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DIASTEREOSELECTIVE SYNTHESIS OF ERYTHRO- AND THREO-2-HYDROXY-3-METHYL-4-PENTENOIC ACIDS BY THE ESTER ENOLATE CLAISEN REARRANGEMENT OF 2-BUTENYL 2-HYDROXYACETATE

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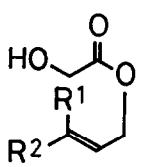
Summary: *The ester enolate Claisen rearrangement of (E)- and (Z)-2-butenyl 2-hydroxyacetates gave erythro- and threo-2-hydroxy-3-methyl-4-pentenoic acids with high diastereoselectivity via silyl ketene acetals, respectively.*

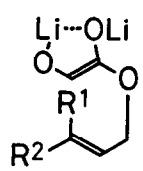
The recent publication of a paper[1] concerning the ester enolate Claisen rearrangement of 2-hydroxyacetate prompts us to disclose our own experiments in this field. In recent years many efforts have been devoted to the diastereoselective synthesis of 2-alkyl-3-hydroxypropionate units[2] characteristic of many macrolide antibiotics.[3] A few studies, however, have been reported for the construction of 3-alkyl-2-hydroxypropionate units,[4-6] which have potential as acyclic units in the synthesis of macrolide antibiotics, especially for verucarin A[5] and pyrrolizidine alkaloids such as crobarbatine[6a] and integerrimine.[6b] In this paper we wish to describe diastereoselective synthesis of *erythro*- and *threo*-2-hydroxy-3-methyl-4-pentenoic acids (3a and 3b) by the ester enolate Claisen rearrangement of (*E*)- and (*Z*)-2-butenyl 2-hydroxyacetate (1a and 1b), respectively. Previous reports on the ester enolate Claisen rearrangement showed that *E* or *Z* geometry of both enolate and allylic moiety controlls product stereochemistry.[7] We assumed predominant formation of an (*E*)-enolate 2 from α-hydroxy esters in terms of a stable chelate structure and expected that diastereoselection for products of the Claisen rearrangement could be controlled by the selection of either (*E*)- or (*Z*)-allylic alcohol. A part of our experimental results was shown in the Table.

When (*E*)-2-butenyl 2-hydroxyacetate (1a, E:Z = 93:7) was treated with lithium diisopropylamide (LDA) in THF at -78 °C and allowed to warm to room temperature during 1 h, the rearranged product was isolated in 13% yield as the corresponding methyl ester 3 by treatment with diazomethane. GLC and NMR analysis[4] of 3 showed

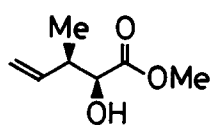


1

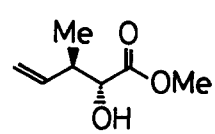
a $R^1 = H, R^2 = Me$ b $R^1 = Me, R^2 = H$



2



3a



3b

Table. The Ester Enolate Claisen Rearrangement of Ester 1[a]

Ester	Base	Additive	Yield of 3 (%)	Ratio of 3α : 3β
1α	LDA	—	13	92: 8 (98: 2)[d]
1α	LDA	Me_3SiCl	40	70:30 (75:25)[d]
1α	LHDS	—	28	90:10 (97: 3)[d]
1α	LHDS	Me_3SiCl	84	92: 8 (98: 2)[d]
1α	LTMP[b]	Me_3SiCl	29	89:11 (96: 4)[d]
1α	LCIA[c]	Me_3SiCl	28	75:25 (81:19)[d]
1β	LHDS	Me_3SiCl	79	3:97 (2:98)[e]

[a] Ester 1 was treated with 3 eq of a base in THF at -78 °C for 2 h. If necessary, 3 eq of trimethylsilyl chloride was added, and then the mixture was allowed to warm to room temperature for 1 h. The products were isolated as methyl esters by TLC. [b] Lithium 2,2,6,6-tetramethylpiperidide. [c] Lithium cyclohexylisopropylamide. [d] Corrected values for the E:Z ratio of 1a (93:7). [e] Corrected value for the E:Z ratio of 1b (1:99).

predominant formation of *erythro*-isomer 3α (3α:3β = 92:8). Among bases investigated, lithium hexamethyldisilylazide (LHDS) was found to be the best one and an addition of trimethylsilyl chloride into a solution of dilithium enolate 2α increased remarkably the yield (84%, 3α:3β =92:8). Considering the E:Z ratio of the starting material 1α (93:7), the stereoselectivity is 98%. In the present reaction, THF is the most suitable solvent. Diethyl ether, 1,2-dimethoxyethane, or THF-HMPA as a solvent decreased the yield of 3, 33, 41, or 6%, respectively. On the other hand, protection of the hydroxy group of 1α as the corresponding methyl or benzyl ether resulted in decreasing the yield (40∿50%) and the stereoselectivity (84∿87%). In contrast to the result of 1α, the similar ester enolate Claisen rearrangement of the Z-isomer 1β (E:Z = 1:99) gave exclusively *threo*-isomer 3β in 79% yield with 97% purity.

Thus, highly diastereoselective synthesis of 2-hydroxy-3-methyl-4-pentenoic acids was achieved from easily available crotyl glycolate, and the present method provides a promising route for the synthesis of natural products.

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