

# The Intramolecular Diyl Trapping Reaction. A Useful Tool for Organic Synthesis

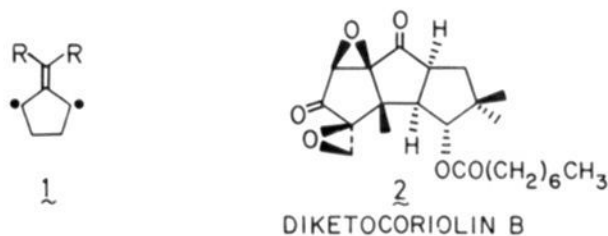
R. DANIEL LITTLE

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

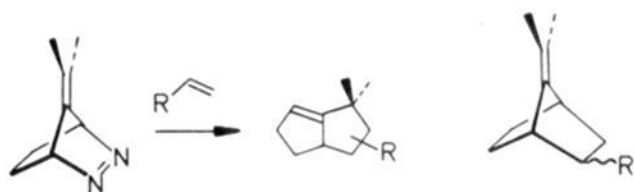
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## Introduction

In the late 1970s we initiated a program whose goal was to utilize 2-alkylidenecyclopentane-1,3-diyls related to trimethylenemethane (e.g., **1**) as intermediates in the synthesis of a variety of natural products. Particular attention was to be placed upon construction of the linearly fused tricyclopentanoid class of sesquiterpenes and of these, the antitumor agent diketocoriolin B (**2**) was selected as the target molecule of greatest interest. At that time, very few methods were available for the construction of these compounds.<sup>1</sup>

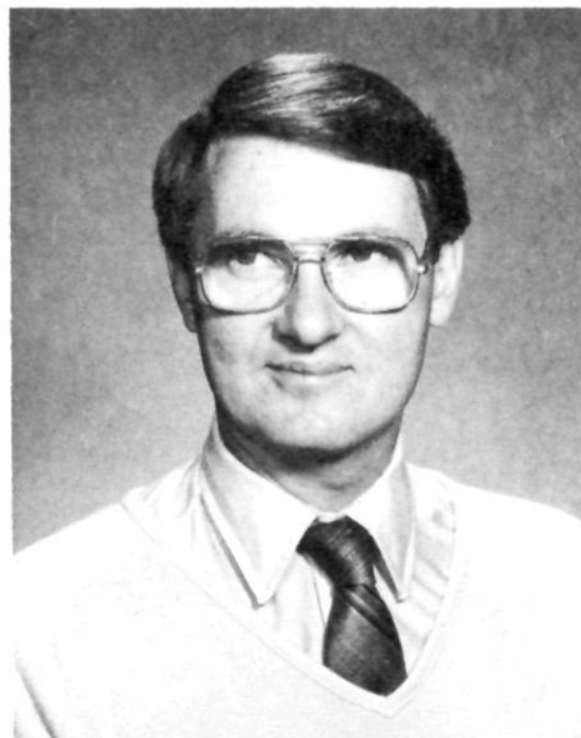


The decision to base our approach upon the use of diyl chemistry was founded upon observations which were first reported by Berson and co-workers in 1972.<sup>2</sup> Thus, they noted that 2-isopropylidenecyclopentane-1,3-diyl **1a** (R = CH<sub>3</sub>) could be trapped with a variety of olefins (diylphiles) provided the olefin was activated by one or more electron-withdrawing groups; in the absence of an olefin, the diyl undergoes dimerization. Two types of cycloaddition products were observed, one possessing a bicyclo[3.3.0]octene ring system and the other a 7-alkylidenebicyclo[2.2.1]heptane skeleton. Fortunately, it was discovered that by operating with a very reactive diylophile and/or at a high concentration of the diylophile, one could obtain the fused product preferentially. In addition, the fused cycloadducts were formed with maintenance of the diylophile stereochemistry, a factor which could be particularly useful in any synthetic applications which might be envisioned.



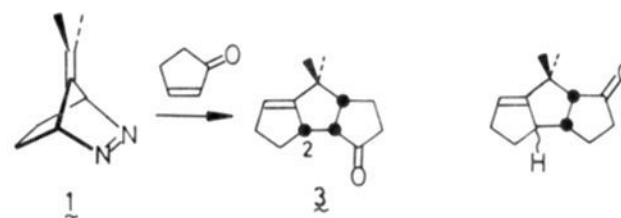
## The Intermolecular Approach

Our initial approach to the linearly fused tricyclopentanoid skeleton utilized an *intermolecular* cycloaddition between two readily available starting materials, namely, the dimethyl diyl **1a** and cyclopentenone.<sup>3</sup> We were pleased to find that the reaction efficiently afforded the desired ring system (isolated yield >90%). However, several disturbing factors were noted. Thus,



Dan Little was born in Superior, WI. He attended schools in Superior and received his B.S. degree in mathematics and chemistry from the University of Wisconsin at Superior. While in college, he participated in the National Science Foundation Undergraduate Research Program on two occasions at the University of South Dakota. He also spent one semester of his senior year at Argonne National Laboratory with Drs. Kaplan and Wilzbach. Graduate studies were carried out at the University of Wisconsin under the direction of Professor Howard Zimmerman and were followed by a year and a half of postdoctoral research at Yale University under the guidance of Professor Jerome Berson. Dr. Little joined the Department of Chemistry at UCSB in late August of 1975 and is now Professor of Chemistry. He maintains a group of 10-12 persons consisting of a mix of graduate and postdoctoral students. In 1980, Dr. Little received an Alfred P. Sloan Foundation Fellowship and was given the Harold Plous Award to recognize excellence in teaching and research by an Assistant Professor. His research interests center upon the development and use in synthesis of the intramolecular 1,3-diyl trapping reaction and organic electrochemistry.

while the reaction did show a slight stereoselection for the formation of the *cis,syn*-ring-fused product **3**, all of

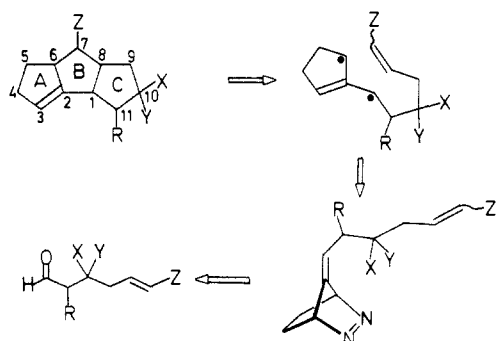


the naturally occurring tricyclopentanoids possess a *cis,anti,cis*-ring fusion. Further, while there was a preference for the formation of **3**, two regioisomers were also isolated. Another disturbing feature stems from a recognition of the fact that the C-C  $\pi$  bond in each product is located in a somewhat awkward position with respect to the possible functionalization of C<sub>2</sub> (coriolin

numbering), a requirement for the achievement of our objectives.

