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α-Fluoro-Benzylphosphonates as Reagents for the Preparation of 1-Fluoro-1-Aryl Alkenes and α-Fluorostilbenes

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Abstract: The preparation of several fluoro-benzylphosphonates Ar-CHF-PO(OEt)$_2$ and their Wadsworth-Emmons type olefination with aldehydes and ketones are described affording fluorostyrenes and fluorostilbenes. Some of these compounds are incorporated into target molecules tested as drug candidates.

Keywords: Fluoro-benzylphosphonates · Fluoroolefins · Horner-Wadsworth-Emmons olefination

Introduction

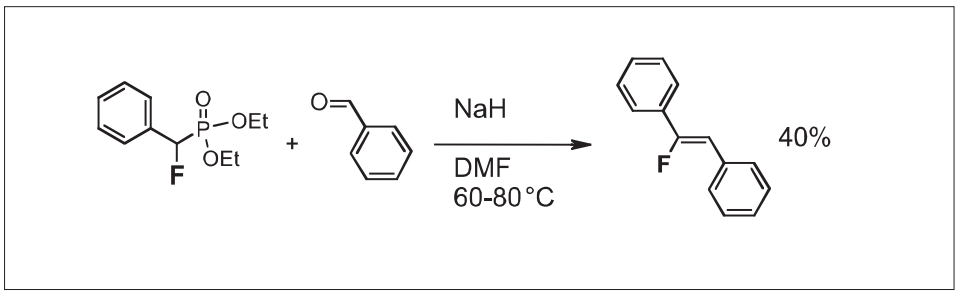
Ylide-type chemistry is well elaborated in the field of fluorine-organic chemistry and has been comprehensively reviewed recently [1]. For example, the reaction of α-fluoro-benzylphosphonate with benzaldehyde to form fluorostilbene (Scheme 1) was reported as early as 1968 [2] but has reached only limited attention until recently [3].

As part of our studies towards the preparation of fluoroolefins and their application in medicinal chemistry [4], we have also investigated this reaction more closely, varying the structure of the carbonyl compound as well as that of the fluoro benzylphosphonate; this paper summarizes the results.

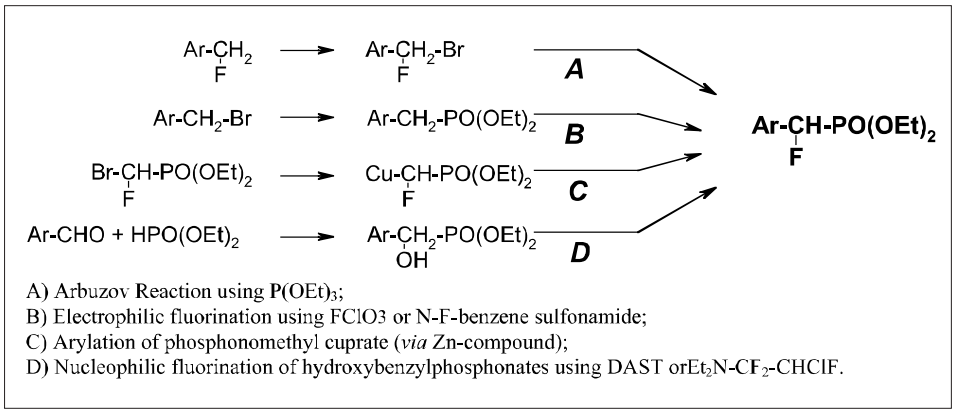
Preparation of Fluoro-benzyl-phosphonates

Several methods have been reported for the preparation of α-fluoro-benzylphosphonates (Scheme 2, A [5], B [6], C [7]); the most widely applicable and also most simple being the conversion of α-hydroxy-benzylphosphonates (D) using DAST [8] or similar fluorinating agents [2].

