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Tandem Claisen - Diels-Alder reactions in organic synthesis

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Tandem Claisen - Diels-Alder reactions in organic synthesis

by

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DEDICATION

This dissertation is dedicated to Neil Ryan Fulton, who will never be able to fully enjoy the wonder of knowledge.

> The joy of learning is often a nightmare for more than 10 million normal, bright, intelligent children - just because no one has recognized their learning difference. Understand their frustration - and begin to understand the problem.
>
> Let no child be demeaned, nor have his wonder diminished, because of our ignorance or inactivity. Let no child be deprived of discovery, because we lack the resources to discover his problem. Let no child - ever doubt himself or his mind because we are unsure of our commitment.
>
> From the Foundation for Children
> With Learning Disabilities

Also, to Julia Holman (1962-1980), who suffered from leukemia. By her very act of being she was able to make life pleasurable for the short 18 years she was with us.

It is my sincerest hope that the knowledge that I have been privileged to have received may some day be returned in a form that will alleviate the suffering of people like Neil and Julia.

I. INTRODUCTION

The Diels-Alder reaction and the Claisen rearrangement have been widely used by organic chemists for the synthesis of naturally occurring compounds. We have developed a very unusual variant of the Diels-Alder reaction and Claisen rearrangement that is being used towards the synthesis of the anthracycline and tetracycline antibiotics. Heating 2-hydroxy-5-allyloxyacetophenone derivatives results in a regiospecific Claisen rearrangement immediately followed by an intramolecular Diels-Alder cycloaddition producing highly functionalized tri and tetracyclic ring systems.

There have been a few reported examples of Claisen rearrangement products undergoing subsequent Diels-Alder reactions. However, the Diels-Alder reaction has always occurred from the intermediate dienone with the dienone acting as the diene and the newly created double bond of the allyl group acting as the dienophile. To our knowledge, the tandem Claisen - Diels-Alder reaction we have developed is the first reported example of a Claisen rearrangement followed by a Diels-Alder reaction where the diene was not part of the aromatic ring upon which the Claisen rearrangement occurred.

This thesis will deal with the development of the tandem Claisen - Diels-Alder reaction and its use in the synthesis of naturally occurring antibiotics.

II. HISTORICAL

A. Claisen Rearrangement

1. Mechanism

In 1913 Claisen and Eisleb reported that allyl phenyl ethers rearrange upon heating to give o-allyl phenols (1). The rearrangement has hence been known as the Claisen rearrangement.

The mechanism of the Claisen rearrangement has been thoroughly studied and is believed to be an orbital symmetry allowed [3.3] sigmatropic shift (2). This process is illustrated in Figure 1 for the parent compound, allyl phenyl ether.

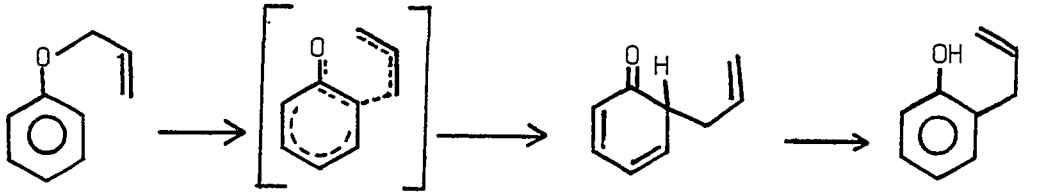
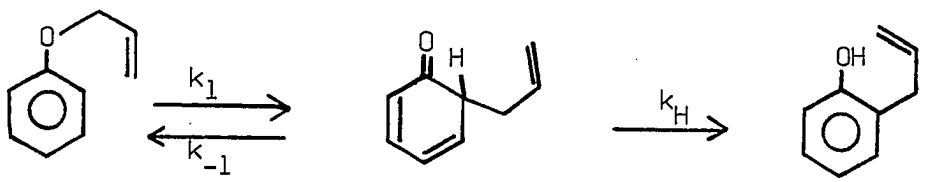


Figure 1. Claisen rearrangement of allyl phenyl ether

The Woodward-Hoffmann rules of orbital symmetry apply to reactions that involve a reorganization of electrons by a concerted pathway. The conservation of orbital symmetry is a powerful concept that organized a very large number of reactions that were originally known as "no mechanism reactions" (3).

The Claisen rearrangement has been shown to proceed in the following manner:



1 2 3

$k_H >> k_{-1}$

The intermediate dienone 2 has not been isolated except for cases where the two ortho positions are substituted. Then, of course, enolization cannot occur. The reaction is first-order with respect to the allyl ether with k_1 being the rate-determining step. One assumes that k_H is much faster than k_1 (3).

The effect of ring substitution on the rate of rearrangement has been studied. Goering and Jacobson determined the relative rates of fifteen m- and p-substituted phenyl allyl ethers by a dilatometric method (4). Overall, substitution had little influence on the rate of rearrangement. Some values for comparison are shown in Table 1.

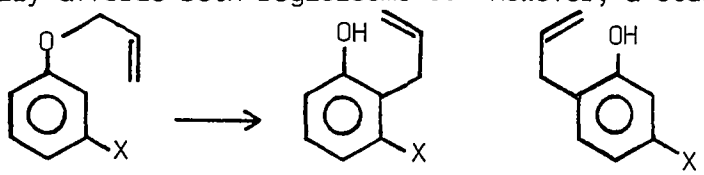
Electron-releasing groups tend to accelerate the rearrangement while electron-withdrawing groups decrease the rate. However, the fastest and slowest rates shown only differ by a factor of 15. Note that all electron-withdrawing groups affect the rate practically the same. The energy of activation, Ea, is affected to a small degree with electron-

Table 1. Rate constants and activation parameters for the rearrangement of substituted allyl phenyl ethers in diphenyl ether (184°)

Substituent	k x 10^5 sec^{-1}	Ea(kcal/mol)	$\Delta S^{\dagger}$(cal/deg.)
p-$N(CH_3)_2$	14.3	34.3	-2
p-OCH_3	4.58	33.6	-6
p-CH_3	2.00	34.8	-5
p-Br	1.58	31.2	-13
NONE	1.52	31.6	-12
p-$COOC_2H_5$	1.115	31.5	-13
p-$COCH_3$	0.994	32	-12
p-NO_2	0.892	31.9	-13
m-$COOC_2H_5$	1.48	29.8	-16

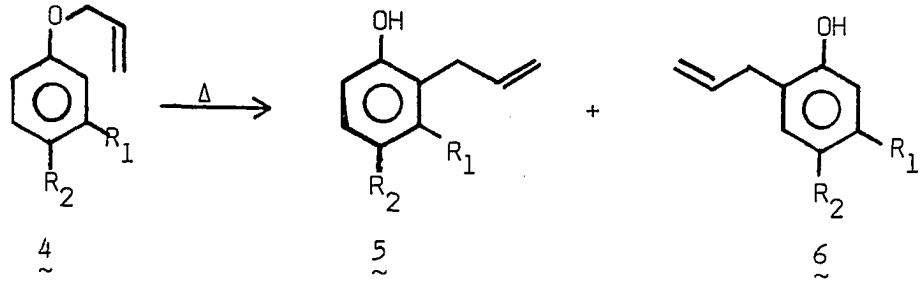
withdrawing groups causing a slight decrease in Ea. The negative values of the entropy of activation, $\Delta S^{\dagger}$, are consistent with a cyclic, highly ordered transition state (5). The negative value of the entropy results from the loss of rotational degrees of freedom in the transition state.

Few studies have been conducted to determine the effect ring substituents have upon the direction of rearrangement of unsymmetrical allyl phenyl ethers. For example, heating of m-substituted allyl phenyl ethers usually affords both regioisomers. However, a study by Bruce and



A B

Roshan-Ali has shown that when X is an electron-withdrawing group by resonance, then A tends to predominate; whereas when X is electron-releasing by resonance, B tends to predominate (6). Bruce and Roshan-Ali examined the Claisen rearrangement of 4, some pertinent results are shown in Table 2.



4 5 6

Table 2. Claisen rearrangement of neat 4 at 220°

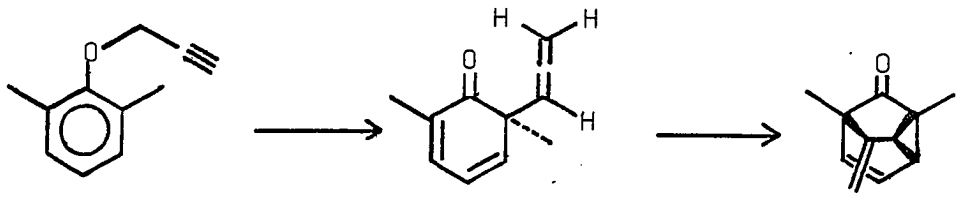
Compound	R_1	R_2	Total Yield	Ratio 5:6
4a	OCH_3	H	86	1:2
b	CH_3	H	85	1:1
c	$COOCH_3$	H	68	6:1
d	$COCH_3$	H	65	2:1
e	$C(CH_3)_3$	OH	61	0:1
f	CH_3	OH	68	11:15
g	$COOCH_3$	OH	83	11:6
h	$COCH_3$	OH	75	1:0

Of special interest are entries 4e and 4h where rearrangement is regiospecific. Heating of 4e results in migration of the allyl group to the less hindered side. Steric hindrance is undoubtedly the controlling factor since 4b and 4f show little or no selectivity. This would be consistent with the much larger A value of a t-butyl group (-4.5 kcal/mol) versus a methyl group (-1.8 kcal/mol) (7). The regiospecificity of 4h is due to intramolecular hydrogen bonding between the phenol hydrogen and the acetyl oxygen atom which results in a six-membered chelated ring. The regiospecific rearrangement had been observed earlier (8).

In the analog of 4h where no hydrogen bonding is present, 4d, a mixture of regioisomers develops. The predominant regioisomer is 5d so the electron-withdrawing acetyl group apparently exerts some controlling influence on the direction of migration. However, the intramolecular hydrogen bonding seems to be the dominant factor in influencing the direction of migration.

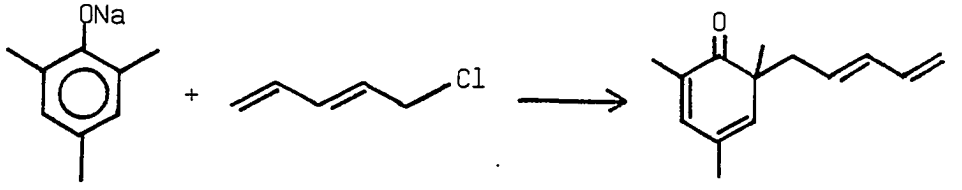
A problem arises though when 4c is compared with 4g. Now it appears that hydrogen bonding actually exerts a negative influence on the regioselectivity of migration. No explanation was suggested for this anomaly.

As mentioned above, there have been a few cases reported where the intermediate dienones have been trapped via an intramolecular Diels-Alder reaction. In these cases, the olefin formed upon rearrangement undergoes cycloaddition with the dienone. The majority of examples reported have been for propargyl ethers such as 7 (9).



7

The dienone 8 has been independently synthesized and found to undergo an intramolecular Diels-Alder reaction producing 9 and 10 in 5% and 35% yield, respectively (10).



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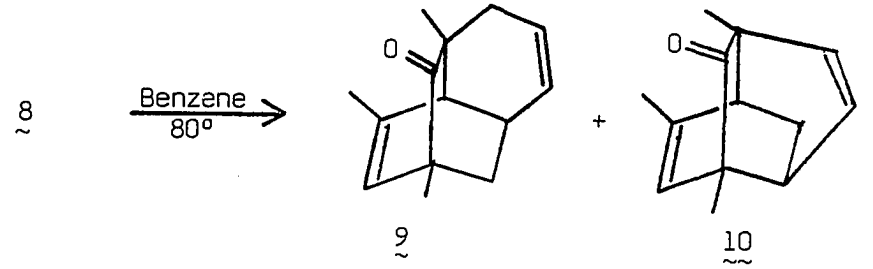


9 10

The dienone 13 (see Figure 2) results from competitive rearrangement of the allyl group in 12 to the para position when the ortho positions contain substituents other than hydrogen or when other factors are involved (e.g. solvent, allyl substituents).

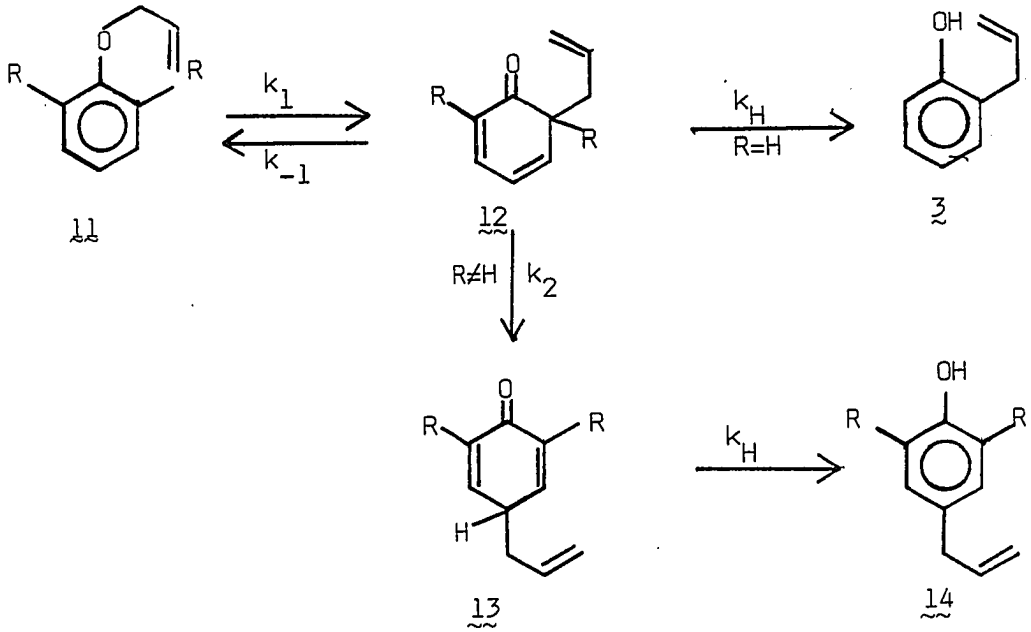


Figure 2. Para Claisen rearrangement

When R = CH_3 in 11 it has been found that $k_2/k\text{-}1$ = 2.7-2.8 (11). Since k_H should be much faster than k_2, the para rearrangement becomes important only when R ≠ H. The para rearrangement product itself results from a [3.3] sigmatropic shift (Cope rearrangement).

The above examples show some of the mechanistic studies done that will be pertinent to this thesis. A review by Rhoads covers mechanistic studies up to 1975 (12).

2. Synthetic applications

One of the guiding principles of synthetic organic chemistry is the development of regio and steroselective reactions and their applications in the synthesis of organic compounds. While the Claisen rearrangement

of aliphatic allyl vinyl ethers has been intensely studied (13), relatively little work has been done with the aromatic Claisen rearrangement.

The most obvious direction one would take is to determine the influence of ring substituents on the regiochemistry of rearrangement. Unfortunately, the few studies done show that ring substituents usually have little directive effect as was illustrated above.

To my knowledge, no attempt has been made recently to review the synthetic uses of the aromatic Claisen rearrangement. Some recent applications of the Claisen rearrangement in organic synthesis are shown in Figure 3.

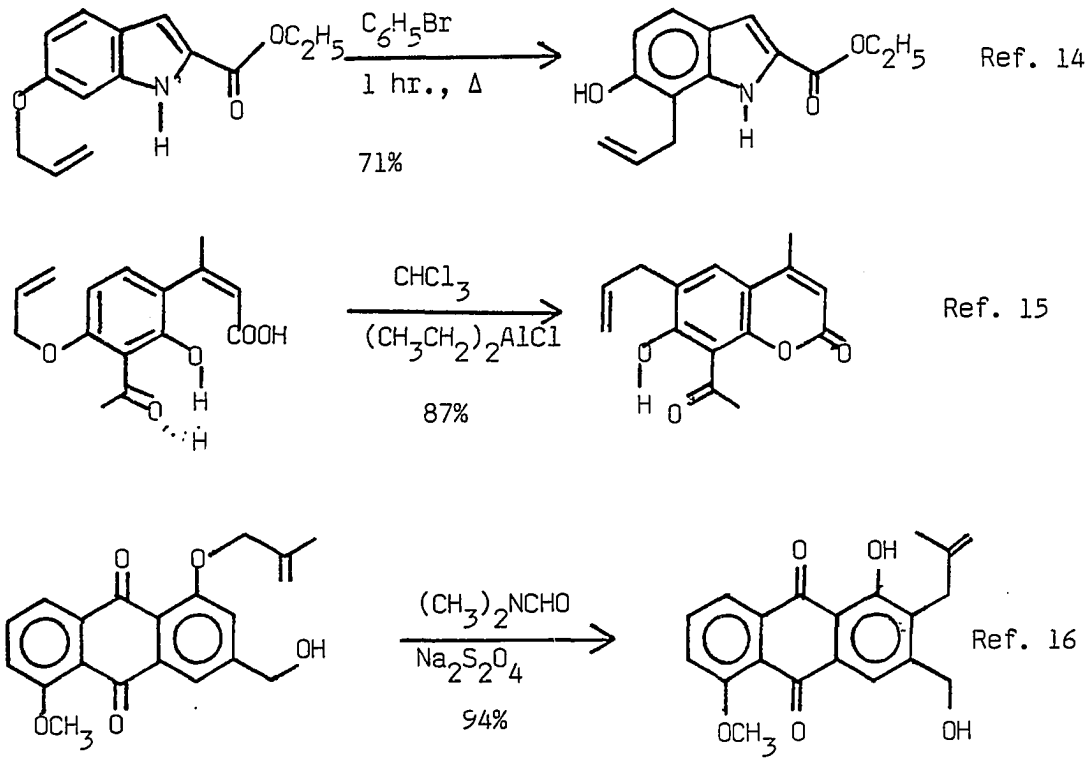
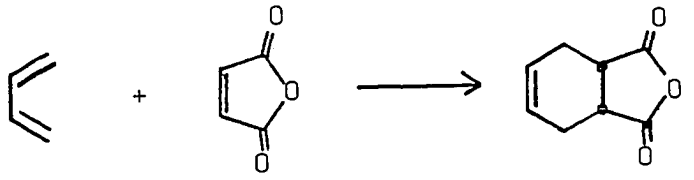


Figure 3. Claisen rearrangement in synthesis

B. Diels-Alder Reaction

1. Mechanism-Theory

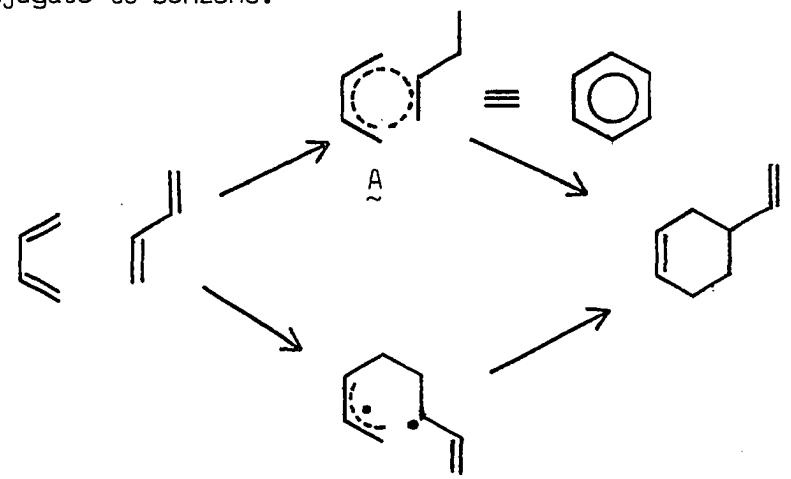
The Diels-Alder reaction was first discovered by Diels and Alder in 1928 when they observed that maleic anhydride added to butadiene (17).



The mechanism of the Diels-Alder reaction has since been intensely studied and is generally accepted as being a concerted, orbital-symmetry allowed [$4\pi + 2\pi$] cycloaddition (2). What this rigorously means, is, that during the course of the reaction "...it is possible to transform continuously the molecular orbitals of reactants (say A + B) into those of the product (C) in such a way as to preserve the bonding character of all occupied molecular orbitals at all stages of the reaction" (18).

There are three general theoretical methods used to describe concerted reactions; aromatic transition states (Dewar (19), Evans (20)), construction of correlation diagrams (Woodward and Hoffmann (2), Longuet-Higgins and Abrahamson (21)), and frontier molecular orbital theory (Fukui (22), Fleming (23a), Houk (23b)). The idea that the Diels-Alder reaction proceeds through an aromatic transition state was suggested by Evans in 1939. He showed that if butadiene dimerized through a six-membered cyclic transition state, A, relative to an acyclic transition state, B, then the energy of activation would be lowered with a resonance

energy of 23.5 Kg. cals. (20). Transition state A is said to be isoconjugate to benzene.



A

B

Dewar described this thought as "...he attributed the facility of the Diels-Alder reaction to the corresponding resonance stabilization of the "aromatic" benzene-like transition state.... He also implies clearly that the Diels-Alder reaction should take place in a single step via such a stabilized cyclic transition state rather than in two steps via a biradical because the linear transition state for the latter would be nonaromatic" (24).

The second analysis of the Diels-Alder reaction involved correlation diagrams. Correlation diagrams require recognition of the molecular orbitals involved in the reaction and classification of the orbitals as symmetric (S) or antisymmetric (A) with respect to the symmetry elements of the transition state (25). One then correlates reactant and prouct molecular orbitals (MOs) of like symmetry. If all the bonding MOs correlate, then the reaction is orbital symmetry allowed. However, if bonding and antibonding MOs correlate, then the reaction is thermally

unfavorable and will not follow the selection rules of orbital symmetry. It is still possible though that a symmetry allowed reaction may proceed by some other multistep mechanism such as a diradical intermediate (25).

The correlation analysis of butadiene reacting with ethylene to form cyclohexene is shown below. In Figure 4 we define the symmetry element of the transition state.

