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Cross metathesis approach to retinoids and other β-apocarotenoids

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ABSTRACT

Cross metathesis (CM) reactions between polyenes, such as β-carotene, canthaxanthin or retinyl acetate, and various alkenes or dienes in the presence of second generation Hoveyda–Grubbs (H II) or Grubbs (G II) catalysts were investigated. Depending on the cross partner different apocarotenoids were obtained. Cross metathesis reactions of retinyl acetate proved to be fully regioselective. Carotenoid CM reactions afforded mixtures of two products due to competing cleavage of the C11–C12 and C15–C15′ double bonds. However, regioselectivity can be controlled by choice of appropriate reaction conditions. The reactions of polyenes with dienes worked better in respect of yields and diastereoselectivities than those with monounsaturated cross partners.

1. Introduction

Natural products containing a conjugated polyene system constitute a large and structurally diverse group of compounds.[1] Some of them, including eicosanolids,[2] polyene macrolides,[3] carotenoids,[4] apocarotenoids,[5] and retinoids[6] show interesting biological activity. Particularly, retinoids (Fig. 1) play an essential role in a variety of biological processes, such as vision, reproduction, cell differentiation, and immune response. Besides being important to normal cell function, all-*trans*-retinoic acid and its natural and synthetic analogues exhibit antitumor activity.[7] One of them, *N*-(4-hyroxyphenyl)retinamide (fenretinide) is currently undergoing clinical trials for the treatment of breast, bladder, renal, and neuroblastoma malignancies.[8]

Due to increasing application of polyenes in medicine, nonlinear optics, cosmetics, and the food industry, the search for efficient synthetic routes to these compounds is becoming increasingly important. Difficulties with controlling the olefin geometry and susceptibility of some polyenes to oxidation and isomerization make their synthesis a difficult and challenging task. Nowadays synthetic chemists are provided with a new tool to construct polyene compounds, i.e., olefin metathesis. Since the development of well defined molybdenum and ruthenium catalysts (Fig. 2), which are now commercially available, olefin metathesis has become one of the most valuable methods of C–C double bond formation.[9] It has found application in the synthesis of a variety of natural products.[10]

Although cross metathesis (CM) reactions of two alkenes, and recently also of an alkene and a conjugated diene, have already been studied,[11] the use of CM to construct longer conjugated polyene systems is very limited.[12] In our previous paper, we reported the CM reaction of β-carotene with ethyl (2*E*,4*E*/*Z*)-3-methylhexa-2,4-dienoate.[13] In spite of the fact that there are many alternative reaction sites in the polyene molecule, the reaction was regio- and diastereoselective. The major product was either ethyl all-*trans*-retinoate or 12′-β-apocaroten-12′-oate, depending on reaction conditions. With this promising preliminary result in hand, we decided

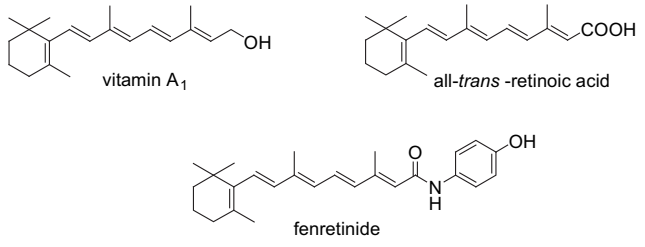

Fig. 1. Natural and synthetic retinoids.

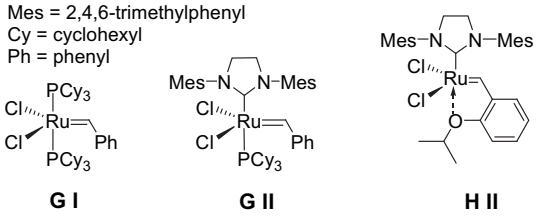

Fig. 2. Examples of the commercially available metathesis catalysts.

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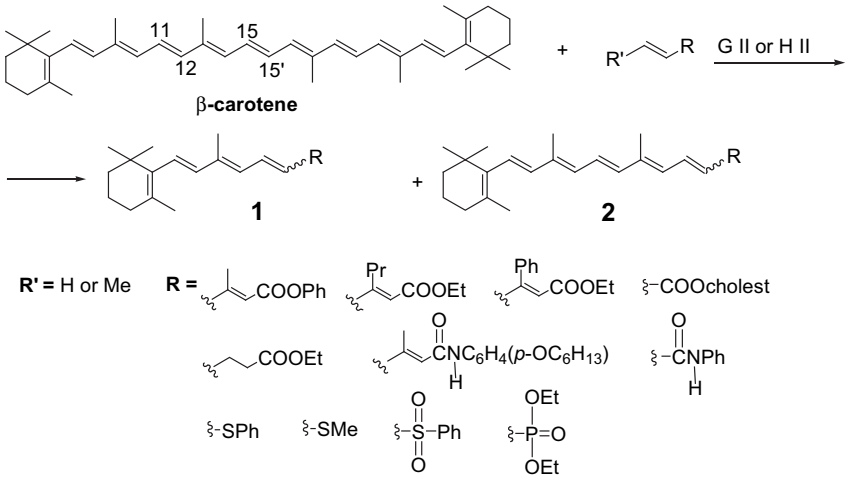
to define the scope and limitation of CM reactions of different polyenes in order to develop the CM methodology of retinoid synthesis, including fenretinide analogues and other apocarotenoids.

2. Results and discussion

Clearly our first goal was to find out if CM of β-carotene with different olefins can also be accomplished effectively and selectively. As cross partners alkenoic and dienoic acid esters, amides, as well as vinyl sulfide, sulfone, and phosphate were chosen (Scheme 1). The experiments were carried out under conditions elaborated in our preliminary study on the β-carotene reaction with ethyl (2*E*,4*E*/*Z*)-3-methylhexa-2,4-dienoate (polyene concentration 0.1 M, 4 equiv of a cross partner, second generation Hoveyda–Grubbs catalyst (H II), toluene, rt). In the case of a disappointing outcome, the reaction conditions were optimized. Various catalysts (G II, H II), catalyst loading (5–20 mol %), amount of a cross partner (1–4 equiv), solvents (CH_2Cl_2, toluene, MeOH), reaction temperature (rt, 40 °C, or 60 °C), and time (20 min–120 h) were tested. The results are summarized in Table 1.



Scheme 1. CM between β-carotene and different cross partners.

