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THE INTRAMOLECULAR DIELS-ALDER REACTION: STEREOCONTROL THROUGH NONSYNCHRONOUS BOND FORMATION?

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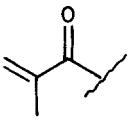
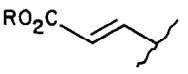
SUMMARY: Nonsynchronous bond formation in the transition state of the intramolecular Diels-Alder reaction is suggested to be an important determinant of the stereochemical outcome of the cyclization.

The intramolecular Diels-Alder reaction (1) promises to be a useful tool in carbocyclic synthesis. Before this reaction can be considered generally useful, however, it would be desirable to be able to predict the stereochemical outcome of a proposed cyclization. Two elements appear to be dominant in controlling this outcome: the length of the chain bridging the diene and the dienophile, and the substitution pattern of the latter.

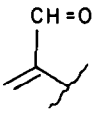
There are three types of activated dienophiles: enone, crotonate, and acrolein. Cyclization of the former two leading to 6/5 systems have been reported (2,3). We describe



ENONE



CROTONATE



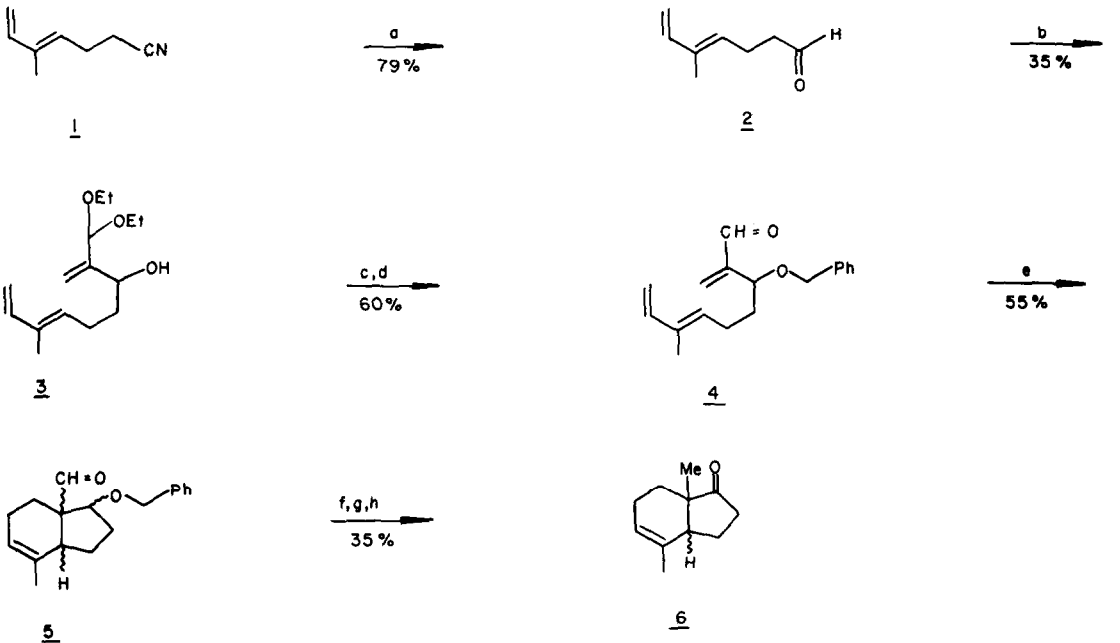
ACROLEIN

here the preparation and cyclization of a triene 4 having the acrolein substitution pattern, and suggest an overall rationalization for the stereochemical control seen in the 6/5 series.

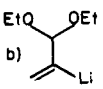
Triene 4 (4) was prepared (Scheme I) from aldehyde 2, readily available by Dibal reduction (5) of nitrile 1 (6). Addition of the anion of acrolein diethyl acetal (7) gave 3, which on benzylation (8) and hydrolysis (9) gave 4. Cyclization (toluene, methylene blue (10), reflux, 18 h) of 4 proceeded smoothly to give 5 as a mixture of diastereomers. This mixture was carried on without further purification to ketone 6 as a mixture of two isomers (^{1}H NMR major: 1.02 angular methyl, 5.44 vinyl; minor: 0.84 angular methyl, 5.30 vinyl; 82:18).

