JOC Article

Intramolecular Reaction of a Phenonium Ion. Novel Lactonization of 4-Aryl-5-tosyloxypentanoates and 4-Aryl-5-tosyloxyhexanoates Concomitant with a Phenyl Rearrangement[1]

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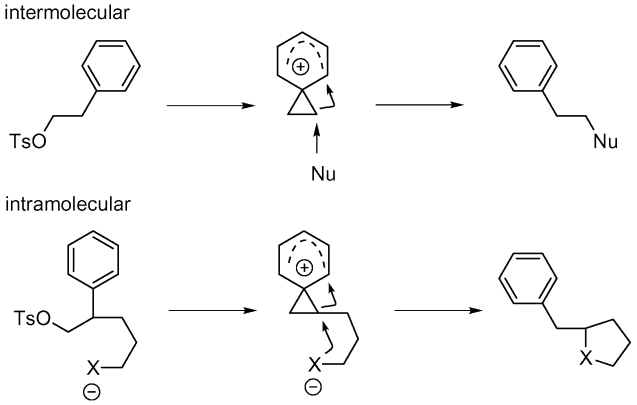
The novel lactonizations of methyl 4-aryl-5-tosyloxypentanoate **1** and 4-aryl-5-tosyloxyhexanoate **3** concomitant with a phenyl rearrangement are reported. The lactonizations were promoted by silica gel or heating in various solvents. By examining the effects of substituents of the aromatic ring on the reactivity, it was found that the reaction proceeded via a phenonium ion. This finding was supported by the stereochemical results for the lactonization of optical active **1**. Silica gel-promoted lactonization of **1** gave only γ-lactone **2**, whereas that of **3** afforded γ-lactone **4** and δ-lactone **5**. These lactonizations proved to be kinetically controlled. On the other hand, when **3c** was heated in CH_3NO_2 at 70 °C, the highly selective formation of **4c** was observed. Further detailed experiments confirmed that the thermal lactonization in CH_3NO_2 was thermodynamically controlled.

Introduction

Symmetrical σ-bridged ethylenebenzenium (phenonium) ions were proposed by Cram to explain the stereochemical results in solvolyses of optically active *threo*- and *erythro*-3-aryl-2-butyltosylates.[2] Brown claimed that these experimental findings could alternatively be explained by considering weakly π-bridged, rapidly equilibrating open ions.[3] This controversy became the most important topic in modern physical organic chemistry, and many reports on this subject have been published.[4] On the basis of the results of these studies, Brown concluded that a continuous spectrum of ions, from open to completely bridged ions, exists depending upon the solvent and substituent in the ions.[5] Furthermore, NMR spectral[6] and theoretical[7] studies have indicated that the intermediate has a σ-bridged phenonium ion structure rather than an equilibrating open ion structure. Despite the impressive advances in phenonium ion chemistry due to the contribution of results of many studies, the ion has not been widely applied to synthetic chemistry. If a phenonium ion has appropriately aligned intramolecular nucleophilic functional groups, a novel type of ring formation induced by the ion should proceed (Scheme 1). Such a reaction should offer possibilities that are not available in the case of an intermolecular reaction. For

SCHEME 1



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† Hokkaido College of Pharmacy.

‡ Toho University.

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(4) For a review, see: (a) Lancelot, C. J.; Cram, D. J.; Schleyer, P. v. R. In *Carbonium Ions*; Olah, G. A., Schleyer, P. v. R., Eds.; Wiley-Interscience: New York, 1972; Vol. III, Chapter 27. (b) Vogel, P. In *Carbocation Chemistry*; Elsevier: Amsterdam, 1985; Chapter 7.

(5) Brown, H. C.; Kim, C. J.; Lancelot, C. J.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1970**, *92*, 5244.

