Diyl Trapping and Electroreductive Cyclization Reactions

R. Daniel Little

Department of Chemistry, University of California, Santa Barbara, Santa Barbara, California 93106

Received July 28, 1995 (Revised Manuscript Received October 3, 1995)

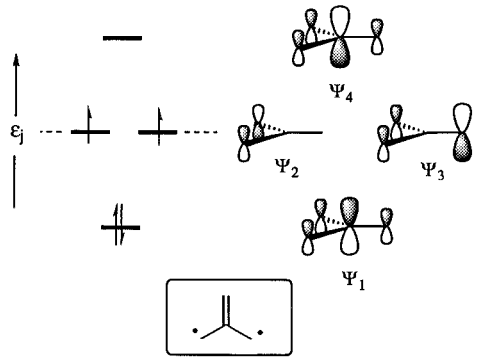
Contents

Dan Little was born and raised in Superior, Wisconsin. He was educated in Superior (University of Wisconsin—Superior, B.S.); in Vermillion, South Dakota (NSF URP programs at the University of South Dakota); at Argonne National Laboratory (undergraduate research program); in Madison, Wisconsin (University of Wisconsin, Ph.D.); and in New Haven, Connecticut (Yale, postdoctoral associate). He is a past recipient of an A. P. Sloan Fellowship, has served as an NIH study section member, was a visiting professor at the University of British Columbia, and is now a professor and vice-chair of the Chemistry Department at University of California, Santa Barbara. A few interests outside of chemistry include music, live theatre, and hiking in the Sierra mountain range. The photo is one of Dan (right) and his son, Jon, atop Mt. Whitney in late July of 1995.

Diyl Trapping Reactions

Introduction

The simple hydrocarbon called trimethylenemethane (TMM, **1**) has been of interest to theoreticians and experimentalists for many years.[1] Simple Hückel molecular orbital calculations indicate the presence of a degenerate pair of non-bonding molecular orbitals, Ψ_2 and Ψ_3, with the shape illustrated below. Clearly, singlet and triplet electronic configurations are possible, and as we shall see, the corresponding singlet and triplet states play a significant role in the chemistry of TMM derivatives.

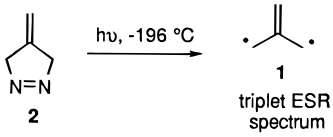


trimethylenemethane (TMM, **1**)

The parent diradical (diyl) was first generated and studied by Dowd in 1966.[2] Thus, irradiation of 4-methylenepyrazoline (**2**) at 77 K afforded TMM. An ESR spectrum consistent with that of a triplet species was observed. Subsequent efforts demonstrated the triplet to be the ground state.

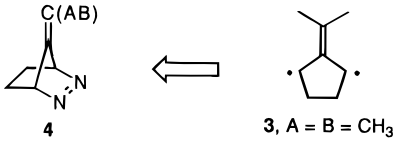
In principle, cycloaddition between TMM and an alkene could lead to the formation of a five-membered ring. Unfortunately, this is not a synthetically viable process. The singlet diyl rapidly closes to form methylenecyclopropane. Since the early efforts which

0009-2665/96/0796-0093$25.00/0



appeared in the 1960s,[3] however, there has been much success in accomplishing a similar transformation by indirect means, *viz.*, using methods which do not involve the parent diyl. Particularly notable contributions come independently from the groups of Binger and Trost, who have developed exceptionally useful methods involving organometallics.[4]

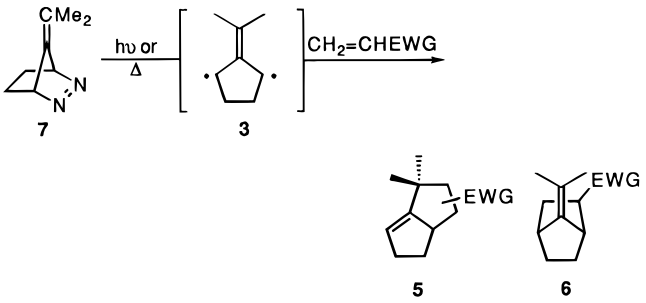
In 1971, Berson and co-workers reported the generation and properties of 2-isopropylidene-1,3-diyl (**3**).[5] This system dimerizes and in so doing gives rise



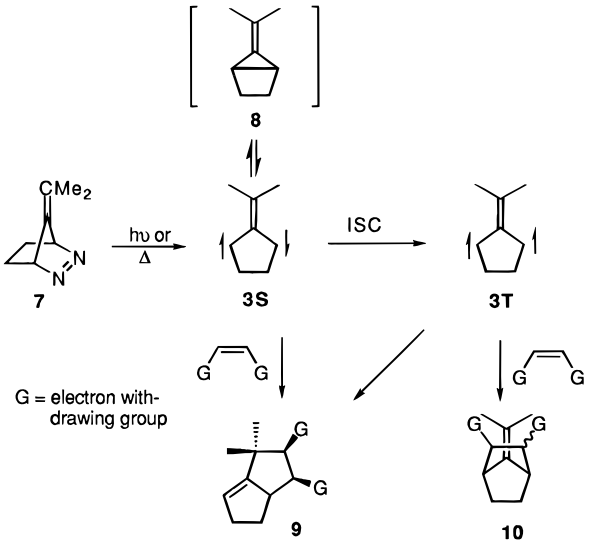
to chemically induced dynamic nuclear polarization (CIDNP) emission signals in the ^{1}H NMR spectrum of the dimers. In an accompanying paper, Closs reported the radical pair theory of CIDNP and concluded that the process involves either a singlet (S) plus triplet (T) or a T plus T combination.[6] Later, Berson and Platz demonstrated the latter to be true.[7]

Diyls are generated either thermally or photochemically from bicyclic azo compounds such as **4**. The temperature required for extrusion of nitrogen varies as a function of the substituents A and B. The most labile system of which we are aware is one where A = B = OCH_3. Here, the loss of nitrogen is readily apparent even at −20 °C.[8] Fortunately, most systems are easy to handle, requiring heating at reflux to facilitate formation of the diyl. A variety of solvents can be used, most often acetonitrile or THF. Photogeneration of the diyl is also readily accomplished using a light filter which allows irradiation of the low-intensity UV maximum which appears near 340 nm.

The isopropylidene diyl **3** can be intercepted by a number of trapping agents, referred to as diylophiles. Diyl **3** behaves as an electron rich system and preferentially undergoes cycloaddition to electron deficient trapping agents to afford fused and bridged adducts, **5** and **6**. Fortunately, the fused system can be generated selectively.[9] This prospect served as the impetus for our initial studies, those designed to explore the intermolecular diyl trapping reaction as a means of accessing systems containing one or more five-membered rings.



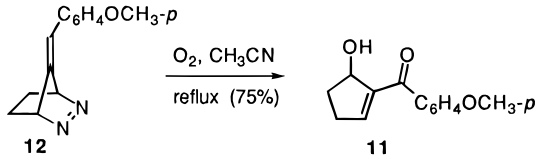
Scheme 1



Much of our work is predicated on pioneering mechanistic studies emanating from the Berson group. Their so-called "cascade mechanism" is one where a thermal or photochemically promoted extrusion of nitrogen leads to the singlet diyl **3S**[10] (Scheme 1). At temperatures above −60 °C, it interconverts rapidly with housane **8**, and also undergoes intersystem crossing to the ground state triplet diyl, **3T**. When the concentration of the diylophile is high and it is very reactive, *e.g.*, with maleic anhydride, then the singlet diyl **3S** can be trapped to selectively afford fused adducts **9**. The relative reactivity of a series of diylophiles has been determined with respect to both the singlet and triplet diyl.[11] For the singlet, the reactivity drops off in the following order: maleic anhydride > maleonitrile > fumaronitrile > dimethyl fumarate > acrylonitrile > methyl acrylate > dimethyl maleate.

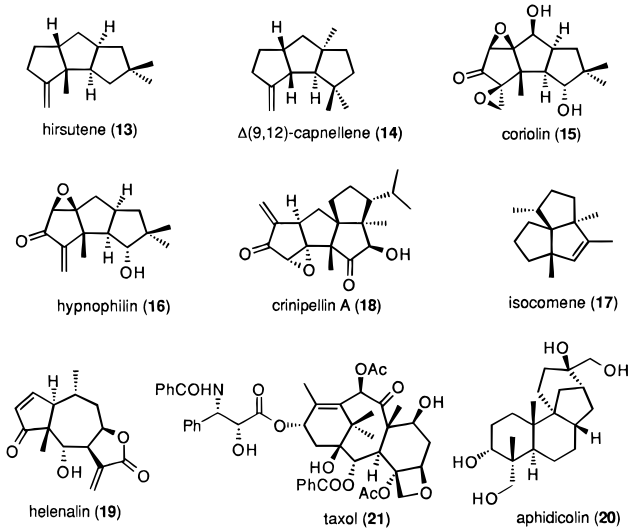
As the diylophile concentration is reduced, the rate of cycloaddition to the singlet decreases, and intersystem crossing becomes competitive. Like triplet nitrenes and carbenes,[12] the triplet diyl **3T** is not very discriminating, affording both fused and bridged products, **9** and **10**. And, unlike cycloaddition involving the singlet where the geometry of the diylophile is maintained (*e.g.*, with dimethyl maleate, G = CO_2CH_3), triplet processes are essentially stereorandom.

The triplet diyl reacts with molecular oxygen.[10, 13] Berson and co-workers used this discovery to quench the formation of triplet-derived cycloadducts. We have also used this protocol in conjunction with several of the examples which are discussed later. The nature of the oxygen-derived adducts varies depending upon whether the substituent appended to the diyl is an alkyl or an aryl group. The process is quite efficient in the latter case, affording the crystalline keto alcohol **11**, for example, in a 75% isolated yield.[14] The reaction with oxygen is so facile, in fact, that in a competition experiment conducted using diazene **12**, it even beats out cycloaddition to the very reactive diylophile dimethyl fumarate. None of the cycloadduct with fumarate was detected.



Diyl Trapping Reactions en Route to Naturally Occurring Materials

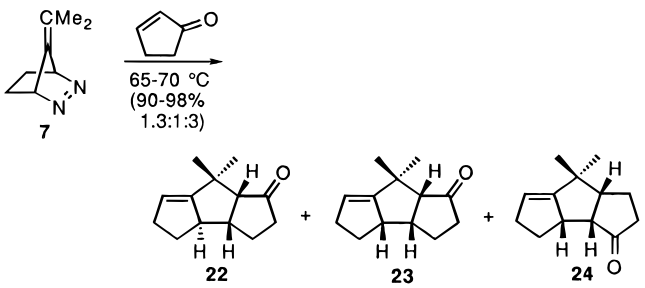
For some time now, we have been interested in the possibility of using the diyl trapping reaction as a key step in the assembly of natural products. Our early efforts focused upon the possibility of constructing systems containing three or more five-membered rings including, for example, the linearly fused tricyclopentanoids, such as hirsutene (**13**), Δ(9,12)-



capnellene (**14**), coriolin (**15**), and hypnophilin (**16**), as well as angularly fused systems like isocomene (**17**), and those with mixed linear and angular architectures, like crinipellin A (**18**). Recently, we have begun to focus our attention upon other frameworks, including, for example, that of helenalin (**19**), aphidicolin (**20**), and taxol (**21**). Our efforts to apply the diyl trapping reaction to the assembly of a number of these systems is described. Rather than discussing the complete details of each synthesis, we have elected to focus on the cycloaddition process.

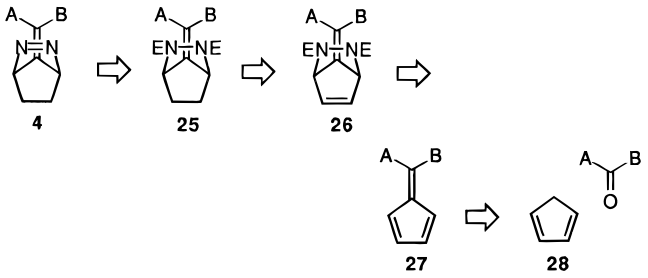
Entry to the Linearly Fused Tricyclopentanoids

The *inter*molecular diyl trapping reaction provides a very direct and simple route to the linearly fused tricyclopentanoid ring system. As illustrated, heating the dimethyl diazene **7** to 70−75 °C in the presence of an excess of cyclopentenone afforded a 90−98% yield of cycloadducts **22**−**24**.[15] Unfortunately, the process displayed essentially no stereo- or regioselectivity, the ratio of cis-syn to cis-anti adducts being a modest 3:1. What is interesting, however, is the fact that the cis-syn isomers dominate. Later, we will see that the cis-anti adduct invariably corresponds to the major product of an *intra*molecular diyl trapping reaction.



Preparation for Cycloaddition

The diyl trapping reaction depends upon the availability of bicyclic azo compounds to serve as diyl precursors. A basic approach to these systems is depicted below. It consists of fulvene formation, Diels-Alder cycloaddition, selective saturation of the Δ-5,6 π bond of **26**, and conversion of the biscarbamate to the diazene linkage. Most often, this chemistry is accomplished in a routine manner. However, both the fulvene-forming step and the final conversion to the diazene linkage required attention before we deemed the methodology suitable for the range of systems desired for study. The following two sections describe some of our efforts to improve both steps.



Fulvene Formation

The standard Thiele method for the construction of fulvenes calls for condensation of an aldehyde or ketone with cyclopentadiene (CpH) and in the presence of an alkoxide.[16] While this is a straightforward procedure, the efficiency is limited by competing aldol condensations. For intramolecular diyl trapping reactions, the aldehyde component is often quite valuable, requiring several steps for its assembly. Consequently, we needed to have access to a more general protocol to avoid wasting valuable material.

In 1963, Freisleben reported an efficient route to fulvenes calling for the use of CpH, the carbonyl component, and diethylamine.[17] As illustrated below, Büchi and co-workers used this methodology in an elegant approach to the spiro[4.5]decane ring system of the spirovetivanes, and a total synthesis of racemic β-vetivone (**32**).[18]

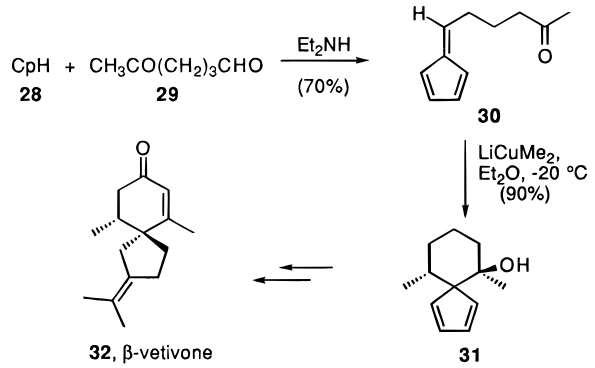
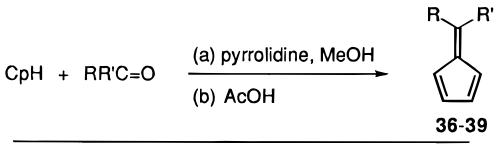
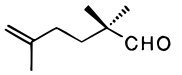
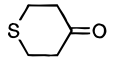


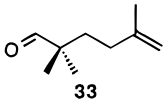
Table 1

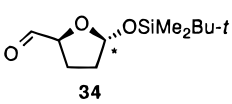


RR'CO	fulvene	time	yield (%)
$(CH_3)_2CHCHO$	**36**	15 min	98
	**37**	17 h	59
	**38**	15 min	69
	**39**	2.25 h	95

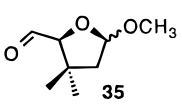
2 mmol RR'CO, 5 mmol CpH, 3 mmol pyrrolidine in 2 mL of methanol; TLC analysis; 3.2 mmol AcOH.

We too found the methodology to be exceptionally versatile, allowing access to a wide range of fulvenes. However, a few systems proved problematic. For example, the hindered aldehyde **33**, a substance


33



34

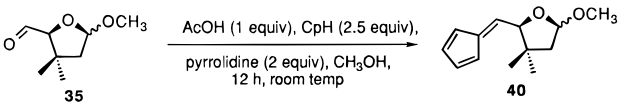


35

needed *en route* to the marine natural product Δ(9,12)-capnellene (**14**), reacted very slowly and afforded only a modest yield of the desired fulvene. Aldehydes **34** and **35** unfortunately also proved troublesome. The former substance was designed to be used in a study of asymmetric induction in the diyl trapping reaction, the latter as an important intermediate *en route* to both coriolin (**15**) and hypnophilin (**16**).

