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Novel Lactonization Induced by the Phenonium Ion

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Abstract: Silica gel promotes the lactonization and the concomitant aryl rearrangement of 4-aryl-5-tosyloxy pentanoates (**3c-j**) to give γ-lactones along with complete inversion in high yields.
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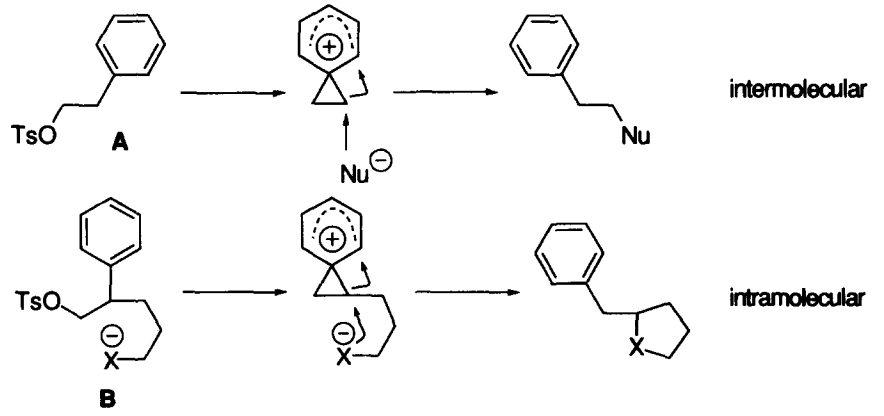
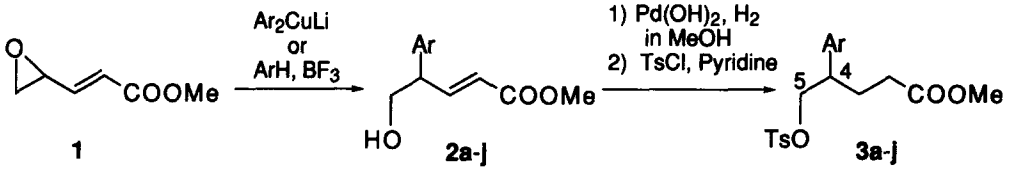
The participation by neighboring aryl groups in the solvolyses of 2-arylethyl tosylates **A** has been one of the most studied topics of modern organic chemistry. The intermediates in these reactions were initially proposed by Cram to be the σ-bridged phenonium ion.[1] Further studies by means of the ^{13}C and ^{1}H NMR method[2] and theoretical calculations[3] have proved unequivocally the presence of the phenonium ion. It has been reported that some nucleophiles, including carboxylate, attack the phenonium ion.[4] If a phenonium ion has an appropriately aligned intramolecular nucleophilic functional group such as **B**, a novel ring formation induced by the phenonium ion will proceed (Chart 1). However, so far as we know, such an intramolecular reaction has not been reported. In this paper, we wish to report the first lactonization via intramolecular nucleophilic attack against the phenonium ion.

Chart 1



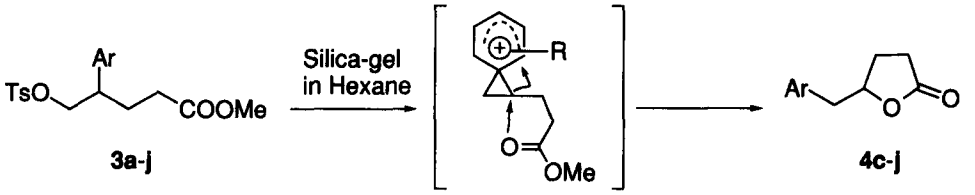
4-Aryl-5-tosyloxy pentanoates (**3a-j**) having an ester group are expected to form the σ-bridged phenonium ion under acidic conditions. Nucleophilicity of ester groups is generally not so high, but if electrophilicity of the phenonium ion is adequately high, the ester group will play the role of a nucleophile to achieve lactonization along with simultaneous loss of the methyl group. In order to clarify this view, **3a-j** were prepared from **1** as shown in Chart 2.[5]

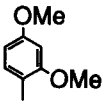
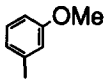
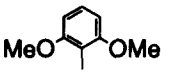
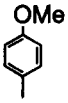
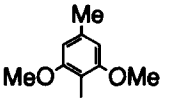
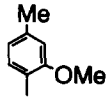
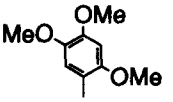
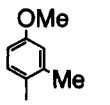
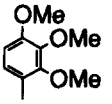
Chart 2



