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New Expedient Route to the Stereoselective Synthesis of Fluorinated 1,3-Diol Derivatives *via* Aluminum Acetals Derived from β -Alkoxy Esters and DIBAL

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Abstract

On treating the aluminum acetal intermediates, generated *in situ* from ethyl 3-benzyloxy-2,2-difluoroalkanoates or 3-benzyloxy-4,4,4-trifluorobutanoate and diisobutylaluminum hydride at -78 $^{\circ}$ for 1 h, with allylic stannanes in the presence of titanium(IV) dichloride diisopropoxide at 0 $^{\circ}$ for 8 h or at -30 $^{\circ}$ for 6 h, the corresponding allylated products, polyfluoro-1,3-diol derivatives, were obtained in good yields with high *anti* stereoselectivity. © 1998 Elsevier Science Ltd. All rights reserved.

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Since fluorine substituents, such as monofluoro, difluoromethylene, and trifluoromethyl, introduced to organic molecules are frequently observed to exert significant effect on their biochemical properties [1], extensive efforts have continually been made to synthesize various types of fluorine-containing biologically active compounds [2]. Regioselectively fluorinated 1,3-diols of defined stereochemistry are a useful class of compounds in organic synthesis, and should be employed as building blocks for preparing fluorinated analogues of organic natural products, many of which involve a 1,3-dioxygenated framework. Therefore, development of a new access to the synthesis of such 1,3-diols and their derivatives would be of exceeding value.

In the course of our research program [3] based upon the concept that fluorinated metal acetals $R_fCH(OR)OM$, capable of essentially existing in preference to their carbonyl forms [4], would act as carbonyl equivalents in organic reactions, we have now attained the stereoselective allylation of the aluminum acetal intermediates 2, derived from fluorinated β -alkoxy esters 1 and diisobutylaluminum hydride (DIBAL) [5], by the action of allylic stannanes and a Lewis acid leading to the *anti* isomers of 1,3-diol derivatives 3. This communication describes the results of these reactions, along with data on the stabilities or reactivities of the intermediates 2.

