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Preparation of 3-fluoro-5-hydroxy-4-[2-phenyl-(*E*)-ethenyl]-2(5*H*)-furanone

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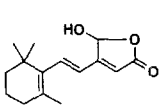
Abstract

Synthesis of 3-fluoro-5-hydroxy-4-[2-phenyl-(*E*)-ethenyl]-2(5*H*)-furanone as an inhibitor of the phospholipase A_2 (PLA_2) was described.

Keywords: Bioactive materials; Inhibitor

1. Introduction

Research on the synthesis of molecules with γ-hydroxybutenolide skeleton which can lead to profound and unexpected results on biological activity has extensively been made in recent years [1–4]. Furthermore, it is well known that the phospholipase A_2 (PLA_2) inhibitory effect of retinoidal-4-ylidenebutenolide **1** and γ-hydroxy-β-styrylbutenolide **2** analogues requires the opening of the lactone ring to form a reactive α,β-unsaturated aldehyde moiety (shown in Scheme 1) [5,6]. Recently, we have reported that the a carbon–carbon double bond modified by a fluorine atom is revealed to have significantly lower LUMO energy level than the corresponding nonfluorinated material and has the similar values for the corresponding p_z orbital coefficients at the reaction sites, which demonstrates the higher electrophilic reactivity of those materials [7,8]. As a continuation of our interest in the synthesis of biologically active materials modified with fluorine(s), we were intrigued by modification of 2-position on the lactone ring with a fluorine atom to increase the reactivity of α,β-unsaturated carbonyl compound.



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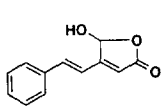

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Our strategy is based on the concept that fluorine-containing molecules might be constructed more easily by employing building blocks with appropriate functionalities. Herein, we report the synthesis of fluorinated analogues of γ-hydroxy-β-styrylbutenolide which is known to act as an anti-inflammatory activity. Especially, we aimed to introduce fluorine atom(s) into a specific position for the purpose of increasing the reactivity of the α,β-unsaturated aldehyde of the hemiacetal ring derived from molecules with γ-hydroxybutenolide skeleton (shown in Scheme 1).

2. Results and discussion

A convenient synthetic route to the desired materials is shown in Scheme 2. To obtain the desired γ-hydroxy-β-styrylbutenolide derivative possessing a fluorine atom, we required the *cis*- and/or *trans*-acetal derivatives (**4**) as a precursor.

At first, compound **3** was thought to undergo a Horner–Emmons reaction upon treatment with NaH–$(EtO)_2$-P(O)$CHFCO_2Et$ system in THF, giving satisfactory conversion into the crude mixture of desired *cis*- and *trans*-compound **4**, and then the mixture was transformed into the fluorinated butenolide derivative **5** by treating with 40% H_2SO_4. Column chromatography on silica gel using a mixture of *n*-hexane–ethyl acetate (1:1) as an eluent, gave pure **5** (19% total yield) [9].

The relative stereochemistry of compounds **4a** and **4b** was determined as follows. Lovey and Pawson [10] have reported the preparation of the geometrical isomers of compound **6** by the reaction of triethyl fluorophosphonoacetate and pyruvaldehyde dimethyl acetal. Their NMR spectral data shown in Table 1 suggest that the four-bond coupling constants ($^4J_{H,F}$) between the C-2 fluorine and C-3 methyl pro-

