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Phosphonium salts: useful synthons for the total synthesis of LTA_4 methyl ester analogues

Mylène Garcia[1], Thierry Durand[1], Agnès Vidal[1], Jean Pierre Vidal[1], Jean Claude Rossi[1]*, Dmitry Kuklev[2], Igor Serkov[2], Vladimir Bezuglov[2]

[1] *Laboratoire de Chimie Biomoléculaire et des Interactions Biologiques associé au CNRS, Universités Montpellier I et II, Faculté de Pharmacie, 15 avenue Ch Flahault, 34060 Montpellier, France;*
[2] *Department of PG & LT, Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, The Russian Academy of Sciences, ul Miklukho-Maklaya 16/10, 117871 GSP 7 Moscow, Russia*

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Summary — Different (ω − 1)-functionalized phosphonium ylides **5** were obtained from commercially available 5-chloropentan-2-one **3** and but-3-yn-1-ol **4** in several steps. Some of the phosphonium ylides obtained were coupled using a Wittig reaction with a chiral epoxydienal **1** (prepared from (−)-2-deoxy-D-ribose **2** as starting material) to afford (ω − 1)-functionalized leukotriene A_4 (LTA_4) methyl ester analogues. The described strategy demonstrates a general and flexible approach to other leukotriene analogues stable to β-oxidation, and/or molecular probes carrying reporter groups to characterize a potential LTC_4 receptor.

leukotriene A_4 analogue / Wittig reaction / (ω − 1)-functionalized phosphonium salt / lipophilic moiety

Résumé — Sels de phosphonium : synthons clés pour la synthèse totale d'analogues de l'ester méthylique du LTA_4. Différents ylures de phosphonium **5** ont été obtenus à partir de composés commerciaux, la 5-chloropentan-2-one **3** et le but-3-yn-1-ol **4** en plusieurs étapes. Certains de ces ylures de phosphonium, utilisés dans une réaction de Wittig, réagissent avec l'époxydiénal chiral **1** (préparé à partir du (−)-2-déoxy-D-ribose **2**), conduisant aux analogues (ω − 1)-fonctionnalisés de l'ester méthylique du leucotriène A_4 (LTA_4). Cette stratégie générale, du fait de sa flexibilité, conduit soit à des analogues de leucotriènes stables à la β-oxydation soit à des porteurs de sondes moléculaires pour caractériser le récepteur potentiel du LTC_4.

analogue du leucotriène A_4 / réaction de Wittig / sel de phosphonium (ω − 1)-fonctionnalisé / partie lipophile

Introduction

Formation of new carbon–carbon double bonds via coupling of phosphorus-stabilized ylides with carbonyl compounds represents one of the major methods in synthetic organic chemistry. The extraordinary usefulness of organophosphorus reagents is proved by the wide application of stereoselective Wittig reactions in the synthesis of natural products [1].

In leukotrienes' series, the Wittig approach has been the most commonly used because of its versatile capability of combining a chiral epoxide unit prepared from chiral precursors [2]. In connection with our studies on the potential applications of leukotriene analogues, we became interested in the synthesis of different (ω − 1)-functionalized leukotriene A_4 analogues (LTA_4 analogues) [3,4]. Three main applications of such analogues have retained our attention. First of all, modulation with (ω − 1)-functionality was an arachidonic acid (AA) metabolism index by means of chemically and metabolically stable leukotriene mimics, because (ω − 1) substitution avoids any β-oxidation [5] on the lipophilic backbone. The second useful application, after fixation of LTC_4 derivative via a spacer attached to a (ω − 1)-functional group, was a purification of cysteinyl-leukotriene receptors by affinity column, on solid phase. The third was the ability of leukotriene C_4 (LTC_4) bearing photoactivatable groups at the (ω − 1) position to serve as molecular probes [6] for characterization and identification of high-affinity binding site LTC_4 receptors [7].

We now report a general and flexible strategy of preparation of (ω − 1)-functionalized LTA_4 methyl esters, starting from chiral epoxydienal **1** arising from (−)-2-deoxy-D-ribose **2** [8] which is coupled by a Wittig reaction to different ylides **5**, easily prepared on a large scale from commercially available 5-chloropentan-2-one **3** and but-3-yn-1-ol **4** (fig 1). This strategy allows us to synthesize LTA_4 analogues, which can be converted into corresponding LTC_4 analogues by treatment with glutathione and/or glutathione analogues.

* Correspondence and reprints

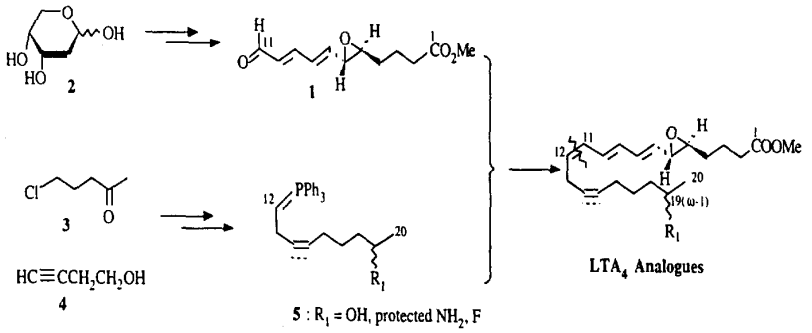

Fig 1. Synthetic pathway of LTA_4 analogues.

It should be stressed that non-saturation into synthon **5** may be introduced as a double or triple bond. This acetylenic function can be a precursor of analogues specifically labelled with tritium or deuterium at 14,15-positions used later for biological studies.

Results and discussion

The retrosynthetic analysis of phosphonium salts (fig 2) summarizes the general synthetic pathway allowing to access to ylides via non-3(Z)-enyl (or non-3-ynyl) triphenylphosphonium salts **6** bearing different functionalities in (ω − 1) position (R_1 = hydroxy, amino or fluoro).

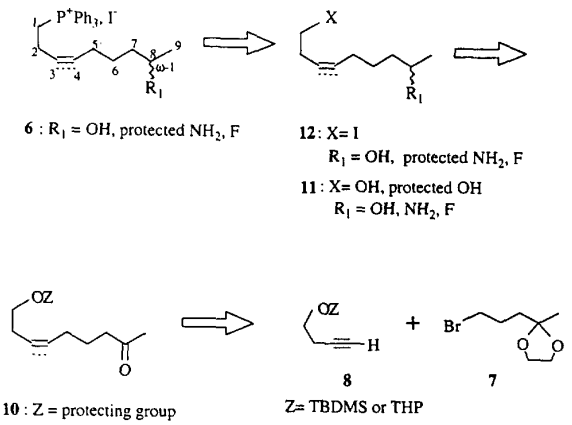

Fig 2. Retrosynthetic analysis of phosphonium salts.

The first step to phosphonium salts **6** is the conversion of chloro compound **3** into the protected bromoketone derivative **7** (59% overall yield) because of its better reactivity as electrophilic reagent during the next coupling with an acetylide [3]. The acetylide route begins by activation of protected but-3-yn-1-ol as silyl ether **8** into its lithium salt (n-BuLi, THF, 0 °C), followed by nucleophilic substitution on 1-bromo-4,4-ethylenedioxypentane **7** in the presence of HMPA [3] to give 9-hydroxynon-6-yn-2-one **9** after deprotection [3]. It may be underlined that ethylenic or acetylenic phosphonium salts can be synthesized from respectively homoallylic or homopropargylic alcohols with a Z double bond (obtained by catalytic reduction of alkyne).

The key intermediates **10** were prepared by protection of the primary hydroxyl group [3]. The procedure leading to **10** with a tetrahydropyranyl (THP) group was published in our previous paper [3]. This derivative led us to different (ω − 1)-functionalized derivatives **11** bearing hydroxyl, amino or fluorine functionalities by reduction or amination of the ketone function and subsequent replacement of the hydroxyl group with a fluorine atom. Then, the access to phosphonium salts **6** via iodo derivatives **12** was realized after selective deprotection of the primary hydroxyl group.

