. *J. Am. Chem. Soc.* **1981**, *103*, 3224.

The dienone **8** (Figure 7) was also shown to react with a number of C-1 substituted 2-methyl-1,3-butadienes. The reactions were carried out in refluxing toluene and without the need of a Lewis Acid. Reaction times varied depending on diene substitution but in all cases product yields exceeded 70%. The *endo* rule was made apparent by this study as the product stereochemical ratios were roughly 60-80% *endo* to 20-40% *exo*. The formyl group of the dienophile consistently directed product regiochemistry to the *ortho* conformation relative to the C-1 substituent of the diene. Products in both dienone **8** studies were easily deformylated through either treatment with silica gel or reflux in methanolic or *t*-butanolic base.[22]

In studies towards the construction of the natural product arisugacin, the oxygen containing heterocycle 3-cyanochromone (**10**, Figure 8) demonstrated [4 + 2] type reactivity with a number of dienes, including 1-methoxy-1,3-butadiene (**11**).[23]



10 **11**

Figure 8: 3-cyanochromone (**10**) with 1-methoxy-1,3-butadiene (**11**).

Reactions with non-activated dienes did not occur under thermal conditions alone and required the use of a Lewis Acid ($TiCl_4$ in this case). Dienes substituted with EWGs did not react with 3-cyanochromone under any conditions. Addition of an electron withdrawing halogen to C-6 of the 3-cyanochromone served to both shorten reaction times and lower required reaction temperatures when compared to comparable reactions with the chromone solely activated with the cyano EWG.

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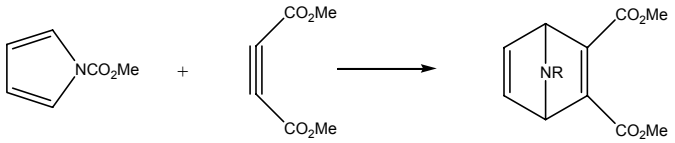
[22] Gore, V. K.; Desai, S. R.; Mayelvaganan, T.; Padmakumar, R.; Hadimani, S. B.; Bhat, S. V. *Tetrahedron.* **1993**, *49*, 2767.
[23] Hsung, R. P. *J. Org. Chem.* **1997**, *62*, 7904.

Related Syntheses: Nitrogen Systems

The use of nitrogen containing heterocycles in the Diels-Alder reaction was initially met with difficulty. Both pyridine and pyrrole are stable aromatic systems that show resistance to cyclization in a manner similar to benzene. However, Acheson and Vernon found an increase in the rate of hydrogenation of pyrrole through the addition of an alkoxycarbonyl group to the nitrogen atom of the ring. Their findings prompted further investigation into the possibility of pyrrole acting as a diene and they were able to eventually isolate the cycloadduct of methyl pyrrole-1-carboxylate (**12**, Figure 9) with dimethyl acetylenedicarboxylate (**13**). They concluded that the "withdrawal of the π electrons from nitrogen by the alkoxycarbonyl group increases the aliphatic character of the ring diene system."[24]



12 **13**

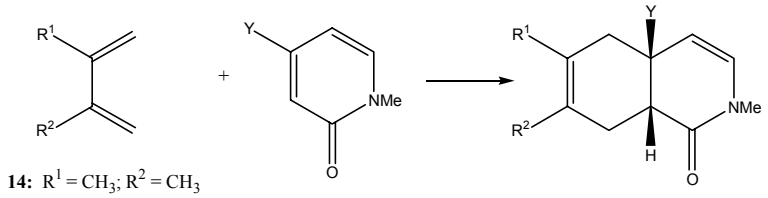
Figure 9: Additon of methyl pyrrole-1-carboxylate (**12**) to dimethyl acetylenedicarboxylate (**13**).

Similar difficulty was initially reported in the attempted cycloaddition reactions between unsubstituted 2-pyridones and dienophiles.[25] The first successful results involved N-methyl-2-pyridone, acting as the diene, with the dienophile benzyne.[26] Several compounds other than benzyne have since been used as dienophiles with N-methyl-2-pyridone. Cycloaddition products have been reported without N-substitution but low yields and complex mixtures have generally resulted. In the case of 2-pyridone, the choice of N-substituent was generally a methyl group (CH_3). An acyl substituent may

[24] Acheson, R. M.; Vernon, J. M. *J. Chem Soc. C.* **1961**, 457.
[25] Acheson, M. R.; Tasker, P. A. *J. Chem Soc. C.* **1967**, 1542.
[26] Sheinin, E. B.; Wright, G. E.; Bell, C. L.; Bauer, L. *J. Heterocyclic Chem.* **1968**, *5*, 859.

be prone to migration to the neighboring oxygen via a Chapman type rearrangement so these were typically avoided. Sulfonyl groups however, under mild to moderate conditions, are resistant to rearrangement and may be used effectively as N-substituents.[27]

The 2-pyridone species can also act as a dienophile if additional EWGs are added to the ring. Two different butadienes, 2,3-dimethyl-1,3-butadiene (**14**, Figure 10) and isoprene (**15**), were shown to react with methyl-2-pyridone (**16**) when it was substituted at the 4 position with a cyano (CN) group.[28]



14: $R^1 = CH_3$; $R^2 = CH_3$
15: $R^1 = CH_3$; $R^2 = H$ **16:** Y = CN, COOMe, or COMe

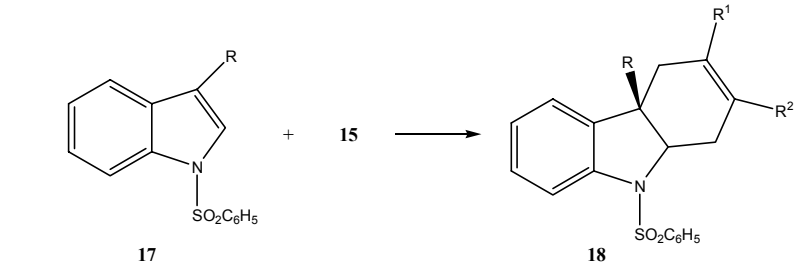
Figure 10: Diels-Alder cycloaddition of substituted butadienes with EWG activated 2-pyridone.

Product yields are highly sensitive to both diene type and choice of EWG added to the pyridone. For example, in the above reaction, both acetyl (COMe) and ester (COOMe) EWGs were used. When the diene was isoprene, the acetyl EWG increased yields from 50 to 98 percent over the ester. When the diene was 2,3-dimethyl-1,3-butadiene, the change from ester to acetyl EWG resulted in a drop in yield from 83 to 42 percent.[29]

Both pyrrole and indole can act as the dienophile component in [4 + 2] cycloaddition reactions when sufficiently activated with EWGs. Wenkert and co-workers utilized 3-acetyl-1-(phenylsulfonyl)pyrrole and 1-(phenylsulfonyl)-3-nitropyrrole as dienophiles in Diels-Alder type reactions with isoprene (**15**, Figure 10). Both formed cycloadducts

[27] Posner, G. H.; Switzer, C. *J. Org Chem.* **1987**, *52*, 1642.
[28] (a) Tomisawa, H.; Kato, H.; Fujita, R.; Hongo, H. *Chem. Pharm. Bull.* **1979**, *27*, 810. (b) Tomisawa, H.; Fujita, R.; Kato, H.; Hayasaka, K.; Kamimura, T.; Hongo, H. *Chem. Pharm. Bull.* **1988**, *36*, 1882.
[29] Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron.* **1992**, *48*, 9111.

successfully but the nitropyrrole was seen to be more reactive than the acetyl substituted analogue. Also, the nitro group was spontaneously ejected under the given reaction conditions (175 ^{o}C, 48 h), thereby eliminating any extra step for the removal of the EWG. Various 3-substituted N-(phenylsulfonyl) indoles were reacted with isoprene under the same conditions as with the pyrroles. Cycloadducts were formed with EWGs $COCONEt_2$ (**17a**, Figure 11), $COCO_2Et$ (**17b**), COMe (**17c**), CHO (**17d**), COOMe (**17e**), and NO_2 (**17f**). Contrary to what might be expected in view of the reactivity of the 2-pyridones, no reaction was observed when the indole was 3-substituted with the electron withdrawing cyano group. Interestingly, no reaction was observed when the EWG was placed on the α instead of β indole carbon.[30]



17

a. R = $COCONEt_2$; **b.** R = $COCO_2Et$; **c.** R = COMe; **d.** R = CHO; **e.** R = COOMe; **f.** R = NO_2

18

a. $R^1 = CH_3$; $R^2 = H$

b. $R^1 = H$; $R^2 = CH_3$

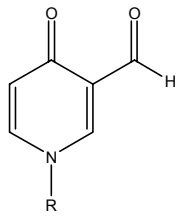
Figure 11: Cycloaddition of substituted indoles with isoprene.

Current Research: The Dienophile

4-Pyridone (**2**, Figure 1) was chosen as the starting material for the development of an activated dienophile for Diels-Alder cycloaddition. The carbonyl group at C-4 is essentially an integrated EWG that can contribute towards dienophilic reactivity under normal demand conditions through the lowering of LUMO energy. It was theorized that addition of EWGs to the nitrogen atom and to C-3 of the 4-pyridone would cause a corresponding raise in reactivity. The substrate thus substituted would contain three

[30] Wenkert, E.; Moeller, P. D. R.; Piettre, S. R. *J. Am. Chem. Soc.* **1988**, *110*, 7188.

activating EWGs and should therefore be likely to form cycloadducts with reacting dienes. A formyl group was chosen as the desired EWG for C-3 substitution and both tosyl (4-$MeC_6H_4SO_2$; **19a**, Figure 12) and *t*-butoxycarbonyl ($COOC(CH_3)_3$; **19b**) groups were considered to be good candidates for N-substitution.



19 (**a**): R = 4-$MeC_6H_4SO_2$
(**b**): R = $COOC(CH_3)_3$

Figure 12: Target pyridone based dienophile.

Dienes

The catalogue of available dienes for the Diels-Alder reaction is substantial.[31] Therefore, an investigation into the reactivity of different dienes with **19** (Figure 12), including considerations of product yield, observed isomer selectivity, and reaction conditions would be required in order to select the best of those obtainable.

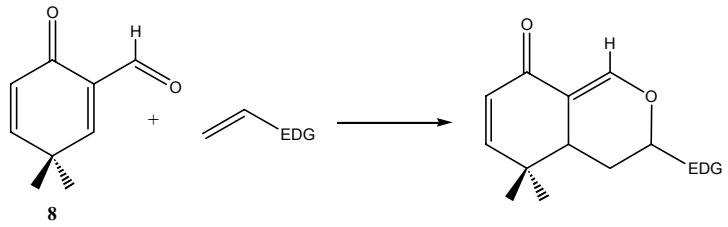
In their work with formyl dienone **8**, Desai et al. utilized dienes produced from the alkylation and subsequent thermolysis of 3-sulfolenes.[32] This method proved to be both a convenient and cost effective way in which to attain a series of variably substituted dienes and will be explored as a possible source of dienes useful to the current research.

Inverse Demand Reactions

Compounds such as formyl dienone **8** can act as the diene in inverse demand Diels-Alder cycloadditions and, when reacted with an EDG substituted dienophile, will

[31] For a comprehensive review of synthetically useful dienes, see: Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder Reaction*; Wiley: New York, 1990.
[32] Desai, S. R.; Gore, V. K.; Mayelvaganan, T.; Padmakumar, R.; Bhat, S. V. *Tetrahedron*, **1992**, *48*, 481.

incorporate the oxygen atom of the formyl group into a bicyclic product (Figure 13).[33] The carbonyl group of the dienone ring still acts as an EWG in this case but is beneficial to the reaction because the pertinent interaction is between the LUMO of the diene and the HOMO of the dienophile.



8

Figure 13: Inverse demand Diels-Alder reaction of formyl dienone **8** with an EDG activated dienophile.

This type of addition can also be imagined to occur with the formyl substituted 4-pyridone based species. An investigation into possible inverse demand reactivity of the 4-pyridone will therefore be made and may be significant as the hypothesized adduct has not yet been reported in the literature.

RESULTS AND DISCUSSION

The first phase of research involved the development of a synthetic route to the dienophile **19** using 4-pyridone as starting material. The sequence based on this substrate is shown in Figure 14, as "Route A".

Route A

The first step in the sequence required selective monobromination at carbon 3 (C-3) α to the carbonyl. The primary result of the reaction of pyridones with molecular bromine (Br_2) is the 3,5-disubstituted product. However, it was found that by maintaining an

[33] Desai, S. R.; Gore, V. K.; Bhat, S. V. *Synth. Commun.* **1992**, *22*, 97.

acidic medium, specifically in the range of 4.2-4.4, mono substitutition becomes favored over disubstitution.[34] An acetic acid/sodium acetate buffer solution was used to obtain the desired pH. In the course of the reaction, the dibrominated minor product precipitated out of solution. The monobrominated product **20** appeared as the major spot in TLC analysis but proved difficult to separate from remaining starting material due to the high polarity of both species. A mixture of both components was carried over to the subsequent sulfonylation step.

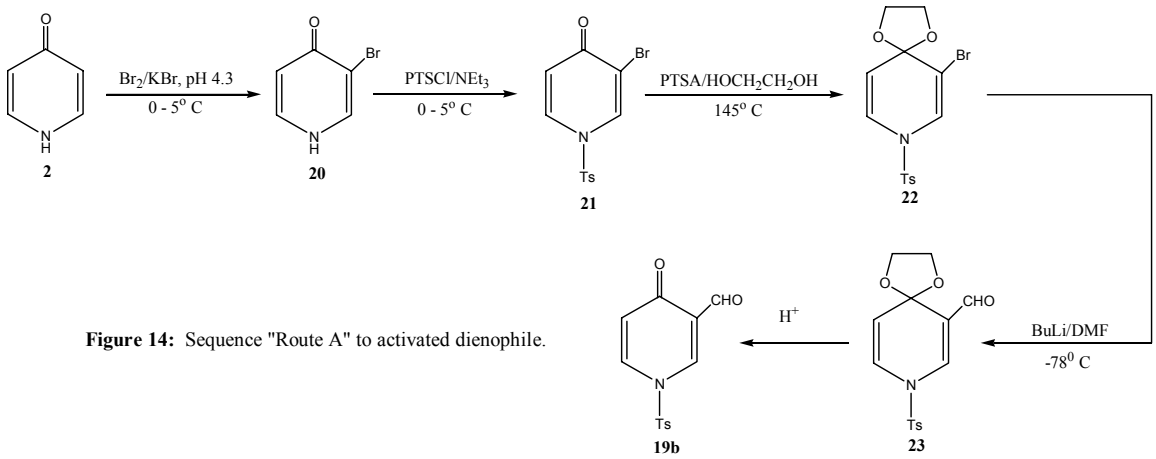


Figure 14: Sequence "Route A" to activated dienophile.

The preparation of sulfonamides via sulfonyl chlorides is well known. The reaction was carried out with *p*-toluenesulfonyl chloride (PTSCl) in the presence of triethylamine (NEt_3). HCl is scavenged by the NEt_3 and is then removed in aqueous washes. The new major product **21** was seen in TLC and verified in ^{1}H NMR analysis by the appearance of two new aromatic region peaks at 7.1 ppm (d, 2H) and 7.5 ppm (d, 2H) as well as a methyl peak at 2.3 ppm (s, 3H). Overall yield based on the starting pyridone was 13%.

Protection of the carbonyl group was next attempted in order to avoid possible alkylation at the site in the subsequent butyllithium (BuLi) catalyzed formylation step. Ethylene glycol is commonly used as a carbonyl protecting group and in the presence of

[34] Tee, O. S.; Paventi, M. *Can. J. Chem.* **1983**, *61*, 2556.

p-toluenesulfonic acid, results in the formation of the cyclic ketal.[35] The reaction was performed in refluxing toluene with a tenfold molar excess of ethylene glycol. TLC revealed the disappearance of the starting material and two new primary spots of both high and low R_f. The placement of spots indicated the possibility of tosyl group cleavage in that the higher spot could likely contain the less polar tosyl group and the lower spot could be the highly polar brominated pyridone. In order to investigate this theory, the starting material was divided into separate flasks and refluxed in either toluene or benzene. After 30 minutes, TLC showed that decomposition of the compound occurred in both solvents, although somewhat less rapidly in the lower boiling benzene. The decomposition products had R_fs comparable to those previously observed so it was concluded that, under acidic and thermal conditions, a more stable pyridone system was found in 3-bromo-4-hydroxypyridine through the dissociation of the tosyl group. Until a more suitable protection strategy could be found, further studies proceeded with 4-piperidone hydrochloride monohydrate (**24**, Figure 16) as starting material.

