Retinoids and Related Compounds. Part 15.[1] Synthesis and Spectral Characterization of Bicyclic Retinals involving the 8–18 or 8–16 Bonded Structure

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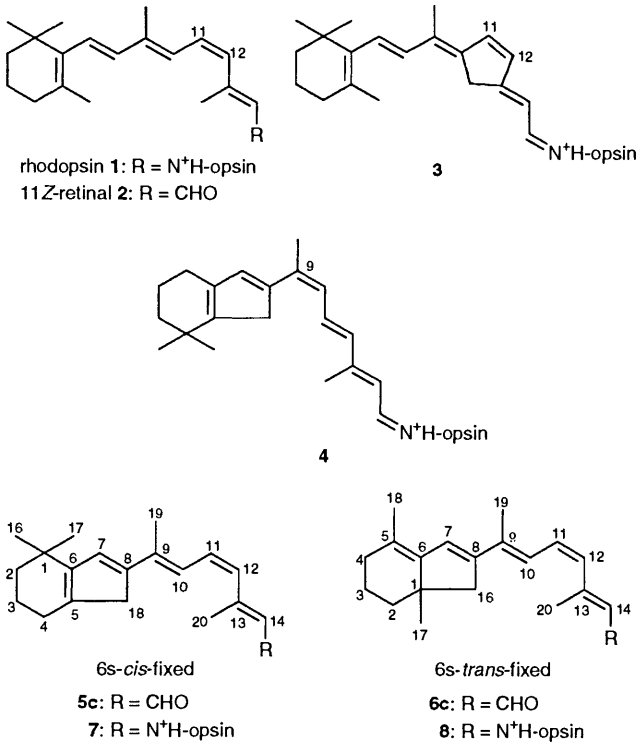
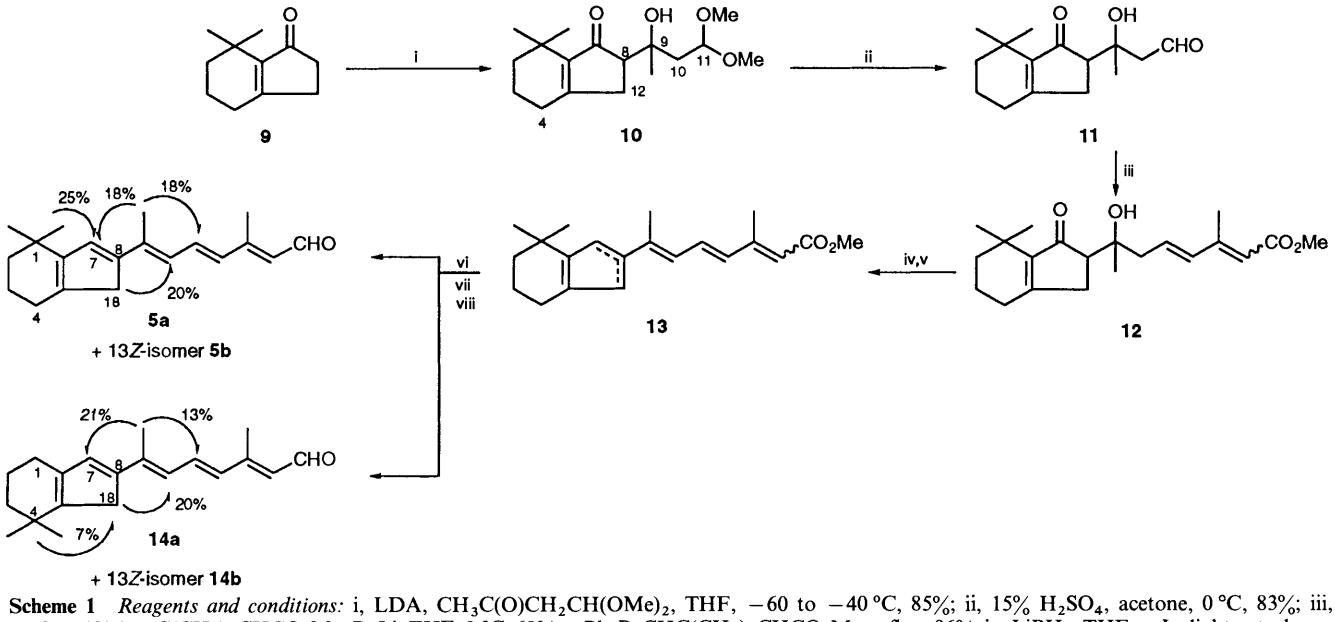
In order to investigate both the chromophore conformation around the trimethylcyclohexene ring and the origin of the induced β-circular dichroism (CD) band in rhodopsin, two C(6)–C(7) single-bond fixed retinal analogues, 6s-*cis*- and 6s-*trans*-locked bicyclic retinals **5** and **6**, have been synthesized. Their spectral characterization is described.

