Unexpected Formation of a [2+2] Cycloaddition Product from Reaction of Methyl 7-Oxabicyclo[2.2.1]hept-2-en-2-carboxylate with a Samarium(II) Reagent

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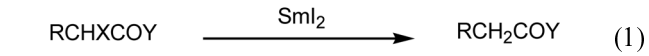
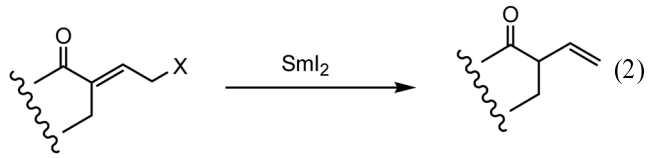
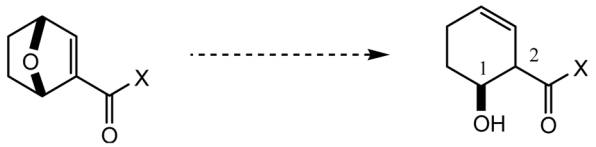
Efficient preparation of functionalized cyclic compounds is one of the main themes in organic synthesis. This is ascribed to the fact that there are many natural products and biological molecules that possess substituted ring structures. Diels-Alder reaction is a good route to construct six-membered ring structures and therefore, we have been interested in utilizing the Diels-Alder adducts to prepare functionalized cyclohexanes.[1] We have also studied the samarium(II) iodide-mediated reactions. One of the efficient reactions mediated by this important one-electron transfer reagent is the reductive cleavage of α-heterosubstituted carbonyl compounds and related substrates shown in the following equation (Eq. 1).[2]



X=OH, OR, O_2CR, halide, $OSiR_3$, OSO_2Ar, SAr, S(O)Ar, $OP(O)(OR)_2$
Y= R, OR

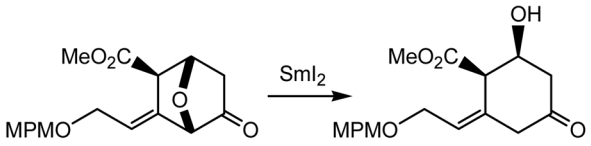


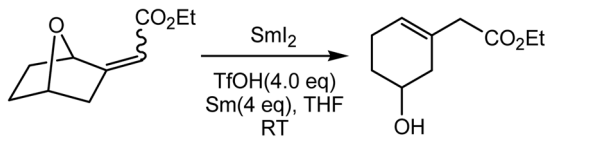
This reaction (elimination of α-heteroatom in carbonyl compounds) can be applicable to carbonyl groups and nitriles containing heteroatoms at the α-position. Furthermore, this samarium(II) iodide-mediated reaction can be extended to vinylogous derivatives and as results, β,γ-unsaturation can be achieved shown in equation 2. We previously utilized this reaction to prepare 3-alkyldenecepham-4-carboxylic acid derivatives.[3] It occurred us that this overall deconjuation reaction could be used for preparing functionalized cyclohexanes, which is summarized in the following scheme.



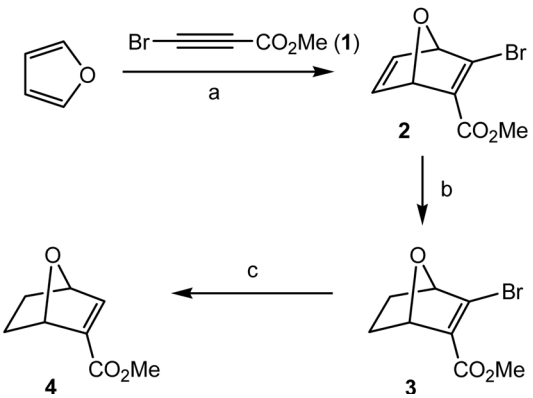
Scheme 1

Literature survey reveals that the similar and related transformations have been reported previously (eq. 3 and 4).[4,5] Also, preparation of the functionalized six-membered ring system by cleavage of carbon-oxygen bond in oxabicyclo-[2.2.1]heptanes with oragnometallic reagents has been studied extensively by Lautens and co-workers.[6] Therefore, it would be interesting to investigate the transformation shown in Scheme 1 to introduce the hydroxyl group to cyclohexane rings with creation of a new stereogenic center at the C-2 position. The double bond could be used for the further elaboration of the ring. Here, we wish to report our results according to this line of research.





