Expeditious and Stereoselective Synthesis of Chiral *trans*-β-Hydroxy-δ-lactone Systems

Masahiro Miyazawa, Erika Matsuoka, Shinobu Sasaki, Satoshi Oonuma, Kimiyuki Maruyama, and Masaaki Miyashita*
Division of Chemistry, Graduate School of Science, Hokkaido University, Sapporo 060

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Expeditious and stereoselective synthesis of chiral *trans*-β-hydroxy-δ-lactone systems starting from γ,δ-epoxy acrylates is described which involves the regioselective ring opening of an epoxide and the intramolecular conjugate addition of a hemiacetal alkoxide anion of δ-hydroxy-α,β-unsaturated esters as key steps.

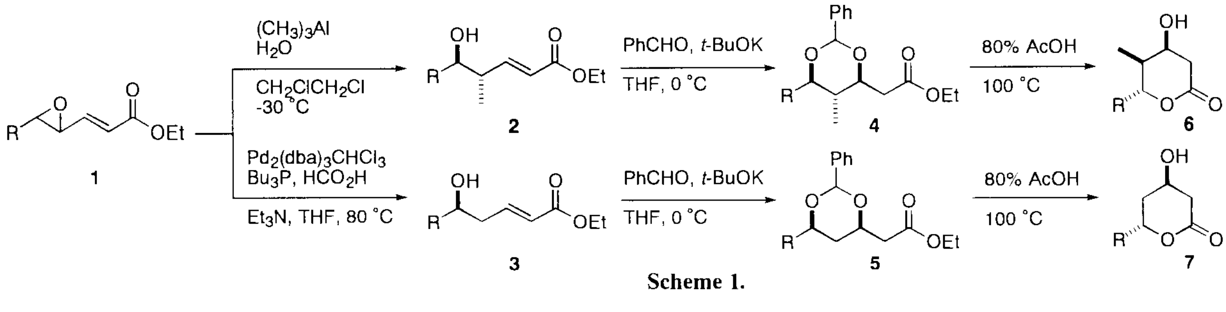
The *trans*-β-hydroxy-δ-lactone structure has been known to be specifically important for the 3-hydroxy-3-methylglutaryl coenzyme A (HMG Co-A) reductase inhibiting activities of medicinally important compactin,[1] mevinolin, and NK-104,[2] and has elicited attention from synthetic chemists. Although many synthetic methods for *trans*-β-hydroxy-δ-lactones starting from chiral sources such as sugars, malic acid, and glycidol have been reported, most of them require multisteps or have synthetic limitations that both enantiomers are not available.[3]

Recently we have reported the stereoselective synthesis of the C_1-C_7 segment of (+)-discodermolide,[4] a potent immunosuppressive agent, having the fully substituted *trans*-β-hydroxy-δ-lactone structure in which the stereospecific methylation of a γ,δ-epoxy acrylate by trimethylaluminum and the intramolecular conjugate addition of a benzylidene acetal alkoxide anion of the resulting δ-hydroxy-α,β-unsaturated ester were involved as key steps. Since the above methodology has considerable synthetic potential and seemed to provide an efficient entry into the *trans*-β-hydroxy-δ-lactone system, we investigated its generality in detail. We report here the expeditious and stereoselective synthetic methods for the chiral *trans*-β-hydroxy-δ-lactone systems starting from γ,δ-epoxy acrylates.

Two synthetic routes were designed for the purpose (Scheme 1). One is the route to *trans*-β-hydroxy-γ-substituted-δ-lactones **6** via the regioselective alkylation of γ,δ-epoxy acrylates **1** and subsequent intramolecular conjugate addition of a benzylidene acetal alkoxide anion of **2**, and another is that to *trans*-β-hydroxy-γ-unsubstituted-δ-lactones **7** by way of the palladium catalyzed hydrogenolysis of γ,δ-epoxy acrylates **1** followed by the acetalization of the resulting δ-hydroxy-α,β-unsaturated ester **3**. In the former route, we used the stereospecific methylation reaction of γ,δ-epoxy acrylates **1** by trimethylaluminum ($(CH_3)_3Al$) which has been developed by us since both the anti compounds **2** and the syn compounds are stereospecifically obtainable from (*E*)-epoxy acrylates and (*Z*)-epoxy acrylates, respectively, in excellent yields.[5] On the other hand, in the latter route, the palladium catalyzed hydrogenolysis of **1** with formic acid was employed for the synthesis of δ-hydroxy-α,β-unsaturated esters **3**.[6] The common starting materials, γ,δ-epoxy acrylates **1**, can be easily prepared from the corresponding chiral epoxy alcohols via Swern oxidation followed by Horner-Emmons reaction.