### The Intramolecular 1,3-Diyl Trapping Reaction

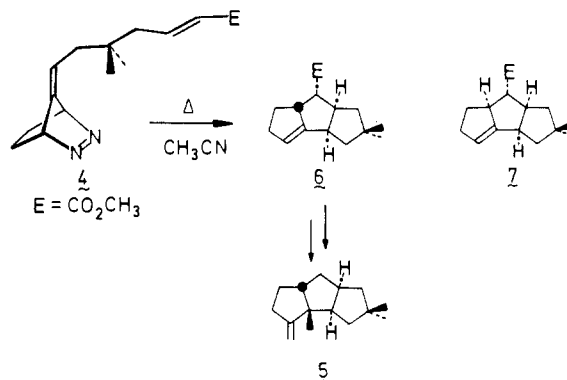
Faced with these results, we decided that it would be appropriate to devise an alternative approach, one which continued to use a diyl trapping reaction as the key step and designed to avoid a number of the problems inherent to the intermolecular route.<sup>4</sup> To that end, we reasoned that the *intramolecular* approach outlined below might prove particularly appropriate. Clearly, since the diylophile is incorporated within the same molecule as the diyl, one is not faced with the necessity of removing the excess diylophile upon completion of the reaction. More importantly, the intramolecular strategy avoids the BC-ring regiochemical ambiguities of the intermolecular route, since the location of the substituents destined to become those of rings B and C is fixed on the chain (the tether) linking the diyl to



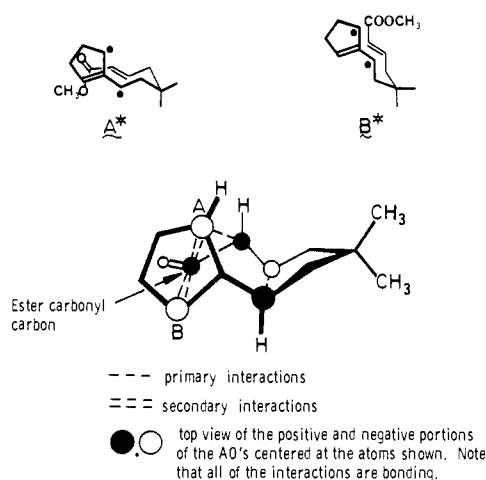
the diylophile and on the diylophile itself. Finally, the A-ring C-C  $\pi$  bond is located in a position well-suited for the addition of substituents at C<sub>2</sub> and for elaboration of the A-ring functionality found in diketocoriolin B (2) as well as other linearly fused tricyclopentanoids.

The first intramolecular 1,3-diyl trapping reaction was carried out using diazene 4 as the diyl precursor.<sup>5</sup> This substrate was selected with the idea that, should the reaction proceed in the desired sense, then the product could be converted to the simple hydrocarbon hirsutene (5). An activated diylophile was selected since we were aware that in the intermolecular cycloaddition, dimerization of the diyl is competitive with cycloaddition when an unactivated diylophile is used. Obviously, one might have argued that the difference in rates between inter- and intramolecular processes would be enough to make up for differences due to the absence of an electron-withdrawing group. Nevertheless, we opted for this rather conservative approach and were delighted with the results. Two products 6 and 7 were isolated in a ratio of 87:13 and an isolated yield of >85%. In contrast with the intermolecular process, the major product 6 possessed the desired *cis,anti*-ring-junction stereochemistry. Notice too that the *trans* diylophile stereochemistry was maintained. Compound 6 was converted to hirsutene (5), albeit somewhat awkwardly due to the necessity of removing the ester unit located at C<sub>7</sub>; more will be said about this point later.

While we were pleased with these results and were able to demonstrate that the methodology was applicable to the construction of a natural product, we were more intrigued by the stereoselective formation of the *cis,anti*-ring-fused product and by the possibility of



formulating a model which would allow one to predict the course of other intramolecular diyl trapping reactions. Accordingly, we assumed that following the departure of nitrogen, the reaction is kinetically controlled and, therefore, that an adequate model must focus upon the accurate formulation of transition-state representations. For the case at hand, the extended and folded pseudo-chair representations A\* and B\* were suggested,



and of the two, the extended formulation was considered to be of lower energy than the folded for electronic reasons. Thus, in analogy with the Diels-Alder reaction, we reasoned that the bonding secondary orbital interactions shown above between the ester carbonyl carbon and the diyl ring carbons A and B might lower the energy of A\* relative to B\*, thereby leading to the formation of an excess of the *cis,anti* product.<sup>6</sup> However, we noted that if this argument was accurate, then it was subject to experimental test.

Suppose, for a moment that a diylophile with a (*Z*)-olefin geometry was used and consider the extended and folded pseudo-chair transition state representations C\* and D\*; assume that the geometry about the diyl-

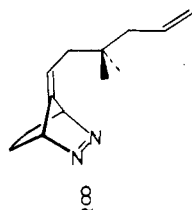


phile C-C  $\pi$  bond will not be lost. Then, if the secondary orbital interactions provide the stereochemical controlling feature for the reaction, one would predict the preferential formation of the *cis,syn* rather than the *cis,anti* product.

In practice, the *cis,anti* product was still dominant, although the preference was reduced from 87:13 to 75:25.<sup>5b</sup> This was the first of a series of results which,

when taken together, indicate that electronic factors play an insignificant role in controlling the outcome of intramolecular diyl trapping reactions in comparison with the role played by conformational and nonbonded interactions. Finally, the diylophile stereochemistry was maintained in both of the products, thereby demonstrating that the reaction is stereospecific with respect to maintaining diylophile stereochemistry and stereoselective in its preference for the formation of *cis*,*anti*-ring-fused product.

