Pergamon

Tetrahedron Letters, Vol. 38, No. 35, pp. 6209-6212, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01400-7

Synthesis of Fluorinated Analogs of Polyunsaturated Fatty Acid Metabolites (4 HNE, 13 HODE)

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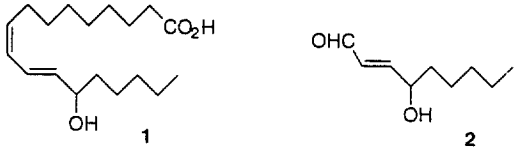
Abstract *: The first synthesis of the fluorinated analogs of the biologically very active fatty acid metabolites (4-hydroxynonenal and coriolic acid) is reported. The key step is the regioselective fluorination of allylic acetal 3.* © 1997 Published by Elsevier Science Ltd.

Many polyunsaturated fatty acid metabolites act as lipid mediators. Such derivatives are almost ubiquitous and probably the best known of them are obtained *via* the arachidonic acid cascade: Prostaglandins, Prostacycline, Thromboxane, Hetes, Leukotrienes...[1] Due to their potent biological activities, all these compounds have been extensively studied during the last 20 years. Metabolites from other essential fatty acids, such as linoleic acid for instance, are also important since they are found both in mammals and in plants. This is the case with 13 HODE **1**, also called coriolic acid: it is acting as a self-defense agent against rice blast disease,[2] it displays unique calcium ionophoric properties,[3] it is also present in sera of patients with familial mediterranean fever and may have a role in its pathogenesis [4]; furthermore it acts as a vessel wall chemorepellant,[5] it is an inhibitor of platelet agregation [6] and platelet adhesion in human endothelium cell cultures[7] and appears involved in tumor cell adhesion.[8] To be mentioned also is the cytotoxic 4-hydroxynon-2-enal **2** which could mediate many pathophysiological effects occuring in cells and organs in response to oxidative stress and lipid peroxidation.[9]



Scheme 1

It is well known that introduction of fluorine atoms in a molecule can induce strong modifications of their chemical and biological properties and this is already demonstrated in various families of biomolecules.[10] However, in the field of polyunsaturated fatty acids and their oxygenated metabolites, this approach has not been

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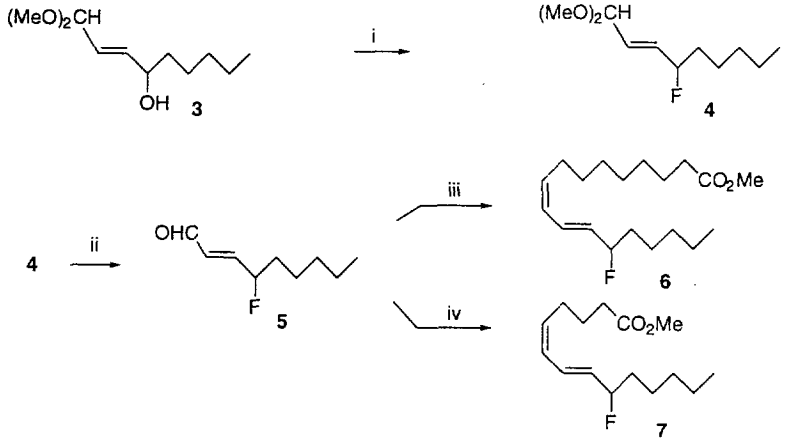
much used[11] except for prostaglandins[12] and prostacyclin[13] derivatives. A few examples of arachidonic acid[14], Hetes[15] and leukotrienes[16] analogs have also been reported but it is interesting to note that most of them are gem difluoro or trifluoromethyl derivatives. *To the best of our knowledge, in these series, there is no example of analogs with a single fluorine atom in allylic position.* In order to have a better understanding of the biological properties of these lipid mediators and to obtain new structure-function relationships it appears important to prepare such selectively monofluorinated analogs. As part of this program, the purpose of this paper is to describe the first synthesis of the fluorinated analogs of 4HNE **5**, and also of the 13 HODE **6**,[17] together with its tetranorderivative **7** (which is also a known metabolite of 13 HODE),[18] as their methyl esters.