Synthesis of (ω− 1)-functionalized phosphonium salts

Figure 3 summarizes the synthesis of (ω − 1)-hydroxy phosphonium salt **18**. The ketone function of ethylenic key intermediate **10a** was reduced to a secondary alcohol **13** under mild conditions ($NaBH_4$ in methanol, 30 min at room temperature) with 85% yield. This alcohol was protected by conversion into silyl ether **14** as previously described [3]. Selective THP deprotection of derivative **14** was carried out in the presence of dimethylaluminium chloride (Me_2AlCl) in

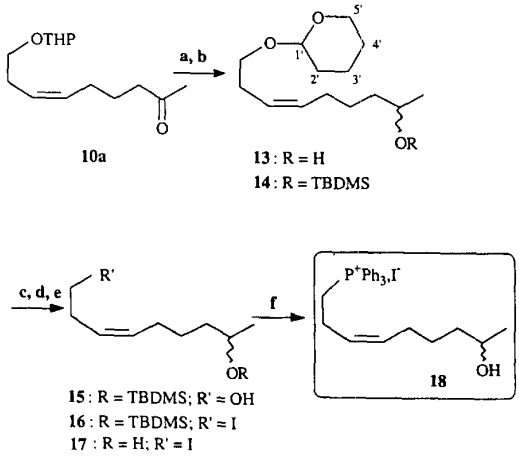

Fig 3. Synthesis of compound **18**. Reagents and conditions: **a**: 0.7 equiv $NaBH_4$/MeOH, rt, 30 min, 85%; **b**: 1.1 equiv TBDMSiCl, 1.2 equiv DBU/CH_2Cl_2, rt, 16 h, 89%; **c**: 2.0 equiv Me_2AlCl/CH_2Cl_2, rt, 4 h, 83%; **d**: 1.3 equiv PPh_3, 1.4 equiv I_2, 1.4 equiv Imidazole/Xylene, 80 °C, 5 min, 83%; **e**: HCl/THF, rt, 7 h, 88%; **f**: 1.3 equiv PPh_3/CH_3CN, reflux, 48 h, 85%.

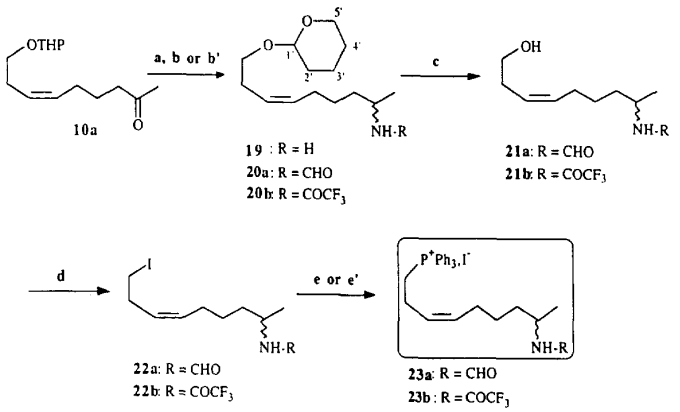

Fig 4. Synthesis of compound **23a/b**. Reagents and conditions: **a**: 0.7 equiv $NaBH_3CN$, 10 equiv CH_3CO_2–NH_4^+/MeOH, rt, 48 h, 83%; **b**: 2.0 equiv DCCI, 4 equiv HCO_2H/pyridine–$CHCl_3$, 4 h, 0 °C, 85%; **b'**: 8 equiv $(CF_3CO)_2O$, 11 equiv Et_3N/CH_2Cl_2, rt, 2 h, 98%; **c**: 0.1 equiv PPTS/EtOH, 55 °C, 4 h, 96–98%; **d**: 1.3 equiv PPh_3, 1.4 equiv I_2, 1.4 equiv imidazole/xylene, 60–80 °C, 15–30 min, 92%; **e**: 1.1 equiv PPh_3/toluene–CH_3CN = 1:1, 80 °C, 24 h, 94%; **e'**: 1.1 equiv PPh_3/CH_3CN, 80 °C, 24 h, 92%.

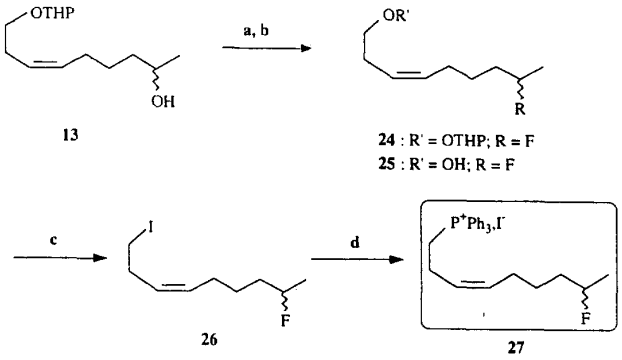

Fig 5. Synthesis of compound **27**. Reagents and conditions: **a**: 1.7 equiv MSTF/CH_2Cl_2, 5 min, −50 °C, 75%; **b**: HCl 10%/THF, 60 °C, 2 h, 82%; **c**: 1.3 equiv PPH_3, 1.4 equiv I_2, 1.4 equiv imidazole/xylene, 80 °C, 15 min, 85%; **d**: 1.3 equiv PPh_3/toluene, 90 °C, 24 h, 87%.

dichloromethane with good yield, thus avoiding any deprotection of silyl ether [3]. In order to perform the iodination of the primary hydroxyl group in compound **15**, we have developed [9] a simple and rapid reaction (5 min) using triphenylphosphine, iodine and imidazole as reagents in a xylene solution at 80 °C. At least, silyl ether deprotection in the presence of HCl 1N in THF and conversion into phosphonium salt led to compound **18**, with good yield.

The synthesis of (ω − 1)-protected amino phosphonium salt **23** starts from the same intermediate **10a** (fig 4). The carbonyl function was converted into an amino group in the presence of sodium cyanoborohydride and ammonium acetate in methanol [10] giving the expected compound **19** in quantitative yield. In order to explore the stability and capability of the amino protecting groups, two protections have been considered, either as formyl derivative **20a** prepared under standard conditions with an excess of formic acid and *N*,*N'*-dicyclohexylcarbodiimide (DCC) [11] or trifluoroacetamide **20b** obtained with trifluoroacetic anhydride and triethylamine in dichloromethane. In the case of formyl-protected derivative **20a**, our first attempt of THP deprotection in the presence of Me_2AlCl, under the same conditions as previously indicated to obtain compound **15**, led to simultaneous deprotection of the formyl group. To overcome this problem, THP deprotection was carried out in the presence of pyridinium *para*-toluenesulfonate (PPTS) in ethanol with good yields on both intermediates **20a** and **20b**. The iodination reaction described above affords iodo compounds **22a** and **22b** which were transformed into corresponding phosphonium salts **23a** and **23b** with 67% overall yield respectively. The formyl protecting group has been left because of its weak stability during the Wittig reaction.

The (ω − 1)-fluoro phosphonium salt **27** was synthesized according to the scheme outlined in figure 5. Reaction of the hydroxy compound **13** with morpholinosulfur trifluoride (MSTF) (Aldrich) [12] in dry CH_2Cl_2 generates the fluoro derivative **24** in 75% yield. Deprotection of the THP group with 10% aqueous HCl affords the fluoro alcohol **25** in 82% yield. The iodo derivative **26** was obtained in 85% yield with the same procedure as previously described, and transformed into (ω − 1)-fluoro phosphonium salt **27** with 87% yield. This strategy has been published in our previous note [4]. The technical points are given in the Experimental section.

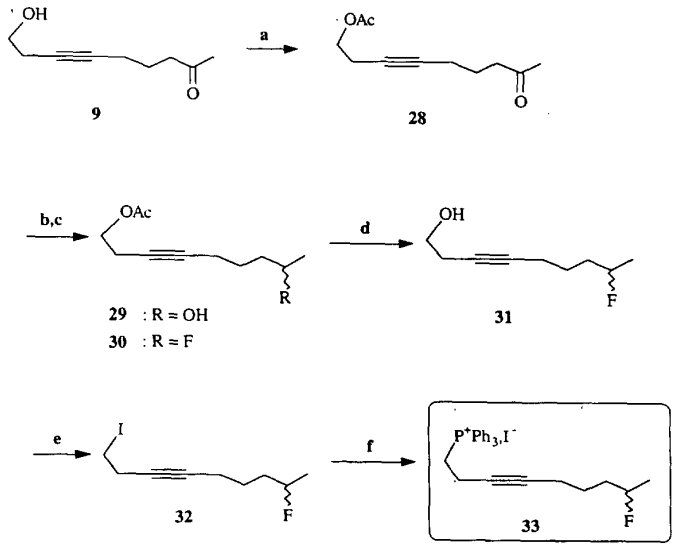

Fig 6. Synthesis of compound **33**. Reagents and conditions: **a**: Ac_2O–DMAP/pyridine–benzene, rt, 18 h, 90%; **b**: $NaBH_4$/MeOH, 100%; **c**: MSTF/CH_2Cl_2, −45 °C, 40 min, 40%; **d**: K_2CO_3/MeOH, rt, 30 min, 87%; **e**: I_2–PPh_3–imidazole/xylene, 60–80 °C, 30 min, 81%; **f**: PPh_3/toluene, 24 h, reflux, 88%.

Finally, the acetylenic (ω − 1)-fluoro phosphonium salt **33** (fig 6) was prepared from starting compound **9** [3] according to the same methodology we have developed for derivative **27**. The protective group introduced at position 1 is an acetyl group. Acetylation of **9** with acetic anhydride in pyridine (2:1) in the presence of a catalytic amount of DMAP gave **28** in 90% yield. Reduction of the keto group in **28** with sodium borohydride afforded quantitatively **29** that was converted to fluorononynol acetate **30** by reaction with MSTF. Pure **30** was obtained in 40% yield after chromatography on silica gel column as well as a complex mixture of close migrating by-products. Removal of the acetate group in the presence of potassium carbonate in methanol smoothly led to fluorononynol **31** in 87% yield. The previous iodination reaction led to iodo compound **32** which was transformed into the corresponding acetylenic ($\omega-1$)-fluoro phosphonium salt **33** with good yield.

