A Facile Ring Enlargement Reaction *via* β-Oxido Carbenoid[1)]

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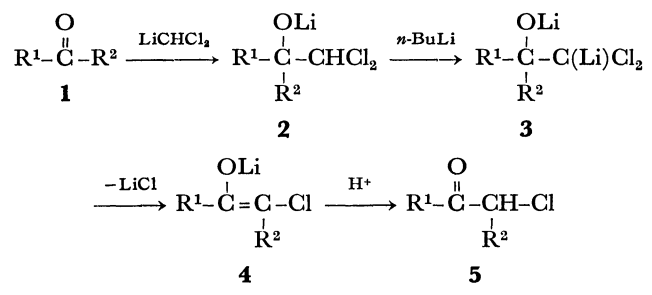
A general method of transforming a cyclic ketone to the next higher ring homolog chlorinated at the α-carbon or alternatively to its parent ketone is described. Treatment of a dichloromethyllithium-carbonyl adduct **2** with butyllithium affords a β-oxido carbenoid **3** at low temperature. Upon warming, **3** decomposes to a lithium enolate **4**, which is quenched with diluted hydrochloric acid to give the α-chloro ketone **5**. Cycloalkanone is converted to a one-carbon ring enlarged halogenated ketone. Meanwhile, dibromomethylcarbinol **7** is transformed to the halogen-free ketone **8** *via* monobromo β-oxido carbenoid upon treatment with butyllithium. α-Methyl substituted ketone is exclusively converted to the β-methyl substituted homolog and therefore *dl*-muscone is synthesized from cyclotetradecanone according to this new method.

The construction of the desired medium or large ring structure can be performed easily by ring enlargement of readily available cyclic compounds.[2)] The one-carbon ring expansion is most important and has been attained by either (a) diazomethane reaction[3)] or (b) the Tiffeneau-Demjanov rearrangement.[4)] However, preparative disadvantages arise from either the complex mixture being formed in the method (a) or from the number of steps required in the method (b).[5)] In addition, regioselectivity can hardly be expected when these methods are applied to an α-substituted or an α,β-unsaturated cyclic ketone. In this report we describe a new method, which is not only simple and convenient, but is highly regioselective. The method is based on smooth decomposition of a β-oxido carbenoid to a lithium enolate.

Synthesis of α-Chloro Ketones.[1a,6)] Nucleophilic addition of dichloromethyllithium to a carbonyl component **1** proceeds smoothly at low temperature to afford a lithium (dichloromethyl)alkoxide **2**. Treatment of the solution with butyllithium at −95 °C, gradual warming to 0 °C, and quenching with diluted hydrochloric acid yielded a one-carbon homologated α-chloro ketone **5**. The reaction obviously involves initial formation of the dilithiated intermediate, β-oxido carbenoid **3**, followed by decomposition to the enolate **4** as shown in Scheme 1.

From benzaldehyde (**1a**), phenacyl chloride (**5a**) was obtained in 72% yield. The possible phenyl migration



a: R^1=Ph, R^2=H
b: R^1=*n*-C_8H_{17}, R^2=H
c: R^1=2-furyl, R^2=H
d: R^1=$(CH_3)_2C{=}CH(CH_2)_2C(CH_3){=}CH$–, R^2=H
e: R^1, R^2=$-(CH_2)_{11}-$
f: R^1, R^2=$-(CH_2)_4-$

Scheme 1.

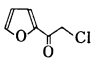
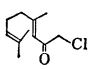
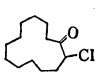
producing PhCHClCHO was anticipated, but the NMR assay of the reaction product indicated the absence of any isomer other than **5a** before and after purification.

The reaction of PhCDO (98% D content)[7)] gave PhCOCHDCl (97% D content) after recrystallization from the crude product. This is a token indicating the intermediacy of the enolate **4a** resulting from intramolecular carbene insertion to the adjacent C–H bond of β-oxido carbenoid.

