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CHIRALITY TRANSFER IN THE ESTER ENOLATE CLAISEN REARRANGEMENT OF (R)-1-METHYL-(E)-2-BUTENYL HYDROXYACETATE AND ITS APPLICATION TO THE STEREOCONTROLLED PHEROMONE SYNTHESIS

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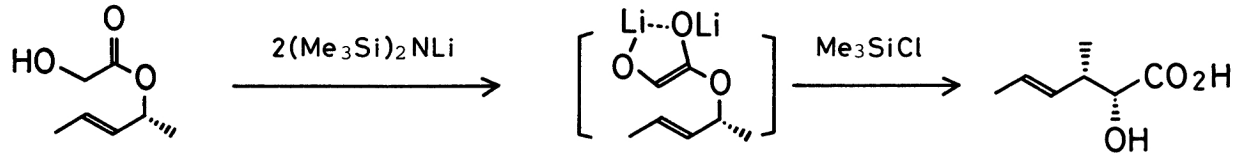
The ester enolate Claisen rearrangement of (*R*)-1-methyl-(*E*)-2-butenyl hydroxyacetate provides complete asymmetric transfer along with 98% erythroselectivity to give (2*R*,3*S*)-2-hydroxy-3-methyl-(*E*)-4-hexenoic acid. Its synthetic utility is demonstrated by the stereocontrolled synthesis of optically active pheromones.

One of the most important problems in the synthetic chemistry is the construction of carbon skeleton with both diastereo- and enantioselectivities, since there are many complicated organic compounds with several successive chiral carbons in nature. We now report here the enantioselectivity in the ester enolate Claisen rearrangement of (*R*)-1-methyl-(*E*)-2-butenyl hydroxyacetate as illustrated by the following equation.



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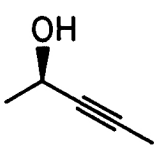
Recently we have demonstrated that the ester enolate Claisen rearrangement of 2-butenyl hydroxyacetate exhibits an extremely high degree of diastereoselectivity to afford 2-hydroxy-3-methyl-4-pentenoic acids;[1] *i.e.*, the use of the allylic ester with *E* form or with *Z* form gives the *erythro* or *threo* acid, respectively, with 98% of diastereoselectivity. On the other hand, previous reports on the Claisen rearrangement to transmit the substrate chirality to the newly created chiral center in the product have been described on the two distinct types of the chirality transfer. The one is 1,3-chirality transfer along the allylic array, which is shown by the Claisen rearrangement using chiral (*E*)- or (*Z*)-6-methylhept-2-en-4-ol derivatives under a variety of conditions with 97-99% chirality transmission leading to a chiral 3,7-dimethyloct-4-enoic acid.[2] The other one is 1,4-chirality transfer by the introduction of newly formed chiral carbon through the ester enolate Claisen rearrangement of a chiral allylic propionate to afford a chiral 2-methyl-4-alkenoic acid with exclusive chirality transmission.[3] The application of these chirality transfers to the natural product synthesis has been demonstrated by the synthesis of tocopherol in the former example[2] and an



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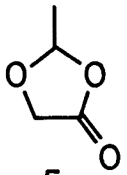

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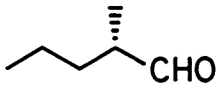

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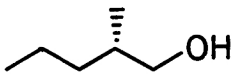

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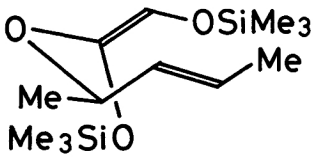

