A NOVEL NUCLEOPHILIC ADDITION TO α-FLUORO-α-TRIFLUOROMETHYL-γ-LACTONES

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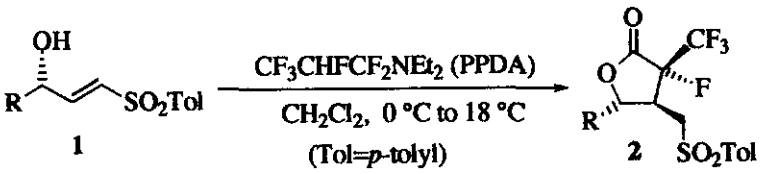
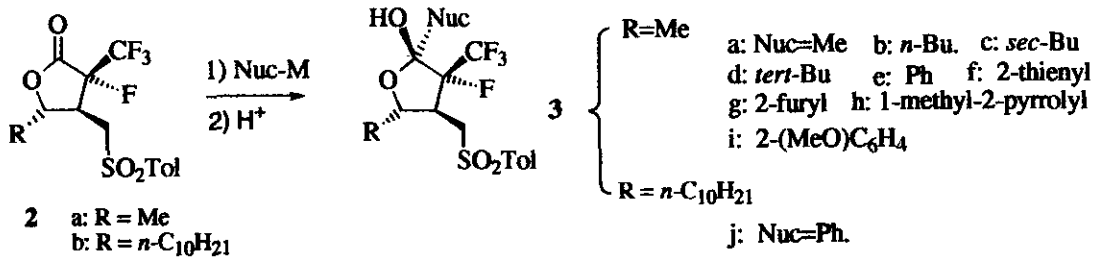
Abstract - α-Fluoro-β-(*p*-tolylsulfonylmethyl)-α-trifluoromethyl-γ-lactones (**2**) show high reactivity for various nucleophiles to afford cyclic hemiketals (**3**). Reduction of **3** with lithium aluminium hydride brought about reductive ring-opening to give 2-fluoro-3-(*p*-tolylsulfonylmethyl)-2-(trifluoromethyl)alkane-1,4-diols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

Fluorinated organic compounds are well known to show unique chemical, physical, and biological properties.[1-3] Our interest is to evaluate the compounds bearing a fluoro(trifluoromethyl)methylene moiety ($CF_3CF<$: **A**) instead of the ethylidene moiety ($CH_3CH<$) that is found in a wide range of biological active compounds, but there have appeared only a few papers[2,4,5] that relate to this intriguing moiety (**A**). Recently we also discovered a stereospecific formation of α-fluoro-β-(*p*-tolylsulfonylmethyl)-α-trifluoromethyl-γ-lactones (**2**) in the reaction of (*E*)-γ-hydroxy-α,β-unsaturated sulfones (**1**) with a hexafluoropropene-diethylamine adduct (PPDA).[6]


(A)



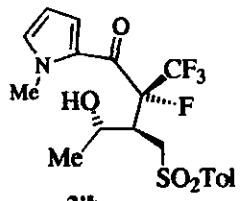
During our further investigation on the reactivity of these unique γ-lactones aiming to develop their synthetic utility, we found that **2** has high ability to receive various nucleophiles. In this communication, we wish to describe the nucleophilic addition to **2** to give a cyclic hemiketal (**3**)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



2 a: R = Me
b: R = n-$C_{10}H_{21}$

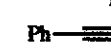
the subsequent stereoselective reduction to produce 2-fluoro-3-(*p*-tolylsulfonylmethyl)-2-trifluoromethyl-alkane-1,4-diols (**5** and **6**, respectively). These findings open a novel route to preparation of many kinds of fluoro(trifluoromethyl)methylene-containing compounds.

