The Versatile Trimethylenemethane Diyl; Diyl Trapping Reactions − Retrospective and New Modes of Reactivity

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The diyl trapping reaction has been applied as the key step in the assembly of a variety of ring systems. An overview of the various modes of reactivity of the trimethylenemethane (TMM) diyl is presented, detailing both the mechanistic features affecting selectivity as well as several applications directed towards the synthesis of a variety of natural products. Also highlighted are two new areas of focus, atom transfer and diyl-induced vinylcyclopropane ring opening.

This *Microreview* highlights the chemistry of trimethylenemethane-like diradicals (TMM diyls) within the framework of our studies of the diyl trapping reaction, a process characterized by cycloaddition, either inter- or intramolecular, between the diyl and a diylophile.[1] As illustrated in Scheme 1, a relatively wide variety of ring systems can be accessed using this approach, particularly so the intramolecular variation.

We also describe two promising new areas of research involving these versatile materials, namely, atom transfer and fragmentation/cyclization.

Background

The parent diradical, TMM (**1**), has been of interest for many years.[2] While the first reports appeared in the literature in 1949,[3] it was not until 1966 that the late Paul Dowd

Dan Little (center) was born and raised in Superior, Wisconsin. He received the bachelor of science degree in mathematics and chemistry from the University of Wisconsin, Superior. During that time, he spent two rewarding summers at the University of South Dakota and one semester at Argonne National Laboratory. Following undergraduate work, he moved to Madison, Wisconsin where he obtained his Ph.D. with Howard Zimmerman at the University of Wisconsin. A delightful and rewarding postdoctoral stay at Yale University with Jerome Berson preceded a move to UCSB. A past recipient of Sloan and Plous Awards, Dan is now professor and chairman of the UCSB Chemistry Department. His research interests are relatively broad ranging from the chemistry highlighted in the present Microreview to organic electrochemistry.

Amy Kim Allan (left) was born in Seoul, Korea and moved to Los Angeles, California at the age of two. She received her bachelor of science degree from the California State University at Los Angeles in 1993 and is currently working towards a Ph.D. at the University of California, Santa Barbara in the research group of Professor Little. The focus of her present research includes the application of an atom transfer process of a TMM (trimethylenemethane) diyl towards the natural product rudmollin, and mechanistic studies of DNA cleavage by a TMM diyl.

Georgia Law Carroll (right), a native Californian, received her bachelor of science degree from the University of California, Santa Barbara, graduating in 1989 with high honors. After working in industry for three years, she returned to UCSB in 1993 to pursue her doctoral degree with Professor Little. Currently, her areas of research focus upon synthetic strategies directed toward phorbol analogs utilizing electroreductive cyclization methods, and also the investigation of TMM initiated vinylcyclopropane cleavages.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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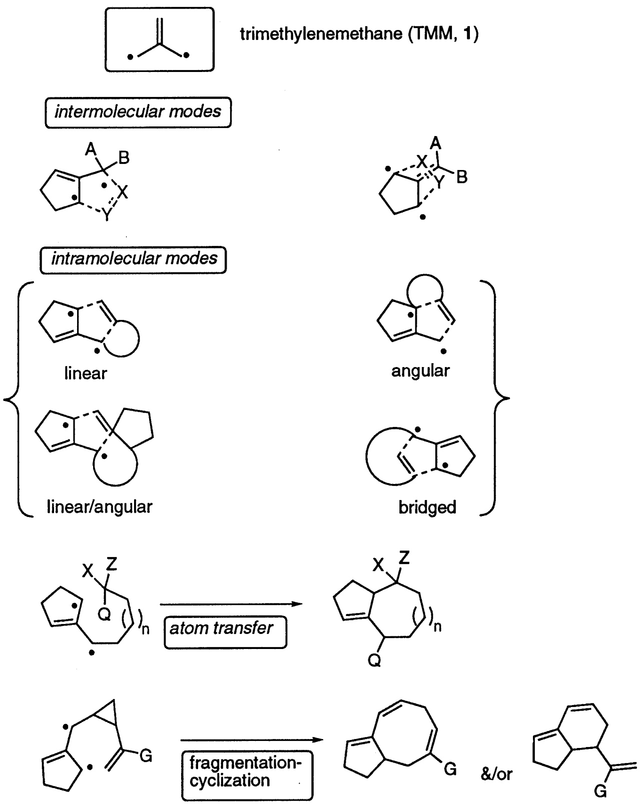
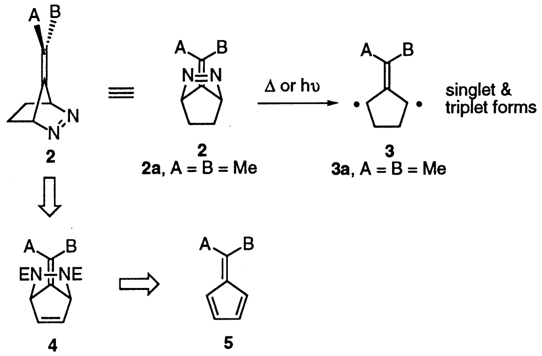
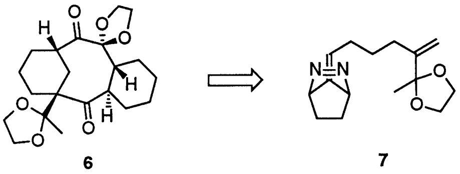
Scheme 1



Scheme 2



Scheme 3



was actually able to synthesize and study this material using ESR spectroscopy at low temperatures.[4] In accord with early theoretical predictions, TMM (**1**) did indeed display a triplet spectrum, and evidence was accumulated to demonstrate that it corresponded to the ground state.

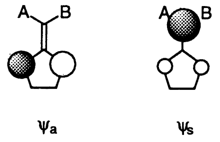
The foundation for much of our work, particularly the early studies, was provided by Berson and coworkers.[5][6] Among many other things, they examined cycloadditions between the 2-isopropylidenecyclopentane-1,3-diyl (**3a**) and a variety of diylophiles.[6] Their work led to formulation of the "cascade mechanism"[5b] that has been used as a mechanistic rationale for much of the chemistry described herein.

