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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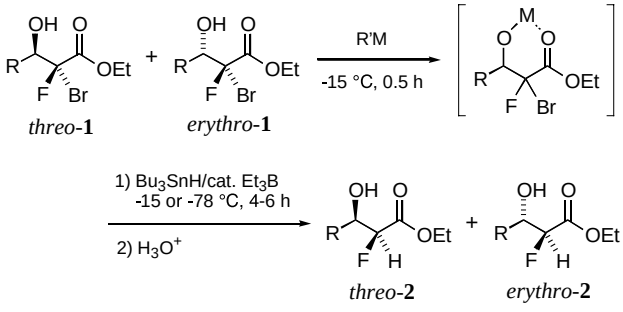
(Received November 1, 2001; CL-011095)

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 reduction[7] 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.



threo-**1** *erythro*-**1** *threo*-**2** *erythro*-**2**

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).

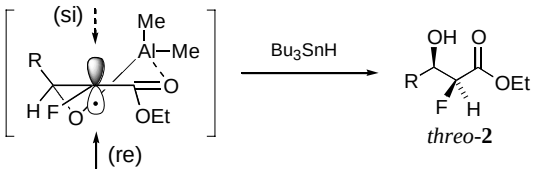
The procedure for the reaction of **1a** is typical. To a toluene solution of **1a** (1.0 equiv) was dropwise added Me_3Al (1 M = 1 mol dm^{-3} in hexane, 1.1 equiv) at −15 °C under an argon atmosphere. After stirring for 0.5 h, Bu_3SnH (2.0 equiv) and Et_3B (1 M in hexane, 0.1 equiv) were successively 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 Bu_3SnH/cat. Et_3B

Entry	β-Hydroxy ester **1** R	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_2Zn	$PhCH_3$	−78	6	**2a**	80	57 : 43
4	Ph	41 : 59	*i*-Bu_2AlH	$PhCH_3$	−78	6	**2a**	69	76 : 24
5	Ph	39 : 61	Et_3Al	$PhCH_3$	−78	6	**2a**	77	89 : 11
6	Ph	39 : 61	Me_3Al	$PhCH_3$	−78	6	**2a**	80	95 : 5
7	Ph	39 : 61	Me_3Al	$PhCH_3$	−15	4	**2a**	84	95 : 5
8	Ph	43 : 57	Me_3Al	CH_2Cl_2	−15	4	**2a**	80	95 : 5
9	Ph	43 : 57	Me_3Al	THF	−15	4	**2a**	80	53 : 47
10	*p*-MeC_6H_4	40 : 60	Me_3Al	$PhCH_3$	−15	4	**2b**	95	93 : 7
11	*p*-$MeOC_6H_4$	49 : 51	Me_3Al	$PhCH_3$	−15	4	**2c**	89	94 : 6
12	(*E*)-MeCH = CH	43 : 57	Me_3Al	$PhCH_3$	−15	4	**2d**	73	86 : 14
13	Pr	40 : 60	Me_3Al	$PhCH_3$	−15	4	**2e**	75	91 : 9
14	Hex	54 : 46	Me_3Al	$PhCH_3$	−15	4	**2f**	72	90 : 10
15	*i*-Pr	37 : 63	Me_3Al	$PhCH_3$	−15	4	**2g**	68	93 : 7
16	*t*-Bu	54 : 46	Me_3Al	$PhCH_3$	−15	4	**2h**	66	96 : 4
17	Pr	100 : 0	Me_3Al	$PhCH_3$	−15	4	**2e**	86	91 : 9
18	Pr	100 : 0	Me_3Al	$PhCH_3$	−78	6	**2e**	75	95 : 5
19	Pr	0 : 100	Me_3Al	$PhCH_3$	−15	4	**2e**	73	90 : 10
20	Pr	0 : 100	Me_3Al	$PhCH_3$	−78	6	**2e**	81	89 : 11

[a]Measured by ^{19}F NMR. [b]The yields refer to pure products isolated by column chromatography on silica gel. [c]Determined by ^{19}F 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 Me_3Al 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.[7e–g] This radical may be reduced with Bu_3SnH 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

1 "Biomedical Frontiers of Fluorine Chemistry," ed. by I. Ojima, J. R. McCarthy, and J. T. Welch, American Chemical Society, Washington, D.C. (1996); J. T. Welch and S. Eswarakrishnan, "Fluorine in Bioorganic Chemistry," John Wiley & Sons, New York (1991); J. T. Welch, *Tetrahedron*, **43**, 3123 (1987); R. Filler and Y. Kobayashi, "Biomedical Aspects of Fluorine Chemistry," Kodansha & Elsevier Biomedical, Tokyo (1982).