(6) (a) Olah, G. A.; Head, N. J.; Rasul, G.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1995**, *117*, 875. (b) Manner, J. A. M.; Cook, J. A., Jr.; Ramsey, B. G. *J. Org. Chem.* **1974**, *39*, 1199. (c) Olah, G. A.; Porter, R. D. *J. Am. Chem. Soc.* **1971**, *93*, 6877. (d) Olah, G. A.; Porter, R. D. *J. Am. Chem. Soc.* **1970**, *92*, 7627. (e) Olah, G. A.; Comisarow, M. B.; Namanworth, E.; Ramsey, B. *J. Am. Chem. Soc.* **1967**, *89*, 5259.

(7) (a) Sieber, S.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1993**, *115*, 6987. (b) Yamabe, S.; Tanaka, T. *Nippon Kagaku Kaishi* **1986**, 1388. (c) Loupy, A.; Ancian, B. *Tetrahedron Lett.* **1975**, 951. (d) Hehre, W. J. *J. Am. Chem. Soc.* **1972**, *94*, 5919.

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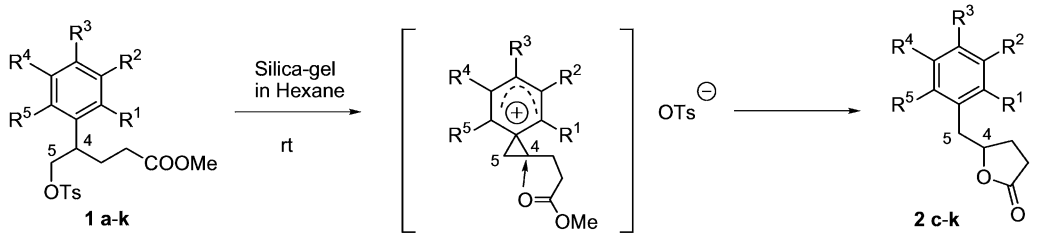
TABLE 1. Lactonization of Methyl 4-Aryl-5-tosyloxypentanoates



entry	tosylate	R^1	R^2	R^3	R^4	R^5	yield (%)	time (h)
1	**1a**	H	H	H	H	H	no reaction	
2	**1b**	H	OMe	H	H	H	no reaction	
3	**1c**	H	H	OMe	H	H	83	144
4	**1d**	OMe	H	Me	H	H	86	48
5	**1e**	Me	H	OMe	H	H	85	48
6[a]	(*S*)-**1e** (79%ee)	Me	H	OMe	H	H	74	48
7	**1f**	OMe	H	OMe	H	H	81	3
8	**1g**	OMe	H	H	H	OMe	96	5
9	**1h**	OMe	H	Me	H	OMe	91	2
10[b]	**1h**	OMe	H	Me	H	OMe	95	120
11[c]	**1h**	OMe	H	Me	H	OMe	99 (**2h**:**1h** = 2:1)[d]	270
12	**1i**	Me	H	OMe	H	OMe	81	4
13	**1j**	OMe	H	OMe	OMe	H	84	5
14	**1k**	OMe	OMe	OMe	H	H	84	72

[a] This lactonization produced (*S*)-**2e** (77%ee). [b] This lactonization was carried out in Et_2O and hexane (1:1). [c] This lactonization was carried out in AcOEt and hexane (1:1). [d] The yield of crude mixture of **2h** and **1h** is shown. The ratio was estimated by ^{1}H NMR.

example, a low-nucleophilic functional group such as an ester group would be expected to couple with the phenonium ion in an intramolecular reaction. We therefore examined the solvolyses of various β-arylalkyltosylates with an internal ester group.

