Fluorinated Analogs of Retinoids: Stereocontrolled Synthesis Employing Fluoroisoprenoidal Horner Ylides

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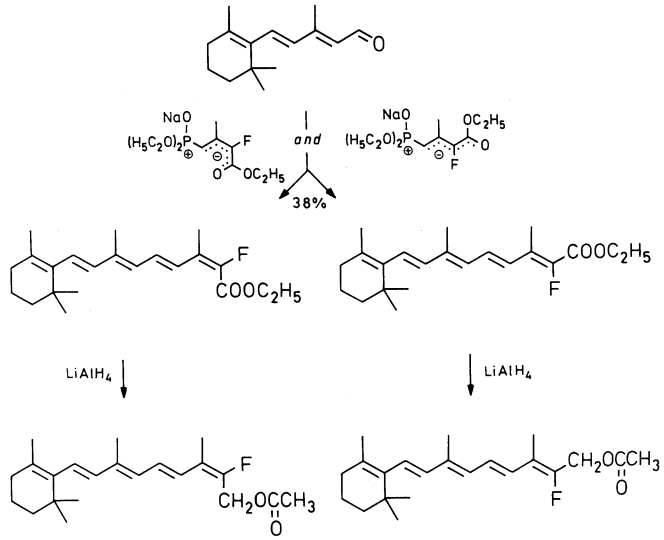
Received June 27, 1998

Keywords: Fluoro analogs of vitamin A / Horner-Wittig reaction / Fluoroisoprenoid building blocks / Stereoselectivity / Hydrolysis of chlorofluorocyclopropanes

An improved method for the preparation of ethyl 2-fluoro-3-methyl-2-butenoate (**3**) is described. The two stereoisomers [(*E*)-**4** and (*Z*)-**4**] obtained after γ-bromination can be separated and can be individually converted into the corresponding diethyl phosphonates. The PO-ylides generated by α-deprotonation of the latter lose their stereochemical integrity by rapid torsional equilibration of the ester tail. Thus, Horner-Wittig reactions accomplished with benzaldehyde and (*Z*)- or (*E*)-(β-ionylidene)-acetaldehyde lead inevitably to stereorandomization at the terminal, ethoxycarbonyl-bearing double bond affording (*E*)- and (*Z*)-isomers in 50:50 to 15:85 ratios, depending on the reaction conditions. The new double bond, however, is formed with perfect *trans*-selectivity.

Fluorinated retinoids have a great potential for the treatment of dermatologic diseases (in particular, psoriasis) and cancer[1]. In a landmark article[2], Machleidt et al. disclosed the preparation of the first fluorinated retinoid analogs. Submitting *all-trans*-(β-ionylidene)acetaldehyde to a Horner-Wittig condensation with an alkoxycarbonyl-carrying C_5-*PO*-ylide, they obtained a (13*E*) and (13*Z*) mixture of ethyl 14-fluororetinoate in 38% yield. A small quantity of the presumed (*Z*)-isomer was isolated as a stereochemically pure sample upon crystallization at low temperature. Reduction of the esters with lithium aluminum hydride and subsequent acetylation afforded the (13*E*) and (13*Z*) stereoisomeric 14-fluororetinyl acetates.



All structural assignments were tentative, however. They essentially relied on the appearance of two spots on the thin-layer chromatography plate and on the ultraviolet absorption maxima of the reaction mixtures. Moreover, the stereochemical integrity had been sacrificed from the very beginning, the *PO*-ylide being generated from a phosphonic ester prepared by Michaelis-Arbusov reaction between triethyl phosphite and a (*Z/E*)-mixture of ethyl 4-bromo-2-fluoro-3-methyl-2-butenoate. We deemed it worthwhile to repeat these reactions using stereochemically well-defined components and to monitor the composition of product mixtures with modern analytical and NMR spectroscopic means.

A convenient entry to ethyl 2-fluoro-3-methyl-2-butenoate (**3**; "fluorodimethylacrylate") was developed on the basis of our chlorofluorocarbene cycloaddition/solvolytic ring-opening method[3]. Ethyl isobutyrate was converted into the corresponding *O*-ethyl *O*-trimethylsilyl ketene acetal **1** (81%). The chlorofluorocarbene cycloadduct **2** prepared from the latter was not isolated but immediately hydrolyzed to afford ethyl 2-fluoro-3-methyl-2-butenoate (**3**) in 75% yield. The ω-bromo derivative **4** obtained by treatment with *N*-bromosuccinimide as a 1:2 (*E/Z*) mixture (83%) was separated into its components by careful fractional distillation. The pure isomers (*Z*)-**4** and (*E*)-**4** were heated in the presence of triethyl phosphite until no more ethyl bromide was evolved. Distillation afforded the corresponding diethyl phosphonates (*Z*)-**5** and (*E*)-**5** (85% and 51%, respectively).

