Retinoids and related compounds. Part 26.[1] Synthesis of (11*Z*)-8,18-propano- and methano-retinals and conformational study of the rhodopsin chromophore †

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In order to clarify the conformation of the chromophore in rhodopsin, especially the effect of the torsional angle around the C6–C7 single bond on the CD spectrum, 8,18-propano- and methano-retinal **4** and **5** were prepared *via* the palladium-catalyzed coupling reaction of vinyl triflates derived from bicyclic ketones **10** and **27** with methyl (*E*)-3-(trimethylstannyl)but-2-enoate. In a binding experiment with bovine opsin, retinal analogs **4** and **5** afforded the new rhodopsin analogs. Although the opsin shifts of these pigments were similar to that of the native rhodopsin, CD spectra exhibited the characteristic feature owing to the locked structures of retinal analogs. This fact strongly indicates that the CD spectra were significantly influenced by the torsional angles around the 6–7 and 8–9 single bonds of the chromophore in the protein.

In the visual pigment rhodopsin (Rho) **1** (Fig. 1), the chromophore (11*Z*)-retinal **2** is bound to the ε-amino group of the apoprotein lysine residue through a protonated Schiff base (PSB),[2] and exhibits a characteristic circular dichroism (CD) signal at α and β bands in the visible (VIS) and near-ultraviolet (UV) region [α-band: 487 nm (+7.5), β-band: 335 nm (+15.4)], in spite of CD-silence in both the (11*Z*)-retinal and apoprotein opsin.[3] It is of particular interest for the conformational analysis of the Rho chromophore to elucidate the origin of the CD bands of Rho, since the CD spectrum gives precise information about the interaction between the chromophore and the protein in the photo-bleaching intermediate of Rho.[3,4] We have found that the α-CD band originates from the torsion around the 12–13 single bond of the chromophore and that the twisted 6s-single bond strongly affects the β-band of Rho using the retinal analog, in which the 12–13 or 5–6 single bond of retinal was fixed by the five-membered ring.[5] Very recently, we have also shown that the torsional angle around the 6–7 single bond of retinal chromophore in Rho is very close to that of 8,18-ethanoretinal **3**, in which the C8 and C18 positions of **2** are connected by an ethylene group, from the comparison of opsin shift and CD spectrum of the artificial pigment with those of native rhodopsin.[6] In this paper, we describe the synthesis of (11*Z*)-8,18-propano- and methano-retinal **4** and **5**, which have one more or fewer methylene group than does **3**, and their interaction with bovine opsin in order to clarify the effect on the CD spectrum of a change of the torsional angle around the 6–7 single bond in the chromophore, including a full account of our preliminary communication.[7]

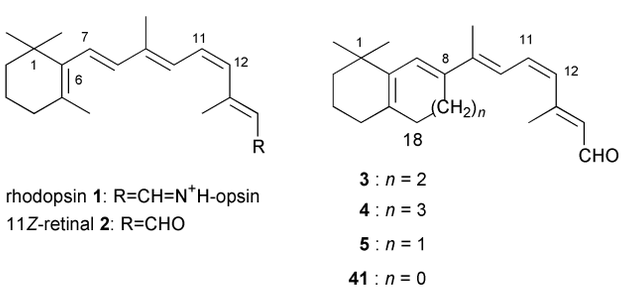

Fig. 1

Results and discussion

(11*Z*)-8,18-Propanoretinal 4. The bicyclic ketone **10** was prepared from the β-keto ester **6** *via* the Dieckmann condensation in the same manner as described for the preparation of **3**[8] in seven steps (11% yield, Scheme 1). The reaction of **10** with trimethylsilylethynylcerium(III) reagent[9] smoothly proceeded to afford the alcohol **11** in 87% yield. The attempted conversion of **11** to the corresponding β-ionone analog **12′** using formic acid[10] was unsuccessful, because the conjugated geometrical double-bond isomer **12** was obtained as a sole product in poor yield. From this fact, we speculated that the thermodynamic energy difference between the olefinic compounds **12** and **12′** was not enough to produce the more conjugated olefin **12** in the dehydration process due to a torsion of the 6–7 (ref. 11) single bond of the bicyclic ring skeleton. To circumvent this problem, we tried to perform dehydration after elongation of the side chain.

Hydration of **11** was achieved by the usual manner using mercury(II) oxide and sulfuric acid to give the ketone **13** in 68% yield. After acetylation of the hydroxy group in **13**, the Horner–Emmons reaction of **14** with a C-2 phosphonate gave the nitrile **15** as a mixture of newly produced double-bond isomers. In the diisobutylaluminium hydride (DIBAL-H) reduction of **15**, isomerization of the double bond and deacetylation of the acetoxy group occurred at the same time to afford the aldehyde **16** as a single product. Dehydration of **16** by thionyl dichloride gave the more conjugated aldehyde **17** as the sole product in moderate yield (Scheme 2). The structure of **17** was

† Electronic supplementary information (ESI) available: UV-VIS and ^{1}H NMR data are available for retinal, 8,18-propanoretinal and 8,18-methanoretinal isomers. See http://www.rsc.org/suppdata/p1/b1/b104394n/

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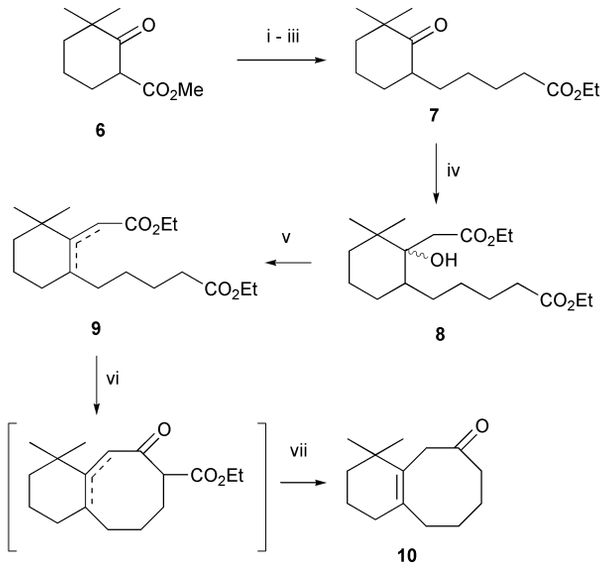
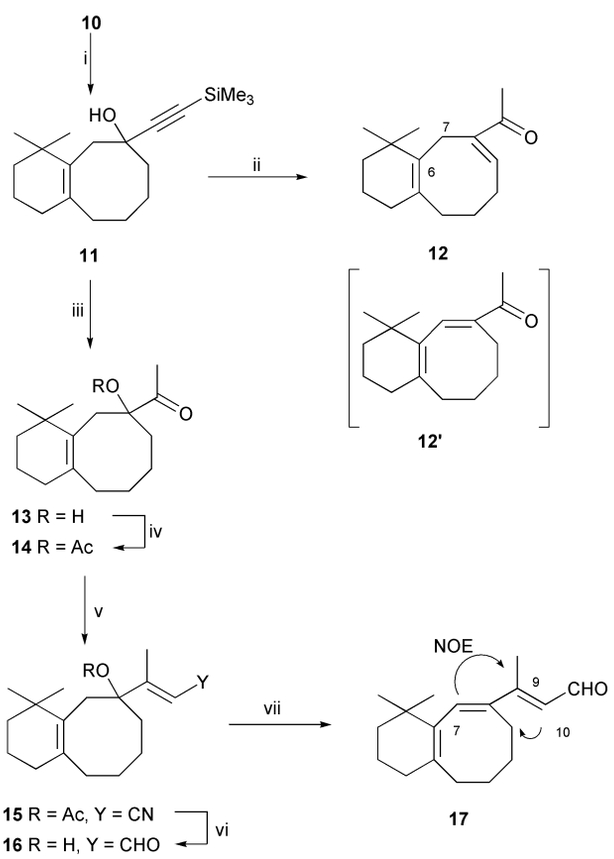


Scheme 1 *Reagents and conditions (and yields)*: i, NaH, $Br(CH_2)_4$-CO_2Et, reflux, ii, c. HCl, reflux; iii, c. H_2SO_4, EtOH, reflux (49% from **6**); iv, LDA, AcOEt, THF, −70 °C (91%); v, $SOCl_2$, pyridine, 0 °C (95%); vi, *t*-BuOK, *o*-xylene, reflux, viii, $MgCl_2·6H_2O$, DMSO, 160 °C (27% from **9**).

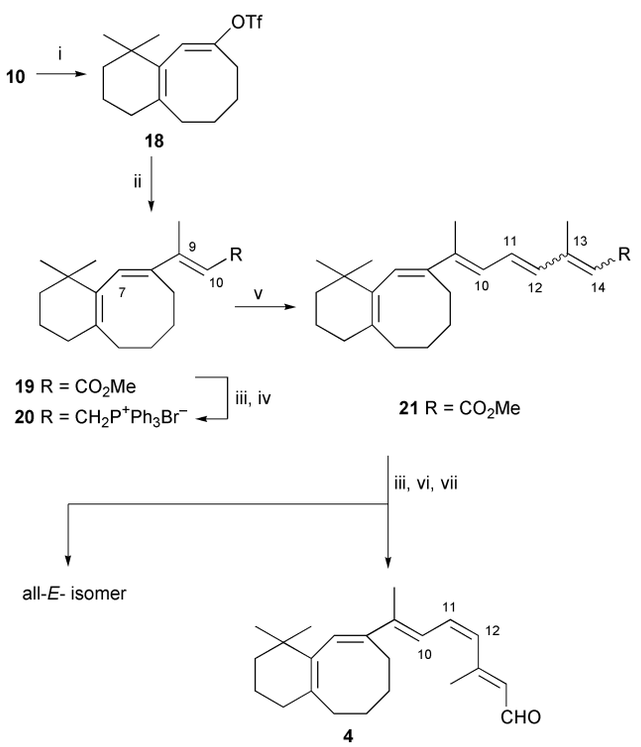


Scheme 2 *Reagents and conditions (and yields)*: i, TMS C≡CCeCl_2, THF, −70 °C (87%); ii, 85% HCOOH, 90 °C, (3%); iii, HgO, H_2SO_4, 120 °C, (68%); iv, Ac_2O, Et_3N, DMAP, 100 °C (72%); v, *n*-BuLi, (^{i}-PrO)$_2$P(O)CH_2CN, THF, 0 °C (75%); vi, DlBAL-H, CH_2Cl_2, 0 °C (57%); vii, $SOCl_2$, pyridine, 0 °C (95%).

confirmed from the nuclear Overhauser effect (NOE) experiment in its ^{1}H NMR spectrum, in which both the cross-peaks between the olefinic proton in the side chain (10 position) with the methylene protons and the methyl protons at the 9 position with the olefinic proton at 7 position were detected.

Although we could obtain the trienyl aldehyde **17**, it required many steps and the total yield is not satisfactory, so we tried another approach for the synthesis of trienyl compound **19**. It is well known that the palladium-catalyzed cross-coupling reaction of a vinyl group and an aryl triflate with organometallics is a powerful tool for the preparation of alkenes and alkynes.[12] So, we adopted this methodology for the preparation of β-ionylideneaceto ester analog **19**. Treatment of vinyl triflate **18**, derived from **10** in 57% yield by the reaction of *N*,*N*-bis-(trifluoromethylsulfonyl)aniline (Tf_2NPh) and lithium diisopropylamide (LDA) in 1,2-dimethoxyethane (DME), with methyl (*E*)-3-trimethylstannylbut-2-enoate[13] in the presence of palladium diacetate and triethylamine afforded the coupling product **19** in 39% yield, accompanied by the recovery of triflate **18** (28%).