The cycloalkylidene diyls **3** that have formed the focus of our efforts can be generated either thermally or photochemically from bicyclic diazenes, **2**.[1] We routinely use the route portrayed in Scheme 2. It has proven versatile enough to handle the wide variety of systems we have examined and is for the most part, the method of choice.

Diyl trapping reactions are exceptionally easy to conduct. In fact, it is not unreasonable to say that they are easier than most since they simply require heating or photolysis until the starting material disappears, removal of the solvent and isolation of the product(s). While early studies[1] were conducted on a small scale, we now realize that it is simple to scale the process to preparative levels, and do so with ease. For example, in a recent effort designed to gain access to the ABC-ring system of Taxol® analog **6**, we routinely used more than 15 g (ca. 58 mmol) of the diyl precursor **7** in an intramolecular cycloaddition that consistently proceeded in >80% yield.[7]

The temperatures used to generate the diradical range from an extreme of −20 °C for the onset of nitrogen loss (**2**, A = B = OMe),[8] to the reflux temperature of a number of different solvents, often acetonitrile or THF. In nearly all cases, the latter conditions are employed. As far as we are aware, the low temperature extreme is limited to the one example cited. In that instance, the presence of the electron-donating groups renders loss of nitrogen a symmetry allowed process. This is so because the electron-donating substituents perturb the formally degenerate TMM NBMO's in such a manner that the diyl HOMO is the antisymmetric orbital, ψ_a (Figure 1). The phase properties of this orbital match those of the π^* orbital of nitrogen, thereby rendering the process allowed.[8] It is interesting to note that even though the symmetric orbital, ψ_s, corresponds to the HOMO in most cases studied, the temperatures required for loss of nitrogen are still relatively low, e.g., refluxing THF or acetonitrile. Thus, the formal "forbiddeness" is reflected by only a modest increase in the temperature needed to induce diyl formation. Typical Arrhenius activation energies for loss of nitrogen range from 28.8 for diazene **2a**, to 26.4 kcal/mol when the more highly stabilized monophenyl diyl (**3**, A = Ph, B = H) is formed.[9]

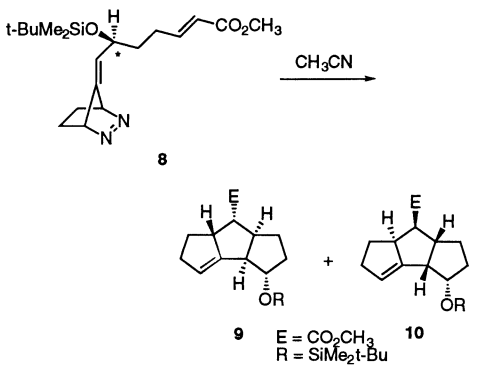
Figure 1



Asymmetric Induction: Thermolysis vs. Photolysis

Photochemical generation of the diyl offers a number of advantages, the most important being that the process can be initiated at low temperatures. This can lead to enhanced selectivity in instances where operation at an elevated temperature might trigger a competitive pathway. The chemistry of the diyl derived from diazene **8**, for example, has been studied extensively.[10] It was generated both thermally and photochemically. Several important points emerged. First, the products and product distribution obtained in both the thermally and photochemically promoted process proved identical when conducted at a common temperature, viz., 50 °C. That temperature was low enough to assure a negligible thermal contribution to the photchemically initiated transformation. We concluded that under these conditions, the same intermediate is formed regardless of its mode of generation. Secondly, it was possible to obtain high levels of asymmetric induction, particularly in the photoinitiated instance. Thus, despite the fact that ds values of as high as 92% were achieved when the reaction was conducted at 81 °C, this value rose as the temperature was lowered, reaching a value of 98% in the corresponding photochemically initiated process conducted at −31 °C (Table 1).

Table 1

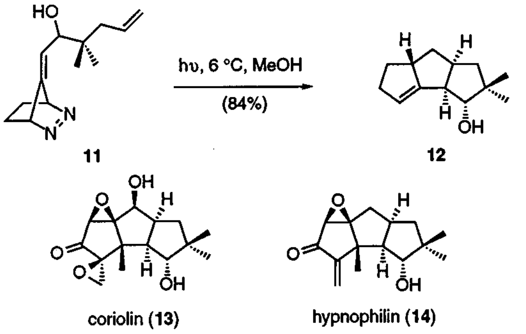


conditions	(°C)	ratio **9/10**	% ds
hν	−31	49	98
hν	−2	24	96
hν	7	26	96
hν	50	14	93
Δ	50	15	94
Δ	66	13	93
Δ	81	12	92

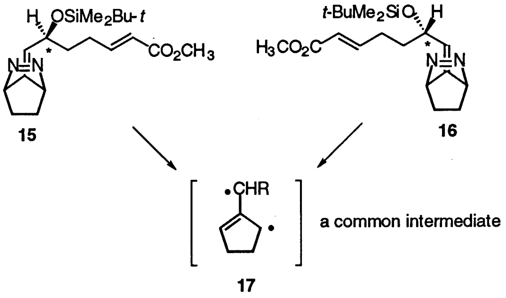
We capitalized on these findings in the key step of our total synthesis of the anti-cancer agents (*d,l*)-coriolin (**13**)[11][12] and (*d,l*)-hypnophilin (**14**).[11][12] Thus, irradiation of diazene **11** at 6 °C through a Pyrex filter, led cleanly to the formation of **12** in an 84% yield.

Another point of interest and much practical importance is the fact that regardless of the mode of generation of the diyl, the same product distribution and yield is obtained independent of the geometry about the exocyclic π-bond of the diazene.[10] This implies a very *important* and *general* point, one exemplified in the chemistry of the diastereomeric diazenes **15** and **16**: the same diyl intermediate **17** is formed from each diazene. Thus, free rotation occurs about the exocyclic bond of the diyl. Consequently, in synthesizing a substrate to be used in, for example, a total synthesis effort or a mechanistic investigation, one need not be concerned about the presence of diastereomeric alkenes.