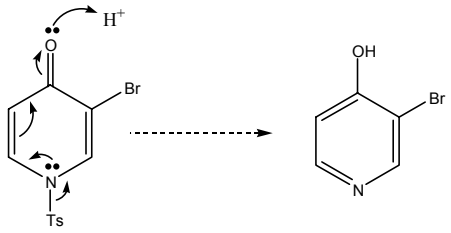


Figure 15: Proposed decomposition occuring in "Route A" protection step.

Route B

It was believed that 4-piperidone would more likely maintain the tosyl EWG during the protection step. The drive towards aromaticity seen in the pyridone species would not be present in 4-piperidone due to the lack of any conjugated system within its structure.

[35] Oliveto, E. P.; Smith, H. Q.; Gerold, C.; Weber, L.; Rausser, R.; Hershberg, E. B. *J. Am. Chem. Soc.* **1954**, *77*, 2224.

The challenge in this case then became not monobromination but rather the selective introduction of a double bond to the system. A single double bond between C-2 and C-3 would be the only site available to bromination and, following substitution with the formyl group, the only site for dienophilic reactivity.

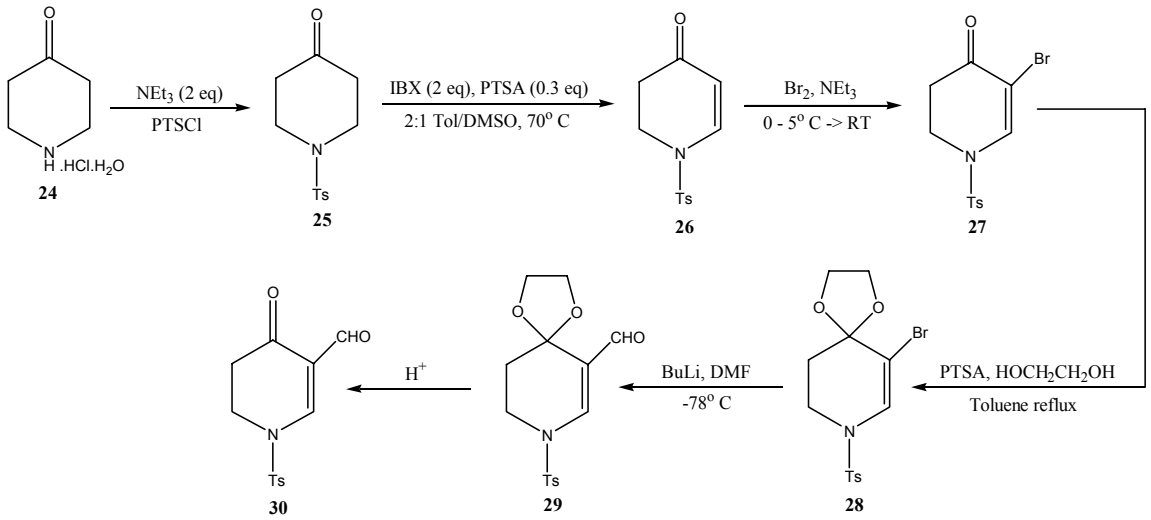


Figure 16: Sequence "Route B" to activated dienophile.

The initial tosylation step was carried out with two equivalents of NEt_3 in order to complex both bound and evolved HCl. Yields were near quantitative in repeated trials.

One method attempted for the introduction of the double bond involved the mild brominating reagent phenyl trimethyl ammonium tribromide (PTT).[36] The net result of PTT monobromination at C-3, followed by dehydrohalogenation with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), would theoretically be the formation of a double bond.[37] Reactions performed on the tosylated piperidone substrate however yielded no major product and a complex reaction mixture. Further optimization of this strategy was not pursued.

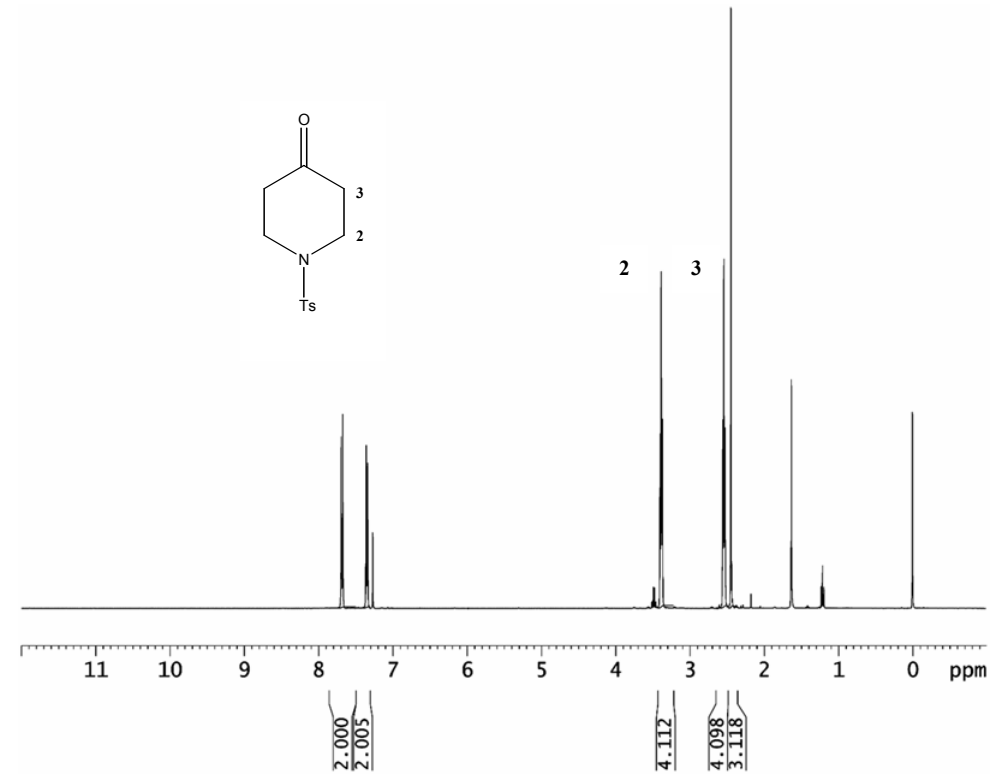
[36] Gensler, W. J.; Solomon, P. H. *J. Org. Chem.* **1973**, *38*, 1726.
[37] Geen, G. R.; Mann, I. S.; McKillop, M. V. M. *Tetrahedron.* **1998**, *54*, 9875.

2-Iodoxybenzoic acid (IBX) has been shown to possess uniquely selective oxidizing capacity and has proven to be particularly useful for the introduction of unsaturation adjacent to carbonyl functionalities.[38] Thorough research into the possible synthetic application of IBX has only recently begun as its use was initially limited due to reported explosiveness and insolubility. The asymmetric introduction of unsaturation within the piperidone system **25** (Figure 16) via IBX as proposed in "Route B" would qualify as a novel addition to information currently available in the literature.

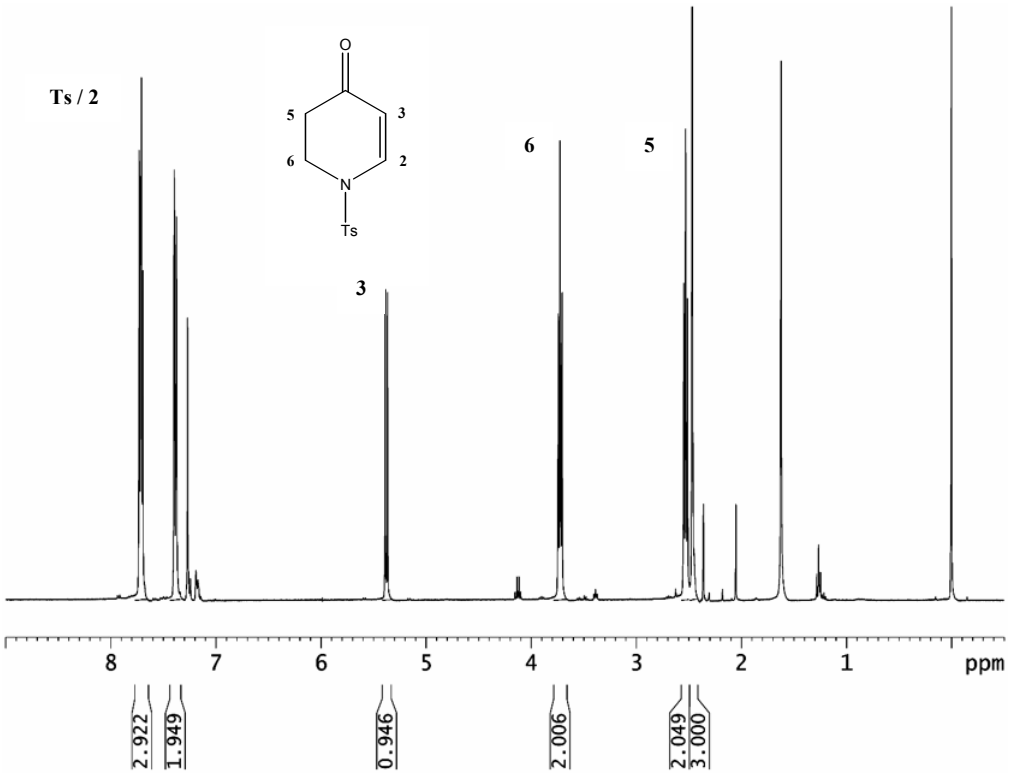
After several attempts, reaction conditions appeared to be maximized utilizing 2 equivalents (eq) IBX in a 2:1 toluene/dimethyl sulfoxide (DMSO) solution held at 70^{o} C for at least 6 h. HPLC analysis of reaction mixtures in 45:55 MeOH/H_2O gave retention times as 4.73 minutes (m) for **25** and 5.74 m for **26**. ^{1}H NMR of **25** (A, Figure 17) gave peaks at 2.44 ppm (s, 3H), 7.34 (d, 2H), 7.68 (d, 2H) for the *p*-toluene portion of the tosyl group and peaks at 2.52-2.55 (t, 4H) and 3.37-3.40 (t, 4H) corresponding to the two sets of chemically equivalent piperidone ring hydrogens. The compound **26** (B, Figure 17) showed new integration values for the two piperidone hydrogen peaks (2 in **26** from 4 in **25**) and two new separate 1H peaks at 5.38 and 7.70 ppm. The two new peaks both appeared as doublets and the two 2H peaks remained as triplets, which is consistent with multiplicities expected for the asymmetric introduction of a double bond.

The addition of catalytic PTSA had been reported to enhance reaction rate and product yield in comparable cycloalkane reactions and was therefore investigated as a possible improvement upon the above conditions.[39] After 24 h reaction time, HPLC analysis of PTSA catalyzed versus control reaction samples showed a difference in product

[38] Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y. -L. *J. Am. Chem. Soc.* **2002**, *124*, 2245.
[39] Nicolaou, K. C.; Zhong, Y. –L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596.



A



B

Figure 17: ^{1}H NMR spectra for **25** (A) and **26** (B).

concentration of 82% versus 32%, indicating that the use of PTSA (0.3 eq) was indeed beneficial. Unless left for over 48 h, solid remained undissolved in solution throughout the course of this reaction. The solid appeared to maintain near constant volume so most likely it consisted of a gradually increasing portion of the reduced form of IBX as it was being consumed. The observed dissolution of solid accompanying longer reaction times can most probably be attributed to the decomposition of the reduced reagent. Repeated trials of the PTSA catalyzed reaction gave consistent purified product yields of 40-50%.

The remaining steps in "Route B" (Figure 16) were based on a method reported by Smith et al. for the production of 2-hydroxymethyl-2-cyclopentenone.[40] Vinyl bromination, α to the carbonyl, was achieved by treatment with molecular bromine, followed by dehydrobromination with NEt_3. The monobrominated product **27** was verified through ^1H NMR (A, Figure 18), which showed the disappearance of the upfield vinyl proton, previously seen at 5.38 ppm for **26**, and slight downfield shift of the remaining vinyl proton to 8.10 ppm. This shift can be attributed to deshielding of the C-2 proton caused by the addition of the bromine atom to the double bond.

Product yields were highly sensitive to the relative ratio of Br_2 to substrate. When compared to trials run with higher molar equivalencies, the use of one equivalent Br_2 appeared to minimized the occurrence of dibrominated side products. Side products were observed under all reaction conditions however and typical recrystallized yields of the desired product did not exceed 40%. ^1H NMR of the major side product gave a similar spectrum to **27** but instead of two 2H triplets for the saturated C-5 and C-6 carbons, a 1H triplet (most likely the C-5 proton) and two 1H doublet of doublet peaks appeared (the

[40] Smith, III, A. B.; Branca, S. J.; Guaciaro, M. A.; Wovkulich, P. M.; Korn, A. *Organic Syntheses*. CV7, 271.

now chemically non-equivalent C-6 protons). The data led to the conclusion that the substrate can easily undergo disubstitution to form the 3,5-dibrominated product. In an effort to reduce the amount of side products formed in this step, an alternative method was attempted using the more mild brominating reagent PTT. HPLC analysis of PTT reaction mixtures however showed no product that corresponded to the RT of previously synthesized **27** (3.40 m; 40:60 MeOH/H_2O) so bromination via Br_2/Net_3 was maintained.

The synthesis of **27** provided the non-conjugated analogue of compound **21**. Believed to be now resistant to decomposition, **27** was subjected to carbonyl protection under the same PTSA/ethylene glycol in refluxing toluene conditions as had been employed in "Route A" (Figure 14). TLC after 3.5 h showed only a small amount of remaining starting material, a primary product spot and secondary spot of higher R_f, as well as several faint spots of lower R_f. The product composition of the reaction mixture was not significantly affected by either additional reflux or extended room temperature (RT) stirring. Purification via preparative TLC did not provide clean separation of components even after two attempts. Qualitative analysis of the ^1H NMR spectrum of the slightly impure product **28** (B, Figure 18) showed two new 2H peaks in the 3.5-4.5 ppm region, in addition to all characteristic peaks of **27**. The integrations and chemical shifts of these new peaks were consistent with what would be expected for protons of the cyclic ketal as formed through ethylene glycol.

Although it still remained a possible route to the activated dienophile of interest, further work along "Route B" was paused at this point. An alternative strategy was developed which could eliminate the need for both bromination and protection steps.