Deprotonation of either phosphonate isomer, (*E*)-**5** or (*Z*)-**5**, with sodium hydride in diethyl ether and subsequent combination with (*E*)-(β-ionylidene)acetaldehyde at 0°C afforded the same (13*E*) and (13*Z*) 1:1 mixture (approx. 50%) of ethyl (9*E*,11*E*)-14-fluororetinoate [(*E*,*E*,*E*)-**6** and (*E*,*E*,*Z*)-**6**]. However, the (13*E*)- and (13*Z*)-isomers were

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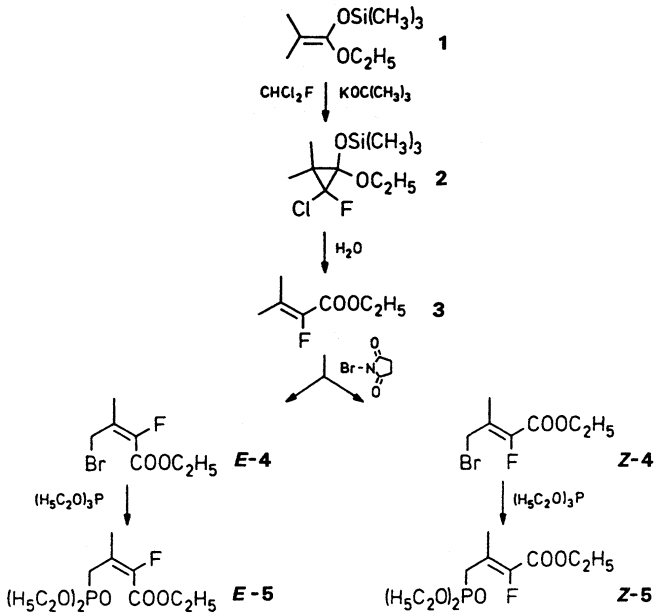
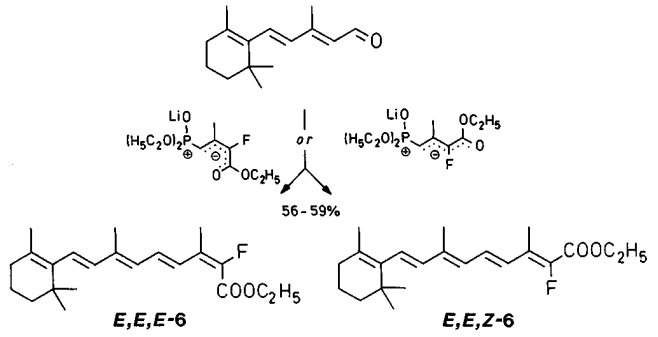
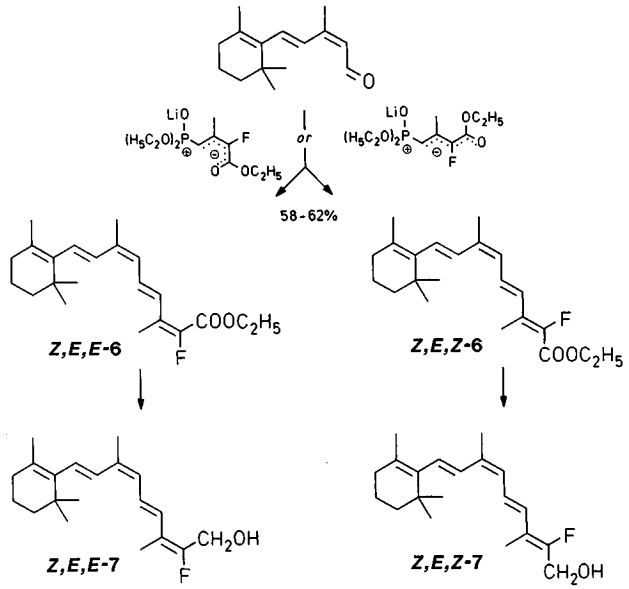


