Tetrahedron Letters No. 46, pp 3975 - 3978, 1975. Pergamon Press. Printed in Great Britain.

THE STEREOSELECTIVE GENERATION OF ESTER ENOLATES

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(Received in USA 9 August 1975; received in UK for publication 2 October 1975)

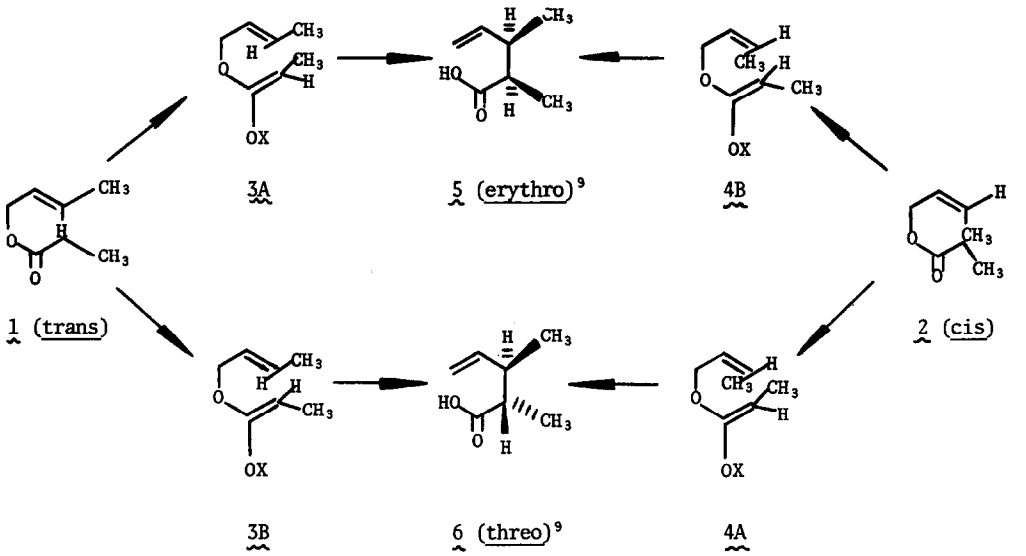
In the course of a continuing investigation of the characteristics and synthetic utility of the Claisen rearrangement of allyl ester enolates[2], attention was directed toward the stereochemical outcome of the process. Of interest were the effect of the very mild reaction conditions used on the isomer ratio of the newly developed double bond, and the extent to which it was possible to control the stereochemistry about the newly formed carbon-carbon single bond. Theoretical considerations[3] and ample precedence[4] show that for 1,5-diene systems lacking structural constraints, the chair-like conformation of the transition state is preferred for the rearrangement, and that as a result, the stereochemical consequences at both of these sites may be predicted from the stereochemistry of the starting material. The result of investigations in these[5] and other laboratories[6] on the first of these points has demonstrated the expected high degree of stereochemical control in the formation of the new double bond.

More surprising are the results of a program designed to test the second point and in which the stereochemistry of the acids formed on rearrangement of trans-(1) and cis-(2) crotyl propionates was the probe (TABLE I).

Previous work, particularly that of Schmid[4b] on the isomeric crotyl propenyl ethers, indicates that the stereochemistry of the products from such rearrangements will depend on the geometry of the double bonds involved. While the geometry of the double bond in the allyl portion of the starting esters can be fixed in advance, there was no apparent reason to expect significant stereochemical control during the ester enolization process.

It was found, however, that the character of the solvent used for the reaction played an important role in determining the erythro/threo ratio in the rearranged products. Assuming a chair-like transition state[4a], the results of these rearrangements indicate that in THF the formation of Z-enolates 3A(X=Li) and 4A(X=Li) is favored, while the geometrically isomeric E-enolates 3B(X=Li) and 4B(X=Li) predominate when the solvent is changed to 23% HMPA-THF. In this work both the enolate anions (3 and 4, X=Li) and the tert.-butyldimethylsilyl ketene acetals (3 and 4, X=t-BuMe$_2$Si) were used for the rearrangement reactions, but it should be noted that the enolate anion is only preparatively useful in the case of 3A isomer. The lower yields experienced when the other isomeric anions were employed may reflect variations in the activation energies[3b] and/or a lower stability of these enolates in the presence of HMPA at temperatures above -78°. In no case was there any evidence of stereochemical equilibration of the enolate anions initially formed under kinetically controlled conditions[8].

TABLE I. Stereochemistry of Carbon-Carbon Bond Formation.

