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12-Substituted-13,14-dihydroretinols designed for affinity labeling of retinol binding- and processing proteins

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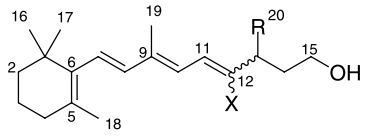
Abstract—All-*trans*- and 11-*cis*-retinol derivatives substituted with various electron-withdrawing groups at C_{12} were designed to be affinity labels for retinol binding and processing proteins. Unlike other non-selective highly reactive affinity labels, these compounds carry a Michael acceptor type substitution at C_{12} of the polyene chain. Therefore, they are expected to be highly selective towards such proteins that have a nucleophilic residue near the C_{11} position of their retinol ligand. The synthetic route for these compounds is based on the Emmons–Horner reaction of a C15 aldehyde with an appropriate phosphonate bearing the desired electron-withdrawing group to be incorporated at the C_{12} position of the retinol skeleton.

1. Introduction

Retinoids and their metabolites are essential for many physiological processes such as vision, gene transcription, cell proliferation and differentiation, hormone level regulation, immune function and morphogenesis.[1] The regulation of these processes is mediated via retinoid-binding proteins (RBP). RBP range from a variety of retinoid-processing and metabolizing enzymes via retinoid receptors, to different transport proteins designed to protect and transfer these sensitive and lipophilic compounds to their cell target, as well as mediators of retinoid action.[2] RBP can be found as soluble proteins both intra- and extracellularly, while others are present as integral membrane-bound minor constituents. The multiplicity of retinoid isomers and chemical forms (alcohols, aldehydes, acids and esters) requires different protein structures and binding sites, in order to bind the appropriate ligand with high selectivity and affinity.

Affinity labeling has been used as a tool in the study of these proteins' structure and function and for their isolation and purification. Most of the affinity labels of various RBPs were synthetic retinoids bearing highly reactive functional groups such as azide,[3] diazirene,[3a,4] allyl bromide,[5] haloketone and ester[6] or diazoketone and ester.[3a,4a,b,7] As such, they lack the specificity within the large family of RBPs, a major disadvantage when attempting to tag a specific minor constituent protein.[6a]

In a previous study, we synthesized a set of 13-substituted-13,14-dihydroretinols as potential affinity labels of retinol-binding proteins.[8] Most of these compounds were found to be not stable enough for biological studies. Thus, the present paper describes the design and synthesis of a family of stable 12-substituted all-*trans*- and 11-*cis*-retinol derivatives (Fig. 1) that would act as mild, highly specific affinity labels for retinol-binding proteins containing a nucleophilic residue in the binding pocket of the protein. One specific target in mind was the enzyme *trans* retinyl ester isomerohydrolase, which has been postulated to carry out its catalytic activity via a nucleophilic attack at the substrate C_{11} position.[1a,9]



	X	R
1	CN	H
2	CN	CH_3
3	CHO	H
4	CHO	CH_3
5	CO_2Et	H
6	CO_2Et	CH_3

Figure 1.

Keywords: Retinol analogs; Retinol binding proteins; *trans* Retinyl ester isomerohydrolase; Affinity labeling; Michael acceptors.
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2. Results and discussion

2.1. Design of the C_{12}-substituted retinol analogs

Substitution of an electron-withdrawing group at C_{12} of the retinol polyene skeleton can efficiently render the C_{11} position an electrophilic core of the molecule, yielding an electrophilic retinoid of a Michael acceptor type (Fig. 2).

The C_{13}–C_{14} bond in the synthetic retinol analogs is saturated, in contrast to the native ligand. This prevents cross-conjugation to the 12-substituted electron-withdrawing group, thus, increasing its electrophilicity. In addition, in the context of the *trans* retinyl ester isomerohydrolase, the saturated C_{13}–C_{14} bond prevents the natural isomerization from taking place, ensuring that the C_{12}-substituted compounds are not substrates for the enzyme.

Both 13-de-methyl and 13-methyl analogs were prepared, since this substitution may affect the isomeric distribution of the new synthetic 12-substituted retinol analogs. The 13-de-methyl analogs are expected to exhibit higher stability of their 11-*cis* isomer, relative to the corresponding 13-methyl counterparts (see below). This is especially relevant taking into account the fact that the 11-*cis* isomer of retinoids is of high biological importance. Thus, both the all-*trans* and the 11-*cis* isomers of the various new compounds were synthesized.

Since many 13-demethyl retinoids are biologically active[10] or bind their biological target,[11] the omission of this methyl in some of the new affinity label compounds should not prohibit their activity.

2.2. Synthesis

A convergent strategy for the synthesis of the 12-substituted retinol analogs **1**–**6** was employed, based on the assembly of two fragments, the all-*trans* isomer of the C15 aldehyde **15** and an appropriate four-carbon chain phosphonate, via the Emmons–Horner condensation (Fig. 3). The phosphonates contain the precursors of the electron-withdrawing group functionalities.

2.2.1. Preparation of the phosphonate units. Four different phosphonates were prepared for the synthesis of the six 12-substituted retinol analogs by a common synthetic strategy, i.e. condensation of an *O*-protected halo alcohol with an appropriate phosphonate bearing the desired substituent (Scheme 1).

Thus, 3-bromopropanol protected either with *tert*-butyldimethylsilyl or with tetrahydropyran was condensed with the sodium salt of diethyl cyanomethylphosphonate (producing

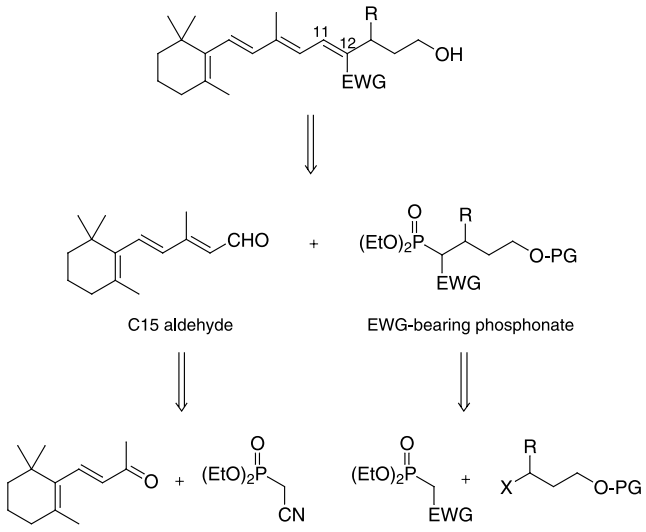


Figure 3.

cyano phosphonate **7**) or triethyl phosphonoacetate (yielding ester phosphonate **11**), respectively.

The corresponding methylated analogs **10** and **14** were prepared from 1,3-butanediol by protection of the primary alcohol (yielding also some secondary alcohol protection), substitution of the free secondary hydroxyl with iodide (**9** and **13**)[12] and condensation with the appropriate phosphonates. The condensation on the secondary alkyl iodides was more difficult and required drastic conditions: 55–60 °C for 5 days in the presence of HMPA in dry THF.

Phosphonates **10** and **14** have a few chiral centers, only one of which will remain in the corresponding final products. They were both synthesized as a mixture of diastereomers. These compounds are quite rigid, in respect to their C_3–C_4 bond. Their relative configurations and conformations were determined by the $^3J_{H,H}$ and $^3J_{P,C}$ coupling constants in the ^1H and ^{13}C NMR spectra. While the ester phosphonate **14** was present in solution as a mixture of both the *anti* and the *gauche* conformations (in both diastereomers), both diastereomers of the cyano phosphonate **10** were present mainly in the *gauche* conformation, without any significant contribution from the *anti* conformation (Fig. 4). This is probably due to the very small size of the cyano substituent.

2.2.2. Condensation. The synthesis of the 12-substituted retinol analogs from C15 aldehyde **15**[13] and the appropriate phosphonates is described in Scheme 2. All the condensation reactions between aldehyde **15** and the different phosphonates, as well as all subsequent reactions were carried out under dim red light, in order to avoid undesired isomerizations along the polyene skeleton.

The Emmons–Horner condensation between all-*trans*

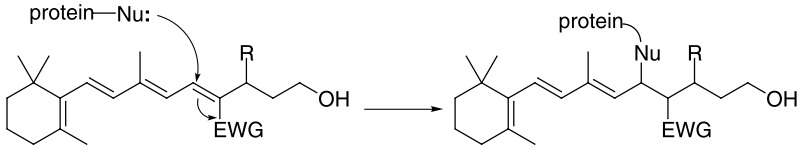
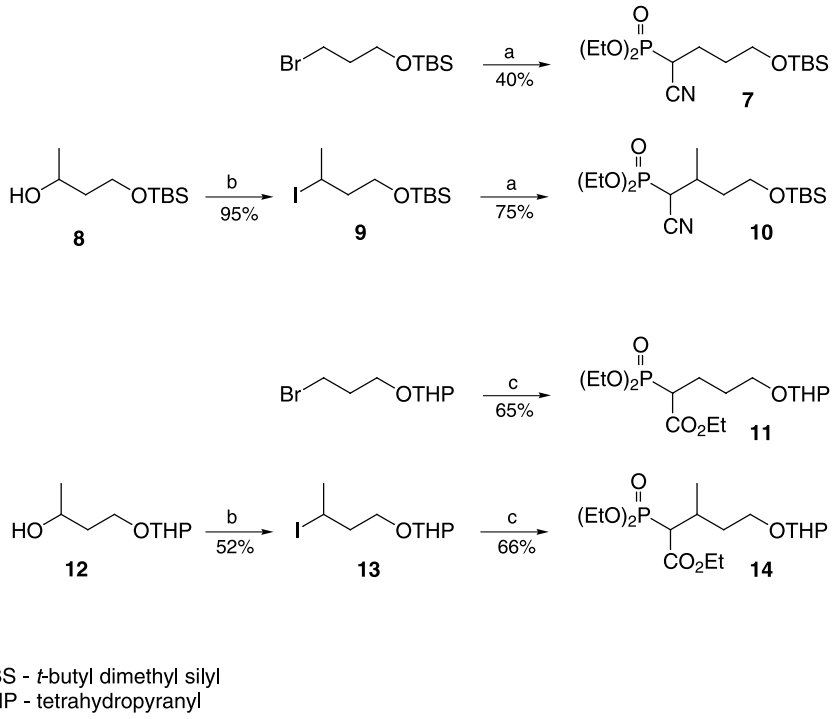


Figure 2.



Scheme 1. Reagents and conditions: (a) $(EtO)_2P(O)CH_2CN$, NaH, dry THF/HMPA. (b) I_2, PPh_3, imidazole, CH_2Cl_2. (c) $(EtO)_2P(O)CH_2CO_2Et$, NaH, dry THF/HMPA.

aldehyde **15** and either phosphonate **7** or **11** readily produced a mixture of two isomers about the newly formed C_{11}–C_{12} double bond of **16** and **20**: 11-*Z* (will be referred to as 'all-*trans*' in respect to the full length retinol skeleton) and 11-*E* (11-*cis* in the retinol terminology) (Scheme 2). Minor amounts of the 9-*cis* isomer of **20** were also isolated. Deprotection and separation of the isomers afforded the all-*trans* and the 11-*cis* isomers of retinol analogs **1** and **5**, respectively.