Scheme 4



Scheme 5



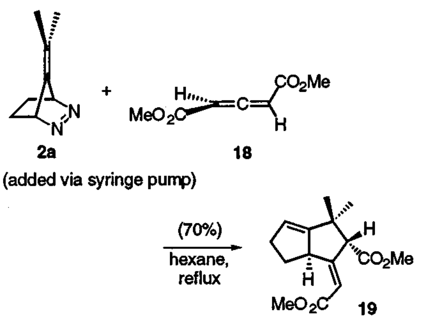
Intermolecular Modes of TMM Reactivity: Allenes as Diylophiles and Construction of Heterocycles

TMM diyls participate in a relatively wide range of reactions, and despite their short lifetimes (e.g., in the case of **3a**, 0.28 ns[5b] for the singlet and 916 ns[13] for the triplet), they are capable of undergoing remarkably selective processes. Some we have already encountered in the chemistry described thus far. The electron-rich diyls that have been most frequently studied can be intercepted by electron-deficient alkenes,[1][6] and alkynes[14] to assemble carbocyclic frameworks. Recently, allenes have also been shown to be effective trapping agents.[15] For example, we have explored the intermolecular cycloaddition chemistry of the symmetrical allene diester **18** and diazene **2a**. Cycloaddition afforded compound **19**, in a triplet derived process as a single regio- and stereoisomer.

The best yield, 70%, was obtained when a ca. 2.5 mM solution of the diazene was added slowly to a 51 mM solution of allene in refluxing hexanes; similar results were obtained in THF, though the yield was slightly less (64%).

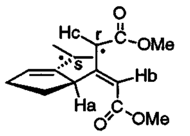
To rationalize the stereochemical outcome we suggest that diradical preferentially adopts a geometry wherein the plane of the five-membered ring and the five-carbon side

Scheme 6



chain are nearly perpendicular. Of the geometries available, that portrayed in structure **20** minimizes non-bonded interactions relative to alternatives. σ-Bond formation between carbons C_r and C_s leads to the observed adduct, **19**.

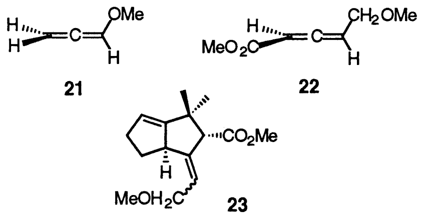
Figure 2



20

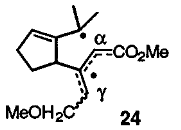
We also explored the chemistry of allenes, **21** and **22**. The former, being electron rich at one end of the π-system, and essentially neutral at the other, might be expected to intercept the diyl at the neutral end. It did not. The latter, under the optimal reaction conditions described above, did undergo cycloaddition to afford in a 50% yield, a single regioisomer which was isolated as a mixture of stereoisomers, **23**.

Figure 3



This regiochemical outcome is of interest. We suggest that its origin might simply be in the difference in the size of the coefficients at the potential reacting sites, C_α and C_γ, in the SOMO of diradical **24**. The former being larger, should, and does correspond to the preferred reaction site. Such selectivity is reminiscent of the kinetic α-selectivity observed in alkylation of extended enolates.[16]

Figure 4



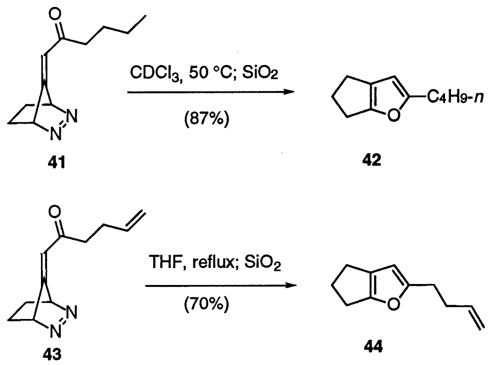
24

Heterocycles can also be constructed via cycloadditions to azo dicarboxylates, or to the π-portion of C=O, C=S, and C=N containing substrates. Examples are provided in Table 2.[14] Entries 2, 3, and 6 are particularly notable. The second and third illustrate two points of interest. Notice, for example, that for the same diylophile, diethyl oxomalonate, the trapping reaction can either be selective, as in the third entry, or non-selective, as portrayed by entry two. The formation of each product can be rationalized by assuming a diyl HOMO controlled process wherein the symmetric orbital, π_S (Figure 1), functions in that capacity.[8a] The difference between the two processes clearly resides in the nature of the diyl; in one case, the exocyclic carbon is unsubstituted while in the other, it bears a sterically more demanding *gem* methyl unit. The selectivity expressed in the reaction of diyl **25** with the diylophile presumably reflects both the direction and magnitude of polarization of the diyl HOMO/diylophile LUMO, as well as the absence of unfavorable steric interactions. We suggest, but do not have a sufficient number of examples to verify with certainty, that selectivity of this nature might be the rule in intermolecular cycloadditions to the diprotio diyl **25**.

The sixth entry is of interest for it also portrays a selective process, and because in the absence of Lewis acid, no reaction was observed. Presumably, the acid decreases the HOMO−LUMO energy gap and accentuates the polarization of the LUMO.[8a][14]

Heterocycles are also accessible using an interesting version of the intramolecular process that is illustrated by the conversion of diazenes **41** and **43** to the bicyclic furans **42** and **44**, following chromatography over silica gel (SiO_2).[17] In these cases, the carbonyl formally behaves as the cycloaddition partner. Obvious variations on the theme suggest that replacement of oxygen by nitrogen, sulfur or another heteroatom ought to provide access to other heterocyclic systems. This area of research remains open for exploration.