The substrate for ring opening (Scheme 1) by samarium-(II) iodide could be obtained by a synthetic route utilizing Diels-Alder reactions (Scheme 2). Furan was reacted with



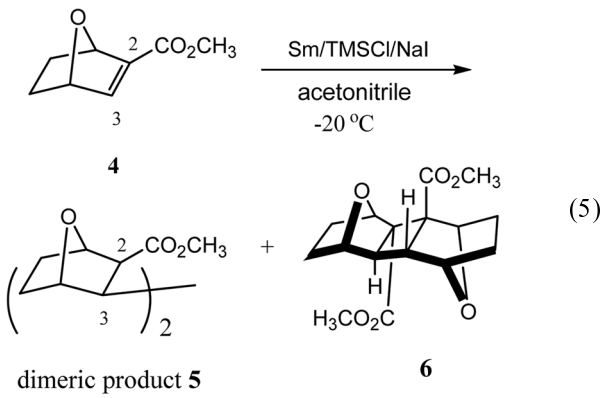
Scheme 2. a) Benzene, 80 °C, 24 h (25%) b) H_2, Pd/C (83%) c) Zn/HOAc, H_2O (85%)

methyl 3-bromopropiolate (**1**)[7] in benzene to produce the Diels-Alder product (**2**).[8] Selective reduction of electron rich C-C double bond was achieved by catalytic hydrogenation followed by treatment with zinc in acetic acid to offer ester **4** that is the desired substrate for the samarium(II) iodide-mediated reaction.

The ester **4** was treated with samarium(II) iodide which was generated from the reaction of Sm metal and CH_2I_2 in THF. No product was observed from the reaction in THF with or without addition of HMPA. However, reaction with a samarium(II) reagent in acetonitrile ($Sm/Me_3SiCl/NaI$)[9] provided two products. Mass spectra revealed that molecular weights of less polar (**5**) and more polar (**6**) compounds (according to R_f values) were 310 (yield = 34%) and 308 (yield = 48%), respectively. Obviously, neither of these products was the expected ring-opened compound. With NMR and MS analyses the less polar product (MW = 310) was likely to be formed by dimerization. When we performed the reaction at −20 °C the highest yield was obtained.

Identity of the more polar compound (MW = 308) was not obvious by NMR and MS analysis. Structural assignment of **6** was achieved by X-ray diffraction (Fig. 1). Surprisingly, the product was formed apparently by a [2+2] cycloaddditon.

Based upon the molecular weight and (both ^1H and ^{13}C) NMR data the less polar compound is formed most likely by dimerization at the β-position. Formation of the dimerization



(5)

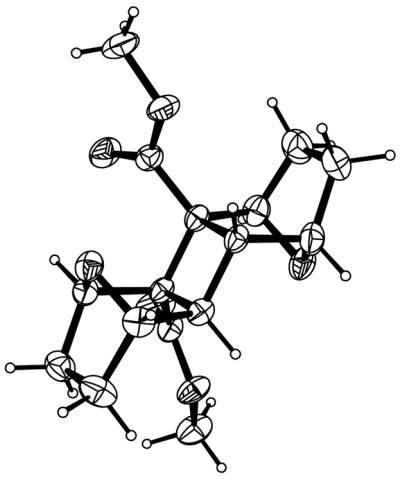


Figure 1. X-ray crystal structure of the product **6**.