The visual pigment rhodopsin (Rh) **1** found in vertebrate retina contains the protonated Schiff base of 11*Z*-retinal **2** as a photoactive chromophore which is bound to the terminal ε-amino group of lysine-296 of the apoprotein opsin.[2,3] Both 11*Z*-retinal and opsin fail to show optical activity in the visible and near-UV part of the spectrum, but Rh **1** has a characteristic circular dichroism (CD) signal at the α- and β-bands. It is of particular interest for the conformational analysis of the chromophore of Rh to elucidate the origin of the CD bands of Rh, since the CD spectrum gives precise information about the interaction between the chromophore and the protein in photobleaching intermediates of Rh.[4–6] In previous papers,[7–9] we proposed that the origin of the α-CD band of Rh is due to the twisted 12s-bond in the chromophore by use of the 5-membered Rh analogue **3**, having a non-twisted conformation around a 12s-*trans* bond. The CD spectra of **3** showed a negligible α-band [β-band: 336 nm (+11.6)] in comparison with that of Rh [α-band: 487 nm (+7.5), β-band: 335 nm (+15.4)]. This is strong evidence supporting the theory of a twisted chromophore proposed for the induction of the α-CD band in Rh. On the other hand, CD data of the bicyclic Rh analogue **4** [α-band: 512 nm (+13.6), β-band: 326 nm (−2.1)], having 6s-*cis* fixed chromophore suggested that the β-band of Rh originates from the twist of the 6–7 single bond. The 9*Z*-chromophore of **4**, however, left ambiguity as to the conformation around the 6–7 bond in the 11*Z* form. In order to investigate the origin of the β-CD band of Rh, two kinds of retinal analogues, 11*Z*-6s-*cis*-fixed bicyclic retinal **5** and 11*Z*-6s-*trans*-fixed bicyclic retinal **6**, were prepared and incorporated into bovin opsin to provide the artificial Rh analogues **7** and **8**, respectively. Details of the CD data of the analogues **7** and **8** and the conformational study of the chromophore were discussed in the previous paper.[10] Here we report a full account of the synthesis of the bicyclic retinals **5** and **6**.



Results and Discussion

6*s*-cis-*Locked Bicyclic Retinal* **5** (*Scheme* 1).—Aldol condensation[11] of 2,3,4,5,6,7-hexahydro-7,7-dimethyl-1*H*-inden-1-one **9**[12] with 3-oxobutanal dimethyl acetal in the presence of lithium diisopropylamide (LDA) gave the hydroxy acetal **10** (85%) as a mixture of diastereoisomers which, without separation, was deprotected with 15% H_2SO_4 to afford the hydroxy aldehyde **11** (83% yield). A Horner–Emmons reaction of **11** with the C-5 ester phosphonate gave the diene ester **12** (68% yield) as a mixture of 4 isomers (13*E*- and 13*Z*-isomers for each of the two diastereoisomers) which, without separation, after reduction of the ketone group with $LiBH_4$ was dehydrated with I_2 to provide the conjugated pentaene ester **13** (20% from **12**). Conversion of the ester group in compound **13** into the aldehyde group led to a mixture of conjugated pentaene aldehydes **5** and **14** (52%), the repeated purification of which by a combination of column chromatography (CC) and preparative high performance liquid chromatography (HPLC) in the dark furnished 4 bicyclic retinal isomers (**5a**:**5b**:**14a**:**14b** = 1.7:1.4:1.2:1.0). The structures of the isomers were determined on the basis of the UV–visible (VIS) and ^1H NMR spectral data compared with those of all-*E*-retinal and another all-*E*-bicyclic retinal **15** (Table 1).[13] Confirmation of their stereostructure was based on measurements of nuclear Overhauser effects (NOE). A positive NOE (25%) between C-1-gem-Me and 7-H in **5a** was observed in combination with the absence of that observed between C-1-gem-Me and 18-H_2, indicating this structure (Scheme 1). On the other hand, a 7% NOE between C-4-gem-Me and 18-H_2 was observed in **14a**. 11*Z*-6s-*cis*-Locked bicyclic retinal **5c** was obtained from the photoirradiation mixture of the all-*E* form. Irradiation products of **5a** using a daylight fluorescent lamp (30 W) in MeOH exhibited the HPLC chromatogram shown in Fig. 1. Although the main product was the 9*Z*-isomer **5d**, the 11*Z*-isomer **5c** was also isolated very carefully by preparative HPLC in the dark. These structures were determined from ^1H NMR; the 9*Z*-geometry was identified from the upfield shift of the



