

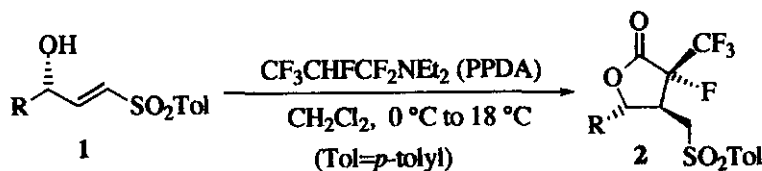
## A NOVEL NUCLEOPHILIC ADDITION TO $\alpha$ -FLUORO- $\alpha$ -TRIFLUOROMETHYL- $\gamma$ -LACTONES

Ken-ichi Ogu,<sup>a</sup> Yusuke Saito, Motohiro Akazome, and Katsuyuki Ogura\*

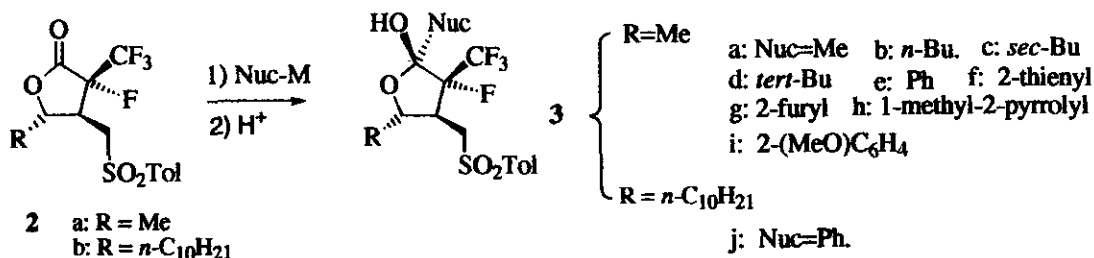
Department of Applied Chemistry, Faculty of Engineering and <sup>a</sup>Graduate School of Science and Technology, Chiba University, 1-33 Yayoicho, Inageku, Chiba 263, Japan

**Abstract** -  $\alpha$ -Fluoro- $\beta$ -(*p*-tolylsulfonylmethyl)- $\alpha$ -trifluoromethyl- $\gamma$ -lactones (**2**) show high reactivity for various nucleophiles to afford cyclic hemiketals (**3**). Reduction of **3** with lithium aluminium hydride brought about reductive ring-opening to give 2-fluoro-3-(*p*-tolylsulfonylmethyl)-2-(trifluoromethyl)alkane-1,4-diols (**4**) in a stereoselective manner.

Fluorinated organic compounds are well known to show unique chemical, physical, and biological properties.<sup>1-3</sup> Our interest is to evaluate the compounds bearing a fluoro(trifluoromethyl)methylene moiety (CF<sub>3</sub>CF<: **A**) instead of the ethylidene moiety (CH<sub>3</sub>CH<) that is found in a wide range of biological active compounds, but there have appeared only a few papers<sup>2,4,5</sup> that relate to this intriguing moiety (**A**). Recently we also discovered a stereospecific formation of  $\alpha$ -fluoro- $\beta$ -(*p*-tolylsulfonylmethyl)- $\alpha$ -trifluoromethyl- $\gamma$ -lactones (**2**) in the reaction of (*E*)- $\gamma$ -hydroxy- $\alpha,\beta$ -unsaturated sulfones (**1**) with a hexafluoropropene-diethylamine adduct (PPDA).<sup>6</sup>



During our further investigation on the reactivity of these unique  $\gamma$ -lactones aiming to develop their synthetic utility, we found that **2** has high ability to receive various nucleophiles. In this communication, we wish to describe the nucleophilic addition to **2** to give a cyclic hemiketal (**3**) and a lactol (**4**) as well as



the subsequent stereoselective reduction to produce 2-fluoro-3-(*p*-tolylsulfonylmethyl)-2-trifluoromethyl-alkane-1,4-diols (**5** and **6**, respectively). These findings open a novel route to preparation of many kinds of fluoro(trifluoromethyl)methylene-containing compounds.

