Titanium-promoted highly stereoselective synthesis of α,α-difluoro-β,γ-dihydroxyester. Simple route to 2-deoxy-2,2-difluororibose

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Abstract

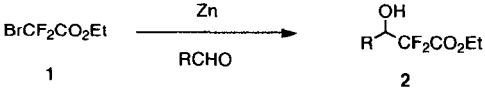
The highly stereoselective synthesis of α,α-difluoro-β,γ-dihydroxyesters is described Reformatsky reaction of bromo- or iododifluoroacetate with D-glyceraldehyde provided (3*R*, 4*R*)-2,2-difluoro-4,5-*O*-cyclohexylidene-3-triethylsiloxypentanoic acid ethyl ester in high yield, with more than 95% diastereoselectivity, by asymmetric induction promoted by Cp_2TiCl_2. The reaction affords a simple and practical route to 2-deoxy-2,2-difluororibose

Introduction

Intensive efforts have been underway worldwide for many years to explore novel anticancer and antiviral agents. Recently new types of nucleosides fluorinated in the sugar moiety have been developed as potent candidates for anticancer [1] or antiviral [2, 3] agents. Among them 2′-deoxy-2′,2′-difluorocytidine (gemcitabine) [1] was identified as a novel antimetabolite with a broad spectrum of potent antitumor activity [4].

In accord with the development of difluorinated bioactive compounds, new synthetic methods [5–8] to introduce difluoroacetyl units were reported. Fried *et al.* [5] first reported Reformatsky reaction of ethyl bromodifluoroacetate **1**. However, the reaction required high temperature to activate the substrate, and due to the instability of the reactive intermediate the yield and selectivity have been limited. Taguchi and coworkers have studied the reactivity of methyl iododifluoroacetate **3** [9] for coupling [10], aldol [6, 7] and addition [11] reactions. They found silyl ketene acetal **4** to be an intermediate for the aldol reaction and anti-selectivity of the reaction in the case of chiral aldehydes.

We focused on the Reformatsky reaction to construct stereodefined α,α-difluoro-β,γ-dihydroxycarbonyl sequences using chiral glyceralde-



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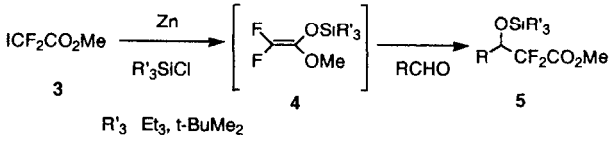


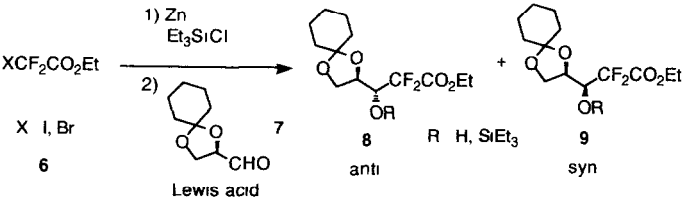
(2)

hydes by asymmetric induction. We herein report the titanium-promoted highly stereoselective synthesis of an α,α-difluoro-β,γ-dihydroxy ester under mild conditions, and offer a simple and practical route to 2-deoxy-2,2-difluororibose.

Results and discussion

Requirements to achieve enhanced face differentiation of this type of Reformatsky reaction involve proper activation of the substrate by Lewis acid and conformational preference by blocking one prochiral face of the substrate through stereoelectronic effects of the chiral center.

Our approach started with the selection of the substrate without external catalyst. The reaction of 2,3-*O*-cyclohexylidene-D-glyceraldehyde **7** [12], readily available from D-mannitol, with ethyl iododifluoroacetate **6** (X = I) treated with Zn–Et_3SiCl in CH_3CN by Kobayashi's method [6] provided an 85:15 mixture of *anti*-**8** (R = $SiEt_3$) and *syn*-**9** (R = $SiEt_3$) isomers in 60% yield (Scheme 1). To assay the Reformatsky reaction in the presence of Lewis acid, we chose the cyclohexylidene glyceraldehyde **7** because 2,3-*O*-isopropylidene-D-glyceraldehyde and 2,3-*O*-dibenzyl-D-glyceraldehyde showed lower diastereoselectivity (up to 80% selectivity).



