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Regioselective cleavage of the cyclic ethereal bond of 7-oxabicyclo[2.2.1]heptane derivatives mediated by samarium(II) iodide

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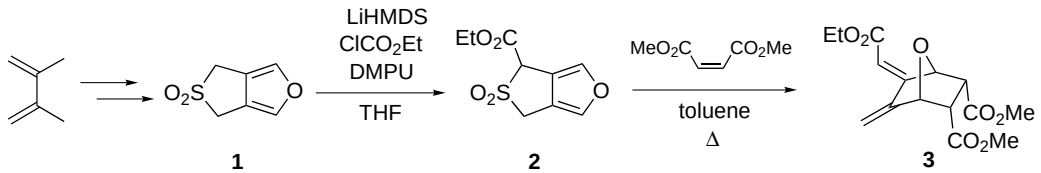
Abstract—It was established that exclusively high regioselective C–O bond cleavage of 7-oxabicyclo[2.2.1]heptane skeletons, which are unique Diels–Alder products of furans, under mild conditions using samarium(II) iodide and samarium powder yields cyclohexanol derivatives or aromatic compounds. © 2001 Elsevier Science Ltd. All rights reserved.

7-Oxabicyclo[2.2.1]heptane derivatives, which can be readily prepared by Diels–Alder reactions with furans, are very useful compounds for stereoselective synthesis of natural products bearing multisubstituted cyclohexanol units after regioselective cleavage of the ethereal C–O bond. However, in general, little or no regioselectivity in the C–O bond cleavage reactions was observed under nucleophilic conditions.[1,2] Most of these examples utilize nucleophiles such as metal hydrides, alkyllithiums, Grignard reagents and cuprates, which limit application to non-multifunctional compounds.

On the other hand, we have developed the chemistry of furan-annulated sulfolene **1** and its derivatives.[3] These compounds behave as dienes in Diels–Alder reactions and 3,4-dimethylenefuran synthons due to the smooth cheletropic elimination of sulfur dioxide after cycloadditions.[4] Thus, we planned the regioselective cleavage of the ethereal bond of Diels–Alder adduct **3** derived from furan-annulated sulfolene **2**, since the ring opening product would be an important key compound for the synthesis of natural products such as vitamin D analogues (Scheme 1).[4e]

Diels–Alder adducts such as **3** bearing a carbonyl moiety cannot be treated by DIBAL-H and Grignard reagents for C–O bond cleavage reactions, and since usual reductions with samarium(II) iodide proceed under mild and neutral conditions, we considered samarium(II) iodide to be a suitable reagent to open the ethereal rings. It has been reported that the reductive C–O bond cleavage can occur at the α-position to carbonyls or the γ-position to α,β-unsaturated carbonyls by samarium(II) iodide.[5] It is worth noting that not only alkoxycarbonyl groups but also alkoxy groups can be eliminated by divalent samarium. Substrate **3** bearing an α,β-unsaturated ester moiety may be suitable for samarium(II)-mediated reductive elimination to cleave C–O bond regiospecifically at the γ-position. However, it can be predicted that the ring opening of bicyclic ether **3** is difficult because of stereoelectronic effects described later. There have only been a few



Scheme 1.

Keywords: samarium and compounds; cleavage reactions; regiocontrol; Diels–Alder reactions; furans; sulfur heterocycles.

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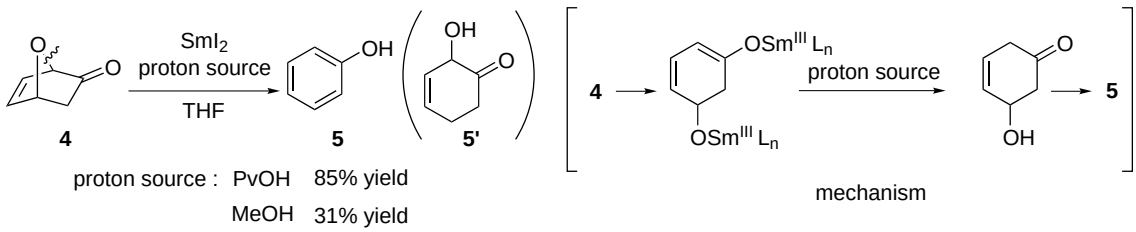
reports on the samarium(II)-mediated ring opening reaction of cyclic ethers,[6] and there have been no reports on the C–O bond cleavage of the substrates such as **3** with a rigid conformation. In this study, we first investigated the ring opening reactions of 7-oxabicyclo[2.2.1]hept-5-en-2-one (**4**),[7] which is more reactive than **3**, using a combination of samarium(II) iodide and various proton sources as preliminary experiments.