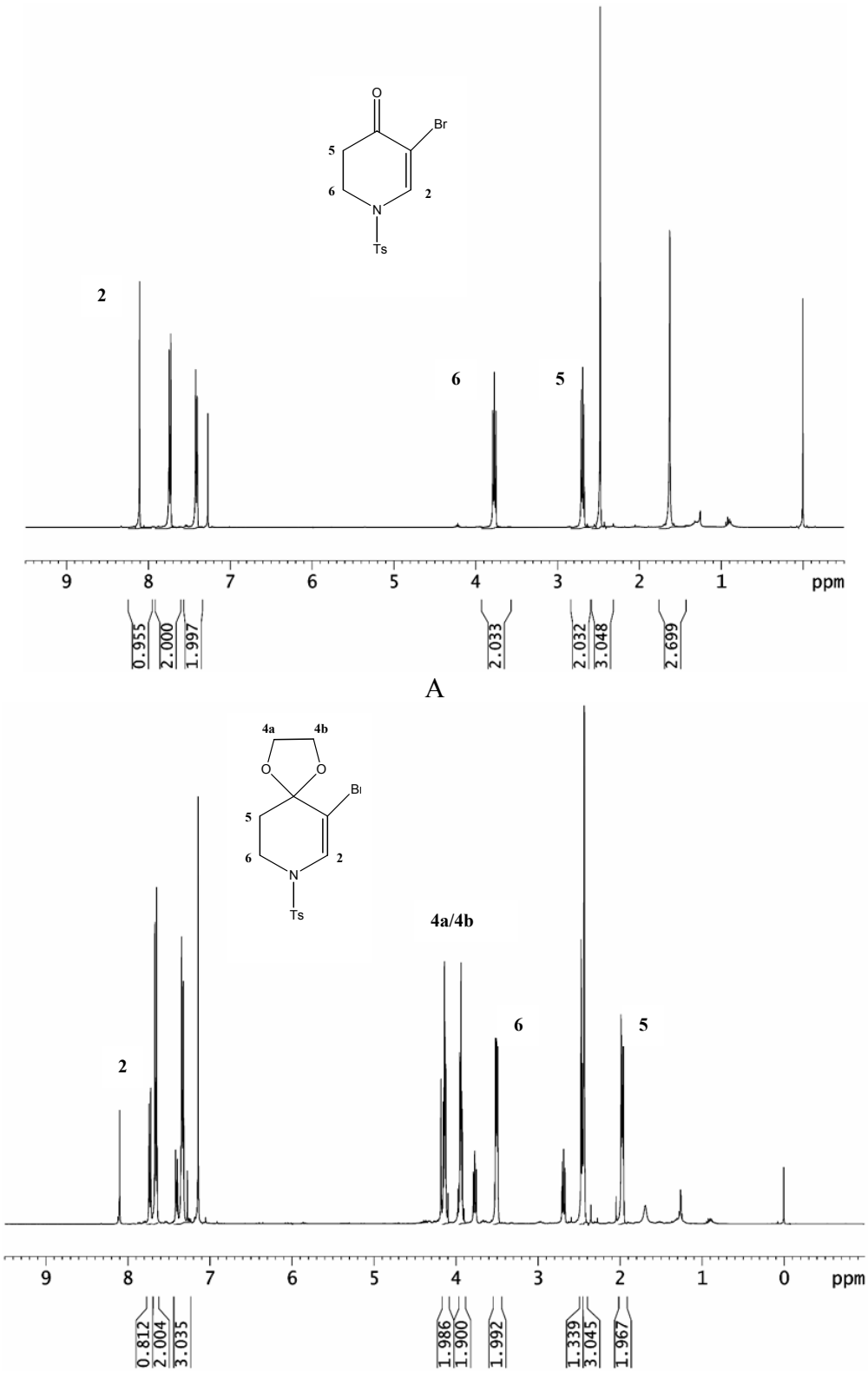
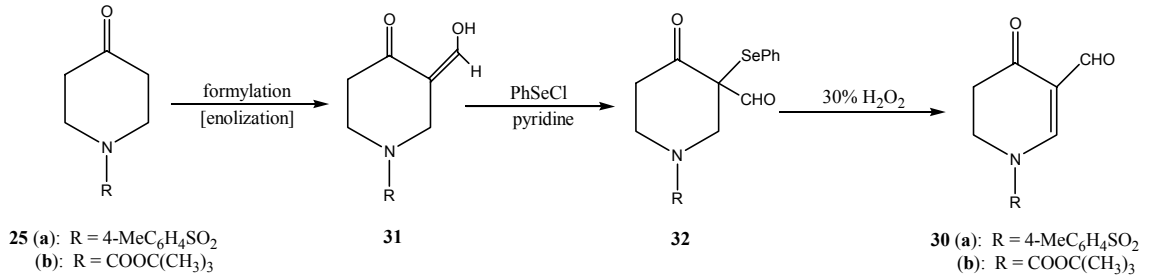


Figure 18: ^{1}H NMR spectra for **27** (A) and **28** (B).

Route C

Enolizable *β*-dicarbonyl compounds can be converted into their unsaturated derivatives through selenation, using a 1:1 phenylselenenyl chloride/pyridine complex, followed by oxidation with 30% H_2O_2.[41] A C-3 formylated 4-piperidone such as **31** (Figure 19) would possess the *β*-dicarbonyl functionality that could, if behaving like the structurally analogous cyclohexanone systems, undergo selenation and subsequent oxidation to form the dienophile of interest (**30a** = tosyl N-substituted; **30b** = *tert*-butoxycarbonyl N-substituted). Both the previously synthesized compound **25** and the commercially available N-(*tert*-Butoxycarbonyl)-4-piperidone **25b** could serve as starting materials. The primary challenge of "Route C" was then to find a way in which to selectively introduce a formyl group to C-3 of the piperidone nucleus.



25 (**a**): R = 4-$MeC_6H_4SO_2$
(**b**): R = $COOC(CH_3)_3$

31

32

30 (**a**): R = 4-$MeC_6H_4SO_2$
(**b**): R = $COOC(CH_3)_3$

Figure 19: General sequence for "Route C" pathway to activated dienophile**.**

It was thought that treatment of **25** with 1 equivalent of strong base would cause selective deprotonation and carbanion formation α to the carbonyl, at C-3. Addition of an appropriate electrophile could then result in formylation at the site. The initial attempt to produce **31** used the commercially available compound **25b** as the substrate, lithium diisopropylamide (LDA) as the base, and *N*-*N*-dimethylformamide (DMF) as the potential source of the formyl group. Formation of the carbanion was performed at -78°C

[41] Liotta, D.; Barnum, C.; Puleo, R.; Zima, G.; Bayer, C.; Kezar, III, H. S. *J. Org. Chem.* **1981**, *46*, 2920.

in order to reduce the possibility of product decomposition and/or uncontrolled deprotonation. TLC 1.5 h following the addition of DMF showed that the majority of starting material had disappeared and a new product was being formed. Recrystallization of the recovered clear oil gave an overall 46% yield of unidentified white crystals. ^{1}H NMR analysis of the recovered product however gave results inconsistent with what was to be expected for the formylated structure **31**. Two 9H peaks were seen at 1.46 and 1.50 ppm respectively, which implied possible polymerization of **25b**. Broad peaks corresponding to the piperidone ring hydrogens remaining between 2 and 4 ppm. Also, if successful addition of the formyl group had taken place, a new downfield peak associated with the proton of the formyl group would have been seen but no such peak appeared in the spectrum.

Literature review at this point revealed a related synthesis in the production of 1-hydroxy-2-methylpent-1-en-3-one from 3-pentanone.[42] Treatment of 3-pentanone with sodium hydride (1 eq), followed by ethyl formate (1 eq) gave mono-addition of the formyl group α to the carbonyl. This reaction was run under dry conditions using **25b** again as substrate. Quenching with 1 N HCl after 24 h produced violent bubbling, which indicated the presence of still unreacted sodium hydride. TLC showed a distinct product to have formed which was recrystallized in hexane and submitted for ^{1}H NMR analysis. The spectrum correlated almost exactly with that of starting material **25b**, with the addition of a 3H peak at 1.45 ppm. Further characterization of the compound was not pursued as it was believed that a more potent base than sodium hydride would be necessary to promote carbanion formation.

[42] Myles, D. C.; Bigham, M. H. *Organic Syntheses*, CV 9, 548.

The third attempt at formylation using **25b** as substrate maintained ethyl formate as the potential source of the formyl substituent with the base altered to the more highly reactive LDA. A distinct product appeared in TLC analysis after 24 h reaction time. Column purification gave a final 47% yield of the major product. The ^{1}H NMR differed significantly from previously submitted candidates for the formylated product **31** (A, Figure 21) in that the piperidone ring hydrogen peak integrations at 2.48 and 3.60 ppm had changed from 4H to 2H. These peaks both remained as triplets. A third peak at 4.20 ppm integrated for 2H and appeared as a singlet. This correlated with expected results for the protons of C-2 given that the adjacent C-3 was now formylated and in its enol form, as shown for compound **31**. An additional peak appeared far downfield at 8.50 ppm and this was believed to be the proton bonded to the formyl carbon. When the field of analysis was broadened out to 16 ppm, a small peak integrating to between 0.5 and 1H at roughly 14.10 ppm could be seen. Spectra of product from this and repeated versions of the same experiment also showed enhanced integration of the *t*-butoxy 9H proton peak to between 9.5 and 10H. It was believed that the additional observed split peak areas corresponded to the hydroxyl proton of the formyl group that was hydrogen bonding to the adjacent carbonyl at C-4. As **31** existed as an intermediate in the route to the desired dienophile, extensive characterization of the compound was remitted in favor of a more complete investigation into the possible product of the proposed selenation/oxidation sequence.

Following column purification, the believed compound **31** was dissolved in dichloromethane and treated with the 1:1 phenylselenenyl chloride/pyridine complex. The role of pyridine in the transformation from **31** to **32** is not fully understood; however,

in similar reactions with enolized 3-formyl cycloalkane systems, its presence significantly reduced the appearance of side products.[43] The pyridine may complex HCl evolved from the addition of the phenylseleno moiety to C-3 but if so, remains soluble in the dichloromethane even in its salt form as no precipitation of solid was observed during the selenation phase of the reaction. After TLC analysis showed the disappearance of the starting material and new product formation, the pyridine and any salts formed were removed through extraction with 10% HCl solution. Neither purification nor characterization of the intermediate compound **32** was attempted at this time. Instead, oxidation with H_2O_2 was carried out on the crude product mixture contained in the recovered, Na_2SO_4 dried dichloromethane extractions. It had been reported that phenylselenocarbonyl compounds, when treated with hydrogen peroxide, will oxidize into the selenoxide and then eliminate to form the α,β-unsaturated carbonyl moiety.[44] It was believed that this process would occur in the present system to form the desired dienophile **30b** as shown in Figure 20.

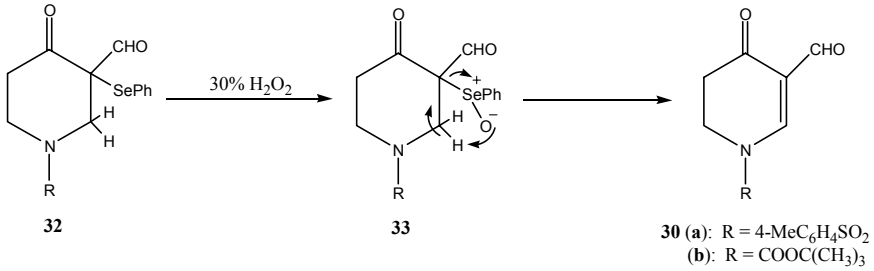
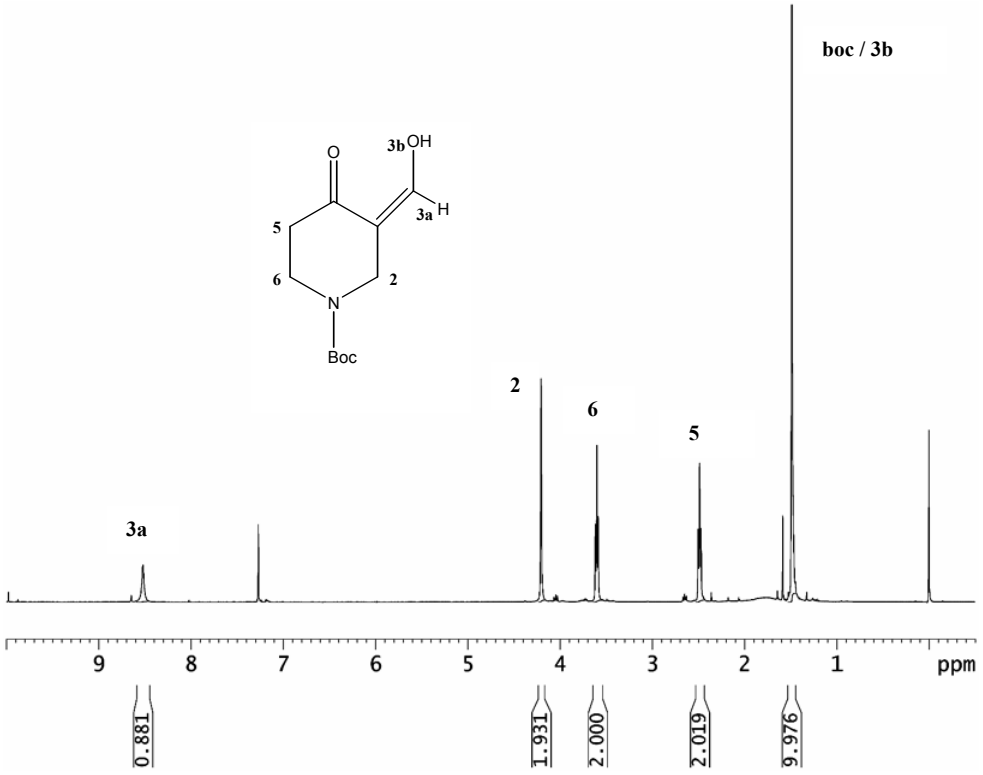


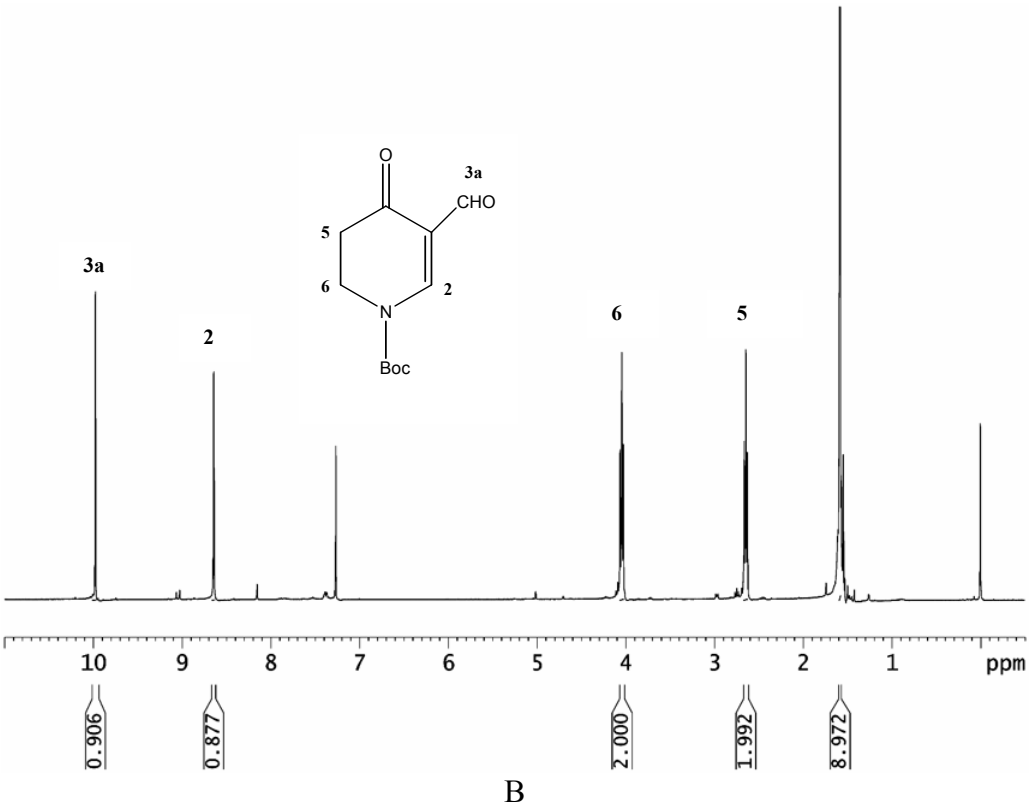
Figure 20: Mechanism of oxidation in "Line C" pathway to activated dienophile**.**

Initial inspection of the ^{1}H NMR spectrum (B, Figure 21) for the column purified major product showed two 2H triplet peaks similar to those seen in the spectrum of **31**, although appearing slightly further downfield (2.65 and 4.05 ppm versus 2.48 and 3.60).

[43] Liotta, D.; Barnum, C.; Puleo, R.; Zima, G.; Bayer, C.; Kezar, III, H. S. *J. Org. Chem.* **1981**, *46*, 2920.
[44] Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137.



A



B

Figure 21: ^{1}H NMR spectra of **31** (A) and **30b** (B).

A raise in chemical shift for these protons, which are believed to correspond to C-5 and C-6 respectively, would be consistent with the introduction of unsaturation into the piperidone ring. A large 9H singlet at 1.58 ppm could be seen, which indicated that the *t*-butoxycarbonyl (boc) group had been maintained in the product. The singlet peak that had corresponded to the protons of C-2 in compound **31** (4.20 ppm, 2H) was no longer present in the spectrum of the product. Instead, two new singlet peaks appeared. The first of these, at 8.65 ppm, was believed to represent the remaining vinyl proton at C-2. The second peak was within the characteristic range for aldehyde protons at 9.97 ppm so most likely corresponded to the proton of the CHO group at C-3. These spectral changes together indicated that successful introduction of the double bond had taken place and the formyl group at C-3 was no longer in its enol form.

