

Highly Stereoselective Radical Reduction of α -Bromo- α -fluoro- β -hydroxy Esters with Tributyltin Hydride Leading to *threo*- α -Fluoro- β -hydroxy Esters

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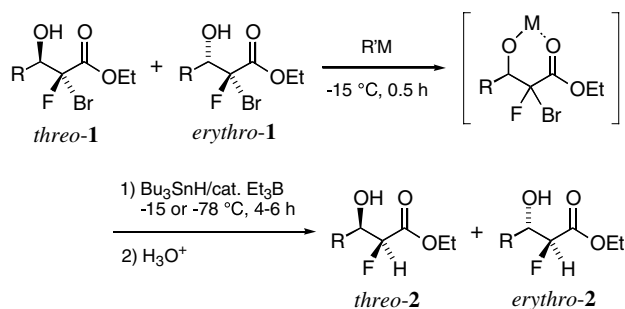
(Received November 1, 2001; CL-011095)

α -Bromo- α -fluoro- β -hydroxy esters, prepared as isomeric mixtures by the zinc-mediated coupling reaction of dibromofluoroacetate with aldehydes at -20°C , were successively treated with trimethylaluminium at -15°C for 0.5 h and with tributyltin hydride in the presence of a catalytic amount of triethylborane at -15°C for 4 h or at -78°C for 6 h to give preferentially the *threo*-isomers of the corresponding α -fluoro- β -hydroxy esters in good yields.

α -Fluoro- β -hydroxy acid derivatives are very important and fundamental compounds for preparing a variety of regioselectively monofluorinated natural substances, which attract much attention in biological chemistry due to frequent occurrence of their unique bioactivities.¹ It is general for the access to such fluorinated β -hydroxy acid derivatives to utilize either the aldol reaction of the metal enolates of monofluoroacetic acid esters^{2,3} and amides^{2,4} or the Reformatsky reaction of bromofluoroacetate,⁵ but these reactions suffer the lack of stereoselectivity. Therefore, the development of a stereocontrolled route to the synthesis of α -fluoro- β -hydroxy acid derivatives is strongly required.

In close connection with our recent success in the zinc-mediated coupling reaction between ethyl dibromofluoroacetate and various aldehydes leading efficiently to α -brominated α -fluoro- β -hydroxy esters **1**,⁶ we set out to investigate the radical reduction⁷ of such α -bromo esters **1** with hydrogen transfer reagents, under consideration that it could constitute a stereoselective synthetic method for the α -fluoro- β -hydroxy esters.

This communication discloses the preliminary results demonstrating that the sequential reaction of **1** with trimethylaluminium and with tributyltin hydride in the presence of a catalytic amount of triethylborane proceeds with high levels of diastereoselection, preferentially yielding the *threo*-isomers of the reduction products **2**. To our best knowledge, the present reaction provides us with the first highly stereoselective means for constructing an α -monofluoro- β -hydroxy ester moiety of interest.



First, the reaction of **1a**, readily prepared as an isomeric

mixture from dibromofluoroacetate and benzaldehyde,⁶ with tributyltin hydride (Bu_3SnH) (2 equiv) was carried out in the presence of 10 mol% of triethylborane (Et_3B) in toluene at -78°C for 6 h. ^{19}F NMR of the crude products indicated the formation of **2a**⁸ consisting of 51 : 49 *threo*- and *erythro*-isomers^{9,10} (Entry 1). When the β -hydroxy ester **1a** was allowed to react with an organometallic reagent, followed by treating with Bu_3SnH and a catalytic amount of Et_3B at -78°C for 6 h, the isomer distribution of **2a** was improved definitely (Entries 2–6). Out of the metallic reagents examined, such as butyllithium, diethylzinc, diisobutylaluminium hydride, triethylaluminium (Et_3Al), and trimethylaluminium (Me_3Al), the latter two reagents gave better results. Thus, the reaction of an aluminium β -alkoxy ester, generated *in situ* from **1a** and Et_3Al or Me_3Al , with Bu_3SnH and catalytic Et_3B at -78°C for 6 h occurred with good stereoselectivity, leading to the *threo*- and *erythro*-isomers of **2a** with a ratio of 89 : 11 or 95 : 5, respectively, in good yield (Entries 5 and 6). It should be noted that even on conducting the reaction at -15°C for 4 h, high stereoselectivity could be realized (Entry 7). Dichloromethane was employed as the solvent comparable to toluene (Entry 8). However, tetrahydrofuran was not a suitable solvent: The reaction of **1a** using Me_3Al in THF under similar conditions proceeded in a nearly nonstereoselective fashion (Entry 9).