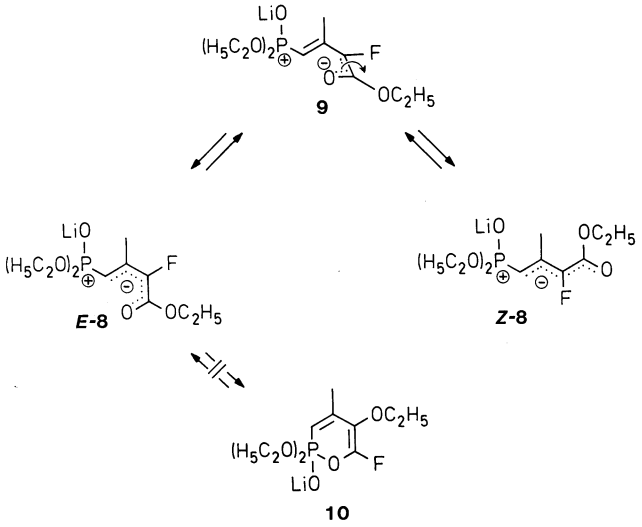
formed in a 1:7 ratio and in improved yields (56−59%) when sodium hydride was replaced by lithium diisopropylamide (LIDA) in tetrahydrofuran, no matter whether the aldehyde was added at 0°C or at −75°C to the *PO*-ylide derived from one of the stereoisomeric phosphonates **5**. In other words, the new double bond emerges from the Horner-Wittig reaction indeed *trans*-selectively, as reported[2], but the configuration of the ester tail is invariably randomized.



Reactions with other aldehydes revealed identical stereochemical patterns: *trans*-selectivity and stereoconvergence for the new double bond and the unsaturated ester tail, respectively. Benzaldehyde and phosphonate (*E*)-**5** gave a 1:2 mixture of ethyl (2*E*,4*E*)- and (2*Z*,4*E*)-2-fluoro-3-methyl-5-phenyl-2,4-pentadienoate (63%) when sodium hydride was used to generate the *PO*-ylide. A 1:7 mixture was obtained in 69−75% yield when the phosphonates (*E*)-**5** or (*Z*)-**5** were deprotonated with lithium diisopropylamide. (*Z*)-(β-Ionylidene)acetaldehyde afforded a 1:1 mixture (54−60%) of (13*E*)- and (13*Z*)-isomers of ethyl (9*Z*,11*E*)-14-fluororetinoate [(*Z*,*E*,*E*)-**6** and (*Z*,*E*,*Z*)-**6**] when the deprotonation of the phosphonates was accomplished with sodium hydride or potassium *tert*-butoxide in tetrahydrofuran, and a 1:6 mixture (58−60%) when lithium diisopropyl amide was employed as the base. Upon reduction with lithium aluminum hydride, the corresponding 14-fluororetinols [(*Z*,*E*,*E*)-**7** and (*Z*,*E*,*Z*)-**7**] were obtained.



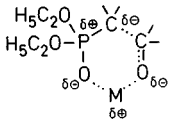
The loss of the stereochemical integrity of the ester part must have happened at the level of the *PO*-ylide **8**. Unlike congeners derived from allylic phosphonates[4] and phosphane oxides,[5] ylides carrying a crotonate side chain are obviously prone to rapid torsional isomerization. The ease with which the latter process can occur demonstrates how little energy is required to trim back the optimally delocalized *PO*-ylide to an enephosphonio enolate **9**, which can act as the transition state for the (*Z*/*E*) equilibration. One may feel inclined to invoke a second equilibrium linking the betaine (*E*)-**8** further to a cyclic phosphorane **10**. However, as can be judged from the absence of any high-field ^{31}P-NMR signal, the latter intermediate exists only in negligible concentrations, at best.



The phosphonates have to be treated with lithium diisopropylamide (in tetrahydrofuran) at −50°C and with sodium hydride (in diethyl ether or tetrahydrofuran) at 0°C to assure reasonably fast *PO*-ylide formation. Subsequently,

it affects neither the yields nor the stereochemistry is affected on addition of aldehyde is added at −75°C or 0°C. In contrast to these findings, the stereochemical outcome of Horner-Wittig reactions between a related, though fluorine-free *PO*-ylide and a (*Z/E*)-isomeric mixture of (β-ionylidene)acetaldehyde has been claimed to depend strongly on the addition temperature[6].

The metal effect on the (13*E*)/(13*Z*) stereoisomeric product composition can be plausibly rationalized by assuming that the *PO*-ylide and the aldehyde combine via a six-membered, cyclic transition state (**11**), at which the metal (M = lithium or sodium) is more or less effectively chelated by two negative charged oxygen atoms. At the moment, however, nothing is known about whether the adduct can undergo reversible decomposition and, if so, to what extent.



11

All configurations have been unambiguously assigned on the basis of $^3J_{HF}$ constants. Fluorine attached to olefinic sites is known to couple with hydrogen atoms at *cis*- and *trans*-allylic positions across the double bond to the extent of 4.0−4.5 and 2.8−3.5 Hz, respectively[7][8][9].

