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A DIASTEREO- AND ENANTIOSELECTIVE MICHAEL ADDITION OF CHIRAL AMIDE ENOLATES TO α,β-UNSATURATED ESTERS A STEREOSELECTIVE SYNTHESIS OF (+)-DEHYDROIRIDODIOL AND (-)-ISODEHYDROIRIDODIOL

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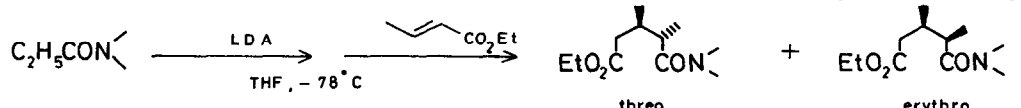
Abstract: (+)-Dehydroiridodiol and (-)-isodehydroiridodiol were synthesized stereoselectively using the diastereo- and enantioselective Michael addition of chiral amide enolates to α,β-unsaturated esters.

The stereocontrolled construction of the adjacent tertiary carbons using the Michael type reaction is a useful method for the synthesis of various natural products. We have previously reported the diastereoselective Michael addition of ester enolates to α,β-unsaturated esters.[1, 2] In this communication, we wish to describe a diastereo- and enantioselective Michael addition of chiral amide enolates to the unsaturated esters and its successful application to the stereoselective synthesis of (+)-dehydroiridodiol (1) and (-)-isodehydroiridodiol (2).[3]

At first, the stereochemistry of the reaction of various lithiated propionamides and crotonates was examined (Scheme 1). The results are summarized in Table 1. As N-propionylpyrrolidine gave threo-adduct highly stereoselectively (entry 1), the asymmetric synthesis was performed using (S)-N-propionylprolinol (3).[4] Optically active threo-2,3-dimethylglutaric acid (4) was obtained in 79% d.e. (entry 2). Erythro-selective Michael addition was achieved by employing (S)-N-methyl-N-propionylvalinol (5) or trans-2,5-bis(methoxymethoxymethyl)-pyrrolidine amide[5] (entries 8 and 9). In general, bulky amides show erythro-selectivity (entries 1,2 vs 9; entry 4 vs 7; entry 6 vs 8). As amide enolates are known to prefer (Z)-form,[6] we presume the transition state as shown in the Figure 1. This model also seems to account for the relatively small effect of the β-substituents of unsaturated esters on the stereoselectivity; For example,

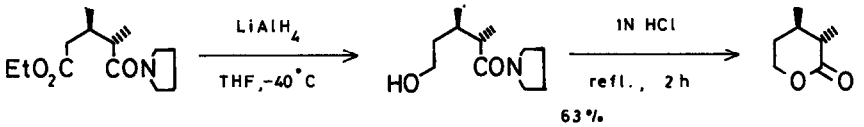


Scheme 1.

Table 1. The Michael Addition of Lithiated Tertiary Amides to Crotonates.[a]

entry	-N<	yield (%)	threo : erythro[b]	d.e. (%)
1	-N⟨ ⟩	86	>20 : 1[c]	—
		92	20 : 1	—
2	-N⟨ ⟩ (OH) 3	84[h]	7 : 1[d]	79[e]
3	-N⟨ ⟩	85	3 : 1	—
4	$-NMe_2$	92	2 : 1	—
5	-N⟨ ⟩ (Me)	88	1 : 1	—
6	$-NCH_2CH_2OH$	67[f]	1 : 1	—
7	$-N(i\text{-}Pr)_2$	85	1 : 2	—
8	-N(Me)(CH(CH$_3$)$_2$)(CH$_2$OH) 5 (OMOM)	76[f, g, h]	1 : 10	74[e]
9	-N⟨ ⟩ (OMOM)	76	1 : 15	≥ 80[i]

[a] The reaction was carried out with ethyl crotonate in THF at -78 °C using LDA as the base, unless otherwise noted.
[b] The ratio was determined by ^{13}C-NMR. The chemical shift of C-3 methyl group of threo-isomer: δ 15.7 ± 0.3; erythro-isomer: δ 18.5 ± 0.5.
[c] The reaction was carried out in ether. The adduct was converted to lactone according to the following procedures without epimerization.