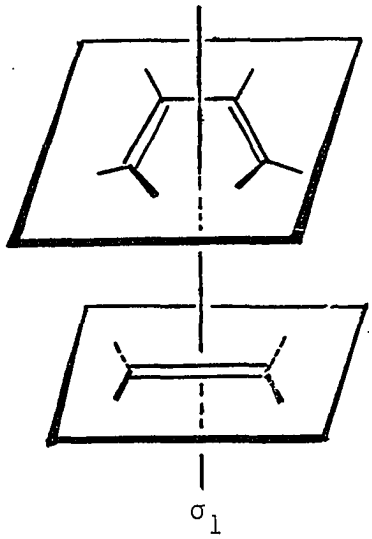


Figure 4. Symmetry element of butadiene and ethylene

The relevant MOs (π and π^*), relative energies, and respective symmetries for butadiene are (26):

$$\psi_4 = 0.37\ (\phi_1 - \phi_4) - 0.60\ (\phi_2 - \phi_3) \qquad E = \alpha - 1.62\beta \qquad A$$

$$\psi_3 = 0.60\ (\phi_1 + \phi_4) - 0.37\ (\phi_2 + \phi_3) \qquad E = \alpha - 0.62\beta \qquad S$$

$$\psi_2 = 0.60\ (\phi_1 - \phi_4) + 0.37\ (\phi_2 - \phi_3) \qquad E = \alpha + 0.62\beta \qquad A$$

$$\psi_1 = 0.37\ (\phi_1 + \phi_4) + 0.60\ (\phi_2 + \phi_3) \qquad E = \alpha + 1.62\beta \qquad S$$

Likewise, for ethylene:

$$\psi_2 = 0.707\ (\phi_1 - \phi_2) \qquad E = \alpha - \beta \qquad A$$

$$\psi_1 = 0.707\ (\phi_1 + \phi_2) \qquad E = \alpha + \beta \qquad S$$

These MOs are then correlated with the two resultant π- and four σ-orbitals of cyclohexene as shown in Figure 5. Note there is no correlation of bonding with antibonding MOs.

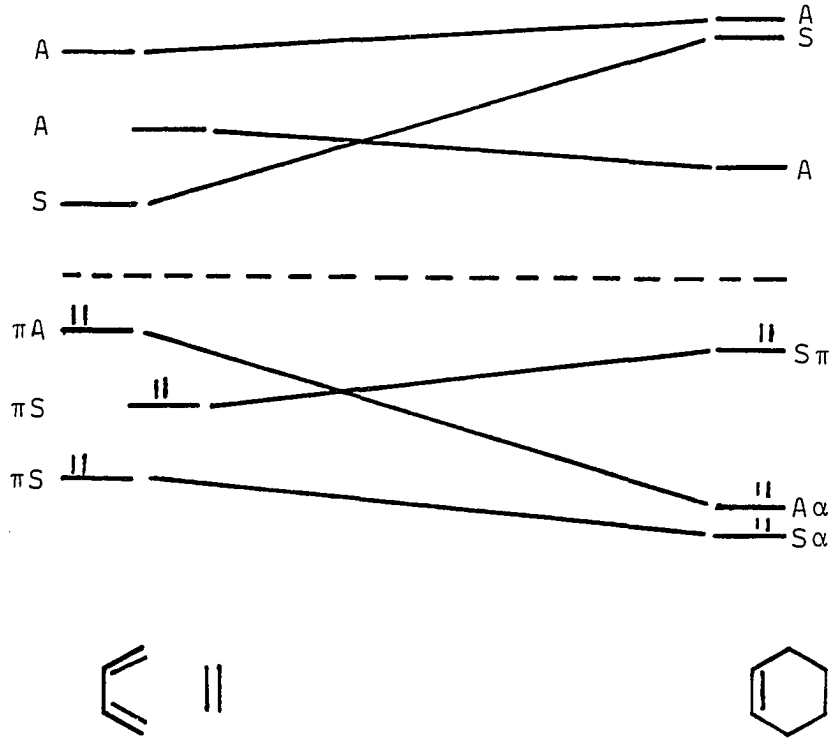
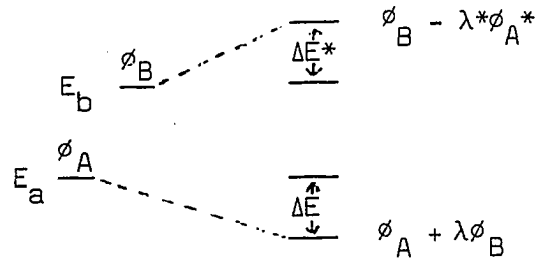


Figure 5. Correlation diagram for butadiene + ethylene

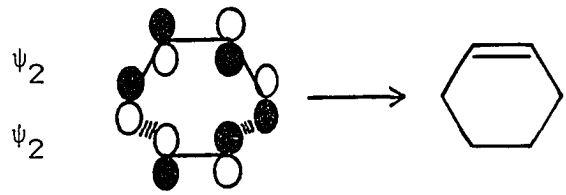
Frontier molecular orbital (FMO) theory is the method most commonly used in practice by synthetic organic chemists. The FMO method uses perturbation theory conclusions that when two MOs interact, a bonding (ϕ_A) with an antibonding (ϕ_B), the change in energy (stabilization) of the resultant MOs is inversely proportional to the difference in energy between ϕ_A and ϕ_B. In other words, the closer ϕ_A and ϕ_B are in energy, the greater the change in energy (ΔE) (23b).



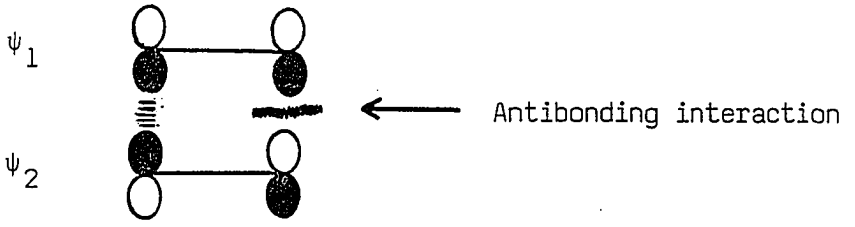
Before interaction After interaction

Since it would be difficult (time-consuming) to consider all the MOs during a reaction, FMO theory approximates perturbation theory by considering only the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of the reactants. These two MOs are of greatest importance since they lie closest in energy, and thus, relative to the lower- and higher-lying MOs, they contribute the most towards stabilization of the resultant MOs. FMO theory is then just a first approximation of perturbation theory.

Thus, for the Diels-Alder reaction of butadiene with ethylene, one examines the HOMO of one component interacting with the LUMO of the other component. As one can see from above, the HOMO of butadiene interacting with the LUMO of ethylene involves the two frontier MOs of lowest energy. The interaction is represented pictorially as:



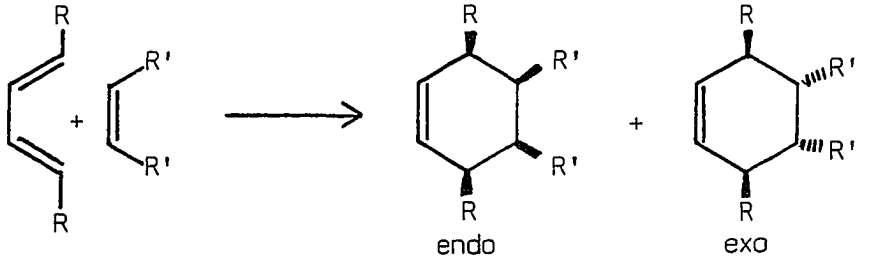
The important point is that when the orbitals interact there are only bonding interactions. This is compared with the [2π + 2π] cycloaddition of two ethylene molecules where an antibonding interaction now occurs.



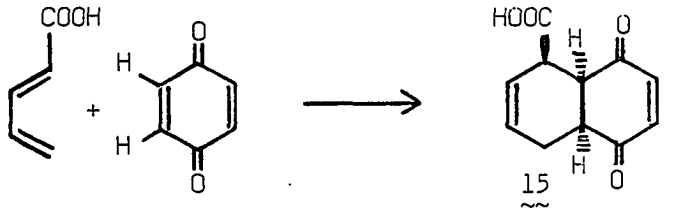
The main benefit of the FMO method is that if the relative coefficients and relative MO energies are known, one can predict the regioselectivity, and sometimes the endo/exo steroselectivity (27), of the Diels-Alder reaction (vide infra). The ability to correctly predict regioselectivity is extremely important for synthesis.

2. Mechanism-Experimental observations

One of the distinguishing characteristics of the Diels-Alder reaction is its sterospecificity. Functional groups that are cis on the dienophile are syn in the product, likewise for the diene.

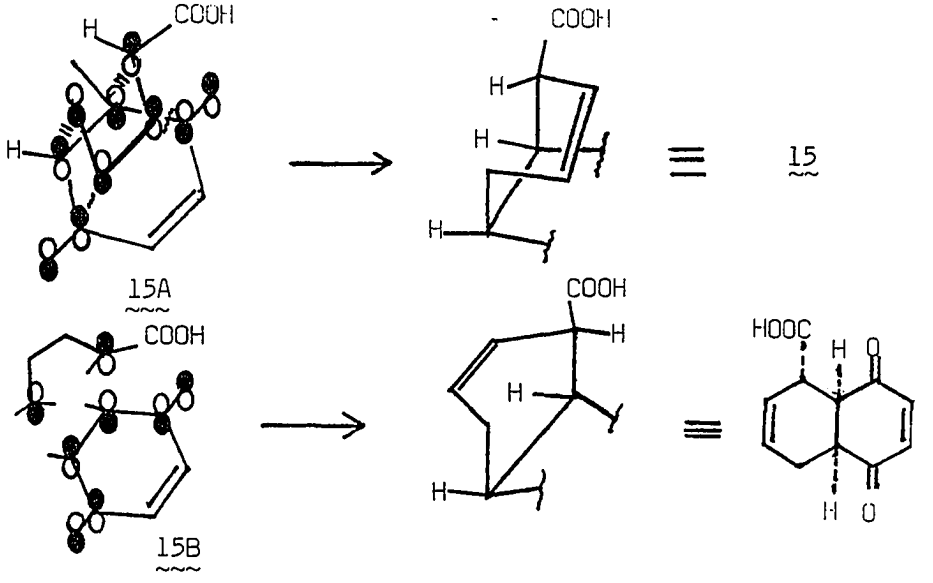


The relative sterochemistry (if R is syn or anti to R') is determined by whether addition occurs to give the kinetically favorable endo adduct or the thermodynamically favorable exo adduct. The endo adduct is said to arise by the "rule of maximum accumulation of unsaturation" (Alder rule) in the transition state (28). The actual physical basis of endo addition is thought to be nonbonding attractive forces (secondary orbital overlap) between the π-systems of the diene and dienophile (29). For example, in Woodward and coworkers synthesis of reserpine, trans-vinylacrylic acid added to benzoquinone to produce the endo adduct 15



15

via transition state 15A. The alternate exo adduct would arise via transition state 15B (30).

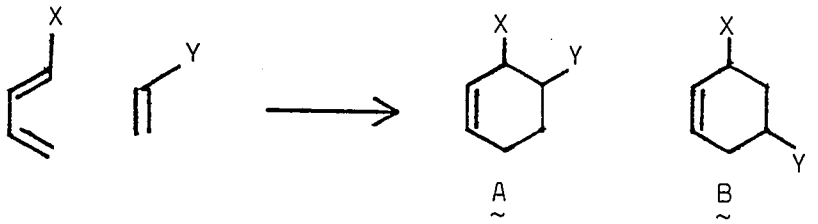


While the Alder rule was originally defined for cyclic dienes, Diels-Alder reactions tend to show a preference for the endo adduct in the absence of overriding steric constraints. Secondary orbital overlap interactions are generally weak interactions so the free energy difference ($\Delta G^{\dagger}$) between the exo and endo transition states is quite small. By the use of equation 1 the free energy difference has

$$\Delta G^{\dagger}_{exo} - \Delta G^{\dagger}_{endo} = 4.575\ T \log (endo/exo) \qquad 1$$

been found to range from 0.5 to 1.7 kcal/mol (31). Non bonding interactions can often exceed this energy range; 1,3-diaxial methyl-methyl interaction has a ΔH^{o} of 3.7 kcal/mol, ΔH^{o} between the s-trans and s-cis forms of butadiene is 2.3 kcal/mol, etc. (32). Thus, there exists a subtle interplay between steric hindrance and secondary orbital overlap in the transition state. This can lead to erroneous prediction of product sterochemistry, especially for acyclic dienes and dienophiles.

The regioselectivity of the Diels-Alder reaction is rationalized



A ~ B ~

by FMO theory. When X is electron-releasing and Y electron-withdrawing, then the "ortho" product A is found to predominate. The formation of A can be predicted using the following generalizations developed by Houk (33):

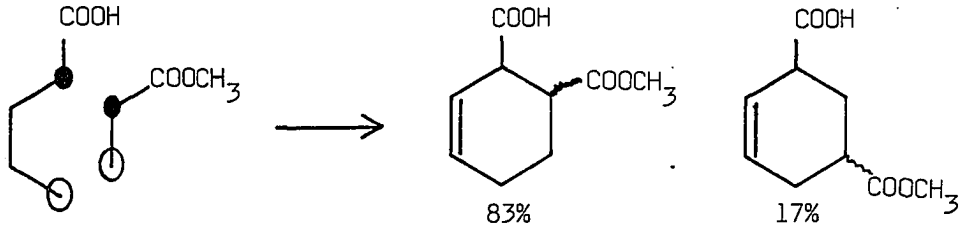
1. The principal stabilization of the transition state will arise from interaction of the HO-LU pair of addend frontier orbitals which are closest in energy.
2. The larger terminal coefficient on each addend will become bonded preferentially in the transition state.

The first generalization was dealt with in section B-1. The second will now be discussed. The coefficients are derived from calculations and have been tabulated by Houk (33). Houk has explained regioselectivity by "...the stabilization energy will be larger when the larger terminal coefficients and the smaller terminal coefficients of the two interacting orbitals overlap, which gives a larger net overlap in the numerator of the second-order perturbation expression, and thus, a

$$\Delta\epsilon = \frac{\beta^2}{\epsilon_a - \epsilon_b} \qquad \beta = \text{resonance integral between orbitals a and b.}$$

larger transition state stabilization, than if a large coefficient on one orbital interacts with a small on the second at both bond-forming centers" (23b). This is pictured in Figure 6.

In the addition of trans-vinylacrylic acid with methyl acrylate



the ortho product predominates as one would predict based on coefficient size (34). Note that orbitals of like symmetry bind. This point is of primary importance and must be obeyed.

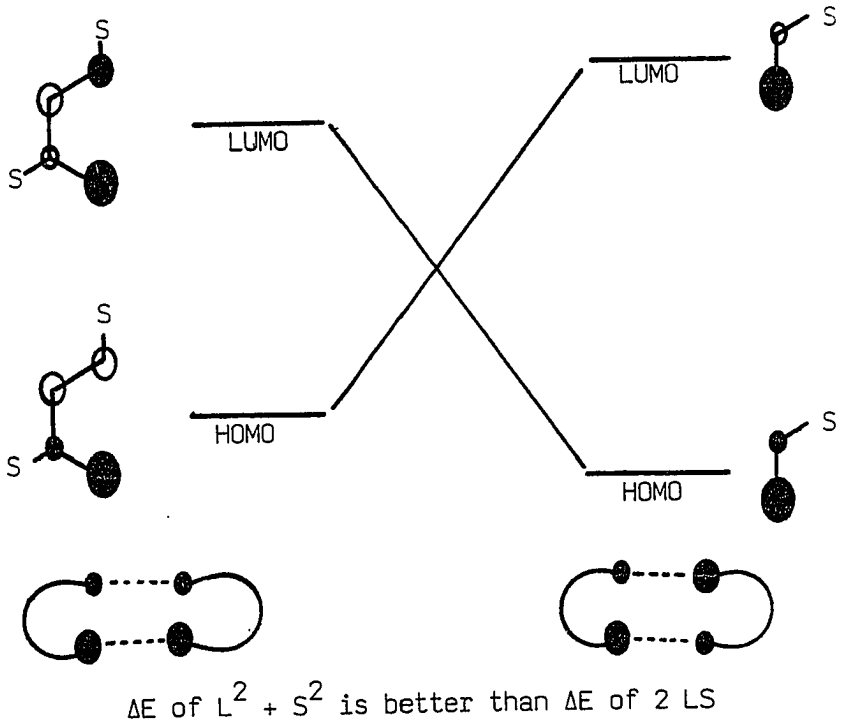
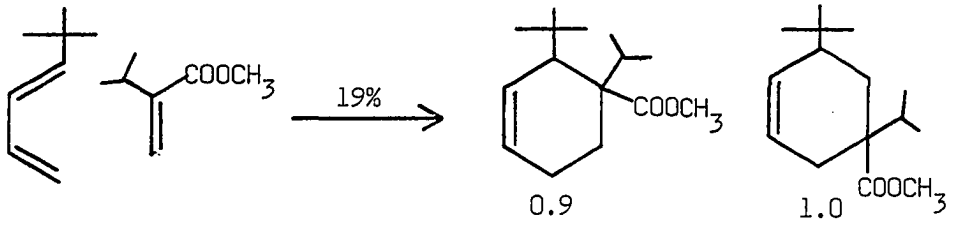


Figure 6. Frontier orbital interactions controlling regioselectivity in Diels-Alder reactions

As with steroselectivity, steric hindrance in the transition state can result in formation of B (above) even though A would be the predicted product based solely on coefficient magnitudes.

The following example was taken from a table in a review by Sauer (35). He states though that the product regiochemistry should be interpreted with care since the yields were low and the products were often determined by degradation.



Clearly, great care is needed for the prediction of steroselectivity and regioselectivity when there exists the possibility of steric hindrance in the transition state.

Kinetically, the rate of the Diels-Alder reaction is greatly dependent on the structure of the components. In general, electron-withdrawing groups on the dienophile and electron-releasing groups on the diene enhance the rate of reaction. The rate increase results from the decrease in the energy gap between the HOMO and the LUMO of the components. The reaction is second-order overall and first-order with respect to both components.

Thermodynamically, the Diels-Alder reaction possesses activation entropies of -40 to -30 cal/K mol (36). This low negative value is ascribed to a considerable loss of translational and rotational degrees of freedom in the transition state and is said to be consistent with the cyclic, highly ordered transition state required for a concerted reaction. The energy of activation in the gas phase ranges from 15-30 kcal/mol (36).

Mechanistic studies of the Diels-Alder reaction have been the subject of several excellent reviews (31,36). The concepts and values shown above for the intermolecular Diels-Alder reaction will be of importance in later discussion of the intramolecular Diels-Alder reaction.

3. Synthetic applications

The intermolecular Diels-Alder reaction has developed into perhaps the most important method of ring construction. Its ability to construct ring systems with fixed, relative sterochemistry is unparalleled by normal annulation methodology. The intramolecular version, where the diene and dienophile are connected by a bridge (see Figure 7) has only recently come into its own and has been the subject of several recent reviews (37-39).

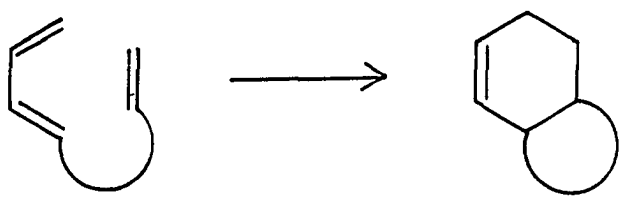
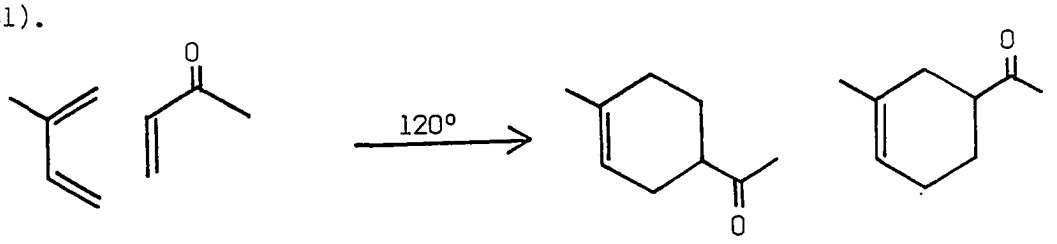


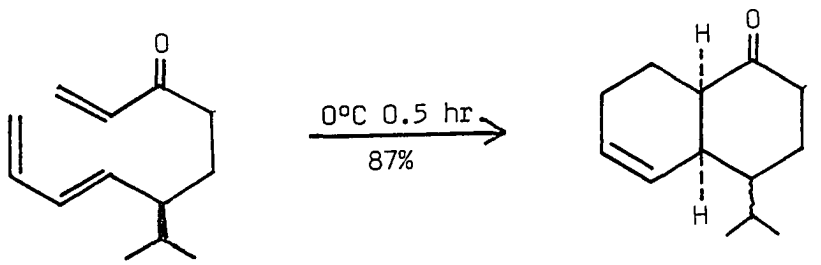
Figure 7. The intramolecular Diels-Alder (IMDA)

The IMDA reaction is unimolecular (first-order) with a much more positive $\Delta S^{\dagger}$ value than the intermolecular Diels-Alder reaction. The positive increase in $\Delta S^{\dagger}$ is due to the spatial proximity of reaction

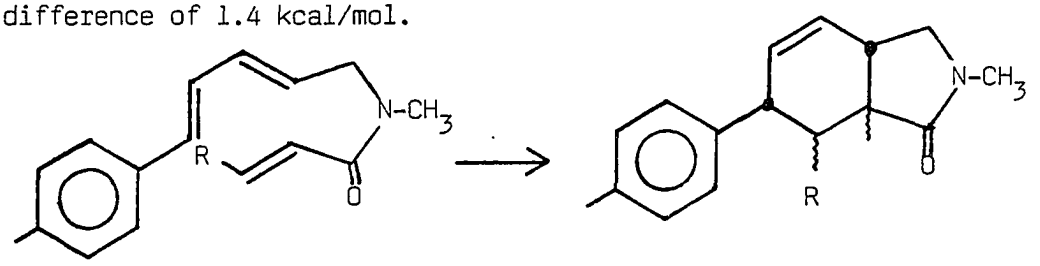
partners (37). This often allows the use of components that would react poorly, if at all, intermolecularly. Also, components that do add intermolecularly often add in the IMDA reaction under much less severe conditions. For example, isoprene adds to methyl vinyl ketone at 120°C (40), whereas the intramolecular counterpart occurs at 0°C (41).