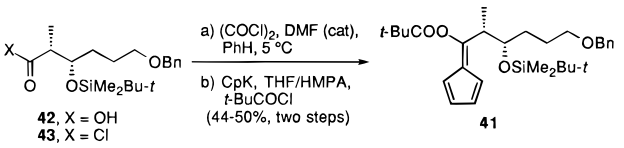
Motivated by these difficulties, we devised what turns out to be an effective variant of the Freisleben procedure, calling simply for the use of pyrrolidine in methanol, in place of diethylamine.[19] Significantly improved yields and rather dramatically increased reaction rates were observed in a number of instances. For example, a 98% yield of 6-isopropylfulvene (**36**) was isolated after only 15 min using pyrrolidine, while only 40% was obtained after 2.5 h using diethylamine. Also, the hindered fulvene **37**, needed in the capnellene synthesis, was isolated in a 59% yield (not optimized) after 17 h at room temperature using pyrrolidine, while after 24 h, *none* was obtained using diethylamine. A few additional examples are provided in Table 1. Erden and coworkers have recently further explored the scope and limitations of the methodology, comparing it with other methods and extending its applicability to the use of α,β-unsaturated carbonyl compounds and aldols.[20]

One additional example merits comment. As indicated above, aldehyde **35** was designed to serve as an intermediate *en route* to the natural products coriolin (**15**) and hypnophilin (**16**). Using the protocol described above, we could never obtain yields of the requisite fulvene **40** which were greater than 40−45%. Since fulvene formation was slower in this instance than any of several other cases that were examined, we were able to detect the formation of an intermediate (imine?) which slowly transformed to **40**. However, prolonged reaction times also led to the slow decomposition of the fulvene, so that it proved advantageous to work up the reaction after 24 h. While attempting to improve the yield, we discovered that the rate of fulvene formation increased dramatically when acetic acid was added directly to the reaction mixture. These conditions are reminiscent of those often associated with Knoevenagel condensation reactions. Thus, after only 12 h at room temperature in the presence of 1 equiv of AcOH, we were able to obtain fulvene **40** in a 55% yield, over two steps (Swern and fulvene formation).



35 **40**

We have also devised a general method which allows the preparation of 6-(silyloxy)-, and 6-(acyloxy)fulvenes.[21] For example, we were able to construct **41**, a system needed in conjunction with the phorbol ester analog study described below, by treating acid chloride **43** with CpK and 5 equiv of pivaloyl chloride at temperatures between −32 and −42 °C.

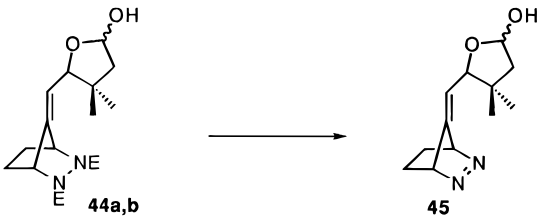


42, X = OH
43, X = Cl
41

Conversion to the Diazene

Of the methods which exist for the conversion of a biscarbamate to an azo linkage, few are sufficiently general to meet the multitude of uses to which azo compounds are called.[22] We have found two procedures to be reasonably general, though not without occasional difficulty. As usual, determination of the preferred route often requires exploration, so that the specific requirements of the system being assembled can be taken into account. At the present time, we are exploring alternative methodologies which appear promising.[23] The results will be disclosed elsewhere.

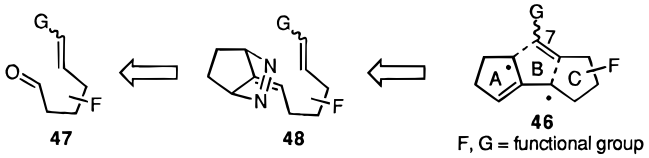
The use of bis(2,2,2-trichloroethoxy) azodicarboxylate as a dienophile in the Diels-Alder reaction with a fulvene is advantageous in that the reaction occurs more rapidly than those using, for example, DEAD or its dimethyl analog.[24] Once the Δ-5,6 π bond of the [2.2.1] adduct is reduced, either *via* selective atmospheric pressure hydrogenation or by using diimide generated *in situ*, then the conversion to the azo linkage can conveniently be carried out in one of three ways: (a) using zinc or zinc-copper couple,[25] (b) *via* an electrochemically promoted reductive cleavage,[22] or (c) *via* saponification using hydroxide or anhydrous hydroxide.[26] Treatment of the resulting intermediate with potassium ferricyanide, or any of a variety of other oxidants, affords the azo unit. While the oxidation with ferricyanide invariably works, it is occasionally accompanied by the formation of emulsions.



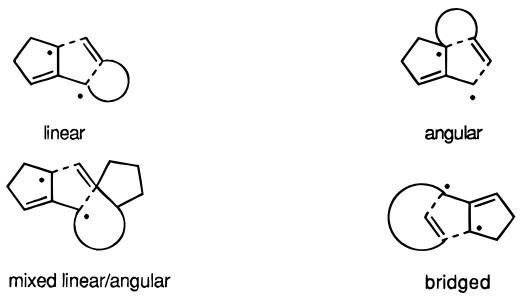
E	conditions	yield (%)
a, $CO_2CH_2CCl_3$	a) -1.7V, DMF, $LiClO_4$ b) $K_3Fe(CN)_6$, H_2O	73
b, CO_2CH_3	a) KOH, EtOH, reflux, 1.5 h b) $K_3Fe(CN)_6$, H_2O, 0 °C	76-86

Intramolecular Variant

It soon became clear that many of the problems inherent to the intermolecular diyl trapping reaction could be solved in a natural manner using an intramolecular variant. For example, the relationship between B- and C-ring substituents in tricyclopentanoids is determined by their relationship to one another on the tether and diylophile. The functionality appended to the pro-C_7 carbon, a site which is often functionalized in natural products, is determined by that appended to the diylophile. Following the general route described above for the synthesis of bicyclic diazenes, the major task in preparing for an intramolecular diyl trapping reaction becomes one of constructing the functionalized unit **47**, or its synthon.

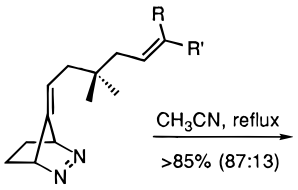


When generalized in the manner portrayed below, it is clear that the intramolecular cycloaddition pathway could provide access to the carbon framework of each of the natural products illustrated in Scheme 1.

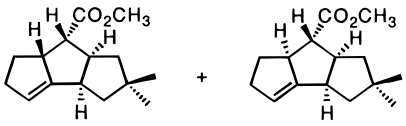


Initial Studies

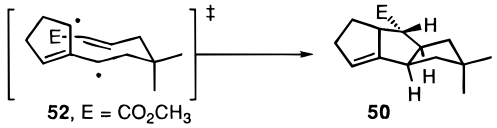
The first systems to be examined were diazenes **49a** and **49b**, the former bearing an *E*- and the latter a *Z*-substituted diylophile.[27] Diazene **49a** was heated at reflux in acetonitrile. As with other diyl trapping reactions, the course of the process was monitored by TLC, reflux being discontinued when the diazene was consumed. Workup is invariably very easy, calling simply for the removal of solvent, followed by the use of standard separation techniques. In this instance, cycloadducts **50** and **51** were obtained in an 87:13 ratio and a combined isolated yield of >85%. The cis-anti adduct **50** predominated, as is customary for intramolecular cycloaddition. This is in contrast to the outcome of the intermolecular diyl trapping reaction of **7** with cyclopentenone which was discussed previously; there, the cis-syn adducts formed preferentially.[15]



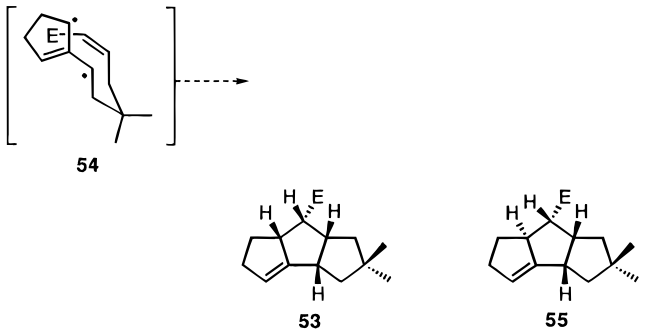
49a, R = H, R' = CO_2CH_3
49b, R = CO_2CH_3, R' = H



To rationalize the ring junction stereochemical preference, we developed a model which views the cycloaddition as a kinetically controlled process, where the lowest energy transition state corresponds to the extended pseudochair formulation, **52**, illustrated below.



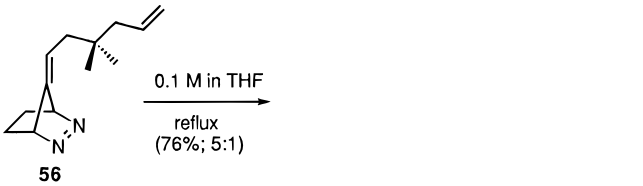
We initially postulated the existence of bonding secondary orbital overlap interactions between the carbonyl carbon of the ester, E, and the odd electron centers located on the diyl ring of **52**.[27, 28] To test this notion, we synthesized diazene **49b**, one bearing a *Z*-substituted diylophile. As illustrated, if secondary interactions dominate, then the cis-syn adduct **53**, resulting from the folded pseudochair transition state conformation **54**, should correspond to the major product. In practice, the cis-anti adduct **55** still predominated, a 75:25 ratio of **55** to **53** being obtained.



It is noteworthy that the diylophile stereochemistry was maintained in this instance. This piece of information, combined with the fact that it was also

maintained using the diazene **49a**, indicates that these intramolecular diyl trapping reactions are stereospecific insofar as the diylophile stereochemistry is concerned. We conclude that cycloaddition is either a concerted process or that formation of the second σ bond occurs at a rate which exceeds that of bond rotation and loss of stereochemistry.

Subsequent experiments estimated that the magnitude of the putative secondary interactions was similar to that associated with rotation about a C—C σ bond. Clearly, this is a value which is so small that one is well advised not to associate it with a specific interaction.[28] Diazene **56** does not have an electron-withdrawing substituent appended to the diylophile. Consequently, secondary orbital interactions are not possible. Given the preceding commentary, it is amusing to note that the cis-anti to cis-syn product ratio (**57**/**58**), corresponded exceptionally well to the value one would have predicted by factoring out the small contribution due to secondary interactions.[29] We conclude that secondary orbital interactions do not play a significant role in determining the stereochemical course of diyl trapping reactions.

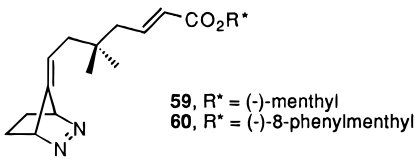


Both of the cis-anti ring-fused adducts **50** and **57** proved to be useful intermediates *en route* to the mold metabolite hirsutene (**13**). With **57**, of course, the ester need not be removed. Consequently, it provided a much more direct route to the natural product.[29,30]

In retrospect, perhaps the most important lesson to be learned from the work just described is that short-lived, highly reactive diradicals can serve as useful intermediates in organic synthesis.

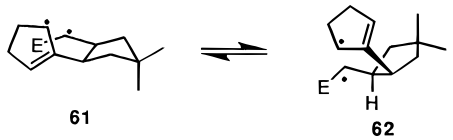
Asymmetric Induction

Our efforts in this area first explored the influence of a chiral ester appended to the terminal carbon of the diylophile; both the (−)-menthyl and (−)-8-phenylmenthyl esters, **59** and **60**, were examined. On



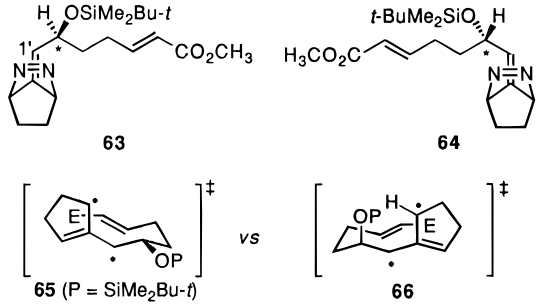
the basis of the transition state model just described, it seemed reasonable to expect that the larger the ester, the greater its influence in biasing the diastereoface of the diylophile which is exposed to the diyl, and therefore the diastereoselectivity of the cycloaddition process. Unfortunately, both auxiliaries afforded essentially the same, abysmal, 5−10% diastereomeric excess (de).[31]

We suggest that in these cases, cycloaddition occurs in a stepwise manner. In this way, the ester can remain as far away as possible for as long as possible, allowing formation of the first five-membered ring to occur essentially without any influence from the auxiliary. If this is so, then one would anticipate that the size of the ester would express itself in the formation of the second, rather than the initial, σ bond. Consider, for example, the equilibrating structures **61** and **62**. In **61**, the ester units are located



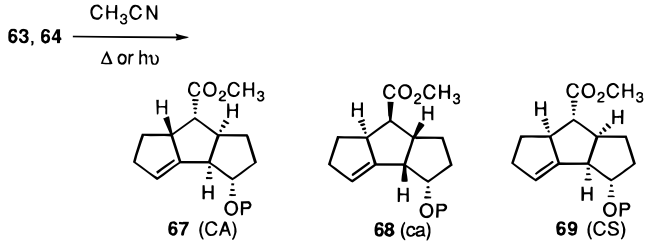
under the five-membered ring of the allylic radical, in a position where steric interactions promise to be significantly larger than in the alternative formulation **62**. σ bond formation in **61** leads to the cis-anti adduct, while the cis-syn adduct is derived from **62**. If these ideas are credible, then the cis-anti/cis-syn product ratio ought to decrease as the size of the ester increases. This was indeed the case, the value changing from 9:1 to 5.6:1 to 3.3:1 as the ester varied from methyl to menthyl to 8-phenylmenthyl.

We turned our attention to a system bearing a stereogenic center on the tether linking the diyl and diylophile.[32] Since one of our objectives was to complete a total synthesis of coriolin (**15**) and hypnophilin (**16**), we elected to append an ether to a site destined to bear the requisite substituent at C_{11} in both natural products. The foundation for the total synthesis efforts was provided by a detailed study of the diyls derived from the diastereomeric diazenes **63** and **64**, systems differing only in the orientation



of the tether appended to $C_{1'}$.[33] It was reasoned that the OP unit ought to prefer the pseudoequatorial orientation portrayed in transition state formulation **65**, rather than the alternative pseudoaxial form **66** which is associated with *si*-face attack of the diyl on the diylophile.

Cycloaddition was studied over a broad range of temperatures, from −31 to 81 °C, the diyl being generated both thermally (50 °C $\leq T \leq$ 81 °C) and photochemically (−31 °C $\leq T \leq$ 50 °C). The same products and product ratios were obtained at 50 °C, regardless of the mode of generation of the diyl, suggesting that both the thermal and photochemical routes lead to the same intermediate. Furthermore, the diastereomeric diazenes **63** and **64** afford the



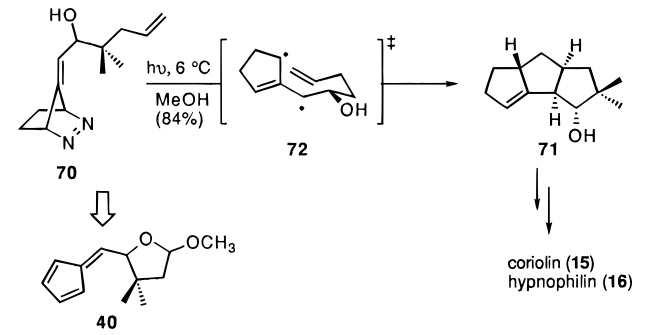
same products and product ratios, indicating free rotation about the ring to the exocyclic carbon−carbon bond and the existence of a time-average planar and nitrogen-free diyl. Yields for the adducts shown consistently exceeded 90%. The major product in all cases was the cis-anti ring-fused cycloadduct **67**, that predicted using transition state formulation **65**. Diastereoselectivities in the cis-anti series, that is CA/ca, ranged from 92% in refluxing acetonitrile to 98% when the diyl was generated photochemically at −31 °C.

