Enantioselective Synthesis of C11–C17 Segment of Mycinolide IV Using Samarium(II) Iodide-mediated Aldol Reaction

Yasuyuki Ogawa,[†,††] Kiichi Kuroda,[†,††] and Teruaki Mukaiyama*[†,††]
[†]*Center for Basic Research, The Kitasato Institute, 6-15-5 (TCI) Toshima, Kita-ku, Tokyo 114-0003*
[††]*Kitasato Institute for Life Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641*

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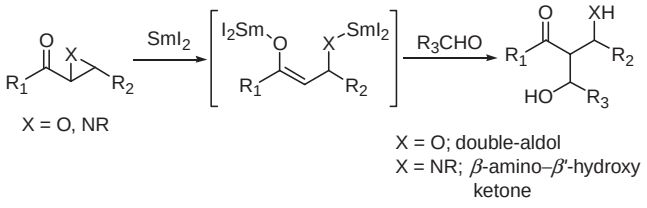
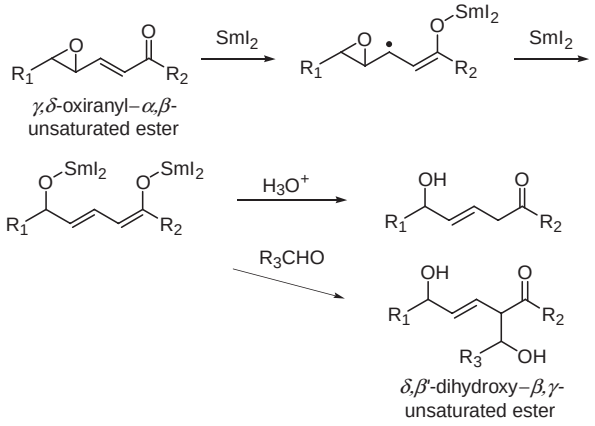
δ,β'-Dihydroxy–β,γ-unsaturated esters were stereoselectively synthesized by aldol reaction of aldehydes with samarium enolates that were generated by epoxide-fragmentation of γ,δ-oxiranyl–α,β-unsaturated esters using two moles of samarium(II) iodide. This samarium(II) iodide-mediated aldol reaction was applied successfully to the enantioselective synthesis of C11–C17 segment of Mycinolide IV.

Samarium(II) iodide (SmI_2) is known as a powerful one-electron reducing agent and is widely used in organic synthesis.[1] Preparation of 3-hydroxy-2-(1-hydroxyalkyl)alkyl ketones (double-aldols) or 3-amino-2-(1-hydroxyalkyl)alkyl ketones (β-amino–β'-hydroxy ketones) by SmI_2-mediated aldol reaction of aldehydes with oxiranyl ketones or aziridinyl ketones was recently reported (Scheme 1),[2,3] which were then successfully applied to synthesis of taxane skeleton.[4]



Scheme 1.

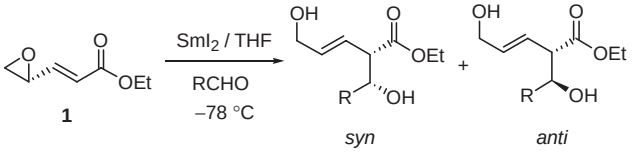
In addition, preparation of δ-amino–β'-hydroxy–β,γ-unsaturated esters by SmI_2-mediated aldol reaction of aldehydes with γ,δ-aziridinyl–α,β-unsaturated esters was reported.[5] Further, this SmI_2-mediated aldol reaction was successfully applied to the asymmetric one by introducing chiral oxazolidinone to unsaturated aziridine. Next, the use of γ,δ-oxiranyl–α,β-unsaturated esters instead of γ,δ-aziridinyl–α,β-unsaturated esters was studied and aldol adducts thus formed here were considered to be δ,β'-dihydroxy–β,γ-unsaturated esters (Scheme 2). As three functional groups and trans double bond are involved in these compounds, they can be considered new building blocks for the synthesis of natural products or bioactive compounds.



Scheme 2.

In the first place, SmI_2-mediated aldol reaction of (2′*R*,2*E*)-3-(oxiran-2′-yl)acrylic ethyl ester (**1**)[6] with several aldehydes was examined (Table 1). Reaction of **1** with benzaldehyde gave the corresponding δ,β'-dihydroxy–β,γ-unsaturated ester **1a** (32/68 mixture of *syn* and *anti* isomers) in moderate yield along with a small amount of δ-hydroxy–β,γ-unsaturated ethyl ester (Entry 1). The yield of **1a** slightly decreased because reduction of benzaldehyde simultaneously took place under these conditions. On the other hand, reaction of **1** with aliphatic aldehydes proceeded smoothly to give the corresponding δ,β'-dihydroxy–β,γ-unsaturated esters **1b**–**1f** in excellent yields (Entries 2–6). This aldol reaction proceeded to form *E*-olefin selectively with complete α-regioselectivity but diastereoselectivity (*syn*/*anti* = 23/77–49/51) was not observed.