Scheme 1 *Reagents and conditions:* i, LDA, $CH_3C(O)CH_2CH(OMe)_2$, THF, −60 to −40 °C, 85%; ii, 15% H_2SO_4, acetone, 0 °C, 83%; iii, $(EtO)_2P(O)CH_2C(CH_3)$=$CHCO_2Me$, BuLi, THF, 0 °C, 68% or Ph_3P=$CHC(CH_3)$=$CHCO_2Me$, reflux, 96%; iv, $LiBH_4$, THF; v, I_2, light petroleum, reflux, 20%; vi, LAH, Et_2O, 0 °C; vii, MnO_2, CH_2Cl_2, 52%; viii, preparative HPLC

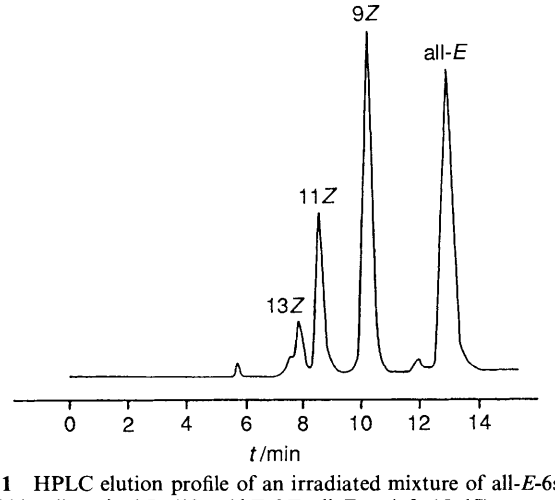
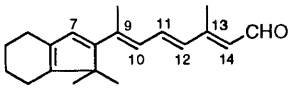


Fig. 1 HPLC elution profile of an irradiated mixture of all-*E*-6s-*cis*-fixed bicyclic retinal **5a** (13*Z*:11*Z*:9*Z*:all-*E* = 4:9:15:17)

Table 1 ^{1}H NMR data for 6s-*cis*-fixed bicyclic retinals **5a** and **15**



		All-*E* **5a**	All-*E* **15**
^{1}H NMR	9-Me	2.09 (s)	2.11 (s)
(200 MHz)	13-Me	2.33 (s)	2.34 (s)
(δ, $CDCl_3$)	7-H	6.63 (s)	6.47 (s)
	10-H	6.36 (d, *J* 11.5)	6.43 (d, *J* 11)
	11-H	7.15 (dd, *J* 15, 11.5)	7.21 (dd, *J* 15, 11)
	12-H	6.36 (d, *J* 15)	6.42 (d, *J* 15)
	14-H	5.98 (d, *J* 8.5)	5.98 (d, *J* 8)
	CHO	10.10 (d, *J* 8.5)	10.10 (d, *J* 8)

10-H signal and the downfield shift of the 11-H signal in comparison with the all-*E*-isomer **5a** (Fig. 2). As the 11*Z*-isomer **5c** was extremely unstable in $CDCl_3$, its ^{1}H NMR spectrum was measured in C_6D_6. The $J_{11,12}$ value (12 Hz) and the downfield shift of 10-H (δ 6.77) provided the confirmation of the 11*Z*-configuration compared with those of the all-*E*-isomer **5a** in C_6D_6. As known from the data of retinal isomers shown in

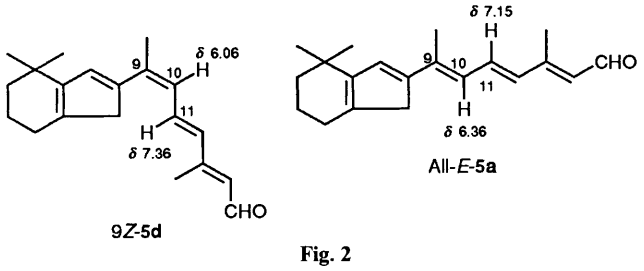


Fig. 2

Tables 2 and 3, 13- and 9-methyl signals and 11- and 12-olefinic proton signals are strongly shielded by the solvent effect. This trend is also observed in the 6s-*cis*-fixed bicyclic retinals **5**. In addition, the chemical shift differences between the 11*Z*-isomer **5c** and the all-*E*-isomer **5a** are close to those of 11*Z*-retinal relative to all-*E*-retinal. The ^{1}H NMR of other isomers of **5** measured in C_6D_6 were also assigned by comparison with the chemical shifts and their differences among retinal isomers in C_6D_6 (Table 2), which are useful data in the assignment of unstable retinal analogues. Isomer **5c** showed an absorption maximum at 422 nm (EtOH). This is the longest wavelength observed so far for 11*Z*-retinal analogues, suggesting that the chromophore in **5c** has a high coplanarity in a C(5)–C(8) part (Table 4).