A crucial point of this reaction was the selection of an acid. Carboxylic acids and hydrochloric acid were considered to be not appropriate in order to avoid the competitive intermolecular reaction. Furthermore, a mild acid was preferred to suppress the side reactions such as polymerization. Actually, a mixture of the substrates **3a-j** (ca. 150 mg) and hexane (5 ml) was stirred for an adequate time at room temperature in the presence of silica gel (500 mg) satisfying the requirements described above, and the expected lactonization products (**4c-j**) were obtained. It was found that an attack of the ester group to the σ-bridged phenonium ion proceeded selectively at the C_4 position to give only γ-lactones.

Table Effect of Substituents in the Phenyl Ring



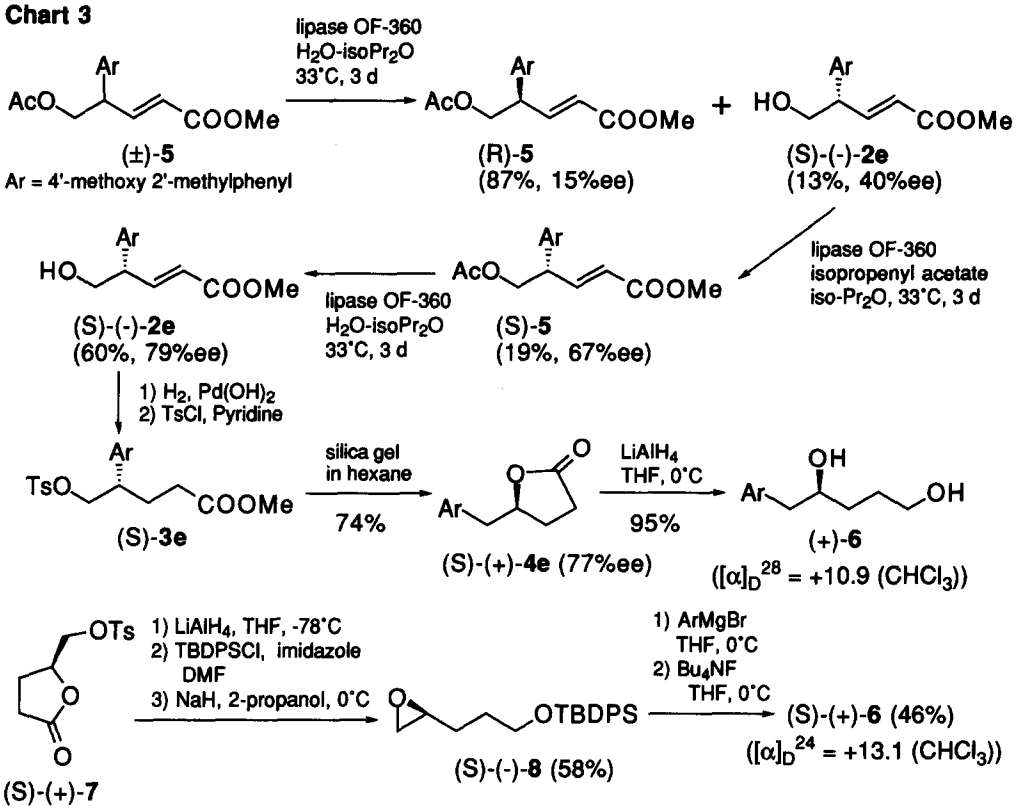
Substrates	Ar	Products **4c-e** (yield %)	Time	Substrates	Ar	Products **4f-j** (yield %)	Time
3a		no reaction		**3f**		81%	3 h
3b		no reaction		**3g**		96%	5 h
3c		74%	6 d	**3h**		91%	2 h
3d		86%	2 d	**3i**		84%	5 h
3e		85%	2 d	**3j**		84%	3 d