α-Hydroxy-benzylphosphonates **2** are easily accessible by the base-catalyzed ad-



Scheme 1. Initial report of Bergman



Scheme 2. Preparation of α-fluoro-benzylphosphonates

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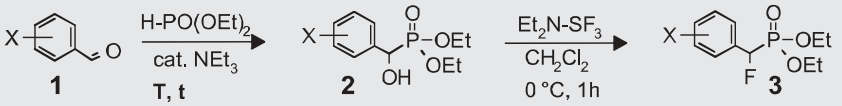
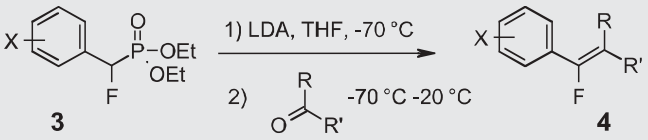
Table 1. Preparation of α-hydroxy- and α-fluoro-benzylphosphonates **2** and **3**



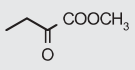
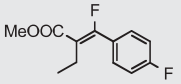
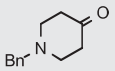
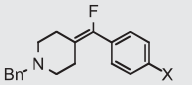
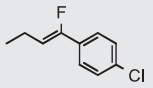
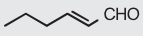
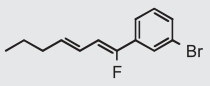
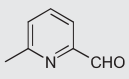
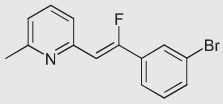
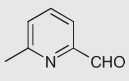
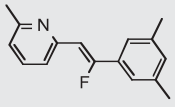
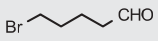
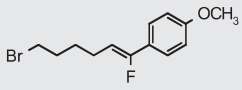
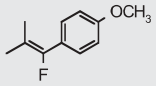
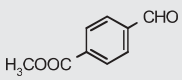
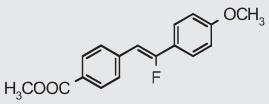
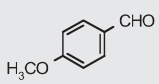
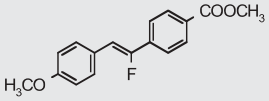
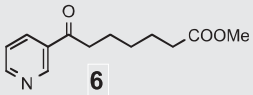
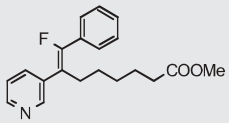
	X	T	t	mp 2	Yield 3
a	H	60 °C	24 h	83 °C	52%
b	*p*-F	70 °C	16 h	–	59%
c	*p*-Cl	70 °C	16 h	67 °C	57%
d	*m*-Br	90 °C	24 h	–	51%
e	*p*-OMe	40 °C	60 h	121 °C	80%
f	*p*-COOMe	40 °C	3 h	108 °C	66%
g	3,5-Me_2	25 °C[a]	1 h*	–	91%

[a]NaOMe catalyzed reaction

Table 2. Preparation of α-fluoro-styrene derivatives by base-induced Wadsworth-Emmons



reaction of diethyl α-fluoro-benzylphosphonate with aldehydes and ketones

entry	3, X=	Carbonyl-compound	4 (only (Z)-isomer depicted)		yield	(Z)/(E)
1	*p*-F			**a**	82%	50:50
2	*p*-F			**b**	76%	–
3	*p*-Cl			**c**	72%	–
4	*p*-Cl			**d**	98%	50:50
5	*m*-Br			**e**	78%	50:50
6	*m*-Br			**f**	33 %	50:50
7	3,5-$(CH_3)_2$			**g**	30 %	32:68
8	*p*-OCH_3			**h**	52%	60:40
9	*p*-OCH_3			**i**	78%	–
10	p-OCH3			**j**	68%	50:50
11	*p*-$COOCH_3$			**k**	73%	15:85
12	H	 **6**		**l**	32%	50:50