Results

Table 1 summarizes the results of the solvolytic lactonization of 4-aryl-5-tosyloxypentanoates **1a**−**k**.[8] As we expected, pentanoates **1c**−**k** having *o*- and *p*-methoxy groups underwent a solvolytic rearrangement concomitant with lactone ring closure upon treatment with silica gel in hexane to yield only γ-lactones **2c**−**k** in good yields. On the other hand, pentanoates **1a,b** having no *o*- and *p*-methoxy groups did not react. Their reactivities were remarkably affected by the substituent patterns in the aromatic ring. The lactonization of **1c** was completed in 6 days. Compounds **1d,e** were somewhat more reactive than was **1c**. The lactonization of tosylates **1f**−**j**, which have two methoxy groups in the *ortho* or *para* positions, was completed in a few hours. On the other hand, the reactivity of **1k** was much less than that of **1f**−**j** in spite of their having *o*- and *p*-methoxy groups. Increasing the polarity of the solvent makes the reaction rate slower (Table 1, entries 9−11). It was found that the lactonization proceeded with inversion of the stereo center by performing it with optically active tosylate (*s*)-**1e**.[9,10]

Silica gel promoted lactonization of **3**[8] produced δ-lactone **5** along with γ-lactone **4** (Table 2). Interestingly, the ratio of **4** and **5** depended on the presence of *ortho* substituents. The solvolytic lactonization of **3a** and **3c** having no *ortho* substituent afforded γ-lactone **4a**,**c** and δ-lactone **5a**,**c** with a ratio of ca. 1:1 (entries 1 and 3). On the other hand, the same reaction of **3b**, **3d**, and **3e** bearing a methoxy or methyl group at the *ortho* position resulted in preferential formation of δ-lactone (entries 2, 8, and 9).

Since we were particularly interested in the effect of *o*-methyl group on regioselectivity, we carried out acetolyses of β-aryl tosylates **6a,b**[11] and **7a,b**[11] (Table 3) in order to clarify the generality of the effect of an *o*-methyl group. Solvolysis of **6a** proceeded smoothly at 70 °C to give an inseparable mixture of **8a** and **9a** in 73% yield at a ratio of 1:1.3. The ratio of acetates **8a** and **9a** was determined by comparing the respective proton peaks at the benzyl position in ^{1}H NMR. Solvolysis of **7a** under the same conditions afforded a mixture of **8a** and **9a** in 74% yield at a ratio of 1:1.5. The ratios of the products in these acetolyses are not significantly different. Interestingly, when solvolyses of **6b** and **7b** having an *o*-methyl group were performed under the same conditions, a remarkable difference in the ratio of products was observed. The ratio of **8b** and **9b** was 3:1 in the solvolysis of **6b**, while it was 1:8 in the solvolysis of **7b**.

Solvolytic lactonization of **3c** also occurred in various heating solvents at 70 °C without silica gel (Table 2, entries 4, 6, and 7). The ratio of **4c** and **5c** depended

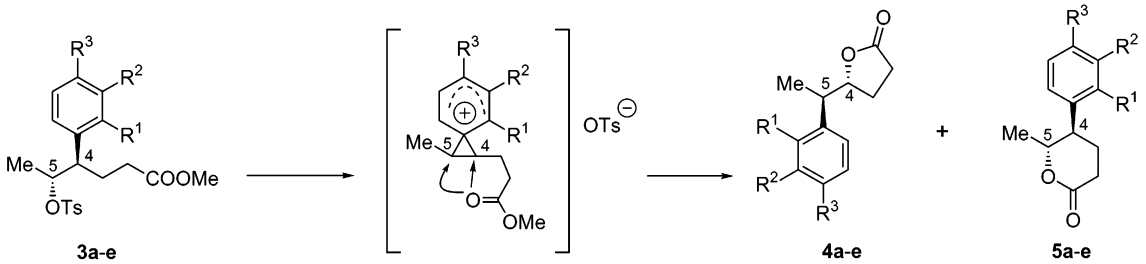
(8) Compounds **1a**−**k**, **3a**−**e**, and **10** were synthesized from methyl 4-aryl-5-hydroxy-2-pentenoate or methyl 4-aryl-5-hydroxy-2-hexenoate. For detailed procedure, see Supporting Information. See also: (a) Ono, M.; Yamamoto, Y.; Todoriki, R.; Akita, H. *Heterocycles* **1994**, *37*, 181. (b) Ono, M.; Todoriki, R.; Yamamoto, Y.; Akita, H. *Chem. Pharm. Bull.* **1994**, *42*, 1590. (c) Ono, M.; Yamamoto, Y.; Akita, H. *Chem. Pharm. Bull.* **1995**, *43*, 553. (d) Ono, M.; Ogura, Y.; Hatogai, K.; Akita, H. *Tetrahedron: Asymmetry* **1995**, *6*, 1829. (e) Nagumo, S.; Irie, S.; Akita, H. *J. Chem. Soc., Chem. Commun.* **1995**, 2001. (f) Nagumo, S.; Irie, S.; Akita, H. *Chem. Pharm. Bull.* **1996**, *44*, 675. (g) Nagumo, S.; Irie, S.; Hayashi, K.; Akita, H. *Heterocycles* **1996**, *43*, 1175. (h) Akita, H.; Umezawa, I.; Takano, M.; Matsukura, H.; Oishi, T. *Chem. Pharm. Bull.* **1991**, *39*, 3094.