This work was supported by the *Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung* (grant 20−49′307−96), Bern, the *Hoffmann-LaRoche AG*, Basel, and the *Bundesamt für Bildung und Wissenschaft* (contract 97.0083), Bern, in the framework of the TMR project "Fate-MP".

Experimental Section

For working routine and abbreviations see recent publications (e.g., ref.[10]) which have emanated from this laboratory. ^{1}H-, ^{13}C-, ^{19}F-, and ^{31}P-NMR spectra were recorded at 400, 101, and 188 MHz, respectively, trichlorofluoromethane and 85% aqu. phosphonic acid (external standard) being used as the shift reference in the two latter cases.

1. Starting Materials

(β-Ionylidene)acetaldehyde: Butyllithium (0.10 mol), from which the commercial solvent (hexanes) had been stripped off, was dissolved in precooled (−75°C) tetrahydrofuran (50 ml). Always at −75°C, (*Z*)-2-bromovinyl ethyl ether (11 ml, 15 g, 0.10 mol) and, 10 min later, β-ionone (20 ml, 19 g, 0.10 mol) and finally, after the mixture had been allowed to reach 25°C, 6 M hydrochloric acid (10 ml) were added. The homogeneous solution was kept 2 h at 25°C, it was concentrated with a rotatory evaporator to approximately one quarter of its former volume. Water (40 ml) was added and the mixture is rapidly extracted with diethyl ether (3 × 25 ml). The combined organic layers were washed with a saturated aqueous solution of sodium hydrogen carbonate (2 × 25 ml) and brine (25 ml) before being dried. Distillation afforded the product as a 1:2 (*Z/E*) mixture according to gas chromatography (30 m, silicon rubber DB−1, 170°C; 30 m, polyalcohol DB−WAX, 180°C); bp 95−98°C/0.05 Torr; n_D^{20} 1.5737; 18 g (72%). − The material was absorbed on silica gel (100 ml) and eluted with 1:10 (v/v) mixture (approx. 2.0 l) of ethyl acetate and hexanes from a column (∅ 7.0 cm) filled with more silica (2.0 l). Pure (*Z*)-isomer appeared first, being followed by a mixed fraction (5.0 g) and eventually pure (*E*)-isomer was collected. − (*Z*)-*Isomer* (stereochemical purity ≥ 97%): 2.5 g (14%); n_D^{20} = 1.5662. − ^{1}H NMR: δ 10.17 (d, *J* = 8.2 Hz, 1 H), 7.09 (d, *J* = 16.2 Hz, 1 H), 6.63 (d, *J* = 16.2 Hz, 1 H), 5.87 (d, *J* = 8.2 Hz, 1 H), 2.13 (s, 3 H), 2.05 (t, *J* = 6.2 Hz, broad, 2 H), 1.6 (m, 2 H), 1.5 (m, 2 H), 1.05 (s, 6 H). − (*E*)-*Isomer* (stereochemical purity ≥ 97%): 5.5 g, (31%); n_D^{20} 1.5746. − ^{1}H NMR: δ 10.13 (d, *J* = 8.3 Hz, 1 H), 6.75 (d, *J* = 16.2 Hz, broad, 1 H), 6.21 (d, *J* = 16.2 Hz, 1 H), 5.94 (d, *J* = 8.3 Hz, broad, 1 H), 2.31 (d, *J* = 0.8 Hz, 3 H), 2.0 (m, 2 H), 1.6 (m, 2 H), 1.5 (m, 2 H), 1.06 (s, 6 H).

1-Ethoxy-2-methyl-1-(trimethylsilyloxy)propene (**1**): At −75°C, ethyl isobutyrate (33 ml, 29 g, 0.25 mol) and, 30 min later, chlorotrimethylsilane (83 ml, 72 g, 0.66 mol) were added to a solution of lithium diisopropylamide prepared by mixing diisopropylamine (40 ml, 27 g, 0.28 mol) in tetrahydrofuran (0.30 l) and butyllithium (0.28 mol) in hexanes (0.18 l). Most of the volatiles were removed by distillation through a Widmer column (20 cm long). Pentane (40 ml) and kieselgur (diatomaceous earth, Celite) were added. The filtrate was concentrated and distilled; bp 33−35°C/2 Torr (ref.[11]: bp 60°C/20 Torr); n_D^{20} 1.4153; 38 g (81%). − ^{1}H NMR: δ 3.77 (q, *J* = 7.1 Hz, 2 H), 1.58 (s, 3 H), 1.52 (s, 3 H), 1.22 (t, *J* = 7.1 Hz, 3 H), 0.20 (s, 9 H).