71 = 29



The entropic factor has been experimentally verified by Gschwend and Meier (42). They found that 16 cyclized to 17 with an $\Delta S^{\dagger}$ of -16 e.u. whereas, as mentioned above, bimolecular Diels-Alder reactions have an $\Delta S^{\dagger}$ from -30 to -40 e.u. Compound 17 was obtained in an endo to exo ratio of 15:2, which corresponds to an activation energy difference of 1.4 kcal/mol.



16 R = C_6H_5 17 R = C_6H_5

Some examples of the IMDA reaction are illustrated in Figure 8.

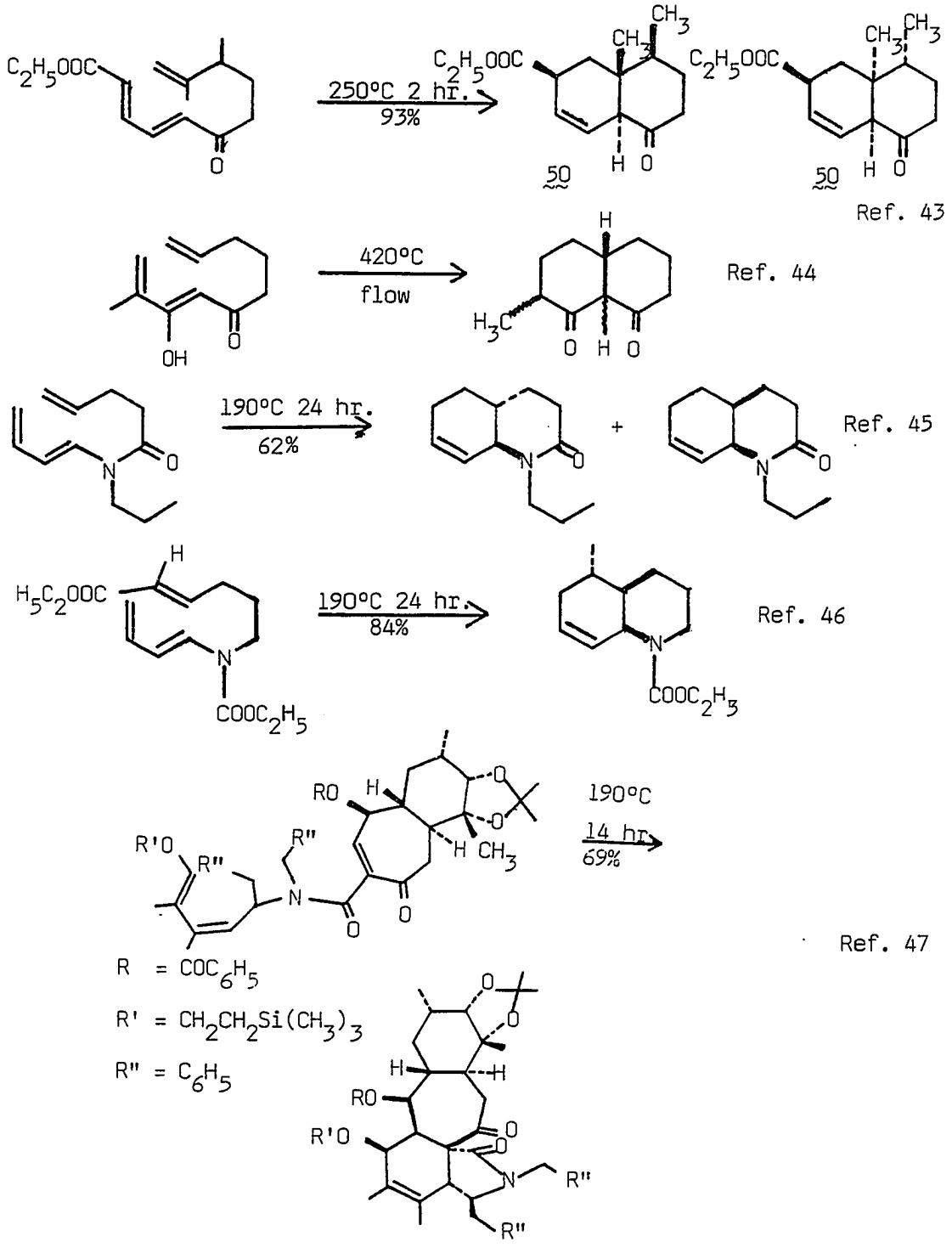
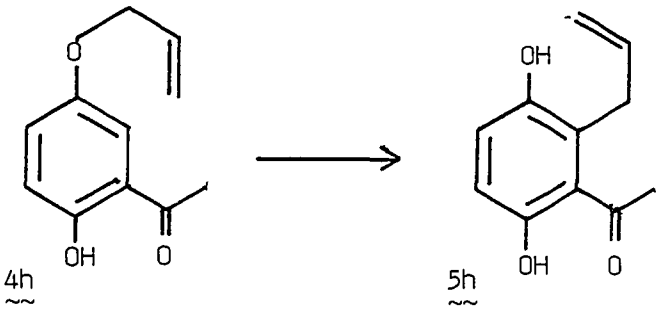


Figure 8. IMDA in organic synthesis

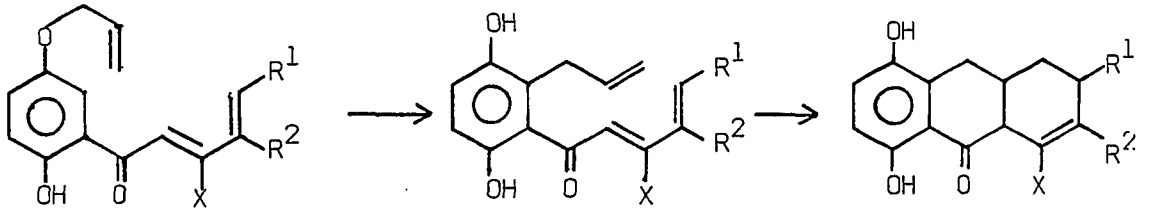
III. RESULTS AND DISCUSSION

In 1936 Baker and Lothian discovered that 2-hydroxy-5-allyloxy-acetophenone, 4h, underwent a regiospecific Claisen rearrangement to produce 2,5-dihydroxy-6-allylacetophenone (8).



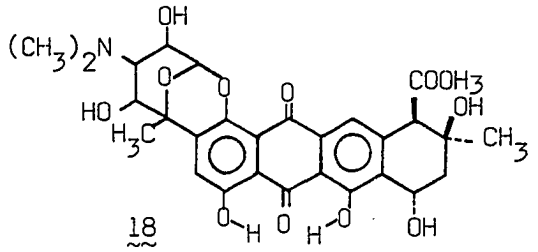
4h 5h

This rearrangement was recently rediscovered in our laboratories at which time the idea arose of utilizing this Claisen rearrangement towards the synthesis of the anthracycline and tetracycline antibiotics. We envisioned a horizontal dissection of the tetracyclic ring systems leading to an intramolecular Diels-Alder reaction. The dienophile component of the Diels-Alder reaction would arise from the Claisen rearrangement. The investigation of the following transformation was then initiated.



X = H, OH

I will first discuss our studies towards the anthracyclines (e.g. Nogalamycin, 18, (48)) followed by a discussion on the tetracyclines (e.g. 6-demethyl-6-deoxytetracycline, 19, (49)). This will be followed by a discussion in Part IV of proposed factors responsible for the unusual Claisen rearrangement specificity of 4h.



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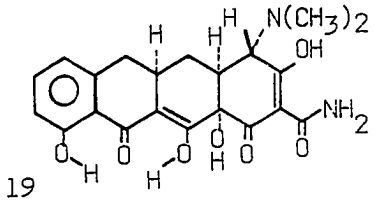
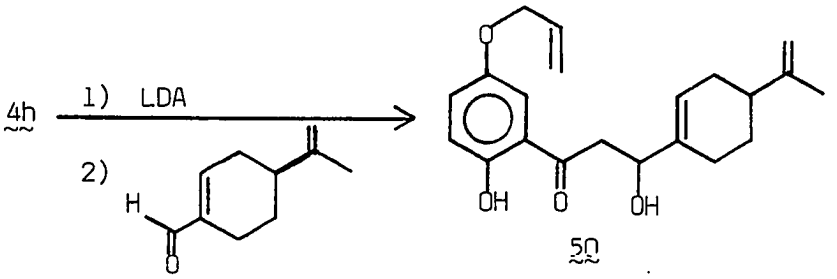


19

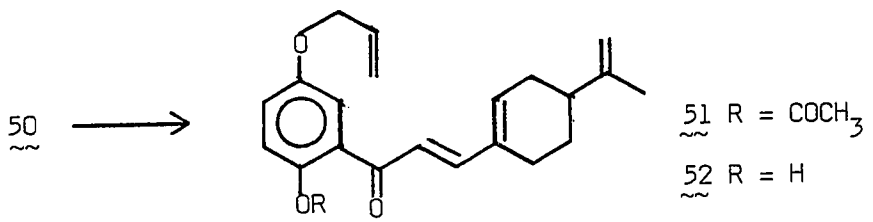
A. Anthracycline Study

Compound 52 was chosen as the initial system to test the viability of the tandem Claisen - Diels-Alder reaction (TCDA). Dianion formation of 4h (8) with lithium diisopropylamide (LDA) followed by addition of commercially available (s)-(-)-perillaldehyde gave the sensitive aldol product 50 in 68% yield.



50

Attempted dehydration of 50 with a catalytic amount of p-toluenesulfonic acid (pTSA) resulted mainly in a retro-aldol reaction. We then decided to acylate 50 and eliminate the resultant acetate. Upon acylation (50) we were surprised to discover that in situ elimination had occurred to produce 51 directly from 50 in 82% yield. The presence of triethylamine (Et_3N) and 4-dimethylaminopyridine (DMAP) undoubtedly effected elimination. The acylation was generally performed on the crude aldol mixture since silica gel chromatography of the aldol mixture resulted in a substantial amount of retro-aldol formation. Methanolysis of 51 then afforded 52 as an orange, waxy solid.



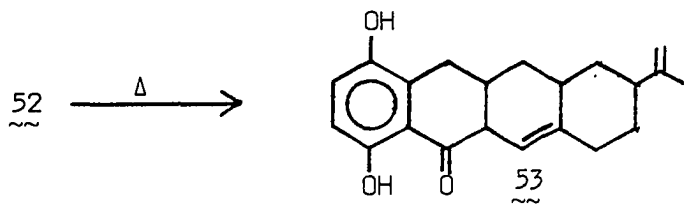
51 R = $COCH_3$

52 R = H

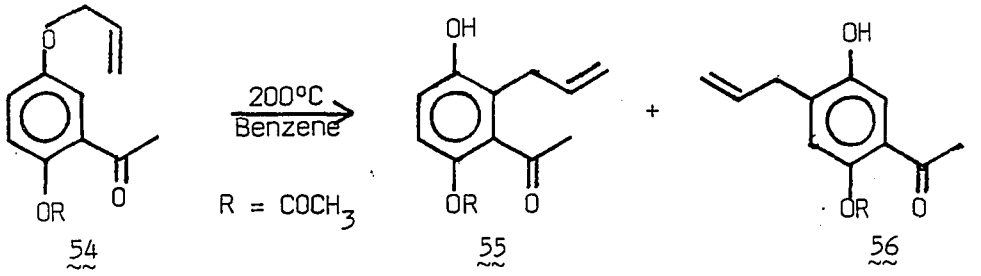
We later discovered that 52 could be produced directly from 4h and perillaldehyde in 45% yield by performing the aldol condensation with the lithium salt of 2,6-di-t-butyl-4-methylphenol (LiBHT). This phenol, otherwise known as BHT, is a common preservative in breads. The LiBHT base was developed by Corey and Chen as a strong, non-nucleophilic base for use in carboxylation reactions (51). To my knowledge, LiBHT has seen little if any use in organic synthesis as a base for aldol condensations.

Thermolysis experiments were first performed on the aldol product 50 and on the acetate 51. Thermolysis of 50 (200°C) with or without a catalytic amount of pTSA resulted only in decomposition or retro-aldol reaction, respectively. Liquid phase thermolysis of 51 (benzene, 200-280°C; N,N-dimethylaniline, reflux) led only to decomposition. Gas phase thermolysis of 51 under flash vacuum pyrolysis conditions (410°C at 2.5 x 10^{-4} torr, 520°C at 5.1 x 10^{-5} torr, and 580-600°C at 1.2 x 10^{-5} torr) and under nitrogen flow conditions (350°C and 405°C, a 0.1 M benzene solution was added dropwise to a hot tube packed with quartz cylinders) afforded recovered 51 and decomposition products (52, 53).

The phenol 52, however, smoothly underwent the tandem Claisen - Diels-Alder reaction to afford 53 in 70% yield.



Obviously, removal of the acetyl group was crucial for the success of the TCDA reaction. Why, though, is not obvious since the acetate 54 undergoes the Claisen rearrangement to produce 55 and 56 in a ratio of 2.6 to 1. Since hydrogen bonding between the phenol hydrogen and the

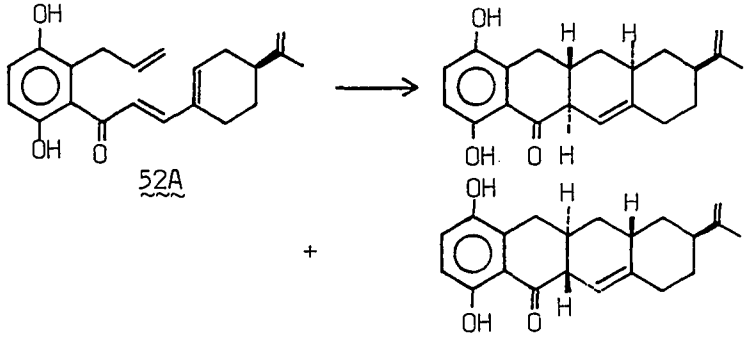


adjacent carbonyl is so crucial, perturbation of this apparently completely destroys the electronic and/or conformational requirements necessary for the success of the TCDA reaction.

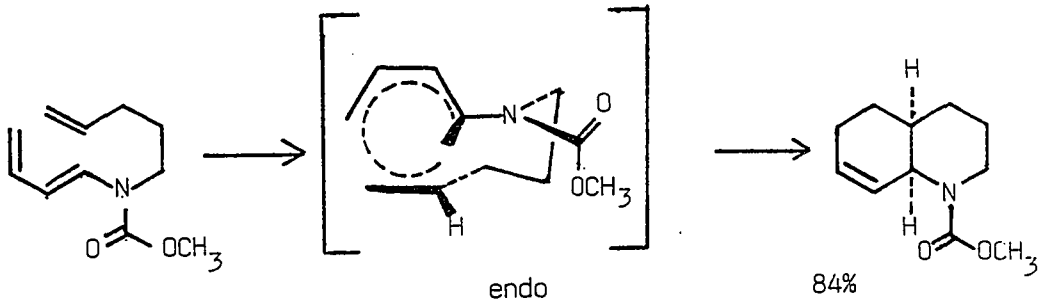
Qualitatively, the rate-determining step of the TCDA reaction appears to be the Claisen rearrangement step. This is based solely on the fact that none of the intermediate Claisen product could be isolated by stopping the reaction before completion.

Compound 53 was a ca 1:1 mixture of diastereomers as evidenced by the complexity of the 300 MHz proton and carbon NMR spectra. The relative sterochemistry about the ring junctions could not be determined.

If the Diels-Alder reaction proceeds through an exo transition state then the following two diastereomers would be produced containing a trans-fused ring junction. An endo transition state would afford cis-fused products.

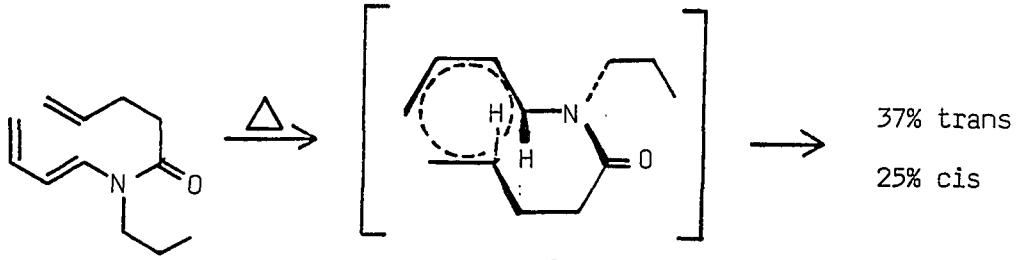


I feel an exo transition state is more likely based on the following argument. One of the main factors influencing steroselectivity in IMDA reactions is coplanarity of the diene π-system with another π-system that is directly in conjugation with the diene. Oppolzer and Frŏstl have shown that such coplanarity directs the endo or exo conformation of the transition state (46). Cyclization of amide 57 proceeds



endo 84%

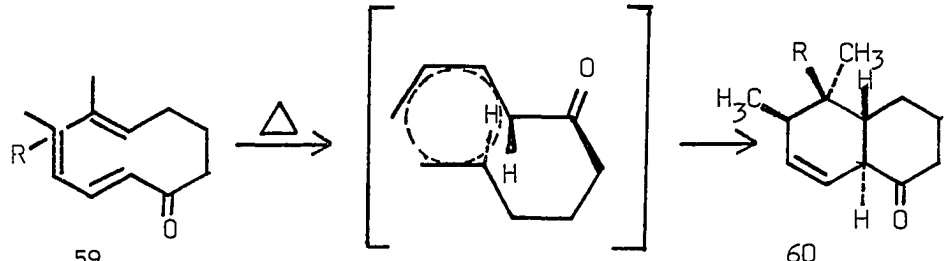
through an endo transition state. The alternate exo transition state leads to poor overlap between the amide and diene π-systems. Cycloaddition of amide 58 affords the trans-fused [4.4.0] system as the main product. Cyclization through an exo transition state now results in better π-overlap between the amide and diene.



58 exo

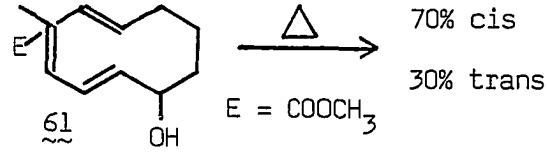
Similarly, Roush and Hall have found that cyclization of 59 proceeds through a transition state in which the carbonyl group remains coplanar with the diene to afford the trans-fused compound 60 as the

major product (54). However, when the carbonyl group is protected as the ethylene glycol ketal, then cyclization leads to an 89:19 ratio of cis- to trans-fused products. One could argue that steric hindrance



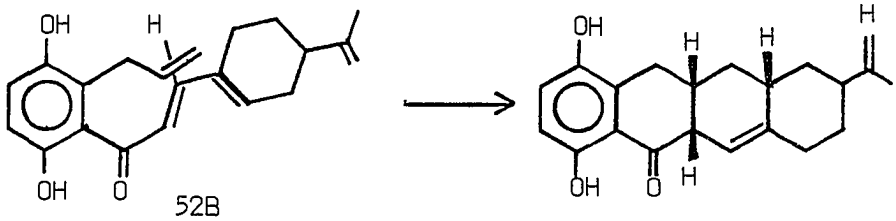
59 R = $COOCH_3$ 60

due to the ketal directs the conformation of the transition state. However, 61 also gave cis-fused cycloadducts as the major products.



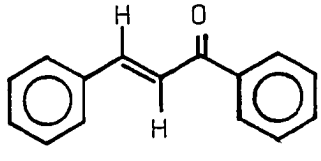
61

In our case, cyclization of 52 through an exo transition state would result in retention of coplanarity between the carbonyl and diene groups to afford trans-fused products. Coplanarity could also be retained if cyclization proceeded through the s-trans form of 52A, 52B. This would result in an endo addition to form cis-fused adducts.

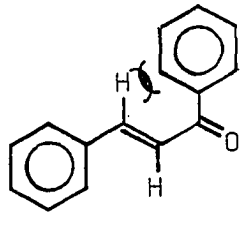


52B

However, a study by Montaudo and coworkers suggest that the s-cis form, 52A, should be the preferred conformation. Using proton NMR, they measured the lanthanide induced shifts (LIS) of several α,β-unsaturated aldehydes, ketones, esters, and amides (55). This data was then used with parameters from a computorized LIS simulation process to calculate the population ratios between the s-cis and s-trans conformers. They determined that 63% (molar fraction percent) of E-4-phenyl-3-buten-2-one exists as the s-cis conformer and that 83% of E-1,3-diphenyl-2-propen-1-one(chalcone), 62, exists as the s-cis conformer. Steric hindrance in the s-trans conformers causes the predominance of the s-cis conformers.



62 c-cis



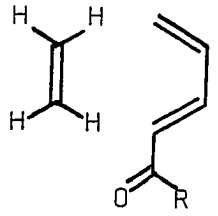
62 c-trans

In our case, conformer 52A (s-cis) should then be preferred over conformer 52B (s-trans). As is readily seen, formation of 52B introduces a great deal of strain into the molecule due to nonbonding interactions between the allyl group and the diene system. In fact, conformer 52B can be achieved only if rotation about the carbon-carbon bond between the carbonyl and aryl group occurs. However, this rotation would weaken or destroy the hydrogen bonding which was shown to be crucial for the success of the TCDA reaction.

The question of sterochemistry is important insofar as the IMDA reaction is concerned. Identification of cis- or trans-fused adducts would increase the general knowledge concerning the subtle factors involved in product steroselectivity. In our case, the relative sterochemistry does not matter since the sterocenters at the ring junctions will ultimately be destroyed.

The terms exo and endo will be used in the sense shown above. It is actually incorrect to speak of an exo or endo transition state since secondary orbital overlap is not possible. However, the terms are commonly used when discussing IMDA reactions of the type at hand, so the terms will be retained for the sake of consistency.

It is interesting to digress at this point and examine the isolated components of the cycloaddition in terms of FMO theory. In a "normal" intermolecular Diels-Alder reaction the components would not react rapidly because of the large energy gap between the frontier MOs. The presence of the conjugated carbonyl group will lower the energy



of the diene HOMO relative to a nonsubstituted diene, increasing the energy gap between the frontier MOs. Relative to the "normal" case, where an electron-releasing group is on the diene, the energy gap between the frontier MOs for the reaction above will be larger. According to perturbation theory, the resultant MOs will be less stable than for the normal case.

However, the cycloaddition under examination may actually involve the dienophile HOMO interacting with the diene LUMO. The reversal from the "normal" case is known as inverse electron demand. One can draw this conclusion using the approximate FMO energies determined by Houk (33) as shown in Figure 9.