Table 1
CM reactions between β-carotene and different cross partners

Entry	Cross partner R'/R	Reaction conditions[a]	Yield[b,c] (*E*/*Z*)[d]	
			Product **1**	Product **2**
1[13]	**R'** = Me **R** = COOEt	H II, 4 equiv of olefin, toluene, 24 h, rt	9[e] (30:1)	38[e] (23:1)
2[13]	**R'** = Me **R** = COOEt	H II, 4 equiv of olefin, toluene, 96 h, rt	31%[f] (9:1)	15%[f] (>15:1)
3	**R'** = Me **R** = COOPh	H II, 4 equiv of olefin, toluene, 24 h, rt	6%[e] (20:1)	50%[e] (100:1)
4	**R'** = Me **R** = COOPh	H II, 4 equiv of olefin, toluene, 96 h, rt	33%[f] (30:1)	57%[f] (60:1)
5	**R'** = Me **R** = COOPh	G II, 4 equiv of olefin, toluene, 96 h, rt	4%[e] (30:1)	23%[e] (100:1)
6	**R'** = Me **R** = COOcholest	H II, 4 equiv of olefin, toluene, 24 h, rt	9%[e] (6:1)	30%[e] (10:1)
7	**R'** = Me **R** = COOcholest	H II, 4 equiv of olefin, toluene, 96 h, rt	12%[f] (5:1)	8%[f] (8:1)
8	**R'** = H **R** = COOEt	H II, 3 equiv of olefin, toluene, 96 h, rt	20%[d] (1.5:1)	6%[d] (5:1)
9	**R'** = H **R** = Pr, COOEt	Various conditions	<1%[e]	<1%[e]
10	**R'** = H **R** = Ph, COOEt	Various conditions	<1%[e]	<1%[e]
11	**R'** = Me **R** = CNC6H4(*p*-OC6H13)	H II, 2 equiv of olefin, CH_2Cl_2, 96 h, rt	22%[f] (>80:1)	32%[f] (20:1)
12	**R'** = Me **R** = CNPh	H II, 1.1 equiv of olefin, 72 h, rt, toluene/CH_2Cl_2	19%[f] (3:1)	21%[f] (3:1)

[a] Catalyst (15 mol %) was used in all experiments.
[b] Yields were calculated in relation to β-carotene and were divided by two due to the symmetry of β-carotene molecule.
[c] The remaining material was mainly the unreacted β-carotene, although its stereochemical purity was not analyzed.
[d] Diastereomeric ratio determined by NMR or HPLC analysis.
[e] Yield obtained by quantitative HPLC analysis.
[f] Isolated yield.

It appeared that both second generation catalysts (G II, H II) effectively promote the examined reactions. In most experiments slightly better product yields were achieved in the presence of H II. All reactions promoted with these catalysts proceeded with similar regioselectivity with respect to β-carotene. Two double bonds C11–C12 and C15–C15′ in the polyene molecule were cleaved during CM reactions. Analyzing the results obtained in the series of β-carotene reactions with unsaturated esters (Table 1, entries 1–8), a conclusion can be drawn that shorter reaction time, less active catalyst, and more demanding substrates favor formation of product **2**. However, compounds **2** can undergo secondary CM reactions to give products **1**. Therefore the more forcing conditions (longer reaction time, more active catalyst, and higher catalyst loading) give higher yields of products **1**. In most cases, the regio- and stereoselectivity can be, to some extent, controlled by selection of the reaction conditions. All ester products in optimized experiments were obtained in rather moderate yields. Interestingly, higher conversion and better diastereoselectivity was achieved in reactions with 3-methylhexa-2,4-dienoates (Table 1, entries 1–5) than those with monounsaturated esters (ethyl pent-4-enoate or cholesteryl crotonate, Table 1, entries 6–8). The higher conversion and better diastereoselectivity attained in reactions of β-carotene with 3-methylhexa-2,4-dienoates than in those with monounsaturated cross partners can be explained by the likely formation of chelate intermediates in the latter case. We assume that during reactions with ethyl pent-4-enoate a new alkylidene ruthenium complex is formed with the oxygen atom of the carbonyl group coordinated to the metallic center (Fig. 3). Such six-membered chelate intermediates were proposed earlier by Taylor for homoallylic alcohol CM[14] and by Grubbs for γ-δ unsaturated amide CM reactions.[15] As chelation decreases catalyst turnover it would result in lower product yields. In the case of reaction of β-carotene with cholesteryl crotonate formation of a four-membered chelate intermediate could be considered.[15]

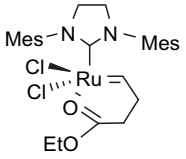


Fig. 3. Proposed structure of chelation in CM reaction with ethyl pent-4-enoate.

We also examined reactions of β-carotene with ethyl penta-2,4-dienoates substituted at C-3 by a substituent larger than a methyl group (*n*-propyl or phenyl, Table 1, entries 9 and 10). However, to our surprise the reactions with these substrates failed. Despite testing various reaction conditions (type and amount of catalyst, amount of cross partner, solvent, temperature, and additives, e.g., chlorocatecholborane) only trace amounts (<1%) of products were obtained.

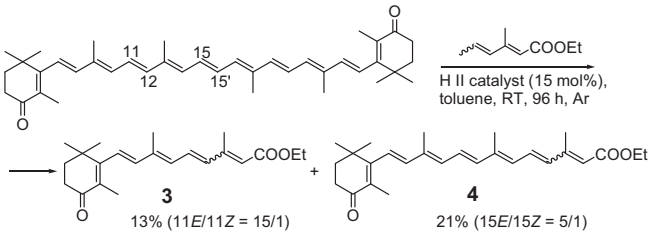
Having in mind the synthesis of fenretinide analogues, we also investigated β-carotene reactions with amide cross partners (Table 1, entries 11, 12 and Scheme 2). In comparison with the results of reactions with unsaturated esters, the amide substrates provided CM products in slightly lower yields but with similar selectivities. *O*-*n*-Hexylfenretinide (Table 1, entry 11) was obtained in 22% yield along with its analogue possessing a longer polyenic chain. Both products showed high *E*-diastereoselectivity (*E*/*Z* better than 20:1). Also fenretinide analogues were synthesized according to this strategy, using *N*-phenylcrotonamide as a cross partner (Table 1, entry 12). However, the *E*/*Z* ratio of products was less satisfactory (3:1). Interestingly, the same products were obtained in the reaction between β-carotene and *N*-phenylsorbamide (Scheme 2) but with better *E*-diastereoselectivity (at least 10:1).

In contrast to the previously reported CM reactions of sorbamide,[11b] *N*-phenylsorbamide exhibited different regioselectivity in reactions with β-carotene—the internal C2–C3 double bond proved to be more reactive than the C4–C5 double bond.

Although many examples of successful CM reactions of vinyl sulfides, sulfones, and phosphates are known in the literature,[16] the reactions of β-carotene with such olefins failed, ever under harsh reaction conditions.