The reaction was carried out by adding a SmI_2 (2.2 equiv.) solution in THF[8] to a THF solution of **4** in the presence of a proton source (2.2 equiv.) such as methanol. Surprisingly, phenol (**5**) was obtained exclusively (Scheme 2). We speculated that this compound **5** was produced through a dehydration–aromatization process after cleavage of the C–O bond at the α-position of ketone **4**. No opposite C–O bond cleavage product **5′** was observed. Pivalic acid as a proton source gave **5** in a higher yield than methanol. This can be an efficient synthetic method of multisubstituted phenols, when multisubstituted substrates, prepared by Diels–Alder reactions of multisubstituted furans with ketene equivalents, are used instead of **4**.

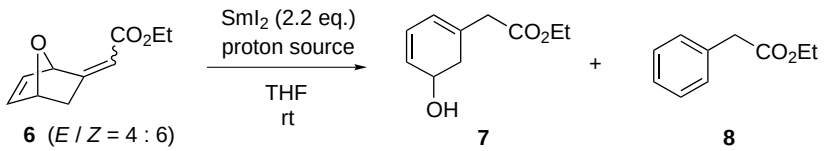
Next, we investigated the reductive ring opening of α,β-unsaturated ester **6** ($E/Z=4:6$) prepared from ketone **4** via a Horner–Wadsworth–Emmons reaction. The results are summarized in Table 1. In entry 1, the ring opening product **7** was obtained through C–O bond cleavage at the γ-position followed by kinetic protonation at the α-position of the resultant trienolate intermediate, though in a low yield. Starting material **6** was recovered in a relatively high percentage. Other entries gave phenylacetate **8** via dehydration (aromatization) after the formation of **7** along with the recovery of **6**. The addition of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), which was often used as a Lewis base instead of HMPA, to the reaction system was inefficient (entry 3).

To prevent the ring opening product from aromatization, we prepared the bicyclic saturated substrate **9** by hydrogenation of **4** followed by carboxyolefination, and then carried out the samarium(II)-mediated reactions under various conditions (Table 2). All entries gave β,γ-unsaturated ester **10** through regiospecific ring opening followed by kinetic protonation at the α-position of dienolate intermediate. Using weak acid such as methanol and ethylene glycol, **10** was obtained in low yields along with recovery of the starting **9** (entries 1–3). Although strong acid such as trifluoroacetic acid (TFA)[9] or trifluoromethanesulfonic acid (TfOH) was used to achieve higher yields, the isolated yields were up to 33% (in entries 4–6). A strong Lewis base DMPU as an additive was also ineffective (entry 5). The addition of $Sm(OTf)_3$ as a Lewis acid, which could activate ethereal oxygen, was ineffective (entry 7). However, zero valent samarium powder was extremely effective to give **10** in a higher yield (entry 8).[10] A SmI_2–Sm system was effective because it had a stronger reducing ability



Scheme 2.

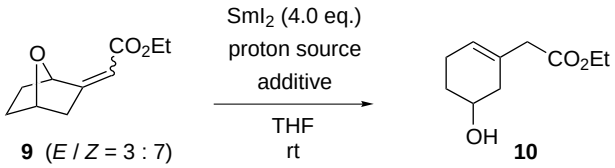
Table 1. Ring opening-aromatization reactions by samarium(II) iodide



Entry	Proton source	Yield (%)		
		7[a]	**8**[a]	**6** (recovery)
1	MeOH (2.2 equiv.)	16 (63)	(Trace)	74
2	PvOH (2.2 equiv.)	–	6 (21)	76
3[b]	MeOH (2.2 equiv.)	–	(Trace)	81
4[c]	MeOH (2.2 equiv.)	–	37 (69)	46
5	MeOH (4.4 equiv.)	–	14 (17)	17
6	MeOH (4.4 equiv.)	–	6 (12)	47
7	$(CH_2OH)_2$ (2.2 equiv.)	–	27 (65)	59

[a] Values in parentheses were conversion yields (%).
[b] DMPU (8.8 equiv.) was added.
[c] SmI_2 (4.4 equiv.) was used.