The isolation and purification of some of the all-*trans*-retinol analogs was problematic due to unconstrained isomerization about the C_{11}–C_{12} double bond. We therefore decided to re-introduce the Me-20 group to the retinol analogs. This should decrease the rate of isomerization, owing to steric hindrance between H-10 and the Me-20 group in the 11-*cis* isomer.[14] Furthermore, re-introduction of the methyl group to C_{13} makes these 12-substituted retinol analogs better mimics of the native substrate of the enzyme.

Thus, the 13-methyl substituted analogs were synthesized similarly, starting with phosphonates **10** and **14**, which carry both the nitrile and ester functionalities, respectively, and the future Me-20 groups. The condensation reaction of the

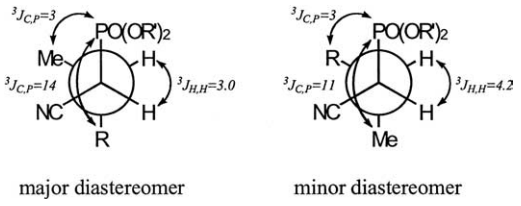
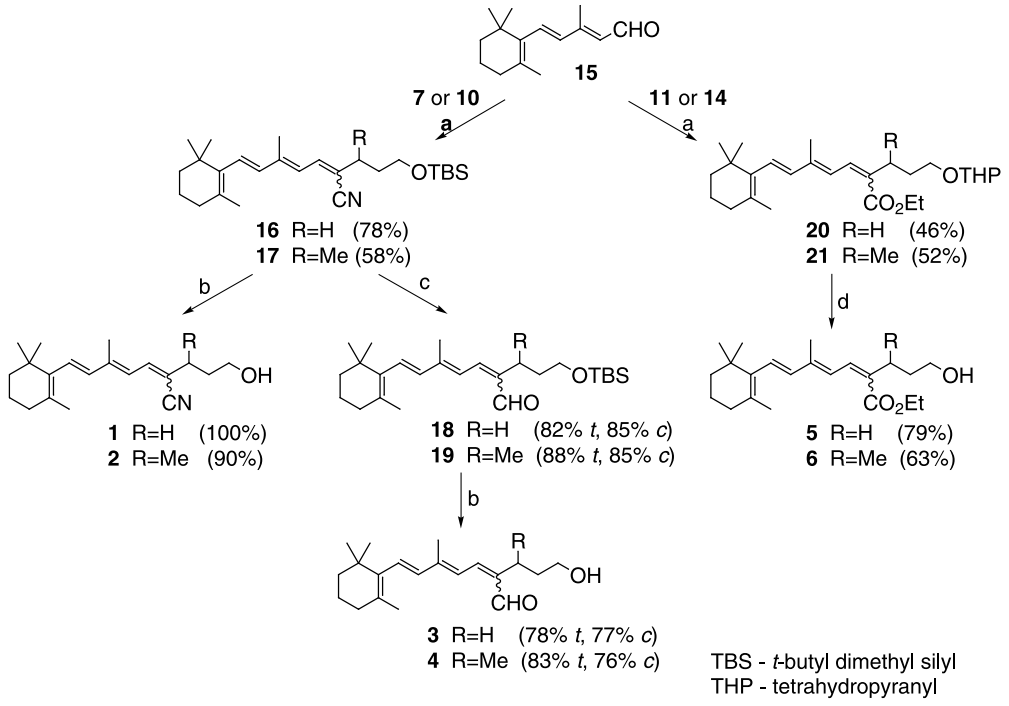


Figure 4.

phosphonates with aldehyde **15** produced mainly the all-*trans* isomer of **17** and **21**, with only minor amounts of the 11-*cis* isomer. Thus, the introduction of Me-20 indeed fulfilled the expectation of stabilizing the all-*trans* isomer due to increased steric repulsion in the 11-*cis* isomer. The all-*trans* and 11-*cis* isomers of the final products, 12-cyano-13,14-dihydroretinol **2** and 12-carbethoxy-13,14-dihydroretinol **6**, were readily obtained by mild deprotection of **17** and **21**, respectively.

During the synthesis of **21**, the basic conditions of the Emmons–Horner reaction promoted some dimerization of aldehyde **15** by the Robinson annulation reaction.[15]

Cyano intermediates **16** and **17** were also used for the synthesis of the 12-formyl retinol analogs **3** and **4**, respectively. In order to produce separately each isomer, the subsequent reduction of the nitrile group and deprotection were carried out separately for each isomer of **16** and **17**. DIBAL-H reduction followed by removal of the silyl protecting group successfully furnished the desired products 12-formyl-13-demethyl-13,14-dihydroretinol **3** and 12-formyl-13,14-dihydroretinol **4**. The above procedure preserved the isomeric integrity of the starting materials 11-*cis* **16**, 11-*cis* **17** and all-*trans* **17**. However, similar treatment of all-*trans* **16** yielded a mixture of all-*trans* and 11-*cis* *O*-protected-12-formyl retinol **18**, even when all reactions and workups were carried out in the dark at 4 °C. Deprotection of all-*trans* **18** again produced a mixture of all-*trans* and 11-*cis* **3**, along with some 9-*cis* product. The best results (a 1:1 mixture of all-*trans*: 11-*cis*) were obtained when the aldehyde reduction product was subjected to deprotection immediately, without any purification step. These results demonstrate once again the stabilizing effect



Scheme 2. Reagents and conditions: (a) NaH, dry THF. (b) $Bu_4N^+F^-$, dry THF. (c) (i) DIBAL-H, hexane, −78 °C. (ii) SiO_2/H_2O, ether. (d) PPTS, EtOH, 55 °C.

of the 13-methyl substitution on the all-*trans* isomer of the retinol analogs.

The chemical stability of aldehyde derivatives **3** and **4**, both in terms of isomerization and degradation, was poor. Only when kept dry at −20 °C, was the 11-*cis* isomer stable against isomerization for several months. The all-*trans*-isomer was much more labile. Nitriles **1** and **2** and esters **5** and **6** were quite stable under argon atmosphere at 20 °C.

3. Conclusions

In this paper we present the design and synthesis of a family of retinol analogs substituted at C_{12} with electron withdrawing groups as potential selective affinity labels for retinol binding- and processing proteins. Both 11-*cis* and all-*trans* isomers of aldehyde, cyano and ester substituted retinol analogs and 13-demethyl retinol analogs were prepared via an efficient convergent procedure, based on Emmons–Horner condensation reaction between C15 aldehyde and an appropriate phosphonate unit bearing the desired C_{12} functional group. These compounds are now being tested as inhibitors of the enzyme *trans* retinyl ester isomerohydrolase.

4. Experimental

4.1. General

All operations involving synthesis and manipulation of full-length retinoids were performed under dim red light. ^1H and ^{13}C NMR spectra were recorded at 300 or 600, and 75 or 150 MHz, respectively, in $CDCl_3$ (TMS as an internal standard), unless otherwise indicated. ^{31}P NMR spectra were recorded at 81 MHz in $CDCl_3$ (85% H_3PO_4 as an external reference). ^1H NMR assignments were supported by COSY and NOESY experiments, while ^{13}C NMR assignments were supported by distortionless enhancement by polarization transfer (DEPT), heteronuclear multiple quantum correlation (HMQC) and heteronuclear multiple bond connectivity (HMBC) experiments. *J* values are given in Hz. The NMR signals are assigned according to the atom numbering of the retinoid skeleton (Fig. 1). All-*trans*, 11-*cis* or 9-*cis* configurations refer to the configuration of the retinol skeleton. UV spectra were recorded on a diode array spectrophotometer in dichloromethane. Mass spectra were recorded in DCI mode with methane, unless otherwise stated. TLC was performed on E. Merck 0.2 mm precoated silica gel F-254 plates, and viewed by UV light and vanillin.[16] Chromatography refers to flash column chromatography,[17] carried out on silica gel 60 (230–400 mesh ASTM, E. Merck). Anhydrous solvents were dried and freshly distilled: THF and diethyl ether (referred to as ether) from sodium/benzophenone, CH_2Cl_2 from $CaCl_2$ and DMF from 4 Å molecular sieves.

4.2. Synthesis

1-*tert*-Butyldimethylsilanyloxy-3-butanol **8**[18] and C15 aldehyde **15**[13b] were prepared as previously described.

4.2.1. Diethyl 4-*tert*-butyldimethylsilanyloxy-1-cyanobutyl phosphonate (7). *General procedure A*. Diethyl cyanomethylphosphonate (7.7 g, 0.04 mol), was added dropwise to a suspension of NaH (80% in mineral oil, 1.42 g) and NaI (0.5 g) in dry THF (120 mL) and HMPA (20 mL) under Ar atmosphere. After full consumption of NaH, 1-(*tert*-butyldimethylsilanyloxy)-3-bromopropane

(5.0 g, 0.022 mol) was added and the reaction mixture was stirred at rt for 3 days. The solvent was evaporated and the residue was dissolved in ether and washed twice with water. The organic phase was dried ($MgSO_4$), filtered and evaporated. Chromatography ($CHCl_3$: ether, 1:3) afforded the product as colorless oil (40% yield). ^{1}H NMR δ 4.23 (m, J=7.2 Hz, 4H, CH_2OP), 3.70 (ddd, J=10.5, 5.5, 5.1 Hz, 1H, H-4), 3.64 (ddd, J=10.5, 6.5, 5.0 Hz, 1H, H-4), 3.04 (ddd, J=23.4, 10.5, 4.8 Hz, 1H, H-1), 2.12–1.79 and 1.73–1.64 (m, 4H, H-2, H-3), 1.38 (m, 6H, Me), 0.89 (s, 9H, *t*-Bu), 0.05 (s, 6H, $SiMe_2$). ^{13}C NMR δ 116.2 (d, J=9.1 Hz, CN), 63.8 (d, J=7.0 Hz, COP), 63.5 (d, J=6.9 Hz, COP), 61.7 (C-4), 30.3 (d, J=11.9 Hz, C-3), 29.7 (d, J=143.8 Hz, C-1), 25.7 (*t*-Bu), 24.0 (d, J=4.2 Hz, C-2), 18.1 (C-*t*-Bu), 16.2 (d, J=5.6 Hz, 2×Me), −5.6 (C–Si). ^{31}P NMR δ 18.8. HRMS *m/z* calcd for $C_{16}H_{35}NO_4SiP$ (MH^+) 364.2073, found 364.2053.

4.2.2. *tert*-Butyl-3-iodobutoxy dimethylsilane (9). *General procedure B*. **8** (3.0 g, 0.015 mol) in dry CH_2Cl_2 (16 mL) was added to a solution of triphenylphosphine (5.9 g, 0.022 mol), imidazole (1.6 g, 0.023 mol) and iodine (5.7 g, 0.022 mol) in dry CH_2Cl_2 (60 mL). After 3 h at rt, the solvent was evaporated. The residue was triturated with *n*-hexane and the organic phase was washed with sat. $Na_2S_2O_3$, dried ($MgSO_4$), filtered and evaporated to give **9** as colorless oil (95% yield). ^{1}H NMR δ 4.35 (dqd, J=9.6, 6.9, 4.5 Hz, 1H, H-3), 3.76 (ddd, J=10.5, 5.7, 4.5 Hz, 1H, H-1), 3.65 (ddd, J=10.2, 8.1, 4.8 Hz, 1H, H-1), 1.99 (ddt, J=14.7, 9.6, 4.8 Hz, 1H, H-2), 1.97 (d, J=6.9 Hz, 3H, Me-4), 1.79 (dddd, J=18.6, 8.1, 5.4, 4.5 Hz, 1H, H-2), 0.91 (s, 9H, *t*-Bu), 0.08 and 0.07 (s, 3H, SiMe). ^{13}C NMR δ 68.2 (C-3), 62.7 (C-1), 39.9 (C-2), 25.8 (*t*-Bu), 23.3 (C-4), 18.1 (C-*t*-Bu), −5.6 (C–Si). MS (CI/ isobutane) *m/z* 315 (MH^+), 257 ($MH^+ - t$-Bu).