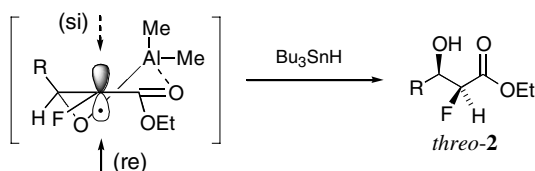
The procedure for the reaction of **1a** is typical. To a toluene solution of **1a** (1.0 equiv) was dropwise added Me_3Al (1 M = 1 mol dm^{-3} in hexane, 1.1 equiv) at -15°C under an argon atmosphere. After stirring for 0.5 h, Bu_3SnH (2.0 equiv) and Et_3B (1 M in hexane, 0.1 equiv) were successively added to the reaction mixture and the whole was stirred at -15°C for 4 h. A solution of 4-*t*-butyl-2,6-dimethylphenol (0.1 M in toluene, 0.5 mL) was added to the reaction mixture. After stirring at that temperature for 15 min, the mixture was poured into a cold NH_4Cl and 10% HCl mixed solution. The resultant mixture was extracted with ether, followed by drying over anhydrous Na_2SO_4 . Evaporation of the solvents and column chromatography on silica gel using hexane- AcOEt gave analytically pure product **2a** in 84% yield.

Table 1 summarizes the results of the reactions of other β -hydroxy esters **1** bearing various substituents R. Regardless of the types of R, such as aryl, *n*-alkyl, and branched alkyl substituents, the reactions of **1** under the conditions described above took place in a highly stereoselective manner, except for the reaction of **1d** (Entry 12), to afford the *threo*-isomers of **2**⁸ preferentially in good yields (Entries 10, 11, 13–16). Of much significance is that the stereoselectivity of the reaction did not depend appreciably on the isomer ratios of the starting esters **1** employed (Entries 17–20).

Table 1. Reduction of α -bromo- α -fluoro- β -hydroxy esters **1** with Bu₃SnH/cat. Et₃B