The transformation of **19** into the Wittig salt **20** was accomplished by the sequence of lithium aluminium hydride ($LiAlH_4$) reduction and treatment with triphenylphosphine hydrobromide. The Wittig reaction of **20** with methyl (*E*)-3-formylcrotonate[14] was achieved using NaOMe as a base to give the ester **21** in 84% yield as a mixture of geometrical isomers. Without isolation of this mixture, the final conversion of **21** to the corresponding aldehyde was established according to the usual method of $LiAlH_4$ reduction and manganese(IV) dioxide (MnO_2) oxidation, and the 11*Z*-isomer **4** was isolated in pure form by repeated preparative high-performance liquid chromatography (HPLC) in the dark (Scheme 3). The structures of **4** and its all-*E*-isomer were determined on the basis of their ^{1}H NMR spectra. The assignments of all signals were carried out by a comparison of chemical-shift values with those of retinal isomers in CD_3OD (see Supplementary information).



Scheme 3 *Reagents and conditions (and yields)*: i, LDA, Tf_2NPh, DME, rt, (57%); ii, $Me_3Sn(Me)C{=}CHCO_2Me$, $Pd(OAc)_2$, DMF, rt, (39%); iii, $LiAlH_4$, Et_2O; iv, $Ph_3P·HBr$; v, NaOMe, OHC(Me)C=$CHCO_2Me$, CH_2Cl_2, (84% from **19**); vi, MnO_2, CH_2Cl_2, (27% from **20**); vii, prep HPLC.

(11*Z*)-8,18-Methanoretinal 5. A preparation of (all-*E*)-8,18-methanoretinal **5′** had been reported by Lugtenburg and co-workers,[15] *via* the β-ionone analog **22** (Fig. 2). The transformation of the β-ionone analog into the corresponding (11*Z*)-retinal *via* the Wittig reaction between the analog of β-ionylideneethyltriphenylphosphonium salt and the appropriate C5 aldehyde is well established.[6,16] To adopt this methodology for the synthesis (11*Z*)-8,18-methanoretinal **5**, our first attempt

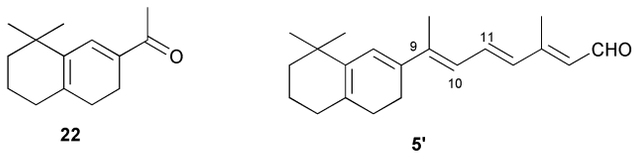


Fig. 2

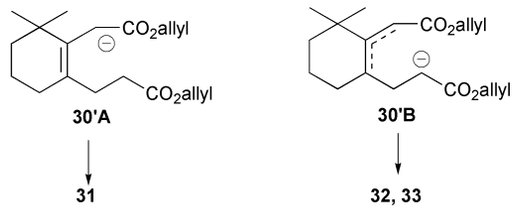
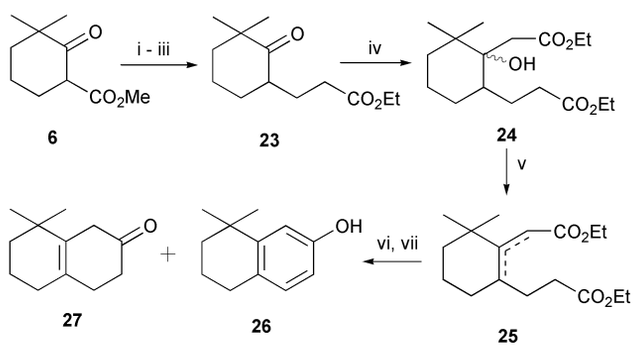


Fig. 3

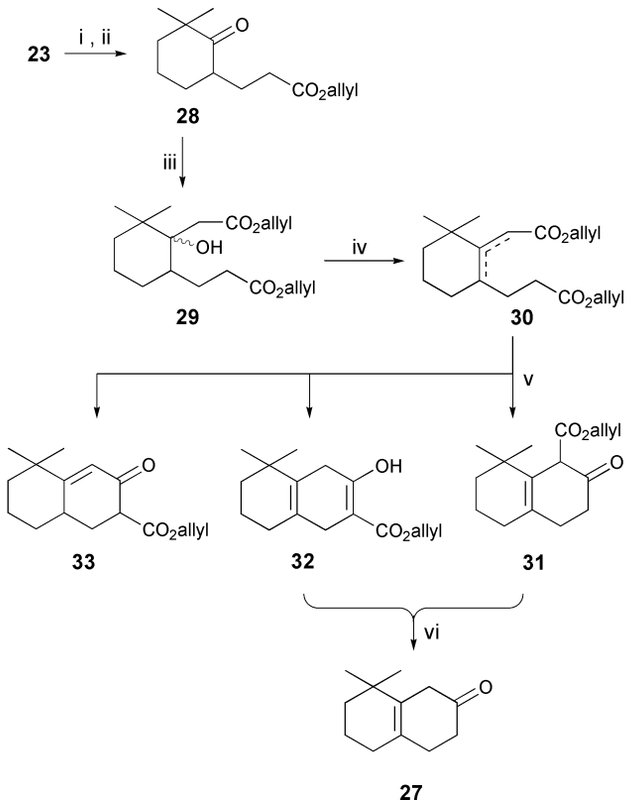
at the preparation of **22** according to the previously reported method being unsuccessful, we decided to develop our original method.

The Dieckmann condensation of the diester **25**, prepared from the β-keto ester **6** in the same manner as that described for the preparation of **9** in five steps (49% yield), and subsequent deethoxycarbonylation, gave the aromatized phenol **26** and the bicyclic ketone **27** in 7% and 14% yield, respectively (Scheme 4). It seemed that the conditions used in these reactions were too drastic to produce the ketone **27** because the yield was low and the phenol **26** was obtained as a by-product.



Scheme 4 *Reagents and conditions (and yields)*: i, NaOEt, CH_2=$CHCO_2Et$, rt, ii, c. HCl, reflux; iii, c. H_2SO_4, EtOH, reflux (82% from **6**); iv, LDA, AcOEt, THF, −70 °C (73%); v, $SOCl_2$, pyridine, 0 °C (82%); vi, *t*-BuOK, *o*-xylene, reflux; vii, $MgCl_2 \cdot 6H_2O$, DMSO, 160 °C (21% from **25**).

Tsuji *et al.*[17] reported a dealkoxycarbonylation of an allyl ester using a palladium catalyst under mild conditions. Thus, to apply this methodology to the preparation of bicyclic ketone **27**, diallyl ester **30** was prepared from the ester **23** in four steps (60% yield). Initially, the Dieckmann condensation of the diester **30** under mild conditions was tried. When LDA in THF at 0 °C was used as a base, three cyclized products **31**, **32** and **33** were obtained in 10%, 21% and 18% yield, respectively. These structures were determined on the basis of their ^{1}H NMR spectra. On the other hand, in the case of using lithium tetramethylpiperidide (LiTMP), the two cyclized products **32** and **33** were generated in 33% and 29% yield, respectively. This fact was easily understandable upon consideration of the anionic reaction intermediate. Thus, in the case of a small base such as LDA, two different anionic intermediates **30′A** and **30′B** (Fig. 3) were generated to give three products. On the other hand, in the case of a bulky base, only a single intemediate **30′B** was produced, to afford the two cyclized products. Deallyloxycarbonylation of a mixture of **31** and **32** proceeded smoothly by treatment with formic acid and triethylamine in the presence of palladium(II) acetate and triphenylphosphine to afford the desired ketone **27** in 68% yield (Scheme 5).



Scheme 5 *Reagents and conditions (and yields)*: i, c. HCl; ii, DCC, DMAP, CH_2=$CHCH_2OH$, CH_2Cl_2, rt, 86% from **23**; iii, LDA, AcOallyl, THF, −70 °C, 82%; iv, $SOCl_2$, pyridine, 0 °C (85%); v, LDA, THF, 0 °C, (49%) or LiTMP, THF, 0 °C (62%); vi, $Pd(OAc)_2$, PPh_3, HCO_2H, Et_3N, rt, 68% from **31** and **32**.

Subsequently, we focused our attention on the transformation of the ketone **27** into the (11*Z*)-retinal analog. The trienyl ester **35** was prepared by the palladium-catalyzed cross-coupling reaction of the triflate **34**, derived from **27** (58%), with methyl (*E*)-3-(trimethylstannyl)but-2-enoate in 62% yield. According to the same procedure described for the preparation of (11*Z*)-8,18-propanoretinal **4**, the ester **35** was converted to the Wittig salt **36** followed by condensation with methyl (*E*)-3-formylcrotonate to give the two products **37** and **38** as a mixture of double-bond isomers. Without isolation of this mixture, upon the transformation of the esters **37** and **38** into the corresponding aldehydes by $LiAlH_4$ reduction and subsequent MnO_2 oxidation, the desired (11*Z*)-8,18-methanoretinal **5** was not detected at all, and the aromatized aldehyde **39** was obtained as an isomeric mixture. It seemed that aromatization of **37** had occurred during the oxidation step (Scheme 6).

To avoid aromatization of the dihydrobenzene ring, (*E*)-3-formylbut-2-enenitrile[18] was used in a condensation of the Wittig salt **36**, because it is well known that a nitrile group can easily be converted to an aldehyde group by DIBAL-H reduction. The Wittig reaction of **36** with (*E*)-3-formylbut-2-enenitrile proceeded to afford the pentaenyl nitrile **40** in 24% yield as a mixture of geometrical isomers. Without isolation of these isomers, the transformation of **40** into the corresponding aldehyde mixture was achieved by DIBAL-H reduction in 44% yield. The 11*Z*-isomer **5** was isolated in pure form by repeated preparative HPLC in the dark (Scheme 7). The structures of **5** and its isomers were determined on the basis of their ^{1}H NMR spectra, and the assignments of all signals were carried out by a comparison of chemical-shift values with those of retinal isomers (see Supplementary information).

Binding with bovine opsin. Binding experiments of **4** and **5** with bovine opsin purified according to the previously reported

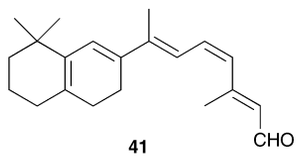
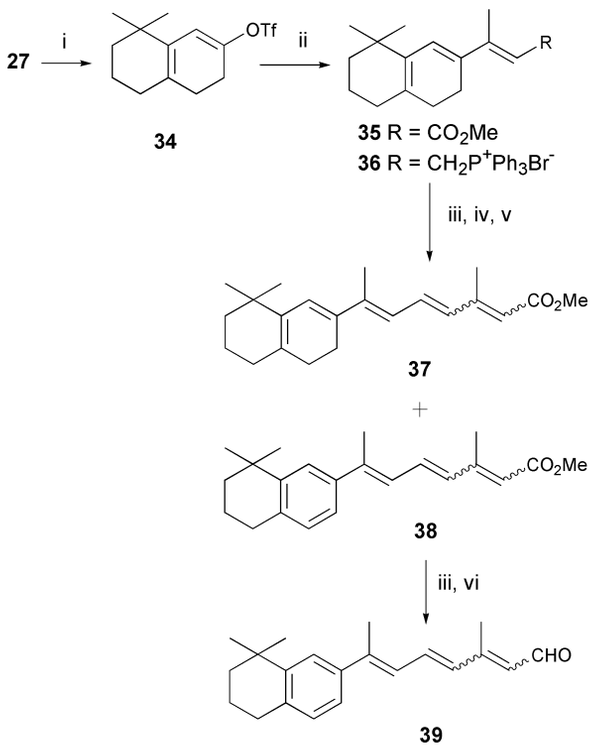
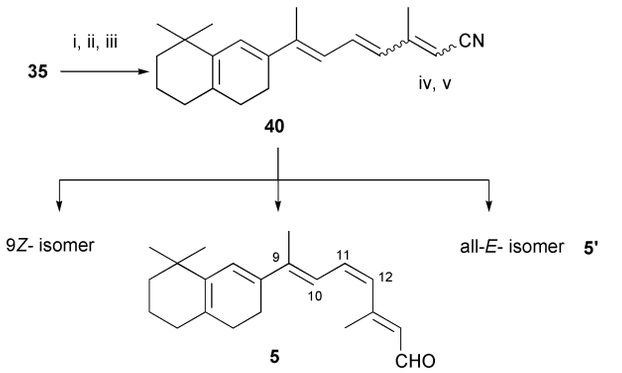


Fig. 4



Scheme 6 *Reagents and conditions (and yields)*: i, LDA, Tf_2NPh, DME, rt, (58%); ii, $Me_3Sn(Me)C{=}CHCO_2Me$, $Pd(OAc)_2$, DMF, rt, (62%); iii, $LiAlH_4$, Et_2O; iv, $Ph_3P{\cdot}HBr$; v, NaOMe, OHC(Me)C=$CHCO_2Me$, CH_2Cl_2 (28% from **35**); vi, MnO_2, CH_2Cl_2.



