New syntheses of haloketo acid methyl esters and their transformation to halolactones by reductive cyclization*

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A new method for haloketo acid methyl ester synthesis on the basis of the ring-opening of cyclic α,β-unsaturated ketones followed by halogenation under mild conditions is reported. Di- and tri-haloketo acid methyl esters are conveniently synthesized *via* the hydrolytic ring-opening reaction through this method. Halolactones were readily obtained from these haloketo acid methyl esters by reductive cyclization employing $NaBH_4$ and trifluoroacetic acid. Derivatizations of the obtained halolactone utilizing the *exo*-halomethylene moiety were also demonstrated.

Key words: haloketo acid methyl ester, halolactone, hydrolytic ring-opening reaction, reductive cyclization, cyclic β-diketone.

Halolactones are useful synthetic intermediates[1] for derivatization to various compounds including natural products with interesting biological activities. Recently, several biologically active halolactones have also been reported.[2—4] Halolactones are typically synthesized by halocyclizations of olefinic acids, such as iodo-, bromo-, and chlorolactonizations (Scheme 1, ***A***).[5—15]. However, the halolactonization reaction offers limited control of the regioselectivity of *endo*- and *exo*-cyclizations in the case of internal alkenes. The classical intramolecular cyclization strategies based on the condensation of hydroxy acids are advantageous since a mixture of these *exo*- and *endo*-lactones are not formed in principle. This halolactonization requires an excess amount of an organic base and diluted hydroxy acids in order to avoid dimer formation,[16—20] whereas the cyclization of hydroxy acid methyl esters under acidic or basic conditions readily provides lactones without a dimer byproduct.[21—24] Moreover, the strategy of halolactone synthesis using carboxylic acid methyl esters with a halohydrin moiety derived by the reduction of haloketo acid methyl esters as a synthetic intermediate does not produce the corresponding dimer and regioisomeric byproducts (Scheme 1, ***B***).

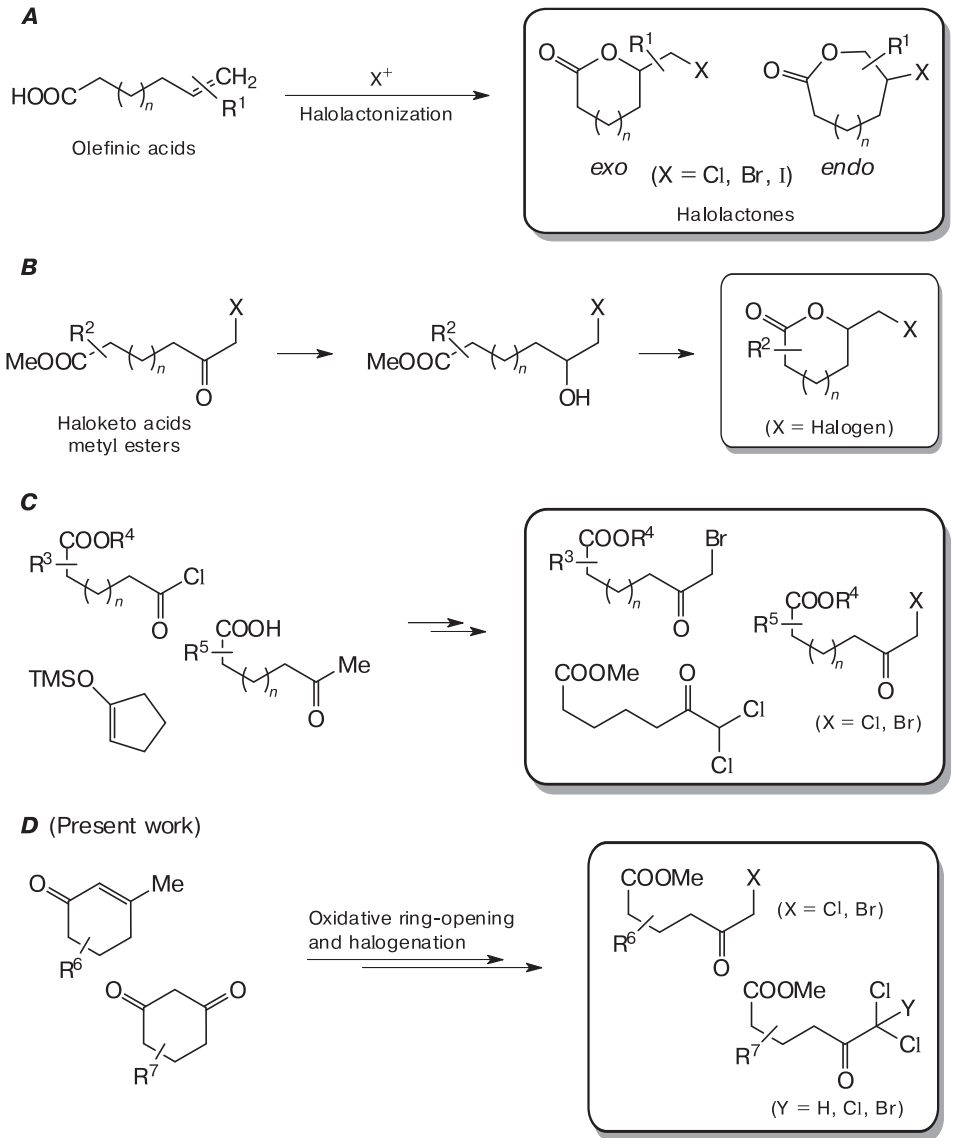
The previously reported method for the synthesis of monohaloketo acid methyl esters (Scheme 1, ***C***) typically involved the use of diazomethane as the C(1)-carbon source.[25,26] On the next step, diazomethyl ketone, generated from acyl chloride, is converted to monohaloketo acid methyl ester by the reaction with dry hydrogen halide. Alternatively, monobromoketo acid alkyl esters can be synthesized from keto acids by their reactions with molecular bromine using alcohol as a co-solvent under heating.[27] There is only one example of the synthesis of dichloroketo acid methyl ester by the ring-opening of bicyclic compound.[28] However, selective synthesis of substituted dichloroketo acid methyl esters may be difficult through this method, because regioisomers of silyl enol ethers may be formed during the synthesis of the substrate.

