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STEREOCHEMICAL CONTROL IN TYPE I INTRAMOLECULAR ENE REACTIONS OF 1,6-DIENES: TRENDS IN REACTIVITY AND SELECTIVITY UPON SUBSTITUTION

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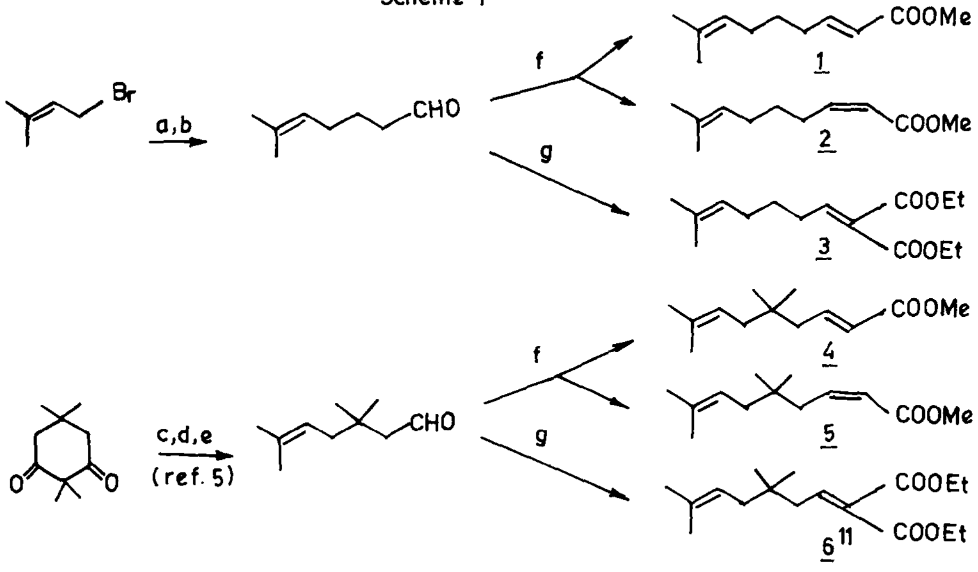
Abstract: The effects of varying the activating groups in the enophile and of geminal substitution in the connecting chain on the rates and stereoselectivities of the title reactions have been investigated.

In spite of the global efforts directed at understanding the stereochemical outcome in the intramolecular Diels-Alder reactions,[1] comparative studies on the reactivity and stereoselection imposed by activating groups on the enophile and/or substitution in the chain in the mechanistically related but synthetically less exploited intramolecular ene reaction[2,3] are at best limited. As part of a synthetic approach toward cyclopentanoid natural products,[4] we had occassion to examine these aspects in the thermal cyclization using the six 1,6-dienes, 1 - 6, and in this letter we wish to report the preliminary results of our investigation.

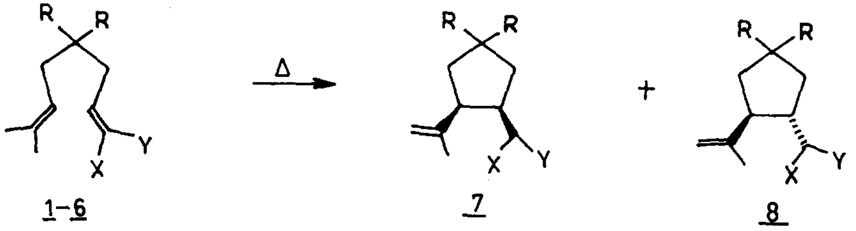
The parent dienes, 1 - 6, were synthesized following standard synthetic techniques as summarized in Scheme 1.

Scheme 1[10]



(a) $ClMgCH_2CH_2CH_2OMgCl$; (b) PCC; (c) $NaBH_4$; (d) TsCl; (e) t-BuOK/t-BuOH;
(f) $(MeO)_2P(O)CH(Na)COOMe$, then separation of the (E,Z)-mixture (9:1) by PLC; (g) $H_2C(COOEt)_2$/ piperidinium acetate

Preparative cycloadditions ($_{\pi}2_s$ + $_{\pi}2_s$ + $_{\sigma}2_s$) were carried out in sealed ampoules[6] without solvent under a blanket of nitrogen (eq 1). The product ratios[7,8] were determined by high-field NMR (200-MHz)[9] and are listed in Table I.



(1)

Table I. Stereoselectivities of the intramolecular ene reactions of 1,6-dienes

Educt	R	X	Y	Reaction Conditions	Combined Yield (%)§	Products[10] %7	%8
1	H	COOMe	H	253°C/40h	80	76	24
2	H	H	COOMe	253°C/40h	75	43	57
3	H	COOEt	COOEt	255°C/5h	70	13	87
4	Me	COOMe	H	222°C/35h	85	72	28
5	Me	H	COOMe	222°C/35h	80	40	60
6	Me	COOEt	COOEt	117°C/65h	80	20	80

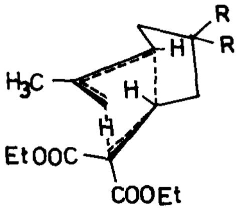
§Isolated after chromatography on silica gel.