The spectroscopic data (^{1}H-, ^{13}C- and ^{31}P NMR) for all phosphonium salts are summarized in table I.

The *Z*-stereochemistry of the double bond in position 3,4 was preserved all along the synthesis and was confirmed by ^{1}H NMR (360 MHz) on (ω − 1)-fluoro phosphonium salt **27** ($J_{3,4}$ = 10.5 Hz) because of a good separation of 3-H and 4-H in its spectrum.

Synthesis of LTA_4 analogues

The crucial step of this synthesis was the Wittig reaction between unstabilized phosphonium ylides generated in situ from phosphonium iodides and epoxydienal **1** (fig 7). All these reactions were carried out in dry THF in the presence of freshly distilled HMPA (6:1) at −78 °C, using *n*-butyllithium as a base. The best result was obtained with 3 equiv of anhydrous phosphonium salt and 1 equiv of epoxydienal **1**. (ω − 1)-OH and alkyne-(ω − 1)-fluoro phosphonium salts **18** and **33** gave corresponding (ω − 1)-OH and 14,15-dehydro-(ω − 1)-fluoro LTA_4 methyl esters with respectively 50% and 80% yields, but could not be isolated in pure form because of the difficulty of separation by chromatography and/or their instability. On the other hand, (*RS*)-19-fluoro and CF_3CONH LTA_4 methyl esters **34a** and **34b** (diastereoisomer mixture) were obtained, in 15 min, with respectively 84% and 51% yields after purification by flash chromatography on basic silica gel column. The new established double bond has pure 11(*Z*) stereochemistry ($J_{11,12}$ = 11.0 Hz). It is important to stress that the coupling reactions should be carried out under extremely dry conditions (see Experimental section). We have detected the formation of phosphorus species that were characterized as phosphine oxides **35**. In order to demonstrate the corresponding structures, phosphonium salts were transformed into the expected phosphine oxides **35** by treatment under alcaline condition (30% aqueous NaOH) at 75 °C. The spectroscopic data of phosphine oxides summarized in table II were identical with data of Wittig by-products.

The UV, ^{1}H, ^{13}C NMR, COSY and HMQC spectra of LTA_4 analogues are in accordance with the corresponding structures, and verification of the purity of the compounds was completed by HPLC trials (table III). Transformation of these derivatives into LTC_4 analogues is in progress.

Conclusion

We have synthesized ($\omega-1$)-OH, -NHCHO, -$NHCOCF_3$ and -fluoro phosphonium salts **18**, **23a** and **23b**, **27** and **33** using the same general strategy from 5-chloropentan-2-one **3** and but-3-yn-1-ol **4** as starting materials, via a lithium acetylide to have access to the key intermediate **10**, from which the (ω − 1)

Table I. Spectroscopic data of phosphonium salts ($CDCl_3$, δ ppm).

NMR[a,b]		***18***	***23a***[c]	***23b***	***27***[d]	***33***
1H	1-H	3.68–3.8 (m, 3H)	3.43–3.74 (m, 2H)	3.56–3.66 (m, 2H)	3.67–3.77 (m, 2H)	3.82–3.94 (m, 2H)
	2-H	2.36–2.47 (m, 2H)	2.23–2.57 (m, 2H)	2.36–2.47 (m, 2H)	2.36–2.47 (m, 2H)	2.7–2.83 (m, 2H)
	3-H	5.45–5.58 (m, 1H)	5.28–5.48 (m, 2H)	5.41–5.5 (m, 1H)	5.53–5.61 (m, 1H, 10.5)	–
	4-H	5.35–5.44 (m, 1H)	5.28–5.48 (m, 2H)	5.3–5.40 (m, 1H)	5.33–5.42 (m, 1H, 10.5)	–
	5-H	1.8–1.9 (m, 2H)	1.78–2.0 (m, 2H)	1.83–1.92 (m, 2H)	1.78–1.87 (m, 2H)	1.71–1.8 (m, 2H)
	6-H 7-H	1.27–1.42 (m, 4H)	1.2–1.5 (m, 4H)	1.17–1.67 (m, 4H)	1.28–1.53 (m, 4H)	1.17–1.54 (m, 4H)
	8-H	3.68–3.8 (m, 3H)	3.8–4.1 (m, 1H)	3.85–3.98 (m, 1H)	4.43–4.66 (dm, 1H, 48.6$^+$)	4.4–4.66(dm, 1H, 50$^+$)
	9-H	1.13 (d, 3H, 6.0)	1.1 (d, 3H, 7.3)	1.2 (d, 3H, 6.7)	1.24 (dd, 3H, 6.2, 24$^+$)	1.26 (dd, 3H, 6.2, 24$^+$)
	OH	1.77 (sb, 1H)	–	–	–	–
	NH	–	6.94 (db, 1H)	7.12 (db, 1H)	–	–
	CHO	–	8.08 (s, 1H)	–	–	–
	H_{arom}	7.64–7.86 (m, 15H)	7.6–7.92 (m, 15H)	7.65–7.84 (m, 15H)	7.66–7.86 (m, 15H)	7.6–7.88 (m, 15H)
^{13}C	C-1	23.3 (48*)	23.4 (48*)	23.2 (48.5*)	23.5 (54*)	23.1 (55*)
	C-2	20.3	20.2	20.2	20.3	13.2 (5.1*)
	C-3	125.8 (14.7*)	125.6 (14.5*)	126.0 (15*)	126.4 (18*)	76.6 (7.0*)
	C-4	132.7	133.4	132.4	132.1	84.8
	C-5	27.1	27.0	26.7	27.0	18.2
	C-6	25.4	25.7	25.6	24.8	23.8 (4.3**)
	C-7	38.5	35.7	35.2	36.2 (27**)	35.8 (21**)
	C-8	67.3	43.8	46.3	90.8 (162**)	90.3 (164.4**)
	C-9	23.5	21.0	20.2	21.0 (18**)	20.9 (22**)
	Protection	–	161.1 (CHO)	156.6 (CO, 36**) 115.9 (CF_3, 286**)	–	–
	$C_{arom\ IV}$	117.8 (85.9*)	117.8 (86.2*)	117.7 (85*)	118.0 (81*)	117.7 (86.3*)
	C_{arom}	130.3	130.4	130.3	130.5	130.1
		130.8	130.8	130.8	130.7	130.6
		133.4	133.5	133.3	133.7	133.6
		133.8	133.8	133.7	133.8	134.0
		135.2	135.2	135.3	135.2	135.2
^{31}P	P	24.8		24.9	24.9	25.4

[a] Assignments of atoms are indicated on compound **6** (fig 2). ^1H NMR (360 MHz), ^{13}C NMR (25 MHz) and ^{31}P NMR (81.015 MHz). [b] Data between parentheses indicate multiplicity of signal (m = multiplet, s = singlet, d = doublet, b = broad), integration and coupling constants in Hertz ($^+J_{H,F}$), and for ^{13}C NMR only coupling constants are indicated ($^*J_{C,P}$ or $^{**}J_{C,F}$). [c] ^1H NMR (100 MHz). [d] ^{13}C NMR (90 MHz).

functionalization was introduced. The $(\omega - 1)$-$NHCOCF_3$ and -fluoro phosphonium salts **23b** and **27** gave, using a Wittig reaction via unstabilized phosphonium ylides, $(\omega - 1)$-$NHCOCF_3$ and -fluoro LTA_4 analogues stable to β-oxidation. This kind of compounds will be useful as leukotriene analogues with potential modified biological activity. Another useful aspect of these analogues is the synthesis of molecular probes for the characterization of a potential LTC_4 receptor and/or cysteinyl-leukotriene receptors ($Cys LT_2$) in various cells [13].

Experimental section

All reactions were performed under nitrogen. THF was freshly distilled from sodium-benzophenone, absolute methanol and ethanol from magnesium, dry toluene and xylene from sodium, triethylamine, cyclohexane and ether were obtained by distillation from KOH, dry dichloromethane from CaH_2, ethyl acetate from $CaCl_2$ and acetonitrile quality HPLC (FSA Laboratory supplies) was used. HMPA was distilled from molecular sieves 4A. Reactions were monitored by TLC on Merck aluminium sheets, silica gel 60 F_{254}, and spots were visualized using UV_{254} light and heating with a *p*-anisaldehyde solution. Silica gel 60 Merck (70–230 mesh) was used for purification of crude products by chromatography. Melting points (uncorrected, capillary tubes) were measured on a Büchi Tottoli apparatus.

