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Halolactonization Reaction Using N-haloimides[1)]

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Abstract□ Novel halactolactonizations using NBS (2), NIS(3), and NSP (4) in dry DMF were found to be the most reasonable and efficient procedures. The participation of $X^{\oplus}$ as the cyclization initiator could be clearly rationalized by experimental results and the regioselectivities of formed halolactones were reasonably elucidated by weakly bridged carbonium ion intermediate.

Keywords□ N-chlorosuccinimide, N-bromosuccinimide, N-iodosuccinimide, N-bromophthalimide, N-bromosaccharin, haloactonization, bromolactonization, N,N-dimethylformamide.

The reaction of a halonium ion intermediate, resulting from an electrophilic attack of a cyclization reagent on the double bond of an olefinic acid, with an internal nucleophile a CO_2H or $CO_2^{\ominus}$ group, is known as halolactonization[3)]. Since halolactonization is highly regio- and stereoselective, it has been valuably applied to synthetic organic chemistry[6)].

By means of halogen atoms of produced halolactones, halolactonization can be classified into three greups; chlorolactonization, bromolac tonization, and iodolactonization, and iodolactonization has been of a great utility value in synthetic organic chemistry[7)]. However, iodolactonization has been performed by treating the olefinic acid with KI and I_2 in basic (eg., $NaHCO_3$) aqueous medium[7)]. These drastic reaction conditions put limit on its scope and especially cause difficulty to the olefinic acid with important functional or protecting groups. Recently amild procedure involing the reaction of thallum salt of the olefinic acid with I_2 in ether was reported[8)], and two novel reactions, phenyl seleno-[9a,b,c,d)] and phenylsulfenolactonization[9c,e)] comparable to halolactonization in synthetic organic chemistry were developed. As far as far as we know, from the viewpoint of the convenienience, reagent for above-mentioned cyclizations, thallium ethoxide[8)], phenylselenochloride[9a,b,c)], phenylselenosuccinimide[9d)], phenylselenophthalimide[9a)] and phenylsulfur chloride [9c,e)] are all rather expensive, very toxic and/or unstable.

Eight years ago, one of us took part in the study of synthesis of optically active α-hydroxy acids using asymmetric halolactonizactonization of (S)-N-(α,β-unsaturatedacyl)prolines with N-bromosuccinimide (NBS) (2) in presence of potassiumetert-butoxide or without in dry N,N-dimethylformamide[10)]. This result was so impressive that we set about investigation on the possibility of its application to usual halolactonization, its limitations, and mechanism in connection with the studies of novel reactions of N-haloimides in aprotic polar solvents.

RESULTS AND DISCUSSION

Besides NBS, we used N-chlorosuccinimide (NCS) (1), N-iodosuccinimide (NIS) (3), N-bromophthalimide (NBP) (4) and N-bromosaccharin (NBSC) (5) as halolactonization reagents

1), 2a), 2b): See Literature Cited

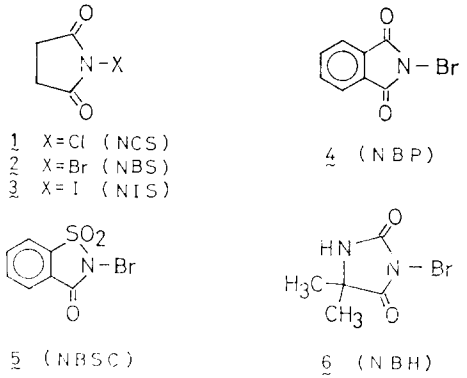

Fig. 1

as shown in Figure 1. And dry N, N-dimethylformamide (DMF), among some aprotic polar solvents, turned out the most appropriate solvent for halolactonization. Unlike the preceeding bromolactonization, potassium tert-butoxide was exclusively ruled out (vide infra).

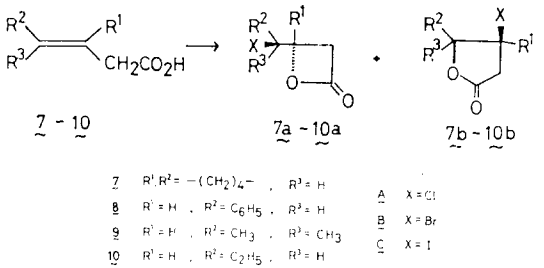

Fig. 2

Halolactonization of olefinic acids (**7**~**10**) showed following results (Fig. 2 and Table I).

