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Lactonization of Methyl 4-Aryl-5-tosyloxyhexanoate *via* a Phenonium Ion.

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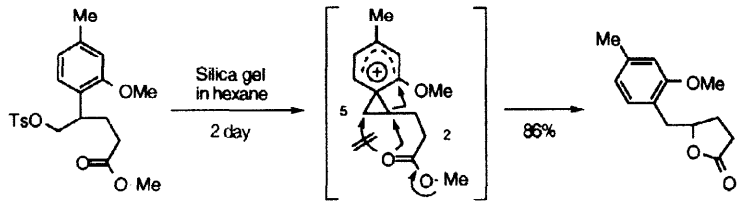
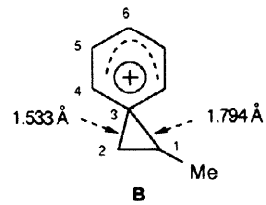
Abstract: Lactonization of methyl 4-aryl-5-tosyloxy hexanoate 3 via a phenonium ion gave γ-lactone 4 selectively under thermodynamical conditions while it afforded δ-lactone 5 preferentially under kinetic conditions.

The presence of the σ-bridged phenonium ion has been widely accepted based on stereochemical,[1] kinetic,[2] spectroscopic,[3] and theoretical evidence.[4] The features of the phenonium ion have been explored from many aspects. However, the intramolecular reaction of the ion has been rarely reported. We recently reported the novel lactonization of methyl 4-aryl-5-tosyloxypentanoate (**1**) concomitant with aryl rearrangement.[5]

Chart 1



Figure



In the intermediary phenonium ion (**A**), the ester group selectively attacked the C_4 position to give only γ-lactones. The selectivity could be rationalized by two different factors. One is an electronic factor. In the solvolysis of 2-phenyl-1-propyl tosylates in 80% EtOH, the highly selective phenyl rearrangement *via* the phenonium ion (**B**) has also been observed.[6] *Ab initio* MO calculation of **B** showed that the methyl group, attached to the cyclopropane site, caused the elongation of the C_1-C_3 bond to give the intermediate geometry in the "symmetrical bridge-asymmetric open" spectrum (Figure).[7] Thus, the positive character of the C_1 atom in **B** might be higher than that of the C_2 atom. In the case of **A**, it is equally suggested that the regioselectivity in the cyclization arises from the more highly positive character of the C_4 atom than that of the C_5 atom. The other is a stereoelectronic factor. According to the Baldwin rule, the 5-exo-tetrahedral cyclization is easy, while the 6-endo tetrahedral cyclization is generally difficult.[8,9] To clarify which factor was more essential for the regioselectivity and to extend the synthetic value of this new reaction, we carried out the lactonization of methyl 4-aryl-5-tosyloxyhexanoate (**3a-e**) *via* the phenonium ion, whose C_4 and C_5 positions were electronically unbiased.

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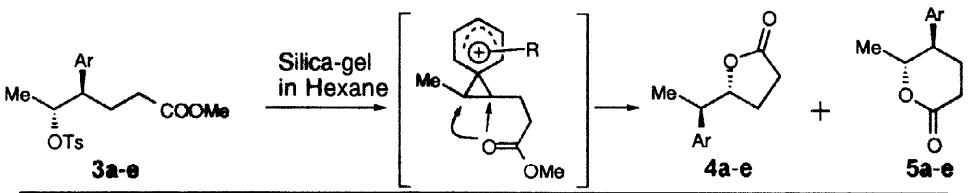
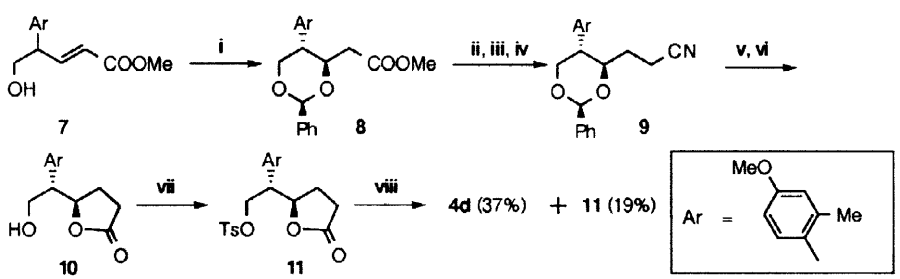
Table 1