^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ using tetramethylsilane as internal standard on a Bruker AMX-360 spectrometer or a Bruker AC-100 spectrometer, ^{19}F NMR spectra were recorded in $CDCl_3$ using CCl_3F as internal standard on a Bruker CPX-200 and ^{31}P NMR spectra were recorded in $CDCl_3$ using H_3PO_4 as external standard on a Bruker 200 spectrometer at room temperature. Chemical shifts are expressed in ppm and data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, b = broad), integration, assignments and coupling constants J in Hz. Assignments were made with the aid of DEPT spectra and/or homonuclear and heteronuclear 2D spectra. For a better understanding of spectroscopic data, assignments used for ^1H NMR and ^{13}C NMR data are all the same, indicated on compound **6** (fig 2), except compound **34** (fig 7).

IR spectra were obtained on a Beckman Acculab-2 spectrophotometer using films on NaCl cells for liquid or KBr disks for solid. Absorption wave numbers are expressed in cm^{-1}.

Elemental analyses were performed by the Service Central d'Analyse du CNRS, Vernaison, France.

UV spectra were recorded on a Varian DMS 90 spectrophotometer. For LTA_4 analogues, there are three absorption wave numbers, reported in nm, corresponding to λ_{max} and two shoulders (characteristic of a natural trienic system).

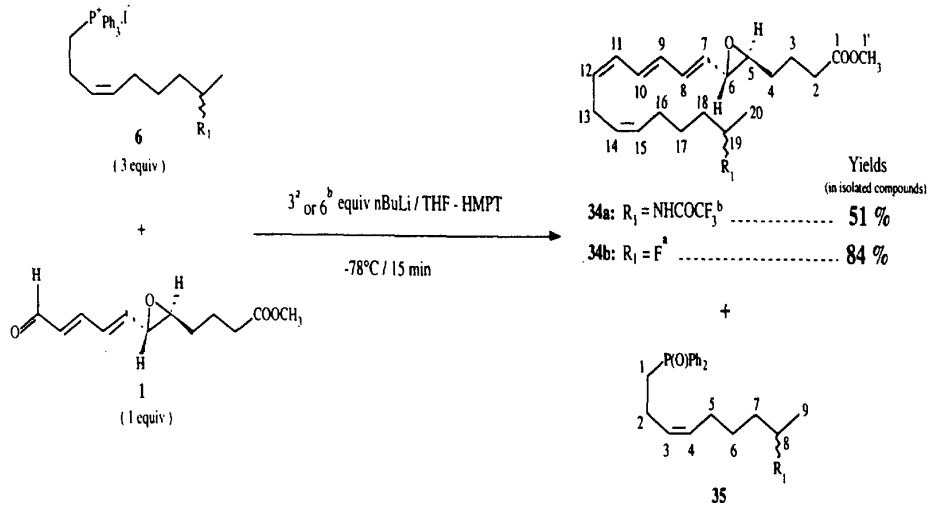

Fig 7. Synthesis of LTA_4 analogues **34** by Wittig reaction.

Table II. Spectroscopic data of phosphine oxides **35** ($CDCl_3$, δ ppm).

NMR[a]		R_1 = *OH*	R_1 = *NHCOCF*$_3$	R_1 = *F*[b]	R_1 = *F (triple bond on C-3 C-4)*
^{1}H	1-H 2-H	2.12–2.5 (m, 4H)	2.15–2.5 (m, 4H)	2.21–2.36 (m, 4H)	2.35–2.58 (m, 4H)
	3-H 4-H	5.16–5.5 (m, 2H)	5.1–5.55 (m, 2H)	5.27–5.4 (m, 2H)	–
	5-H	1.8–2.07 (m, 2H)	1.85–2.10 (m, 2H)	1.89–1.97 (m, 2H)	1.9–2.11 (m, 2H)
	6-H 7-H	1.03–1.50 (m, 4H)	1.1–1.6 (m, 4H)	1.2–1.64 (m, 4H)	1.26–1.76 (m, 4H)
	8-H	3.58–3.9 (m, 1H)	3.8–4.17 (m, 1H)	4.44–4.67 (dm, 1H, 49)	4.17–5.0 (dm, 1H, 50)
	9-H	1.13 (d, 3H, 6.2)	1.2 (d, 3H, 7.2)	1.25 (dd, 3H, 6.2, 24.1)	1.25 (dd, 3H, 6.2, 24)
	OH	–	–	–	–
	NH	–	6.75 (db, 1H)	–	–
	CHO	–	–	–	–
	H_{arom}	7.3–7.87 (m, 10H)	7.25–7.87 (m, 10H)	7.4–7.77 (m, 10H)	7.26–7.84 (m, 10H)
^{13}C	C-1	29.8 (70)	29.7 (70)	29.9 (70)	29.6 (70)
	C-2	19.3 (3.3)	19.3 (3.2)	19.4	11.7
	C-3	128.3 (15.2)	128.8 (15.3)	128.7 (15.3)	79.1 (19)
	C-4	130.4	130.3	130.6	80.2
	C-5	26.9	26.7	26.8	18.4
	C-6	25.6	25.7	25.0	24.4
	C-7	38.6	35.5	36.3 (21)	35.9 (21)
	C-8	67.4	46.4	90.7 (164)	90.4 (163)
	C-9	23.5	20.2	20.9 (23)	20.9 (22)
	Protection	–	156.6 (CO, 36) 119.6 (CF_3, 288)	–	–
	$C_{IV\ arom}$	134.8	134.6	133.0 (99)	134.4
	C_{arom}	128.4	128.4	128.7	128.4
		128.8	128.9	128.8	128.8
		130.5	130.5	130.7	130.5
		130.9	130.8	130.8	130.9
		131.6	131.7	131.7	131.8
^{31}P	P	32.6	32.5	32.5	31.4

[a] ^{1}H NMR (100 MHz), ^{13}C NMR (25 MHz) and ^{31}P NMR (81.015 MHz). [b] ^{1}H NMR (360 MHz) and ^{13}C NMR (90 MHz)

HPLC data were obtained on a Waters 490 multiwavelength detector at room temperature. Solvents were filtered through a 0.5 μm filter (Millipore) and degassed with an ultrasonic bath, before use.

Starting materials were purchased from commercial suppliers and compounds **9** and **10a** were synthesized using the methodology previously described [3]. LTA_4 analogues need to be kept at −40 °C, under nitrogen, out of the light and in a diluted solution cyclohexane/ethyl acetate with 2% triethylamine, to prevent their degradation.

9-(Tetrahydropyran-2-yloxy)non-6(Z)-en-2-ol ***13***

This reaction is realized more quickly with methanol as solvent instead of ethanol [3]. A solution of sodium borohydride (144 mg, 3.81 mmol) in dry MeOH (12 mL) was stirred at

Table III. Spectroscopic data of (ω − 1)-functionalized LTA_4 methyl ester **34a** and **b** ($CDCl_3$, δ ppm).

^1H NMR (360 MHz)	R_1 = NHCOCF$_3$	R_1 = F	^{13}C NMR (90 MHz)	R_1 = NHCOCF$_3$	R_1 = F
1′-H	3.65 (s, 3H)	3.65 (s, 3H)	C-1′	51.5	51.5
1-H	–	–	C-1	173.6	173.6
2-H	2.36 (t, 2H, 7.3)	2.36 (t, 2H, 7.4)	C-2	33.5	33.5
3-H	1.70–1.84 (m, 2H)	1.74–1.84 (m, 2H)	C-3	21.3	21.3
4-H	1.56–1.70 (m, 2H)	1.37–1.7 (m, 6H)	C-4	31.3	31.4
5-H	2.81–2.86 (m, 1H)	2.82–2.87 (m, 1H)	C-5	60.5	60.5
6-H	3.12 (dd, 1H, 2.0, 7.9)	3.11 (dd, 1H, 1.9, 7.9)	C-6	58.3	58.3
7-H	5.31–5.46 (m, 4H)	5.3, 5.48 (m, 4H)	C-7	129.7	130.1
8-H	6.41–6.56 (m, 2H)	6.41–6.55 (m, 2H)	C-8	134.4	134.5
9-H	6.18 (dd, 1H, 10.8, 14.8)	6.18 (dd, 1H, 10.8, 14.8)	C-9	131.3	131.5
10-H	6.41–6.56 (m, 2H)	6.41–6.55 (m, 2H)	C-10	128.8	128.8
11-H	6.0 (t, 1H, 11.0)	6.0 (t, 1H, 10.9)	C-11	128.4	128.4
12-H	5.31–5.46 (m, 4H)	5.3, 5.48 (m, 4H)	C-12	131.5	131.5
13-H	2.92 (t, 2H, 6.1)	2.93 (t, 2H, 6.7)	C-13	26.2	26.2
14-H	5.31–5.46 (m, 4H)	5.3, 5.48 (m, 4H)	C-14	127.9	127.6
15-H	5.31–5.46 (m, 4H)	5.3, 5.48 (m, 4H)	C-15	130.1	130.2
16-H	2.03–2.12 (m, 2H)	2.06–2.12 (m, 2H)	C-16	26.8	27.0
17-H	1.34–1.44 (m, 2H)	1.37–1.7 (m, 6H)	C-17	25.7	25.0
18-H	1.46–1.56 (m, 2H)	1.37–1.7 (m, 6H)	C-18	35.9	36.3, 36.5 (22)
19-H	3.95–4.07 (m, 1H)	4.52–4.73 (dm, 1H, 50)	C-19	46.4	89.9, 91.7 (164)
20-H	1.20 (d, 3H, 6.6)	1.3 (dd, 3H, 6.1, 23.8)	C-20	20.4	20.9, 21.1 (23)
Protection	–	–			–
UV (cm^{-1}, Et_2O)			HPLC*		
λ_{max}	279	277		18 min 30[a]	8 min[b]
Shoulders	269, 290	269, 290			

* Analytic column Si 60 5 μm MERCK, cyclohexane/ethyl acetate/NEt_3, 85:15:1 as eluent, flow rate: 1.125 mL/min[a], 0.675 mL/min[b], λ = 280 nm.

