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The Hydrogenation of β-Hydroxy-γ-Fluoro-γ-Ethylenic Esters as an Efficient Approach to the Fluorohydrin Substructure

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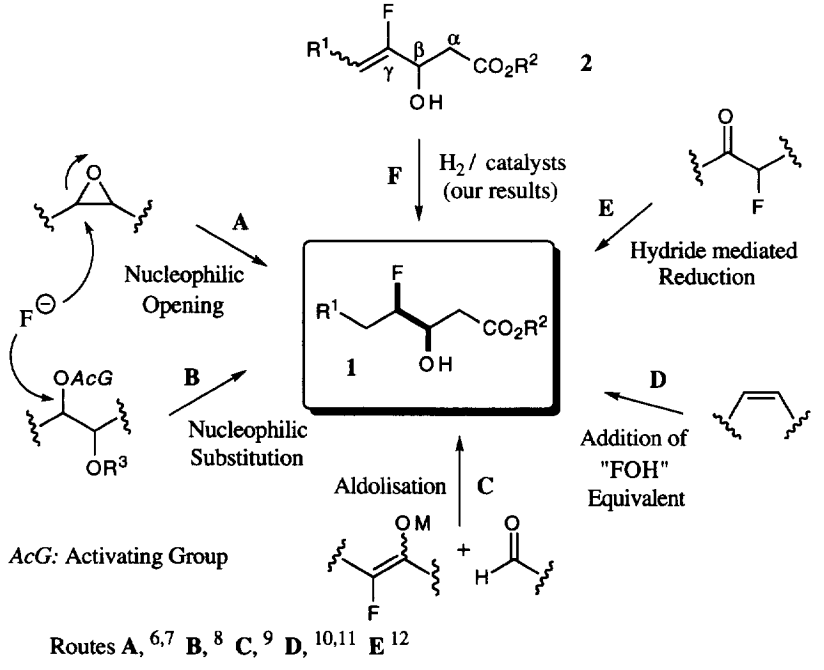
***Abstract** : A novel high-yielding preparation of the fluorohydrin moiety is depicted based on the reductive hydrogenation of β-hydroxy-γ-fluoro-γ-ethylenic esters. Several useful homogeneous as well heterogeneous conditions are disclosed and discussed in this communication.*

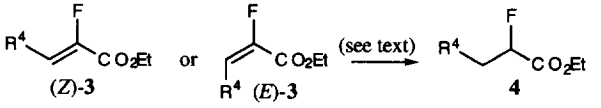
In the context of our continuous interest towards the biochemical and enzymatic characterization of the vegetal acyl-coenzyme-A elongases partially purified from leek microsomes, [1-3] we designed mechanism-based potential fluorinated suicide inhibitors **1** which incorporate the fluorohydrin moiety as an attractive substructure. According to the known electronic and steric properties of fluorine versus hydrogen, this atom exchange has been successfully exploited for the inhibition of many targeted enzymes of biochemical interest. [4,5]



Routes **A**, [6,7] **B**, [8] **C**, [9] **D**, [10,11] **E** [12]

As depicted above, the current literature data made obvious several valuable *one-step* routes to the fluorohydrin moiety except the reductive hydrogenation of the β-hydroxy-γ-fluoro-olefins **2** (route **F**) which could

be viewed as another potential general synthetic access not described previously. Although some recent results dealing with the hydrogenation of electronically deficient fluorinated enoates **3** to reduced esters **4** have been previously described, [13-19] these works did not mention the special case of precursors of type **2**.