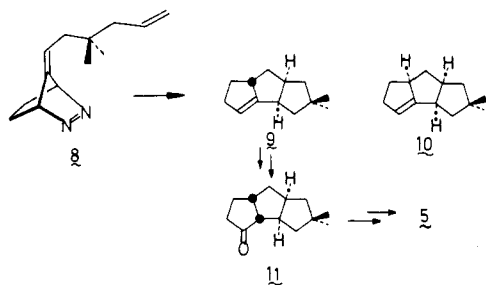
**Use of an Unactivated Diylophile.** We turned our attention toward an investigation of the chemistry of the diyl derived from diazene **8**.<sup>7</sup> Through this study



we intended to (1) determine whether, like its intermolecular counterpart, diyl dimerization is competitive with the intramolecular diyl trapping reaction when an unactivated diylophile is present; (2) determine the *cis*,*anti* to *cis*,*syn* product ratio for a system wherein the bonding secondary orbital interactions referred to above cannot be operable; (3) reduce the number of steps required to construct hirsutene (**5**).

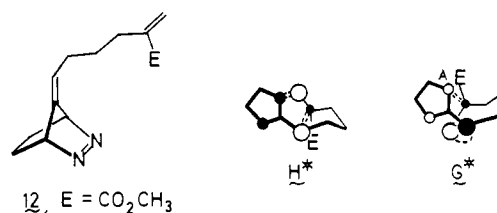
In practice, dimerization was not competitive with trapping. This result hardly seems surprising if one reasons that the intramolecular nature of the process should be sufficient to compensate for the decrease in trapping rate due to the use of an unactivated diylophile. However, as we shall see, one must exercise a considerable bit of caution in attempting to draw the conclusion that dimerization will not be competitive with trapping in *each* case wherein an unactivated diylophile is used.

Two linearly fused tricyclopentanoids **9** and **10** were isolated in a ratio of 5:1 and in a nonoptimized yield of 76%. Once again the *cis*,*anti* product was formed in preference to the *cis*,*syn*; **9** was easily converted to



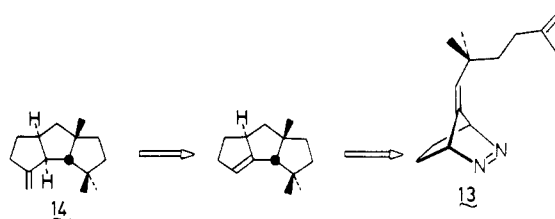
ketone **11**, thereby converging with our previous synthesis of hirsutene (**5**) and reducing the total number of steps required by five. The decrease in ring-fusion stereoselectivity from 87:13 using the diyl derived from **4** to 5:1 in the present instance is of significance in that, at least in principle, it reflects a decrease due to the absence of the transition-state energy lowering secondary orbital interactions. However, the change in product ratios is small enough to make one question whether the secondary orbital interactions play any role in determining the stereochemical outcome of these reactions.

To further illustrate the very minor role played by electronic effects in determining the course of the diyl trapping reaction, we site the chemistry of the diyl derived from diazene **12**.<sup>8</sup> It was selected for study because, based upon the simple frontier molecular orbital analysis illustrated below, one would predict that the preferred product should possess the tricyclo-[5.3.1.0<sup>2,6</sup>]- rather than the tricyclo[6.3.0.0<sup>2,6</sup>]undecene ring system. Both can arise *via* thermally allowed pathways. However, notice that in *G\**, overlap between the atomic orbital centered at the  $\beta$ -carbon in the diylophile LUMO with the atomic orbital centered at the exocyclic carbon of the diyl HOMO, allows the larger of the two AO coefficients in each pair of MO's to interact. Similarly, the interaction between center  $C_A$  and the  $\alpha$ -carbon of the diylophile matches the smaller coefficient of the diyl HOMO with the smaller coefficient of the diylophile LUMO. The alternative, *H\**, matches the larger with the smaller coefficient in



each pair of interacting orbitals. FMO theory suggests that the former pathway should be preferred.<sup>9</sup> In practice, we were unable to detect the formation of *any* product resulting from the predicted preferred mode of reaction! Only products possessing the tricyclo-[6.3.0.0<sup>2,6</sup>]undecene ring system were produced.

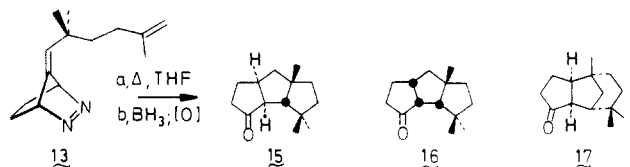
**Capnellene. Another Unactivated Diylophile, but Different Results.** The chemistry of the diyl derived from diazene **8** demonstrated that intramolecular trapping can successfully compete with diyl dimerization despite the use of an unactivated diylophile. As a result, we decided to construct diazene **13**, one



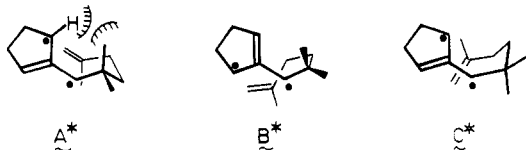
devoid of diylophile activation, en route to the marine natural product  $\Delta^9(12)$ -capnellene (**14**).<sup>10</sup> Diazene **13** differs from **8** in two important ways. First, as dictated by the structure of the target molecule, the *gem*-methyl group has been relocated and the diylophile, while unactivated, is substituted with two alkyl groups.

Compound **13** was easy to synthesize in a reasonably large quantity and in short order. However, unlike all of the other intramolecular 1,3-diyl trapping reactions which we had conducted, we were greatly surprised and distressed to discover that the <sup>1</sup>H NMR spectrum of the crude reaction mixture indicated that very little of the desired monomeric product had formed. Instead, the reaction mixture consisted mainly of diyl dimer. To obtain the desired material required that the concentration of the diyl be low enough to allow the intramolecular trap to occur at a rate faster than the dimerization. Accordingly, syringe pump techniques were

utilized. Even then, however, the reaction displayed characteristics which differed greatly from all previous examples. In particular, three rather than two monomeric products, 15–17, were isolated in a ratio of 1.6:1:6.6, respectively. Furthermore, as discerned by single-crystal X-ray analysis, the major product 17 was not a linearly fused tricyclopentanoid, but instead possessed a tricyclo[5.3.1.0<sup>2,6</sup>]undecane ring system.



