Pergamon

Tetrahedron 55 (1999) 13779–13790

TETRAHEDRON

Stereocontrolled Synthesis of Retinoids Functionalized at C-13 by Suzuki Coupling Reactions

Rosana Alvarez, Beatriz Iglesias and Angel R. de Lera*

Departamento de Química Física e Química Orgánica, Universidade de Vigo, 36200 Vigo, SPAIN

Received 9 July 1999; revised 6 September 1999; accepted 23 September 1999

Abstract. The retinal analogues (13*Z*)-13-bromo-13-desmethylretinal (**3**) and (13*E*)-20,20,20-trifluororetinal (**4**) have been efficiently synthesized using the palladium-catalyzed cross-coupling of boronic acid **8** and electrophiles **9** and **10**, respectively. For the first analogue, the coupling of **8** and the *gem*-dibromide **9** took place with high stereoselectivity. The configuration of the C13–C14 double bond in **4** relied on the stereoselective preparation and coupling of alkenyltriflate *Z*-**10** from β-ketoester **15**. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Retinoids; Suzuki reactions; Stereocontrol; Polyenes.

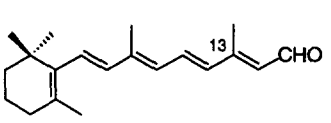
For the last twenty years, metal-catalyzed cross-coupling reactions have become an indispensable tool for C–C bond formation involving unsaturated species such as vinyl, alkynyl and aryl moieties.[1] As a consequence, the often tedious classical procedures to access conjugated polyenes can now be confidently replaced by the metal-catalyzed cross-coupling processes.[1] In particular, palladium-catalyzed cross-coupling reactions have been found, in general, to be chemo- and stereoselective. The retention of configuration of the coupling partners has been mechanistically predicted and further corroborated by experimental results. The field of retinoid synthesis has also benefited from the development of these contemporary catalytic stereocontrolled methods, thus helping to overcome the often difficult separation of double-bond isomers obtained by classical synthesis involving double bond-forming condensations (Wittig, HWE, Julia–Lythgoe...).[2] As representative of the class of polyene natural products, synthetic endeavors directed towards the stereocontrolled synthesis of retinoids[3] are expected to have general application for polyene synthesis. In this respect, we[4] and others[5] have contributed to the development of variants of the reliable Suzuki[6] and Stille[7] cross-coupling reactions for the stereocontrolled synthesis of retinoids using alkenyl boronic acids and alkenyl stannanes, respectively. A recent report[8] describing selective functionalizations at C-13 of the retinoid skeleton by Stille coupling prompted us to disclose our own results in this area.

Bacteriorhodopsin (BR), the light-harvesting protein found in the purple membrane of *Halobacterium salinarum*, uses *trans*-retinal (**1**) as the chromophore responsible for light absorption (568 nm).[9] The excitation triggers a photocycle which induces a proton translocation across the bacterial membrane. The photochemical excitation of BR_{568} induces a *trans* to *cis* isomerization of the terminal C13–C14 double bond to afford intermediate J_{625} in which the chromophore is 13-*cis*-retinal (**2**). Other intermediates, differing in C13–C14 geometry and/or in protonation states of the Schiff base protein-bound chromophore, have also been spectroscopically characterized on the photocycle before BR reaches its original state BR_{568}. Upon replacing the native retinal **1** by synthetic analogues artificial protein-chromophore complexes are obtained. This technique can also be combined with the site-directed mutagenesis of the apoprotein, particularly affecting the residues

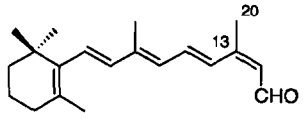
PII: S0040-4020(99)00861-3

comprising the binding pocket,[10] to generate artificial BR's that generally show differences in absorption maxima and/or protonation capabilities. These comprehensive studies involving native and artificial BRs have contributed to increase the knowledge of a biological proton-pump.[9b]