Scheme 7 *Reagents and conditions (and yields)*: i, $LiAlH_4$, Et_2O; ii, $Ph_3P{\cdot}HBr$; iii, NaOMe, OHC(Me)C=CHCN, CH_2Cl_2 (24% from **35**); iv, DIBALH, hexane (44%); v, prep. HPLC.

method [19] were carried out in a 3-[(3-cholamidopropyl)dimethylammonio]propane-1-sulfonate–phosphatidyl choline (CHAPS–PC) mixture to afford the novel rhodopsin analogs. The PSBs of **4** and **5** with *n*-butylamine were formed by the usual method. The absorption maxima, opsin shifts and CD data of artificial pigments derived from **3**–**5** and retinal analog (**41**, Fig. 4; $n = 0$ in Fig. 1), whose 8 and 18 positions were directly connected, are shown in Table 1 and Fig. 5 with those of native rhodopsin.

We had not expected that the opsin shift of **4** would exhibit almost the same value as that of **3**, although the torsion angles around the cyclohexene ring and the polyene side chain in **3** and **4** are very different, *e.g.* 50–55 and 80–85°, respectively, from an examination of their Dreiding models. This fact indicates that such a difference in torsional angle between compounds **3** and **4** does not cause a significant effect on the opsin shift. In addition, this speculation was supported by the fact that the opsin shift of **5**, in which the torsional angle of the C6–7 single bond is about 30°, is very close to those of **3** and **4** (only 150 cm^{-1} in difference). In contrast, from a comparison of CD spectra, we found important features in the both α- and β-bands. Thus, the intensity of the α-band increased according to increasing torsional angle around the C6–7 single bond (**5** ⟶ **3** ⟶ **4**), whereas the intensity of the β-band decreased. In addition, in respect of the change of the intensity-degree in both α- and β-bands, the difference of the β-band is greater than that of the α-band. In connection with the fact that the bicyclic retinal **41** had no twisted conformation around the C6–7 single bond, which was fixed by the five-membered ring, and also exhibits the β-band,[6] it is strongly suggested that the origin of the β-band would be the total combination of both the twisted conformations of the C6–7 and C8–9 single bonds of the chromophore.

In summary, an important conclusion was obtained from the above experiments that the β-band was affected by the torsional angle of the C6–7 single bond and that the origin of the β-band was expected to be the total combination of the twisted conformation of both the C6–7 and C8–9 single bonds in the retinal chromophore.

Experimental

Ether refers to diethyl ether, and hexane to *n*-hexane. *n*-BuLi was used as a solution in hexane. UV-VIS spectra were recorded on a JASCO Ubest-55 instrument, and IR or FT-IR spectra on a Shimadzu IR-27G or Shimadzu FT-IR-4200 spectrometer. ^1H NMR spectra at 200 MHz or 500 MHz were measured on a Varian XL-200 or a Varian VXR-500 superconducting FT-NMR spectrometer with tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded on a Varian VXR-500 instrument operating at 125 MHz. Mass spectra were determined on a Hitachi M-4100 spectrometer. Analytical HPLC was carried out on a Shimadzu LC-5A instrument with a Shimadzu photodiode array UV-VIS detector SPD-M6A

Table 1 Absorption maxima, CD data and opsin shift of rhodopsin and its analogs

Chromophores (compound no.)	Aldehydes [a] λ_{max}/nm	PSB [b] λ_{max}/nm	Rhodopsin [c] CD/nm λ_{max}/nm	(mdeg/absorption) α-band	β-band	Opsin shifts $\Delta\nu$/cm^{-1}
6,7-Bicyclic retinal **3**	386	457	503 [d]	491 [d] (+8.2)	335 [d] (+17.0)	2000
6,8-Bicyclic retinal **4**	374	440	483	475 (+11.0)	340 (+12.0)	2000
6,6-Bicyclic retinal **5**	416	496	546	545 (+5.5)	340 (+32.0)	1850
6,5-Bicyclic retinal **41**	422	506	539 [e]	526 [e] (+12.3)	332 [e] (+31.0)	1200
(11*Z*)-Retinal **2**	377	440	498 [e]	489 [e] (+8.7)	332 [e] (+17.5)	2650

[a] In ethanol. [b] In methanol. [c] In CHAPS–PC mixture. [d] Ref. 6. [e] Ref. 5*b*.

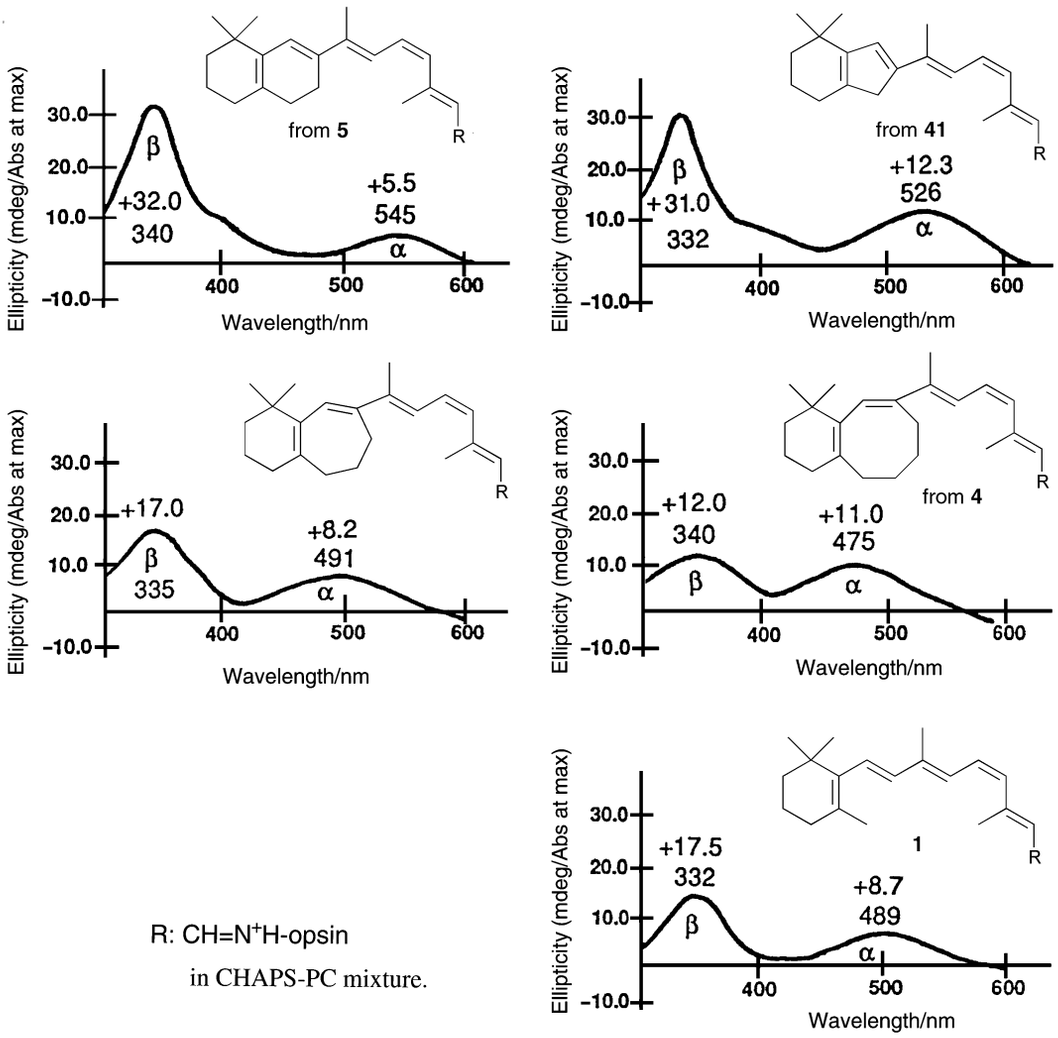


Fig. 5

using a column, LiChrosorb Si-60 (5 μm), 0.4 × 30 cm. Preparative HPLC was conducted on a Shimadzu LC-6A instrument with a Shimadzu UV-VIS detector, SPD-6AV. Column chromatography (CC) under reduced pressure was performed by using Merck silica gel 60. All reactions were carried out in a nitrogen atmosphere. THF and ether were purified by distillation from benzophenone ketyl–sodium under nitrogen. Other solvents used for reaction were dried prior to use. NaH was a 60% dispersion in mineral oil and used after washing with dry hexane. Other chemicals were of reagent grade and used without purification. Standard work-up means that the organic layers were finally washed with brine, dried over anhydrous sodium sulfate (Na_2SO_4), filtered, and concentrated *in vacuo* below 30 °C using a rotary evaporator.

Synthesis of (11*Z*)-8,18-propanoretinal 4

Ethyl 5-(3,3-dimethyl-2-oxocyclohexyl)pentanoate 7. To a suspension of NaH (60% dispersion in oil; 3.4 g, 0.085 mol) in THF (65 cm^3) and DMF (7 cm^3) was added a solution of β-keto ester **6**[8] (12.2 g, 0.066 mol) in THF (70 cm^3) at 0 °C. After stirring of the mixture for 15 min at room temperature, a solution of ethyl 5-bromopentanoate (28 g, 0.13 mmol) in THF (70 cm^3) was added dropwise and the resulting mixture was heated under reflux for 18 h. After cooling, the mixture was poured into 10% HCl (100 cm^3) and the organics were extracted with ether (2 × 100 cm^3), followed by standard work-up. The residue was purified by CC (ether–hexane, 1 : 4) to give ethyl 5-(1-methoxycarbonyl-3,3-dimethyl-2-oxocyclohexyl)pentanoate (14.5 g, 70%) as a colorless oil, δ_H ($CDCl_3$) 1.03 (3H, s, Me), 1.07 (3H, s, Me), 1.25 (3H, t, *J* = 7 Hz, $CO_2CH_2CH_3$), 1.3–1.8 (9H, m, CH_2 × 4 and CH_2 × 1/2), 1.8–2.1 (2H, m, CH_2), 2.2–2.4 (2H, m, CH_2), 2.5–2.6 (1H, m, CH_2 × 1/2), 3.66 (3H, s, CO_2CH_3), 4.14 (2H, q, *J* = 7 Hz, $CO_2CH_2CH_3$).

A mixture of this keto diester (17 g, 54.5 mmol) and c. HCl (70 cm^3) was refluxed for 18 h. After cooling, water (150 cm^3) was added, and the organics were extracted with ether (3 × 80 cm^3), followed by standard work-up to give the crude acid. To the residue were added anhydrous ethanol (160 cm^3) and c. H_2SO_4 (1 cm^3) and the resulting mixture was refluxed for 20 h. After cooling, the mixture was poured into water (100 cm^3) and the organics were extracted with ether (2 × 100 cm^3), followed by standard work-up. The residue was purified by CC (ether–hexane, 1 : 6) to afford the keto ester **7** (9.7 g, 70%) as a pale yellow oil, ν_{max} ($CHCl_3$)/cm^{-1} 1725, 1700; δ_H ($CDCl_3$) 1.04 (3H, s, Me), 1.19 (3H, s, Me), 1.27 (3H, t, *J* = 7 Hz, $CO_2CH_2CH_3$), 1.4–1.9 (11H, m, CH_2 × 5 and CH_2 × 1/2), 2.12 (1H, ddt like, *J* = 13, 6, 3 Hz, CH_2 × 1/2), 2.32 (2H, t, *J* × 7 Hz, CH_2), 2.54 (1H, m, CH), 4.17 (2H, q, *J* × 7 Hz, $CO_2CH_2CH_3$) [Found (HRMS): M^+, 254.1898. Calc. for $C_{15}H_{26}O_3$: *M*, 254.1880].