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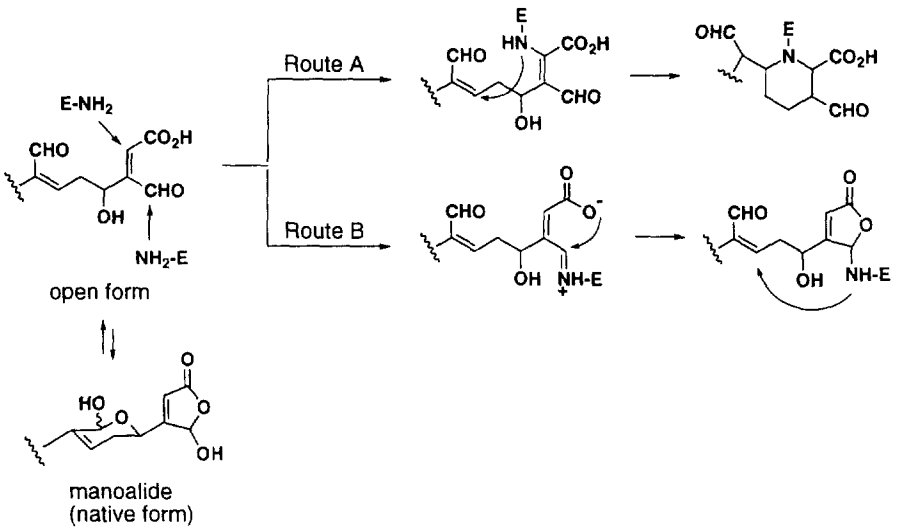
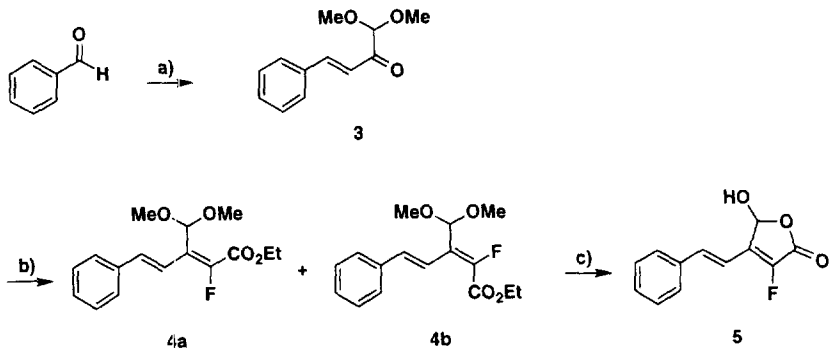


Scheme 1. Proposed schemes for the reaction of manoalide and manoalogue with cobra venom phospholipase A2: (A) involving two conjugate additions, or (B) involving conjugate addition following Schiff base formation.



Scheme 2. (a) $MeCOCH(OMe)_2$, pyrrolidine, MeOH, reflux (b) $(EtO)_2P(O)CHFCO_2Et$, NaH, THF (c) 40% H_2SO_4, 1,4-dioxane.

tons in compound **6** follow a pattern of $^4J_{H,F}$ (*E*-isomer) $>{}^4J_{H,F}$ (*Z*-isomer) [11,12]. From this result, it seems that the comparison of the coupling constant ($J_{F,H}$) supports the assignment of the geometrical isomers. The comparison of their NMR spectral data has led to the assignment of **4a** (*E*-isomer; $J_{F,H}=2.4$ Hz) and **4b** (*Z*-isomer; $J_{F,H}=1.2$ Hz) (shown in Fig. 1).

For compound **5**, the in vitro phospholipase A_2 (PLA_2) inhibitory effect was determined. The reported IC_{50} values represent the concentration of inhibitor producing 50% inhibition of phospholipase A_2 (PLA_2) inhibitory effect. Table 2 shows the results for compounds with the established phospholipase A_2 (PLA_2) inhibitory effect of manoalide, retinoic acid analogues, as a reference [9]. A comparison of IC_{50} values demonstrated the potential of this compound **5** as an phospholipase A_2 (PLA_2) inhibitor. However, phospholipase A_2 (PLA_2) inhibitory effect of compound **5** retained weak activity.

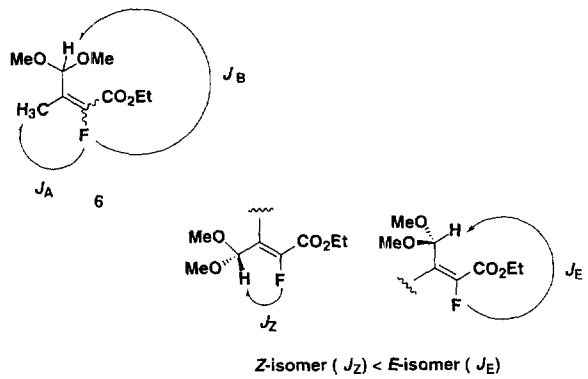


Fig. 1. Comparison of the NMR coupling constants.

Table 1
H–F coupling constants

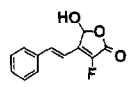
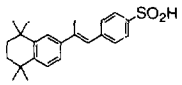
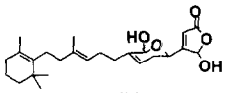
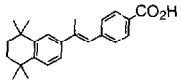
	J_A	J_B
E-isomer	4.40	2.45
Z-isomer	3.18	1.47

3. Experimental

3.1. General procedure

All commercially available reagents were used without further purification. Chemical shifts of ^1H (500 MHz) and

Table 2
Phospholipase A_2 (PLA_2) inhibitory effect of compound in vitro

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
	3.0	 Retionic acid analogue-A	6.6
 manoalide	0.2	 Retionic acid analogue-B	12.0

^{13}C NMR spectra were recorded in ppm (δ) downfield from the following internal standard (Me_4Si, δ 0.00, or $CHCl_3$, δ 7.24). The ^{19}F (470 MHz) NMR spectra were recorded on a Varian XR 500 instrument, the chemical shifts being indicated in ppm downfield from the external $CFCl_3$ in $CDCl_3$. Yields quoted are those of the products actually isolated.