In this study, we have developed a new synthetic route to haloketo acid methyl esters through the ring-opening of cyclic α,β-unsaturated ketones and cyclic β-diketones and their sequential transformation to halolactones by reductive cyclization. The halolactone formation belongs to the condensation-type cyclization without the potent problem of regioselectivity (see Scheme 1, ***B***). The monohaloketo acid methyl esters can be obtained by regioselective halogenation of the corresponding keto acid methyl ester precursors that are accessible by oxidative cleavage[29] of 3-methyl-2-cyclohexenones (Scheme 1, ***D***). Di- and tri-haloketo acid methyl esters can be alternatively synthesized by the hydrolytic ring-opening of 2,2-dichlorocyclohexane-1,3-diones (see Scheme 1, ***D***).

* Based on the materials of the International Conference "Catalysis and Organic Synthesis" (ICCOS-2019) (September 15—20, 2019, Moscow, Russian Federation).

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 9, pp. 1804—1810, September, 2020.
1066-5285/20/6909-1804© 2020 Springer Science+Business Media LLC

Scheme 1

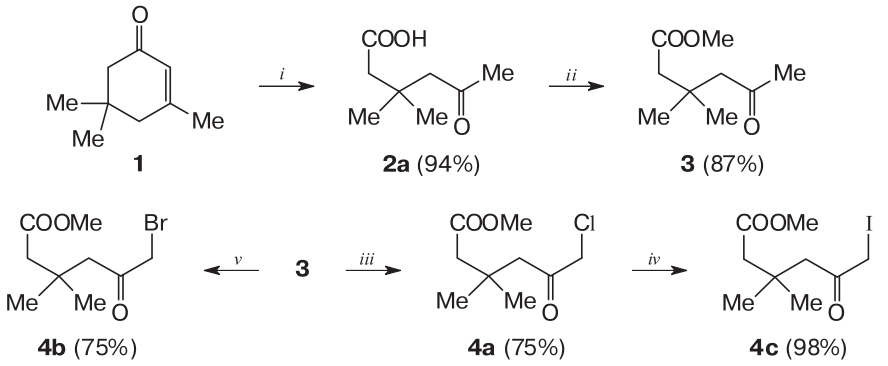


Results and Discussion

The representative scheme for the preparation of monohaloketo acids as a substrate for a reductive lactonization is illustrated in Scheme 2. Keto acid **2a** was produced by the oxidative cleavage of cyclic α,β-unsaturated ketone **1**.[29] Keto acid methyl ester **3** derived from keto acid **2a** in 87% yield was converted to monochloroketo acid methyl ester **4a** and monobromoketo acid methyl ester **4b** in good yield by reacting with 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) and *N*-bromosuccinimide (NBS), respectively, in the presence of silica gel. Monoiodoketo acid methyl ester **4c** was prepared by the Finkelstein reaction of compound **4a**. The ring-opening alcoholysis of dichloro-β-diketone, which was obtained by the chlorination of dimedone,[30] using Na_2HPO_4 in MeOH afforded dichloroketo acid methyl ester **5a** in 97% yield (Scheme 3). In addition, this ring-opening alcoholysis in the presence of *N*-chlorosuccinimide (NCS) and NBS, respectively, gave pure trichloroketo acid methyl ester **5b** and monobromo dichloroketo acid methyl ester **5c** in high yields (see Scheme 3).

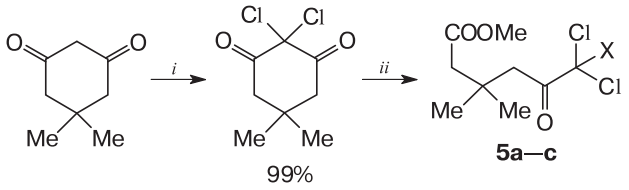
Next, the reductive cyclization of the thus-obtained haloketo acid methyl esters **4** and **5** using $NaBH_4$ and trifluoroacetic acid (TFA) to produce halolactones was examined (Scheme 4). After the reduction of the substrates using $NaBH_4$ in MeOH at 0 °C, the intramolecular condensation reaction of the resulting methyl esters with the halohydrin moiety was subsequently carried out by the treatment with TFA at room temperature. This method

Scheme 2



Reagents and conditions: *i*. Oxone®, $RuCl_3$, MeCN, H_2O, RT, 3 h; *ii*. CDI, MeOH, RT, 30 min; *iii*. DCDMH, MeOH, SiO_2; *iv*. NaI, acetone, RT, 1 h; *v*. NBS, MeOH, SiO_2, RT, 6 h.

Scheme 3



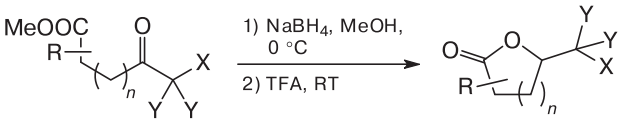
Compounds **5**	X	Yield (%)
a	H	97
b	Cl	96
c	Br	89

Reagents and conditions: *i*. aq. NaOCl, AcOH, MeOH, 0 °C, 30 min; *ii*. Na_2HPO_4, MeOH (for **5a**) or Na_2HPO_4, MeOH, NCS (for **5b**), or Na_2HPO_4, MeOH, NBS (for **5c**), room temperature (RT), 0.5—1 h.

