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A novel synthesis of γ-lactones by tandem epoxide opening-cyclization reaction mediated by samarium(II) diiodide

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Abstract

Various epoxy esters readily reacted with SmI_2 (2 equiv) in the presence of ethyl bromoacetate (1 equiv) and HMPA (6 equiv) under mild conditions (THF, −78 °C, 2 h, Ar) providing the corresponding γ-lactones via tandem epoxide opening-cyclization reaction in good to excellent yields.

Keywords: Samarium diiodide; γ-Lactone; γ-Butyrolactone; Tandem reaction

γ-Lactones have attracted much attention in organic and medicinal chemistry due to the extensive occurrence in numerous biologically active natural products,[1] and also versatile utility as synthetic intermediates in the synthesis of a wide range of bioactive compounds.[2] Therefore, a number of new synthetic route for γ-lactones have been reported in recent years,[3] for example, Ni-catalyzed reductive cyanation of alkynols,[3a] selective reaction of aldehydes/ketones with carbene-catalyzed conjugate umpolung of α,β-unsaturated aldehydes,[3b] reaction of alkyl phenyl selenides with *p*-toluenesulfonic acid,[3c] Pd-catalyzed cyclization of unsaturated malonates,[3d] Pd-catalyzed carbonylative cyclization of β-bromovinyl aldehydes,[3e] and diastereoselective osmylation of unsaturated *syn*-aldol adduct with OsO_4/NMO.[3f]

We have recently reported an efficient synthesis of 1,3-dioxolane derivatives from acrylic acid esters bearing an oxiranylmethoxy substituent at β-position utilizing samarium(II) diiodide[4] under mild reaction conditions.[5a] This initial result together with the great importance of γ-lactones in organic and medicinal chemistry prompted us to devise a new synthetic route to γ-lactones based on our samarium diiodide chemistry.[5] We herein wish to report an efficient synthesis of γ-lactone derivatives from epoxy esters (ethyl/methyl α-oxiranylmethylacetate derivatives) via tandem epoxide opening-iodocyclization reaction using SmI_2 as a key reagent under mild conditions (Table 1).

Initial tandem reaction was studied by using appropriate epoxy malonates **2a**–**e**,[6] and optimum reaction conditions involved the addition of SmI_2 (2 equiv) in THF to a solution of substrate **2**, ethyl bromoacetate (1 equiv) and HMPA (6 equiv) in dry THF at −78 °C and stirring the resulting solution at −78 °C for ca. 2 h under Ar. After usual work-up, γ-lactones **3a**–**e** were obtained in 80–85% yields as a mixture (1:1) of diastereomers (runs 1–5).[7] These optimized reaction conditions were successfully extended to a simple epoxy ester **2f** affording γ-lactone **3f** in 90% yield (run 6).

To determine the scope of this new tandem reaction, a diverse set of functionalized epoxy esters (**2h**–**l**) were also tested with SmI_2 under the same reaction conditions (Table 2).

This attempted tandem reaction of **2h**–**j** is important from the synthetic point of view since it enables rapid access to the cis-fused bicyclic γ-lactones (**3h**–**j**), which