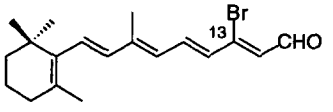
Figure 1



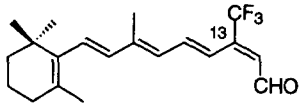
1 *trans*-retinal



2 13-*cis*-retinal



3 13-bromo-13-desmethylretinal
(13*Z*)-13-bromo-13-desmethylretinal

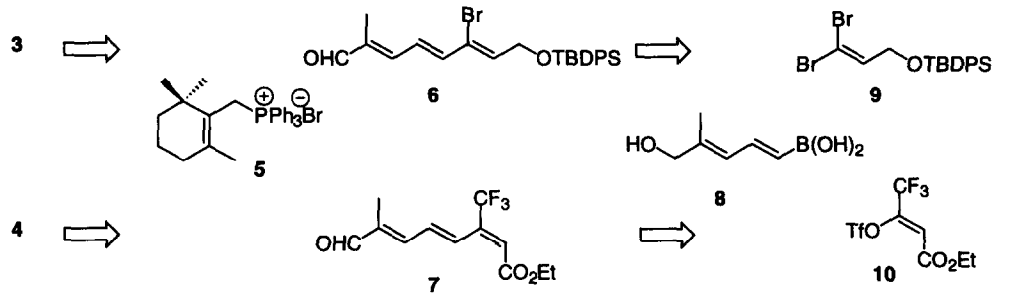


4 13-*cis*-20,20,20-trifluororetinal
(13*E*)-20,20,20-trifluororetinal

Other properties of BR, such as long-term stability against thermal and photochemical degradation during a large number of proton-translocation cycles,[11] and the capability to form well-ordered thin Langmuir-Blodgett films or to be immobilized in sol-gel glass,[12] make natural and artificial BRs attractive candidates for photochromic applications (optical recording, photoimaging, photovoltaic devices etc.).[11] Analogues that endow changes in absorption properties are highly desirable in the study of BR as a prototype of photosensitive protein-retinal complexes that show the ability to respond to changes in their environmental conditions with reversible changes in absorption properties and refractive index. In connection with a project aimed at studying the proton uptake and release of BR analogues with synthetic retinal derivatives,[13] we required access to artificial protein complexes showing absorption maxima red shifted relative to native BR. Apart from the strongly red-shifted BRs derived from azulenic retinals (λ_{max} up to 830 nm, depending upon substitution),[14] two other derivatives, both functionalized at the C13 position, that show ground-state absorption spectra shifted to the red relative to native BR (λ_{max}= 568 nm)[9] have been described, namely (13*Z*)-13-bromo-13-desmethylretinal (**3**) (*trans*-13-bromo-13-desmethylretinal, artificial BR at λ_{max}= 595 nm)[15] and (13*E*)-20,20,20-trifluororetinal (**4**) (13-*cis*-20,20,20-trifluororetinal, artificial BR at λ_{max}= 624 nm)[16a].

We therefore set out to synthesize stereoselectively the two aforementioned retinal analogues (**3** and **4**) in the common convergent fashion outlined in Scheme 1, which features Suzuki cross-coupling reactions involving dienylboronic acid **8** and the appropriate electrophile as the key step. Availability of the starting materials helped to dictate the choice of the electrophile cross-coupling components, to give **3** and **4**, as alkenyldibromide **9** and alkenyl triflate **10**, respectively. Both alkenyl triflates and alkenyl bromides are known to couple with alkenyl boronic acids if the appropriate recommended reaction conditions are followed, which further attests to the generality of the Suzuki coupling.[6] Since the retinoid C7–C8 double bond can be obtained with high stereoselectivity using a Wittig condensation of C_{10} aldehydes and the ylide of the C_{10} fragment **5**,[2c] the complete retinoid side chain for both analogues could be accessed provided that both the preparation of triflate *Z*-**10** and the coupling of electrophiles **9** and *Z*-**10** were found to proceed stereoselectively.

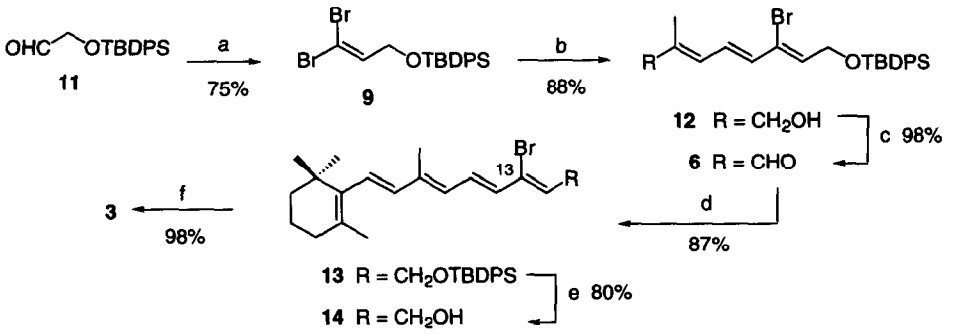
Scheme 1



Synthesis of (13Z)-13-bromo-13-desmethylretinal (3)

The Suzuki coupling of alkenyl *gem*-dibromides such as **9** has been shown to proceed stereoselectively due to the considerable rate differences between the bromides with *Z* or *E* configuration relative to the substituent, with the reaction proceeding in favour of the latter.[17] In the event, the required dibromide **9**, derived from aldehyde **11**[18] by the Corey–Fuchs procedure,[19] coupled to known boronic acid **8**[4c] under the mild conditions developed by Kishi [$Pd(PPh_3)_4$, 10% aqueous TlOH, THF, 25 °C],[20] to afford geometrically homogeneous trienylalcohol **12**, in accordance with expectations, in 88% yield. Trienal **6**, obtained in almost quantitative yield by MnO_2 oxidation of trienol **12**, was treated with the ylide derived from phosphonium salt **5**[15] (*n*-BuLi, THF, –30 to 25 °C) to afford the Wittig condensation product, pentaene **13**, in good yield (87%), with complete control of the C7–C8 bond geometry. Finally, deprotection of silyl ether **13** afforded (13Z)-13-bromo-13-desmethylretinol (**14**), which was oxidized under the same conditions as indicated above to provide the target compound (13Z)-13-bromo-13-desmethylretinal (**3**). This analogue has previously been obtained in low yield by addition of HBr to the corresponding tetraen-13-ynal.[15]

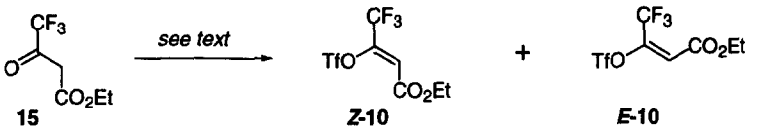
Scheme 2[a]



[a] Reagents and reaction conditions: (a)PPh_3, CBr_4, CH_2Cl_2, 0 --> 25 °C (75%); (b) Boronic acid **8**, $Pd(PPh_3)_4$, 10% aq. TlOH, THF, 25 °C (88%); (c) MnO_2, CH_2Cl_2, 25 °C (98%); (d) phosphonium salt **5**, *n*-BuLi, THF, -30 -> 0 °C (87%); (e) nBu_4NF, THF, 25 °C (80%); (f) MnO_2, CH_2Cl_2, 25 °C (98%).

Synthesis of (13E)-20,20,20-trifluororetinal (4)

The stereoselectivity of the bond-forming reactions depicted in Scheme 1 relies, for the synthesis of **4**, on the preparation of geometrically homogeneous alkenyl triflate *Z*-**10** from the convenient precursor ethyl trifluoroacetoacetate (**15**).