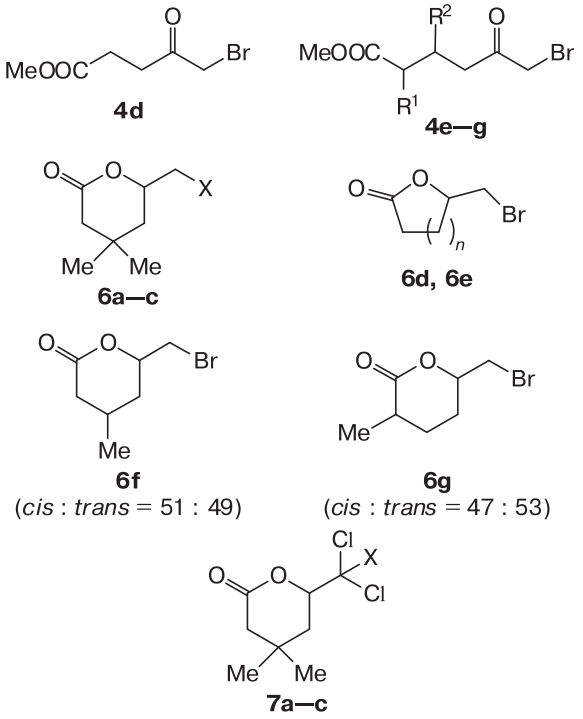
afforded highly pure halolactones **6** and **7** without chromatographic purification in both the reduction and cyclization steps. Thus, 3,3-dimethyl-substituted monochloro-δ-lactone **6a** and monobromo-δ-lactone **6b** were obtained by the lactonization of the corresponding methyl esters **4a** and **4b** in high yield. However, monoiodoketo acid methyl ester **4c** did not form monoiodo-δ-lactone **6c**. This is because the elimination of the iodine atom in the substrate **4c** was caused during the reduction with $NaBH_4$.

Unsubstituted monobromo-γ-lactone **6d** and monobromo-δ-lactone **6e** were obtained in satisfactorily yields by the lactonizations of the corresponding methyl esters **4d** and **4e**, respectively. 4-Methyl-substituted monobromo-δ-lactone **6f** and 3-methyl-substituted monobromo-δ-lactone **6g** were also obtained in good yields from the corresponding methyl esters **4f** and **4g**, respectively; no significant difference in the *cis*/*trans* ratio of products **6f** and **6g** was observed. 3,3-Dimethyl-substituted dichloro-δ-lactone **7a** and trichloro-δ-lactone **7b** were afforded in high yields by the lactonization of the corresponding dichloro- and trichloromethyl esters **5a** and **5b**, respectively. Whereas monobromo dichloro-δ-lactone **7c**

Scheme 4



X = H or halogen; Y = H or Cl



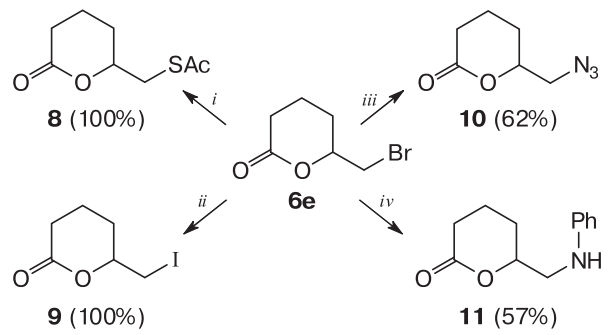
$R^1 = R^2 = H$ (**4e**), $R^1 = H$, $R^2 = Me$ (**4f**), $R^1 = Me$, $R^2 = H$ (**4g**)
X = H (**7a**), Cl (**6a**, **7b**), Br (**6b**, **7c**), I (**6c**)
n = 1 (**6d**), 2 (**6e**)

Compound	Yield (%)	Compound	Yield (%)
6a	98	**6f**	96
6b	99	**6g**	99
6c	0	**7a**	97
6d	90	**7b**	99
6e	97	**7c**	0

was not detected during the lactonization of monobromo dichloroketo acid methyl ester **5c** due to the facile reduction of the weak carbon—bromine bond. Instead, in this case dichloro-δ-lactone **7a** was obtained in 96% yield.[31—33] This method is particularly convenient to synthesize lactones **7a** and **7b** since no purification was required in all steps from dimedone (see Schemes 3 and 4).

Finally, derivatizations of **6e** were demonstrated in Scheme 5. The bromo-substitution reaction for the derivatization of bromolactone must be conducted under mild pH conditions because the ring-opening of lactone would occur under strong basic conditions. The treatment of **6e** with potassium thioacetate (AcSK) in THF at 60 °C quantitatively afforded lactone **8** tethered with the thioester moiety. Halogen substitution to produce iodolactone **9** was accomplished by the Finkelstein reaction at 60 °C. Such iodolactones can be converted to aryl lactones[34] and olefinic lactones[35] by $C(sp^3)—C(sp^2)$ cross-coupling reactions. In addition, iodolactones are known as the useful precursor of lactones with thioether[34] and ester[34,36,37] moieties. The reaction between **6e** and NaN_3 in DMF at 80 °C under neutral pH conditions afforded azide lactone **10** in moderate yield. The C—N coupling between **6e** and aniline to form the amine lactone **11** occurred under weak basic conditions at reflux. In the synthesis of biologically active compounds, bromolactones were sometimes used for the elongation of aliphatic side chains.[38—40]

Scheme 5



Reagents and conditions: *i*. AcSK, THF, 60 °C, 12 h; *ii*. NaI, acetone, 60 °C, 6 h; *iii*. NaN_3, DMF, 80 °C, 7 h; *iv*. $PhNH_2$, $NaHCO_3$, MeCN, reflux, 24 h.

In summary, herein we reported the reductive cyclization using $NaBH_4$ and TFA for haloketo acid methyl esters **4** and **5** obtainable by new synthetic routes to synthesize halolactones **6** and **7**; this method differs from the conventional method based on the halolactonization strategy employing olefinic acids. Our methodology provides versatility for the introduction of the substituents in the halolactone structures because the halolactones derived from cyclic olefins and cyclic β-diketones can be obtained in good yields. There is a remarkable advantage in using this method: purification is not necessary for the lactonization sequence and di- and tri-chlorolactones can be readily obtained in high yields. Regarding the halogen functionality, derivatizations are possible while maintaining the lactone structure. Therefore, this method would become a practical and convenient alternative to synthesize haloketo acid methyl esters and halolactones.

