

## SAMARIUM(II) IODIDE-MEDIATED INTRAMOLECULAR ALDOL-TYPE CYCLIZATION

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Abstract - The  $\alpha$ -substituted  $\alpha,\beta$ -epoxy ketone having a formyl group in the molecule reacted with samarium(II) iodide to afford cyclized spiro ketones formed by an intramolecular aldol-type reaction. However, in the presence of proton source the ratio of spiro products decreased and the yield of hydrindanone increased. The  $\alpha$ -substituted  $\alpha,\beta$ -unsaturated cyclopentenone derivative smoothly cyclized into the same hydrindanone.

The development of synthetic reaction for C-C bond formation is important in organic synthesis. We have been interested in developing a new C-C bond formation reaction using a radical process, electrolysis<sup>1</sup> and/or  $\text{SmI}_2$ .<sup>2</sup> Previously, we reported cyclization of  $\alpha,\beta$ -unsaturated cyclopentenones with formyl groups to hydrindanones using  $\text{SmI}_2$ .<sup>3</sup> The stereochemistries of hydrindanones depend on the conditions with/without the proton source and/or HMPA. Thus *cis* or *trans* stereochemistry of the products can now be predicted.<sup>3</sup> A variety of regio- and stereoselective reductive coupling reactions using  $\text{SmI}_2$  have been widely used for synthesis of natural products and many reviews on this matter have appeared.<sup>4</sup> It is known that  $\alpha,\beta$ -epoxy ketone is reduced by  $\text{SmI}_2$  to form  $\beta$ -hydroxy ketones in good yield.<sup>5</sup> The radical-type C-C bond formation by sequential epoxide fragmentation/radical cyclizations mediated by  $\text{SmI}_2$  has been reported by Molander *et al.*<sup>6</sup> The aldol-type C-C bond formation reaction of  $\alpha,\beta$ -epoxy ketone using  $\text{SmI}_2$  in excellent yield and selectivity has been recently reported by Mukaiyama *et al.*<sup>7</sup> This prompted us to report our recent results of aldol reactions mediated by  $\text{SmI}_2$ . The  $\alpha$ -substituted  $\alpha,\beta$ -epoxy ketone having a formyl group in the molecule reacted with  $\text{SmI}_2$  to afford cyclized spiro ketones formed by an intramolecular aldol-type reaction.

The epoxide (**1**) (mixture of diastereoisomers, 3:2)<sup>8</sup> was first treated with  $\text{SmI}_2$  in THF at 0°C for 1 h to yield three products (**2**, **3**, and **4**) in the ratio of 47:27:26 in 89% yield (Table 1, entry 1). The ratio was determined by GC-MS. Because compound (**2**) gave crystals, the X-Ray analysis was carried out to establish the spiro structure.<sup>9</sup> As epoxide (**1**) was a mixture of diastereoisomers,<sup>8</sup> spiro product (**2**) must

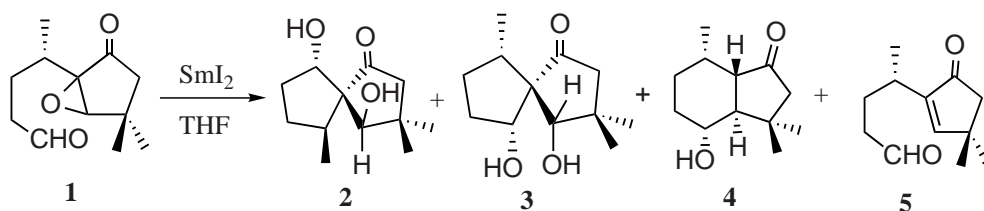


Table 1. Results of the reaction of **1** with  $\text{SmI}_2$ .<sup>a</sup>

entry	$\text{SmI}_2$ (eq)	additive (eq)	temp ( $^{\circ}\text{C}$ )	time (h)	yields (%) ( <b>2:3:4:5</b> ) <sup>b</sup>
1	12.0	—	0	1	89 (47:27:26:0)
2	6.0	MeOH (10)	0	0.5	62 (5:40:55:0)
3	8.0	MeOH (10)	-78	1	53 (0:24:38:38)

<sup>a</sup> The reaction was carried out in THF.