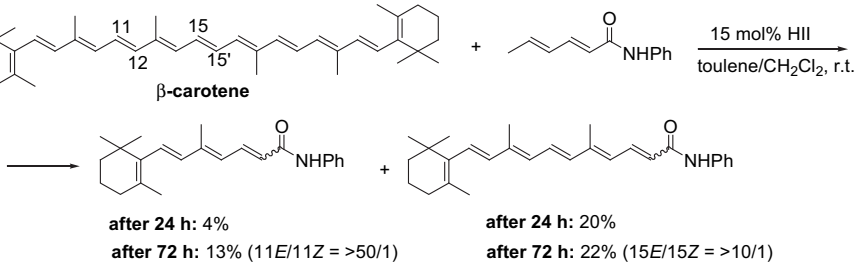
Generally, various β-apocarotenoids (including retinoids, 13-β-apocarotenoids, 12′-β-apocarotenoids, and 14′-β-apocarotenoids) may be obtained in one-step by CM reactions of β-carotene, albeit in moderate yields.

In our further study, the CM reactions of other polyenes—canthaxanthin and retinyl acetate were also examined. Canthaxanthin is the oxygenated analogue of β-carotene, possessing two carbonyl groups in positions 4 and 4′. It was of interest to check if the reactivity of the polyene system conjugated with carbonyl groups remains the same, as in the case of β-carotene, and also what is the regio- and diastereoselectivity of CM reactions of such system. The reaction of canthaxanthin with ethyl (2*E*,4*E*/*Z*)-3-methylhexa-2,4-dienoate was carried out under standard conditions (Scheme 3). After 96 h ethyl 4-oxoretinoate (**3**, 13%) and ethyl 4-oxo-12′-apo-β-caroten-12′-oate (**4**, 21%) were isolated from the reaction mixture.[17] All trans isomers of these products predominated. The obtained result shows that both carotenoids behave similarly in CM reactions, however conversion was much lower for cantaxanthin (60% of unreacted substrate was recovered).



Scheme 3. CM between cantaxanthin and ethyl (2*E*,4*E*/*Z*)-3-methylhexa-2,4-dienoate.

In the case of cantaxanthin reaction with (2*E*,4*E*/*Z*)-*N*-(4-hexyloxyphenyl)-3-methylhexa-2,4-dienamide after 24 h the



Scheme 2. CM between β-carotene and *N*-phenylsorbamide.

all-*trans*-amide **5** (Fig. 4) was selectively obtained in 17% yield. Only a trace amount (<1%) of 4-oxoretinamide was formed. This result and the previous one demonstrated that the presence of additional carbonyl groups in the molecule slightly diminished the reactivity of the C11–C12 double bond in cantaxanthin when compared with β-carotene. The isolated pure amide **5** upon standing in chloroform solution spontaneously underwent partial transformation to its isomer (presumably rotamer), the structure of which was not unequivocally established. The mixture of isomers could be separated by preparative HPLC, but within a few hours both pure isomers afforded again the same equilibrium mixture of isomers.

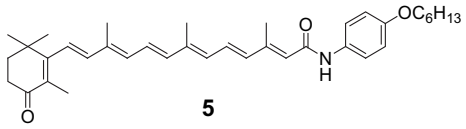
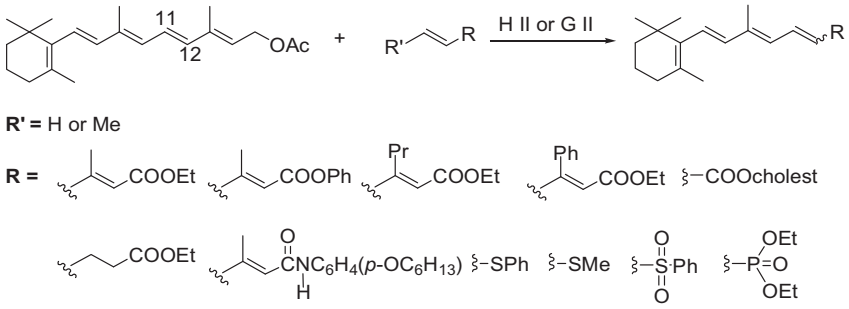


Fig. 4. Product of cantaxanthin CM reaction with (2*E*,4*E*/*Z*)-*N*-(4-hexyloxyphenyl)-3-methylhexa-2,4-dienamide.

In the next stage, CM reactions of retinyl acetate with different dienes and alkenes (Scheme 4) were investigated. The results are shown in Table 2.

As could be expected, in all cases the C11–C12 double bond of retinyl acetate was selectively cleaved. The reactions with (2*E*,4*E*/*Z*)-3-methylhexa-2,4-dienoic acid esters proceeded smoothly under promotion of the Hoveyda–Grubbs second generation catalyst (H II) as well as Grubbs second generation catalyst (G II) to afford the desired retinoates in satisfactory yields and with high diastereoselectivities (Table 2, entries 1–3). The product yield of reaction with the less reactive analogous dienoic amide proved to be a bit lower (Table 2, entry 8). *O*-*n*-Hexylfenretinide was obtained in 26% yield with an excellent diastereoselectivity (Table 2, entry 8). Surprisingly, once again, reactions with alkenoic acid esters (Table 2, entries 4 and 5) proceeded much less effectively and less diastereoselectively. For example, the reaction with ethyl pent-4-enoate afforded the desired product only in 10% yield as a mixture of 11*E*/11*Z* isomers in the 5:1 ratio (Table 2, entry 5). As the main product tetraene **6** (33%, Fig. 5) was obtained through the undesirable



Scheme 4. CM reactions between retinyl acetate and different cross partners.

Table 2
CM reactions between retinyl acetate and different cross partners

Entry	Cross partner R'=R	Reaction conditions[a]	Yield (*E*/*Z*)[b,c] Product
1	**R'** = Me **R** = COOEt	H II, 4 equiv of olefin, toluene, 96 h, rt	55%[e] (40:1)
2	**R'** = Me **R** = COOEt	G II, 4 equiv of olefin, toluene, 96 h, rt	35%[e] (80:1)
3	**R'** = Me **R** = COOPh	H II, 4 equiv of olefin, toluene, 96 h, rt	40%[e] (50:1)
4	**R'** = Me **R** = COOcholest	H II, 4 equiv of olefin, toluene, 96 h, rt	31%[e] (1.8:1)
5	**R'** = H **R** = COOEt	H II, 2 equiv of olefin, toluene, 96 h, rt	10%[e,f] (5:1)
6	**R'** = H **R** = Pr COOEt	H II, 4 equiv of olefin, toluene, 96 h, rt	<1%[e]
7	**R'** = H **R** = Ph COOEt	H II, 4 equiv of olefin, toluene, 96 h, rt	<1%[e]
8	**R'** = Me **R** = CNC6H4(p-OC6H13)	H II, 1.2 equiv of olefin, toluene/CH_2Cl_2, 96 h, rt	26%[d] (95:1)

[a] Catalyst (15 mol %) was used in all experiments.
[b] Diastereomeric ratio determined by NMR or HPLC analysis.
[c] The remaining material was mainly the unreacted retinyl acetate.
[d] Isolated yield.
[e] Yield obtained by quantitative HPLC analysis.
[f] Tetraene **6** was the major reaction product (33%).

metathesis reaction. The derivatives of sorbic acid (Scheme 5) were regioselectively cleaved at the C2–C3 double bond, yielding mainly 13β-apocarotenoid products of CM reactions with retinyl acetate. Ethyl 13-apo-β-carotenoate as well as 13-apo-β-carotenamides were obtained in low yields (10%–15%).