Experimental

^1H and ^{13}C NMR spectra were recorded on an ECS 400 NMR spectrometer (JEOL Ltd., Tokyo, Japan) at 400 and 100 MHz, respectively, using $CDCl_3$ as a solvent. The chemical shifts are given in the δ scale relative to Me_4Si as an internal standard. Steric and interactive analyses were performed by 1D nuclear Overhauser enhancement and exchange spectroscopy (NOESY) using the double pulsed field gradient spin echo-nuclear Overhauser effect (DPFGSE-NOE) method under the appropriate mixing time and relaxation delay. Infrared (IR) spectra were recorded by a JASCO FT/IR-4200 spectrometer (JASCO Co., Tokyo, Japan) on diffuse reflectance method using KBr pellets. Electron impact high resolution mass spectra (HRMS) obtained by the electron ionization (EI) method were recorded on a JMS-700 spectrometer (JEOL).

Methyl 5-bromo-4-oxopentanoate (**4d**), methyl 6-bromo-5-oxohexanoate (**4e**), methyl 6-bromo-3-methyl-5-oxohexanoate (**4f**), and methyl 6-bromo-2-methyl-5-oxohexanoate (**4g**) were synthesized from the corresponding keto acids **2b—e** by the earlier reported method.[27]

Methyl 3,3-dimethyl-5-oxohexanoate (3). To a solution of 3,3-dimethyl-5-oxo-hexanoic acid **2a**[29] (3.95 g, 25.0 mmol) in CH_2Cl_2 (62.5 mL), 1,1′-carbonyldiimidazole (CDI, 4.46 g, 27.5 mmol) was added. The mixture was stirred at room temperature for 0.5 h and MeOH (12.5 mL) was added. After 15 min of continuous stirring, the solvent was removed by evaporation. The product was extracted with hexane by sonication and the extract was filtered through filter paper. Removal of the solvent by evaporation gave product **3** (3.75 g, 87%) as a colorless oil. ^1H NMR, δ: 1.09 (s, 6 H), 2.12 (s, 3 H), 2.46 (s, 2 H), 2.57 (s, 2 H), 3.64 (s, 3 H). ^{13}C NMR, δ: 28.0, 31.9, 32.5, 44.3, 51.2, 52.3, 172.7, 208.2. ^1H and ^{13}C NMR data are consistent with those reported in the literature.[30]

Methyl 6-bromo-3,3-dimethyl-5-oxohexanoate (4b). To a solution of compound **3** (517 mg, 3.00 mmol) in MeOH (30 mL) containing silica gel (3.0 g), NBS (1.34 g, 7.50 mmol) was added. After the mixture was stirred at room temperature for 6 h, the silica gel was removed by filtration, washed with MeOH and the solvent was removed by evaporation. The product was extracted with hexane by sonication and the extract was filtered through filter paper for dehydration. The filtrate was concentrated by evaporation and the residue was purified by silica gel chromatography with AcOEt—hexane (1 : 9) to afford product **4b** (568 mg, 75%) as a colorless oil. ^1H NMR, δ: 1.11 (s, 6 H), 2.47 (s, 2 H), 2.78 (s, 2 H), 3.65 (s, 3 H), 3.91 (s, 2 H). ^{13}C NMR, δ: 28.2, 32.8, 35.9, 44.0, 48.4, 51.3, 172.6, 200.9. IR, ν/cm^{-1}: 3651, 3559, 3444, 2960, 2876, 2638, 2327, 2029, 1733, 1437, 1390, 1356, 1232, 1156, 1052, 1026, 887, 812, 737, 640, 619. HR-MS (EI), found: *m/z* 251.0279 $[M + H]^+$. Calculated for $C_9H_{16}BrO_3$: 251.0283.

Methyl 6-iodo-3,3-dimethyl-5-oxohexanoate (4c). To a solution of methyl 6-chloro-3,3-dimethyl-5-oxohexanoate (**4a**)

(82.7 mg, 0.40 mmol) in acetone (4 mL), NaI (71.9 mg, 0.48 mmol) was added. After the mixture was stirred at room temperature for 1 h, the solvent was removed by evaporation. The product was extracted with CH_2Cl_2 and the extract was filtered through filter paper. Removal of the solvent by evaporation gave product **4c** (116.4 mg, 98%) as a pale-yellow oil. ^{1}H NMR, δ: 1.10 (s, 6 H), 2.47 (s, 2 H), 2.86 (s, 2 H), 3.65 (s, 3 H), 3.82 (s, 2 H). ^{13}C NMR, δ: 8.4, 28.0, 32.7, 44.1, 48.1, 51.3, 172.6, 202.0. IR, ν/cm^{-1}: 3649, 3545, 3434, 2953, 2874, 2020, 1728, 1436, 1357, 1231, 1159, 1022, 928, 885, 720, 598. HR-MS (EI), found: *m/z* 298.0066 $[M]^+$. Calculated for $C_9H_{15}O_3I$: 298.0066.

Preparation of keto acid 2b—e (general procedure). Keto acids **2b—e** were synthesized by a modified version of the previously described procedure.[29] To a solution of the corresponding α,β-unsaturated ketone (5.0 mmol) and $RuCl_3$ (10.4 mg, 0.05 mmol) in a mixture of MeCN (30 mL) and water (20 mL), a mixture of Oxone® (4.61 g, 7.5 mmol) and $NaHCO_3$ (1.93 g, 23 mmol) was added by portions over a period of 10 min at room temperature. After the mixture was stirred at room temperature for 21 h, the solvent was removed by evaporation. The resulting aqueous solution was acidified by addition of concentrated H_2SO_4 (0.25 mL). The product was extracted with CH_2Cl_2 (5×80 mL) and the extracted product was purified by extraction with a saturated $NaHCO_3$ aqueous solution (80 mL). After washing with CH_2Cl_2 (10 mL), the aqueous solution was acidified to pH 1 with concentrated H_2SO_4. The product was extracted with CH_2Cl_2 (5×40 mL) and the extract was filtered through filter paper for dehydration. Removal of the solvent by evaporation gave the corresponding keto acids **2b—e**.

