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Synthesis of Arylalkylmonofluorophosphonates as *Myo*-Inositol monophosphatase Ligands.

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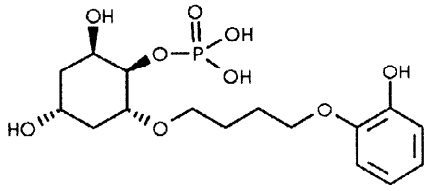
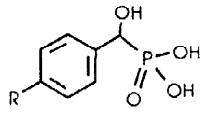
Abstract: Arylalkylmonofluorophosphonates were prepared by condensation of arylalkylaldehydes with the lithium salt of diethyl 1-fluoro-1-(trimethylsilyl)-methylphosphonate. Reduction and hydrolysis sequences gave the final products. These compounds do not inhibit the *myo*-inositol monophosphatase.

Myo-inositol monophosphatase seems to be a key enzyme in the cellular inositol phosphate cycle. Its uncompetitive inhibition by lithium salts, [1-4] modulating the cell signalling[5], seems to be the mode of action of the manic depression therapy. These treatments are limited by the side effects which could lead to coma or death.[6-9] Discovery of new inhibitors of this enzyme could result in alternative therapies.

Structure-activity relationship studies were developped by differents groups.[10] These studies relied on either systematic structural variations or took X-Rays, NMR and modelling analyses into account.[11-15] Among numerous others, compounds **1-3** have demonstrated interesting binding potencies as competitive inhibitors.[16-18]



1



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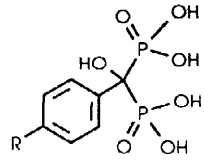

3

These results suggested the synthesis of arylalkylmonofluorophosphonates analogues. Due to the fluor electronegativity, the monofluorophosphonate function has pK_A similar to the one of the corresponding phosphate. These analogues could be able to be complexed similarly to the natural ligands into the enzyme active site, but, could not be hydrolyzed. Moreover, the phenolic moiety could occupy the space area of the mechanistic water as for the phenolic group of **1**.

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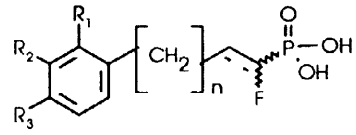
Here, we report the synthesis of arylalkylmonofluorophosphonates 4.



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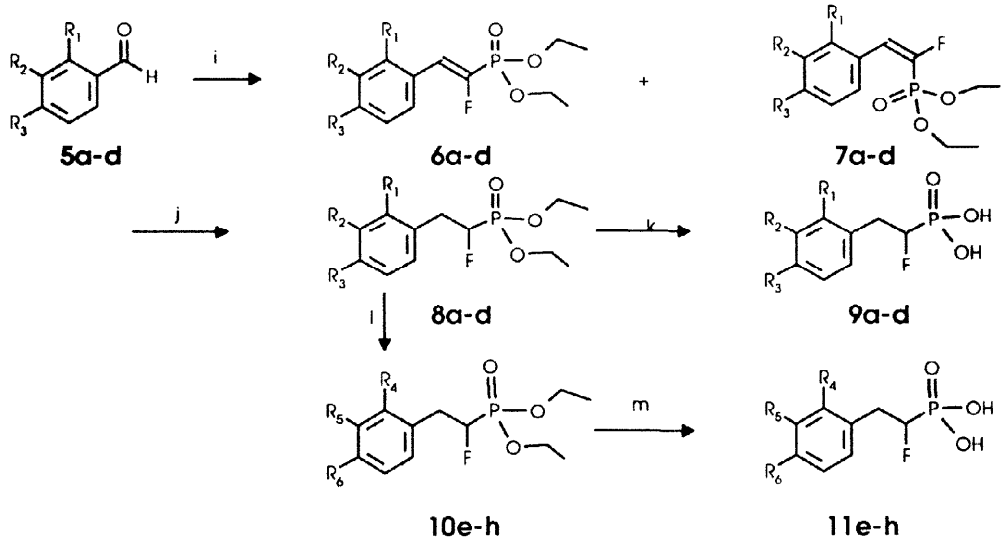
Compounds, where n = 0, were prepared starting from substituted benzaldehydes **5a-d** (scheme 1). Reaction of these benzaldehydes with the lithium salt of diethyl 1-fluoro-1-(trimethylsilyl)-methylphosphonate[19-23] yielded a 1/1 *cis/trans* mixture of the alkenes **6a-d** and **7a-d**.[20] Reduction of the double bond by hydrogenation using Pd/C as catalyst gave the corresponding fluoroalkanes **8a-d**. The phosphonic esters were hydrolysed[24] to give the free phosphonic acids **9a-d** which were stabilized as ammonium salts. The phenolic group could be deprotected by treatment with BBr_3[25] giving the phenol **10e-h**, which were transformed to the free phosphonic acids **11e-h** by means of trimethylsilyliodide.[24]