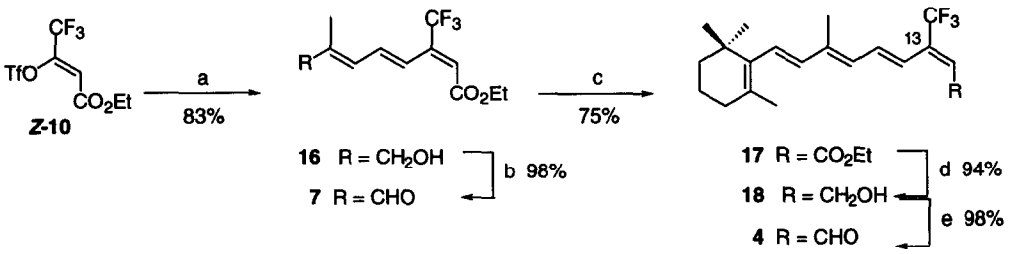
Following precedents by Houpis[21] on the generation of vinyl triflates from the corresponding β-ketoesters, we first treated **15** with NaH in THF at 0 °C followed by addition of triflic anhydride (Tf_2O). The reaction proved to be unacceptably slow, yielding, after 40 min, a mixture of products with starting material predominating. After extended reaction times and with higher temperatures (25 °C, 3 h), a jelly-like reaction mixture was formed, from which no desired product could be isolated. Changing the solvent to DMF with *N,N*-bis(trifluoromethanesulfonyl)-*N*-phenyltriflimide (Tf_2NPh) as a trapping agent did improve the reactivity of **15**, but the product *Z*-**10** was difficult to isolate from the reaction mixture. Use of the more reactive triflating agent, developed by Comins,[22] was also unproductive. Success was finally achieved with KH/DME and Tf_2O at –78 °C[23] and these conditions provided *Z*-**10** in 75% yield. The use of silyl amide bases, as described by Crisp and Meyer,[24] was also optimized for the production of *Z*-**10**. Treatment of **15** with NaHMDS and Tf_2O at –78 °C for 2.5 h afforded *Z*-**10** in 37% yield, whereas the combination KHMDS/Tf_2O in THF led to *Z*-**10** in 31% yield. A higher yielding reaction used LiHMDS in THF/HMPA to generate the lithium enolate, followed by quenching of the reaction with Tf_2NPh,[25] and afforded a satisfactory 86% yield of *Z*-**10**.

In order to complement the efficient preparation of *Z*-**10**, a variety of reaction conditions for the generation of the geometric isomer, vinyl triflate *E*-**10**, from β-ketoester **15** were thoroughly examined. The use of hindered amines has frequently been described as the procedure of choice for the synthesis of *E*-vinyl triflates from β-ketoesters.[26] Attempts to produce *E*-**10** by treatment of **15** with Tf_2O in the presence of Et_3N in CH_2Cl_2 also led to the production of *Z*-**10**, regardless of the reaction conditions (–78 °C, 5 h: 57%; 25 °C, 18 h: 43%; 45 °C, 13 h: 49%). Likewise, when di-*tert*-butylmethylpyridine was used in CH_2Cl_2 in conjunction with Tf_2O at 40 °C,[27] *Z*-**10** was isolated in 81% yield. Other conditions included LDA in THF and Tf_2O at –30 °C for 2 h, which led mainly to recovered **15** after quenching the reaction mixture. Upon increasing the reaction temperature to 25 °C and stirring for 20 h, a mixture containing mostly starting material, *Z*-**10** and an unidentified reaction product (which might correspond to *E*-**10**) was formed, as shown by examination of the ^{1}H-NMR spectrum of the reaction mixture. However, the yields for **10** were unacceptably low and this route was not pursued further. It is also worthy of note that the use of Hünig's base in CH_2Cl_2 and of Cs_2CO_3 in CH_3CN to induce the generation of triflate(s) led to failure, with starting material recovered in both cases.

Once Z-**10** had been successfully obtained, we used the optimized conditions for coupling triflates to boronic acids (2M Na_2CO_3, DME, 80 °C), described by Suzuki,[28] to afford ester **16** in 80% yield, with retention of configuration in both coupling partners. Oxidation of the alcohol group in **16** to give aldehyde **7** (MnO_2, CH_2Cl_2, 98%) set the stage for the Wittig condensation with phosphonium salt **5** in the presence of *n*-BuLi. This reaction afforded ethyl (13*E*)-13-*cis*-20,20,20-trifluororetinoate (**17**) in good yield (75%). Conversion of **17** to the desired

compound **4** was effected in two steps; firstly, reduction to alcohol **18** using DIBAL-H (94%) and then oxidation to **4** following the general MnO_2 procedure (98%). Retinal analogue **4** is prone to photochemical degradation[16] and should be handled with suitable precautions. The spectroscopic data for **4** matched those published for the same product obtained by Horner–Emmons and Peterson olefin elongation procedures.[16]

Scheme 3[a]



[a] Reagents and reaction conditions: (a) Boronic acid **8**, $Pd(PPh_3)_4$, Na_2CO_3 2M, DME, 80 °C (83%); (b) MnO_2, CH_2Cl_2, 25 °C (98%); (c) phosphonium salt **5**, *n*-BuLi, THF, -30 -> 0 °C (75%); (d) DIBAL-H, THF, -78 -> 0 °C (94%); (e) MnO_2, CH_2Cl_2, 25 °C (98%).