Bromolactonization of **7** with NBS, NBP, NBSC gave γ-bromo-β-lactone **7aB** as a sole product in 88%, 79%, and 11% yields respectively. Of particular interest it is that iodolactonization of **7** with NIS led to the exclusive formation of β-iodo-γ-lactone **7bC** Halolactonization of **8** and **9** with NBS and NIS were separately effected to afford β-bromo-γ-lactone (**8bB**, **9bB**) or β-iodo-γ-lactone (**8bC**, **9bC**) as a sole product; **8bB** (54%), **9bB** (41%); **8bC** (66%), **9bC**[24] (16%). By treating **10** with NIS 50% yields of β-iodo-γ-lactone (**10cC**) as a sole product was obtained, but with NBS, both 30% yields of γ-bromo-β-lactone (**10aB**) and 49% yields of β-bromo-γ-lactone (**10bB**). However chlorolactonization of **8** and **10** with NCS barely gave 2.8% and

Table 1: Halolactonizations of 3-olefinic acids with following reagents (1.3 mol. eq.) at 2025°C for 20 hrs. under N_2.

Run No.	3-olefinic acid	Reagent	Yield (%)	
			a	b
1	7[11a]	NBS	88	0
2	7	NIS	0	56[8,11a]
3	7	NBP	79	0
4	7	NBSC	11	0
5	7	NBH[15]	91	0
6	8[11b]	NCS	(6.1)[23]	
7	8	NBS	0	54
8	8	NIS	0	66[8]
9	9[11c]	NBS	0	41
10	9	NIS	0	16[24]
11	10[11d]	NCS	(2.8)[23]	
12	10	NBS	30	49
13	10	NIS	0	50

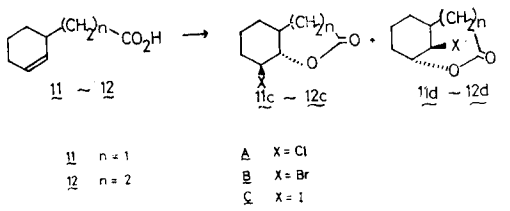

Fig. 3

Table II: Halolactonizations of olefinic acids 11 & 12(1.0eq.) with following reagents (1.3 mol. eq.) at 2025°C for 20 hrs. under N_2.

Run No.	3-Olefinic acid	Reagent	Halolactone(c) Yield (%)
1	11[12]	NCS	1.8[23]
2	11	NBS	83
3	11	NIS	83[11a,25]
4	11	NBP	90
5	11	NBSC	35
6	11	NBH[15]	82
7	12[12]	NBS	72
8	12	NIS	71
9	12	NBP	68
10	12	NBH[15]	82

6.1% yields of neutral components.

Halolactonization of cyclic-4-olefinic acid(**11**) and cyclic-4-olefinic acid (**12**) gave following results (Figure 3 and Table II).

Chlorolactonization of **11** with NCS gave 1.8 % of δ-chloro-γ-lactone **11cA** and this low reactivity of NCS agreed with the case of 3-olefinic acid as shown in Table 1. By using NBS, NBP, and NBSC, bromolatonizations of **11** were performed to give **11cB** in 83%, 90%, and 35 % yields respectively. By these results, NBS and NBP are more reactve reagents than NCS for halolactonization. Iodolactonization of **11** with NIS was effected to give iodolactone **11cC** in high yields (80%) as much as bromolactonization with NBS, and NBP. By treating **12** with NBS and NBP, ϵ-bromo-δ-lactone **12cB** was obtained in 72% and 68% yields.

The Heterolytic Cleavage of N-X Bond

It is not unambigous whether the cyclization initiator is $X^{\oplus}$ ($Cl^{\oplus}$, $Br^{\oplus}$, and $I^{\oplus}$) which is generated by a heterolytic cleavage of a N-X bond of the halolactonization reagent (**1**~**6**) in an aprtic polar solvent, dry DMF, or $X^{\delta\oplus}$ which has partial positive charge through inductive effect.

More recently we performed the asymmetric bromolactonization[13] of **7** by means of (S)(--)-3-bromo-5-phenylhydantoin in hope that if the reaction entity is $X^{\oplus}$ rather than $X^{\delta\oplus}$, the optically active bromolactone should be obtained, but the asymmetric bromolactonization was not accomplished. This result indicates the participation of $X^{\oplus}$ as the cyclization initiator.