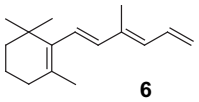


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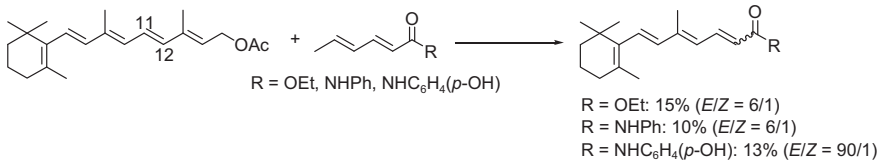
Fig. 5. Main product of retinyl acetate CM with ethyl pent-4-enoate.



Scheme 5. CM reactions between retinyl acetate and sorbic acid derivatives.

Analogously, as in the case of β-carotene, there was no reactions of retinyl acetate with vinyl sulfone, sulfide or phosphate.

3. Conclusions

In summary, CM reactions between polyenes (β-carotene, canthaxanthin, retinyl acetate) and various alkenes and dienes were investigated. Only reaction of retinyl acetate was fully regioselective and yielded, depending on the structure of a cross partner, different apocarotenoids (i.e., retinoids, 13-apocarotenoids). In the case of carotenoid reactions, mixtures of two products **1** and **2** were formed. However, appropriate choice of conditions improved the reaction regio- and diastereoselectivity. Surprisingly, higher yields were obtained in polyene CM reactions with dienes than in those with monounsaturated substrates. This can be rationalized taking into account higher electron density at the terminal double bonds in dienes. The reactivity of dienes in CM reactions depends both on electronic and steric factors. Indeed, the more electron-withdrawing the substituent (ArNH–, EtO–, PhO–) at the carbonyl group, the better the yield of CM reactions. A very important role plays substituent at C-3 in dienes. A bulky substituent (*n*-propyl, phenyl) at this position suppresses completely the reaction, probably due to steric hindrance in the intermediate ruthenium complex (Fig. 6), which prevents the partner olefin from approaching the reaction site. The methyl group allows CM reactions to occur but at the same time it discriminates between different approaches of the partner olefin and favors intermediates leading to *E*-configurated products (reactions are highly *E*-diastereoselective). When there is no substituent at C-3, a different mode of CM reactions was observed. The reactions occurred with C2–C3 double bond cleavage. The lower yields observed for reactions of polyenes with alkenoic esters may result from carbonyl chelation to the ruthenium center (Fig. 3) and in consequence, diminished catalyst activity.

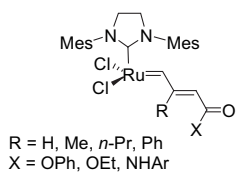


Fig. 6. Ruthenium complex formed in CM reaction with (2*E*,4*E*/*Z*)-3-methylhexa-2,4-dienoic acid derivatives.

In our opinion, CM reactions of different retinoids and carotenoids provide an alternative, one-step route to apocarotenoids, including retinoids. The cross metathesis seems to be a fast and useful approach to the synthesis of small samples of various apocarotenoids for biological and structural studies.

4. Experimental

4.1. General information

All manipulations of retinoids, such as isolation, purification, etc. were performed in argon atmosphere. All retinoids were stored in argon atmosphere at −20 °C. Toluene and dichloromethane for CM reactions were distilled over calcium hydride under argon just prior to use.

NMR spectra were recorded with a Bruker Avance II 400 spectrometer using $CDCl_3$ solutions with TMS as the internal standard (only selected signals in the ^1H NMR spectra are reported). Infrared spectra were recorded on a Nicolet series II Magna-IR 550 FT-IR spectrometer in chloroform solutions. Mass spectra were obtained at 70 eV with AMD-604 spectrometer. UV/vis spectra were recorded in dichloromethane. The reactions were analyzed by TLC or HPLC method. The products were isolated by column chromatography performed on 70–230 mesh silica gel (J. T. Baker) or by semipreparative HPLC.

HPLC analysis: HPLC was performed with LabAlliance apparatus comprised of pumps (III Pump series), UV/vis detector (525 Dual-wavelength) and injection valve (Rheodyne Model 7725i). Analytical HPLC was carried out with a Supelco-Si column (5 μm), 0.46×25 cm, and semipreparative HPLC with SMT–Silica (5 μm), 1.0×25 cm, eluting solvent was 98.5:1.5 *n*-hexane/ethyl acetate, isocratic, the flow rate: 3.4 ml/min. The elution pattern of retinoids was monitored continuously by UV at 340 or 365 nm.

4.2. General procedure for CM reactions

To the solution of a polyene (c=9.7×10^{-2} or 4.9×10^{-2} M) and of Hoveyda (Grubbs) second generation catalyst (15 mol %) in dry toluene (or dichloromethane or methanol) olefin (1–4 equiv) was added dropwise. The reaction mixture was stirred at rt under argon atmosphere. Then the mixture was analyzed by HPLC and purified by semipreparative HPLC or column chromatography.

4.3. Synthesis

4.3.1. Phenyl retinoate. UV/vis (dichloromethane) λ_{max} (ε)=370 nm (43,650); IR ($CHCl_3$) ν_{max} 1723, 1579, 1493, 1220, 1127, 968 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.05 (s, 6H), 1.49 (m, 2H), 1.64 (m, 2H), 1.74 (s, 3H), 2.037 (s, 3H), 2.040 (m, 2H), 2.42 (s, 3H), 6.01 (s, 1H), 6.17 (d, J=16.1 Hz, 1H), 6.20 (d, J=11.4 Hz, 1H), 6.29 (d, J=15.0 Hz, 1H), 6.32 (d, J=16.1 Hz, 1H), 6.39 (d, J=12.0 Hz, 1H), 7.09 (dd, J=11.4, 15.0 Hz, 1H), 7.13 (m, 2H), 7.23 (m, 1H), 7.39 (m, 2H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 13.0 (CH_3), 14.1 (CH_3), 19.2 (CH_2), 12.9 (CH_3)21.7 (CH_3), 29.0 (2× CH_3), 33.1 (CH_2), 34.3 (C), 39.6 (CH_2), 117.2 (CH), 121.8 (2× CH), 129.1 (CH), 125.5 (CH), 130.2 (C), 129.3 (2× CH), 129.4 (CH), 137.2

(CH), 131.9 (CH), 134.8 (CH), 140.4 (C), 137.7 (C), 150.8 (C), 155.5 (C), 165.5 (C); LRMS (EI): *m/z* (%): 376 (M^+, 41), 283 (124), 267 (12); HRMS (ESI): *m/z* calcd for $C_{26}H_{32}O_2Na$ (MNa^+): 399.2300, found: 399.2303.

