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MECHANISTIC RATIONALIZATION OF AN APPARENTLY NON-STEREOSPECIFIC INTRAMOLECULAR DIELS-ALDER REACTION.

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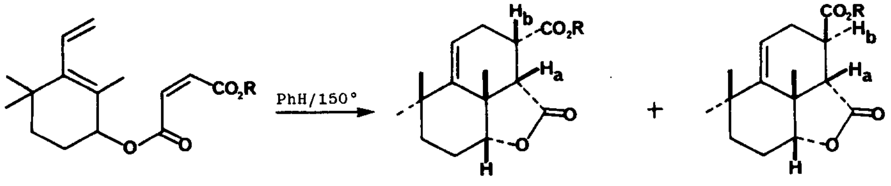
SUMMARY: The loss of dienophile stereochemistry in the conversion of 1/4 into 3/6 is shown to result from epimerization α- to the lactone carbonyl via 9.

It was recently reported[1] that the maleate ester 1, on heating at 150°C in benzene (sealed tube), gave the two tricyclic lactones 2 (14%), and 3 (42%). The assigned stereochemistry was based upon nuclear Overhauser enhancements (n. O. e.'s). Clearly, this observation apparently violates one of the basic tenets of the Diels-Alder reaction - that the stereochemistry of the dienophile is preserved in the cyclohexenyl product.[2] Recent extensive studies of the intramolecular Diels-Alder reaction[3] have suggested that in many cases the reaction proceeds preferentially via a geometry (in the transition state) in which the connecting linkage between diene and dienophile is exo-, and the stereochemistry of the newly formed ring fusion is determined by the non-bonded interactions, rather than electronic factors. There are no examples where the stereochemistry of the dienophile is not retained in the product. In this paper we confirm the original stereochemical assignments by single crystal X-ray crystallography; and through deuterium labelling have located the origin of this unexpected stereochemical result.

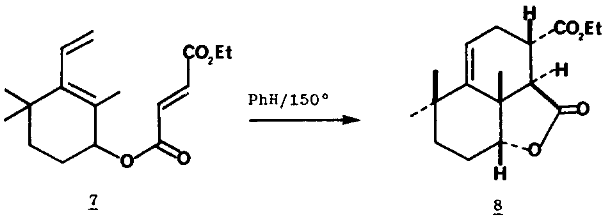


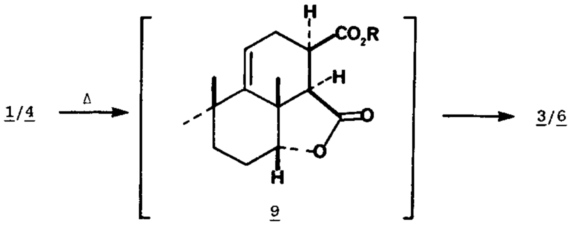
1 (R = Et) 4 (R = Me)

2 (R = Et) 5 (R = Me)

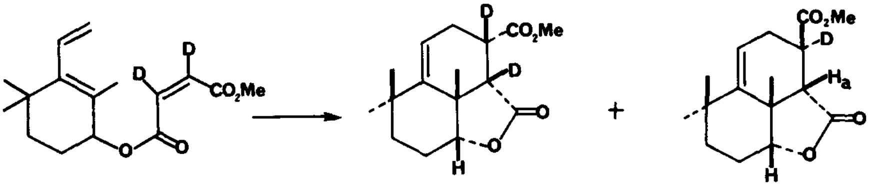
3 (R = Et) 6 (R = Me)

The minor isomer 2, m.p. 106.5 - 107°C, gave suitable crystals for X-ray analysis, FIGURE 1,[4] whereas, the major isomer 3 is an oil. In the methyl ester series 4, the corresponding isomer 6, m.p. 58 - 59°C, gave suitable crystals for X-ray analysis, FIGURE 2.[4] If the formation of 3/6 from 1/4[5] is simply the result of dienophile isomerism prior to cyclization, the corresponding fumarate derivative 7[5] should give the same tricyclic lactone. In the event, heating 7 at 150°C/36h. gave the lactone 8 (48%),[6] m.p. 97.5 - 98°C, whose structure was based on n. O. e. measurements and confirmed by X-ray analysis, FIGURE 3.[4] Clearly, the formation of the trans-lactone 8 excludes a dienophile isomerization pathway. The lactones 3/6 do not epimerize α- to the ester or lactone carbonyl group under conditions used for their formation. The only reasonable explanation for the loss of dienophile stereochemistry is that epimerization α- to the lactone carbonyl group has taken place subsequent to the Diels-Alder cyclization. In other words, the kinetic product from thermolysis of 1/4 is 9, which is transformed into 3/6 in situ.