6s-trans-*Locked Bicyclic Retinal* **6** (*Scheme* 2).—Treatment of 2,6-dimethylcyclohexanone with the lithium derivative prepared from butyllithium (BuLi) and the prop-2-ynyl alcohol THP ether gave the alcohol **16** in quantitative yield. After deprotection, the resulting diol **17** was cyclized under acidic conditions[12] to provide the bicyclic enone **18** (44%) as an enantiomeric mixture. The structure of this new compound **18** was determined from ^{1}H and ^{13}C NMR data (see Experimental section). This reaction mechanism was rationalized by MacAlpine *et al.*[12] Attempts to obtain compound **6** by use of the same route as the preparation of **5** and **14** (Scheme 1) were unsuccessful at the dehydration stage. The methoxycarbonyl group was introduced at the α-position in the ketone **18** with dimethyl carbonate in the presence of NaH to afford the keto ester **19** (92%). Subsequent reduction of **19** with $NaBH_4$ followed by protection of the resulting hydroxy group with *tert*-butyldimethylsilyl (TBS) group provided **20** (55% from **19**)

Table 2 ^{1}H NMR chemical shifts of 6s-*cis*-fixed bicyclic retinals **5** and retinals. The chemical shift differences of each isomer relative to all-*E*-isomers are given in parentheses

		All-*E*-**5a**	13*Z*-**5b**	11*Z*-**5c**	9*Z*-**5d**
^{1}H NMR (200 MHz) (δ, C_6D_6)	9-Me	1.89	1.89 (0)	1.85 (−0.04)	1.91 (+0.02)
	13-Me	1.79	1.65 (−0.14)	1.85 (+0.06)	1.78 (−0.01)
	7-H	6.62	6.62 (0)	6.60 (−0.02)	6.63 (−0.01)
	10-H	6.23	6.30 (+0.07)	6.77 (+0.54)	5.90 (−0.33)
	11-H	6.91	6.84 (−0.07)	6.47 (−0.44)	7.21 (+0.30)
	12-H	6.12	7.27 (+1.15)	5.61 (−0.51)	6.08 (−0.04)
	14-H	6.05	5.76 (−0.29)	6.22 (+0.17)	5.97 (−0.08)
	CHO	10.07	10.21 (+0.14)	10.02 (−0.05)	10.03 (−0.04)
		All-*E*-retinal	13*Z*-retinal	11*Z*-retinal	9*Z*-retinal
^{1}H NMR (500 MHz) (δ, C_6D_6)	9-Me	1.78	1.78 (0)	1.74 (−0.04)	1.86 (+0.08)
	13-Me	1.74	1.59 (−0.15)	1.76 (+0.02)	1.62 (−0.12)
	7-H	6.36	6.37 (+0.01)	6.34 (−0.02)	6.37 (+0.01)
	10-H	6.02	6.05 (+0.03)	6.59 (+0.57)	5.89 (−0.13)
	11-H	6.84	6.74 (−0.10)	6.38 (−0.46)	7.07 (+0.23)
	12-H	6.04	7.07 (+1.03)	5.59 (−0.45)	5.97 (−0.07)
	14-H	5.96	5.75 (−0.21)	6.11 (+0.15)	5.94 (−0.02)
	CHO	10.02	10.15 (+0.13)	9.91 (−0.11)	9.95 (−0.07)

Table 3 ^{1}H NMR data for all-*E*- and 11*Z*-6s-*trans*-fixed bicyclic retinals and all-*E*- and 11*Z*-retinals