The acetal **3** is easily obtained from fumaraldehyde dimethylacetal, as described.[19] Reaction with DAST gives exclusively and in good yield (73%) the fluorinated analog **4**.



i: DAST (1 equiv.), CH_2Cl_2, -50°C, 5 min. (73%). ii: HCO_2H (40 equiv.), CH_2Cl_2, room temp., 3 h. then *solid* Na_2CO_3 (50 equiv.) (74%). iii: $Ph_3P^+(CH_2)_8CO_2MeBr^-$ (2 equiv.), THF, LiHMDS (2 equiv.), -15°C, 30 min. then at -30°C HMPA (20 equiv.) and at -80°C **5**; 2 hours from -80°C to -10°C then aq. NH_4Cl (80%). iv: $Ph_3P^+(CH_2)_4CO_2HBr^-$ (2 equiv.), THF, LiHMDS (4 equiv.), -15°C, 30 min. then at -30°C HMPA (20 equiv.) and **5** at -80°C; 2 hours from -80°C to -20°C then addition of Na_2CO_3 (3 equiv.) and Me_2SO_4 (6 equiv.), room temp. 2 hours, (68%).

Scheme 2

Reaction of **4** with formic acid[20] gives the 4 HNE analog **5** in good yield. Under the same conditions as used for the natural products,[21] Wittig reactions of **5** give the target molecules **6** and **7** in good yields and with good stereoselectivities (Z:E ≥ 95:5 by NMR).

From the organofluorine chemistry point of view, two aspects have to be noticed:

- usually, the nucleophilic fluorination of allylic or polyenic alcohols is neither regio- nor stereoselective whatever the fluorinating agent.[22] The complete selectivity observed in the case of **4** indicates a new and interesting effect of the acetal group.

- the stability of these functionalized allylic fluorides, both under very acidic and strongly basic conditions is also noteworthy and will be important for future synthetic developments in these series.[23,24]

In conclusion, we have described a very short and efficient synthesis of monofluorinated analogs of three lipid mediators. Their biological properties are under study and corresponding results will be reported in due course. Furthermore, this approach could be easily extended to other derivatives, for instance in using **5** as a

versatile key intermediate. Research dealing with the control of stereochemistry during this fluorination and its application to the enantioselective synthesis of such derivatives is actively pursued in our laboratory.

ACKNOWLEDGEMENTS
We thank Prof. J.C. Rossi, Drs Y. Le Floc'h and J. Doyon for fruitful discussions. We acknowledge the French-Algerian cooperation program for financial support.

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23 However, it should be pointed out that both for the TLC analysis and the flash chromatographic purification of these compounds, the silica gel must be pretreated with eluents containing triethylamine.

24 All new compounds exhibited spectral and analytical data consistent with the corresponding structures; ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) with TMS as standard. ^{19}F NMR (376 MHz) with CCl_3F as external reference (^{19}F shifts applied from CCl_3F have negative values). ^{13}C NMR spectra are obtained under proton decoupling conditions and our data indicate the carbon-fluorine coupling constants. When appropriate, signal assignments have been confirmed by 2D NMR experiments.

4: TLC [Ether + light boiling Petroleum Ether 1:1 with Et_3N (2%)]: R*f*= 0.7 ^{1}H NMR ($CDCl_3$): 0.89 (t, 3H, J= 6.9, H-9), 1.4-1.2 (m, 6H), 1.9-1.4 (m, 2H, H-5); 3.320, 3.325 (s, 6H, OCH_3); 4.83 (ddd, 1H, J= 3.3, 1.2, J_{HF}= 2.4, H-1); 4.93 (dq, 1H, J= 6.1, J_{HF}= 48.6, H-4); 5.71 (dddd, 1H, J= 15.8, 3.0, 1.2, J_{HF}= 4.4, H-2); 5.91 (dddd, 1H, J= 15.8, 5.7, 1.1, J_{HF}= 14.7, H-3). ^{19}F NMR δ= -177,7. ^{13}C NMR 13.9 (C-9), 22.4 (C-8), 24.2 (J= 4.5, C-6), 31.4 (C-7), 35.1 (J= 21.9, C-5), 52.5, 52.4 (OCH_3), 92.3 (J= 168.0, C-4), 101.7 (C-1), 128.4 (J= 11.0, C-2), 132.9 (J= 19.7, C-3).