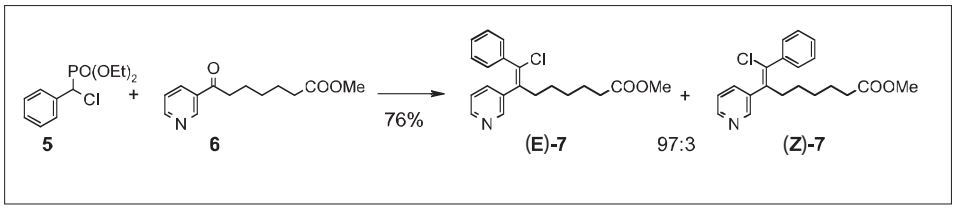
dition of diethylphosphite to aldehydes [9]. Thus mixtures of the aromatic aldehyde, diethylphoshite and triethylamine (molar ratio 1:1:0.1) are stirred without solvent at elevated temperature (Table 1). Upon completion of the reaction, most of the mixtures solidify and may be used directly in the following step. Alternatively, the solid compounds **2** may be isolated by triturating with hexane and recrystallized. For a representative example see [10]. The conversion to the corresponding α-fluoro-benzylphosphonates **3** is simply achieved by treating solutions of **2** in dichloromethane with diethylamino sulfur trifluoride at 0 °C.

The methoxy-substituted derivative **3e** was reported to be not accessible by this route [1][8]. Following the procedures outlined in reference [11] the preparation of diethyl 4-methoxy-α-fluoro-benzylphosphonate **3e** proved to be reproducible.

Wadsworth-Emmons Olefination of Fluorophosphonates

Having a simple way to access a wide variety of α-fluoro-benzylphosphonates **3**, these compounds were used for the preparation of fluoroolefins. In a standard procedure [12], compounds **3** were treated with lithium diisopropylamide (LDA) as a base at low temperature and subsequently reacted with carbonyl compounds (Table 2). Aliphatic and aromatic aldehydes and ketones are equally reactive forming α-fluorostyrenes and α-fluorostilbenes **4** in moderate to excellent yields.

In the case of aldehydes and unsymmetrical ketones, mixtures of (*E*)- and (*Z*)-isomers are obtained in a ratio usually around 1:1. As Burton has already pointed out for the simple unsubstituted **3a**, this ratio is virtually unaffected by the reaction conditions and only slightly altered by solvent or salt additives [3]. Some examples in Table 2 however indicate that the substituent in the phosphonate has an influence on the stereochemical outcome of the reaction. Reacting *p*-methoxy fluorophosphonate **3e** with methyl 4-formylbenzoate (entry 10) affords the fluorostilbene **4j** in a 1:1 ratio of (*E*)- and (*Z*)-isomers. Exchanging the substituents in the starting materials (hence, reaction **3f** with *p*-anisaldehyde, entry 11) has a substantial effect on the stereoselectivity; the corresponding fluorostilbene **4k** is obtained predominantly as its (*E*)-isomer (*cis*-stilbene). Another interesting observation is the selectivity of the reaction of the chlorophosphonate **5** [13] with ketone **6** (Scheme 3) to afford almost exclusively the (*E*)-chloroolefine **7** in contrast to the corresponding fluoro-phosphonate **3a** giving raise to a 1:1 mixture of fluoroolefines **4l** (Table 2, entry 12).