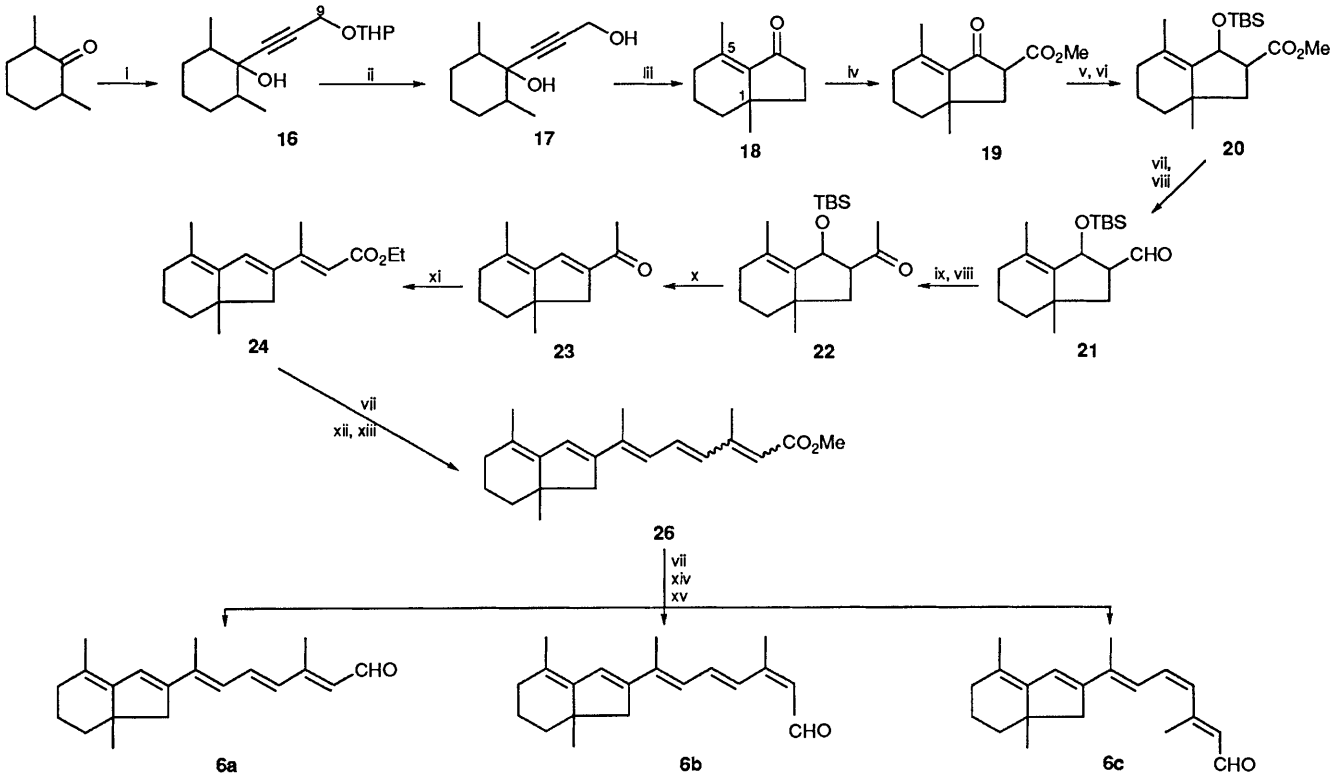
		All-*E*-**6a**	All-*E*-retinal	11*Z*-**6c**	11*Z*-retinal
^{1}H-NMR (200 MHz) (δ, $CDCl_3$)	1-Me	1.05 (s)	1.04 (s)	1.05 (s)	1.02 (s)
	5-Me	1.74 (s)	1.72 (s)	1.74 (s)	1.71 (s)
	9-Me	2.10 (s)	2.03 (s)	2.06 (s)	1.99 (s)
	13-Me	2.33 (s)	2.33 (s)	2.39 (s)	2.36 (s)
	7-H	6.56 (s)	6.36 (d, *J* 16.5)	6.55 (s)	6.32 (d, *J* 16)
	10-H	6.26 (d, *J* 12)	6.20 (d, *J* 12)	6.61 (d, *J* 10)	6.54 (d, *J* 13)
	11-H	7.15 (dd, *J* 15, 12)	7.15 (dd, *J* 15.4, 12)	6.70 (t-like, *J* 10)	6.69 (dd, *J* 13, 11.5)
	12-H	6.40 (d, *J* 15)	6.37 (d, *J* 15.4)	5.95 (d, *J* 10)	5.92 (d, *J* 11.5)
	14-H	5.98 (d, *J* 8.5)	5.98 (d, *J* 8)	6.08 (d, *J* 8)	6.07 (d, *J* 8)
	CHO	10.12 (d, *J* 8.5)	10.12 (d, *J* 8)	10.10 (d, *J* 8)	10.10 (d, *J* 8)

Table 4 UV–VIS absorption maxima for retinal analogues, their PSB and rhodopsin analogues

		5	PSB of **5**	**7**	**6**	PSB of **6**	**8**	Retinal	PSB of retinal	Rhodopsin
UV–VIS λ_{max}(EtOH)/nm	All-*E*	425			425			383		
		295			295					
	13*Z*	420			407			375		
		297			280			257		
	11*Z*	422	506[a]	539[b]	405	495[a]	545[b]	376.5	440[a]	498[b]
		299			310			290		
		229			258			254		
					227 (sh)					
	9*Z*	416			402			373		
		295			301 (sh)					
					257					
					222					

[a] In MeOH. [b] In CHAPS–PC mixture.

