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A new metal mediated stereocontrolled synthesis of allylic fluorides

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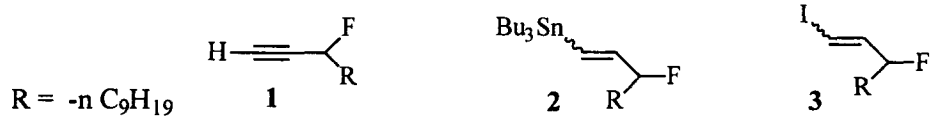
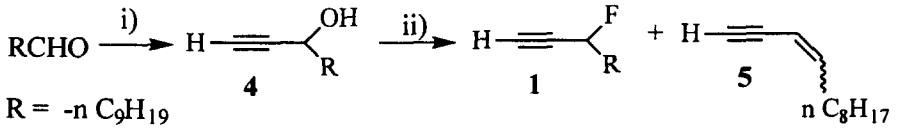
Abstract *: Propargylic fluorides are converted in a short sequence involving hydrostannylation, iodination and Pd catalysis into new stereodefined polyunsaturated systems with a fluorine atom in the allylic position.* © 1999 Published by Elsevier Science Ltd. All rights reserved.

The introduction of fluorine atoms into biomolecules strongly modifies their physical and biological properties leading, for instance, to useful drugs or interesting pharmacological tools. [1] The regio-and stereochemical control in the monofluorination at the position vicinal to unsaturated systems is however still a difficult problem.[2] We have reported recently that some chiral transition metal complexes [Fe[3], Cr[4], Re[5]] efficiently control the dehydroxy-fluorination and this is especially useful in the case of final target molecules or for late intermediates. A complementary approach is to prepare monofluorinated key building blocks that can be elaborated later into the desired target molecules. Such a strategy has been elegantly demonstrated for instance in the case of α-fluorinated carbonyl compounds. [6] Acetylenic derivatives are now widely used for stereocontrolled synthesis of polyunsaturated systems via short sequences including hydro- or carbo-metallation followed by transition metal catalysed C-C bond formation. [7] The purpose of this communication is to demonstrate, for the first time, that such a sequence is compatible with a propargylic fluoride. Using derivative **1**, selected as a model, we have prepared the novel vinyl stannanes **2** and iodides **3** and then converted **3** utilising Pd catalysed reactions into enynes **7** and dienes **8** bearing a single fluorine atom in allylic position.



The synthesis of **1** (Scheme 1) is straightforward since the reaction of diethylaminosulfurtrifluoride (DAST)[8] with alcohol **4** gives **1** (51% yield) with a small amount of **5** (easily separated by chromatography). [9]



Scheme 1 : i) H—≡— MgBr (1eq), THF, RT, 0.5h, 80% ; ii) DAST (1eq), CH_2Cl_2, RT, 0.2h, then Na_2CO_3, **1** (51%) and **5** (11%).

In agreement with the results obtained with other propargylic alcohols, [10] this dehydroxy-fluorination leads exclusively to the propargylic fluoride. [11]

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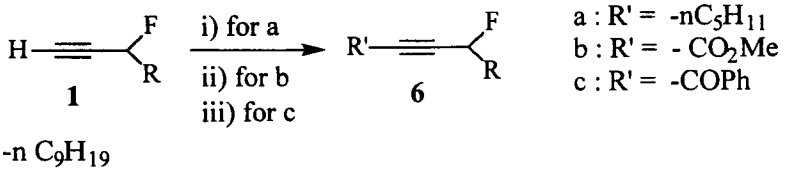
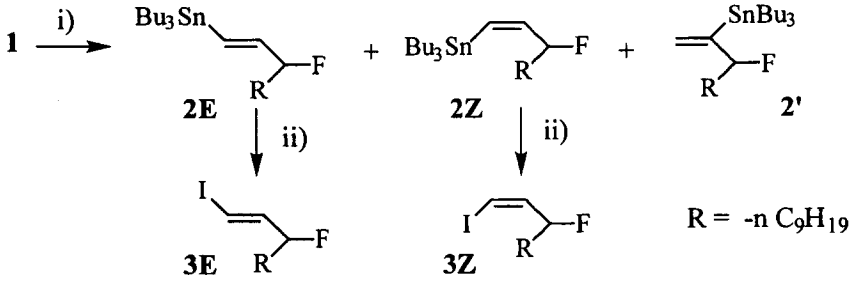
The introduction of substituents on the triple bond was checked first (Scheme 2) : starting from **1**, alkylation, esterification and Sonogashira type reactions are easily performed ; there is neither inhibition of these reactions by the fluorine atom nor decomposition of the molecules.