From Table I and II, the reactivities of N-halosuccinimides follow the order; NIS≃NBS≫NCS. It is considered to be connected with the extent of solvation of $I^{\oplus}$, $Br^{\oplus}$, and $Cl^{\oplus}$ with dry DMF[14]. It can be another elucidation of the heterolytic cleavage of N-X bond.

For the purpose of rationalizing the participation of $X^{\oplus}$ (i.e., $Br^{\oplus}$) with the effect of counter anions (**1a**~**6a**) on reactivity as depicted in Figure 4 and designing the more convenient reagents by choosing the recommendable anion parts, bromolactonization employing NBS, NBP, NBSC, and 3-bromo-5, 5-dimethethylhydantoin (NBH) (**6**)[15] were performed. If there are the same participation of $X^{\oplus}$ as in the afore-mentioned N-halosuccinimide (**1**, **2**, **3**), relative reactivities appear to follow the order; NBP> NBH>NBS≫NBSC, since dissociation constants of conjugated acids such as succinimide (**1b**)[16a], phthalimide (**4b**)[16a], saccharin (**5b**)[16b], and 5,5-dimethylhydantoin(6b)[16c], are 3.2×10^{-10}, 5×10^{-9}, 2.1×10^{-12}, and 6.46×10^{-10} respectively.

For the purpose of comparing the effect of

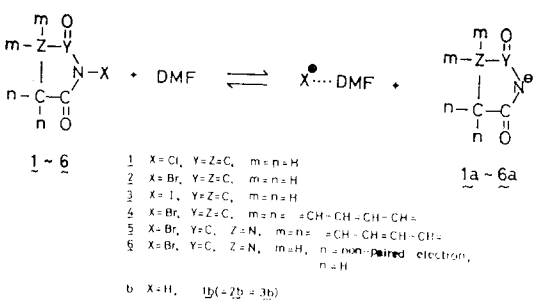

Fig. 4

1a~**6a** bromolactonization of **11** was effected to provide following reactivities; NBP (90%)> NBS (83%)>NBH (82%)>NBSC (35%) (Table II, Run Nos. 2, 4, 5, 6). It is completely in accordance with the order expected from the dissociation constants[17]. Therefore, it is thought to be apparent that the dissociation constants of **1b**, **4b**, **5b**, and **6b** affect the relative reactivities.

From the three kinds of the eluctdation, we come to the conclusion that this novel halolactonization is initiated by $X^{\oplus}$ generated from the N-X bond of the halolactonization in dry DMF.

The Role of the Anion (**1a**~**6a**)

Of special importance it is that the anion (**1a**~**6a**) can convert an olefinic acid, the substrate for halolactonization into a salt of the olefinic acid, which is requisite to usual halolactonization[7]. **1a**~**6a** are capacle of playing the same role as the base in case of general halolactonization condition in addition to the afore-mentioned role of $X^{\oplus}$ as the cyclization initiator For this reason, our novel procedure is the most reasonable and effective method, which can perfectly make up the drawback of usual iodolactonization, viz. aqueous basic media.

The Stereoselectivity

The halonlum ion formed from the reaction of the salt of the olefinic acid with the aforementioned $X^{\oplus}$, reacts with a intramolecular nucleophile, a carboxylate anion of the salt in the mode of intramolecular S_N reaation as the well-rationalized mechanism[7]. Therefore this reaction is considered to be perfectly stereoselective.

Recently the very high streeoselectivity of halolactonization arising from the complete trans-addition was proved by utilizing asymmetric synthesis of α-hydroxy acids from α,β unsaturated acids[10,18], and in case of the total synthesis employing halolactonization, the absolute configurations have been determined by X-ray crystallography[5b,5c]. Hence, the relative configuration of halolactones obtained by our procedure was tentatively assigned. The sole value of $J_{4,5}$ of NMR spectrum of **8bB** is accu rately read to 6.0 Hz, but from this spin-spin coupling constant it appear to be impossible to assign trans or cis[19].

The Regioselectivity

Although in case of 3-olefinic acids (Fig. 2) the formation of γ-halo β-lactone (**7a**~**10a**) and/or β-halo-γ-lactone (**7b**~**10b**) was expected, bromolactonization of **7** with NBS, NBP, and NBSC gave **7aB** exclusively but of **10** with NBS gave **10aB** and **10bB** in the ratio of 30 to 49 (Table I, Run Nos. 1, 3, 4, 12).