Scheme 7

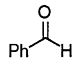
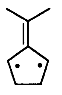
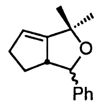
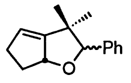
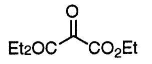
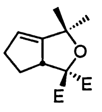
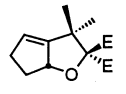
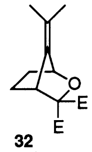
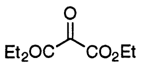
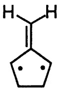
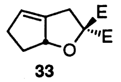
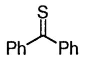
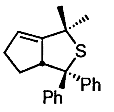
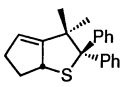
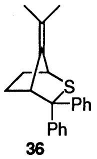
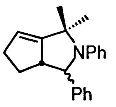
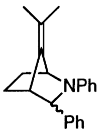
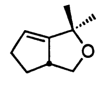


Intramolecular Diyl Trapping and Oxygen Quenching: A Diagnostic Tool

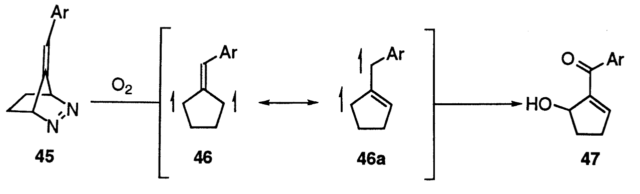
Molecular oxygen also intercepts the diyl.[18] In cases where an aryl substituted diazene is used (**45**), the chemistry is clean and affords respectable yields (> 70%) of enone **47** (e.g. Ar = *p*-$CH_3OC_6H_4$).[19]

When the aryl group is replaced by an alkyl group, the chemistry is more complex. For example, when diazene **48**

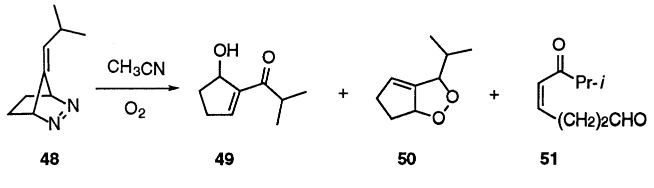
Table 2

entry	diylophile	diyl	cycloadducts (isolated yields)
1		 **2a**	 **26**, 33% β - Ph **27**, 4% α - Ph  **28**, 37% β - Ph **29**, 4% α- Ph
2		**2a**	 **30** 27%  E = CO_2Et **31** 19%  **32** 17%
3		 **25**	 **33** 75%
4		**2a**	 **34** 50%  **35** 22%  **36** 19%
5	PhN=CHPh	**2a**	 **37**, 3% α - Ph **38**, 37% β - Ph  **39** 35%
6	(CH_2O) $ZnCl_2$	**2a**	 **40** 87%

Scheme 8



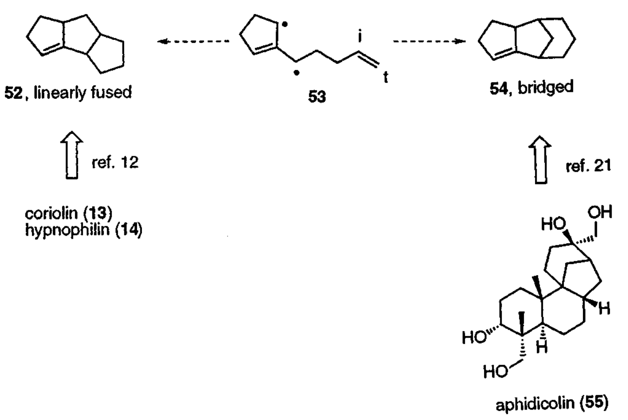
Scheme 9



is heated in refluxing acetonitrile in the presence of a steady stream of oxygen, three products, **49**, **50**, and **51** are isolated.[19]

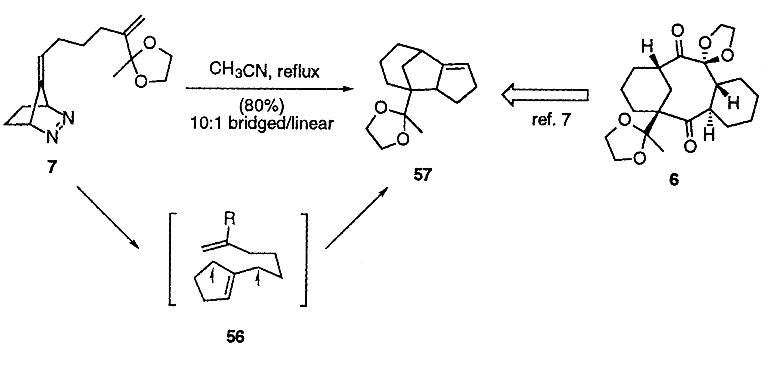
The reaction with oxygen serves as a diagnostic for the intervention of triplet chemistry and has been used as a mechanistic tool.[5b][18] While in principle both the singlet and triplet diyl can react with molecular oxygen, a combination of the low oxygen concentration available under the reaction conditions, combined with the short lifetime and rapid rate of intersystem crossing of the singlet to the triplet, allows only the triplet diyl to react. Thus, oxygen behaves as a triplet quencher. Use of this technique proved invaluable in our search for a means to achieve regioselection in the intramolecular cycloaddition leading to the regioisomeric linearly fused (**52**) and bridged (**54**) tricyclic skeletons illustrated in Scheme 10.[20] As a result of these studies, we are now able to selectively form either regioisomer, and by design. This is important, particularly within the context of applying the methodology to the total synthesis of natural products possessing these skeletons [e.g., coriolin (**13**),[12] hypnophilin (**14**),[12] aphidicolin (**55**)], or those that might be readily derived from them (e.g. **6**). At this time, our efforts focus on utilizing this attribute of the intramolecular diyl trapping reaction to access aphidicolin(**55**)[21] as well as Taxol® analogs such as **6** and structurally more complex and potentially bioactive materials.[7]

Scheme 10



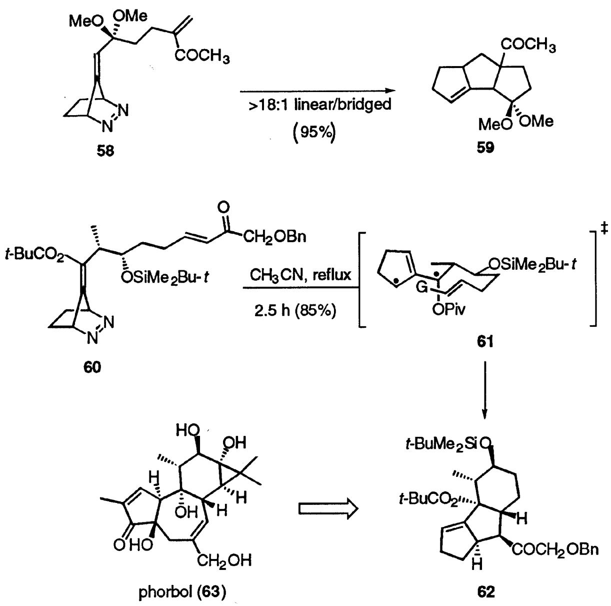
Invariably, bridged adducts **54** are triplet derived and formed selectively in those cases where a "large" alkyl group is appended to the internal carbon of the diylophile, that is, to C_i of structure **53**. Here, a 6-*endo-trig* cyclization is preferred over the alternative 5-*exo-trig* pathway. The transformation of diazene **7** to the bridged cycloadduct **57** via triplet diyl **56** illustrates this point, and also provided us an opportunity to explore model studies that led to the synthesis of Taxol® analog **6**.[7]

