

Total Synthesis of the 13,13 Difluoro Analog of the 13 HODE

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Abstract: The first total synthesis of the 13,13 difluoro analog of 13 HODE, via the novel fluorinated synthons (5) and (2), is reported. The key advantages of using a propargylic route for the introduction of the gem difluoro moiety are highlighted below.

Keywords: Fluorine; DAST; 13 HODE; lipids.

INTRODUCTION

The introduction of fluorine atom(s) strongly modifies the physical, chemical and biological properties in a molecule [1]. This explains why fluorinated compounds are intensively studied and used in areas as diverse as pharmaceuticals, agrochemicals and polymers, for instance. In fluorobioorganic chemistry the selective replacement of strategic C-H or C-OH bonds by C-F, as well as exchange of CH₂ or O by CF₂ moieties, could lead to important informations regarding the structure and mechanism of action of enzymatic systems. It could as well give compounds, which are more stable from the chemical point of view and/or have a better bioactivity [2, 3]. We have been involved for the last few years in a program dealing with the synthesis and biological evaluation of fluorinated analogs of polyunsaturated fatty acid metabolites [4]. This led us to develop a novel propargylic route for the first enantioselective synthesis of (1a), which is the fluorinated analog of the 13-hydroxyoctadecadienoic acid (13 HODE) (1b) [5]. The latter derivative is a well known metabolite of linoleic acid with potent biological properties in various human diseases, such as cancer, inflammation or cardiovascular problems, as well as in the inhibition of spore germination of rice blast fungus [6]. In order to complete our structure-activity relationships in this family of compounds, and to better understand the role of the fluorine atoms, it appeared interesting to prepare also the gemdifluorinated analog (1c) (Fig. 1) [7].

Therefore, the purpose of this letter is:

- to report the first total synthesis of compound (1c),
- to demonstrate that the propargylic route is again particularly flexible and efficient for the preparation of such derivatives with a gemdifluoro group in allylic position.

SYNTHESIS

The most direct route towards the target molecule involved a disconnection between the carbons 9 and 10

through a Wittig type reaction: this led to the difluoroaldehyde (2) and the known phosphonium salt (3) that we have already used in our synthesis of (1a) [4]. For the preparation of the key intermediate (2), two possibilities have been considered (Scheme 1):

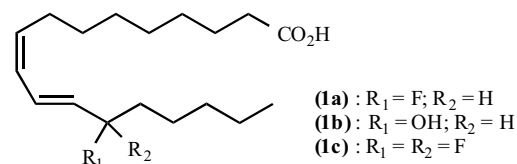
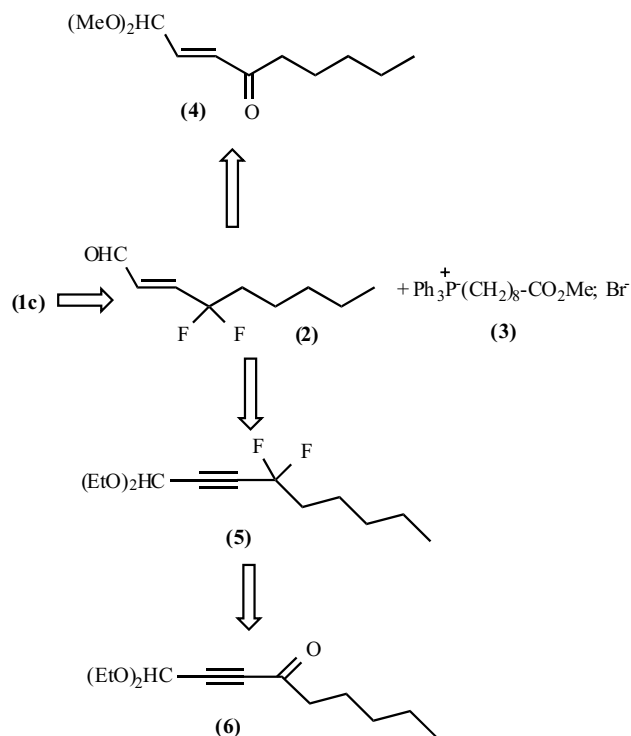


Fig. (1).



Scheme 1.

- Either the difluorination of the easily accessible enone (4),
- or the introduction of the double bond at a later stage in the synthesis, via a semi-hydrogenation of a triple bond; in