(9) For the synthesis of (*S*)-**1d**, see Supporting Information.

(10) Absolute configuration of (*S*)-**2d** was detected by chemical conversion. For detail, see Supporting Information.

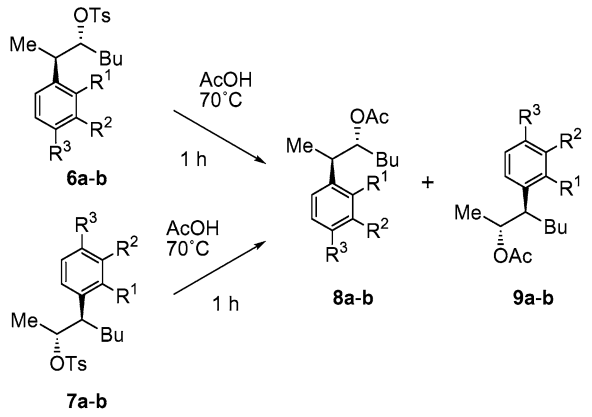
(11) Compounds **6a,b** and **7a,b** were synthesized from **4c,d** and **5c,d**, respectively. For detailed procedure, see Supporting Information.

TABLE 2. Silica Gel Promoted Lactonization of 4-Aryl-5-tosyloxyhexanonates



entry	tosylate	R^1	R^2	R^3	solvent	additive	temp	**4** (yield, %)	**5** (yield, %)	ratio (**4**:**5**)	time (h)
1	**3a**	H	H	OMe	hexane	silica gel	rt	30	42	1:1.4	20
2	**3b**	OMe	H	H	hexane	silica gel	rt	11	67	1:6	10
3	**3c**	H	OMe	OMe	hexane	silica gel	rt	34	36	1:1.05	46
4	**3c**	H	OMe	OMe	CH_3NO_2		70 °C	61	3	20:1	5
5	**3c**	H	OMe	OMe	CH_3NO_2	MS4Å	70 °C	20	57	1:2.85	5
6	**3c**	H	OMe	OMe	^{t}BuOH		70 °C	31	39	1:1.3	14
7	**3c**	H	OMe	OMe	CH_3COOH		70 °C	29	41	1:1.4	0.5
8	**3d**	Me	H	OMe	hexane	silica gel	rt	7	73	1:10	15
9	**3e**	OMe	H	Me	hexane	silica gel	rt	14	68	1:5	6

