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A New Reagent for the Preparation of Chiral HMGA (3-Hydroxy-3-methylglutaric Acid) Esters and Amides. Synthesis of (*R*)- and (*S*)-β-Carboxymethyl-β-methyl-β-lactones by Asymmetric Desymmetrization of HMGA Anhydride

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Abstract: (*R*)- and (*S*)-β-carboxymethyl-β-methyl-β-lactones, new reagents for the preparation of chiral HMGA (3-hydroxy-3-methylglutaric acid) esters and amides were developed through the asymmetric desymmetrization of HMGA anhydride. The reagent was smoothly reacted with various alkoxide without racemization to afford the desirable half-esters. On the other hand, the reaction with various amine in refluxing toluene gave a racemic amide. The chiral HMGA amide was prepared using the corresponding methyl ester of the reagent.

HMGA (3-hydroxy-3-methylglutaric acid, previously named dicrotalic acid[1]), which exists as HMGCoA in organisms, is a key intermediate in the biosynthesis of terpenoids, steroids, and carotenoids[2] and is often included in secondary metabolites as a half-ester,[3] amide-ester,[4] and mixed diester.[1,5] All of them are chiral compounds with definite stereochemistry (Fig. 1).

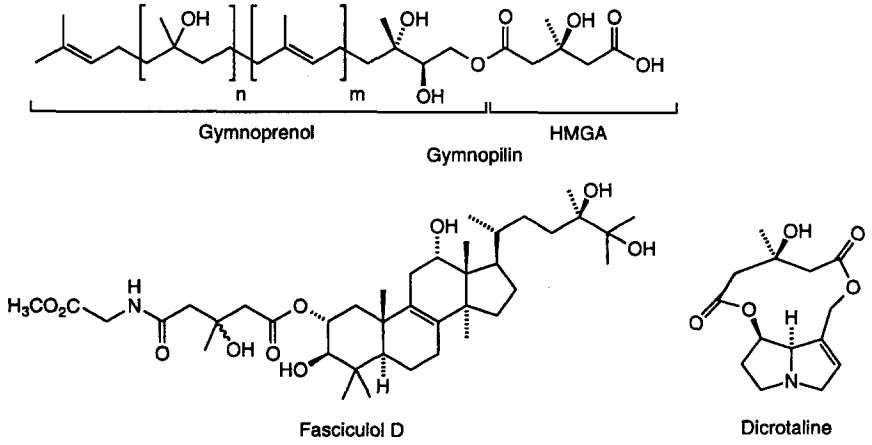
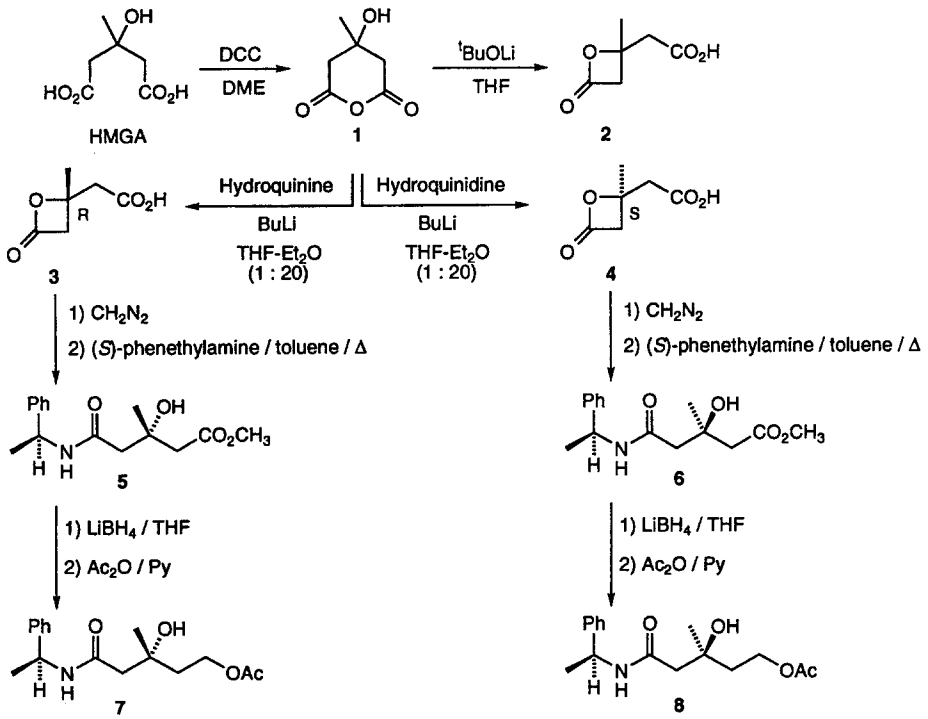


Fig. 1 Some natural compounds containing chiral HMGA fragments.