The conversion of cyclic ketones to the one-carbon ring enlarged chloro ketones was performed under similar conditions. Sequential treatment of cyclododecanone (**1e**) with dichloromethyllithium at −78 °C and then with butyllithium at −30 °C afforded 46% of 2-chlorocyclotridecanone (**5e**).

Similarly, nonanal (**1b**), furfural (**1c**), citral (**1d**), and cyclopentanone (**1f**) gave the one-carbon homologated chloro ketones in the yield as shown in Table 1.

Table 1. Preparation of α-chloro ketone

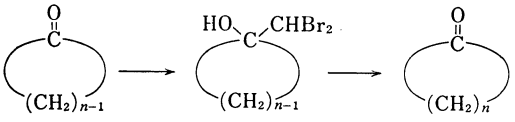
Carbonyl compd	α-Chloro ketone	Yield, %
PhCHO **1a**	$PhCOCH_2Cl$ **5a**	72
$CH_3(CH_2)_7CHO$ **1b**	$CH_3(CH_2)_7COCH_2Cl$ **5b**	62
 **1c**	 **5c**	62
 **1d**	 **5d**	51
 **1e**	 **5e**	46
 **1f**	 **5f**	64

One-Carbon Ring Enlargement of Cyclic Ketones. The next problem was the synthesis of halogen-free ketones under one-carbon homologation, which required generation of monohalo β-oxido carbenoids. This was attained by the lithium-halogen exchange proceeding upon treatment of lithium (dibromomethyl)alkoxide with

butyllithium.

The dibromides **7** were readily prepared from cyclic ketones **6** by the previous method.[8] Treatment with butyllithium in tetrahydrofuran (THF) gave the homologous ketones **8** as shown in Table 2. Thus a two step, facile transformation of a cyclic ketone to a next higher ring homolog has been established.

Table 2. Preparation of cycloalkanones from 1-dibromomethylcycloalkanols



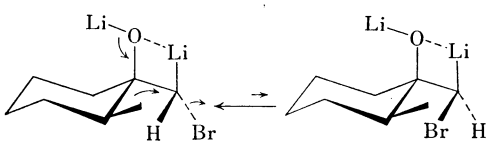
6 **7** **8**

Dibromide	n	Product	Yield, %
7a	12	**8a**	89
7b	8	**8b**	87
7c	7	**8c**	80
7d	6	**8d**	70
7e	5	**8e**	92

Regioselectivity in the Ring Enlargement Reaction. 2-Methylcyclohexanone gives the dibromide **9b**, whose treatment with butyllithium afforded methylcycloheptanone. Yields and isomer ratios under various reaction conditions are listed in Table 3. Thus, the regioselectivity is highly dependent upon the nature of solvent and the reaction temperature. When the reaction was conducted at −95 °C in ether, 3-methylcycloheptanone (**10b**) was obtained with high selectvity (97: 3). At −45 °C a significant amount of 2-methylcycloheptanone was produced. THF as a solvent was characterized by higher selectivity giving 3-methyl ketone **10b** almost exclusively. In ether, **10b** still dominated, but significant amount of 2-methyl ketone **11b** was produced at −78 °C. In hexane solvent the regioselectivity was scarcely observed, and the yield was poor. The low yield in THF was ascribed to the thermal lability of dibromide **9b** even at −78 °C.

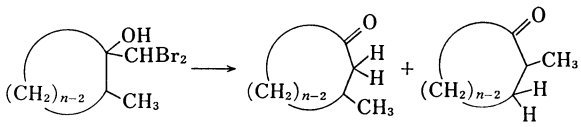
The high selectivity was observed as well in the larger ring system. Under similar procedure the dibromide **9c** (n=12) afforded 96% isolated yield of 3-methylcyclotridecanone (**10c**) in 99% selectivity.

