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Intramolecular Reactivity of a Captodative Bis-Diene

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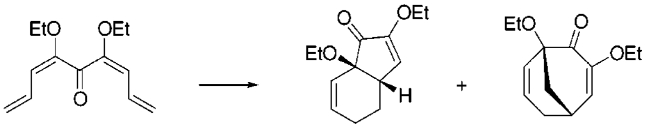
ABSTRACT



A 1,1-captodative bis-diene (3) has been prepared from crotonaldehyde diethyl acetal through an elimination−metalation sequence. This compound has been reacted with electron-rich and electron-deficient dienophiles. Under both thermal and high-pressure conditions, no intermolecular reaction was observed, the fused (4) and bridged (5) intramolecular bicyclic adducts being recovered. The reduction of the central carbonyl group has led to the corresponding allylic alcohol which, in thermal cycloaddition conditions, also provides an intramolecular adduct that aromatizes in the medium.

Multifunctional molecules are attractive synthetic targets because of their implication in serial-primer reactions such as cascade, tandem, domino, etc., processes.[1] Bis-dienes belong to these promising classes of structures since they can be employed in double cycloadditions involving two dienophiles, which can be the same or different, and therefore lead to a rapid increase of molecular complexity in a reduced step-count.[2] The potential of double reactions has also been pointed out by Poss and Schreiber within the frame of the two-directional chain growth strategy[3] and has received important synthetic applications.[4]

The interest of our groups in dienes chemistry[5] led us to consider the case of bis-dienes of type **3**. Such compounds, bearing both an electron-rich and an electron-deficient substituent on the same carbon atom, are to be considered as captodative (cd) according to H. G. Viehe's original studies.[6] If the behavior of cd olefins in [2 + 2] reactions is relatively well documented, the corresponding dienes have been almost left aside, especially in [4 + 2] additions. The cd and bis-dienic characters of **3** are likely to endow this compound with a peculiar reactivity, eventually amplified by its large conjugation. The antagonistic effects of the substituents render the behavior of **3** in cycloaddition reaction particularly difficult to predict, a direct or inverse-demand as well as spin-paired diradical (considering the pro-radical aspect of the quaternary carbons) pathways being a priori possible.

A direct synthetic access to **3** is described in Scheme 1. The LICKOR treatment of crotonaldehyde diethyl acetal leads to the expected elimination−metalation process.[7] The intermediate vinylic organometallic **2** can be trapped at low

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[1] (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Eng.* **1993**, *32*, 131−163. (b) Radl, S. *Aldrichima Acta* **1997**, *30*, 97−100.

[2] (a) Hudlicky, T. *Chem. Rev.* **1996**, *96*, 3−30. (b) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167−176.

[3] Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9−17.

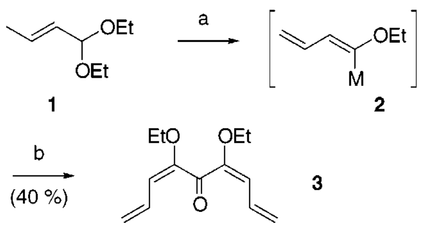
[4] Inter alia: (a) Spino, C.; Liu, G. *J. Org. Chem.* **1993**, *58*, 817−819. (b) Gorman, D. B.; Gassman, P. G. *J. Org. Chem.* **1995**, *60*, 977−985. (c) Marchionni, C.; Vogel, P.; Roversi, P. *Tetrahedron Lett.* **1996**, *37*, 4149−4152. (d) Winkler, J. D.; Holland, J. M.; Peters, D. A. *J. Org. Chem.* **1996**, *61*, 9074−9075. (e) Lautens, M.; Fillion, E. *J. Org. Chem.* **1997**, *62*, 4418−4427.

[5] See, for instance: (a) Balma Tivola, P.; Deagostino, A.; Fenoglio, C.; Mella, M.; Prandi, C.; Venturello, P. *Eur. J. Org. Chem.* **1999**, 2143−2147. (b) Guillam, A.; Toupet, L. Maddaluno, J. *J. Org. Chem.* **1998**, *63*, 5110−5122.