<sup>b</sup> Yields are isolation yields and ratios of products were determined by GC-MS.

have been derived from the  $\beta$ -epoxide. The  $^1\text{H}$  NMR and IR spectra of the second product (**3**) showed the presence of two methine protons at  $\delta$  3.85 (1H, s) and 4.52 (1H, dd,  $J=8.0, 5.2$  Hz) bearing hydroxyl groups ( $3300\text{ cm}^{-1}$ ).<sup>10</sup> The  $^1\text{H}$  NMR spectrum of **3** is very similar to that of **2**, indicating that these are isomers each other. The 2D NMR analysis established the stereostructure of **3** as depicted in the formula.<sup>11</sup> This compound must be derived from the  $\alpha$ -epoxide of **1**. Compound (**4**) showed the presence of a hydroxyl ( $3450\text{ cm}^{-1}$ ) and a carbonyl ( $1730\text{ cm}^{-1}$ ) group as well as three methyl groups in the IR and  $^1\text{H}$  NMR spectra. The 2D NMR analysis established the stereostructure of **4** to be a *trans*-hydrindanone as depicted in the formula.<sup>11</sup> In entry 2, MeOH was added as a proton source and the products were **2**, **3**, and **4** in the ratio of 5:40:55 in 62% yield. However, at  $-78^{\circ}\text{C}$  the rate of the reaction was slowed down and the yield dropped to 53% (entry 3). Moreover the fourth product (**5**) was obtained and compound (**2**) was not formed.

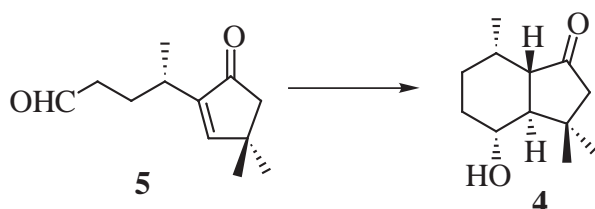


Table 2. Results of the reaction of **5** with  $\text{SmI}_2$ .<sup>a</sup>

entry	$\text{SmI}_2$ (eq)	additive(eq)	temp ( $^{\circ}\text{C}$ )	time (h)	yield (%) of <b>4</b> <sup>b</sup>
1	3	HMPA(5)	0	0.5	27
2	6	MeOH(5)	0	1.25	25

<sup>a</sup> The reaction was carried out in THF.

<sup>b</sup> Yields are isolation yields.

Then, a keto aldehyde (**5**) was treated with  $\text{SmI}_2$  in THF in the presence of HMPA to give a hydrindanone (**4**) as a sole product (Table 2, entry 1). When MeOH was added to the reaction mixture as a proton source, the same product (**4**) was obtained in 25% yield (entry 2).<sup>12</sup>