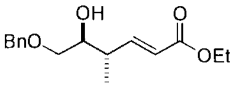
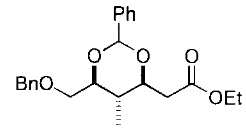
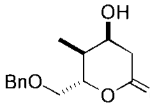
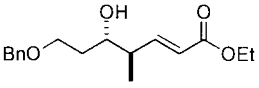
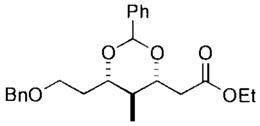
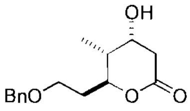
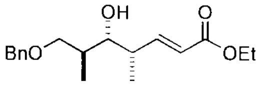
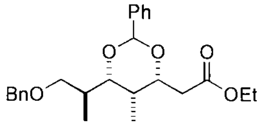
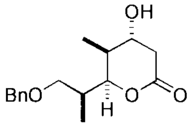
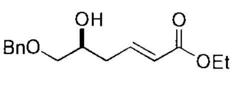
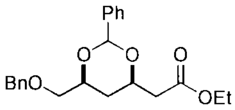
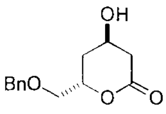
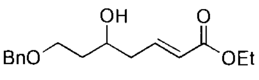
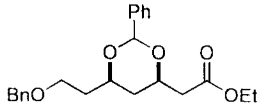
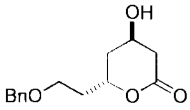
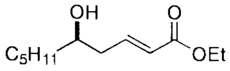
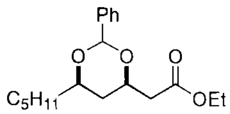
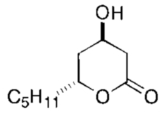
Practical reactions were carried out as follows. The methylation of γ,δ-epoxy acrylates **1** was performed with $(CH_3)_3Al$ (2 M solution in hexane, 10 equiv.) in 1,2-dichloroethane in the presence of water (6 equiv.) at -30 °C for 1-2 h. All the methylation reactions proceeded stereospecifically at the γ-position giving rise to the sole product, **2a**, **2b**, and **2c**, in 94, 97, and 97% yields, respectively (Table 1, entries 1-3). On the other hand, the palladium catalyzed hydrogenolysis of **1** was carried out with $Pd_2(dba)_3CHCl_3$ (0.025 equiv.), Bu_3P (0.013 equiv.), formic acid, and triethylamine in THF at 80 °C. The reduction occurred exclusively at the γ-position giving **3a**, **3b**, and **3c**, in 86, 74, and 87% yields, respectively, (Table 1, entries 4-6). *Z*-Olefinic isomers were not formed in these reactions. Conversion of **2** and **3** into the benzylidene acetals **4** and **5**, respectively, was successfully performed by the Evans protocol.[7] Namely, to a solution of the hydroxy ester **2** or **3** in THF was added benzaldehyde (1.1 equiv.) and *t*-BuOK (0.1 equiv.) at 0 °C and the mixture was stirred for 15 min in the cold. Then the above manipulation was repeated until the starting material disappeared on TLC. Subsequently, the reaction mixture was treated with phosphate buffer (pH 7) and extracted with ethyl acetate, and the crude product was purified by silica gel column chromatography. The results are summarized in Table 1. Each product was a mixture of diastereoisomers concerning the benzylic position and the equatorial isomer was always predominant (> 95%). Interestingly, the isolated yields of the γ-substituted products **4** (entries 1-3) were higher than those of the unsubstituted products **5** (entries 4-6).

The final conversion of the benzylidene acetals **4** and **5** into the target molecules, *trans*-β-hydroxy-δ-lactones **6** and **7**, respectively, was carried out in 80% aqueous AcOH at 90-110 °C. Under these conditions, all the benzylidene acetals except **5a** gave directly the corresponding β-hydroxy-δ-lactones in high yields (Table 1). In the case of **5a**, the intermediate dihydroxy ester remained unchanged under the conditions. Eventually, the



Scheme 1.

Table 1. Stereoselective synthesis of *trans*-β-hydroxy-δ-lactones from δ-hydroxy-α,β-unsaturated esters

Entry	Substrate (%)		Acetal (%)		Lactone (%)		$[\alpha]_D$
1	 **2a**	94	 **4a**	69	 **6a**	75	+18.4 (c 1.01, $CHCl_3$)
2	 **2b**	97	 **4b**	93	 **6b**	85	-40.4 (c 1.08, $CHCl_3$)
3	 **2c**	97	 **4c**	81	 **6c**	83	-24.0 (c 1.05, $CHCl_3$)
4	 **3a**	86	 **5a**	49	 **7a**	46	(lit. +6.59)[9]
5	 **3b**	74	 **5b**	56	 **7b**	68	racemate
6	 **3c**	87	 **5c**	72	 **7c**	88	+ 33.8 (c 1.0, $CHCl_3$) (lit. +37.7)[10]

lactonization of **5a** was achieved by treatment of the dihydroxy ester with a catalytic amount of *p*-TsOH in benzene at 80 °C, albeit in somewhat low yield (entry 4).

The lactones **7a** and **7b** (entries 4 and 5) thus obtained serve as potential intermediates for the synthesis of the δ-lactone moiety of compactin, mevinolin, and NK-104. On the other hand, the lactone **7c** (entry 6) is a natural product 8-hydroxy-8,9-dihydromassoialactone ((*4R,6R*)-(+)-4-hydroxy-6-pentyl-valerolactone).[8]

In summary, we found the convenient synthetic method for chiral *trans*-β-hydroxy-δ-lactones including γ-substituted and unsubstituted ones starting from γ,δ-epoxy acrylates.

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