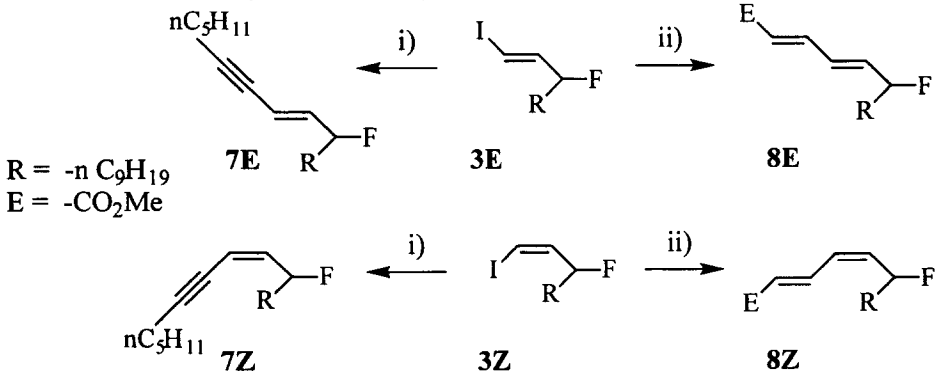
Scheme 2 : i) nBuli, THF-HMPA (3:1), -78°C→-40°C, 0.6h, then $nC_5H_{11}Br$ (2eq), -60°C→ -30°C, 3h, **6a** (76%), ii) nBuli, THF -78°C, 0.5h then $ClCO_2Me$ (1.2eq) 1h then RT 4h, **6b** (66%) ; iii) Pd $(PPh_3)_4$ (0.1eq) CuI (0.1eq), Ph COCl (5eq), Et_3N, RT, 18h, **6c** (41%).

The hydrostannylation of **1**, under classical radical type reaction conditions,[12] occurs smoothly giving (77% overall yield) a 5:4:1 mixture of the E and Z isomers of vinylstannane **2** together with the regioisomer **2'** ; these compounds can be separated by chromatography (Scheme 3).



Scheme 3 : i) Bu_3SnH (1.1eq), AIBN (0.02eq), 90°C, 1h, **2E** (39%), **2Z** (30%), **2'** (8%) ; ii) I_2 (1eq), $CHCl_3$, RT, 1h, **3E** (69%), **3Z** (62%).

Iodination of both derivatives **2E** and **2Z** gives the vinyliodides **3**, stereospecifically and in good yields. The stereochemistry of these compounds is easily established from the NMR data. [13] These new iodides can be used both in Sonogashira type reactions [14] (using Linstrumelle reaction conditions [15]) or in Heck type reactions [16], under Jeffery's conditions [17] (Scheme 4).



Scheme 4 : i) Pd $(PPh_3)_4$ (0.05eq); heptyne (5eq), CuI (0.05eq), Et_3N, RT, 5h, **7E** (53%), **7Z** (48%) ; ii) Pd $(OAc)_2$ (0.06eq), methyl acrylate (2eq), K_2CO_3 (2.5eq), NBu_4Br (1eq), DMF, RT, 6h, **8E** (65%), **8Z** (60%).

In both cases, the reactions are stereospecific, [18] leading to the corresponding polyunsaturated target molecules **7** and **8** with complete stereocontrol. [19] In the latter case, it is noteworthy that this approach is complementary to the use of iron-carbonyl complexes which lead only to E, E dienes. [3]

In conclusion we have developed a new, short, and stereodefined sequence to polyunsaturated systems with a single fluorine atom in the allylic position. This strategy will be of interest in the preparation of monofluorinated analogs of various natural products (pheromones, polyunsaturated fatty acid metabolites, ...). The control of the absolute configuration at the stereogenic centre is another key point in this process. Therefore, the stereoselectivity of the dehydroxy-fluorination in propargylic systems is currently under active study by our group.

Acknowledgments : we thank Dr D. Bremmer for fruitful comments. We acknowledge the Region Bretagne for a fellowship to V.M.

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9 NMR data for **1** :
δ_H ($CDCl_3$) : 5.10(dtd, 1H, J_{HF} = 48.3, J_{HH} = 6.6, J_{HH} = 2.0), 2.68(dd, 1H, J_{HF} = 5.6, J_{HH} = 2.0), 1.96-1.77 (m, 2H), 1.58-1.42(m, 2H), 1.42-1.21(m, 12H), 0.90(t, 3H, J_{HH} = 6.8). δ_C ($CDCl_3$) : 82.4(J_{CF} = 167.1), 80.6(J_{CF} = 25.9), 76.2(J_{CF} = 10.5), 35.8(J_{CF} = 22.1), 31.9, 29.55, 29.52, 29.4, 29.2, 24.4,(J_{CF} = 4.2),22.8, 14.2. δ_F ($CDCl_3$) : -175.45.Anal. $C_{12}H_{21}F$.

