ASPECTS OF THE INTRAMOLECULAR DIELS-ALDER REACTIONS OF SOME 1,3,8-TRIENIC ESTERS[1]

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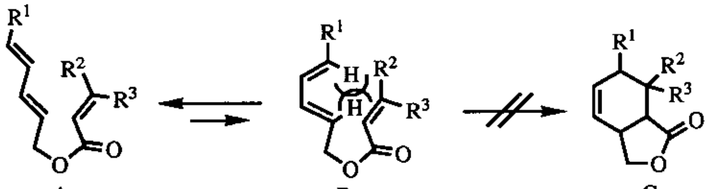
Abstract--The intramolecular cycloadditions of a number of 1,3,8-trienes containing monoester or diester function were examined. The unsaturated ester (**4**) gave the unexpected dimeric lactone (**10**) in the absence and presence of Et_2AlCl. On the other hand, the thermolyses of the triene mono- and diesters (**6**) and (**9**) in the presence of Lewis acid afforded mixtures of the corresponding cycloadducts and those epimers (**16**) and (**23**) respectively.

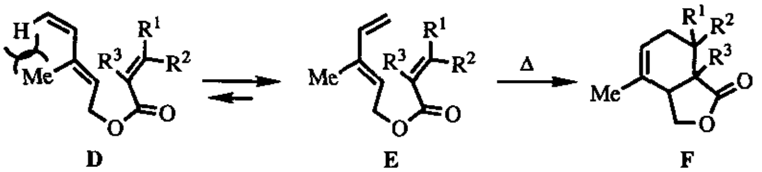
The intramolecular Diels-Alder reaction promises to become widely used in the synthesis of natural products.[2] The reaction has been used to synthesize many interesting ring systems and has already been applied to a variety of problems in natural products chemistry.[3] Although a number of stereochemical studies of intramolecular Diels-Alder reaction have been reported,[4] the stereochemical aspects of the reactions of 1,3,8-trienic esters are not yet well investigated due probably to the lack of reactivity of them[5] (eq. 1).



A **B** **C**

1 $R^1=R^2=R^3=H$
2 $R^1=Me, R^2=R^3=H$ (eq. 1)
3 $R^1=R^2=R^3=Me$

Since the hydroisobenzofuranone ring system (**C**) is an important synthon found in naturally occurring drimenin-type terpenoids, we were prompted to examine synthetic entries to **C** that featured the thermal cyclization of more functionalized trienic esters (**4**~**9**) (eq. 2).



(eq. 2)

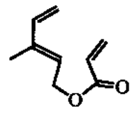
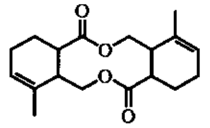
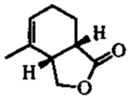
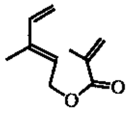
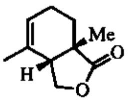
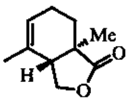
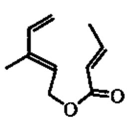
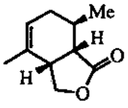
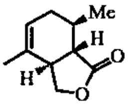
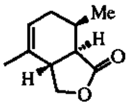
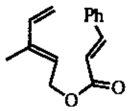
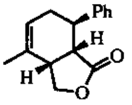
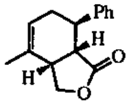
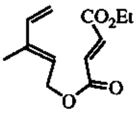
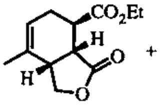
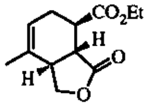
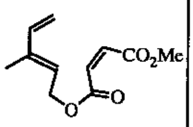
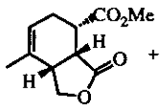
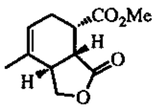
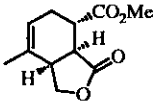
4	$R^1=R^2=R^3=H$	**7**	$R^1=Ph, R^2=R^3=H$
5	$R^1=R^2=H, R^3=Me$	**8**	$R^1=CO_2Et, R^2=R^3=H$
6	$R^1=Me, R^2=R^3=H$	**9**	$R^1=H, R^2=CO_2Me, R^3=H$

The requisite trienic esters (**4**~**9**) for these preliminary studies were conveniently prepared by standard synthetic reactions involving the esterification of the appropriate carboxylic acids with the unsaturated alcohol whose conformation is kept to minimize the allylic strain.[6] At the very inception of our attempts to induce the thermal cyclizations of the trienes (**4**~**9**), it became apparent that the conditions to effect their intramolecular [4+2] cycloadditions would be considerably drastic. The thermal cyclizations were performed by heating solutions of individual substrates in dilute toluene solution (10 % w/v) at 160 °C until the reactions were judged complete by tlc analysis. The Lewis acid catalyzed reactions were also performed for each substrates at the same conditions (Table).