Since the energy difference (ΔE) is smaller for the inverse case, the resultant MOs should be more stable than for the normal case. Also, orbital overlap between addends should be greater in the inverse case for 52.

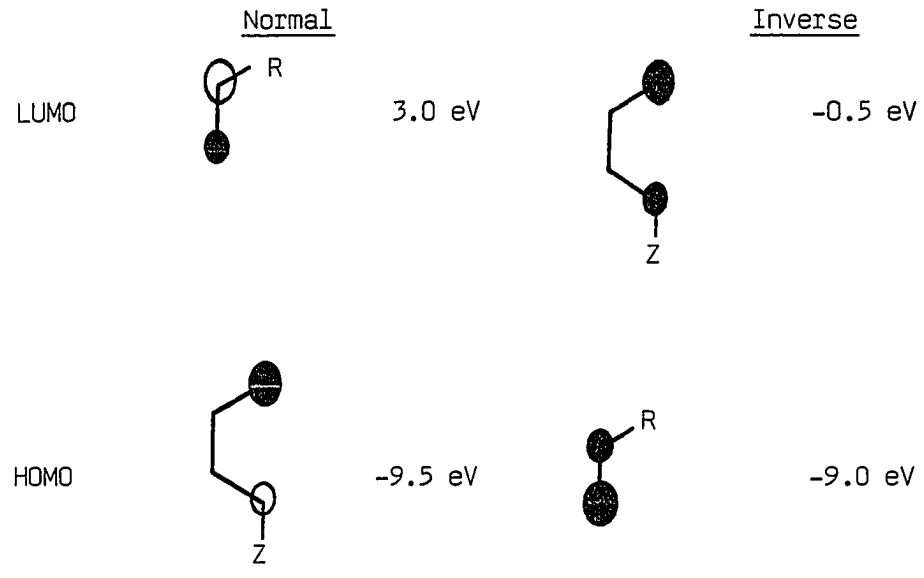
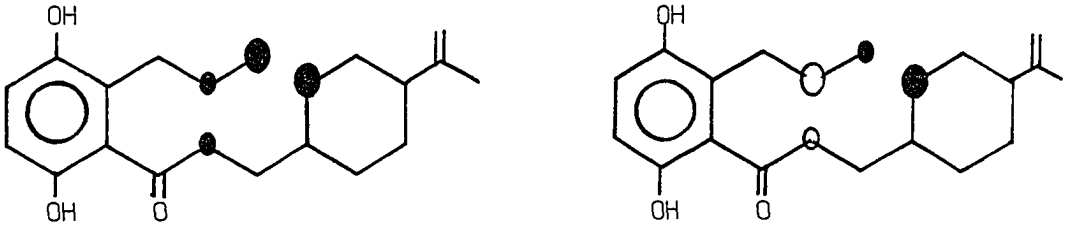


Figure 9. Relative MO energies of "normal" and inverse electron demand case

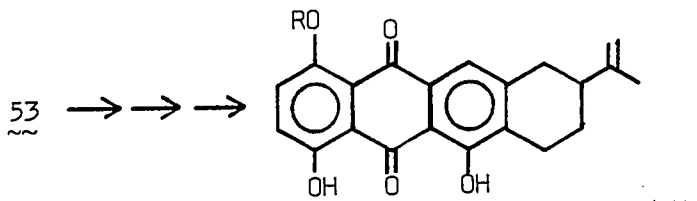


$Diene_{LUMO}$ + $Dienophile_{HOMO}$ (Inverse)

$Diene_{HOMO}$ + $Dienophile_{LUMO}$ (Normal)

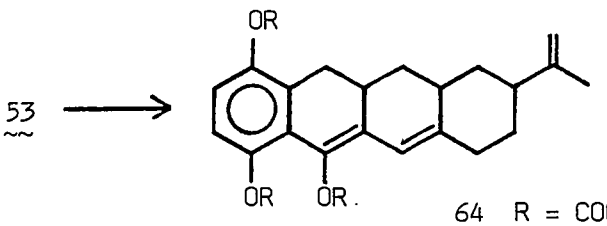
The actual HOMO-LUMO pair involved is simply a matter of conjecture. It is interesting to note that ΔE(LUMO-HOMO) for a Diels-Alder reaction where an electron-releasing group is on the diene and an electron-withdrawing group is on the dienophile is 8.5 eV (for 1-substituted diene), the same energy as for the inverse electron demand case in Figure 9. IMDA reactions of compounds with similar electronic components as in 52 are quite common (39, 56).

With 53 in hand, we embarked on oxidation studies in the hope of obtaining the anthraquinone 63. Protection of the easily oxidized



63 R ≠ H

hydroquinone proved difficult due to the apparent base sensitivity of 53. Addition of 1-2 equivalents of base followed by the protecting unit (dimethyl sulfate, acetic anhydride, methyl iodide, or t-butyldimethylsilyl chloride) led only to darkening of the reaction mixture with isolation of small amounts of unidentifiable products. However, it proved possible to prepare the triacetate 64 in 80% yield.



64 R = $COCH_3$

Unfortunately, we were unable to find any oxidizing agent that would transform 64 into any useful intermediate. The following oxidants were used: triphenylcarbenium tetrafluoroborate (57), triphenylcarbenium tetrafluoroacetate (58), N-bromosuccinimide (57), N-chlorosuccinimide (57), selenium dioxide (59), manganese dioxide (60), pyridinium chlorochromate, t-butyl chromate (61), 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (57, 62), platinium on activated carbon (57), palladium on activated carbon (57), and excess Br_2/base.

The main problem involved competitive reaction of the isopropenyl group. The isopropenyl group was required in the synthesis since it would later have been transformed into an acetyl group. Attempted dehydrogenation by the triphenylcarbenium reagents resulted only in recovery of very small amounts of reaction products. In the case of triphenylcarbenium trifluoroacetate (in situ generation from triphenylmethanol and trifluoroacetic acid), the main reaction product appeared to be that resulting from Markovnikov addition of trifluoroacetic acid across the isopropenyl group. This was suggested by the proton NMR spectrum which was largely identical with 64 except for complete loss of the isopropenyl group at 1.7 - 1.8 ppm and 4.7 to 4.9 ppm concurrent with a large singlet arising at 1.5 ppm. Methanolysis of this product (potassium carbonate and methanol) resulted in a hydroxyl absorption in the infrared spectrum at 3180 - 3600 cm^{-1}.

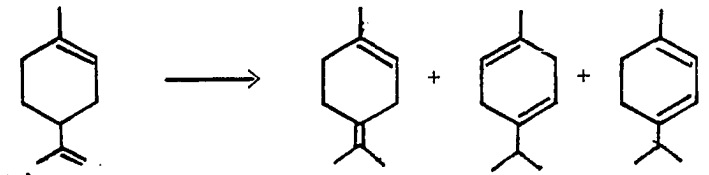
Attempted benzylic halogenation led either to recovered starting material (at short reaction times, ca 5 hours) or minor amounts of unidentifiable products. In these cases, it appeared that the dienol acetate component was undergoing preferential reaction as evidenced by a complete loss of diene proton absorption in the proton NMR at 6.0 ppm. Use of N-chlorosuccinimide was interesting in that its major oxidation product had a proton NMR spectrum identical with the minor oxidation product obtained from DDQ. The structure of this common product could not be determined.

Attempted benzylic oxidation with selenium dioxide in aqueous ethanol or dioxane led to several products in which the main reaction pathway appeared to be oxidation of the isopropenyl group. Attempted benzylic oxidation with pyridinium chlorochromate and t-butyl chromate resulted only in decomposition of 64.

Dehydrogenation with DDQ followed a complex reaction pathway in which a host of products were obtained. Dehydrogenation over transition metal catalysts resulted in recovery of 64 with Pt/C (refluxing cumene) and decomposition of 64 with Pd/C.

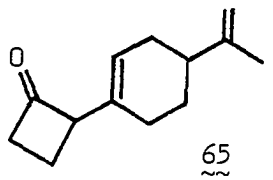
Finally, in a tour de force, the triacetate was subjected to perbromination (3 equivalence bromine) followed by thermal (boiling benzene) or base-induced (lithium chloride/lithium carbonate/hexamethylphosphoramide (63), 1,5-diazabicyclo[4.3.0]non-5-ene (64), or potassium t-butoxide/t-butanol complex (65)) elimination reactions on the crude perbromination product. Only intractable materials were obtained in all attempts.

It became obvious throughout these oxidations that the sensitivity of the isopropenyl group towards isomerization and competitive oxidation was the hindering factor. In retrospect, this is not surprising since it is known in the menthane series (e.g. perillaldehyde and limonene) that Lewis acids and Brnsted-Lowry acids readily cause isomerization of the isopropenyl group to form mainly the corresponding dihydrobenzene derivatives (66). Isomerization conditions in the literature though are usually fairly harsh.



Limonene

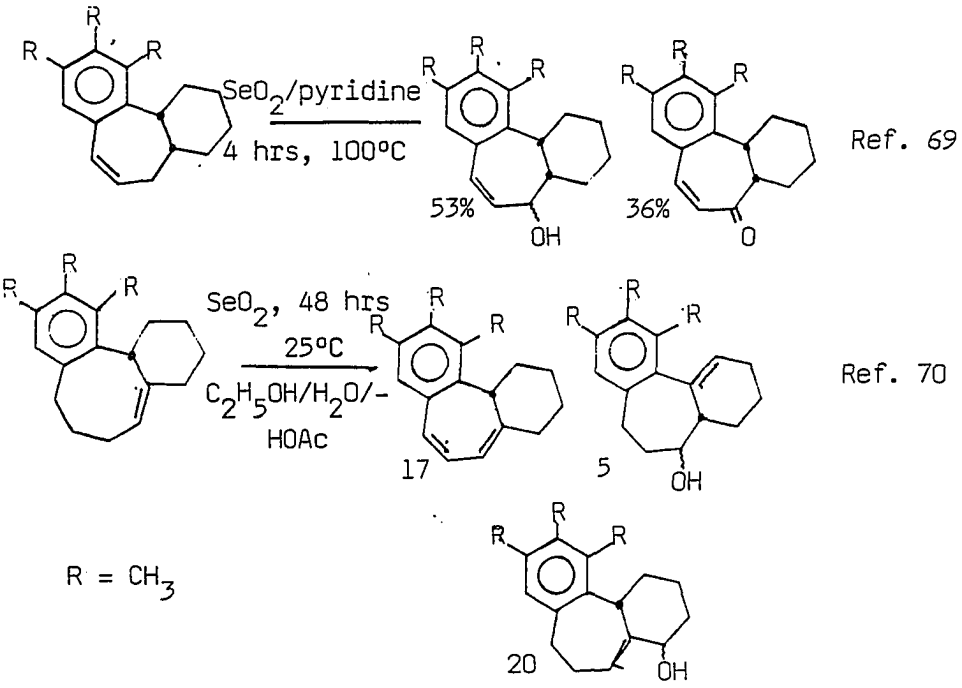
Cohen and coworkers have reported that treatment of 65 with a strong acid results in migration of the isopropenyl double bond into the ring and disproportionation of the resulting dihydrobenzene (67).



65

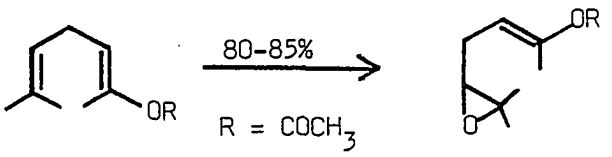
The majority of oxidants used proceed via radical or carbocation intermediates. Compound 64 contains six carbon atoms that, upon oxidation, have the potential of forming resonance stabilized radicals

or carbocations. In the formation of radicals the bond dissociation energy (D) of the C-H bond is indicative of radical stability. The larger the D value, the less stable the radical. The D_{278} of $C_6H_5CH_2$-H is 85 kcal/mol while that of $H_2C{=}CHCH_2$-H is 88.4 kcal/mol (68). With this similarity of stability coupled with the number of potential oxidation sites, it is not surprising that selective oxidation of 64 failed. While there are many examples of benzylic and allylic carbon atoms undergoing oxidation, there are actually few reported cases where both allylic and benzylic centers were present in the same molecule (see 57, 59, 62). The following two examples are typical:



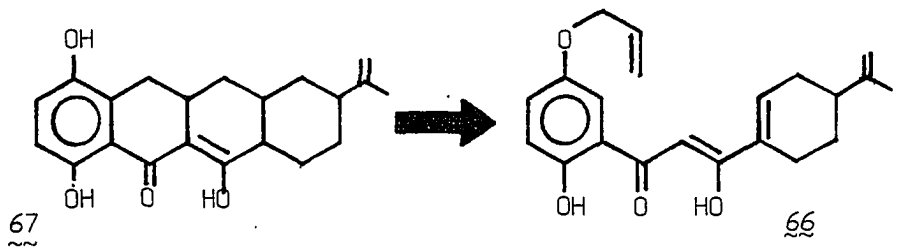
In general, reaction conditions had to be carefully defined and strictly adhered to.

To surmount the oxidation problems we decided to oxidatively cleave the isopropenyl double bond and protect the resultant ketone. Unfortunately, no selectivity between the dienol acetate moiety and the isopropylidene group was observed with sodium periodate/osmium tetroxide (71), m-chloroperoxybenzoic acid (MCPBA), and buffered m-chloroperoxybenzoic acid (72). Anderson and Veysoglu have reported that buffered MCPBA (sodium bicarbonate) can selectively epoxidize a double bond in the presence of an enol acetate (72). Apparently, the dienol acetate



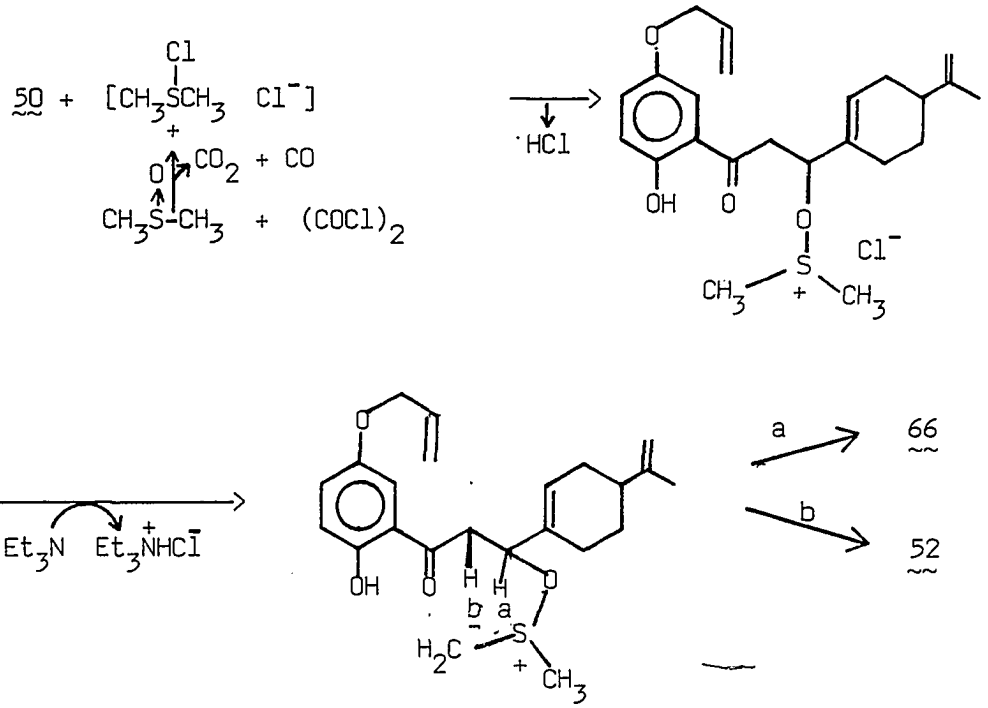
moiety in 64 possesses an electronic environment different enough from an enol acetate that selective epoxidation of the isolated double bond is no longer possible.

At this stage we reasoned that if a β-diketone was present in 53, then the selenium chemistry of Liotta and coworkers could be utilized to effect aromatization (73). We then turned our attention to the construction of 67, which in turn would arise from TCDA reaction of 66.



67 66

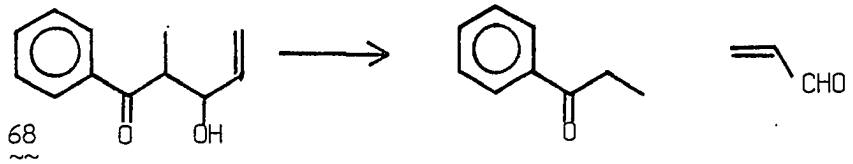
We initially attempted oxidation of 50. However, oxidation of 50 to the corresponding β-diketone could not be accomplished. Oxidation with manganese dioxide (74) resulted in a retro-aldol reaction. Oxidation with Swern's reagent (dimethyl sulfoxide, oxalyl chloride, triethylamine) resulted in dehydration, producing 52 (75). Oxidation with buffered pyridinium chlorochromate (76) resulted in decomposition of 50. Dehydration with Swern's reagent can be rationalized by the following mechanism:



Pathway b is apparently favored due to the acidity of the proton alpha to the carbonyl group.

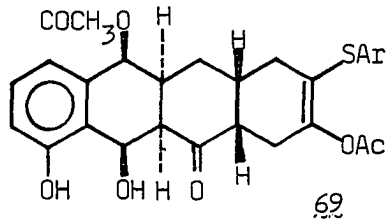
Smith and Levenberg have noted similar difficulties with oxidation of β-hydroxyketones to β-diketones (77). Of eight oxidants Swern's reagent and Collins reagent gave the best results. They noted that

oxidation of 68 yielded only the retro-aldol products. Trost and coworkers also had difficulty in the oxidation of 69 to the β-diketone (78). Manganese dioxide proved to be the optimum reagent with the



68

yield being critically dependent on the amount of oxidant and solvent used.

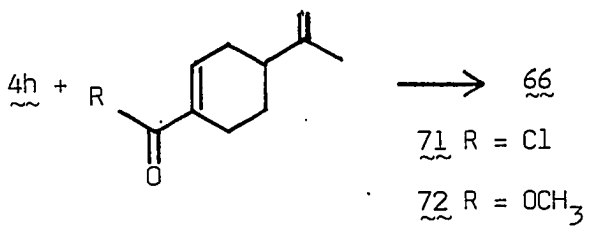


69

It is possible to avoid the oxidation step by using an acid chloride or carboxylic acid ester in place of the aldehyde during the aldol reaction. This will produce the β-diketone directly. The Claisen condensation (79) and the acetoacetic ester condensation (80) have been extensively used for the production of β-diketones and β-ketoesters, respectively. However, yields tend to be poor unless the reaction conditions are rigorously defined. Since the Claisen and acetoacetic ester condensations are often performed in an alcohol solvent, esters were the only acylating agents possible. When methods for the kinetic generation of enolate anions in aprotic media were developed (81), the use of acid chlorides as the acylating agent became possible. The main difficulty encountered with the extremely reactive

acid chlorides is O-acylation of the enolate anion. O-acylation is said to result from a reactant-like transition state with the high charge density at the oxygen atom of the enolate anion leading to O-acylation (82). The competing O-acylation can often be minimized by inverse addition (83 a,b).

In order to synthesize 66 by the above methods the following transformation had to be achieved:



We initally explored acylation with perillyl chloride, 71. Oxidation (84) of (s)-(-)-perillaldehyde afforded perillic acid, 70, which was converted to 71. Formation of the acid chloride from the acid proceeded in 90% crude yield. Upon distillation, decomposition would occur with the purified yield being only 30%. In order to test the general reactivity of o-hydroxyacetophenones, we condensed the dianion of o-hydroxyacetophenone with perillyl chloride under inverse addition conditions using LDA as the base. Examination of the crude reaction mixture by proton NMR revealed approximately 60-70% conversion of o-hydroxyacetophenone to the β-diketone.

Condensation of 4h with 71 gave erratic results with 46% being the maximum yield of 66. Yields usually varied from 30-40%. Under optimized reaction conditions, use of LDA as base afforded a 33% yield of 66, while use of lithium 2,2,6,6-tetramethylpiperidide (LiTMP) as base afforded a 46% yield of 66.

The low yields appeared to be a factor of the purity of 71. Dianion formation (LiTMP) of 4h at -78°C followed by addition of perillaldehyde afforded 50. Examination of the crude reaction mixture by proton NMR revealed less than 10% of unreacted ketone. Based on this, enolate formation of 4h proceeded in approximately 90% yield, but the enolate is apparently quenched by impurities present in 71.

In hope of improving the yield of 66, we turned to condensation of 4h with 72. Under no conditions did condensation occur! Use of LiTMP, LiBHT, potassium hydride, or potassium t-butoxide/t-butanol complex as base afforded recovered starting materials. Sodium hydride led to decomposition of the starting materials or product while sodium ethoxide led only to ester exchange.

A literature search revealed that intramolecular acylation was possible for certain systems. The Baker-Venkataraman reaction (79) involves an intramolecular acyl transfer as shown in Figure 10. Although the intramolecular acyl transfer appeared to be limited to the transfer of aromatic acyl groups, we decided to investigate the reaction to see if it could be extended to aliphatic acyl groups.

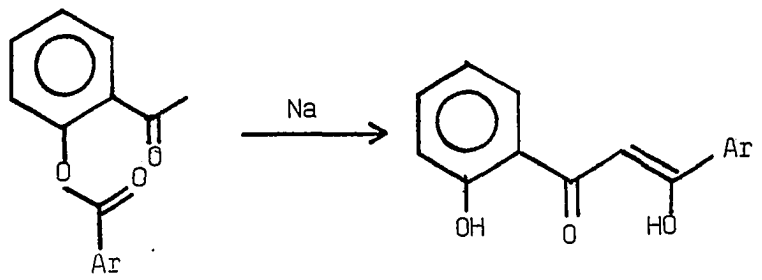
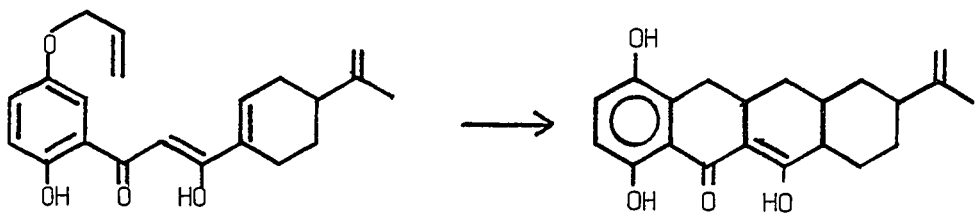


Figure 10. The Baker-Venkataraman reaction

In general, formation of the sodium phenoxide (sodium hydride) followed by addition of an acid chloride furnished the corresponding ester. Intramolecular acyl transfer was then accomplished using the potassium t-butoxide/t-butanol complex. While the two step process was initially done with isolation of the ester, it was discovered that the overall transformation could be accomplished in one reaction vessel with comparable yields. The results of this study have recently been published (85).