The regioselectivity is rationalized by assuming the contribution of β-oxido carbenoid **12** and **13** (from the dibromide **9b**) to be in equilibrium. The absence of repulsion between bulky bromine and methyl group should favor **12** thermodynamically over **13**. Curved arrows indicate that simultaneous elimination of Br^- and selective migration of methyl substituted carbon should afford the observed 3-methylcycloheptanone (**10b**) in preference.



12 **13**

Table 3. Product distribution of ring expansion reaction of 1-dibromomethyl-2-methylcycloalkanol



9 **10** **11**

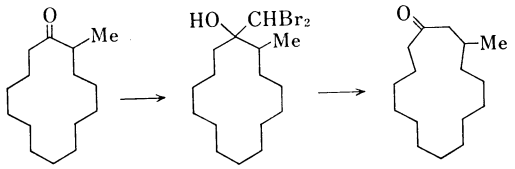
Dibromide	n	Temp[b] °C	Solvent	Isomer distribution **10**:**11**	Yield[d] % (**10**+**11**)
9a-*trans*[e]	5	−78	THF	69:31	90
9a-*cis*[e]	5	−78	THF	49:51	73
9b[f]	6	−78	THF	98:2	29[g]
9b	6	−95	THF	99:1	51
9b	6	−45	ether	86:14	62
9b	6	−78	ether	95:5	82
9b	6	−95	ether	97:3	86
9b	6	−78	hexane	66:34	71
9b	6	−95	hexane	65:35	68
9c[h]	12	−78	THF	99:1	(96)
9d[i]	14	−78	THF	97:3[j]	(79)

a) Prepared according to the previously reported procedure.[8] b) Cooling bath temperature. c) Determined by GLPC assay on analytical samples before bulk purification. d) The yields were determined by analytical GLPC using an internal standard: isolated yields in parentheses. e) Reaction of cyclopentanone with dibromomethyllithium afforded **9a** in a ratio of *trans*: *cis*=7: 3. The isomers were separated by preparative TLC. The stereochemical course of the reaction was estimated by the analogy in similar systems. See, for example, E.C. Ashby and J. T. Laemmle, *Chem. Rev.*, **75**, 521 (1975). f) Only one isomer was detected from the reaction of dibromomethyllithium and 2-methylcyclohexanone. 2-Methylcyclohexanone is known to be attacked from the equatrial side to a large extent. It has been suggested that the 2-methyl group introduces a pseudo-axial hydrogen into the molecule which increases hindrance of attack from the axial side; see G. Chauviere, Z. Welvart, D. Eugene, and J. Richer, *Can. J. Chem.*, **47**, 3285 (1969). g) Low yield of this reaction was due to the thermal lability of dibromide **9b** even at −78 °C. h) Mixture of stereoisomers (≈4:1 by NMR assay). i) Mixture of stereoisomers (≈8: 1 by NMR assay). j) Estimated by NMR analysis.

The effectiveness of THF may be attributed to the increased stability of the β-oxido carbenoid because of the solvation of THF for lithium atom.[5] Since the β-oxido carbenoid is stabilized more in THF than in less polar solvent such as ether or hexane, the species is supposed to have enough time for establishment of the equilibrium **12**⇄**13**, which should result in the observed high regioselectivity.

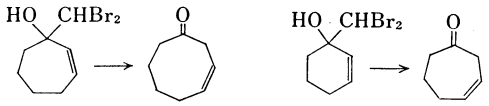
The novel reaction of remarkable regioselectivity has a wide applicability as exemplified by the following *dl*-muscone synthesis.[9] Addition of dibromomethyllithium to 2-methylcyclotetradecanone (**14**) afforded 1-

dibromomethyl-2-methylcyclotetradecanol (**9d**) in 78% yield. The dibromide **9d** was transformed into *dl*-muscone (**10d**) exclusively (≈97% of selectivity) in 79% yield by the reaction with butyllithium.



14 **9d** **10d**

The present method is successfully applied also to the regioselective ring enlargement of α,β-unsaturated cyclic ketone affording β,γ-unsaturated ketone. Treatment of the dibromide **15a** and **15b** with butyllithium gave 3-cyclooctenone (**16a**) (85% yield, 98% of selectivity) and 3-cycloheptenone (**16b**) (76% yield, 95% of selectivity) respectively.