Scheme 1

Addition of Lewis acids enhanced the condensation reaction under mild conditions and improved diastereoselection in some cases The results are summarized in Table 1. After extensive survey of Lewis acids, the addition of bis(cyclopentadienyl)titanium dichloride [13] (Cp_2TiCl_2) promoted by far the best asymmetric induction and led almost exclusively to the *anti* isomer (entry 7). More significantly, only a catalytic amount (10%) of Cp_2TiCl_2 is also effective for the face discrimination to provide more than 90% *anti*selectivity in high yields (entries 8 and 10).

TABLE 1

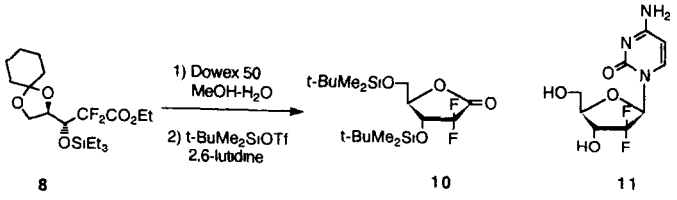
Synthesis of α,α-difluoro-β,γ-dihydroxyesters (**8** and **9**) in the presence of Lewis acid

Run	X	Lewis acid[a]	Conditions	R	Yield (%)	*anti syn*[b]
1	I	none	0 °C, 40 min	Et_3Si	60	85:15
2	I	BF_3 OEt_2	−40 °C, 1 h	H	47	91 9
3	I	Me_2AlCl	−40 °C, 20 min	H	80	78 22
4	I	Cp_2ZrCl_2	−40 °C, 40 min then 23 °C, 1 h	H	41	83 17
5	I	$Ti(O_i\text{-}Pr)_4$	−40 °C, 1 5 h	H	50	78 22
6	I	$TiCl_4$	−40 °C, 4 h	H	74	89 11
7	I	Cp_2TiCl_2	−40 °C, 1 5 h then 23 °C, 1 h	Et_3Si	68	>95 5
8	I	Cp_2TiCl_2[c]	−40 °C, 1 h then 23 °C, 1 h	Et_3Si	80	90 10
9	Br	Cp_2TiCl_2	−40 °C, 2 h then 23 °C, 1 h	Et_3Si	84	>95 5
10	Br	Cp_2TiCl_2[c]	−40 °C, 2 h then 23 °C, 1 h	Et_3Si	92	91 9

[a] 1 1 equiv of Lewis acid was employed unless otherwise noted
[b] The ratio of *anti* and *syn* isomers was determined by ^{19}F NMR
[c] A catalytic amount (0 1 equiv) of Lewis acid was employed

In addition, the reaction utilized commercially available ethyl bromodifluoroacetate **6** (X = Br) and gave over 95% diastereoselectivity in 84% yield (entry 9).

In view of the general utility of the process, we synthesized 3,5-bis-*O*-(t-butyldimethylsilyl)-2-deoxy-2,2-difluoro-1-oxoribose, **10** [1], a key intermediate to 2′-deoxy-2′,2′-difluorocytidine **11**. Silyl ether **8** (R = $SiEt_3$) was treated with ion-exchange resin (Dowex 50) and subsequently silylated by t-butyldimethylsilyl triflate to afford the 1-oxoribose **10** in 85% yield. The ribose **10** can be readily converted to 2′-deoxy-2′,2′-difluorocytidine **11** by the usual methods [1] (Scheme 2)



Scheme 2

The exceptional diastereofacial selectivity could be explained on the basis of the Felkin–Anh model [14] (Fig. 1). Sterically hindered Cp_2TiCl_2 should be coordinated to the carbonyl oxygen, and the nucleophile attacks from the less crowded Si face.

In conclusion, we have developed an efficient method for the highly stereoselective synthesis of α,α-difluoro-β,γ-dihydroxyesters from glycer-

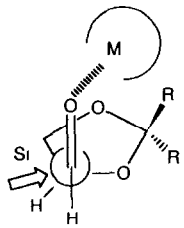


Fig 1 Favored transition state

aldehydes and bromo- or iododifluoroacetate. We have also provided a simple and practical route to 2-deoxy-2,2-difluororibose.

Experimental

IR spectra were recorded on a JASCO IR-810 spectrometer. NMR spectra were taken on JEOL GX-270 spectrometer. The reference was tetramethylsilane for ^1H spectra and $CFCl_3$ for ^{19}F spectra. All chemical shifts were recorded downfield from the reference.