5: TLC [Ether + light boiling Petroleum Ether 1:1 with Et_3N (2%)]: R*f*= 0.57 ^{1}H NMR ($CDCl_3$): 0.92 (t, 3H, J= 6.9, H-9), 1.58-1.30 (m, 6H), 1.80-1.70 (m, 2H, H-5), 5.21 (dm, J= 7.0, 4.0, 1.6, J_{HF}= 48.4, H-4), 6.32 (dddd, J= 15.8, 7.8, 1.6, J_{HF}= 1.1, H-2), 6.78 (ddd, J= 15.8, 4.0, J_{HF}= 19.9, H-3), 9.60 (dd, J= 7.7, J_{HF}= 1.7, H-1). ^{19}F NMR δ= -184.7. ^{13}C NMR 14.0 (C-9), 22.4 (C-8), 24.2 (J= 4.0, C-6), 31.4 (C-7), 34.5 (J= 21.2, C-5), 91.5 (J= 174.4; C-4), 131.0 (J= 9.0, C-2), 153.3 (J= 20.0, C-3), 192.9 (C-1). IR (neat): 1698.

6: TLC [Ether + light boiling Petroleum Ether 1:1 with Et_3N (2%)]: R*f*= 0.69 ^{1}H NMR ($CDCl_3$): 0.90 (t, 3H, J= 6.8, H-18), 1.45-1.30 (m, 14H), 1.83-1.50 (m, 4H), 2.19 (dt, 2H, J= 7.6, 7.2, H-8), 2.32 (t, 2H, J= 7.6, H-2), 3.68 (s, 3H, $CO_2\underline{CH}_3$), 4.95 (dq, 1H, J= 6.9, J_{HF}= 48.8, H-13), 5.52 (dt, 1H, J= 10.2, 7.8, H-9), 5.68 (ddd, 1H, J= 15.2, 6.9, J_{HF}= 12.6, H-12), 6.00 (t, 1H, J= 10.8, H-10), 6.56 (ddd, 1H, J= 15.2, 11.1, J_{HF}= 4.1, H-11). ^{19}F NMR δ= -171.8. ^{13}C NMR 13.9 (C-18), 22.4 (C-17), 24.4 (J= 4.4, C-15), 24.8, 27.7 (J= 0.6, C-8), 28.93, 28.99, 29.02, 29.4 (J= 0.7, C-7), 31.5 (C-16), 34.0 (C-2), 35.5 (J= 22.6, C-14), 51.4 (CO_2CH_3), 93.7 (J= 164.8, C-13), 127.3 (J= 2.8, C-10), 127.9 (J= 12.0, C-11), 130.7 (J= 18.2, C-12), 134.2 (J= 3.4, C-9), 174.2 (C-1). IR (neat): 1730.

7: TLC [Ether + light boiling Petroleum Ether 1:1 with Et_3N (2%)]: R*f*= 0.7 1H NMR ($CDCl_3$) 0.91 (t, 3H, J= 6.8, H-14), 1.50-1.30 (m, 6H), 1.70-1.50 (m, 2H, H-10), 1.75 (qt, 2H, J= 7.4, H-3), 2.26 (q, 2H, J= 7.4, H-4), 2.35 (t, 2H, J= 7.4, H-2), 3.69 (s, 3H, CO_2CH_3), 4.94 (dq, 1H, J= 6.6, J_{HF}= 49.1, H-9), 5.49 (dt, 1H, J= 10.3, 7.8, H-5), 5.72 (ddd, 1H, J= 15.2, 6.8, J_{HF} = 13.0, H-8), 6.04 (dd, 1H, J= 11.1, 10.3, H-6), 6.53 (ddd, 1H, J= 15.2, 11.1, J_{HF}= 4.0, H-7). ^{19}F NMR δ= -172.5 ^{13}C NMR 14.0 (C-14), 22.5 (C-13), 24.4 (J= 4.4, C-11), 24.7 (J= 1.0, C-3), 27.0 (J= 0.8, C-4), 31.6 (C-12), 33.3 (C-2), 35.5 (J= 22.6, C-10), 51.5 (CO_2CH_3), 93.6 (J= 165.3, C-9), 127.5 (J= 12.0, C-7), 128.4 (J= 2.7, C-6), 131.4 (J= 18.2, C-8), 132.5 (J= 3.3, C-5), 173.9 (C-1). IR (neat): 1735.

(*Received in France* 7 *June* 1997; *accepted* 9 *July* 1997)