Because the process was examined over a broad temperature range, we were able to determine the differences in free energies, enthalpies, and entropies of activation, $\Delta\Delta G^{\ddagger}$, $\Delta\Delta H^{\ddagger}$, and $\Delta\Delta S^{\ddagger}$, respectively. The CA/ca ratio (**67**/**68**) was shown to be enthalpically determined. This is consistent with the ideas embodied in transition structures **65** and **66**, where the existence of the nonbonded interactions referred to above leads to a preference for **65**. Interestingly, the cis-syn product **69** was shown to be *entropically* disfavored relative to the major product, **67**.

Application to Coriolin (15) and Hypnophilin (16)

With the foundation provided by the studies just described, it remained for us to demonstrate further the synthetic utility of the diyl trapping methodology. We elected to synthesize racemic coriolin (**15**)[34] and hypnophilin (**16**),[34,35] being confident that enantiomerically pure materials could be assembled if desired.

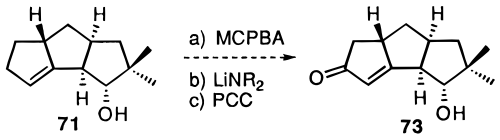
The key cycloaddition step was studied in a variety of solvents, and the diyl was generated both thermally and photochemically.[35] As illustrated, the conversion of diazene **70** to the desired tricyclopentanoid, **71**, occurred in a highly stereoselective man-



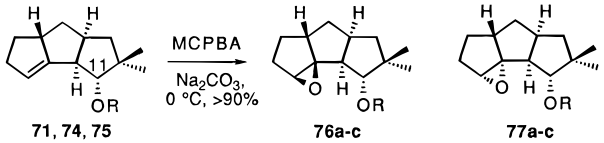
ner, and in an 84% isolated yield. In this instance, the transition state model **72** portrayed above does very well in rationalizing the stereochemical outcome. However, it will be shown later that, in certain cases, the model requires modification.

Progress from cycloadduct **71** to each natural product proved relatively straightforward, with the exception of one completely unanticipated result, which is discussed below.

Formation of a trans-Fused [3.3.0] Subunit. To set the stage for a Rickborn−Crandall fragmentation leading to enone **73**,[36] we treated alcohol **71** with MCPBA in methylene chloride, expecting to form a single epoxide.



We were very surprised to discover the formation of an 80/20 mixture of two adducts, **76a** and **77a**, in >90% yield.[35] The ratio proved to be dependent upon



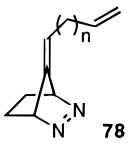
starting alkene	R	products	ratio
71	H	**76a**, **77a**	80/20
74	COPh	**76b**, **77b**	27/73
75	$SiMe_2Bu$-*t*	**76c**, **77c**	0/100

the size of the OR unit appended to C_{11}. When a bulky silyl ether was used (**75**), a single product formed, **77c**. Desilylation afforded the minor epoxy alcohol **77a**, which was produced in the initial epoxidation of **71**. X-ray analysis of the corresponding benzoate **77b**, the major adduct derived from the epoxidation of **74**, demonstrated conclusively the presence of a trans-fused A,B-ring system. Thus, despite the fact that the parent trans-fused bicyclo[3.3.0]octane is ∼8 kcal/mol less stable than its cis-fused counterpart, such systems can be assembled, and in high yield.

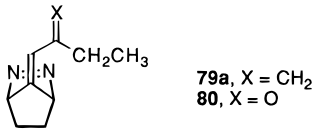
Our rationale reaffirms the importance of simple tools *viz.*, molecular models and conformationally meaningful drawings. Thus, despite the fact that the C_{11} OR unit is formally on the α-side of the tricyclic framework, models clearly indicate that the BC-ring fusion positions the substituent so that it is *above* the π bond of the A ring. Large R groups would, therefore, be expected to direct epoxidation to the opposite side, as observed.

Influence of Tether Length: Construction of Heterocycles

The length of the tether joining diyl to diylophile has a significant influence on the course of the cycloaddition process. Systems varying in length from zero to four atoms have been studied (**78**, n = 0−4), and an overview of the chemistry is presented.



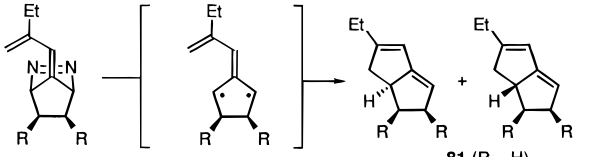
Zero-Carbon Tether. Of course, the expression "zero-carbon tether" refers to instances where no atoms separate the diyl and diylophile, *i.e.*, where they are linked directly, as in structures **79a** and **80**.



79a, X = CH_2
80, X = O

These systems are of interest for several reasons. First, the diazenes lose nitrogen at a rate greater than that observed when an insulating unit intervenes. For example, the Arrhenius activation energy for nitrogen loss from **63**, the diazene used in the asymmetric induction study described above, is 27.0 kcal/mol, and that for the dimethyl diazene **7** is 28.8 kcal/mol. In contrast, it is only 25.6 kcal/mol for both **79a** and **80**.[37,38]

One of the first examples to illustrate the chemistry of these systems involved the conversion of diazene **79a** to the bicyclic diene **81** (R = H), upon heating



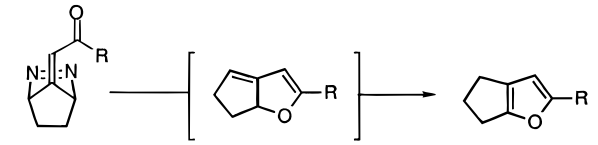
79a, R = H
79b, R = D

82

81 (R = H)
83 (R = D) **84** (R = D)

the former to reflux in acetonitrile.[37,38] In principle, this transformation could have occurred *via* a concerted eight-electron process, or through the intermediacy of a TMM diyl, **82**. To differentiate between these possibilities, the deuterated diazene **79b** was synthesized and studied. A concerted process would have afforded a single diene, **83**. In fact, a 1/1 mixture of dienes **83** and **84** was obtained, thereby implicating the existence of an intermediate, most likely the time-average planar, nitrogen-free diyl, **82**.[37]

Reasonably facile access to bicyclic furans is provided using this methodology, simply by heating the diazene to reflux in the solvent of choice. For example, enones **85** and **86** are converted to furans



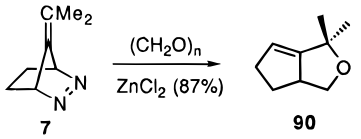
85, 86 **89** **87, 88**

R	conditions	adduct	yield (%)
85, *n*-C_4H_9	$CDCl_3$, 50 °C; SiO_2	**87**	87
86, CH_2=$CHCH_2CH_2$	THF, reflux; SiO_2	**88**	70

87 and **88** in 87% and 70% yield, respectively.[39] The initially formed adduct, **89**, is converted to the corresponding furan upon chromatography over silica gel. While we have not tested the idea, it seems reasonable to speculate that the replacement of C=O with C=NR might provide an entry to nitrogen-containing heterocycles.

Heterocycles are also accessible using the *inter*molecular diyl trapping reaction. We were nevertheless somewhat surprised to discover that TMM diyls can cycloadd across C=O, C=N, and C=S bonds. Suitable diylophiles included benzaldehyde, diethyl ketomalonate, *N*-phenylbenzalimine, thiobenzophenone, and formaldehyde (from paraformaldehyde).[40]

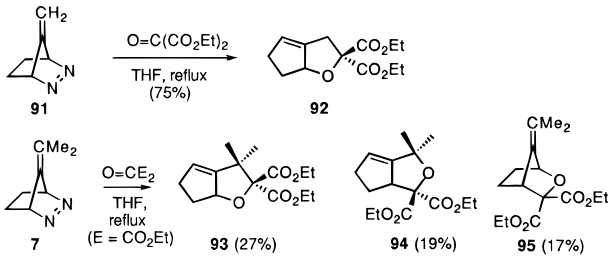
As with other intermolecular cycloadditions, however, many of these reactions are regiorandom. We know of two exceptions.[40] In one, the cycloaddition of formaldehyde to the dimethyl diyl **3** in the presence of zinc chloride leads exclusively to **90**. In the



7 **90**

absence of zinc chloride, cycloaddition does not occur. The Lewis acid facilitates depolymerization of the paraformaldehyde. We also suspect that it reduces the energy difference between the diyl HOMO and the diylophile LUMO and accentuates the polarization of the diylophile LUMO in a manner which leads preferentially to the observed regiochemical outcome. It is interesting to also note that diyl dimers were not detected; in nearly all of the other cycloaddition reactions to heteroatom-containing diylophiles, dimers are formed. We suggest that this observation is a reflection of the rate acceleration for cycloaddition which manifests itself as a consequence of the reduced HOMO/LUMO energy gap.

Diethyl ketomalonate adds regiospecifically to the diprotio diyl derived from diazene **91** to afford **92** in a 75% yield.[40] In stark contrast, a mixture of regioisomers **93**−**95** is obtained in the cycloaddition to the dimethyl diyl **3**. Presumably, the difference

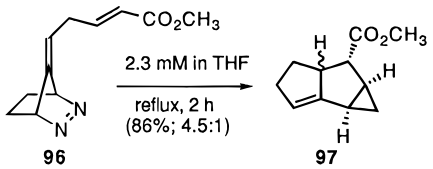


91 **92**

7 **93** (27%) **94** (19%) **95** (17%)

between the dimethyl and diprotio cases simply reflects the role of steric factors in these cycloadditions. This simple idea is certainly worth noting, since we almost always use the dimethyl diyl **3** as a prototypical case when exploring new examples of diyl trapping reactions. It may very well be that the regiochemical outcome of a number of the reactions we have examined could be made more selective simply by using the diprotio analog.

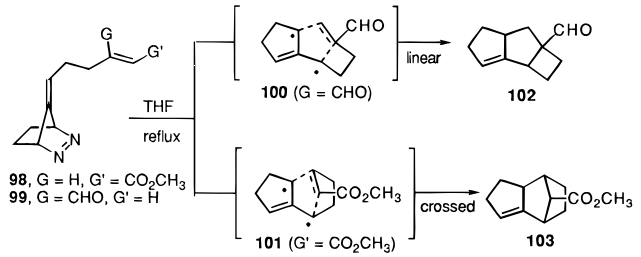
One and Two-Atom Tethers. When one methylene unit separates the diyl and diylophile as in diazene **96**, the tricyclo[6.1.0.$0^{2,6}$]nonene **97** results, *i.e.*, the product is linearly fused.[41]



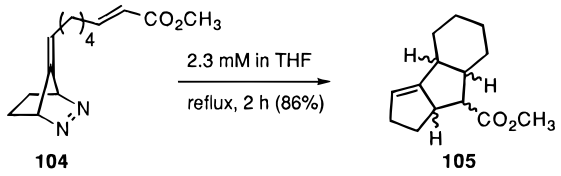
96 **97**

One begins to see the emergence of a different regiochemical pattern when the length of the tether

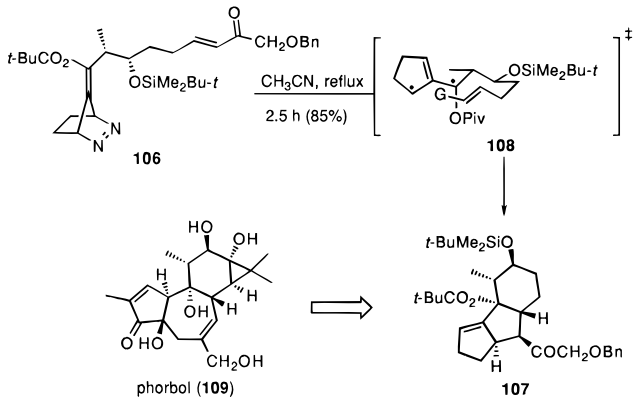
is two. In a manner reminiscent of photo-[2 + 2]-cycloaddition reactions, we find both "linear" and "crossed" cycloaddition pathways in the chemistry of diazenes **98** and **99**.[42,43]



Four-Atom Tether. When the tether length is four, two contrasting examples emerge.[44] The first system, diazene **104**, is devoid of substituents on the tether, and undergoes cycloaddition to afford a 1:1:1:1 mixture of stereoisomers in a combined 86% yield. No stereoselectivity is observed.



In stark contrast, the enantiomerically pure diazene **106** undergoes the intramolecular diyl trapping reaction to afford tricycle **107** in 85% yield.[44] This

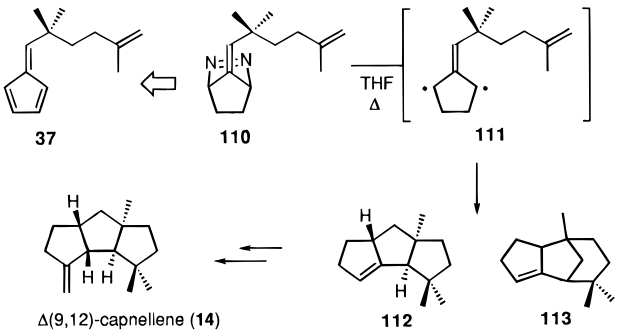


was gratifying, as our intent has been to use it as a precursor to analogs of the phorbol esters. We attribute the difference between the cycloadditions to conformational effects. In the absence of substituents which tend to bias the cycloaddition geometry as in **104**, there are several nearly equal energy reaction paths. The methyl and silyl ether units in **106**, on the other hand, prefer to occupy pseudoequatorial orientations, as shown in the transition state formulation **108**, thereby directing the stereochemical outcome.

Δ(9,12)-Capnellene (**14**)

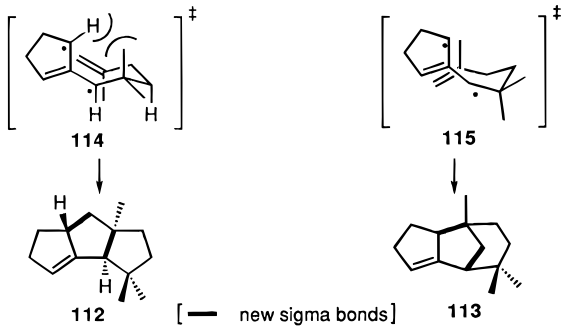
This simple marine natural product presented an unexpected challenge, one which ultimately forced us to revise our transition state model for the intramolecular diyl trapping reaction. While initially disconcerting, this exercise has proven rewarding insofar as it motivated us to learn more about the fundamental factors which govern the course of diyl trapping reactions, and has opened the door to allow access to ring systems previously considered inaccessible using diyl chemistry.

Diazene **110** was synthesized using fulvene **37** as a key intermediate.[45] We envisioned **110** to be ideally suited to our needs. It was not. Cycloaddition afforded the expected linearly fused system **112** as well as nearly an equal amount of the previously unobserved bridged regioisomer **113**. These materi-



als proved difficult to isolate as hydrocarbons and were converted to the expected ketones *via* hydroboration-oxidation. The structure of the bridged ketone was confirmed by X-ray crystallographic analysis.

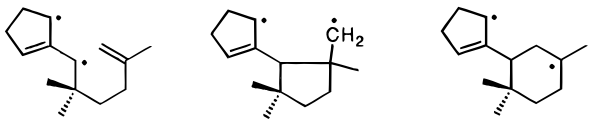
We were surprised to obtain **113**. Application of the transition state model for the intramolecular diyl trapping reaction in systems possessing a three-atom tether failed to predict its formation. Why? Examination of transition state **114** suggests several possibilities. The most obvious difference between the present case and those studied previously was the existence of the *gem*-dimethyl unit appended to the carbon adjacent to the diyl, and the methyl group appended to the internal carbon of the diylophile. As illustrated in **114**, the positioning of these substitu-



ents sets up a series of energy raising nonbonded interactions between hydrogen and methyl groups. That between the *gem*-methyl unit and the diyl ring hydrogen is alleviated if the alternative transition state formulation **115** is assumed. Perhaps it was simply the presence and location of the *gem*-dimethyl unit that was responsible for the formation of the bridged adduct.

