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Diastereoselective Synthesis of *erythro*- and *threo*-2-Hydroxy-2,3-dialkyl-4-alkenoic Acids by the Ester Enolate Claisen Rearrangement of Allyl 2-Hydroxyalkanoates

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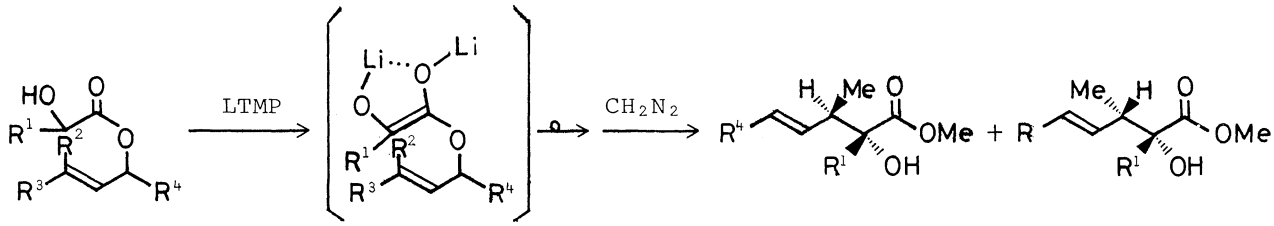
The ester enolate Claisen rearrangement of (E)- and (Z)-allyl 2-hydroxyalkanoates diastereoselectively gives *erythro*- and *threo*-2-hydroxy-2,3-dialkyl-4-alkenoic acids, respectively.

One of the most important problem in organic synthesis is the construction of carbon skeleton with high diastereoselectivity. In our previous paper, we reported the diastereoselective synthesis of *erythro*- and *threo*-2-hydroxy-3-methyl-4-pentenoic acids by the ester enolate Claisen rearrangement of 2-butenyl 2-hydroxyacetate.[1] The high chirality transfer in the rearrangement using optically active allyl alcohols was effectively applied to the syntheses of optically active natural products.[2] We wish to report here the highly diastereoselective synthesis of 2-hydroxy-2,3-dialkyl-4-alkenoic acids possessing four-substituted carbon at α-position, which could not be attained by the usual ester enolate Claisen rearrangement due to the general lack of stereocontrol of E or Z enolate formation.[3]

Allyl 2-hydroxyalkanoate (**1**), which was prepared by either the ester exchange[4] of ethyl 2-hydroxyalkanoates or 2,5-dimethyl-1,3-dioxolane-4-one[5] with allyl alcohols, was treated with lithium 2,2,6,6-tetramethylpiperidide (LTMP) (3 equiv.) in THF at -78 °C for 2 h. The reaction mixture was allowed to warm up to 0 °C over 3 h and stirred for 2 h at 0 °C. After an extractive workup and esterification with diazomethane, methyl 2-hydroxy-2,3-dialkyl-4-alkenoate (**3**) was isolated by silica gel TLC. The result of the ester enolate Claisen rearrangement of **1** is summarized in Table 1.

Ester **3** was synthesized with high diastereoselectivity depending on geometrical isomer of allyl alcohol part, that is, (E)-allyl ester (R^2 = H, R^3 = CH_3) afforded *erythro*-**3**, while (Z)-allyl ester (R^2 = CH_3, R^3 = H) yielded *threo*-**3**. The



1 **2** **threo-3** **erythro-3**

R^2, R^3 = H or Me

Table 1. The Ester Enolate Claisen Rearrangement of Ester 1

	R^1	R^2	R^3	R^4	Yield / %	*threo* : *erythro*[a)]
1a	C_2H_5	H	CH_3	CH_3	82	3 : 97
1b	C_2H_5	CH_3	H	CH_3	77	96 : 4
1c	CH_3	H	CH_3	CH_3	69	5 : 95
1d	CH_3	CH_3	H	CH_3	60	89 : 11
1e	CH_3	H	CH_3	H	15	6 : 94
1f	CH_3	H	CH_3	Si^tBuMe_2	56	1 : 99

a) The ratio was determined by GLC using a capillary column (FFAP-50m).

secondary allyl esters (R^4 = CH_3 and Si^tBuMe_2) gave **3** in much higher yields than primary allyl ester (R^4 = H). In addition, sterically bulky substituent, tert-butyldimethylsilyl group increased the diastereoselectivity to the ratio of 1 : 99. LTMP was much superior to lithium hexamethyldisilazide and lithium diisopropylamide as a base in the rearrangement of **1c**. Trap of the enolate **2a** with chlorotrimethylsilane,[1)] in contrast to the previous result of the reaction of 2-hydroxyacetate, decreased the diastereoselectivity down to 45 : 55. The configuration of the rearrangement products was assigned by ^{1}H NMR.[5,6)] The product **3c** is known as a useful precursor of crobarbatic acid lactone.[7)]

Thus, the highly diastereoselective synthesis of 2-hydroxy-2,3-dialkyl-4-alkenoic acid **3** was achieved from (E)- and (Z)-allyl 2-hydroxyalkanoate **1** by the ester enolate Claisen rearrangement in terms of the chelate effect of lithium cation as illustrated in **2**.

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6) **3a**: ^{1}H NMR (CCl_4); δ 0.76(d, 3H, J = 7 Hz), 1.40 − 1.80(m, 5H), 2.10 − 2.60(m, 1H), 3.30(s, 1H), 3.73(s, 3H), 5.20 − 5.50(m, 2H). **3b**: ^{1}H NMR (CCl_4); δ 0.85(d, 3H, J = 7 Hz), 1.40 − 1.80(m, 5H), 2.10 − 2.60(m, 1H), 3.30(s, 1H), 3.67 (s, 3H), 5.20 − 5.50(m, 2H). **3c**: ^{1}H NMR ($CDCl_3$); δ 0.86(d, 3H, J = 7 Hz), 1.23(s, 3H), 1.7 (d, 3H, J = 5 Hz), 2.35(m, 1H), 3.00(s, 1H), 3.73(s, 3H), 5.1 − 5.8(m, 2H). **3d**: ^{1}H NMR (CCl_4); δ 0.97(d, 3H, J = 7 Hz), 1.25(s, 3H), 1.6(d, 3H, J = 5 Hz), 2.1 − 2.6(m, 1H), 3.35(s, 1H), 3.65(s, 3H), 5.2 − 5.4(m, 2H). **3e**: ^{1}H NMR ($CDCl_3$); 0.95(d, 3H, J = 7 Hz), 1.35(s, 3H), 2.48(m, 1H), 3.13(s, 1H), 3.79 (s, 3H), 4.9 − 6.2(m, 3H). **3f**: ^{1}H NMR (CCl_4); δ 0(s, 6H), 0.9(s, 9H), 0.95(d, 3H, J = 7 Hz), 1.23(s, 3H), 2.15 − 2.62(m, 1H), 2.95(s, 1H), 3.73(s, 3H), 5.26 − 6.2 (m, 2H).
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