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_3COOD/D_2O. 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.[7] Under similar conditions, various alkyllithiums 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-openning product (**3'h**) in a ratio of 3:2.[8] Pure **3h** could be isolated by recrystallization and its stereochemical structure was shown by X-Ray crystallography[7] to be same to **3a**. When the isolated **3h** was allowed to stand in $CDCl_3$, 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



3'h

Table 1. Nucleophilic Addition to **2**

Entry	2	NucM (equiv)	Solvent	Temp./Time	Product	Yield	(Ratio) [a]
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**	*n*-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**	*sec*-BuLi (3.3)	Ether	-78 °C/0.5 h	**3c**	97%	[b]
7	**2a**	*tert*-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**	 (2.2)	THF	-78 °C/2 h	**3f**	95%	(>99:1)
12	**2a**	 (2.2)	THF	-78 °C/1 h	**3g**	94%	(>99:1)
13	**2a**	 (2.2)	THF	-78 °C/1 h	**3h**	27%	(>99:1)
14	**2a**	 (2.2)	THF	0 °C/2 h	**3i**	73%	(>99:1)
15	**2a**	 (2.2)	THF	-78 °C/1 h	**3j**	91%	(93:7)

[a] By 300 Hz ^{1}H NMR.

[b] Two diasteremers that are based on the chiral center of *sec*-butyl group were formed in a 66:34 ratio.

[c] 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[9] 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**).

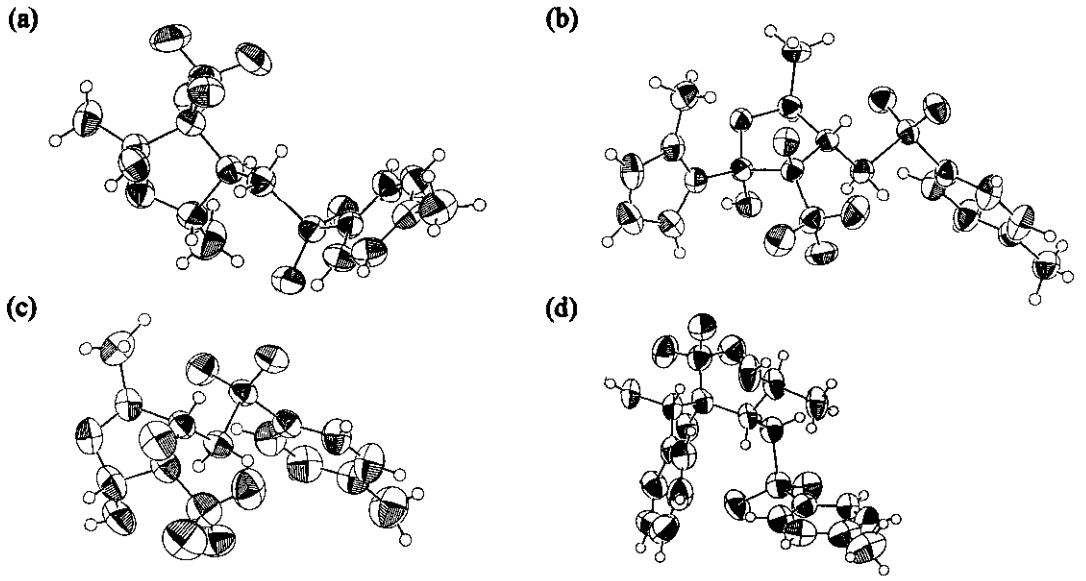
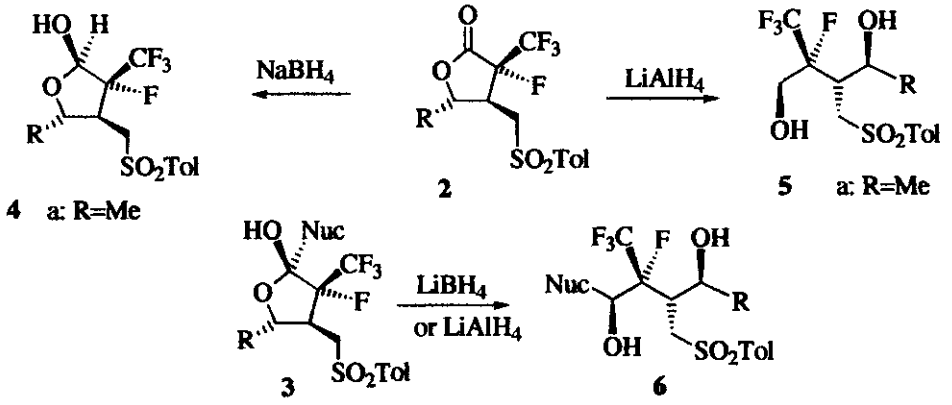
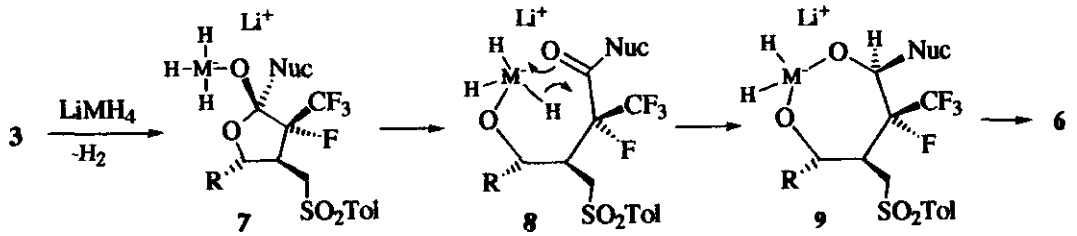