4.3.2. Phenyl 12′-apo-β-caroten-12′-oate. UV/vis (dichloromethane) λ_{max} (ε)=414 (26,220); IR ($CHCl_3$) ν_{max} 1722, 1590, 1552, 1493, 1126, 967 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.05 (s, 6H); 1.48 (m, 2H), 1.63 (m, 2H), 1.73 (s, 3H), 2.00 (s, 3H), 2.03 (m, 2H), 2.06 (s, 3H), 2.42 (s, 3H), 6.02 (s, 1H), 6.15 (m, 2H), 6.20 (d, *J*=12.4 Hz, 1H), 6.27 (d, *J*=11.4 Hz, 1H), 6.38 (d, *J*=15.0 Hz, 1H), 6.41 (d, *J*=15.0 Hz, 1H), 6.78 (dd, *J*=11.4, 15.0 Hz 1H), 7.08 (dd, *J*=11.6, 15.0 Hz, 1H), 7.13 (m, 2H), 7.23 (m, 1H), 7.39 (m, 2H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 13.1 (CH_3), 14.1 (CH_3), 12.8 (CH_3), 19.2 (CH_2), 29.0 (2× CH_3), 21.8 (CH_3), 33.1 (CH_2), 34.3 (C), 39.6 (CH_2), 117.4 (CH), 127.0 (CH), 121.8 (2× CH),125.5 (CH), 129.3 (2× CH), 127.5 (CH), 130.4 (CH), 129.7 (C), 135.2 (CH), 130.8 (CH), 131.9 (CH), 137.4 (C), 136.5 (CH), 137.6 (CH), 140.5 (C), 137.8 (C), 150.8 (C), 155.4 (C) and 165.4 (C); LRMS (ESI): *m/z* 465 (MNa^+); HRMS (ESI): *m/z* calcd for $C_{31}H_{38}O_2Na$ (MNa^+): 465.2770, found: 465.2785.

4.3.3. Cholesteryl (all E) 13-apo-β-caroten-13-oate. UV/vis (dichloromethane) λ_{max} (ε)=336 (47,013); IR ($CHCl_3$) ν_{max} 1693, 1598, 1272, 1148 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 0.69 (s, 3H), 0.876 (d, *J*=6.6 Hz, 3H), 0.881 (d, *J*=6.6 Hz, 3H), 0.93 (d, *J*=6.5 Hz, 3H), 1.04 (s, 6H), 1.05 (s, 3H), 1.74 (s, 3H), 2.01 (m, 2H), 2.05 (s, 3H), 2.38 (m, 2H), 4.70 (m, 1H), 5.40 (d, *J*=5.0 Hz, 1H), 5.86 (d, *J*=5.0 Hz, 1H), 6.16 (m, 2H), 6.39 (d, *J*=15.4 Hz, 1H), 7.71 (dd, *J*=12.0, 15.0 Hz, 1H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 11.9 (CH_3), 13.0 (CH_3), 19.2 (CH_2), 18.7 (CH_3), 19.4 (CH_3), 21.0 (CH_2), 21.7 (CH_3), 22.6 (CH_3), 22.8 (CH_3), 23.8 (CH_2), 24.3 (CH_2), 27.9 (CH_2), 28.0 (CH), 28.2 (CH_2), 28.9 (2× CH_3), 31.87 (CH), 31.92 (CH_2), 33.1 (CH_2), 34.2 (C), 35.8 (CH), 36.2 (CH_2), 36.6 (C), 37.0 (CH_2), 38.2 (CH_2), 39.6 (CH_2), 39.7 (CH_2), 42.3 (C), 50.0 (CH), 56.1 (CH), 56.7 (CH), 73.7 (CH), 120.5 (CH), 122.6 (CH), 127.3 (CH), 130.65 (C), 130.73 (CH), 136.7 (CH), 137.5 (C), 139.8 (C), 140.5 (CH), 144.2 (C), 167.0 (C); LRMS (ESI): *m/z* 1280 ($2MNa^+$), 683 (MNa^++MeOH), 651 (MNa^+); HRMS (ESI): *m/z* calcd for $C_{44}H_{68}O_2Na$ (MNa^+): 651.5117, found: 651.5131.

4.3.4. Cholesteryl (11Z) 13-apo-β-caroten-13-oate. UV/vis (dichloromethane) λ_{max} (ε)=334 (23,900); IR ($CHCl_3$) ν_{max} 1698, 1598, 1273 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 0.69 (s, 3H), 0.87 (d, *J*=6.6 Hz, 3H), 0.88 (d, *J*=6.6 Hz, 3H), 0.93 (d, *J*=6.5 Hz, 3H), 1.04 (s, 6H), 1.05 (s, 3H), 1.72 (s, 3H), 2.02 (m, 2H), 2.08 (s, 3H), 2.38 (m, 2H), 4.70 (m, 1H), 5.40 (d, *J*=4.3 Hz, 1H), 5.86 (d, *J*=15.0 Hz, 1H), 6.16 (m, 2H), 6.39 (d, *J*=15.6 Hz, 1H), 7.71 (dd, *J*=11.9, 15.0 Hz, 1H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 11.9 (CH_3), 13.0 (CH_3), 18.7 (CH_3), 19.2 (CH_2), 19.4 (CH_3), 21.0 (CH_2), 21.7 (CH_3), 22.6 (CH_3), 22.8 (CH_3), 23.8 (CH_2), 24.3 (CH_2), 27.9 (CH_2), 28.0 (CH), 28.2 (CH_2), 28.9 (2× CH_3), 31.90 (CH), 31.93 (CH_2), 33.1 (CH_2), 34.3 (C), 35.8 (CH), 36.2 (CH_2), 36.6 (C), 37.1 (CH_2), 38.3 (CH_2), 39.5 (CH_2), 39.6 (CH_2), 39.8 (CH_2), 42.3 (C), 50.1 (CH), 56.2 (CH), 56.7 (CH), 73.8 (CH), 120.5 (CH), 122.6 (CH), 127.3 (CH), 130.6 (C), 130.7 (CH), 136.8 (CH), 137.5 (C), 139.8 (C), 140.5 (CH), 144.2 (C), 166.9 (C); LRMS (ESI): *m/z* 1280 ($2MNa^+$), 683 (MNa^++MeOH), 651 (MNa^+); HRMS (ESI): *m/z* calcd for $C_{44}H_{68}O_2Na$ (MNa^+): 651.5117, found: 651.5131.