First, we examined the nucleophilic reaction of methyllithium to **2a**. When **2a** was treated with 1.1 equiv of methyllithium in ether at -78 °C, the expected adduct (**3a**) was produced in 23% yield and a large amount (63%) of the starting **2** was recovered. This phenomenon is probably due to the concomitant hydrogen abstraction at the position adjacent to the *p*-tolylsulfonyl group. Indeed, the incorporation of deuterium at the methylene of **3a** was observed by quenching the reaction with CH<sub>3</sub>COOD/D<sub>2</sub>O. The use of more than 2 equiv of methyllithium improved the yield of **3a** (Table 1, Entries 1-3), which reached 97% with 3.3 equivalents of methyllithium. Of the two possible diastereomers, only one isomer of **3a** was detected in the reaction mixture. The stereochemical structure of this isomer, which is shown in Figure 1, was confirmed by a single-crystal X-Ray analysis.<sup>7</sup> Under similar conditions, various alkylolithiums added to **2** in ether or THF (Table 1, Entries 4-7). Notably the addition of *tert*-butyllithium occurred smoothly to give the corresponding adduct (**3d**) in 96% yield. This indicates that the carbonyl group of **2** is highly electrophilic. The lithio derivatives of some arene and heterocyclic aromatics are reactive enough to give **3** in high yields as shown in Table 1 (Entries 8-14). Phenylmagnesium bromide also added to **2**, but the yield was somewhat low (84%). For all of the cyclic hemiketals (**3**) except for **3h** and **3j**, only one diastereomer was observed. In the case of **3h** which bears an *N*-methylpyrrol ring, intractable by-products were formed to make the yield of **3h** lower. It is noteworthy that, in a solution, **3h** exists in equilibrium with a ring-opening product (**3'h**) in a ratio of 3:2.<sup>8</sup> Pure **3h** could be isolated by recrystallization and its stereochemical structure was shown by X-Ray crystallography<sup>7</sup> to be same to **3a**. When the isolated **3h** was allowed to stand in CDCl<sub>3</sub>, equilibration occurred smoothly to give a mixture of **3h** and **3'h** (3:2). This phenomenon was not observed for other cyclic hemiacetals, probably because a thermodynamically controlled equilibrium between

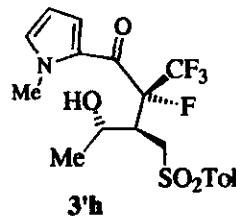






Table 1. Nucleophilic Addition to 2

Entry	2	NucM (equiv)	Solvent	Temp./Time	Product	
					Yield	(Ratio) <sup>a</sup>
1	2a	MeLi (1.1)	Ether	-78 °C/2 h	3a	23% (>99:1)
2		(2.2)	Ether	-78 °C/2 h	3a	94% (>99:1)
3		(3.3)	Ether	-78 °C/2 h to r.t./2 h	3a	97% (>99:1)
4	2a	<i>n</i> -BuLi (3.3)	Ether	-78 °C/2 h	3b	99% (>99:1)
5		(3.3)	THF	-78 °C/0.5 h	3b	97% (>99:1)
6	2a	<i>sec</i> -BuLi (3.3)	Ether	-78 °C/0.5 h	3c	97% (>99:1)
7	2a	<i>tert</i> -BuLi (3.3)	THF	-78 °C/0.5 h	3d	96% (>99:1)
8	2a	PhLi (3.3)	THF	-78 °C/0.5 h	3e	94% (>99:1)
9	2b	PhLi (3.0)	THF	-78 °C/0.5 h	3e	91% (>99:1)
10	2a	PhMgBr (3.3)	Ether	-78 to 0 °C/0.5 h	3e	84% (>99:1)
11	2a	 Li (2.2)	THF	-78 °C/2 h	3f	95% (>99:1)
12	2a	 Li (2.2)	THF	-78 °C/1 h	3g	94% (>99:1)
13	2a	 Li (2.2)	THF	-78 °C/1 h	3h	27% (>99:1)
14	2a	 Li (2.2)	THF	0 °C/2 h	3i	73% (>99:1)
15	2a	Ph—C≡C—Li (2.2)	THF	-78 °C/1 h	3j	91% (93:7)

<sup>a</sup> By 300 Hz <sup>1</sup>H NMR.

<sup>b</sup> Two diastereomers that are based on the chiral center of *sec*-butyl group were formed in a 66:34 ratio.