[d] The adduct was hydrolized (2N HCl, refl., 2h) to give threo-2,3-dimethylglutaric acid in 68% yield, $[\alpha]_D^{24}$ -19 ° (c2.4, $CHCl_3$).
[e] Determined by ^{13}C-NMR of bis[(S)-phenethylamide], prepared by using WSC.[7] The absolute configuration is shown below.
[f] The adduct was hydrolized (2N HCl, refl., 2h), and the yield of erythro-2,3-dimethylglutaric acid is shown, $[\alpha]_D^{24}$ -11 ° (c1.0, $CHCl_3$) for entry 8.
[g] The reaction was carried out in ether-THF (2:1).
[h] Methyl crotonate was used.
[i] Determined by ^{13}C-NMR of the adduct.

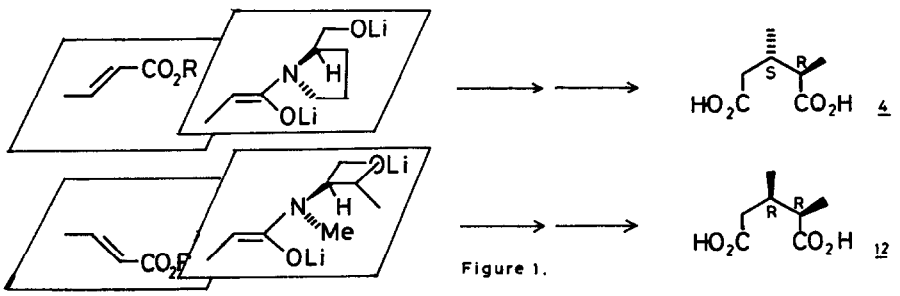
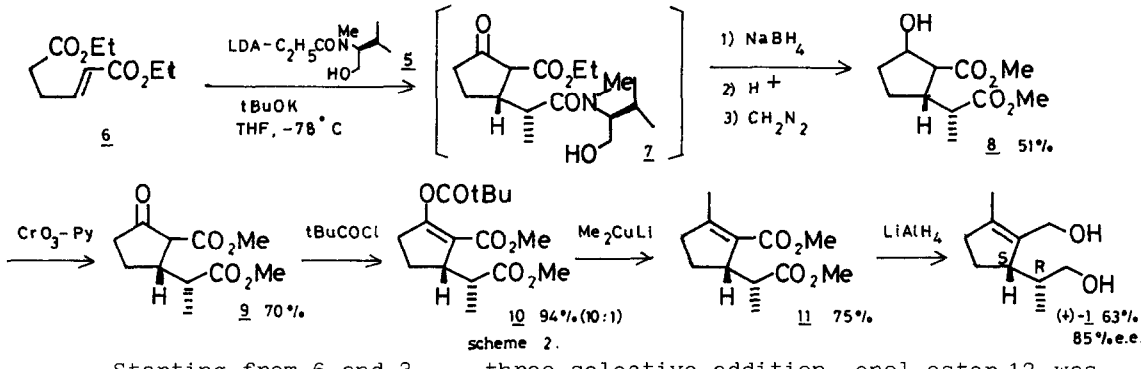


Figure 1.

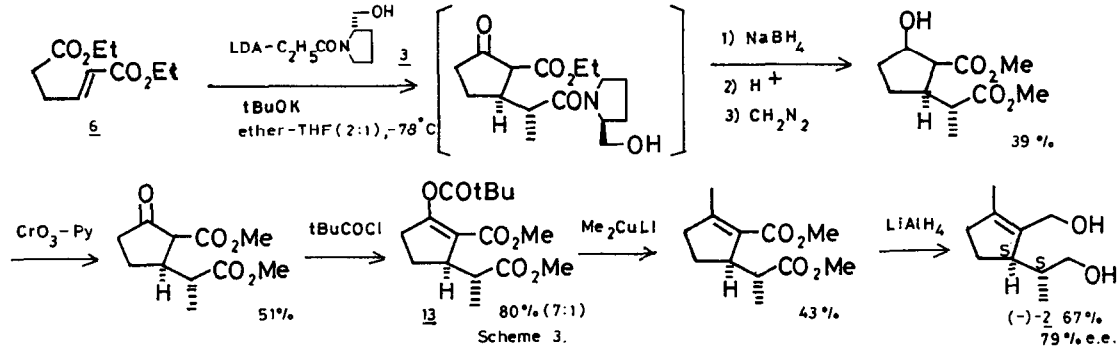
the reaction of 3 and ethyl 2-decenoate afforded the corresponding glutaric acid in 10 : 1 ratio (threo : erythro) and in 80% d.e.[8]