HMGA is a prochiral compound and by its regioselective monoesterification leads to chiral compounds. This kind of conversion, called asymmetric desymmetrization, has been performed by enzymes[6] and also by chemical syntheses.[7] The (*S*)-(+)-HMGA monomethyl ester was synthesized through hydrolysis of the corresponding dimethyl ester by enzymes,[8] and it could be used for the chiral HMGA esterification of various alcohols. However, the major disadvantages of this monomethyl ester as the esterification reagent are the

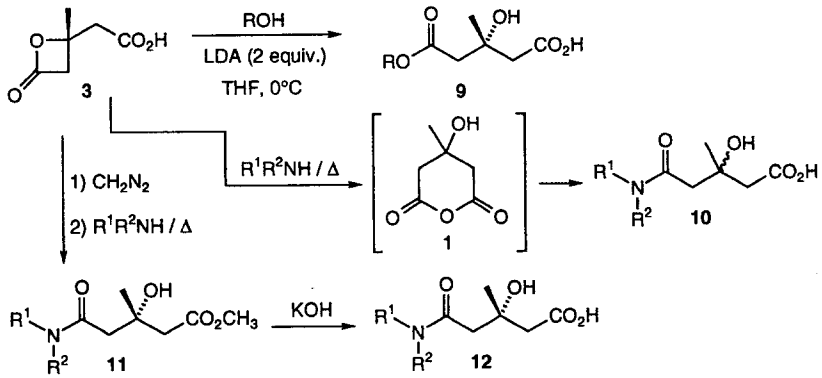
lack of an (*R*)-(-)-isomer and the need for deprotection (hydrolysis of the methyl ester after preparation of the mixed ester). The title compound, a β-lactone, would be the most useful reagent for the chiral HMGA esterification because it is easily condensed with an alkoxide without using a condensation reagent and it directly gives the desired half-ester.

HMGA was synthesized by the known method[9] and it was converted to HMGA anhydride **1** with DCC in DME (Scheme 1). Treatment of the anhydride with lithium *tert*-butoxide in THF afforded the *dl*-β-lactone **2**. For the asymmetric synthesis of the β-lactone, a chiral base with a less nucleophilic nature was employed. To a solution of hydroquinine (1.1 equiv) dissolved in a minimum amount of THF was added BuLi (1.1 equiv) at 0℃. After stirring for 15 min, the solution was cooled to -78℃, to which the HMGA anhydride dissolved in a minimum amount of THF was slowly added. After stirring for 15 min, the solution was diluted 20 times with dry Et_2O[10] precooled to -78℃ through a canular. The resulting cloudy solution was stirred for 30 min at -78℃ and then for 2 h at 0℃. The reaction was quenched by the addition of 1N HCl to adjust the pH to 2~3 and extracted with AcOEt to give the desired (*R*)-(-)-β-lactone **3** in 70% yield with more than 90% ee. The optical purity was checked by ^{1}H-NMR after conversion of the acid to the amide **5**[11] (i) CH_2N_2, ii) (*S*)-phenethylamine in toluene at 100℃). The absolute configuration was determined by leading the ester **5** to the known acetate **7**[3(d)] through reduction of the ester with $LiBH_4$ in THF followed by acetylation with Ac_2O in pyridine. The (*S*)-(+)-β-lactone **4** was also obtained using hydroquinidine in the above reaction in 70% yield with more than 90% ee. These β-lactones were recrystallized from CCl_4 for the measurement of optical rotation.[12]



Scheme 1

The chiral β-lactone was successfully used for the esterification reaction to give the chiral half-ester (Scheme 2). Some alcohols, such as octanol, cyclohexanol, 3-pentanol, farnesol and gymnoprenol,[13] were exposed to the condensation reaction using LDA (2.0 equiv.) as the base. The reaction smoothly proceeded to afford the corresponding HMGA half-esters without racemization which was checked by ^{1}H-NMR after further conversion of the resulting half-ester to an amide of (*S*)-phenethylamine with DCC. The limitation of the condensation reaction was met with phenol whose less nucleophilic property resulted in no reaction. On the other hand, the β-lactone reacted with various amines, such as hexylamine, cyclohexylamine, pyrrolidine and phenethylamine in hot toluene to give amides with complete racemization probably through the HMGA anhydride. The chiral amide was prepared from the methyl ester of the β-lactone with amines in hot toluene without racemization. The resulting amide-ester was easily hydrolized to afford the corresponding amide-acid.



Scheme 2

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10. Addition of the ether was essential to achieve the high enantioselectivity. It may supress the dissociation of the chiral complex consisting of HMGA anhydride and the chiral base.
11. Diastereomeric amide **5** and **6** were clearly discriminated by ^{1}H-NMR.
12. (*R*)-(-)-β-lactone **3**; m.p. 52°-54℃; $[\alpha]_D$ -56.0° (*c* 1.59, $CHCl_3$); ^{1}H-NMR (400MHz, $CDCl_3$) δ1.72 (3H, s), 2.95 (1H, d, *J*=16.3Hz), 3.02 (1H, d, *J*=16.3Hz), 3.30 (1H, d, *J*=16.3Hz), 3.58 (1H, d, *J*=16.3Hz).
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