A Facile Synthesis of Chiral γ-Butyrolactones in Extremely High Enantioselectivity Mediated by Samarium(II) Iodide

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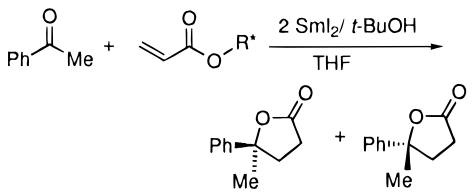
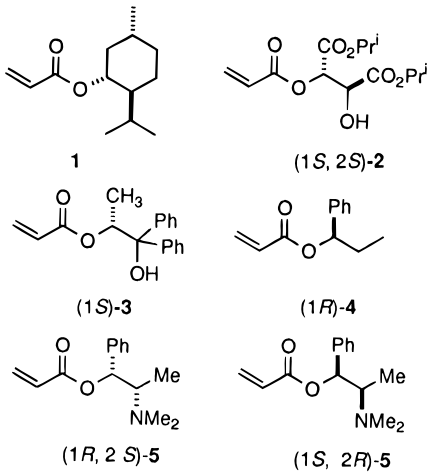
The lactone functionality is present in a large variety of natural products and biologically active compounds. For example, certain functionalized chiral γ-butyrolactones are sex attractant pheromones for several insect species and some are utilized as flavoring components. They also constitute a particularly useful class of synthons and chiral building blocks. Because the physiological activity of these γ-butyrolactones often depends on the enantiomeric purity and absolute configuration especially for insect sex pheromones, highly selective asymmetric synthesis of chiral γ-butyrolactones has been of current interest and is an important subject. Recent useful examples of the chemical synthesis of chiral γ-butyrolactones are as follows: transformation of (i) chiral natural products;[1] (ii) chiral allylic alcohols;[2] (iii) chiral propagyl alcohols;[3] (iv) stoichiometric or catalytic chiral induction with chiral organometallic reagents.[4] Although these methods are useful for the synthesis of chiral γ-butyrolactones, they suffer from certain drawbacks. In most of these methods, a multistep process (i.e., more than four steps) is required to reach the desired γ-butyrolactones.

In previous papers, we reported the facile and effective synthesis of racemic γ-butyrolactones by the reaction of α,β-unsaturated esters with ketones or aldehydes mediated by samarium(II) iodide.[5] An interesting feature of the reaction is the stereochemistry. Thus, 3,4-disubstituted-γ-butyrolactones are produced by the reaction of crotonic acid ester and aldehydes in favor of the *cis* isomer (70:30 to 99:1).[5,6] Samarium(II) iodide often produces highly stereoselective reactions as the result of chelation control of the samarium atom with the oxygen or nitrogen moiety in organic molecules.[7] Highly selective intra- and intermolecular 1,2- and 1,3-asymmetric inductions are typical examples of chelation control.[8] In our previous γ-butyrolactone synthesis described above, if chiral α,β-unsaturated esters could be used in the reaction some steric interactions between the organic molecule and samarium metal would be expected to lead to chiral induction. Indeed a chiral γ-butyrolactone was obtained in high enantiomeric purity when *N*-methylephedrine was used as a chiral auxiliary. We would like to present here the facile and highly enantioselective synthesis of γ-butyrolactones by the reaction of acrylates and crotonates derived from chiral *N*-methylephedrine with ketones or aldehydes.