4.3.5. Cholesteryl (all E) 14′-apo-β-caroten-14′-oate. UV/vis (dichloromethane) λ_{max} (ε)=390 (19,200); IR ($CHCl_3$) ν_{max} 1693, 1615, 1563, 1305, 1155 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 0.69 (s, 3H), 0.87 (d, *J*=6.6 Hz, 3H), 0.88 (d, *J*=6.6 Hz, 3H), 0.93 (d, *J*=6.5 Hz, 3H), 1.04 (s, 6H), 1.05 (s, 3H), 1.73 (s, 3H), 2.00 (s, 3H), 2.04 (m, 2H), 2.07 (s, 3H), 2.38 (m, 2H), 4.71 (m, 1H), 5.40 (d, *J*=4.6 Hz, 1H), 5.88 (d, *J*=15.0 Hz, 1H), 6.10–6.28 (m, 4H), 6.36 (d, *J*=14.7 Hz, 1H), 6.83 (dd, *J*=11.4, 15.0 Hz, 1H), 7.69 (dd, *J*=12.0, 15.0 Hz, 1H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 11.9 (CH_3), 12.8 (CH_3), 13.2 (CH_3), 18.7 (CH_3), 19.3 (CH_2), 19.4 (CH_3), 21.1 (CH_2), 21.7 (CH_3), 22.6 (CH_3), 22.8 (CH_3), 23.8 (CH_2), 24.3 (CH_2), 27.9 (CH_2), 28.0 (CH), 28.2 (CH_2), 29.0 (2× CH_3), 31.91 (CH_2), 31.94 (CH), 33.1 (CH_2), 34.3 (C), 35.8 (CH), 36.2 (CH_2), 36.7 (C), 37.1 (CH_2), 38.3 (CH_2), 39.5 (CH_2), 39.7 (CH_2), 39.8 (CH_2), 42.3 (C), 50.1 (CH), 56.2 (CH), 56.7 (CH), 73.8 (CH), 120.8 (CH), 122.6 (CH), 128.0 (CH), 128.3 (CH), 128.5 (CH), 129.8 (C), 130.1 (CH), 136.0 (CH), 137.5 (CH), 138.3 (C), 139.8 (C), 140.2 (CH), 142.9 (C), 144.2 (C), 166.9 (C); LRMS (ESI): *m/z* 717 (MNa^+); HRMS (ESI): *m/z* calcd for $C_{49}H_{74}O_2Na$ (MNa^+): 717.5586, found: 717.5599.

4.3.6. Ethyl (11E/Z) 13-nor-13,14-dihydroretinoate. UV/vis (dichloromethane) λ_{max} (ε)=290 (14,200); IR ($CHCl_3$) ν_{max} 1727, 1604, 1265 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.02 (s, 6H), 1.27 (t, *J*=7.1 Hz, 3H), 1.47 (m, 2H), 1.62 (m, 2H), 1.70 (s, 3H), 1.90 (s, 3H), 2.01 (t, *J*=6.2 Hz, 2H), 2.36 (s, 3H), 2.43 (m, 2H), 2.47 (m, 2H), 4.15 (q, *J*=7.1 Hz, 2H), 5.71 (dt, *J*=6.7, 15.0 Hz, 1H), 5.99 (d, *J*=11.2 Hz, 1H), 6.03–6.15 (m, 2H), 6.46 (m, 1H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 12.5 (CH_3), 14.2 (CH_3), 14.3 (CH_3), 19.3 (CH_2), 21.4 (CH_3), 21.7 (CH_3), 28.4 (CH_2), 28.9 (2× CH_3), 33.0 (CH_2), 34.2 (C, CH_2), 39.6 (CH_2), 60.3 (CH_2), 126.3 (CH), 128.0 (CH), 128.9 (C), 129.4 (CH), 132.1 (CH), 134.5 (C), 137.7 (CH), 137.9 (C), 173.0 (C), LRMS (EI): *m/z* (%) 316 (M^+, 72), 301 (3), 157 (39), 145 (64), 91 (100); HRMS (EI): *m/z* calcd for $C_{21}H_{32}O_2$ (M^+): 316.2402, found: 316.2411.

4.3.7. Ethyl (15E/Z) 12′-apo-13′-nor-13′,14′-dihydro-β-caroten-12′-oate. ^1H NMR (400 MHz; $CDCl_3$) δ 1.03 (s, 6H), 1.27 (t, *J*=7.1 Hz, 3H), 1.49 (m, 2H), 1.62 (m, 2H), 1.72 (s, 3H), 1.92 (s, 3H), 1.97 (s, 3H), 2.03 (t, *J*=6.2 Hz, 2H), 2.36 (s, 3H), 2.44 (m, 2H), 2.48 (m, 2H), 4.15 (q, *J*=7.1 Hz, 2H), 5.74 (dt, *J*=6.6, 14.3 Hz, 1H), 6.05–6.15 (m, 4H), 6.30 (d, *J*=15.0 Hz, 1H), 6.44 (m, 1H), 6.61 (dd, *J*=11.3, 14.9 Hz, 1H). A very unstable compound—it decomposed during ^{13}C NMR analysis.

4.3.8. N-(4-Hexyloxyphenyl)retinamide. UV/vis (dichloromethane) λ_{max} (ε)=370 (63,700); IR ($CHCl_3$) ν_{max} 3434, 1663, 1580, 1511, 1242, 1156 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 0.92 (t, *J*=6.9 Hz, 3H), 1.04 (s, 6H), 1.35 (m, 4H), 1.46 (m, 4H), 1.63 (m, 2H), 1.73 (s, 3H), 1.77 (m, 2H), 2.01 (s, 3H), 2.03 (m, 2H), 2.43 (s, 3H), 3.94 (t, *J*=6.6 Hz, 2H), 5.79 (s, 1H), 6.15 (m, 2H), 6.29 (m, 2H), 6.86 (m, 2H), 6.99 (dd, *J*=11.5, 14.8 Hz, 1H), 7.07 (br s, 1H), 7.45 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 12.9 (CH_3), 13.6 (CH_3), 14.0 (CH_3), 19.2 (CH_2), 21.7 (CH_3), 22.6 (CH_2), 25.7 (CH_2), 29.0 (2× CH_3), 29.2 (CH_2), 31.6 (CH_2), 33.1 (CH_2), 34.3 (C), 39.6 (CH_2), 68.3 (CH_2), 114.9 (2× CH), 121.36 (CH), 121.42 (CH), 121.5 (C), 128.4 (CH), 129.5 (2× CH), 129.9 (C), 130.2 (CH), 131.2 (C), 135.4 (CH), 137.3 (CH), 137.7 (C), 139.1 (C), 150.2 (C), 155.9 (C); LRMS (ESI): *m/z* 973 ($2MNa^+$), 498 (MNa^+); HRMS (ESI): *m/z* calcd for $C_{32}H_{45}NO_2Na$ (MNa^+): 498.3348, found: 498.3358.