Using the modified Baker-Venkataraman reaction, we were able to produce 66 from 4h and 71 in 68% yield. The β-diketone exists completely as its enol form as observed from the proton NMR spectrum by a sharp singlet at 6.2 ppm and at 15.2 ppm. Thermolysis of 66 afforded 67 in 68% yield.



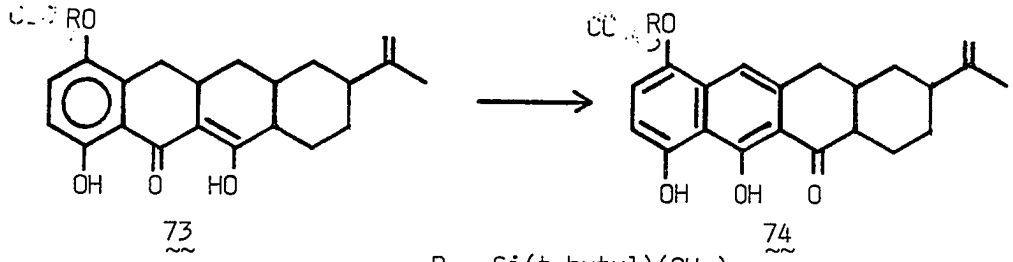
66 67

The cyclization is one of the few known examples where the enol form of a β-diketone is used as a diene in a Diels-Alder reaction.

Our effort to aromatize 67 to the corresponding naphthol centered on the work of Liotta and coworkers (73). They have shown that the 1:1 complex of phenylselenenyl chloride and pyridine will add across β-diketones to form the α-phenyl selenide, which, upon in situ oxidation to the selenoxide, undergoes syn elimination to afford the unsaturated β-diketone. The complex appears to add via nucleophilic substitution of the complex by the β-diketone (73, 86). With this in mind the hydroquinone was monoprotected as the t-butyldimethylsilyl ether (87). The ability to selectively protect 67 demonstrates the greater nucleophilicity of the nonhydrogen-bonded hydroxyl group relative to the hydrogen-bonded ones. The decision to protect 67 proved correct since addition of 67 to the phenylselenenyl chloride/pyridine complex followed by oxidation led to a complex reaction mixture.

With the monosilyl compound 73 in hand we proceeded with its aromatization. While experiments on this subject are still in progress, initial attempts with phenylselenenyl chloride appear promising. The

aromatization is being complicated by the formation of a disilyl compound during the silylation step. However, the yield of the aromatization step may be low (vide infra).

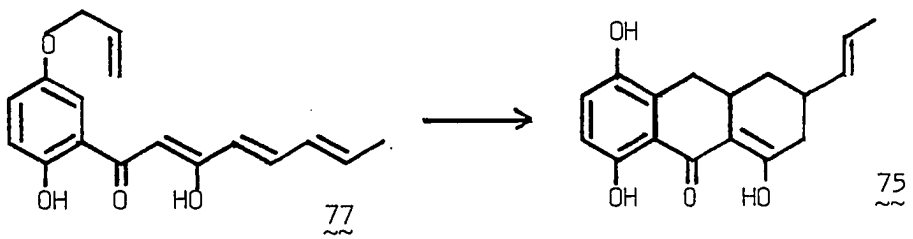


73 74

R = Si(t-butyl)$(CH_3)_2$

During this period the idea arose of developing a common intermediate for both the anthracyclines and tetracyclines. Compound 75 was chosen to test this idea. From 75, addition of a ring on the hydroquinone side would lead to the anthracyclines while addition of a ring on the opposite side would lead to the tetracyclines. This divergent concept is illustrated in Figure 11.

Compound 75 was prepared in the same fashion as 67. Baker-Venkataraman reaction of 4h and sorbyl chloride, 76, led to 77 in 71% yield. Thermolysis of 77 afforded the key intermediate 75 in 50-60% yield. Under optimum conditions a 66% yield of 75 could be obtained.



77 75

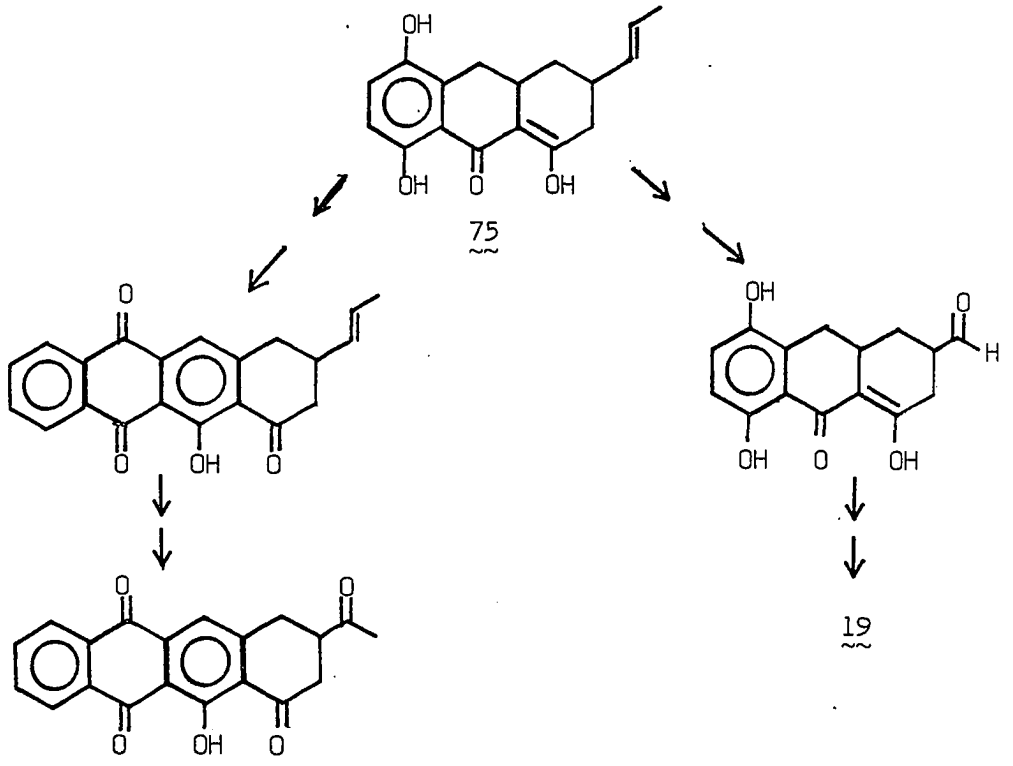
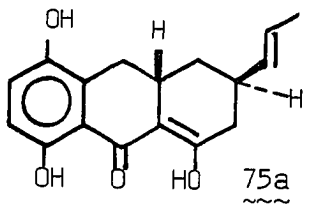


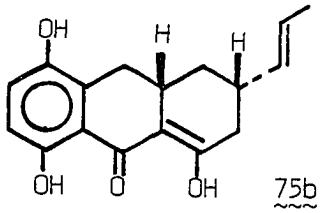
Figure 11. Divergent strategy from 75

Thermolysis of 77 yielded two main products, compound 75 and an unidentified and slightly more polar compound in approximately 10% yield. The more polar compound is highly crystalline and possesses the same molecular weight of 75 by low resolution mass spectroscopy. It has a different fragmentation pattern and a very complex 300 MHz proton NMR spectrum. No attempt was made to determine the structure of the more polar compound because of its low yield.

By C-13 NMR, 75 appears to be a mixture of diastereomers. However, 300 MHz NMR shows the ratio of diastereomers is greater than 10:1. Whether the major diastereomer is 75a or 75b is unclear.



75a

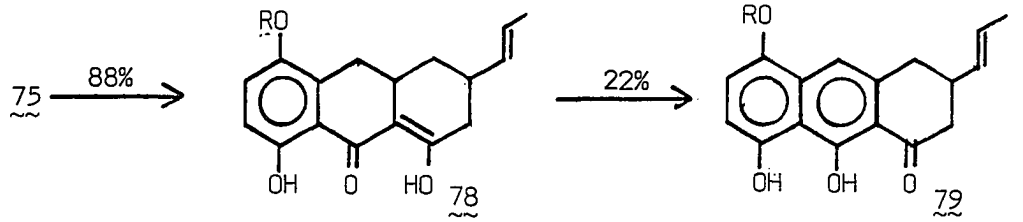


75b

An exo transition state would result in 75a, whereas 75b would arise from an endo transition state. In principle, 75b could arise from an exo transition state if 77 underwent double bond isomerization (presumably by trace amounts of acid coupled with the high reaction temperatures) before the Diels-Alder reaction. Isomerization, however, would result in an inner substituent on the diene which is known to retard Diels-Alder reactions. Therefore, isomerization prior to cyclization seems unlikely.

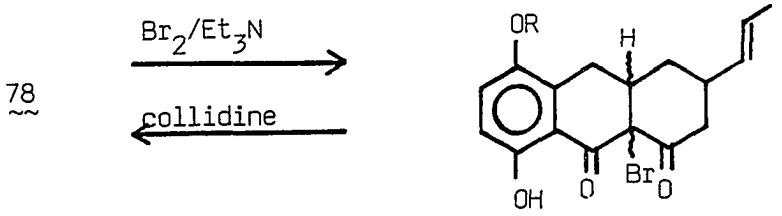
In practice, the cis-trans relationship in 75 is not important since the relative sterochemistry will be destroyed during aromatization to the anthracyclines. Also, epimerization of a suitable intermediate would establish the cis relationship of methine protons required for the tetracyclines.

In our approach towards the anthracyclines, the naphthoquinone 81 appeared to be a useful intermediate. The initial approach involved monosilylation of 75 to give 78 followed by selenoxide elimination to afford 79.



R = Si(t-butyl)$(CH_3)_2$

Faced with the low yield of the elimination step we decided to explore the more traditional method of bromination-dehydrobromination. It proved possible to selectively brominate the β-diketone portion of 78 if an excess of triethylamine was used. However, attempted elimination in refluxing collidine (88) led to less than 15% of 79 with the remainder of the material being the β-diketone 78 as determined by proton NMR and comparison of the ultraviolet spectra of 78, 79 and 80 with ultraviolet spectra reported by Kende and coworkers for similar systems (88).



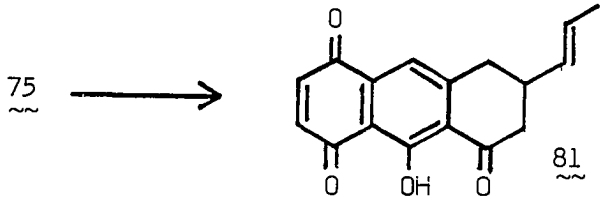
80 R = Si(t-butyl)$(CH_3)_2$

A possible explanation for the lack of dehydrobomination is suggested by the infrared spectrum of 80. Carbonyl absorption at 1735 cm^{-1} corresponds to an equatorially situated bromine or, at least a situation where the carbon-bromine bond is codirectional - coplanar with the carbon-oxygen bond of the nonconjugated carbonyl group (89 a,b). If the methine hydrogen beta to the bromine is axial, then the hydrogen and bromine atoms will have a syn relationship, resulting in the inhibition of an E2 anti elimination process.

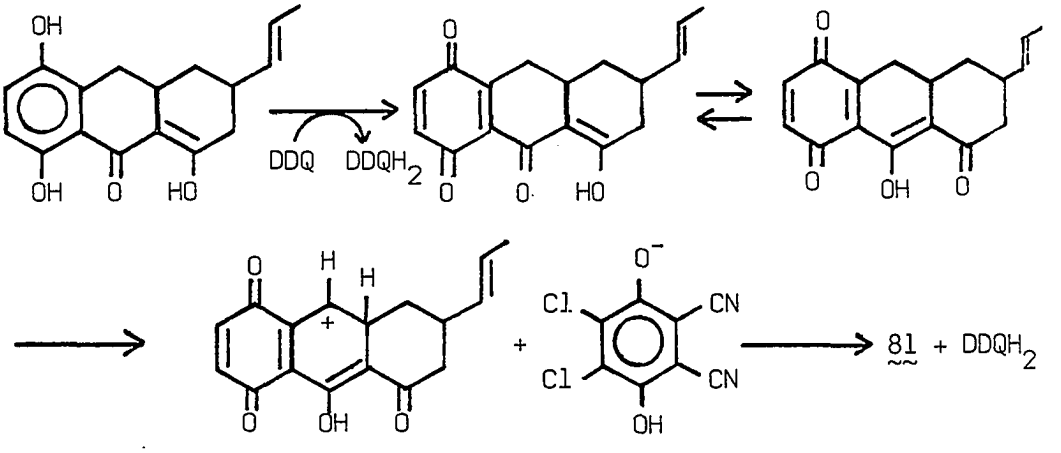
It is surprising that the dehydrobromination failed since 80 is extremely similar to a system reported by Kende and coworkers (88) where dehydrobromination occurred in 84% yield. The only possible conclusion is that 80 exists in a conformation that inhibits dehydrobromination from occurring. How the β-diketone arose from the α-bromo-β-diketone is unknown unless the bromide was displaced by collidine via nucleophilic substitution followed by quenching of the resultant enolate during workup. Difficulties associated with dehydrohalogenations of α-chloro-β-diketones and α-halo-β-ketoesters have been previously noted (90 a,b).

Since formation of the naphthoquinone 81 by elimination reactions proved unsatisfactory, we decided to explore the possibility of oxidizing 75 directly to 81. This was possible with DDQ. The optimum reaction condition was 2 hours at ambient temperature. An increase in reaction temperatures (boiling benzene) or time (24 hours) led to reduced yields of 81 or propene isomerization. Although the

proton NMR of the crude naphthoquinone was clean, there was always a large amount of 2,3-dichloro-5,6-dicyano-1,4-benzohydroquinone ($DDQH_2$) present as determined by the mass balance. The $DDQH_2$ proved extremely difficult to remove as it appeared to have solubility properties very similar to 81. Silica gel chromatography failed while base extraction of crude 81 led only to formation of an inseparable emulsion. The latter is not surprising since juglone is known to be unstable under alkaline conditions (91).

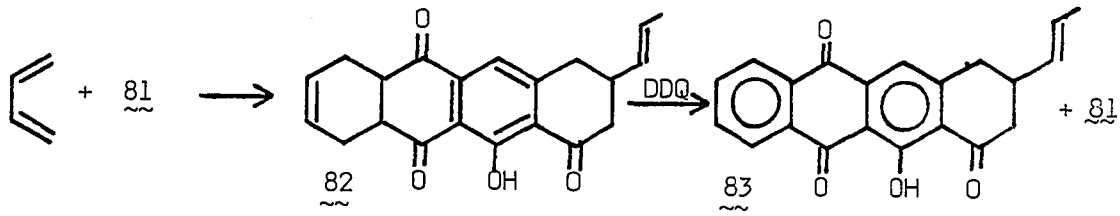


It is interesting that oxidation of 78 with DDQ afforded only recovered starting material. Apparently, dehydrogenation of the hydroquinone to the quinone precedes dehydrogenation of the middle ring. The following mechanism seems likely:



While a hydride transfer intermediate is pictured, the alternate radical intermediate is also possible and should lead to similar results. Also, it is important to note that under optimized reaction conditions the propene group is not affected as contrasted with the isopropenyl group in 64.

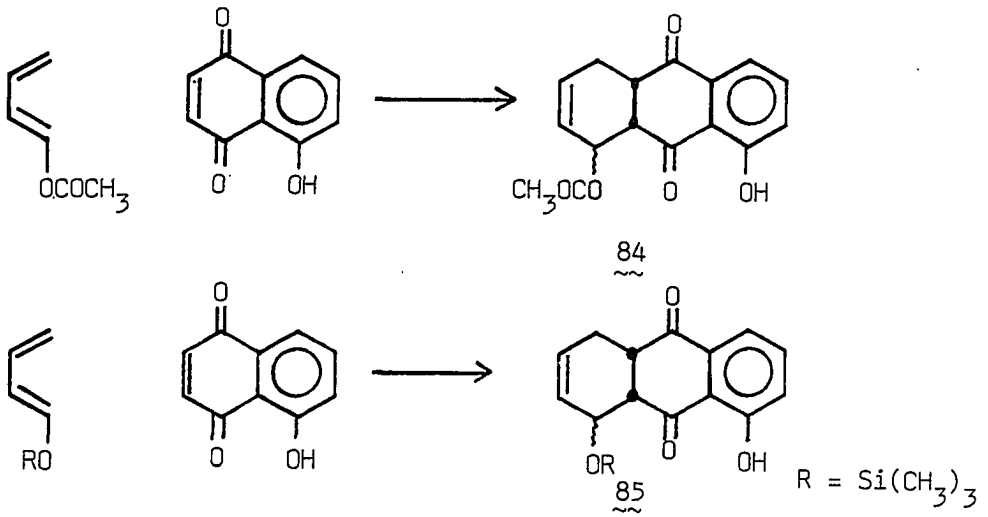
Since the crude yield of 81 appeared to be acceptable, we decided to proceed with the crude material and purify the mixture at a later point. Initial cycloaddition reactions with butadiene, 1-acetoxybutadiene, and 1-trimethylsilyloxybutadiene were discouraging. While adducts were obtained, they tended to be unstable to silica gel chromatography. Oxidation of the purified Diels-Alder adduct 82 afforded the desired anthraquinone, 83, in low yield.



The majority of product consisted of the naphthoquinone 81, which is quite interesting since 81 was not present in the Diels-Alder adduct 82! However, examination of the 300 MHz proton NMR spectrum of 82 revealed the presence of the hydroquinone of 81. Since the hydroquinone was not present in the naphthoquinone 81, then it must have been formed during the Diels-Alder reaction with butadiene. Examination of the various Diels-Alder adducts and reaction products thereon by

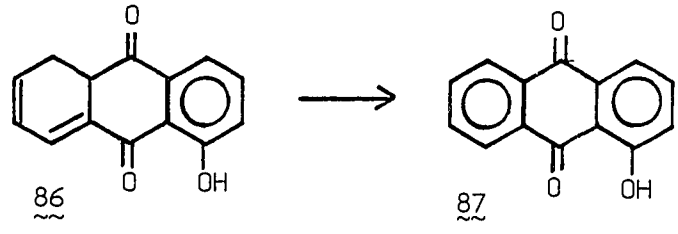
300 MHz proton NMR often revealed the presence of the hydroquinone of 81. Perhaps disproportionation type reactions are occurring in which hydrogen is transferred from the Diels-Alder adducts to the naphthoquinone 81.

Because of the difficulties, a model system was chosen upon which methodology to achieve aromatization could be developed. The Lewis acid catalyzed addition of 1-acetoxybutadiene with juglone has recently been reported by Trost and coworkers (78). The resultant adduct, 84, along with that from the reaction of 1-trimethylsilyloxybutadiene and juglone, 85, were used as model systems.

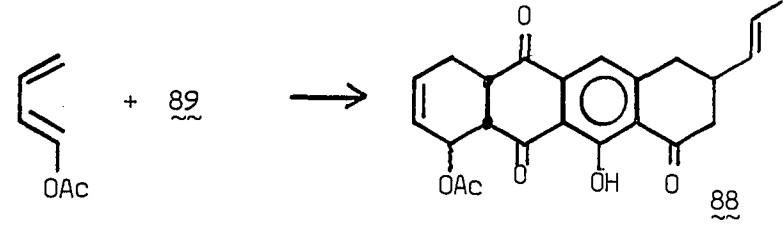


The regioselectivity of the 1-trimethylsilyloxybutadiene reaction is based on analogy with 1-acetoxybutadiene, which has been shown to have the regioselectivity shown (78). It is interesting to note that 85 is completely stable to silica gel chromatography.

Addition of potassium carbonate to a methanolic solution of the acetate 84 afforded a 64% yield of 1-hydroxy-9,10-anthraquinone, 87. Likewise, addition of triethylamine to the silyl ether adduct 85 afforded 87 in an unpurified yield of 94%. Presumably, both base mediated aromatizations are proceeding through intermediate 86, which, upon enolization to the corresponding anthraquinol, readily undergoes aerial oxidation to 87.



Extending this methodology to the case at hand, 81 was reacted with 1-acetoxybutadiene under Lewis acid catalysis to afford adduct 88 with complete disappearance of the naphthoquinone. Adduct 88 was unstable to chromatography, but analysis of the crude reaction mixture



by mass spectroscopy and proton NMR confirmed the presence of 88, although the yield is unknown.

The crude adduct was then exposed to potassium carbonate in methanol for 1 hour at 0°C. A fairly clean reaction resulted but analysis of the purified product by mass spectroscopy showed none of the desired anthraquinone. Similar results were obtained with the corresponding trimethylsilyloxy adduct. The use of triethylamine on either adduct also showed little promise.

We then decided to reinvestigate the butadiene adduct 82. The optimum reaction conditions for the Diels-Alder reaction producing 82 arose from the methodology of Fieser and Dunn (92). An ethanolic solution of buradiene and 81 was heated at 100°C in a sealed tube for 1 hour. Unfortunately, all attempts to aromatize 82 by the methods above failed to give any useful intermediates in preparative yield.

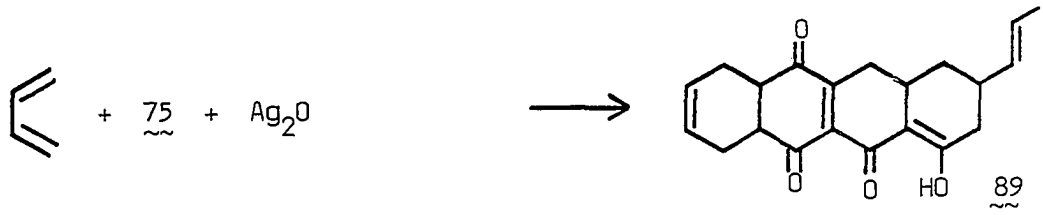
The failure to induce aromatization of the Diels-Alder adducts of 81 is confusing, since literature precedent exsits for very similar systems. For example, the adduct of 2,3-dimethylbutadiene and naphthoquinone is readily aromatized by alcoholic potassium hydroxide in the presence of air (93). The overall yield for both steps is 90%. This, along with our earlier studies with the juglone adducts, would suggest facile aromatization of the Diels-Alder adducts.

