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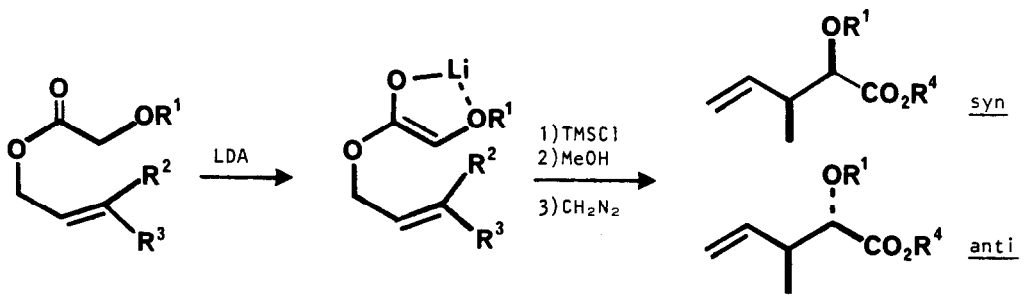
ENOLATE CLAISEN REARRANGEMENT OF GLYCOLATE ESTERS

James Kallmerten* and Thomas J. Gould
Department of Chemistry, Syracuse University
Syracuse, New York 13210

Summary: The enolate Claisen rearrangement of O-protected allylic glycolates yields functionalized acyclic systems with high syn and anti stereoselectivity. This procedure is the key step in a short synthesis of threo-4-methylheptan-3-ol, an aggregation pheromone of the European elm bark beetle.

The Claisen rearrangement of ester enolates[1] is an important method for the stereocontrolled construction of acyclic systems.[2] In connection with our synthetic studies on the Nargenicin antibiotics, we have examined the diastereoselective conversion of allylic glycolates (i.e., 1) to highly functionalized acyclic systems by the ester enolate procedure. We anticipated that the vicinal alkoxy substituent in 1 would prejudice the enolate geometry in favor of the E isomer since this intermediate can support an internal chelate. The result of this enolate control should be enhanced stereochemical induction in the rearranged product. Examples of the enolate Claisen rearrangement of α-alkoxy esters in cyclic systems have been described.[3] Bartlett has recently reported the rearrangement of acyclic lactate and mandelate esters as well as the rearrangement of the dianion of a glycolate ester.[4,5] Our studies in this area have been concerned with O-protected glycolates, and we now report that the enolate Claisen rearrangement of these compounds proceeds with high stereoselectivity to give either syn or anti products.



1a; $R^1 = R^3 = CH_3$, $R^2 = H$
1b; $R^1 = CH_2Ph$, $R^2 = H$, $R^3 = CH_3$
1c; $R^1 = R^2 = CH_3$, $R^3 = H$
1d; $R^1 = CH_2Ph$, $R^2 = CH_3$, $R^3 = H$

2a; $R^1 = CH_3$, $R^4 = H$
2b; $R^1 = CH_2Ph$, $R^4 = H$
3a; $R^1 = R^4 = CH_3$
3b; $R^1 = CH_2Ph$, $R^4 = CH_3$

We initially examined the rearrangement of the glycolate esters of E and Z crotyl alcohol.[6] Treatment of the E-O-methyl glycolate 1a with lithium diisopropylamide (LDA) followed by sily-

lation, warming to room temperature and hydrolysis afforded acid 2a. Esterification of 2a with diazomethane gave the diastereomeric esters 3a-syn and 3a-anti in 61% yield as a 89:11 mixture.[7] Similarly, the O-benzyl glycolate 1b afforded esters 3b-syn and 3b-anti in 51% overall yield as a 87:13 mixture. In each case, the major diastereomer was shown to possess the syn stereochemistry by comparison with an authentic sample.[8] Rearrangement of the Z crotyl glycolates afford the anti diastereomer as the major product. Thus the O-methyl and O-benzyl esters 1c and 1d gave 3 as syn:anti mixtures of 8:92 (74%) and 7:93 (43%) respectively.

We obtain optimum yields and diastereomer ratios by inverse addition of LDA to a solution of the glycolate ester in THF at -78°, followed by immediate addition of trimethylsilyl chloride and warming to room temperature (Table I). The procedure works equally well in THF or ether. Generation of the enolate at -40° gives a slightly higher diastereomer ratio accompanied by a significant decrease in yield. Similar results were obtained from enolate formation in the presence of added metal salts. Generation of the enolate under kinetic conditions (addition of ester to a solution of LDA) gives a diminished diastereomer ratio. These results support the formation of an internal chelate as a factor in the diastereoselectivity of the rearrangement, since under equilibrating conditions (i.e., inverse addition of base) the E enolate is expected to be thermodynamically preferred.