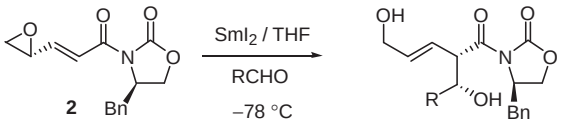
Table 1. SmI_2-mediated aldol reaction of γ,δ-oxiranyl–α,β-unsaturated ester **1** and various aldehydes



Entry	Aldehyde R	Product	Yield/%	(*syn*/*anti*)
1	Ph	**1a**	65	(32/68)
2	Et	**1b**	85	(40/60)
3	$Ph(CH_2)_2$	**1c**	86	(49/51)
4	*i*-Pr	**1d**	91	(43/57)
5	*c*-Hex	**1e**	95	(37/63)
6	*t*-Bu	**1f**	89	(23/77)

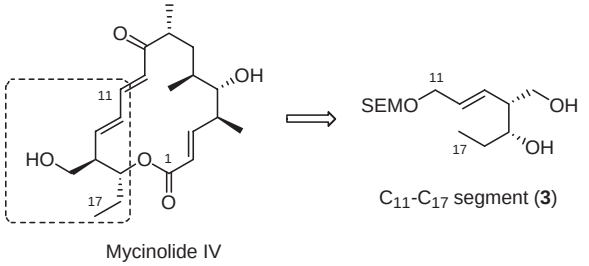
Then, this aldol reaction was applied to the asymmetric one by introducing a chiral oxazolidinone to the unsaturated epoxide as in the case of unsaturated aziridine. In the first place, the reaction of (2′*R*,4″*R*,2*E*)-4″-benzyl-3″-[3-(oxiran-2′-yl)acryloyl]-oxazolidin-2″-one (**2**) with 3-phenylpropanal was examined (Table 2, Entry 1).[7] This asymmetric aldol reaction proceeded smoothly and afforded the corresponding product **2a** in high yield with high *syn* diastereoselectivity (dr = 7.8/1). In addition, the corresponding products were also obtained in good to high yields with high diasteoselectivities when other aldehydes were used (Entries 2–4).

Table 2. SmI_2-mediated asymmetric aldol reaction



Entry	Aldehyde R	Product	Yield/%	dr[a]
1	$Ph(CH_2)_2$	**2a**	85	7.8/1
2	Et	**2b**	89	9.3/1
3	*i*-Pr	**2c**	72	8.1/1
4	*c*-Hex	**2d**	68	7.9/1

[a]Diasteromeric ratio

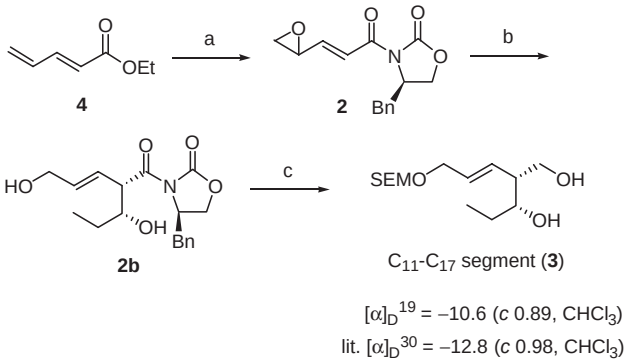


Scheme 3.

As the asymmetric SmI_2-mediated aldol reaction was thus established, this aldol reaction was applied to the synthesis of natural products to show its utility. Then, synthesis of C11–C17 segment of Mycinolide IV (**3**) was tried. Mycinolide IV, isolated from *Micromonospora griseorubida* sp. nov., is the 16-membered macrolide antibiotic and the aglycon of mycinamicin IV. As C11–C17 segment (**3**) has two chiral centers and trans double bond, the above mentioned aldol reaction would be effectively employed in the construction of this compound (Scheme 3).