4-Oxopentanoic acid (2b) was synthesized from 3-methylcyclopent-2-enone in 49% yield as a colorless oil. ^{1}H NMR, δ: 2.20 (s, 3 H), 2.63 (t, 2 H, *J* = 6.4 Hz), 2.76 (t, 2 H, *J* = 6.6 Hz), 7.5—12.0 (br.s, 1 H). ^{13}C NMR, δ: 27.8, 29.8, 37.7, 178.7, 206.7. ^{1}H and ^{13}C NMR data are consistent with those reported in the literature.[41]

5-Oxohexanoic acid (2c) was synthesized from 3-methylcyclohex-2-enone in 64% yield as a colorless oil. ^{1}H NMR, δ: 1.90 (quint, 2 H, *J* = 7.3 Hz), 2.16 (s, 3 H), 2.40 (t, 2 H, *J* = 7.3 Hz), 2.55 (t, 2 H, *J* = 7.3 Hz), 7.4—11.8 (br.s, 1 H). ^{13}C NMR, δ: 18.5, 30.0, 32.9, 42.3, 179.3, 208.2. ^{1}H and ^{13}C NMR data are consistent with those reported in the literature.[41]

3-Methyl-5-oxohexanoic acid (2d) was synthesized from 3,5-dimethylcyclohex-2-enone in 61% yield as a colorless oil. ^{1}H NMR, δ: 1.01 (d, 3 H, *J* = 6.9 Hz), 2.15 (s, 3 H), 2.27 (dd, 1 H, *J* = 15.6 Hz, *J* = 6.9 Hz), 2.37 (d, 1 H, *J* = 5.9 Hz), 2.40 (d, 1 H, *J* = 7.8 Hz), 2.44—2.61 (m, 2 H). ^{13}C NMR, δ: 19.9, 26.0, 30.4, 40.5, 49.7, 178.6, 208.1. IR, ν/cm^{-1}: 2962, 1709, 1407, 1370, 1162, 1087, 957, 911. HR-MS (EI), found: *m/z* 144.0787 $[M]^+$. Calculated for $C_7H_{12}O_3$: 144.0786.

2-Methyl-5-oxohexanoic acid (2e) was synthesized from 3,6-dimethylcyclohex-2-enone[42] in 66% yield as a colorless oil. ^{1}H NMR, δ: 1.21 (d, 3 H, *J* = 7.3 Hz), 1.72—1.84 (m, 1 H), 1.84—1.96 (m, 1 H), 2.16 (s, 3 H), 2.44—2.61 (m, 3 H). ^{13}C NMR, δ: 17.1, 27.1, 30.0, 38.5, 41.0, 182.4, 208.3. IR, ν/cm^{-1}: 2973, 1707, 1464, 1415, 1362, 1170, 1127, 1068, 910, 810, 747. HR-MS (EI), found: *m/z* 145.0864 $[M + H]^+$. Calculated for $C_7H_{13}O_3$: 145.0865.

Methyl 6,6-dichloro-3,3-dimethyl-5-oxohexanoate (5a). To a solution of 2,2-dichloro-5,5-dimethylcyclohexane-1,3-dione[30] (418 mg, 2.0 mmol) in MeOH (10 mL), Na_2HPO_4 (142 mg, 1.0 mmol) was added. After the mixture was stirred at room temperature for 0.5 h, the residual Na_2HPO_4 was removed by filtration and washed with MeOH. The solvent was removed by evaporation, the product was extracted with hexane by sonication, and the extract was filtered through filter paper. Removal of the solvent by evaporation gave ester **5a** (466 mg, 97%) as a colorless oil. ^{1}H NMR, δ: 1.14 (s, 6 H), 2.50 (s, 2 H), 2.97 (s, 2 H), 3.65 (s, 3 H), 5.83 (s, 1 H). ^{13}C NMR, δ: 28.1, 32.6, 44.0, 44.3, 51.3, 70.5, 172.4, 195.7. ^{1}H and ^{13}C NMR data are consistent with those reported in the literature.[30]

Methyl 6,6,6-trichloro-3,3-dimethyloxohexanoate (5b). To a solution of 2,2-dichloro-5,5-dimethyl-cyclohexane-1,3-dione[30] (2.09 g, 10.0 mmol) and NCS (1.60 g, 12.0 mmol) in MeOH (100 mL), Na_2HPO_4 (7.10 g, 5.0 mmol) was added. After the mixture was stirred at room temperature for 1 h, the residual Na_2HPO_4 was removed by filtration and washed with MeOH. The solvent was removed by evaporation, the product was extracted with hexane by sonication and the extract was filtered through filter paper. Removal of the solvent by evaporation gave ester **5b** (2.65 g, 96%) as a colorless oil. ^{1}H NMR, δ: 1.17 (s, 6 H), 2.58 (s, 2 H), 3.23 (s, 2 H), 3.66 (s, 3 H). ^{13}C NMR, δ: 27.7, 32.8, 42.7, 44.1, 51.3, 96.7, 172.3, 189.2. IR, ν/cm^{-1}: 2953, 2879, 1735, 1437, 1391, 1353, 1230, 1196, 1153, 1121, 1075, 1012, 881, 831, 748, 696, 651, 624, 555. HR-MS (EI), found: *m/z* 275.0016 $[M + H]^+$. Calculated for $C_9H_{14}Cl_3O_3$: 275.0009.

Methyl 6-bromo-6,6-dichloro-3,3-dimethyl-5-oxohexanoate (5c). To a solution of 2,2-dichloro-5,5-dimethylcyclohexane-1,3-dione[30] (418 mg, 2.0 mmol) and NBS (534 mg, 3.0 mmol) in MeOH (10 mL), Na_2HPO_4 (142 mg, 1.0 mmol) was added. After the mixture was stirred at room temperature for 0.5 h, the residual Na_2HPO_4 was removed by filtration and washed with MeOH. The solvent was removed by evaporation, the product was extracted with hexane by sonication and the extract was filtered through filter paper. Removal of the solvent by evaporation gave ester **5c** (568 mg, 89%) as a colorless oil. ^{1}H NMR, δ: 1.18 (s, 6 H), 2.59 (s, 2 H), 3.30 (s, 2 H), 3.67 (s, 3 H). ^{13}C NMR, δ: 27.7, 32.9, 42.3, 44.1, 51.4, 81.7, 172.3, 189.5. IR, ν/cm^{-1}: 2954, 2877, 1738, 1437, 1392, 1348, 1230, 1153, 1072, 1013, 930, 888, 826, 705, 625, 536. HR-MS (EI), found: *m/z* 318.9499 $[M + H]^+$. Calculated for $C_9H_{14}BrCl_2O_3$: 318.9503.