Further confirmation of the dienophile **30b** was found through ^{13}C NMR analysis (A, Figure 22). Nine distinct carbons were present in the compound and nine peaks were seen in the spectrum. Three peaks, upfield at 30, 35, and 42 ppm, were believed to correspond to 1) the three equivalent methyl carbons of the boc group, and 2/3) the two non-equivalent saturated ring carbons. The peak at 86 ppm was attributed to the central carbon of the boc group bonded to oxygen. The peak at 114 ppm most likely represented the sp^2 C-3 carbon. The other carbon of the double bond, C-2 adjacent to the nitrogen atom of the piperidone ring, gave a peak at 150 ppm. Also at 150 ppm was a small peak believed to be the carbonyl carbon of the boc group bonded to the nitrogen atom. The two remaining peaks, at 188 and 191 ppm, fell within the expected area for the two carbonyls found at C-4 of the ring and within the aldehyde (CHO) group attached to C-3.

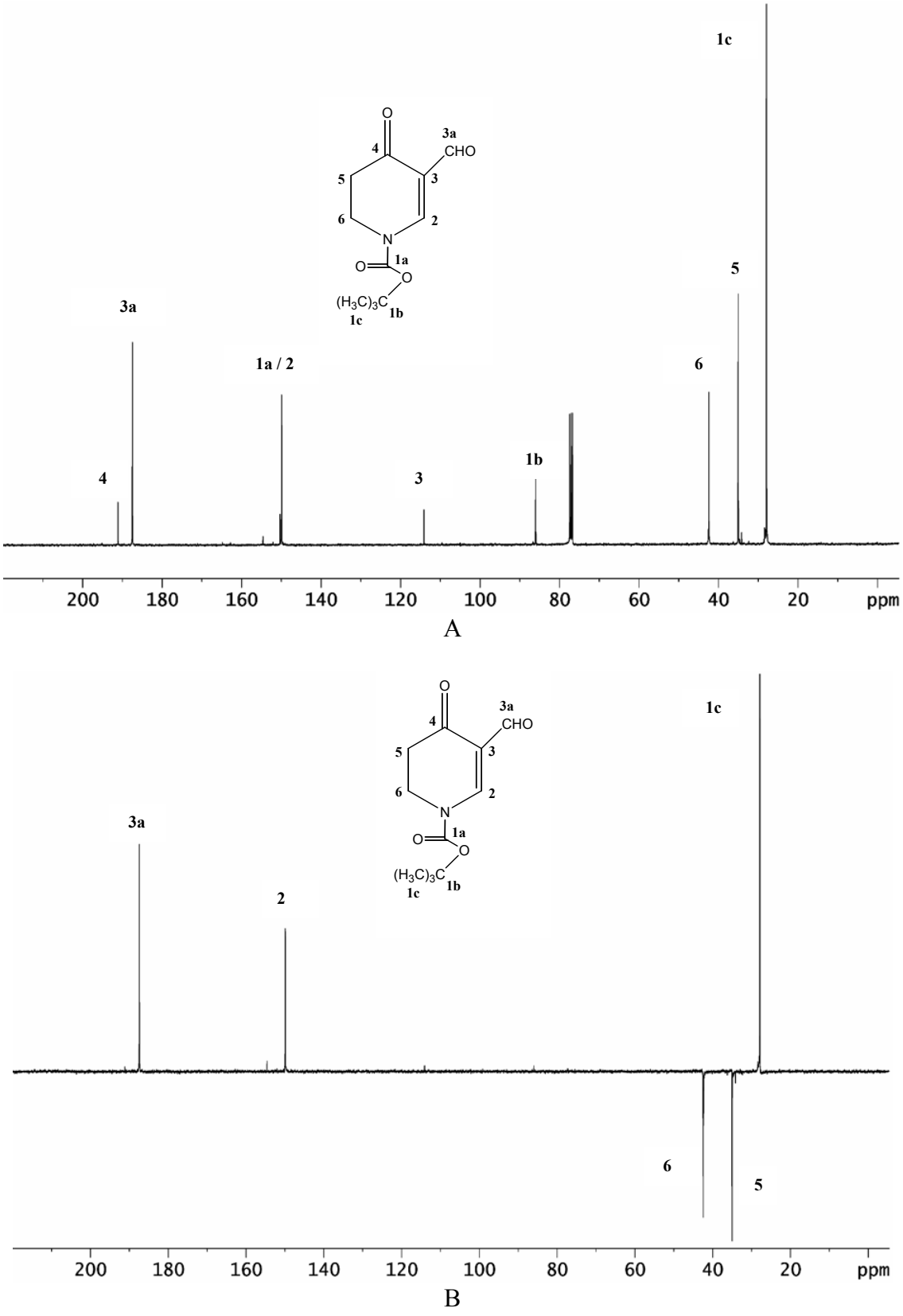


Figure 22: ^{13}C (A) and ^{13}C DEPT (B) spectra for **30b**.

A ^{13}C Distortionless Enhancement by Polarization Transfer (DEPT) scan gave two negative peaks at 35 and 42 ppm (B, Figure 22). This supported the assignment of these peaks as the methylene carbons C-5 and C-6. A positive peak at 28 ppm indicated the three methyl groups of the boc. Additional positive peaks at 150 ppm and 188 ppm indicated the methine carbons C-2 (of the double bond) and formyl group CHO respectively. The four quaternary carbons of compound **30b** (seen at 86, 114, 150, and 191 ppm in the ^{13}C NMR spectrum) were implied by the absence of their corresponding peaks in the DEPT spectrum. Repeated execution of "Route C" with the N-boc substituted piperidone starting material gave consistent NMR results for the product dienophile. Overall yields were typically between 30-40%.

The synthetic route developed for the production of the activated dienophile **30b** (Figure 19) was next applied to substrate **25a** in an effort to produce the dienophile **30a**. A method for the synthesis of **25a** (Figure 16) had previously been found through work along "Route B" so this starting material was readily available. Reaction of **25a** with LDA/ethyl formate gave a product mixture that was difficult to completely purify by column chromatographic methods but, based on comparison to the spectrum for the N-boc substituted intermediate, appeared to contain the formylated compound **31**. The selenation/oxidation sequence was carried out as before and the final pure product, believed to be compound **30a**, was isolated in overall 15% yield.

The ^{1}H NMR spectrum (A, Figure 23) showed two 2H triplet peaks (2.62 and 3.84 ppm) for the protons of the saturated ring carbons C-5 and C-6, one 3H singlet (2.48 ppm) and two 2H doublets (7.42 and 7.77 ppm) corresponding to the tosyl group protons, one 1H singlet (8.60 ppm) for the vinylic proton at C-2, and one 1H singlet (9.93 ppm)

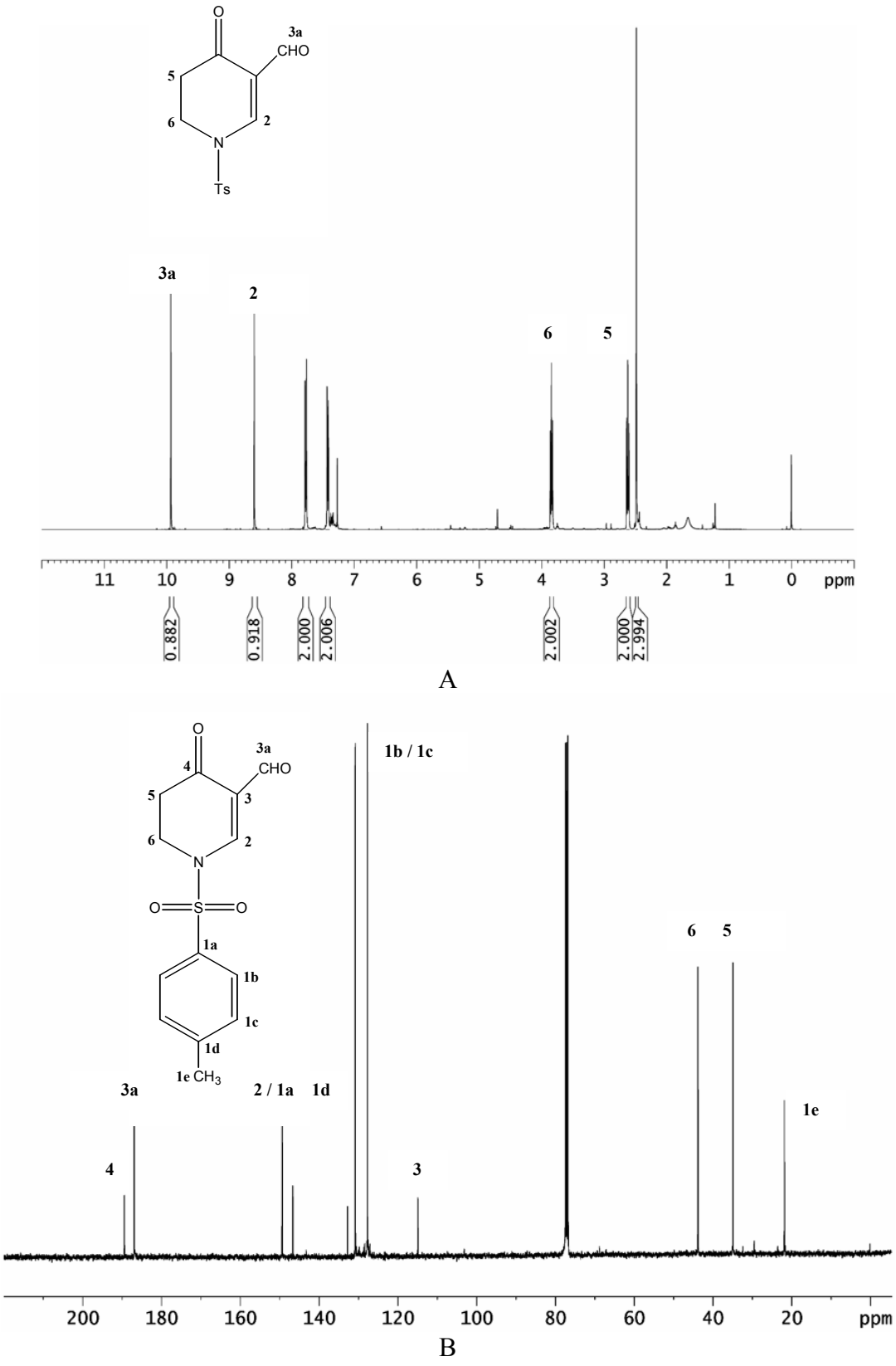


Figure 23: ^{1}H (A) and ^{13}C (B) NMR spectra for **30a**.

far downfield which could only represent the formyl group proton. ^{13}C NMR data for **30a** (B, Figure 23) compared closely to that of compound **30b** (A, Figure 22). The peaks for the five carbons of the piperidone ring, as well as for the carbon of the formyl group, all appeared within 2 ppm of those seen in the **30b** spectrum. Five peaks exclusive to compound **30a** could also be seen. These most likely represented the five other non-equivalent carbons contained in the tosyl EWG. The chemical shifts of the peaks supported this assumption in that one appeared at 22 ppm, which would be typical for the methyl group carbon, and the others were at 128, 131, 133, and 147 ppm, shifts more typical of aromatic ring carbons.

In an effort to further broaden the selection of available dienophiles for pending Diels-Alder reactivity studies, both 2- and 4-nitrobenzenesulfonyl (NBS) chlorides were reacted with 4-piperidone. Both N-substituted compounds were formed cleanly and in high yield, as had been the case with PTSCl. When prepared for formylation, the 4-NBS substituted compound was found to be insoluble (in THF) and was set aside. The 2-NBS compound was soluble but gave a complex mixture after treatment with LDA/ethyl formate. These groups had been chosen because they are more potent EWGs than either the boc or tosyl groups and could therefore serve to more highly activate the dienophile. However, it appeared that the strong electron withdrawing capacity of 2-NBS caused unwanted side reactions. The possibility that the piperidone ring had opened was considered. It was decided at this point that **30a** and **30b** would be used as the primary dienophiles in the subsequent Diels-Alder cycloaddition studies. These compounds possessed the favorable combination of being both significantly activated and synthetically accessible.

Diels-Alder Studies

"Route C" served to establish a reliable synthetic route to the activated dienophiles of interest. However, it remained to be seen if the compounds would actually undergo [4 + 2] Diels-Alder cycloaddition. The latter half of the current research was therefore directed towards the investigation of this issue. Basic reactivity of the compounds was first established. Following that, dienes of various degrees of activation were used in order to develop a greater understanding of dienophile reactivity. Mild reaction conditions (room temperature, no catalyst) were generally used as a starting point but investigation into the effect of several Lewis Acids on product outcome became necessary. A summation of the Diels-Alder reactions attempted is given in Table 1.

Inverse Demand Reactions

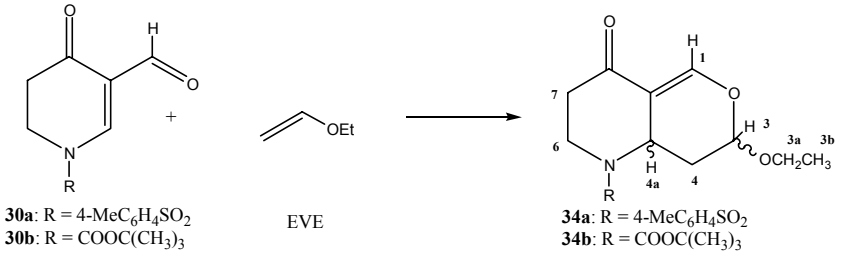
The most straightforward way in which to assess the potential capacities of compounds **30a** and **30b** for cycloaddition was through the use of inverse demand conditions (Figure 24). Ethyl vinyl ether (EVE) can be used as the dienophile and, because it dissolves both **30a** and **30b**, can be employed as the solvent, which allows for the reaction to be performed neat. The first test reaction utilized roughly 5mg of **30b** reacted with a 10-20 fold molar excess of EVE. After 24h at room temperature and without convection, a clear product could be seen by TLC. The product was recovered by simple evaporation of residual EVE. ^{1}H NMR of the sample gave a complex spectrum that, at first inspection, implied the possible need of product purification prior to sample analysis.

Table 1: Summary of Diels-Alder reactions.

Experiment #	Dienophile	Diene	Solvent	Temp. (^{o}C)	Lewis Acid	Time (h)	Reaction?
1	EVE*	30b*	(neat)	RT	N/A	24	**Yes**
2	EVE	30b	toluene	80	N/A	24	**Yes**
3	EVE	30a*	(neat)	75	N/A	24	**Yes**
4	30a	PPD*	toluene	125	N/A	24	No
5	30a	PPD	toluene	RT	$AlCl_3$	20	No
6	30a	Dan.*	toluene	RT	N/A	24	**Yes**
7	30a	isoprene	toluene	100	N/A	24	No
8	30a	isoprene	THF	RT	BF_3 etherate	84	Minor
9	30a	isoprene	DCM	RT	BF_3 etherate	24	Mix
10	30a	DTB*	toluene	RT	N/A	24	**Yes**
11	26	DTB	toluene	RT	N/A	24	No
12	26	DTB	toluene	80	N/A	24	No
13	30a	DTB	toluene	0-5	N/A	24	Minor
14	DADC*	DTB	benzene	5-RT	N/A	24	**Yes**
15	30b	DTB	toluene	RT	N/A	2	**Yes**
16	30b	DTB	toluene	0-5	N/A	24	**Yes**
17	30b	DTB	THF	-78	N/A	24	No
18	30b	isoprene	toluene	RT	N/A	18	No
19	30b	isoprene	toluene	110	N/A	18	No
20	30b	isoprene	DCM	RT	BF_3 etherate	24	No
21	30b	isoprene	DCM	RT	$SnCl_4$	24	No
22	30b	isoprene	DCM	RT	$TiCl_4$	24	No

*EVE = ethyl vinyl ether; 30b = N-boc-3-formyl-5,6-dihydropyridin-4-one; 30a = N-tosyl-3-formyl-5,6-dihydropyridin-4-one; PPD = 1-phenyl-2,4-pentadiene; Dan. = "Danishefsky's diene" (1-methoxy-3-trimethylsiloxy-1,3-butadiene); DTB = 1-dimethylamino-3-*tert*-butyldimethylsiloxy-1,3-butadiene; DADC = diethyl acetylenedicarboxylate. Highlighted experiments were repeated in order to verify results.

The reaction was performed a second time under the same conditions but using 1 mmol (0.2g) **30b** in order to facilitate pure product isolation. After 24h at room temperature, TLC showed remaining starting material as well as the same distinct product spot that had been seen previously. The mixture was transferred to a high-pressure tube and brought to 80^{o} C in order to investigate possible furthering of the reaction by heating. TLC after 4h did not show significant change in the product distribution so this was discontinued. Column chromatography gave 0.13g of the major product for a yield of 50%. ^{1}H NMR of the product (A, Figure 25) gave a spectrum very similar to that attained from the first trial, which implied that the reaction proceeds smoothly and without significant side product formation. The suspected product **34b** appeared as a 60:40 mixture of two isomers. The coupling constants for the two observed isomers were nearly identical but of slightly different chemical shift, which implied that the pair could be the diastereomeric endo and exo isomers assuming a similar confirmation. This could be possible due to the flexibility of the ring system as caused by the presence of nitrogen.