Considering that **7** and **10** were α,α,β-trisubstituted and α,β-disubstituted olefins, the regioselectivity can be rationalized, emploing weakly bridged carbonium ion intermediate[20] **7f**~**10f** and **7g**~**10g** rather than the covalent bromonium intermediate (**7e**~**10e**) (Fig. 5). That is, the exclusive formation of **7aB** implied the entire contribution of **7gB** and in case of 10, it is not unambigous whether the formation of **10aB** and **10bB** is due to the whole contribution of **10gB** as in case of **7** followed by rearrangement of **10aB** into **10bB** or the both contribution of **10gB** and **10fB.** However, we consider the latter more

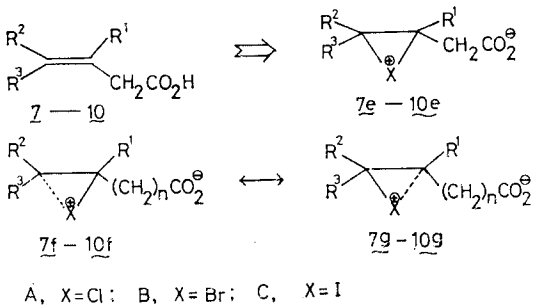

Fig. 5

feasible, since **10** is α,β-disubstituted olefin while **7** is α,α,β-trisubstituted.

Iodolactonization of **7** and **10** with NIS gave β-iodo-γ-lactone (**7bC, 10bC**) as more recently reported cyclization reactions of **7** with iodine[8], $PhSeCl$[9a,b,c], and $PhSCl$[9c,e].

In connection with bromolactonization of **7** and **10**, we can come to the conclusion that initially formed α-iodo-β-lactones **7aC, 10aC** were rearranged to thermodynamically contolled products **7bC, 10bC** as the case of phenylselenlactonization[9a,b,c], but γ-bromo-β-lactones **7aB, 10aB** were not rearranged. It is worthy of note that this result indicate the reactivity of Br, I, PhSe, and PhSe, and PhS as a leaving group; I≃PhSe≃PhS>Br. This suggest bromolactonization, which can be regio-and stereoselectively performed in excellent yields with NBS, NBP, and NBH[2,15], the more practical method for synthetic organic chemistry.

Bromolactonization and iodolactonization of **8** and **9** gave exclusively **8bB, 8bC** and **9bB, 9bC**[24]. It can be elucidated by the fact that in both cases **8fB, 8fC** and **9fB, 9fC** only contribute to the formation of β-bromo-γ-lactone (**8bB, 9bB**) or β-iodo-γ-lactone (**8bC, 9bC**[24]) because **8** is α-alkyl-β-phenyl substituted olefin and **9** is α-alkyl-β,β-dimethyl.

Although from 4-olefinic acid (**11**) the formation of δ-halo-γ-lactone (**11cB** and **11cB**) and/or γ-halo-δ-lactone (**11dB** and **11dC**) were anticipated as shown in Figure 2, **11cB** or **11cC** was obtained as a sole product. The exclusive formation of **11cB** or **11cC** appear to be rationalized by the favorable contribution of the entropy of activation, though according to the mode of substituted olefin **11gB** and **11gC** make the same contribution to the intermediate as **11fB** and **11fC** (Figure 6).

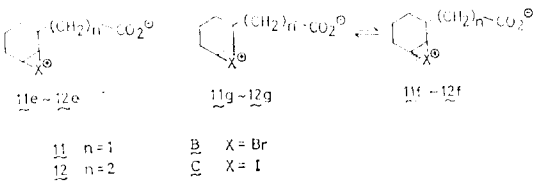

Fig. 6

In bromolactonization of 5-olefinic acid (**12**), though the formation of ϵ-halo-δ-lactone(**12cB** and **12cC**) and/or δ-halo-ϵ-lactone (**12dB** and **12dC**) was suggested, **12cB** and **12cC** were obtained as sole products. This fact can be explained by the same reason as for 4-olefinic acid (**11**).

EXPERIMENTAL METHODS

All melting points were uncorrected. IR spectra were measured with a Beckman IR 20A Infrared Spectrometer and were reported in ν_{max} cm^{-1}. ^1H NMR spectra were recorded on a Perkin-Elmer R32 NMR Spectrometer and were reported in δ from Me_4Si as an internal standard. Mass spectra measurement were executed with a AEI MS 1073 Spectrometer. Only the strongest and/or structually most important peaks were reported for IR and Mass spectra. All reactions were carried out by using anhyd. solvent and the combined organic extracts obtained in each experment were dried over anhyd. $MgSO_4$ followed by successive filtration and evaporation in vacuo. All yields referred to chromatographically and spectroscopically (^1H NMR) homogenous materials. NIS and NCS were available from Tokyo Kasei Kogyo Co.,

LTD., and NBP[21] and NBSC[23] were prepared according to the literatures.