Lactonization (general procedure). To a solution of haloketo acid methyl ester (0.20 mmol) in anhydrous MeOH (1 mL), $NaBH_4$ (9.1 mg, 0.24 mmol) was added. After the mixture was stirred at 0 °C for 0.5 h, the reaction was quenched by addition of water (200 μL) and 2*M* HCl aqueous solution (200 μL). The product was extracted with CH_2Cl_2 (2×20 mL). The extract was filtered with filter paper for dehydration and the solvent was removed by evaporation to obtain the corresponding alcohol. To the thus obtained alcohol, TFA (0.5 mL) was added, the resulting mixture was stirred at room temperature for 1 h and then diluted with CH_2Cl_2 (20 mL). After the reaction was quenched by addition of a saturated $NaHCO_3$ solution (20 mL), the product was extracted with CH_2Cl_2 (2×20 mL) and the extract was filtered with filter paper for dehydration. The removal of the solvent by evaporation gave the corresponding lactones **6a,b,d—g** and **7a,b**.

6-Chloromethyl-4,4-dimethyltetrahydropyran-2-one (6a) was synthesized from compound **4a** in 98% as a colorless oil. ^{1}H NMR, δ: 1.11 (d, 6 H, *J* = 3.2 Hz), 1.66 (dd, 1 H, *J* = 13.9 Hz, *J* = 12.3 Hz), 1.81 (dq, 1 H, *J* = 14.0 Hz, *J* = 2.0 Hz), 2.26 (d, 1 H, *J* = 17.2 Hz), 2.41 (dd, 1 H, *J* = 17.2 Hz, *J* = 2.1 Hz), 3.68 (d, 2 H, *J* = 4.6 Hz), 4.62 (ddd, 1 H, *J* = 11.9 Hz, *J* = 9.0 Hz,

J = 4.8 Hz). ^{13}C NMR, δ: 26.8, 29.8, 30.8, 39.0, 43.7, 46.3, 76.2, 170.6. IR, ν/cm^{-1}: 3493, 2961, 2873, 1739, 1469, 1431, 1373, 1313, 1239, 1208, 1153, 1087, 1058, 1034, 966, 924, 822, 732, 654, 628, 577. HR-MS (EI), found: m/z 177.0685 [M + H]$^+$. Calculated for $C_8H_{14}ClO_2$: 177.0682.

6-Bromomethyl-4,4-dimethyltetrahydropyran-2-one (6b) was synthesized from compound **4b** in 99% as a colorless oil. ^{1}H NMR, δ: 1.10 (d, 6 H, J = 4.1 Hz), 1.62 (dd, 1 H, J = 14.0 Hz, J = 11.9 Hz), 1.86 (dq, 1 H, J = 14.2 Hz, J = 2.0 Hz), 2.26 (d, 1 H, J = 17.2 Hz), 2.40 (dd, 1 H, J = 16.9 Hz, J = 2.1 Hz), 3.53 (d, 2 H, J = 5.0 Hz), 4.59 (dtd, 1 H, J = 11.9 Hz, J = 5.0 Hz, J = 4.0 Hz). ^{13}C NMR, δ: 26.9, 29.8, 30.8, 34.5, 40.1, 43.7, 75.8, 170.5. IR, ν/cm^{-1}: 3476, 3030, 2957, 2871, 2732, 1468, 1421, 1372, 1308, 1239, 1197, 1151, 1083, 1043, 991, 966, 925, 858, 817, 788, 676, 641. HR-MS (EI), found: m/z 221.0179 [M + H]$^+$. Calculated for $C_8H_{14}BrO_2$: 221.0177.

5-Bromomethyldihydrofuran-2-one (6d) was synthesized from compound **4d**[43] in 90% as a colorless oil. ^{1}H NMR, δ: 2.08—2.19 (m, 1 H), 2.40—2.51 (m, 1 H), 2.53—2.73 (m, 2 H), 3.55 (dd, 1 H, J = 11.0 Hz, J = 5.7 Hz), 3.58 (dd, 1 H, J = 11.0 Hz, J = 4.6 Hz), 4.72—4.80 (m, 1 H). ^{13}C NMR, δ: 26.2, 28.4, 34.1, 77.9, 176.3. ^{1}H and ^{13}C NMR data are consistent with those reported in the literature.[44]

6-Bromomethyltetrahydropyran-2-one (6e) was synthesized from compound **4e**[45] in 97% as a colorless oil. ^{1}H NMR, δ: 1.67—1.78 (m, 1 H), 1.82—2.05 (m, 2 H), 2.09—2.18 (m, 1 H), 2.48 (ddd, 1 H, J = 18.1 Hz, J = 9.8 Hz, J = 7.1 Hz), 2.63 (dddd, 1 H, J = 18.1 Hz, J = 6.6 Hz, J = 4.6 Hz, J = 1.2 Hz), 3.49 (dd, 1 H, J = 10.8 Hz, J = 6.1 Hz), 3.55 (dd, 1 H, J = 11.0 Hz, J = 4.6 Hz), 4.48—4.56 (m, 1 H). ^{13}C NMR, δ: 18.2, 26.3, 29.4, 33.8, 78.6, 170.4. ^{1}H and ^{13}C NMR data are consistent with those reported in the literature.[46]

6-Bromomethyl-4-methyltetrahydropyran-2-one (6f) was synthesized from compound **4f** in 96% as a colorless oil. IR, ν/cm^{-1}: 3442, 2958, 1733, 1457, 1422, 1382, 1234, 1086, 1053, 1022, 989, 926, 890, 869, 796, 658. HR-MS (EI), found: m/z 207.0018 [M + H]$^+$. Calculated for $C_7H_{12}BrO_2$: 207.0021.

