

CROTONATES AS DIENOPHILES IN HIGH PRESSURE-INDUCED DIELS-ALDER
CYCLOADDITIONS : COMPARED INTRA AND INTERMOLECULAR SITUATIONS

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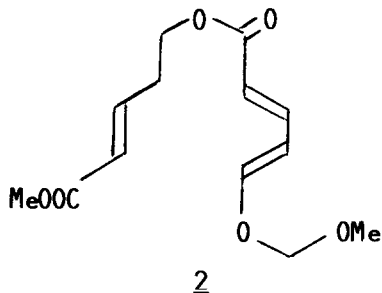
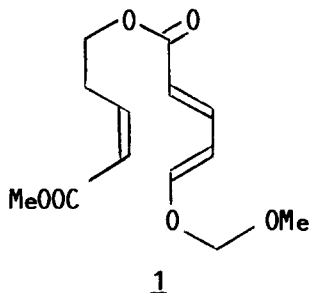
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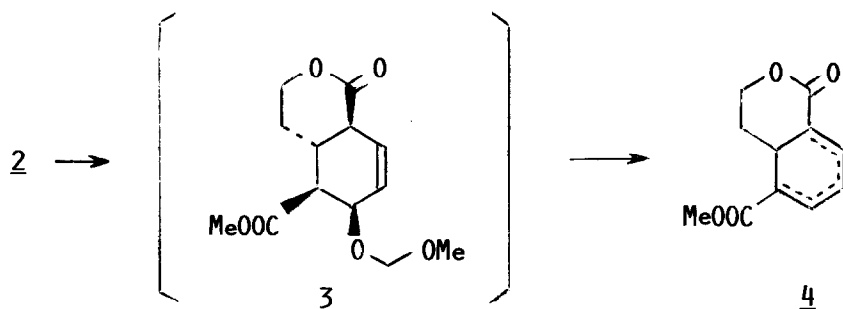
Summary : The cyclization reactions of trienes 1 and 2 related intermolecular systems (5+6) and (9+10) have been investigated.

Bicyclic lactones such as 3 and 7 should be potential synthetic intermediates for an approach to the yohimbine-type indole alkaloids¹. In principle these compounds could be prepared by either an *intra* or *intermolecular* Diels-Alder cycloaddition between an appropriately substituted diene and a crotonate derivative as the dienophile. In both cases, the required (*E,E*) diene component would bear an electron withdrawing substituent at position 1 and an electron donor substituent at position 4, a peculiar situation found in a new class of dienes we have previously synthesized². In this paper we would like to report two sets of experiments relating the behavior of such dienes toward *Z* and *E* crotonate-type dienophiles, in both *intra* and *intermolecular* situations.

Intramolecular cycloadditions^{3a}.

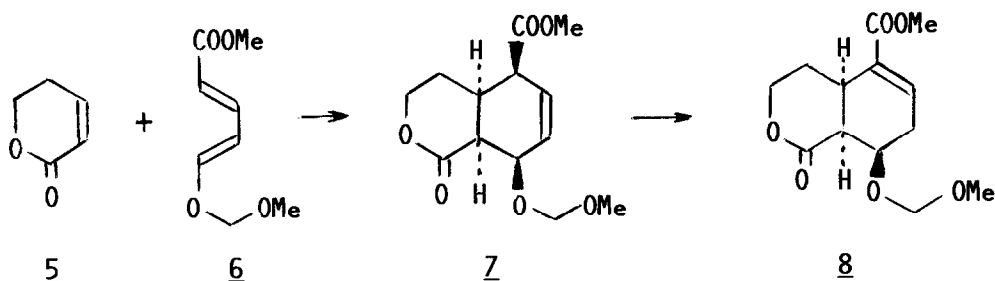
Starting from trienes 1 and 2, none of the expected cycloadducts were obtained under various thermal⁵ or Lewis acid-catalyzed⁶ conditions. When triene 1 was subjected to 17 kbar pressure^{3b,7} at 20°C no reaction occurred; at 70°C only unreacted starting material and polymers were recovered. Under the same conditions, triene 2 afforded a mixture of isomeric dienes⁸ 4, albeit in low yield (<20 %). The expected adduct 3 probably underwent facile (1-2 diaxial) elimination of the alkoxy group, leading to dienes 4.



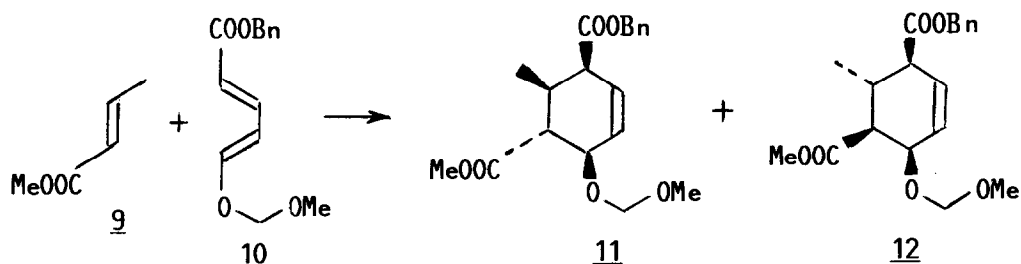


Intermolecular cycloadditions.