TABLE 3. Acetolysis of *β*-Arylheptyltosylates

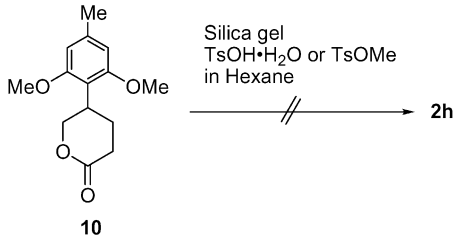


entry	tosylate	R^1	R^2	R^3	**8** + **9** (yield, %)	ratio (**8**:**9**)
1	**6a**	H	OMe	OMe	73	1:1.3
2	**7a**	H	OMe	OMe	74	1:15
3	**6b**	Me	H	OMe	78	3:1
4	**7b**	Me	H	OMe	72	1:8

strongly on the solvent. The lactonization in ^{t}BuOH or CH_3COOH afforded a slight excess of *δ*-lactone **5c**, while the reaction in CH_3NO_2 gave *γ*-lactone **4c** preferentially. Interestingly, when the change in the composition of the reaction mixture with the passage of time was confirmed by monitoring of TLC, **5c** proved to be preferentially formed at an early stage also in CH_3NO_2. The addition of 4 Å molecular sieves (MS4Å) to the heating solution of **3c** in CH_3NO_2 caused a reversal of the selectivity to give **5c** as a major product (entry 5).

To elucidate the reaction mechanisms of silica gel promoted lactonization and thermal lactonization, we performed the following experiment using isolated **4c** and **5c**. When **5c** was treated with TsOH·H_2O (1 equiv) in CH_3NO_2 at 70 °C, **4c** was obtained in 99% yield after 2 h. The ring transformation of **5c** in CH_3COOH proceeded slowly to give **4c** in 94% yield after 48 h. The ring transformation in ^{t}BuOH did not proceed. It is noteworthy that the ring transformation did not proceed when TsOMe was used instead of TsOH·H_2O (1 equiv). When

SCHEME 2



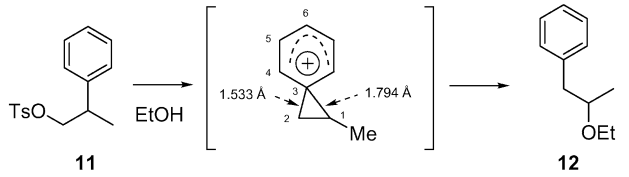
5c was treated with TsOH·H_2O (1 equiv) and silica gel in hexane at room temperature, the rate of ring transformation was remarkabaly slow and **4c** was obtained in only 5% yield after 46 h. On the other hand, the conversion of **4c** into **5c** was not observed under any of the conditions described above. Finally, conversion of **10**[8] into **2h** did not occur upon treatment with silica gel/TsOH (1 equiv) or silica gel/TsOMe in hexane (Scheme 2).

Discussion

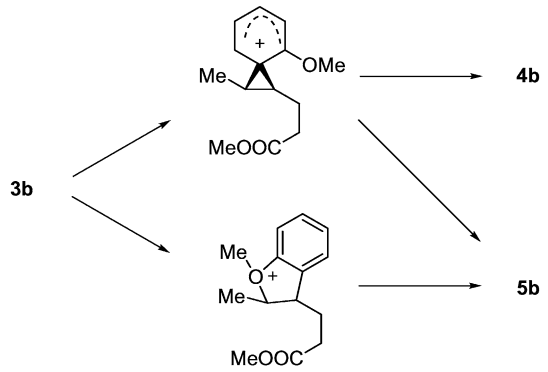
The silica gel promoted lactonization of **1** and **3** is thought to proceed via a phenonium ion on the basis of the following facts: (1) a complete or partial phenyl rearrangement occurs to produce **2** and **4**, (2) the reactivity of **1** depends on the substituent patterns in the aromatic ring, (3) the lactonization proceeds with complete inversion at the C_4 position, and (4) the relative configuration of **5** is trans. The reaction seems to take place on the surface of silica gel,[12] because the reaction rate of **1h** is very slow in ether/hexane (1:1) or AcOEt/hexane (1:1). It is noteworthy that isolated **4c** and **5c** were almost not interconverted upon treatment with