First, 2,4-pentadienoic acid ethyl ester (**4**) was treated with *m*-CPBA and γ,δ-oxiranyl-α,β-unsaturated ester was obtained (Scheme 4). Then, it was converted to γ,δ-oxiranyl-α,β-unsaturated imide as a mixture of two diastereomers by hydrolysis and successive introduction of chiral oxazolidinone that followed. Next, asymmetric SmI_2-mediated aldol reaction was attempted. Treatment of **2** and propanal with 2 equiv. of SmI_2 at $-78\,^{\circ}C$ cleanly afforded the aldol adduct **2b** in high yield (85%) with high diastereoselectivity (dr = 8.7/1). Concerning the reactivity and stereoselectivity, the results were the same either when a mixture of diastereomers or a single isomer was used. Undesired isomers were separated easily by column chromatography. The primary hydroxy group of **2b** was selectively protected with 2-(trimethylsilyl)ethoxymethyl (SEM) group followed by reduction with $LiBH_4$ afforded C11–C17 segment of Mycinolide IV (**3**). This compound had already been obtained by an entirely different procedure in the total synthesis of Mycinolide IV.[8] Successful use of the aldol adduct **2b** in the enantioselective synthesis of C11–C17 segment of Mycinolide IV also confirmed stereochemical assignment of this compound.

It is noted that the stereoselective synthesis of δ,β'-dihydroxy-β,γ-unsaturated esters from γ,δ-oxiranyl-α,β-unsaturated esters and aldehydes was developed via the samarium enolates by using two moles of SmI_2. In addition, this aldol reaction



Scheme 4. Reagents and conditions: a) *m*CPBA, $ClCH_2CH_2Cl$, 60 °C (60%); LiOH, dioxane-MeOH-H_2O, 0 °C; PivCl, Et_3N, (4*R*)-4-benzyl-2-oxazolidinone, LiCl, 0 °C (52% in 2 steps). b) SmI_2, EtCHO, THF, −78 °C (85%, dr = 8.7:1). c) SEMCl, $^iPr_2NEt$, CH_2Cl_2, 0 °C (85%); $LiBH_4$, THF–EtOH, 0 °C (87%).

was successfully applied to the enantioselective synthesis of C11–C17 segment of Mycinolide IV. Further investigation of this reaction is now in progress.

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References

1 a) G. A. Molander, *Chem. Rev.*, **92**, 29 (1992). b) G. A. Molander and C. R. Harris, *Chem. Rev.*, **96**, 307 (1996). c) G. A. Molander and C. R. Harris, *Tetrahedron*, **54**, 3321 (1998).
2 a) T. Mukaiyama, H. Arai, and I. Shiina, *Chem. Lett.*, **2000**, 580. b) T. Mukaiyama, K. Pudhom, K. Yamane, and H. Arai, *Bull. Chem. Soc. Jpn.*, **76**, 413 (2003).
3 T. Mukaiyama, Y. Ogawa, and K. Kuroda, *Chem. Lett.*, **33**, 1472 (2004).
4 a) K. Pudhom, H. Arai, K. Yamane, and T. Mukaiyama, *Chem. Lett.*, **2002**, 87. b) J. Matsuo, Y. Ogawa, K. Pudhom, and T. Mukaiyama, *Chem. Lett.*, **33**, 124 (2004). c) Y. Ogawa, K. Kuroda, J. Matsuo, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, in press.
5 Y. Ogawa, K. Kuroda, and T. Mukaiyama, *Chem. Lett.*, **34**, 372 (2005).
6 M. Miyazawa, N. Ishibashi, S. Onhuma, and M. Miyashita, *Tetrahedron Lett.*, **38**, 3419 (1997).
7 Typical experimental procedure is as follows (Table 2, Entry 1): to a mixture of **2** (36.3 mg, 0.133 mmol) and 3-phenylpropanal (26.7 mg, 0.200 mmol) in THF (4 mL) at −78 °C under an argon atmosphere was added a solution of SmI_2 in THF (0.1 M, 3.30 mL, 0.330 mmol). After the reaction mixture was stirred for 30 min at −78 °C, the reaction mixture was quenched with saturated aq ammonium chloride and was diluted with ethyl acetate. It was extracted with ethyl acetate, and the organic layer was washed with brine and dried over anhydrous sodium sulfate. The crude product was obtained after evaporation of the solvent under reduced pressure and purification by thin-layer chromatography afforded *syn*-**2a** (41.2 mg, 76%) and other isomer (5.3 mg, 9.7%).
8 a) K. Suzuki, T. Matsumoto, T. Tomooka, K. Matsumoto, and G. Tsuchihashi, *Chem. Lett.*, **1987**, 113. b) S. Takano, Y. Sekiguchi, and K. Ogawasawara, *Heterocycles*, **33**, 743 (1992).

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