Substrates	Ar	4 (yield)	5 (yield)	Ratio (4 : 5)	Time
3a	4'-methoxyphenyl	30%	42%	1 : 1.4	20 h
3b	2'-methoxyphenyl	11%	67%	1 : 6	10 h
3c	3',4'-dimethoxyphenyl	34%	36%	1 : 1.05	46 h
3d	4'-methoxy-2'-methylphenyl	7%	73%	1 : 10	15 h
3e	2'-methoxy-4'-methylphenyl	14%	68%	1 : 5	6 h

The results are summarized in Table 1. Typical procedure is as follows. A mixture of substrates **3**[10] (ca. 150 mg), silica gel (500 mg) and hexane (5 ml) was stirred for an adequate time at room temperature and then filtered. The filtrate was washed with sat. $NaHCO_3$ aq., concentrated and purified by column chromatography with silica gel. In all cases, γ-lactone (**4a-e**) and δ-lactone (**5a-e**) were obtained. The structures of the products were assigned on the basis of spectroscopic data. The stereochemistry of δ-lactone **5a-e** can be assigned as *anti* based on the coupling constant (10.5 Hz) between C_4-H and C_5-H in the ^{1}H-NMR spectrum. The stereochemistry of δ-lactone **5a-e** suggested that these compounds were formed not by the direct substitution of the tosyloxy group with the ester group, but by passing through the phenonium ion as well as γ-lactone **4a-e**.[11]

Chart 3

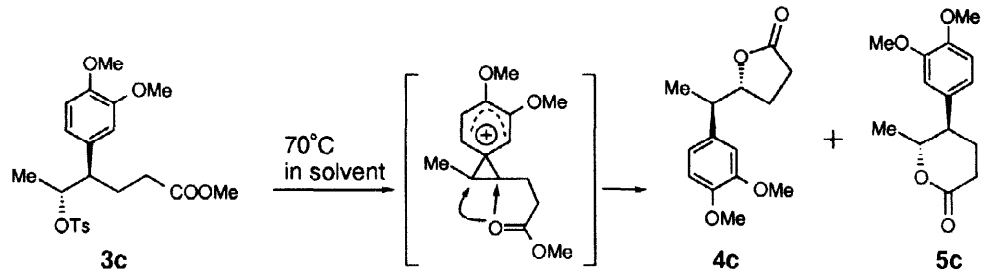


Conditions: i) PhCHO, ^{t}BuOK (21%) ii) $LiAlH_4$ (94%) iii) TsCl,Pyridine (74%) iv) NaCN (96%) v) KOH in EtOH, H_2O, reflux (60%) vi) Dowex in MeOH:H_2O (1:1), reflux (93%) vii) TsCl, Pyridine (85%) viii) $NaBH_4$ (5 eq.) in DMSO at 80°C

γ-Lactone **4d** was prepared by an alternative route as shown in Chart 3 to determine its relative configuration. The reaction of alcohol (**7**) with benzaldehyde in the presence of ^{t}BuOK afforded ketal (**8**) in 21% yield.[12] The coupling constant (10.7 Hz) between C_3-H and C_4-H in the ^{1}H-NMR spectrum of **8** suggested that its relative configuration was *trans*. Reduction of **8** with $LiAlH_4$ followed by a sequence of tosylation and cyanation afforded cyanate (**9**). Hydrolysis of **9** under basic conditions followed by treatment with Dowex in refluxing MeOH and H_2O gave γ-lactone (**10**). Conversion of **10** into **4d** was achieved by a sequence of tosylation and reduction with $NaBH_4$ in DMSO at 80°C. The ^{1}H-NMR spectroscopic data of the product was identical with that of **4d** obtained by lactonization *via* the phenonium ion. The relative configuration of **4d** was thus determined to be *anti*.

Isolated **4c** and **5c** were independently treated with 1 equivalent of TsOH and silica gel in hexane at room temperature for 46 h to clarify whether the interconversion between **4** and **5** occurred or not. As a result, it was shown that **5c** was scarcely converted into **4c** (**4c** : **5c** = 1 : 15). No isomerization was observed in the case of **4c**. Consequently, the ratio between **4** and **5** in Table 1 was attributed to the kinetically controlled regioselectivity for cyclization of the phenonium ion. Selective formation of γ-lactones **4a-e** was not observed in the lactonization of **3a-e**, while the lactonization of **1** proceeded selectively to form only γ-lactone **2**. If the stereoelectronic factor (Baldwin rule) contributed to the lactonization *via* the phenonium ion, γ-lactone would be preferentially formed in both cases. Thus, it can be concluded that the regioselectivity of the novel lactonization *via* the phenonium ion is controlled by the electronic factor.