Figure 1. X-Ray Sturctures.[7] a) **3a**. b) **3h**. c) **4a**. d) **6** (Nuc=Ph, R=Me).

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 corresconding **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 diisopropylaluminium 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 β-keto alkoxide, which participates in a six-membered chelation, and the subsequent attack of hydride from the side opposite to the adjacent trifluoromethyl group.[4c] 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_3 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 appoarch of the hydride from the CF_3 site.



In conclusion, we found that α-fluoro-α-trifluoromethyl-γ-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)-methydene group.

ACKNOWLEDGMENT

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7. X-Ray crystallographic data were collected with Cu Kα (λ = 1.54178 Å) 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 $P2_1/c$, a = 11.544(3) Å, b = 14.756(4) Å, c = 10.284(3) Å, β = 104.18(2)°, V = 1698.6(8) Å^3, Z = 4, R = 0.0455, Rw = 0.0385.

   Crystal data of **3h** (major) : monoclinic, space group $P2_1/a$, a = 21.160(5) Å, b=7.542(2) Å, c =12.922(3) Å, β =104.32(2)°, V =1998.2(9) Å^3, Z = 4, R = 0.053, Rw = 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, β =115.80(3)°, V = 3246(2) Å^3, Z = 8, R = 0.0491, Rw = 0.0545.

   Crystal data of **6** (Nuc=Ph, R=Me)•Et_2O : monoclinic, space group $P2_1/a$, a=12.241(3) Å, b= 22.240(7) Å, c = 9.589(3) Å, β = 94.79(2)°, V = 2601(1) Å^3, Z = 4, R = 0.0526, Rw = 0.0579.
8. A mixture of **3h** and **3'h** showed an IR absorption at 1647 cm^{-1}. In ^{1}H NMR ($CDCl_3$), a quintet-like signal at δ 4.39 [$CH_3C\underline{H}$(OH)-] became a quartet-like signal on treatment with D_2O because the coupling constant between the protons of $C\underline{H}$(OH)- and $C\underline{H}(CH_2SO_2Tol)$ was very small if any.
9. The diastereomeric ratio was 93:7 just after crystalline **4a** was dissolved in $CDCl_3$. The ratio changed slowly to 73:27 (after 19 h at room temperture). On treatment of **4a** with CF_3COOH in CD_3OD, the epimerization occurred smoothly to give rise to the diastereomeric ratio of 76:24.

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