0 °C. Then, a solution of 9-(tetrahydropyran-2-yloxy)non-6(*Z*)-en-2-one **10a** (1.4 g, 5.83 mmol) in dry MeOH (12 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature, and the stirring was continued for 30 min. After concentration of the solvent under reduced pressure, the residue was diluted with Et_2O and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure, to afford 1.41 g (100%) of crude hydroxy compound **13**, which was purified by chromatography with cyclohexane/EtOAc from 5% to 30%. 1.2 g (85%) of pure alcohol **13** was obtained (R_f = 0.40 cyclohexane/EtOAc 70:30). IR spectra, ^1H NMR (360 MHz, $CDCl_3$) spectra were identical to spectra previously obtained [3].

^{13}C NMR (25.178 MHz, $CDCl_3$): 23.31 (C-9), 19.40, 25.29, 25.57, 27.03, 27.78, 30.52, 38.52 (C-2 C-5 C-6 C-7 C-2′ C-3′ C-4′), 62.10, 66.88 (C-1 C-5′), 67.70 (C-8), 98.53 (C-1′), 125.75, 131.36 (C-3 C-4).

Anal ($C_{14}H_{26}O_3$) calc: C 69.37, H 10.82, O 19.81; found: C 69.29, H 10.87, O 19.89.

8-[(Tert-butyldimethylsilyl)oxy]-1-(tetrahydropyran-2-yloxy)non-3(Z)-ene **14**

Under the same conditions previously described [3], **13** gave compound **14** (89%) after chromatography on silica gel (cyclohexane/EtOAc 95:5). Spectroscopic data were given in the literature [3], except the following ^{13}C NMR data (25.178 MHz, $CDCl_3$): −4.82, −4.50 (Si(CH_3)$_2$), 18.02 (SiC(CH_3)$_3$), 19.48, 25.39, 25.79, 27.24, 27.87, 30.61, 39.21 (C-2 C-5 C-6 C-7 C-2′ C-3′ C-4′), 23.74 (C-9), 25.79 (SiC(CH_3)$_3$), 61.92, 66.76 (C-1 C-5′), 68.21 (C-8), 98.58 (C-1′), 125.57, 131.70 (C-3 C-4).

8-[(Tert-butyldimethylsilyl)oxy]non-3(Z)-en-1-ol **15**

Under the same conditions previously described [3], **14** gave the alcohol **15** (83%) after purification by chromatography (cyclohexane/EtOAc 95:5). Spectroscopic data were given in the literature [3], except the following ^{13}C NMR data (25.178 MHz, $CDCl_3$): −4.85, −4.53 (Si(CH_3)$_2$), 17.95 (SiC(CH_3)$_3$), 23.68 (C-9), 25.77 (SiC(CH_3)$_3$), 25.70, 27.23, 30.68, 39.14 (C-2 C-5 C-6 C-7), 62.01 (C-1), 68.40 (C-8), 125.21, 132.68 (C-3 C-4).

1-Iodo-8-[(tert-butyldimethylsilyl)oxy]non-3(Z)-ene **16**

A solution of compound **15** (1.285 g, 4.72 mmol), triphenylphosphine (1.623 g, 6.19 mmol) and imidazole (443 mg, 6.52 mmol) in dry xylene (37 mL) was heated to 60 °C. Then, iodine in powder form (1.727 g, 6.81 mmol) was added by small portions, and stirring was continued at 60–80 °C during 5 min. After cooling, the mixture was washed with sat aqueous $NaHCO_3$ under vigorous stirring for 10 min, and the aqueous layer was extracted with Et_2O. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The yellow solid residue obtained was purified by flash chromatography with cyclohexane/CH_2Cl_2 from 5 to 20%, and afforded 1.5 g (83%) of the pure iodo derivative **16** as a pale pink oil (R_f = 0.90 cyclohexane/EtOAc, 90:10 or 0.55 cyclohexane/CH_2Cl_2, 90:10). ^1H NMR spectrum was identical to spectra previously obtained [3].

^{13}C NMR (25.178 MHz, $CDCl_3$): −4.72, −4.40 (Si(CH_3)2), 5.35 (C-1), 18.09 (SiC(CH_3)$_3$), 23.80 (C-9), 25.87 (SiC(CH_3)$_3$), 25.63, 27.44, 31.49, 39.24 (C-2 C-5 C-6 C-7), 68.40 (C-8), 127.87, 132.47 (C-3 C-4).

Anal ($C_{15}H_{31}OSiI$) calc: C 47.11, H 8.18, O 4.19, I 33.21; found: C 46.94, H 8.17, O 4.25, I 33.07.

9-Iodonon-6(Z)-en-2-ol **17**

To a solution of **16** (50 mg, 0.13 mmol) in dry THF (1 mL) at room temperature was added HCl 1 N (362 μL, 0.36 mmol). The resulting solution was stirred at room temperature for 7 h. After evaporation of the solvent under reduced pressure, the residual oil was diluted with EtOAc, and washed successively with water and saturated $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography with a gradient of 10–30% EtOAc in heptane as eluent, to afford 31 mg of pure alcohol **17** (88%) (R_f = 0.31 heptane/EtOAc, 70:30).

IR: 3 500–3 200 (O–H), 3 010 (=C–H), 2990–2820 (C–H), 1 650 (C=C).

^{1}H NMR (360 MHz, $CDCl_3$): 1.16 (d, 3H, 9-H, $J_{8,9}$ = 6.2 Hz), 1.34–1.50 (m, 4H, 6-H 7-H), 1.65 (s, 1H, OH), 1.92–2.20 (m, 2H, 5-H), 2.47–2.75 (m, 2H, 2-H), 3.12 (t, 2H, 1-H, $J_{1,2}$ = 7.3 Hz), 3.61–3.92 (m, 1H, 8-H), 5.12–5.62 (2m, 2H, 3-H, 4-H).

^{13}C NMR (90 MHz, $CDCl_3$): 5.39 (C-1), 23.55, 25.6, 27.34, 31.48, 38.81 (C-2, C-5, C-6, C-7, C-9), 67.95 (C-8), 128.15, 132.18 (C-3, C-4).

Anal ($C_9H_{17}OI$) calc: C 40.29, H 6.39, O 5.97, I 47.35; found: C 40.18, H 6.11, O 5.79, I 47.32.

(8-Hydroxynon-3(Z)-enyl)triphenylphosphonium iodide **18**

To a solution of iodo derivative **17** (277 mg, 1.03 mmol) in dry CH_3CN was added Ph_3P (351 mg, 1.34 mmol). The resulting suspension was stirred at reflux for 48 h. The solvent was removed under reduced pressure, then the crude product was washed twice with ether, affording 466 mg (85%) of pure phosphonium salt **18** as a white powder.

Mp: 138–139 °C (ether).

Spectroscopic data: see table I.

9-(Tetrahydropyran-2-yloxy)non-6(Z)-en-2-amine **19**

A solution of 9-(tetrahydropyran-2-yloxy)non-6(*Z*)-en-2-one **10a** (300 mg, 1.25 mmol), sodium cyanoborohydride (55 mg, 0.87 mmol), and anhydrous ammonium acetate (960 mg, 12.5 mmol) in absolute MeOH (6 mL) was stirred at room temperature for 48 h. After evaporation of the solvent under reduced pressure, the residual solid was dissolved in water (5 mL). Then, the resulting solution was saturated at 0 °C with NaCl and KBr pellets. The product was extracted vigorously with CH_3Cl (3 × 15 mL). After drying the organic layer over anhydrous Na_2SO_4, filtration and concentration under vacuum, the crude amine was obtained as a colorless oil (quantitative yield) and was used either directly without further purification for the following protection, or was immediately purified by flash chromatography with a gradient of 2–5% MeOH in CH_2Cl_2 as eluent, to afford 251 mg (83%) of the pure amine (R_f = 0.55 $CHCl_3$/MeOH, 85:15).