15a **16a** **15b** **16b**

Experimental

The IR spectra were determined on a Shimadzu IR-27-G spectrometer; the mass spectra on a Hitachi RMU-6L mass spectrometer; the GLPC analyses on a Yanagimoto GCG-550F; and NMR spectra on a Varian EM-360 spectrometer. The chemical shifts are given in δ with TMS as the internal standard. The analyses were carried out by the staff at the the Elemental Analyses Center of Kyoto University. All the experiments were carried out under an atmosphere of dry nitrogen, preparative thin layer chromatography (PLC) on silica gel PF-254 plates (Merck) with benzene as an eluent, and preparative column chromatography on silica gel Wakogel C-100 (Wako). THF was purified by distillation from $LiAlH_4$. Ether and hexane were dried over Na metal.

Preparation of Dichloromethyllithium. To a stirred solution of dichloromethane (0.18 ml, 2.8 mmol) in dry THF (5 ml) butyllithium (2.4 mmol) was added drop by drop at −95°C. The resulting solution was stirred for 0.5 h at the same temperature and used immediately.

Preparation of Phenacyl Chloride. Benzaldehyde (212 mg, 2.0 mmol) was added slowly to a stirred solution of dichloromethyllithium (2.4 mmol) at −95 °C. The reaction mixture was stirred for 2 h at the same temperature. To the solution, butyllithium (3.6 mmol) was added dropwise at −95 °C. The resulting mixture was warmed gradually to 0 °C for 20 min, and then quenched with 1M hydrochloric acid. The aqueous layer was separated and extracted with ether 3 times. All organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Preparative TLC of the residue gave 223 mg (72%) of phenacyl chloride: IR (KBr) 1699, 1600 cm^{-1}; NMR (CCl_4) δ 4.52 (s, 2H), 7.30—8.05 (m, 5H); mass *m/e* (%) 156 (1), 105 (100).

PhCDO was obtained from benzil by the method of Burgstahler.[7]

PhCOCHDCl: NMR (CCl_4) δ 4.52 (s, 1H); mass *m/e* (%) 157 (1), 105 (100).

The reactions of aldehydes, such as furfural, nonanal, and citral, were carried out according to the above procedure, and the yields of the corresponding chloromethyl ketones are summarized in Table 1. The spectral and analytical data of the products are listed below.

1-Chloro-2-decanone: IR (neat) 1719 cm^{-1}; NMR (CCl_4) δ 3.89 (s, 2H); mass *m/e* (%) 190 (1), 141 (59), 57 (100).

2-(Chloroacetyl)furan: IR (neat) 1682 cm^{-1}; NMR (CCl_4) δ 4.46 (s, 2H), 7.23—7.72 (m, 3H); mass *m/e* (%) 146 (8), 95 (100); Found: C, 50.0; H, 3.6%. Calcd for $C_6H_5ClO_2$: C, 49.9; H, 3.5%.

1-Chloro-4,8-dimethyl-3,7-nonadien-2-one: IR (neat) 1710 cm^{-1}; NMR (CCl_4) δ 3.84 (s, 2H); mass *m/e* (%) 202 (1), 69 (100); Found: C, 65.5; H, 8.7%. Calcd for $C_{11}H_{17}ClO$: C, 65.8; H, 8.5%.

Preparation of 2-Chlorocyclotridecanone. To a stirred solution of dichloromethyllithium (2.4 mmol), a solution of cyclododecanone (364 mg, 2.0 mmol) in dry THF (2 ml) was added slowly at −78 °C. The resulting solution was stirred for 1.5 h at the same temperature, and for 0.5 h at −26 °C. To the solution butyllithium (6.0 mmol) was added at the same temperature. The resulting mixture was warmed gradually to 0 °C for 20 min, and then quenched with 1M hydrochloric acid. After extraction with ether, the combined organic layers were washed, dried, and then concentrated under reduced pressure. The residue was purified by preparative TLC affording 212 mg (46%) of 2-chlorocyclotridecanone: IR (neat) 1715 cm^{-1}; NMR (CCl_4) δ 4.20 (m, 1H); mass *m/e* (%) 232 (3), 98 (74), 55 (100). The preparation of 2-chlorocyclohexanone was carried out under the same procedure, and the yield is given in Table 1.