In order to determine the absolute configuration of the optically active glutarates, and show the utility of the present asymmetric synthesis, a total synthesis of (+)-1 and (-)-2 was performed (Scheme 2 and 3). Our synthetic strategy is based on the Michael induced intramolecular acylation:[9] Diethyl 2-hexendioate (6)[10] was used as the starting material. Erythro-selective addition cyclization process using 6 and lithiated 5 in THF at -78 °C in the presence of potassium t-butoxide[9] gave cyclopentanone 7. In order to avoid decarboxylation 7 was reduced ($NaBH_4$, EtOH, 0 °C, 30 min), hydrolyzed (2N HCl, refl., 2h), and esterificated (CH_2N_2, ether, 0 °C, 30 min). The resulted diastereomeric mixture of hydroxyester 8 was converted to ketoester 9 (pyridine-CrO_3, CH_2Cl_2, r.t., 30 min). Introduction of methyl group was achieved by a two-steps procedure (i. t-BuCOCl, Et_3N, HMPA, 0 °C to r.t., 2h; ii. Me_2CuLi, ether, -78 to -25 °C, 1h).[11] The diastereoselectivity of the initial Michael addition was determined at the stage of enol ester 10 (erythro : threo = 10 : 1). Finally, diester 11 was reduced ($LiAlH_4$, ether, r.t., 30 min) and (+)-(3S, 8R)-1 was obtained, $[\alpha]_D^{24}$ +15 ° (c2.2, $CHCl_3$); 85% e.e. by MTPA-method.[3,12] Thus, the absolute configuration of erythro-glutaric acid 12 (Table 1, entry 8) should be (2R, 3R).



scheme 2.

Starting from 6 and 3 —— threo-selective addition, enol ester 13 was obtained in 7:1 selectivity. By a similar procedures as above, (-)-(3S, 8S)-2



Scheme 3.

was synthesized (79% e.e.) $[\alpha]_D^{24}$ -13° (c0.9, $CHCl_3$).[3, 12] Thus, 4 should have (2R, 3S)-configuration (Table 1, entry 2).

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8 As crotonate approaches from the (less hindered) si-face of lithiated 3 and 5, the configuration of the enolates is presumed as Figure 1, in which two OLi groups are repulsive. The diastereoselectivities are determined by the degree of steric repulsion between the alkoxycarbonyl group of crotonate and the amine part of enolates.
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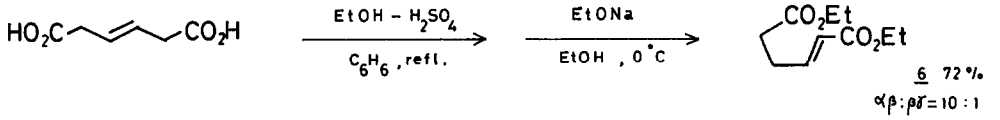
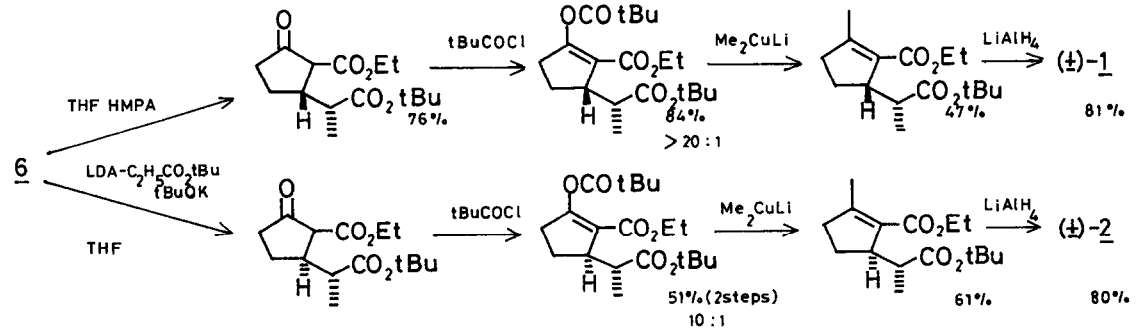


11 K. E. Harding and C. Tseng, J. Org. Chem., 43, 3974 (1978).
12 Racemic (±)-1 and (±)-2 were synthesized as follows.



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