Table 2. Ring opening reactions by samarium(II) iodide



9 (E / Z = 3 : 7) **10**

Entry	Proton source	Additive	Yield (%)	
			10[a]	**9** (recovery)
1	MeOH (4.4 equiv.)	–	11 (100)	89
2	$(CH_2OH)_2$ (2.2 equiv.)	–	11 (100)	89
3[b]	$(CH_2OH)_2$ (4.4 equiv.)	–	22 (100)	78
4[b]	TFA (4.4 equiv.)	–	24 (81)[c]	71
5	TFA (4.4 equiv.)	DMPU (16 equiv.)	15 (67)[c]	78
6	TfOH (4.4 equiv.)	–	33 (90)[c]	64
7	TfOH (4.4 equiv.)	$Sm(OTf)_3$ (0.5 equiv.)	31 (100)[c]	69
8	TfOH (4.0 equiv.)	Sm (4.0 equiv.)	65[c]	–

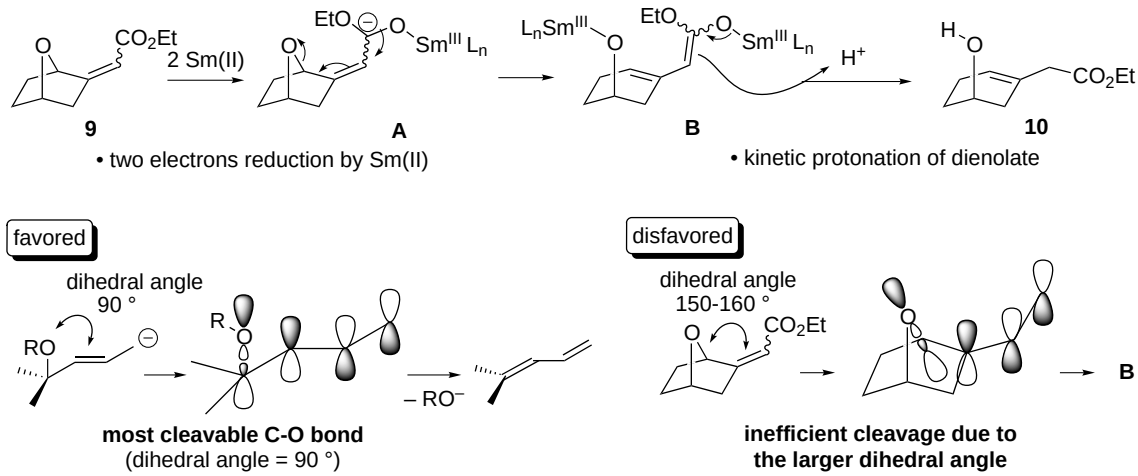
[a] Values in parentheses were conversion yields (%).
[b] The reaction was performed at 40°C.
[c] THF-polymerization product was also obtained as a by-product.

than SmI_2 and because of the regeneration of low valent samarium from Sm(III) reduced by Sm(0).[10]

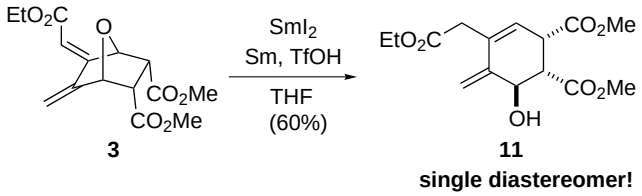
The reason for the low yields except for entry 8 is due to the stereoelectronic effect (Scheme 3). C–O bond cleavage is considered to readily occur if the direction of the C–O bond is fixed perpendicularly to the olefinic plane because of the resulting new C–C π-bond formation. However, according to MM2 calculations, the dihedral angle of bicyclic substrate **9** was estimated to be between 150 and 160°. Thus, the ring opening of the 7-oxabicyclo[2.2.1]heptane derivative is difficult to achieve and it is an important point that our SmI_2–Sm system overcomes this problem. The reaction was considered to proceed mainly through a stepwise mechanism.

Finally, we investigated the ring opening of multifunctional substrate **3** derived from furan-annulated sulfolene **1**. As expected, multisubstituted cyclohexanol derivatives **11** was obtained as a single diastereomer (Scheme 4).[11] An application of stereoselective synthesis for an A-ring moiety of vitamin D analogues is currently underway in our laboratory.

In summary, we have developed an efficient synthetic route to multisubstituted cyclohexanols and aromatic compounds by samarium(II)-mediated ring opening reactions of 7-oxabicyclo[2.2.1]heptane derivatives. This is the first example of regiospecific cleavage of the C–O bond of 7-oxabicyclo[2.2.1]heptane derivatives bearing the carbonyl function.