4.3.9. N-(4-Hexyloxyphenyl)-12′-apo-β-caroten-12′-amide. UV/vis (dichloromethane) λ_{max} (ε)=480 (16,300); IR ($CHCl_3$) ν_{max} 3433, 1663, 1596, 1511, 1241, 1157 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 0.92 (t, *J*=6.9 Hz, 3H), 1.04 (s, 6H), 1.35 (m, 4H), 1.48 (m, 4H), 1.63 (m, 2H), 1.73 (s, 3H), 1.78 (m, 2H), 2.00 (s, 3H), 2.04 (s, m, 5H), 2.43 (s, 3H), 3.94 (t, *J*=6.6 Hz, 2H), 5.80 (s, 1H), 6.12–6.24 (m, 4H), 6.31 (d, *J*=15.0 Hz, 1H), 6.37 (d, *J*=15.0 Hz, 1H), 6.74 (dd, *J*=11.4, 14.5 Hz, 1H), 6.86 (m, 2H), 6.98 (dd, *J*=10.9, 14.0 Hz, 1H), 7.06 (br s, 1H), 7.45 (d, *J*=8.2 Hz, 2H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 12.8 (CH_3), 13.0 (CH_3), 13.6 (CH_3), 14.0 (CH_3), 19.3 (CH_2), 21.8 (CH_3), 22.6 (CH_2), 25.7 (CH_2), 29.0 (2× CH_3), 29.2 (CH_2), 31.6 (CH_2), 33.1 (CH_2), 34.3 (C), 39.6 (CH_2), 68.3 (CH_2), 114.8 (2× CH), 121.4 (CH), 121.6 (CH), 126.4 (CH), 127.3 (2× CH), 129.6 (2× C), 130.2 (CH), 130.5 (CH), 131.0 (CH), 135.9 (CH), 136.7 (CH), 137.0 (C), 137.6 (CH), 137.9 (C), 139.2 (C), 150.1 (C), 155.9 (C), 164.8 (C); LRMS (ESI): *m/z* 564 (MNa^+); HRMS (ESI): *m/z* calcd for $C_{37}H_{51}NO_2Na$ (MNa^+): 564.3817, found: 564.3826.

4.3.10. N-Phenyl-13-apo-β-caroten-13-amide. UV/vis (dichloromethane) λ_{max} (ε)=342 (13,500); IR ($CHCl_3$) ν_{max} 3431, 1674, 1597, 1522, 1438 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.05 (s, 6H), 1.49 (m, 2H), 1.63 (m, 2H), 1.73 (s, 3H), 2.03 (m 2H), 2.08 (s, 3H), 5.99 (d, *J*=14.5 Hz, 1H), 6.15–6.20 (m, 2H), 6.40 (d, *J*=16.2 Hz, 1H), 7.12 (m, 2H), 7.35 (m, 2H), 7.59 (br s, 2H), 7.82 (dd, *J*=12.0, 14.5 Hz, 1H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 13.0 (CH_3), 19.2 (CH_2), 21.7 (CH_3), 28.9 (2× CH_3), 33.1 (CH_2), 34.3 (C), 39.6 (CH_2), 119.7 (CH), 124.3 (CH), 127.1 (2× CH), 129.0 (3× CH), 129.1 (C), 130.6 (C), 130.7 (CH), 136.8 (2× CH), 137.6 (C), 138.4 (C), 144.2 (C); LRMS (ESI): *m*/*z* 358 (MNa^+); HRMS (ESI): *m*/*z* calcd for $C_{23}H_{29}NONa$ (MNa^+): 358.2147, found: 358.2145.

4.3.11. N-Phenyl-14′-apo-β-caroten-14′-amide. UV/vis (dichloromethane) λ_{max} (ε)=382 (52,100); IR ($CHCl_3$) ν_{max} 3430, 1671, 1599, 1522, 1438 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.05 (s, 6H), 1.48 (m, 2H), 1.63 (m, 2H), 1.73 (s, 3H), 2.01 (s, 3H), 2.04 (m, 2H), 2.10 (s, 3H), 6.00 (d, *J*=14.4 Hz, 1H), 6.13–6.28 (m, 4H), 6.37 (d, *J*=15.0 Hz, 1H), 6.84 (dd, *J*=11.5, 15.0 Hz, 1H), 7.11–7.21 (m, 2H), 7.35 (m, 2H), 7.59 (m, 2H), 7.81 (dd, *J*=12.0, 14.4 Hz, 1H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 12.9 (CH_3), 13.2 (CH_3), 19.2 (CH_2), 21.7 (CH_3), 29.0 (2× CH_3), 33.1 (CH_2), 34.3 (C), 39.6 (CH_2), 119.8 (CH), 124.2 (CH), 128.0 (CH), 128.3 (CH), 129.0 (4× CH), 129.8 (C), 130.1 (2× CH), 136.0 (CH), 137.5 (2× CH), 137.8 (C), 138.2 (C), 138.56 (C), 138.59 (C), 144.2 (C); LRMS (ESI): *m*/*z* 424 (MNa^+); HRMS (ESI): *m*/*z* calcd for $C_{28}H_{35}NONa$ (MNa^+): 424.2616, found: 424.2617.

4.3.12. N-(4-Hydroxyphenyl)-13-apo-β-caroten-13-amide. UV/vis (dichloromethane) λ_{max} (ε)=348 (13,300); IR ($CHCl_3$) ν_{max} 3432, 3313, 1663, 1592, 1514. 1265 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.03 (s, 6H), 1.47 (m, 2H), 1.61 (m, 2H), 1.71 (s, 3H), 2.02 (m, 2H), 2.06 (s, 3H), 4.90 (br s, 1H), 5.94 (d, *J*=14.5 Hz, 1H), 6.15 (m, 2H), 6.37 (d, *J*=15.8 Hz, 1H), 6.80 (d, *J*=8.8 Hz, 2H), 7.04 (br s, 1H), 7.43 (m, 2H), 7.78 (dd, *J*=12.0, 14.5 Hz, 1H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 13.0 (CH_3), 19.2 (CH_2), 21.7 (CH_3), 28.9 (2× CH_3), 33.1 (CH_2), 34.3 (C), 39.6 (CH_2), 115.7 (2× CH), 127.1 (CH), 128.3 (4× CH), 130.53 (2× C), 130.54 (CH), 136.8 (C, CH), 137.6 (C), 144.0 (C), 146.0 (C); LRMS (ESI): *m*/*z* 374 (MNa^+); HRMS (ESI): *m*/*z* calcd for $C_{23}H_{29}NO_2Na$ (MNa^+): 374.2096, found: 374.2102.