Another idea was also entertained, though at the time its importance was thought to be negligible. We considered the possibility of a stepwise cycloaddition, rather than the concerted pathway which had served so well in other instances with three-atom tethers. In so doing, one notes that the linearly fused material

formally arises *via* an initial 5-*exo-trig* cyclization



116 **116a** (5-exo path) **116b** (6-endo path)

onto an alkene which is substituted with a methyl group. On the other hand, the bridged adduct results formally from a 6-*endo-trig* cyclization onto the opposite end of the alkene. In analogy with monoradical chemistry,[46] one notes that in cases such as these, the rate of the 6-*endo-trig* cyclization exceeds that of the alternative, though the rate differences are generally small. Could it be that one ought to apply the ideas of monoradical cyclization to diyl chemistry? Which is the more important factor, the presence and location of the geminal alkyl substituents or the alkyl group on the internal carbon of the diylophile?

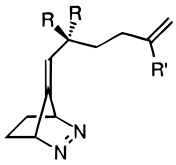
Reversal of Regiochemistry

As indicated, we were initially perplexed by the failure of our model to predict the formation of the bridged adduct **113**. Two factors motivated our efforts to understand what was wrong. The first was that we were simply curious. The second was a realization that many natural products possess the bicyclo[3.2.1] subunit found in the bridged regioisomer, so understanding the factors which control the regiochemical outcome ought to significantly improve the opportunity to use the diyl trapping reaction *en route* to such systems.

On reflection, it is clear that several important clues were ignored, unfortunately, at the outset of our studies. The most important point was that, unless diazene **110** was added slowly to a solution of THF or acetonitrile at reflux, significant quantities of diyl dimers were isolated.[45] Until this system was studied, dimer formation had either not been observed or the amount formed proved so small that it was not deemed important. As indicated previously, Berson and co-workers demonstrated that dimers of the dimethyl diyl **3** arise *via* the combination of two triplet diradicals.[7] We had assumed that intramolecular diyl trapping reactions would occur faster than intersystem crossing from the first formed singlet to the triplet diyl. Could it be that the chemistry of diyl **111** reflected that of the triplet or both the singlet and triplet manifolds?

In an attempt to sort out the relative importance of geminal substitution *vs* the nature of the substituent appended to the diylophile, we synthesized and examined the chemistry of the diyls derived from diazenes **117a**−**c**, the first two having geminal substituents but no alkyl group on the diylophile and the third being devoid of the geminal substituents but possessing a hydroxymethylene unit on the diylophile. Once again, to our surprise, geminal substitution turned out to play an imperceptible role. The only one of the three systems to provide a significant quantity of the bridged cycloadduct was **117c**.[47]

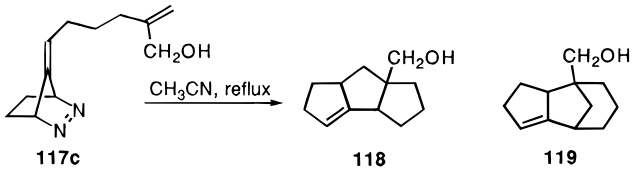
To address the possibility that both the singlet and triplet diradicals could be participants, we examined



117a-c

R	R'	major product/comments
a, CH_3	H	linear
b, OCH_3	H	linear
c, H	CH_2OH	essentially 1:1 bridged /linear

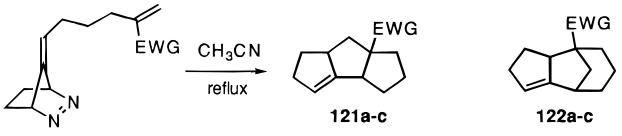
the chemistry of **117c** in the presence of molecular oxygen.[47] Bridged adduct formation was completely quenched, and the amount of linearly fused adduct **118** was reduced from 44 to 17%. If one assumes that the low steady state concentration of oxygen coupled with the large intersystem crossing rate from singlet to triplet diyl combine to make the triplet diyl the only interceptable intermediate, then these results indicate that all of the bridged and a portion of the linearly fused adducts are triplet derived.



117c **118** **119**

comments	
no oxygen	1:1.2 linear/bridged; 90% combined yield
with oxygen	no bridged & yield of linear decreases from 44 to 17%

The chemistry of diazenes **120a**−**c** illustrates that linearly fused adducts are formed very efficiently when an electron-withdrawing group is appended to either carbon of the diylophile. Product formation could not be quenched with molecular oxygen, indicating that these materials are singlet derived.[47]



120a-c **121a-c** **122a-c**

EWG	yield (%)	% linear
a, CO_2CH_3	88	>95
b, CHO	93	88
c, $COCH_3$	98	91

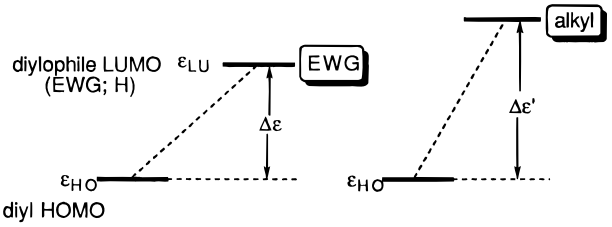
Electron spin resonance (ESR) experiments add credibility to these conclusions.[48] For both diazenes **117c** and **120a**, a triplet signal was observed. Apparently, at the low temperature which is associated with the photogeneration of the diyl in the ESR cavity, the intersystem crossing rate exceeds that of cycloaddition. Thus, even though an electron-withdrawing group leads to singlet chemistry from **120a** at elevated temperatures, the same singlet, when generated at −120 °C, intersystem crosses to the triplet.

To verify that the triplet responsible for the ESR spectrum was also that associated with the cycloaddition chemistry, we dissolved diazene **117c** in ethylene glycol, cooled the solution in liquid nitrogen, and irradiated the sample for 8 h. Upon warming to room temperature, analysis of the product mixture

demonstrated the formation of the same adducts, **118** and **119**, and in the same ratios as predicted on the basis of the oxygen quenching studies.[48]

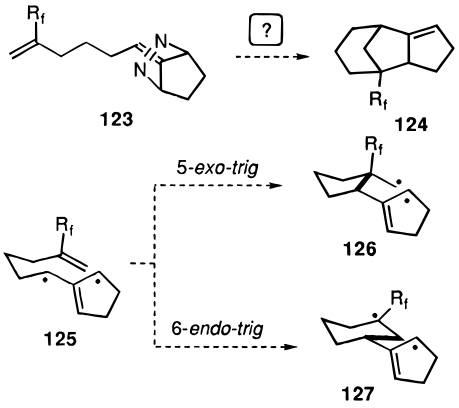
We suggest that these differing reactivity patterns can be understood using frontier molecular orbital theory, coupled with the Berson cascade mechanism illustrated previously. According to the latter, the first formed interceptable intermediate is the singlet diyl. Originally, we were of the opinion that intramolecular cycloaddition would occur fast enough to render intersystem crossing (ISC) to the triplet manifold noncompetitive. This does indeed seem to be the case when an electron-withdrawing group is appended to the diylophile. But as evidenced by the findings described above, this is not always true; triplet chemistry can and does intervene.

Since the triplet diyl affords the bridged cycloadducts, we wondered whether it would be possible to optimize production of the triplet and simultaneously optimize the amount of bridged product formed. We assume that the reason cycloaddition of the singlet diyl is rapid is related to the existence of a comparatively small diyl HOMO/diylophile LUMO energy gap, ΔE, the situation most likely to occur when an electron-withdrawing group is appended to the diylophile. If ΔE were larger, then that rate ought to decrease, thereby providing time for ISC to become competitive. Conceptually, this is an easy objective to achieve: merely replace the electron-withdrawing group with an alkyl substituent.[47]

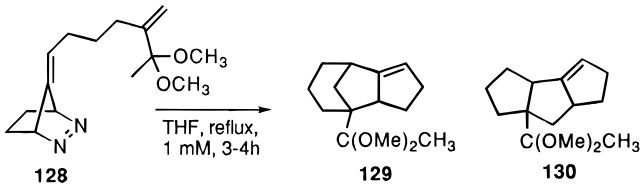


Once the triplet forms, it can choose either a stepwise 5-*exo-trig* or a 6-*endo-trig* cyclization pathway for the initial carbon−carbon bond forming event. The former converts **125** to **126**, an intermediate which will suffer progressively larger nonbonded interactions as the size of the diylophile substituent, R_f, increases. The alternative cyclization, **125** to **127**, alleviates these, particularly if the radical site bearing R_f assumes either a planar or time-average planar geometry, thereby allowing it to maximize its separation from the remainder of the molecule. The preferences for five- *vs* six-membered ring formation are expected to be similar to those expressed in monoradical cyclizations.[46] A plan emerges: to optimize formation of the bridged cycloadduct, append a large alkyl group, R_f, to the internal carbon of the diylophile in **123**. To add versatility and the possibility of functional group elaboration, select a large, *functionalized* alkyl group.

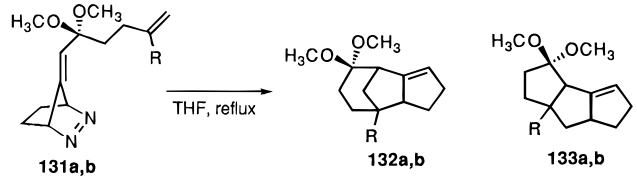
We were able to test these ideas; fortunately, the plan proved viable. The equation illustrated below demonstrates the dramatic influence the size of the alkyl group has on determining the bridged/linear regioisomer distribution. Thus, for the comparatively small CH_2OH unit of **117c**, a 1.2:1 ratio (**118**/**119**)



was obtained, while for the large dimethyl ketal found in **128**, it increased to 16:1 (**129**/**130**).[47]



The influence of both steric and electronic factors is illustrated in the chemistry of diazenes **131a** and **131b**.[47] The dimethyl ketal **131a** affords the bridged adduct **132a** to the near exclusion of its fused counterpart **133a**. In stark contrast, the corresponding enone **131b** provides the linearly fused adduct **133b** selectively, and in high yield.



R	bridged/linear	yield (%)
a, $C(OCH_3)_2CH_3$	16 : 1	70 (cycloaddition and deketalization)
b, $COCH_3$	1: >18	95

In summary, we highlight the following points: (1) The presence of geminal alkyl substituents adjacent to the first carbon exocyclic to the diyl ring has no apparent influence on the regiochemical outcome, an idea which is in complete discord with our initial thoughts. (2) The regiochemical controlling factor is the nature of the substituent appended to the diylophile. Electron-withdrawing groups (EWG) attached to either carbon result in the selective formation of linearly fused systems. In contrast, the presence of an alkyl group on the internal carbon of the diylophile leads to variable amounts of both linear and bridged adducts, depending upon the size of the substituent. The larger the group, the greater the preference for formation of the bridged material. (3) Both the singlet and the triplet diyl play an important role in this chemistry, the former providing a linear adduct when an electron-withdrawing group is appended to the diylophile, the latter being the precursor of the bridged isomer.

As a result of these studies we are now able to selectively form either the bridged or the linearly

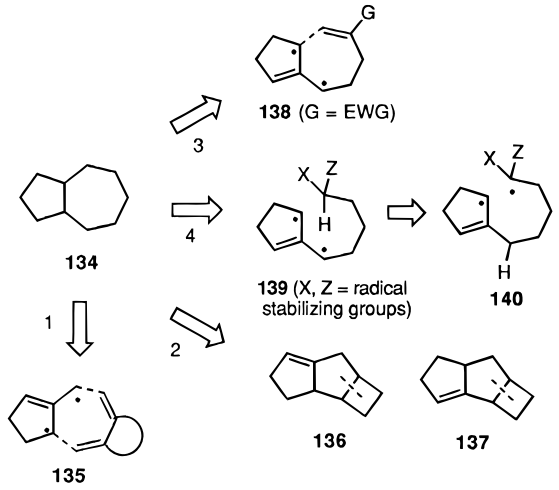
fused regioisomer by design. At this time, our efforts focus on utilizing this attribute of the intramolecular diyl trapping reaction to access aphidicolin (**20**) as well as taxol analogs.[49] These studies are progressing nicely and the details of the work will be reported elsewhere.

Access to Other Ring Systems

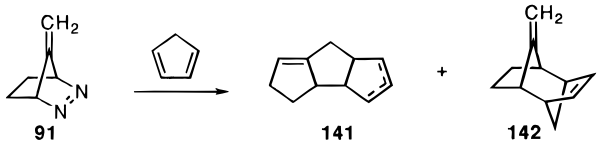
With access to both linearly fused and bridged tricyclic systems assured, we elected to examine several strategies which promised to deliver bicyclic systems (**134**), particularly those of the [5.3.0] and [6.3.0] types, which are common to a significant number of natural products.

Several of the strategies we either have examined or continue to explore are illustrated in Scheme 2.

Scheme 2

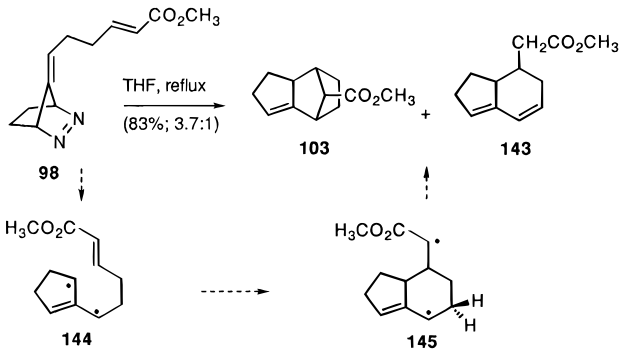


The apparently most direct route to the [5.3.0] ring system (route 1), calls for the interception of the diyl with a 1,3-diene and does have precedent in the literature. Thus, Berson and co-workers demonstrated that cyclopentadiene was able to trap the diyl resulting from the diprotio diazene **91**, to afford both



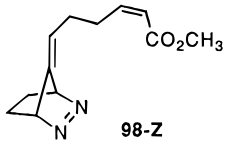
1,2- and 1,4-cycloadducts **141** and **142**, respectively.[50] In addition, Dowd and co-workers were able to trap the parent trimethylenemethane using 1,3-butadiene.[51] Despite these successes, our efforts to generalize and formulate a method of broad synthetic utility have not met with much success.

Another conceptually simple method calls for an inter- or intramolecular cycloaddition leading to the tricyclic skeleton **136** or **137**, respectively, followed by cleavage of the endocyclic C−C bond, as indicated (route 2, Scheme 2). To examine the intramolecular pathway, we synthesized diazenes **98** and **98-*Z*** and examined the subsequent diyl trapping reactions.[42] To our surprise, the desired linearly fused system was not produced. Instead, a 3.7 to 1 ratio of diene **143** and the bridged tricycle **103** was obtained in a combined 83% yield. The simplest rationale suggests



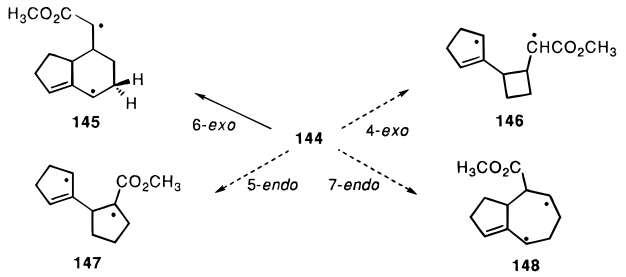
that the process occurs in a stepwise, rather than a concerted manner. Thus, a 6-*exo-trig* cyclization of the initially formed diyl **144** leads to a new diradical **145**, which engages both in σ bond formation leading to **103**, and transfer of a hydrogen atom to the exocyclic odd electron center to afford diene **143**.

Further indication of the stepwise nature of the process was obtained by examining the chemistry of the diyl derived from diazene **98-*Z***, one possessing a



Z-substituted diylophile.[42] Unlike the analogous system, **49b**, where the alkene geometry was maintained, it was lost in the present instance. Presumably, the geometric constraints imposed by a two-atom tether preclude the facile formation of the linearly fused framework, the diyl electing instead to undergo 6-*exo-trig* cyclization leading to the ester-stabilized diyl **145**. The results imply that there is sufficient time to rotate about the exocyclic C−C bond and lose stereochemistry, an otherwise uncommon event in diyl trapping chemistry.