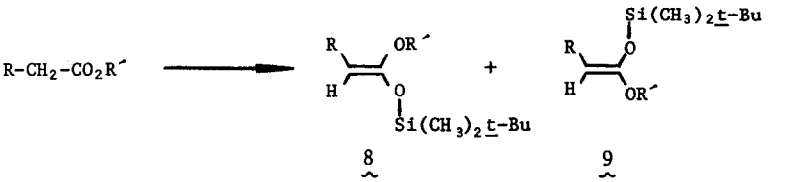


ESTER	CONDITIONS	SOLVENT	YIELD	ERYTHRO/THREO[12]	ENOLATE GEOMETRY[13]
1 (trans)	Anion[10]	100% THF	86%	92/8	Z
1 (trans)	Ketene Acetal[11]	100% THF	79%	87/13	Z
1 (trans)	Anion[10]	23% HMPA-THF	21%	13/87	E
1 (trans)	Ketene Acetal[11]	23% HMPA-THF	73%	19/81	E
2 (cis)	Anion[10]	100% THF	6%	25/75	Z
2 (cis)	Ketene Acetal[11]	100% THF	75%	11/89	Z
2 (cis)	Anion[10]	23% HMPA-THF	—	—	—
2 (cis)	Ketene Acetal[11]	23% HMPA-THF	75%	86/14	E

Using the preparatively more practical reaction conditions in which the ester enolate is trapped as the silyl ketene acetal, the subsequent Claisen rearrangement affords good yields of that acid (5 or 6) expected from the enolization conditions chosen. This result greatly expands the synthetic utility of this sequence, for the rearrangement not only results in the intramolecular formation of a new carbon-carbon bond but also accomplishes this task in a highly stereoselective fashion.

A variety of simple esters and one ketone were examined under similar conditions in order to establish the generality of this process. The results are recorded in TABLE II.

TABLE II. Effect of Structure on Ratio of Enolates.[14]



8 9

Ester	R	R'	8/9 (THF)[15]	8/9 (23% HMPA-THF[15]
7a	C_2H_5	CH_3	91/9	16/84
7b	$(CH_3)_3C$	CH_3	97/3	9/91
7c	C_2H_5	$(CH_3)_3C$	95/5	23/77
7d	C_6H_5	CH_3	29/71	5/95
	3-Pentanone		77/23[16]	5/95[16]

Recent reports relating enolate anion geometry to the stereochemical outcome of such intermolecular reactions as the aldol condensation[17] and alkylation reactions[18] indicate that the described means for the stereochemical control of the enolization process may have significant general synthetic value.

Acknowledgements

The support of this work by the National Science Foundation and the National Institutes of Health is gratefully acknowledged.

References and Notes

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8) In addition to that cited in TABLE I, further evidence on this point will be presented in the forthcoming definitive paper.

9) The stereochemistry of the erythro- and threo- acids 5 and 6 was established by ozonization of a mixture of the acids containing 90% of the isomer in question (O_3, EtOAc, HOAc, -10°C; H_2O_2, 25°C): erythro-acid 5 → meso-dimethyl succinic acid (70%) and threo-acid 6 → d,l-dimethyl succinic acid (72%).

10) The neat ester (5.0 mmol) was added to 1.1 equiv. of LDA in the indicated solvent (0.3 M) at -78°C. After 2.0 min the mixture was allowed to warm to room temperature (30 min) and stir for 2 hr. The mixture was diluted with 5% aqueous NaOH solution and washed with ether. The acids were isolated after acidification of the basic solution, ether extraction, and then evaporative distillation 90°C, (2 mm).

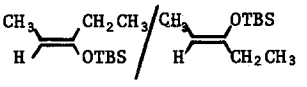
11) Following the enolization procedure described above (see 10) for the anion, TBSCl was added to the mixture. A standard solution of TBSCl in HMPA was utilized when the solvent was 100% THF; a solution in hexane was used when the solvent was 23% HMPA-THF. The mixture was then allowed to warm to room temperature (30 min) and then heated at 65°C for 1 hour. The resulting silyl esters were isolated by pentane extraction and then hydrolyzed with 2% hydrochloric acid in aqueous THF. The resulting acids were isolated as described in (10) above.

12) This ratio was determined after conversion of a sample of the acid mixture to the corresponding methyl esters (excess diazomethane, ether, 0°C). The esterification reaction mixture was analyzed directly by glpc: 90°C; 1/8" x 27' 15% Carbowax 20 M on Chromasorb W AW DMCS; carrier gas helium, 20 ml/min; not corrected for sensitivities. Retention times: erythro-5 (methyl ester), 54 min; threo-6 (methyl ester), 58 min.

13) Geometry assigned to the predominate isomer formed is based on the stereochemistry of the predominate acid generated from rearrangement and inferred from a chair-like transition state for the Claisen rearrangement.

14) The esters were enolized with 1.1 equiv. LDA at -78° and then the enolates were trapped with t-butyldimethylchlorosilane.

15) Ratio determined by NMR analysis of the isolated mixture.

16) Ratio represents: 

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