

Synthesis and SmI₂-Induced Ring Expansion Reactions of Activated Cyclopropyl Ketone Derivatives Containing Ester Group

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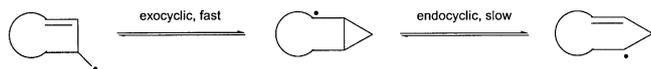
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Alkyl (n+1)-oxobicyclo[n.1.0]alkane-1-carboxylates have been prepared from phosphoniosilylation and cyclopropanation of α,β -unsaturated ketones, and alkyl 4-oxocycloalkanecarboxylates have been prepared in good yield *via* endocyclic ring expansion reactions of activated cyclopropyl ketone derivatives containing ester group mediated by 3 equiv of SmI₂-induced single electron transfer in THF/MeOH.

Introduction

Recent advances in the ring opening reactions of three-membered rings have led to the steadily increasing utilization of cyclopropyl derivatives as reagents for organic synthesis.¹⁻³ In this respect, ring opening of the cyclopropyl-carbinyl radical has proved to be a useful strategy for ring expansion because cleavage of the three-membered ring takes place easily and the usually disfavored entropy effect associated with medium and large size ring formation can be avoided.⁴⁻⁶ However, the literature on bicyclo[n.1.0] radicals reveals a preference for stereoelectronically controlled exocyclic radical ring opening as opposed to thermodynamically favored endocyclic ring opening.⁷⁻¹¹ The exocyclic cleavage has been achieved usually under the reaction con-

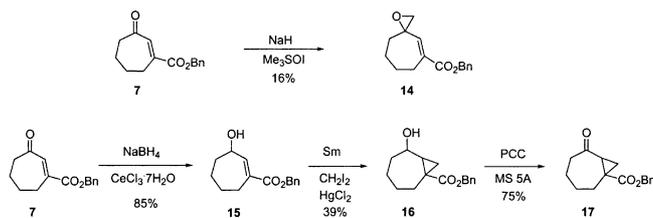


ditions such as electrolysis,¹² samarium iodide,¹³ alkali metal^{14,15} and photochemical electron transfer.¹⁶ Recently, it was reported that methyl 5-oxobicyclo[4.1.0]heptane-1-carboxylate was converted into methyl 4-oxocycloheptanecarboxylate under radical condition (*n*-Bu₃SnH/AIBN).¹⁷ However, this reaction was carried out under harsh conditions, and the yield was only 69%. As part of our continuing effort to expand the synthetic utility of cyclopropanes, we reported the preparation of 3-alkenylcyclohexanones *via* exocyclic ring opening reactions of bicyclo[n.1.0]-2-heptanones¹⁸ as well as cyclopentanones, furans, and unsymmetrical dialkenyl ketones from ring opening reaction of 1-alkenyl 1-methoxy cyclopropane derivatives containing anion stabilizing groups.^{19,20} We also reported SmI₂-induced ring expansion reactions of alkyl (n+1)-oxobicyclo[n.1.0]alkane-1-carboxylates.²¹ In this full article, we wish to report the scopes, limitations, and mechanism for synthesis and an efficient SmI₂-

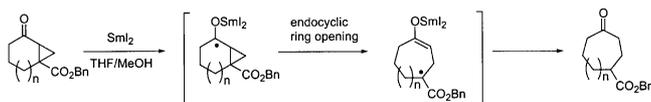
induced ring opening reaction of activated cyclopropyl ketone derivatives containing ester group *via* endocyclic bond cleavage as outlined in Scheme 1 including the experimental details.