(3R, 4R)- and (3S, 4R)-2,2-difluoro-4,5-O-cyclohexylidene-3-triethylsiloxypentanoic acid ethyl ester ***8*** *and* ***9***

To a suspension of activated zinc powder (157 mg, 2.4 mmol) in CH_3CN (3 ml) was added ethyl bromodifluoroacetate **6** (X = Br) (256 μl, 2 mmol) at 23 °C. After stirring for 10 min, Et_3SiCl (369 μl, 2.2 mmol) was added at 0 °C and the stirring was continued for 10 min. After cooling to −40 °C, a solution of 2,3-*O*-cyclohexylidene-D-glyceraldehyde 7 (170 mg, 1 mmol) in CH_3CN (1 ml) and Cp_2TiCl_2 (274 mg, 1.1 mmol) were added to the mixture. The mixture was stirred at −40 °C for 1.5 h, then allowed to warm to 23 °C and stirred for 1 h. Ether (10 ml) and saturated $NaHCO_3$ were added at 0 °C, stirred for 5 min and filtered through Celite. The filtrate was separated, washed with brine and dried over $MgSO_4$. Flash chromatography on silica gel (AcOEt:hexane = 1:50 − 1:20) provided a mixture of *anti*-**8** (R = $SiEt_3$) and *syn*-**9** (R = $SiEt_3$) isomers (343 mg, 0.84 mmol, 84% yield, **8.9** > 95:5). R_f = 0.58 (AcOEt:hexane = 1:9). IR($CHCl_3$):1775, 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.64–0.70 (6H, m), 0.92–1.00 (9H, m), 1.36 (3H, t, J = 7.1 Hz), 1.30–1.60 (10H, m), 3.90 (1H, dd, J = 5.5, 8.4 Hz), 4.01–4.04 (1H, m), 4.19–4.35 (4H, m). ^{19}F NMR ($CDCl_3$) *anti*-isomer. −113 ppm (dd, ^2J(F–F) = 260 Hz, ^2J(H–F) = 7.5 Hz), −122 ppm (dd, ^2J(F–F) = 260 Hz, ^3J(H–F) = 15.8 Hz); *syn* isomer: −110 ppm (dd, ^2J(F–F) = 260 Hz, ^3J(H–F) = 7.9 Hz), −119 ppm (dd, ^2J(F–F) = 260 Hz, ^3J(H–F) = 11.9 Hz).

2-Deoxy-2,2-difluoro-1-oxoribose

Dowex 50 (H^+) (15 g) was added to a solution of ester **8** (2.94 g, 7.20 mmol, >95% purity) in 30 ml of MeOH–H_2O (2:1) at 23 °C. After

stirring at 23 °C for 96 h, the mixture was filtered and concentrated *in vacuo*. The residue was purified by column chromatography (YMC-ODS-A60, reverse-phase C_{18}, H_2O then 10% MeOH–H_2O) to give lactone (1.14 g, 6.78 mmol). ^1H NMR (D_2O) δ: 3.43–3.61 (m, 3H), 3.95 (m, 1H). ^{19}F NMR (D_2O) −116 ppm (dd, ^2J(F–F) = 255 Hz, ^3J(H–F) = 9.5 Hz), −122 ppm (dd, ^2J(F–F) = 255 Hz, ^3J(H–F) = 16.3 Hz).

3,5-Bis-O-(t-butyldimethylsilyl)-2-deoxy-2,2-difluoro-1-oxoribose ***10***

2,6-Lutidine (156 μl, 1.34 mmol) and then t-butyldimethylsilyl triflate (332 μl, 1.45 mmol) were added to the above lactone in CH_2Cl_2 (1 ml) at 0 °C. The mixture was stirred at 23 °C for 9 h. After dilution with AcOEt (10 ml) and washing with 1 N HCl, saturated $NaHCO_3$ and brine, the crude product was chromatographed on silica gel (AcOEt:hexane 1:50 -1:5) to give disilyl ether **10** (191 mg, 0.482 mmol) having spectra consistent with those reported in the literature [1]. IR ($CHCl_3$):2950, 2930, 2855, 1818, 1770, 1250, 1150, 1122 and 1095 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.1–0.2 (m, 12H), 0.84 (s, 9H), 0.91, (s, 9H), 3.81 (m, 1H), 3.96 (m, 1H), 4.28 (m, 1H), 4.55 (m, 1H).

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