Scheme 11



On the other hand, linearly fused materials **52** are derived from either spin state. They can be produced selectively in a singlet-selective process in those cases wherein an electron-withdrawing group is appended to either of the carbons C_i or C_t of the diylophile (Scheme 10).[20] The transformations portrayed in Scheme 12 are illustrative. The second case shows promise as an entry to the tumor-promoting phorbol esters.[22]

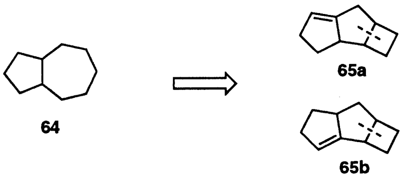
Scheme 12



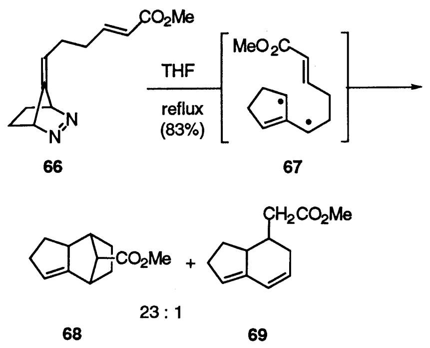
Another instance where oxygen quenching was used to determine the nature of the reactive spin state, arose as a consequence of our interest in adapting the intramolecular diyl trapping reaction to the synthesis of tricyclic adducts such as **65 a, b**. Fragmentation of the σ bond common to the four and five-membered rings promised to deliver the bicyclo[5.3.0] ring system **64** that is common to many natural products.[23] To accomplish this objective, we synthesized and examined two diazenes,[24][25] **66** and **70**, differing in the location of the electron-withdrawing group appended to the diylophile. When it was positioned at the terminal site (**66**), the reaction failed to produce the desired skeleton. Instead, a stepwise process occurred via an initial 6-*exo-trig* cyclization of **67**.[24]

In contrast, when positioned on the internal carbon (**70**), both the *cis,syn* linearly fused tricycle **71** and triene **72**, were isolated in yields ranging from 66–85%.[25] Both products

Scheme 13

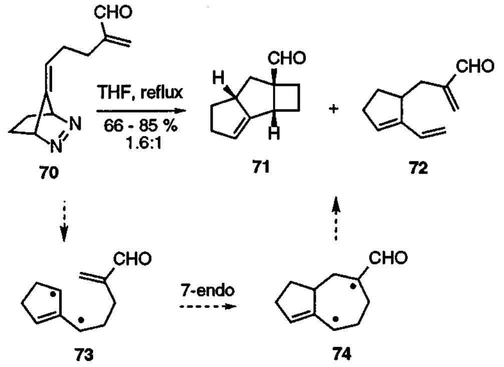


Scheme 14



suggest the intervention of the 1,4-diyl **74** formed on 7-*endo-trig* cyclization of the initial TMM diyl **73**. Oxygen quenching studies were used to determine the spin state responsible for the formation of each adduct, triene **72** being triplet derived, while the linearly fused product **71** was formed from both the singlet and triplet manifolds.[25]

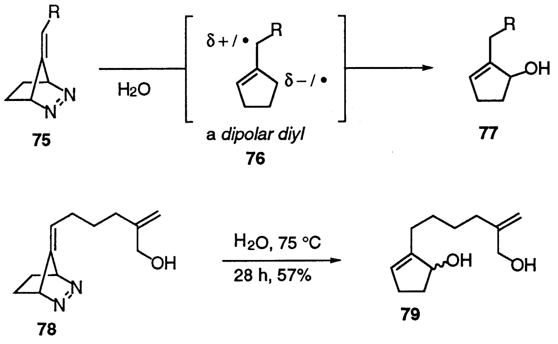
Scheme 15



Reaction with Water and DNA Cleavage by a TMM Diyl

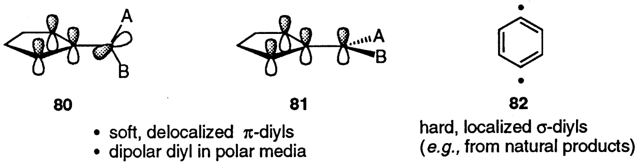
In nearly all cases, diyl trapping reactions are conducted in an organic solvent. We have, however, found occasion to explore the chemistry in an aqueous or semi-aqueous medium.[26][27] Dramatic differences are observed. Qualitatively, when the dielectric constant of the medium is >48 at 60 °C, the intermediate displays dipolar character and undergoes reaction with water.[26] Even in the case of diazene **78**, an instance where the intermediate could be intercepted intramolecularly by an alkene, the reaction with water proved competitive leading to the formation of diol **79**.

Scheme 16



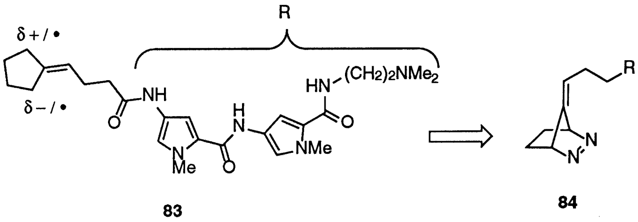
Recently, we explored the behavior of the intermediate **83** formed from a diazene in the presence of DNA,[27] the thought being that it might be capable of engaging in chemistry that leads to DNA cleavage in a fashion similar to that of the naturally occurring antitumor agents.[28] TMM diyls differ substantially from those derived from the natural materials in that those of the TMM variety correspond to soft, delocalized species **80** and **81**, rather than hard, localized, exceptionally reactive σ diyls **82** and are therefore expected to be less reactive. The concern, but also the intrigue, was that the intermediate might prove unreactive.