In summary, the Suzuki reaction has been extended to the preparation of retinal analogues with substituents (CF_3, Br) replacing the native methyl group at the C13-position. The highly stereoselective nature of the Suzuki coupling allows the stereocontrolled synthesis of the polyene skeleton, avoiding the separation of geometric isomers that was required in previous approaches to **3** and **4**. The trifluoromethylated building block *Z*-**10** should prove useful[29] in the preparation of trifluoromethylated organic molecules, which are known to have significantly different properties to the parent methylated compounds.[30]

Experimental Section

General. Solvents were dried according to published methods and distilled before use. HPLC grade solvents were used for the HPLC purification. All other reagents were commercial compounds of the highest purity available. Manganese(IV) oxide was obtained from Aldrich Chemical Co. Analytical thin-layer chromatography (TLC) was performed using Merck silica gel (60 F-254) plates (0.25 mm) precoated with a fluorescent indicator. Column chromatography was performed using Merck silica gel 60 (particle size 0.040–0.063 μm). Proton (^1H) and carbon (^{13}C) magnetic resonance spectra (NMR) were recorded on Bruker AMX-300 [300 MHz (75 MHz for ^{13}C)] and AMX-400 [400 MHz (100 MHz for ^{13}C)] Fourier transform spectrometers, and chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane (TMS, 0 ppm), benzene (C_6H_6, 7.20 ppm for ^1H) or chloroform ($CHCl_3$, 7.24 ppm for ^1H and 77.00 ppm for ^{13}C) as internal reference. ^{13}C multiplicities (s, singlet; d, doublet; t, triplet; q, quartet) were assigned with the aid of the DEPT pulse sequence. Infrared spectra (IR) were obtained on a MIDAC Prospect Model FT-IR spectrophotometer. Absorptions are recorded in wavenumbers (cm^{-1}). UV spectra were recorded on an HP5989A spectrophotometer using MeOH as solvent. Absorption maxima are reported in nm. Melting points (m.p.) were taken on a Kofler apparatus and are uncorrected. Low-resolution mass spectra were taken on an HP59970 instrument operating at 70 eV. High-resolution mass spectra were taken on a VG Autospec M instrument. All operations involving synthesis and/or manipulation of retinoids were done under subdued light.

***tert*-Butyldiphenylsilyl 3,3-Dibromoprop-2-en-1-yl Ether (9).** Carbon tetrabromide (1.07 g, 3.22 mmol) was slowly added to a cooled (0 °C) solution of triphenylphosphine (1.58 g, 6.04 mmol) in CH_2Cl_2 (20 mL). After stirring at 0 °C for 30 min, a solution of aldehyde **11**[18] (0.40 g, 1.34 mmol) in CH_2Cl_2 (5 mL) was added and the mixture was stirred at 0 °C for 1 h. The mixture was diluted with Et_2O (100 mL), filtered through a Celite® pad, washed with saturated aqueous $NaHCO_3$ solution (3 x 10 mL), H_2O (2 x 10 mL) and brine (3 x 10 mL), dried (Na_2SO_4) and concentrated. The residue was purified by chromatography (SiO_2, 100% hexane) to yield 0.46 g (75%) of dibromide **9** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.8–7.7 (m, 4H, ArH), 7.6–7.4 (m, 6H, ArH), 6.68 (t, J = 5.8 Hz, 1H, H_2), 4.25 (d, J = 5.8 Hz, 2H, $2H_1$), 1.11 (s, 9H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4 (d, C_2), 136.0 (d, 4 x Ar), 133.5 (s, 2 x Ar), 130.3 (d, 2 x Ar), 128.3 (d, 4 x Ar), 90.0 (s, C_3), 64.9 (t, C_1), 27.3 (q, *t*-Bu), 19.6 (s, *t*-Bu); FTIR (NaCl) υ 3067 (m, C–H), 2934 (s, C–H), 2859 (s, C–H), 1467 (m), 1428 (m), 1369 (w), 1106 (s), 703 (s) cm^{-1}; MS *m/z* (%) 399 (M^+ – *t*-Bu, 52), 397 (M^+ – *t*-Bu, 100), 395 (M^+ – *t*-Bu, 47), 290 (53), 263 (73), 261 (72), 211 (26), 181 (24), 91 (10); HRMS (M^+– *t*-Bu) calcd. for $C_{15}H_{13}{}^{79}Br^{81}BrOSi$ 396.9082, found 396.9070.

(2*E*,4*E*,6*Z*)-6-Bromo-8-[(*tert*-butyldiphenylsilyl)oxy]-2-methylocta-2,4,6-trien-1-ol (12). After stirring a suspension of $Pd(PPh_3)_4$ (0.09 g, 0.08 mmol) in THF (10 mL) at 25 °C for 5 min, a solution of dibromide **9** (0.36 g, 0.78 mmol) in THF (5 mL) was added, and the mixture was stirred for 15 min. Boronic acid **8** (0.20 g, 1.41 mmol) in THF (5 mL) was then added, followed by 10% aqueous TlOH solution (6.82 mL, 3.14 mmol), and the final mixture was stirred at 25 °C for 1 h. The mixture was then diluted with Et_2O (7 mL) and filtered through a Celite® pad, with thorough washing with Et_2O. The filtrate was washed with saturated aqueous $NaHCO_3$ solution and the aqueous phase extracted with Et_2O (3 x 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Purification of the residue by chromatography (SiO_2, 80:20 hexane/ethyl acetate) afforded 0.32 g (88%) of **12** as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.8–7.7 (m, 4H, ArH), 7.6–7.4 (m, 6H, ArH), 6.68 (dd, J = 14.2, 11.5 Hz, 1H, H_4), 6.2–6.1 (m, 3H, H_3 + H_5 + H_7), 4.49 (d, J = 5.8 Hz, 2H, $2H_8$), 4.12 (br, 2H, $2H_1$), 1.11 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7 (s), 136.0 (d, 4 x Ar), 133.8 (s), 133.7 (d), 130.7 (d), 130.2 (d, 2 x Ar), 129.8 (d), 128.0 (d, 4 x Ar), 124.0 (s), 123.7 (d), 68.6 (t), 64.7 (t), 27.1 (q, 3x, *t*-Bu), 19.6 (s), 14.9 (q); FTIR (NaCl) υ 3600–3200 (s, br, OH), 3067 (w, C–H), 2934 (m, C–H), 2859 (m, C–H), 1645 (m), 1429 (m), 1107 (s), 703 (s) cm^{-1}; UV (MeOH) λ_{max} 278 nm; MS *m/z* (%) 443 (M^+ – CH_3O, 2), 441 (M^+ – CH_3O, 4), 439 (M^+ – CH_3O, 2), 303 (12), 263 (31), 261 (32), 200 (23), 199 (100), 195 (18), 155 (10), 155 (11), 135 (14); HRMS (M^+ – CH_3O) calcd. for $C_{24}H_{28}{}^{79}BrOSi$ 439.1093, found 439.1086.