4.2.3. Diethyl 4-*tert*-Butyldimethylsilanyloxy-1-cyano-2-methylbutyl phosphonate (10). Compound **10** was prepared according to general procedure A with diethyl cyanomethylphosphonate (5.7 g, 0.032 mol), NaH (60% in mineral oil, 1.2 g) and **9** (5.4 g, 0.017 mol) in dry THF (160 mL) and HMPA (24 mL) at 55 °C for 5 days. Chromatography (hexane/ether 1:1) afforded the product as a 2:1 diastereomeric mixture of colorless oil (75% yield, 20% recovery of SM). ^{1}H NMR δ 4.23 (m, 4H, CH_2OP), 3.70 (m, 2H, CH_2-4), 3.39 (dd, J=25.2, 3.0 Hz, 1H, H-1), 2.98 (dd, J=24.6, 4.2 Hz, 1H, H-1), 2.39 and 2.10 (bm, 1H, H-2), 1.62 (m, 2H, CH_2-3), 1.38 (m, 6H, CH_3CH_2O), 1.22 (d, J=6.9 Hz, 3H, 2-Me), 1.18 (dd, J=6.9, 0.9 Hz, 3H, 2-Me), 0.89 (s, 9H, *t*-Bu), 0.05 (s, 6H, $SiMe_2$). ^{13}C NMR δ 115.0 (d, J=9.0 Hz, CN), 63.8, 63.7, 63.42 and 63.37 (d, J=6.7 Hz, COP), 60.7 and 60.1 (C-4), 38.4 (d, J=13.5 Hz, C-3), 36.9 (d, J=143.2 Hz, C-1), 35.9 (d, J=3.3 Hz, C-3), 35.2 (d, J=143.2 Hz, C-1), 29.6 and 29.2 (d, J=3.3 Hz, C-2), 25.8 (*t*-Bu), 18.7 (d, J=11.2 Hz, 2-Me), 18.1 (C-*t*-Bu), 17.2 (2-Me), 16.3 (d, J=5.9 Hz, CH_3CH_2O), −5.4, −5.5, −5.6 (C–Si). ^{31}P NMR δ 18.8 and 18.2. HRMS *m/z* calcd for $C_{16}H_{35}NO_4PSi$ (MH^+) 364.2073, found 364.2053.

4.2.4. Ethyl 2-diethoxyphosphoryl-5-(tetrahydropyran-2-yloxy)-pentanoate (11). The product was obtained according to general procedure A with triethyl phosphonoacetate (1.0 g, 4.5 mmol), NaH (80% in mineral oil, 0.17 g) and 2-(3-bromopropoxy)-tetrahydropyran (0.5 g, 2.2 mmol) in dry THF (8 mL) at rt for 2 days. Chromatography (*n*-hexane/ether 1:1) afforded the product (a diastereomeric mixture) as colorless oil (65% yield). ^{1}H NMR δ 4.57 (t, J=3.3 Hz, 1H, H-2′), 4.18 (m, 6H, CH_2OCO and CH_2OP), 3.84 (ddd, J=11.4, 7.8, 3.6 Hz, 1H, H-6′), 3.74 (m, 1H, H-5), 3.48 (m, 1H, H-6′), 3.38 (m, 1H, H-5), 3.00 (ddd, J=22.5, 10.5, 4.5 Hz, 1H, H-2), 2.1–1.5 (m, 10H, H-3, H-4, H-3′, H-4′, H-5′), 1.34 and 1.33 (t, J=7.2 Hz, 3H, phosphonate-Me), 1.29 (t, J=7.2 Hz, 3H, ester-Me). ^{13}C NMR δ 169.0 (d, J=4.5 Hz, C-1), 98.6 and 98.5 (C-2′), 66.5 and 66.4 (C-6′), 62.5 (d, J=6.6 Hz, COP), 62.4 (d, J=6.8 Hz, COP), 62.0 (C-5), 61.2 (CH_2OCO), 45.33 and 45.30 (d, J=131.3 Hz, C-2), 30.5 (C-3′), 28.2 (d, J=14.5 Hz, C-4), 28.1 (d, J=14.8 Hz, C-4), 25.3 (C-5′), 23.89 and 23.86 (d, J=4.8 Hz, C-3), 19.3 (C-4′), 16.2 (d, J=5.4 Hz, phosphonate-Me), 14.0 (ester-Me). ^{31}P NMR δ 23.3. HRMS *m/z* calcd for $C_{11}H_{24}O_6P$ (MH^+-THP) 283.1311, found 283.1317, calcd for $C_{11}H_{22}O_5P$ (MH^+ − THP-H_2O) 265.1146, found 265.1148.

4.2.5. 1-(Tetrahydropyran-2-yloxy)-3-butanol (12).[19] 1,3-Dihydroxybutane (1.0 g, 11 mmol), 3,4-dihydro-2*H*-pyran (1.0 g, 12 mmol) and catalytic amount of PPTS (0.28 g, 1.1 mmol) were stirred in dry CH_2Cl_2 (25 mL) at rt for 4 h. Evaporation and chromatography (*n*-hexane/ether 1:1 and then 3:1) afforded the product **12** (about 1:1 diastereomeric mixture) as colorless oil (45% yield), along with some 3-protected (5%) byproduct. ^{1}H NMR δ 4.50 and 4.49 (t, J=4.5 Hz, 1H, H-2′), 3.87, 3.78 and 3.55–3.39 (m, 5H, H-1, H-3, H-6′), 3.16 (s, 1H, OH), 1.63 and 1.44 (m, 8H, H-2, H-3′, H-4′, H-5′), 1.11 (d, J=6.3 Hz, 3H, Me-4). ^{13}C NMR δ 98.8 and 98.6 (C-2′), 66.8 and 66.2 (C-3), 65.7 and 65.6 (C-1), 62.4 and 61.9 (C-6′), 38.1 and 38.0 (C-2), 30.5 and 30.3 (C-3′;), 25.1 (C-5′), 23.12 and 23.07 (C-4), 19.4 and 19.2 (C-4′). HRMS *m/z* calcd for $C_9H_{17}O_3$ ($(M-H)^+$) 173.1178, found 173.1183.

4.2.6. 2-(3-Iodobutoxy)-tetrahydropyran (13). Compound **13** was prepared according to general procedure B with triphenylphosphine (5.24 g, 0.02 mol), imidazole (1.36 g, 0.02 mol), iodine (5.1 g, 0.02 mol) in dry CH_2Cl_2 (27 mL) and **12** (2.9 g, 0.017 mol, contaminated with about 10% of the 3-protected isomer) in dry CH_2Cl_2 (13 mL). The product, a 1:1 diastereomeric mixture contaminated by 17% of a 1:1 diastereomeric mixture of *O*-THP-1-iodo-3-butanol, was obtained as colorless oil (52% overall yield). ^{1}H NMR δ 4.61 (t, J=3.0 Hz, 1H, H-2), 4.59 (dd, J=4.2, 2.7 Hz, 1H, H-2), 4.37 (dqd, J=9.3, 6.9, 4.5 Hz, 1H, H-3′), 4.35 (dqd, J=10.8, 6.9, 4.5 Hz, 1H, H-3′), 3.90 (m, 2H, H-6, H-1′), 3.85 (ddd, J=12, 7, 3 Hz, 1H, H-6), 3.81 (ddd, J=9.9, 7.8, 5.4 Hz, 1H, H-1′), 3.52 (m, 3H, 2×H-6, H-1′), 3.45 (ddd, J=9.9, 8.1, 4.8 Hz, 1H, H-1′), 2.08 (m, 1H, H-2′), 1.97 (d, J=6.9 Hz, 3H, Me-4′), 1.91 (m, 1H, H-2′), 1.81 (m, 1H, H-4), 1.71 (m, 1H, H-3), 1.60–1.50 (m, 4H, H-3, H-4, 2×H-5,). ^{13}C NMR δ 99.4 and 98.4 (C-2), 67.1 and 66.8 (C-1′), 62.5 and 62.0 (C-6), 42.6 (C-2′), 30.6 and 30.5 (C-3), 29.0 and 29.0 (C-4′), 26.6 and 26.2 (C-3′), 25.38 and 25.36 (C-5), 19.4 and 19.2 (C-4). MS (CI/NH_3) *m/z* 285 (MH^+), 155 (M − HI). HRMS *m/z* calcd for $C_9H_{16}O_2I$ (M − H) 283.0195, found 283.0196.

4.2.7. Ethyl 2-diethoxyphosphoryl-3-methyl-5-(tetrahydropyran-2-yloxy)-pentanoate (14). Compound **14**

was obtained according to general procedure A with triethyl phosphonoacetate (4.9 g, 0.022 mol), NaH (80% in mineral oil, 0.81 g) and **13** (2.5 g, 8.8 mmol, with 17% impurity of the 3-protected isomer) in dry THF (40 mL) and HMPA (10 mL) at 70 °C for 5 days. Chromatography (ether) afforded the product as a diastereomeric mixture (colorless oil, 66% yield). ^{1}H NMR δ 4.59 (dd, J=4.5, 2.7 Hz, 1H, H-2′), 4.57 (dd, J=4.1, 2.9 Hz, 1H, H-2′), 4.20 (q, J=7.1 Hz, 2H, CH_2OCO), 4.16 (m, 4H, CH_2OP), 3.88 (m, 1H, H-6′), 3.80 (m, 1H, H-5), 3.52 (m, 1H, H-6′), 3.42 (m, 1H, H-5), 2.98 (dd, J=21.3, 7.1 Hz, 1H, H-2), 2.96 (dd, J=21.2, 7.2 Hz, 1H, H-2), 2.85 (dd, J=28.2, 5.3 Hz, 1H, H-2), 2.50 and 2.42 (m, 1H, H-3), 2.01 (m, 2H, H-4), 1.83 (m, H-4′), 1.70 (m, H-3′), 1.6–1.5 (m, H-4, H-3′, H-4′, H-5′), 1.33 (m, 3H, phosphonate-Me), 1.30 (t, J=7.1 Hz, 3H, ester-Me), 1.20 and 1.10 (d, J=6.8 Hz, 3H, 3-Me). ^{13}C NMR δ 169.0, 168.8 and 166.7 (d, J=5.3 Hz, CO), 98.9, 98.8 and 98.6 (C-2′), 65.2 and 64.8 (C-5), 63.6 and 62.8 (d, J=7 Hz, COP), 62.4 and 62.1 (C-6′), 59.9 (CH_2OCO), 51.1 and 51.0 (d, J=134.5 Hz, C-2), 48.4 (d, J=128.0 Hz, C-2), 47.6 (d, J=131.6 Hz, C-2), 35.0 (d, J=11.6 Hz, C-4), 34.9 (d, J=11.3 Hz, C-4), 30.7 (C-3′), 28.7 (d, J=3.9 Hz, C-3), 25.5 (C-5′), 22.6 (d, J=6.6 Hz, 2-Me), 19.8 and 19.5 (C-4′), 16.4 (d, J=5.6 Hz, phosphonate-Me), 14.2 (ester-Me). ^{31}P NMR δ 23.3. HRMS *m/z* calcd for $C_{17}H_{34}O_7P$ (MH^+) 381.2042, found 381.1960.