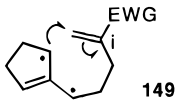
While these results are of interest with respect to learning the fundamental characteristics of diyl trapping chemistry, the work did not afford a route to the desired framework. Why? Of the options available to diyl **144**, the stepwise 6-*exo-trig* cycliza-



tion pathway was preferred over the alternative 4-*exo-trig* as well as the 5- and 7-*endo-trig* possibilities. This is not surprising, given the relative rates of monoradical cyclization and that the 6-exo mode leads to a radical which is stabilized by an electron-withdrawing group.[46,52,53] The 4-*exo* and 7-*endo* options could have led to the desired framework, but that chemistry was not expressed.

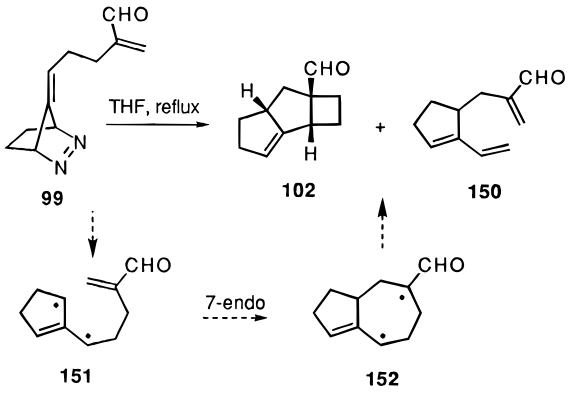
We wondered whether it was possible to tip the balance from the 6-*exo-trig* toward the 7-*endo* mode

by placing a radical stabilizing group on the internal carbon of the diylophile, C_i, in the manner portrayed below.[43,53]



149

Diazene **99** was assembled to explore this idea.[43] The cis-syn linearly fused tricycle **102** and triene **150**, were isolated in yields ranging from 66−85%, and in a ratio of 1.6−1.65 to 1. Of interest was the



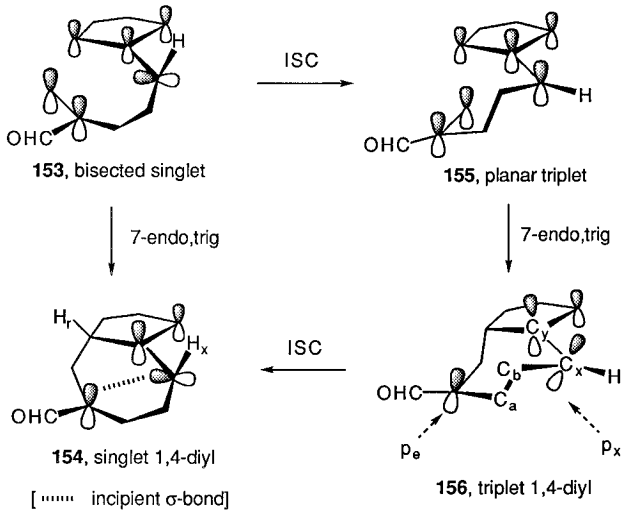
99 102 150 151 152

isolation of only the cis-syn tricycle. This contrasts dramatically with our previous work leading to linearly fused tricyclopentanoids where the cis-anti linearly fused systems invariably constituted the major stereoisomer.[29,30,34,35]

Both products suggest the intervention of the 1,4-diyl **152** formed on 7-*endo-trig* cyclization of the initial TMM diyl **151**. σ bond formation leads to the tricycle **102**, while cleavage of the intervening σ bond affords triene **150**. These results indicate that it is possible to achieve a switch between the 6-*exo-trig* and 7-*endo-trig* cyclization modes of the initially formed diradical.

Oxygen-quenching studies were used to determine the spin state responsible for the formation of each adduct.[43] Scheme 3 summarizes the results. The triene **150** is triplet derived, while the linearly fused product **102** is formed from both the singlet and triplet manifolds. The observed cis-syn selectivity

Scheme 3



153, bisected singlet 155, planar triplet

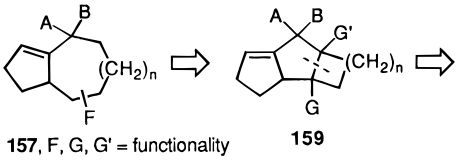
154, singlet 1,4-diyl 156, triplet 1,4-diyl

[····· incipient σ-bond]

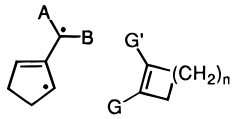
presumably derives from the fact that the TMM diyl initially generated from **99** is likely to be the bisected singlet **153**. This geometry predisposes the tether and diylophile so that, upon 7-*endo-trig* cyclization to afford **154**, hydrogens H_x and H_r are oriented cis to one another. In addition, the p-orbital located on the carbon exocyclic to the five-membered ring and the odd electron center positioned α to the aldehyde are pointed toward one another in a manner which ought to facilitate formation of the cis-syn adduct **102**. Competitive ISC from the bisected singlet 1,3-diyl **153** to the planar triplet **155**, followed by 7-*endo-trig* cyclization, leads to the triplet 1,4-diyl **156**. Here, the p-orbitals, p_x and p_e, are parallel to the intervening σ bond, C_a-C_b, and are therefore stereoelectronically well-suited to facilitate cleavage of that bond, leading to the formation of triene **150**. Note that the geometric change from the bisected to the planar TMM (**153** to **155**), and between the 1,4-diyls **156** and **154**, involves rotation about the bond C_x-C_y, a process which ought to promote the spin-orbit coupling needed to facilitate intersystem crossing.[54]

Intermolecular Cycloaddition Pathways to the [n.3.0] Framework

Recent efforts have focused upon gaining direct access to the fused ring system **157** *via* intermolecu-



157, F, G, G' = functionality 159



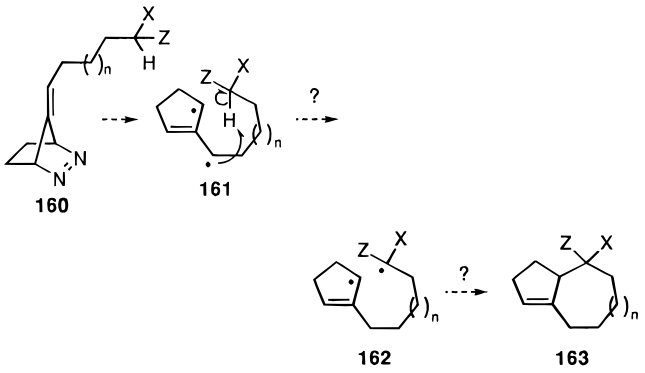
158

lar diyl trapping reactions. In these instances, functionalized diylophiles, **158**, have been selected to facilitate ring opening of the initial adduct, **159**. This work has been quite successful, providing access to bicyclo[7.3.0], -[6.3.0], and -[5.3.0] ring systems.[55] Details will be presented in a full paper.

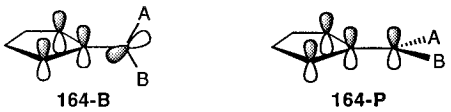
Alternative Reactivity Patterns. Atom Transfer[56]

We are interested in exploring new, non-cycloaddition reaction pathways involving TMM diyls. We wondered, for example, if it was possible for these systems to engage in atom transfer processes leading to "radical translocation".[57] The basic idea is displayed below. In principle, diyls of the type portrayed by structure **162** ought to be accessible *via* atom transfer involving the TMM diyl **161**. Once formed, **162** is expected to readily engage in σ bond formation leading to the desired bicyclo[*n*.3.0] framework. If workable, then the process promises to provide a new area for detailed mechanistic and synthetic exploration.

The issue, of course, is one of determining whether TMM diyls are capable of participating in atom transfer reactions. The problem is that these soft, delocalized diyls are not expected to be anywhere

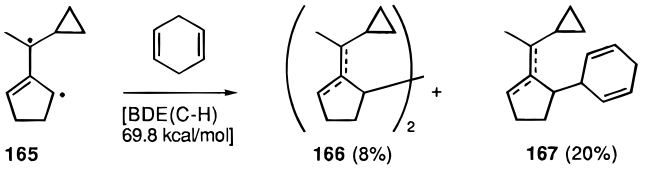


near as reactive as their localized counterparts. If one assumes a planar geometry for the TMM, as is often the case for the triplet diyl, then the odd electrons in **164-P** are delocalized over four centers,



and are consequently not expected to be very reactive. The bisected form, **164-B**, which is most often associated with the singlet, promises to be more reactive, given the reduced delocalization. Its involvement in atom transfer would, therefore, be a reasonable prospect were it not for the fact that the lifetime of the singlet is limited by the rate of intersystem crossing to the triplet, an event which is likely to occur so rapidly that only the fastest events are expected to be competitive. Atom transfer to a TMM diyl is not expected to be among those processes.

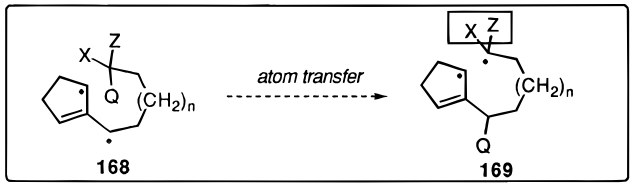
The first indication that atom transfer was possible stemmed from the work of Adam and Finzel.[58] They demonstrated that diyl **165** abstracts a hydrogen atom from 1,4-cyclohexadiene leading to dimer **166**, and to **167**, the latter resulting from radical-radical recombination.



Our plan is outlined in Table 2. The idea was to design a system where the process would at least be thermodynamically feasible. In this vein, we were guided in our selection of radical stabilizing groups, X and Z, and by the existence of C−H bond dissociation energy tables (BDE[C−H]).[56,59] Ideally, the loss in TMM delocalization energy should be offset by the radical stabilizing ability of X and Z. Whether the kinetic barrier could be surmounted would have to await experimental testing. If fortunate, then kinetic and thermodynamic effects would couple to make atom transfer a viable proposition.

In practice, neither one or two electron-donating groups (X = OH, Z = H; X = Z = OMe) nor one electron-withdrawing group (X = H, Z = CN) proved effective. Diyl dimerization occurred instead of atom transfer. On the basis of these findings, we suggest,

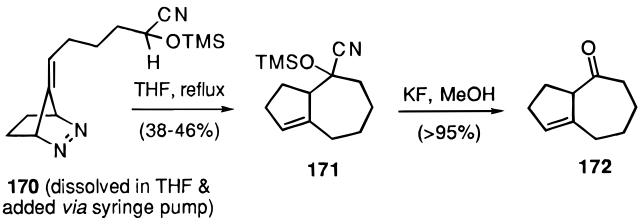
Table 2



X	Z	radical	BDE(C-H), kcal/mol
OH	H	$\cdot CH_2OH$	94.0
H	CN	$\cdot CH_2CN$	92.9
OMe	OMe	$\cdot CH(OH)_2$	91.9
OH	CO_2Me	$\cdot CH(OH)CO_2H$ [$\cdot CH(OH)CHO$]	84.8 [79.1]
OTMS	CN	$\cdot CH(OH)CN$	82.6

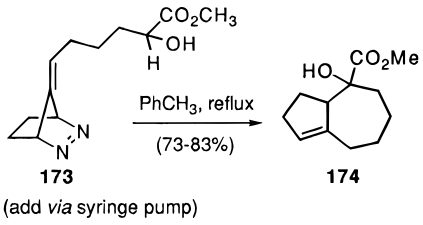
but certainly have not proven, that when the C−H bond dissociation energy is greater than or equal to 90 kcal/mol, atom transfer is unlikely to occur. Fortunately, when X is an electron-donating group and Z is electron-withdrawing, success is achieved; the captodative radical formed upon atom transfer presumably provides the proper balance of kinetic and thermodynamic factors to allow the transformation to occur.[56]

Our first successful case corresponded to the silyl-protected cyanohydrin **170**.[56] In this instance, the



[5.3.0] adduct **171** was obtained in yields ranging from 38 to 46%. While not efficient, we were exceptionally pleased to discover that the basic idea could be implemented. Simple desilylation of **171** cleanly and efficiently afforded ketone **172**.

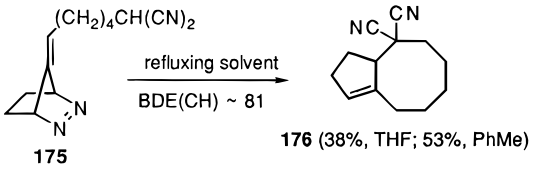
Atom transfer also occurs from the α-hydroxy ester **173**.[56] As in the previous case, the diazene was added *via* syringe pump to a solution of refluxing THF. In this instance, the [5.3.0] adduct **174** was isolated in



40−45% yield. The best results were obtained when the reaction was conducted in higher boiling solvents. For example, in refluxing toluene or in *n*-octane at the same temperature (*i.e.* that of toluene at reflux), the yield of the [5.3.0] adduct **174** rose to the respectable and synthetically useful range, 73−83%. In response, there was a reduction in the principle competing process: diyl dimerization.

We assume the temperature dependence reflects the fact that the rate of dimerization changes slowly, while that for atom transfer increases significantly as the temperature is raised. This is reasonable, given that dimerization simply involves radical−radical combination, while atom transfer involves bond cleavage and ought to have a sizable enthalpic component.

Eight-membered rings are also accessible using this methodology.[56] In this case, atom transfer occurs when X = Z = CN, *i.e.*, when both radical-stabilizing substituents are electron-withdrawing. As illustrated, the efficiency of this reaction also improves in response to an increase in temperature.



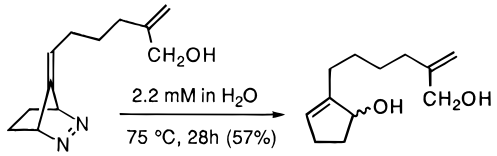
175 **176** (38%, THF; 53%, PhMe)

We suggest that the triplet diyl is the reactive species in these processes. As indicated previously, the lifetime of the initially formed singlet is limited by the rate of intersystem crossing to the triplet manifold, a process which for the dimethyl diyl **3** occurs at a rate of $\sim 10^8$ s^{-1}.[60] Given that the rate constants for 1,5-hydrogen transfer in monoradicals are typically in the range of 10^6 s^{-1},[61] it seems most unlikely that the transfer would occur more rapidly than that to a TMM diyl. Furthermore, the competitive nature of atom transfer and diyl dimerization, a process which for **3** is known to occur *via* the combination of two triplets, suggests that atom transfer to a TMM diyl involves the triplet.

Studies are underway to assess the scope of the atom transfer process, focusing particularly upon the opportunity to explore the transfer of functionality, as well as its possible application to natural product synthesis.

Other Modes of Reactivity. Reaction with Water[62]

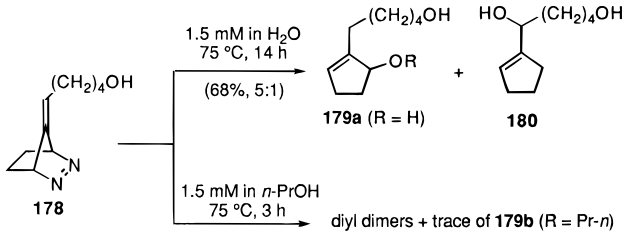
In an effort to improve the stereo- and regioselectivity of the intramolecular diyl trapping reaction, we elected to heat diazene **117c** in water. The idea was



117c **177**

that the hydrophobic tether might coil in a manner differing from that observed in organic solvents, leading to a change in product selectivity. Much to our surprise, the usual cycloaddition products were accompanied by a 57% isolated yield of diol **177**, a previously unobserved material which clearly results from the interception of an intermediate by water.[47,62] Thus, instead of modifying cycloaddition selectivity, a new mode of reactivity was observed.