The problem may lie with impurities present in 81. Fieser and Dunn have stated that naphthoquinones reacted well with dienes only when highly purified starting materials were used (92). They mentioned

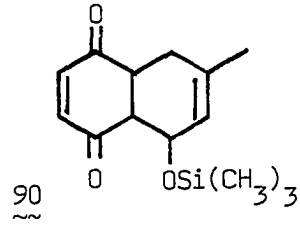
that traces of impurities in the naphthoquinones seemed to promote extensive decomposition during the Diels-Alder reaction. This would be coupled with the fact that the actual amount of material used in the experiments was uncertain since 81 could not be thoroughly purified. If the DDQ oxidation of 75 to 81 proceeded in low yield, then we were dealing with much smaller quantities than originally thought. This means that even if the aromatization step proceeded well, it would be difficult to determine since the final amount of purified material obtained (i.e. 83) was very small.

The main difference between our system and those in the literature is the carbonyl group in the A ring (anthracycline nomenclature). The only problem the carbonyl group might cause would be base mediated side reactions via the corresponding enolate anion. However, this seems unlikely. To my knowledge, there are no aromatizations present in the literature on systems similar to the case at hand.

We decided to return to the hydroquinone 75 and determine if it could be used in Diels-Alder reactions via the corresponding benzoquinone. Following the methodology of Kraus and Taschner (94), 75 was oxidized in situ with silver(I) oxide in the presence of butadiene at ambient temperatures for 24 hours. The adduct 89 was obtained in a purified yield of 35%. Compound 89 also proved to be unstable to silica gel chromatography. Unlike 81, Diels-Alder reaction in acetonitrile, a more polar solvent, led to extensive decomposition during the reaction.

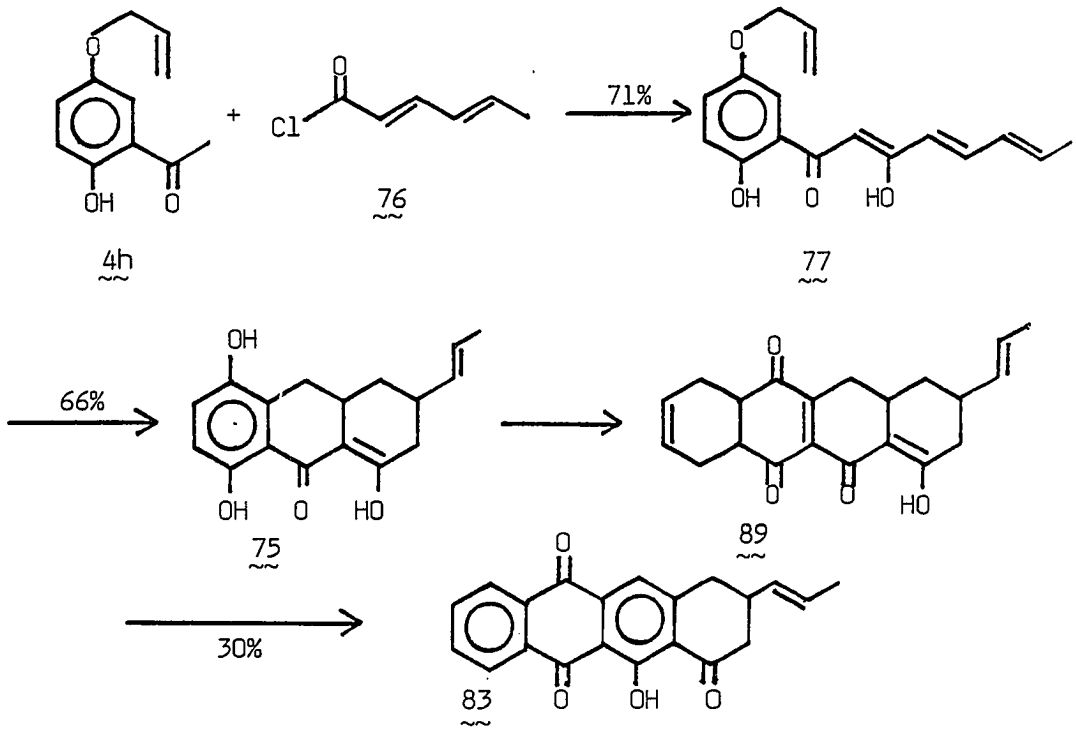


The instability of 89 appears to derive from the enedione unit. Similar instability has been observed by Richard Angus of Professor Johnson's group for molecules containing an enedione moiety (95). Krohn and Brosher have recently reported that compound 90 was "rather labile" (96).



Aromatization of 89 with an excess of triethylamine resulted only in total decomposition of 89. However, when pure 89 was mixed with a catalytic amount of triethylamine, the desired anthraquinone, 83, was obtained in a purified yield of 37%. The aromatization is almost certainly assisted by air although the reaction itself was conducted under a nitrogen atmosphere. Presumably, oxygen present in the triethylamine and solvent (benzene) was responsible.

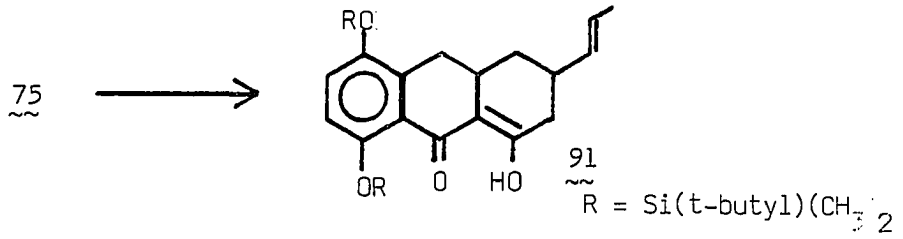
Likewise, bubbling air through a solution of 89 in 5% ethanolic potassium hydroxide (93) afforded anthraquinone 83 in an overall yield of 30% from the hydroquinone 75. The optimum route to date is summerized below.



In just four steps we are able to produce a functionalized anthracycline precursor from readily available starting materials in an overall yield of 14%.

B. Tetracycline Study

Our efforts towards the tetracyclines originates with the disilyl compound 91, which is prepared from 75 in 95% yield. The disilyl compound exists as the free β-diketone as the chemical



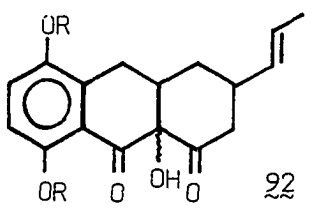
shift of the hydrogen bonded proton (16.3 ppm) corresponds to that reported for benzoylacetone (16.27 ppm) (97).

The initial plan was to oxidatively cleave the propenyl group to the corresponding carboxaldehyde and to react the aldehyde group with an appropriate Wittig reagent. Conjugate addition of dimethylamine followed by an intramolecular condensation would then afford the tetracycline precursor. Intramolecular condensations are well documented in tetracycline syntheses and are in fact, the standard method of producing the A ring (49).

Initial attempts at oxidative cleavage were performed on what was thought to be the trisilyl derivative of 91. It was later discovered, due to the large downfield shift of the hydrogen bonded proton, to be only the disilyl compound. Not surprisingly, oxidative cleavage was generally unsuccessful because of the greater nucleophilicity of the β-diketone unit.

Oxidative cleavage with osmium tetroxide/sodium periodate (71) was erratic with an aldehyde being produced in low yield. Attempts to form the corresponding diol of 91 from the propenyl group with osmium tetroxide/potassium chlorate (98) and osmium tetroxide/t-butylhydroperoxide (99) led to disappearance of the propenyl group but a complex reaction mixture resulted. Examination of the mixtures by 300 MHz proton NMR revealed what appeared to be overoxidation products of the diol, i.e. an aldehyde absorption at 9.7 ppm and absorptions from 2-3 ppm which could correspond to 1,2-hydroxyketones. Overoxidation of diols is not unheard-of in metal oxidations (100). It is noteworthy that the β-diketone unit appeared to have survived; however, the region from 16-16.5 ppm was complex consisting of 3 to 4 peaks.

Epoxidation of 91 with m-chloroperbenzoic acid (72) resulted in a clean reaction producing a compound with a lower R_f value than 91. However, the retention of the propenyl group along with a hydroxy absorption and carbonyl absorption (1725 cm^{-1}) in the infrared spectrum suggested the formation of 92.



92 R = Si(t-butyl)$(CH_3)_2$

Bromination of 91 resulted in a mixture of products. Infra-red absorption at 1715 cm^{-1} suggests formation of a α-bromo-β-diketone compound. However, a hydrogen bonded absorption at 14.5 ppm is also present. The propenyl group remained untouched. These results are not unexpected as Bienvenue-Goetz and Dubois have shown that 2,4-pentadione adds bromine approximately 1000 times faster than, for example, trans-1-phenyl-1-propene. (101).

Selective ozonolysis of 91 using the methodology of Veysoglu and coworkers (102) with sudan red 7B as the indicator dye was also unsuccessful. Reductive workup with dimethyl sulfide afforded a mixture of products along with an aldehyde (9.77 ppm) but the results were erratic. Reductive workup with sodium borohydride (103) led to complete disappearance of the propenyl group, but it was also clear that cleavage of the β-diketone unit had occurred.

With these results in hand, it was obvious that protection of the β-diketone was necessary. However, under no conditions was protection possible. Silylation with t-butyldimethylsilyl chloride returned only starting material. Likewise, methyl chloroformate/pyridine, diazomethane/ethanol (104), and methanesulfonyl chloride/potassium carbonate (105) afforded 91. Chan and Brownbridge have shown that 4-phenylbut-3-en-2-one can be protected as the trimethylsilyl enol ether but extension of their methodology to 91 resulted in only partial protection (106). Subjection of 91 to sodium hydride and

dimethyl sulfate resulted in a mixture of products along with recovery of 91.

The difficulties encountered in protecting the β-diketone unit are probably due in part to the known hydrolytic instability of o-alkyl and o-acyl β-diketones. For example, Veysoglu and Mitscher have shown that the t-butyldimethylsilyl enol ether of 2,4-pentadione acts as a silyl transfer reagent with alcohols (107). In fact, the above compound in dimethylformamide reacts rapidly with water to afford 2,4-pentadione and t-butyldimethylsilanol.

Work is currently in progress to circumvent these difficulties.

IV. MECHANISTIC ANALYSIS OF THE CLAISEN REARRANGEMENT OF o-HYDROXYACETOPHENONES

One of the guiding principles of science is that of prediction. The ability to logically deduce the occurrence of events with the information we have at hand. Prediction is one of the cornerstones of science; without it progress would be impossible.

Wherever an event occurs that disrupts the pattern of predictability, it is extremely important to examine the event and attempt to determine (explain) why nature has taken a course that contradicts that which was expected. History has proven the correctness of this approach. In chemistry, one of the prime examples of recent times is the development of the conservation of orbital symmetry. The theoretical basis had been present for some time. However, it was not until Woodward found it curious that an electrocyclic reaction produced the opposite sterochemistry of that what was predicted during the synthesis of vitamin B12 (108) that the development of the conservation of orbital symmetry occurred in the form known today.

For these reasons, I feel it is important to examine the Claisen rearrangement of 2-hydroxy-5-allyloxyacetophenone in more than a cursorily manner. Chemical experience would not predict the complete regiospecificity of rearrangement of 4h. Based on analogy from Table 2, it would not be surprising if the majority of rearrangement product consisted of 5h, however, it is surprising that the rearrangement

proceeds to produce only 5h. To my knowledge, why this is so has not been rigorously addressed.

There are many effects that have been used to explain selectivity during organic reactions. Some of the more common are: the stereoelectronic effect (109), steric hindrance, electron density, bond order, substituent effects during aromatic substitution, frontier molecular orbital control (23a), and coordination control. Many of these are interrelated and it is rare if only one effect is occurring. As such, it is often difficult to fully explain why a certain selectivity is observed, especially during the transformations of complex molecules. In the case at hand, π-bond order seems to be the controlling factor although the problem is more complex than to invoke just bond order.

When Baker and Lothian (8) first discovered the rearrangement of 4h they rationalized the specificity of rearrangement in terms of bond fixation of one of the Kekule resonance forms in 4h, "... chelation between the hydroxyl and the acetyl group in o-hydroxyacetophenones depends upon the mutual unsaturation of the carbon atoms bearing these groups and therefore leads to stabilization of one of the Kekule form...." Therefore, the direction of rearrangement was thought to be a consequence of the intramolecular hydrogen bonding. However, they also showed that 2-methoxy-5-allyloxyacetophenone produced 5-hydroxy-2-methoxy-6-allylacetophenone upon rearrangement in 94% yield. The same direction of rearrangement was observed although chelation was now impossible. This was dismissed by saying that while no proof was obtained for a stable

Kekule form of 4h, the results were "in harmony" with such a view. It is interesting that in our hands, 2-methoxy-5-allyloxyacetophenone produced a 2:1 mixture of regioisomers upon Claisen rearrangement.

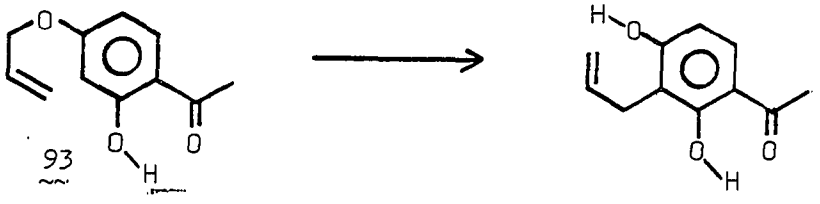
Dewar later expressed a similar view using more modern terminology in a theoretical paper dealing with electrophilic substitution of substituted benzene compounds (110). He states that in 1,2,4-trisubstituted benzenes, the bond order of the annular bond between an electron-releasing group and an electron-withdrawing group is increased. The increase in bond order then causes an alternation of bond order about the benzene ring. The increase in bond order between the two groups "insulates" the groups from the rest of the ring by bonds of low order; electrophilic substitution is then directed by the third group and substitution occurs at the ortho position to which the group is attached by the bond of highest order. Note that substitution is dependent only upon the electronic nature of the substituents. Of course, one cannot directly apply the results of ionic reactions to that of concerted reactions, but the recognition of an increase in bond order between groups is important.

The existence of an alteration of bond order in o-hydroxyacetophenones has been suggested to explain experimental results obtained by Marcinkiewicz (111). The relevant data is in Table 3.

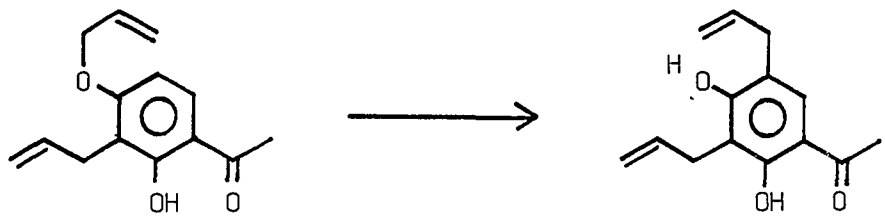
Table 3. Rate constants and activation parameters for the Claisen rearrangement of o-hydroxyacetophenones

Compound	k (186°C)	$\Delta E^{\dagger}$ (kcal/mol)	ΔS (e.u.)
2-hydroxy-5-allyoxy-acetophenone 4h	6.8×10^{-4} sec^{-1}	28.7	-12
2-hydroxy-4-allyloxy-acetophenone 93	3.8×10^{-4} sec^{-1}	27.0	-16
2-hydroxy-3-allyl-4-allyoxyaceto-phenone 94	2.7×10^{-5} sec^{-1}	33.9	- 7.1

Claisen rearrangement of 93 resulted in migration of the allyl group to carbon -3. This would be consistent with an increase in bond order between C-3 and C-4 due to the intramolecular hydrogen bonding.



The author's main point was that while 94 rearranged, the energy of activation ($\Delta E^{\dagger}$) was higher than 4h and 96. He says that the increase in $\Delta E^{\dagger}$ is due to rearrangement about the bond having the lower bond order. That is, the bond order about C-3 and C-4 is greater than that about C-4 and C-5. From Table 1, the energy of activation of allyl

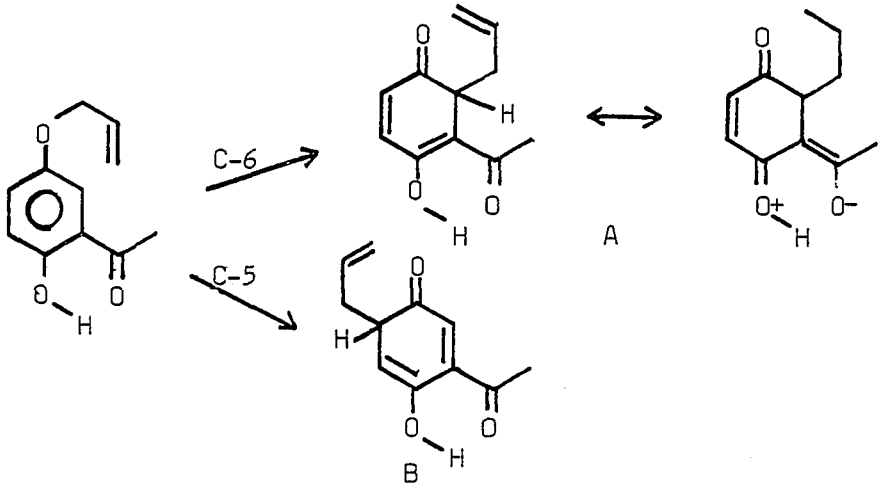


94

phenyl ether is 31.6 kcal/mol. Since the π-bond orders of allyl phenyl ether should be very similar, then it appears that the hydrogen bonding induces a change in π-bond order that can cause a small, though perhaps significant lowering of $\Delta E^{\dagger}$. However, a meta electron-withdrawing group (see Table 1) also lowered $\Delta E^{\dagger}$ relative to allyl phenyl ether. This shows that while hydrogen bonding is important, it is not wholly responsible for selectivity during rearrangement. Based on these results, it appears that Claisen rearrangement about the bond of higher bond order involves the lower energy pathway.

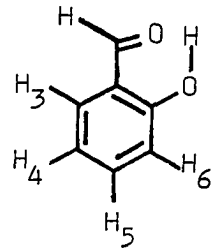
Kruse and Cha have recently attempted to explain the regiochemistry of electrophilic substitution and Claisen rearrangement in aromatic systems (112). In short, they propose the following principle: in the absence of overwhelming steric constraints, aromatic substitution will occur via a transition state which most closely resembles the valence-bond-resonance form of lowest energy. This proposal was based on the thought that functional groups which control reactivity by changing transition-state energies should also perturb ground-state

π-electron densities. This proposal holds well for the case at hand. An examination of the two possible transition-states suggests why rearrangement occurs to C-6.



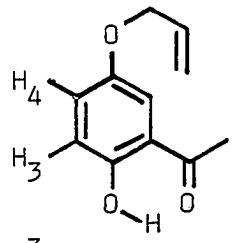
Intuitively, one would feel that A is the valence-bond resonance form of lowest energy since π-electron delocalization can occur through four conjugated π-bonds whereas in B only three π-bonds are directly conjugated.

Other experimental evidence for bond order alteration has been given by Schaefer and coworkers (113). It has been suggested for some time that examination of the three-bond coupling constants in aromatic compounds might give information of the relative bond orders in the compound. Appreciable deviations from coupling constants predicted on an additivity basis would suggest partial double bond fixation by substituent interactions. They measured the proton NMR $^{3}J^{H,H}$ values for salicylaldehyde at a field of 100 MHz. They found that $^{3}J_{34}$ = 8.435 Hz, $^{3}J_{45}$ = 7.258 Hz, and $^{3}J_{56}$ = 7.709 Hz. The coupling constants

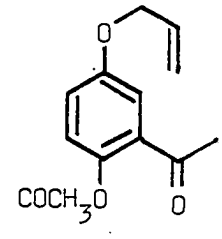


were said to differ from those predicted on an additivity basis by +0.33 Hz, -0.07 Hz, and +0.11 Hz, respectively. These results suggest that the C-3 - C-4 bond order (ρ_{34}) and ρ_{56} is greater than ρ_{45}.

This idea has been extended to the case at hand as shown below.



$\underset{\sim\sim}{4h}$ $^3J_{34}$=9 Hz



$\underset{\sim\sim}{54}$ $^3J_{34}$ = 8.84 Hz

Assuming that an acetoxy group affects the magnitude of coupling the same as a hydroxy group, loss of hydrogen bonding results in a slightly smaller coupling constant, ΔJ = 0.16 Hz. This suggests that ρ_{34} in $\underset{\sim\sim}{4h}$ is greater than ρ_{34} in $\underset{\sim\sim}{54}$, which in turn makes ρ_{56} in $\underset{\sim\sim}{4h}$ greater than ρ_{56} in $\underset{\sim\sim}{54}$. In line with Dewar's work, this suggests why $\underset{\sim\sim}{4h}$ shows greater selectivity than $\underset{\sim\sim}{54}$ during the Claisen rearrangement. It does not, though, explain why $\underset{\sim\sim}{4h}$ is completely regiospecific.

I am unaware of any molecular orbital calculations that have been published for o-hydroxyacetophenones in which the bond order was calculated. We have performed a simple Hückel calculation on $\underset{\sim\sim}{4h}$ to

see if any alterations in bond order exists (114). The following basic parameters for the Coulomb and resonance integrals of the hetero atoms were used (115):

$$\alpha_{=O} = \alpha + \beta$$

$$\alpha_{-O-} = \alpha + 2\beta$$

$$\beta_{C=O} = \beta$$

$$\beta_{C-O} = 0.7\beta$$

To our delight, an alteration in bond order was observed with $\rho_{56} = 0.62$ and $\rho_{45} = 0.58$. So even at this level of calculation it is possible to show that the bond order in 4h is definitely altered due to the substituent groups present. Although the difference in bond orders are small, it is significant that a difference was at least observed. Higher order calculations of the semi-empirical type would have to be performed on 4h in order to more clearly determine the relationship of the substituent groups and hydrogen bonding with bond order.

By the discussion above, it is possible to rationalize in part the selectivity observed for the Claisen rearrangement of o-hydroxy-acetophenones. However, the question appears to be very complicated and there are undoubtedly several effects present that ultimately determine the regioselectivity of rearrangement.