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- [6] 13 HODE is also called coriolic acid; the most important biological properties of this derivative have been indicated in ref [4].
- [7] To the best of our knowledge, only two other fluorinated analogues of 13 HODE have been prepared previously: the 14,14 difluorocoriolic acid by the group of Kornilov see: Kornilov, A.M.; Kulik, I.B.; Sorochinsky, A.E.; Kukhar, V.P. *Tetrahedron: Asymmetry*, **1995**, *6*, 199; and the 9 fluorocoriolic acid by the group of Hara see: Yoshida, M.; Hara, S.; Fukuhara, T.; Yoneda, N. *Tetrahedron Lett.*, **2000**, *41*, 3887.
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- [16] All new compounds have spectral and analytical data in agreement with the indicated structures. The data for **(1c)** and the key fluorinated intermediates are the following:
(5) ¹H NMR(400 MHz, CDCl₃) δ (ppm) 5.32 (t, *J* = 3.0 Hz, 1H), 3.73 (dq, *J* = 7.1 Hz, *J*_{HF} = 2.3 Hz, 2H), 3.60 (dq, *J* = 7.1 Hz, *J* = 2.3 Hz, 2H), 2.08-1.97 (m, 2H), 1.59-1.51 (m, 2H), 1.33 (m, 2H), 1.24 (t, *J* = 7.0 Hz, 6H), 0.90 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 114.67 (t, *J* = 233.0 Hz), 90.84, 81.93 (t, *J* = 6.7 Hz), 78.00 (t, *J* = 41.3 Hz), 61.32 (t, *J* = 4.7 Hz), 39.05 (t, *J* = 25.6 Hz), 31.10, 22.40, 15.02, 13.88; ¹⁹F NMR (376.5 MHz, CDCl₃) δ (ppm) -84.21 (td, *J* = 15.0 Hz, *J* = 3.1 Hz); MS (EI) 70 eV calcd for C₁₃H₂₂O₂F₂ [M]⁺: 248.15879; found 249.1588.
(10) ¹H NMR (400 MHz, CDCl₃) δ (ppm) 5.76 (ddt, *J* = 12.0 Hz, *J* = 7.8 Hz, *J*_{HF} = 1.6 Hz, 1H), 5.65 (dt, *J* = 14.1, *J* = 12.6 Hz, 1H), 5.37 (dq, *J* = 7.7 Hz, *J*_{HF} = 0.8 Hz, 1H), 3.68 (qd, *J* = 7.1 Hz, 2H), 3.55 (dq, *J* = 7.1, 2H), 1.98-1.90 (m, 2H), 1.52-1.44 (m, 2H), 1.35-1.30 (m, 4H), 1.23 (t, *J* = 7.1 Hz, 6H), 0.90 (t, 6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 133.70 (t, *J* = 5.0 Hz), 127.28 (t, *J* = 28.2 Hz), 122.11 (t, *J* = 239.7 Hz), 97.04, 61.72, 38.37 (t, *J* = 26.1 Hz), 31.40, 22.39, 21.79 (t, *J* = 4.1 Hz), 15.21, 13.87; ¹⁹F NMR (376.5 MHz, CDCl₃) δ (ppm) -92.03 (q, *J* = 15.7 Hz); MS (EI) 70 eV m/z calcd for C₁₃H₂₄O₂F₂ [M]⁺: 250.17444; found : 250.1748.
(11) ¹H NMR (400 MHz, CDCl₃) δ (ppm) 10.14 (dt, *J* = 7.9 Hz, *J* = 1.5 Hz, 1H), 6.46 (td, *J*_{HF} = 15.6 Hz, *J* = 12.2 Hz, 1H), 6.07 (ddt, *J* = 12.2 Hz, *J* = 7.9 Hz, *J* = 1.9 Hz, 1H), 2.09-1.97 (m, 2H), 1.54-1.47 (m, 2H), 1.37-1.30 (m, 4H), 0.90 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 191.33 (t, *J* = 4.9 Hz), 140.57 (t, *J* = 29.4 Hz), 133.28 (t, *J* = 3.8 Hz), 121.78 (t, *J* = 241.1 Hz), 38.33 (t, *J* = 25.5 Hz), 31.22, 22.28, 21.75 (t, *J* = 4.0 Hz), 13.78; ¹⁹F NMR (376.5 MHz, CDCl₃) δ (ppm) -90.06 (q, *J* = 16.1 Hz); MS (EI) 70 eV m/z calcd for C₈H₁₂F [M - ·CHO-HF]⁺: 127.09230; found : 127.0916.
(2) ¹H NMR (400 MHz, CDCl₃) δ (ppm) 9.66 (d, *J* = 7.5 Hz, 1H), 6.67 (dt, *J* = 15.9 Hz, *J*_{HF} = 10.8 Hz, 1H), 6.45 (ddt, *J* = 16.0 Hz, *J* = 7.5 Hz, *J* = 2.0 Hz, 1H), 2.04-1.92 (m, 2H), 1.51-1.43 (m, 2H), 1.35-1.31 (m, 4H), 0.90 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 192.15, 146.28 (t, *J* = 28.8 Hz), 133.30 (t, *J* = 7.2 Hz), 120.57 (t, *J* = 239.9 Hz), 36.82 (t, *J* = 25.5 Hz), 31.28, 22.31, 21.67 (t, *J* = 4.1 Hz), 13.82; ¹⁹F NMR (376.5 MHz, CDCl₃) δ (ppm) -99.35 (dtd, *J* = 16.2 Hz, *J* = 10.7 Hz, *J* = 2.0 Hz); MS (EI) 70 eV m/z calcd for C₈H₁₂F [M - ·CHO-HF]⁺: 127.09230; found : 127.0928.
(1c) ¹H NMR (400 MHz, CDCl₃) δ (ppm) 12.32 (s, 1H), 6.85-6.75 (m, 1H), 6.00 (t, *J* = 11.3 Hz, 1H), 5.72-5.58 (m, 2H), 2.36 (t, *J* = 7.5 Hz, 2H), 2.21 (q, *J* = 7.1 Hz, 2H), 1.97-1.85 (m, 2H), 1.68-1.58 (m, 2H), 1.53-1.30 (m, 14 H), 0.90 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 179.87, 136.80, 128.47 (t, *J* = 9.4 Hz), 126.52 (t, *J* = 1.7 Hz), 126.31 (t, *J* = 26.5 Hz), 122.08 (t, *J* = 237.9 Hz), 37.61 (t, *J* = 26.9 Hz), 34.05, 31.46, 29.33, 29.06, 29.04, 27.80, 24.89, 22.41, 22.05 (t, *J* = 4.1 Hz), 13.92; ¹⁹F NMR (376.5 MHz, CDCl₃) δ (ppm) -95.36 (q, *J* = 15.0 Hz); MS (EI) 70 eV m/z calcd for C₁₈H₂₉O₂F [M-HF]⁺: 296.21516; found : 296.21402.