(2*E*,4*E*,6*Z*)-6-Bromo-8-[(*tert*-butyldiphenylsilyl)oxy]-2-methylocta-2,4,6-trienal (6). General procedure for the oxidation of allylic alcohols with MnO_2: To a solution of alcohol **12** (0.30 g, 0.64 mmol) in CH_2Cl_2 (15 mL) was added MnO_2 (1.0 g, 11.46 mmol). After being stirred at 25 °C for 2 h, the mixture was filtered through a Celite® pad, with thorough washing with CH_2Cl_2. The solvent was evaporated and the residue purified by chromatography (silica gel, 95:5 hexane/ethyl acetate) to obtain 0.29 g (98%) of trienal **6** as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 9.49 (s, 1H, H_1), 7.8–7.6 (m, 4H, ArH), 7.5–7.3 (m, 6H, ArH), 7.0–6.9 (m, 2H, H_4 + H_5), 6.59 (d, J = 11.4 Hz, 1H, H_3), 6.46 (t, J = 5.4 Hz, 1H, H_7), 4.53 (d, J = 5.4 Hz, 2H, $2H_8$), 1.93 (s, 3H, C_2-CH_3), 1.09 (s, 9H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.0 (d, C_1), 147.0 (d), 140.0 (s, C_2), 139.4 (d), 138.7 (d), 136.0 (d, 4 x Ar), 133.6 (s, 2 x Ar), 130.3 (d, 2 x Ar), 128.4 (d), 128.2 (d, 4 x Ar), 122.0 (s, C_6), 64.8 (t, C_8), 27.2 (q, *t*-Bu), 19.6 (s, *t*-Bu), 10.2 (q, C_2-CH_3); FTIR (NaCl) υ 2929 (s, C–H), 2857 (s, C–H), 1680 (s,

C=O), 1615 (m), 1427 (w), 1109 (s), 704 (s) cm^{-1}; UV (MeOH) λ_{max} 312 nm; MS *m/z* (%) 469 (M^+, 1), 468 (1), 429 (3), 427 (3), 331 (20), 301 (33), 264 (18), 263 (100), 261 (98), 211 (28), 199 (35), 198 (55), 181 (28), 155 (14), 135 (29); HRMS (M^+) calcd. for $C_{25}H_{29}O_2{}^{81}BrSi$ 470.1099, found 470.1083.

(13Z)-13-Bromo-13-desmethylretinyl *tert*-Butyldiphenylsilyl Ether (13). General procedure for the Wittig reaction: To a cooled (–78 °C) solution of (2,6,6-trimethylcyclohex-1-en-1-yl)methyl triphenylphosphonium bromide (**5**) (0.18 g, 0.38 mmol) in THF (8 mL) was slowly added *n*-BuLi (0.22 mL, 1.73 M in THF, 0.38 mmol). After stirring for 30 min, a solution of trienal **6** (0.15 g, 0.32 mmol) in THF (8 mL) was added and the mixture was stirred at –78 °C for 1 h and at 25 °C for 3 h. 10% aqueous HCl was then added until neutral pH was reached, and the mixture was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with H_2O (3 x 10 mL) and brine (3 x 10 mL), dried (Na_2SO_4) and evaporated. Purification of the residue by chromatography (SiO_2, hexane) afforded 0.16 g (87%) of **13**. ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 4H, ArH), 7.5–7.3 (m, 6H, ArH), 6.92 (dd, J = 14.1, 11.7 Hz, 1H, H_{11}), 6.3–6.1 (m, 5H, H_7 + H_8 + H_{10} + H_{12} + H_{14}), 4.49 (d, J = 5.5 Hz, 1H, $2H_{15}$), 2.02 (t, J = 6.4 Hz, 2H, $2H_4$), 1.99 (s, 3H, C_9-CH_3), 1.72 (s, 3H, C_5-CH_3), 1.6–1.4 (m, 4H, $2H_2$ + $2H_3$), 1.06 (s, 9H, *t*-Bu), 1.03 (s, 6H, C_1-$2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0 (s), 138.1 (s), 137.8 (d), 136.1 (s), 136.0 (d, 4 x Ar + CH), 133.7 (s, 2 x Ar), 133.2 (d), 130.8 (d), 130.2 (d, 2 x Ar), 128.9 (d), 128.3 (d), 128.2 (d, 4 x Ar), 124.3 (s), 64.8 (t, C_{15}), 39.9 (t), 34.7 (s, C_1), 33.5 (t), 29.1 (q, 2x, C_1-$2CH_3$), 27.1 (q, 3x, *t*-Bu), 22.2 (q, C_9-CH_3), 19.7 (t), 19.6 (s, *t*-Bu), 13.4 (q, C_5-CH_3); MS *m/z* (%) 588 (M^+, 13), 525 (14), 508 (40), 415 (31), 335 (14), 263 (8), 261 (7), 200 (18), 199 (100), 77 (14), 74 (10); HRMS (M^+) calcd. for $C_{35}H_{45}{}^{79}BrOSi$ 588.2423, found 588.2432.