It is clear from data decribed in the next page that the allylic strain in the diene plays a minor role in determining the reactivity of the intramolecular Diels-Alder reaction. Surprisingly, when **4** was heated in the absenece and presence of Lewis acid, the dimeric lactone (**10**) was obtained. To our knowledge, it is a quite rare example under such conditions. As excepted,[9] only the trans-hydroisobenzofuranones (**15**) and (**22**) underwent epimerization α to the lactone carbonyl group. It is immediately striking that the reactivity of the [4+2] cycloaddition of terminally activated **8** and **9** increases as previously reported.[10]

Further studies of the intramolecular Diels-Alder reactions of other oxygen-containing trienes are in progress to test the validity of some of the conclusions drawn herein and to explore further the scope and synthetic utility of such processes. The results of these investigations will be reported in due course.

Table

conditions[c]	Reaction Products[a, b]	
substrates	160 °C	Et_2AlCl[d] / 160 °C
 4	 10 (23%)	 + 10 (6.4%) 11 (10%)[e]
 5	—	 +  12 (1.8%) 13 (1.8%)
 6	—	 +  +  14 (3%) 15 (5%) 16 (3%)
 7	 +  17 (3%) 18 (8%)	17 (2%) + 18 (4%)
 8	 +  19 (11%) 20 (34%)	19 (10%)
 9	 +  21 (23%) 22 (45%)	21 (22%) +  23 (45%)

a) Stereochemistries of the products were established by nmr spectroscopic studies of the separated adducts and/or their transformed products.

b) The yields of adducts were determined independently by isolation, and by intergation of the resonances due to the olefinic proton in the nmr spectra of reaction mixtures.

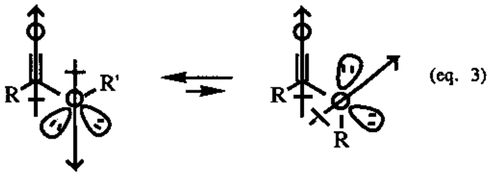
c) All thermal cyclizations were performed in sealed tubes using toluene as solvent.

d) Lewis acid (0.2 M) based on 1,3,8-trienic ester was used.

e) ref. 7.

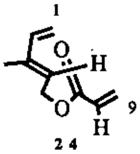
REFERENCES AND NOTES

1. Dedicated to Professor Edward C. Taylor on the occasion of his 70th birthday.
2. W. Carruthers, 'Cycloaddition Reactions in Organic Synthesis', Pergamon Press, 1990, and refs. cited therein.
3. A few recent examples: a) D. A. Evans and W. C. Black, *J. Am. Chem. Soc.*, 1992, **114**, 2260. b) S. R. Wilson and L. Jacob, *J. Org. Chem.*, 1992, **57**, 4380. c) D. L. Comins and R. S. Al-awar, *J. Org. Chem.*, 1992, **57**, 4098.
4. A few recent examples: a) S. M. Sieburth and L. Fensterbank, *J. Org. Chem.*, 1992, **57**, 5279. b) D. Craig and J. C. Reader, *Tetrahedron Lett.*, 1992, **33**, 6165. c) G. Stork, T. Y. Chan, and G. A. Breault, *J. Am. Chem. Soc.*, 1992, **114**, 7578.
5. a) H. O. House and T. H. Cronin, *J. Org. Chem.*, 1965, **30**, 1061. b) E. Ciganek, *Org. React.*, 1984, **32**, 1. c) The propensity of esters to exist nearly totally in the transoid geometry (eq. 3) due to dipole repulsions is well-known.[11] In the s-trans conformation, the diene and dienophile are not properly disposed to cyclize.



G **H**

6. F. Johnson, *Chem. Rev.*, 1968, **68**, 375.
7. Recently we have independently suggested that Diels-Alder reactions of this type occur by concerted but *nonsynchronous* transition states in which bond formation between one pair of carbon atoms precedes at the other termini.[8] In this reaction, bond formation between C-1 and C-9 is more advanced in the transition state and formation of the nine-membered ring is considered to occur more readily *via* the *syn* transition state (**24**).



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8. M. Toyota, T. Seishi, M. Yokoyama, and K. Fukumoto, *Tetrahedron Lett.*, 1992, **33**, 4581.
9. P. Magnus and C. Walker, *Tetrahedron Lett.*, 1986, **27**, 651.
10. a) J. D. White, B. G. Sheldon, B. A. Solheim, and J. Clardy, *Tetrahedron Lett.*, 1978, 5189. b) J. D. White and B. G. Sheldon, *J. Org. Chem.*, 1981, **46**, 2773.
11. a) H. Nakanishi and M. Oki, *Bull. Chem. Soc. Jpn.*, 1970, **43**, 2558. b) H. Wennerstrom, S. Forsen, and B. Roos, *J. Phys. Chem.*, 1972, **76**, 2436. c) H. Nakanishi, H. Fujita, and O. Yamamoto, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 214. d) J. K. Wilmshurst, *J. Mol. Spectrosc.*, 1957, **1**, 201.

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