While we were able to convert 15 to  $\Delta^{9(12)}$ -capnellene (14), we were more intrigued by the peculiar observations described above than by completion of the total synthesis. We felt compelled to try and come to grips with the reasons for this behavior, to reshape our model, so that in future endeavors one could more intelligently plan and use the trapping reaction. Accordingly, consider the three transition-state representations illustrated below. The first A\* illustrates the extended



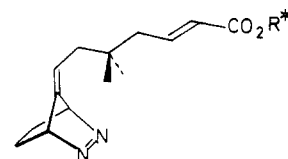
pseudo-chair representation which we have previously considered to be of lowest energy. In this case, however, A\* suffers from energy raising pseudo-1,3-diaxial interactions as well as an interaction between the pseudoaxially oriented methyl group located on the tether and the ring hydrogen, as illustrated; these interactions were absent in each of the systems examined previously.<sup>11</sup> Assumption of representation B\* apparently does not lower the energy. On the other hand, transition-state representation C\* is devoid of the energy raising interactions. Thus, based simply upon a qualitative evaluation of the relative magnitudes of non-bonded interactions in each of the transition-state representations, one can conclude that C\* is of lower energy.

However, we believe that this description is incomplete. For example, why does the diyl derived from 13 undergo dimerization under conditions wherein the others do not? The elegant mechanistic studies of Berson and co-workers as well as the theoretical treatment of diradical dimerization provided by Closs, clearly indicate that diyl 1a dimerizes by a triplet-plus-triplet combination.<sup>12</sup> We propose that the dimers formed from 13 arise in the same way and suggest that one or more of the monomeric products also arise from the diyl triplet. In corroboration of this hypothesis is our recent discovery that *both* the formation of the dimeric and the monomeric products is completely quenched when the trapping reaction is conducted in the presence of molecular oxygen.<sup>13</sup>

In the present case, therefore, it is reasonable to suggest that the trapping reaction proceeds in a stepwise rather than a concerted fashion. Within this framework, it is of interest to reexamine the transition-state representations illustrated above. Let us

assume that the formation of the smaller of the two rings occurs first and analyze the process as though we were dealing with monoradical cyclization of a substituted 5-hexenyl radical.<sup>14</sup> Then, representation A\* portrays a 5-exo, trig cyclization onto a carbon atom which bears a methyl group, while C\* displays a 6-endo, trig closure. Ordinarily, when considering the rates of competitive monoradical cyclization, the rate of formation of a five-membered ring is greater than that of the six, *except* when the carbon onto which the radical center is closing is substituted with an alkyl group, as is the case for the reaction of 13. Thus, we suggest that a combination of factors, the relative importance of which is unknown, operate together and lead to the observation of products wherein the "usual" linear regiochemistry is reversed. Additional studies designed to probe the validity and generality of this model are in progress.<sup>15</sup>

**Asymmetric Induction.** In an effort to devise methodology which would allow the construction of optically pure coriolin and learn more about the fundamental features which govern the course of the intramolecular 1,3-diyl trapping reaction, we embarked upon an investigation of two plans designed to achieve asymmetric induction. The first was conceptually quite vague and relied heavily upon literature precedent for the use of menthyl and 8-phenylmenthyl ester chiral auxiliaries;<sup>16</sup> it required the synthesis of diazenes 18a and 18b. In practice, neither system worked satisfac-



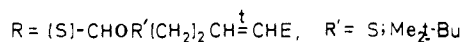
18a, (-)-menthyl ester  
18b, (-)-8-phenylmenthyl ester



torily. Regardless of the nature of the ester, no more than a 5% diastereomeric excess (de) was obtained.<sup>17</sup>

The results indicate that the chiral auxiliary plays an insignificant role in determining the direction of coiling of the acyclic chain. The experimental observations can be reconciled by suggesting that, like the chemistry discussed above, these reactions also proceed in a stepwise fashion and that the formation of the smaller of the two rings precedes the formation of the larger. In this fashion, one can envision approach of the diylophile to the diyl as occurring when the ester is in a conformation which removes this large unit from the proximity of the reacting centers. Initial bond formation can then occur before much, if any, asymmetric influence of the chiral ester can be achieved.

The other approach seemed more sound from the outset, but was more difficult to test due to the existence of a variety of technical problems which were encountered in the construction of the required diazene 19.<sup>18</sup> The plan calls for fixing the absolute configura-



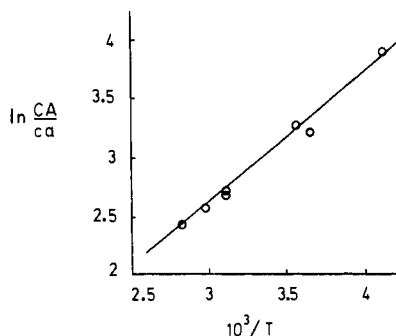


Figure 1.

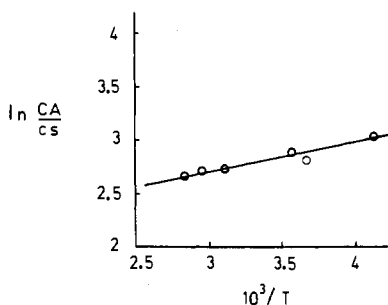
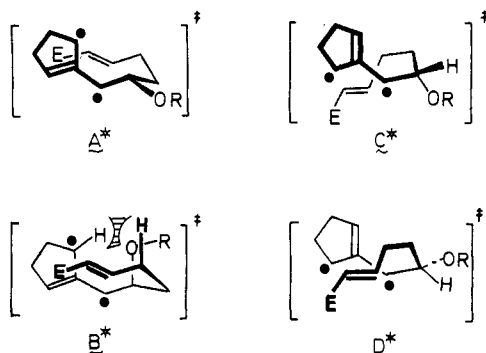


Figure 2.

tion at one of the carbons linking the diyl to the diylophile and is most simply visualized by reference to the transition-state representations A\*–D\* shown below. We deliberately chose to use an -OR unit and to fix the configuration at the center indicated since both are required if the methodology is to be applicable to the total synthesis of, for example, coriolin and diketocoriolin B. Focus upon A\* and B\* since these lead to the cis,anti-ring fusion which is common to all of the naturally occurring linearly fused tricyclopentanoids. We reasoned that representation A\* would be of lower energy than B\* on enthalpic grounds and that asym-



metric induction should be obtained in an amount related to the difference in energy between the two formulations. The latter suffers from energy-raising pseudo-1,3-diaxial interactions as well as that due to interaction between -OR and the diyl ring hydrogen as illustrated.