Results and Discussion

Alkyl (n+1)-oxobicyclo[n.1.0]alkane-1-carboxylates were prepared from phosphoniosilylation²² and cyclopropanation of α,β -unsaturated ketones. We used many reagents (zinc-copper couple, ethylzinc iodide, and etc.) to obtain cyclopropane derivatives from β -benzyloxycarbonyl- α,β -unsaturated ketones and found that trimethyloxosulfoxonium iodide gave the best results.²³ Some experimental results are shown in the Table 1. In case of cyclopropanation of 3-benzyloxycarbonyl-2-cyclohepten-1-one (**7**), the epoxide **14** was produced in 16% yield instead of the desired compound **17**. Benzyl 6-oxobicyclo[5.1.0] octane-1-carboxylates (**17**) was prepared from α,β -enones **7** using 1,2-reduction,²⁴ cyclopropanation,²⁵ followed by oxidation.²⁶



Initial studies were performed with benzyl 5-oxobicyclo[4.1.0]heptane-1-carboxylate **10** (Table 2). When a solution of samarium(II) iodide was added to a solution of **10** in THF, benzyl 4-oxocycloheptanecarboxylate (**20**) was obtained in 44% yield. HMPA and DMPU as additives were ineffective for increasing the yield. We next turned our attention to the uses of alcohols, known to be very effective proton source for SmI₂-induced single electron transfer reaction.²⁷ When methanol was added to reaction mixture, the desired compound **20** was obtained in 89% yield. When an equimolar amount of SmI₂ was added to **10**, **20** was obtained in 27% yield, and the starting material was recovered in 67% yield. The use of 2 to 3 equiv of SmI₂ gave better results, yielding **20** in 62% and 89% yield, respectively. Thus, the remaining



Scheme 1

Table 1. β -Benzoyloxycarbonylation and Cyclopropanation of α,β -Unsaturated Ketones

Product	Isolated Yield/%	Product	Isolated Yield/%		
	1	58		8	6
	2	80		9	21
	3	86		10	38
	4	55 ^a		11	38 ^a
	5	40		12	35 ^b
	6	43		13	62
	7	19			

^aMethyl chloroformate in stead of benzyl chloroformate was used.
^b70:30 ratio of diastereomer.

Table 2. Determination of Amount of SmI₂

Equiv of SmI ₂	Reaction time (h)	Isolated yield, % ^a
1	8	27(67)
1.5	10	45(46)
2	10	62(28)
3	0.03	89(0)

^aThe numbers in parentheses indicate the isolated yields of starting material

reactions were carried out with 3 equiv of SmI₂ for each mol of alkyl (n+1)-oxobicyclo[n.1.0]alkane-1-carboxylate (Table 2).

Table 3 summarizes the experimental results and illustrates the efficiency and scope of the present method. Monocyclic compound **8** (entry 1, Table 3) reacted readily and gave a good yield of 5-keto ester **18**. In case of bicyclo[4.1.0] system (entries 4 and 5, Table 3) containing methyl groups, the reaction afforded the desired compounds **21** and **22**. When SmI₂ was added to a bicyclo[3.1.0] (entry 2, Table 3) and [5.1.0] (entry 6, Table 3) compound under

Table 3. Ring Expansion Reactions of Alkyl (n+1)-Oxobicyclo[n.1.0]alkane-1-carboxylates

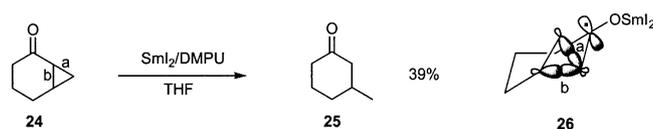
Entry	Starting material	Product	Isolated Yield/%
1			51
2			83
3			89 94 ^a 44 ^b
4			71(56:44) ^c
5			85
6			85

^aMethyl ester instead of benzyl was used. ^bMethanol was not used.
^cDiastereomer ratio

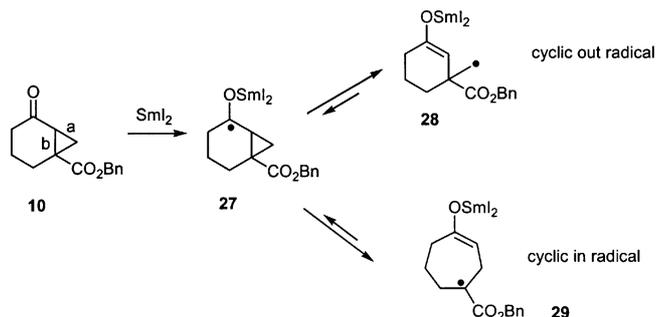
the same conditions, the desired products **19** and **23** were obtained in 83, and 85% yields, respectively.

