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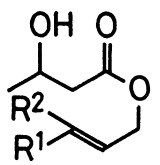
ESTER ENOLATE CLAISEN REARRANGEMENT OF 2-BUTENYL 3-HYDROXYBUTANOATE

Tamotsu FUJISAWA,* Kazuhisa TAJIMA, Masamichi ITO, and Toshio SATO
Chemistry Department of Resources, Mie University, Tsu, Mie 514

The ester enolate Claisen rearrangement of (*E*)- or (*Z*)-2-butenyl 3-hydroxybutanoate was found to give predominantly each one of four isomers of 3-methyl-4-methoxycarbonyl-5-hydroxy-1-hexene by the selection of the reaction conditions *via* the enolate dianions or silyl ketene acetals.

Recently the syntheses of the macrolides and ionophores with continuous asymmetric carbons have prompted many organic chemists to develope a methodology of the stereocontrolled construction of acyclic systems.[1] Although the typical methods which have been used to control the diastereoselectivity of two asymmetric carbons involve the aldol condensation,[2] epoxidation of olefinic compounds,[3] the opening reaction of epoxy alcohols,[4] and the Claisen[5a,b] and [2,3]-Wittig rearrangement,[6] there are a few reports on the regulation of three continuous asymmetric carbons.[2,7] In the previous paper,[8] we have reported the ester enolate Claisen rearrangement of (*E*)- or (*Z*)-2-butenyl glycolate to afford the corresponding *erythro* or *threo*-2-hydroxy-3-methyl-4-pentenoic acid[9] with high diastereoselectivity. To expand the scope of the diastereoselective carbon-carbon bond formation by the ester enolate Claisen rearrangement, the rearrangement of 2-butenyl 3-hydroxybutanoate (1a or 1b) is noted to induce three continuous asymmetric centers of the rearrangement product by the chelate effect of lithium cation as 2. We now describe here that the ester enolate Claisen rearrangement of (*E*)- or (*Z*)-2-butenyl 3-hydroxybutanoate (1a or 1b) could give predominantly each one of the four isomers of 3-methyl-4-methoxycarbonyl-5-hydroxy-1-hexene (3a-d) by the selection of the reaction conditions, *via* the enolate dianions or silyl ketene acetals.



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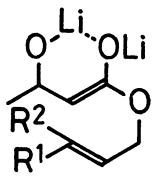
a: R^1 = Me, R^2 = H
b: R^1 = H, R^2 = Me



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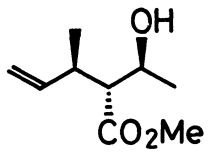
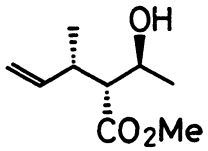
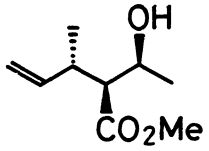
(*E*)-2-Butenyl 3-hydroxybutanoate (1a), which is easily available *via* the reaction of diketene and (*E*)-2-buten-1-ol followed by reduction with $NaBH_4$, was treated with 3 equivalent of lithium hexamethyldisilaside (LHDS) in THF at -30 °C and the reaction mixture was allowed to warm to room temperature, and further refluxed for 2 h. Esterification with diazomethane gave a mixture of three diastereomers of 3a (11%), 3b (85%), and 3c (4%) in 52% yield. The structure of