(13Z)-13-Bromo-13-desmethylretinol (14). To a solution of silyl ether **13** (0.15 g, 0.26 mmol) in THF (4 mL) was added *n*-Bu_4NF (0.38 mL, 1 M in THF, 0.38 mmol). After being stirred at 25 °C for 90 min, the mixture was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$ solution (3 x 10 mL). The aqueous layer was extracted with Et_2O (3 x 15 mL) and the combined organic extracts were washed with brine (3 x 10 mL), dried (Na_2SO_4), filtered and concentrated. Purification by chromatography (SiO_2, 80:20 hexane/ethyl acetate) yielded 0.07 g (80%) of **14** as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (dd, J = 14.0, 11.7 Hz, 1H, H_{11}), 6.3–6.1 (m, 5H, H_7 + H_8 + H_{10} + H_{12} + H_{14}), 4.44 (d, J = 6.1 Hz, 2H, $2H_{15}$), 2.00 (s, 3H, C_9-CH_3), 2.0–1.9 (m, 2H, $2H_4$), 1.71 (s, 3H, C_5-CH_3), 1.6–1.4 (m, 2H, $2H_2$ + $2H_3$), 1.02 (s, 6H, C_1-$2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6 (s), 138.2 (s), 137.7 (d), 131.8 (d), 131.5 (d), 130.3 (s), 129.9 (d), 128.8 (d), 128.7 (d), 126.8 (s), 62.9 (t, C_{15}), 39.9 (t), 34.7 (s, C_1), 33.5 (t), 30.2 (q, 2x, C_1-$2CH_3$), 22.2 (q), 19.6 (t), 13.3 (q); FTIR (NaCl) υ 3600–3200 (br, OH), 2925 (s, C–H), 2860 (s, C–H), 1451 (m), 1364 (m), 1022 (m), 965 (m) cm^{-1}; UV (MeOH) λ_{max} 330 nm; MS *m/z* (%) 352 (M^+, 56), 351 (13), 350 (58), 271 (32), 183 (26), 159 (25), 157 (32), 149 (58), 123 (31), 119 (38), 109 (40), 105 (48), 95 (43), 91 (52), 83 (37), 81 (44), 69 (100); HRMS (M^+) calcd. for $C_{19}H_{27}{}^{81}BrO$ 352.1225, found 352.1226.

(13Z)-13-Bromo-13-desmethylretinal (3). In accordance with the general procedure described above, the reaction of alcohol **14** (0.06 g, 0.19 mmol) and MnO_2 (0.31 g, 3.49 mmol) in CH_2Cl_2 (4 mL) afforded, after purification by chromatography (SiO_2, 95:5 hexane/ethyl acetate), 0.06 g (98%) of (13Z)-13-bromo-13-desmethylretinal (**3**). ^1H NMR (400 MHz, C_6D_6) δ 10.20 (d, J = 6.8 Hz, 1H, H_{15}), 7.45 (dd, J = 14.0, 11.7 Hz, 1H, H_{11}), 6.41 (d, J = 16.1 Hz, 1H, H_7), 6.28 (d, J = 16.1 Hz, 1H, H_8), 6.13 (d, J = 6.8 Hz, 1H, H_{14}), 6.00 (d, J = 11.7 Hz, 1H, H_{10}), 5.83 (d, J = 14.0 Hz, 1H, H_{12}), 2.00 (t, J = 6.1 Hz, 2H, $2H_4$), 1.78 (s, 6H, C_9-CH_3 + C_5-CH_3), 1.6–1.4 (m, 4H, $2H_2$ + $2H_3$), 1.13 (s, 6H, C_1-$2CH_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 10.06 (d, J = 7.0 Hz, 1H, H_{15}), 7.55 (dd, J = 13.9, 11.9 Hz, 1H, H_{11}), 6.43 (d, J = 16.1 Hz, 1H, H_7), 6.39 (d, J = 13.9 Hz, 1H,

H_{12}), 6.34 (d, J = 7.0 Hz, 1H, H_{14}), 6.26 (d, J = 11.9 Hz, 1H, H_{10}), 6.19 (d, J = 16.1 Hz, 1H, H_8), 2.09 (s, 3H, C_9-CH_3), 2.04 (t, J = 6.1 Hz, 2H, $2H_4$), 1.73 (s, 3H, C_5-CH_3), 1.6–1.4 (m, 4H, $2H_2$ + $2H_3$), 1.04 (s, 6H, C_1-$2CH_3$); FTIR (NaCl) υ 2923 (s, C–H), 2855 (s, C–H), 1662 (s, C=O), 1550 (s), 1152 (s), 961 (m) cm^{-1}; UV (MeOH) λ_{max} 394 nm; MS *m/z* (%) 350 (M^+, 84), 348 (85), 269 (56), 199 (31), 173 (24), 169 (27), 159 (26), 157 (24), 149 (53), 145 (30), 143 (37), 141 (36), 133 (41), 131 (35), 129 (43), 123 (30), 121 (36), 119 (68), 115 (47), 109 (37), 107 (39), 105 (71), 95 (55), 91 (100), 83 (55); HRMS (M^+) calcd. for $C_{19}H_{25}{}^{81}BrO$ 350.1068, found 350.1080.

Ethyl (*Z*)-3-[(Trifluoromethanesulphonyl)oxy]-3-trifluoromethylprop-2-enoate (*Z*-10). Ethyl trifluoroacetoacetate (**15**) (1.0 g, 5.44 mmol) was added to a solution of di-*tert*-butylmethylpyridine (1.78 g, 8.70 mmol) in CH_2Cl_2 (50 mL), at 0 °C, and the mixture was stirred for 10 min. After the addition of Tf_2O (1.3 mL, 7.62 mmol), the mixture was stirred at 0 °C for 20 min and at 40 °C for 30 min, cooled down to 25 °C, filtered and the solvent evaporated. The residue was purified by chromatography (SiO_2, 100% hexane) to afford 1.38 g (81%) of a brown oil identified as *Z*-**10**. ^1H NMR (300 MHz, $CDCl_3$) δ 6.53 (s, 1H, H_2), 4.34 (q, J = 7.1 Hz, 2H, O$\underline{CH_2}CH_3$), 1.35 (t, J = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0 (s, C_1), 141.7 (s), 120.8 (s), 118.4 (sq, $^1J_{CF}$ = 276.8 Hz), 118.2 (d, C_2), 63.1 (t, O$\underline{CH_2}CH_3$), 14.2 (q, $OCH_2\underline{CH_3}$); UV (MeOH) λ_{max} 270 (sh), 282, 292 nm; MS *m/z* (%) 316 (M^+, 100), 207 (14), 191 (29), 149 (19), 97 (19), 91 (15), 85 (16), 83 (21), 71 (28), 70 (17), 69 (25).