Table I. Effect of Conditions on Rearrangement of Glycolate 1a

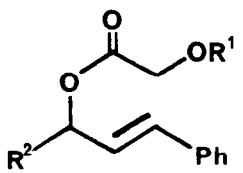
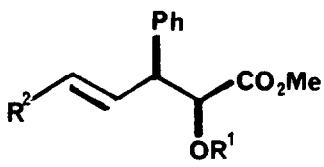
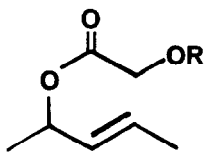
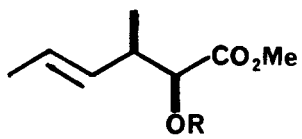
Entry	Conditions[a]	Yield of 2[b]	Ratio syn:anti[c,d]
1	inverse addition of LDA, THF, -78°	61%	8.3:1
2	inverse, ether, -78°	66%	9.0:1
3	inverse, DME, -40°	52%	8.6:1
4	inverse, THF, -40°	47%	9.0:1
5	inverse, THF, -78°, 2 eq. $MgBr_2$[e]	36%	10.8:1
6	ester added to LDA, THF, -78°	66%	6.8:1

a) generation of enolate is followed in each case by addition of 1.1 eq TMSCl, warming to room temperature over 1 hour, addition of MeOH and standard workup.
b) yields are for distilled material; c) ratios determined by GC analysis of methyl esters 3 on a 6 m 13% Carbowax 20M column using a Varian CDS-111 integrator;
d) starting glycolate ester is a 98:2 E:Z mixture, ratios are uncorrected; e) $MgBr_2$ added to ester prior to addition of LDA.

Additional examples of the glycolate Claisen procedure are shown in Table 2. Rearrangement of cinnamyl glycolates (entries 1-3) is remarkably stereoselective affording only the syn products[9] in each case. Similarly, the pentenyl glycolate 8b gives a single diastereomer, while the corresponding O-methyl glycolate 8a affords an 18:1 mixture of 10a-syn : 10a-anti. These observations are consistent with the assumption that increased steric demands will favor a chair-like transition state for the rearrangement. As expected, rearrangement of secondary glycolates (entries 3-5) results in exclusive formation of the E olefins;[10] we were unable to detect any of the isomeric Z olefins in the product mixtures.

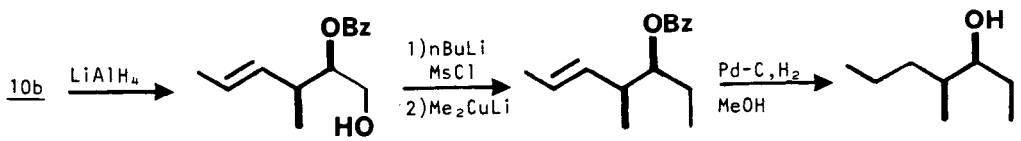
The glycolate Claisen modification affords highly functionalized, acyclic systems which can undergo further stereoselective transformations, and should prove useful for the synthesis of acyclic natural products. For example, the O-silylated analog of ester 3 has been previously converted to verrucarinolactone.[11] We have employed the glycolate rearrangement in a short

Table 2. Rearrangement of Cinnamyl and Pentenyl Glycolates

Entry	Ester	Major Product[a]	Yield[b]	syn:anti[c]
1	 4a; R^1= CH_3, R^2= H	 6a; R^1= CH_3, R^2= H	36	>40:1[d] OV
2	4b; R^1= CH_2Ph, R^2= H	6b; R^1= CH_2Ph, R^2= H	31	>40:1[d] OV
3	5; R^1= R^2= CH_3	7; R^1= R^2= CH_3	50	>40:1[d] OV
4	 8a; R= CH_3	 10a; R= CH_3	73	18:1 C
5	8b; R= CH_2Ph	10b; R= CH_2Ph	44	40:1 OV

a) Inverse addition of LDA to ester in THF at -78°; b) based on chromatographed and/or distilled material; c) ratios were determined by GC analysis using a 6 m 10% OV-225 (OV) or a 6 m 13% Carbowax 20M(C) column; d) no anti isomer was detected by GC or ^{13}C NMR.

synthesis of racemic threo-4-methylheptan-3-ol, 13, an aggregation pheromone of the European elm bark beetle.[12] Reduction of ester 10b with $LiAlH_4$ affords alcohol 11, which is converted to 12 by mesylation and treatment with lithium dimethylcuprate. Hydrogenation of 12 gives the desired threo alcohol 13, which was identical in all respects with an authentic sample.[13] Application of the glycolate Claisen rearrangement to the synthesis of other natural products is currently under investigation.