trans-Isomer of **6f**. ^{1}H NMR, δ: 1.13 (d, 3 H, J = 6.9 Hz), 1.71—1.81 (m, 1 H), 1.97—2.06 (m, 2 H), 2.17—2.31 (m, 1 H), 2.56—2.66 (m, 1 H), 3.47 (dd, 1 H, J = 10.8 Hz, J = 6.7 Hz), 3.55 (dd, 1 H, J = 10.8 Hz, J = 5.1 Hz), 4.58—4.68 (m, 1 H). ^{13}C NMR, δ: 20.9, 23.7, 32.9, 33.3, 37.3, 75.7, 170.9.

cis-Isomer of **6f**. ^{1}H NMR, δ: 1.08 (d, 3 H, J = 6.2 Hz), 1.33—1.46 (m, 1 H), 2.04—2.16 (m, 4 H), 2.65—2.77 (m, 1 H), 3.47—3.55 (m, 2 H), 4.46—4.55 (m, 1 H). ^{13}C NMR, δ: 21.4, 26.4, 34.2, 35.1, 37.9, 78.4, 170.3.

6-Bromomethyl-3-methyltetrahydropyran-2-one (6g) was synthesized from compound **4g** in 99% as a colorless oil. ^{1}H and ^{13}C NMR data for compound **6g** are consistent with those reported in the literature.[47]

trans-Isomer of **6g**. ^{1}H NMR, δ: 1.32 (d, 3 H, J = 7.1 Hz), 1.53—1.69 (m, 2 H), 2.02—2.20 (m, 2 H), 2.41—2.54 (m, 1 H), 3.51 (dd, 2 H, J = 5.7 Hz, J = 2.3 Hz), 4.47—4.58 (m, 1 H). ^{13}C NMR, δ: 17.2, 27.5, 27.7, 34.5, 36.0, 79.3, 173.3.

cis-Isomer of **6g**. ^{1}H NMR, δ: 1.25 (d, 3 H, J = 6.8 Hz), 1.73—1.88 (m, 2 H), 2.07—2.20 (m, 2 H), 2.56—2.68 (m, 1 H), 3.45 (dd, 1 H, J = 10.9 Hz, J = 6.1 Hz), 3.53 (dd, 1 H, J = 11.0 Hz, J = 5.3 Hz), 4.47—4.58 (m, 1 H). ^{13}C NMR, δ: 16.2, 25.06, 25.10, 33.1, 33.3, 76.7, 174.9.

6-Dichloromethyl-4,4-dimethyltetrahydropyran-2-one (7a) was synthesized from compound **5a** in 97% as a colorless oil. ^{1}H NMR, δ: 1.14 (d, 6 H, J = 8.5 Hz), 1.81 (dd, 1 H, J = 14.0 Hz, J = 11.7 Hz), 1.98 (dq, 1 H, J = 14.0 Hz, J = 2.4 Hz), 2.29 (dd, 1 H, J = 17.3 Hz, J = 0.7 Hz), 2.43 (dd, 1 H, J = 17.3 Hz, J = 2.3 Hz), 4.74 (ddd, 1 H, J = 11.6 Hz, J = 3.7 Hz, J = 4.6 Hz), 5.89 (d, 1 H, J = 3.7 Hz). ^{13}C NMR, δ: 26.3, 29.6, 30.6, 35.0, 43.7, 72.5, 79.4, 169.3. IR, ν/cm^{-1}: 3476, 2959, 2874, 1742, 1469, 1373, 1234, 1152, 1096, 1054, 994, 964, 920, 896, 824, 770, 751, 656, 574. HR-MS (EI), found: m/z 211.0289 [M + H]$^+$. Calculated for $C_8H_{13}Cl_2O_2$: 211.0293.

4,4-Dimethyl-6-trichloromethyltetrahydropyran-2-one (7b) was synthesized from compound **5b** in 99% as a white powder. ^{1}H NMR, δ: 1.15 (s, 3 H), 1.17 (s, 3 H), 1.81 (dd, 1 H, J = 14.0 Hz, J = 11.4 Hz), 2.23 (ddd, 1 H, J = 14.0 Hz, J = 2.5 Hz, J = 4.8 Hz), 2.31 (dd, 1 H, J = 17.4 Hz, J = 0.7 Hz), 2.47 (dd, 1 H, J = 17.4 Hz, J = 2.5 Hz), 4.86 (dd, 1 H, J = 11.4 Hz, J = 4.8 Hz). ^{13}C NMR, δ: 26.1, 29.8, 30.5, 37.3, 43.3, 85.1, 99.4, 168.6. IR, ν/cm^{-1}: 3468, 2961, 2874, 1756, 1471, 1371, 1268, 1226, 1155, 1107, 1068, 1031, 969, 924, 901, 822, 783, 768, 678, 635, 615, 583, 534. HR-MS (EI), found: m/z 244.9910 [M + H]$^+$. Calculated for $C_8H_{12}Cl_3O_2$: 244.9903.

***S*-[(6-Oxotetrahydro-2*H*-pyran-2-yl)methyl] ethanethioate (8).** To a solution of compound **6e** (38.6 mg, 0.20 mmol) in THF (1 mL), AcSK (30.4 mg, 0.40 mmol) was added. After the mixture was stirred at 60 °C for 12 h, the solvent was removed by evaporation. The product was dissolved in CH_2Cl_2 and the extract was filtered through filter paper. Removal of the solvent by evaporation gave product **8** (37.7 mg, quantitative yield) as a pale-yellow oil. ^{1}H NMR, δ: 1.58 (dtd, 1 H, J = 13.8 Hz, J = 11.1 Hz, J = 5.4 Hz), 1.79—2.07 (m, 3 H), 2.38 (s, 3 H), 2.46 (ddd, 1 H, J = 18.1 Hz, J = 9.2 Hz, J = 7.1 Hz), 2.59 (dddd, 1 H, J = 17.9 Hz, J = 7.1 Hz, J = 5.0 Hz, J = 1.2 Hz), 3.14 (dd, 1 H, J = 14.3 Hz, J = 6.3 Hz), 3.22 (dd, 1 H, J = 14.3 Hz, J = 5.4 Hz), 4.36—4.45 (m, 1 H). ^{13}C NMR, δ: 18.2, 26.7, 29.3, 30.5, 33.6, 78.9, 170.9, 195.1. IR, ν/cm^{-1}: 3509, 2952, 1732, 1693, 1419, 1356, 1239, 1138, 1044, 960, 934, 754, 631. HR-MS (EI), found: m/z 189.0584 [M + H]$^+$. Calculated for $C_8H_{13}O_3S$: 189.0585.