<sup>c</sup> A ring-opening product (3'h), which existed in equilibrium with 3h, was formed in 13% yield.

their isomers leaned to one side. We also found that sodium borohydride effectively converts 2a to a lactol (4a): To a solution of 2a in methanol was added sodium borohydride (2.3 mol-equiv) under ice-cooling and the resultant mixture was further stirred at the same temperature for 6 h. By the usual workup, the lactol (4a) was isolated in 93% yield along with a small amount (5%) of a diol (5a). This lactol (4a) consists of two diastereomers<sup>9</sup> and its major isomer also has a stereochemical structure similar to that of 3a. (Figure 1) Lithium aluminium hydride (LAH) could not interrupt the reduction at the stage of the lactol (4a), but further reduction proceeded to produce a ring-opening product, 2-fluoro-3-(*p*-tolylsulfonylmethyl)-2-trifluoromethylpentane-1,4-diol (5a) in 94% yield (LAH 3.0 mol-equiv. in THF; rt/70 min). This reduction was applicable to the reductive ring-opening of the cyclic hemiketals (3).

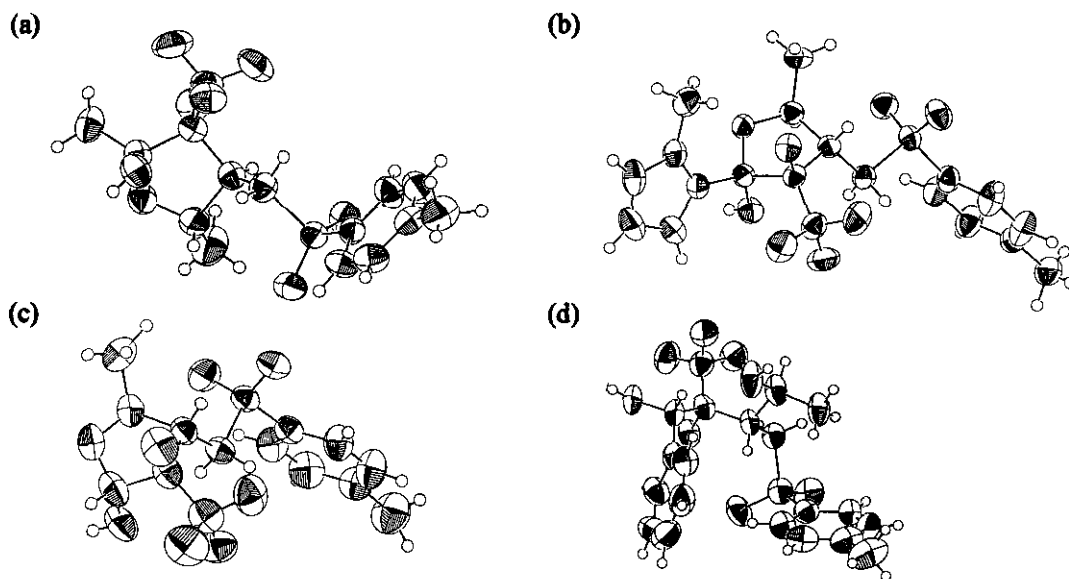
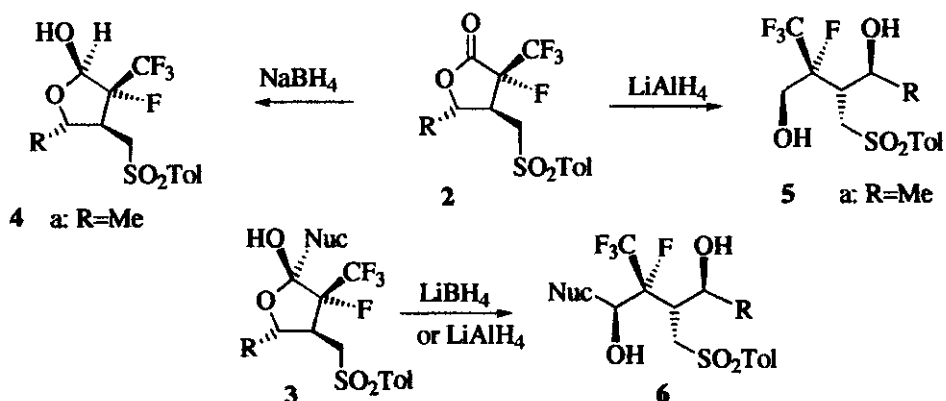
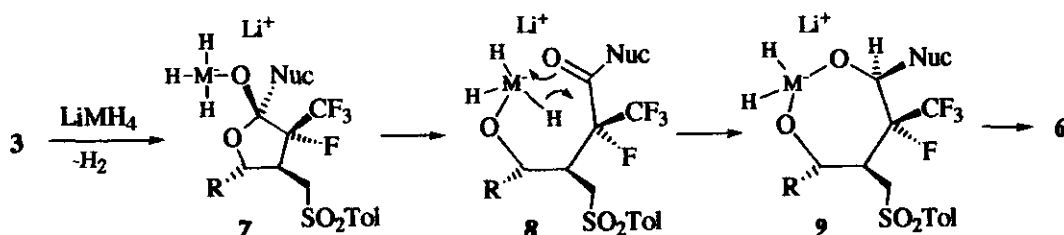