30a: R = 4-Me$C_6H_4SO_2$
30b: R = $COOC(CH_3)_3$

EVE

34a: R = 4-Me$C_6H_4SO_2$
34b: R = $COOC(CH_3)_3$

Figure 24: Inverse demand reaction of synthesized compounds **30a** and **30b** with ethyl vinyl ether (EVE).

Proton assignments were facilitated by comparison to those made for protons of the related benzopyranone structure shown in Figure 13.[45] The protons of the boc group were here unique but appeared undisturbed in the product (s, 1.50, 9H). Several other

[45] For proton assignments of the benzopyranone compound, see: Desai, S. R.; Gore, V. K.; Bhat, S. V. *Synth. Commun.* **1992**, *22*, 97.

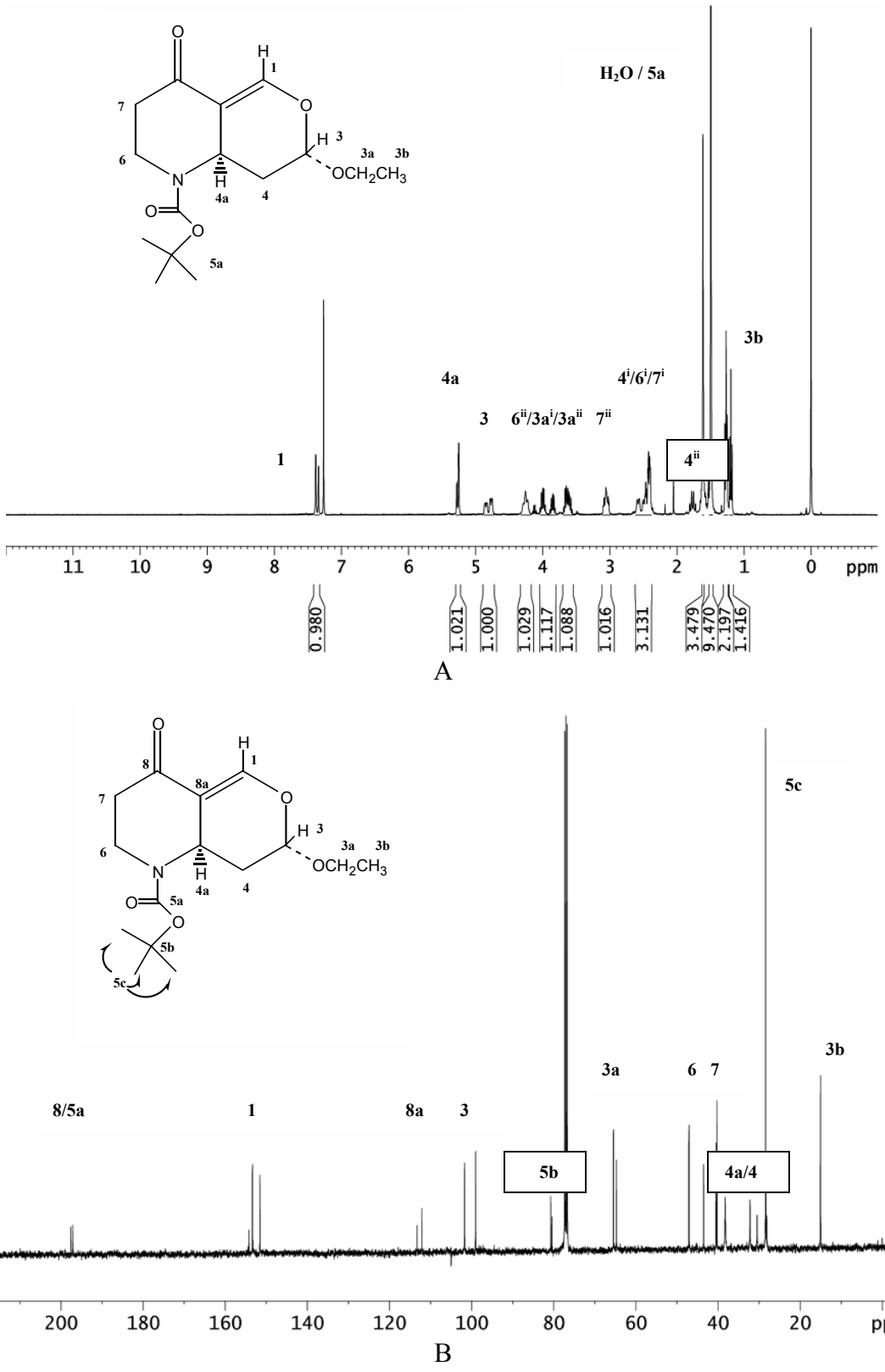


Figure 25: ^{1}H (A) and ^{13}C (B) NMR spectra for inverse demand product **34b.**

protons compared closely to those reported for the benzopyranone, including H-1 (d, 7.38, 1H, *J* = 2), H-3 (dd, 4.81, 1H, *J* = 2.5, 11.3), H-3a (dq, 3.64 and 3.9, 1H each, *J* = 7.2, 9.5), H-3b (t, 1.27, 3H, *J* = 7.1), and H-4 (dt, 1.70 and 2.50, 1H each, *J* = 9.3, 11.8, 12.3). The proton at H-4a appeared considerably further downfield from that of the benzopyranone analogue (5.26 as compared to 2.77) most probably due to the additional deshielding caused by the adjacent nitrogen atom in **34b**. Four additional protons were observed, two at 2.4 ppm, one at 4.0, and another at 4.2. The only remaining unassigned protons belonged to the saturated carbons numbered in Figure 25 as 6 and 7. Analysis by two-dimensional Correlation Spectroscopy (2D COSY) confirmed that these protons coupled each other. Molecular modeling of **34b** shows that the four protons maintain different chemical environments; however, the two appearing close together were believed to be the equatorial protons whereas those further downfield were thought to be the more deshielded axial protons.

The ^{13}C spectrum for **34b** (B, Figure 25) showed 13 distinct carbons corresponding to the 13 chemically non-equivalent carbons found in the compound. Most of these appeared as closely matched pairs of approximately 60:40 height ratio, presenting with slight differences in chemical shift between the two isomers. As with the proton assignments, several of the carbon chemical shifts of **34b** matched closely to those reported for the benzopyranone, including C-1 (152 ppm in **34b** versus 152 for the benzopyranone), C-3 (100 compared to 101), C-3a (65 to 65), C-3b (15 to 15), C-4 (31 to 29), C-4a (40 to 40), and C-8a (112 to 112). C-8 appeared somewhat more downfield (198 compared to 186) in **34b** compared to benzopyranone, again most probably due to the presence of nitrogen within the ring. Three signals (28, 81, and 196 ppm) represented

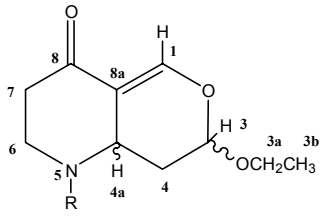
the carbons of the boc group. The remaining two signals corresponded to C-6 and C-7 and were assigned through comparison to the carbon spectrum of the synthesized dienophile **30b**.

The inverse demand reaction with EVE was also carried out using the tosyl substituted compound **30a** as substrate. No product was seen after 24h at room temperature. However, heating the mixture to 75^{o} C in a sealed pressure tube for 24h did result in product formation. The difference in required reaction conditions between the boc and tosyl substituted compounds (room temperature versus 75^{o} C) implied that the boc derivative may be somewhat more reactive than the tosyl.

The ^{1}H NMR spectrum for **34a** possessed several similar characteristics to that obtained for compound **34b** (see Table 2). A mixture of isomers could again be seen but the tosyl substituted substrate appeared to be more selective as the peak ratio of isomers in this case was approximately 75:25. The chemical shifts for protons H-1, H-3, H-3a, H-3b, H-4, and H-4a were all closely comparative between the two compounds (see Table 2). The four protons of C-6 and C-7 appeared at slightly different chemical shifts but in relatively the same position within the spectrum. Two-dimensional COSY of **34a** provided verification of the suspected proton couplings.

The ^{13}C NMR spectrum gave 15 distinct peaks for the 15 chemically non-equivalent carbons in the compound. Many of these peaks appeared again as pairs but the difference in height between the peaks of each pair was here more dramatic than for **34b**. The chemical shifts matched to within 2 ppm of those seen for **34b**, except for those corresponding to the carbons of the tosyl group (see Table 2).

Table 2: ^{1}H, ^{13}C NMR chemical shift values for inverse demand products **34a** and **34b**.



34a: R = 4-$MeC_6H_4SO_2$
34b: R = $COOC(CH_3)_3$

Proton #	34a (ppm)	34b (ppm)		Carbon #	34a (ppm)	34b (ppm)
1	7.4	7.3		**1**	153	152
3	4.6	4.8		**3**	99	100
3a (2H)	3.7 / 4.0	3.6 / 3.9		**3a**	65	65
3b	1.3	1.3		**3b**	15	15
4 (2H)	2.0 / 2.7	1.7 / 2.5		**4**	33	31
4a	5.3	5.3		**4a**	41	40
5a*	7.7	1.5		**5a***	144	196
5b*	7.3	-		**5b***	130	81
5c*	2.4	-		**5c***	127	28
6 (2H)	2.2 / 3.9	2.4 / 4.3		**5d***	136	-
7 (2H)	2.0 / 3.4	2.4 / 3.0		**5e***	22	-
				6	47	45
				7	38	38
				8	196	198
				8a	110	112

*These values correspond to tosyl (**34a**) or boc (**34b**) electron withdrawing groups.

Normal Demand Reactions

In order to synthesize the target decahydroquinoline system, the dienophiles needed to be reacted under normal demand conditions. The first dienes to be used were derived from 3-sulfolene (**35**). It was believed that the sulfolene would serve as a useful template for the synthesis of variably activated dienes because they may be easily alkylated through reaction with alkyl halides.

The first attempt at alkylation utilized benzyl bromide as the source of EDG. The reaction gave a mixture of four products, two groups of two spots as seen by TLC. NMR analysis showed the two spots of higher R_f to be dialkylated compounds. The third spot was not completely characterized due to its appearance as a complex mixture in ^{1}H NMR. The fourth spot correlated with expected results for the monoalkylated product as seen in ^{1}H NMR analysis. The isolated yield was 25%. This product was then subjected to thermolysis via reflux in toluene. TLC after 1 hour showed no remaining starting material and a single major spot of higher R_f. ^{1}H NMR of the column purified product showed 12 protons (**A**, Appendix A). Five of these were in the aromatic region (phenyl substituent). The three protons at C-2, 3, and 4 of the diene appeared distinctly as multiplets. Two doublet peaks represented the terminal C-5 protons and one other peak, a singlet integrating for 2H, indicated the two equivalent protons of C-1. The spectral data taken together confirmed the formation of the desired diene **36** (Figure 26), 1-phenyl-2,4-pentadiene (PPD).

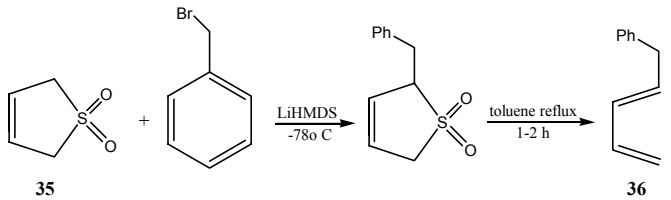


Figure 26: Alkylation and thermolysis pathway to diene 1-phenyl-2,4-pentadiene (PPD).

Having established that thermolysis of the alkylated sulfolene provided a clean route to the desired diene, the first normal demand reaction was run in situ with the dienophile **30a** added directly to the refluxing toluene mixture. TLC after 24 h reflux showed the starting materials to be still present. These results prompted the first investigation into possible Lewis Acid catalyzed reaction of the dienophiles. The dienophile **30a** was dissolved in toluene at room temperature and 0.9 eq of aluminum chloride ($AlCl_3$) was added to the solution, followed by the addition of PPD. The reaction was monitored by TLC over a 24-hour period. No product was observed so the mixture was set up for reflux. A product appeared after 1 h and the mixture was held at reflux temperature for a total of 4 h before workup. The product was column purified and submitted for ^1H NMR analysis. The recovered compound however appeared to be the tosyl group (most likely as TsOH), which had apparently been ejected from the dienophile under the combined Lewis Acid with reflux conditions. The unsuccessful results of the reactions with PPD led to the conclusion that the use of a diene with higher reactivity (i.e. more highly activated with EDGs) might be necessary in order to promote cyclization. The first of these to be chosen was the commercially available Danishefsky's diene (1-methoxy-3-trimethylsiloxy-1,3-butadiene).[46]

Danishefsky's diene has been shown to undergo cycloaddition reaction with the closely analogous system 3-formylchromone.[47] Published experiments do not report the need for Lewis Acid catalysis and may be run at room temperature. The reaction was attempted with the dienophile **30a**, dissolved in toluene at room temperature. TLC

[46] For reactivity and synthesis of this diene, see: (a) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807. (b) Danishefsky, S.; Kitahara, T. *J. Org. Chem.* **1975**, *40*, 538.
[47] (a) Cremins, P. J.; Saengchantara, S. T.; Wallace, T. W. *Tetrahedron*, **1987**, *43*, 3075. (b) Sabitha, G. *Aldrichimi. Acta,* **1996**, *29*, 15.

analysis of the mixture over the course of 24 hours showed the gradual diminishing of starting material concentration. Two primary product spots were seen, one with an R_f slightly higher than that of the dienophile and one at significantly lower R_f. Attempts to purify the reaction mixture were met with difficulty and the final sample submitted for ^1H NMR was not completely pure. The spectrum as obtained showed elements from both starting diene and dienophile as well as a significant number of other peaks. Characterization was further complicated by the fact that partial decomposition of the diene was reportedly common, occurring typically through either the loss of the methoxy or the trimethylsilyl groups. The possibility also existed that the formyl group at C-3 of the dienophile had been ejected through treatment with silica gel. It was believed that the reactivity of Danishefsky's diene may have in fact exceeded that required for dienophile cyclization and further work with it was not pursued. The next several experiments utilized the less activated diene, isoprene (**15**, Figure10).

Despite the lack of reaction observed between **30a** and PPD, isoprene was seen as a potentially valuable diene. It is very inexpensive and also, if it could be made to form a cycloadduct with the dienophiles, would form the desired decahydroquinoline system without a great deal of secondary substituents. A total of eight different experiments were run with isoprene as the diene, three with **30a** and five with **30b**.

Isoprene did not react with either dienophile at room temperature or with simple heating, even up to 195^o C. Any products seen by TLC were generally of higher R_f than would be expected for a nitrogen and oxygen containing cycloadduct. NMR analysis ruled out the possibility of cycloaddition, as the recovered compounds appeared to be simple aromatic systems. The isoprene, used in at least tenfold molar excess with respect

to the dienophile, was most likely polymerizing under the high pressure and heat of the reaction conditions. Boron trifluoride etherate (BF_3 etherate) was employed as a possible catalyst to room temperature reactions with both dienophiles. Addition of 0.5 molar equivalent BF_3 etherate produced no reaction in either case. Tin (IV) chloride and titanium (IV) chloride were also investigated as possible substrate specific catalysts but neither achieved a discernable product. The further use of isoprene, while attractive, was abandoned in favor of a return to experiments employing a more highly activated diene.

1-Dimethylamino-3-*tert*-butyldimethylsiloxy-1,3-butadiene (**DTB**, Figure 27) was believed to be a potentially useful diene as it had been shown to react with a large number of dienophiles to give products in high yield and with near complete regioselectivity.[48] The diene was synthesized in two steps, based on a method reported by Rawal et al.[49] The commercially available acetylacetaldehyde dimethyl acetal (Figure 27) was first treated with dimethylamine in methanol at room temperature. The product oil was vacuum distilled and the purified intermediate was then added dropwise to a solution of sodium bis(trimethylsilyl)amide (NaHMDS) in tetrahydrofuran (THF), which had been cooled in a dry ice-acetone bath. The reaction was allowed to equilibrate to room temperature. Extraction with ether, followed by filtering, concentration, and vacuum distillation gave the desired diene in overall 75% yield.