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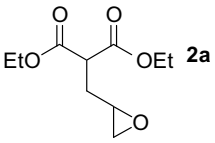
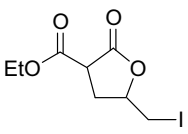
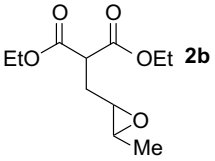
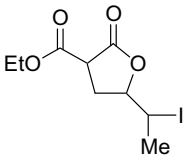
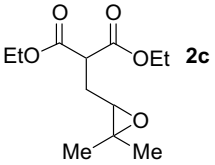
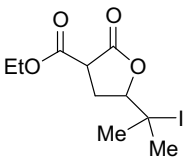
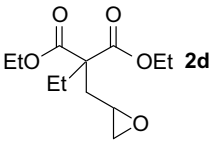
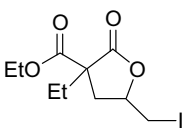
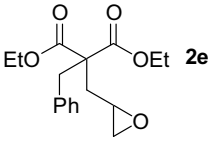
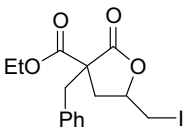
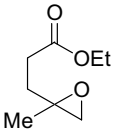
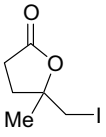
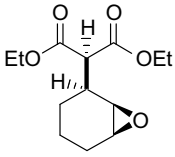
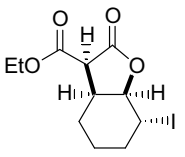
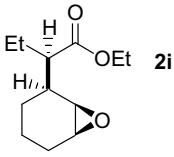
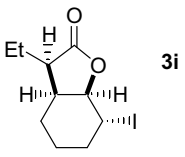
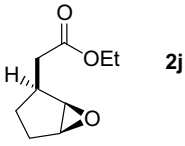
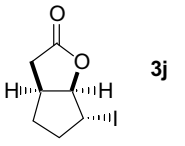
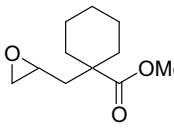
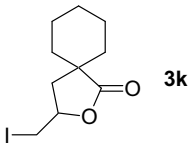
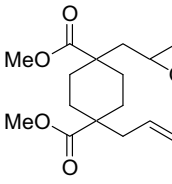
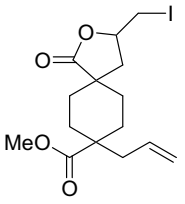
Table 1
Tandem epoxide opening-cyclization of epoxy esters **2** to various γ-lactones **3** mediated by SmI_2[a]

Run	Substrate	Product	Yield[b,c] (%)
1	 **2a**	 **3a**	85[d]
2	 **2b**	 **3b**	82[d]
3	 **2c**	 **3c**	80[d]
4	 **2d**	 **3d**	82[d]
5	 **2e**	 **3e**	83[d]
6	 **2f**	 **3f**	90

[a] Reagents and conditions: **2**, $BrCH_2CO_2Et$ (1 equiv), SmI_2 (2 equiv), HMPA (6 equiv), −78 °C, 2 h, Ar.
[b] Isolated yields after flash column chromatography.
[c] Structures were determined by NMR and mass spectra.
[d] Isolated as a mixture (1:1) of diastereomers by ^1H NMR.

Table 2
Tandem epoxide opening-cyclization of epoxy esters **2** to cis-fused bicyclic and spiro γ-lactones **3** mediated by SmI_2[a]

Run	Substrate	Product	Yield[b,c] (%)
1	 **2h**[d]	 **3h**	85[e,f]
2	 **2i**	 **3i**	81[f,g]
3	 **2j**	 **3j**	84[f,g]
4	 **2k**	 **3k**	91
5	 **2l**	 **3l**	91

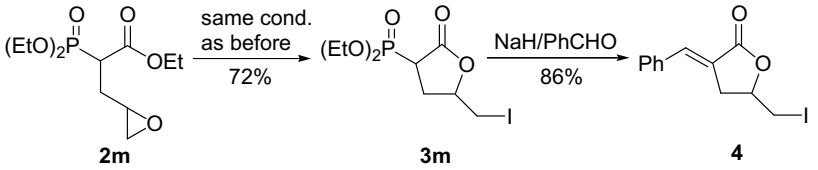
[a] Reagents and conditions: **2**, $BrCH_2CO_2Et$ (1 equiv), SmI_2 (2 equiv), HMPA (6 equiv), −78 °C, 2 h, Ar.
[b] Isolated yields after flash column chromatography.
[c] Structures were determined by NMR and mass spectra.
[d] Used as a mixture (10:1) of diastereomers by ^1H NMR.
[e] Isolated as a mixture (10:1) of diastereomers by ^1H NMR.
[f] Stereochemistry was confirmed by NOE experiment.
[g] ^{13}C NMR indicated that a single diastereomer was formed.

are known to be valuable intermediates for natural product synthesis.[8] Substrate **2h** (a mixture (10:1) of diastereomers by ^1H NMR) afforded a mixture (10:1) of **3h** as a major diastereomer (run 1), while substrates **2i**,**j** gave the corresponding γ-lactones **3i**,**j** as a single diastereomer (runs 2 and 3). The assigned structure and stereochemistry of **3h**–**j** were fully supported by NMR, mass spectra together with NOE experiments. The spiro γ-lactone fragment has proven to be an important subunit in several classes of bioactive compounds.[9] As indicated by runs 4 and 5 in Table 2, substrates **2k**,**l** were transformed cleanly into spiro γ-lactones **3k**,**l** in excellent yields.