	Ester 1		Stannane			Temp.	Time	Yield*/%	Isomer ratio ^b	Yield ^a /%
Entry	X	R	R'	Lewis acid	Solvent	/°C	/h	of 3	syn : anti	of 4
1	F	Ph	Me	ZnBr ₂	CH ₂ Cl ₂	r.t.	4	71	19:81	3
2	F	Ph	Me	ZnI ₂	CH_2Cl_2	r.t.	4	75	18:82	4
3	F	Ph	Me	BF ₃ •OEt ₂	CH_2Cl_2	r.t.	4	39	25 : 75	tr
4	F	Ph	Me	TiCl ₄	CH_2Cl_2	r.t.	4	29		10
5	F	Ph	Me	$(i-PrO)_2TiCl_2$	CH ₂ Cl ₂	r.t.	4	71	14:86	7
6	F	Ph	Me	(<i>i</i> -PrO) ₂ TiCl ₂	THF	r.t.	4	9		tr
7	F	Ph	Me	(<i>i</i> -PrO) ₂ TiCl ₂	Toluene	r.t.	4	75	10:90	2
8	F	Ph	Me	(<i>i</i> -PrO) ₂ TiCl ₂	Toluene	0	4	59	7:93	7
9	F	Ph	Me	(<i>i</i> -PrO) ₂ TiCl ₂	Toluene	0	8	79	5:95	10
10	F	p-MeC ₆ H ₄	Me	(<i>i</i> -PrO) ₂ TiCl ₂	Toluene	0	8	73	7:93	tr
11	F	p-MeOC ₆ H ₄	Me	(i-PrO)2TiCl2	Toluene	0	8	69	8:92	tr
12	F	p-ClC ₆ H ₄	Me	(i-PrO)2TiCl2	Toluene	0	8	68	7:93	6
13	F	p-FC ₆ H ₄	Me	(<i>i</i> -PrO) ₂ TiCl ₂	Toluene	0	8	71	12:88	9
14	F	2-Furyl	Me	(i-PrO)2TiCl2	Toluene	0	8	70	14:86	tr
15	F	PhCH=CH	Me	(<i>i</i> -PrO) ₂ TiCl ₂	Toluene	0	8	60	22:78	15
16	F	<i>n</i> -Pr	Me	(i-PrO) ₂ TiCl ₂	Toluene	0	8	68	47:53	tr
17	F	c-Hex	Me	(i-PrO)2TiCl2	Toluene	0	8	54	46 : 54	tr
18	F	Ph	н	(i-PrO) ₂ TiCl ₂	Toluene	0	8	52	8:92	19
19	F	p-MeC ₆ H ₄	Н	(i-PrO) ₂ TiCl ₂	Toluene	0	8	59	10:90	19
20	F	p-MeOC ₆ H ₄	Н	(<i>i</i> -PrO) ₂ TiCl ₂	Toluene	0	8	76	5:95	10
21	F	p-FC ₆ H₄	Н	(i-PrO)2TiCl2	Toluene	0	8	57	7:93	6
22	F	<i>n</i> -Pr	Н	$(i-PrO)_2TiCl_2$	Toluene	0	8	53	40 : 60	22
23	Н	CF ₃	Me	(<i>i</i> -PrO) ₂ TiCl ₂	CH_2CI_2	0	2	92	35 : 65	tr
24	Н	CF ₃	Me	(<i>i</i> -PrO) ₂ TiCl ₂	Toluene	0	2	92	23:77	tr
25	Н	CF ₃	Me	(i-PrO) ₂ TiCl ₂	Toluene	-30	6	77	7:93	tr
26	Н	CF ₃	Н	(i-PrO)2TiCl2	Toluene	-30	6	76	8:92	tr
27°	н	CF ₃	н	(<i>i</i> -PrO) ₂ TiCl ₂	Toluene	-30	6	80	6:94	tr

 Table 1

 Allylation of the aluminum acetals 2 generated in situ from fluorinated esters 1 and DIBAL

^a The yields refer to pure products isolated by column chromatography on silica gel.

^h Measured by ¹⁹F NMR of the crude products prior to isolation. The stereochemical assignment was made on the basis of comparison

of chemical shifts and couplings of **3** with those of closely related fluoro compounds reported previously [6,7].

^c Dibutyldi(2-propenyl)stannane (1.0 equiv.) was used instead of tributyl(2-propenyl)stannane.

The starting esters 1a and 1b were readily accessible by the Reformatsky reaction of bromodifluoroacetate with aldehydes [8] followed by benzylation and by the benzylation of commercially available 3-hydroxy-4,4,4-trifluorobutanoate, respectively. When the ester 1a (R = Ph) was reduced with DIBAL (1.1 equiv.) in CH_2Cl_2 at -78 °C for 1 h and subsequently treated with methallylstannane (2 equiv.) in the presence of $ZnBr_2$ (1.25 equiv.) at room temperature for 4 h, the corresponding allylated product 3a was obtained as a 19 : 81 mixture of the *syn* and *anti* isomers in 71% yield, together with a trace amount of reduction product 4a (Entry 1). The absence of $ZnBr_2$ decreased the yield of 3a to 42% while it increased the yield of 4a (39%). As regards Lewis acids other than $ZnBr_2$, ZnI_2 and $(i-PrO)_2TiCl_2$ could be used effec-



tively, but $BF_3 \circ OEt_2$ and $TiCl_4$ were not efficient (Entries 2-5). Toluene was a suitable solvent as well for the reaction (Entries 5-7). Eventually, the reduction of **1a** (R = Ph) with DIBAL followed by allylation in the presence of $(i-PrO)_2TiCl_2$ in toluene at 0 °C for 8 h was found to provide the most satisfactory result; **3a** was obtained in 79% yield and with 95% of *anti* stereoselection (Entry 9). As summarized in Table 1, the reactions of **1a** carrying a variety of aryl substituents under the same conditions proceeded with high *anti* stereoselectivity to afford **3a** in fair to good yields (Entries 10-14 and 18-21). However, the esters **1a** having alkyl substituents under went the reaction in an almost nonstereoselective manner (Entries 16, 17, and 22), though the reason for this stereochemical outcome is unclear.