In practice, diazenes **19a** and **19b** were obtained as a separable mixture of diastereomers about C<sub>1</sub>; the absolute configuration at C<sub>2</sub> was fixed. Deazetation was conducted in acetonitrile over a temperature range from -31 to +81 °C; each diastereoisomer was examined independently. The reactions which were performed over the range from -31 to +50 °C, were initiated photochemically while those in the range of +50 to +81 °C were initiated thermally. Thus, +50 °C was a tem-

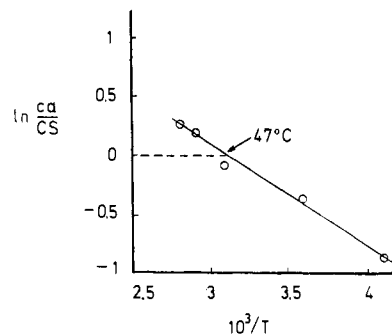
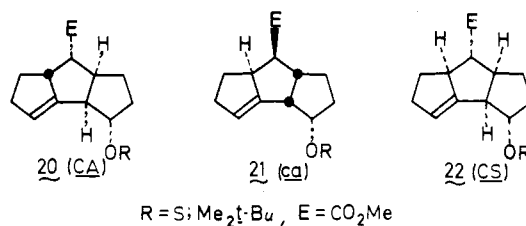


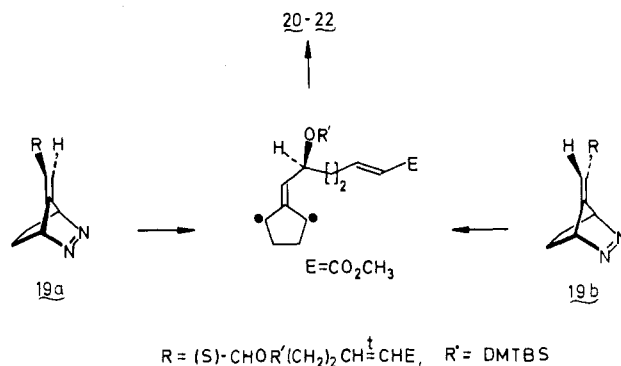
Figure 3.

perature which was common to both the thermal and photochemical runs. Invariably, the three products **20–22** were obtained in high yield (> 90%) in a very clean reaction, and in ratios which were dependent upon temperature but independent of mode of generation of the diyl. The major product **20** (CA) possessed both the



required relative and absolute stereochemistry to allow it to be used in total synthesis efforts.

In principle, the diastereomeric diazenes **19a** and **19b** could have given rise to different product distributions if, for example, some bond formation between the



diylophile and the incipient 1,3-diyl occurred prior to the complete loss of nitrogen. When diazene **19b** was used, we observed not only the same products **20–22** but also the same product ratios as were obtained in the case of the diastereomer **19a**. These results strongly suggest that in both cases, complete cleavage of the C–N bonds occurs prior to any C–C bond formation between the 1,3-diyl and the diylophile. That is, both diastereomers lead to the same cyclopenta-1,3-diyl which behaves as a time-averaged planar intermediate.

Table I and Figures 1–3 illustrate the systematic way in which the tricyclopentanoid product ratios varied as a function of temperature. Notice that the ratio of the two cis,anti-ring-fused products (**20/21** = CA/ca) ranged from 11.7:1, corresponding to 92.1% ds, to 48.5:1, corresponding to a very respectable and synthetically useful 98% ds.<sup>19</sup> Plots of ln [product ratio] vs. 1/T were linear and allowed a determination of the differences in enthalpies and entropies of activation for the processes leading to each pair of products. Notice

TABLE I. Product Ratios of the Linearly Fused Tricyclopentanoids 20-22 Obtained from Thermolysis and Photolysis of Diazenes 19a and 19b in Acetonitrile at Various Temperatures

| temp, °C         | CA/ca (% ds)      | CA/CS      | ca/CS       |
|------------------|-------------------|------------|-------------|
| -31 <sup>b</sup> | 48.5 ± 1.7 (98)   | 20.0 ± 0.7 | 0.41 ± 0.02 |
| -2 <sup>b</sup>  | 24.2 ± 0.7 (96)   | 16.7 ± 0.2 | 0.69 ± 0.01 |
| 7 <sup>b</sup>   | 26.2 ± 0.9 (96.3) | 17.7 ± 0.2 | 0.68 ± 0.02 |
| 50 <sup>b</sup>  | 14.1 ± 0.3 (93.4) | 14.7 ± 0.7 | 1.05 ± 0.06 |
| 50 <sup>c</sup>  | 14.7 ± 0.1 (93.6) | 15.1 ± 0.2 | 1.03 ± 0.01 |
| 66 <sup>c</sup>  | 12.8 ± 0.6 (92.8) | 15.0 ± 0.9 | 1.18 ± 0.12 |
| 81 <sup>c</sup>  | 11.7 ± 0.2 (92.1) | 14.2 ± 0.9 | 1.22 ± 0.08 |

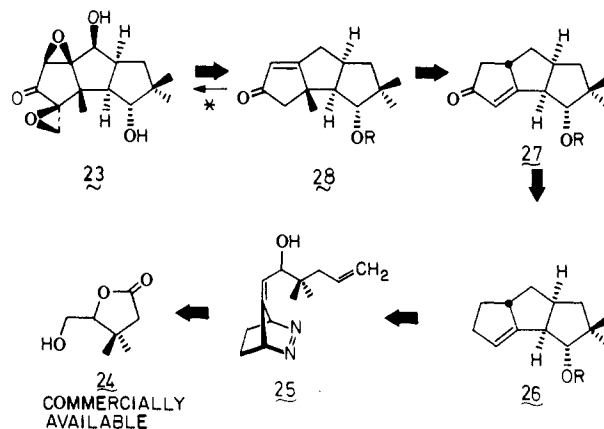
<sup>a</sup> Average ± standard deviation of at least three capillary GC injections. <sup>b</sup> Photochemical deazetation (Pyrex filter). <sup>c</sup> Thermal deazetation.

that the slope of the plot of  $\ln [CA/ca]$  vs.  $1/T$  is significantly greater than that for  $\ln [CA/CS]$  vs.  $1/T$ , reflecting the significantly greater change in product ratio for the former pair over a fixed temperature range. Notice, too, that in accord with our original plan, the difference in the CA/ca product ratio is governed by differences in enthalpy of activation and, surprisingly, that the cis,syn product **22** (CS) is entropically disfavored relative to the major cis,anti product **20** (CA) (see Table II). Finally, the plot for the two minor products ca and CS reveals an interesting feature. That is, at 47 °C, an isokinetic point is observed.<sup>20</sup> There, of course, the ratio of the two minor products is unity; above that temperature, the ca product dominates, while below it, CS is in excess of ca.