On the basis of the NMR data, it was felt that 6 so prepared was largely cis. This point was confirmed by an alternative preparation of 6 (Scheme II). Thus, addition of propenyl magnesium bromide to 2 followed by oxidation gave enone 8. Based on the work of Sutherland (2), cyclization of 8 should preferentially yield cis 6. In the event, thermolysis of 8 (toluene,

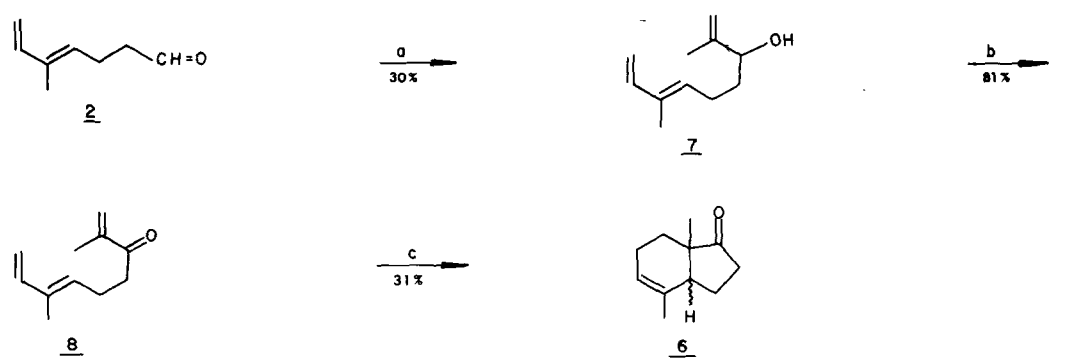
Scheme I



1 2 3 4 5 6

a) Dibal; H_2O, H_2SO_4. b)  c) NaH,  , $(C_3H_7)_4NI$, THF, RT, 18h. d) $(HO_2C)_2$, CH_2Cl_2 / H_2O, Silica gel, RT, 18h. e) Toluene, methylene blue, 110°, 18h. f) $NH_2NH_2 \cdot H_2O$, KOH, Triethylene glycol, Reflux, 18h. g) Na, ℓNH_3 / THF h) Jones reagent, Acetone, RT, 10 min.

Scheme II

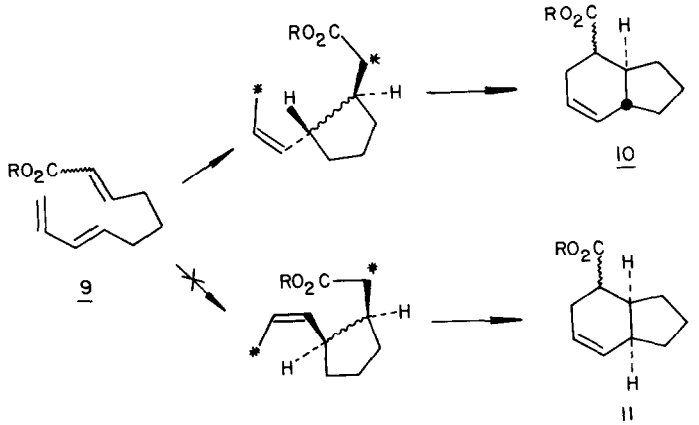


2 7 8 6

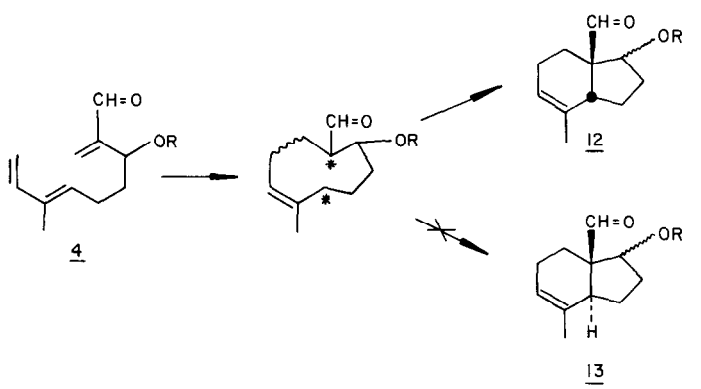
a) MgBr, THF b) Oxalyl chloride/ DMSO; Et_3N. c) Toluene, methylene blue, 190°, sealed tube, 18h.

methylene blue (10), sealed tube, 190°, 18 h) yielded 6 as a mixture of the same major and minor isomers (69:31).

There remains the question of why the crotonate dienophile should give a trans and the acrolein dienophile a cis ring fusion. Possibly, this could be due to a "concerted but non-synchronous" transition state for the cyclization. The "star-star" transition state for the Diels-Alder reaction has long been a useful memonic for predicting the orientation of addition of a dienophile to a diene (11). Application of this concept to the tethered intramolecular case, where orientation is predetermined, has some interesting stereochemical consequences (12) Thus, one would predict that triene 9 would first partially form the five-membered ring. As a staggered transition state would be sterically preferable to the eclipsed variant, one would predict that the trans hydrindan 19 would be favored over cis 11. This is in fact observed, regardless of whether such a trans ring fusion is the product of endo or exo addition (3).



If nonsynchronous bond formation were an important control element, cyclization of 4 would proceed through the "nine membered ring" transition state. Should this be the case, steric constraints would favor collapse to the cis hydrindan 12, again the observed product of the cyclization.



With the stereochemical outcome of cyclizations leading to 6/5 systems firmly in hand from these model studies, it will now be possible to employ such cyclizations in natural product synthesis.

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