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

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Abstract—The α-substituted α,β-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 α-substituted α,β-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[1] and/or SmI_2.[2] Previously, we reported cyclization of α,β-unsaturated cyclopentenones with formyl groups to hydrindanones using SmI_2.[3] 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.[3] A variety of regio- and stereoselective reductive coupling reactions using SmI_2 have been widely used for synthesis of natural products and many reviews on this matter have appeared.[4] It is known that α, β-epoxy ketone is reduced by SmI_2 to form β-hydroxy ketones in good yield.[5] The radical-type C-C bond formation by sequential epoxide fragmentation/radical cyclizations mediated by SmI_2 has been reported by Molander *et al.*[6] The aldol-type C-C bond formation reaction of α, β-epoxy ketone using SmI_2 in excellent yield and selectivity has been recently reported by Mukaiyama *et al*.[7] This prompted us to report our recent results of aldol reactions mediated by SmI_2. The α-substituted α,β-epoxy ketone having a formyl group in the molecule reacted with SmI_2 to afford cyclized spiro ketones formed by an intramolecular aldol-type reaction.

The epoxide (**1**) (mixture of diastereoisomers, 3:2)[8] was first treated with 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.[9] As epoxide (**1**) was a mixture of diastereoisomers,[8] spiro product (**2**) must

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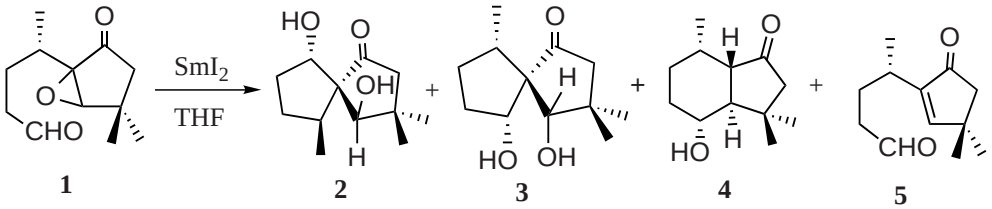
This paper is dedicated to Professor Shô Itô on the occasion of his 77th birthday.



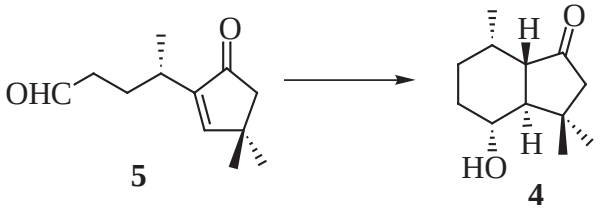
1 **2** **3** **4** **5**

Table 1. Results of the reaction of **1** with SmI_2.[a]

entry	SmI_2 (eq)	additive (eq)	temp (˚C)	time (h)	yields (%) (**2**:**3**:**4**:**5**)[b]
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)

[a] The reaction was carried out in THF.
[b] Yields are isolation yields and ratios of products were determined by GC-MS.

have been derived from the β-epoxide. The ^{1}H NMR and IR spectra of the second product (**3**) showed the presence of two methine protons at δ 3.85 (1H, s) and 4.52 (1H, dd, J=8.0, 5.2 Hz) bearing hydroxyl groups (3300 cm^{-1}).[10] The ^{1}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.[11] This compound must be derived from the α-epoxide of **1**. Compound (**4**) showed the presence of a hydroxyl (3450 cm^{-1}) and a carbonyl (1730 cm^{-1}) group as well as three methyl groups in the IR and ^{1}H NMR spectra. The 2D NMR analysis established the stereostructure of **4** to be a *trans*-hydrindanone as depicted in the formula.[11] 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˚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.



5 **4**

Table 2. Results of the reaction of **5** with SmI_2.[a]

entry	SmI_2 (eq)	additive(eq)	temp (˚C)	time (h)	yield (%) of **4**[b]
1	3	HMPA(5)	0	0.5	27
2	6	MeOH(5)	0	1.25	25

[a] The reaction was carried out in THF.
[b] Yields are isolation yields.

Then, a keto aldehyde (**5**) was treated with 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).[12]