[6] (a) Viehe, H. G.; Merenyi, R.; Stella, L.; Janousek, Z. *Angew. Chem., Int. Ed. Chem.* **1979**, *18*, 917−932. (b) Viehe, H. G.; Janousek, Z.; Merenyi, R.; Stella, L. *Acc. Chem. Res.* **1985**, *18*, 148−154. (c) Viehe, H. G.; Merenyi, R.; Janousek, Z. *Pure Appl. Chem.* **1988**, *60*, 1635−1644.

10.1021/ol991000a CCC: $18.00

Scheme 1[a]

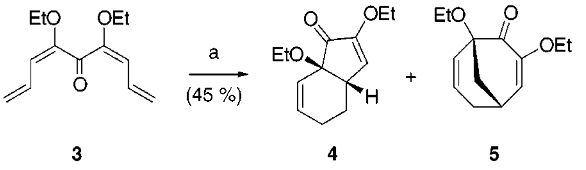


[a] (a) BuLi, *t*-BuOK, THF, −90 °C. (b) $(EtO)_2CO$, THF, −90 °C.

temperature by diethyl carbonate, yielding **3** in 40% yield, as a stable oily compound that can be chromatographed on silica gel. The well-established stereoselectivities of the elimination and metalation steps explain the recovery of a single *E,E′*-isomer.

The bis-diene was first treated with *N*-phenylmaleimide in toluene and benzonitrile at reflux or with neat ethyl acrylate, in the presence of trace amounts of hydroquinone. To our surprise, none of the expected intermolecular single or double adducts were obtained. Two products were instead isolated out of the reaction mixture. They are the [4.3.0] and [3.3.1] bicyclic compounds **4** and **5**, respectively, recovered in 45% overall yield and in a 2:1 ratio (Scheme 2).

Scheme 2[a]



[a] Toluene or benzonitrile, reflux, 22 h (**4**/**5** = 2:1).

Adducts **4** and **5** can be derived from an intramolecular cycloaddition on **3**, one terminal olefin of the bis-diene acting as a dienophile with respect to the other dienic moiety. These two adducts would in this case correspond to the transoid and cisoid arrangements, respectively, of the dienophilic fragment with respect to the diene (Figure 1). In both cases, a single exo transition state would occur, as deduced from the stereochemical outcome of the reaction. This exo selectivity, not uncommon for intramolecular cyclizations,[8] would probably stem from the highly rigid structure of the olefinic tether.

An AM1 semiempirical theoretical study has then been undertaken on **3**, to evaluate the relative stabilities of its reactive conformers. The absolute more stable arrangement corresponds to a totally unfolded transoid−transoid (tt) situation (Figure 2), in which the carbonyl group lies more or less antiparallel to the methoxy ones. In this situation, the olefinic moieties are far apart and cannot interact.

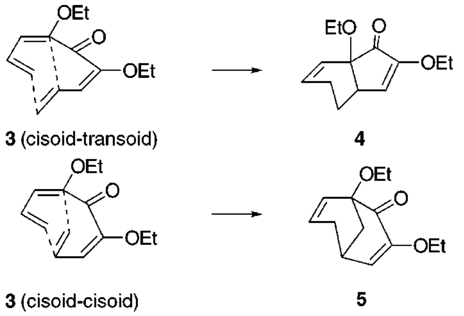


Figure 1. Possible topologies of transition states during the intramolecular cyclization of bis-diene **3**.

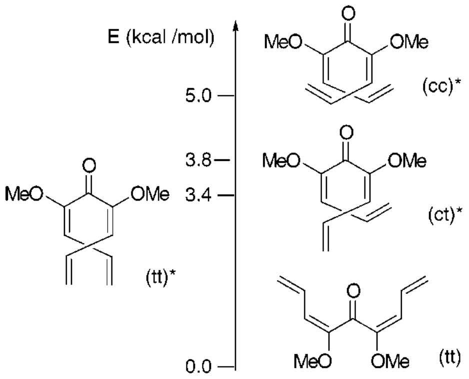


Figure 2. Model conformers for bis-diene **3**.