Ethyl 2-Fluoro-3-methyl-2-butenoate (**3**): At −75°C, precooled dichlorofluoromethane (22 ml, 31 g, 0.20 mol) was added to the slurry of potassium *tert*-butoxide (26 g, 0.23 mol) in hexanes (0.20 l) in which 1-ethoxy-2-methyl-1-(trimethylsilyloxy)propene (37 g, 0.20 mol) had been dissolved. After vigorous stirring for 1 h at −75°C, the mixture was allowed to reach 25°C. Water (0.15 l) was added, the organic phase decanted and the aqueous one extracted with diethyl ether (3 × 50 ml). The combined organic layers were washed with brine (2 × 50 ml), dried, and evaporated. Upon distillation a colorless liquid was collected; bp 54−55°C/10 Torr (ref.[8]: 54°C/10 Torr); n_D^{20} 1.4278; 22 g (75%). − ^{1}H NMR: δ 4.28 (q, *J* = 7.2 Hz, 2 H), 2.12 (d, *J* = 3.2 Hz, 3 H), 1.88 (d, *J* = 4.2 Hz, 3 H), 1.34 (t, *J* = 7.2 Hz, 3 H).

Ethyl 4-Bromo-2-fluoro-3-methyl-2-butenoate (**4**): The 1:2 (*Z/E*)-mixture (83%) was prepared from ethyl 2-fluoro-3-methyl-2-butenoate (**3**; 18 ml, 19 g, 0.13 mol) by reaction with *N*-bromosuccinimide in refluxing tetrachloromethane as described in the literature[2]. The stereoisomers were separated by careful fractionation using a Fischer "Spaltrohr" column. − (*E*) *Isomer* (≥ 97%) pure): bp 89−92°C/5 Torr; n_D^{20} 1.4801; 15.0 g (51%). − ^{1}H NMR: δ 4.55 (d, *J* = 1.5 Hz, 2 H), 4.32 (q, *J* = 7.2 Hz, 2 H), 2.00 (d, *J* = 4.5 Hz, 3 H), 1.36 (t, *J* = 7.2 Hz, 3 H). − ^{19}F NMR: δ −121.1. − (Z) *Isomer* (≥ 97% pure): bp 92−94°C/5 Torr; n_D^{20} 1.4818; 2.5 g (8.5%). − ^{1}H NMR: δ 4.30 (d, *J* = 7.3 Hz, 2 H), 4.08 (q, *J* = 3.3 Hz, 2 H), 2.22 (d, *J* = 3.6 Hz, 3 H), 1.35 (t, *J* = 7.3 Hz, 3 H). − ^{19}F-NMR: δ −122.0.

Ethyl (E)-4-Diethoxyphosphoryl-2-fluoro-3-methyl-2-butenoate [Diethyl (E)-3-Ethoxycarbonyl-3-fluoro-2-methyl-2-propenylphosphonate, (*E*)**-5**]: Ethyl (*E*)-bromo-2-fluoro-3-methyl-2-butenoate (**4**; 4.7 ml, 5.6 g, 25 mmol) and triethyl phosphite (4.3 ml, 4.2 g, 25 mmol) were mixed and slowly, in the course of 1 h, heated to 140°C at which temperature no more ethyl bromide was evolved. The product was obtained as a colorless liquid upon distillation; bp 110−112°C/0.4 Torr; n_D^{20} 1.4513; 6.0 g (85%). − ^{1}H NMR: δ 4.28 (q, *J* = 7.3 Hz, 2 H), 4.1 (m, 4 H), 3.30 (dd, *J* = 23.9, 1.2 Hz, 2 H), 2.00 (dd, *J* = 4.5, 4.2 Hz, 3 H), 1.35 (t, *J* = 7.3 Hz, 3 H), 1.30 (t, *J* = 7.0 Hz, 6 H). − ^{19}F NMR: δ −123.7 (d, *J* = 18.3 Hz). − ^{31}P NMR: δ 29.5. − MS: 284 (100%) [M^+ + 2], 283 (87%) [M^+ +

1], 282 (19%) [M^+]. − $C_{11}H_{20}FO_5P$ (282.25): calcd. C 46.81, H 7.14; found C 46.85, H 7.08%.