The purpose of this communication is to report our own successful results and comments in this field. Considering the two structures **1** and **2**, the control of the expected side reactions of hydrogenolysis of the C-F bonds, (*E*)-/(*Z*)-isomerization of the 4,5-double bond, alkene migration and dehydration of our hydroxylated precursors **2** are of major concern. [14,15,18,19]

Table 1. Hydrogenation of (*E*)-/(*Z*)-**2** ($R^1 = C_{15}H_{31}$, R^2 = Et) [2] and (*E*)-**3** ($R^4 = C_{17}H_{35}$) [2]

Entry	Substrate	Solvent	Catalyst / P_{H2} (bar)	Time (h) at 20 °C	Results [a]
1	(*E*)-**2** [b]	95 % EtOH	Pd-C ($BaSO_4$) / 1	3	Recovery of (*E*)-**2**
2	"	"	Pd-C / 1	"	(*Z*)-**2**
3	"	H_2O	"	8	(*Z*)-**2** + **1** : (1 / 1)
4	"	H_2O or 95 % EtOH	"	18	**1**
5	"	Et_2O	"	24	Recovery of (*E*)-**2**
6	"	"	Pd-C / 50	18	(*Z*)-**2** + **1** : (1 / 1)
7	(*Z*)-**2** [b]	"	Pd-C / 1	3	**1**
8	(*E*)-**3** [c]	95 % EtOH	Pd-C / 1	1	**4**
9	"	Et_2O	"	1	**4**
10	(*E*)-**3** [d]	"	"	0.5	(*Z*)-**3** (90 %) + (*E*)-**3** (< 5 %) + **4** (< 5 %)
11	(*E*)-**2** [e]	THF	$[Rh(DIPHOS)(NOR)]^+BF_4^-$ / 75	16	**1**
12	"	"	$[Rh(DIPHOS)(NOR)]^+BF_4^-$ / 1	48	Recovery of (*E*)-**2**
13	"	PhH	$[Ph_3P]_3RhCl$ / 75	16	**1**
14	"	"	$[Ph_3P]_3RhCl$ / 1	48	Recovery of (*E*)-**2**

a. Yields are relative to isolated compounds and exceed 90 % unless otherwise stated. Compositions of filtrated mixtures are checked using ^1H-/^{19}F-NMR analyses. The reduced fluorinated compounds **1** are always isolated as a 1 / 1 mixture of the *syn* / *anti* isomers as determined by ^{19}F-NMR (C_6F_6 as reference); ***b.*** 10 % Pd-C (9 % weight), substrate (33 mM); ***c.*** 10 % Pd-C (6 % weight), substrate (33 mM); ***d.*** 10 % Pd-C (6 % weight), substrate (16 mM); ***e.*** homogeneous catalyst (5 % molar), the substrate (65 mM); DIPHOS = 1,2-bis(diphenylphosphino)ethane, NOR = norbornadiene.

Our original results in this field are highlighted in the two Tables 1 and 2:

(1) following several trials, valuable hydrogenation conditions for the reduction of (*E*)-/(*Z*)-**2** en route to the fluorohydrin substructure have been disclosed in homogeneous (entries 11 and 13) as well as heterogeneous media (entries 4 and 7) validating our initial concept,

(2) in agreement with the known related literature, [13-19] Pd-C based catalysts are the most efficient ones for the reduction of (*E*)-**2** and (*Z*)-**2** under heterogeneous conditions in water or 95 % EtOH (Table 1, entry 4) and in ethyl ether (entry 7) in yields exceeding 90 %. Interestingly, under analoguous conditions, a Pd-C catalyst poisoned by $BaSO_4$ leads only to recovery of the precursor (*E*)-**2** with no reduction (entry 1 *versus* entry 4).

(3) to the best of our knowledge, the described reduction conditions disclosed here using a cationic rhodium catalyst (entry 11) or the Wilkinson catalyst (entry 13) are new and particularly efficient with no side reactions detectable by NMR techniques. These reduction conditions have potential for their asymmetric versions,

(4) using heterogeneous conditions, (*E*)-**2** is less reactive in ethyl ether than in protic polar solvents. For example, entry 6 indicates that a increased hydrogen pressure (50 bars) is required for reduction affording a 1 / 1 mixture of (*Z*)-**2** and **1** till precursor consumption, while complete in water or 95 % EtOH using a low hydrogen pressure (1 bar) (entry 4). Moreover, the comparison of entries 4 and 5 is in line with this particular remark,