Scheme 3. Reaction of chlorophosphonat **5** with ketone **6**

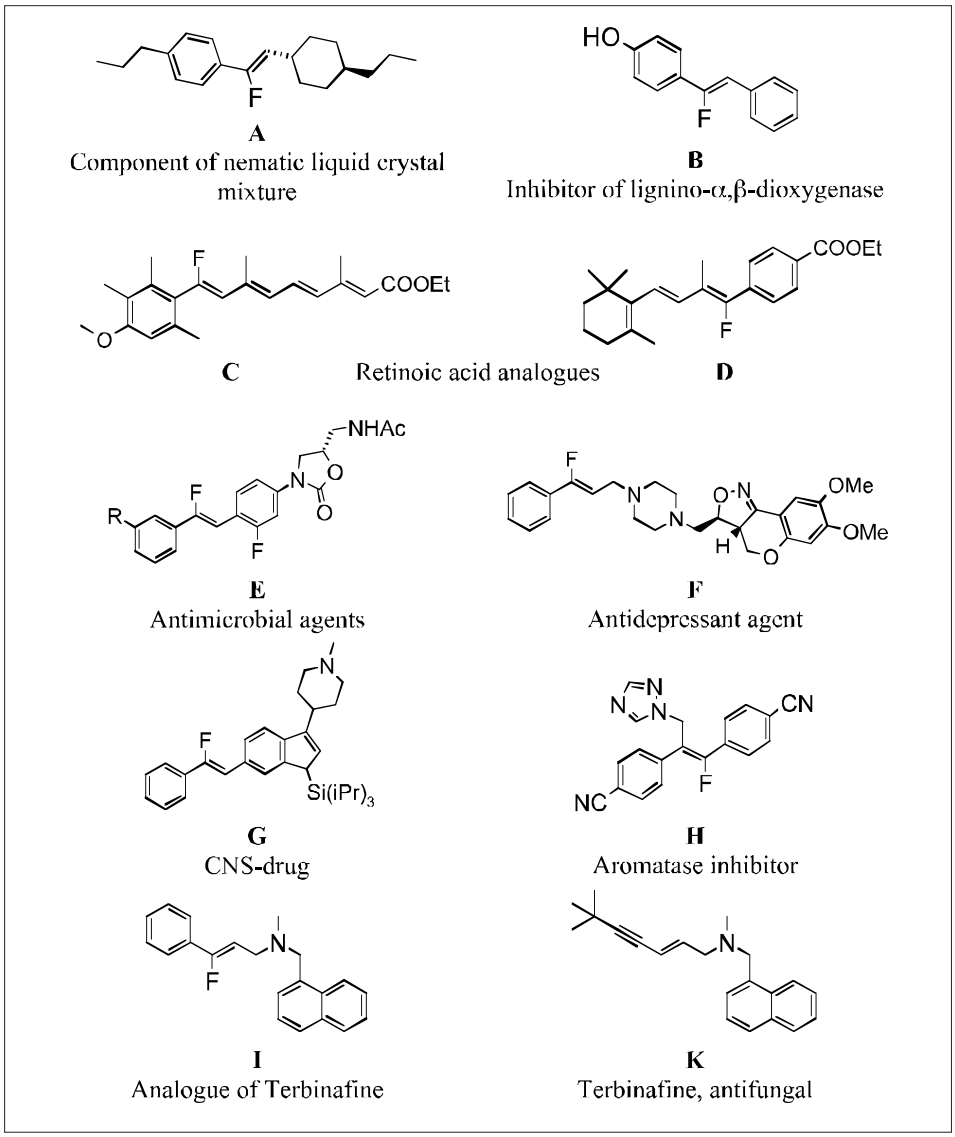
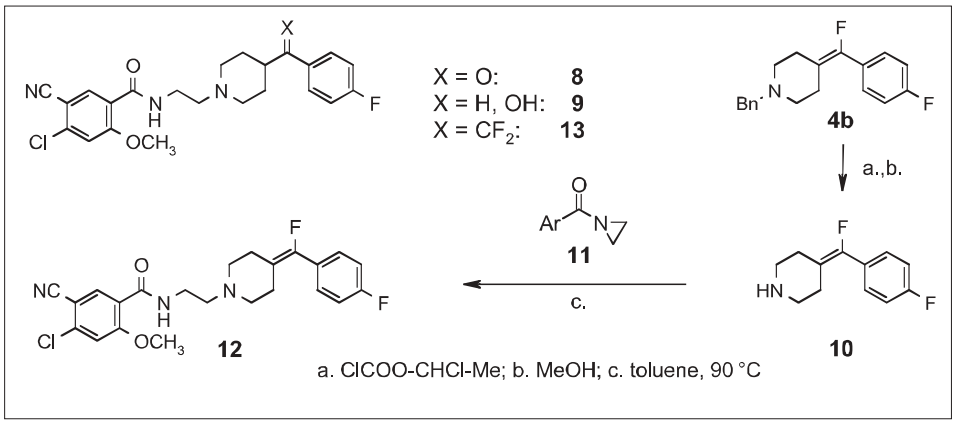