2-Chlorocyclohexanone: IR (neat) 1720 cm^{-1}; NMR (CCl_4) δ 4.32 (m, 1H); mass *m/e* (%) 134 (10), 117 (50), 55 (100).

Preparation of Cyclotridecanone. 1-Dibromomethylcyclododecanol (365 mg, 1.0 mmol) was dissolved in dry THF (3 ml) under nitrogen and cooled to −78 °C. To the stirred solution butyllithium (1.3 ml of a 1.6M hexane solution, 2.1 mmol) was added dropwise over a period of 30 min. The resulting pale yellow solution was stirred for 30 min at −78 °C and 5 min at 0 °C, quenched by pouring into ice cold 1 M hydrochloric acid, and extracted with ether 3 times. The ethereal layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford cyclotridecanone in 89% yield after preparative TLC on silica gel using benzene as an eluent: IR (neat) 1715 cm^{-1}; mass *m/e* (%) 196 (26), 55 (100).

The preparations of cycloalkanones, such as cyclohexanone, cycloheptanone, cyclooctanone, and cyclononanone were carried out according to the above procedure, and the yields of cycloalkanones are listed in Table 2. The product was identified by the comparison of its spectral data or mp of 2,4-dinitrophenylhydrazone derivative with those of the authentic specimen.

Reaction of 1-Dibromomethyl-2-methylcyclopentanol with Butyllithium. To a THF (5 ml) solution of 1-dibromomethyl-2-methylcyclopentanol (272 mg, 1.0 mmol), butyllithium (2.2 mmol) was added dropwise over a period of 10 min at −78°C. The resulting pale yellow solution was stirred for 1 h at −78 °C and 5 min at 0 °C, quenched by pouring into ice cold 1M hydrochloric acid, and extracted with ether. The GLPC analysis of the ethereal layers was performed using cycloheptanone as an internal standard. The yields and isomer ratios are given in Table 3.

Reaction of 1-Dibromomethyl-2-methylcyclohexanol with Butyllithium. The reactions under various conditions were carried out similarly as described above. The GLPC analyses of the ethereal layers were performed using cyclooctanone as an internal standard, and the results are summarized in Table 3.

Preparation of 3-Methylcyclotridecanone. To a solution of 1-dibromomethyl-2-methylcyclododecanol (370 mg, 1.0 mmol) butyllithium (2.2 mmol) was added dropwise over a period of 10 min at −95 °C. The resulting solution was stirred for 1 h at the same temperature and 5 min at 0 °C. Usual work up afforded a colorless oil after preparative TLC on silica gel using benzene as an eluent. Before and after purification, GLPC analyses showed that the oil contains 99% of 3-methylcyclotridecanone (yield 96%): IR (neat) 1710, 1370, 1124, 780 cm^{-1}; NMR (CCl_4) δ 0.95 (d, J=6, 3H), 1.06—1.88 (m, 18H), 2.00—2.60 (m, 5H); mass *m/e* (1) 210 (22), 125 (23), 110 (42), 55 (100).