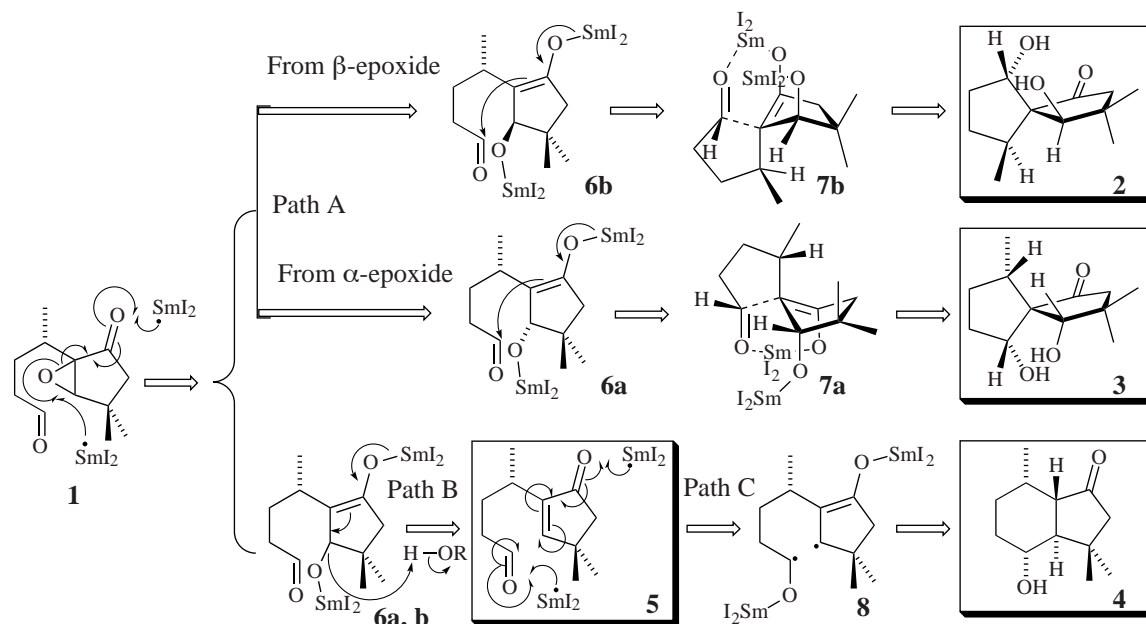


Figure 1. Proposed reaction mechanism.

These results suggest the possible reaction mechanism as shown in Figure 1. As Molander<sup>5</sup> and Mukaiyama *et al.*<sup>7</sup> pointed out, this reaction must proceed *via* samarium enolate like **6a, b** (Figure 1),<sup>12</sup> which attacks the formyl group to yield bis-aldols (**2**) and (**3**) *via* intermediates (**7b**) and (**7a**), respectively. While in the case of **5**, the radical at the  $\beta$ -position of the carbonyl group attacked the formyl group to afford the hydrindanone (**4**).

In conclusion, compound (**1**) gives **2** or **3** *via* path A (intramolecular aldol-type cyclization) and **4** *via* path B and C. In contrast to the epoxide (**1**), compound (**5**) affords **4** *via* path C. This is the first example of intramolecular aldol-type reaction mediated by  $\text{SmI}_2$  to yield spiro systems.