11 12 13

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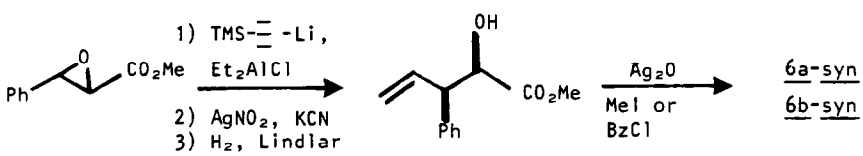
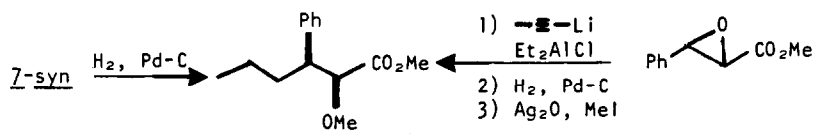
References and Notes

1. R. E. Ireland, R. H. Mueller and A. K. Willard, J. Amer. Chem. Soc. 98, 2868 (1976).
2. For a review of acyclic stereocontrol via electrocyclic processes see: P. A. Bartlett, Tetrahedron 36, 2 (1980).
3. a) R. E. Ireland, S. Thaisrivongs and C. S. Wilcox, J. Amer. Chem. Soc. 102, 1155 (1980); b) R. E. Ireland, S. Thaisrivongs, N. Vanier and C. S. Wilcox, J. Org. Chem. 45, 48 (1980); c) J. K. Whitesell, R. S. Matthews and A. M. Helbing, ibid. 45, 4135 (1980); d) J. K. Whitesell, R. S. Matthews and A. M. Helbing, ibid. 43, 784 (1978).
4. P. A. Bartlett, D. J. Tanzella and J. F. Barstow, J. Org. Chem. 47, 3941 (1982). Two other reports of the glycolate dianion procedure have recently appeared: D. J. Ager and R. C. Cookson, Tetrahedron Letts. 3419 (1982); T. Sato, K. Tajima and T. Fujisawa, ibid. 729 (1983)
5. Whitesell and coworkers examined the rearrangement of O-methyl glycolates for several acyclic cases and in some cases obtained rearranged products although in low yield (Ref. 3c).
6. The O-alkylated esters are easily prepared by reaction of the corresponding acid chloride with an alcohol.
7. The E crotyl alcohol used in this study contained 2% of the corresponding Z isomer; the Z alcohol contained 7% of the E isomer. No attempt has been made to correct the observed ratios for these impurities.
8. Authentic samples of 3a-syn and 3b-syn were prepared by alkylation (Ag_2O, MeI or BzCl) of the known methyl 2-hydroxy-3-methylpent-4-enoate.[4] A similar scheme was used to prepare samples of 6a-syn and 6b-syn:



The stereochemistry of ester 7 was established by the scheme:



The assignments of esters 10a-syn and 10b-syn are based on conversion of the latter to threo alcohol 13 and into ester 10a (Li/NH_3, then Ag_2O, MeI).

9. Samples of the syn diastereomers 6a, 6b, 7 and 10b were subjected to epimerization (LDA, NH_4Cl) to afford a mixture of syn and anti diastereomers. The limit of detection for our GC and ^{13}C analysis is less than 2% of anti isomer.
10. D. J. Faulkner and M. R. Petersen, Tetrahedron Letts., 3243 (1969); D. J. Faulkner and M. R. Petersen, J. Amer. Chem. Soc. 95, 553 (1973).
11. W. R. Roush, T. A. Blizzard and F. Z. Basha, Tetrahedron Letts. 2331 (1982).
12. G. T. Pearce, W. E. Gore, R. M. Silverstein, J. W. Peacock, R. A. Cuthbert, G. N. Lanier and J. B. Simeone, J. Chem. Ecol. 1, 115 (1975). For a chiral synthesis see: K. Mori, Tetrahedron 33, 289 (1977).
13. An authentic sample of racemic 13 was obtained by preparative GC of a mixture of the alcohol diastereomers kindly provided by Prof. G. N. Lanier of the SUNY College of Environmental Science and Forestry. We are grateful to Prof. R. M. Silverstein of SUNY-ESF for comparison spectra of the threo alcohol.

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