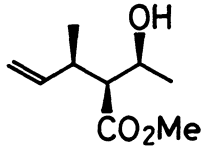
3a (3,4)-T (4,5)-E



3b (3,4)-E (4,5)-E



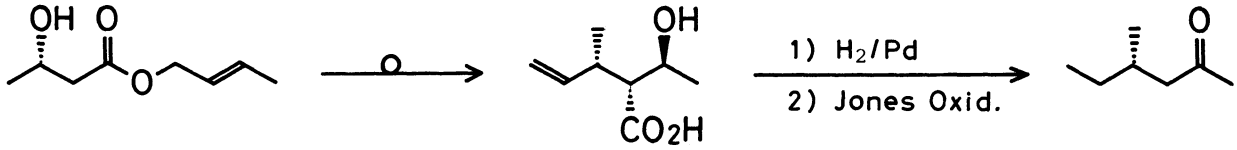
3c (3,4)-T (4,5)-T



3d (3,4)-E (4,5)-T

E: Erythro T: Threo

the major component 3b was confirmed by the following method. To determine the relative stereochemistry between C-4 and C-5, the aldol reaction of methyl 3-methyl-4-pentenoate[5a] with acetaldehyde was carried out to give (4,5)-*erythro* products 3a and 3b (LDA, THF, -78 °C) and (4,5)-*threo* products 3c and 3d (LDA, THF-HMPA, -78 °C). The decoupling ^{1}H NMR spectrum of the methyne proton at C-5 of the former aldol products showed J_{45} = 7.0 Hz, contrasted with that of the carbinol methyne proton of the latter products, J_{45} = 4.5 Hz.[10] Accordingly, the stereochemistry at C-4 and C-5 of the major rearrangement product was determined as the *erythro* configuration by the comparison of the coupling constant and the capillary GLC analysis (PEG 20M, 50 m). Further, to determine the relative stereochemistry of C-3 and C-5, the (*S*)-hydroxy acid 5 ($[\alpha]_D$ +3.8° (c 3.89, $CHCl_3$)), obtained by the ester enolate Claisen rearrangement of (*E*)-2-butenyl (*S*)-3-hydroxybutanoate[11] (4, $[\alpha]_D$ +33.6° (c 0.91, EtOH), 74%ee[12]) under the same conditions as mentioned above, was converted to 4-methyl-2-hexanone (6, $[\alpha]_D$ +1.1° (c 0.38, $CHCl_3$)) by the hydrogenation and successive Jones oxidation. Ketone 6 was found to be of *S* configuration by the comparison with the reported data of (*S*)-(+)-isomer ($[\alpha]_D$ +7.9° (c 0.632, $CHCl_3$)).[13] Thus the major rearranged product 3b was established to have the (3,4)-*erythro* (4,5)-*erythro* configuration.[14]



4 5 6

To obtain a higher diastereoselectivity and chemical yield, several conditions for the base or solvent were examined. Lithium diisopropylamide (LDA) or lithium 2,2,6,6-tetramethylpiperidide (LTMP) as a base gave the rearrangement products (3a-c) in 33 or 24% yields, respectively, in which the diastereoselectivity decreased to 77 or 65% of (3,4)-*erythro* (4,5)-*erythro*-3b. A retro-aldol reaction was found to occur simultaneously as a side reaction. The use of nonpolar solvent, such as hexane or toluene, instead of THF resulted in reducing this side reaction, which increased the chemical yield of the corresponding rearrangement product (3a-d) to 71 or 76%, respectively, but decreased the diastereoselectivity at C-3 and C-4 of 3a-d to ca. 1:1. Thus the degree of stereoselection at C-3 and C-4 was found to depend critically upon the polarity of solvent. Furthermore more polar 1,2-dimethoxyethane (DME) as a solvent gave the rearrangement product (3a-d) in 58% yield with 85% diastereoselectivity for 3b. Accordingly DME was found to be most suitable solvent in regard to the chemical yield and diastereoselectivity.

Table 1. The Ester Enolate Claisen Rearrangement of Esters 1a and 1b[a)]