which, on reduction with lithium aluminium hydride (LAH) and subsequent Swern oxidation, was converted into the aldehyde **21** (77%). Addition of the methyl group to the aldehyde **21** using a Grignard reagent followed by Swern oxidation gave the ketone **22** (85%) which was transformed into the dienone **23**, possessing a β-ionone-type chromophore by deprotection with tetrabutylammonium fluoride (TBAF). Its absorption maximum is at a longer wavelength (312 nm in EtOH) than that of β-ionone, suggesting the coplanarity of chromophoric system in the dienone **23**. The transformation of **23** into the bicyclic retinal **6** was achieved by application of the usual procedure of retinal synthesis. Two-carbon unit elongation of the dienone **23** by the Horner–Emmons reaction gave only the 9*E*-triene ester **24** (63%). The stereostructure of the ester **24** was determined by comparison of its ^{1}H NMR spectrum with those of 9*E*- and 9*Z*-ethyl β-ionylideneacetate **25** (Fig. 3). LAH reduction of the ester **24** and subsequent treatment of the resulting triene alcohol with triphenylphosphine hydrobromide (Ph_3P·HBr) gave the corresponding Wittig salt which, without purification, was condensed with methyl (*E*)-4-formyl-3-methylbut-2-enoate in the presence of NaOMe as a base to provide the pentaene ester **26** as a mixture of geometrical isomers (42% from **24**). The ester **26** was converted into an isomeric mixture of 6s-*trans*-locked bicyclic retinal **6** (38%) by LAH reduction and MnO_2 oxidation. Separation and purification of the mixture by preparative



Scheme 2 *Reagents and conditions:* i, $HC{\equiv}CCH_2OTHP$, BuLi, Et_2O, quant.; ii, 5% H_2SO_4, acetone, quant.; iii, P_2O_5, CH_3SO_3H, 44%; iv, NaH, $(MeO)_2CO$, benzene, reflux, 92%; v, $NaBH_4$, MeOH; vi, TBSCl, Et_3N, DMAP, CH_2Cl_2, 55%, vii, LAH, Et_2O, 0 °C; viii, Swern oxid., **21** 77% from **20**, **22** 85% from **21**; ix, MeMgBr, THF, 0 °C; x, TBAF, THF, 83%; xi, $(EtO)_2P(O)CH_2CO_2Et$, BuLi, THF, reflux, 63%; xii, $Ph_3P{\cdot}HBr$, MeOH; xiii, $OHCC(CH_3){=}CHCO_2Me$, NaOMe, CH_2Cl_2, 0 °C, 42% from **24**; xiv, MnO_2, CH_2Cl_2, 38% from **26**; xv, preparative HPLC

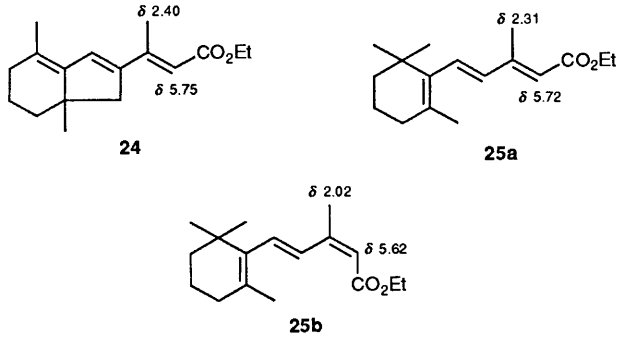


Fig. 3

HPLC in the dark led to three pure isomers [all-*E*:11*Z*:13*Z* = 20:5:7]. Their structures were confirmed on the basis of the UV–VIS (Table 4) and ^1H NMR data (Table 3) by comparison with those of respective retinal isomers.[14] Both 6*s*-*cis*- and 6*s*-*trans*-locked retinals have longer absorption maxima than those of native retinal (Table 4). This suggests that compounds **5** and **6** have greater chromophoric coplanarity due to the rigidly fixed structures. Absorption data of rhodopsin analogues **7** and **8** are listed in Table 4. Compound **8** showed an absorption maximum at 545 nm which is located at a wavelength longer than that (539 nm) of compound **7**. The absorption maxima of the aldehyde **6** and its protonated Schiff base (PSB), however, showed shorter wavelengths than those of the aldehyde **5** and its corresponding PSB. These results suggest that in the organic solvent, compound **5** and its PSB containing the cyclopentadiene chromophore have higher coplanarity in the whole conjugated structure than compound **6** and upon reaction with the protein, compound **5** is incorporated in the more strongly twisted conformation [presumably at the C(8)–C(9) single bond[10]] than that of compound **6**.

Experimental

M.p.s are uncorrected. BuLi was used as a solution in hexane. UV–VIS spectra were recorded on a Shimadzu UV 200 or UV 200S or UV-160 instrument (ε values are given in $dm^3\ mol^{-1}\ cm^{-1}$) 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 using tetramethylsilane as an internal reference. Mass spectra were determined on a Hitachi M-80 double focusing GC mass spectrometer. CC was performed on silica gel Merck Art. 7739 using a short column with glass filter under reduced pressure. Preparative TLC was performed on silica gel plates (Merck silica gel $60F_{254}$ precoated plates, 0.25 or 0.5 mm thickness). Analytical HPLC was carried out on a Shimadzu LC-5A instrument with a Shimadzu photodiode array UV–VIS detector SPD-M6A 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, using a column LiChrosorb Si-60 (5 μm), 1.0 × 30 cm. Unless otherwise stated, solvent extracts were dried over anhydrous sodium sulfate and all operations were carried out under nitrogen or argon. The extract or the filtrate was concentrated under reduced pressure at < 30 °C using a rotary evaporator.