V. CONCLUSION

The tandem Claisen - Diels-Alder reaction has proven to be an effective means of synthesizing linear, polycyclic compounds that can efficiently transform into anthraquinone intermediates for the anthracyclines. The divergent strategy from 75 allows the formation of anthraquinone 83 in just 4 steps from readily available starting materials in an overall yield of 14%. The common intermediate 75 can also be transformed into a potent tetracycline intermediate in just 2 steps.

Highlights of the strategy are the modification of the Baker-Venkataraman reaction, use of an enol form of a β-diketone as a diene in an intramolecular Diels-Alder reaction, use of the regiospecific Claisen rearrangement of 4h, and the facile aromatization of 89 to 83.

Use of the tandem Claisen - Diels-Alder reaction will allow for the rapid formation of natural products containing a linear tri or tetracyclic ring system.

VI. EXPERIMENTAL

A. General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Tetrahydrofuran (THF) and diethyl ether were distilled from lithium aluminium hydride prior to usage. Methylene chloride was distilled from phosphorus pentoxide. Benzene was distilled from sodium benzophenone ketyl. N,N-dimethylformamide (DMF) was dried over 4Å molecular sieves. Acetonitrile was distilled from calcium hydride. All reactions were conducted under a nitrogen atmosphere, and all extracts were dried over anhydrous sodium sulfate. Apparatus for experiments requiring anhydrous conditions was flame-dried under a stream of nitrogen or was dried in an oven at 150°C for 12 hours. Flash chromatography was performed on Kieselgel 60, mesh 230-400. Column chromatography was performed on Grace silica gel, grade 62, mesh 60-200. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Beckman IR-4250 or Acculab 2 spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian EM-360 spectrometer. High field (300 MHz) proton spectra were obtained using a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Splitting patterns are designated as s (single), d (doublet), t (triplet), and m (multiplet); addition of br indicates a broadened pattern. Carbon-13 NMR spectra were determined on a JOEL

FX-90Q or Nicolet NMC-1280 spectrometer and are reported in ppm relative to the central peak of $CDCl_3$ (77.06 ppm) or D_6-acetone (27.0 ppm). Ultraviolet spectra were obtained on a Perkin-Elmer 320 UV-Vis spectrophotometer. High resolution mass spectra were recorded on a AEI-MS 902 high resolution mass spectrometer. Low resolution mass spectra were recorded on a Finnegan 4023 mass spectrometer. Elemental analyses were determined by Galbraith Laboratories, Inc.

1. 2-Hydroxy-5-allyloxyacetophenone 4h

Allylation of 2,5-dihydroxyacetophenone (20 g, 0.131 mol) with allyl bromide (16.8 g, 0.139 mol) and potassium carbonate (18.4 g, 0.133 mol) in 60 ml of acetone was accomplished by the reported procedure (8). Recrystallization from hot ethanol followed by repeated recrystallization of the mother liquor afforded 17.94 g (71%) of 4h as small, pale yellow prisms (mp 57-58°C).

MHz 300, NMR ($CDCl_3$) δ 2.709 (s, 1 H), 4.635 (d, 2 H, J = 5.2 Hz), 5.30 (d, 1 H, J = 9.7 Hz), 5.47 (d, 1 H, J = 17.2 Hz), 6.11 (m), 6.93 (d, 1 H, J = 9 Hz), 7.253 (dd, 1 H, J = 9.3 Hz), 7.47 (d, 1 H, J = 3 Hz), 11.915 (s, 1 H). C-13 NMR ($CDCl_3$) 26.402, 69.971, 115.233, 117.574, 119.070, 119.265, 124.922, 133.311, 150.675, 156.918, 203.740 ppm. IR (Nugol mull) 1650, 1620, 1465, 1210, 800 cm^{-1}.

2. 3-[4-(2-Propenyl)cyclohexenyl]-3-hydroxy-1-[5-(allyloxy)-2-hydroxyphenyl]prop-1-one 50

A 0.5 M solution of 4h (0.293 g, 1.53 mmol) in THF was added dropwise to a preformed solution of LDA (3.28 mmol) in 6.6 ml THF

cooled to -78°C and the resultant light green solution was stirred at -78°C for 1 hour. A 0.5 M solution of perillaldehyde (0.232 g, 1.54 mmol) in THF was added dropwise at -78°C. After stirring at -78°C for 15 minutes the reaction was quenched with acetic acid (0.18 ml, 3.1 mmol) at -78°C, warmed to room temperature, poured into 30 ml of water, and extracted twice with 30 ml of ether. The combined ether layers were dried and concentrated in vacuo. Flash chromatography (116) using 1:8 ethyl acetate/hexane yielded 0.335 g (68%) of 50 as a light yellow oil.

NMR ($CDCl_3$) δ 1.7 (br s, 3 H), 2.0 (m, 1 H), 2.1-2.5 (br m, 6 H), 2.7-2.9 (br t, 1 H, J = 3 Hz), 3.1-3.2 (m, 2 H), 4.53 (d, 2 H, J = 5 Hz), 4.7 (br s, 2 H), 5.13-5.6 (three m, 2 H), 5.64-6.17 (m, 1 H), 6.93 (d, 1 H, J = 7 Hz), 7.0 (d, 1 H, J = 7 Hz), 7.16 (s, 1 H), 11.8 (s, 1 H). IR (neat) 3500, 3080, 2910, 1640, 1610, 1585, 1260, 1100 cm^{-1}.

3. 3-[4-(2-Propenyl)cyclohexenyl]1-1[5-(allyloxy)-2-acetoxyphenyl]prop-2-en-1-one 51

To a solution of 50 (0.4083 g, 1.19 mmol) in 3 ml CH_2Cl_2 was added acetic anhydride (0.259 g, 2.54 mmol), triethylamine (0.254 g, 2.51 mmol), and 4-dimethylaminopyridine (0.0155 g, 0.13 mmol). The mixture was then refluxed for 10 hours. The mixture was cooled to room temperature and washed sequentially with 1N HCl, saturated sodium bicarbonate, and water. The methylene chloride layer was dried and concentrated in vacuo. Flash chromatography using 1:4 ethyl acetate/hexane afforded 0.3649 g (84%) of 51 as a pale yellow oil.

NMR ($CDCl_3$) δ 1.7 (br s, 3 H), 2.0 (m, 1 H), 2.1-2.5 (br m, 6 H), 2.2 (s, 3 H), 4.53 (d, 2 H, J = 5 Hz), 4.7 (br s, 2 H), 5.13-5.6 (three m, 2 H), 5.76-6.17 (m, 1 H), 6.17-6.43 (m, 1 H), 6.2-6.43 (m, 1 H), 6.7 (s, 1 H), 6.9-7.2 (m, 4 H). IR (neat) 3100, 2920, 1765, 1665, 1650, 1620, 1580, 1490, 1325, 1285, 1175 cm^{-1}. MS, m/e (%) 366 (42), 324 (100), 283 (38), 223 (24), 203 (39), 177 (50), 137 (74).

4. 3-[4-(2-Propenyl)cyclohexenyl]-1-[5-(allyloxy)-2-hydroxyphenyl]prop-2-ene-1-one 52

To a solution of 51 (0.9926 g, 2.71 mmol) in 5 ml of methanol was added potassium carbonate (0.3758 g, 2.72 mmol) at 0°C. The resultant dark orange solution was stirred at 0°C for 15 minutes. The mixture was acidified with 1N HCl and poured into water, extracted twice with methylene chloride, dried, and concentrated in vacuo. Flash chromatography using 1:15 ethyl acetate/hexane afforded 0.653 g (74%) of 52 as an orange solid (mp 58-59°C).

MHz 300, NMR ($CDCl_3$) δ 1.6 (m, 1 H), 1.770 (s, 3 H), 1.962 (m, 1 H), 2.177-2.445 (m, 5 H), 4.523 (d, 2 H, J = 5.2 Hz), 4.762 (d, 2 H, J = 10 Hz), 5.314 (d, 1 H, J = 10.5 Hz), 5.429 (d, 1 H, J = 17.5 Hz), 6.001-6.105 (m, 1 H), 6.372 (s, 1 H), 6.91 (d, 1 H, J = 9 Hz), 6.92 (d, 1 H, J = 15.3 Hz), 7.112 (dd, 1 H, J = 9, 2.8 Hz), 7.32 (d, 1 H, J = 2.3 Hz), 7.53 (d, 1 H, J = 15.3 Hz), 12.452 (s, 1 H). C-13 NMR ($CDCl_3$) 20.817, 24.740, 27.029, 32.213, 40.657, 70.124, 109.331, 114.732, 117.192, 117.919, 119.151, 119.881, 124.238, 133.404,

135.219, 141.300, 148.512, 148.743, 150.585, 157.928, 174.626 ppm. IR (neat) 2920, 1645, 1560, 1475, 1280, 1250, 1160 cm^{-1}. UV (MeOH) 270, 334, 380 nm. MS, m/e (%) 324 (84), 283 (30), 223 (26), 203 (31), 187 (36), 137 (100), 135 (82), 133 (47).

5. Preparation of 52 with LiBHT

The phenol BHT (7.59 g, 34.4 mmol) was added to a 250 ml two neck flask equipped with an addition funnel and dissolved in 70 ml of ether. The solution was cooled to -78°C and n-butyl lithium (15 ml of a 2.2 M solution, 33 mmol) was added dropwise. A white precipitate developed and the mixture was warmed to room temperature. A mixture of 4h (3.0 g, 15.6 mmol) and perillaldehyde (2.3 g, 15.4 mmol) in 32 ml of ether was added dropwise at room temperature over 25 minutes. During addition, the solution turned from white to orange with a clear red solution resulting upon the end of addition. After stirring at room temperature for 1 hour the solution was cooled in an ice bath and quenched with acetic acid (2 ml, 34.8 mmol). The mixture was poured into water and extracted twice with ether. The combined ether layers were dried and concentrated in vacuo. Chromatography of the mixture using hexane (to remove the BHT) followed by 1:15 ether/hexane gave 2.22 g (45%) of 52.

6. 7,10-Dihydroxy-6-oxo-2-(2-propenyl)-1,2,3,4,5a,6,11,11a,12,12a-decahydronaphthacene 53

To a dry culture tube was added 52 (0.2519 g, 0.78 mmol) and a trace of hydroquinone as an antioxidant. A 0.1 M solution was made

by adding 7.8 ml of benzene and nitrogen was bubbled through the mixture for 5-10 minutes. A teflon-lined cap was screwed on and the mixture was heated at 200-210°C for 10 hours. After cooling and concentration in vacuo, the mixture was flash chromatographed using 1:2 ether/hexane to afford 0.156 g (62%) of 53 as a mixture of diastereomers. An analytic sample was crystallized from 1:4 ether/hexane (mp. 139°C, yellow to orange; 155-160°C).

MHz 300, NMR ($CDCl_3$) δ 1.735 and 1.770 (two s, 3 H), 1.8-3.0 (m, 14 H), 3.03-3.12 (two m, 1 H), 4.717 (s, 2 H), 6.019 (s, 1 H), 6.71 (d, 1 H, J = 9 Hz), 6.96 (d, 1 H, J = 9 Hz), 12.032 and 12.358 (two s, 1 H). C-13 NMR ($CDCl_3$) 20.966, 26.204, 27.143, 29.251, 30.571, 30.818, 34.262, 37.078, 38.406, 38.855, 109.219, 115.853, 124.628, 128.306, 138.509, 139.830, 141.418, 144.324, 149.278, 157.889, 194.556 ppm. IR ($CDCl_3$) 3380, 2910, 1635, 1455, 1180 cm^{-1}. UV (MeOH) 216 (sh), 278, 388 nm. MS, m/e (%) 324 (100), 281 (76), 263 (54), 177 (99.6), 152 (70), 151 (69). Elemental analysis calculated for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.91; H, 7.51.

7. 2-Acetoxy-5-alloxyacetophenone 54

The ketone 54 was isolated by chromatography from the acylation of the crude reaction mixture from 50 as a low melting solid (mp. 15-25°C).

MHz 300, NMR ($CDCl_3$) δ 2.500 (s, 3 H), 2.751 (s, 3 H), 4.670 (d, 2 H, J = 5 Hz), 5.50 (d, 1 H, J = 10 Hz), 5.65 (d, 1 H, J = 17 Hz), 6.25-6.40 (m, 1 H), 7.33 (d, 1 H, J = 8.82 Hz), 7.401 (dd, 1 H, J =

8.86, 2.7 Hz), 7.624 (d, 1 H, J = 2.7 Hz). IR (neat) 1765, 1685, 1480, 1180 cm^{-1}.

8. Claisen rearrangement of 54

Thermolysis of 54 (0.186 g, 0.78 mmol) was accomplished using the procedure developed for 53. Flash chromatography of the reaction mixture using 1:2 ether/hexane afforded 0.0917 g (50%) of 55 and 0.035 g (19%) of 56.

9. 2-Acetoxy-5-hydroxy-6-allylacetophenone 55

MHz 300, NMR ($CDCl_3$) δ 2.238 (s, 3 H), 2.445 (s, 3 H), 3.299 (br d, 2 H, J = 6 Hz), 4.969-5.069 (m, 2 H), 5.841-5.971 (m, 1 H), 6.413 (s, 1 H), 6.719 (d, 1 H, J = 8.75 Hz), 6.882 (d, 1 H, J = 8.75 Hz).

10. 2-Acetoxy-4-allyl-5-hydroxyacetophenone 56

MHz 300, NMR ($CDCl_3$) δ 2.339 (s, 3 H), 2.453 (s, 3 H), 3.378 (br d, 2 H, J = 6.6 Hz), 5.104-5.164 (m, 2 H), 5.872-5.985 (m, 1 H), 6.556 (s, 1 H), 6.836 (s, 1 H), 7.139 (s, 1 H).

11. 6,7,10-Triacetoxy-2-(2-propenyl)-1,2,3,4,11,11a,12,12a-octahydronaphthacene 64

To a solution of 53 (0.325 g, 1 mmol) in 4 ml of methylene chloride was added acetic anhydride (0.324 g, 3.2 mmol), triethylamine (0.327 g, 3.2 mmol), and 4-dimethylaminopyridine (0.042 g, 0.345 mmol). The mixture was stirred at room temperature for 4 hours, washed with

1N HCl and water, dried, and concentrated *in vacuo*. Flash chromatograph using 1:4 ethyl acetate/hexane afforded 0.351 g (78%) of **64** as a pale yellow foam.

NMR ($CDCl_3$) δ 1.7 (br s, 3 H), 2.23 (s, 3 H), 2.28 (s, 6 H), 2.0-2.5 (m, 13 H), 4.83 (m, 2 H), 6.05 (s, 1 H), 6.77 (d, 2 H, *J* = 2 Hz). IR ($CDCl_3$) 3090, 2930, 2860, 1755, 1460, 1360, 1180 cm^{-1}. UV (MeOH) 248, 304 (sh), 314, 330 (sh) nm. MS, m/e (%) 450 (8), 408 (37), 366 (79), 322 (27), 297 (100).

12. Perillic acid **70**

A solution of sodium chlorite (1.8 g of commercial 80%, 16 mmol) in 16 ml of monobasic monohydrate sodium phosphate pH 4 buffer was added dropwise to perillaldehyde (2.0 g, 13.3 mmol) and 2-methyl-2-butene (14 ml, 132 mmol) in 70 ml of t-butanol at room temperature. The resultant light yellow solution was stirred at room temperature for 20 hours. It was made basic with 6N NaOH (pH 10) and the majority of t-butanol was removed at reduced pressure. The residue was added to water and extracted twice with hexane. The aqueous layer was acidified with 6N HCl to pH 2 and extracted with 3 x 100 ml of ether. The combined ether layers were dried and concentrated *in vacuo*. Azeotropic distillation with benzene yielded 1.29 g (59%) of **70** as a white solid. An analytical sample was crystallized from 50% ethanol (mp. 134-135°C).

NMR ($CDCl_3$) δ 1.7 (br s, 3 H), 2.0 (m, 1 H), 2.1-2.5 (m, 6 H), 4.7 (s, 2 H), 7.4 (br s, 1 H), 11.3 (s, 1 H). IR ($CDCl_3$) 3400-2700 (br), 1680, 1635 cm^{-1}.

13. Perillyl chloride 71

A mineral oil dispersion of 50% sodium hydride (0.295 g, 6.1 mmol) was added to a 50 ml three-neck flask and washed twice with 6 ml of hexane with a syringe under a nitrogen atmosphere. The washed sodium hydride was suspended in 12 ml of benzene and a 1 M solution of 70 (0.994 g, 6 mmol) in benzene was added dropwise at 0°C. After stirring for 5 minutes oxalyl chloride (0.53 ml, 6.1 mmol) was added dropwise. The resultant heterogenous mixture was warmed to room temperature and stirred for 3 hours. Filtration and concentration of the filtrate afforded 1.04 g (81%) of a light yellow oil. Bulb-to-bulb distillation (1 torr, 75-80°C) afforded 0.349 g (31%) of 71 as a colorless oil.

NMR ($CDCl_3$) δ 1.7 (br s, 3 H), 2.0 (m, 1 H), 2.1-2.5 (m, 6 H), 4.7 (br s, 2 H), 7.4 (br s, 1 H). IR (neat) 3080, 2920, 1740, 1635, 1140 cm^{-1}.

14. Methyl perillate 72

To the acid 70 (0.266 g, 1.6 mmol) in 3 ml of methylene chloride was added excess diazomethane. The solution was concentrated in vacuo to afford 0.286 g (100%) of 72.

NMR ($CDCl_3$) δ 1.7 (br s, 3 H), 2.0 (m, 1 H), 2.1-2.5 (m, 6 H), 3.7 (s, 3 H), 4.7 (s, 2 H), 7.0 (br s, 1 H). IR (neat) 3100, 2960, 1710, 1650, 1430, 1250 cm^{-1}.

15. 3-[4-(2-Propenyl)cyclohexenyl]-3-ol-1-[5-(allyloxy)-2-hydroxy-phenyl]-prop-2-en-1-one 66

a. LiTMP method A 0.5 M solution of LiTMP in THF was prepared by adding 2.3 M nBuLi (1.7 ml, 3.9 mmol) to 2,2,6,6-tetramethylpiperidine (0.67 ml, 4 mmol) in 8 ml of THF at 0°C. After cooling the solution to -78°C, a 0.5 M solution of 4h (0.365 g, 1.9 mmol) in THF was added dropwise. The resultant mixture was stirred at -78°C for 30 minutes and then added to a precooled 0.5 M solution of 71 (0.349 g, 1.9 mmol) in THF at -78°C via a cannula under positive nitrogen pressure. The resultant solution was stirred at -78°C for 30 minutes and then quenched with excess acetic acid at -78°C. The mixture was warmed to room temperature, poured into water and extracted twice with ether. The combined ether layers were dried and concentrated in vauco. Flash chromatography using 1:10 ether/hexane afforded 0.296 g (46%) of 66 as a yellow wax. The spectral data were identical with that given below.

b. Baker-Venkataraman reaction Condensation of 4h (0.50 g, 2.6 mmol) with 71 (0.48 g, 2.6 mmol) was accomplished using the procedure recently published (85). Chromatography using 1:10 ether/hexane afforded 0.60 g (68%) of 66.

MHz 300, NMR ($CDCl_3$) δ 1.776 (s, 3 H), 2.0 (m, 1 H), 2.1-2.3 (m, 2 H), 2.4-2.5 (m, 4 H), 4.515 (d, 2 H, J = 5.2 Hz), 4.77 (d, 2 H, J = 11.6 Hz), 5.311 (d, 1 H, J = 10.2 Hz), 5.427 (d, 1 H, J = 17 Hz),

6.01-6.07 (m, 1 H), 6.232 (s, 1 H), 6.906 (d, 1 H, 9 Hz), 7.036-7.099 (m, 2 H), 7.173 (d, 1 H, J = 3 Hz), 11.712 (s, 1 H), 15.076 (s, 1 H). IR (neat) 3200-2900 (br), 2930, 1635, 1565, 1480, 1280, 1180 cm^{-1}. UV (MeOH) 226, 254 (sh), 330 (sh), 344, 374 nm. Elemental analysis calculated for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.07, H, 7.17.

16. 5,7,10-Trihydroxy-6-oxo-2-(2-propenyl)-1,2,3,4,4a,6,11,11a,12,12a-decahydronaphthacene 67

Cyclization of 66 (0.561 g, 1.65 mmol) was accomplished using the procedure developed for 53. The cyclization was complete after 13 hours at 210°C. Flash chromatography of the reaction mixture using 1:2 ether/hexane afforded 0.385 g (68%) of 67 as a viscous oil. The oil solidified upon standing overnight in a refrigerator (mp. 204-207°C).

MHz 300, NMR ($CDCl_3$) δ 1.451 (m, 1 H), 1.735 (s, 3 H), 1.926 (m, 1 H), 2.09-2.246 (m, 3 H), 2.389-2.438 (m, 3 H), 2.820 (br s, 1 H), 3.091 (dd, 1 H, J = 15.6, 4.33 Hz), 4.765 (d, 2 H, J = 10.8 Hz), 6.653 (d, 1 H, J = 8.7 Hz), 7.00 (d, 1 H, J = 8.7 Hz), 7.297 (br s, 1 H), 11.3 (s, 1 H), 14.5 (s, 1 H). C-13 NMR (D_6-acetone) 19.666, 23.175, 29.232, 29.525, 32.535, 37.357, 38.988, 39.868, 43.641, 105.751, 107.849, 114.039, 122.592, 122.675, 127.141, 144.721, 147.751, 154.785, 178.665, 193.307 ppm. IR (CCl_4) 3450, 2960, 2880, 1620, 1585, 1475,

1300, 1200 cm^{-1}. UV (MeOH) 224, 254 (sh), 270 (sh), 344, 380 (sh) nm. MS (M/e) 340. Elemental analysis calculated for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 73.97; H, 7.22.

17. 10-(t-Butyldimethylsiloxy)-5,7-dihydroxy-6-oxo-2-(2-propenyl)-1,2,3,4,4a,6,11,11a,12,12a-decahydronaphthacene 73

To the hydroquinone 67 (0.385 g, 1.13 mmol) in 4 ml of DMF was added t-butyldimethylsilyl chloride (0.195 g, 1.29 mmol) and imidazole (0.193 g, 2.83 mmol). An exothermic reaction ensued and the resultant solution was stirred at room temperature for 3 hours. The reaction mixture was added to water and ether and acidified to pH 5 with 1N HCl. The layers were separated and the aqueous layer was extracted twice with ether. The combined ether layers were washed with water, dried, and concentrated in vacuo. Flash chromatography using 1:20 ether/hexane afforded 0.3217 g (65%) of a mixture of mono and disilyl ethers as a wax.