Whereas attempts of cycloaddition starting from the partners (5+6) and (9+10) under both thermal or Lewis acid-catalyzed conditions also failed, *activation by the combination of high pressure and moderate temperatures was successful*: the expected adducts were obtained in both cases. Thus lactone 5⁹ (a *Z* crotonate-like dienophile) and diene 6¹⁰ led to cycloadduct 7¹¹ (17 kbar, 50°C, CH₂Cl₂, 48 h, 75 % yield) which smoothly isomerized (Na₂CO₃, MeOH-H₂O, 20°C, 2 days, quantitative) into the bicyclic conjugated ester 8¹².



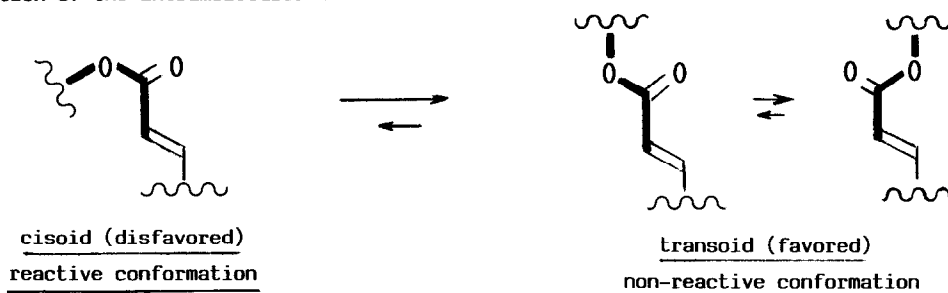
Under similar conditions (17 kbar, 70°C, CH₂Cl₂, 48 h) (*E*) crotonate 9 and diene 10¹⁰ afforded nearly equimolar amounts of the two isomeric cycloadducts 11 and 12¹³, in an overall yield of 40 %.



Discussion

It is known that crotonate-type alkenes act as poor dienophiles in Diels-Alder cycloadditions. Dauben, for example¹⁴, noted that the reactivity of crotonates as dienophiles is very much less than that of their acrylic counterparts in intermolecular situations. However the related intramolecular reactions required less drastic conditions^{3a}. Focusing our attention first on the reactivity of trienes 1 and 2, irrespective of the experimental conditions employed, none of the expected adducts were obtained, a vexing result in view of the fact that such intramolecular processes are favored entropically¹⁵.

We assume as does Martin¹⁶, and others, that the loss of reactivity of these trienes is due to dipolar interactions which strongly destabilize the cisoid conformation¹⁷ of the ester portion of the diene system, thereby resulting in an increase in the energy of activation of the intramolecular transition state.



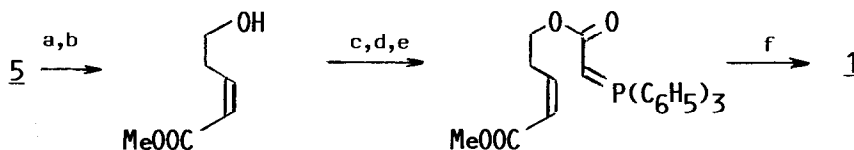
Contrary to the above intramolecular situation, the related intermolecular cycloadditions readily led to the expected adducts. Nevertheless we must note the lack of (*endo*) selectivity in the cycloaddition of (*E*) crotonate 9, such a failure of the *endo* rule in Diels-Alder cycloadditions using crotonates as dienophiles has been previously reported¹⁸.

Further approaches to indole alkaloids, starting from the readily available bicyclic lactone 7, are now in progress ; the results of these investigations will be reported in due course.

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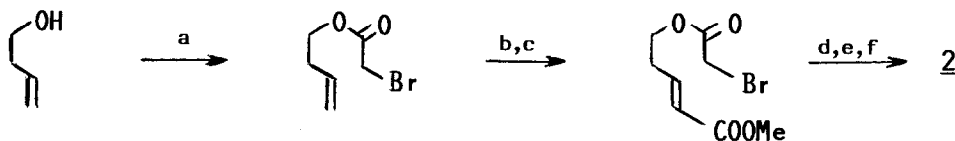
References and Notes

1. For a related strategy, see : J. Ficini, A. Guingant, J. d'Angelo, G. Stork, Tetrahedron letters, 907 (1983) and J. d'Angelo, R.M. Ortuño, J.F. Brault, J. Ficini, C. Riche, J.F. Boucaudy, Tetrahedron Letters, 1489 (1983).
2. a) J. Maddaluno, J. d'Angelo, Tetrahedron Letters, 895 (1983).
As expected, such dienes show an ambident reactivity in Diels-Alder cycloadditions :
b) G. Revial, M. Blanchard, J. d'Angelo, Tetrahedron Letters, 899 (1983).
3. a) For recent reviews on the intramolecular Diels-Alder reaction, see :
A.G. Fallis, Can. J. Chem. 62, 183 (1984) ; E. Ciganek, Org. React. 32, 1 (1984).
b) For a recent review on organic synthesis under high pressure, see :
K. Matsumoto, A. Sera, T. Uchida, Synthesis, 1 (1985).
4. Triene 1 was prepared in 25 % overall yield, according to the following sequence :



a : OH^- then H_3O^+ , b : CH_2N_2 , c : $\text{BrCH}_2\text{COOH/DCC/DMAP}$, d : $(\text{C}_6\text{H}_5)_3\text{P}$, e : NaOH , f :
 $\text{MeO}-\text{CH}_2-\text{CH}=\text{CH}-\text{CHO}$ (prepared according to 2a).