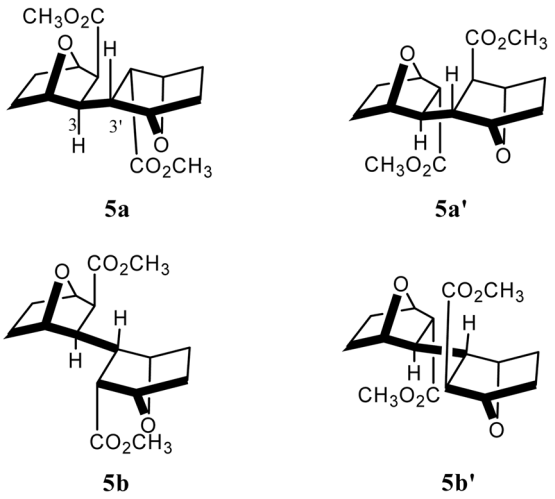


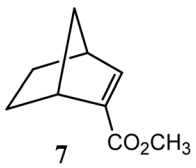
Figure 2. Possible stereochemistry of the dimeric product **5** from the Sm(II)-mediated reaction.

product **5** (Eq. 5) is not surprising, since it has been known that α,β-unsaturated esters are dimerized in either intermolecular or intramolecular fashion by the use of a reduction system, SmI_2-THF-HMPA.[10] At this moment precise stereochemistry of **5** is not clear. Since the ^{13}C NMR spectrum exhibits only 8 peaks implying that the product has a two-fold symmetry, one of the four products (**5a**, **5a'**, **5b**, or **5b'**) as shown in Figure 2 is possible to be the structure of **5** among all the products possible to be formed depending on the stereochemical relationship on 2 or 3 positions.[11]

Formation of a cyclobutane ring from alkenes *via* [2+2] cycloaddition mediated by a samarium(II) reagent has not been reported. Although literature survey reveals that unexpected metal-catalyzed [2+2] cycloaddition of bisenones has been reported using a cobalt reagent in the presence of silane,[12] the reported dimerization proceeds apparently through a different mechanism. It is not clear how the product **6** is formed at this moment.

Assuming the first step of the process is the electron transfer to the enoate, the resulting radical at the β-position seems not to be able to overlap with the C-O bond in the 1-oxabicyclo[2.2.1]heptane.[5] Therefore, instead of undergoing ring-opening reaction, the radical could react with the other molecule to dimerize and eventually produce the [2+2] cycloaddition product.

This reaction seems to have a narrow scope. Under the same reaction condition ester **7** did not produce the corresponding cycloaddition product. Extended reaction time simply resulted in decomposition of the reactant.



In conclusion, we have observed the formation of an interesting [2+2] cycloaddition product mediated by a

samarium(II) reagent from reaction of a α,β-unsaturated ester system in addition to formation of a dimerized product.

Experimental Section

All materials and solvents were purchased from either Sigma-Aldrich or Tokyo Chemical Industry Co. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX-300. The chemical shifts are reported in ppm on δ scale downfield from TMS, and signal patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad peak.

Methyl 3-bromo-7-oxabicyclo[2.1.1]hepta-2,5-dien-2-carboxylate (2).[8] A solution of methyl 3-bromo-2-propynoate (**1**)[7] (3 g, 18.4 mmol), furan (5.4 mL, 73.6 mmol) in benzene (50 mL) was degassed by passing nitrogen gas for 2 min at 0 °C. The solution was heated in a pressure tube at 80 °C for 24 h with stirring. The solution was concentrated. Purification by flash chromatography (hexane:ethyl acetate = 7:1) provided the desired Diels-Alder product **2** as a dark yellowish liquid (1.06 g, 25%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (dd, 1H, J = 5.3, 1.8 Hz, C*H*CHOBr), 7.16 (dd, 1H, J = 5.3, 1.8 Hz, CHC*H*OCCOOMe), 5.66 (t, 1H, J = 1.7 Hz, bridgehead C*H*), 5.29 (t, 1H, J = 1.7 Hz, bridgehead C*H*), 3.76 (s, 3H, OCH_3).