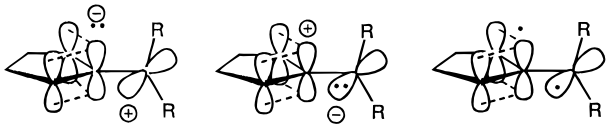
We have examined other substrates and have found the reaction to be general, at least within the context of the systems studied.[62] Interestingly, the course of the reaction is markedly influenced by solvent polarity. For example, diazene **178** is con-



178 **179a** (R = H) **180**

verted in 68% yield to a 5:1 mixture of diols **179a** and **180** when the process is conducted in water at 75 °C. In contrast, when the solvent is *n*-propanol, only diyl dimers form, along with a trace of ether **179b**, the latter being evidenced by capillary column gas chromatography. These and other data suggests that when the dielectric constant of the medium is less than 16 at 60 °C (*e.g.*, with *n*-PrOH), the diradical character is expressed and diyl dimers form; when it is equal to or greater than 48 (30% *n*-PrOH/water), dipolar reactivity prevails.

We suggest that in a polar medium, the intermediate behaves as a dipolar diradical, that is, a species which expresses neither purely zwitterionic or purely diradical character, but a hybrid of these.[62] In fact, given that the dominant water-trapped regioisomer is invariably one where the hydroxyl group is appended to the five-membered ring, we suggest that the major contributor to the formulations **181**−**183** portrayed below, is **182**. This also seems reasonable, given that the combination of an allyl cation and an orthogonal carbanion, ought to be of lower energy than alternative, **181**.

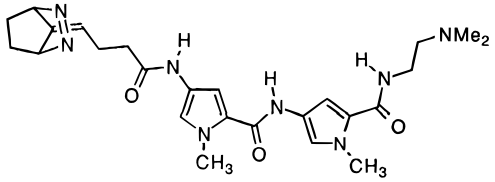


181 **182** **183**

Reactions with DNA. Cleavage Mechanism: Diradical or Dipolar Diradical?

Are soft, delocalized TMM diyls capable of cleaving DNA in a manner reminiscent of the hard, σ-diyls derived from natural products,[63] and if so, by what mechanism?

To address these questions, we designed and synthesized diazene **184**.[64] The idea, of course, is

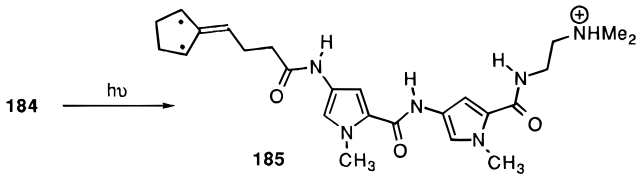


184

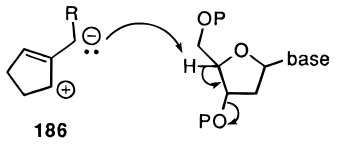
that the shape of the recognition unit roughly matches the helical twist of DNA, with the dipyrrole dicarboxamide units serving as sites for hydrogen bonding to the base pairs and the terminal dimethylamino group as a protonation site leading to a positively

charged unit which is attracted electrostatically to the negatively charged DNA.

When **184** is *irradiated* at room temperature in the presence of 517 and 167 base pair restriction fragments of 5′-^{32}P end-labeled pBR322, cutting does occur, and preferentially in AT-rich regions of the minor groove.



On the basis of detailed studies of the cleavage sites, the mode of binding to the double-stranded DNA oligomer 5′-CGCAAAAGGC-3′•5′-GCCTTTT-GCG-3′, and computer modeling,[64,65] we conclude that the diyl **185** can be positioned so that atom abstraction from the sugar−phosphate backbone is a reasonable possibility. We suggest that there are three pathways which could lead to cleavage: (1) Direct hydrogen atom abstraction. Given that TMM diyls are capable of participating in an intramolecular hydrogen atom transfer[56] and that binding to DNA can be likened onto an intramolecular setting, we suggest that direct hydrogen atom abstraction from the sugar−phosphate backbone of DNA may constitute a viable path. (2) As indicated, triplet TMM diyls react readily with molecular oxygen.[13,14] In so doing, a new, more reactive oxygen-centered radical is produced. Perhaps it could initiate cleavage by hydrogen atom abstraction. (3) In water, one can best describe the intermediate formed on extrusion of nitrogen as a dipolar diradical.[62] It is possible, therefore, that under the highly polar conditions which are associated with the experiments conducted in the presence of DNA, that this character is also expressed? We suggest a new pathway for DNA cleavage involving an E_2 elimination promoted by the "dipolar diyl" **186**, in the manner depicted below. Such a process would lead directly to 3′/5′-cleavage.

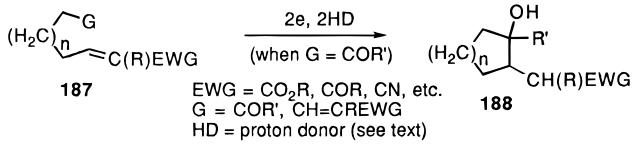


Which of these pathways is operable, if any? At this time, we do not know. However, efforts to elucidate the pathway and to design and study new systems are underway.[66] The results of these efforts will be reported in due course.

Electroreductive Cyclization Reactions[67,68]

Introduction[69]

In this section, we detail some of our efforts in the area of organic electrochemistry, focusing particularly on the use of intramolecular electroreductive cyclization chemistry. This process is characterized by σ bond formation between two formally electrophilic carbons, often, but not always, the β-carbon of an electron deficient alkene, and the carbonyl carbon of a remotely tethered subunit. To accomplish this transformation requires the reduction of an electrophore, the electron deficient alkene **187**, for example. The resulting radical anion, or the carbanion which is obtained by protonation and the addition of a second electron, possesses nucleophilic character, thereby facilitating cyclization in the manner illustrated below.



This process is a variation on a theme developed many years ago by Baizer and co-workers in their pioneering studies of electrohydrodimerization and electrohydrocyclization processes.[70] The former is best known for its application to the synthesis of adiponitrile used in the Monsanto process leading to Nylon 6-6.

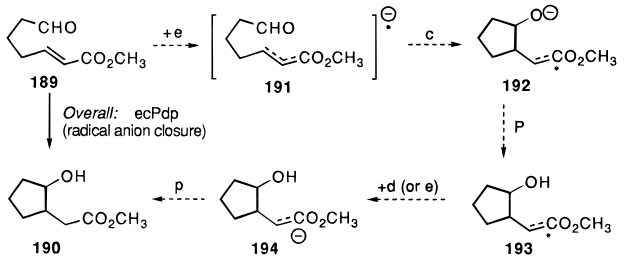
Overall, these processes require the consumption of two electrons and two protons. It is easy to monitor current consumption using a simple, commercially available coulometer.[69,71] Of course, electrochemical transformations can also be monitored in the usual manner (TLC, spectroscopy, etc). The structure and acidity of effective proton donors vary from mineral to carbon acids. Often, a simple dialkyl malonate is effective, though they can pose problems insofar as they are sometimes difficult to separate from the adduct(s).

Electrochemical processes are conducted under what is referred to as either "constant current" or "controlled-potential" conditions. The former is often preferred, because it is least expensive as it does not require acquisition of a potentiometer, and reaction times are often much shorter. The disadvantage of this method, of course, is that in order to maintain a constant current, the potential must change. It becomes more negative or positive, depending upon whether or not a reduction or an oxidation is being investigated in order to maintain the constant current condition. Controlled-potential methods allow one to set the potential to a value which corresponds to the reduction or oxidation wave of the electrophore, much the same way that the use of some type of filtering system allows one to selectively irradiate a particular chromophore in a photochemical process. And just as one obtains a UV spectrum to determine the appropriate filter prior to conducting a photolysis, so one obtains the analogous cyclic voltammogram (CV) corresponding to the material to be studied electrochemically. It describes how the current changes as a function of variation in potential. Current flow corresponds to the existence of a redox process, one which can occur reversibly or irreversibly during the potential scan. In the former, an electron is added and removed during the forward and reverse scans, respectively. In the latter, a follow-up process occurs at a rate exceeding that of the oxidation, assuming, of course, that the forward scan corresponds to a reduction. All of the systems we have studied display irreversible CV curves, at all of the scan rates which were examined.

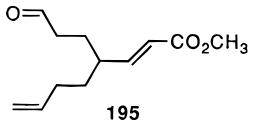
Mechanism

In collaboration with Professor A. J. Fry, we have studied the electroreductive cyclization reaction in reasonable mechanistic detail.[68] Our initial thought was that the process simply occurred *via* the cyclization of the radical anion derived, for example, from **187** in the first reduction step. A moment's reflection, however, reveals that there are many more mechanistically viable pathways, especially when one realizes that the transformation involves five steps, two electron transfers (symbolized below by "e" and "d", the latter corresponding to a homogeneous process), two protonations ("p"), and cyclization ("c"). In principle, these could occur in any order, and with any one of the steps being rate-determining.

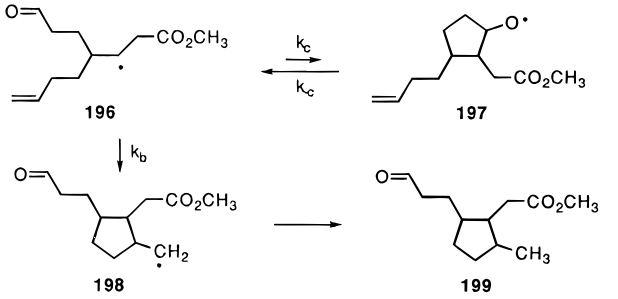
Of the literally hundreds of pathways that were formulated, the list was trimmed to four using linear sweep voltammetry (LSV) and chemical arguments.[68] The LSV method is an exceptionally powerful one for analyzing electrochemical processes. It is based on the independent research of Savéant and of Parker.[72] From LSV studies, it was concluded that a single heterogeneous electron transfer precedes the rate-determining step, cyclization is first-order in substrate, and proton transfer occurs before or in the rate-determining step. The candidates include (a) e−c−P−d−p (radical anion closure), (b) e−P−c−d−p (radical closure), (c) e−p−C−d−p (radical closure), and (d) e−P−d−c−p (anion closure). The first of these cases is portrayed below to illustrate the use of the notation; when a symbol appears as a capital letter, it refers to the rate-determining step.



To sort among these possibilities, we designed and synthesized compound **195**, one where in principle, there exists an equal opportunity for closure onto the alkene and/or the aldehyde.[6]

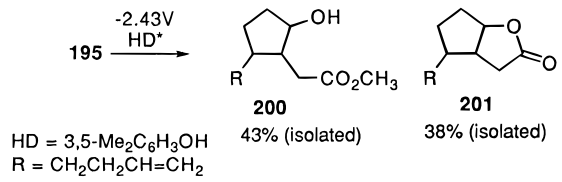


Consider first, the possibility of radical cyclization involving **196**, it being formed after electron transfer



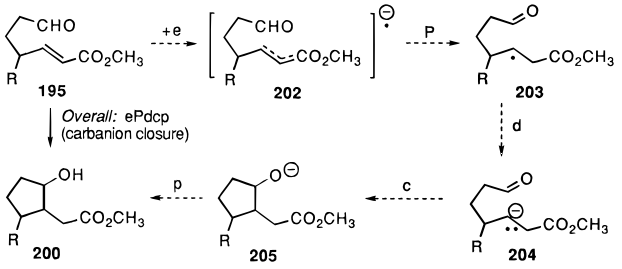
("e") and rate-determining protonation ("P"). Clearly, **196** has the option of undergoing either a 5-*exo-trig* cyclization onto an alkene or an aldehyde, with both rate constants approximating 10^5 s^{-1}.[46,73] We assume, as is most often the case, that the former process is irreversible, while ring opening of the anion occurs with a rate constant of $\sim 10^8$ s^{-1}.[46,73] Should **198** form, it follows that at least some of aldehyde **199** ought to be detected.

In practice, reduction of **195** (−2.43 V vs SCE) in the presence of 3,5-dimethylphenol as a proton donor, tetra-*n*-butylammonium hexafluorophosphate as the



supporting electrolyte, and DMF as the solvent led to the γ-hydroxy ester **200** and lactone **201**.[68] No sign of any material resulting from cyclization onto the alkene was detected. We conclude that radical cyclization does not occur in this instance and that the homogeneous electron transfer rate exceeds that of a 5-*exo-trig* radical cyclization, thereby implying the operation of either a radical anion or carbanion cyclization pathway.

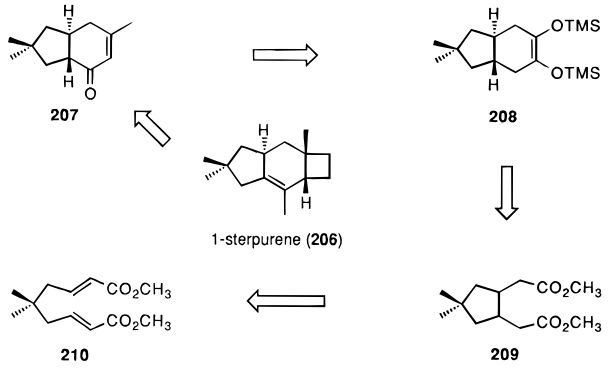
The radical anion pathway (e−c−P−d−p) requires a rate-determining protonation *after* cyclization, *i.e.*, a slow protonation of a hard oxyanion. However, such proton transfer rates are usually diffusion-controlled, so this seems unlikely.[74] On the other hand, the carbanion closure (e−P−d−c−p) portrayed below requires a very reasonable suggestion that the



rate-determining step corresponds to protonation of the soft, weakly basic radical anion **202**, prior to cyclization;[74,75] this is the mechanism we prefer. One must use caution, however, realizing that these conclusions are drawn for the particular set of substrates which were examined. In some cases, radical anion cyclization remains a viable option.

Applications to Synthesis. 1-Sterpurene (206)

Our first application of electroreductive cyclization methodology to natural product synthesis was in conjunction with a total synthesis of 1-sterpurene (**206**).[76] This isolactarane corresponds to one of the neutral metabolites isolated from the fungus *Stereum purpureum*, the causative agent of the so-called silver leaf disease which is associated with a variety of trees and shrubs. Our strategy focuses on three key steps: (a) electrochemical cyclization of the bis

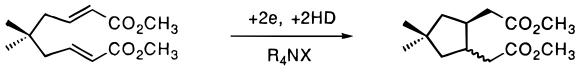


unsaturated ester **210** to produce the five-membered ring of **209**, (b) a Ruhlman-modified acyloin condensation to provide the six-membered ring (**209** to **208**), and (c) a photo-[2+2]-cycloaddition to generate the third ring.

In practice, reduction of **210** afforded the cyclopentyl diesters **209a,b** in 58−87% yield as a mixture of cis and trans isomers. As noted in Table 3, both the yield and stereoselectivity varied in response to changes in electrode and proton donor. Environmental factors clearly make the use of a glassy carbon electrode preferable. The *trans*-diester **209a** invariably corresponded to the major adduct, with the highest selectivity being achieved in the presence of cerium(III) chloride. We suspect that the latter is involved in a chelation process which predisposes an intermediate toward trans-selectivity. However, additional studies are needed to verify such a claim, preferably using soluble lanthanides as chelating agents.

The remainder of the sequence, culminating in the total synthesis of 1-sterpurene (**206**), proceeded as planned.

Table 3

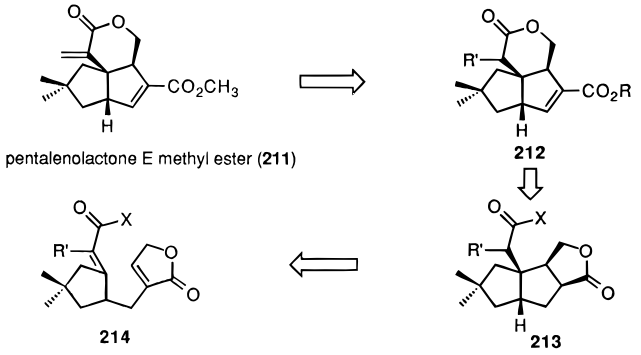


electrode	proton source	trans/cis ratio	yield (%)	additive*
Hg	AcOH, H_2O	2.6:1	82-87	none
Hg	$CH_2(CO_2Et)_2$	7.5:1	66	none
glassy carbon	$CH_2(CO_2Et)_2$	7.1:1	73	none
Cu	$CH_2(CO_2Et)_2$	11.6:1	58	none
Hg	$CH_2(CO_2Et)_2$	14.8:1	73	1.3 equiv $CeCl_3$

* suspension in acetonitrile.