3.2. 3-Fluoro-5-hydroxy-4-[2-phenyl-(E)-ethenyl]-2(5H)-furanone 5

3.2.1. Preparation of compound 3

Benzaldehyde (2.12 g, 20 mmol), pyruvaldehyde dimethyl acetal (4.73 g, 40 mmol), and pyrrolidine (0.043 g, 0.6 mmol) were dissolved in methanol (50 ml). The solution was refluxed for 2 h under an argon atmosphere, and then the mixture was diluted with ethyl acetate followed by drying over $MgSO_4$ and evaporation. 1,1-Dimethyl-4-phenylbut-3-en-2-one (**3**) was obtained by column chromatography with hexane–ethyl acetate (8:1) as eluent in 64% yield.

^1H NMR ($CDCl_3$): δ 3.46 (6 H, s), 4.75 (1 H, s), 7.08 (1 H, d, J = 16.1 Hz), 7.81 (1 H, d, J = 16.1 Hz), 7.32–7.68 (5 H, m).

3.2.2. Preparation of compound 4

To a suspension of NaH (0.50 g, 21 mmol) in dried THF (20 ml) under an argon atmosphere, a solution of ethyl diethylfluorophosphonoacetate (5.09 g, 21 mmol) in dried THF (10 ml) was added at 0°C, and then the mixture was stirred at room temperature for 30 min. The compound **3** (3.82 g, 18.5 mmol) in dried THF (10 ml) was added and the whole was stirred for 8 h. The reaction was quenched with sat. NH_4Cl aq., and oily materials were extracted with diethyl ether and washed with brine. After drying over $MgSO_4$, the solvents were removed. Compound (**4**) was obtained by column chromatography with hexane–ethyl acetate (9:1) as eluent in 87% yield (E/Z ratio = 3.2:1).

E-isomer: ^1H NMR ($CDCl_3$): δ 1.40 (3 H, t, J = 7.3 Hz), 3.48 (6 H, s), 4.36 (2 H, q, J = 7.1 Hz), 5.45 (1 H, dd, $J_{H,F}$ = 1.2, J = 0.7 Hz), 7.29 (1 H, d, J = 16.6 Hz), 7.25–7.53 (6 H, m), 7.74 (1 H, dt, J = 16.5, 1.5 Hz); ^{19}F ($CDCl_3$): δ −125.7 (br) ppm.

Z-isomer: ^1H NMR ($CDCl_3$): δ 1.39 (3 H, t, J = 7.3 Hz), 3.48 (6 H, s), 4.34 (2 H, q, J = 7.1 Hz), 6.11 (1 H, dd, $J_{H,F}$ = 2.4, J = 0.7 Hz), 6.95 (1 H, d, J = 16.6 Hz), 7.25–7.53 (5 H, m), 7.57 (1 H, d, J = 16.4 Hz); ^{19}F NMR ($CDCl_3$): δ −120.4 (d, J = 2.1 Hz) ppm.

3.2.3. Preparation of compound 5

A solution of compound **4** (4.48 g) and 40% H_2SO_4 (30 ml) in 1,4-dioxane (60 ml) was refluxed for 2 h, and the mixture was cooled to room temperature. The mixture was poured into ice-water. Oily materials were extracted with diethyl ether, and washed with brine, After drying over $MgSO_4$, the solvent was removed. 3-Fluoro-5-hydroxy-4-[2-phenyl-(*E*)-ethenyl]-2(5*H*)-furanone (**5**) was obtained by column chromatography with hexane–ethyl acetate (1:1) as eluent in 34% yield.

^1H NMR ($CDCl_3$): δ 4.25 (1 H, br), 6.23 (1 H, d, J = 4.7 Hz), 6.92 (1 H, d, J = 16.6 Hz), 7.25 (1 H, d, J = 16.6 Hz), 7.37–7.56 (5 H, m): ^{19}F NMR ($CDCl_3$): δ −145.5 (d, J = 4.5 Hz) ppm.

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