6-(Iodomethyl)tetrahydro-2*H*-pyran-2-one (9). To a solution of compound **6e** (38.6 mg, 0.20 mmol) in acetone (4 mL), NaI (149.9 mg, 1.00 mmol) was added. After the mixture was stirred at 60 °C for 6 h, the solvent was removed by evaporation. The product was dissolved in CH_2Cl_2 and the extract was filtered through filter paper. Removal of the solvent by evaporation gave product **9** (48.0 mg, quantitative yield) as a pale-yellow oil. ^{1}H NMR, δ: 1.26 (dtd, 1 H, J = 14.2 Hz, J = 11.1 Hz, J = 5.4 Hz), 1.83—2.04 (m, 2 H), 2.14—2.24 (m, 1 H), 2.47 (ddd, 1 H, J = 18.1 Hz, J = 9.7 Hz, J = 7.2 Hz), 2.64 (dddd, 1 H, J = 18.1 Hz, J = 6.9 Hz, J = 4.8 Hz, J = 1.4 Hz), 3.33 (dd, 1 H, J = 18.1 Hz, J = 6.5 Hz), 3.38 (dd, 1 H, J = 18.1 Hz, J = 4.7 Hz), 4.25—4.35 (m, 1 H). ^{13}C NMR, δ: 7.5, 18.2, 28.0, 29.2, 78.8, 170.5. IR, ν/cm^{-1}: 3433, 2953, 1734, 1461, 1440, 1415, 1351, 1245, 1170, 1077, 1026, 933, 870, 854, 818, 757, 621, 530. HR-MS (EI), found: m/z 239.9644 [M]$^+$. Calculated for $C_6H_9O_2I$: 239.9647.

6-(Azidomethyl)tetrahydro-2*H*-pyran-2-one (10). To a solution of compound **6e** (38.6 mg, 0.20 mmol) in DMF (1 mL), NaN_3 (26.0 mg, 0.40 mmol) was added. After the mixture was stirred at room temperature for 7 h, the solvent was removed by evaporation. The product was dissolved in CH_2Cl_2 and the extract was filtered through filter paper. The filtrate was concentrated by evaporation and the residue was purified by silica gel chromatography (CH_2Cl_2) to obtain product **10** (19.2 mg, 62%) as a colorless oil. ^{1}H NMR, δ: 1.58—1.80 (m, 1 H), 1.80—2.06

(m, 3 H), 2.42—2.55 (m, 1 H), 2.57—2.70 (m, 1 H), 3.46 (dd, 1 H, J = 13.2 Hz, J = 5.1 Hz), 3.52 (dd, 1 H, J = 13.0 Hz, J = 4.6 Hz), 4.41—4.50 (m, 1 H). ^{13}C NMR, δ: 18.4, 25.1, 29.5, 54.4, 78.6, 170.5. IR, ν/cm^{-1}: 3452, 2941, 2104, 1720, 1445, 1250, 1189, 1162, 1059, 974, 934, 845, 781, 668, 634, 557. HR-MS (EI), found: m/z 156.0771 $[M + H]^+$. Calculated for $C_6H_{10}N_3O_2$: 156.0773.

6-[(Phenylamino)methyl]tetrahydro-2*H*-pyran-2-one (11). To a solution of compound **6e** (38.6 mg, 0.20 mmol) in MeCN (1 mL), aniline (93.1 mg, 1.00 mmol) and $NaHCO_3$ (84.0 mg, 1.00 mmol) were added. After the mixture was refluxed with stirring for 24 h, the solvent was removed by evaporation. The filtrate was concentrated by evaporation and the residue was purified by silica gel chromatography (AcOEt—hexane (1 : 1)) to obtain product **11** (23.4 mg, 57%) as a white powder. ^{1}H NMR, δ: 1.50—1.78 (m, 1 H), 1.78—2.02 (m, 3 H), 2.36—2.55 (m, 1 H), 2.55—2.68 (m, 1 H), 3.31 (dd, 1 H, J = 13.7 Hz, J = 7.3 Hz), 3.44 (dd, 1 H, J = 14.2 Hz, J = 3.7 Hz), 4.51—4.60 (m, 1 H), 6.66 (d, 2 H, J = 7.8 Hz), 6.76 (t, 1 H, J = 7.5 Hz), 7.20 (dd, 2 H, J = 10.5 Hz, J = 9.6 Hz). ^{13}C NMR, δ: 18.3, 25.5, 29.5, 48.4, 78.9, 113.4, 118.4, 129.4, 147.2, 171.4. IR, ν/cm^{-1}: 3383, 3050, 2951, 1731, 1603, 1507, 1461, 1439, 1378, 1328, 1241, 1166, 1058, 1030, 992, 933, 876, 755, 696, 666, 639, 613, 598, 564, 535, 515. HR-MS (EI), found: m/z 205.1100 $[M]^+$. Calculated for $C_{12}H_{15}NO_2$: 205.1103.

This work was financially supported by a Grant-in-Aid for Scientific Research C (JSPS KAKENHI (C) Grant Number 19K05466) from JSPS and the Uruma Fund for the Promotion of Science. T.D. acknowledges support from the Ritsumeikan Global Innovation Research Organization (R-GIRO) project.

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Received September 30, 2019;
in revised form March 18, 2020;
accepted July 8, 2020