

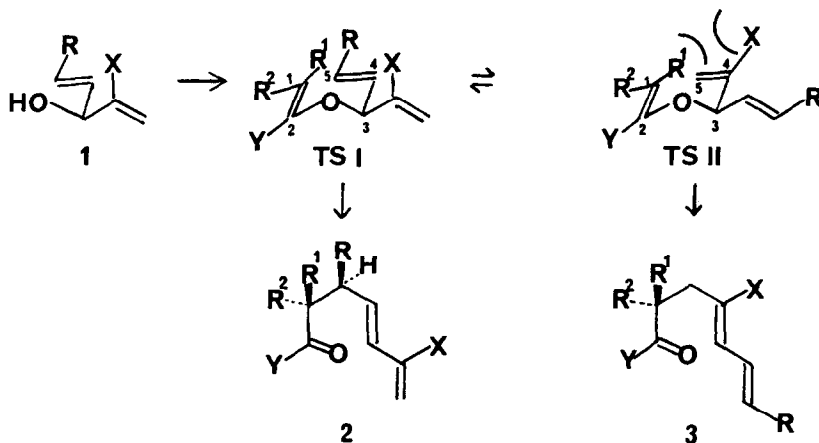
REGIOSELECTIVITY IN THE CLAISEN REARRANGEMENT OF BIS-ALLYLIC ALCOHOLS:  
ELECTRONIC AND STERIC EFFECTS OF C-4 SUBSTITUENTS

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Enol ethers of 1,4-dien-3-ols in which one allylic double bond is substituted with a methoxyl or alkyl group at C-4 undergo Claisen rearrangement in which the unsubstituted olefin participates preferentially. Rearrangement to the substituted olefin has been shown to be retarded by both electronic and steric effects.

Although the stereochemical consequences of the various modifications of the Claisen rearrangement<sup>1</sup> have been investigated in some detail and applied in numerous synthetic schemes,<sup>2</sup> the examination of the regiochemistry of Claisen processes in which more than one allylic double bond can participate has been limited.<sup>3,4</sup>

An unanticipated experimental result in our laboratories<sup>5</sup> suggested that, for enol ethers of 1,4-dien-3-ols in which one allylic double bond is substituted with a good electron donating group at C-4 (see transition state conformers TS I and TS II below), rearrangement to the alternative double bond is greatly preferred.



To test this premise, we prepared allylic alcohols **1a** and **1b** and subjected them to Claisen rearrangement under the orthoester<sup>6</sup> and amide acetal<sup>6,7</sup> conditions. The ratios of regioisomeric products are shown in Table I, entries 1-4.

From these results, we conclude that in the reactions of **1b** the methyl group retards rearrangement to be substituted olefinic bond by a small steric effort. In the reactions of **1a**, rearrangement of the substituted olefinic bond is inhibited by an electronic effect as well as by the steric effect which one can attribute to the methoxyl group. The observed selectivities are in accord with Carpenter's prediction<sup>8</sup> that an electron-donating substituent at position 4 of the allyl vinyl ether system<sup>9</sup> would slow the rate of the Claisen rearrangement.

Table I - Ratios of Regioisomers in Claisen Rearrangements of 1,4-Dien-3-ols

entry	alcohol	rearrangement conditions <sup>a</sup>	X	R	Y	R <sup>1</sup>	R <sup>2</sup>	ratio <sup>b</sup> 2:3	Yield <sup>c</sup>
1	1a	A	OMe	H	OEt	H	H	95:5	91
2	1a	B	OMe	H	NMe <sub>2</sub>	H	H	97:3	91
3	1b	A	CH <sub>3</sub>	H	OEt	H	H	65:35	79
4	1b	B	CH <sub>3</sub>	H	NMe <sub>2</sub>	H	H	74:26	93
5	1b	C	CH <sub>3</sub>	H	OLi	H	H	74:26	43
6	1b	C	CH <sub>3</sub>	H	OLi	CH <sub>3</sub>	H	92:8	75
7	1b	D	CH <sub>3</sub>	H	OLi	H	CH <sub>3</sub>	75:25	56
8 <sup>d</sup>	1c	C	CH <sub>3</sub>	CH <sub>3</sub>	OLi	CH <sub>3</sub>	H	93:7	64
9 <sup>d</sup>	1d	C	CH <sub>3</sub>	CH <sub>2</sub> CH <sub>3</sub>	OLi	CH <sub>3</sub>	H	93:7	64

(a) A: CH<sub>3</sub>C(OEt)<sub>3</sub>, cat. EtCOOH, 140°. B: CH<sub>3</sub>(OMe)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, 140°. C: LDA, THF, -78°→25°. D: LDA, 23%HMPA-THF, -78°→25°.

(b) Ratios were determined by integration of <sup>1</sup>H nmr resonances (250 MHz) which were assigned to each regioisomer by alternate syntheses.

(c) Yields refer to isolated, distilled products.

(d) In order to avoid epimerization α to the carboxy group in these rearrangements, it was necessary to quench the reaction mixtures after less than 10 minutes at room temperature.

The prospect of improving regioselectivity in the reactions of alkyl-substituted dienols led us to study the rearrangement of the enolates of esters of 1b-d (Ireland-Claisen conditions).<sup>10</sup> The results of these studies (Table I, entries 5-9) imply that it is the R<sup>1</sup>/X interaction in conformation TSII which disfavors that transition state. In each case where R<sup>1</sup>=H, regioisomer 2 predominates and in each case where R<sup>1</sup>=CH<sub>3</sub>, regioisomer 2 is the almost exclusive product.

In the rearrangements of the (Z)-enolates of propionates 1c and 1d (Table I, entries 8 and 9), a diene system is generated regioselectively and simultaneously with the two adjacent chiral centers. The potential of this dienol rearrangement for total synthesis has been demonstrated and will be reported elsewhere.

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