(12) For example, see: (a) Nagumo, S.; Suemune, H.; Sakai, K. *Tetrahedron Lett.* **1991**, *32*, 5585. (b) Nagumo, S.; Suemune, H.; Sakai, K. *Tetrahedron* **1992**, *48*, 8667. (c) Motorina, I. A.; Sviridova, L. A.; Golubeva, G. A.; Bundel, Y. G. *Tetrahedron Lett.* **1989**, *30*, 117. (d) Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. S. *J. Org. Chem.* **1986**, *51*, 404. (e) Mandai, T.; Moriyama, T.; Nakayama, Y.; Sugino, K.; Kawada, M.; Otera, J. *Tetrahedron Lett.* **1984**, 5913. (f) Tamagaki, S.; Suzuki, K.; Takagi, W. *Chem. Lett.* **1982**, 1237. (g) Tsuboi, S.; Fujita, H.; Muranaka, K.; Seko, K.; Takeda, A. *Chem. Lett.* **1982**, 1909. (h) Bartlett, P. D.; Blakeney, A. J.; Kimura, M.; Watson, W. H. *J. Am. Chem. Soc.* **1980**, *102*, 1383.

SCHEME 3



SCHEME 4



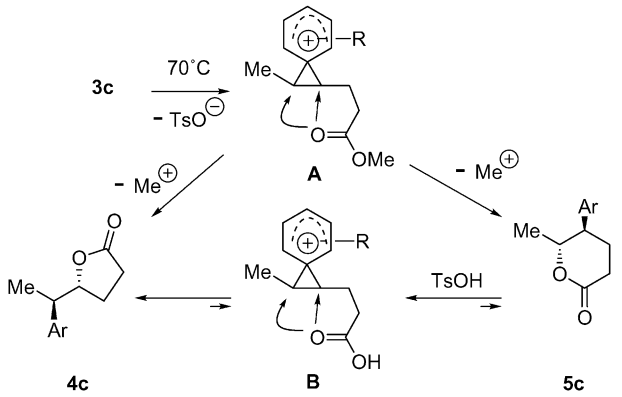
silica gel/TsOH or TsOMe in hexane at room temperature. These results confirm that the regioselectivity of the lactonization of **3** is mostly kinetically controlled. Likewise, exclusive formation of **2** in the lactonization of **1** can be considered to also be kinetically controlled because treatment of **10** with silica gel and TsOH showed no conversion into **3** (Scheme 2).

The regioselectivity of **1** and that of **3** are attributed to an electronic factor under kinetic conditions. A phenonium ion derived from **1** includes methylene (C_5) and methine carbon (C_4) on the cyclopropane ring and reacts with the internal ester group at the C_4 position, whose positive character is greater than that at the C_5 position. On the other hand, the C_4 and C_5 positions of a phenonium ion derived from **3** can be considered to be electronically unbiased. This electronic situation should contribute to the ratio (ca. 1:1) in the solvolytic lactonization of tosylates **3a** and **3c** having no *ortho* substituent. Yamabe et al. reported the ab initio MO calculation of a phenonium ion derived from *β*-aryltosylate **11**, which is the same type of phenonium ion as that derived from **1** (Scheme 3).[7b] The optimized geometry of the phenonium ion by this calculation showed that the methyl group, attached to the cyclopropane site, caused elongation of the C_1-C_3 bond. Indeed, the solvolysis of tosylates **11** in 80% EtOH proceeded regioselectively to give **12**.[13]

Interestingly, the silica gel promoted lactonization of **3b**, **3d**, and **3e**, bearing a methoxy or methyl group at the *ortho* position, shows the preferential formation of *δ*-lactones. The selectivity for the lactonization of **3b** or **3e** can be rationalized by considering that the reaction occurs by way of a phenonium ion and an oxonium ion as intermediates, as shown in Scheme 4. In this scenario, cyclization of the phenonium ion should produce both lactones at a ratio of ca. 1:1, whereas that of the oxonium ion should give only *δ*-lactone. Ramsey et al. reported the presence of such an oxonium ion based on the ionization of *o*-anisylethyl chloride in $SbF_5 \cdot SO_2$ at −70 °C and

(13) Raber, D. J.; Harris, J. M.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1971**, *93*, 4829.