4.2.8. *O*-TBS-12-cyano-13-demethyl-13,14-dihydroretinol (16). Compound **16** was prepared according to general procedure A with phosphonate **7** (0.42 g, 1.2 mmol), NaH (60% in mineral oil, 0.04 g) and aldehyde **15** (0.54 g, 2.5 mmol) in dry THF (35 mL) at rt for 18 h. Chromatography (*n*-hexane/ether 25:1) afforded the two separated clean isomers (all-*trans*: 11-*cis* 3:1) as yellow oils in 78% yield. All -*trans*. ^{1}H NMR δ 6.98 (d, J=12.0 Hz, 1H, H-11), 6.43 (d, J=12.0 Hz, 1H, H-10), 6.38 (d, J=16.2 Hz, 1H, H-7), 6.19 (d, J=16.2 Hz, 1H, H-8), 3.64 (t, J=6.0 Hz, 2H, CH_2-15), 2.39 (t, J=7.5 Hz, 2H, CH_2-13), 2.03 (t, J=6.0 Hz, 2H, CH_2-4), 1.97 (s, 3H, Me-19), 1.75 (m, 2H, CH_2-14), 1.72 (s, 3H, Me-18), 1.62 (m, 2H, CH_2-3), 1.46 (m, 2H, CH_2-2), 1.03 (s, 6H, Me-16, 17), 0.89 (s, 9H, *t*-Bu), 0.05 (s, 6H, $SiMe_2$). ^{13}C NMR δ 142.5 (C-9), 140.4 (C-11), 137.3, (C-6), 136.6 (C-8), 130.9 (C-7 and C-5), 125.5 (C-10), 118.5 (CN), 111.1 (C-12), 61.3 (C-15), 39.6 (C-2), 34.2 (C-1), 33.1 (C-4), 31.2 (C-13), 30.9 (C-14), 28.9 (C-16, C-17), 25.9 (*t*-Bu), 21.7 (C-18), 19.1 (C-3), 18.2 (C-*t*-Bu), 12.9 (C-19), −5.4 (C–Si). UV λ_{max} 334 nm. HRMS *m/z* calcd for $C_{26}H_{44}NOSi$ (MH^+) 414.3192, found 414.3202. 11-*cis*. ^{1}H NMR δ 7.13 (d, J=12.3 Hz, 1H, H-11), 6.41 (d, J=15.9 Hz, 1H, H-7), 6.26 (d, J=12.3 Hz, 1H, H-10), 6.14 (d, J=16.2 Hz, 1H, H-8), 3.63 (t, J=6.0 Hz, 2H, CH_2-15), 2.43 (t, J=7.5 Hz, 2H, CH_2-13), 2.03 (t, J=6.0 Hz, 2H, CH_2-4), 1.99 (d, J=0.9 Hz, 3H, Me-19), 1.77 (m, 2H, CH_2-14), 1.70 (d, J=0.9 Hz, 3H, Me-18), 1.60 (m, 2H, CH_2-3), 1.47 (m, 2H, CH_2-2), 1.02 (s, 6H, Me-16, 17), 0.89 (s, 9H, *t*-Bu), 0.04 (s, 6H, $SiMe_2$). ^{13}C NMR δ 143.6 (C-9), 139.6 (C-11), 137.4, (C-6), 136.6 (C-8), 131.4 (C-7), 130.9 (C-5), 122.9 (C-10), 121.5 (CN), 111.1 (C-12), 61.3 (C-15), 39.5 (C-2), 34.2 (C-1), 33.1 (C-4), 31.2 (C-14), 28.8 (C-16, C-17), 25.9 (*t*-Bu), 24.9 (C-13), 21.7 (C-18), 19.1 (C-3), 18.2 (C-*t*-Bu), 12.8 (C-19), −5.4 (C–Si). HRMS *m/z* calcd for $C_{26}H_{44}NOSi$ (MH^+) 414.3192, found 414.3203.

4.2.9. *O*-TBS-12-cyano-13,14-dihydroretinol (17). Compound **17** was prepared according to general procedure A with phosphonate **10** (0.88 g, 2.4 mmol), NaH (60% in mineral oil, 0.09 g) and aldehyde **15** (1.05 g, 4.8 mmol) at rt for 3 days. The isomeric mixture (all-*trans* and 11-*cis* in a 9:1 ratio, and some 9-*cis* which was formed upon standing) was purified by chromatography (hexane/ether 25:1), yielding yellow oil in 58% yield. All-*trans*. ^{1}H NMR δ 6.99 (d, J=11.7 Hz, 1H, H-11), 6.45 (d, J=11.7 Hz, 1H, H-10), 6.39 (d, J=16.2 Hz, 1H, H-7), 6.21 (d, J=16.2 Hz, 1H, H-8), 3.65 (dt, J=10.2, 5.4 Hz, 1H, H-15), 3.55 (ddd, J=10.2, 7.8, 5.4 Hz, 1H, H-15), 2.67 (sextet, J=6.9 Hz, 1H, H-13), 2.04 (t, J=6.0 Hz, 2H, CH_2-4), 1.98 (s, 3H, Me-19), 1.73 (d, J=0.9 Hz, 3H, Me-18), 1.66 (m, 4H, CH_2-14 and CH_2-3), 1.48 (m, 2H, CH_2-2), 1.19 (d, J=6.9 Hz, Me-20), 1.04 (s, 6H, Me-16, 17), 0.90 (s, 9H, *t*-Bu), 0.05 (s, 6H, $SiMe_2$). ^{13}C NMR δ 142.5 (C-9), 139.3 (C-11), 137.3 (C-6), 136.6 (C-8), 130.84 (C-5), 130.8 (C-7), 125.5 (C-10), 117.3 (CN), 116.9 (C-12), 60.2 (C-15), 39.6 (C-2), 38.2 (C-14), 35.6 (C-13), 34.2 (C-1), 33.1 (C-4), 28.9 (C-16, C-17), 25.9 (*t*-Bu), 21.7 (C-18), 20.0 (C-20), 19.1 (C-3), 18.2 (C-*t*-Bu), 12.9 (C-19), −5.4 (C–Si). UV λ_{max} 332 nm. HRMS *m/z* calcd for $C_{27}H_{46}NOSi$ (MH^+) 428.3349, found 428.3350. 11-*cis*. ^{1}H NMR δ 7.11 (d, J=12.0 Hz, 1H, H-11), 6.41 (d, J=15.6 Hz, 1H, H-7), 6.32 (d, J=12.3 Hz, 1H, H-10), 6.15 (d, J=15.9 Hz, 1H, H-8), 3.65 (dt, J=10.5, 5.4 Hz, 1H, H-15), 3.53 (m, 1H, H-15), 3.11 (dq, J=14.1, 6.9 Hz, 1H, H-13), 2.04 (t, J=6.0 Hz, 2H, CH_2-4), 1.99 (d, J=0.9 Hz, 3H, Me-19), 1.71 (s, 3H, Me-18), 1.68 (m, 2H, CH_2-14), 1.62 (m, 2H, CH_2-3), 1.48 (m, 2H, CH_2-2), 1.16 (d, J=6.9 Hz, Me-20), 1.03 (s, 6H, Me-16, 17), 0.88 (s, 9H, *t*-Bu), 0.04 (s, 6H, $SiMe_2$). ^{13}C NMR δ 143.6 (C-9), 138.9 (C-11), 137.4 (C-6), 138.7 (C-8), 131.2 (C-7), 129.1 (C-5), 122.9 (C-10), 120.1 (CN), 117.1 (C-12), 61.1 (C-15), 39.5 (C-2), 38.3 (C-14), 34.2 (C-1), 33.1 (C-4), 28.9 (C-16, C-17), 28.5 (C-13), 25.9 (*t*-Bu), 21.7 (C-18), 19.5 (C-20), 19.1 (C-3), 18.2 (C-*t*-Bu), 12.8 (C-19), −5.8 (C–Si). UV λ_{max} 334 nm. HRMS *m/z* calcd for $C_{27}H_{46}NOSi$ (MH^+) 428.3349, found 428.3320. 9-*cis*. ^{1}H NMR δ 7.06 (d, J=11.7 Hz, 1H, H-11), 6.55 (d, J=15.6 Hz, 1H, H-8), 6.35 (d, J=12 Hz, 1H, H-10), 3.62 (dt, J=10.2, 5.4 Hz, H-15), 3.57 (m, H-15), 2.67 (sextet, J=6.6 Hz, 1H, H-13), 2.04 (d, J=1.2 Hz, 3H, Me-19), 2.03 (t, J=6.0 Hz, 2H, CH_2-4), 1.73 (d, J=0.9 Hz, 3H, Me-18), 1.66 (m, 4H, CH_2-14, CH_2-3), 1.48 (m, 2H, CH_2-2), 1.17 (d, J=6.9 Hz, Me-20), 1.03 (s, 6H, Me-16, 17), 0.90 (s, 9H, *t*-Bu), 0.05 (s, 6H, $SiMe_2$).

4.2.10. All-*trans*-*O*-TBS-12-formyl-13-demethyl-13,14-dihydroretinol (18). *General procedure C*. All-*trans* **16** (0.29 g, 0.7 mmol) was dissolved in *n*-hexane (10 mL) under Ar atmosphere. The solution was cooled to −78 °C and DIBAL-H (1 M in hexane, 1.2 mL) was added. The reaction was stirred at −78 °C for 35 min. Wet silica gel and ether were added and the reaction mixture was stirred at 0 °C overnight. The mixture was filtered through Celite. The Celite was then washed with ethyl acetate. The organic phase was dried ($MgSO_4$), filtered and evaporated. The obtained isomeric mixture (11-*cis* and all-*trans* in 1:3.5 ratio) was separated by chromatography (*n*-hexane/ether/ethyl acetate 4:2:1) (yellow oils, 82% yield). ^{1}H NMR (acetone-d_6) δ 10.40 (s, 1H, CHO), 7.46 (d, J=12.6 Hz, 1H, H-11), 7.25 (d, J=12.9 Hz, 1H, H-10), 6.48 (d, J=16.2 Hz, 1H, H-7), 6.32 (d, J=16.2 Hz, 1H, H-8), 3.64 (t, J=6.3 Hz,

2H, CH_2-15), 2.35 (dd, J=8.1, 7.2 Hz, 2H, CH_2-13), 2.07 (d, J=1.2 Hz, 3H, Me-19), 2.03 (m, CH_2-4), 1.73 (d, J=0.6 Hz, 3H, Me-18), 1.64 (m, 4H, CH_2-14 and CH_2-3), 1.49 (m, 2H, CH_2-2), 1.06 (s, 6H, Me-16, 17), 0.92 (s, 9H, *t*-Bu), 0.07 (s, 6H, $SiMe_2$). ^{13}C NMR δ 189.8 (CHO), 142.5 (C-9), 140.1 (C-11), 137.5 (C), 137.4 (C-8), 137.36 (C), 130.0 (C-7), 129.9 (C), 122.3 (C-10), 62.0 (C-15), 39.4 (C-2), 33.9 (C-1), 32.7 (C-4), 32.1 (C-14), 28.4 (C-16, C-17), 26.9 (C-13), 25.4 (*t*-Bu), 21.1 (C-18), 18.9 (C-3), 17.9 (C-*t*-Bu), 11.4 (C-19), −6.1 (C–Si). UV λ_{max} 352 nm. HRMS *m/z* calcd for $C_{26}H_{45}O_2Si$ (MH^+) 417.3189, found 417.3243.