On the basis of these results, it seems reasonable to suggest that one electron transfer to ketone from samarium iodide produced the intermediate cyclopropylcarbonyl radical (**27**), which then undergoes cleavage to the ring expanded product (**29**). In this reaction, the ester group plays important roles. It assists the ring opening reaction of the cyclopropylcarbonyl radical by stabilizing the formed radical. The stabilization of the radical center usually favor radical scissions of cyclopropanes bearing radical-stabilizing functional groups such as an ester or phenyl group. It is also possible to suggest an anionic mechanism because 3 equivalents of samarium iodide was essential to complete the ring expansion reaction.

Motherwell²⁸ reported that exobond (a) cleavage occurred to give 3-methylcyclohexanone (**25**) in 39% yield when bicyclo[4.1.0]-2-heptanone (**24**) was treated with samarium iodide. To explain the two contrasting results, we propose that stereoelectronic effects initially favor the cleavage of bond "a" in **24** because the cyclopropane "a" σ -bond has better orbital overlap with the sp^2 orbital of the adjacent ketyl radical as seen in structures **26**. However, bond "b" is almost orthogonal to the sp^2 orbital of the ketyl radical.



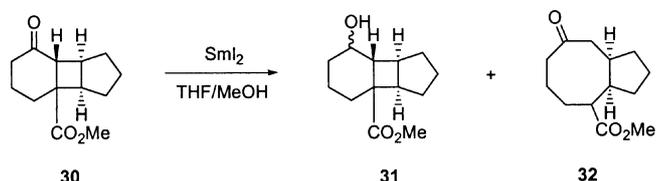
Our observation means that both *endo*- and *exo*-bond



Scheme 2

cleavage involve cyclopropylmethyl radicals and potentially can involve a reversible ring-closure process; however, bond cleavages are highly favored because of the release of ring strain energy, as shown in scheme 2. Reclosure could become more facile in **28**, because no substituent is present and the center is less hindered. At this point, cleavage of bond "b" likely occurs, leading to the resonance-stabilized radical intermediate **29** in which the reverse reaction is possible, but less likely.¹⁷

Methyl 8-oxotricyclo[5.4.0.0]undecane-1-carboxylates (**30**)²⁹ was treated with 3 equivalents of samarium iodide in THF/MeOH to produce the desired compound (**32**) in 10% yield together with alcohol **31** in 7% yield. **32** was obtained in 11% yield when **30** was treated with photochemical electron transfer method.¹⁶ Yields of these methods were low because the ring strain of 4-membered ring was less than that of cyclopropane.



In summary, SmI₂ provides a new and useful route to cleave the bridged bond of alkyl (n+1)-oxobicyclo[n.1.0]-alkane-1-carboxylates which was prepared from phosphoni-osilylation and cyclopropanation of α,β -unsaturated ketones to produce various alkyl 4-oxocycloalkanecarboxylates. Because the exocyclic cleavage of cyclopropyl ketone derivatives was reported mainly in prior work, the present method contrasts with the existing synthetic methods.