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12 It was noticed that the ratio of the three stannanes appears somewhat dependent on the origin of the hydride. The result in Scheme 3 was obtained using a commercially available (Acros) Bu_3SnH. Starting with a freshly prepared Bu_3SnH a mixture of **2E** (63%), **2Z** (23%) and **2'** (13%) was isolated in a similar yield. Furthermore, it is interesting to note that Pd catalysed hydrostannylation gives a 60:40 mixture of **2'** (33% yield) and **2E** (22% yield). The stannylcupration gives only decomposition products.

13 NMR data for **2** and **3** :
2Z : δ_H ($CDCl_3$) : 6.52(dt, 1H, J_{HH} = 6.6, J_{HH} = J_{HF} = 13.3), 6.14(d, 1H, J_{HH} = 13.3), 4.71(dq, 1H, J_{HF} = 48.8, J_{HH} = 6.6), 1.63(quint, 2H, J_{HH} = 6.6), 1.39-1.21(m, 32H), 0.89(t, 3H, J_{HH} = 7.1), 0.88 (t, 9H, J_{HH} = 7.1). δ_C ($CDCl_3$) : 145.6(J_{CF} = 18.1), 133.2(J_{CF} = 12.9), 95.7(J_{CF} = 166.9), 35.7(J_{CF} = 22.4), 31.9, 29.5, 29.4, 29.3, 29.1, 27.3, 24.9(J_{CF} = 4.3), 22.7, 14.1, 13.7, 10.6. δ_F ($CDCl_3$) : -174.31($J_{F\text{-}Sn}$ = 18.8)
2E : δ_H ($CDCl_3$) : 6.24(dd, 1H, J_{HH} = 18.8, J_{HF} = 2.6), 6.00(ddd, 1H, J_{HH} = 18.8, J_{HF} = 11.7, J_{HH} = 5.6), 4.80(dq, 1H, J_{HF} = 48.8, J_{HH} = 5.6), 1.48(quint, 2H, J_{HH} = 6.0), 1.38-1.20(m, 32H), 0.90(t, 9H, J_{HH} = 7.1), 0.88 (t, 3H, J_{HH} = 7.1). δ_C ($CDCl_3$) : 146.1(J_{CF} = 19.5), 131.4(J_{CF} = 8.0), 95.9(J_{CF} = 167.5), 35.1(J_{CF} = 22.1), 31.9, 29.55, 29.53, 29.4, 29.3, 29.0, 27.3, 24.7(J_{CF} = 4.5), 22.7, 14.1, 13.7, 9.4. δ_F ($CDCl_3$) : -174.25($J_{F\text{-}Sn}$ = 9.4 Hz). Anal.$C_{24}H_{49}FSn$.
3Z : δ_H ($CDCl_3$) : 6.47(d, 1H, J_{HH} = 8.0), 6.40(dt, 1H, J_{HF} = 11.2, J_{HH} = 7.9), 5.10(dtd, 1H, J_{HF} = 48.2, J_{HH} = 7.6, J_{HH} = 4.9), 1.82-1.55(m, 2H), 1.51-1.20(m, 14H), 0.88(t, 3H, J_{HH} = 7.1). δ_C ($CDCl_3$) : 139.6(J_{CF} = 25.2), 95.1(J_{CF} = 164.0), 83.9(J_{CF} = 13.7), 34.2(J_{CF} = 22.5), 31.9, 29.5, 29.4, 29.34, 29.30, 24.3(J_{CF} = 3.8), 22.7, 14.1. δ_F ($CDCl_3$) : -179.04.
3E : δ_H ($CDCl_3$) : 6.59(ddd, 1H, J_{HH} = 14.6, J_{HF} = 13.3, J_{HH} = 6.0), 6.47(ddd, J_{HH} = 14.6, J_{HF} = 2.8, J_{HH} = 1.1), 4.81(dtdd, J_{HF} = 48.3, J_{HH} = 7.2, J_{HH} = 6.0, J_{HH} = 1.1), 1.79-1.55(m, 2H), 1.48-1.20 (m, 14H), 0.88(t, 3H, J_{HH} = 7.1). δ_C ($CDCl_3$) : 144.2(J_{CF} = 19.4), 94.2(J_{CF} = 171.6), 79.4(J_{CF} = 14.5), 34.7(J_{CF} = 22.1), 31.9, 29.48, 29.44, 29.3, 29.1, 24.4(J_{CF} = 4.2), 22.7, 14.1. δ_F ($CDCl_3$) : -176.77. Anal. $C_{12}H_{22}FI$.