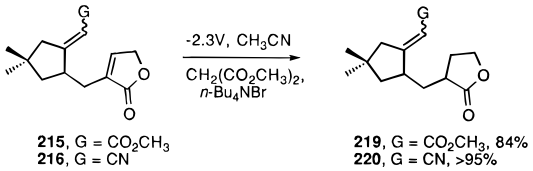
An Approach to Pentalenolactone E Methyl Ester (211)[77]

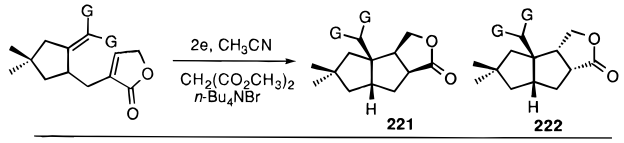
Pentalenolactone E methyl ester (**211**), an angularly fused sesquiterpene lactone, was first isolated and characterized by Cane and Rossi.[78] This interesting material attracted reasonable attention, ultimately leading to the development of several novel approaches for its construction. Our approach, one which though not complete has afforded a number of interesting and potentially useful discoveries, is illustrated below. Key to the successful implementation of the plan is the synthesis of butenolide **214**, the electrochemically promoted cyclization of **214** to the tricyclic γ-lactone **213**, ring opening of the latter to convert the linearly fused system to the angularly



fused six-membered ring lactone **212**, and functional group elaboration leading to the natural product **211**.

Butenolides **215**−**218** were assembled.[77] Both **215** and **216**, one tethered to an α,β-unsaturated ester, the other to an unsaturated nitrile, failed to undergo cyclization. Instead, the C=C π bond of the butenolide was reduced, leading cleanly and efficiently to saturation of that bond. In contrast, the corresponding alkylidene malonate **217** as well as the alkylidene malonitrile **218** both cyclize to afford a mixture of the cis-anti-cis and cis-syn-cis linearly fused lactones **221** and **222**.





G	potential (V vs SCE)	combined yield (%)	ratio (**221**/**222**)
217, CO_2CH_3	-2.1	90	1:1
218, CN	-1.6	23	1:1

That **217** and **218** undergo cyclization, while **215** and **216** do not, points to one of the significant advantages of controlled-potential electrochemical methodology over alternative, non-electrochemical methods. That is, one can vary the potential to match the electrophore. In this instance, when the butenolide is the easier electrophore to reduce, cyclization fails. By switching from a singly to a doubly activated electrophore, the roles reverse. Cyclization occurs from the latter onto the butenolide. We suspect that the reason for this behavior is related to the higher basicity of the radical anion which is produced upon reduction of **215** and **216**, compared to that of the more highly delocalized and presumably less basic species resulting from the reduction of **217** and **218**. In the former cases, acid−base chemistry dominates cyclization.

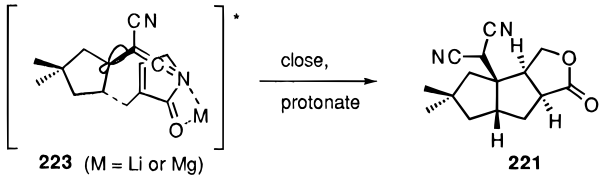
Another interesting feature of the electrochemistry of the doubly activated systems **217** and **218** can be discerned from the data presented in Table 4. First, the dinitrile is easier to reduce than the malonate. While this is a common trait of such systems, the difference in peak potentials is striking, corresponding to as much as 0.5 V, or ~11 kcal. Second, the

Table 4

G	potential (V vs SCE)	combined yield (%)	ratio	electrolyte
CO_2CH_3	−2.1	90	1/1	*n*-Bu_4NBr
CN	−1.6	23 (+25% starting material)	1/1	*n*-Bu_4NBr
CN	−1.7	77	3/1	$LiClO_4$
CN	−1.6	62	11/1	$Mg(ClO_4)_2$

stereoselectivity changes significantly depending upon the choice of supporting electrolyte, varying from zero (*i.e.*, a 1/1 mixture of stereoisomers) when *n*-Bu_4NBr is used to as high as 11/1 (**221**/**222**) in the presence of $Mg(ClO_4)_2$. Finally, we note that the major product corresponds to the cis-anti-cis adduct **221**, as required in the construction of pentalenolactone *E*-methyl ester (**211**).

We suggest that the stereoselectivity may have its origin in the ability of lithium and magnesium to serve as coordinating metals. For example, in the case of **218** undergoing cyclization in the presence of magnesium perchlorate, it seems reasonable to postulate the existence of an intermediate such as **223**,

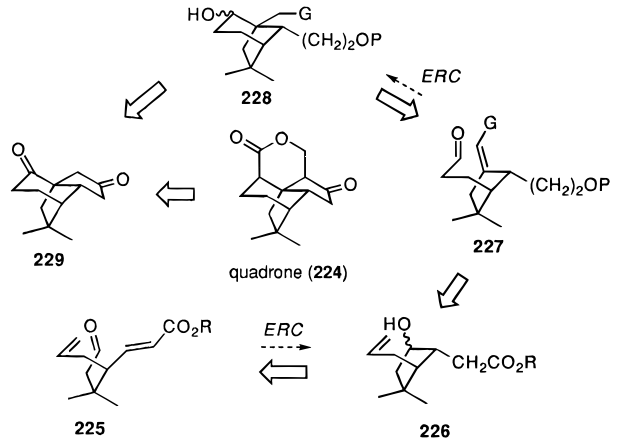


where the metal is associated with the butenolide as well as the reduced alkylidene malononitrile. Metal coordination to the nitrogen end of the CN unit in the intermediate is precedented in carbanion chemistry.[79] This effectively places the β carbon above that of the corresponding carbon in the butenolide. σ bond formation therefore establishes all but one stereocenter, it being determined in the final protonation of the enolate. That it should occur to afford a cis ring fusion is entirely reasonable given the substantial energy difference between cis- and trans-fused bicyclo[3.3.0] ring systems.[35]

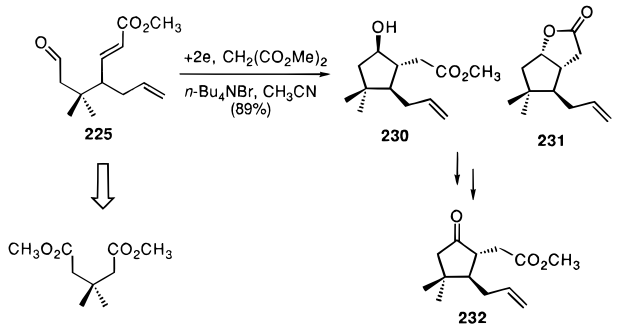
Compound **221** appears to be a reasonable precursor to the natural product. Efforts to complete the sequence are planned.

Formal Total Synthesis of Quadrone (224)

The utility of electroreductive cyclization chemistry is demonstrated quite nicely in its application to a formal total synthesis of quadrone (**224**).[80] This fungal metabolite isolated from *Aspergillus terreus*, displays *in vivo* and *in vitro* cytotoxicity. Of course, it has received much attention and has led to the development of new synthetic methods and strategies. Our approach focuses upon three transformations, two involving σ bond formation *via* electroreductive cyclization (ERC) and serving to convert **225** to **226** and **227** to **228**, the third being an oxidative cyclization used to generate **229** and the third of four rings.

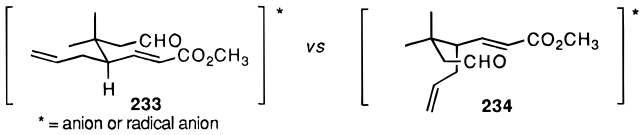


Compound **225** was synthesized in a straightforward manner from dimethyl 3,3-dimethylglutarate.

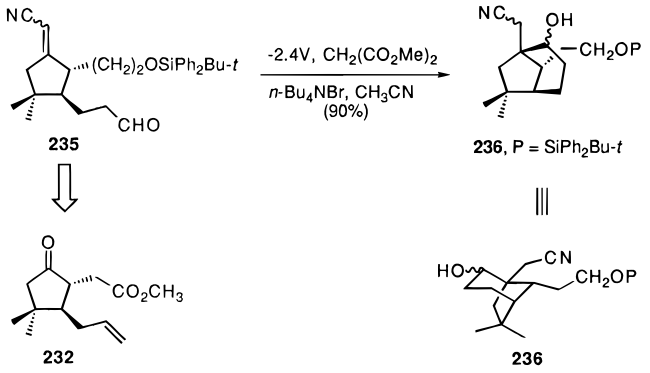


Controlled-potential reduction of **225** in the presence of dimethyl malonate as a proton donor afforded a mixture of two products, the γ-hydroxy ester **230** and lactone **231**, in a combined yield of 89%. Since these materials were epimeric at a center destined to become sp^2 hybridized, each was converted to a common intermediate, **232**.

We attribute the selective formation of materials with the ester and allyl units trans to one another, to the preference for the allyl unit to occupy a pseudoequatorial, rather than a pseudoaxial orientation in the product determining transition state. Compare, for example, transition state formulation **233** with **234**. This stereochemical outcome is fortunate, as later on in the sequence, it is necessary for the allyl unit (after functional group modification) to swing across the top face of the cyclopentyl ring system during the conversion of **227** to **228**. Were the substituents cis to one another, this would not be possible.

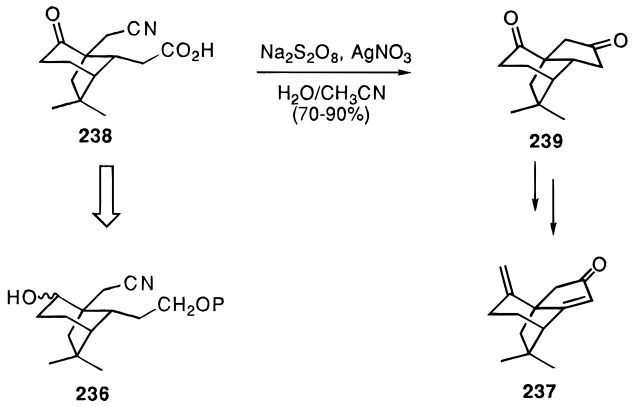


Keto ester **232** was converted to the unsaturated nitrile **235** in a routine manner. The latter proved to be an exceptionally useful intermediate. We were concerned that the electroreductive cyclization might not work in this case due to the significant steric demands which are associated with the formation of a σ bond to the fully substituted β carbon of the unsaturated nitrile. Our fears were allayed, however, by the discovery that the controlled-potential



reduction of **235** at −2.4 V in the presence of dimethyl malonate as the proton donor afforded a 90% isolated yield of the requisite [3.2.1] adduct **236**.

To complete our route, converging with Kende's synthesis at enone **237**,[81] required simple functional group modification of **236** in a manner which would

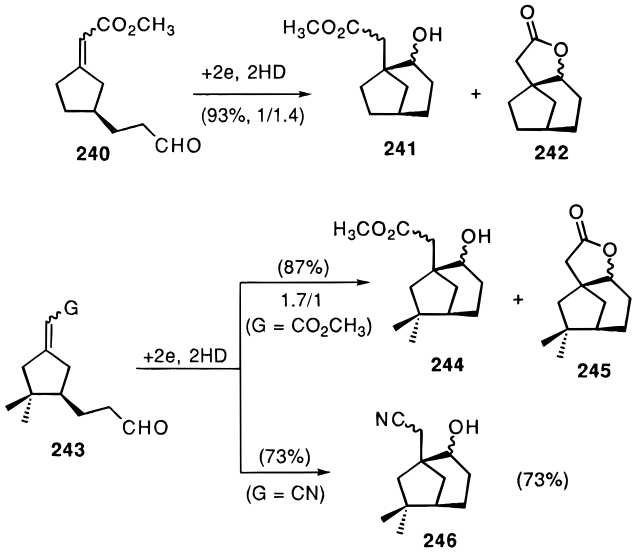


set the stage for formation of the third ring. Initially, we planned to use a Dieckmann condensation, but considering the nature of the functionality in **236**, we decided that a more direct approach was desirable. The thought was to utilize a scheme which would position the carbonyl unit of the new ring in the desired location and simultaneously excise the extra carbon. While the methodology has not seen widespread use in synthesis, the method of Nikishin and co-workers proved ideally suited to our needs.[82] Thus, simple functional group manipulation converted **236** to the nitrile acid **238**. When treated with sodium peroxydisulfate in water/acetonitrile at 60 °C, **238** undergoes decarboxylation, cyclization, and hydrolysis to afford the desired diketone **239** in yields ranging from 70 to 90%. Its conversion to enone **237** completed our effort, one which highlighted the use of two electroreductive cyclizations.

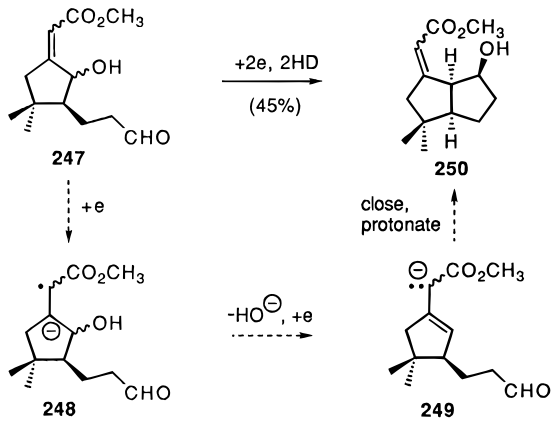
The [3.2.1] Framework

Scope and Limitations[83]

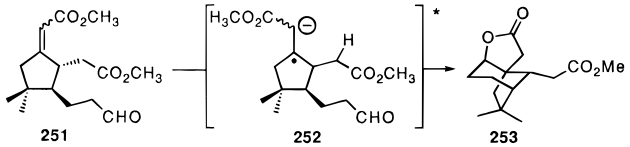
As indicated by the conversion of **235** to **236**, the electroreductive cyclization reaction provides an excellent method for the assembly of the bicyclo[3.2.1]-octane ring system. Several additional examples are portrayed in the following equations. In general, we prefer to use an unsaturated nitrile rather than the corresponding ester, as this avoids lactone formation.



As with any transformation, this methodology is not without limitations. For example, the γ-hydroxy unsaturated ester **247**, a substance we planned to use *en route* to quadrone, failed to undergo the desired cyclization.[83] Instead, elimination occurred, presumably leading to the extended enolate **249**, which condenses onto the aldehyde unit to afford the [3.3.0] adduct **250** in a 45% yield.

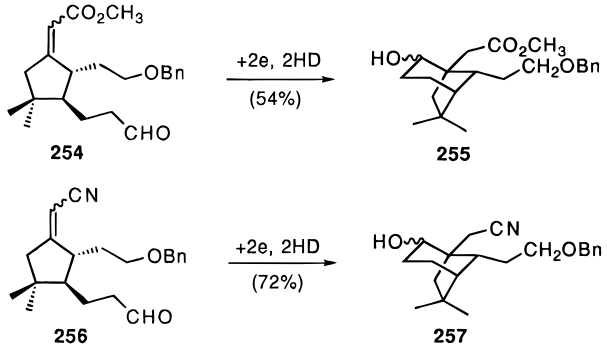


Another occasionally troublesome process is related to the tendency of some substrates to preferentially, or competitively, undergo acid−base chemistry.[83,84] Of course, this is not surprising, considering the nature of the putative intermediates. One system where this process diminishes the efficiency of the electroreductive cyclization is that of compound **251**.