Figure 5



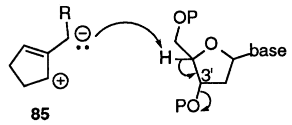
Diazene **84** was synthesized to explore these issues.[27] When irradiated at room temperature in the presence of 517 and 167 base pair restriction fragments of 5′-^{32}P end-labeled pBR322, cutting does occur, and preferentially in AT-rich regions of the minor groove.

Figure 6



We suggest that there are three pathways that could lead to cleavage: (1) Direct hydrogen atom abstraction. Given that TMM diyls are capable of participating in an intramolecular hydrogen atom transfer,[29] and that binding to DNA can be likened to 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 above, triplet TMM diyls react read-

Figure 7



ily with molecular oxygen.[18][19] 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.[26] 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, as shown in Figure 7. Such a process would lead directly to 3′/5′-cleavage. At this time, we do not know which, if any of these pathways is operable. Efforts to elucidate the pathway are underway.[30]

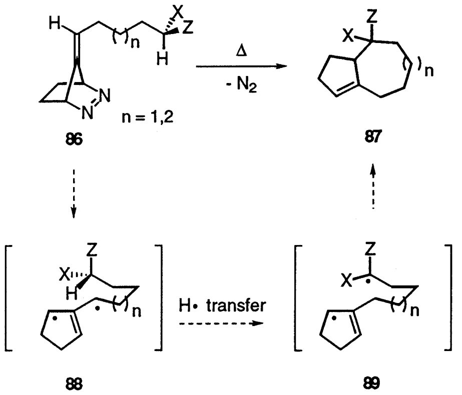
Novel Reaction Pathways

Two additional modes of reactivity have recently been discovered, namely, intramolecular atom transfer[29][31] and diyl-induced vinylcyclopropane fragmentation.[32] Both appear to have substantial potential as powerful new synthetic tools, and each provides a fertile territory for study mechanistically.

Intramolecular Atom Transfer Reactions of TMM Diyls

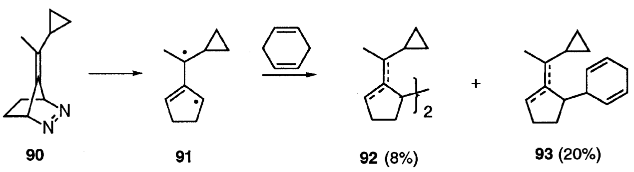
Our ongoing interest in the discovery of alternative reaction pathways for TMM diyls led us to examine the possibility of achieving atom transfer. The basic idea is summarized in Scheme 17; the overall transformation leads to the facile construction of functionalized bicyclo[5.3.0] and [6.3.0] carbocyclic ring systems.[29] The abundance of natural products containing medium-sized rings makes this methodology a promising route toward many useful targets.

Scheme 17



In the previously described diyl-trapping reactions with alkenes and other diylophiles, no occasion of H-atom transfer from solvent (e.g., acetonitrile, THF, 2-methyltetrahydrofuran, methanol and ethylene glycol) was ever observed to be a competing process. The ability of TMM diyls to participate in hydrogen atom abstraction was first demonstrated by Adam and Finzel.[33] They reported that products **92** and **93** were derived from intermolecular hydrogen atom transfer to TMM diyl **91**, and comprised 28% of the reaction mixture when thermolysis was carried out in a solution of benzene containing 0.1 M 1,4-cyclohexadiene as hydrogen atom donor.

Scheme 18



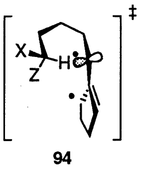
Our thought was to devise a system where the process portrayed in Scheme 17 would both be thermodynamically and kinetically feasible. The substrates were designed so that following a 1,5- or 1,6 hydrogen-atom transfer (depending on tether length), the new radical center would be stabilized by the substituents X and Z. The newly formed 1,7- or 1,8-diradical **89** could then engage in carbon−carbon bond formation leading to the desired bicyclo[5.3.0] or [6.3.0] adduct.

When Does Atom Transfer Occur with TMM Diyls?

The triplet TMM diradical benefits from a significant resonance stabilization energy particularly if it possesses the planar geometry illustrated in structure **81** (Figure 5). Upon atom transfer, there is a loss of TMM delocalization energy and for the reaction to be exothermic, the •CXZ radical stabilization must compensate for that loss. Thus a critical factor ensuring the viability of the atom transfer process arises from the careful selection of the stabilizing substituents X and Z. We also remained keenly aware of the need to surmount a kinetic barrier. Would TMM diradicals be sufficiently reactive to do so?

The transition-state representation, **94**, portrayed in Figure 8, easily accommodates a collinear geometry for the 1,5 H-atom transfer. Theoretical studies reported by Dannenberg indicated that the optimal transition state is one that places the atom to be transferred directly between the donating and abstracting nuclei in a collinear geometry.[34]

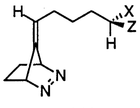
Figure 8



Taking these geometric and enthalpic considerations into account, a series of substituted diazenes **95−99** were synthesized and the chemistry of the resulting diyls examined.[29] The choices of X and Z were guided primarily by the C−H bond dissociation energy values of Leroy.[35] In

Table 3, the BDE(C−H) values are displayed for a variety of functionalized diazenes.

Table 3



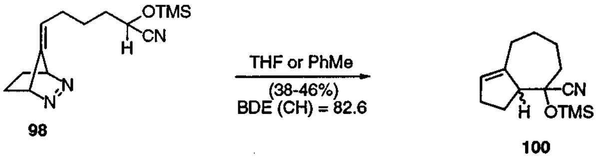
95-99

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

For the substrates with BDE's >90 kcal/mol, atom transfer did not proceed; instead diyl dimerization occurred, even at low concentrations controlled via syringe pump addition. This value suggests an upper limit for atom transfer. In the cases that were successful, both substituents were either electron-withdrawing, or captodative (**98** and **99**). Attempts to achieve atom transfer in substrates bearing one or two electron-donating groups (**95** and **97**), or one electron-withdrawing group (**96**) were ineffective and no products derived from atom transfer were isolated. Deuterium labeling studies verified that the transfer took place intramolecularly.[36]

Initially, the readily available TMS-cyanohydrin **98** seemed to be an ideal system, yet the diastereomeric products **100** were only formed in yields ranging from 38−46%. Competing side reactions with the cyanohydrin functionality seemed to be the reason for the poor yields.