Several unilaterally folded (and therefore still inert) conformers are found in a 2 kcal/mol range above the tt steady state. It indeed takes a double folding to bring both diene and dienophile moieties in a same region of space and to obtain conformers that can be regarded as possible pre-transition-state arrangements, as discussed in Lightstone and Bruce's Near Attack Conformation (NAC) theory[9] or in Parrill and Dolata's Facilitated Transition Hypothesis.[10] The more stable doubly folded form (tt)* lies 3.4 kcal/mol above the fundamental tt situation, albeit it remains obviously unable to cycloadd. Two pre-transition-type local minima have finally been identified, the (ct)* at 3.8 kcal/mol, and the (cc)* at 5.0 kcal/mol higher (Figure 2). For all these conformers, the *E,E′* geometry of the system precludes the carbonyl group to lie in the planes defined by each diene. Of note are the relative energies of the (ct)* and (cc)* situations that on thermodynamic basis, fairly account for the proportions of adducts **4** and **5** recovered.

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(7) (a) Venturello, P. *J. Chem. Soc., Chem. Commun.* **1992**, 1032−1033. (b) Fossey, J.; Ghigo, G.; Tonachini, G.; Venturello, P. *Tetrahedron* **1997**, *53*, 7937−7946.

(8) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187−238.

(9) Lightstone, F. C.; Bruice, T. C. *J. Am. Chem. Soc.* **1994**, *116*, 10789−10790.

(10) Parrill, A. L.; Dolata, D. P. *Tetrahedron Lett.* **1994**, *35*, 7319−7322.

The captodative character of **3** also prompted us to take into account eventual diradical mechanisms. In Figure 3 are presented possible nonconcerted pathways to **4** and **5**.

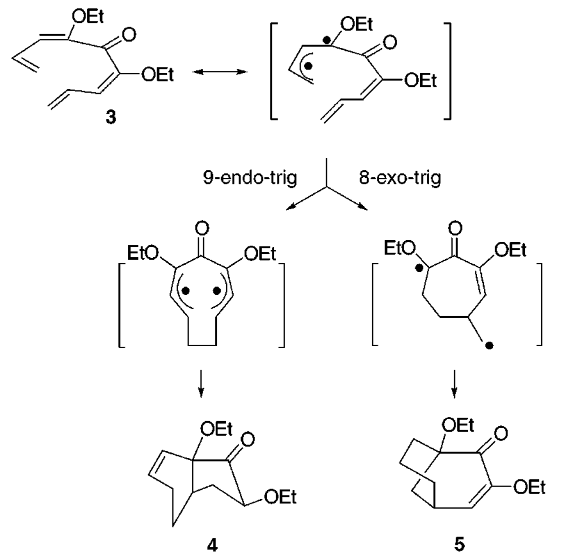
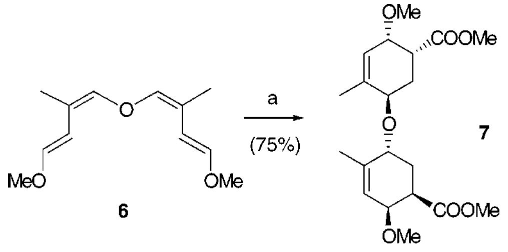


Figure 3. Possible nonconcerted routes to **4** and **5**.

Considering that the allylic radical could be relatively less stabilized than the cd one, the [4.3.0] cyclization product **4** would occur through a 9-endo-trig ring closure while the [3.3.1] skeleton of **5** would be due to a 8-exo-trig process. Albeit not covered by Baldwin's original rules,[11] these medium-size ring formations seem compatible with the geometrical constraints imposed by the approach of the intermediate radical on the trigonal carbon. The relative rigidity of these systems could explain the stereoselectivity of the cylizations, and the double stabilization of the intermediate symmetrical diradical along the 9-endo-trig route could account for the preference in **4**, provided these ring-closing steps allow some reversibility. One should however keep in mind that in all experiments described above, small amounts of hydroquinone have been added to avoid (in principle) radical side reactions.