Scheme 1



Scheme 2



We first surveyed the enantioselectivity in the reaction of acetophenone with various acrylates derived from chiral *sec*-alcohols as a probe reaction. We chose easily accessible and inexpensive chiral auxiliaries for economic reasons. The reaction was usually carried out as follows. To the THF solution of samarium(II) iodide was added a mixture of acetophenone, the acrylate derivative, and *t*-BuOH simultaneously at −78 °C (Scheme 1). The mixture was stirred at that temperature for 1 h, and then the solution was gradually warmed to room temperature over a period of 5−6 h. The chemical yields and enantiomeric excesses (ee) of 4-methyl-4-phenyl-γ-butyrolactone prepared from the reaction with acrylate derivatives are as follows (Scheme 2): L-menthol (**1**) (39%, 8% ee), (2*S*,3*S*)-diisopropyl tartarate (**2**) (43%, 28% ee), (2*S*)-1,1-diphenyl-1,2-propanediol (**3**)[9] (64%, 54% ee), (*R*)-1-phenyl-1-propanol[10] (purity, 97% ee) (**4**) (68%, 74% ee), and (1*R*,2*S*)-*N*-methylephedrine (**5**)[11] (86%, 90% ee). The ee value of the product was determined by GC using a chiral capillary column (Astec, Chiraldex GT-A, 30 m).

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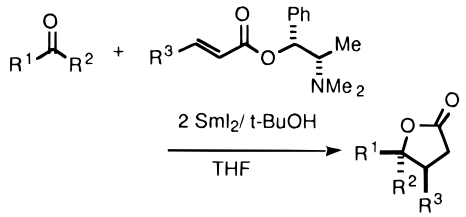
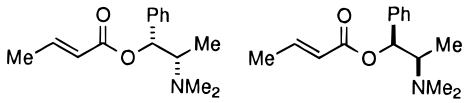
Table 1. Samarium(II) Iodide Mediated Asymmetric Synthesis of γ-Butyrolactones by the Reaction of Carbonyl Compounds with *N*-Methylephedrinyl Acrylate and Crotonate



entry	ester	R^1	R^2	R^3	yield (%)[a]	*cis*:*trans*[a]	ee (%, *cis*)[b]	$[\alpha]^{25}_D$[c]	config.
1	(1*R*, 2*S*)-**5**	C_6H_{13}	Me	H	86		43	+3.47	*d*
1		Ph	Me	H	86		90	−34.1	*S*
3		Ph	Et	H	74		69	−37.5	*d*
4		*n*-C_5H_{11}	H	H	43		93	+37.4[e]	*R*
5		$PhCH_2CH_2$	H	H	45		>99	+39.2	*d*
6		*t*-Bu	H	H	57		94	+31.1[f]	*S*
7		*c*-C_6H_{11}	H	H	51		96	+26.2	*d*
8		*i*-Pr	H	H	43		93	+35.6	*S*
9	(1*S*, 2*R*)-**5**	Ph	Me	H	88		88	+38.0[g]	*R*
10		Ph	Et	H	72		70	+44.6	*d*
11		*n*-C_5H_{11}	H	H	43		93	−35.9	*S*
12		$PhCH_2CH_2$	H	H	55		>99	−41.9	*d*
13		*t*-Bu	H	H	52		96	−31.1[h]	*R*
14		*c*-C_6H_{11}	H	H	45		93	−20.2	*d*
15	(1*R*, 2*S*)-**6**	*n*-Bu	H	Me	55	97:3	94	+73.8	(3*R*,4*R*)
16		*n*-C_5H_{11}	H	Me	59	98:2	95	+75.2	*d*
17		*t*-Bu	H	Me	69	99:1	95	+38.4	*d*
18		*c*-C_6H_{11}	H	Me	76	99:1	96	+55.7	*d*
19	(1*S*, 2*R*)-**6**	*n*-Bu	H	Me	57	97:3	96	−74.3[i]	(3*S*,4*S*)
20		*n*-C_5H_{11}	H	Me	59	98:2	93	−78.2	*d*
21		*t*-Bu	H	Me	68	99:1	94	−40.1	*d*
22		*c*-C_6H_{11}	H	Me	74	99:1	97	−56.8	*d*