Halolactonization

To the stirred 8.5% solution of a olefinic acid (1 mol. eq.) in dry DMF under nitrogen at 0°C (only for iodolactonization) or 20~25°C (for chloro-and bromolactonization) was added the 20% of a halolactonization reagent (1.3 mol. eq.) during 30 minutes. After being stirred at 20~25°C for 20 hours, the reaction mixrure was diluted with ethyl acetate, and the organic solution was sucessively washed with 5% Na HCO_3, H_2O, and sat. NaCl. Filtration and evaporation in vacuo gave crude halolactones, which were then columnchromatogrammed on a silica gel.

Bromolactonization of 7[11a]

Spiro [5,3]-1-oxacyclononan-2-one (**7aB**) (yield: NBS, 88%; NBP, 79%; NBSC, 11%): colorless, crystalline solid, mp 67°C (EtOAc-Benzene=1 : 10); Rf 0.42 (Hexane: Benzen=1: 10); IR (nujol) $\nu_{max}^{cm^{-1}}$ 1825 (β-lactone); NMR (CCl_4) δ 1.30~2.50 (m, 8H, $CH_2\times4$), 3.04 (1H, d, J=16.0 Hz, one of CH_2CO_2), 3.30 (1H, d, J=16.0 Hz, one of CH_2CO_2); Anal. Cacd. for $C_8H_{11}O_2Br$, C, 43.82; H, 5.06 Found C, 43.70; H, 5.09.

Bromolactonization of 8[11b]

4-Bromo-5-phenyltetrahydrofuran-2-one(**8bB**) (yield: NBS, 54%); colorless, crystalline solid, mp 55°C (EtOAc: Benzene=1 : 10); Rf 0.71 (Benzene:EtOAc:EtOH=20:2:3); IR (nujol) $\nu_{max}^{cm^{-1}}$ 1780 (γ-lactone); NMR (CCl_4) δ 2.85 (1H, dd, J=18 and 7.2 Hz, one of CH_2CO_2), 3.12 (1H, dd, J=18 and 6.6 Hz, one of CH_2CO_2), 4.10~4.45 (1H, m, CHBr), 5.55 (1H, d, J=6.0 Hz, CHO), 7.37 (5H, s, aromatics); Anal. Cacd. for $C_{10}H_9O_2Br$; C, 49.86; H, 3.77; Found C, 50.00; H, 3.77.

Bromolactonization of 9[11c]

4-Bromo-5,5-dimethyltetrahydrofuran-2-one(**9bB**) (yield: NBS, 41%): colorless, crystalline solid, mp 57°C (EtOAc: Benzene=1:1); IR (nujol) $\nu_{max}^{cm^{-1}}$ 1775 (γ-lactone); NMR (CCl_4) δ 1.53 (3H, s, CH_3), 1.56 (3H, s, CH_3), 2.83 (1H, dd, J=15 and 7.6 hz, one of CH_2CO_2), 3.17 (1H, dd, J=15 and 7.6Hz, one of CH_2CO_2), 4.37 (1H, dd, J=8.0 and 7.6 Hz, CHBr); Anal. CaCd. for $C_6H_9O_2Br$; C, 37.33; H, 4.70; Found C, 37.13; H, 4.81.

Bromolactonization of 10[11d]

4-(1-Bromoethyl)-oxetane-2-one (**10aB**) (yield: NBS, 30%): colorless, caramel; Rf 0.77 (Benzene: EtOAc: EtOH=20:2:3); IR (neat) $\nu_{max}^{cm^{-1}}$ 1835 (β-lactone); NMR (CCl_4) δ 1.13 (3H, t, J=7.7 Hz, CH_3), 1.52~2.42 (2H, m, CH_2), 3.27 (1H, dd, J=15 and 5.0Hz, one of CH_2CO_2), 3.59 (1H, dd, J=15 and 5.4 Hz, one of CH_2CO_2), 3.98 (1H, dt, J=3.6 and 7.7Hz, CHBr), 4.30~4.60 (1H,m, CHO).