Figure 1. X-Ray Structures.<sup>7</sup> a) 3a. b) 3h. c) 4a. d) 6 (Nuc=Ph, R=Me).

When **3e** was treated with lithium borohydride (LBH) (26 h) or LAH (4 h) in THF at from 0 °C to room temperature, the corresponding 1,4-diol (**6e**) was obtained in 96% or 64 % yields, respectively. The diastereomeric ratio of **6e** was 91:9 or 93:5, respectively. The structure of the major diastereomer was determined by a single-crystal X-Ray analysis (Figure 1(d)). The stereoselectivity in the reduction of **3** with LAH was affected by the bulkiness of the substituent (R): the stereoselectivity increases as the substituent becomes bulkier [R=Me 70:30 (61% yield), *n*-Bu 80:20 (86%), Ph 93:7 (64%), *tert*-Bu >99:1 (89%)]. It should be noted that, by reduction with LAH, a 60:40 diastereomeric mixture of **3h** and **3'h** (69:31) gave only one diastereomer of the corresponding **6** in 77% yield. Recently, Ishihara and his coworkers found a highly stereoselective reduction of a 2-fluoro-3-hydroxy-2-(trifluoromethyl)alkyl



ketones with LAH or diisopropylaluminum hydride (DIBAL-H) in a 1,2-*syn* diastereoselective manner, in which the high 1,2-*syn* stereoselectivity was ascribed to the first formation of the corresponding  $\beta$ -keto alkoxide, which participates in a six-membered chelation, and the subsequent attack of hydride from the side opposite to the adjacent trifluoromethyl group.<sup>4c</sup> This explanation can be extended to that for the present reaction: At first, the hydroxyl group of **3** reacts with LBH or LAH to form an alkoxide (**7**). Then the hydride approaches the carbonyl group via a seven-membered transition-state (**8**) while avoiding the CF<sub>3</sub> group to give the 1,4-diol (**6**) with a high stereoselectivity. The bulkier alkyl (R) group is thought to make the stereoselectivity higher because it undergoes a steric repulsion by carbonyl group in the approach of the hydride from the CF<sub>3</sub> site.



In conclusion, we found that  $\alpha$ -fluoro- $\alpha$ -trifluoromethyl- $\gamma$ -lactones (**2**) exhibit high reactivity for nucleophiles to form the cyclic hemiketals (**3**) and the lactols (**4**) which, by the subsequent reduction with LBH or LAH, can be converted to the 2-fluoro-3-(*p*-tolylsulfonylmethyl)-2-trifluoromethyl-1,4-diol derivatives (**5** and **6**) in a stereoselective manner. We are now investigating the derivation of the 2-fluoro-2-trifluoromethyl-1,4-diol derivatives (**5** and **6**) into useful compounds bearing a fluoro(trimethyl)-methydenes group.

#### ACKNOWLEDGMENT

This work was supported by a Grant-in-Aid for Scientific Research (No. 07405041) from the Ministry of Education, Science, Sports and Culture of Japan and "Research for the Future" Program (JSPS-RFTF96P00304) from the Japan Society for the Promotion of Science.

#### REFERENCES AND NOTES

- (a) "Biomedical Aspects of Fluorine Chemistry", ed. by R. Filler and Y. Kobayashi, Kodansha Ltd., Tokyo and Elsevier Biomedical, Amsterdam, 1982. (b) J. T. Welch and S. Eswarakrishnan, "Fluorine in Bioorganic Chemistry" John Wiley & Sons, New York, 1990. (c) G. Resnati,

*Tetrahedron*, 1993, **49**, 9385.