**Total Synthesis of Hypnophilin. Formal Total Synthesis of Coriolin (23).** From the outset, one of our objectives has been to use the diyl trapping reaction in a total synthesis of coriolin (**23**) and/or diketocoriolin B. Given the background material discussed above, we felt confident that we could intelligently use the intramolecular version of the diyl trapping reaction to achieve these objectives.

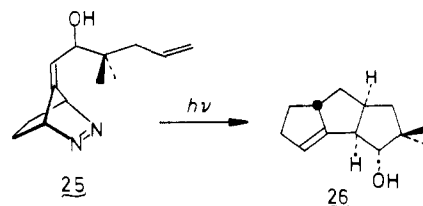
A retrosynthetic analysis of the coriolin (**23**) problem is illustrated.<sup>21</sup> The synthesis began with the commercially available furanone **24** which, in turn, was converted to diazene **25**. It, rather than any of several alternative diyl precursors was selected based upon our knowledge of the chemistry discussed above. In particular, compare the substitution pattern on the tether with that of diazenes **8** and **19** and notice, therefore, the use of an unactivated diylophile without the fear of competitive diyl dimerization. Notice too, the placement of the OR unit in the same location as in our studies of asymmetric induction, a position which is destined to become the C<sub>11</sub> carbon of coriolin (**23**) and hypnophilin.

The diyl trapping reaction was conducted at a variety of temperatures, in both thermally and photochemically induced extrusions of nitrogen. When carried out in refluxing acetonitrile (2.5 h), five products, one major



\* CONVERGENT POINT

(**26**) and the others minor, could be detected by capillary column gas chromatographic analysis. The ratio of the major (**26**) to the sum of the minor products corresponded to 4:1 and the combined, isolated yield was 93%. Photodeazetation at 6 °C afforded a 9:1 ratio of products (major/sum of minor) from which the major product **26** could be isolated in an 84% yield. When



the transformation was accomplished photochemically at -60 °C in methanol rather than acetonitrile as the solvent, the reaction displayed remarkably high stereoselectivity; the ratio of the major to the sum of the minor products rose to 65:1.<sup>22</sup> In general, as demonstrated by this example and our study of asymmetric induction (vide supra), stereoselectivity increases as the temperature decreases.

En route to coriolin (**23**), the interesting discovery was made that epoxidation of alcohol **29a** as well as ester **29b**, led to the formation of two, rather than the expected one epoxide (Scheme I). As illustrated, both cis and the highly strained and unexpected trans-fused epoxide were formed.<sup>23</sup>

The stereochemical assignments were confirmed by single-crystal X-ray data which was obtained for the benzoate **33**. Interestingly, *only* the trans-fused epoxide is formed upon epoxidation of the silyl ether **29c**. These initially surprising results become easy to understand (in retrospect) after an examination of the X-ray data. In particular, when the benzoate is viewed from the side, it becomes clear that the ester unit provides a very large steric blockade toward attack of the peracid upon the  $\beta$ -face of the olefin, one which is sufficiently large

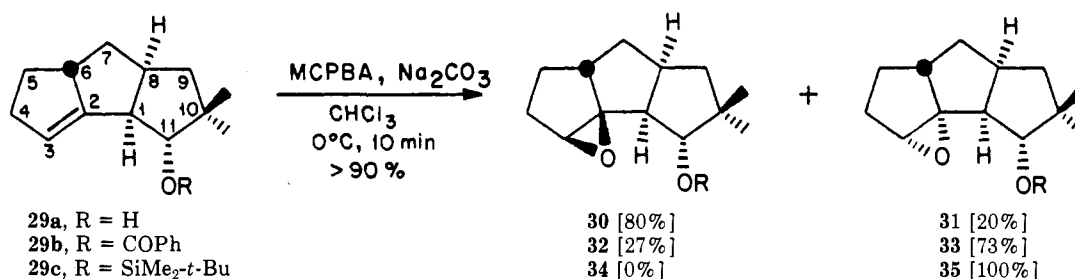
TABLE II. Differences in Enthalpy, Entropy, and Free Energy<sup>a</sup> of Activation for the Formation of Tricyclopentanoids 20-22 (CA, ca, and CS, Respectively)

| A  | B  | $\Delta\Delta H_{A-B}^{*b}$ | $\Delta\Delta S_{A-B}^{*c}$ | $\Delta\Delta G_{A-B}^{*a,b} (A/B)^d$ |              |              |
|----|----|-----------------------------|-----------------------------|---------------------------------------|--------------|--------------|
|    |    |                             |                             | 81 °C                                 | 25 °C        | -31 °C       |
| CA | ca | -2.14                       | -1.3                        | -1.69 (11.0)                          | -1.76 (19.5) | -1.83 (44.9) |
| CA | CS | -0.50                       | +3.9                        | -1.87 (14.3)                          | -1.65 (16.2) | -1.43 (19.6) |
| ca | CS | +1.65                       | +5.2                        | -0.12 (1.2)                           | +0.11 (0.83) | +0.40 (0.44) |

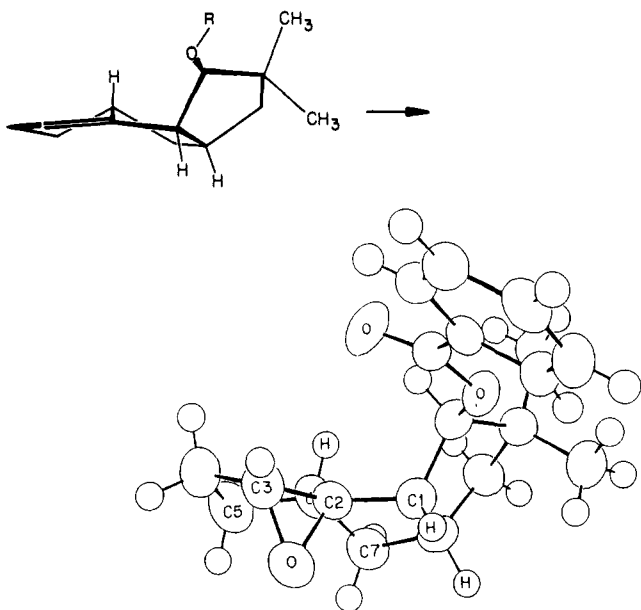
<sup>a</sup> Calculated values. <sup>b</sup> In kcal/mol. <sup>c</sup> In cal/(mol deg) (eu). <sup>d</sup> Calculated product ratio at the indicated temperatures.