4.2.11. 11-*cis*-*O*-TBS-12-formyl-13-demethyl-13,14-dihydroretinol (18). The 11-*cis* isomer was similarly prepared according to general procedure C with 11-*cis* **16** (0.09 g, 0.22 mmol) and DIBAL-H (1 M in hexane, 0.35 mL) in *n*-hexane (5 mL). Chromatography (*n*-hexane/ether/ethyl acetate 4:2:1) provided pure 11-*cis* **18** (yellow oil, 85% yield). ^{1}H NMR δ 9.47 (s, 1H, CHO), 7.24 (d, J=12.3 Hz, 1H, H-11), 6.52 (d, J=11.7 Hz, 1H, H-10), 6.49 (d, J=16.2 Hz, 1H, H-7), 6.27 (d, J=15.9 Hz, 1H, H-8), 3.61 (t, J=6.3 Hz, 2H, CH_2-15), 2.45 (dd, J=8.1, 7.5 Hz, 2H, CH_2-13), 2.10 (d, J=1.2 Hz, 3H, Me-19), 2.05 (t, J=6.3 Hz, 2H, CH_2-4), 1.74 (d, J=0.9 Hz, 3H, Me-18), 1.61 (m, 4H, CH_2-14 and CH_2-3), 1.48 (m, 2H, CH_2-2), 1.06 (s, 6H, Me-16, 17), 0.91 (s, 9H, *t*-Bu), 0.06 (s, 6H, $SiMe_2$). ^{13}C NMR δ 194.6 (CHO), 145.4 (C-9), 144.9 (C-11), 141.0, (C-6), 137.4 (C-5 or C-12), 137.0 (C-8), 131.7 (C-7), 131.2 (C-12 or C-5), 124.5 (C-10), 62.6 (C-15), 39.6 (C-2), 34.3 (C-1), 33.2 (C-4), 32.1 (C-14), 28.9 (C-16, C-17), 25.9 (*t*-Bu), 21.8 (C-18), 20.5 (C-13), 19.1 (C-3), 18.3 (C-*t*-Bu), 12.9 (C-19), −5.3 (C–Si). UV λ_{max} 354 nm. HRMS *m/z* calcd for $C_{26}H_{45}O_2Si$ (MH^+) 417.3189, found 417.3184.

4.2.12. All-*trans*-*O*-TBS-12-formyl-13,14-dihydroretinol (19). All-*trans* **19** was prepared according to general procedure C with all-*trans* **17** (0.33 g, 0.77 mmol) and DIBAL-H (1 M in Hexane, 1.4 mL) in *n*-hexane (10 mL). The product was obtained as yellow oil (88% yield). ^{1}H NMR δ 10.32 (s, 1H, CHO), 7.26 (d, J=12.6 Hz, 1H, H-11), 7.00 (d, J=12.9 Hz, 1H, H-10), 6.42 (d, J=16.2 Hz, 1H, H-7), 6.20 (d, J=15.9 Hz, 1H, H-8), 3.56 (t, J=6.6 Hz, 1H, CH_2-15), 2.88 (sextet, J=6.9 Hz, 1H, H-13), 2.03 (d, J=1.2 Hz, and t, J=6 Hz, 5H, Me-19 and CH_2-4), 1.76 (m, 1H, H-14), 1.72 (d, J=0.9 Hz, 3H, Me-18), 1.62 (m, 3H, H-14, CH_2-3), 1.47 (m, 2H, CH_2-2), 1.10 (d, J=6.9 Hz, Me-20), 1.03 (s, 6H, Me-16, 17), 0.88 (s, 9H, *t*-Bu), 0.02 (s, 6H, $SiMe_2$). ^{13}C NMR δ190.2 (CHO), 143.3 (C-4°), 141.6 (C-4°), 138.9 (C-11), 137.5 (C-4°), 137.2 (C-8), 130.9 (C-7), 130.7 (C-4°), 122.0 (C-10), 61.5 (C-15), 39.5 (C-2), 39.1 (C-14), 34.2 (C-1), 33.1 (C-4), 30.4 (C-13), 28.9 (C-16, C-17), 25.9 (*t*-Bu), 21.7 (C-18), 20.6 (C-20), 19.1 (C-3), 18.3 (C-*t*-Bu), 12.3 (C-19), −5.3 (C–Si). UV λ_{max} 354 nm. HRMS *m/z* calcd for $C_{27}H_{46}O_2Si$ ($M^{\cdot+}$) 430.3267, found 430.3223.

4.2.13. 11-*cis*-*O*-TBS-12-formyl-13,14-dihydroretinol (19). 11-*cis* **19** was prepared according to general procedure C with 11-*cis* **17** (0.69 g, 1.6 mmol) and DIBAL-H (1 M in Hexane, 2.9 mL) in *n*-hexane (21 mL). The product was obtained as yellow oil in 85% yield. ^{1}H NMR δ 9.43 (d, J=2 Hz, 1H, CHO), 7.19 (d, J=12.0 Hz, 1H, H-11), 6.53 (d, J=12.0 Hz, 1H, H-10), 6.46 (d, J=15.9 Hz, 1H, H-7), 6.22 (d, J=16.2 Hz, 1H, H-8), 3.55 (dt, J=10.8, 5.7 Hz, 1H, H-15), 3.43 (ddd, J=10.4, 7.8, 5.4 Hz, 1H, H-15), 3.09 (m, 1H, H-13), 2.08 (d, J=1.2 Hz, 3H, Me-19), 2.03 (CH_2-4), 1.77 (m, 1H, H-14), 1.71 (d, J=0.9 Hz, 3H, Me-18), 1.64 (m, 3H, H-14, CH_2-3), 1.48 (m, 2H, CH_2-2), 1.19 (d, J=7.2 Hz, Me-20), 1.03 (s, 6H, Me-16, 17), 0.87 (s, 9H, *t*-Bu), 0.00 and −0.02 (s, 3H, SiMe). ^{13}C NMR δ 195.1 (CHO), 145.8 (C-11), 145.3 (C-4°), 144.0 (C-4°), 137.4 (C-4°), 137.1 (C-8), 131.6 (C-7), 131.1 (C-4°), 124.5 (C-10), 61.2 (C-15), 39.2 (C-2), 36.7 (C-14), 34.2 (C-1), 32.8 (C-4), 28.9 (C-16, C-17), 27.9 (C-13), 25.9 (*t*-Bu), 21.7 (C-18), 19.1 (C-3), 18.7 (C-20), 18.2 (C-*t*-Bu), 12.9 (C-19), −5.3 (C–Si). UV λ_{max} 356 nm.

4.2.14. *O*-THP-12-carbethoxy-13-demethyl-13,14-dihydroretinol (20). Compound **20** was prepared according to general procedure A with phosphonate **11** (0.84 g, 2.3 mmol), NaH (60% in mineral oil, 0.085 g) and aldehyde **15** (1.0 g, 4.6 mmol) in dry THF at rt for 2 days. The obtained isomeric mixture (11-*cis* as a major product, along with some all-*trans* and 9-*cis*) was purified and partially separated by chromatography (*n*-hexane/ether, 20:1) (yellow oil, 46% yield). 11-*cis*. ^{1}H NMR δ 7.63 (d, J=12.3 Hz, 1H, H-11), 6.35 (d, J=16.2 Hz, 1H, H-7), 6.33 (d, J=12.0 Hz, 1H, H-10), 6.18 (d, J=16.2 Hz, 1H, H-8), 4.55 (dd, J=4.5, 3.0 Hz, H, H-2′), 4.22 (q, J=7.2 Hz, 2H, CH_2OCO), 3.86 (ddd, J=11.1, 7.5, 3.3 Hz, 1H, H-6′), 3.74 (dt, J=9.9, 6.3 Hz, 1H, H-15), 3.47 (m, 1H, H-6′), 3.37 (dt, J=9.9, 6.3 Hz, 1H, H-15), 2.58 (dt, J=13.5, 7.5 Hz, 1H, H-13), 2.50 (dt, J=13.5, 6.9 Hz, 1H, H-13), 2.03 (d, J=1.2 Hz, 3H, Me-19), 2.02 (t, J=6.3 Hz, 2H, CH_2-4), 1.80–1.48 (m, CH_2-3, CH_2-14, CH_2-3′, CH_2-4′, CH_2-5′), 1.70 (d, J=0.9 Hz, 3H, Me-18), 1.46 (m, 2H, CH_2-2), 1.31 (t, J=7.2 Hz, 3H, ester-Me), 1.03 (s, 6H, Me-16, 17). ^{13}C NMR δ 168.3 (CO_2), 142.9 (C-9), 137.5 (C-6), 137.3 (C-8), 134.5 (C-11), 130.3 (C-12), 130.2 (C-5), 129.8 (C-7), 124.6 (C-10), 98.8 (C-6′), 66.6 (C-15), 62.1 (C-2′), 60.3 (C-21), 39.5 (C-2), 34.1 (C-1), 33.0 (C-4), 30.7 (C-5′), 29.4 (C-14), 28.8 (C-16, 17), 25.4 (C-3′), 23.4 (C-13), 21.6 (C-18), 19.5 (C-4′), 19.1 (C-3), 14.2 (C-22), 12.8 (C-19). UV λ_{max} 334 nm. HRMS *m/z* calcd for $C_{27}H_{42}O_4$ ($M^{\cdot+}$) 430.3083, found 430.3073. All-*trans*. ^{1}H NMR δ 7.03 (d, J=12.0 Hz, 1H, H-10), 6.79 (d, J=12.0 Hz, 1H, H-11), 6.34 (d, J=15.6 Hz, 1H, H-7), 6.01 (d, J=15.6 Hz, 1H, H-8), 4.57 (dd, J=3.9, 2.7 Hz, 1H, H-2′), 4.22 (q, J=7.2 Hz, 2H, CH_2OCO), 3.86 (m, 1H, H-6′), 3.75 (m, 1H, H-15), 3.49 (m, 1H, H-6′), 3.36 (dt, 1H, H-15), 2.46 (m, 2H, CH_2-13), 1.94 (s, 3H, Me-19). 9-*cis*. ^{1}H NMR δ 7.69 (d, J=12.3 Hz, 1H, H-11), 6.88 (d, J=15.3 Hz, 1H, H-8), 6.28 (d, J=12.0 Hz, 1H, H-10), 6.09 (d, J=15.9 Hz, 1H, H-7). HRMS *m/z* calcd for $C_{27}H_{42}O_4$ ($M^{\cdot+}$) 430.3083, found 430.3054.