[a] Yields and diastereomeric ratios were determined by GC. [b] Determined by GC using a chiral capillary column (Astec, GT-A, 30 m). [c] In MeOH (c = 0.2−1.0). [d] Not determined. [e] Reported value: $[\alpha]^{25}_D$ = +45.8 (c = 1, MeOH); ref 3a. [f] Reported value: $[\alpha]^{25}_D$ = +43.5 (c = 1.92, $CHCl_3$); ref 2. [g] Reported value: $[\alpha]^{25}_D$ = +72.4 (c = 1.3, $CHCl_3$); ref 4r. [h] Reported value: $[\alpha]^{25}_D$ = −44.6 (c = 2.00, THF); ref 2. [i] Reported value: $[\alpha]^{25}_D$ = −74.0 (c = 0.2, MeOH); ref 1d,e.

Scheme 3



(1*R*, 2*S*)-**6** (1*S*, 2*R*)-**6**

Since *N*-methylephedrine was found to be the most effective chiral auxiliary, we next examined the reaction of various ketones and aldehydes with (1*R*,2*S*)- and (1*S*,2*R*)-(**5**). Table 1 summarizes the results of the asymmetric coupling reaction. Chiral 4-substituted-γ-butyrolactones were obtained with high ee values in many cases, and the highest ee (>99% ee) was achieved with 3-phenylpropanal (Table 1, run 5), although the yields and selectivities have not yet been optimized. Starting from the acrylate isomers of (1*R*,2*S*)-**5** and (1*S*,2*R*)-**5**, the (*S*)- and (*R*)-isomers of the corresponding γ-butyrolactones were produced. The reversal of the enantioselectivity shows that the enantioselectivity depends on the configuration of ephedrine. This method for γ-butyrolactone synthesis is superior to other methods with respect to simplicity of the synthetic procedure, which involves simply mixing the two starting compounds with samarium(II) iodide and the use of inexpensive *N*-methylephedrine as a chiral auxiliary. The *N*-methylephedrine is easily separated from the product during acidic workup by aqueous extraction and can be recovered.

With crotonates derived from *N*-methylephedrine, the *cis*-isomer of the 3,4-disubstituted-γ-butyrolactone was produced predominantly (97:3 to 99:1) with a high enantioselectivity (93−97% ee) with most of the aldehydes examined here. The reaction with cyclohexanecarboxaldehyde gave the highest diastereo- (*cis*:*trans* = >99:<1) and enantioselectivities (>97% ee) with 76% chemical yield. In the reaction of pentanal with the crotonate isomers of (1*R*,2*S*)-**6** and (1*S*,2*R*)-**6** (Scheme 3), the (3*R*,4*R*)- and (3*S*,4*S*)-isomers of whisky lactones were produced, respectively (Table 1, runs 15 and 20).[1d,e]

As described in our previous paper, in the first stage of the reaction, one electron is transfered from samarium(II) iodide to the ketone or the aldehyde to produce a ketyl radical.[5] The mechanism of the reaction includes the ketyl radical and alkene coupling reaction where the diastereoselectivity is determined. Because addition of HMPA (hexamethylphosphoric triamide) to the reaction system resulted in production of a completely racemic mixture of the γ-butyrolactone, it is safely to say that chelation control by samarium atom would play an important role in the asymmetric induction. The extinction of enantioselectivity by addition of HMPA suggests that HMPA might block the chelation of the samarium atom with the ester group. However, origins of the selectivity have not been determined yet.[12]

In conclusion, this method provides a facile and effective method for the synthesis of optically active 4-substituted- or *cis*-3,4-disubstituted-γ-butyrolactones. Starting from various aldehyes and ketones, a wide range of chiral γ-butyrolactones including natural lactones can be readily prepared in high enantiopurity.

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Supporting Information Available: ^{1}H NMR and GC (by a chiral capilary column) spectra of chiral acrylates, crotonates, and γ-butyrolactones and experimental procedures for preparation and the reaction of chiral *N*-methylephedrinyl crotonate with an aldehyde in preparative scale (69 pages). See any current masthead page for ordering and Internet access instructions.

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