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18 NMR data for **7Z, 7E, 8Z, 8E** :
7Z : δ_H ($CDCl_3$) : 5.87(dt, 1H, J_{HH} = 8.3, J_{HH} = J_{HF} = 10.8), 5.62(dqd, 1H, J_{HH} = 10.8, J_{HH} = J_{HF} = 2.2, J_{HH} = 1.0), 5.41(dddtd, 1H, J_{HF} = 48.7, J_{HH} = 5.4, J_{HH} = 8.3, J_{HH} = 1.0), 2.33(tt, 2H, J_{HH} = 7.1, J_{HH} = J_{HF} = 1.7), 1.60-1.48 (m, 4H),1.43-1.22 (m, 18H), 0.91(t, 3H, J_{HH} = 7.1), 0.88(t, 3H, J_{HH} = 7.1). δ_C ($CDCl_3$) : 139.2(J_{CF} = 22.6), 112.6(J_{CF} = 12.2), 97.2(J_{CF} = 1.8), 91.2(J_{CF} = 161.3), 76.0(J_{CF} = 4.2), 35.0(J_{CF} = 22.9), 31.9, 31.0, 29.54, 29.53, 29.4, 19.2, 14.1, 14.0. δ_F ($CDCl_3$) : -176.02 .
7E : δ_H ($CDCl_3$) : 6.02(ddd, 1H, J_{HH} = 15.9, J_{HF} = 14.2, J_{HH} = 6.4), 5.72(ddq, 1H, J_{HH} = 15.9, J_{HF} = 3.6, J_{HH} = 1.4), 4.87(dqd, 1H, J_{HF} = 48.3, J_{HH} = 6.4, J_{HH} = 1.1), 2.30(tt, 2H, J_{HH} = 7.0, J_{HH} = J_{HF} = 1.7), 1.75-1.49(m, 4H), 1.43-1.22(m, 18H), 0.90(t, 3H, J_{HH} = 7.1), 0.88(t, 3H, J_{HH} = 7.0). δ_C ($CDCl_3$) : 139.2(J_{CF} = 18.3), 112.6(J_{CF} = 14.0), 92.9(J_{CF} = 167.9), 92.5(J_{CF} = 2.5), 77.9(J_{CF} = 2.4), 35.2(J_{CF} = 22.2), 31.9, 31.1, 29.5, 29.4, 29.3, 29.2, 28.3, 24.6(J_{CF} = 4.4), 22.7, 22.2, 19.4, 14.1, 14.0. δ_F ($CDCl_3$) : -176.15. Anal. $C_{19}H_{33}F$.
8Z : δ_H ($CDCl_3$) : 7.54(dd, 1H, J_{HH} = 15.3, J_{HH} = 11.8), 6.24(t, 1H, J_{HH} = 11.8), 5.96(d, 1H, J_{HH} = 15.3), 5.84(dt, 1H, J_{HH} = 8.2, J_{HH} = J_{HF} = 11.2), 5,40(dq, 1H, J_{HF} = 48.8, J_{HH} = 7.6), 3.77(s, 3H), 1.88-1.50(m, 2H), 1.49-1.17(m, 14H), 0.88(t, 3H, J_{HH} = 7.1). δ_C ($CDCl_3$) : 167.4, 138.7(J_{CF} = 1.5), 137.4(J_{CF} = 20.6), 129.2(J_{CF} = 9.5), 124.2(J_{CF} = 2.6), 89.4(J_{CF} = 164.4), 51.1, 36.0(J_{CF} = 22.5), 32.2, 29.9, 29.75, 29.71, 29.6, 24.9(J_{CF} = 4.2), 23.1, 14.5. δ_F ($CDCl_3$) : -174.45.
8E : δ_H ($CDCl_3$) : 7.26(dd, 1H, J_{HH} = 15.3, J_{HH} = 11.2), 6.39(dd, 1H, J_{HH} = 16.3, J_{HH} = 11.2), 6.09(dt, 1H, J_{HH} = 5.6, J_{HH} = J_{HF} = 16.3), 5.93(d, 1H, J_{HH} = 15.3), 5.04(dq, 1H, J_{HF} = 48.3, J_{HH} = 5.6), 3.76(s, 3H), 1.79-1.57 (m, 2H),1.49-1.19 (m, 14H), 0.88(t, 3H, J_{HH} = 7.1). δ_C ($CDCl_3$) : 167.6, 143.8(J_{CF} = 1.5), 140.2(J_{CF} = 18.7), 129.0(J_{CF} = 12.2), 122.5(J_{CF} = 1.9), 92.7(J_{CF} = 169.4), 52.0,35.6(J_{CF} = 21.7), 32.2, 29.87, 29.84, 29.7, 29.6, 25.0(J_{CF} = 4.2), 23.1, 14.5. δ_F ($CDCl_3$) : -179.27. Anal. $C_{16}H_{27}FO_2$.
19 Preliminary studies indicate that Stille or Suzuki type reactions are possible , but the yields are low (20-30%).