4.2.15. *O*-THP-12-carbethoxy-13,14-dihydroretinol (21). Compound **21** was prepared according to general procedure A with phosphonate **14** (1.2 g, 3.2 mmol), NaH (60% in mineral oil, 0.12 g) and aldehyde **15** (0.65 g, 3.0 mmol) in dry THF at rt for 3 days. Chromatography (*n*-hexane/ether 25:1) afforded a complex diastereoisomeric mixture of the all-*trans* and 11-*cis* isomers, as well as minor amounts of a product derived from the phosphonate of the 3-protected butanediol (yellow oil, 52% yield). ^{1}H NMR δ 7.60, 7.58 and 7.57 (d, J=12.3 Hz, 1H, H-11), 6.79 (J=

12.0 Hz, 2H-10), 6.73 (dd, J=12.0, 0.9 Hz, 1H, H-11), 6.71 (dd, J=12.0, 0.9 Hz, 1H, H-11), 6.42 (d, J=12.3 Hz, 1H, H-10), 6.41–6.30 (m, 2H-10, 4H-7), 6.27 (d, 12 Hz, 1H, H-10), 6.25 (d, J=16.2 Hz, 1H, H-7), 6.19 (d, J=16.2 Hz, 1H, H-8), 6.17 (d, J=15.9 Hz, 1H, H-8), 6.16 (d, J=16.2, 1H, H-8), 6.15 (d, J=15.9 Hz, 1H, H-8), 6.13 (d, J=15.6 Hz, 1H, H-8), 4.71 (dd, J=4.2, 3 Hz, 1H, H-2′), 4.63 (dd, J=4.8, 3.0 Hz, 1H, H-2′), 4.54 (t, J=3.3 Hz, 1H, H-2′), 4.52 (dd, J=4.7, 2.7 Hz, 1H, H-2′), 4.40 (dd, J=4.5, 2.7 Hz, 1H, H-2′), 4.23, 4.20, 4.19, 4.18, (q, J=6.9 Hz, 2H, ester-CH_2), 3.95–3.10 (m, H-13, CH_2-15 and CH_2-6′), 2.78 (m, 1H, H-13), 2.63 (ddd, J=13.8, 10.8, 6 Hz, 1H, H-13), 2.45 (m, 1H, H-13), 2.02, 2.01, 2.00, 1.95 and 1.94 (d, J=1.2 Hz, 3H, Me-19), 1.98 (m, 2H, CH_2-4), 1.9–1.4 (m, 12H, CH_2-2, CH_2-3, CH_2-14, CH_2-3′, CH_2-4′, CH_2-5′), 1.70 (d, J=0.9 Hz, 3H, Me-18), 1.70, 1.69 and 1.68 (s, 3H, Me-18), 1.317, 1.29 (t, J=6.9 Hz, 3H, ester-Me), 1.25 (d, J=6.3 Hz, 3H, Me-20), 1.21 (d, J=7.2 Hz, 3H, Me-20), 1.18 (t, J=6.9 Hz, 3H, ester-Me), 1.15 (d, J=6.9 Hz, 3H, Me-20), 1.13 (d, J=6.0 Hz, 3H, Me-20), 1.02, 1.02, 1.01, 1.00 and 0.99 (s, 6H, Me-16, 17). UV λ_{max} 334 nm. HRMS *m/z* calcd for $C_{28}H_{44}O_4$ 444.3240, found 444.3214.

4.2.16. 12-Cyano-13-demethyl-13,14-dihydroretinol (1). *General procedure D*. A mixture of all-*trans* and 11-*cis* (2.6:1) **16** (0.34 g, 0.8 mmol) was dissolved in dry THF (10 mL). A solution of $Bu_4N^+F^-$ (1 M in THF, 0.88 ml) was added and the reaction mixture was stirred at rt for 1 h. After evaporation of the solvent, the isomers were separated by chromatography (ethyl acetate/hexane 1:2) (yellow oils, 100% yield). All-*trans*. ^{1}H NMR δ 7.02 (d, J=11.9 Hz, 1H, H-11), 6.43 (d, J=11.9 Hz, 1H, H-10), 6.39 (d, J=16.1 Hz, 1H, H-7), 6.20 (d, J=16.1 Hz, 1H, H-8), 3.71 (t, J=6.2 Hz, 2H, CH_2-15), 2.43 (t, J=7.5 Hz, 2H, CH_2-13), 2.03 (t, J=6.2 Hz, 2H, CH_2-4), 1.99 (s, 3H, Me-19), 1.84 (quintet, J=7.4 Hz, 2H, CH_2-14), 1.72 (s, 3H, Me-18), 1.62 (m, 2H, CH_2-3), 1.47 (m, 2H, CH_2-2), 1.03 (s, 6H, Me-16, Me-17). ^{13}C NMR δ 142.8 (C-9), 140.6 (C-11), 137.2 (C-6), 136.4 (C-8), 131.0 (C-7), 130.8 (C-5), 125.3 (C-10), 118.4 (CN), 110.6 (C-12), 61.0 (C-15), 39.5 (C-2), 34.1 (C-1), 33.0 (C-4), 31.1 (C-14), 30.8 (C-13), 28.8 (C-16, C-17), 21.6 (C-18), 19.0 (C-3), 12.9 (C-19). UV λ_{max} 334 nm. HRMS *m/z* calcd for $C_{20}H_{30}NO$ (MH^+) 300.2327, found 300.2310. 11-*cis*. ^{1}H NMR δ 7.15 (d, J=12.1 Hz, 1H, H-11), 6.43 (d, J=16.1 Hz, 1H, H-7), 6.26 (d, J=12.1 Hz, 1H, H-10), 6.16 (d, J=16.1 Hz, 1H, H-8), 3.71 (t, J=6.1 Hz, 2H, CH_2-15), 2.47 (t, J=7.4 Hz, 2H, CH_2-13), 2.03 (t, J=6.6 Hz, 2H, CH_2-4), 2.00 (s, 3H, Me-19), 1.85 (quintet, J=7.6 Hz, 2H, CH_2-14), 1.72 (s, 3H, Me-18), 1.62 (m, 2H, CH_2-3), 1.47 (m, 2H, CH_2-2), 1.03 (s, 6H, Me-16, Me-17). ^{13}C NMR δ 144.1 (C-9), 139.8 (C-11), 137.4 (C-6), 136.5 (C-8), 131.7 (C-7), 131.0 (C-5), 122.6 (C-10), 121.5 (CN), 110.6 (C-12), 61.4 (C-15), 39.5 (C-2), 34.2 (C-1), 33.1 (C-4), 30.9 (C-14), 28.9 (C-16, C-17), 24.9 (C-13), 21.7 (C-18), 19.1 (C-3), 12.9 (C-19). UV λ_{max} 336 nm. HRMS *m/z* calcd for $C_{20}H_{30}NO$ (MH^+) 300.2327, found 300.2311.

4.2.17. 12-Cyano-13,14-dihydroretinol (2). Retinol analog **2** was prepared according to general procedure D with **17** (0.3 g, 0.7 mmol, a mixture of isomers) and $Bu_4N^+F^-$ (1 M in THF, 0.8 ml) in dry THF (10 mL). The product isomeric mixture was purified and separated by chromatography (ethyl acetate/hexane 1:2) (yellow oils, 90% yield). All-*trans*. ^{1}H NMR δ 7.04 (d, J=11.7 Hz, 1H, H-11), 6.44 (d, J=11.7 Hz, 1H, H-10), 6.38 (d, J=15.9 Hz, 1H, H-7), 6.20 (d, J=15.9, 1H, H-8), 3.67 (m, 1H, H-15), 3.62 (m, 1H, H-15), 2.66 (dquintet, J=8.1, 6.6 Hz, 1H, H-13), 2.49 (t, J=7.8 Hz, 1H, OH), 2.03 (t, J=6.3 Hz, 2H, CH_2-4), 1.99 (d, J=1.2 Hz, 3H, Me-19), 1.75 (m, 2H, CH_2-14), 1.72 (s, 3H, Me-18), 1.62 (m, 2H, CH_2-3), 1.47 (m, 2H, CH_2-2), 1.23 (d, J=6.6 Hz, 3H, Me-20), 1.03 (s, 6H, Me-16, 17). ^{13}C NMR δ 142.9 (C), 139.4 (C-11), 137.3 (C), 136.5 (C-8), 131.0 (C-7), 130.8 (C), 125.3 (C-10), 117.2 (CN), 116.6 (C), 59.9 (C-15), 39.5 (C-2), 38.1 (C-14), 35.5 (C-13), 34.1 (C-1), 33.0 (C-4), 28.8 (C-16, 17), 21.6 (C-20), 20.0 (C-18), 19.1 (C-3), 13.0 (C-19). UV λ_{max} 334 nm. HRMS *m/z* calcd for $C_{21}H_{31}NO$ (M^+) 313.2406, found 313.2410. 11-*cis*. ^{1}H NMR δ 7.13 (d, J=12.3 Hz, 1H, H-11), 6.42 (d, J=15.9 Hz, 1H, H-7), 6.33 (d, J=12.1 Hz, 1H, H-10), 6.16 (d, J=15.9, 1H, H-8), 3.71 (dt, J=10.7, 5.4 Hz, 1H, H-15), 3.60 (dt, J=10.7, 6.6 Hz, 1H, H-15), 3.08 (sextet, J=6.9 Hz, 1H, H-13), 2.04 (d, J=5.4 Hz, 2H, CH_2-4), 2.00 (d, J=1 Hz, 3H, Me-19), 1.76 (td, J=6.9, 5.7 Hz, 2H, CH_2-14), 1.71 (d, J=1 Hz, 3H, Me-18), 1.62 (m, 2H, CH_2-3), 1.48 (m, 2H, CH_2-2), 1.19 (d, J=6.9 Hz, 3H, Me-20), 1.033 (s, 3H, Me-16), 1.026 (s, 3H, Me-17). ^{13}C NMR δ 144.2 (C-9), 139.0 (C-11), 137.4 (C-6), 136.6 (C-8), 131.6 (C-7), 131.1 (C-5), 125.6 (CN), 116.9 (C-12), 60.2 (C-15), 39.6 (C-2), 37.9 (C-14), 34.3 (C-1), 33.1 (C-4), 29.0 (C-16), 28.9 (C-17), 28.8 (C-13), 21.8 (C-18), 19.6 (C-20), 19.1 (C-3), 12.9 (C-19). HRMS *m/z* calcd for $C_{21}H_{31}NO$ (M^+) 313.2406, found 313.2395. 9-*cis*. ^{1}H NMR δ 7.10 (d, J=11.7 Hz, 1H, H-11), 6.56 (d, J=15.9 Hz, 1H, H-8), 6.38 (d, J=15.9 Hz, 1H, H-7), 6.37 (d, J=11.7, 1H, H-10), 3.71 (dt, J=10.8, 6.0 Hz, 1H, H-15), 3.62 (ddd, J=10.8, 7.5, 1.8 Hz, 1H, H-15), 2.65 (dquintet, J=8.1, 6.9 Hz, 1H, H-13), 2.06 (d, J=0.9 Hz, 3H, Me-19), 2.05 (t, J=6 Hz, 2H, CH_2-4), 1.76 (m, 2H, CH_2-14), 1.74 (d, J=0.9 Hz, 3H, Me-18), 1.64 (m, 2H, CH_2-3), 1.49 (m, 2H, CH_2-2), 1.21 (d, J=6.9 Hz, 3H, Me-20), 1.04 (s, 6H, Me-16, 17). ^{13}C NMR δ 142.0 (C-9), 138.1 (C-11), 137.7 (C-6), 132.2 (C-8), 130.6 (C-5), 128.8 (C-7), 123.8 (C-10), 117.1 (CN), 116.1 (C-12), 60.1 (C-15), 39.4 (C-2), 38.0 (C-14), 35.5 (C-13), 34.2 (C-1), 33.0 (C-4), 28.9 (C-16, 17), 21.8 (C-18), 20.9 (C-20), 19.9 (C-19), 19.1 (C-3).