The results are summarized in Table 1. The structures of the products were assigned on the basis of spectroscopic data. As a representative example, the FAB-MS spectrum of **4e** showed M^++1 peak at m/z 221. The IR absorption suggested the existence of γ-lactone (1775 cm^{-1}). The ^{1}H-NMR spectrum exhibited signals for two benzilic-H (δ 2.86, *dd*, *J* = 7.0, 15.0 Hz, 1 H: δ 3.05, *dd*, *J* = 7.0, 15.0 Hz, 1 H), the proton at the C_4 position (δ 4.68, *dt*, *J* = 6.3, 7.0 Hz), and aromatic protons (δ 7.07, *d*, *J* = 8.3 Hz, 1 H: δ 6.73, *d*, *J* = 2.4 Hz, 1 H: δ 6.70, *dd*, *J* = 8.3, 2.4 Hz, 1 H). Tosylates **3a** and **3b** did not react at all. Tosylates **3c-j** possessing a methoxy group at least at the 2', 4' and 6' positions of the phenyl ring underwent lactonization accompanied by phenyl rearrangement to form γ-lactones **4c-j** in good yields. Lactonization of substrates possessing two methoxy groups at the 2', 4' and 6' positions except for **3j** proceeded in a few hours. The lower reactivity of tosylate **3j** than that of **3i** is interesting. In the case of **3j**, resonance effect by the methoxy group at the 2' position might be decreased, because overlap of its lone pair and the π-orbital of the benzene ring is sterically inhibited by two adjacent substituents (carbon side chain and methoxy group at the 3' position). Consequently, the reactivity of **3j** is close to that of substrates **3c-e** possessing only one methoxy group at the 2', 4' and 6' positions. On the other hand, because **3i** has no substituent at the 2' position, the lone pair of the methoxy group at the 2' position gives a much greater overlap with the π-orbital of the benzene ring. Thus, the reactivity of **3i** is close to that of **3f-h** possessing two methoxy groups at the 2', 4' and 6' positions.

Next, optically active **3e** was synthesized in order to clarify the stereochemistry at the C_4 position of the lactonization by way of the phenonium ion. Enzymatic hydrolysis of acetate (**5**) using lipase OF-360 from *Candida rugosa* afforded (S)-(-)-**2e** (13%, 40%ee) and (R)-(+)-**5** (87%, 15%ee). As optical purities of these compounds were not appreciably high, enzymatic acetylation of (S)-(-)-**2e** obtained was carried out using lipase OF-360 to give (S)-**5** (19%, 67%ee). Furthermore, enzymatic hydrolysis of (S)-**5** obtained was repeated to give (S)-**2e** (60%, 79%ee, $[\alpha]_D^{27}$ = -2.5 (c = 1.08, $CHCl_3$)). In order to confirm the absolute configuration, (-)-**2e** was successfully converted to the structurally defined dimethyl (2S)-methylpentanedioate (79%ee, $[\alpha]_D^{21}$ = +13.9 (c = 0.78, $CHCl_3$)) which was consistent with an authentic sample (90%ee, $[\alpha]_D^{21}$ = +15.8 (c = 0.72, $CHCl_3$)) derived from (S)-**2d**.[6] Thus, the absolute configuration of (-)-**2e** was determined to be S.[7] Conversion of (S)-**2e** into (S)-**3e** was carried out according to the synthesis of racemic **3e**. The lactonization *via* the phenonium ion of (S)-**3e** (79%ee) by silica gel gave (+)-**4e** (74%) with retained optical purity (77%ee). The optical purity of (S)-(-)-**2e** and (+)-**4e** was determined by HPLC analysis using a CHIRALCELL OD (250×4.6 mm) column. In order to determine the absolute configuration, (+)-**4e** was converted into diol (+)-(**6**) ($[\alpha]_D^{28}$ = +10.9 (c = 0.95, $CHCl_3$)). The authentic diol **6** was also synthesized from lactone (S)-(+)-(**7**),[8] whose absolute configuration has been already determined. Reduction of (S)-**7** with $LiAlH_4$ followed by selective silylation of the primary hydroxy group and epoxide formation with NaH gave epoxide (S)-(-)-(**8**) in 58% yield. Coupling of (S)-**8** with an aryl Grignard reagent followed by desilylation afforded diol (S)-(+)-**6** ($[\alpha]_D^{24}$ = +13.1 (c = 1.39, $CHCl_3$), corresponds to 96%ee). The sign of the optical rotation of (+)-**6** obtained by LAH reduction of (+)-**4e** was the same as that of (S)-(+)-**6** synthesized from (S)-(+)-**7**. Thus, the absolute configuration of (+)-**4e** was determined to be S. These results suggested that the lactonization of substrates **3c-j** proceeded with complete inversion at the C_4 position.

In conclusion, we have described the first finding that the phenonium ion causes migration of an aryl group along with intramolecular attack by a nucleophilic functional group to form lactone compounds in high yield. Other applications to the synthesis of natural products are in progress.

Chart 3



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