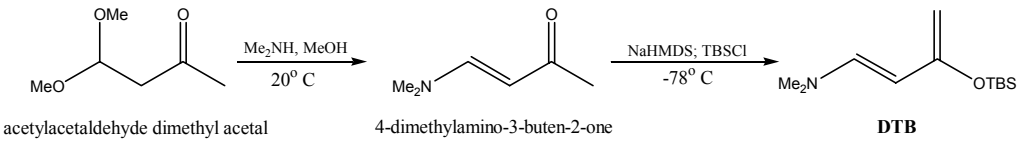


Figure 27: Synthesis of activated diene 1-dimethylamino-3-*tert*-butyldimethylsiloxy-1,3-butadiene (DTB).

[48] Rawal, V. H.; Kozmin, S. A.; Janey, J. M. *J. Org. Chem.* **1999**, *64*, 3039
[49] Rawal, V. H.; Kozmin, S. A.; He, S. *Organic Syntheses.* Vol. 78, p.152.

Reaction products were observed between DTB and both dienophiles **30a** and **30b.** Conditions appeared to be optimized with toluene as the solvent, held at room temperature with stirring for at least 2 h. Both dienophiles formed a yellow product, as observed on the TLC plate. A strongly polar solvent system (1:9 methanol/chloroform) needed to be employed in order to raise the compound of interest above baseline. Starting materials were still present within the reaction mixtures of both dienophiles, albeit in relatively low concentrations in comparison to the product. Perhaps due to the polarity of the product, purification was difficult and required two separate column treatments. The second column was run in 100% ethyl acetate and appeared to provide the desired compounds in high purity.

The tosyl and boc N-substituents appeared undisturbed in the ^{1}H NMR spectra of the products (Figure 29). The spectra for the compounds both showed 15 protons in addition to those present within their respective N-substituent. One of the more revealing features of the DTB adduct spectra was the absence of *t*-butyldimethylsilyl peaks, which indicated that the group had been ejected in the course of the reaction. Alternatively, a singlet peak, integrating for 6H (3.3 ppm), implied that the dimethylamino group of the diene had been maintained in the product. Two protons appeared in the aromatic region (7.8 and 7.9 ppm), two appeared in between 4.0 and 5.0 ppm, and five were between 2.0 and 3.5 ppm.

^{13}C NMR analysis showed 15 peaks present for the recovered product of the reaction between DTB and the boc substituted dienophile **30b** (B, Figure 30). The tosyl substituted dienophile **30a** reacted with DTB to give a product with a nearly identical

^{13}C spectrum (A, Figure 30) to that of the boc product, discounting the peaks associated with the N-substituents (see Table 3).

The data implied that the two dienophiles were forming the same fundamental product. Two carbonyl peaks were seen near 195 ppm. DEPT analysis showed three methylene carbons and indicated 6 quaternary carbons to be present. Both the boc and tosyl substituents contain 2 quaternary carbons, so the remaining 4 were within the rest of the compound. Three possible structures for the DTB adducts were developed and considered based on the data provided by ^{1}H and ^{13}C NMR spectroscopy.

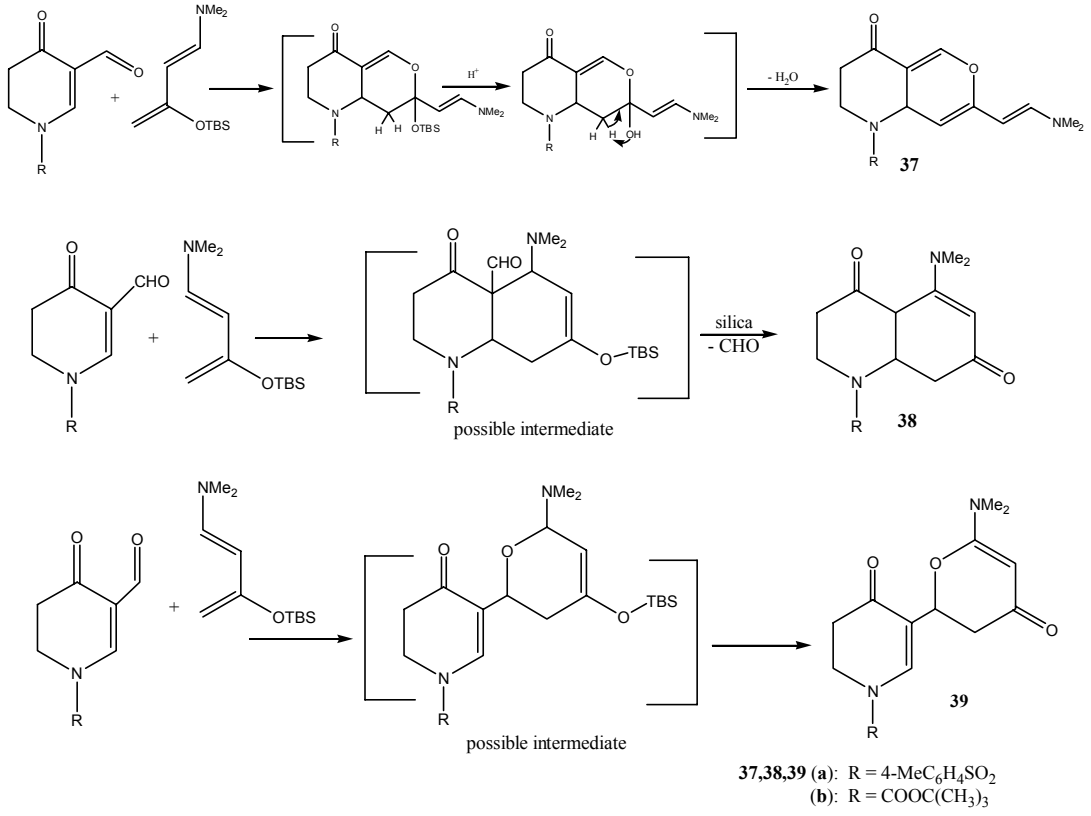


Figure 28: Inverse demand (**37**), normal demand (**38**), and heterodienophile (**39**) proposed structures for the reaction of dienophiles **30a** and **30b** with DTB.

Structure **37** would be the product formed through inverse demand reactivity of the dienophile, as had been seen in reactions with ethyl vinyl ether. The pyran system could be formed through protonation of the deprotected oxygen of the OTBS group, followed

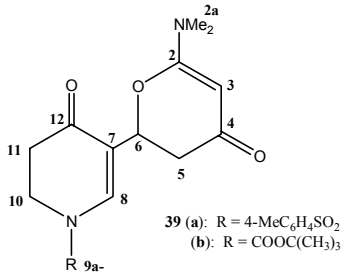
by dehydration. The extensive conjugation through the pyran ring progressing out towards the dimethylamino substituent could serve as some explanation for the observed yellow color of both recovered products. The correct number of carbons, based on spectral data, was maintained in this structure. The number and general multiplicity of the protons as drawn in **37** also correlated with NMR data. The faults of this structure included the lack of a third methylene carbon, as had been seen by DEPT, and the lack of a second carbonyl group. This led to the consideration of a possible normal demand product.

Following the loss of the TBS group, the attached oxygen will assume a ketone functionality when the DTB functions as a normal demand diene. The formyl substituent at C-3 of the dienophile was believed to be lost during treatment with silica gel as no aldehyde proton could be seen in the ^{1}H NMR spectra. The structure **38** (Figure 28) represents the normal demand product with the dimethylamino group oriented in accordance with the *ortho* rule of addition. The major advantages of this structure over **37** were that it incorporated the two observed carbonyls, as well as the third methylene carbon. However, while it contains the correct number of protons, it has one carbon less than the number shown in NMR analysis.

It was believed that the carbon of the formyl group must have been maintained in the product as this was the only way to account for all peaks present in the ^{13}C NMR spectra. The formyl group may be incorporated through inverse demand reaction, as shown within the structure of **37**. An alternative to this would be for the carbonyl of the formyl group to act as a heterodienophile. Reaction with DTB would form a dihydropyranone ring following the loss of the TBS group, which would be bridged to C-3 of the original

dienophile (**30a** or **30b**), as depicted in structure **39** (Figure 28). This structure contained the correct number of protons and carbons, including the three methylene and six quaternary carbons, as well as the two carbonyls. Structure **39** appeared to correlate with the data to a greater extent than either **37** or **38** so proton and carbon assignments were based on the assumption that this was in fact the synthesized compound.

Table 3: ^{1}H and ^{13}C NMR data for DTB adducts **39a** and **39b**.



Proton #	39a ppm	39b ppm		Carbon #	39a ppm	39b ppm
1	-	-		**1**	-	-
2	-	-		**2**	121	122
2a	3.3	3.3		**2a**	41 / 48	41 / 48
3	7.8	7.8		**3**	135	134
4	-	-		**4**	194	195
5	2.6 / 2.8	2.5 / 2.8		**5**	38	38
6	4.9	4.9		**6**	52	50
7	-	-		**7**	104	104
8	7.9	7.9		**8**	153	153
9a	7.7	1.5		**9a**	144	154
9b	7.3	-		**9b**	130	80
9c	2.6	-		**9c**	127	28
10	3.5 / 4.0	3.1 / 4.3		**9d**	138	-
11	2.2 / 2.3	2.5 / 2.5		**9e**	22	-
				10	44	42
				11	40	40
				12	195	196

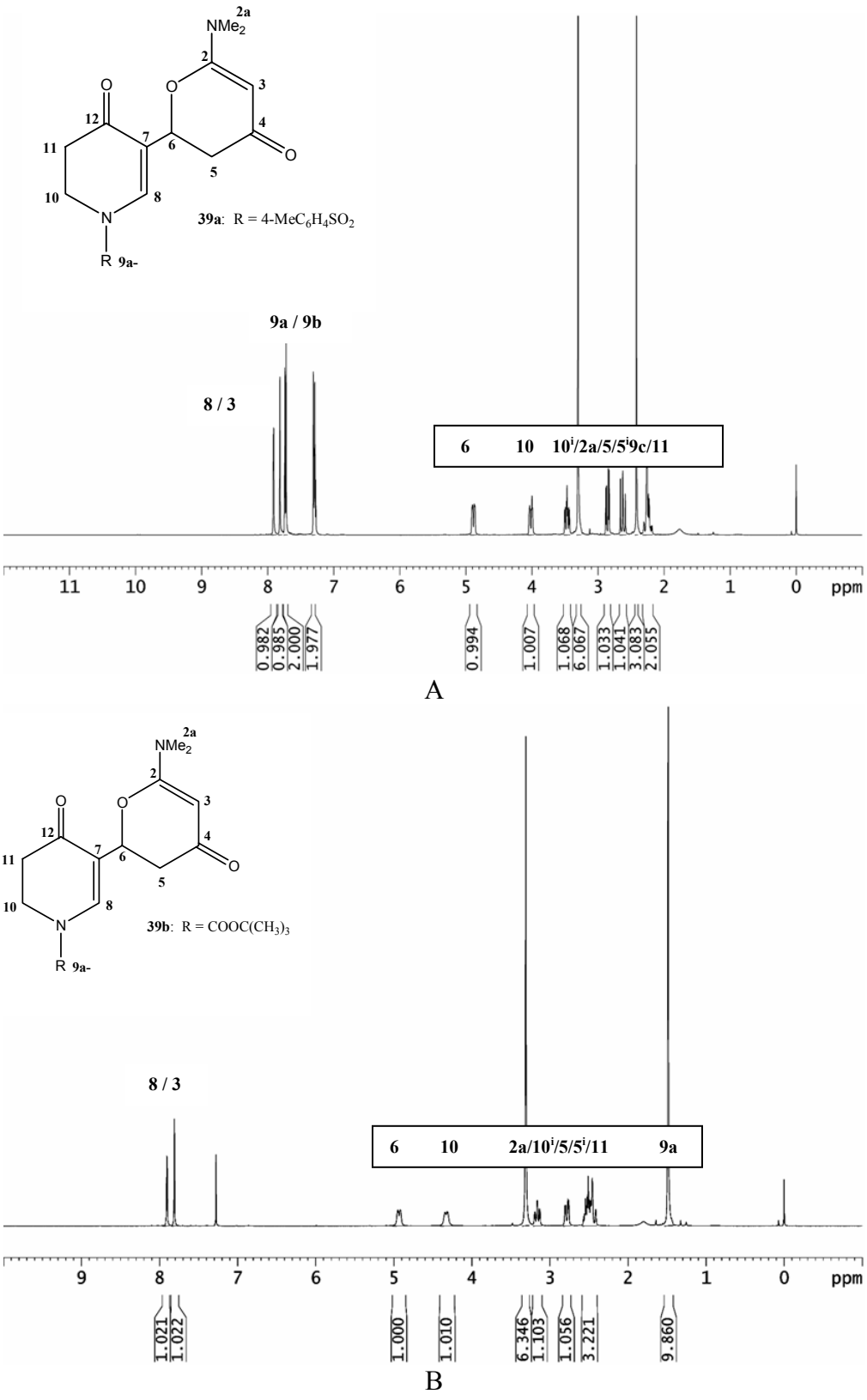
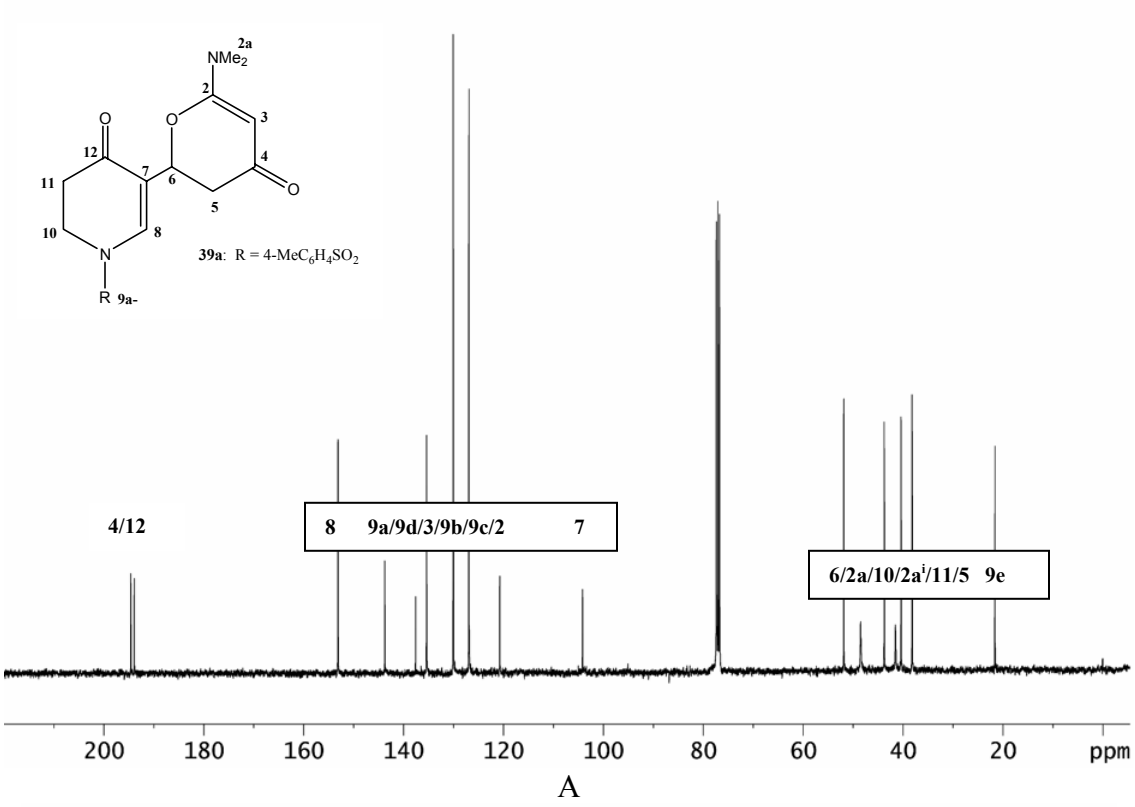
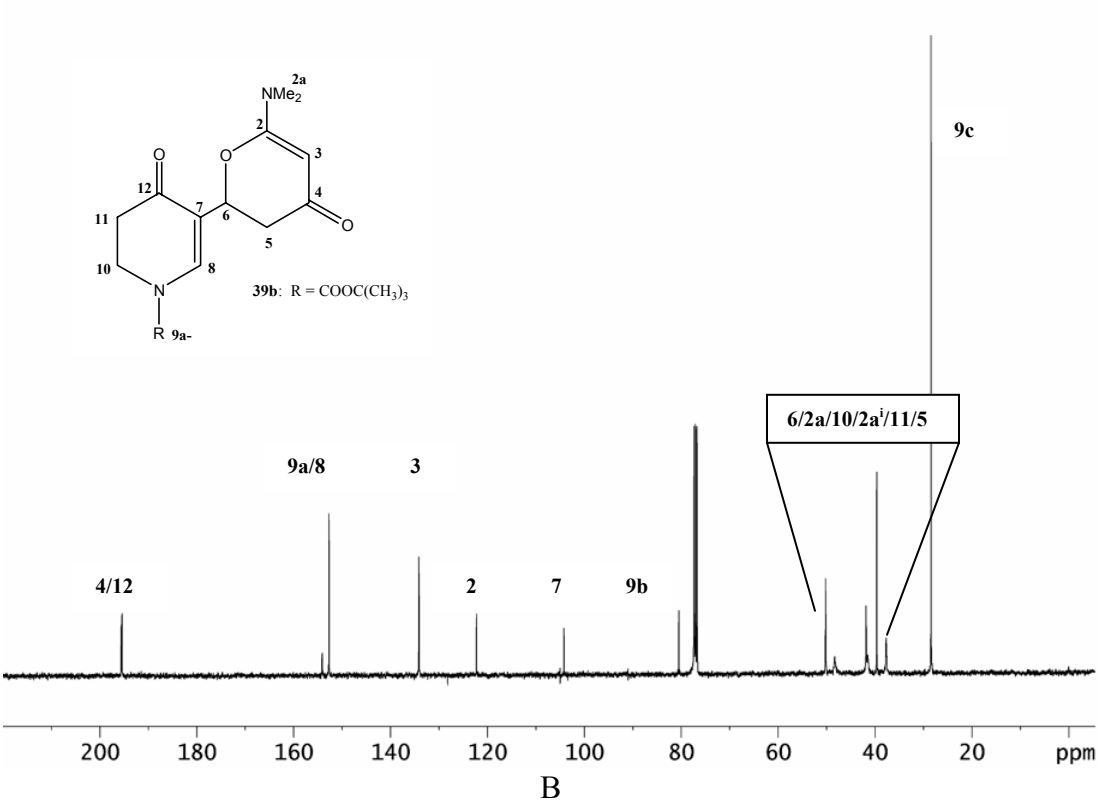


Figure 28: ^{1}H NMR spectra for DTB adducts **39a** (A) and **39b** (B).