Ethyl 5-(2-ethoxycarbonylmethyl-2-hydroxy-3,3-dimethylcyclohexyl)pentanoate 8. To a stirred solution of LDA, prepared from *n*-BuLi (1.7 M hexane solution; 24.8 cm^3, 42.3 mmol) and diisopropylamine (4.27 g, 42.3 mmol) in THF (30 cm^3), was added a solution of ethyl acetate (4.1 cm^3, 42.3 mmol) in THF (7 cm^3) at −70 °C, and the resulting mixture was stirred for an additional 30 min. A solution of the keto ester **7** (3.58 g,

14 mmol) in THF (10 cm^3) was added at −70 °C and the mixture was further stirred for 2 h. After addition of saturated aq. NH_4Cl (80 cm^3) and evaporation of the solvent, the organics were extracted with ether (3 × 70 cm^3), followed by standard work-up. The residue was purified by CC (ether–hexane, 1 : 5) to give a mixture of stereoisomers **8** (4.41 g, 91%) as a pale yellow oil. NMR analysis indicated that the ratio of stereoisomers was 2 : 1; ν_{max} ($CHCl_3$)/cm^{-1} 3470, 1720, 1710; δ_H ($CDCl_3$) 0.88 (1/3 × 3 H, s, Me), 0.92 (2/3 × 6H, s, Me × 2), 1.02 (1/3 × 3H, s, Me), 1.25 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 1.29 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 1.1–1.9 (13H, m, CH_2 × 6 and CH), 2.31 (2H, t, J = 7 Hz, CH_2), 2.38 (2/3 × 1H, d, J = 16 Hz, CH_2COO), 2.42 (1/3 × 1H, d, J = 16 Hz, CH_2COO), 2.56 (2/3H, d, J = 16 Hz, CH_2COO), 2.60 (1/3H, d, J = 16 Hz, CH_2COO), 4.16 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 4.20 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 4.33 (2/3 × 1H, s, OH, disappeared with D_2O), 4.92 (1/3 × 1H, s, OH, disappeared with D_2O) [Found (HRMS): M^+, 342.2421. Calc. for $C_{19}H_{34}O_5$: *M*, 342.2404].

Dehydration of 8. To a solution of the hydroxy diester **8** (9.65 g, 28.2 mmol) in pyridine (120 cm^3) was added thionyl dichloride (2.4 cm^3, 34 mmol) at 0 °C, and the resulting mixture was stirred for 10 min. The reaction was quenched with 5% HCl (200 cm^3) in an ice-bath, and the organics were extracted with ether (3 × 80 cm^3), followed by standard work-up. The residue was purified by CC (ether–hexane, 1 : 6) to give a mixture of diesters **9** (8.70 g, 95%) as a colorless oil. NMR analysis indicated that the *endo* and *exo* double-bond isomers were present in the ratio of 5 : 1. Analytical samples were obtained respectively by further CC using the same eluent.

Endo-isomer. ν_{max} ($CHCl_3$)/cm^{-1} 1730; δ_H ($CDCl_3$) 0.98 (6H, s, Me × 2), 1.28 (6H, t, J = 7 Hz, $CO_2CH_2CH_3$ × 2), 1.4–1.7 (9H, m, CH_2 × 4 and CH_2 × 1/2), 1.9–2.1 (3H, m, CH_2 and CH_2 × 1/2), 2.2–2.4 (2H, m, CH_2), 3.04 (2H, s, CH_2COO), 4.14 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 4.15 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$) [Found (HRMS): M^+, 324.2312. Calc. for $C_{19}H_{32}O_4$: *M*, 324.2299].

Exo-isomer. ν_{max} ($CHCl_3$)/cm^{-1} 1725, 1710, 1620; δ_H ($CDCl_3$) 1.14 (3H, s, Me), 1.16 (3H, s, Me), 1.28 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 1.31 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 1.4–1.9 (12H, m, CH_2 × 6), 2.34 (2H, t, J = 7 Hz, CH_2), 3.8–3.9 (1H, m, CH), 4.18 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 4.19 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 5.82 (1H, s, =CH) [Found (HRMS): M^+, 324.2290. Calc. for: $C_{19}H_{32}O_4$: *M*, 324.2299].

4,4-Dimethyl-1,2,3,4,7,8,9,10-octahydrobenzocycloocten-6(5*H*)-one 10. A solution of the diester **9** (80 mg, 0.24 mmol) in *o*-xylene (2 cm^3) was added dropwise to a stirred suspension of *t*-BuOK (0.14 g, 1.2 mmol) in *o*-xylene (12 cm^3) at 160 °C. The mixture was further stirred for 5 min at this temperature, and then cooled to room temperature. Saturated aq. NH_4Cl (100 cm^3) was added, and the organic layer was separated. The aqueous layer was extracted with ether (2 × 10 cm^3), and the combined organic extracts were treated as standard work-up. The residue was purified by CC (ether–hexane, 1 : 7) to give an isomeric mixture of the β-keto esters (35.3 mg, 52%) as a colorless oil.

The mixture of β-keto esters (35.3 mg) and $MgCl_2 \cdot 6H_2O$ (0.1 g, 5 eq.) in DMSO (4 cm^3) was heated at 160 °C for 3 h. After cooling, water (25 cm^3) was added and the organics were extracted with ether (3 × 10 cm^3), followed by standard work-up. The residue was purified by CC (ether–hexane, 1 : 6) to afford the bicyclic ketone **10** (13.6 mg, 27%) as a colorless oil. ν_{max} ($CHCl_3$)/cm^{-1} 1690; δ_H ($CDCl_3$) 0.98 (6H, s, Me × 2), 1.4–1.5 (2H, m, CH_2), 1.5–1.8 (6H, m, CH_2 × 3), 2.0–2.1 (4H, m, CH_2 × 2), 2.4–2.5 (2H, m, CH_2), 3.15 (2H, s, CH_2) [Found (HRMS): M^+, 206.1690. Calc. for $C_{14}H_{22}O$: *M*, 206.1669].

9-Hydroxy-1,1-dimethyl-9-(2-trimethylsilylethynyl)-1,2,3,4,5,6,7,8,9,10-decahydrobenzocyclooctene 11. To a stirred suspension of anhydrous cerium(III) chloride (0.8 g, 3.3 mmol) in THF (13 cm^3) was added dropwise at −70 °C a solution of lithium trimethylsilylacetylene, prepared from trimethylsilylacetylene (0.45 cm^3, 3.3 mmol) and *n*-BuLi (1.7 M hexane solution; 1.9 cm^3, 3.3 mmol) in THF (6 cm^3). After stirring had been continued for 1 h, a solution of **10** (260 mg, 1.3 mmol) in THF (6 cm^3) was added and the resulting mixture was stirred for an additional 3 h at −70 °C. The reaction mixture was quenched with saturated aq. NH_4Cl (20 cm^3) and filtered through Celite. The filtrate was extracted with ether (3 × 20 cm^3), followed by standard work-up. The residue was purified by CC (ether–hexane, 1 : 7) to afford the acetylenic alcohol **11** (333 mg, 87%) as a colorless oil, ν_{max} ($CHCl_3$)/cm^{-1} 3600, 2250; δ_H ($CDCl_3$) 0.16 (9H, s, $SiMe_3$), 1.10 (3H, s, Me), 1.13 (3H, s, Me), 1.4–1.8 (10 H, m, CH_2 × 5), 1.88 (1H, br s, OH, disappeared with D_2O), 1.9–2.1 (4H, m, CH_2 × 2), 2.57 (1H, d, J = 14 Hz, CH_2 × 1/2), 2.66 (1H, d, J = 14 Hz, CH_2 × 1/2) [Found (HRMS): M^+, 304.2237. Calc. for $C_{19}H_{32}OSi$: *M*, 304.2221].

9-Acetyl-1,1-dimethyl-1,2,3,4,5,6,7,10-octahydrobenzocyclooctene 12. A mixture of the acetylenic alcohol **11** (105 mg, 0.35 mmol) and 85% HCOOH (0.6 cm^3) was heated at 90 °C for 4.5 h. After cooling, the reaction mixture was neutralized with cold 5% NaOH in an ice-bath. The organics were extracted with ether (3 × 20 cm^3), followed by standard work-up. The residue was purified by CC (ether–hexane, 1 : 5) to afford the ketone **12** (2.8 mg, 3%) as a pale yellow oil; δ_H ($CDCl_3$) 1.00 (6H, s, Me × 2), 1.4–1.8 (8H, m, CH_2 × 3 and [CH_2 × 1/2] × 2), 1.8–2.0 (2H, m, [CH_2 × 1/2] × 2), 2.0–2.2 (2H, m, CH_2), 2.34 (3H, s, $COCH_3$), 3.00 (2H, br s, CH_2), 6.88 (1H, tt, J = 8, 2 Hz, =CH).

9-Acetyl-9-hydroxy-1,1-dimethyl-1,2,3,4,5,6,7,8,9,10-decahydrobenzocyclooctene 13. A mixture of acetylenic alcohol **11** (19.7 mg, 0.065 mmol), HgO (yellow, 42 mg, 0.19 mmol) and 1.5 M H_2SO_4 (1 cm^3) in THF (4 cm^3) was heated at 120 °C for 40 min. After cooling, NH_4Cl was added and the organics were extracted with CH_2Cl_2 (3 × 20 cm^3), followed by standard work-up. The residue was purified by CC (ether–hexane, 1 : 5) to afford the hydroxy ketone **13** (11 mg, 68%) as a pale yellow oil, ν_{max} ($CHCl_3$)/cm^{-1} 3500, 1705; δ_H ($CDCl_3$) 0.91 (3H, s, Me), 1.10 (3H, s, Me), 1.3–1.9 (14H, m, CH_2 × 7), 2.05 (1H, d, J = 16 Hz, CH_2 × 1/2), 2.28 (3H, s, $COCH_3$), 2.61 (1H, d, J = 16 Hz, CH_2 × 1/2), 3.33 (1H, s, OH, disappeared with D_2O) [Found (HRMS): M^+, 250.1917. Calc. for $C_{16}H_{26}O_2$: *M*, 250.1931].

9-Acetoxy-9-acetyl-1,1-dimethyl-1,2,3,4,5,6,7,8,9,10-decahydrobenzocyclooctene 14. A solution of the hydroxy ketone **13** (52 mg, 0.20 mmol) in triethylamine (3 cm^3) were added acetic anhydride (0.4 cm^3, 4.2 mmol) and DMAP (50 mg, 0.40 mmol) at 0 °C, and the resulting mixture was heated at 100 °C for 2 h. After cooling, 10% HCl was added and the organics were extracted with ether (3 × 20 cm^3), followed by standard work-up. The residue was purified by CC (ether–hexane, 1 : 7) to afford the acetoxy ketone **14** (44 mg, 72%) as a pale yellow oil, ν_{max} ($CHCl_3$)/cm^{-1} 1730, 1720; δ_H ($CDCl_3$) 0.93 (3H, s, Me), 1.09 (3H, s, Me), 1.3–1.7 (8H, m, CH_2 × 4), 1.7–2.0 (4H, m, CH_2 × 2), 2.09 (3H, s, COMe), 2.12 (3H, s, OAc), 2.1–2.4 (2H, m, CH_2), 2.54 (1H, d, J = 16 Hz, CH_2 × 1/2), 2.72 (1H, d, J = 16 Hz, CH_2 × 1/2) [Found (HRMS): M^+, 292.2030. Calc. for $C_{18}H_{28}O_3$: *M*, 292.2037].