Synthesis of 6*s*-cis-*Locked Bicyclic Retinal* **5**: (±)-2,3,4,5,6,7-*Hexahydro*-2-(1-*hydroxy*-3,3-*dimethoxy*-1-*methylpropyl*)-7,7-*dimethylinden*-1-*one* **10**.—To a solution of LDA (18.0 mmol, prepared from 2.51 cm^3 of diisopropylamine and 18.0 mmol of BuLi) in tetrahydrofuran (THF) (18 cm^3) was added a solution of the bicyclic ketone **9** (2.95 g, 18 mmol) in THF (29 cm^3) at −60 °C. After the reaction mixture had been stirred for 1 h, 3-oxobutyraldehyde dimethyl acetal (4.75 g, 36.0 mmol) was added to it and stirring continued at −40 °C for 1 h. The

reaction was quenched by the addition of saturated aqueous NH_4Cl, after which the mixture was extracted with Et_2O. The combined extracts were washed with brine, dried and evaporated to give a residue which was purified by CC (Et_2O–hexane, 1:2). This afforded a mixture of diastereoisomers **10** (4.55 g, 85%) as a pale yellow oil, some of which was separated by CC (Et_2O–hexane, 1:2) to give the less polar compound **10a** and the more polar compound **10b**. Compound **10a**: $\nu_{max}(CHCl_3)/cm^{-1}$ 3475 (OH), 1685 (C=O) and 1630 (C=C); $\nu_{max}(CCl_4)/cm^{-1}$ 3520 (intramolecular hydrogen bond); δ_H(200 MHz; $CDCl_3$) 1.05 (3 H, s, 9-Me), 1.16 and 1.18 (each 3 H, each s, gem-Me), 2.29 (2 H, t, *J* 6, 4-H_2), 2.57 (2 H, s, 12-H_2), 3.34 and 3.37 (each 3 H, each s, 2 × OMe), 4.73 (1 H, dd, *J* 6 and 4, 11-H) and 4.48 (1 H, s, OH) (Found: M^+ − OMe, 265.180. $C_{16}H_{25}O_3$ requires *M* − OMe, 265.180). Compound **10b**: $\nu_{max}(CHCl_3)/cm^{-1}$ 3475 (OH), 1685 (C=O) and 1630 (C=C); δ_H(200 MHz; $CDCl_3$) 1.07 (3 H, s, 9-Me), 1.15 and 1.17 (each 3 H, each s, *gem*-Me), 2.30 (2 H, t, *J* 6, 4-H_2), 2.51 (2 H, s, 12-H_2), 3.35 and 3.38 (each 3 H, each s, 2 × OMe), 4.36 (1 H, s, OH) and 4.74 (1 H, t-like, *J* 5.5, 11-H) (Found: M^+ − OMe, 265.180. $C_{16}H_{25}O_3$ requires *M* − OMe, 265.180).

(±)-2,3,4,5,6,7-*Hexahydro*-2-(2-*formyl*-1-*hydroxy*-1-*methylethyl*)-7,7-*dimethylinden*-1-*one* **11**.—To a solution of the acetal **10** (1.0 g, 3.38 mmol) in acetone (25 cm^3) was added 15% H_2SO_4 (1 cm^3) at 0 °C. The mixture was stirred at 0 °C for 6 h and then poured into water. The water layer was extracted with Et_2O and the extracts were washed with brine, dried and evaporated to give a residue which was purified by CC (Et_2O–benzene, 1:9) to afford the title compound **11** (0.70 g, 83%) as a pale yellow oil. A portion of the oil was separated by preparative TLC (Et_2O–benzene, 1:4) to yield the less polar compound **11a** and the more polar compound **11b**. Compound **11a**: $\nu_{max}(CHCl_3)/cm^{-1}$ 3450 (OH), 1720 (CHO), 1685 (cyclopentenone) and 1630 (C=C); δ_H(200 MHz; $CDCl_3$) 1.14 and 1.17 (each 3 H, each s, gem-Me), 1.22 (3 H, s, 9-Me), 2.39 (1 H, dd, *J* 15 and 3, 10-H), 2.66 (1 H, dd, *J* 15 and 2, 10-H), 4.79 (1 H, br s, OH) and 9.95 (1 H, dd, *J* 3 and 2, CHO) (Found: M^+, 250.158. $C_{15}H_{22}O_3$ requires *M*, 250.157). Compound **11b**: $\nu_{max}(CHCl_3)/cm^{-1}$ 3450 (OH), 1720 (CHO), 1685 (cyclopentenone) and 1630 (C=C); δ_H(200 MHz; $CDCl_3$) 1.14 (3 H, s, 9-Me), 1.17 (6 H, s, gem-Me), 2.46 (1 H, dd, *J* 15 and 3, 10-H), 2.58 (1 H, dd, *J* 15 and 2.5, 10-H), 4.95 (1 H, br s, OH) and 9.95 (1 H, t-like, *J* 3, CHO) (Found: M^+, 250.156. $C_{15}H_{22}O_3$ requires *M*, 250.157).