A



B

Figure 29: ^{13}C NMR spectra for adducts **39a** (A) and **39b** (B).

CONCLUSIONS

The compounds N-*t*-butoxycarbonyl-3-formyl-5,6-dihydropyridin-4-one (**30b**) and N-tosyl-3-formyl-5,6-dihyropyridin-4-one (**30a**) were synthesized in two and three steps respectively. The developed compounds appeared to be best suited for inverse demand reaction with dienophiles activated with EDG. The formyl group at C-3, in conjugation with the double bound between C-2 and C-3, acted as a diene which, when reacted with ethyl vinyl ether, resulted in the formation of a pyran ring fused to the 4-pyridone derivative. The synthesis of the inverse demand products was highly repeatable with ethyl vinyl ether acting as the dienophile. Very few side products were seen but isomeric ratios were 60:40 with the boc substituted compound and 75:25 with the analogous tosyl substituted compound.

Normal demand Diels-Alder reactions between the synthesized compounds and non-activated dienes were largely unsuccessful. Only when the diene was highly activated did cycloaddition take place. However, the addition appeared to involve the carbonyl of the formyl group acting as a heterodienophile. The compounds as synthesized were not then shown to be particularly useful substrates for the formation of the decahydroquinoline system. The reactions between **30a** and **30b** and 1-dimethylamino-3-*tert*-butyldimethylsiloxy-1,3-butadiene produced the dihydropyridone C-3 bridged to the dihydropyranone with complete regioselectivity. Typical purified yields exceeded 20% and the reactions could be run under mild conditions.

The compounds as synthesized may yet serve as useful substrates towards the creation of the target decahydroquinoline system but additional investigation into a more

appropriate selection of diene would need to be done. This research has further emphasized the high degree of substrate specificity inherent in Diels-Alder [4 + 2] cycloaddition chemistry that can, in many cases, contribute unexpected complexity to what might appear to be an otherwise straightforward reaction.

EXPERIMENTAL

General. All reagents were obtained from Aldrich Chemical, except for ethyl formate and 4-piperidone hydrochloride monohydrate, which were both from Avocado (Alfa Aeser), and *o*-iodoxybenzoic acid, which was from Quality Chemical Laboratories. All standard solvents used were Burdick and Jackson. The dry solvents pyridine, toluene, and THF were from Drisolve. All silica used in column chromatography was Whitman brand, 250A, 230-400 mesh. All organic filtrates were dried with sodium sulfate. Rotary evaporations were carried out on Buchi and Labconco rotary evaporators. HPLC analyses were performed on a Hewlett Packard Series 1100 HPLC equipped with an Agilent 1100 autosampler, a Waters Nova-Pak C-18 60A, 4μm, 3.9mm x 150mm column, and Agilent Chemstation software. TLC analyses were carried out with aluminum backed Silicycle brand plates, 250μm SiO_2 coated. Infrared spectroscopic data was obtained via a Mattson Polaris Spectrophotometer 299B. All IR experiments were performed as a film on NaCl plates and units were processed in cm^{-1}. All NMR data was obtained via a Bruker 400MHz Avance DRX spectrometer. ^{1}H NMR experiments utilized the Bruker "zg30" pulse program, ^{13}C NMR experiments used the "zgdc" program, H-H COSY experiments used pulse program "cosy45", and HMQC data were

obtained through "invbtp". Chemical shifts were processed and subsequently reported in parts per million (ppm), referenced to trimethylsilane (0.00 ppm). All samples were submitted in $CDCl_3$ solvent. Melting points were determined using a 120 volt Mel-Temp apparatus and are reported in degrees Celsius.

N-tosyl-4-piperidone (25). To a 2L RBF, 20g (130 mmol) 4-piperidone hydrochloride monohydrate, 600mL THF, 40mL (286 mmol, 2.2 eq), and 27.3g (143 mmol, 1.1 eq) PTSCl were added and left to stir at room temperature for 24 h. The mixture was then transferred to a 2L separatory funnel with an additional 500mL ethyl acetate (EA), washed twice with 500mL portions of DI, once with saturated brine solution, and dried. The filtrate was rotovaporated to near dryness and transferred to a 500mL RBF. The solution crystallized upon transfer and was redissolved in a minimum amount of EA with stirring in a hot water bath at 60^{o} C. Recrystallization with hexane yielded 26g (78%) white crystals recovered by filtration and dried under high vacuum: ^{1}H NMR 7.68 (d, 2H, J = 8.0), 7.35 (d, 2H, J = 8.0), 3.38 (t, 4H, J = 6.1, 12.3), 2.53 (t, 4H, J = 6.1,12.3), 2.44 (s, 3H); mp. 131-132.

N-tosyl-5,6-dihydropyridin-4-one (26). In a 2L RBF, 20g (79 mmol) of **25**, 600mL 2:1 toluene/dimethyl sulfoxide, 44.2g (158 mmol, 2 eq) *o*-iodoxybenzoic acid (IBX), and 4.5g (24 mmol, 0.3 eq) PTSA were added, in that order and left to stir at 75^{o} C for 6h. The mixture was removed from the oil bath and allowed to cool to room temperature. Ethyl acetate (500mL) was added. Solid remaining in the mixture was filtered and the filtrate was washed with 50% sodium bicarbonate ($NaHCO_3$) solution. Residual white solid in the filtrate was removed by Celite filtration. The filtrate was washed again with 50% $NaHCO_3$, once with saturated brine solution, and dried. The crude recovered

product was column purified (15:85 EA/toluene) and fractions containing the pure product were combined and dried under high vacuum to give 8.7g (44%) tan solid: ^{1}H NMR 7.71 (dd, 3H, *J* = 2.6, 5.6, 8.3), 7.38 (d, 2H, *J* = 8.0), 3.72 (t, 2H, *J* = 7.2, 14.5), 2.53 (t, 2H, *J* = 7.2, 14.5), 2.46 (s, 3H); mp. 108-110.

N-tosyl-3-bromo-5,6-dihydropyridin-4-one (27). To a 100mL RBF, 2.1g (8.4 mmol) **26** was added, dissolved in 8mL dichloromethane, and cooled to 0-5^o C. A solution of 1.34g molecular bromine (Br_2) in 10mL dichloromethane was made in a 25mL RBF, transferred to a 25mL addition funnel, and added dropwise to the reaction flask over the course of 30 minutes. Reaction color was faint red after complete addition of Br_2 and a total reaction time of 1.5h. A solution of 1.75mL (12.5 mmol, 1.5 eq) triethylamine in 10mL dichloromethane was made and added to the reaction flask over 20 minutes. After an additional 10 minutes, the reaction mixture was removed from the ice bath and left to stir for 1.5h. The solution was washed one time each with 2N HCl, deionized water (DI), $NaHCO_3$, and brine. This removed most of the color. A column was run in 10:90 EA/toluene solution. Recrystallization in EA at 70^o C with added hexane produced white crystals which were isolated in 36% yield: ^{1}H NMR 8.10 (s, 1H), 7.73 (d, 2H, *J* = 6.7), 7.40 (d, 2H, *J* = 7.7), 3.77 (t, 2H, *J* = 7.0, 14.5), 2.68 (t, 2H, *J* = 7.0, 14.5), 2.48 (s, 3H).

Ethylene glycol protection of 27. To a 100mL RBF, 0.5g (1.5 mmol) **27** was dissolved in 65mL toluene and set to stir. A catalytic amount of PTSA was added, followed by 0.5g (7.6 mmol, 5 eq) ethylene glycol. The flask was fitted with a Dean Stark trap and condenser and heated to 165^o C in an oil bath. The reaction was set to reflux for a total of 6h and then allowed to cool to room temperature. The mixture was

transferred to a 250mL separatory funnel with 50mL EA and washed with 50mL portions of $NaHCO_3$, DI, and brine. The organic layer was recovered, dried, and rotovaporated to give an orange/brown oil. Purification by preparative TLC (100% toluene mobile phase) gave the desired product **28** in 20% yield: ^{1}H NMR 8.1 (s, 1H), 7.65 (d, 2H, J = 8.3), 7.33 (d, 2H, J = 8.0), 4.13 (m, 2H), 3.93 (m, 2H), 3.50 (m, 2H), 2.45 (t, 2H, J = 5.7), 2.47, (s, 3H).

General procedure for the formylation of N-substituted piperidones (31). The substituted (boc or tosyl) 4-piperidone (5.2g, 20.5 mmol) and a stir bar were added to a 250mL Schleink flask and placed under vacuum, then gas flush, and the cycle was repeated. Dry THF was added via cannula to half fill the flask (~125mL). The flask was set in a dry ice/acetone bath to stir and equilibrate to -77^o C. After 15 minutes, 1M (in hexanes) lithium bis(trimethylsilyl)amide (22.6mL, 22.6 mmol, 1.1 eq) was added dropwise via syringe. After 30 minutes, 1.7mL ethyl formate (21.6 mmol, 1.05 eq) was added dropwise via syringe. After 15 minutes, the flask was removed from the ice bath to equilibrate to RT. Solution color was dark yellow. The solution was acidified after 24h using 60mL 1 N HCl. The mixture was transferred to a 1L separatory funnel with 300mL EA and 250mL DI. The EA was washed once more with DI and the washes were combined and extracted with 200mL additional EA. The EA portions were combined, dried, filtered, and rotovaporated to yield a dark yellow oil that after column purification (1:1 EA/dichloromethane) gave 2.9g, or a 50% yield: **31a** (tosyl) ^{1}H NMR 14.05 (s, 0.6H), 8.57 (s, 1H), 7.69 (d, 2H, J = 8.2), 7.35 (d, 2H, J = 8.1), 3.88 (s, 2H), 3.28 (t, 2H, J = 6.1), 2.56 (t, 2H, J = 6.0), 2.44 (s, 3.4H). **31b** (boc) ^{1}H NMR 8.52 (s, 1H), 4.20 (s, 2H), 3.60 (t, 2H, J = 7.6, 7.2), 2.48 (t, 2H, J = 7.6, 7.2), 1.48 (s, 10H).

General procedure for the oxidation of 31 to compounds 30a and 30b. To a 500mL RBF, 2.1g (10.8 mmol, 1.05 eq) phenylselenenyl chloride (PhSeCl) was added with a stir bar and dissolved at RT in 150mL dichloromethane. This was set in an ice bath and after 15 minutes, 0.9mL (11.3 mmol, 1.1 eq) dry pyridine was added via syringe. The formylated compound **31** (2.9g, 10.3 mmol) was dissolved in dichloromethane and transferred via pipette to the PhSeCl mixture 15 minutes following pyridine addition. The flask was removed from the ice bath after 15 minutes, transferred to a separatory funnel, and washed twice with 80mL portions of 10% HCl. The dichloromethane layer was recovered, dried, and filtered back into the cleaned reaction flask. This was returned to the ice bath and after 10 minutes, 0.8mL (0.1mL per 1.3 mmol 31) 30% H_2O_2 was added dropwise via syringe. Two additional 0.8mL portions of 30% H_2O_2 were added in 10 minute intervals. Each addition lightened solution color somewhat. The reaction mixture was transferred to a 500mL separatory funnel and washed twice each with DI and brine. The dichloromethane was recovered, dried, filtered, and rotovaporated. TLC (2:8 EA/toluene) showed the major product to have an R_f of 0.2. Column purification (2:8 EA/toluene) gave 1.6g product, a yield of 55%, and an overall yield of 28% based on the starting piperidones: **30a** ^{1}H NMR 9.93 (s, 1H), 8.60 (s, 1H), 7.77 (d, 2H, J = 8.3), 7.42 (d, 2H, J = 8.2), 3.84 (t, 2H, J = 7.2, 7.3), 2.62 (t, 2H, J = 7.4, 7.6), 2.48 (s, 3H); ^{13}C NMR 189.4, 186.9, 149.6, 146.6, 132.7, 130.8, 127.7, 114.9, 43.7, 34.9, 21.8; IR 2856.67, 1700.16, 1565.37. 1374.09, 1174.06; mp. 96-102. **30b** ^{1}H NMR 9.96 (s, 1H), 8.65 (s, 1H), 4.05 (t, 2H, J = 7.3, 7.4), 2.65 (t, 2H, J = 7.4, 7.3), 1.59 (s, 9H); ^{13}C NMR 191.2, 187.5, 150.3, 150.0, 114.1, 86.0, 42.4, 35.0, 28.4, 28.0, 27.9; IR 2981.17, 1743.69, 1675.37, 1570.04, 1248.45; mp. 90-94.

Alkylation of 3-sulfolene (35). A 250mL Schleink flask containing a stir bar and 3-sulfolene (2.4g, 20 mmol) was evacuated and flushed with gas twice in succession. Dry THF was added to approximate half volume. Benzyl bromide (4.8mL, 40 mmol, 2 eq) was added via syringe. The flask was then set in a dry ice/acetone bath to chill to -78^{o} C. After 15 minutes, 20mL (20mmol, 1 eq) 1M lithium bis(trimethylsilyl)amide was added to the flask dropwise via syringe. The flask was then removed from the dry ice bath and allowed to equilibrate to RT over the course of 1.5h. The reaction was then quenched with 50mL ammonium chloride and transferred to a separatory funnel. The solution was diluted in EA, washed with DI and brine, dried, filtered, and rotovaporated to yield a dark oil. Two sets of two spots were seen by TLC. Column purification (2:8 EA/hexane) gave 1.1g of the product (spot of lowest R_f by TLC) for a 26% yield: ^{1}H NMR 7.34 (t, 2H, J = 6.9, 7.5), 7.26 (m, 3H), 6.03 (m, 1H), 5.93 (m, 1H), 3.94 (m, 1H), 3.77 (m, 2H), 3.38 (dd, 1H, J = 5.7, 14.0), 2.81 (dd, 1H, J = 9.9, 14.0).