(5) some heterogeneous conditions dealing with the reduction of (*E*)-**2** afford also a mixture of the isomeric (*Z*)-**2** and **1** (entries 3 and 6) or even (*Z*)-**2** isomerically pure as judged by ^1H-, ^{13}C- and ^{19}F-NMR (entry 2). This unexpected result has never been described in the available literature and would constitute a new powerful access to (*Z*)-fluoroalkenes of pure geometry as compared to other poorly stereoselective methods. [20-28] Additionally, it is worthwhile to note that our described homogeneous conditions do not afford any detectable traces of (*Z*)-**2** (entries 11-14),

(6) (*Z*)-**2** can be considered more reactive than isomeric (*E*)-**2** since, under analogous conditions, it is reduced efficiently to **1** (entry 7, quantitative yield) while (*E*)-**2** cannot be reduced (entry 5),

Table 2. Hydrogenation of fluorinated substrates possessing a chemically modified carboxyl group at C(1) [2]

Entry	Substrate **2** ($R^1 = C_{15}H_{31}$)	Solvent	Catalyst / P_{H2} (bar)	Time (h) at 20 °C	Results [a]
15	(*E*)-**2** (R^2 = H) [b]	H_2O / 95 % EtOH 1 / 1	Pd-C / 1	16	**1** (R^2 = H)
16	(*E*)-**2** (R^2 = NHS) [b]	95 % EtOH	"	"	**1** + (*Z*)-**2**: 3 / 2 (R^2 = NHS)
17	(*E*)-**2** (R^2 = NHS) [e]	PhH	$[Ph_3P]_3RhCl$ / 75	16	**1** (R^2 = NHS)
18	(*Z*)-**2** (R^2 = NHP) [e]	"	"	"	**1** (R^2 = NHP)

NHS: succinimido, NHP: phtalimido (the indicated superscripts are the same as in the Table 1)

(7) questioned by the possible involvement of the hydroxyl group at C(3) on the course of the (*E*)-**2** reduction, we considered the case of (*E*)-**3** submitted to similar heterogeneous conditions (entries 8-10). (*E*)-**3** can be quantitatively reduced in **4** (95 % EtOH or Et_2O, 1 h, entries 8 and 9) while diminishing the reaction time to 0.5 h in ethyl ether allowed us to isolate the isomeric (*Z*)-**3** (entry 10, 90 % yield) accompanied with less than 5 % of **4**. Therefore, the isomerization of the fluoroalkene (*E*)-**2** to the corresponding isomeric (*Z*)-**2** cannot be inferred

to the presence of the allylic hydroxyl group. This particular result adds also further support to the previous point (5),

(8) as reported above (Table 2), some heterogeneous or homogeneous reduction conditions were usefully applied to fluorinated unsaturated precursors modified chemically at position C(1) (*E*)-**2** (R^2 = H or NHS) and (*Z*)-**2** (R^2 = NHP) affording the corresponding fluorohydrins in yields exceeding 90 % (entries 15-18). Interestingly, (*E*)-**2** (R^2 = NHS) was found less reactive than (*E*)-**2** (R^2 = Et) under similar conditions (compare entry 4 of Table 1 and entry 16 of Table 2).

In conclusion, following multiple trials of reduction of various fluorinated functionalized alkenes, we disclose efficient homogeneous as well as heterogeneous conditions leading to our required potential suicide inhibitors **1** which contain the targeted fluorohydrin substructure. Whatever conditions, yields of isolated fluorohydrins always exceed 90 % emphasizing on the lack of major side reactions during the reduction processes making valuable this methodology for an efficient access to the fluorohydrin substructure. Another point of great synthetic interest is the observed total isomerization of (*E*)-fluoro-olefins to the corresponding isomeric (*Z*)-ones under some optimized experimental conditions. This new procedure can be viewed as a useful alternative for the obtention of (*Z*)-fluoro-olefins. This particular point will be our future concern in the laboratory.