Fig. Applications of fluorostyrenes and fluorostilbenes (references in the text)



Scheme 4. Analogues of dopamine antagonist **8**

Applications

Some potential applications have appeared in the literature (Fig.): Fluorostilbene **A** and related compound are claimed to give nematic liquid crystal mixtures with improved physical properties [14]; α-fluoro-*p*-hydroxy-stilbene **B** is a potent inhibitor of LSD (ligninostilbene-α,β-dioxygenase) [15]; fluorinated retinoic acid analogues **C** and **D** have been tested as anticancer drugs [5a][6a]; a novel series of antimicrobials **E** are described by Sciotti *et al*. (Abbott Laboratories) [16]; substituted isoxazole **F** and indole **G** are prepared and tested as antidepressants [17]; stilbene derivative **H** was tested as aromatase inhibitor and antifungal agent [18]; a screening program for antifungal agents in our company included also fluoroolefine **I** [19], however the final marketed drug Lamisil® contains the alkyne derivative Terbinafine **K**.

The development of the dopamine antagonist **8** as an antipsychotic agent was discontinued due to its rapid metabolism to the corresponding alcohol **9** (Scheme 4). We therefore were looking for metabolically stable compounds containing groups mimicking the labile carbonyl group: **12**, **13**. Compound **4b** was debenzylated and the amine **10** thus obtained was reacted with the N-aroyl-aziridine **11** affording fluoroolefine analogue **12**. It shows only moderate biological activity, similar to that of the difluoromethylene analogue **13**.

α-Fluorinated-β-pyridyl-substituted styroles **4f** and **4g** (Table 2), were tested as antagonists of subtype **5** of the metabotropic glutamate receptor and are therefore of potential interest for the treatment of a number of diseases [20].

The acids **14** and **15** prepared from the esters **4l** and **7** (Scheme 5) resemble the structural requirements of thrombaxane A_2 synthesis inhibitors (a basic nitrogen in distinct distance to a carboxylic acid) [21] and are therefore strong inhibitors of human platelet aggregation.

During a program to discover LTB_4 antagonists as new anti-inflammatory agents, the Eli-Lilly antagonist LY223982 [22] (Scheme 6) was modified. Part of this effort was an attempt to understand the SAR of the *p*-methoxystyrene olefin which seemed to be important for antagonist activity. Unfortunately, introducing a fluorine substituent in α-position of the styrene moiety (target compound **16**) had the opposite effect: the building block **4h** turned out to be unstable; dissolved in $CDCl_3$, **4h** remained unchanged for about 3 days but then decomposed completely and rapidly to form a product lacking the fluoroolefin moiety. Closer examination revealed the formation of the ketone **17** (the analogue **18** was inactive in the biological assay). This phenomenon is easily explained by the presence of

a *p*-MeO group which stabilizes a transient carbocation formed by protonation of the fluoroolefin moiety and by the formation of HF inducing the autocatalytic effect. Similar observations have been made by Rolando in an attempt to cleave MOM-protected *p*-hydroxy-α-fluorostilbenes [23].

Alternatives, Summary, and Outlook

Despite the utility of the Wadsworth-Emmons method described here, modern Stille and Suzuki reactions have been commonly used to generate the fluoroolefins (Scheme 7). These Pd-catalyzed reactions of arylboronic acids or stannanes with fluorinated vinyl bromides or aryl iodides with fluorinated vinylstannanes are stereoselective and have found some applications [15][16][24]. However, the preparation of bromo-fluoro olefins and fluorovinylstannanes in pure (*E*) or (*Z*) form are laborious.