Table 2



3c **4c** **5c**

Entry	Solvent	**4c** (yield)	**5c** (yield)	Ratio (**4c** : **5c**)	Time
1	CH_3NO_2	61%	3%	20 : 1	5 h
2	CH_3CN	60%	23%	2.6 : 1	6 h
3	AcOEt	44%	29%	1.5 : 1	10 d
4	^{t}BuOH	31%	39%	1 : 1.3	14 h
5	CH_3COOH	29%	41%	1 : 1.4	0.5 h

Next, we examined the lactonization of **3c** in various heated solvents without silica gel. The results are summarized in Table 2. The lactonization in ^{t}BuOH or CH_3COOH afforded a slight excess of δ-lactone **5c**, while the reaction in CH_3NO_2, CH_3CN or AcOEt gave γ-lactone **4c** preferentially. However, it was confirmed by monitoring the change in the composition of the reaction mixture with the passage of time that **5c** was preferentially formed at an early stage in also CH_3NO_2 and CH_3CN.

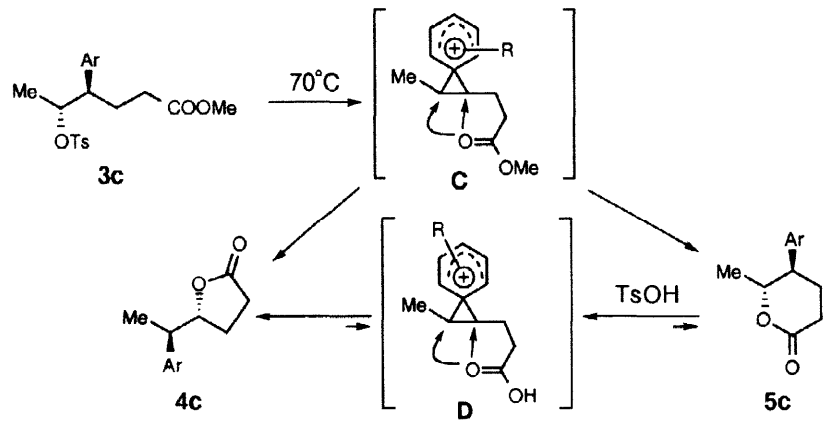
Table 3

δ-lactone **5c** —TsOH•H_2O, 70°C, in solvent→ γ-lactone **4c**

Entry	Solvent	**4c** (yield)	**5c** (yield)	Time
1	CH_3NO_2	99%	1%	2 h
2	CH_3CN	91%	5%	26 h
3	AcOEt	90%	2%	7 d
4	^{t}BuOH	0%	74%	2 d
5	CH_3COOH	94%	5%	2 d

Furthermore, treatment of isolated **5c** with 1 equivalent of $TsOH \cdot H_2O$ in various solvents at 70°C effected the phenyl rearrangement to afford **4c** (Table 3). This conversion did not proceed in the case of using TsOMe instead of TsOH. On the other hand, TsOH scarcely promoted conversion of isolated **4c** into **5c**. These findings suggested the reaction mechanism as shown in Chart 4 for the lactonization of tosylate **3c** in heated solvent without silica-gel. The phenonium ion **C**, which was spontaneously formed from **3c** at 70°C, undergoes the 6-endo cyclization selectively to give **5c** as a major product and then MeOH and TsOH are simultaneously formed.[13] The acid promotes conversion of **5c** into **4c** *via* the phenonium ion **D**. Consequently, the selectivities in Table 2 might be affected by the balance between the disappearance rate of **3c** and the rate in the conversion of **5c** into **4c**.

Chart 3



In conclusion, it was found the lactonization of **3** *via* the phenonium ion gave γ-lactone **4** selectively under thermodynamically controlled conditions while it afforded δ-lactone **5** preferentially under kinetically controlled conditions. At present we do not know the reason why the formation of **5** is kinetically favored over that of **4**. Further mechanistic studies and synthetic applications are now in progress in our group.

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13 Probably, the generated methyl cation and tosylate anion react with a trace amount of H_2O, which was included in the reaction solvent, to give TsOH and MeOH.