References and Notes

1. Cassagne, C.; Lessire, R.; Bessoule, J.-J.; Moreau, P.; Creach, A.; Schneider, F.; Sturbois, B. *Prog. Lipids Res.* **1994**, *33*, 55-69.
2. Lucet-Levannier, K. *Conception et Synthèses d'Inhibiteurs d'Elongases d'Acides Gras chez les Végétaux Supérieurs*, Thesis, University of Paris-Sud, 1995.
3. Lucet-Levannier, K.; Lellouche, J.-P.; Mioskowski, C. *J. Am. Chem. Soc.* **1995**, *117*, 7546-7547.
4. Welch, J. T. *Tetrahedron* **1987**, *43*, 3123-3197.
5. Silverman, R. B. *Mechanism-Based Enzyme Inactivation: Chemistry and Enzymology*; CRC Press, Inc. : Boca Raton, 1988 ; Vol. I and II.
6. Duhamel, P.; Leblond, B.; Poirier, J.-M. *J. Chem. Soc., Chem. Comm.* **1993**, 476-477.
7. Shimizu, M.; Yoshioka, H. *Tetrahedron Lett.* **1988**, *29*, 4101-4104.
8. Szarek, W. A.; Hay, G. W.; Perlmutter, M. M. *J. Chem. Soc., Chem. Comm.* **1982**, 1253-1254.
9. Kitazume, T.; Kobayashi, T. *Synthesis* **1987**, 187-188.
10. Berrier, C.; Jacquesy, M. P.; Jouannetaud, J. C.; Vidal, V. *Tetrahedron* **1990**, *46*, 815-826.
11. Migliorese, K. G.; Appelman, E. H.; Tsangaris, M. N. *J. Org. Chem.* **1979**, *44*, 1711-1714.
12. Corey, E. J.; Yang Yi, K.; Matsuda, S. P. T. *Tetrahedron Lett.* **1992**, *33*, 2319-2322.
13. Saburi, M.; Shao, L.; Sakurai, T.; Uchida, Y. *Tetrahedron Lett.* **1992**, *33*, 7877-7880.
14. Martinet, P.; Sauvêtre, R.; Normant, J.-F. *J. Fluorine Chem.* **1991**, *52*, 419-432.
15. Allmendinger, T.; Dandois, C.; Walliser, B. *Tetrahedron Lett.* **1991**, *32*, 2735-2736.
16. Burton, D. J.; Mettille, F. J. *Fluorine Chemistry Reviews*; Tarrant, T. Ed.; Marcel Dekker: New-York, 1967; Vol. 1.; pp. 315-358.
17. Hudlický, M. *Chemistry of Organic Fluorine Compounds*; Halsted Press Ed.: New-York, 1976.
18. Hudlický, M. *J. Fluorine Chem.* **1979**, *14*, 189-199.
19. Hudlický, M. *J. Fluorine Chem.* **1989**, *44*, 345-359.
20. Ishihara, T.; Kuroboshi, M. *Chem. Lett.* **1987**, 1145-1148.
21. Welch, J. T.; Herbert, R. W. *J. Org. Chem.* **1990**, *55*, 4782-4784.
22. Boche, G.; Fährmann, U. *Chem. Ber.* **1981**, 114.
23. Bessière, Y.; Ngoc-Huê Savary, D.; Schlosser, M. *Helv. Chim. Acta* **1977**, *60*, 1739-1746.
24. Allmendinger, T. *Tetrahedron* **1991**, *47*, 4905-4914.
25. Clemenceau, D.; Cousseau, J. *Tetrahedron Lett.* **1993**, *34*, 6903-6906.
26. Kitazume, T.; Ishikawa, N. *Chem. Lett.* **1981**, 1259-1260.
27. McCarthy, J. R.; Matthews, D. P.; Stemerick, D. M.; Huber, E. W.; Bey, P.; Lippert, B. J.; Snyder, R. D.; Sunkara, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 7439-7440.
28. Pirrung, M. C.; Rowley, E. G.; Holmes, C. P. *J. Org. Chem.* **1993**, *58*, 5683-5689.

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