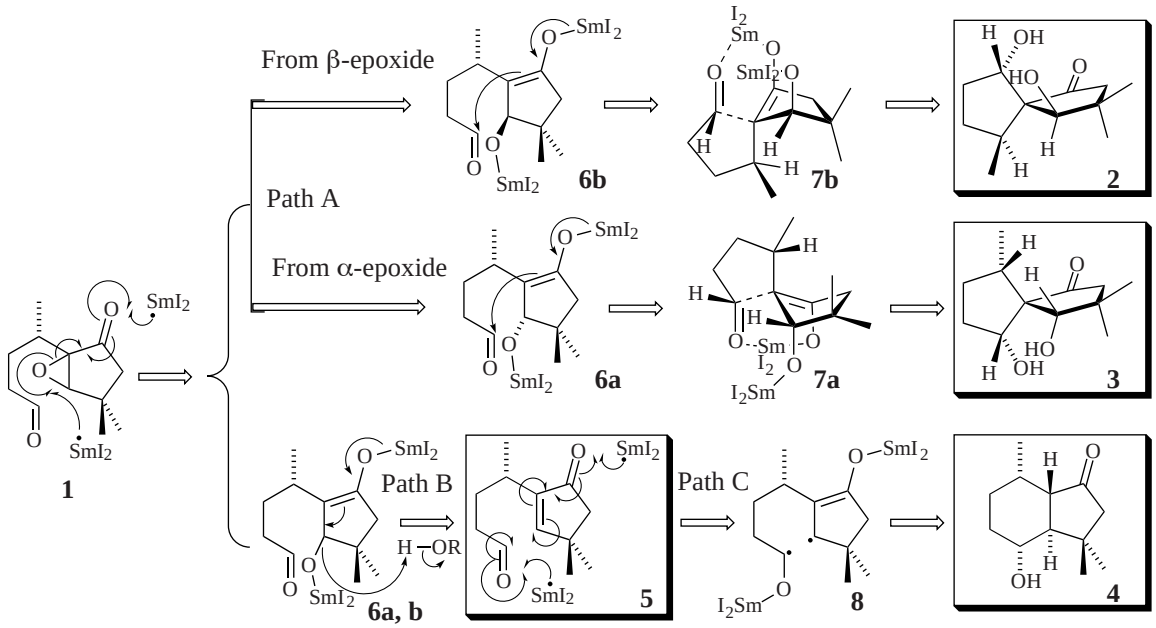


Figure 1. Proposed reaction mechanism.

These results suggest the possible reaction mechanism as shown in Figure 1. As Molander[5] and Mukaiyama *et al*.[7] pointed out, this reaction must proceed *via* samarium enolate like **6a**, **b** (Figure 1),[12] 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 β-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 SmI_2 to yield spiro systems.

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6 (a) G. A. Molander and C. d. P. Losada, *Tetrahedron*, 1998, **54**, 5819. (b) G. A. Molander and C. d. P. Losada, *J. Org. Chem.*, 1997, **62**, 2935.
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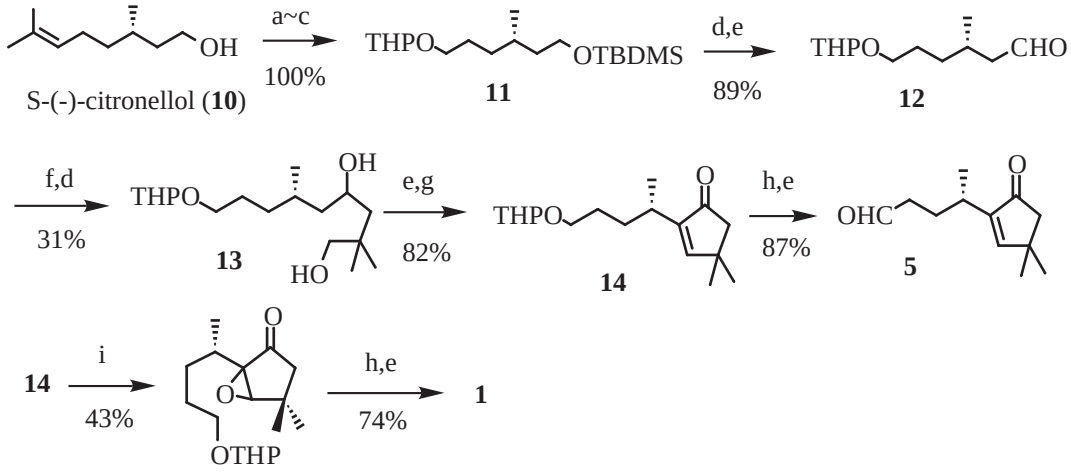
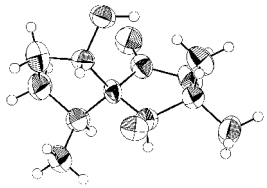
8. Compounds (**1**) and (**5**) were prepared from **10** as shown below. Epoxides **15** and **1** were not separated after several trials, and the stereochemistries could not be determined.



(a) TBDMSCl , Et_3N ; (b) O_3; then $NaBH_4$; (c) DHP, PPTS , CH_2Cl_2 ; (d) TBAF, THF, rt , 1 h; (e) Swern oxid; (f) $TBDMSOCH_2CMe_2CH_2MgBr$, THF, rt; (g) 5%KOH, THF, 70˚C; (h) TsOH, MeOH-H_2O, rt; (i) 4M NaOH, H_2O_2, MeOH, rt

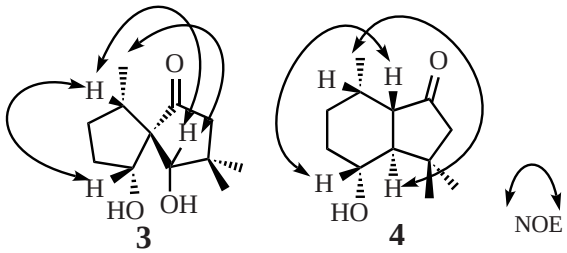
9. X-Ray data of **2** : Mr=218.00, Monoclinic, $P2_1$, a=10.902(3), b=6.370(2), c=9.389(2)Å, β=114.25(2)˚, V=594.5(3) $Å^3$, Z=2, Dx=1.217 Mg m^{-3}, Dm=1.200 Mg m^{-3}, R=0.054, 509 observed reflections.



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

10. **3**: IR: 3300, 1730cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD) 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); ^{13}C NMR (50 MHz, CD_3OD) δ 15.0 (CH_3), 21.5 (CH_3), 28.6 (CH_3), 31.4 (CH_2), 34.9 (CH_2), 39.1 (C), 44.1 (CH), 55.6 (CH_2), 66.7 (C), 75.0 (CH), 82.7 (CH), 220.0 (CO); MS (CI) *m/z* 213 $(M+H)^+$, 195 (base); HRMS (CI) *m/z* 213.1519 $(M+H)^+$ $C_{12}H_{21}O_3$ 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.