(2*E*/*Z*)-3-(6-Acetoxy-4,4-dimethyl-1,2,3,4,5,6,7,8,9,10-decahydrobenzocycloocten-6-yl)but-2-enenitrile 15. To a stirred solution of diisopropyl cyanomethylphosphonate (64 mg, 0.36 mmol) in THF (3 cm^3) was added a hexane solution of *n*-BuLi (1.6 M; 0.22 cm^3, 0.36 mmol) at 0 °C. After stirring of the mixture for 30 min, a solution of the acetoxy ketone **14** (21 mg, 0.072 mmol) in THF (2 cm^3) was added slowly at 0 °C, and the resulting mixture was stirred for 48 h at room temperature. The reaction was quenched with saturated aq. NH_4Cl (10 cm^3), and

the organics were extracted with ether (3 × 20 cm^3), followed by standard work-up. The residue was purified by CC (ether–hexane, 1 : 6) to provide the nitrile **15** (17 mg, 75%) as a mixture of stereoisomers. NMR analysis indicated that the double-bond stereoisomers were present in the ratio 4 : 3; ν_{max} ($CHCl_3$)/cm^{-1} 2250, 1725, 1620; δ_H ($CDCl_3$) 0.93 (3/7 × 3H, s, Me), 0.95 (4/7 × 3H, s, Me), 1.10 (3/7 × 3H, s, Me), 1.13 (4/7 × 3H, s, Me), 1.3–2.0 (12 H, m, CH_2 × 6), 2.04 (4/7 × 3H, s, OAc), 2.05 (3/7 × 3H, s, OAc), 2.10 (3/7 × 3H, s, CH_3), 2.14 (4/7 × 3H, s, CH_3), 2.2–2.4 (2H, m, CH_2), 2.54 (1H, d, J = 16 Hz, CH_2 × 1/2), 2.63 (1H, d, J = 16 Hz, CH_2 × 1/2), 5.27 (4/7H, s, =CH), 5.70 (3/7H, s, =CH) [Found (HRMS): M^+, 315.2207. Calc. for $C_{20}H_{29}NO_2$: *M*, 315.2197].

(2*E*)-3-(6-Hydroxy-4,4-dimethyl-1,2,3,4,5,6,7,8,9,10-decahydrobenzocycloocten-6-yl)but-2-enal 16. To a solution of the nitrile **15** (27 mg, 0.09 mmol) in CH_2Cl_2 (2 cm^3) was added dropwise DIBAL-H (0.03 cm^3, 0.17 mmol) in dry CH_2Cl_2 (1 cm^3) at 0 °C. After stirring of the mixture for an additional 10 min at 0 °C, the excess of DIBAL-H was destroyed by addition of moist silica gel. The silica gel was filtered off, and the filtrate was extracted with CH_2Cl_2 (3 × 10 cm^3), followed by standard work-up. The residue was purified by CC (ether–hexane, 1 : 4) to provide the aldehyde **16** (13 mg, 57%) as a single stereoisomer, λ_{max} (EtOH)/nm 240; ν_{max} ($CHCl_3$)/cm^{-1} 3600–3200, 1665; δ_H ($CDCl_3$) 0.93 (3H, s, Me), 1.12 (3H, s, Me), 1.40–1.48 (2H, m, CH_2), 1.50–1.60 (3H, m, CH_2 and CH_2 × 1/2), 1.60–1.70 (4H, m, CH_2 × 2), 1.76–1.88 (2H, m, [CH_2 × 1/2] × 2), 1.83 (1H, s, OH, disappeared with D_2O), 2.14–2.22 (2H, m, [CH_2 × 1/2] × 2), 2.19 (1H, d, J = 15 Hz, CH_2 × 1/2), 2.26 (3H, d, J = 1 Hz, CH_3), 2.42 (1H, td, J = 14, 4 Hz, CH_2 × 1/2), 2.63 (1H, d, J = 15 Hz, CH_2 × 1/2), 6.29 (1H, dq, J = 8, 1 Hz, =CH), 10.08 (1H, d, J = 8 Hz, CHO) [Found (HRMS): M^+, 276.2099. Calc. for $C_{18}H_{28}O_2$: *M*, 276.2088].

(2*E*)-3-(4,4-Dimethyl-1,2,3,4,7,8,9,10-octahydrobenzocycloocten-6-yl)but-2-enal 17. As the same manner described for the preparation of **9**, dehydration of the hydroxy aldehyde **16** (13 mg, 0.047 mmol) was achieved. The crude product was purified by CC (ether–hexane, 1 : 6) to give the trienal **17** (13 mg, 95%) as a pale yellow oil, λ_{max} (EtOH)/nm 314, 281; ν_{max} ($CHCl_3$)/cm^{-1} 1660, 1600; δ_H ($CDCl_3$) 0.88 (3H, s, Me), 0.99 (3H, s, Me), 1.3–2.5 (14H, m, CH_2 × 7), 2.30 (3H, s, Me), 6.14 (1H, d, J = 8 Hz, =CH), 6.67 (1H, t-like, J = 2 Hz, =CH), 10.14 (1H, d, J = 8 Hz, CHO) [Found (HRMS): M^+, 258.1990. Calc. for $C_{18}H_{26}O$: *M*, 258.1983].

4,4-Dimethyl-1,2,3,4,7,8,9,10-octahydrobenzocycloocten-6-yl trifluoromethanesulfonate 18. To a stirred solution of LDA, prepared from *n*-BuLi (1.7 M hexane solution; 1.17 cm^3, 1.9 mmol) and diisopropylamine (0.27 cm^3, 1.9 mmol) in DME (6 cm^3) was added a solution of the ketone **10** (157 mg, 0.76 mmol) in DME (2 cm^3) at 0 °C, and the resulting mixture was stirred for an additional 1 h. A solution of Tf_2NPh (0.33 mg, 0.8 mmol) in DME (2 cm^3) was added at 0 °C and the mixture was further stirred for 3 h at rt. After addition of saturated aq. NH_4Cl (30 cm^3), the organics were extracted with ether (3 × 70 cm^3), followed by standard work-up. The residue was purified by CC (ether–hexane, 1 : 9) to give the triflate **18** (147 mg, 57%) as a pale yellow oil, λ_{max} (EtOH)/nm 237; ν_{max} ($CHCl_3$)/cm^{-1} 1410, 1135; δ_H ($CDCl_3$) 1.00 (6H, s, Me × 2), 1.4–1.7 (8H, m, CH_2 × 4), 1.9–2.2 (4H, m, CH_2 and [CH_2 × 1/2] × 2), 2.3–2.4 (2H, m, [CH_2 × 1/2] × 2), 6.10 (1H, t, J = 2 Hz, =CH) [Found (HRMS): M^+, 338.1168. Calc. for $C_{15}H_{21}F_3O_3S$: M, 338.1163].

Methyl (2*E*)-3-(4,4-dimethyl-1,2,3,4,7,8,9,10-octahydrobenzocycloocten-6-yl)but-2-enoate 19. To a stirred solution of the triflate **18** (69 mg, 0.2 mmol) and methyl (*E*)-trimethylstannylbut-2-enoate[13] (75 mg, 0.24 mmol) in DMF (1 cm^3) was added $Pd(OAc)_2$ (1.6 mg, 3 mol%) at room temperature under nitrogen. The resulting mixture was stirred for an additional 24 h at room temperature. After addition of saturated aq. NH_4Cl (20 cm^3), the organics were extracted with ether (3 × 20 cm^3), followed by standard work-up. The residue was purified by HPLC [LiChrosorb Si-60 (5 μm), 1 × 25 cm, hexane–ether (98 : 2), detection in wavelength 240 nm, flow rate 2.2 cm^3 min^{-1}] to afford the trienyl ester **19** (20 mg, 39%) as a pale yellow oil, accompanied by the recovery of triflate **18** (19 mg, 28%); λ_{max} (EtOH)/nm 270, 295; ν_{max} ($CHCl_3$)/cm^{-1} 1715, 1615; δ_H ($CDCl_3$) 0.84 (3H, s, Me), 1.05–1.14 (2H, m, [CH_2 × 1/2] × 2), 1.12 (3H, s, Me), 1.46–1.52 (2H, m, CH_2), 1.58–1.64 (1H, m, CH_2 × 1/2), 1.64–1.72 (2H, m, CH_2), 1.76 (1H, t, J = 8.5 Hz, CH_2 × 1/2), 1.82–1.87 (2H, m, CH_2), 1.95 (2H, br t, J = 10.5 Hz, [CH_2 × 1/2] × 2), 2.22 (1H, dt, J = 18.5, 4 Hz, CH_2 × 1/2), 2.39 (3H, s, Me), 2.46 (1H, dd, J = 14, 8.5 Hz, CH_2 × 1/2), 3.73 (3H, s, CO_2CH_3), 5.97 (1H, br s, =CH), 6.54 (1H, t, J = 1.5 Hz, =CH); δ_C ($CDCl_3$) 15.75 (Me), 19.63 (CH_2), 23.98 (CH_2), 24.31 (CH_2), 27.61 (CH_2), 28.12 (Me), 28.60 (Me), 30.90 (CH_2), 33.82 (CH_2), 34.11 (C), 38.92 (CH_2), 50.99 (OMe), 114.75 (CH), 129.94 (CH), 134.98 (C), 136.33 (C), 142.42 (C), 155.35 (C), 168.06 (CO) [Found (HRMS): M^+, 288.2065. Calc. for $C_{19}H_{28}O_2$: *M*, 288.2087].

(11*Z*)-8,18-Propanoretinal 4. A solution of the trienyl ester **19** (55 mg, 0.18 mmol) in dry Et_2O (2 cm^3) was added to a stirred suspension of $LiAlH_4$ (14 mg, 0.36 mmol) in dry Et_2O (5 cm^3) at 0 °C under nitrogen, and the resulting mixture was stirred for an additional 15 min. The excess of $LiAlH_4$ was destroyed by the successive addition of moist Et_2O and water, and the mixture was extracted with Et_2O. The extract was washed with brine, dried (Na_2SO_4) and concentrated to afford the crude alcohol, which was used the next reaction without further purification.

Triphenyphosphine hydrobromide (84 mg, 0.24 mmol) was added dropwise to a stirred solution of the crude alcohol in methanol (2 cm^3), and the resulting mixture was stirred for 20 h at room temperature. Evaporation of the solvent gave a residue, which was washed with ether to provide the Wittig salt **20**.

A solution of the Wittig salt in CH_2Cl_2 (2 cm^3) was added to a stirred solution of methyl (*E*)-3-formylcrotonate[14] (30 mg, 0.24 mmol) in MeOH (2 cm^3, containing NaOMe, 0.24 mmol) at 0 °C. The resulting mixture was stirred for 1 h, and water (5 cm^3) was added. After removal of the solvent, the residue was extracted with ether. The extract was washed with brine and then dried over Na_2SO_4. The solvent was removed *in vacuo* to give a crude product, which was purified by CC (ether–hexane, 1 : 9) to afford the pentaenyl ester **21** (56 mg, 84% from **19**) as a mixture of stereoisomers.

A solution of the ester **21** (56 mg) in dry Et_2O (5 cm^3) was added to a stirred suspension of $LiAlH_4$ (12 mg, 0.32 mmol) in dry Et_2O at 0 °C. After the mixture had been stirred at 0 °C for 15 min, the excess of $LiAlH_4$ was destroyed by the successive addition of moist Et_2O and water, and the whole was twice extracted by Et_2O. The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give the hydroxy compound as a pale yellow amorphous product.