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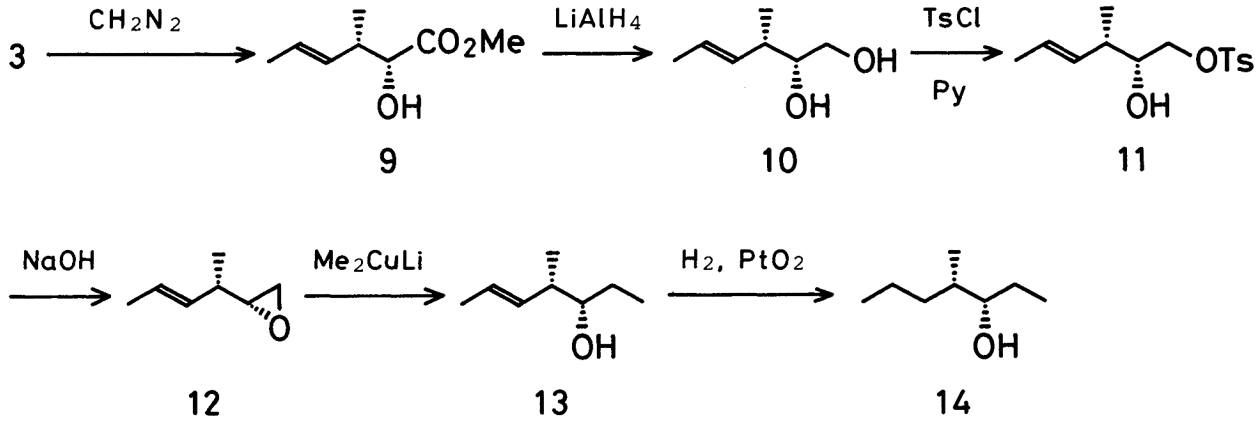
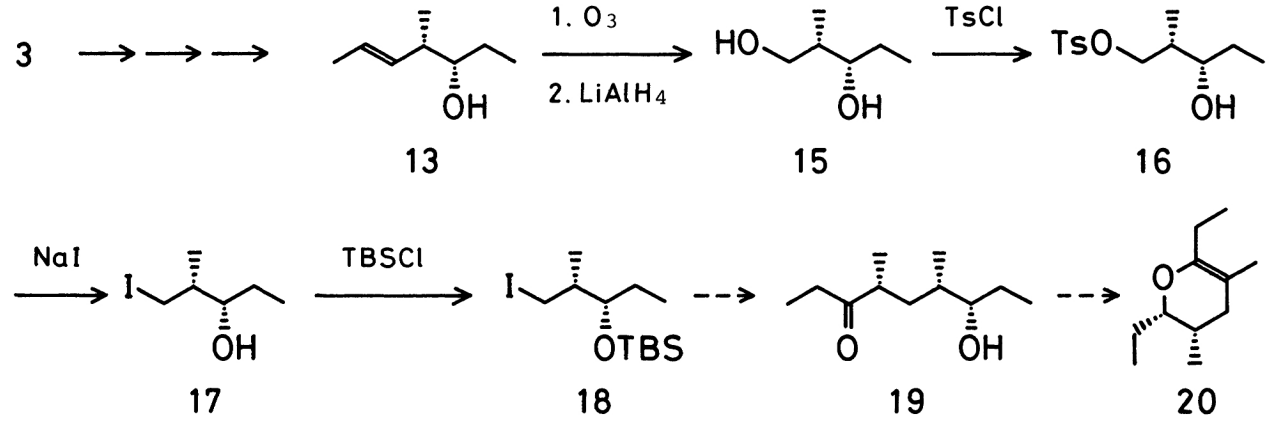
antibiotic calcimycin in the latter example.[3] Thus, the use of the chiral allylic ester in the case of the Claisen rearrangement of hydroxyacetate can be expected to afford 2-hydroxy-4-alkenoic acid with two chiral carbons at C-2 and C-3 positions.[4]

First, we examined the ester enolate Claisen rearrangement of (*R*)-1-methyl-(*E*)-2-butenyl hydroxyacetate (1, $[\alpha]_D^{23}$ +77.17° (c 0.93, $CHCl_3$))[5] which was derived from an optically resolved propargyl alcohol 4[6] with 91% ee ($[\alpha]_D^{23}$ +46.01° (c 0.92, dioxane)) by the partial hydrogenation with metallic sodium in liq. ammonia followed by treatment with 2-methyl-1,3-dioxolane-4-one (5). The ester 1 was added to 3 equiv. of lithium hexamethyldisilazide in THF at -78 °C and the reaction mixture was stirred for 2 h. After adding 3 equiv. of chlorotrimethylsilane as a trapping reagent of dianion 2, the reaction mixture was allowed to warm to room temperature for 2 h and then stirred continuously for 2 h at this temperature to afford a 71% yield of (2*R*,3*S*)-2-hydroxy-3-methyl-4-hexenoic acid (3, $[\alpha]_D^{23}$ -28.88° (c 1.01, $CHCl_3$)), in which the ratio of *erythro* and *threo* isomers was 98:2 as determined by Glpc analysis of the corresponding methyl esters obtained by treatment of 3 with diazomethane. In order to determine the sense of chirality transmission, the product 3 was transformed into 2-methyl-1-pentanol (7), whose optical rotation has been reported ($[\alpha]_D^{20}$ -12.0° (c 2.5, MeOH), 90% ee, *S* configuration)).[8] Thus the double bond of the acid 3 was saturated by a catalytic hydrogenation on platinum, and then the oxidation with sodium metaperiodate[9] gave 2-methyl-1-pentanal (6, $[\alpha]_D^{23}$ +18.49° (c 0.63, Et_2O)), which was reduced by lithium aluminum hydride to afford 2-methyl-1-pentanol (7, $[\alpha]_D^{23}$ -12.14° (c 1.04, MeOH)). The optical rotation shows that the alcohol has *S* configuration with 91% of enantiomeric excess as compared with the reported value. Considering the enantiomeric excess (91% ee) of the starting propargyl alcohol 4, the chirality transmission in the ester enolate Claisen rearrangement was perfect through 1,3-chirality transfer. In addition it is noted that the rearrangement shows a 98% of erythroselectivity. These results can be reasonably explained by the intermediate 8, which is formed by trapping the dianion 2 of an (*E*)-enolate with stable chelate structure derived from the α-hydroxy ester 1, with chlorotrimethylsilane. The chair like transition state with a chiral methyl group at the thermodynamically stable equatorial position gave the (2*R*,3*S*)-2-hydroxy-3-methyl-4-hexenoic acid (3) with high diastereoselectivity and with high chirality transmission.