2 T. Ishihara, *J. Synth. Org. Chem. Jpn.*, **50**, 347 (1992), and references cited therein; J. T. Welch and S. Eswarakrishnan, "Fluorine-Containing Molecules; Structure, Reactivity, Synthesis, and Applications," ed. by J. F. Liebman, A. Greenberg, and W. R. Dolbier, Jr., VCH Publishers, New York (1988), Chap. 7, pp 123-147.

3 J. T. Welch and R. W. Herbert, *J. Org. Chem.*, **55**, 4782 (1990); J. T. Welch and J. S. Plummer, *Synth. Commun.*, **19**, 1081 (1989).

4 J. T. Welch and S. Eswarakrishnan, *J. Org. Chem.*, **50**, 5403 (1985).

5 S. Brandänge, O. Dahlman, and L. Mörch, *J. Am. Chem. Soc.*, **103**, 4452 (1981); E. T. McBee, O. R. Pierce, and D. L. Christman, *J. Am. Chem. Soc.*, **77**, 1581 (1955).

6 T. Ishihara, T. Matsuda, K. Imura, H. Matsui, and H. Yamanaka, *Chem. Lett.*, **1994**, 2167.

7 For selected general reviews, see: a) D. P. Curran, N. A. Porter, and B. Giese, "Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications," VCH publishers, New York (1996). b) W. Smadja, *Synlett*, **1994**, 1. c) N. A. Porter, B. Giese, and P. D. Curran, *Acc. Chem. Res.*, **24**, 296 (1991). d) B. Giese, *Angew. Chem., Int. Ed. Engl.*, **28**, 969 (1989). For a selected review and papers dealing with stereocontrolled reactions using Lewis acids, see: e) P. Renaud and M. Gerster, *Angew. Chem., Int. Ed. Engl.*, **37**, 2563 (1998). f) Y. Guindon and J. Rancourt, *J. Org. Chem.*, **63**, 6554 (1998). g) Y. Guindon, Z. Liu, and G. Jung, *J. Am. Chem. Soc.*, **119**, 9289 (1997). h) C. Ha, O. M. Musa, F. N. Martinez, and M. Newcomb, *J. Org. Chem.*, **62**, 2704 (1997).

8 Spectroscopic and analytical data of the products **2** were in good accord with the assigned structures.

9 The relative stereochemical nomenclature proposed by Noyori *et al.* is applied in this work. See: R. Noyori, I. Ishida, and J. Sakata, *J. Am. Chem. Soc.*, **105**, 1598 (1983).

10 The configurational assignment of the products **2** was made on the basis of the relative magnitudes of vicinal H-F couplings[11] for acetonides[12] prepared by the reduction of **2** with lithium aluminium deuteride followed by acetalization with 2,2-dimethoxypropane.

11 T. Ishihara, M. Kuroboshi, K. Yamaguchi, and Y. Okada, *J. Org. Chem.*, **55**, 3107 (1990). T. Yamazaki, T. Yamamoto, and T. Kitazume, *J. Org. Chem.*, **54**, 83 (1989).

12 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, $CDCl_3$) 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); ^{19}F NMR (84.1 MHz, $CDCl_3$, $CFCl_3$) δ = −204.3 (dd, J = 47.2, 1.2 Hz, 1F). For the *erythro*-isomer, ^1H NMR (300 MHz, $CDCl_3$) 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); ^{19}F NMR (84.1 MHz, $CDCl_3$, $CFCl_3$) δ = −194.7 (dd, J = 50.2, 8.7 Hz, 1F).