Additionally, the present reaction protocol could nicely be applied to the ester **1b** (Entries 23-27), providing high distribution of the *anti* isomers and good yields of **3b**.



In order to estimate the stabilities or reactivities of the aluminum acetals 2, we attempted trapping them with trimethylsilyl triflate (Me₃SiOTf) [9] under various conditions, as shown in Table 2. Thus, when *in-situ* generated 2a (R = Ph) or 2b was made to react with Me₂SiOTf (1.1 equiv.) and pyridine (3 equiv.) in CH₂Cl₂ at -78 °C for 3 h, the corresponding silvlated acetal 5 was obtained as a diastereomeric mixture (Entries 1 and 4). Even the reaction of 2a, which was kept at 0 °C for 1 h, with Me₃SiOTf and pyridine at 0 °C for 3 h gave rise to 5a in 77% yield (Entry 2). The presence of ZnBr, (1.25 equiv.) led to an increase of the yield of 4a (Entry 3). On the other hand, 2b was entirely converted into the reduction product 4b under similar conditions in the absence or presence of the Lewis acid (Entries 5 and 6). Consequently, the reduction products 4 are likely to arise from a Meerwein-Ponndorf-Verley-type reduction [10] of **2**. The data obtained herein suggest that the aluminum intermediates 2a and 2b prefer an acetal form to an aldehyde at least below 0 °C, and 2b is more susceptible to the reduction and allylation than **2a**. This difference in the reactivity may primarily be ascribed to an electronic effect exerted by electronegative fluorine substituents; the fluorines remote from the acetal functionality can render polarization (or activation) of the C-OEt bond in 2 more feasible. The

Aluminum acetal 2				Temp.	Time	Yield ^a of 5		Isomer ratio ^h	Yield ^a of 4	
Entry 1	x	R Ph	Lewis acid	/℃ -78	/h 3	1%		syn : anti	1%	
	F					5a	68	78:22	tr	
2°	F	Ph	none	0	3	5a	77	77:23	6	
3°	F	Ph	ZnBr ₂	0	3	5a	47	62:38	22	
4	н	CF,	none	-78	3	5 b	75	81:19	0	
5°	н	CF ₃	none	0	3	5 b	tr	_	76	
6 ^d	н	CF_3	ZnBr ₂	0	2	5 b	0	_	74	

Table 2 Trapping of the aluminum acetals **2** with trimethylsilyl triflate and pyridine

* The yields are of pure products isolated by flash column chromatography on silica gel.

^b Determined by ¹⁹F NMR analysis of the crude products prior to isolation. The stereochemical assignment was tentatively made

from comparison of chemical shifts and couplings of 5 with those of closely related fluoro compounds reported previously [6,7]. 'After being stirred at 0 $^{\circ}$ C for 1 h, the mixture was treated with Me₃SiOTf and pyridine at 0 $^{\circ}$ C for a specified period.

^d No Me₃SiOTf and pyridine were added to the reaction mixture.

above described allylation seems to occur *via* a cyclic oxocarbenium ion 2° , which may undergo the chelation-controlled addition [11] of allylstannanes to result in the predominant formation of the *anti* isomers of the products 3.

In short, we have demonstrated that the aluminum acetal intermediates 2, generated *in situ* from fluorinated β -benzyloxy esters and DIBAL, participate well in the reaction with allylic stannanes in the presence of (i-PrO)₂TiCl₂ under mild conditions to afford preferentially the *anti* isomers of fluorinated 1,3-diol derivatives 3. The present reaction can serve as a new convenient method for the synthesis of such compounds of defined stereochemistry.

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