Ethyl (Z)-4-Diethoxyphosphoryl-2-fluoro-3-methyl-2-butenoate [Diethyl (Z)-3-Ethoxycarbonyl-3-fluoro-2-methyl-2-propenylphosphonate, (*Z*)-**5**]: Prepared and isolated as described in the preceding paragraph using ethyl (*Z*)-4-bromo-2-fluoro-3-methyl-2-butenoate [(*Z*)-**4**]; bp 94−96°C/0.3 Torr (ref.[2]: bp 85−86°C/0.01 Torr; (*Z*/*E*) mixture); n_D^{20} 1.4522; 6.1 g (87%). − ^{1}H NMR: δ 4.29 (q, *J* = 7.1 Hz, 2 H), 4.1 (m, 4 H), 3.30 (dd, *J* = 23.9, 3.2 Hz, 2 H), 2.00 (dd, *J* = 3.9, 3.6 Hz, 3 H), 1.34 (t, *J* = 7.1 Hz, 3 H), 1.30 (t, *J* = 7.0 Hz, 6 H),−^{19}F NMR: δ −123.5 (d, *J* = 9.2 Hz). − ^{31}P NMR: δ 29.4. − MS: 284 (100%) [M^+ + 2], 283 (87%) [M^+ + 1], 282 (19%) [M^+]. − $C_{11}H_{20}FO_5P$ (282.25): calcd. C 46.81, H 7.14; found C 46.91, H 7.18%.

2. Olefination Reactions

Ethyl (13E)- and (13Z)-(9E,11E)-14-Fluororetinoate[2] [(*E*,*E*,*E*)-**6** and (*E*,*E*,*Z*)-**6**]: At −50°C, ethyl (*E*)-4-diethoxyphosphoryl-2-fluoro-2-butenoate (*E*-**5**; 2.3 ml, 2.8 g, 10 mmol) and, 10 min later, (*E*)-(β-ionylidene)acetaldehyde (1.8 ml, 2.2 g, 10 mmol) were added to a solution of lithium diisopropylamide (obtained by the instantaneous reaction between diisopropylamine and butyllithium, both 10 mmol) in tetrahydrofuran (25 ml) and hexanes (7 ml). When the reaction mixture had reached 25°C, water (0.5 ml) was added, and the mixture was absorbed on silica gel (25 ml) and evaporated to dryness. The powder was poured on top of a column filled with more silica gel (75 ml) and eluted with a 1:20 (v/v) mixture of ethyl acetate and hexanes. A viscous, yellow oil was obtained which, according to NMR, contained (13*E*) and (13*Z*) isomers in the approximate ratio of 14:86 (ref.[2]: ethyl 13-(*Z*)-14-fluororetinoate; mp 87°C); n_D^{20} 1.6065; 1.9 g (56%). − ^{1}H NMR: δ 6.96 (dd, *J* = 15.2, 11.3 Hz, 1 H), 6.78 (dd, *J* = 15.2, 1.5 Hz, 0.9 H), 6.71 (dd, *J* = 15.2, 1.5 Hz, 0.1 H), 6.29 (d, *J* = 16.1 Hz, 1 H), 6.22 (d, *J* = 11.3 Hz, 1 H), 6.14 (d, *J* = 16.1 Hz, 0.9 H), 6.12 (d, *J* = 16.1 Hz, 0.1 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 2.28 (d, *J* = 3.2 Hz, 2.6 H), 2.02 (d, *J* = 4.5 Hz, 0.4 H), 2.01 (3 H, s), 2.0 (m, 2 H), 1.75 (s, 0.4 H), 1.71 (s, 2.6 H), 1.6 (m, 2 H), 1.5 (m, 2 H), 1.36 (t, *J* = 7.1 Hz, 0.4 H), 1.35 (t, *J* = 7.1 Hz, 2.6 H), 1.05 (s, 0.8 H), 1.03 (s, 5.2 H).

In the same way, using phosphonate *Z*-**5** as starting material, a 12:88 (13*E*/13*Z*) mixture of ethyl (9*E*,11*E*)-14-fluororetinoate [(*E*,*E*,*E*)-**6** and (*E*,*E*,*Z*)-**6**] was obtained; 2.0 g (59%).