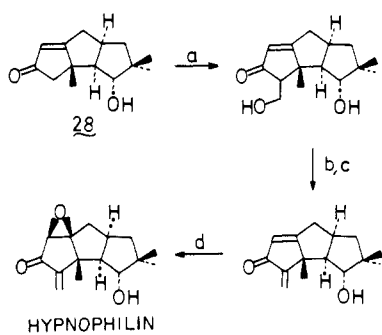
## SCHEME I



to overcome the increase in strain energy which is attendant upon formation of the trans-fused AB-ring system.



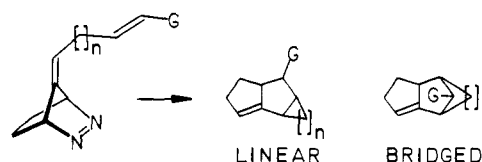
Finally, tricyclopentane 28, a compound which provided a point of convergence with existing routes to coriolin (23),<sup>24</sup> proved to be a useful intermediate in the first total synthesis of hypnophilin.<sup>25</sup>



(a) LDA, THF, -78 °C; CH<sub>2</sub>O, -30 °C; (b) *p*-TsCl, C<sub>6</sub>H<sub>5</sub>N; (c) DBU; (d) NaHCO<sub>3</sub>, H<sub>2</sub>O<sub>2</sub>, THF, H<sub>2</sub>O

**Variation of Tether Length.** Having achieved our initial objective, we felt it appropriate to explore the potential utility of the intramolecular 1,3-diyl trapping reaction in the construction of ring systems other than the linearly fused tricyclopentane. While many potentially interesting and useful avenues of exploration exist, one of our initial ventures addressed the simple question: Will the nature of the ring system formed be dependent upon the length of the chain (the tether) which connects the diyl to the diylophile? In principle, two types of products one possessing a tricyclo[6.*n*.0.0<sup>2,6</sup>] (a linearly fused product) and the other a tricyclo-

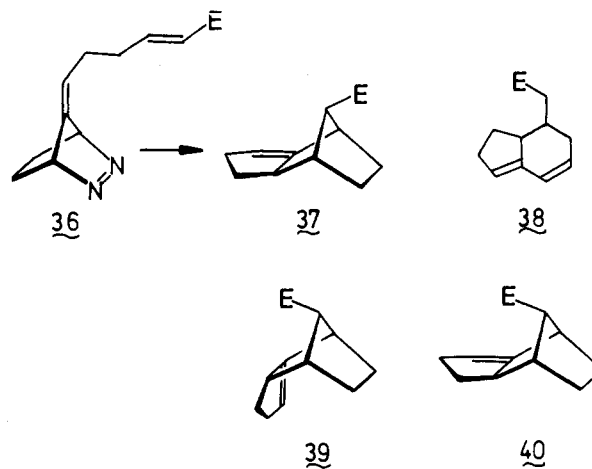
[5.*n*.1.0<sup>2,6</sup>] (a bridged adduct) ring system could be formed.



The results of experiments conducted using tether lengths of one-four are summarized below. Notice that linearly fused products are formed when *n* = 1, 3, and 4, but not when *n* = 2. Also, keep in mind that in certain cases (vide supra), two regiochemical outcomes have been observed when *n* = 3.<sup>26</sup>

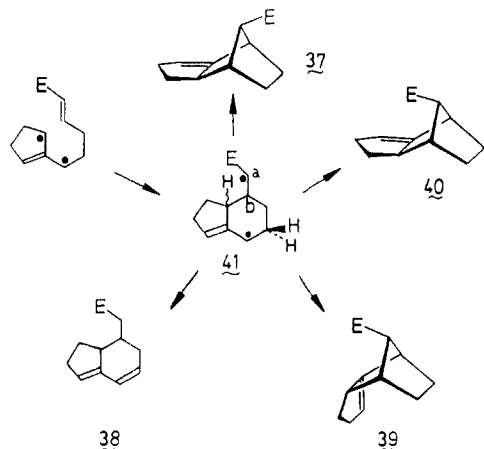
| <i>n</i> | nature of product(s) obtained |
|----------|-------------------------------|
| 1        | linear                        |
| 2        | see below                     |
| 3        | linear/reverse                |
| 4        | linear                        |

Four products 37-40 are produced in an 83% isolated yield and in a ratio of 16:5:1.5:1, upon thermal deazetation of diazene 36 (*n* = 2); no linearly fused product could be detected or identified.<sup>27</sup> These results



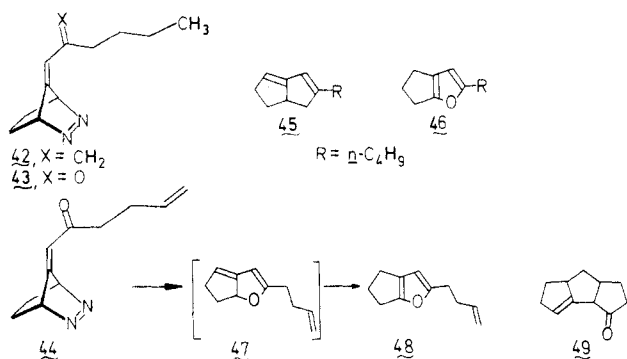
can be understood by application of some of the "ground rules" which govern the cyclization of a monoradical onto an olefin.<sup>14</sup> Assume, once again, that the trapping reaction proceeds in a stepwise fashion and that the smaller of the rings is formed first. Then, the initial closure could lead either to a four- or a six-membered ring; the former affords a cyclobutyl- and the latter a cyclohexylcarbinyl radical. It has been established that the equilibrium between the cyclobutylcarbinyl and homoallyl radicals lies on the side of the latter while that between the alternative pair lies on the side of the cyclohexylcarbinyl radical.<sup>28</sup> Consequently, one might predict that closure to a four-membered ring could go undetected, as observed. Once

cyclization to the bicyclo[4.3.0]nonene intermediate **41** has occurred, then rotation about the  $C_a-C_b$  bond followed by bonding between the two odd-electron centers leads to the major product **37** while hydrogen atom abstraction and collapse to a C-C  $\pi$  system affords diene **38**. Both the loss of diophile stereochemistry



and the hydrogen-atom abstraction events are without precedent in all cases of the intramolecular 1,3-diyI trapping reaction which have been studied to date.