The utility of the present method was further demonstrated in effective syntheses of some pheromones possessing contiguous chiral carbons. One of the component of the attractant pheromone for the smaller European elm bark beetle *(Scolytus multistriatus)*[10] has the structure of (3*S*,4*S*)-(-)-4-methylheptan-3-ol (14).[11] These configurations were constructed by utilizing the skeleton of (2*R*,3*S*)-2-hydroxy-3-methyl-4-hexenoic acid (3), obtainable by the ester enolate Claisen rearrangement of (*R*)-1-methyl-(*E*)-2-butenyl hydroxyacetate (1). The hydroxy methyl ester (9, $[\alpha]_D^{23}$ -45.73° (c 0.94, $CHCl_3$)) derived from the corresponding acid 1[12] was reduced by lithium aluminum hydride to the diol 10 ($[\alpha]_D^{23}$ -58.12° (c 1.03, $CHCl_3$)) in 79% yield, whose primary hydroxy group was selectively tosylated in 82% yield. Then the epoxide 12 ($[\alpha]_D^{23}$ -30.21° (c 0.99, $CHCl_3$), *erythro* : *threo* = 94:6) obtained by treatment of 11 with an equivalent of sodium hydroxide in methanol at room temperature for 30 min, was cleaved by an attack of lithium dimethylcuprate, and the catalytic hydrogenation with platinum gave the desired (3*S*,4*S*)-4-methyl-3-heptanol (14, $[\alpha]_D^{23}$ -18.78° (c 1.20, hexane), lit.[11] $[\alpha]_D^{22}$ -21.7° (c 0.572, hexane)) with an enantiomeric excess of 83%.[13]

Next, the same procedure was applied to the synthesis of the precursor of serricornin (19) and anhydro serricornine (20),[14] the sex pheromone of the female cigarette beetle, *Lasioderma serricorne* (F.). 3-Methyl-5-hepten-2-ol (13, $[\alpha]_D^{23}$ -16.54° (c 1.10, Et_2O), *erythro* : *threo* = 94:6), prepared by the same procedure as mentioned above, was ozonized and reduced with lithium aluminum hydride to afford the diol 15 ($[\alpha]_D^{23}$ +2.41° (c 1.08, $CHCl_3$)) in 88% yield. Selective tosylation of the primary



hydroxy group and treatment with sodium iodide gave the iodide 17. The secondary hydroxy group was protected by *t*-butyldimethylsilyl group to give a known compound 18 ($[\alpha]_D^{23}$ +10.99° (c 0.78, $CHCl_3$), lit.[15] $[\alpha]_D^{23}$ +11.7° (c 3.75, $CHCl_3$), ≥85% ee) in 66% yield. Transformation of 18 into serricornine (19) and anhydro serricornine (20) has been reported by Mori's group[16] and Hoffmann's group.[15]

As mentioned above, the ester enolate Claisen rearrangement of an optically active allyl glycolate proceeds with high diastereoselectivity and with high chirality transmission to give 2-hydroxy-3-alkyl-4-alkenoic acid, which is a promising method for the synthesis of natural products with contiguous chiral carbons.

References

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4) For the general ester enolate Claisen rearrangement with asymmetric transfer, see; R. E. Ireland and M. D. Varney, *J. Am. Chem. Soc.*, 106, 3668 (1984), and references cited therein.
5) (*R*)-1-Methyl-(*E*)-2-butenyl 2-hydroxyacetate was synthesized by the following method. (*R*)-(*E*)-3-Penten-2-ol derived from (*R*)-3-pentyn-2-ol[6] in 70% yield by partial hydrogenation with metallic sodium in liquid ammonia, was treated with one equiv of butyllithium at -60 °C in THF. After 30 min 1,3-dioxolane-2-methyl-4-one[7] was added and then the reaction mixture was allowed to warm to -20 °C for 4 h. The ester was obtained by distillation in 48% yield. Bp: 120 °C/20 mmHg (Kugelrohr).
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12) In this case 98% ee of (*R*)-1-methyl-(*E*)-2-butenyl hydroxyacetate (1, $[\alpha]_D^{23}$ +81.15° (c 1.09, $CHCl_3$)) was used.
13) The enantiomeric excess was calculated from the optical rotation value of 3*R* 4*R* isomer $[\alpha]_D^{23.5}$ +22.7° (c 0.264, hexane).[11]
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