Ethyl (13E)- and (13Z)-(9Z,11E)-14-Fluororetinoate [(*Z*,*E*,*E*)-**6** and (*Z*,*E*,*Z*)-**6**]: As described above, ethyl (*E*)-4-diethoxyphosphoryl-2-fluoro-2-butenoate (*E*-**5**; 2.3 ml, 2.8 g, 10 mmol) and, 10 min later, (*Z*)-(β-ionylidene)acetaldehyde (1.8 ml, 2.2 g, 10 mmol) were added to a solution of lithium diisopropylamide in tetrahydrofuran (25 ml) and hexanes (7 ml) kept at −50°C. When the reaction mixture had reached 25°C, water (0.5 ml) was added and the mixture was absorbed on silica get (25 ml) and evaporated to dryness. The powder was poured on top of a column filled with more silica gel (75 ml) and eluted with a 1:20 (v/v) mixture of ethyl acetate and hexanes. A viscous, yellow oil was obtained which, according to NMR, consisted of (13*E*) and (13*Z*) isomers in the approximate ratio of 15:85; n_D^{20} 1.6074; 2.0 g (58%). − ^{1}H NMR: δ 7.46 (d, *J* = 15.2 Hz, 0.2 H), 7.06 (dd, *J* = 15.2, 11.5 Hz, 0.8 H), 7.69 (dd, *J* = 15.2, 11.5 Hz, 0.2 H), 6.71 (d, broad, *J* = 15.2 Hz, 0.8 H), 6.65 (d, *J* = 15.6 Hz, 0.8 H), 6.64 (d, *J* = 15.5 Hz, 0.2 H), 6.29 (d, broad, *J* = 15.6 Hz, 0.8 H), 6.22 (d, broad, *J* = 15.6 Hz, 0.2 H), 6.15 (d, *J* = 11.5 Hz, 0.2 H), 6.13 (d, broad, *J* = 11.5 Hz, 0.8 H), 4.29 (q, *J* = 7.1 Hz, 1.7 H), 4.28 (q, *J* = 7.1 Hz, 0.3 H), 2.27 (d, *J* = 3.1 Hz, 2.6 H), 2.03 (d, *J* = 4.5 Hz, 0.5 H), 2.0 (m, 2 H), 2.01 (s, 2.6 H), 1.98 (s, 0.5 H), 1.75 (s, 2.6 H), 1.74 (s, 0.5 H), 1.6 (m, 2 H), 1.5 (m, 2 H), 1.36 (t, *J* = 7.1 Hz, 0.5 H), 1.35 (t, *J* = 7.1 Hz, 2.6 H), 1.04 (s, 5.2 H), 1.03 (s, 0.8 H). − ^{19}F NMR: δ −127.4. − MS: 347 (46%) [M^+ + 1], 346 (100%) [M^+], 345 (41%) [M^+ − 1], 331 (45%), 311 (41%). − $C_{22}H_{31}FO_2$ (346.48): calcd. C 76.26, H 9.02; found C 76.07, H 8.96%.

In the same way, using phosphonate (*Z*)-**5** as the starting material, ethyl (13*E*)- and (13*Z*)-(9*Z*,11*E*)-14-fluororetinoate [(*Z*,*E*,*E*)-**6** and (*Z*,*E*,*Z*)-**6**] was obtained as a 13:87 mixture of (13*E*) and (13*Z*) isomers; 2.1 g (62%). When sodium hydride, in diethyl ether or tetrahydrofuran, or potassium *tert*-butoxide in tetrahydrofuran were used instead of lithium diisopropylamide, (9*Z*,11*E*)-14-fluororetinoate [(*Z*,*E*,*E*)-**6** and (*Z*,*E*,*Z*)-**6**] was produced in 56, 59, and 53% yield and with (13*E*/13*Z*) ratios of 45:55, 50:50, and 48:52, respectively.

Ethyl (2E)- and (2Z)-(4E)-2-Fluoro-3-methyl-5-phenyl-2,4-pentadienoate: At −50°C, ethyl (*E*)-4-diethoxyphosphoryl-2-fluoro-2-butenoate (*E*-**5**) (2.3 ml, 2.8 g, 10 mmol) and, 10 min later, benzaldehyde (1.0 ml, 1.1 g, 10 mmol) were added to a solution of lithium diisopropylamide in tetrahydrofuran (25 ml) and hexanes (7 ml). When the reaction mixture had reached 25°C, water (20 ml) and diethyl ether (20 ml) were added and the two phases were separated. The aqueous layer was extracted with diethyl ether (3 × 25 ml). The combined organic layers was washed with brine (20 ml), then dried. After evaporation of the solvent, the residue was distilled; bp 100−102°C/0.4 Torr; 1.7 g (75%). According to NMR, (2*E*)- and (2*Z*)-isomers were present in the ratio of 14:86. Crystallization from pentanes (at 0°C) gave the pure (2*Z*)-isomer as a white needles; mp 40−42°C. The yield decreased slightly (to 70%) while the stereochemical ratio remained the same (14:86) when an analogous reaction was carried out with the (*Z*)-isomer of the phosphonate (*Z*-**5**). − ^{1}H-NMR: δ 7.5 (m, 2 H), 7.3 (m, 4 H), 6.90 (d, *J* = 16.3 Hz, 0.8 H), 6.88 (d, *J* = 16.3 Hz, 0.2 H), 4.32 (q, *J* = 7.3 Hz, 2 H), 2.34 (d, *J* = 3.3 Hz, 2.6 H), 2.11 (d, *J* = 4.5 Hz, 0.4 H), 1.37 (t, *J* = 7.3 Hz, 3 H). − ^{19}F-NMR: δ −126.2. − MS: 235 (24%) [M^+ + 1], 234 (55%) [M^+], 161 (100%), 146 (89%). − $C_{14}H_{15}FO_2$ (234.27): calcd. C 71.78, H 6.45; found C 72.09, H 6.23%.