4.2.18. All-*trans*-12-formyl-13-demethyl-13,14-dihydroretinol (3). All-*trans* **3** was prepared according to general procedure D with all-*trans* **18** (0.11 g, 0.26 mmol) and $Bu_4N^+F^-$ (1 M in THF, 0.26 mL) in dry THF (7 mL). It was purified by chromatography (hexane/ethyl acetate 5:1), providing a mixture of 1:1 all-*trans* and 11-*cis* **3**, along with small amounts of the 9-*cis* congener (yellow oil, 78% yield). ^{1}H NMR δ 10.34 (s, 1H, CHO), 7.38 (d, J=12.6 Hz, 1H, H-11), 6.99 (d, J=12.6 Hz, 1H, H-10), 6.44 (d, J=16.2 Hz, 1H, H-7), 6.20 (d, J=16.2 Hz, 1H, H-8), 3.59 (t, J=6 Hz, 2H, CH_2-15), 2.38 (t, J=7.2 Hz, 2H, CH_2-13), 2.03 (m, 5H, Me-19 and CH_2-4), 1.73 (s, 3H, Me-18), 1.64 (m, 4H, CH_2-14 and CH_2-3), 1.48 (m, 2H, CH_2-2), 1.04 (s, 6H, Me-16, 17). ^{13}C NMR δ 190.7 (CHO), 144.0 (C-9), 142.0 (C-11), 137.5 (C), 136.9 (C-8), 131.4 (C-7), 131.0 (C), 121.5 (C-10), 61.4 (C-15), 39.5 (C-2), 34.2 (C-1), 33.1 (C-4), 32.6 (C-14), 28.9 (C-16, C-17), 26.5 (C-13), 21.8 (C-18), 20.2 (C-13), 19.1 (C-3), 12.4 (C-19). UV λ_{max} 354 nm. HRMS *m/z* calcd for $C_{20}H_{30}O_2$ (M^+) 302.2246, found 302.2283.

4.2.19. 11-*cis*-12-Formyl-13-demethyl-13,14-dihydroretinol (3). 11-*cis* **3** was prepared from 11-*cis* **18** according to general procedure D as yellow oil in 77% yield. It was further purified by HPLC on a 5μ PVA-Sil (250×4.6 mm, 1.20 Å, YMC) column, using a mixture of 7% dioxane in hexane at a flow rate of 1.5 mL/min. Retention time: 26.3 min. 98% purity. λ_{max} (hexane)=342 nm, ε=18600. ^{1}H NMR δ 9.48 (s, 1H, CHO), 7.30 (d, J=12.3 Hz, 1H, H-11), 6.51 (d, J=15.9 Hz, 1H, H-7), 6.49 (d, J=12.3 Hz, 1H, H-10), 6.27 (d, J=16.2 Hz, 1H, H-8), 3.53 (t, J=6.0 Hz, 2H, CH_2-15), 2.52 (t, J=7.2 Hz, 2H, CH_2-13), 2.12 (s, 3H, Me-19), 2.05 (t, J=6.0 Hz, 2H, CH_2-4), 1.75 (s, 3H, Me-18), 1.66 (m, 4H, CH_2-14 and CH_2-3), 1.49 (m, 2H, CH_2-2), 1.06 (s, 6H, Me-16, 17). ^{13}C NMR δ 195.5 (CHO), 146.5 (C-9), 146.0 (C-11), 140.2 (C), 137.4 (C), 136.8 (C-8), 132.4 (C-7), 131.5 (C), 124.0 (C-10), 60.9 (C-15), 39.5 (C-2), 34.2 (C-1), 33.2 (C-4), 31.7 (C-14), 28.9 (C-16, C-17), 21.8 (C-18), 19.5 (C-13), 19.1 (C-3), 13.0 (C-19). UV λ_{max} 354 nm. MS m/z 303 (MH^+).

4.2.20. All-*trans*-12-formyl-13,14-dihydroretinol (4). All-*trans* **4** was prepared according to general procedure D with all-*trans* **19** and (0.52, 1.2 mmol) $Bu_4N^+F^-$ (1 M in THF, 1.2 mL) in dry THF (14 mL). The product, all-*trans* isomer, was obtained as a yellow oil (83%). ^{1}H NMR (acetone-d_6) δ 10.33 (s, 1H, CHO), 7.38 (d, J=12.6 Hz, 1H, H-11), 7.15 (d, J=12.9 Hz, 1H, H-10), 6.48 (d, J=16.2 Hz, 1H, H-7), 6.28 (d, J=16.2 Hz, 1H, H-8), 3.45 (td, J=6.5, 2.4 Hz, 1H, H-15), 3.43 (td, J=6.5, 2.4 Hz, 1H, H-15), 2.89 (sextet, J=7.2 Hz, 1H, H-13), 2.06 (d, J=1.2 Hz, 3H, Me-19), 2.03 (t, J=6.6 Hz, 2H, CH_2-4), 1.73 (d, J=0.9 Hz, 3H, Me-18), 1.63 (m, 4H, CH_2-14 and CH_2-3), 1.48 (m, 2H, CH_2-2), 1.12 (d, J=6.3 Hz, Me-20), 1.03 (s, 6H, Me-16, 17). ^{13}C NMR δ 192.1 (CHO), 144.8 (C), 143.4 (C), 140.5 (C-11), 139.0 (C), 138.6 (C-8), 131.7 (C-7), 130.4 (C), 123.8 (C-10), 61.3 (C-15), 40.8 (C-2), 38.3 (C-14), 35.4 (C-1), 34.2 (C-4), 30.8 (C-13), 29.7 (C-16, C-17), 22.5 (C-18), 21.1 (C-20), 20.4 (C-3), 12.9 (C-19). UV λ_{max} 354 nm. HRMS m/z calcd for $C_{21}H_{32}O_2$ (M^+) 316.2402, found 316.2425.

4.2.21. 11-*cis*-12-Formyl-13,14-dihydroretinol (4). 11-*cis* **4** was similarly prepared. The product, 11-*cis* isomer exclusively, was obtained as a yellow oil (76%). It was purified by HPLC on a 5μ PVA-Sil (250×4.6 mm, 1.20 Å, YMC) column, using a mixture of 7% dioxane in hexane at a flow rate of 1.5 mL/min. Retention time: 23.1 min. 93% purity. λ_{max} (hexane)=336 nm, ε=22400. ^{1}H NMR (acetone-d_6) δ 9.48 (d, J=1.8 Hz, 1H, CHO), 7.39 (d, J=12.3 Hz, 1H, H-11), 6.72 (d, J=12.0 Hz, 1H, H-10), 6.55 (d, J=16.2 Hz, 1H, H-7), 6.35 (d, J=16.2 Hz, 1H, H-8), 3.42 (m, CH_2-15), 3.15 (dqd, J=6.9, 6.6, 1.8 Hz, 1H, H-13), 2.14 (d, J=1.2 Hz, 3H, Me-19), 2.05 (m, CH_2-4), 1.94 (m, H-14), 1.74 (d and m, J=0.9 Hz, Me-18 and H-14), 1.64 (m, CH_2-3), 1.48 (m, CH_2-2), 1.20 (d, J=7.2 Hz, 3H, Me-20), 1.064 and 1.056 (s, 3H, Me-16 and Me-17). HRMS m/z calcd for $C_{21}H_{32}O_2$ (M^+) 316.2402, found 316.2415.

4.2.22. 12-Carbethoxy-13-demethyl-13,14-dihydroretinol (5). *General procedure E.* PPTS (0.017 g, 0.07 mmol) was added to a solution of 11-*cis* **20** (0.3 g, 0.7 mmol) in ethanol (10 mL). The mixture was stirred at 55 °C for 1.5 h, cooled to rt and the solvent was evaporated to half its volume. The mixture was diluted with ether, washed with water, dried ($MgSO_4$) filtered and evaporated, providing a mixture of 11-*cis*, 9-*cis* and all-*trans* isomers in a ratio of 30:2:1, respectively. Chromatography (hexane/ether 2:1) afforded clean 11-*cis* **5** as yellow oil and a fraction containing the three isomers (79% overall yield). 11-*cis*. ^{1}H NMR δ 7.62 (d, J=12.3 Hz, 1H, H-11), 6.34 (d, J=15.9 Hz, 1H, H-7), 6.28 (d, J=12.3 Hz, 1H, H-10), 6.17 (d, J=15.9 Hz, 1H, H-8), 4.20 (q, J=7.2 Hz, 2H, ester-CH_2), 3.55 (t, J=6.3 Hz, 2H, CH_2-15), 2.52 (t, J=7.2 Hz, 2H, CH_2-13), 2.01 (d, J=0.9 Hz, 3H, Me-19), 1.98 (t, J=6.3 Hz, 2H, CH_2-4), 1.68 (m, 5H, CH_2-14 and Me-18), 1.58 (m, 2H, CH_2-3), 1.42 (m, 2H, CH_2-2), 1.29 (t, J=6.9 Hz, 3H, ester-Me), 1.00 (s, 6H, Me-16, 17). ^{13}C NMR δ 168.9 (CO_2), 143.5 (C-9), 137.4 (C-6), 137.2, (C-8), 134.9 (C-11), 130.3 (C-12), 130.2 (C-7), 129.7 (C-5), 124.3 (C-10), 61.3 (C-15), 60.6 (ester-CH_2), 39.5 (C-2), 34.1 (C-1), 33.0 (C-4), 32.3 (C-14), 28.8 (C-16, 17), 22.5 (C-13), 21.6 (C-18), 19.1 (C-3), 14.2 (ester-CH_3), 12.8 (C-19). UV λ_{max} 340 nm. HRMS m/z calcd for $C_{22}H_{34}O_3$ ($M^{\cdot+}$) 346.2508, found 346.2490. All-*trans*. ^{1}H NMR δ 6.99 (d, J=12.0 Hz, 1H, H-10), 6.82 (d, J=12.0 Hz, 1H, H-11), 6.33 (d, J=16 Hz, H-7), 6.13 (d, J=16.2 Hz, 1H, H-8), 4.21 (q, J=7.2 Hz, 2H, ester-CH_2), 3.62 (t, J=6.3 Hz, 2H, CH_2-15), 2.42 (t, J=7.2 Hz, 2H, CH_2-13), 2.01 (CH_2-4), 1.94 (d, J=1.2 Hz, 3H, Me-19), 1.70 (s, 3H, Me-18), 1.58 (m, 2H, CH_2-3), 1.42 (m, 2H, CH_2-2), 1.29 (t, J=7.2 Hz, 3H, ester-Me), 0.98 (s, 6H, Me-16, 17). ^{13}C NMR δ 169.1 (CO_2), 141.7 (C-9), 137.8 (C-8), 135.7 (C-11), 129.4 (C-7), 126.3 (C-10), 61.9 (C-15), 60.3 (ester-CH_2), 39.6 (C-2), 34.2 (C-1), 33.1 (C-4), 32.4 (C-14), 28.9 (C-16, 17), 22.3 (C-13), 21.8 (C-1O-8), 19.2 (C-3), 14.3 (ester-CH_3), 12.9 (C-19). UV λ_{max} 338 nm. HRMS m/z calcd for $C_{22}H_{34}O_3$ ($M^{\cdot+}$) 346.2508, found 346.2547. 9-*cis*. ^{1}H NMR δ 7.72 (d, J=12.3 Hz, 1H, H-11), 6.70 (d, J=15.9 Hz, 1H, H-8), 6.33 (d, J=15.9 Hz, 1H, H-7), 6.19 (d, J=12.3 Hz, 1H, H-10), 4.19 (q, J=6.9 Hz, 2H, ester-CH_2), 3.56 (t, J=6.3 Hz, 2H, CH_2-15), 2.51 (t, J=7.2 Hz, 2H, CH_2-13), 2.02 (CH_2-4), 2.02 (d, J=1.2 Hz, 3H, Me-19), 1.71 (d, J=0.9 Hz, 3H, Me-18), 1.58 (m, 2H, CH_2-3), 1.42 (m, 2H, CH_2-2), 1.28 (t, J=7.2 Hz, 3H, ester-Me), 1.01 (s, 6H, Me-16, 17).