Scheme 3.



Scheme 4.

Acknowledgements

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References

1. Review: Woo, S.; Keay, B. A. *Synthesis* **1996**, 669–686.
2. Recent example: Lautens, M.; Renaud, J.-L.; Hiebert, S. *J. Am. Chem. Soc.* **2000**, *122*, 1804–1805 and references cited therein.
3. Review: Ando, K.; Takayama, H. *Heterocycles* **1994**, *37*, 1417–1439.
4. (a) Suzuki, T.; Kubomura, K.; Fuchii, H.; Takayama, H. *J. Chem. Soc., Chem. Commun.* **1990**, 1687–1689; (b) Suzuki, T.; Kubomura, K.; Takayama, H. *Chem. Pharm. Bull.* **1991**, *39*, 2164–2166; (c) Ando, K.; Akadegawa, N.; Takayama, H. *J. Chem. Soc., Chem. Commun.* **1991**, 1765–1767; (d) Ando, K.; Akadegawa, N.; Takayama, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2263–2268; (e) Ando, K.; Hatano, C.; Akadegawa, N.; Shigihara, A.; Takayama, H. *J. Chem. Soc., Chem. Commun.* **1992**, 870–873; (f) Hayashi, T.; Kawanami, Y.; Konno, K.; Takayama, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2387–2388; (g) Konno, K.; Sagara, S.; Takayama, H. *Heterocycles* **1994**, *39*, 51–54; (h) Konno, K.; Maki, S.; Sagara, S.; Takayama, H. *Tetrahedron Lett.* **1995**, *36*, 1865–1866.
5. Reviews: (a) Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *42*, 6573–6614; (b) Inanaga, J. *J. Synth. Org. Chem. Jpn.* **1989**, *47*, 200–211; (c) Molander, G. A. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, pp. 251–282; (d) Molander, G. A. *Org. React.* **1994**, *46*, 211–367; Related to our reports: (e) Mikami, K.; Yoshida, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *109*, 892–894; (f) Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Yamaoka, M.; Yoshida, A.; Mikami, K. *Tetrahedron Lett.* **1997**, *38*, 2709–2712; (g) Yoshida, A.; Mikami, K. *Synlett* **1997**, 1375–1376; (h) Yoshida, A.; Hanamoto, T.; Inanaga, J.; Mikami, K. *Tetrahedron Lett.* **1998**, *39*, 1777–1780; (i) Mikami, K.; Yamaoka, M.; Yoshida, A.; Nakamura, Y.; Takeuchi, S.; Ohgo, Y. *Synlett* **1998**, 607–608; (j) Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Yamaoka, M.; Yoshida, A.; Mikami, K. *Tetrahedron* **1999**, *55*, 4595–4620.
6. Ring opening of tetrahydrofuranones is quite hard, see: (a) Linderman, R. J.; Cusack, K. P.; Kwochka, W. R. *Tetrahedron Lett.* **1994**, *35*, 1477–1480; ring opening of tetrahydropyrans bearing ketones on the side chain: (b) Enholm, E. J.; Schreier, J. A. *J. Org. Chem.* **1995**, *60*, 1110–1111.
7. Vieira, E.; Vogel, P. *Helv. Chim. Acta* **1982**, *65*, 1700–1706; **1983**, *66*, 1865–1871.
8. Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698.
9. SmI_2–TFA system: Studer, A.; Curran, D. P. *Synlett* **1996**, 255–257.
10. SmI_2–Sm system: (a) Ogawa, A.; Takami, N.; Sekiguchi, M.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992**, *114*, 8729–8730; (b) Ogawa, A.; Nanke, T.; Takami, N.; Sumino, Y.; Ryu, I.; Sonoda, N. *Chem. Lett.* **1994**, 379–380; (c) Murakami, M.; Hayashi, M.; Ito, Y. *Synlett* **1994**, 179–180.
11. Typical experimental method is as follows: To a solution of **3** (30 mg, 0.1 mmol) in THF (1 mL) were added TfOH (35 μL, 0.4 mmol), Sm powder (58 mg, 0.4 mmol), and then a 0.1 M solution of SmI_2 in THF (4 mL, 0.4 mmol) at room temperature under an argon atmosphere. After stirring until the color of the reaction mixture turned from blue-green into yellow, the reaction mixture was poured into sat. $NaHCO_3$. Usual work-up followed by silica gel column chromatography gave product **11** (16 mg, 60%).