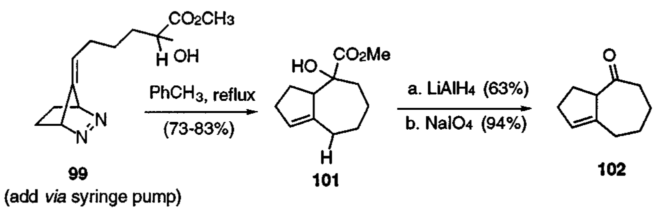
Scheme 19



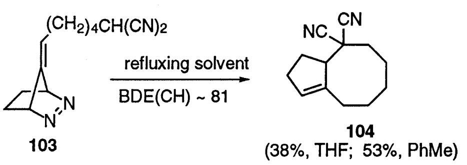
The best case examined thus far is that of hydroxy ester **99**. Thus, when it was added by syringe pump to refluxing toluene, a 1:1 mixture of diastereomeric adducts **101** were formed in 73−83% yields, along with about 10% of the diyl dimers. The product was readily transformed to ketone **102**. In general, the best results were obtained when the reaction was conducted in refluxing toluene or in *n*-octane at the reflux temperature of toluene.

This methodology also provides a concise route to eight-membered rings and is to be used in a future total synthesis. Thus far, we have found that atom transfer occurs when X = Z = CN, i.e., when both radical stabilizing substituents are electron-withdrawing, as illustrated by the conversion of diazene **103** to the (6.3.0) adduct **104**. The efficiency of this reaction improves relative to the competing diyl dimerization with an increase in temperature. This was also true of the conversion of **99** to **101**.

Scheme 20



Scheme 21

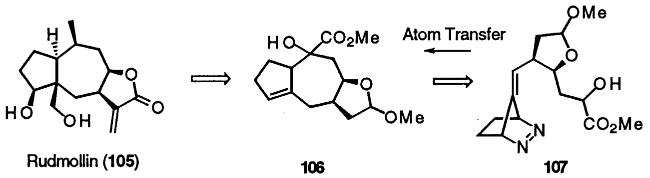


We suggest that the temperature dependence reflects the fact that the rate of dimerization changes slowly, while that for atom transfer increases significantly as the temperature is raised. This is reasonable, given that dimerization simply involves radical−radical combination, while atom transfer involves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

We believe that the planar, fully delocalized, triplet TMM diyl, **81** (Figure 5), is associated with the atom transfer process. The lifetime of the initially formed and more reactive bisected singlet (**80**) is limited by the rate of intersystem crossing (ISC), a process which has been measured to be about 10^8 s^{-1}[37] for the dimethyl substituted diyl **2a**. Rate constants for typical 1,5 H-atom transfers are in the range of 10^6 s^{-1},[38] a process which is an hundred-fold slower than the ISC of the TMM diyl from the singlet to the triplet manifold. Hypothetically, the singlet could participate in atom transfer if the rate was faster than that of ISC, which seems most unlikely. In addition, the competitive formation of diyl dimers, which is known to occur from the combination of two triplets, supports our view that atom transfer is triplet derived.

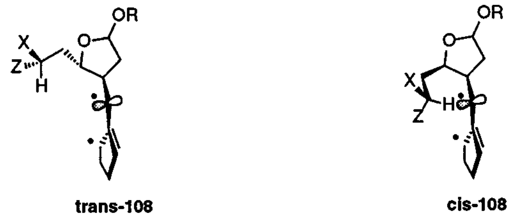
These initial investigations have provided a firm foundation for ongoing discoveries in this new area of TMM diyl chemistry. Both synthetic and mechanistic issues are presently being explored in the setting of a total synthesis effort. The pseudoguaianolide, rudmollin (**105**) which exhibits activity against a leukemic cell line, was chosen as the target structure.[39] Although rudmollin (**105**) has been synthesized,[40] the structural features of a trans-fused bicyclo[5.3.0] where a *cis*-fused α-methylene-γ-butyrolactone is appended to the seven-membered ring seemed ideal to test our methodology. If atom transfer occurred, then the highly functionalized tricycle **106** would be assembled quickly. Successful execution of this strategy promised to provide the foundation upon which to base the synthesis of a variety of natural products.

Scheme 22



The presence of the lactol unit in diazene **107** clearly alters the flexibility of the tethering unit relative to the examples cited thus far. In principle, the attendant decrease in degrees of freedom might facilitate the atom transfer event. Furthermore, the opportunity to synthesize and examine the chemistry of both *cis* and *trans* fused lactols promised to shed light on the geometric requirements associated with the process. Models suggest that the *cis* lactol places the hydrogen being transferred in a favorable collinear geometry, whereas the *trans* system does not allow attainment of the collinear relationship (Figure 9). Both diazenes have been synthesized and we are currently evaluating the outcome.

Figure 9

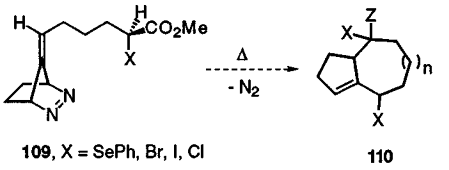


Another promising area of this atom transfer research focuses upon determining what atoms besides hydrogen may undergo similar chemistry.[41] Mechanistically, this endeavor addresses the enthalpic issues since other bonds of the type C−X (X= I, Br, Cl, SePh, SR) have lower energies than that of C−H. Rather than the need for a doubly activated system, it is feasible that with the halogens and the chalcogenides, a mono-activated group may provide sufficient radical stabilization to allow the process to occur. At present, substrates of ester diazene **109** are being synthesized and will be subjected to the typical conditions described earlier. Of course it is highly desirable, to have such diversity. The incorporation of other groups such as selenium or halogen into the resulting bicyclic products will provide very useful handles for manipulation leading to more diverse and structurally complex molecules.