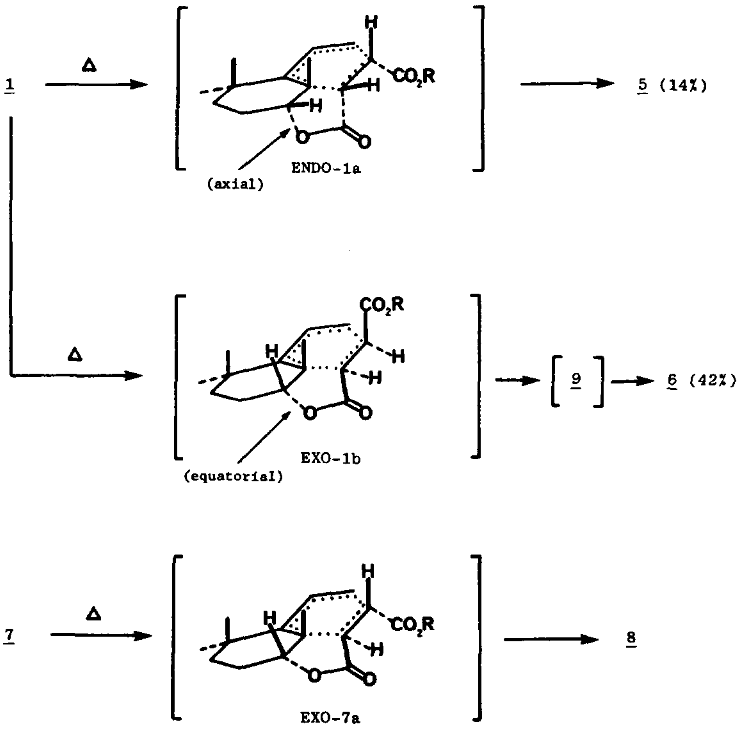




Thermolysis of 1 at 150°C/PhH, in the presence of CD$_3$OD (25 equiv.), gave 3 with 71% exchange of Ha for deuterium. More convincingly, thermolysis of 10[5] under the usual conditions gave 11 and 12. The ^{1}H NMR spectrum of 12 shows Ha as a singlet δ 3.10, and the absence of Hb; whereas, 6 has Ha as a doublet δ 3.19. The mass spectra of 11 and 12 showed molecular ions at m/e 280 and 279 respectively, consistent with the incorporation of two deuterium atoms and a single deuterium. Epimerization of 9 has taken place on the surface of the glassware, resulting in the loss of one deuterium atom. SCHEME 1 depicts the various transition states involved in these cyclizations, which are best rationalized by product-like transition states. The preference for 1b over 1a, even though it leads to 9 which is more strained, is explained by the presence of more equatorial substituents in the transition state. Silylation of the glassware did not give 3/6/12, only extensive decomposition was observed.



10 11 12



SCHEME 1

In summary, the observations described here should be a caution in interpreting the stereochemical outcome of intramolecular Diels-Alder reactions in terms of strictly kinetic products. The protocol of deuterium labelling to detect epimerization processes on the hydrophilic surface of the reaction vessel should find applications to other types of stereochemical problems, where assumptions concerning kinetic products have been made without due experimental evidence.

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1. P.R. Jenkins, K.A. Menear, P. Menear, P. Barraclough, and M.S. Nobbs, J. Chem. Soc., Chem. Commun., 1984, 1423.
2. Natural Products Synthesis Through Pericyclic Reactions. A.C.S. Monograph 180, Washington DC, 1983.
3. J.D. White, B.G. Sheldon, B.A. Solheim, and J. Clardy, Tetrahedron Letters, 1978, 5189; W.R. Roush, J. Am. Chem. Soc., 1978, 100, 3599; W.R. Roush, J. Org. Chem., 1979, 44, 4008; W.R. Roush, A.I. Ko, H.R. Gillis, J. Org. Chem., 1980, 45, 4264; W.R. Roush and H.R. Gillis, J. Org. Chem., 1980, 45, 4267 and references cited therein, particularly 18; J.D. White and B.G. Sheldon, J. Org. Chem., 1981, 46, 2273; "It is noteworthy that no evidence could be found for cycloaddition products in which the configurational fidelity of the dienophile had been lost."; R.K. Boeckman,Jr. and S.S. Koo, J. Am. Chem. Soc., 1982, 104, 1033.
4. Crystallographic details are available on microfiche from the Indiana University Chemistry Library - request Structure Report No. 85020 for FIGURE 1; 85044 for FIGURE 2; 85019 for FIGURE 3.
5. Compounds 1, 4, 7 and 10 were prepared in good yield from diene alcohol, 13[7] and the maleate or fumarate esters via DCC mediated coupling.

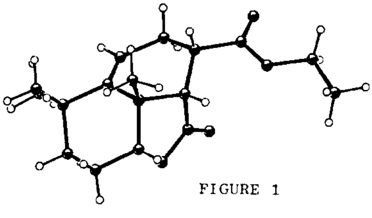

FIGURE 1

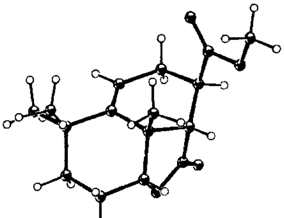

FIGURE 2

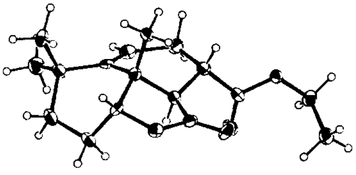

FIGURE 3

6. Corrected yield for recovered starting material. Only a small amount (5%) of another Diels-Alder cyclized product was observed in this reaction.
7. T. Leapheart, Ph.D. thesis, 1983, Indiana University.
8. For a recent example where the ester group in 1/4/7 is an aldehyde, see:- F.E. Ziegler, B.H. Jaynes, and M.T. Saindane, Tetrahedron Letters, 1985, 3307.

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