IR: 3 400–3 200 (2 bands NH_2), 3 010 (=C–H), 2 960, 2 820 (C–H), 1 580 (NH_2).

^{1}H NMR (100 MHz, $CDCl_3$): 1.0 (d, 3H, 9-H, $J_{8,9}$ = 6.0 Hz), 1.2–1.85 (m, 10H, 6-H 7-H 2′-H 3′-H 4′-H), 1.90–2.15 (m, 2H, 5-H), 2.32 (q, 2H, 2-H, J = 6.4 Hz), 2.65–2.97 (m, 1H, 8-H), 3.2–3.95 (m, 4H, 1-H 5′-H), 4.57 (m, 1H, 1′-H), 5.18–5.58 (m, 2H, 3-H 4-H).

^{13}C NMR (25.178 MHz, $CDCl_3$): 23.82 (C-9), 19.53, 25.41, 26.37, 27.27, 27.90, 30.64, 39.64 (C-2 C-5 C-6 C-7 C-2′ C-3′ C-4′), 46.79 (C-8), 62.20, 66.97 (C-1 C-5′), 98.64 (C-1′), 125.77, 131.51 (C-3 C-4).

N-Formyl-9-(tetrahydropyran-2-yloxy)non-6(Z)-en-2-amine **20a**

A solution of *N*,*N*′-dicyclohexylcarbodiimide (DCC) (3.29 g, 2 equiv) in dry $CHCl_3$ was cooled at 0 °C under vigorous stirring. Then was slowly added a solution of formic acid 2M in $CHCl_3$ (16 mL, 4 equiv). The mixture was stirred 20 min at 0 °C and added dropwise to a solution of crude compound **19** (1.923 g, 7.98 mmol) in dry pyridine (20 mL) at 0 °C (formation of a white suspension). The stirring was continued 4 h at 0 °C, then the reaction mixture was allowed to warm to room temperature and Et_2O (180 mL) was added. The white precipitate was filtered under vacuum and the resulting solution was concentrated under reduced pressure. The residue was diluted with Et_2O and washed 3 times with water. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography with cyclohexane/ethyl acetate from 30% to 80% as eluent to give 1.817 g (85%) of pure compound **20a** (R_f = 0.10 cyclohexane/EtOAc, 60:40).

^{1}H NMR (100 MHz, $CDCl_3$): 1.03 (d, 3H, 9-H, $J_{8,9}$ = 6.9 Hz), 1.2–2.35 (m, 14H, 2-H 5-H 6-H 7-H 3′-H 4′-H 2′-H), 3.1–4.22 (m, 5H, 1-H 5′-H 8-H), 4.45 (m, 1H, 1′-H), 5.1–5.5 (m, 2H, 3-H 4-H), 6.35 (m, 1H, NH), 8.0 (s, 1H, CHO).

^{13}C NMR (25.178 MHz, $CDCl_3$): 20.80 (C-9), 19.53, 25.34, 25.88, 26.92, 27.82, 30.62, 36.14 (C-2 C-5 C-6 C-7 C-2′ C-3′ C-4′), 43.85 (C-8), 62.26, 66.94 (C-1 C-5′), 98.72 (C-1′), 126.00, 130.82 (C-3 C-4), 160.63 (CHO).

Anal ($C_{15}H_{27}O_3N$) calc: C 66.87, H 10.11, O 17.83; found: C 66.95, H 10.10, O 17.89.

8-Formamidonon-3(Z)-en-1-ol **21a**

To a solution of compound **20a** (1.658 g, 6.16 mmol) in absolute EtOH (53 mL), was added pyridinium *p*-toluenesulfonate (PPTS) (154 mg, 0.1 equiv). The mixture was heated at 55 °C under stirring for 4 h. After cooling, the solvent was evaporated under reduced pressure, and the residual oil was taken up with ether and washed with brine. The etheral phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The alcohol **21a** was obtained, after purification by chromatography with CH_2Cl_2/MeOH of 0% to 4% as eluent gradient, 1.097 g (96%) as a colorless oil (R_f = 0.19 CH_2Cl_2/MeOH, 95:5).

^{1}H NMR (360 MHz, $CDCl_3$): 1.04 (d, 3H, 9-H, $J_{8,9}$ = 6.6 Hz), 1.22–1.40 (m, 4H, 6-H 7-H), 1.87–2.05 (m, 2H, 5-H), 2.20 (q, 2H, 2-H, J = 6.8 Hz), 3.5 (t, 2H, 1-H, $J_{1,2}$ = 6.75 Hz), 3.85–3.98 (m, 1H, 8-H), 5.23–5.4 (m, 2H, 3-H 4-H), 6.50 (m, 1H, NH), 7.96 (s, 1H, CHO).

^{13}C NMR (25.178 MHz, $CDCl_3$): 20.57 (C-9), 25.67, 26.63, 30.57, 35.77 (C-2 C-5 C-6 C-7), 43.57 (C-8), 61.67 (C-1), 125.77, 131.47 (C-3 C-4), 160.90 (CHO).

N-Formyl-9-iodonon-6(Z)-en-2-amine **22a**

As described for the synthesis of compound **16**, in the same amounts, the iodination on compound **21a** (100 mg, 0.54 mmol) gave in 30 min, after purification by flash chromatography using silica gel 60 Merck (35–70 mesh) with CH_2Cl_2/EtOAc from 10% to 20% as eluent, 146 mg (92%) of the pure iodo derivative **22b** as a colored oil (R_f = 0.29 CH_2Cl_2/EtOAc, 80:20).

^{1}H NMR (360 MHz, $CDCl_3$): 1.13 (d, 3H, 9-H, $J_{8,9}$ = 6.6 Hz), 1.28–1.47 (m, 4H, 6-H 7-H), 1.94–2.07 (m, 2H, 5-H), 2.54–2.63 (m, 2H, 2-H), 3.09 (t, 2H, 1-H, $J_{1,2}$ = 7.25 Hz), 3.97–4.10 (m, 1H, 8-H), 5.22–5.50 (m, 2H, 3-H 4-H), 6.50 (m, 1H, NH), 8.05 (s, 1H, CHO).

^{13}C NMR (25.178 MHz, $CDCl_3$): 5.58 (C-1), 20.80 (C-9), 25.68, 26.95, 31.22, 36.13 (C-2 C-5 C-6 C-7), 43.77 (C-8), 128.02, 131.72 (C-3 C-4), 160.52 (CHO).

Anal ($C_{10}H_{18}ONI$) calc: C 40.67, H 6.15, O 5.42, I 43.01; found: C 40.62, H 6.02, O 5.47, I 43.22.

(8-Formamidonon-3(Z)-enyl)triphenylphosphonium iodide **23a**

The experimental procedure was the same as for preparation of compound **18**, in a mixture of toluene/CH_3CN (1:1) as solvent. The reaction was completed after 24 h and compound **23a** was obtained, after the usual treatment, as a pale yellow powder with 94% yield (R_f = 0.55 CH_2Cl_2/MeOH, 90:10).

Spectroscopic data: see table I.

9-(Tetrahydropyran-2-yloxy)N-(trifluoroacetyl)-non-6(Z)-en-2-amine **20b**

To a stirred solution of the purified compound **19** (222 mg, 0.92 mmol) in dry CH_2Cl_2 (17 mL), at 0 °C, triethylamine (1.41 mL, 0.01 mol) was added dropwise, followed by trifluoroacetic anhydride (1.04 mL, 7.36 mmol). After stirring at 0 °C for 15 min, the mixture was allowed to warm to room temperature and the stirring was continued for 2 h. Then, after treatment at 0 °C with sat aqueous $NaHCO_3$, the product was extracted with CH_2Cl_2. The organic layer was washed with brine until neutrality, then was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography with a gradient of 0–5% MeOH in CH_2Cl_2 to recover 304 mg (98%) of the pure protected compound **20b** as an oil (R_f = 0.74 CH_2Cl_2/MeOH, 95:5 or 0.39 cyclohexane/EtOAc, 75:25).

IR: 3 400–3 180, 3 090 (N–H), 3 010 (=CH), 2 990–2 820 (C–H), 1 720–1 680 (C=O), 1 660 (C=C), 1 540 (C–N).

^{1}H NMR (100 MHz, $CDCl_3$): 1.08 (d, 3H, 9-H, $J_{8,9}$ = 6.52 Hz), 1.0–1.8 (m, 10H, 6-H 7-H 2′-H 3′-H 4′-H), 1.8–2.08 (m, 2H, 5-H), 2.08–2.34 (m, 2H, 2-H), 3.15–4.04 (m, 5H, 1-H 8-H 5′-H), 4.45 (m, 1H, 1′-H), 5.13–5.5 (m, 2H, 3-H 4-H), 6.95 (m, 1H, NH).