A mixture of the resulting hydroxy compound and active MnO_2 (700 mg, 8 mmol) in dry CH_2Cl_2 (6 cm^3) was shaken at room temperature for 2 h and then filtered through Celite. Evaporation of the filtrate gave an oil, which was purified by CC (ether–hexane, 1 : 9) to yield an isomeric mixture of the aldehydes (14 mg, 27%) as an orange oil. Separation of the isomers was achieved by preparative HPLC [LiChrosorb Si-60 (7 μm) 1 × 25 cm; hexane–ether (98 : 2), 5 cm^3 min^{-1}, 350 nm] to give 11*Z*-isomer **4** and all-*E*-isomer in the ratio 7 : 12.

11Z-Isomer 4. λ_{max} (MeOH, ε/dm^3 mol^{-1} cm^{-1})/nm 258.5 (13 100), 374 (17 600); ν_{max} (KBr)/cm^{-1} 1660, 1575; δ_H (CD_3OD) 0.86 (3H, s, Me), 1.14 (3H, s, Me), 1.06–1.20 (2H, m, [CH_2 × 1/2] × 2), 1.48–1.54 (2H, m, CH_2), 1.57–1.63 (1H, m, CH_2 × 1/2), 1.63–1.72 (2H, m, CH_2), 1.72–1.80 (1H, m, CH_2 × 1/2),

1.86–1.90 (2H, m, CH_2), 1.96–2.01 (1H, m, CH_2 × 1/2), 2.01–2.06 (1H, m, CH_2 × 1/2), 2.05 (3H, s, Me), 2.24–2.30 (1H, m, CH_2 × 1/2), 2.39 (3H, d, J = 1 Hz, Me), 2.51 (1H, dd, J = 12.5, 8.5 Hz, CH_2 × 1/2), 6.02 (1H, br d, J = 8.5 Hz, =CH), 6.06 (1H, br d, J = 10 Hz, =CH), 6.44 (1H, br s, =CH), 6.83 (1H, d, J = 11.5 Hz, =CH), 6.86 (1H, dd, J = 11.5, 10 Hz, =CH), 10.05 (1H, d, J = 8.5 Hz, CHO); δ_C (CD_3OD) 14.37 (Me), 18.30 (Me), 20.76 (CH_2), 25.28 (CH_2), 26.17 (CH_2), 28.64 (Me), 29.20 (Me), 30.76 (CH_2), 31.92 (CH_2), 33.07 (C), 35.05 (CH_2), 40.23 (CH_2), 123.63 (CH), 128.24 (CH), 130.86 (CH), 131.74 (CH), 133.08 (C), 133.47 (CH), 135.70 (C), 137.96 (C), 142.98 (C), 144.20 (C), 193.36 (CHO) [Found (HRMS): M^+, 324.2422. Calc. for $C_{23}H3_{32}O$: M, 324.2451].

All-E-isomer. λ_{max} (MeOH, ε/dm^3 mol^{-1} cm^{-1})/nm 378.5 (36 800); ν_{max} (KBr)/cm^{-1} 1660, 1575; δ_H (CD_3OD) 0.87 (3H, s, Me), 1.14 (3H, s, Me), 1.04–1.22 (2H, m, [CH_2 × 1/2] × 2), 1.48–1.54 (2H, m, CH_2), 1.60–1.74 (3H, m, CH_2 and CH_2 × 1/2), 1.78–1.86 (1H, m, CH_2 × 1/2), 1.86–1.89 (2H, m, CH_2), 1.94–2.02 (2H, m, [CH_2 × 1/2] × 2), 2.11 (3H, d, J = 0.5 Hz, Me), 2.24–2.32 (1H, m, CH_2 × 1/2), 2.38 (3H, d, J = 1 Hz, Me), 2.60 (1H, dd, J = 13.5, 8.5 Hz, CH_2 × 1/2), 5.98 (1H, br d, J = 8 Hz, =CH), 6.46 (1H, br s, =CH), 6.51 (1H, br d, J = 11 Hz, =CH), 6.52 (1H, d, J = 15 Hz, =CH), 7.36 (1H, dd, J = 15, 11 Hz, =CH), 10.07 (1H, d, J = 8 Hz, CHO); δ_C (CD_3OD) 13.23 (Me), 15.14 (Me), 20.81 (CH_2), 25.33 (CH_2), 26.08 (CH_2), 28.39 (CH_2), 28.67 (Me), 29.22 (Me), 31.96 (CH_2), 35.05 (CH_2), 35.21 (C), 40.28 (CH_2), 127.76 (CH), 128.46 (CH), 129.72 (CH), 135.22 (CH), 135.76 (C), 136.11 (CH), 138.04 (C), 143.33 (C), 144.21 (C), 158.22 (C), 193.52 (CHO) [Found (HRMS): M^+, 324.2448. 22. Calc. for $C_{23}H_{32}O$: M, 324.2451].

Synthesis of (11*Z*)-8,18-methanoretinal 5

Ethyl 3-(3,3-dimethyl-2-oxocyclohexyl)propanoate 23. To a stirred solution of the keto ester **6** (5.00 g, 27 mmol) in benzene (100 cm^3) and NaOEt (0.55 g, 8.2 mmol) was added a solution of ethyl acrylate (5.4 g, 54 mmol) in benzene (25 cm^3) at 0 °C under nitrogen, and the resulting mixture was stirred for an additional 6 h. After addition of saturated aq. NH_4Cl (60 cm^3), the organics were extracted with benzene (3 × 80 cm^3), followed by standard work-up. The residue was purified by CC (hexane–ether, 4 : 1) to afford ethyl 3-(1-methoxycarbonyl-3,3-dimethyl-2-oxocyclohexyl)propanoate as a pale yellow oil, ν_{max} (KBr)/cm^{-1} 1740, 1730; δ_H ($CDCl_3$) 1.08 (3H, s, Me), 1.12 (3H, s, Me), 1.15 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 1.5–2.6 (10H, m, CH_2 × 5), 3.68 (3H, s, CO_2CH_3), 4.11 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$).

This keto diester was converted to the ester **23** according to the same manner as described for the preparation of **7**, in 82% yield (5.1 g) as a pale yellow oil, ν_{max} ($CHCl_3$)/cm^{-1} 1730, 1705; δ_H ($CDCl_3$) 1.04 (3H, s, Me), 1.17 (3H, s, Me), 1.25 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 1.4–2.6 (11H, m, CH_2 × 5 and CH), 4.17 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$) [Found (HRMS): M^+, 226.1553. Calc. for $C_{13}H_{22}O_3$: M, 226.1567].

Allyl 3-(3,3-dimethyl-2-oxocyclohexyl)propanoate 28. A mixture of ethyl 3-(1-methoxycarbonyl-3,3-dimethyl-2-oxocyclohexyl)propanoate (6.64 g, 23 mmol), prepared as described for the preparation of **23**, and c. HCl (70 cm^3) was refluxed for 18 h. After cooling of the mixture, water (150 cm^3) was added and the organics were extracted with ether (3 × 80 cm^3), followed by standard work-up to give the crude acid.

To a stirred solution of this crude acid, DMAP (40 mg, 0.33 mmol) and allyl alcohol (5.30 g, 92 mmol) in CH_2Cl_2 (90 cm^3) was added a solution of DCC (5.39 g, 25 mmol) in CH_2Cl_2 (40 cm^3) at 0 °C, and the resulting mixture was further stirred for an additional 2 h at room temperature. After filtration of the precipitate, the filtrate was concentrated under reduced pressure. The residue was purified by CC (ether–hexane, 1 : 6) to afford the keto ester **28** (4.79 g, 86%) as a pale yellow oil, ν_{max} ($CHCl_3$)/cm^{-1} 1720, 1700; δ_H ($CDCl_3$) 1.03 (3H, s, Me), 1.17 (3H, s, Me), 1.4–2.7 (11H, m, CH_2 × 5 and CH), 4.56 (2H, dt, J = 5.5, 1.5 Hz, $CO_2CH_2CH{=}CH_2$), 5.24 (1H, dq, J = 10, 1.5 Hz, $CO_2CH_2CH{=}CH_2$), 5.28 (1H, dq, J = 17, 1.5 Hz, $CO_2CH_2CH{=}CH_2$), 5.8–6.0 (1H, m, $CO_2CH_2CH{=}CH_2$) [Found (HRMS): M^+, 238.1560. Calc. for $C_{14}H_{22}O_3$: M, 238.1568].

Ethyl 3-(2-ethoxycarbonylmethyl-2-hydroxy-3,3-dimethylcyclohexyl)propanoate 24. This compound was prepared from the keto ester **23** (6.8 g, 30 mmol) and ethyl acetate (5.3 g, 60 mmol) in 73% yield (6.8 g) as a pale yellow oil according to the same procedure as described for the preparation of **8**. NMR analysis indicated that the ratio of stereoisomers was 1 : 3; ν_{max} ($CHCl_3$)/cm^{-1} 3450, 1720, 1710; δ_H ($CDCl_3$) 0.92 (6H, s, Me × 2), 1.25 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 1.29 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 1.4–2.4 (11H, m, CH_2 × 5 and CH), 2.46 (1/4 × 1H, d, J = 16 Hz, CH_2COO), 2.48 (3/4 × 1H, d, J = 16 Hz, CH_2COO), 2.52 (3/4 × 1H, d, J = 16 Hz, CH_2COO), 2.53 (1/4 × 1H, d, J = 16 Hz, CH_2COO), 4.12 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 4.16 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 4.40 (3/4 × 1H, s, OH, disappeared with D_2O), 4.93 (1/4 × 1H, s, OH, disappeared with D_2O) [Found (HRMS): M^+, 314.2104. Calc. for $C_{17}H_{30}O_5$: M, 314.2091].

Allyl 3-(2-allyloxycarbonylmethyl-2-hydroxy-3,3-dimethylcyclohexyl)propanoate 29. This compound was prepared from the keto ester **28** (4.90 g, 21 mmol) and allyl acetate (6.10 g, 61 mmol) in 82% yield (5.74 g) as a mixture of diastereoisomers according to the same procedure described for the preparation of **8**. NMR analysis indicated that the ratio of stereoisomers was 1 : 2; ν_{max} ($CHCl_3$)/cm^{-1} 3450, 1725; δ_H ($CDCl_3$) 0.86 (1/3 × 3H, s, Me), 0.92 (2/3 × 6H, s, Me × 2), 1.01 (1/3 × 3H, s, Me), 1.3–2.4 (11H, m, CH_2 × 5 and CH), 2.50 (1/3 × 1H, d, J = 18 Hz, CH_2COO), 2.54 (2/3 × 1H, d, J = 18 Hz, CH_2COO), 2.63 (2/3 × 1H, d, J = 18 Hz, CH_2COO), 2.66 (1/3 × 1H, d, J = 18 Hz, CH_2COO), 4.24 (2/3 × 1H, s, OH, disappeared with D_2O), 4.58 (4H, dt, J = 6, 1.5 Hz, $CO_2CH_2CH{=}CH_2$ × 2), 4.81 (1/3 × 1H, s, OH, disappeared with D_2O), 5.2–5.4 (4H, m, $CO_2CH_2CH{=}CH_2$ × 2), 5.8–6.0 (2H, m, $CO_2CH_2CH{=}CH_2$ × 2) [Found (HRMS): M^+, 338.2086. Calc. for $C_{19}H_{30}O_5$: M, 338.2091].

Dehydration of 24. The diester **25** was prepared from the hydroxy diester **24** (1.65 g, 5 mmol) and thionyl dichloride (0.75 cm^3, 10 mmol) in 82% yield (1.39 g) as a mixture of double-bond isomers according to the same procedure as described for the preparation of **9**. NMR analysis indicated that the *endo* and *exo* double-bond isomers were present in the ratio 3 : 1. Analytical samples were obtained by further CC (ether–hexane, 1 : 6), respectively.