NMR ($CDCl_3$) δ 0.02 (two s, 9 H), 1.0 (s, 14 H), 1.7 (s, 3 H), 2.2-2.5 (m, 14 H), 4.7 (br s, 2 H), 6.6 (d, 1 H, J = 7 Hz), 6.9 (d, 1 H, J = 7 Hz), 11.5 (s, 1 H), 14.0 (s, 1 H). IR ($CDCl_3$) 2920, 2860, 1610, 1575, 1460, 1250, 1010 cm^{-1}. UV (MeOH) 220, 266 (sh), 342 nm. MS, m/e (%) 511[disilyl-$(CH_3)_3C$, 22], 453 (M^+ for monosilyl, 100), 397 (28).

18. Sorbyl chloride (2,4-hexadienyl chloride) 76

Sorbic acid (5.23 g, 46.4 mmol) was added to a dry three-neck flask equipped with a reflux condenser and stir bar. To the solid sorbic acid was added oxalyl chloride (10.1 ml, 115 mmol) dropwise

with stirring. After it appeared that gas evolution had ceased, the yellow solution was refluxed for 30 minutes. It was cooled and concentrated in vacuo. Bulb-to-bulb distillation (1 torr, 70°C) afforded 5.4 g (89%) of 76 as a colorless oil.

NMR ($CDCl_3$) δ 2.0 (d, 3 H, J = 6 Hz), 5.9-6.7 (m, 3 H, H-2, H-4, H-5), 7.3-7.7 (m, 1 H, H-3). IR (neat) 3020, 1740, 1635, 1590, 1320, 1110, 1015, 985, 750 cm^{-1}.

19. 3-Hydroxy-1-[5-(allyloxy)-2-hydroxyphenyl]octa-2,4-6-trien-1-one 77

Condensation of 4h (5.0 g, 26 mmol) with sorbyl chloride (3.43 g, 26.3 mmol) in DMF was accomplished using the procedure recently published (85). Recrystallization from hot ethanol followed by repeated recrystallization of the mother liquor afforded 5.38 g (72%) of 77 as pale yellow needles (mp. 132-134°C).

MHz 300, NMR ($CDCl_3$) δ 1.884 (d, 3 H, J = 6 Hz), 4.51 (d, 2 H, J = 5.23 Hz), 5.304 (d, 1 H, J = 10.4 Hz), 5.417 (dd, 1 H, J = 17.5, 1.1 Hz), 5.93 (d, 1 H, J = 15.17 Hz), 6.006-6.082 (m, 1 H), 6.099 (s, 1 H), 6.181-6.240 (m, 2 H), 6.902 (d, 1 H, J = 8.96 Hz), 7.081 (dd, 1 H, J = 8.92, 2.8 Hz), 7.129 (d, 1 H, J = 2.8 Hz), 7.214-7.297 (m, 1 H), 11.820 (s, 1 H), 14.662 (s, 1 H). C-13 NMR ($CDCl_3$) 18.661, 70.166, 96.309, 113.477, 117.639, 119.005, 119.460, 123.427, 124.142, 130.710, 133.571, 138.969, 140.790, 151.065, 157.178, 175.647, 195.286 ppm. IR ($CDCl_3$) 3200-2800 (br), 1615, 1530, 1470, 1420, 1250 cm^{-1}. UV (MeOH) 224 (sh), 260 (sh), 284, 370, 396 nm. MS, m/e (%) 286 (9), 245 (6), 177 (13), 95 (100). Elemental analysis calculated for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.52; H, 6.48.

20. 4,5,8-Trihydroxy-10-oxo-2-(1-propenyl)-1,2,3,9,9a,10-hexahydroanthracene 75

Cyclization of 77 (2.0 g, 7.0 mmol) was accomplished using the procedure developed for 53. The cyclization was complete after 10 hours at 210°C. Flash chromatography of the reaction mixture using 1:2 ether/hexane afforded 1.314 g (66%) of 75. An analytical sample was crystallized from warm benzene as pale yellow plates (mp. 181-182°C).

MHz 300, NMR ($CDCl_3$) δ 1.645 (d, 3 H, J = 3.6 Hz), 1.886-1.944 (m, 1 H), 2.236 (br t, 1 H, J = 14.6 Hz), 2.355 and 2.412 (two br s, 1 H), 2.644-2.8 (m, 4 H), 3.067 (dd, 1 H, J = 15.37, 4.62 Hz), 4.53 (s, 1 H), 5.469 (m, 2 H), 6.694 (d, 1 H, J = 9 Hz), 6.915 (d, 1 H, J = 9 Hz), 11.539 (s, 1 H), 14.703 (s, 1 H). C-13 NMR (D_6-acetone) 16.401, 27.506, 32.125, 33.484, 33.937, 106.338, 114.089, 115.365, 122.781, 123.649, 126.759, 132.001, 144.489, 154.661, 176.935, 192.060 ppm (two carbon absorptions overlapping). IR ($CDCl_3$) 3380, 2910, 1610, 1570, 1460, 1310, 1270, 1200 cm^{-1}. UV (MeOH) 220 (sh), 250, 268 (sh), 340, 380 (sh) nm. Elemental analysis calculated for $C_{17}H_{18}O_4$: C, 7131; H, 6.34. Found: C, 71.17; H, 6.27. High resolution mass spectrum for $C_{17}H_{18}O_4$ requires 286.12051; measured 286.12023.

21. 8-(t-Butyldimethylsiloxy)-4,7-dihydroxy-10-oxo-2-(1-propenyl)-1,2,-3,9,9a,10-hexahydroanthracene 78

Monosilylation of 75 (0.120 g, 0.42 mmol) with t-butyldimethylsilyl chloride (0.077 g, 0.51 mmol) and imidazole (0.068 g, 1.0 mmol)

was accomplished using the procedure developed for 73. Chromatography using 1:20 ether/hexane afforded 0.148 g (88%) of 78 (mp. 98-99°C).

NMR ($CDCl_3$) δ 0.20 (s, 6 H), 1.0 (s, 9 H), 1.7 (br d, 3 H, J = 4 Hz), 1.8-3.2 (m, 8 H), 5.5 (br s, 2 H), 6.63 (d, 1 H, J = 9 Hz), 6.93 (d, 1 H, J = 9 Hz), 12.17 (s, 1 H), 15.3 (s, 1 H). IR (neat) 3100-2900 (br), 1605, 1575, 1460, 1255, 1200, 820 cm^{-1}. UV (MeOH) 220, 264, 272, 340, 370 (sh) nm.

22. 8-(t-Butyldimethylsiloxy)-5,10-dihydroxy-4-oxo-2-(1-propenyl)-1,2,3,4-tetrahydroanthracene 79

Pyridine (0.07 ml, 0.87 mmol) was added to a red solution of phenylsilenyl chloride (0.127 g, 0.66 mmol) in 1 ml of methylene chloride at 0°C. The resultant pale yellow solution was stirred at 0°C for 15 minutes. To this was added 78 (0.250 g, 0.625 mmol) in 1 ml of methylene chloride dropwise and stirring was continued for 1 hour at 0°C. With a pipette, the mixture was washed twice with 6 ml of 1N HCl. The solution was recooled to 0°C and 1 ml of 30% hydrogen peroxide was added. After 1 hour at 0°C the mixture was washed twice with water, dried, and concentrated in vacuo. Column chromatography using 1:20 ether/hexane followed by flash chromatography with 1:20 ether/hexane afforded 0.054 g (22%) of 79 as a wax and 0.076 g (30% recovery) of 78. An analytical sample was crystallized from hexane (mp. 142-144°C).

MHz 300, NMR ($CDCl_3$) δ 1.655 (d, 3 H, J = 5.8 Hz), 2.621 (d, 1 H, J = 11 Hz), 2.793-2.856 (m, 3 H), 3.056 (d, 1 H, J = 11 Hz), 5.5-5.59 (m, 2 H), 6.684 (d, 1 H, J = 8.4 Hz), 6.931 (d, 1 H, J = 8.4 Hz), 7.310 (s, 1 H), 9.387 (s, 1 H), 16.0 (s, 1 H). C-13 NMR ($CDCl_3$) -4.245, 17.916, 18.407, 25.915, 36.578, 37.620, 44.231, 109.798, 110.431, 112.294, 113.195, 120.120, 125.788, 131.871, 132.895, 136.047, 143.203, 152.028, 165.214, 204.502 ppm. UV (MeOH) 220, 268, 334, 420 nm. Elemental analysis calculated for $C_{23}H_{30}O_4Si$: C, 69.31; H, 7.59. Found: C, 69.41; H, 7.38. High resolution mass spectrum for $C_{23}H_{30}O_4Si$ requires 398.1913; measured 398.1913.

23. 4a-Bromo-8-(t-butyldimethylsiloxy)-5-hydroxy-4,10-dioxo-3-(1-propenyl)-1,2,3,4,4a,9,9a,10-octahydroanthracene 80

To a solution of 78 (0.3196 g, 0.80 mmol) in 5 ml of methylene chloride was added triethylamine (0.23 ml, 1.68 mmol) at 0°C. After stirring at 0°C for 15 minutes a bromine (0.8 ml of a 1 M solution in methylene chloride, 0.8 mmol) was added dropwise. The resultant light green solution was stirred at 0°C for 3 hours. The mixture was poured into water containing a pinch of sodium sulfite, shaken, acidified to pH 5 with 1N HCl, and extracted twice with methylene chloride. The combined methylene chloride layers were dried and concentrated in vacuo to give 0.3616 g of the crude bromoketone 80 as a viscous oil.

NMR ($CDCl_3$) δ 0.2 (s, 6 H), 1.0 (s, 9 H), 1.7 (br d, 3 H, J = 5 Hz), 1.8-2.2 (m, 3 H), 2.6-3.2 (m, 5 H), 5.5 (m, 2 H), 6.77 (d, 1 H, J = 9 Hz), 7.07 (d, 1 H, J = 9 Hz), 11.35 (s, 1 H). IR (neat) 3200-2900 (br), 1735, 1720, 1680, 1635, 1580, 1460, 1310, 1250, 1190 cm^{-1}.

24. Attempted dehydrobromination of 80

The bromoketone 80 (0.3616 g, 0.75 mmol) was dissolved in 4 ml of freshly distilled collidine and deoxygenated under reduced pressure. A dry reflux condenser was added and the mixture was plunged into a silicon oil bath preheated to 190°C and the mixture was refluxed for 15 minutes. The dark colored mixture was cooled and poured into ether, washed three times with 2N HCl, washed with water, dried, and concentrated in vacuo to give 0.340 g of a black oil. Column chromatography using 1:20 ether/hexane gave 0.124 g (41%) of 78 and 0.0386 g (15%) of 79.

25. 10-Hydroxy-4-oxo-2-(1-propenyl)-1,2,3,4-tetrahydroanthracene-5,8-dione 81

To a suspension of 75 (0.522 g, 1.83 mmol) in 7.2 ml of benzene was added DDQ (0.91 g, 4 mmol) and the mixture was stirred at room temperature for 2 hours. The mixture was diluted with 40 ml of methylene chloride and filtered through celite to give a black solid. The solid was dissolved in ethyl acetate and quickly passed through silica gel using 1:1 ether hexane to give 0.641 g of a black solid.

NMR ($CDCl_3$) δ 1.7 (br d, 3 H, J = 5 Hz), 2.7-3.1 (m, 5 H), 5.5 (m, 2 H), 6.9 (s, 2 H), 7.4 (s, 1 H), 13.7 (s, 1 H).

In a separate experiment, 75 (0.286 g, 0.83 mmol) was refluxed with DDQ (0.4145 g, 1.83 mmol) in benzene for 24 hours. Workup as above followed by chromatography using 1:1 ether/hexane gave 0.026 g (10%) of pure 81 as a dark brown solid.

MHz 300, NMR ($CDCl_3$) δ 1.69 (d, 3 H, J = 6 Hz), 2.57-2.67 (m, 1 H), 2.847-2.926 (m, 3 H), 3.1-3.173 (m, 1 H), 5.484 and 5.554 (two m, 2 H), 6.922 (s, 1 H), 7.446 (s, 1 H), 13.7 (s, 1 H). C-13 NMR ($CDCl_3$) 17.768, 36.946, 37.243, 45.205, 116.920, 117.474, 121.916, 126.666, 131.836, 136.376, 136.762, 140.878, 151.785, 163.287, 184.284, 202.236 ppm (two carbon absorptions overlapping). IR ($CDCl_3$) 3600-3200 (br), 1670, 1600 cm^{-1}. UV (MeOH) 232, 248, 338, 390 nm. MS, m/e (%) 282 (100), 254 (16), 240 (62), 226 (73), 214 (61).

26. 5-Hydroxy-4,6,11-trioxo-2-(1-propenyl)-1,2,3,4,6,6a,7,10,10a,11-decahydronaphthacene 82

To a solution of crude 81 (0.144 g, 0.25 mmol) in 3 ml of ethanol was condensed butadiene at -78°C. The mixture was warmed to room temperature and plunged into an oil bath heated to 100°C. The mixture was heated for 1 hour. Chromatography using 1:1 ether/hexane gave 0.082 g of 82.

NMR ($CDCl_3$) δ 1.7 (d, 3 H, J = 5 Hz), 2.0-3.2 (m, 13 H), 5.5 (br s, 2 H), 5.77 (br d, 2 H, J = 8 Hz), 7.4 (s, 1 H), 13.5 (s, 1 H). MS, m/e (%) 336 (11), 284 (52), 228 (100).

27. 5-Hydroxy-4-trimethylsiloxy-9,10-dioxo-1,4,4a,9,9a,10-hexahydro- ene anthracene 85

To a solution of juglone (0.039 g, 0.22 mmol) in 0.22 ml of benzene was added 1-trimethysiloxybutadiene (0.27 ml, 1.54 mmol). The solution was stirred at room temperature for 2 hours and concentrated in vacuo. The residue was dissolved in ether and washed with water followed by saturated sodium bicarbonate. The ether layer was dried and concentrated in vacuo. The adduct was quickly passed through silica gel to give 0.0589 g (84%) of 85.

MHz 300, NMR ($CDCl_3$) δ 2.20 (s, 9 H), 2.67 (dm, 1 H, J = 18 Hz), 3.72 (bdd, 1 H, J = 19.4 Hz), 3.78-3.9 (m, 2 H), 4.90 (m, 1 H), 6.25-6.50 (m, 2 H), 7.644 (d, 1 H, J = 8 Hz), 8.000-8.112 (m, 2 H), 12.7 (s, 1 H).

28. 1-Hydroxy-9,10-anthraquinone 87

a. Preparation with potassium carbonate/methanol To a solution of 84 (0.060 g, 0.21 mmol) in 4 ml of methanol was added potassium carbonate (0.0388 g, 0.28 mmol) at 0°C. The mixture was warmed to room temperature and stirred for 30 minutes. The mixture was acidified with 1N HCl, poured into water, and extracted twice with methylene chloride. The combined methlene chloride layers were washed with water, dried, and concentrated in vacuo. Chromatography using 1:4 ether/hexane gave 0.0303 g (64%) of 87 (mp. 199-200°C (dec.)).

MHz 300, NMR (D_6-acetone) δ 7.34 (dd, 1 H, J = 6.73, 2.62 Hz), 7.767-7.805 (m, 2 H), 7.908-7.962 (m, 2 H), 8.236-8.321 (m, 2 H), 12.548 (s, 1 H). MS, m/e (%) 224 (100), 196 (15), 168 (29), 139 (41), 69 (68).

b. Preparation with triethylamine To a solution of 85 (0.058 g, 0.18 mmol) in 3 ml of benzene was added triethylamine (0.05 ml, 0.36 mmol). The mixture was stirred at room temperature for 12 hours. The mixture was concentrated in vacuo to give 0.0376 g (94%) of 87.

29. 7-Acetoxy-5-hydroxy-4,6,11-trioxo-2-(1-propenyl)-1,2,3,4,6,6a,-7,10,10a,11-decahydronaphthacene 88

To a solution of 81 (0.125 g, 0.44 mmol) and 1-acetoxybutadiene (0.37 ml, 3.12 mmol) in a solvent system of 4 ml methylene chloride/3 ml acetonitrile was added 2 drops of boron trifluoride etherate. The mixture was stirred at room temperature for 12 hours. The reaction was quenched with 0.5 ml of methanol and concentrated in vacuo. Chromatography using 1:1 ether/hexane gave 0.071 g of a dark foam.

NMR (D_6-acetone) δ 1.5 (s, 3 H), 1.7 (br s, 3 H), 2.0-3.2 (m, 10 H), 5.5 (br s, 2 H), 6.0 (br m, 2 H), 7.4 (s, 1 H). MS, m/e (%) 394 (500.0x), 376 (500.0x), 368 (500.0x), 351 (500.0x), 228 (100), 200 (45).

30. 4-Hydroxy-2-(1-propenyl)-5,6,11-trioxo-1,2,3,5,6,6a,7,10,10a,-11,12,12a-dodecahydronaphthacene 89

To a dry culture tube was added 75 (0.103 g, 0.36 mmol), silver(I) oxide (0.333 g, 1.44 mmol), and 3 ml of benzene. The mixture was cooled to -78°C under nitrogen and a large excess of butadiene was

condensed into the tube. A teflon-lined cap was screwed on and the mixture was warmed to room temperature. The tube was covered with aluminum foil and stirred at room temperature for 2 days. Dilution of the mixture with methylene chloride and filtration through celite afforded 0.085 g of 89.

NMR ($CDCl_3$) δ 1.7 (br s, 3 H), 1.8-3.3 (m, 14 H), 5.42 (br s, 2 H), 5.72 (br d, 2 H, J = 8 Hz), 15.4 (s, 1 H).

31. 5-Hydroxy-4-oxo-2-(1-propenyl)-1,2,3,4-tetrahydronaphthacene-6,11-dione 83

a. Preparation with ethanolic potassium hydroxide To a solution of the crude adduct 89 (0.085 g, 0.25 mmol) in 4 ml of warm 95% ethanol was added 2 ml of 5% ethanolic potassium hydroxide. Air was bubbled through the solution with stirring for 17 hours. The deep purple mixture was poured into water and ether. The solution was acidified with 6N HCl and the resultant red organic layer was removed and washed twice with saturated sodium chloride. The combined aqueous layers were extracted with ether. The organic layers were combined, dried, and concentrated in vacuo. Chromatography using 1:1 ether/hexane afforded 0.029 g (30% from 75) of 83 (mp 205° (dec)).

MHz 300, MNR ($CDCl_3$) δ 1.70 (d, 3 H, J = 5.8 Hz), 2.575-2.663 (m, 1 H), 2.850-2.957 (m, 3 H), 3.186 (br d, 1 H, J = 13 Hz), 5.4-5.63 (m, 2 H), 7.670 (s, 1 H), 7.802 (br t, 2 H, J = 6.5 Hz), 8.24 (br d, 1 H, J = 7.10 Hz), 8.302 (br d, 1 H, J = 7.04 Hz), 13.994 (s, 1 H).

C-13 NMR ($CDCl_3$) 17.857, 36.913, 37.423, 45.560, 117.350, 118.210, 122.717, 126.400, 126.932, 127.199, 131.992, 132.607, 133.931, 134.080, 134.567, 137.179, 152.482, 164.096, 182.277, 184.183, 200.436 ppm. UV (MeOH) 206, 250, 274 (sh), 394 nm. MS, m/e (%) 332 (81), 290 (32), 275 (60), 264 (100), 152 (43). Elemental analysis calculated for $C_{21}H_{16}O_4$: C, 75.89; H, 4.85. Found: C, 75.50; H, 4.81.

b. Preparation with triethylamine The purified adduct 89 (0.045 g, 0.13 mmol) was dissolved in 2 ml of benzene and 2 drops of triethylamine was added. The mixture was stirred at room temperature for 2 hours. The mixture was poured into water, acidified with 1N HCl, and extracted twice with ether. The combined ether layers were dried and concentrated in vacuo. Chromatography using 1:2 ether/hexane afforded 0.016 g (37%) of 83.

c. Preparation with DDQ from 82 To the adduct 82 (0.076 g, 0.23 mmol) was added DDQ (0.104 g, 0.46 mmol) and the mixture was stirred in benzene at room temperature for 15 hours. The mixture was drowned with methylene chloride and filtered through celite. Chromatography with 1:1 ether/hexane gave 0.048 g of a mixture of 83 and 81. Pertinent data are: MHz 300, NMR ($CDCl_3$) δ 6.927 (s, 1 H), 7.438 (s, 1 H), 7.648 (s, 1 H), 7.8-7.9 (m, 2 H), 8.22 (d, 1 H, J = 7.3 Hz), 8.29 (d, 1 H, J = 7.3 Hz). MS, m/e (%) 332 (19), 282 (35), 228 (100).

32. 5,8-(Di-t-butyldimethylsiloxy)-4-hydroxy-10-oxo-2-(1-propenyl)-1,2,3,9,9a,10-hexahydroanthracene 91

Disilylation of 75 (0.62 g, 2.17 mmol) with t-butyldimethylsilylchloride (1.18 g, 7.83 mmol) and imidazole (1.11 g, 16.3 mmol) in 6 ml of DMF was accomplished using the procedure developed for 73. Chromatography using 1:20 ether/hexane afforded 0.954 g (95%) of 91 as a viscous oil.

NMR ($CDCl_3$) δ 0.2 (s, 18 H), 1.0 (s, 27 H), 1.7 (d, 3 H, J = 5 Hz), 2.0-2.9 (m, 7 H), 3.15 (dd, 1 H, J = 13, 3 Hz), 5.5 (br s, 2 H), 6.63 (d, 1 H, J = 9 Hz), 6.87 (d, 1 H, J = 9 Hz), 16.3 (s, 1 H). C-13 NMR ($CDCl_3$) -4.38, -4.236, -4.165, 17.889, 18.288, 18.542, 25.848, 26.008, 26.174, 28.593, 30.603, 33.678, 35.166, 36.807, 108.584, 120.156, 123.621, 123.983, 124.948, 132.842, 133.852, 145.686, 150.151, 184.256, 184.770 ppm. IR (neat) 2940, 2840, 1575 (br), 1450, 1240 cm^{-1}. MS, m/e (%) 473 (1), 457 (31), 75 (100).

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