Thermolysis of alkylated sulfolene to 1-phenyl-2,4,-pentadiene (36). To a 100mL RBF, 0.3g (1.4 mmol) **35** was added with a stir bar, 30mL toluene, and a catalytic amount of hydroquinone. This was set in an oil bath for reflux (125^{o} C) under nitrogen gas. TLC after 45 minutes showed no remaining starting material: ^{1}H NMR 7.30 (d, 2H, J = 7.3), 7.20 (t, 3H, J = 9.6, 7.6), 6.33 (m, 1H), 6.11 (m, 1H), 5.85 (m, 1H), 5.13 (d, 1H, J = 17.0), 5.00 (d, 1H, J = 10.1), 3.42 (d, 2H, J = 7.0).

Inverse Demand Diels-Alder reaction of ethyl vinyl ether with 30b (34b). To a small vial, 0.2g (1 mmol) **30b** and 1mL (10 mmol, 10 eq) ethyl vinyl ether were added. Mild heat was applied to completely dissolve **30b**. TLC after 24h (5:95 methanol/chloroform) showed a single product spot as well as remaining starting

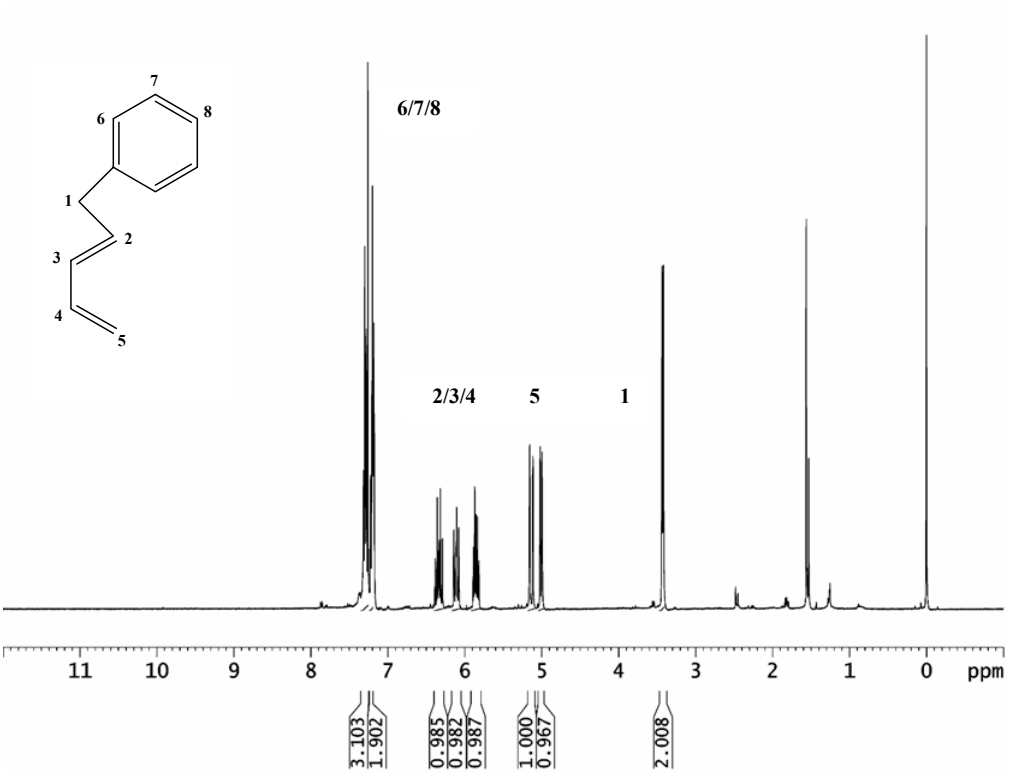
material. Heating at 80° C in a sealed pressure tube did not show change in the product mixture after 4h. Column purification (20:80 EA/hexane – 25:75 – 30:70) gave 0.13g (50%) isolated pure product as a brown oil: ^{1}H NMR (major isomer) 7.38 (d, 1H, *J* = 2.0), 5.26 (d, 1H, *J* = 2.2), 4.81 (dd, 1H, *J* = 2.5, 11.3), 4.26 (t, 1H, *J* = 12.6), 4.00 (m, 1H), 3.63 (m, 1H), 3.04 (m, 1H), 2.47 (m, 3H), 1.72 (m, 1H), 1.50 (s, 9H), 1.27 (t, 3H, *J* = 7.1); ^{13}C NMR (major isomer) 198.0, 196.4, 153.4, 112.1, 99.0, 80.7, 65.4, 47.0, 40.2, 38.2, 32.2, 28.4, 15.0; IR 2976.95, 1685.58, 1595.58, 1411.11, 1164.71.

Inverse Demand Diels-Alder reaction of ethyl vinyl ether with 30a (34a). To a 100mL 9" pressure tube, 0.56g (2 mmol) **30a** and 2mL (20 mmol, 10 eq) were added. This was sealed and set in a preheated oil bath equilibrated to 75° C. After 30 minutes, the solution became brown/orange. TLC after 18h revealed a major product spot and small amount of remaining starting material. Column purification (3:3.5:3.5 EA/hexane/toluene) resulted in the recovery of 0.4g (57%) 34a as a brown oil: ^{1}H NMR (major isomer) 7.72 (d, 2H, *J* = 8.1), 7.38 (d, 1H, *J* = 2), 7.32 (d, 2H, *J* = 8.0), 5.28 (d, 1H, *J* = 2.3), 4.68 (dd, 1H, *J* = 1.9, 4.9), 3.99 (m, 1H), 3.88 (m, 1H), 3.65 (m, 1H), 3.37 (t, 1H, *J* = 14.7), 2.70 (dd, 1H, *J* = 2.7, 13.0), 2.43 (s, 3H), 2.16 (t, 1H, *J* = 2.5), 2.00 (m, 2H), 1.27 (t, 3H, *J* = 7.1); ^{13}C NMR (major isomer) 195.6, 154.4, 144.2, 136.8, 130.1, 127.1, 110.8, 101.7, 65.6, 48.8, 41.0, 38.3, 34.8, 21.6, 15.0; IR 2977.80, 1687.92, 1591.46, 1343.35, 1162.09.

General procedure for production of dihydropyran bridged pyridones 39a and 39b. A 10mL Schleink flask was equipped with a stir bar and 0.3g (1 mmol) **30a**. This was vacuum/gas flushed and 2mL dry toluene was added. After complete dissolution of solid, 0.4g (1.5 mmol, 1.5 eq) of 1-dimethylamino-3-*tert*-butyldimethylsiloxy-1,3-

butadiene was added. The solution became orange. The flask was left under nitrogen atmosphere to stir at RT for 24h. The concentrated product was subjected to column purification (8:2 EA/hexane – 9:2 – 10:0). The recovered compound was recrystallized in EA and hexane to give 0.1g (20%) yellow crystals: **39a** ^{1}H NMR 7.91 (d, 1H, J = 1.9), 7.82 (s, 1H), 7.73 (d, 2H, J = 8.1), 7.29 (d, 2H, J = 8.1), 4.88 (dd, 1H, J = 2.6, 13.3), 4.01 (dd, 1H, J = 3.5, 10.0), 3.47 (dt, 1H, J = 3.8, 11.4), 3.30 (s, 6H), 2.85 (dd, 1H, J = 5.0, 15.5), 2.63 (t, 1H, J = 13.9), 2.42 (s, 3H), 2.26 (m, 2H); ^{13}C NMR 194.6, 194.0, 153.2, 143.8, 137.6, 135.4, 130.1, 127.0, 120.8, 104.2, 51.8, 48.5, 43.7, 41.5, 40.4, 38.2, 21.6; IR 2930.45, 1652.82, 1558.83, 1159.66, 733.60; mp. 121-125. **39b** ^{1}H NMR 7.90 (d, 1H, J = 2.0), 7.81 (s, 1H), 4.87 (d, 1H, J = 12.0), 4.31 (d, 1H, J = 12.1), 3.31 (s, 6H), 3.16 (dt, 1H, J = 11.0), 2.78 (dd, 1H, J = 5.0, 15.3), 2.51 (m, 3H), 1.49 (s, 9H); ^{13}C NMR 195.6, 195.5, 154.1, 152.7, 134.2, 122.3, 104.2, 80.5, 50.2, 48.3, 41.8, 41.5, 39.6, 37.7, 28.4; IR 2976.14, 1694.91, 1562.32, 1422.13, 1174.67; mp. 154-157.

Appendix A: ^{1}H NMR spectra for sulfolene derived diene 1-phenyl-2,4-pentadiene (**A**) and 1-dimethylamino-3-*tert*-butyldimethylsiloxy-1,3-butadiene (**B**).



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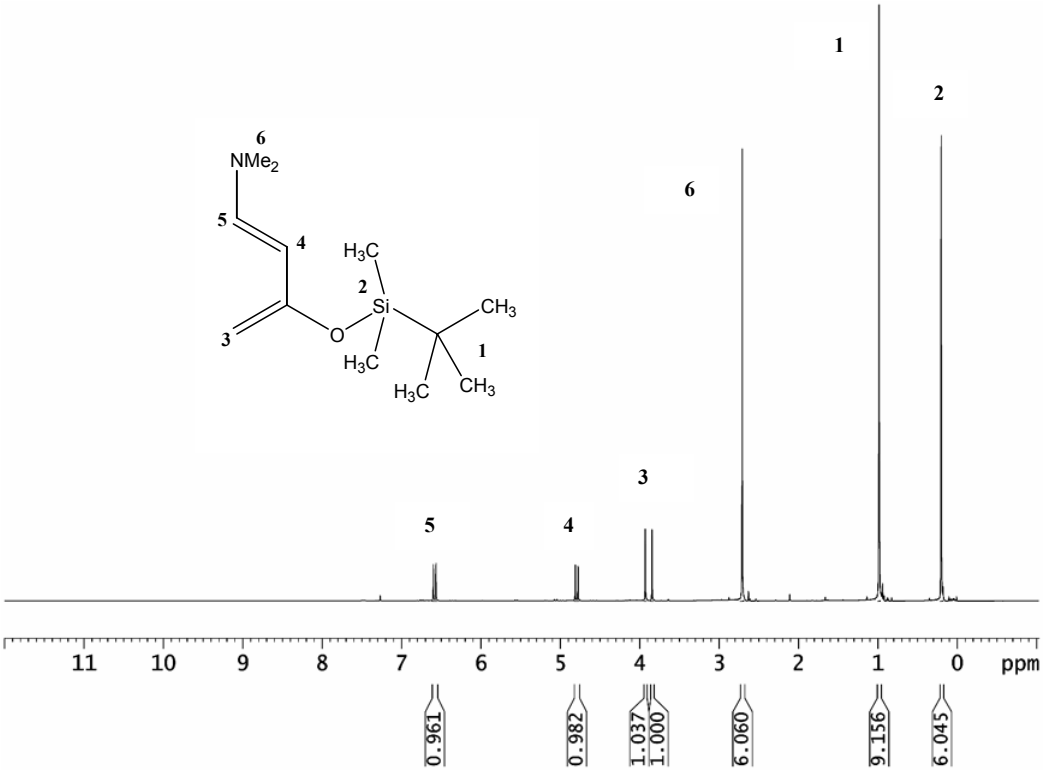
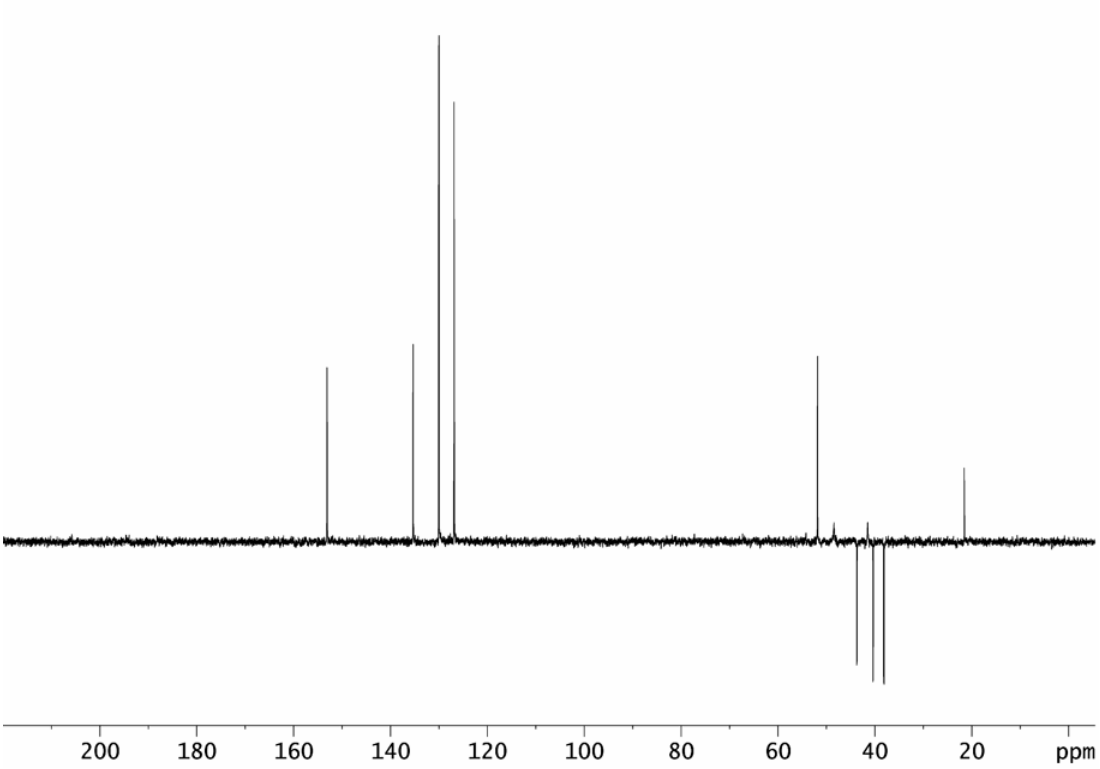
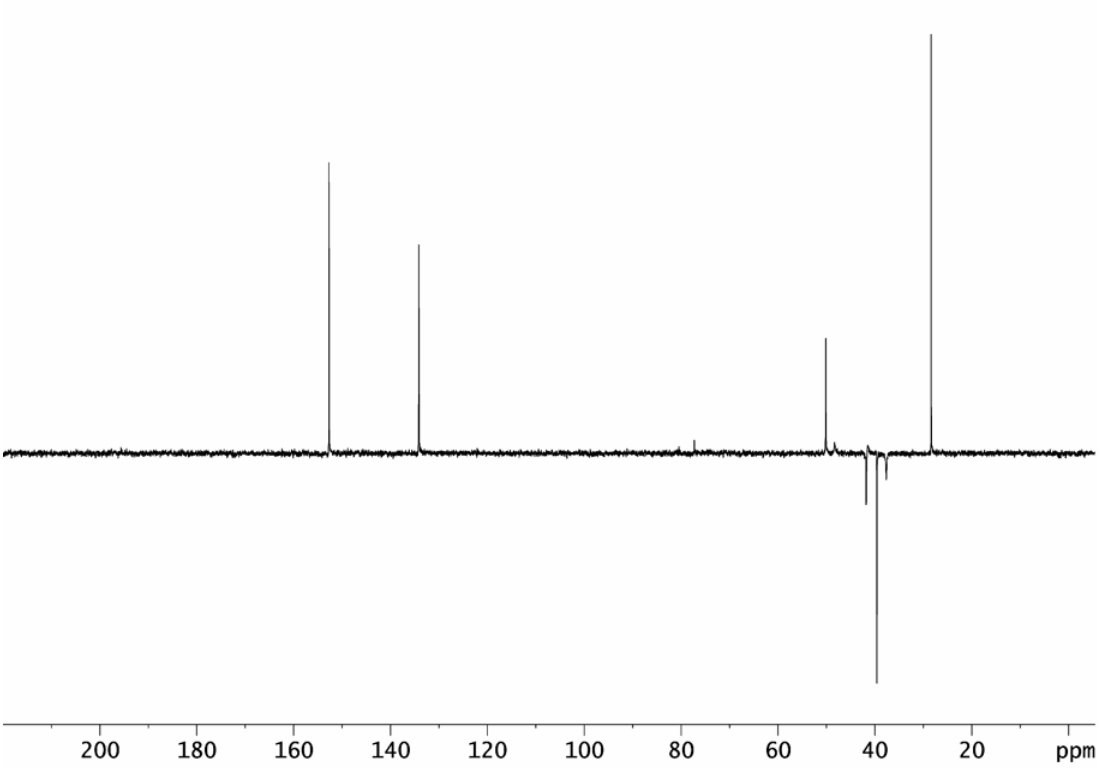


B

Appendix B: ^{13}C DEPT spectra for compounds **39a** (A) and **39b** (B).



A



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