4.2.23. 12-Carbethoxy-13,14-dihydroretinol (6). Compound **6** was prepared according to general procedure E with **21** (0.23 g, 0.5 mmol) and PPTS (0.014 g, 0.06 mmol) in ethanol (10 mL). The product isomeric mixture was separated by chromatography (*n*-hexane/ether 3:1 to 1:1), affording two fractions, of the all-*trans* and the 11-*cis* isomers of **6** (yellow oils, 63% yield). 11-*cis* **6** was further purified by HPLC (inertSil prep-sil, 20×250 mm column, 7% ethyl acetate in *n*-hexane, flow rate 35 mL/min, detection at 324 nm, retention time 37.3 min). All-*trans*. ^{1}H NMR δ 6.81 (d, J=12.1 Hz, 1H, H-10), 6.78 (d, J=11.9 Hz, 1H, H-11), 6.29 (d, J=15.9 Hz, 1H, H-7), 6.15 (d, J=16.1 Hz, 1H, H-8), 4.28 (q, J=7.1 Hz, 2H, ester-CH_2), 3.64 (m, 2H, CH_2-15), 2.85 (sextet, J=7.0 Hz, 1H, H-13), 2.02 (t, J=6.3 Hz, 2H, CH_2-4), 1.98 (s, 3H, Me-19), 1.74 (m, 1H, H-14), 1.70 (s, 3H, Me-18), 1.62 (m, 3H, H-14 and CH_2-3), 1.46 (m, 2H, CH_2-2), 1.35 (t, J=7.2 Hz, 3H, ester-Me), 1.18 (J=7.0 Hz, 3H, Me-20), 1.02 (s, 6H, Me-16, 17). ^{13}C NMR δ 169.0 (CO_2), 141.0 (C-9), 137.8 (C-8), 137.7 (C-6), 135.2, (C-12), 132.0 (C-11), 129.9 (C-5), 129.2 (C-7), 126.0 (C-10), 60.8 (C-15), 60.6 (ester-CH_2), 40.2 (C-14), 39.5 (C-2), 34.2 (C-1), 34.0 (C-13), 33.0 (C-4), 28.9 (C-16,

17), 21.7 (C-18), 20.8 (C-20), 19.2 (C-3), 14.3 (ester-Me), 12.4 (C-19). UV λ_{max} 330 nm. HRMS *m/z* calcd for $C_{23}H_{36}O_3$ ($M^{\cdot+}$) 360.2664, found 360.2671. 11-*cis*. ^{1}H NMR δ 7.61 (d, J=12.3 Hz, 1H, H-11), 6.42 (d, J=12.0 Hz, 1H, H-10), 6.38 (d, J=15.3 Hz, 1H, H-7), 6.19 (d, J=16.2 Hz, 1H, H-8), 4.23 (q, J=7.2 Hz, 2H, ester-CH_2), 3.62 (sextet, J=6.3 Hz, 1H, H-15), 3.55 (ddd, J=10.8, 8.1, 5.7 Hz, 1H, H-15), 3.18 (m, 1H, H-13), 2.04 (m, 5H, CH_2-4 and Me-19), 1.99 (m, 1H, H-14), 1.86 (m, 1H, H-14), 1.73 (d, J=0.9 Hz, 3H, Me-18), 1.61 (m, 2H, CH_2-3), 1.49 (m, 2H, CH_2-2), 1.33 (t, J=7.2 Hz, 3H, ester-Me), 1.25 (d, J=6.9 Hz, 3H, Me-20), 1.05 (s, 3H, Me-16), 1.04 (s, 3H, Me-17). ^{13}C NMR δ 168.5 (CO_2), 143.5 (C-9), 137.5 (C-6), 137.4 (C-8), 134.8 (C-11), 133.8 (C-12), 130.5 (C-5), 130.1 (C-7), 124.0 (C-10), 61.4 (C-15), 60.3 (ester-CH_2), 39.6 (C-2), 38.1 (C-14), 34.3 (C-1), 33.1 (C-4), 29.3 (C-13), 28.99 and 28.96 (C-16 and C-17), 21.8 (C-18), 19.7 (C-20), 19.2 (C-3), 14.3 (ester-Me), 12.9 (C-19). UV λ_{max} 338 nm.

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References and notes

1. (a) Rando, R. R. *Chem. Rev.* **2001**, *101*, 1881–1896. (b) Nau, H., Blaner, W. S., Eds.; *Handb. Exp. Pharma* **1999**, *139*. (c) Packer, L., Ed.; *Methods Enz.* **1990**, *190*.
2. Noy, N. *Biochem. J.* **2000**, *348*, 481–495. (b) Packer L. *Methods Enz.* **1990**, *189*, 193–373.
3. (a) Nakanishi, K.; Crouch, R. *Isr. J. Chem.* **1995**, *35*, 253–272. (b) Sani, B. P.; Wille, J. J.; Dawson, M. L.; Hobbs, P. D.; Bupp, J.; Rhee, S.; Chao, W. R.; Dorsky, A.; Morimoto, H. *Chem. Biol. Interact.* **1990**, *75*, 293–304.
4. (a) Nakanishi, K. *Chem. Pharm. Bull.* **2000**, *48*, 1399–1409. (b) Borhan, B.; Souto, M. L.; Imai, H.; Shichida, Y.; Nakanishi, K. *Science* **2000**, *288*, 2209–2212.
5. Feng, Y.; Menick, D. R.; Katz, B. M.; Beischel, C. J.; Hazard, E. S.; Misra, S.; Ebrey, T. G.; Crouch, R. K. *Biochemistry* **1994**, *33*, 11624–11630.
6. (a) Gollapalli, D. R.; Rando, R. R. *Biochim. Biophys. Acta* **2003**, *1651*, 93–101. (b) Nesnas, N.; Rando, R. R.; Nakanishi, K. *Tetrahedron* **2002**, *58*, 6577–6584. (c) Ruiz, A.; Winston, A.; Lim, Y.-H.; Gilbert, B. A.; Rando, R. R.; Bok, D. *J. Biol. Chem.* **1999**, *274*, 3834–3841. (d) Shi, Y. Q.; Furuyoshi, S.; Hubacek, I.; Rando, R. R. *Biochemistry* **1993**, *32*, 3077–3080. (e) Gawinowicz, M. A.; Goodman, D. S. *J. Protein Chem.* **1985**, *4*, 199–213. (f) Gawinowicz, M. A.; Goodman, D. S. *Biochemistry* **1982**, *21*, 1899–1905.
7. (a) Souto, M. L.; Borhan, B.; Nakanishi, K. *Methods Enz.* **2000**, *316*, 425–435. (b) Souto, M. L.; Um, J.; Borhan, B.; Nakanishi, K. *Helv. Chim. Acta* **2000**, *83*, 2617–2628. (c) Ding, W.-D.; Tsipouras, A.; Ok, H.; Yamamoto, T.; Gawinowicz, M. A.; Nakanishi, K. *Biochemistry* **1990**, *29*, 4898–4904. (d) Boehm, M. F.; Gawinowicz, M. A.; Foucault, A.; Derguini, F.; Nakanishi, K. *J. Am. Chem. Soc.* **1990**, *112*, 7779–7782.
8. Yefidoff, R.; Weiss, L.; Avisar, D.; Albeck, A. *Bioorg. Chem.* **2004**, *32*, 38–50.
9. (a) Gollapalli, D. R.; Rando, R. R. *Biochemistry* **2003**, *42*, 5809–5818. (b) Rando, R. R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 461–480.
10. (a) Corson, D. W.; Kefalov, V. J.; Cornwall, M. C.; Crouch, R. K. *J. Gen. Physiol.* **2000**, *116*, 283–297. (b) Stecher, H.; Prezhdo, O.; Das, J.; Crouch, R. K.; Palczewski, K. *Biochemistry* **1999**, *38*, 13542–13550. (c) Tan, Q.; Nakanishi, K.; Crouch, R. K. *J. Am. Chem. Soc.* **1998**, *120*, 12357–12358. (d) Buczylko, J.; Saari, J. C.; Crouch, R. K.; Palczewski, K. *J. Biol. Chem.* **1996**, *271*, 20621–20630. (e) Wang, Q.; Kochendoerfer, G. G.; Schoenlein, R. W.; Verdegem, J. E.; Lugtenburg, J.; Mathies, R. A.; Shank, C. V. *J. Phys. Chem.* **1996**, *100*, 17388–17394. (f) Cañada, F. J.; Law, W. C.; Rando, R. R. *Biochemistry* **1990**, *29*, 9690–9697.
11. (a) Yan, B.; Xie, A.; Nienhaus, G. U.; Katsuta, Y.; Spudich, J. L. *Biochemistry* **1993**, *32*, 10224–10232. (b) Iwasa, T. *Biochemistry* **1992**, *31*, 1190–1195.
12. Lange, G. L.; Gottardo, C. *Synth. Commun.* **1990**, *20*, 1473–1479.
13. (a) Wada, A.; Hiraishi, S.; Takamura, N.; Date, T.; Aoe, K.; Ito, M. *J. Org. Chem.* **1997**, *62*, 4343–4348. (b) Steinberg, G.; Sheves, M.; Bressler, S.; Ottolonghi, M. *Biochemistry* **1994**, *33*, 12439–12450.
14. (a) Rando, R. R. *Chem. Biol.* **1996**, *3*, 255–262. (b) Rando, R. R.; Chang, A. *J. Am. Chem. Soc.* **1983**, *105*, 2879–2882.
15. Verdegem, P. J. E.; Monnee, C. F.; Mulder, P. P. J.; Luchtenburg, J. *Tetrahedron Lett* **1997**, *38*, 5355–5358.
16. Stahl, E. *Thin-Layer Chromatography*. 2nd ed.; Springer: Berlin, 1969, pp 217–218.
17. Still, W. C.; Kahn, M.; Mitra, A. J. *Org. Chem.* **1978**, *43*, 2923–2925.
18. Hobley, G.; Stuttle, K.; Wills, M. *Tetrahedron* **2003**, *59*, 4739–4748.
19. This compound was previously prepared by various methods: (a) Davis, K. J.; Bhalerao, U. T.; Rao, B. V. *Indian J. Chem., Sect B: Org. Chem. Incl. Med. Chem.* **2001**, *40B*, 656–661. (b) Ogawa, Y.; Mori, H.; Yamada, H.; Kon, K. *J. Antibiot.* **1984**, *37*, 44–56. (c) Nouguier, R. *Tetrahedron Lett.* **1982**, *23*, 2951–2952.