A general method is described to prepare fluoroolefins Ar^1-CF=CH-R^2: aromatic aldehydes Ar^1CHO are converted to α-fluoro-benzylphosphonates which are condensed in a Wadsworth-Emmons reaction with aldehydes and ketones (Scheme 8). Aliphatic fluorophosphonates (similarly prepared by base-catalyzed addition of diethyl phosphite to aliphatic aldehydes R^1CHO followed by OH-F exchange using SF_4) do not readily undergo the Wadsworth-Emmons olefination reaction. The initial report by Blackburn and Parat [25] was not verified [8]. Realization of this goal however would lead to a general method for introducing fluorine substituents at sp^2 and sp^3-centers anywhere into a carbon chain, as fluoroolefins can selectively be hydrogenated [26].

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[4] a) T. Allmendinger, C. Angst, H. Karfunkel, *J. Fluorine Chem.* **1995**, *72*, 247–53; b) G. Bold, T. Allmendinger, P. Herold, L. Moesch, H.P. Schaer, R.O. Duthaler, *Helv. Chim. Acta* **1992**, *75*, 865–82; c) T. Allmendinger, *Tetrahedron* **1991**, *47*, 4905–14; d) T. Allmendinger, E. Felder, E. Hungerbuehler, ACS Symp. Ser. **1991**, *456*, 186–95; e) T. Allmendinger, P. Furet, E. Hungerbuehler, *Tetrahedron Lett.* **1990**, *31*, 7297–300; f) T. Allmendinger, E. Felder, E. Hungerbuehler, *Tetrahedron Lett.* **1990**, *31*, 7301–4; g) J.T. Welch, T. Allmendinger, *Methods Mol. Med.* **1999**, *23* (Peptidomimetics Protocols), 357–384.
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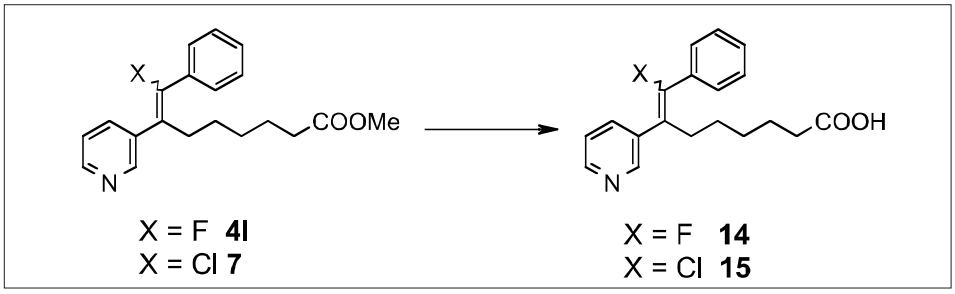
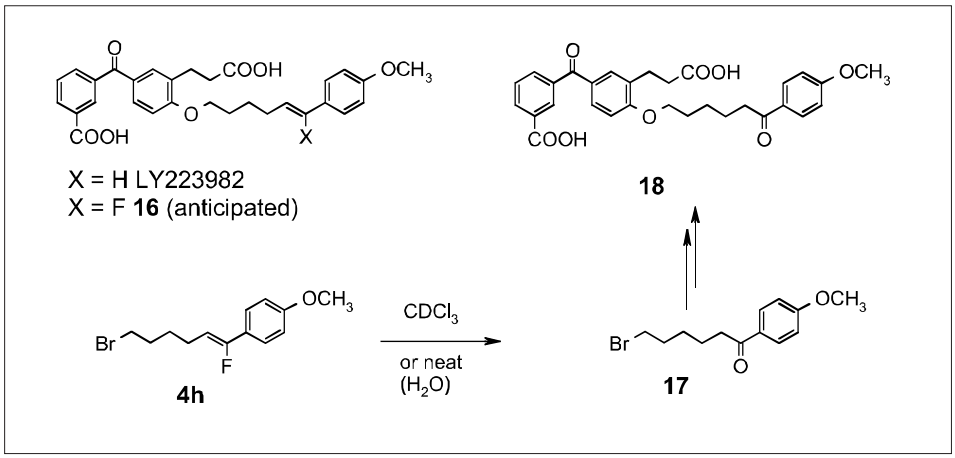
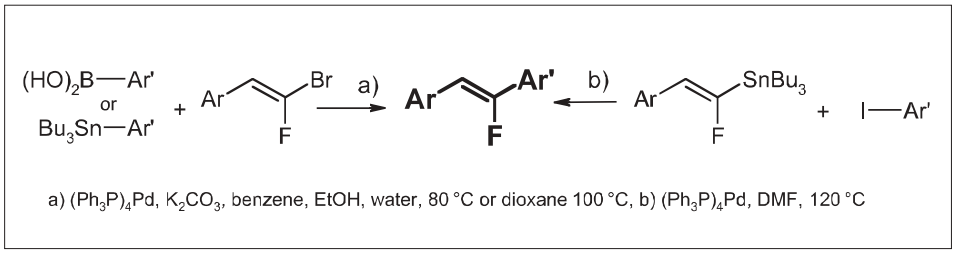