Experimental Section³⁰

Benzyl 5-oxobicyclo[4.1.0]heptane-1-carboxylate (10). A solution of dimethylsulfoxonium methylide was prepared from NaH (81.4 mg, 3.39 mmol) and trimethylsulfoxonium iodide (743.2 mg, 3.38 mmol) in DMSO (4.5 mL) under N₂. After 1 h, a solution of 3-benzoyloxycarbonyl 2-cyclohexen-1-one (597.1 mg, 2.59 mmol) in DMSO (2 mL) was added dropwise over 20 min to a solution of dimethylsulfoxonium methylide. After being stirred for 10 h at room temperature, the solution was poured into ice-cold water (10 mL) and extracted with ether (3 × 50 mL). The combined organic lay-

ers were washed with brine (50 mL), dried with anhydrous MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (EtOAc/hexanes = 1/5) to give benzyl 5-oxobicyclo[4.1.0]heptane-1-carboxylate (240.5 mg, 38%) as a colorless liquid: ¹H NMR (400 MHz, CDCl₃) δ 7.35 (m, 5H), 5.13 (s, 2H), 2.33 (m, 5H), 1.82 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 205.92, 172.49, 135.55, 128.63, 128.38, 128.08, 66.91, 36.52, 33.80, 28.67, 22.12, 17.74, 16.75; IR (film) 3050, 2950, 1710, 1690, 1280 cm⁻¹; MS (CI) calcd for C₁₅H₁₆O₃ [M+H]⁺ 245, found 245.

Benzyl 4-oxocycloheptane carboxylate (20). To a solution of benzyl 5-oxobicyclo [4.1.0]heptane-1-carboxylate (60.4 mg, 0.25 mmol) in THF/MeOH (7 : 1, 0.8 mL) was added dropwise a solution of samarium (II) iodide (8.33 mL, 0.1 M in THF) at room temperature under N₂ until the purple coloration persisted. After 2 min, the reaction mixture was quenched with NaHCO₃ (sat. aq.). The aqueous layer was extracted with ether (3 × 25 mL), and the combined organic layers were washed with water (20 mL), brine (20 mL), dried with anhydrous MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (EtOAc/hexanes = 1/5) to give benzyl 4-oxocycloheptane carboxylate (53.9 mg, 89%) as a colorless liquid: ¹H NMR (400 MHz, CDCl₃) δ 7.23 (m, 5H), 5.00 (s, 2H), 2.43 (m, 5H), 2.01 (m, 2H), 1.80 (m, 2H), 1.59 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 213.53, 174.63, 135.70, 128.45, 128.16, 127.99, 66.25, 46.34, 43.30, 41.37, 32.44, 26.15, 22.22; IR (film) 3050, 2940, 1710, 1670, 1140 cm⁻¹; MS (CI) calcd for C₁₅H₁₈O₃[M+H]⁺ 247, found 247.

Benzyl 4-oxobicyclo[3.1.0]hexane-1-carboxylate (9). ¹H NMR (400 MHz, CDCl₃) δ 7.36 (m, 5H), 5.16 (s, 2H), 2.58 (m, 1H), 2.33 (dd, *J* = 4.34, 4.21 Hz, 1H), 2.21 (m, 3H), 2.0 (dd, *J* = 4.82, 4.55 Hz, 1H), 1.36 (t, *J* = 4.56 Hz, 1H); IR (film) 3050, 2950, 1740, 1280, 1160 cm⁻¹; MS (CI) calcd for C₁₄H₁₄O₃ [M+H]⁺ 230, found 230.

Benzyl 6-oxobicyclo[5.1.0]octane-1-carboxylate (17). ¹H NMR (400 MHz, CDCl₃) δ 7.35 (m, 5H), 5.14 (s, 2H), 2.55 (m, 4H), 1.62 (m, 4H), 1.46 (m, 2H), 1.28 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 208.05, 173.56, 136.11, 129.01, 128.70, 128.36, 67.36, 43.37, 38.01, 30.10, 27.23, 25.78, 25.59, 21.37; IR (film) 3050, 2950, 1720, 1690, 1460, 1310, 1270, 1240, 1160, 1140 cm⁻¹; MS (CI) calcd for C₁₆H₁₈O₃ [M+H]⁺ 259, found 259.