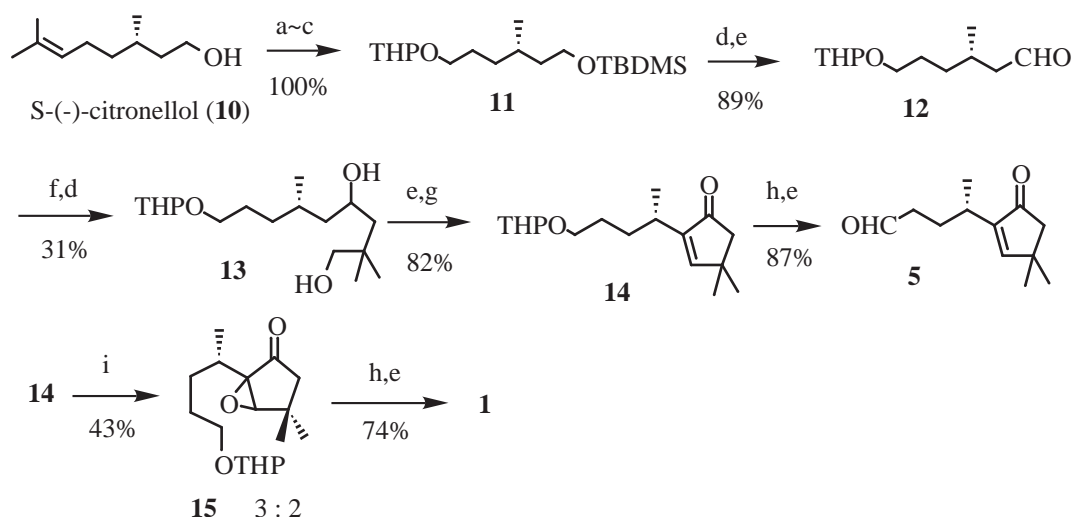
## ACKNOWLEDGMENTS

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## REFERENCES AND NOTES

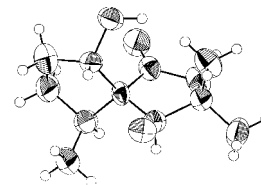
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 8. Compounds (**1**) and (**5**) were prepared from **10** as shown below. Epoxides **15** and **1** were not separated after several trials, and the stereochemistries could not be determined.



(a) TBDMSCl, Et<sub>3</sub>N; (b) O<sub>3</sub>; then NaBH<sub>4</sub>; (c) DHP, PPTS, CH<sub>2</sub>Cl<sub>2</sub>; (d) TBAF, THF, rt, 1 h; (e) Swern oxid; (f) TBDMSOCH<sub>2</sub>CMe<sub>2</sub>CH<sub>2</sub>MgBr, THF, rt; (g) 5% KOH, THF, 70°C; (h) TsOH, MeOH-H<sub>2</sub>O, rt; (i) 4M NaOH, H<sub>2</sub>O<sub>2</sub>, MeOH, rt

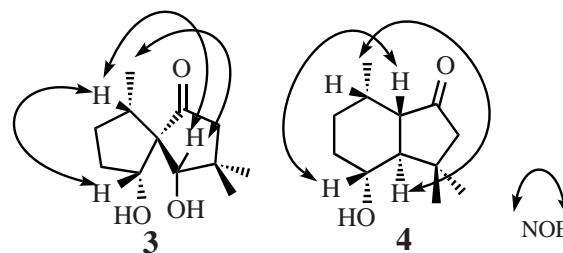
9. X-Ray data of **2** : Mr=218.00, Monoclinic, *P*2<sub>1</sub>, *a*=10.902(3), *b*=6.370(2), *c*=9.389(2),  $\beta$ =114.25(2)°, *V*=594.5(3) Å<sup>3</sup>, *Z*=2, *D*<sub>x</sub>=1.217 Mg m<sup>-3</sup>, *D*<sub>m</sub>=1.200 Mg m<sup>-3</sup>, *R*=0.054, 509 observed reflections.



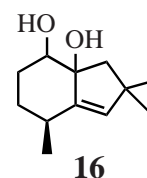
ORTEP drawing of compound (**2**).

10. **3**: IR: 3300, 1730cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>OD) δ 0.91 (3H, d, *J*= 6.9), 1.08 (3H, s), 1.19 (3H, s), 1.69 (2H, m), 1.82 (1H, m), 1.91 (2H, m), 1.95 (1H, d, *J*=18), 2.15 (1H, d, *J*=18), 3.85 (1H, s), 4.52 (1H, dd, *J*=8.0, 5.2); <sup>13</sup>C NMR (50 MHz, CD<sub>3</sub>OD) δ 15.0 (CH<sub>3</sub>), 21.5 (CH<sub>3</sub>), 28.6 (CH<sub>3</sub>), 31.4 (CH<sub>2</sub>), 34.9 (CH<sub>2</sub>), 39.1 (C), 44.1 (CH), 55.6 (CH<sub>2</sub>), 66.7 (C), 75.0 (CH), 82.7 (CH), 220.0 (CO); MS (CI) *m/z* 213 (M+H)<sup>+</sup>, 195 (base); HRMS (CI) *m/z* 213.1519 (M+H)<sup>+</sup> C<sub>12</sub>H<sub>21</sub>O<sub>3</sub> requires 213.1491.

11. The stereochemistries of **3** and **4** were determined by NOESY spectra (the observed NOE's were shown).



12. In this reaction, compound (**16**) was not formed. This is due to the fact that the reduction potential of the carbonyl group is higher than that of the enone system.



**16**