Triene 2 was prepared in 35 % overall yield, as follows :



a : $\text{BrCH}_2\text{COOH/DCC/DMAP}$, b : O_3 then Me_2S , c : $(\text{C}_6\text{H}_5)_3\text{P}=\text{CH}-\text{COOMe}$, d,e,f : id. triene 1.

5. Temperatures higher than 110°C induce thus the destruction of these trienes.
6. For example Et_2AlCl is ineffective, even at 20°C . For successful intramolecular Diels-Alder cycloadditions using such a catalyst, see : K.J. Shea, J.W. Gilman, *Tetrahedron Letters*, 657 (1983).
7. High pressure activation is effective for intramolecular Diels-Alder cycloadditions : N.S. Isaacs, P. Van der Beeke, *Tetrahedron Letters*, 2147 (1982).
8. 4 : $^1\text{H NMR}$ (CCl_4 , 90 MHz) : 6.8 (m 1 H) 5.8 (m 2 H) 3.6 (s 3 H) 3.25 (m 2 H) 2.45 (m 2 H).
9. M. Nakagawa, M. Tonozuka, M. Obi, M. Kiuchi, T. Hino, *Synthesis*, 510 (1974).
10. These dienes were prepared according to 2a.
11. 7 : $^1\text{H NMR}$ (CCl_4 , 90 MHz) : 6.0 (m 2 H) 4.5 (s 2 H) 4.3 (m 4 H) 3.7 (s 3 H) 3.27 (s 3 H) 3.25 (m 1 H) 2.7 (m 2 H) 2.1 (m 1 H).
12. 8 : $^1\text{H NMR}$ (CDCl_3 , 200 MHz) : 7.17 (m 1 H) 4.67 (d $J=7.0$ 1 H) 4.62 (d $J=7.0$ 1 H) 4.35 (m 1 H) 4.22 (m 1 H) 3.97 (ddd $J=8.5$ $J=7.0$ $J=4.5$ 1 H) 3.62 (s 3 H) 3.31 (s 3 H) 3.2 (dd $J=5.5$ $J=4.5$ 1 H) 2.8 (m 1 H) 2.67 (m 1 H) 2.6 (m 1 H) 1.85 (m 1 H) 1.7 (m 1 H).
The proposed stereochemical assignments have been confirmed by double resonance experiment.
13. Compounds 11 and 12 were obtained as an inseparable mixture in the 3:2 relative ratio. $^1\text{H NMR}$ (CDCl_3 , 200 MHz) 11 : 7.35 (s 5 H) 5.71 to 6.08 (m 2 H) 5.14 (s 2 H) 4.68 (m 2 H) 4.45 (dm $J=9$ 1 H) 3.72 (s 3 H) 3.34 (s 3 H) 3.16 (m 1 H) 3.13 (dd $J=11.5$ $J=9$ 1 H) 2.19 (ddq $J=5$ $J=7$ $J=11.5$ 1 H) 0.95 (d $J=7$ 3 H) 12 : 7.35 (s 5 H) 5.71 to 6.08 (m 2 H) 5.17 (s 2 H) 4.61 (m 2 H) 4.27 (m 1 H) 3.71 (s 3 H) 3.3 (s 3 H) 2.82 (dm $J=9.5$ 1 H) 2.63 (ddq $J=12$ $J=9.5$ $J=7$ 1 H) 2.46 (dd $J=12$ $J=4.2$ 1 H) 1.08 (d $J=7$ 3 H).
The proposed stereochemical assignments have been confirmed by double resonance experiment.
14. N.G. Dauben, H.O. Krabbenhoft, *J. Org. Chem.*, 42, 282 (1977).
15. Free energy of activation of intramolecular Diels-Alder cycloadditions are thus lower by 5 to 7 kcal/mol than those for intermolecular additions: W. Oppolzer, *Angew. Chem. Int. Ed.*, 16, 10 (1977).
16. S.F. Martin, S.A. Williamson, R.P. Gist, K.M. Smith, *J. Org. Chem.*, 48, 5170 (1983) and ref. cit. therein.
17. Calculations for the interconversion between cisoid \rightleftharpoons transoid conformations of esters gave thus the estimates $\Delta H = 4 \pm 5$ kcal/mol and $\Delta H^\ddagger = 11 \pm 3$ kcal/mol in the liquid phase : H. Wennerström, S. Forsén, B. Roos, *J. Phys. Chem.*, 76, 2430 (1972).
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