Methyl 3-bromo-7-oxabicyclo[2.2.1]hept-2-ene-2-carboxylate (3). To a solution of Methyl 3-bromo-7-oxabicyclo-[2.1.1]hepta-2,5-dien-2-carboxylate (**2**) (150 mg, 0.65 mmol) in ethanol (7 mL) was added 5% Pd/C (catalytic amount). The mixture was stirred under hydrogen (1 atm, balloon). After the reaction was completed (*ca*. 10 min), the mixture was diluted with ethyl acetate (5 mL) and filtered through celite to remove Pd/C. The filtrate was concentrated and purification by flash chromatorgraphy (hexane:ethyl acetate = 10:1) provide the desired reduced product **3** (121 mg, 80%) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.1-5.3 (m, 1H, CO*H*CBr), 4.8-5.0 (m, 1H, CO*H*CCOO), 3.77 (s, 3H, OCH_3), 1.8-2.0 (m, 2H, CH_2CHOCBr), 1.3-1.5 (m, 2H, CH_2COHCCOO).

Methyl 7-oxabicyclo[2.2.1]hept-2-en-2-carboxylate (4). To a mixture of Methyl 3-bromo-7-oxabicyclo[2.2.1]hept-2-ene-2-carboxylate (**3**) (120 mg, 0.52 mmol) in water (2 mL) was added zinc powder (102 mg, 1.56 mmol) and acetic acid (298 μL, 5.2 mmol). The mixture was stirred (for about 30 min) at room temperature until the reaction was completed. Ethyl acetate (3 mL) was added to the mixture and the organic layer was washed with aq. $NaHCO_3$. After extraction with ethyl acetate (3 × 20 mL), the organic layer was dried ($MgSO_4$) and concentrated. Purification by flash chromatography (hexane:ethyl acetate = 10:1) provided the desired product **4** as a yelowish oil (67 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.0 (d, 1H, J = 1.6 Hz, CHOC*H*), 5.21 (d, 1H, J = 4.1 Hz, C*H*OCCOOMe), 5.0-5.1 (m, 1H, CO*H*CHC), 3.75 (s, 3H, OCH_3), 1.8-2.0 (m, 2H, CHCOH-CH_2CH$_2$), 1.2-1.35 (m, 2H, OCCCOHCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.6, 144.2, 140.8, 79.2, 77.8, 51.6, 23.7, 23.4.

Generation of the samarium(II) reagent (Sm/Me_3Cl/NaI). The samarium(II) reagent was generated according to the literature procedure.[8] Under nitrogen atmosphere to the mixture samarium powder (169 mg, 1.13 mmol) and NaI (505 mg, 3.38 mmol) in acetonitrile (10 mL) was added TMSCl (429 μL, 3.38 mmol) slowly. The turbid solution turned to green with addition of TMSCl. The solution was used for the reaction after stirring for 2 h at room temperature.

Reaction of 4 with a samarium(II) reagent (Sm/Me_3Cl/NaI). To a solution of Methyl 7-oxabicyclo[2.2.1]hept-2-en-2-carboxylate (**4**) (0.30 mmol, 46 mg) in acetonitrile (5 mL) was added the samarium(II) reagent solution (6.6 mL (*ca*. 2.5 eq) of the solution as prepared as above) at –20 °C under nitrogen atmosphere. After stirring for 5 min, *t*BuOH (58 μL) was added to the solution. The resulting solution was stirred at –20 °C for 10 min. The reaction was terminated by addition of water. The solution was extracted with ethyl acetate (3 × 20 mL), and dried. Purification by flash chromatography (hexane:ethyl acetate = 2:1) provided and the dimeric product **5** (16 mg, 34%) the desired [2+2] adduct **6** (22 mg, 48%) as solids. Adduct **6** was recrystalized in ethyl acetate for X-ray crystrallographic analysis.[12]

Dimeric product 5: mp 162-164 °C; R_f 0.45 (hexane: ethyl acetate = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.72 (t, 2H, J = 4.7 Hz, bridgehead C*H*), 4.3-4.4 (m, 2H, bridgehead C*H*), 3.71 (s, 6H, OCH_3), 2.84 (bs, 2H, C*H*COOMe), 2.1-2.3 (m, 2H, CHOC*H*CHCOO), 1.6-1.8 (m, 4H, CH_2CH_2OCH), 1.4-1.6 (m, 4H, CH_2CH_2CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 80.4, 78.0, 53.7, 52.0, 49.9, 29.7, 26.2; HRMS: *m/z* Calcd for $C_{16}H_{22}O_6$: 310.1416. Found: 310.1416.