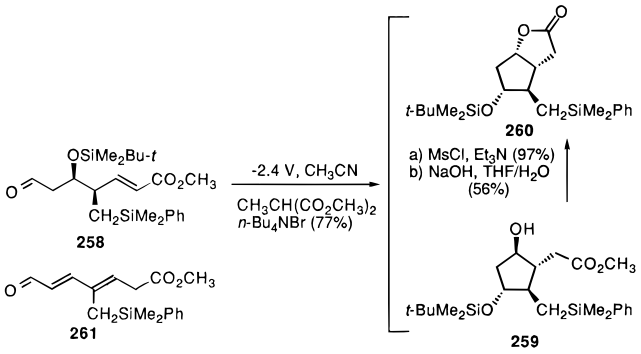


In this reaction, we were not able to isolate more than 35−40% of cyclized material, in this case, lactone **253**. We presume, based on the experiments described below, that the saturated ester serves as a proton source which is able to quench the intermediate **252** responsible for cyclization. When this proton source is rendered unavailable by conversion of the side chain ester to an ether as with compounds **254** and

256, the yield for cyclization increases to 54 and 72%, respectively.

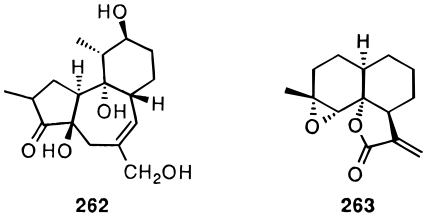


Another example of a case where acid−base chemistry competes with cyclization is found in our efforts to construct an analog of the Corey lactone.[85] The enantiomerically pure unsaturated ester **258** was



assembled and subjected to the conditions indicated in the equation shown above. In this instance, dimethyl methylmalonate was used as the proton donor to avoid 1,4-addition of the conjugate base to **258**. Cyclization afforded a combined 77% isolated yield of the γ-hydroxy ester **259** and the lactone **260**; the former could be converted to the lactone in the straightforward manner portrayed above. Unfortunately, these materials were accompanied by the formation of the conjugated diene **261**, a substance which undoubtedly arises *via* the intervention of acid−base chemistry, leading to β-elimination of the silyloxy unit.

We are currently engaged in efforts to use the electroreductive cyclization methodology *en route* to phorbol analogs (*e.g.* **262**) and have recently completed a total synthesis of the antimalarial agent, desmethyl arteannuin B (**263**).[86] The results of these efforts will be reported on another occasion.



Acknowledgments

We are grateful to the National Science Foundation (NSF) and the National Institutes of Health (NIH) for their support of our programs in the diyl trapping area, and to a joint program sponsored by the NSF and the Electric Power Research Institute (EPRI) for their support of our efforts in organic electrochemistry.

References

(1) (a) Dowd, P. *Acc. Chem. Res.* **1972**, *5*, 242. (b) Weiss, F. *Q. Rev. Chem. Soc.* **1970**, *24*, 278. (c) Moffitt, W. *Trans. Faraday Soc.* **1949**, *45*, 373. (d) Longuet-Higgins, H. C. *J. Chem. Phys.* **1950**, *18*, 265.
(2) Dowd, P. *J. Am. Chem. Soc.* **1966**, *88*, 2587. (b) Baseman, R. J.; Pratt, D. W.; Chow, M.; Dowd, P. *J. Am. Chem. Soc.* **1976**, *98*, 5726.
(3) Day, A. C.; Whiting, M. *Proc. Chem. Soc., London* **1964**, 368.
(4) Chan, D. M. T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, Chapter 3.2.
(5) Berson, J. A.; Bushby, R. J.; McBride, J. M.; Tremelling, M. *J. Am. Chem. Soc.* **1971**, *93*, 1544.
(6) Closs, G. L. *J. Am. Chem. Soc.* **1971**, *93*, 1546.
(7) Platz, M. S.; Berson, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 6743.
(8) (a) Carpenter, B. K.; Little, R. D.; Berson, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 5723. (b) Platz, M. S.; McBride, J. M.; Little, R. D.; Harrison, J. J.; Shaw, A.; Potter, S. E.; Berson, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 5725.
(9) Corwin, L. R.; McDaniel, D. M.; Bushby, R. J.; Berson, J. A. *J. Am. Chem. Soc.* **1980**, *102*, 276.
(10) Berson, J. A. In *Diradicals*; Borden, W. T., Ed.; Wiley: New York, 1982; Chapter 4.
(11) (a) Berson, J. A.; Duncan, C. D.; Corwin, L. R. *J. Am. Chem. Soc.* **1974**, *96*, 6175. (b) Berson, J. A.; Corwin, L. R.; Davis, J. H. *J. Am. Chem. Soc.* **1974**, *96*, 6177.
(12) Wentrup, C. *Reactive Molecules*, Wiley: New York, 1984; Chapter 4.
(13) Berson, J. A. *Acc. Chem. Res.* **1978**, *11*, 446.
(14) Little, R. D.; Losinski-Dang, L.; Venegas, M. G.; Merlic, C. *Tetrahedron Lett.* **1983**, *24*, 4499.
(15) Little, R. D.; Bukhari, A.; Venegas, M. G. *Tetrahedron Lett.* **1979**, 305.
(16) (a) Thiele, J. *Chem. Ber.* **1900**, *33*, 666. (b) Thiele, J. *Justus Liebigs Ann. Chem.* **1906**, *348*, 1.
(17) Freisleben, W. *Angew. Chem.* **1963**, *72*, 576.
(18) Büchi, G.; Bertheot, D.; Decorzant, R.; Grieder, A.; Hauser, A. *J. Org. Chem.* **1976**, *41*, 3208.
(19) Stone, K. J.; Little, R. D. *J. Org. Chem.* **1984**, *49*, 1849.
(20) Erden, I.; Xu, F.-P.; Sadoun, A.; Smith, W.; Sheff, G.; Ossun, M. *J. Org. Chem.* **1995**, *60*, 813.
(21) McLoughlin, J. I.; Little, R. D. *J. Org. Chem.* **1988**, *53*, 3624.
(22) Little, R. D.; Carroll, G. L. *J. Org. Chem.* **1979**, *44*, 4720.
(23) Meehan, S.; Little, R. D. *Abstracts of Papers*; 208th National Meeting of the American Chemical Society, Washington, DC; American Chemical Society: Washington, DC, 1994; ORGN 18.
(24) Little, R. D; Venegas, M. G. *Organic Synthesis*; Wiley: New York, 1990; *Collect Vol. VII*, p 56.
(25) (a) Rastetter, W. H. *J. Am. Chem. Soc.* **1976**, *98*, 6350. (b) Little, R. D.; Bregant, T. M. *Encyclopedia of Reagents for Organic Synthesis*; Wiley: New York, 1995.
(26) Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1976**, *42*, 918.
(27) Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* **1979**, *101*, 7129.
(28) Little, R. D.; Muller, G. W.; Venegas, M. G.; Carroll, G. L.; Bukhari, A.; Patton, L.; Stone, K. *Tetrahedron* **1981**, *37*, 4371.
(29) Little, R. D.; Higby, R. G.; Moeller, K. D. *J. Org. Chem.* **1983**, *48*, 3139.
(30) Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* **1981**, *103*, 2744.
(31) Little, R. D.; Moeller, K. D. *J. Org. Chem.* **1983**, *48*, 4487.
(32) Little, R. D.; Stone, K. J. *J. Am. Chem. Soc.* **1983**, *105*, 6976.
(33) Stone, K. J.; Little, R. D. *J. Am. Chem. Soc.* **1985**, *107*, 2495.
(34) Van Hijfte, L.; Little, R. D. *J. Org. Chem.* **1985**, *50*, 3940.
(35) Van Hijfte, L.; Little, R. D.; Petersen, J. L.; Moeller, K. D. *J. Org. Chem.* **1987**, *52*, 4647.
(36) Kissel, C. L.; Rickborn, B. *J. Org. Chem.* **1972**, *37*, 2060.
(37) Little, R. D.; Billera, C. F. *Tetrahedron Lett.* **1988**, *29*, 5711.
(38) Billera, C. F. M.S. Dissertation, University of California, Santa Barbara, 1988.
(39) Moeller, K. D.; Little, R. D. *Tetrahedron Lett.* **1985**, *26*, 3417.
(40) Little, R. D.; Bode, H.; Stone, K. J.; Wallquist, O.; Dannecker, R. *J. Org. Chem.* **1985**, *50*, 2400.
(41) Campopiano, O. Ph.D. Dissertation, University of California, Santa Barbara, 1986.
(42) Campopiano, O.; Little, R. D.; Petersen, J. L. *J. Am. Chem. Soc.* **1985**, *107*, 3721.
(43) Billera, C. F.; Philipp, C.; Little, R. D. *J. Org. Chem.* **1994**, *59*, 2270.

(44) McLoughlin, J. I.; Brahma, R.; Campopiano, O.; Little, R. D. *Tetrahedron Lett.* **1990**, *31*, 1377.
(45) (a) Little, R. D.; Carroll, G. L. *Tetrahedron Lett.* **1981**, *22*, 4389. (b) Little, R. D.; Carroll, G. L.; Petersen, J. L. *J. Am. Chem. Soc.* **1983**, *105*, 928.
(46) (a) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States;* deMayo, P., Ed.; Academic Press: New York, 1980; Vol.1, Chapter 4 and references therein. (b) Lusztyk, J.; Maillard, B.; Deycard, S.; Lindsay, D. A.; Ingold, K. U. *J. Org. Chem.* **1987**, *52*, 3509.
(47) (a) Masjedizadeh, M. R.; Dannecker-Doerig, I.; Little, R. D. *J. Org. Chem.* **1990**, *55*, 2742. (b) Little, R. D.; Masjedizadeh, M. R.; Moeller, K. D.; Dannecker-Doerig, I. *Synlett* **1992**, 107. (c) We do not mean to imply that geminal substitution has no influence on the course of intramolecular diyl trapping reactions. However, our data does not permit specific commentary regarding how it influences the rate of cycloaddition. Geminal substitution might, as was suggested by a reviewer, facilitate cyclization in a manner similar to that attributed to the Thorpe−Ingold effect. Several years ago, we attempted to address this point qualitatively, by comparing the cycloaddition result for diazene **49a** with that of the same system devoid of *gem*-methyl substitution.[28]
(48) Masjedizadeh, M. R.; Fite, C.; Little, R. D. *Tetrahedron Lett.* **1990**, *31*, 1229.
(49) Ott, M. J.; Little, R. D. *Abstracts of Papers*; 209th National Meeting of the American Chemical Society, Anaheim, CA; American Chemical Society: Washington, DC, 1995; ORGN 208.
(50) Siemionko, R.; Shaw, A.; O'Connell, G.; Little, R. D.; Carpenter, B. K.; Shen, L.; Berson, J. A. *Tetrahedron Lett.* **1978**, 3529.
(51) Dowd, P.; Senqupta, G.; Sachdev, K. *J. Am. Chem. Soc.* **1970**, *92*, 5726.
(52) (a) Balchi, M. D.; Frolow, F.; Hoornaert, C. *J. Org. Chem.* **1983**, *48*, 1841. (b) Batty, D.; Crich, D. *Tetrahedron Lett.* **1992**, *33*, 875. (c) Snider, B. B.; Merritt, J. E. *Tetrahedron* **1991**, *47*, 8663.
(53) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.
(54) Salem, L. *Electrons in Chemical Reactions, First Principles*; Wiley: New York, 1982; pp 208−213.
(55) Leonetti, J.; Little, R. D. *Abstracts of Papers*; 210th National Meeting of the American Chemical Society, Chicago, IL; American Chemical Society: Washington, DC, 1995; ORGN 14.
(56) Billera, C. F.; Little, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 5487.
(57) (a) Curran, D. P.; Shen, W. *J. Am. Chem. Soc.* **1993**, *115*, 6051. (b) Curran, D. P. *Synthesis* **1988**, 417 (Part 1), 489 (Part II).
(58) Adam, W.; Finzel, R. *J. Am. Chem. Soc.* **1992**, *114*, 4563.
(59) Leroy, G.; Sana, M.; Wilante, C. *J. Mol. Struct. (Theochem)* **1991**, *234*, 303.
(60) Kelley, D. F.; Rentzepis, P. M.; Mazur, M. R.; Berson, J. A. *J. Am. Chem. Soc.* **1982**, *104*, 3764.
(61) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151.
(62) (a) Little, R. D.; Brown, L. M.; Masjedizadeh, M. R. *J. Am. Chem. Soc.* **1992**, *114*, 3071. (b) While we suggest the intermediacy of a dipolar, bisected singlet, we realize that this geometry is not necessary to account for the chemistry.
(63) Nicolaou, K. C.; Dai, W. -M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387.
(64) Bregant, T. M.; Groppe, J.; Little, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 3635.
(65) Spielmann, H. P.; Fagan, P. A.; Bregant, T. M.; Little, R. D.; Wemmer, D. E. *Nucleic Acids Res.* **1995**, *23*, 1576.
(66) Ongoing research with Ms. Amy Allan, University of California, Santa Barbara; unpublished results.
(67) Little, R. D.; Fox, D. P.; Van Hijfte, L.; Dannecker, R.; Sowell, G.; Wolin, R. L.; Moëns, L.; Baizer, M. M. *J. Org. Chem.* **1988**, *53*, 2287.
(68) Fry, A. J.; Little, R. D.; Leonetti, J. *J. Org. Chem.* **1994**, *59*, 5017.
(69) Fry, A. J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley: New York, 1989.
(70) (a) A good discussion and set of references can be found: House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin: Menlo Park, 1972; pp 185. (b) Little, R. D.; Baizer, M. M. In *The Chemistry of Enones*, Patai, S. and Rappoport, Z., Eds.; Wiley: New York, 1989; Vol 2, Chapter 14.
(71) Shono, T. *Electroorganic Synthesis*, Academic Press: London, 1991.
(72) (a) Nadjo, L.; Saveant, J. M. *J. Electroanal. Chem.* **1973**, *48*, 113. (b) Andrieux, C. P.; Saveant, J. M. *J. Electroanal. Chem.* **1974**, *53*, 165. (c) Parker, V. D. *Acta Chem. Scand.* **1980**, *34B*, 359. (d) Parker, V. D. In *Topics in Organic Electrochemistry;* Fry, A. J., Britton, W. E., Eds.; Plenum: New York, 1986; Chapter 2.
(73) (a) Tsang, R.; Dickson, J. K., Jr.; Pak, H.; Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1987**, *109*, 3484. (b) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 230.
(74) (a) Kresge, A. J. *Acc. Chem. Res.* **1975**, *8*, 354. (b) Koch, H. F. *Acc. Chem. Res.* **1984**, *17*, 137.
(75) (a) Parker, V. D.; Tilset, M.; Hammerich, O. *J. Am. Chem. Soc.* **1987**, *109*, 7905. (b) Nielsen, M. F.; Hammerich, O.; Parker, V. D. *Acta Chem Scand.* **1986**, *B40*, 101.
(76) Moëns, L.; Baizer, M. M.; Little, R. D. *J. Org. Chem.* **1986**, *51*, 4497.
(77) (a) Bode, H., Ph.D. Dissertation, University of California, Santa Barbara, 1989. (b) Bode, H. E.; Sowell, C. G.; Little, R. D. *Tetrahedron Lett.* **1990**, *31*, 2525.
(78) Cane, D. E.; Rossi, T. *Tetrahedron Lett.* **1979**, 2973.
(79) Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* **1974**, *96*, 5272.
(80) Sowell, C. G.; Wolin, R. L.; Little, R. D. *Tetrahedron Lett.* **1990**, *31*, 485.
(81) Kende, A. S.; Roth, B.; Sanfilippo, P. J.; Blacklock, T. J. *J. Am. Chem. Soc.* **1982**, *104*, 5808.
(82) Nikishin, G. I. In Organic Synthesis: Modern Trends, Chizhov, O, Ed.; Blackwell: Oxford, 1987; p 53.
(83) Little, R. D.; Wolin, R.; Sowell, G. *J. Electrochem. Soc., Jpn (Denki Kagaku)* **1994**, *62*, 1105.
(84) Amputch, M. A.; Little, R. D. *Tetrahedron* **1991**, *47*, 383.
(85) Little, R. D.; Sowell, C. G. In *Electroorganic Synthesis, Festschrift for Manuel M. Baizer*, Little, R. D., Weinberg, N. L., Eds.; Dekker: New York, 1991; pp 323−330.
(86) Unpublished results with Mr. Michael Schwaebe, University of California, Santa Barbara.

CR950017D