^{13}C NMR (25.178 MHz, $CDCl_3$): 19.36, 19.98, 25.30, 25.79, 26.74, 27.78, 30.54, 35.46 (C-2 C-5 C-6 C-7 C-9 C-2′ C-3′ C-4′), 46.34 (C-8), 62.03, 66.84 (C-1 C-5′), 98.59 (C-1′), 115.85 (q, CF_3, $J_{C,F}$ = 286.0 Hz), 126.27, 130.75 (C-3 C-4), 156.57 (q, CO, $J_{C,F}$ = 36.4 Hz).

Anal ($C_{16}H_{26}O_3NF_3$) calc: C 56.94, H 7.77, O 14.23; found: C 56.69, H 7.82, O 14.12.

8-(Trifluoroacetamido)non-3(Z)-en-1-ol **21b**

Under the same conditions described for preparation of compound **21a**, the compound **20b** (1.287 g, 3.82 mmol) gave, after purification by chromatography with cyclohexane/EtOAc from 10% to 30% as eluent gradient, 950 mg (98%) of pure compound **21b** as a pale colored oil (R_f = 0.33 CH_2Cl_2/MeOH, 98:2).

IR: 3 600–3 150 (2 broad bands , OH and NH), 3 090 (NH), 3 010 (=CH), 2 980–2 820 (C–H), 1 720–1 670 (C=O), 1 540 (C–N).

^{1}H NMR (100 MHz, $CDCl_3$): 1.1 (d, 3H, 9-H, $J_{8,9}$ = 6.98 Hz), 1.05–1.6 (m, 4H, 6-H 7-H), 1.85–2.36 (m, 4H, 2-H 5-H), 2.81 (s, 1H, OH), 3.5 (t, 2H, 1-H, $J_{1,2}$ = 6.28 Hz), 3.75–4.1 (m, 1H, 8-H), 5.14–5.56 (m, 2H, 3-H 4-H), 7.27 (m, 1H, NH).

^{13}C NMR (25.178 MHz, $CDCl_3$): 19.83 (C-9), 25.68, 26.55, 30.48, 35.18 (C-2 C-5 C-6 C-7), 46.15 (C-8), 61.78 (C-1), 115.79 (q, CF3, $J_{C,F}$ = 285.8 Hz), 125.77, 131.54 (C-3 C-4), 156.68 (q, CO, $J_{C,F}$ = 36.4 Hz).

9-Iodo-N-(trifluoroacetyl)-non-6(Z)-en-2-amine **22b**

As described for the synthesis of compound **16**, in the same amounts, the iodination of compound **21b** (97 mg, 0.38 mmol) gave in 15 min, after purification by chromatography with heptane/EtOAc (9:1), 128 mg (92%) of the pure iodo derivative **22b** as a colorless oil (R_f = 0.74 cyclohexane/EtOAc, 50:50).

IR: 3 400–3200 and 3 090 (NH, 2 bands), 3 010 (=C–H), 2 990–2 820 (C–H), 1 720–1 670 (C=O), 1 540 (C–N).

^{1}H NMR (100 MHz, $CDCl_3$): 1.2 (d, 3H, 9-H, $J_{8,9}$ = 6.5 Hz), 1.2–1.67 (m, 4H, 6-H 7-H), 2.02 (q, 2H, 5-H, J = 6.1 Hz), 2.58 (q, 2H, 2-H, J = 7.0 Hz), 3.12 (t, 2H, 1-H, $J_{1,2}$ = 7.0 Hz), 3.75–4.75 (m, 1H, 8-H), 5.13–5.64 (m, 2H, 3-H 4-H), 6.37 (m, 1H, NH).

^{13}C NMR (25.178 MHz, $CDCl_3$): 5.54 (C-1), 20.19 (C-9), 25.68, 26.92, 31.28, 35.64 (C-2 C-5 C-6 C-7), 46.37 (C-8), 115.84 (q, CF3, $J_{C,F}$ = 286.0 Hz), 128.53, 131.49 (C-3 C-4), 156.57 (q, CO, $J_{C,F}$ = 36.3 Hz).

Anal ($C_{11}H_{17}ONF_3I$) calc: C 36.36, H 4.72, O 4.41, I 34.96; found: C 36.54, H 4.69, O 4.52, I 34.84.

[8-(Trifluoroacetamido)non-3(Z)-enyl]triphenylphosphonium iodide **23b**

The experimental procedure was the same as for the preparation of compound **18**, in dry CH_3CN as solvent. The reaction from compound **22b** (124 mg, 0.34 mmol) was completed after 24 h and 196 mg (92%) of pure phosphonium salt **23b** was obtained after the usual treatment as a white powder (R_f = 0.65 CH_2Cl_2/MeOH, 90:10).

IR: 3 200, 3 050 (NH), 3 010 (=C–H), 2 980–2 850 (C–H), 1 700 (C=O), 1 540 (C–N).

Spectroscopic data: see table I.

8-Fluoro-1-(tetrahydropyran-2-yloxy)non-3(Z)-ene **24**

To a solution of morpholinosulfur trifluoride (MSTF) (1.15 mL, 9.43 mmol) in dry CH_2Cl_2 (55 mL) at −50 °C, was added dropwise a solution of 9-(tetrahydropyran-2-yloxy)non-6(Z)-en-2-ol **13** (1.328 g, 5.49 mmol) in dry CH_2Cl_2 (11 mL), and the stirring was continued at −50 °C during 5–15 min. The cold mixture was diluted with CH_2Cl_2 and treated with sat aqueous $NaHCO_3$. The separated organic layer was washed with water, brine and was dried over anhydrous Na_2SO_4. Evaporation of the solvent at 20 °C gave a yellow oil that was purified by chromatography with cyclohexane/Et_2O (9:1) as eluent, affording 1.0 g (75%) of pure fluoro compound **24** (R_f = 0.83 cyclohexane/EtOAc, 50:50), and secondary products as defluoro- and iso-compounds.

^{1}H NMR (100 MHz, $CDCl_3$): 1.28 (dd, 3H, 9-H, $J_{8,9}$ = 6.1 Hz, $J_{9,F}$ = 23.9 Hz), 1.37–1.86 (m, 10H, 6-H 7-H 2′-H 3′-H 4′-H), 1.92–2.47 (m, 4H, 2-H 5-H), 3.20–4.00 (m, 4H, 1-H 5′-H), 4.20–5.00 (dm, 1H, 8-H, $J_{8,F}$ = 47 Hz), 4.57 (m, 1H, 1′-H), 5.23–5.54 (m, 2H, 3-H 4-H).

^{13}C NMR (25.178 MHz, $CDCl_3$): 19.48, 25.39, 26.92, 27.87, 30.60 (C-2 C-5 C-6 C-2′ C-3′ C-4′), 20.89 (C-9, $J_{C\text{-}9,F}$ = 22.8 Hz), 36.33 (C-7, $J_{C\text{-}7,F}$ = 20.2 Hz), 62.07, 66.88 (C-1 C-5′), 90.56 (C-8, $J_{C\text{-}8,F}$ = 163.4 Hz), 98.56 (C-1′), 126.10, 131.07 (C-3 C-4).

8-Fluoronon-3(Z)-ęn-1-ol **25**

A solution of compound **24** (192 mg, 0.79 mmol) in a mixture of THF (16 mL) and aqueous 10% HCl (12 mL) was heated at 60 °C for 2 h. After removal of the solvent under reduced pressure, the residue was taken up with brine and was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by chromatography with a gradient of 10–20% EtOAc in cyclohexane, to afford 103 mg (82%) of pure alcohol **25**.

^{1}H NMR (360 MHz, $CDCl_3$): 1.28 (dd, 3H, 9-H, $J_{8,9}$ = 6.3 Hz, $J_{9,F}$ = 23.9 Hz), 1.35–1.77 (m, 4H, 6-H 7-H), 2.08 (q, 2H, 5-H, J = 7 Hz), 2.30 (q, 2H, 2-H, J = 6.7 Hz), 3.62 (t, 2H, 1-H, $J_{1,2}$ = 6.6 Hz), 4.51–4.74 (2m, 1H, 8-H, $J_{8,F}$ = 48 Hz), 5.35–5.56 (2m, 2H, 3-H 4-H).

Anal ($C_9H_{17}OF$) calc: C 67.45, H 10.70, O 9.99; found: C 67.31, H 10.49, O 10.07.

8-Fluoro-1-iodonon-3(Z)-ene **26**

As described for the synthesis of compound **16**, in the same amounts, the iodination of compound **25** (280 mg, 1.75 mmol) gave in 15 min, after purification by chromatography with cyclohexane/EtOAc from 0 to 5%, 401 mg (85%) of the pure iodo derivative **26**.

^{1}H NMR (360 MHz, $CDCl_3$): 1.3 (dd, 3H, 9-H, $J_{8,9}$ = 6.1 Hz, $J_{9,F}$ = 23.7 Hz), 1.40–1.73 (m, 4H, 6-H 7-H), 2.06 (q, 2H, 5-H, J = 7.2 Hz), 2.58–2.65 (m, 2H, 2-H), 3.12 (t, 2H, 1-H, $J_{1,2}$ = 7.2 Hz), 4.51–4.74 (2m, 1H, 8-H, $J_{8,F}$ = 48 Hz), 5.30–5.56 (2m, 2H, 3-H 4-H).