Benzyl 2-methyl-5-oxoheptanoate (18). ¹H NMR (400 MHz, CDCl₃) δ 7.34 (m, 5H), 5.12 (s, 2H), 2.53 (m, 1H), 2.40 (m, 4H), 1.83 (m, 2H), 1.18 (d, *J* = 7.01 Hz, 3H), 1.01 (t, *J* = 7.36 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 211.15, 176.38, 136.47, 128.95, 128.61, 128.55, 66.53, 39.93, 39.18, 36.31, 27.86, 17.55, 8.18; IR (film) 3050, 2950, 1740 cm⁻¹; MS (CI) calcd for C₁₅H₂₀O₃ [M+H]⁺ 249, found 249.

Benzyl 4-oxocyclohexane carboxylate (19). ¹H NMR (400 MHz, CDCl₃) δ 7.29 (m, 5H), 5.09 (s, 2H), 2.73 (m, 1H), 2.39 (m, 2H), 2.27 (m, 2H), 2.16 (m, 2H), 1.99 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 209.94, 173.88, 135.68, 128.57, 128.32, 128.08, 66.49, 40.63, 39.62, 28.42; IR (film)

3050, 2950, 1730, 1200, 1170 cm^{-1} ; MS (CI) calcd for $\text{C}_{14}\text{H}_{16}\text{O}_3$ $[\text{M}+\text{H}]^+$ 233, found 233.

Benzyl 4-methyl-5-oxocycloheptane carboxylate (21). ^1H NMR (400 MHz, CDCl_3) δ 7.27 (m, 5H), 5.05 (s, 2H), 2.48 (m, 3H), 2.09 (m, 1H), 1.85 (m, 4H), 1.62 (m, 2H), 1.0 (d, $J = 6.64$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 215.11, 214.91, 174.95, 174.41, 135.82, 135.80, 128.53, 128.22, 128.07, 66.31, 66.29, 46.46, 46.22, 46.10, 44.37, 40.68, 39.42, 31.82, 31.75, 29.16, 28.30, 26.43, 17.37, 16.72; IR (film) 3050, 2930, 1735, 1705, 1160 cm^{-1} ; MS (CI) calcd for $\text{C}_{16}\text{H}_{20}\text{O}_3$ $[\text{M}+\text{H}]^+$ 261, found 261.

Benzyl 4,4-dimethyl-5-oxocycloheptane carboxylate (22). ^1H NMR (400 MHz, CDCl_3) δ 7.25 (m, 5H), 5.04 (s, 2H), 2.52 (m, 3H), 1.92 (m, 2H), 1.65 (m, 4H), 1.01 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 217.77, 175.43, 136.66, 129.35, 129.03, 128.86, 67.09, 48.27, 47.00, 38.59, 37.76, 28.97, 27.89, 27.38, 25.11; IR (film) 3050, 2950, 1740, 1710, 1460, 1170, 1150 cm^{-1} ; MS (CI) calcd for $\text{C}_{17}\text{H}_{22}\text{O}_3$ $[\text{M}+\text{H}]^+$ 275, found 275.

Benzyl 4-oxocyclooctane carboxylate (23). ^1H NMR (400 MHz, CDCl_3) δ 7.35 (m, 5H), 5.11 (s, 2H), 2.53 (m, 1H), 2.44 (m, 3H), 2.39 (m, 1H), 2.20 (m, 2H), 1.85 (m, 2H), 1.67 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 217.32, 175.46, 136.34, 128.98, 128.64, 128.49, 66.74, 44.18, 41.59, 41.33, 27.55, 27.27, 26.75, 25.33; IR (film) 3050, 2950, 1730, 1690, 1460, 1150 cm^{-1} ; MS (CI) calcd for $\text{C}_{16}\text{H}_{20}\text{O}_3$ $[\text{M}+\text{H}]^+$ 261, found 261.

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- The ^1H and ^{13}C NMR spectra were obtained by Bruker DPX-400 MHz FT-NMR spectrometer in the Central Lab of the Kangwon National University. The gas chromatograms were provided by GC facility, supported by Research Center for Advanced Mineral Aggregate Composite Products.