Endo-Isomer. ν_{max} ($CHCl_3$)/cm^{-1} 1720; δ_H ($CDCl_3$) 0.96 (6H, s, Me × 2), 1.25 (6H, t, J = 7 Hz, $CO_2CH_2CH_3$ × 2), 1.4–1.7 (4H, m, CH_2 × 2), 1.98 (2H, t, J = 5 Hz, CH_2), 2.2–2.5 (4H, m, CH_2 × 2), 3.08 (2H, s, CH_2), 4.14 (4H, q, J = 7 Hz, $CO_2CH_2CH_3$ × 2) [Found (HRMS): M^+, 296.1959. Calc. for $C_{17}H_{28}O_4$: M, 296.1986].

Exo-Isomer. ν_{max} ($CHCl_3$)/cm^{-1} 1725, 1710, 1620; δ_H ($CDCl_3$) 1.12 (3H, s, Me), 1.15 (3H, s, Me), 1.25 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 1.28 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 1.2–2.0 (8H, m, CH_2 × 4), 2.3–2.5 (2H, m, CH_2), 3.7–3.9 (1H, m, CH), 4.13 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 4.15 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 5.86 (1H, s, =CH) [Found (HRMS): M^+, 296.7971. Calc. for $C_{17}H_{28}O_4$: M, 296.1986].

Dehydration of 29. The diester **30** was prepared from the hydroxy diester **29** (944 mg, 2.79 mmol) and thionyl dichloride (664 mg, 5.58 mmol) in 85% yield (757 mg) as a mixture of double-bond isomers according to the procedure described for the preparation of **9**. NMR analysis indicated that the *endo* and *exo* double-bond isomers were present in the ratio 1 : 1. Analytical samples were obtained by further CC (ether–hexane, 1 : 6).

Endo-Isomer. ν_{max} ($CHCl_3$)/cm^{-1} 1725; δ_H ($CDCl_3$) 0.96 (6H, s, Me × 2), 1.4–1.5 (2H, m, CH_2), 1.5–1.7 (2H, m, CH_2), 1.9–2.1 (2H, m, CH_2), 2.2–2.5 (4H, m, CH_2 × 2), 3.12 (2H, s, CH_2), 4.56 (4H, dt, J = 6, 1.5 Hz, $CO_2CH_2CH{=}CH_2$ × 2), 5.2–5.4 (4H, m, $CO_2CH_2CH{=}CH_2$ × 2), 5.8–6.0 (2H, m, $CO_2CH_2CH{=}CH_2$ × 2) [Found (HRMS): M^+, 320.2003. Calc. for $C_{19}H_{28}O_4$: *M*, 320.1986].

Exo-Isomer. λ_{max} (MeOH, ε/dm^3 mol^{-1} cm^{-1})/nm 232; ν_{max} ($CHCl_3$)/cm^{-1} 1730, 1715; δ_H ($CDCl_3$) 1.12 (3H, s, Me), 1.15 (3H, s, Me), 1.4–2.0 (8H, m, CH_2 × 4), 2.4–2.5 (2H, m, CH_2), 3.8–4.0 (1H, m, CH), 4.57 (4H, dq, J = 6, 1.5 Hz, $CO_2CH_2CH{=}CH_2$ × 2), 5.2–5.4 (4H, m, $CO_2CH_2CH{=}CH_2$ × 2), 5.8–6.0 (2H, m, $CO_2CH_2CH{=}CH_2$ × 2), 5.84 (1H, s, =CH) [Found (HRMS): M^+, 320.2000. Calc. for $C_{19}H_{28}O_4$: *M*, 320.1986].

Cyclization and deethoxycarbonylation of 25. In the same manner as described for the preparation of **10**, compounds **26** and **27** were obtained from the diester **25** (150 mg, 0.51 mmol) in 7% (5 mg) and 14% (10 mg) yield, respectively.

Tetrahydro-2-naphthol derivative ***26***. δ_H ($CDCl_3$) 1.24 (6H, s, Me × 2), 1.5–1.9 (4H, m, CH_2 × 2), 2.71 (2H, t, J = 6 Hz, CH_2), 4.53 (1H, s, OH), 6.62 (1H, dd, J = 8, 2.5 Hz, ArH), 6.83 (1H, d, J = 2.5 Hz, ArH), 6.96 (1H, d, J = 8 Hz, ArH).

Bicyclic ketone ***27***. ν_{max} ($CHCl_3$)/cm^{-1} 1705; δ_H ($CDCl_3$) 0.98 (6H, s, Me × 2), 1.4–1.5 (2H, m, CH_2), 1.5–1.7 (2H, m, CH_2), 1.9–2.0 (2H, m, [CH_2 × 1/2] × 2), 2.2–2.5 (4H, m, CH_2 and [CH_2 × 1/2] × 2), 2.84 (2H, br s, CH_2) [Found (HRMS): M^+, 178.1362. Calc. for $C_{12}H_{18}O$: *M*, 178.1357].

Cyclization of 30. (i) To a stirred solution of LDA in THF (15 cm^3, 8.0 mmol) was added a solution of diallyl ester **30** (1.28 g, 4 mmol) in THF (10 cm^3) at 0 °C under nitrogen, and the resulting mixture was stirred for an additional 30 min. After addition of saturated aq. NH_4Cl (40 cm^3), the organics were extracted with benzene (3 × 40 cm^3), followed by standard work-up. The residue was purified by CC (hexane–ether, 6 : 1) to afford the cyclized products **31** (110 mg, 10%), **32** (220 mg, 21%), and **33** (190 mg, 18%), as pale yellow oils.

(ii) Two cyclized products **32** (180 mg, 33%) and **33** (157 mg, 29%) were prepared from the diallyl ester **30** (660 mg, 2.1 mmol) and LiTMP (4.1 mmol) by the same procedure as described in method (i). These compounds were identical with authentic specimens obtained by the previous method.

2,1-Keto-ester ***31***. ν_{max} ($CHCl_3$)/cm^{-1} 1725, 1710; δ_H ($CDCl_3$) 0.95 (3H, s, Me), 0.99 (3H, s, Me), 1.4–1.7 (4H, m, CH_2 × 2), 1.9–2.4 (4H, m, CH_2 × 2), 2.6–2.8 (2H, m, CH_2), 3.96 (1H, s, CH), 4.59 (2H, dt, J = 5.5, 1.5 Hz, $CO_2CH_2CH{=}CH_2$), 5.24 (1H, dq, J = 10, 1.5 Hz, $CO_2CH_2CH{=}CH_2$), 5.32 (1H, dq, J = 17, 1.5 Hz, $CO_2CH_2CH{=}CH_2$), 5.8–6.0 (1H, m, $CO_2CH_2CH{=}CH_2$) [Found (HRMS): M^+, 262.1572. Calc. for $C_{16}H_{22}O_3$: *M*, 262.1567].

Hydroxy-ester ***32***. ν_{max} ($CHCl_3$)/cm^{-1} 3600–3000, 1660, 1615; δ_H ($CDCl_3$) 1.01 (6H, s, Me × 2), 1.4–1.8 (4H, m, CH_2 × 2), 1.93 (2H, br t, J = 6.5 Hz, CH_2), 2.8–3.0 (4H, m, CH_2 × 2), 4.68 (2H, dt, J = 5.5, 1.5 Hz, $CO_2CH_2CH{=}CH_2$), 5.24 (1H, dq, J = 10.5, 1.5 Hz, $CO_2CH_2CH{=}CH_2$), 5.33 (1H, dq, J = 16.5, 1.5 Hz, $CO_2CH_2CH{=}CH_2$), 5.8–6.1 (1H, m, $CO_2CH_2CH{=}CH_2$), 12.01 (1H, s, OH) [Found (HRMS): M^+, 262.1557. Calc. for $C_{16}H_{22}O_3$: *M*, 262.1567].

3,2-Keto-ester ***33***. λ_{max} (EtOH)/nm 240; ν_{max} ($CHCl_3$)/cm^{-1} 1730, 1665, 1605; δ_H ($CDCl_3$) 1.12 (3H, s, Me), 1.14 (3H, s, Me), 1.4–2.1 (6H, m, CH_2 × 2 and [CH_2 × 1/2] × 2), 2.22 (1H, dt, J = 13, 5 Hz, CH), 2.4–2.8 (2H, m, [CH_2 × 1/2] × 2), 3.35 (1H, dd, J = 15, 5 Hz, CH), 4.5–4.7 (2H, m, $CO_2CH_2CH{=}CH_2$), 5.2–5.4 (2H, m, $CO_2CH_2CH{=}CH_2$), 5.8–6.0 (1H, m, $CO_2CH_2CH{=}CH_2$), 6.00 (1H, m, =CH) [Found (HRMS): M^+, 262.1562. Calc. for $C_{16}H_{22}O_3$: *M*, 262.1567].

8,8-Dimethyl-3,4,5,6,7,8-hexahydronaphthalen-2(1*H*)-one 27. To a stirred mixture of $Pd(OAc)_2$ (9 mg, 0.040 mmol) and PPh_3 (22 mg, 0.084 mmol) in THF (25 cm^3) was added a solution of formic acid (0.13 cm^3, 3.3 mmol) and Et_3N (0.58 cm^3, 4.2 mmol) in THF (25 ml) at room temperature under nitrogen. To the resulting mixture was added a solution of cyclized ester **32** (437 mg, 1.67 mmol) in THF (15 ml), and the mixture was stirred for an additional 20 h. After addition of Et_2O and filtration with Celite, the filtrate was concentrated under reduced pressure. The residue was purified by CC (hexane–ether, 6 : 1) to afford the bicyclic ketone **27** (202 mg, 68%) as a pale yellow oil, accompanied by starting ester **32** (90 mg, 21% recovery). Compound **27** was identical with an authentic specimen obtained from the diester **25**.

8,8-Dimethyl-3,4,5,6,7,8-hexahydronaphthalen-2-yl trifluoromethanesulfonate 34. This was prepared from the ketone **27** (217 mg, 2.0 mmol) and Tf_2NPh (1.34 g, 3.7 mmol) by the same method as described for the preparation of **18**, in 58% yield (220 mg); λ_{max} (EtOH)/nm 268; ν_{max} ($CHCl_3$)/cm^{-1} 1415, 1140; δ_H ($CDCl_3$) 0.98 (6H, s, Me × 2), 1.4–1.5 (2H, m, CH_2 × 2), 1.5–1.7 (2H, m, CH_2), 1.9–2.0 (2H, m, [CH_2 × 1/2] × 2), 2.2–2.4 (2H, m, [CH_2 × 1/2] × 2), 2.4–2.6 (2H, m, CH_2), 5.97 (1H, br s, 1-H) [Found (HRMS): M^+, 310.0840. Calc. for $C_{13}H_{17}F_3O_3S$: *M*, 310.0851].

Methyl (2*E*)-3-(4,4-dimethyl-1,2,3,4,7,8-hexahydronaphthalen-6-yl)but-2-enoate 35. This was prepared from the triflate **34** (219 mg, 0.7 mmol) and methyl (*E*)-(trimethylstannyl)but-2-enoate[13] (223 mg, 0.85 mmol) by the same procedure as described for the preparation of **19**, in 62% yield (116 mg) as a pale yellow oil, λ_{max} (EtOH)/nm 339, 227; ν_{max} ($CHCl_3$)/1700, 1600; δ_H($CDCl_3$) 1.04 (6H, s, Me × 2), 1.44–1.54 (2H, m, CH_2), 1.54–1.70 (2H, m, CH_2), 2.00–2.20 (4H, m, CH_2 × 2), 2.24–2.38 (2H, m, CH_2), 2.39 (3H, d, J = 1 Hz, Me), 3.71 (3H, s, CO_2Me), 5.88 (1H, br s, =CH), 6.50 (1H, br s, =CH); δ_C ($CDCl_3$) 17.36 (Me), 21.71 (CH_2), 26.55 (CH_2), 31.01 (Me × 2), 31.96 (CH_2), 33.59 (CH_2), 35.06 (C), 41.54 (CH_2), 53.39 (OMe), 114.83 (CH), 129.58 (CH), 136.45 (C), 137.13 (C), 137.55 (C), 157.22 (C), 170.72 (CO) [Found (HRMS): M^+, 260.1783. Calc. for $C_{17}H_{24}O_2$: *M*, 260.1777].