The synthesis of α-methylene-γ-lactone derivatives has been of great interest due to their biological activities and occurrence in numerous natural products.[10] Scheme 1 demonstrates an additional benefit of our protocol in the synthesis of α-methylene-γ-lactone derivatives. The SmI_2-mediated tandem reaction of α-phosphoryl epoxy ester **2m** gave α-phosphoryl-γ-lactone **3m** in good yield, which in turn reacted readily with benzaldehyde providing α-methylene-γ-lactone **4** in a concise manner.

The plausible reaction mechanism including stereochemical outcome could be rationalized as shown in Figure 1 using **2j** as a starting material.

The reaction appears to be initiated by the formation of samariumiodide complex **A**. Nucleophilic addition of



Scheme 1. Attempted synthesis of α-methylene-γ-lactone **4**.

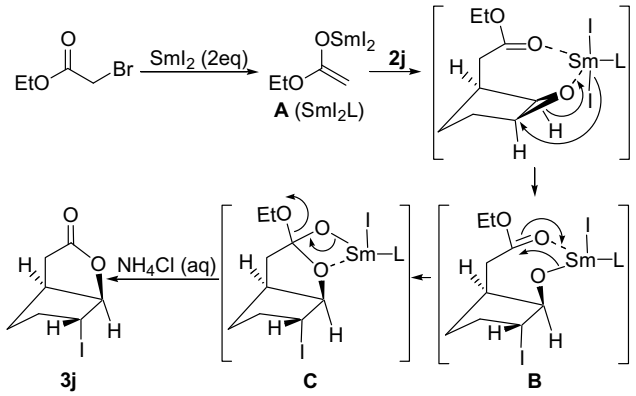


Fig. 1. Plausible reaction mechanism for γ-lactone **3j**.

I^- derived from iodosamarium complex **A** to epoxide **2j**, would deliver an iodohydrin intermediate **B** which, upon hydrolysis, afford **3j** in complete regio- and diastereoselective way.

In conclusion, a novel method for generating γ-lactones from epoxy esters using SmI_2 as a key reagent has been developed. Considering several advantages, for example, easy preparation of starting materials, mild reaction conditions together with good to excellent yields, and furthermore flexibility of this new tandem reaction providing diverse sets of γ-lactones from simple γ-lactones to cis-fused bycyclic/spiro and α-methylene-γ-lactones, this new synthetic route should be a method of choice in the synthesis of various γ-lactone derivatives.

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6. Epoxy esters **2a**–**e** were prepared in two steps via allylation of malonates followed by epoxidation with *m*-CPBA.
7. *Typical synthetic procedure for γ-lactones*: To a precooled (−78 °C) solution of **2a** (0.50 mmol), ethyl bromoacetate (1 equiv) and HMPA (6 equiv) in dry THF (2 mL) was added SmI_2 (2 equiv, 0.1 M solution in THF), and the resulting mixture was stirred at −78 °C for 2 h under Ar. The reaction was quenched by aqueous NH_4Cl solution, and the organic layer was separated. The aqueous layer was extracted with Et_2O (10 mL × 3), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography on SiO_2 using (EtOAc/hexane, 1/3) as an eluent affording pure **3a**. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.22–1.32 (m, 3H), 2.19–2.46 (m, 1H), 2.67–2.80 (m, 1H), 3.26–3.71 (m, 3H), 4.19–4.28 (m, 2H), 4.54–4.69 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 5.7, 7.6, 14.5, 32.7, 47.5, 47.9, 62.8, 62.9, 77.9, 78.1, 167.8, 171.3; HRMS(EI) calcd for $C_8H_{11}IO_4$: 297.9702; found: 297.9713.
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