2. (a) K. Yoshino, M. Ozaki, H. Taniguchi, M. Ito, K. Saitoh, N. Yamasaki, and T. Kitazume, *Jpn. J. Appl. Phys.*, 1987, **26**, L77. (b) N. Shiratori, I. Nishiyama, A. Yoshizawa, and T. Hirai, *ibid.*, 1990, **29**, L2086. (c) N. Shiratori, A. Yoshizawa, I. Nishiyama, M. Fukumasa, A. Yokoyama, T. Hirai, and M. Yamane, *Mol. Cryst. Liq. Cryst.*, 1991, **199**, 129.
3. M. Hübel and D. O'Hagan, *Liebigs Ann. Chem.*, 1995, 583.
4. (a) T. Ishihara, M. Kuroboshi, K. Yamaguchi, and Y. Okada, *J. Org. Chem.*, 1990, **55**, 3107. (b) M. Kuroboshi and T. Ishihara, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 1191. (c) T. Ishihara, K. Yamaguchi, M. Kuroboshi, and K. Utimoto, *Tetrahedron Lett.*, 1994, **35**, 5263.
5. (a) T. Nakai and O. Takahashi, EP350,334 (1990) (*Chem. Abstr.*, 1990, **113**, 39950m). (b) C-P. Qian and T. Nakai, *Tetrahedron Lett.*, 1990, **31**, 7043.
6. K. Ogura, K. Ogu, T. Ayabe, J. Sonehara, and M. Akazome, *Tetrahedron Lett.*, 1997, **38**, 5173.
7. X-Ray crystallographic data were collected with Cu K $\alpha$  ( $\lambda = 1.54178 \text{ \AA}$ ) radiation on a Mac Science MXC18 diffractometer. All computations used "Crystan GM (ver 6.2.1, 1994) or maXus (ver. 1.1, 1997), Computer Program for the Solution and Refinement of Crystal Structure from X-Ray Diffraction Data", Mac Science Co. Ltd.

Crystal data of **3a**: monoclinic, space group P2<sub>1</sub>/c, a = 11.544(3) Å, b = 14.756(4) Å, c = 10.284(3) Å,  $\beta = 104.18(2)^\circ$ , V = 1698.6(8) Å<sup>3</sup>, Z = 4, R = 0.0455, R<sub>w</sub> = 0.0385.

Crystal data of **3h** (major): monoclinic, space group P2<sub>1</sub>/a, a = 21.160(5) Å, b = 7.542(2) Å, c = 12.922(3) Å,  $\beta = 104.32(2)^\circ$ , V = 1998.2(9) Å<sup>3</sup>, Z = 4, R = 0.053, R<sub>w</sub> = 0.071.

Crystal data of **4a**: monoclinic, space group C2/c, a = 19.478(7) Å, b = 12.204(4) Å, c = 15.167(6) Å,  $\beta = 115.80(3)^\circ$ , V = 3246(2) Å<sup>3</sup>, Z = 8, R = 0.0491, R<sub>w</sub> = 0.0545.

Crystal data of **6** (Nuc=Ph, R=Me)•Et<sub>2</sub>O: monoclinic, space group P2<sub>1</sub>/a, a = 12.241(3) Å, b = 22.240(7) Å, c = 9.589(3) Å,  $\beta = 94.79(2)^\circ$ , V = 2601(1) Å<sup>3</sup>, Z = 4, R = 0.0526, R<sub>w</sub> = 0.0579.

8. A mixture of **3h** and **3'h** showed an IR absorption at 1647 cm<sup>-1</sup>. In <sup>1</sup>H NMR (CDCl<sub>3</sub>), a quintet-like signal at  $\delta$  4.39 [CH<sub>3</sub>CH(OH)-] became a quartet-like signal on treatment with D<sub>2</sub>O because the coupling constant between the protons of CH(OH)- and CH(CH<sub>2</sub>SO<sub>2</sub>Tol) was very small if any.
9. The diastereomeric ratio was 93:7 just after crystalline **4a** was dissolved in CDCl<sub>3</sub>. The ratio changed slowly to 73:27 (after 19 h at room temperature). On treatment of **4a** with CF<sub>3</sub>COOH in CD<sub>3</sub>OD, the epimerization occurred smoothly to give rise to the diastereomeric ratio of 76:24.

Received, 24th September, 1997