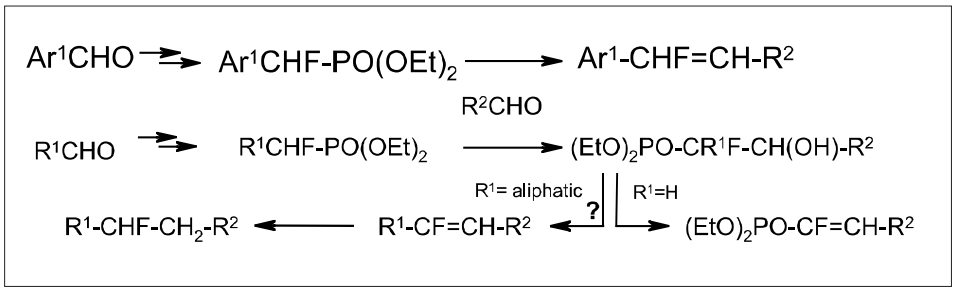
Scheme 5. TxA_2 synthesis inhibitors



Scheme 6. Hydrolysis of *p*-MeO-phenyl substituted fluoroolefin



Scheme 7. 'Modern' Stille and Suzuki reactions to prepare fluorostilbenes



Scheme 8. Reaction of aromatic and aliphatic fluorophosphonates with aldehydes

c) A.R. Sardarian, B. Kaboudin, *Synthetic Comm*. **1997**, *27*, 543.

[10] Diethyl α-hydroxy-4-methoxy-benzylphosphonate (**2e**), typical procedure: A mixture of 13.6 g (0.1 mol) of freshly distilled *p*-anisaldehyde, 14.5 g (0.105 mol) of diethylphosphite and 0.4 g (4 mmol) of triethylamine is heated with stirring at 40 °C for 67 h to obtain **2e** in quantitative yield as a solid which can be used without further purification. Mp. (from ethyl acetate) 121–123 °C. IR (CH_2Cl_2, cm^{-1}): 3373, 3279 (OH), 2985, 1612, 1513, 1239, 1174, 1032, 971. ^{1}H-NMR ($CDCl_3$, 200 MHz, *J* [Hz]): 1.20, 1.27 (2*t*, *J* = 7 each, 3H, 3H, diastereotopic P-O-C-CH_3); 3.80 (*s*, OCH_3); 3.9–4.1 (*m*, 4H, OCH_2); 4.32* (*dd*, $^3J_{HP}$ = 9, $^3J_{HH}$ = 5, OH); 4.94 (dd, $^2J_{HP}$ = 10, $^3J_{HH}$ = 5, O-CH-P); 6.88 (*d*, *J* = 8, aryl-H-C(3), H-C(5)); 7.41 (*dd*, *J* = 8, $^4J_{HP}$ = 2, aryl-H-C-(2), H-C(6)). *OH-signal does not appear always split; if not, the signal at 4.94 is a doublet (*J* = 10) only.