Ethyl (2*E*,4*E*,6*E*)-8-Hydroxy-7-methyl-3-trifluoromethylocta-2,4,6-trienoate (16). A solution of triflate *Z*-**10** (0.62 g, 1.96 mmol) in DME (5 mL) was added to a solution of boronic acid **8** (0.50 g, 3.53 mmol) and $Pd(PPh_3)_4$ (0.23 g, 0.19 mmol) in DME (20 mL). After stirring at 25 °C for 10 min, Na_2CO_3 (3.0 mL, 2 M in H_2O, 5.88 mmol) was added, and the resulting mixture was stirred at 80 °C for 1 h, diluted with Et_2O (15 mL) and washed with brine (3 x 10 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography (silica, 80:20 hexane/ethyl acetate) to afford 0.43 g (83%) of **16** as a yellow solid (m.p.: 58–60 °C, hexane/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 16.0 Hz, 1H, H_4), 7.03 (dd, J = 16.0, 11.0 Hz, 1H, H_5), 6.23 (d, J = 11.0 Hz, 1H, H_6), 6.17 (s, 1H, H_2), 4.22 (q, J = 7.1 Hz, 2H, O$\underline{CH_2}CH_3$), 4.13 (s, 2H, $2H_8$), 1.90 (br s, 1H, OH), 1.84 (s, 3H, C_7-CH_3), 1.30 (t, J = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4 (s, C_1), 145.1 (s), 141.4 (sq, $^2J_{CF}$ = 29.4 Hz, C_3), 134.7 (dq, $^3J_{CF}$ = 5.7 Hz, C_4), 125.0 (d), 124.4 (s), 121.7 (d), 119.1 (dq, $^3J_{CF}$ = 6.2 Hz, C_2), 68.2 (t), 61.4 (t), 15.0 (q), 14.5 (q); FTIR (NaCl) υ 3600–3200 (br, OH), 2987 (m, C–H), 2913 (m, C–H), 1714 (s, C=O), 1613 (s), 1311 (m), 1272 (m), 1203 (s), 1128 (s), 1024 (m), 877 (m) cm^{-1}; UV (MeOH) λ_{max} 320 nm; MS *m/z* (%) 264 (M^+, 64), 246 (9), 219 (20), 190 (25), 189 (100), 187 (27), 165 (24), 141 (44), 91 (29), 77 (17); HRMS (M^+) calcd. for $C_{12}H_{15}F_3O_3$ 264.0973, found 264.0974.

Ethyl (2*E*,4*E*,6*E*)-7-Formyl-3-trifluoromethylocta-2,4,6-trienoate (7). Following the general procedure for the oxidation of allylic alcohols with MnO_2 a solution of alcohol **16** (0.40 g, 1.53 mmol) in CH_2Cl_2 (40 mL) was treated with MnO_2 (2.39 g, 27.54 mmol) at 25 °C for 2 h, to afford, after chromatography (silica gel, 95:5 hexane/ethyl acetate) 0.39 g (98%) of **7** as a yellow solid (m.p.: 54–56 °C, hexane/AcOEt). ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H, CHO), 7.83 (d, J = 16.0 Hz, 1H, H_4), 7.15 (dd, J = 16.0, 11.2 Hz, 1H, H_5), 6.93 (d, J = 11.2 Hz, 1H, H_6), 6.39 (s, 1H, H_2), 4.25 (q, J = 7.1 Hz, 2H, O$\underline{CH_2}CH_3$), 1.91 (s, 3H, $3H_8$), 1.32 (t, J = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8 (d, CHO), 164.7 (s, C_1), 147.1 (d), 142.4 (s, C_7), 140.0 (sq, $^2J_{CF}$ = 29.6 Hz, C_3), 132.7 (d), 128.8 (d), 123.3 (dq, $^3J_{CF}$ = 6.0 Hz), 122.6 (sq, $^1J_{CF}$ = 276.6 Hz, CF_3), 61.9 (t), 14.5 (q), 10.5 (q); FTIR (NaCl) υ 3072 (m, C–H), 2984 (m, C–H), 2930 (m, C–H), 2830 (m, C–H),

1715 (s, C=O), 1677 (s, C=O), 1625 (m), 1383 (m), 1364 (m), 1316 (s), 1275 (s), 1205 (s), 1115 (s) cm^{-1}; UV (MeOH) λ_{max} 314 nm; MS *m/z* (%) 262 (M^+, 35), 243 (11), 233 (100), 217 (39), 216 (83), 215 (37), 214 (22), 213 (34), 189 (50), 188 (30), 159 (21), 141 (31), 91 (58); HRMS (M^+) calcd. for $C_{12}H_{13}F_3O_3$ 262.0817, found 262.0814.