The extreme case of tether-length variation involves the selection of a system wherein, assuming that a diyI is formed, then it and the diophile are linked directly, i.e.,  $n = 0$ . Thus far, we have investigated the chemistry of the three systems **42–44** to determine whether a heteroatom containing diophile could be utilized, thereby leading to the construction of heterocycles, and to determine which of the two  $\pi$  bonds, if either, in **44** would undergo preferential cycloaddition.<sup>29a</sup> The results demonstrated that (a) good yields of product can be obtained (70–87%); (b) heteroatoms can be incorporated into the diophile leading, in these cases, to the formation of bicyclic furans (e.g., **43**  $\rightarrow$  **46**; **44**  $\rightarrow$  **48**);



(c) the initially formed product places one C-C  $\pi$  bond in each of the two rings. Rearrangement of the oxygen-containing products occurs on silica gel to afford the furan ring system (e.g., **47**  $\rightarrow$  **48**); (d) given the choice of forming either the bicyclic furan **48** or the linearly fused system **49**, only the former is produced.

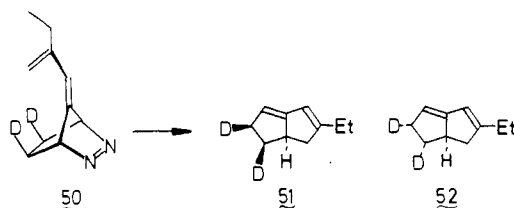
One additional point worth noting is the observation that diazene **42** is converted to **19** in only 1.5 h at 50 °C, while the conversion of **19** to its products requires 40 h at the same temperature. It is tempting to speculate that a thermally allowed [ $\sigma_2 + \pi_2 + \pi_2 + \sigma_2$ ] concerted eight-electron olefin-assisted loss of nitrogen might be responsible for this acceleration. In an attempt to address this issue, we have recently examined

TABLE III

| diophile  | cycloadducts (isolated yields)               | dimer, % |
|---|--|----------|
| PhCHO   | <br>33% $\beta$ -Ph<br>4% $\alpha$ -Ph       | 15       |
| $E_2C=O$<br>E = CO <sub>2</sub> Et                    | <br>(27%) (19%)                              | 14       |
| $E_2C=O$  | <br>(75%) <sup>a</sup>                       | b        |
| Ph <sub>2</sub> C=S                                   | <br>(50%) (22%)                              | 4        |
| PhN=CHPh  | <br>3% $\alpha$ -Ph<br>37% $\beta$ -Ph (34%) | 8        |
| (CH <sub>2</sub> ) <sub>n</sub><br>ZnCl <sub>2</sub>  | <br>(87%) <sup>a</sup>                       | b        |
| EC $\equiv$ CE<br>E = CO <sub>2</sub> CH <sub>3</sub> | <br>(76%)                                    | b        |

<sup>a</sup>Regioisomer and dimer not detected. <sup>b</sup>Dimer not detected.

the chemistry of the deuterated diazene **50**, and have discovered that equal amounts of compounds **51** and **52** are formed.<sup>29b</sup> If the reaction had indeed occurred



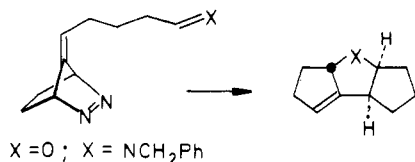
in a concerted fashion, then one would have anticipated the formation of only one of the two observed products. Similarly, if a mix of concerted and stepwise pathways was involved, then one would scarcely expect the formation of equal amounts of **51** and **52**. We propose that these results imply the intervention of a time-average



and planar diyl intermediate.

**Construction of Heterocycles.** Recently, the scope of the diyl trapping reaction was broadened significantly by the discovery that heteroatom-containing olefins can effectively trap diyls, even in the intermolecular mode.<sup>30a</sup> The results, which are summarized in Table III, serve to highlight some of the similarities between the Diels–Alder and the diyl trapping reaction.<sup>30b</sup>

As anticipated, mixtures of regio- and stereoisomers are formed. It is also apparent that the more effective trapping agents correspond to those which bear electron-withdrawing (or radical-stabilizing) groups. For example, in contrast to the cases cited in Table III, simple aliphatic aldehydes and imines do not seem to be capable of trapping the diyl; instead, diyl dimerization ensues. However, these limitations are overcome by utilizing the intramolecular version of the reaction. Two examples are illustrated.<sup>31</sup>



### Concluding Remarks

It is clear that the 1,3-diyl trapping reaction provides a very simple entry into the linearly fused tricyclopentanoid skeleton. Several of the results described above suggest that the reaction will prove to be useful in the construction of a host of other molecules as well. In retrospect, it is rather remarkable that such reactive intermediates have proven to be such serviceable synthetic intermediates. In our opinion, the territory is still fertile; we believe that we are dealing with a potentially very powerful and useful reaction, the scope of which is far from being well-defined. This view should not be regarded negatively, but rather as a challenge to explore the territory in far greater detail and to discover the treasures which await the exploration.

**Acknowledgments.** I am extremely grateful to the gifted and dedicated group of students who have carried out all of the research described herein and whose names appear in the literature citations. It has been a pleasure to be associated with each of them. They have provided a research atmosphere which has made the venture truly enjoyable. I am also pleased to acknowledge the support of the Public Health Service (National Cancer Institute) for their continuing support of this research. Finally, I thank the Alfred P. Sloan Foundation for a fellowship.

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