[11] Diethyl α-fluoro-4-methoxy-benzylphosphonate (**3e**), typical procedure: To the soln. of **2e** (22 g, 80 mmol) in 120 ml of dichloromethane is added (at –5 to 0 °C, during 50 min) a soln. of diethylamino sulfurtrifluoride (DAST, 14.5 g, 90 mmol) in 15 ml of dichloromethane. The organic solution is stirred for 20 min and then washed with water, aq. sodium bicarbonate, and brine. The organic phase is dried over magnesium sulfate and evaporated, the residue is chromatographed on silica (200 g, ethyl acetate) affording 17.7 g (80%) of **3e**. IR (CH_2Cl_2, cm^{-1}): 2984, 1619, 1515, 1240, 1030. ^{1}H-NMR ($CDCl_3$, 300 MHz, *J* [Hz]): 1.22, 1.28 (2*t*, *J* = 7 each, 3H, 3H, diastereotopic P-O-C-CH_3); 3.79 (*s*, OCH_3); 3.9–4.1 (*m*, 4H, OCH_2); 5.57 (*dd*, $^2J_{HF}$ = 44, $^2J_{HP}$ = 7.5, P-CH-F); 6.90 (*d*, *J* = 8, aryl-H-C(3), H-C(5)); 7.40 (*d*, *J* = 8, aryl-H-C-(2), H-C(6)).

[12] Preparation of 6-bromo-1-fluoro-1-(*p*-methoxyphenyl)-1-hexene (**4h**), typical procedure: a soln. of 3.54 g (35 mmol) of diisopropylamine in 25 ml of anhydrous THF is treated with 15 ml of a 2.5 M soln. of n-butyllithium in hexane at –50 to –60 °C and allowed to warm to 0 °C for 10 min. After cooling again, a soln. of diethyl α-fluoro-*p*-methoxybenzylphosphonate (**3e**) (9.12 g) in THF (25 ml) is added during 20 min at –70 °C, followed by the addition of a solution of 5-bromovaleraldehyde in 10 ml of THF. (5-Bromovaleraldehyde was prepared by reduction of 5-bromovaleronitrile with diisobutylaluminum hydride followed by hydrolysis.) The mixture is stirred for 45 min at –70 °C and allowed to warm to r.t. over night. After adding 20 ml of 2N HCl, the mixture is extracted with a mixture of ethyl acetate and hexane. The organic phase is washed with 2N HCl and aq. sodium bicarbonate, dried over sodium sulfate and evaporated to dryness. The residue (10 g of crude product) is purified by flash chromatography on silica eluting with hexane/ethyl acetate 3:2 affording 4.3 g (52%) of **4h** as a 60:40 mixture of (*Z*)- and (*E*)-isomers. IR (CH_2Cl_2, cm^{-1}): 1679 cm^{-1} (C=CF); 1610 (ms), 1513 (s), 1179 (s, C-O-C), 1033 (s), 836 (s, *p*-subst. aromatic C–C). ^{1}H-NMR ($CDCl_3$, 250 MHz, *J* [Hz]); (*Z*)-**4h**: 1.5–1.7 and 1.8–2.0 (2*m*, H-C(4), H-C(5)); 2.30 (*qd*, $^3J_{HH}$ = 6.5, $^4J_{HF}$ = 1.5, CH_2–C=CF); 3.45 (*t*, *J* = 6.5, Br-CH_2); 3.83 (*s*, OCH_3); 5.22 (*dt*, $^3J_{HF}$ = 31, $^3J_{HH}$ = 6.3, CH=CF); 6.88 and 7.43 (each *d*, 6.8 Hz, each 2H, C_6H_4); (*E*)-**4h**: 1.5-1.7 and 1.8-2.0 [each *m*, each 2H, C(4,5)-H]; 2.22 (*q*, 6.3 Hz, CH-C=CF); 3.38 (*t*, 6.3 Hz, CH_2-Br); 3.85 (*s*, 3H, OCH_3); 5.28 (*dt*, $^3J_{HF}$ = 18 Hz, $^3J_{HH}$ = 6, *J* = 3, CH=CF); 6.92 and 7.38 (2*d*, *J* = 6.8 each, 2 aryl-H each.

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