Exactly the same stereoisomeric ratio of 14:86 was found when the phosphonate (*E*)-**5** was consecutively treated in tetrahydrofuran at 0°C with lithium diisopropylamide and benzaldehyde (yield 72%). In contrast, a 33:67 (2*E*,2*Z*) mixture (1.5 g, 64%) was isolated when a suspension of sodium hydride in tetrahydrofuran containing the phosphonate (*E*)-**5** was vigorously stirred at 0°C for 1 h, before benzaldehyde was added at −75°C.

3. Reduction

(13E)- and (13Z)-(9E,11E)-14-Fluororetinol[2] [(*E*,*E*,*E*)-**8** and (*E*,*E*,*Z*)-**8**]: Ethyl 14-fluororetinoate [(*E*,*E*,*E*)-**6**/(*E*,*E*,*Z*)-**6** = 12:88, 1.7 g, 5.0 mmol] was added to the slurry of lithium aluminium hydride (0.38 g, 10 mmol) in diethyl ether (25 ml) and kept at 0°C. After vigorous stirring for 30 min, ethyl acetate (5 ml) was introduced. When the evolution of gas had ceased, the mixture was neutralized with 2 M sulfuric acid (20 ml). The combined organic layers were washed with brine (20 ml) and absorbed on alumina (15 ml). Once dry, the powder was poured on top of a column filled with more alumina (45 ml) and eluted with a 1:9 (v/v) mixture of ethyl acetate and hexanes to afford, according to NMR, (13*E*) and (13*Z*) isomers in the approximate ratio of 12:88 as a faint yellow oil; 0.82 g (54%). − ^{1}H-NMR: δ 6.72 (d, broad, *J* = 15.2 Hz, 0.9 H), 6.62 (dd, *J* = 15.2, 10.9 Hz, 0.9 H), 6.0 (m, 0.2 H), 6.1 (m, 3 H), 4.4 (m, 2 H), 2.01 (t, broad, *J* = 6.3 Hz, 2 H), 1.96 (s, 2.6 H), 1.93 (s, 0.4 H), 1.86 (d, broad, *J* = 3.2 Hz, 3 H), 1.74 (s, 2.6 H), 1.70 (s, 0.4 H), 1.6 (m, 2 H), 1.5 (m, 2 H), 1.04 (s, 0.7 H), 1.02 (s, 5.3 H).

(13E)- and (13Z)-(9Z,11E)-14-Fluororetinol [(*Z*,*E*,*E*)-**8** and (*Z*,*E*,*Z*)-**8**]: In the same way described as above, ethyl 14-fluororetinoate [(*Z*,*E*,*E*)-**6**/(*Z*,*E*,*Z*)-**6** = 13:87, 1.7 g, 5.0 mmol] gave 14-fluororetinol [(*Z*,*E*,*E*)-**8** and (*Z*,*E*,*Z*)-**8**] as a yellowish viscous oil which, according to NMR, contained the (13*E*) and (13*Z*) isomers in the approximate ratio of 13:87; n_D^{20} 1.5662; 0.83 g (55%). – ^{1}H NMR: δ 6.7 (m, 2 H), 6.6 (m, 1 H), 6.20 (d, *J* = 14.9 Hz, 0.1 H), 6.19 (d, *J* = 16.2 Hz, 0.9 H), 6.06 (d, broad, *J* = 10.4 Hz, 0.9 H), 6.00 (d, broad, *J* = 10.2 Hz, 0.1 H), 4.4 (m, 2 H), 2.0 (m, 2 H), 1.97 (3 H, s, broad), 1.8 (m, 4 H), 1.75 (s, 3 H), 1.6 (m, 2 H), 1.5 (m, 2 H), 1.04 (s, 5.2 H), 1.02 (s, 0.8 H). – ^{19}F NMR: δ −116.3 (t, *J* = 23.0 Hz). – MS: 305 (36%) [M^+ + 1], 304 (100%) [M^+], 303 (40%) [M^+ − 1], 289 (27%), 287 (60%), 286 (36%), 269 (20%), 105 (42%), 91 (48%). – $C_{22}H_{29}FO$ (304.45): calcd. C 78.90, H 9.60; found C 79.21, H 9.94%.

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