Preparation of 2-Methylcyclotetradecanone. To a solution of diisopropylamine (0.77 ml, 5.5 mmol) in dry THF (5 ml) butyllithium (5.5 mmol) was added at 0°C and the resulting solution was stirred for 10 min. A solution of cyclotetradecanone (1.05 g, 5.0 mmol) in dry THF (3 ml) was added to the solution, and the reaction mixture was stirred for 30 min at 0°C. To the solution, hexamethylphosphoric triamide (HMPA) (1 ml) and methyl iodide (0.62 ml, 10 mmol) was added at −78 °C. The mixture was stirred for 30 min at the same temperature, and 2 h at room temperature. After extraction with ether, the ethereal layer was concentrated to afford 2-methylcyclotetradecanone (820 mg, 73%) after preparative TLC using benzene as an eluent: IR (neat) 1710, 1020, 720 cm^{-1}; NMR (CCl_4) δ 1.01—2.86 (m, 25H); mass *m/e* (%) 224 (22), 166 (15), 98 (30), 55 (100).

Preparation of 1-Dibromomethyl-2-methylcyclotetradecanol. A well-stirred solution of dibromomethane (0.73 ml) and 2-methylcyclotetradecanone (819 mg, 3.7 mmol) dissolved in dry ether (18 ml) cyclotetradecanone (819 mg, 3.7 mmol), dissolved in dry ether (18 ml) and dry THF (2 ml) was cooled to −78 °C. To the mixture, lithium 2,2,6,6-tetramethylpiperidide (prepared from 2,2,6,6-tetramethylpiperidine (1.14 g, 8.1 mmol) and butyllithium (3.3 ml of 2.4 M hexane solution at 0 °C) was added dropwise over a period of 2 h. The mixture was stirred for 30 min at that temperature. After hydrolysis at −78 °C, the resulting organic layer was extracted with ether, and the extract was washed with 1M hydrochloric acid 3 times and water. The mixture was dried over anhydrous Na_2SO_4, and condensed under reduced pressure to afford 1-dibromomethyl-2-methylcyclotetradecanol (1.14 g, 78%) after preparative TLC using hexane and ether mixture (15: 2) as an eluent: bp 190 °C (bath temp 2 Torr); IR (neat) 3580, 1460, 1154, 978, 708 cm^{-1}; NMR (CCl_4) δ 0.93 (d, J=6, $C\underline{H}_3$ of major isomer), 1.02 (d, J=6, $C\underline{H}_3$ of minor isomer), 5.78 (s, $C\underline{H}Br_2$ of major isomer), 5.86 (s, $C\underline{H}Br_2$ of minor isomer); mass *m/e* (%) 398 (trace), 225 (51), 55 (100). Found: C, 48.1; H, 7.6%. Calcd for $C_{16}H_{30}Br_2O$: C, 48.3; H, 7.6%.

Preparation of dl-*Muscone.* 1-Dibromomethyl-2-methylcyclotetradecanol (183 mg, 0.46 mmol) was dissolved in dry THF (2.5 ml) and cooled to −78 °C. The stirred solution, butyllithium (0.65 ml of a 1.6 M solution, 1.0 mmol) was added dropwise over a period of 10 min. The resulting solution was stirred for 1 h at −78 °C and 5 min at 0 °C, quenched by pouring into ice cold 1M hydrochloric acid, and extracted with ether. The ethereal layer was concentrated to afford *dl*-muscone (86 mg, 79%) after preparative TLC. Before purification, the product was shown by NMR analysis to contain 97% of 3-methylcyclopentadecanone (*dl*-muscone): bp 140 °C (bath temp 2 Torr); IR (neat) 1710, 1370, 1280, 1125, 1055, 790 cm^{-1}; NMR (CCl_4) δ 0.92 (d, J=6.5, 3H), 1.01—1.85 (m, 22H), 1.90—2.50 (m, 5H); mass *m/e* (%) 238 (21), 223 (9), 55 (100). Found: C, 80.4; H, 12.4%. Calcd for $C_{16}H_{30}O$: C, 80.6; H, 12.7%.

Preparations of 3-Cyclooctenone and 3-Cycloheptenone. These β,γ-unsaturated ketones were prepared from 1-dibromomethyl-2-cycloheptenol and 1-dibromomethyl-2-cyclohexenol respectively by the method similar to the preparation of 3-methylcyclotridecanone.

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