Table II. Effects of substituents on reactivity

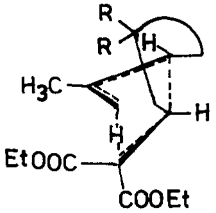
Entry	Educt	T°(C)	$T_{1/2}$§ (min)	$10^{-6}k$,§ s^{-1}	k_a/k_b
a	4	252±1	64	180.63	3.23
b	1	252±1	207	55.88	
a	6	161±1	241	47.96	3.78
b	3	161±1	912	12.66	
a	3	241±1	44	261.26	12.43
b	1	241±1	549	21.03	
a	6	170±1	102	113.24	17.67
b	4	170±1	1803	6.41	

§Determined from NMR by integration of appropriate olefin resonances; accuracy ±10%.

The following trends are apparent from this work (see Tables I & II). (a) Rate of intramolecular ene reaction of 1,6-dienes appears to be not only independent of the ene geometry,[2b] but also largely independent of the enophile geometry.[7b,9b] (b) In contrast to the ene geometry,[2b] the enophilic substitution pattern has a direct bearing on the stereochemical outcome in these reactions. Thus, while the E-dienes (1 & 4) promote cis-selectivity[2b] (preponderance of 7 in the mixture), the Z-dienes (2 & 5) display a marginal preferance[12] for the trans-isomer 8. (c) The trans-selectivity is greatly enhanced in the cases of alkylidene malonates (3 & 6). Although the exo-transistion state **A** is to be invoked (the alternate endo-transition state **B** is highly strained) to account for this stereoselection, the preponderance of the thermodynamically more stable trans-isomer 8 from 3 or 6 might also be the result of a late product-like transition state.[3a] (d) The geminal substitution (4 vs 1 & 6 vs 3) has a small influence (~ 3 - 4 times rate enhancement) on reactivity but has essentially no influence on the stereochemical outcome of the reactions. The buttressing caused by geminal substitution presumably results in an increase of the equilibrium population of cisoid conformers (eq 2) which is reflected in a lowering of the $\Delta S^{\ne}$ for cyclization.[1f] (e) The effect of an additional ester (3 vs 1 & 6 vs 4) on the rates of cyclization (rate enhancements ~ 13-17 times) is somewhat more pronounced than would be expected on the basis of a related study based on intramolecular Diels-Alder reaction.[1f]

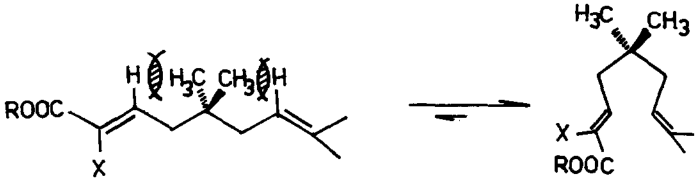


A



B

R= H, Me



X=H, COOR (2)

References and Notes

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5. (a) N.H.Andersen and D.W.Ladner, Synth.Commun., **1978**, 8, 449; (b) E.Wenkert, Y.Gaoni, J.Org.Chem., **1966**, 31, 3809.
6. Silyated Corning tubes were used for these reactions.
7. A seperate set of experiments established the following. (a) No initial cis/trans isomerization ($2 \rightleftharpoons 1$ or $5 \rightleftharpoons 4$) of the starting diene took place; (b) The cyclization proceeded at about the same rate for both dienes (2 vs 1 and 5 vs 4); (c) The ratio of products (7 : 8) obtained from 1 - 6 is, within experimental error, essentially independent of reaction temperature or time. Thus, it appears that the stereochemistry of the reaction is kinetically controlled.
8. A more cogent proof that the reactions ($3 \rightarrow 7/8$ and $6 \rightarrow 7/8$) are indeed kinetically controlled came from the following experiments. Brief exposure of the product mixture (7 and 8, prepared from 3 or 6) to $H_2/(Ph_3P)_3RhCl$ resulted in selective as well as complete elemination of the less abundant cis-isomer presumably by isomerization of the double bond in 7 into the more stable tetra-substituted position (exocyclic to the ring), for a relevant refeence see : J.F.Biellmann and M.J.Jung, J.Amer. Chem.Soc., **1968**, 90, 1673. The product mixture containing 8 thus obtained was then kept at 250°C for 7h and then analysed as usual (see ref. 9e). No trace of conversion to the cis-isomer was visible by 200-MHz NMR analysis in either case.
9. The crude reaction products from 1, 2, 4 and 5 were directly analysed by 200-MHz NMR. The cis/trans ratios were determined by integration of the olefinic reasonances, see : (a) K.Kondo, T.Takemoto and T.Ikenoue, Bull.Chem.Soc.Jpn., **1962**, 35, 1899; (b) P.D.Kennewell, S.S.Matharu, J.Taylor and P.G.Sammes, J.Chem.Soc.(Perk I), **1980**, 2542; (c) W.Oppolzer and K.Thirring, J.Amer.Chem.Soc., **1982**, 104, 4978; (d) W.Oppolzer and C.Robbiani, Helv.Chim.Acta., **1980**, 63, 2010; (e) The crude reaction products from 3 and 6 were similarly analysed after conversion to the acetates (7 and 8, R = Me or H, X = COOEt, Y = H) by the Krapcho protocol (LiCl/aq DMSO/heat).
10. All compounds give spectral data (IR, ^1H-NMR and MS) in accordance with their structures; yields are not optimized.
11. We thank Mr. P.S.V.Subba Rao for the preparation of this compound.
12. (a) Kennwell and coworkers have also made a similar observation, see 9b; (b) for a stereoselective synthesis of Z-unsaturated esters, see W. C. Still and C. Gennari, Tetrahedron Lett., **1983**, 24, 4405.

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