*4.3.13. Ethyl 4-oxoretinoate (**3**, 13%).* UV/vis (dichloromethane) λ_{max} (ε)=360 (44,545); IR ($CHCl_3$) ν_{max} 1702, 1652, 1610, 1590, 1353, 1242, 1156, 970 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.20 (s, 6H), 1.31 (t, *J*=7.1 Hz, 3H), 1.865 (s, 3H), 1.870 (m, 2H), 2.04 (s, 3H), 2.37 (s, 3H), 2.51 (m, 2H), 4.20 (q, *J*=7.1 Hz, 2H), 5.82 (s, 1H), 6.27 (d, *J*=11.0 Hz, 1H), 6.34–6.39 (m, 3H), 6.99 (dd, *J*=11.3, 15.0 Hz, 1H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 12.8 (CH_3), 13.76 (CH_3), 13.81 (CH_3), 14.3 (CH_3), 27.6 (2× CH_3), 34.3 (CH_2), 35.7 (C), 37.4 (CH_2), 59.8 (CH_2), 119.8 (CH), 125.9 (CH), 130.1 (CH), 132.8 (CH), 137.2 (CH), 137.9 (C), 140.5 (CH), 145.0 (C), 152.1 (C), 160.8 (C), 167.0 (C), 199.2 (C); LRMS (ESI): *m*/*z* 365 (MNa^+); HRMS (ESI): *m*/*z* calcd for $C_{22}H_{30}O_3Na$ (MNa^+): 365.2093, found: 365.2105.

*4.3.14. Ethyl 4-oxo-12′-apo-β-caroten-12′-oate (**4**, 21%).* UV/vis (dichloromethane) λ_{max} (ε)=410 (73,073); IR ($CHCl_3$) ν_{max} 1701, 1651, 1595, 1242, 1156, 969 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.20 (s, 6H), 1.30 (t, *J*=7.1 Hz, 3H), 1.86 (m, 2H), 1.89 (s, 3H), 2.02 (s, 3H), 2.04 (s, 3H), 2.37 (s, 3H), 2.52 (m, 2H), 4.19 (q, *J*=7.1 Hz, 2H), 5.81 (s, 1H), 6.26–6.29 (m, 2H), 6.33–6.37 (m, 2H), 6.37 (d, *J*=16.0 Hz, 1H), 6.44 (d, *J*=15.0 Hz, 1H), 6.73 (dd, *J*=11.4, 15.0 Hz, 1H), 6.99 (dd, *J*=11.5, 15.0 Hz, 1H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 12.6 (CH_3), 13.0 (CH_3), 13.8 (CH_3), 14.3 (CH_3), 21.1 (CH_3), 27.7 (2× CH_3), 34.3 (CH_2), 35.7 (C), 37.4 (CH_2), 59.7 (CH_2), 119.4 (CH), 124.6 (CH), 125.8 (CH), 129.9 (C), 130.6 (CH), 132.1 (CH), 134.0 (CH), 135.6 (C), 136.5 (CH), 138.8 (CH), 139.2 (C), 141.0 (CH), 152.3 (C), 161.1 (C), 167.1 (C), 199.3 (C); LRMS (ESI): *m*/*z* 431 (MNa^+); HRMS (ESI): *m*/*z* calcd for $C_{27}H_{36}O_3Na$ (MNa^+): 431.2562, found: 431.2580.

*4.3.15. N-(4-Hexyloxyphenyl)-4-oxo-12′-apo-β-caroten-12′-amide (**5**, 17%).* UV/vis (dichloromethane) λ_{max} (ε)=420 (42,670); IR ($CHCl_3$) ν_{max} 3434, 1653, 1595, 1511, 1470, 1354, 1240, 1157, 969 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 0.92 (t, *J*=6.9 Hz, 3H), 1.21 (s, 6H), 1.35 (m, 3H), 1.46 (m, 2H), 1.78 (m, 3H), 1.86 (m, 2H), 1.88 (s, 3H), 2.02 (s, 3H), 2.04 (s, 3H), 2.43 (s, 3H), 2.52 (t, *J*=6.7 Hz, 2H), 3.95 (t, *J*=6.6 Hz, 2H), 5.82 (s, 1H), 6.27 (m, 2H), 6.35 (m, 2H), 6.44 (d, *J*=15.1 Hz, 1H), 6.73 (dd, *J*=11.6, 15.2 Hz, 1H), 6.87 (d, *J*=8.9 Hz, 2H), 7.00 (dd, *J*=11.9, 14.9 Hz, 1H), 7.07 (br s, 1H), 7.46 (d, *J*=8.9 Hz, 2H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 12.6 (CH_3), 13.0 (CH_3), 13.6 (CH_3), 13.8 (CH_3), 14.0 (CH_3), 22.6 (CH_2), 25.7 (CH_2), 27.7 (2× CH_3), 29.2 (CH_2), 31.6 (CH_2), 34.3 (CH_2), 35.7 (C), 37.4 (CH_2), 68.3 (CH_2), 114.8 (2× CH), 121.4 (CH), 122.1 (CH), 124.5 (CH), 125.7 (CH), 129.9 (2× C), 131.1 (CH), 132.3 (CH), 134.0 (CH), 134.2 (CH), 135.5 (C), 136.8 (CH), 138.78 (C), 138.84 (CH), 141.1 (CH, C), 149.9 (C), 155.9 (C), 161.1 (C), 199.3 (C); LRMS (ESI): *m*/*z* 1134 ($2MNa^+$), 578 (MNa^+); HRMS (ESI): *m*/*z* calcd for $C_{37}H_{49}NO_3Na$ (MNa^+): 578.3610, found: 578.3618.

*4.3.16. 12-Apo-β-carotene (**6**, 33%).* UV/vis (dichloromethane) λ_{max} (ε)=304 (19,600); ^1H NMR (200 MHz; $CDCl_3$) δ 1.03 (s, 6H), 1.48 (m, 2H), 1.63 (m, 2H), 1.71 (s, 3H), 1.93 (s, 3H), 2.02 (m, 2H), 5.18 (m, 2H), 6.03–6.15 (m, 2H), 6.65–6.84 (m, 1H); ^{13}C NMR (50 MHz; $CDCl_3$) δ 12.6 (CH_3), 19.3 (CH_2), 21.7 (CH_3), 28.9 (2× CH_3), 33.0 (CH_2), 34.2 (C), 39.6 (CH_2), 116.7 (CH_2), 127.2 (CH), 129.1 (C), 130.2 (CH), 133.3 (CH), 136.2 (C), 137.5 (CH), 137.8 (C); LRMS (EI): *m*/*z* (%) 216 (M^+, 74), 201 (45), 173 (18), 159 (32), 145 (99) 131 (100); HRMS (EI): *m*/*z* calcd for $C_{16}H_{24}$ (M^+): 216.1878, found: 216.1886.

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Supplementary data

IR, ^1H NMR, ^{13}C NMR, and MS spectra for all compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.06.086.

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