^{13}C NMR (25.178 MHz, $CDCl_3$): 5.45 (C-1), 21.02 (C-9, $J_{C\text{-}9,F}$ = 22.5 Hz), 24.94, 27.13, 31.43 (C-2 C-5 C-6), 36.40 (C-7, $J_{C\text{-}7,F}$ = 19.9 Hz), 90.85 (C-8, $J_{C\text{-}8,F}$ = 163 Hz), 128.61, 131.95 (C-3 C-4).

Anal ($C_9H_{16}IF$) calc: C 40.00, H 5.97, I 47.00; found: C 39.96, H 6.09, I 46.94.

(8-Fluoronon-3(Z)-enyl)triphenylphosphonium iodide **27**

The experimental procedure was identical as for the synthesis of compound **18**, in dry toluene as solvent. Compound **26** (500 mg, 1.85 mmol) gave after 24 h and the usual treatment 857 mg (87%) of pure phosphonium salt **27** as a white powder (R_f = 0.20 $CHCl_3$/MeOH, 85:15).

Mp: 112.5–115.5 °C (ether).

Spectroscopic data: see table I.

9-(Acetyloxy)non-6-yn-2-one **28**

To a solution of 9-hydroxynon-6-yn-2-one **9** (850 mg, 5.52 mmol) in dry benzene (10 mL), acetic anhydride (4 mL) and pyridine (2 mL) were added followed by addition of 4-(dimethylamino)pyridine (30 mg). The slightly warmed up reaction mixture was allowed to stand at room temperature during 18 h. Then methanol was added and the reaction mixture was kept at room temperature for 1 h and was diluted by 2 volumes of pentane, 2 volumes of ether and 15 mL of 2M sodium bisulfate. The organic layer was washed with water and brine, then dried over anhydrous Na_2SO_4 and was evaporated under reduced pressure. The product was used for borohydride reduction without further purification (R_f = 0.76 benzene/EtOAc, 2:1).

MS: m/z 181, 163, 153, 136, 121, 108, 93, 77, 65, 58.

9-(Acetyloxy)non-6-yn-2-ol **29**

The reduction of compound **28** was realized under the same conditions as described for the synthesis of compound **13**. The crude product **29** was used for fluorination without further purification (R_f = 0.5 benzene/EtOAc, 2:1).

MS: m/z 183, 165, 138, 123, 105, 91, 77, 66, 55.

1-(Acetyloxy)-8-fluoronon-3-yne **30**

As described for the synthesis of compound **24**, we obtained from compound **29**, after 40 min of reaction time and the same treatment and purification, the pure compound **30** with 40% yield.

^{1}H NMR (200 MHz, $CDCl_3$): 1.34 (dd, 3H, 9-H, $J_{8,9}$ = 6.2 Hz, $J_{9,F}$ = 25 Hz), 1.48–1.85 (m, 4H, 6-H 7-H), 2.08 (s, 3H, CH_3–CO), 2.12–2.28 (m, 2H, 5-H), 2.42–2.57 (m, 2H, 2-H), 4.13 (t, 2H, 1-H, $J_{1,2}$ = 6.0 Hz), 4.46–4.89 (dm, 1H, 8-H, $J_{8,F}$ = 48 Hz).

^{19}F NMR (188 MHz, $CDCl_3$): −95.77 (d from both *R*- and *S*-fluoro epimers).

8-Fluoronon-3-yn-1-ol **31**

To a solution of compound **30** (320 mg, 1.6 mmol) in methanol (50 mL) was added potassium carbonate (1.2 g). The mixture was stirred 30 min at room temperature, and was diluted with EtOAc and a solution of 2M sodium bisulfate. The organic layer was washed with water and brine, and was dried over anydrous Na_2SO_4. After evaporation of the solvent at 25 °C and purification of a yellow oil residue by column chromatography with cyclohexane/ether of 10% to 30%, **31** was obtained as a pure, slightly yellowish oil.

^{1}H NMR (200 MHz, $CDCl_3$): 1.34 (dd, 3H, 9-H, $J_{8,9}$ = 6.2 Hz, $J_{9,F}$ = 25 Hz), 1.48–1.85 (m, 4H, 6-H 7-H), 2.0 (m, 1H, OH), 2.12–2.28 (m, 2H, 5-H), 2.36–2.48 (m, 2H, 2-H), 3.70 (t, 2H, 1-H, $J_{1,2}$ = 6.0 Hz), 4.48–4.91 (2m, 1H, 8-H, $J_{8,F}$ = 48 Hz).

^{13}C NMR (50.3 MHz, $CDCl_3$): 18.29, 22.77 (C-2 C-5), 20.76 (C-9, $J_{C\text{-}9,F}$ = 23.1 Hz), 24.26 (C-6, $J_{C\text{-}6,F}$ = 4 Hz), 35.70 (C-7, $J_{C\text{-}7,F}$ = 21.7 Hz), 61.06 (C-1), 76.80, 81.39 (C-3 C-4), 90.39 (C-8, $J_{C\text{-}8,F}$ = 165.5 Hz).

8-Fluoro-1-iodonon-3-yne **32**

As described for **16**, in the same amounts, iodination on compound **31** (208 mg, 1.32 mmol) gave 286 mg (81%) of pure compound **32**.

^{1}H NMR (100 MHz, $CDCl_3$): 1.47 (dd, 3H, 9-H, $J_{8,9}$ = 6.1 Hz, $J_{9,F}$ = 24.2 Hz), 1.5–2.06 (m, 4H, 6-H 7-H), 2.14–2.52 (m, 2H, 5-H), 2.78–3.04 (m, 2H, 2-H), 3.4 (t, 2H, 1-H, $J_{1,2}$ = 7.3 Hz), 4.45–5.25 (2m, 1H, 8-H, $J_{8,F}$ = 48 Hz).

^{13}C NMR (25.178 MHz, $CDCl_3$): 2.72 (C-1), 20.89 (C-9, $J_{C\text{-}9,F}$ = 22.5 Hz), 18.49, 24.10, 26.86 (C-2 C-5 C-6), 35.87 (C-7, $J_{C\text{-}7,F}$ = 20.2 Hz), 79.24, 81.73 (C-3 C-4), 90.37 (C-8, $J_{C\text{-}8,F}$ = 163.5 Hz).

Anal ($C_9H_{14}IF$) calc: C 40.30, H 5.26, O 47.35; found: C 40.25, H 5.29, O 47.29.

(8-Fluoronon-3-ynyl)triphenylphosphonium iodide **33**

As described for **18**, compound **32** (280 mg, 1.04 mmol) gave 554 mg (88%) of phosphonium salt **33** as a white powder.

Mp: 107–112 °C.

Spectroscopic data: see table I.

Methyl 19(RS)-trifluoroacetamido- and fluoro-5(S), 6(S)-epoxyeicosa-7(E),9(E),11(Z),14(Z)-tetraenoate ***34a*** *and* ***34b***

A solution of non-3(*Z*)-enyl triphenylphosphonium iodide **23b** or **27** (0.27 mmol, 3 equiv, previously dried under vacuum during 15 h with P_2O_5) in dry THF (2.5 mL) and dry HMPA (500 μL) was stirred under nitrogen at −78 °C. Then was added dropwise *n*-BuLi 1.6 M in hexane (6.6 equiv or 3.6 equiv respectively) and the mixture was stirred for 20 min at −78 °C (the solution became orange). A solution of methyl 5(*S*),6(*S*)-epoxy-11-oxoundeca-7(*E*),9(*E*)-dienoate **1** (20 mg, 0.089 mmol, 1 equiv) in dry THF (0.5 mL) was added dropwise to the mixture. After 15 min, the solution was concentrated under reduced pressure at 20 °C and immediately purified by flash chromatography (deactivated silica gel) with heptane/EtOAc/NEt_3, 98:2:2, and we obtained pure 19(*RS*)-functionalized LTA_4 methyl esters **34a** and **34b** with 51% respectively 84% yields (R_f = 0.61 respectively 0.71 heptane/EtOAc, 50:50).

A competitive reaction is the formation of by-products: phosphine oxides **35**, in spite of dry conditions. About 70% of phosphonium iodide was converted into phosphine oxide during the above Wittig reaction.

Spectroscopic data and HPLC analysis of compound **34**: see table III.

Non-3(Z)-enyl diphenylphosphine oxide ***35***

A solution of non-3(*Z*)-enyl triphenyl phosphonium iodide in a mixture of NaOH/H_2O (30%, w/v) was heated to 75 °C for 15 h. After cooling, the mixture was extracted with $CHCl_3$, and the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography with cyclohexane/EtOAc from 30 to 50%, to yield 80–90% of pure compound **35**.

Spectroscopic data: see table II.

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