[2+2] adduct 6: mp 174-176 °C; R_f 0.27 (hexane:ethyl acetate = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.57 (d, 2H, J = 4.4 Hz, C*H*OCCOOMe), 4.45 (d, 2H, J = 5.1 Hz, C*H*OCHCH), 3.79 (s, 6H, OCH_3), 2.41 (s, 2H, C*H*CH), 1.4-1.8 (m, 8H, 2 x CH_2CH_2CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 80.9, 78.8, 61.3, 52.0, 47.0, 27.6, 26.2; HRMS: *m/z* Calcd for $C_{16}H_{20}O_6$: 308.1259. Found: 308.1257.

Crystal data for 6: $C_{16}H_{20}O_6$, FW = 308.33, triclinic, a = 7.673(1), b = 9.128(1), c = 12.081(1), α = 95.76(1), β = 105.59(1), γ= 113.47(1)°, V = 726.7(2) Å^3, space group $P\bar{1}$, Z = 2, D_{calc} = 1.408 g/cm^3, data range $1° \le \theta \le 70°$, crystal size 0.30 × 0.35 × 0.25 mm^3. Structure solved by direct method and refined by least-squares. The R (wR) is 0.063 (0.102) for 2674 observed reflections ($I \ge 2\sigma(I)$), and 0.065 (0.102) for all the unique (2771) reflections. $-0.51 \le \Delta \le 0.34$ e/Å^3 in the final difference map.[13]

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References

1. For a recent example, see; Choi, J.-H.; Shin, I.-J.; Choi, E.-S.; Cho, C. G. *Bull. Korean Chem. Soc.* **2006**, *27*, 2091 and references therein.

2. Molander, G. A. *Org. React.* **1994**, *46*, 211.
3. Kang, H.-Y.; Cho, Y. S.; Koh, H. Y.; Chang, M. H. *Synth. Commun.* **1993**, *23*, 2977.
4. De Schrijver, J.; De Clercq, P. J. *Tetrahedron Lett.* **1993**, *34*, 4369.
5. Yoshida, A.; Takayama, H. *Tetrahedron Lett.* **2001**, *42*, 3603.
6. Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48.
7. Leroy, J. *Synth. Commun.* **1992**, *22*, 567.
8. Leroy, J. *Tetrahedron Lett.* **1992**, *33*, 2969.
9. (a) Akane, N.; Hatano, T.; Kusui, H.; Nishiyama, H.; Ishii, Y. *J. Org. Chem.* **1994**, *59*, 7902. (b) Kagan, H. B.; Namy, J.-L. In *Lanthanides: Chemistry and Use in Organic Synthesis*; Kobayshi, S., Ed.; Springer: Berlin, 1999; pp 155-198.
10. Inanaga, J.; Handa, Y.; Tabuchi, T.; Otsubo, M.; Yamaguchi, M.; Hanamoto, T. *Tetrahedron Lett.* **1991**, *32*, 6557.
11. Although the exact stereochemical identity of the dimeric product **5** is not clear, either **5b** or **5b'** is more reasonable to be the product observed, since both **5b** and **5b'** are not likely to make a bond between C3-C3' to give a [2+2] cycloaddition product due to the streric hindrance originated by the two *exo*-(for **5b**) or two *endo*-methoxycarbonyl groups (for **5b'**). Therefore, it might be a very tempting scenario that the possibly formed reactive intermediate can be cyclized when the stereochemical relationship of the product is that of either **5a'** (or **5a**). Based on the stereochemistry of the [2+2] cycloaddition product **6**, **5a'** could be the streochemistry of the interemediate which is actually formed. The reactive intermediate involved in the reaction might be either radical or anionic species, although the exact nature of the intermediate is not known.
12. Baik, T.-G.; Luis, A. L.; Wang, L.-C.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 6716.
13. Crystallographic data for the structure reported here have been deposited with the Cambridge Crystallographic Data Centre (Deposition No. CCDC-629168). That data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).