4-Bromo-5-ethyltetrahydrofuran-2-one (**10bB**) (yield; NBS, 49%) colorless, caramel; Rf 0.46 (Benzene: EtOAc: EtOH=20:2:3; IR (neat) $\nu_{max}^{cm^{-1}}$ 1775 (γ-lactone); NMR(CCl_4) δ 1.09 (3H, t, J=6.8 Hz, CH_3), 1.55~2.27 (2H, m, CH_2), 2.78 (1H, dd, J=18 and 6.7Hz, one of CH_2CO_2), 3.95~4.35 (1H, m, CHBr), 4.37~4.65 (1H, m, CHO).

Iodolactonization of 9[11c]

5,5-Dimethyloxolone-2-one(**9bC**)[25](yield;NIS, 16%); pale yellow, caramel, Rf 0.51 (chloroform: EtOAc=20:1); IR(neat) $\nu_{max}^{cm^{-1}}$ 1765(γ-lactone); NMR (CCl_4) δ 1.40 (6H, s, CH_3x2), 2.00 (2H, t, J=8.0 Hz, CH_2CH_2), 2.50 (2H, t, J=8.0 Hz, CH_2CO).

Iodolactonization of 10[11d]

4-Iodo 5-ethyltetrahydrofuran-2-one (**10bC**) (yield: NIS, 50%): pale red, Rf 0.71(Hexane: Ether=1 : 2); IR(neat) $\nu_{max}^{cm^{-1}}$ 1785(γ-lactone): NMR (CCl_4) δ 1.10 (3H, t, J=7.0 Hz, CH_3),

1.40~2.10 (2H, m, CH_2), 2.82 (1H, dd, J= 18.0 and 9.0Hz, one of CH_2CO), 3.12 (1H, dd, J=18.0 and 9.0Hz), 3.88~4.28 (1H, m, CHI), 4.40~4.60 (1H, m, CHO).

Chlorolactonization of **11**[12]

9-Chloro-2-oxabicyclo [4,2,0] nonan-3-one (**11cA**) (yield: NCS, 1.8%); colorless, caramel: Rf 0.60 ($CHCl_3$: EtOAc=5 : 1); IR (neat) $\nu_{max}^{cm^{-1}}$ 1790 (γ-lactone); NMR (CCl_4) δ 0.90~2.90 (7H, m, $CH_2\times3$ and CH), 2.20 (1H, dd, J=18 and 3.0 Hz, one of CH_2CO_2), 2.52 (1H, dd, J=18 and 6.0 Hz, one of CH_2CO_2), 4.2~4.5 (2H, m, CHBr and CHO).

Bromolactonization of **11**[12]

9-Bromo-2-oxabicyclo [4,2,0] nonan-3-one (**11cB**) (yield: NBS, 83%; NBP, 90%; NBSC, 35%); colorless, crystalline solid, mp 59°C, Rf 0.5 (Benzene: EtOAc=10 : 1); IR (nujol) $\nu_{max}^{cm^{-1}}$ 1770 (α-lactone); NMR ($CDCl_3$) δ 1.12~3.02 (7H, m, $CH_2\times3$ and CH), 2.18 (1H, dd, J =22 and 3.2Hz, one of CH_2CO_2), 2.55 (1H, dd, J=22 and 6.0 Hz, one of CH_2CO_2), 1.32~4.60 (2H, m, CHBr and CHO); Anal, Cacd. for $C_8H_{11}O_2Br$; C, 43.86; H, 5.06; Found C, 43.74; H, 5.10.

Bromolactonization of **12**[12]

10-Bromo-2-oxabicyclo [4,4,0] decan-2-one (**12cB**) (yield: NBS, 72%; NBP, 68%); colorless, caramel, Rf 0.46(Benzene:EtOAc:EtOH= 20 : 2 : 3); IR (neat) $\nu_{max}^{cm^{-1}}$ 1740 (δ-lactone); NMR (CCl_4) δ 1.00~3.00 (11H, m, $CH_2\times5$ and CH), 4.35~4.67 (2H, m, CHBr and CHO); Mass m/e 233(M^+).

Iodolactonization of **12**[12]

5-(1-Iodopentyl) tetrahydrofuran-2 one(**12cC**) (yield: NIS, 71%); pale brown oil, Rf 0.53 ($CHCl_3$: EtOAc=9 : 1); IR 0neat) $\nu_{xma}^{cm^{-1}}$ 1735 (δ-lactone); NMR (CCl_4) δ 1.00~3.00 (11H, m, $CH_2\times5$, CH), 4.40~4.70 (2H, m, CHI and CHO).

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