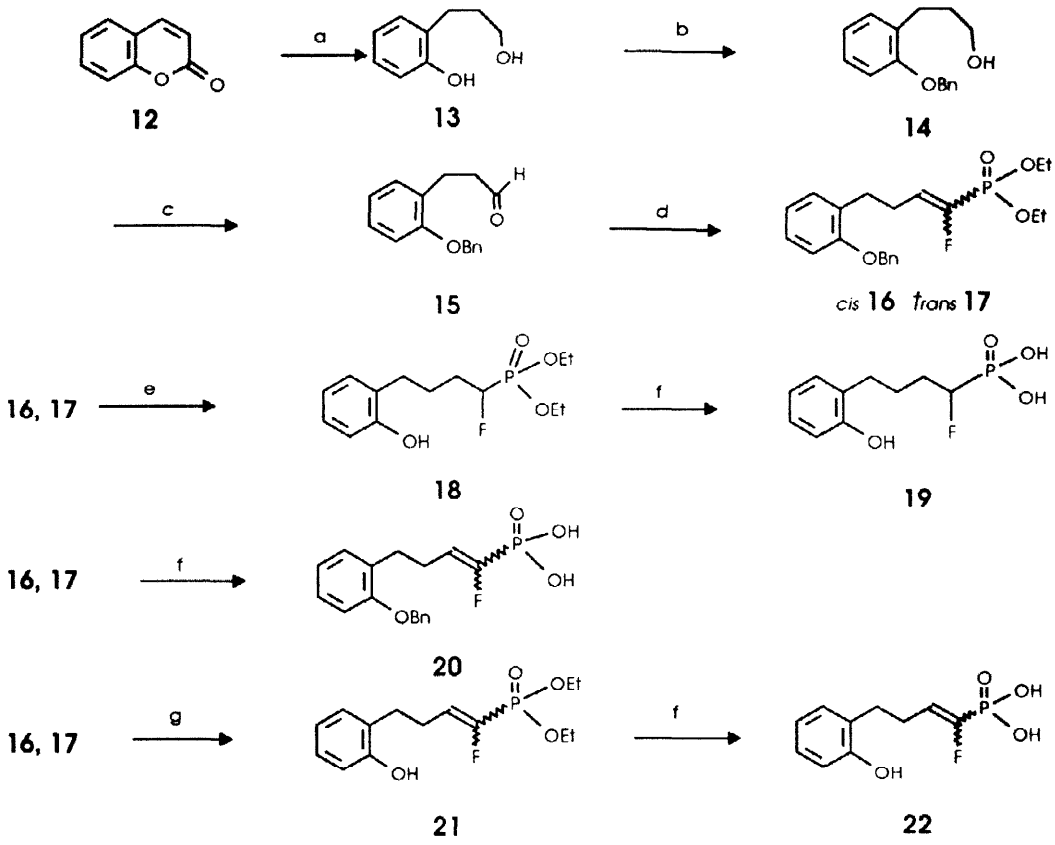


	R_1	R_2	R_3		R_4	R_5	R_6
a	PMBO	H	H	e	OH	H	H
b	H	PMBO	H	f	H	OH	H
c	H	H	PMBO	g	H	H	OH
d	PMBO	H	PMBO	h	OH	H	OH

Scheme 1 : i) LiTMSCFP(O)$(OEt)_2$ 1.2eq, THF, -78°C,30 min → RT 30 min, 73-81%; j) H_2, Pd/C 10%, 5 atm, 15h, RT, 65-88%; k) TMSI, 4 eq, CH_2Cl_2, 0°C, 30 min; l) BBr_3, 3 eq, CH_2Cl_2, -78°C, 2h → RT 12h, 77-88%; m) TMSI, 4 eq, CH_2Cl_2, 0°C, 30 min; PMBO = *p*-methoxybenzyloxy-.[26]

For n = 2, the synthesis started from coumarin **12** (scheme 2). Its reduction with $NaBH_4$ formed the 2-(3-hydroxy) propylphenol **13**. The phenolic function was selectively protected as benzylether **14** and the primary alcohol was oxidized into aldehyde **15** by a Swern

reaction.[27-29] This aldehyde was submitted to the same fluorophosphonate coupling reaction as described above to give the alkenes **16** and **17**. Hydrogenation of the double bond permitted the simultaneous deprotection of the phenol function yielding the fluorophosphonate **18**.



Scheme 2: a) $NaBH_4$, 2.5 eq, EtOH, 0°C 1h, RT 5h, reflux 5h 80%; b) NaH,1.2 eq, BnBr, 1.2 eq, DMF 0°C → RT 2h 30 min, 91%; c) $(COCl)_2$,3 eq, DMSO 4eq, Et_3N, 12 eq, CH_2Cl_2,-78°C 45 min → RT, 98%; d) LiTMSCFP(O)$(OEt)_2$, 79%; e) H_2, Pd/C, 98%; f) TMSI; g) BBr_3; d →g see scheme 1; Bn = benzyl.[26]

Free phosphonic acid **19** was obtained by treatment of compound **18** with trimethylsilyliodide. Trimethylsilyliodide permitted to deprotect selectively the phosphonate esters of **16** and **17**, and gave the derivative **20**. But, the treatment of compound **16** and **17** by means of BBr_3 deprotected selectively the phenolic function and furnished compound **21** which, by treatment with trimethylsilyliodide gave the free phosphonic acid **22**. The compounds **9a-d**, **10e-h**, **19**, **20**, and **22** were inactive toward the inhibition of the *myo*-inositol monophosphatase. A first molecular modelling approach showed that, even if the pK_A could be similar to these of the natural ligands, the fluorine atom seemed less hydrophylic and unable to complex the magnesium cations and the amino-acid residue into the enzyme active site.

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