TMM Diyl-Induced Vinylcyclopropane Fragmentation

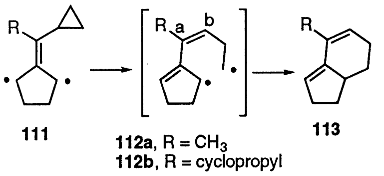
Recent independent studies by Adam[33] and Gajewski[42] have demonstrated that cyclopropyl substituted TMM's **111** undergo ring opening akin to that of a cyclopropylcarbinyl radical.[43] A major difference, of course, is that the former leads to a *di*radical which, when formed with the

Scheme 23



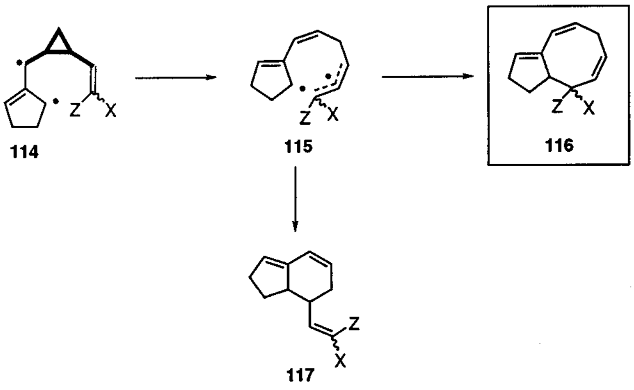
cis-geometry portrayed in **112**, engages in C−C bond formation leading to the bicyclo[4.3.0]nonene ring system **113**.

Scheme 24



Our interest is in the exploration of a variation of this chemistry that has the potential of producing eight-membered rings. To do so, we propose to utilize *vinylcyclopropyl*-substituted systems such as **114**.[44] Illustrated in Scheme 25, the diyl **114** can undergo radical-initiated vinylcyclopropane cleavage resulting in an allylically stabilized intermediate **115**. From here, there are two competing pathways: cyclization to form the [4.3.0] carbocycle **117**, or ring closure to form the eight-membered [6.3.0] product **116**. We are particularly interested in the latter process and wish to investigate the chemistry with the aim of determining the nature of the factors that might lead to selectivity. The large number of naturally occurring materials having an eight-membered ring as a substructure, and the possibility of applying what we learn within this context adds additional appeal.

Scheme 25



Scheme 26

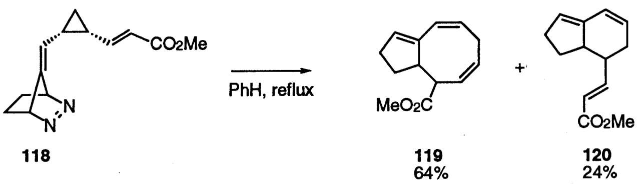
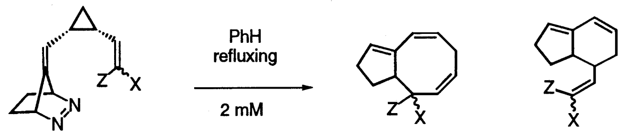
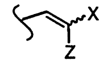
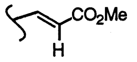
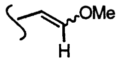
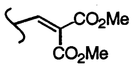
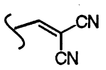


Table 4



118, 121 - 123 **A** **B**

diazene		%A	% B
118		64% (119)	24-26% (120)
121		< 15%	58-62%
122		none observed	83% 2 isomers
123		none observed	81% 2 isomers

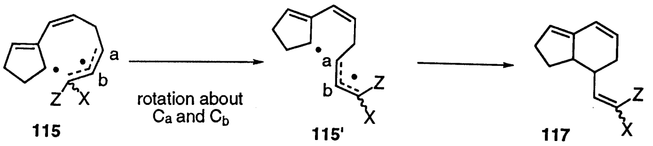
We have conducted preliminary experiments to explore this basic idea, and the results have established the overall viability of the study. Thus, refluxing a 2 mM solution of diazene **118** in benzene for 2.5 h led to the formation of only two materials, **119** and **120**, in a ratio of ca. 2.5:1, with the eight-membered ring predominant. While the selectivity is not yet good, it is in the desired direction and can almost certainly be influenced electronically in a manner that will afford high selectivity. Regardless, the starting material for this study was exceptionally easy to synthesize and consequently, the methodology, even in its present embryonic form, still constitutes a simple, facile entry to the bicyclo[6.3.0] framework.

Our initial plan to achieve selectivity was to use radical stabilizing groups, X and Z, positioned at the terminus of the tether in an attempt to favor formation of the [6.3.0] adduct. Diazenes **118** and **121–123**, possessing electron-donating, electron-withdrawing, and 1,1-diactivated groups were selected for screening. The results of heating 2 mM solutions of these materials in refluxing benzene are summarized in Table 4. It is interesting to compare the results of the case shown above with that of the vinyl ether **121**, and in particular, to note their opposite regiochemical preferences. Thus, when the terminal carbon bears an electron-donating group (**121**), the [4.3.0] adduct is preferred, whereas the presence of an electron-withdrawing group (**118**), leads preferentially to the [6.3.0] product **119**.

The bias observed with the single electron-withdrawing group favoring formation of the eight-membered ring, led us to speculate that geminal activation might improve the selectivity. The two diactivated substrates investigated, **122** and **123**, did undergo fragmentation/cyclization cleanly, each providing only two products in > 80% yield. However, as shown in Table 4, analysis of the reaction mixtures verified that only the six-membered ring carbocycles were produced.

We suggest that there is a delicate balance between electronic and steric factors that must be taken into account in designing systems for additional study. Steric congestion surrounding the radical reactive site for the disubstituted systems (**122** and **123**) may impede cyclization to the eight-membered ring. A rotation about the C_a-C_b bond, as illustrated in Scheme 27, removes the crowding and leads preferentially to the six-membered carbocycle.

Scheme 27



115 **115'** **117**

We are currently preparing a diazene with a sterically demanding group at C_b in an effort to deter the C_a-C_b rotation. We are also planning to examine the electronic effects of captodative systems which are well known for their radical stabilizing ability.[45] Once we better understand the chemistry of these fragmentation/cyclizations, we plan to utilize these diyls in the synthesis of natural products.

We express sincere gratitude to the *National Science Foundation* (NSF) and the *National Institutes of Health* (NIH) for their continued support of our research.

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