Ethyl (13*E*)-20,20,20-Trifluororetinoate (17). In accordance with the general procedure for the Wittig reaction, treatment of phosphonium bromide (**5**) (0.57 g, 1.18 mmol) in THF (20 mL) with *n*-BuLi (0.50 mL, 2.36 M in THF, 1.18 mmol) and addition of trienal **7** (0.26 g, 0.99 mmol) in THF (4 mL) provided, after chromatography (SiO_2, 95:5 hexane/ethyl acetate) 0.28 g (75%) of **17** as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 15.8 Hz, 1H, H_{12}), 7.18 (ddd, *J* = 15.8, 11.6, 1.9 Hz, 1H, H_{11}), 6.34 (d, *J* = 16.0 Hz, 1H, H_7), 6.17 (d, *J* = 11.6 Hz, 1H, H_{10}), 6.16 (d, *J* = 16.0 Hz, 1H, H_8), 6.15 (s, 1H, H_{14}), 4.24 (q, *J* = 7.1 Hz, 2H, $O\underline{CH_2}CH_3$), 2.1–2.0 (m, 2H, $2H_4$), 2.01 (s, 3H, C_9-CH_3), 1.71 (s, 3H, C_5-CH_3), 1.7–1.4 (m, 4H, $2H_2$ + $2H_3$), 1.32 (t, *J* = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$), 1.03 (s, 6H, C_1-$2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6 (s, C=O), 142.9 (s), 141.6 (sq, $^2J_{CF}$ = 28.6 Hz, C_{13}), 138.0 (s), 137.6 (d), 135.7 (d), 131.0 (s), 130.7 (d), 130.4 (d), 123.1 (sq, $^1J_{CF}$ = 276.8 Hz, CF_3), 121.4 (d), 117.7 (dq, $^3J_{CF}$ = 6.3 Hz, C_{14}), 61.3 (t, $O\underline{CH_2}CH_3$), 39.9 (t), 34.7 (s, C_1), 33.6 (t), 29.4 (q, 2x, C_1-$2CH_3$), 22.2 (q), 19.6 (t), 14.6 (q), 13.5 (q); FTIR (NaCl) υ 2929 (m, C–H), 2865 (m, C–H), 1718 (m, C=O), 1579 (m), 1275 (m), 1186 (s), 1135 (s) cm^{-1}; UV (MeOH) λ_{max} 372 nm; MS *m/z* (%) 382 (M^+, 95), 367 (11), 262 (100), 201 (23), 183 (68), 173 (23), 159 (23), 145 (42), 133 (33), 131 (29), 119 (41), 108 (24), 107 (27), 105 (46), 91 (52); HRMS (M^+) calcd. for $C_{22}H_{29}F_3O_2$ 382.2119, found 382.2108.

(13*E*)-20,20,20-Trifluororetinol (18). To a cooled (0 °C) solution of ester **17** (0.28 g, 0.85 mmol) in THF (4 mL) was slowly added DIBAL-H (1.80 mL, 1 M in hexane, 1.80 mmol). After stirring at 25 °C for 2 h, MeOH (2 mL) was added, followed by 5% aqueous HCl (2 mL), and stirring was continued for an additional 30 min. The layers were separated and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (6 x 15 mL) and brine (4 x 15 mL), dried (Na_2SO_4), filtered and concentrated. Purification of the residue by chromatography (silica, 83:15:2 hexane/AcOEt/Et_3N) yielded 0.23 g (94%) of alcohol **18** as a yellow oil. ^1H-NMR (400 MHz, $CDCl_3$) δ 6.60 (dd, *J* = 15.4, 11.3 Hz, 1H, H_{11}), 6.30 (d, *J* = 15.4 Hz, 1H, H_{12}), 6.2–6.0 (m, 4H, H_7 + H_8 + H_{10} + H_{14}), 3.80 (d, *J* = 6.8 Hz, 2H, $2H_{15}$), 1.94 (s, 3H, C_9-CH_3), 1.71 (s, 3H, C_5-CH_3), 1.6–1.4 (m, 4H, $2H_2$ + $2H_3$), 1.02 (s, 6H, C_1-$2CH_3$); FTIR (NaCl) υ 3600–3200 (br, OH), 2929 (s, C–H), 2865 (s, C–H) cm^{-1}; UV (MeOH) λ_{max} 316 nm; MS *m/z* (%) 340 (M^+, 5), 298 (45), 278 (49), 277 (100), 201 (17), 199 (16), 165 (17), 159 (16), 133 (19), 123 (18), 121 (28), 119 (35), 109 (34), 91 (44); HRMS (M^+) calcd. for $C_{20}H_{27}F_3O$ 340.2014, found 340.2015.

(13*E*)-20,20,20-Trifluororetinal (4). Following the general procedure described above, the reaction of alcohol **18** (0.20 g, 0.70 mmol) and activated MnO_2 (1.10 g, 12.60 mmol) in CH_2Cl_2 (15 mL) afforded 0.19 g (98%) of (13*E*)-20,20,20-trifluororetinal **4**[16] as a yellow oil. An analytical sample for characterization was obtained by HPLC purification (Spherisorb W 5 μm/25 x 1 cm, 95:5 hexane/AcOEt, t_R= 10.9 min). ^1H NMR (400 MHz, $CDCl_3$) δ 10.16 (d, *J* = 6.8 Hz, 1H, H_{15}), 7.23 (dd, *J* = 15.3, 11.4 Hz, 1H, H_{11}), 6.92 (d, *J* = 15.3 Hz, 1H, H_{12}), 6.42 (d, *J* = 16.0 Hz, 1H, H_7), 6.29 (d, *J* = 6.8 Hz, 1H, H_{14}), 6.22 (d, *J* = 11.4 Hz, 1H, H_{10}), 6.19 (d, *J* = 16.0 Hz, 1H, H_8), 2.04 (s, 3H, C_9-CH_3), 2.0–1.9 (m, 2H, $2H_4$), 1.61 (s, 3H, C_5-CH_3), 1.6–1.4 (m, 4H, $2H_2$ + $2H_3$), 1.04 (s, 6H, C_1-$2CH_3$).

Acknowledgements. We thank MEC (SAF98-0143, which also supported Dr. Iglesias) and *Xunta de Galicia* (XUGA30106B97) for financial support, and CACTI (Universidade de Vigo) for providing NMR and MS spectra.

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