Wittig reaction of 36. As the same manner as described for the preparation of **21**, the trienyl ester **35** (160 mg, 0.62 mmol) was converted to the Wittig salt **36**, followed by condensation with methyl (*E*)-3-formylcrotonate[14] (106 mg, 0.83 mmol). The crude product was purified by CC (ether–hexane, 1 : 9) to afford the condensed products (56 mg, *ca.* 28% from **35**). Separation of these products was achieved by preparative HPLC [LiChrosorb Si-60 (7 μm) 1 × 25 cm; hexane–ether (97 : 3), 3 cm^3 min^{-1}; 360 nm] to give **37** (all-*E*-:11*Z*-) and **38** (all-*E*-:11*Z*-), all in pure state, in the proportion of 7 : 3 : 5 : 4.

All-E-isomer of ***37***. λ_{max} (EtOH)/nm 385; ν_{max} (KBr)/cm^{-1} 1705, 1590; δ_H 1.10 (6H, s, Me × 2), 1.50–1.60 (2H, m, CH_2), 1.70–1.80 (2H, m, CH_2), 2.10–2.20 (4H, m, CH_2 × 2), 2.11 (3H, s, Me), 2.35–2.45 (2H, m, CH_2), 2.39 (3H, d, J = 1 Hz, Me), 3.73 (3H, s, CO_2Me), 5.84 (1H, br s, =CH), 6.38 (1H, br s, =CH), 6.41 (1H, d, J = 15 Hz, =CH), 6.45 (1H, d, J = 11 Hz, =CH), 7.19 (1H, dd, J = 15, 11 Hz, =CH) [Found (HRMS): M^+, 326.2250. Calc. for $C_{22}H_{30}O_2$: *M*, 326.2244].

11Z-Isomer of ***37***. λ_{max} (EtOH)/nm 376, 293, 225; ν_{max} (KBr)/cm^{-1} 1705, 1590; δ_H 1.05 (6H, s, Me × 2), 1.48–1.54 (2H, m, CH_2), 1.60–1.70 (2H, m, CH_2), 2.01 (3H, s, Me) 2.02–2.13 (4H, m, CH_2 × 2), 2.26–2.36 (2H, m, CH_2), 2.33 (3H, d, J = 1.5 Hz, 13-Me), 3.69 (3H, s, CO_2Me), 5.84 (1H, br s, =CH), 5.94 (1H, br d, J = 11.5 Hz, =CH), 6.33 (1H, br s, =CH), 6.66 (1H, t, J = 11.5 Hz, =CH), 6.76 (1H, br d, J = 11.5 Hz, =CH) [Found (HRMS): M^+, 326.2261. Calc. for $C_{22}H_{30}O_2$: *M*, 326.2244].

All-E-isomer of ***38***. λ_{max} (EtOH)/nm 347, 254; ν_{max} (KBr)/cm^{-1} 1705, 1595; δ_H 1.35 (6H, s, Me × 2), 1.70–1.78 (2H, m, CH_2), 1.80–1.92 (2H, m, CH_2), 2.28 (3H, d, J = 1 Hz, Me), 2.41 (3H, d, J = 1 Hz, Me), 2.80 (2H, t, J = 6 Hz, CH_2), 3.74 (3H, s,

CO_2Me), 5.88 (1H, br s, =CH), 6.50 (1H, d, J = 15 Hz, =CH), 6.62 (1H, br d, J = 11 Hz, =CH), 7.04 (1H, d, J = 8 Hz, ArH), 7.18 (1H, dd, J = 15, 11 Hz, =CH), 7.24 (1H, dd, J = 8, 2 Hz, ArH), 7.49 (1H, d, J = 2 Hz, ArH) [Found (HRMS): M^+, 324.2094. Calc. for $C_{22}H_{28}O_2$: *M*, 324.2088].

11Z-Isomer of ***38***. λ_{max} (EtOH)/nm 340, 250; ν_{max} (KBr)/cm^{-1} 1705, 1590; δ_H 1.29 (6H, s, Me × 2), 1.65–1.70 (2H, m, CH_2), 1.75–1.85 (2H, m, CH_2), 2.20 (3H, s, Me), 2.33 (3H, s, Me), 2.75 (2H, t, J = 6 Hz, CH_2), 3.69 (3H, s, CO_2Me), 5.90 (1H, br s, =CH), 6.00 (1H, d, J = 12 Hz, =CH), 6.66 (1H, t, J = 12 Hz, =CH), 6.90 (1H, br d, J = 12 Hz, =CH), 6.99 (1H, d, J = 8 Hz, ArH), 7.13 (1H, dd, J = 8, 2 Hz, ArH), 7.41 (1H, d, J = 2 Hz, ArH) [Found (HRMS): M^+, 324.2092. Calc. for $C_{22}H_{28}O_2$: *M*, 324.2088].

(11*Z*)-8,18-Methanoretinal 5. In the same manner as described for the preparation of **4**, the trienyl ester **35** (204 mg, 0.78 mmol) was converted to the Wittig salt **36**, followed by condensation with methyl (*E*)-3-formylbut-2-enenitrile[18] (170 mg, 1.79 mmol). The crude product was purified by CC (ether–hexane, 1 : 9) to afford the pentaenyl nitrile **40** (56 mg, 24% from **35**).

To a stirred solution of this nitrile (56 mg) in dry hexane (5 cm^3) was added a hexane solution of DIBAL-H (63 mg, 0.44 mmol) at −70 °C under nitrogen. After the mixture had been stirred at 0 °C for 15 min, the excess of DIBAL-H was destroyed by the successive addition of moist Et_2O and water. The resulting mixture was extracted with hexane, followed by standard work-up. The residue was purified by CC (ether–hexane, 1 : 9) to yield an isomeric mixture of the aldehydes (25 mg, 44%) as an orange oil. Separation of the isomers was achieved by preparative HPLC [LiChrosorb Si-60 (7 μm) 1 × 25 cm; hexane–ether (9 : 1), 5 cm^3 min^{-1}; 360 nm] to give 11*Z*-isomer **5**, 9*Z*-isomer, and all-*E*-isomer **5′** all pure, in the proportions 4.4 : 1 : 2.2.

11Z-Isomer ***5***. λ_{max} (MeOH, ε/dm^3 mol^{-1} cm^{-1})/nm 408 (14 700), 308 (10 200), 233 (8700); ν_{max} (KBr)/cm^{-1} 1660, 1580, 1550; δ_H (CD_3OD) 1.05 (6H, s, Me × 2), 1.50–1.54 (2H, m, CH_2), 1.63–1.68 (2H, m, CH_2), 2.05 (3H, s, Me), 2.06–2.12 (4H, m, CH_2 × 2), 2.33 (2H, t, J = 5.5 Hz, CH_2), 2.40 (3H, d, J = 1 Hz, Me), 6.01 (1H, dq, J = 8.5, 1 Hz, =CH), 6.02 (1H, br d, J = 10.5 Hz, =CH), 6.39 (1H, br s, =CH), 6.81 (1H, br d, J = 11 Hz, =CH), 6.83 (1H, br t, J = 11 Hz, =CH), 10.03 (1H, d, J = 8.5 Hz, CHO); δ_C (CD_3OD) 13.71 (Me), 18.30 (Me), 20.42 (CH_2), 25.06 (CH_2), 29.00 (Me × 2), 30.60 (CH_2), 32.01 (CH_2), 33.61 (C), 40.41 (CH_2), 121.76 (CH), 125.30 (CH), 130.57 (CH), 131.06 (CH), 133.41 (C), 133.76 (CH), 136.64 (C), 136.72 (C), 143.34 (C), 159.18 (C), 193.50 (CHO) [Found (HRMS): M^+, 296.2138. Calc. for $C_{21}H_{28}O$: *M*, 296.2139].

9Z-Isomer. λ_{max} (MeOH, ε/dm^3 mol^{-1} cm^{-1})/nm 366 (9600); ν_{max} (KBr)/cm^{-1} 1660, 1635, 1585; δ_H (CD_3OD) 1.08 (6H, s, Me × 2), 1.52–1.56 (2H, m, CH_2), 1.66–1.72 (2H, m, CH_2), 1.93 (2H, br t, J = 6 Hz, CH_2), 2.07 (3H, s, Me), 2.37 (3H, s, Me), 2.70–2.76 (2H, m, CH_2), 2.83–2.88 (2H, m, CH_2), 5.98 (1H, br d, J = 8 Hz, =CH), 6.13 (1H, br t, J = 4 Hz, =CH), 6.38 (1H, br d, J = 11 Hz, =CH), 6.54 (1H, br d, J = 15 Hz, =CH), 7.33 (1H, dd, J = 15, 11 Hz, =CH), 10.06 (1H, d, J = 8 Hz, CHO) [Found (HRMS): M^+, 296.2144. Calc. for $C_{21}H_{28}O$: *M*, 296.2139].

All-E-Isomer ***5′***. λ_{max} (MeOH, ε/dm^3 mol^{-1} cm^{-1})/nm 416.5 (26 100); ν_{max} (KBr)/cm^{-1} 1660, 1585, 1545; δ_H (CD_3OD) 1.06 (6H, s, Me × 2), 1.50–1.54 (2H, m, CH_2), 1.64–1.70 (2H, m, CH_2), 2.06–2.13 (4H, m, CH_2 × 2), 2.10 (3H, s, Me), 2.34–2.40 (2H, m, CH_2), 2.37 (3H, d, J = 1 Hz, Me), 5.95 (1H, br d, J = 8.5 Hz, =CH), 6.40 (1H, br s, =CH), 6.46 (1H, br d, J = 11.5 Hz, =CH), 6.48 (1H, br d, J = 15 Hz, =CH), 7.35 (1H, dd, J = 15, 11.5 Hz, =CH), 10.05 (1H, d, J = 8.5 Hz, CHO); δ_C (CD_3OD) 13.17 (Me), 14.25 (Me), 20.38 (CH_2), 24.81 (CH_2), 28.97 (Me × 2), 30.60 (CH_2), 32.00 (CH_2), 33.58 (C), 40 38 (CH_2), 125.34 (CH), 125.34 (CH), 126.30 (C), 129.41 (CH), 135.26 (CH), 135.42 (CH), 136.64 (C), 136.70 (C), 143.18 (C), 158.34 (C), 193.41 (CHO) [Found (HRMS): M^+, 296.2140. Calc. for $C_{21}H_{28}O$: *M*, 296.2139].

Binding of retinal analogs with bovine opsin

(11*Z*)-8,18-Alkanoretinal (**4** or **5**) dissolved in a small amount of ethanol was added to the opsin preparation and incubated at 23 °C in the dark for 40 h. The amount of retinal analog added to the opsin preparation was 3–4-fold molar excess over opsin. The formation of artificial pigment was monitored by UV-VIS spectroscopy. The reaction mixture was then applied to a DEAE-Sepharose column (Pharmacia) which had been equilibrated with buffer C [50 mM *N′*-(2-hydroxyethyl)piperazine-*N′*-ethane-2-sulfonic acid (HEPES), 0.6% CHAPS, 0.8 mg cm^{-3} PC, 20% (w/v) glycerol, pH 6.6]. The column was washed with buffer C supplemented with 10 mM hydroxylamine to remove the excess of retinal analog, and then hydroxylamine was removed by washing the column with buffer C. The rhodopsin analog was eluted with buffer C supplemented with 140 mM aq. NaCl.

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