SCHEME 5



^{1}H NMR measurement of the resulting reaction mixture.[6b]

It was surprising that lactonization of **3d** produced *δ*-lactones preferentially, because the methyl group has no nonbonding electrons. The results of the acetolyses using *β*-aryl tosylates **6a,b** and **7a,b** suggest the neighboring effect of *ortho* methyl group similar to that of methoxy group plays an important role in the solvolytic lactonization of **3d**. The fact that ratios of **8a** and **9a** are not significantly different means that only a common intermediate, which should be a phenonium ion, is present in both acetolyses of **6a** and **7a**. On the other hand, the results of the acetolyses of *β*-aryl tosylates **6b** and **7b** confirm the presence of an alternative pathway due to the neighboring effect of the methyl group because the ratios of **8b** and **9b** are remarkably different in the reactions. Although such an alternative pathway should also be present in lactonization of **3d**, the detailed structure of the intermediate has not yet been determined.

The thermal lactonization of tosylate **3c** in CH_3NO_2 is considered to proceed as shown in Scheme 5. At an early stage, the phenonium ion **A**, which was spontaneously formed from **3c** at 70 °C, undergoes 6-endo cyclization selectively to give **5c** as a major product with a ratio of ca. 3:1 (**5c**:**4c**), which is estimated on the basis of the results shown in Table 2, entry 5. Concomitantly, tosyloxy and methyl groups are generated and react with H_2O, which is present in the reaction mixture, to form TsOH and MeOH. When a sufficient amount of TsOH has been generated, **5c** is converted into more thermodynamically stable **4c** via phenonium ion **B** or **A**. Consequently, the preferential formation of **4c** can be observed when **3c** is completely consumed. Addition of MS4Å to the reaction mixture inhibits the generation of TsOH by capturing H_2O to show the preferential formation of **5c** (Table 2, entry 5). The assumption of conversion of **5c** into **4c** is also supported by the fact that isolated **5c** is converted into **4c** upon treatment with $TsOH \cdot H_2O$ in CH_3NO_2 at 70 °C, whereas TsOH does not promote the ring transformation of isolated **4c** into **5c** in CH_3NO_2 at 70 °C. The ring transformation promoted by TsOH is remarkably slow in CH_3COOH and is not observed in ^{t}BuOH. Consequently, the ratio of **4c** and **5c** for the thermal lactonization in CH_3COOH or ^{t}BuOH can be concluded to be kinetically controlled (Table 2, entries 6 and 7).

Conclusion

We have reported a novel lactonization concomitant with a phenyl rearrangement. This lactonization was induced by treatment with silica gel or heating in solvents. On the basis of the substituent effect and stereochemistry, this lactonization is thought to proceed via a phenonium ion. Silica gel promoted lactonization of pentanoates **1** produced only γ-lactones **2**, whereas that of hexanoates **3** gave γ-lactones **4** and δ-lactones **5**. The regioselectivities were dependent on an electronic factor. Thermal lactonization of hexanoate **3c** in CH_3NO_2 afforded thermodynamically stable **4c**, whereas that in CH_3COOH or ^{t}BuOH provided both lactones, whose ratio was close to that of silica gel promoted lactoniztion. The regioselectivity of the thermal lactonization of **3c** in CH_3NO_2 was dependent on the conversion of **5c** into **4c**, which occurred concomitantly.

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Supporting Information Available: Experimental procedures with spectroscopic data for lactonization of **1** and **3** and acetolysis of **6** and **7**, synthesis of **1** including (*S*)-**1d**, **3**, **6** and **7**, the chemical conversion to determine the absolute configuration of (*S*)-**2d** and the alternative synthesis of **4d** for the purpose of determination of its relative configuration; copies of ^{1}H NMR spectra for **4b**, **4e**, **5b**, **5e**, **8a**, **8b**, **9a** and **9b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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