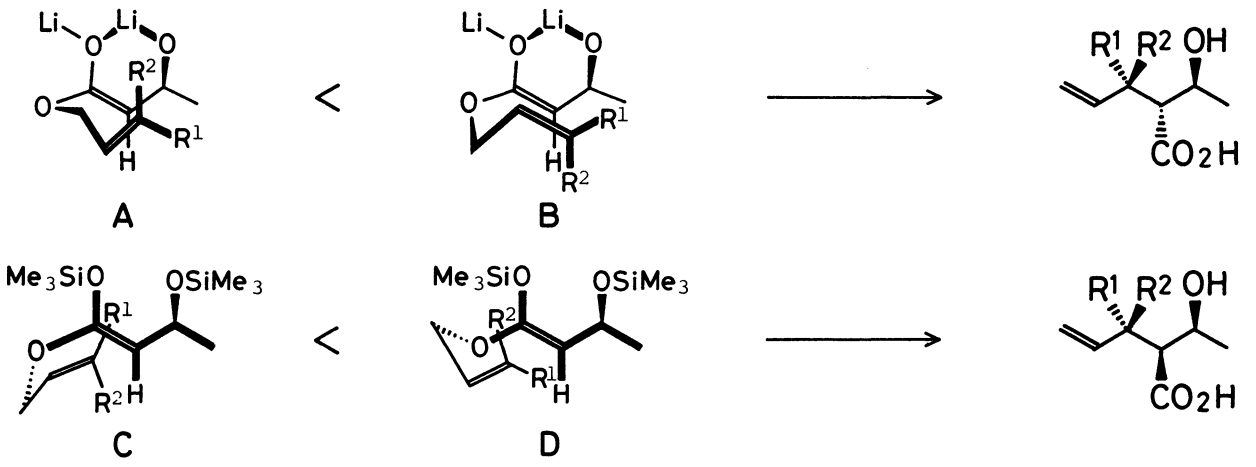
Ester	Solvent	Additive	Yield/%	3a :	3b :	3c :	3d[b)]
1a	DME	None	58	11 :	85 :	4 :	0
1a	THF	Me_3SiCl	37	3 :	18 :	72 :	7
1b	DME	None	31	75 :	19 :	4 :	2
1b	THF	Me_3SiCl	24	25 :	3 :	4 :	68

a) Ester 1 was treated with 3 eq of LHDS in DME or THF at -30 °C. If necessary, 3 eq of trimethylsilyl chloride was added. After the mixture was allowed to warm to room temperature for 1.5 h, the mixture was refluxed for 2 h. The products were isolated as methyl esters by TLC. b) The ratio of diastereomeric mixture was determined by GLC (PEG 20M, 50 m column).

The variation of the diastereoselectivity of 3a-d was further examined using trimethylsilyl chloride as a trapping reagent of dianion 2. After 1a was treated with 3 equivalent of LHDS in THF[15)] at -30 °C for 1 h, trimethylsilyl chloride was added to the reaction mixture and then it was allowed to warm to room temperature, and refluxed for 2 h. The rearrangement product was obtained in 37% yield with 72% selectivity for (3,4)-*threo* (4,5)-*threo*-3c.

In contrast to the results of the rearrangement of (*E*)-2-butenyl 3-hydroxybutanoate (1a), the similar ester enolate Claisen rearrangement of the (*Z*)-2-butenyl 3-hydroxybutanoate (1b) in DME gave (3,4)-*threo* (4,5)-*erythro*-3-methyl-4-methoxycarbonyl-5-hydroxy-1-hexene (3a) with 75% selectivity. Furthermore using trimethylsilyl chloride, 1b gave (3,4)-*erythro* (4,5)-*threo*-3d in 24% yield with 68% selectivity. These results are summarized in Table 1.

The diastereoselectivity can be reasonably explained by consideration of the following transition states. When the ester enolate Claisen rearrangement is performed without trimethylsilyl chloride as a trapping reagent of dianion 2, two favorable states of condensed six-members rings are possible under the boat form by the chelation of lithium cation with oxygen anion.[16)] The conformation of transition state B may be sterically more favorable than that of A, since the later suffers a strain of two rings each other. Thus, (3,4)-*erythro* (4,5)-*erythro*-3b or (3,4)-*threo* (4,5)-*erythro*-3a results from the geometric isomer (*E* or *Z*) of the starting material, respectively, by the ester enolate Claisen rearrangement. On



the other hand, in the another performing with trimethylsilyl chloride, two transition states such as C and D are possible. The chair-like transition state D is more stable than the boat-like transition state C[17] and 2-butenyl part approches to the ester enolate part with a diastereofacial selectivity[18] at the β-carbon of the enolate so that (3,4)-*threo* (4,5)-*threo*-3c or (3,4)-*erythro* (4,5)-*threo*-3d is obtained from each geometric isomer of (*E*)- of (*Z*)-2-butenyl 3-hydroxybutanoate, respectively.

Thus, a diastereoselective synthesis of four isomers of 3-methyl-4-methoxycarbonyl-5-hydroxy-1-hexene (3a-d) was achieved from easily available (*E*)- or (*Z*)-2-butenyl 3-hydroxybutanoate (1a,b) by the ester enolate Claisen rearrangement choosing the reaction conditions.

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