The intramolecular preference of this reaction occurring in an electron direct-demand situation, we thought it appropriate to examine the case of an inverse-demand relationship. At reflux in ethyl vinyl ether for 22 h, **3** yielded a mixture of **4** and **5**, in an almost unchanged ratio. We then resorted to high pressure, placing **3** with either methyl acrylate (in methanol) or neat ethyl vinyl ether under 12 kbar for 48 h at room temperature. No reaction at all could be observed this time, **3** being recovered unchanged in both cases. This absence of reactivity with activated dienophiles is worth noting with respect to the behavior of electron-rich bis-diene **6** in comparable conditions (Scheme 3). Indeed, if the double adduct **7** is obtained in only 29% after 240 h at 80 °C, the yield reaches 75% after 24 h under 13 kbar at room temperature.[12]

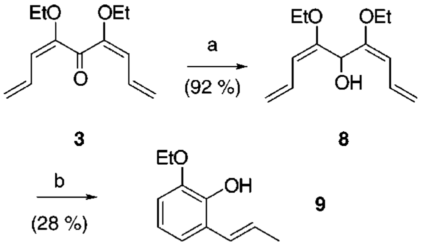
Scheme 3[a]



[a] Methyl acrylate, MeOH, 13 kbar, room temperature, de = 56%.

The LAH reduction of the tethering carbonyl group of **3** has therefore been undertaken, providing alcohol **8** in good yield (Scheme 4).

Scheme 4[a]

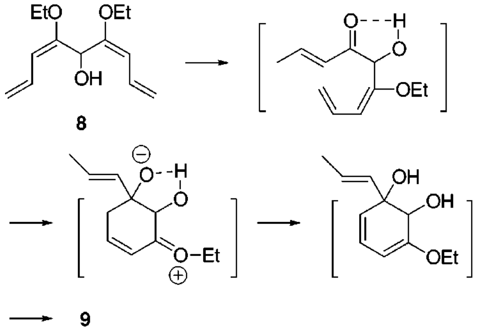


[a] (a) LiAlH$_4$, Et$_2$O, 0−25 °C. (b) Toluene or benzonitrile, reflux.

This new bis-diene, expected to behave as a "regular" electron-rich structure, actually does not add to electrophilic olefins such as *N*-phenylmaleimide or methyl acrylate in toluene or benzonitrile at reflux but rather affords, in both cases, the aromatic product **9** in modest yields.The structure of **9** has been deduced from analytical data and secured by comparison of its proton NMR spectrum with that of a closely related known catechol.[13]

A mechanism, through which this unexpected intramolecular product, which has formally lost one EtOH

Scheme 5



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(11) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734−736.

molecule with respect to starting material **8**, is obtained, can be proposed on the basis of the partial hydrolysis of one enol ether moiety (eventually occurring during the prolonged warming of the reaction medium), followed by an intramolecular Mukaiyama-type reaction (possibly triggered by an intramolecular hydrogen bond between the hydroxy proton and the vicinal carbonyl group) providing the six-membered ring that would aromatize in a final dehydration step (Scheme 5).

In conclusion, this set of cycloaddition experiments on bisdienes **3** and **8** tends to indicate that it is not the cd character of **3** that increases its intramolecular reactivity at the expenses of the intermolecular one. Steric factors, such as the presence of two quaternary ethylenic carbons in both compounds, probably account better for this intramolecular preference.

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(12) Guillam, A.; Toupet, L.; Maddaluno, J. Submitted for publication.

(13) Arnarp, J.; Bielawski, J.; Dahlin, B. M.; Dahlman, O.; Enzell, C. R.; Petterson, Y. *Acta Chem. Scand*. **1989**, *43*, 44−50.