Entry	R	β -Hydroxy ester 1 threo : erythro ^a	R'M	Solvent	Temp. /°C	Time /h	Yield ^b / % of 2	Isomer ratio ^c of 2 threo : erythro
1	Ph	41 : 59	none	PhCH ₃	-78	6	2a 85	51 : 49
2	Ph	41 : 59	BuLi	PhCH ₃	-78	6	2a 57	58 : 42
3	Ph	41 : 59	Et ₂ Zn	PhCH ₃	-78	6	2a 80	57 : 43
4	Ph	41 : 59	<i>i</i> -Bu ₂ AlH	PhCH ₃	-78	6	2a 69	76 : 24
5	Ph	39 : 61	Et ₃ Al	PhCH ₃	-78	6	2a 77	89 : 11
6	Ph	39 : 61	Me ₃ Al	PhCH ₃	-78	6	2a 80	95 : 5
7	Ph	39 : 61	Me ₃ Al	PhCH ₃	-15	4	2a 84	95 : 5
8	Ph	43 : 57	Me ₃ Al	CH ₂ Cl ₂	-15	4	2a 80	95 : 5
9	Ph	43 : 57	Me ₃ Al	THF	-15	4	2a 80	53 : 47
10	<i>p</i> -MeC ₆ H ₄	40 : 60	Me ₃ Al	PhCH ₃	-15	4	2b 95	93 : 7
11	<i>p</i> -MeOC ₆ H ₄	49 : 51	Me ₃ Al	PhCH ₃	-15	4	2c 89	94 : 6
12	(<i>E</i>)-MeCH = CH	43 : 57	Me ₃ Al	PhCH ₃	-15	4	2d 73	86 : 14
13	Pr	40 : 60	Me ₃ Al	PhCH ₃	-15	4	2e 75	91 : 9
14	Hex	54 : 46	Me ₃ Al	PhCH ₃	-15	4	2f 72	90 : 10
15	<i>i</i> -Pr	37 : 63	Me ₃ Al	PhCH ₃	-15	4	2g 68	93 : 7
16	<i>t</i> -Bu	54 : 46	Me ₃ Al	PhCH ₃	-15	4	2h 66	96 : 4
17	Pr	100 : 0	Me ₃ Al	PhCH ₃	-15	4	2e 86	91 : 9
18	Pr	100 : 0	Me ₃ Al	PhCH ₃	-78	6	2e 75	95 : 5
19	Pr	0 : 100	Me ₃ Al	PhCH ₃	-15	4	2e 73	90 : 10
20	Pr	0 : 100	Me ₃ Al	PhCH ₃	-78	6	2e 81	89 : 11

^aMeasured by ¹⁹F NMR. ^bThe yields refer to pure products isolated by column chromatography on silica gel. ^cDetermined by ¹⁹F NMR of the crude products prior to isolation.



The stereoselection observed in the present reaction may be explained as follows. Thus, the α -bromo- β -hydroxy ester **1** is converted by the action of Me₃Al into the aluminium β -alkoxy ester, probably being chelated intramolecularly, which undergoes a bromine abstraction with tributylstannyl radical to generate a chair-like chelated α -ester radical.^{7c-g} This radical may be reduced with Bu₃SnH more easily from its less hindered *re*-face, leading preferentially to the *threo*-isomer of the product **2**.

In summary, we have developed a new, efficient, and stereoselective approach to the *threo*-isomers of α -fluoro- β -hydroxy esters **2** through the radical reduction of α -bromo- α -fluoro- β -hydroxy esters **1**, prepared easily by the Reformatsky reaction of dibromofluoroacetate with aldehydes.

This work was supported by a Grant-in-Aid for Scientific Research (No. 11650893) from the Ministry of Education, Science, Sports, and Culture, Japan.

References and Notes

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- Spectroscopic and analytical data of the products **2** were in good accord with the assigned structures.
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- The configurational assignment of the products **2** was made on the basis of the relative magnitudes of vicinal H-F couplings¹¹ for acetonides¹² prepared by the reduction of **2** with lithium aluminium deuteride followed by acetalization with 2,2-dimethoxypropane.
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- For instance, 4,4-dideuterio-5-fluoro-2,2-dimethyl-6-phenyl-1,3-dioxane derived from **2a**: For the *threo*-isomer, ¹H NMR (300 MHz, CDCl₃) δ = 1.53 (s, 3H), 1.56 (s, 3H), 4.38 (dd, *J* = 47.2, 1.2 Hz, 1H), 4.96 (d, *J* = 31.0 Hz, 1H), 7.25-7.46 (m, 5H); ¹⁹F NMR (84.1 MHz, CDCl₃, CFCl₃) δ = -204.3 (dd, *J* = 47.2, 1.2 Hz, 1F). For the *erythro*-isomer, ¹H NMR (300 MHz, CDCl₃) δ = 1.48 (s, 3H), 1.58 (s, 3H), 4.50 (dd, *J* = 50.2, 8.7 Hz, 1H), 4.78 (dd, *J* = 8.7, 8.7 Hz, 1H), 7.28-7.47 (m, 5H); ¹⁹F NMR (84.1 MHz, CDCl₃, CFCl₃) δ = -194.7 (dd, *J* = 50.2, 8.7 Hz, 1F).