Methyl (E,E/Z,E)-(±)-7-(2,3,4,5,6,7-*Hexahydro*-7,7-*dimethyl*-1-*oxo*-1H-*inden*-2-*yl*)-7-*hydroxy*-3-*methylocta*-2,4-*dienoate* **12**.—BuLi (15% w/v; 3.8 cm^3, 8.9 mmol) was added to a solution of diethyl 3-methoxycarbonyl-2-methylprop-2-enylphosphonate (*E*:*Z* = 3:1) (2.20 g, 8.8 mmol) in THF (5 cm^3) at 0 °C. After the reaction mixture had been stirred for 20 min at room temp., the aldehyde **11** (697 mg, 2.79 mmol) in THF (7 cm^3) was added dropwise to it at 0 °C and stirring continued for a further 30 min. The mixture was then poured into saturated aqueous NH_4Cl and extracted with Et_2O. The extracts were washed with brine, dried and evaporated. The residue was purified by CC (Et_2O–hexane, 1:9) to give the title compound **12** as a mixture of diastereoisomers (total 414 mg, 68%). An aliquot of this was separated by preparative TLC to afford the 13*Z*-isomers **12a** (less polar) and **12b** (more polar) and the 13*E*-isomers **12c** (less polar) and **12d** (more polar). Compound **12a**: $\nu_{max}(CHCl_3)/cm^{-1}$ 3450 (OH), 1710 (CO_2Me), 1670 (cyclopentenone) and 1625 (C=C); δ_H(200 MHz; $CDCl_3$) 1.02 (3 H, s, 9-Me), 1.17 (6 H, s, gem-Me), 2.02 (3 H, s, 13-Me), 3.70 (3 H, s, CO_2Me), 4.91 (1 H, s, OH), 5.64 (1 H, s, 14-H), 6.37 (1 H, ddd, *J* 16, 8 and 6.5, 11-H) and 7.43 (1 H, d, *J* 16, 12-H) (Found: M^+ + H, 347.224. $C_{21}H_{31}O_4$ requires *M* + H, 347.222). Compound **12b**: $\nu_{max}(CHCl_3)/cm^{-1}$ 3450 (OH), 1710 (CO_2Me), 1670 (cyclopentenone) and 1625 (C=C); δ_H(200 MHz; $CDCl_3$) 1.16 (9 H, s, gem-Me and 9-Me), 2.00 (3 H, s, 13-Me), 3.68 (3 H, s, CO_2Me), 4.76 (1 H, s, OH), 5.62 (1 H, s, 14-H), 6.30 (1 H, ddd, *J* 16, 8.5 and 6, 11-H) and 7.54 (1 H, d, *J* 16, 12-H) (Found: M^+, 346.213. $C_{21}H_{30}O_4$ requires *M*, 346.214). Compound **12c**: $\nu_{max}(CHCl_3)/cm^{-1}$ 3450 (OH), 1710 (CO_2Me), 1670 (cyclopentenone) and 1625 (C=C); δ_H(200 MHz; $CDCl_3$) 1.02 (3 H, s, 9-Me), 1.17 (6 H, s, gem-Me), 2.29 (3 H, s, 13-Me), 3.71 (3 H, s, CO_2Me), 4.85 (1 H, s, OH), 5.72 (1 H, s, 14-H), 6.13 (1 H, d, *J* 15, 12-H) and 6.36 (1 H, ddd, *J* 15, 8 and 6.5, 11-H) (Found: M^+ + H, 347.222. $C_{21}H_{31}O_4$ requires *M* + H, 347.222). Compound **12d**: $\nu_{max}(CHCl_3)/cm^{-1}$ 3450 (OH), 1710 (CO_2Me), 1670 (cyclopentenone) and 1625 (C=C); δ_H(200 MHz; $CDCl_3$) 1.17 (9 H, s, gem-Me and 9-Me), 2.27 (3 H, s, 13-Me), 3.70 (3 H, s, CO_2Me), 4.48 (1 H, s, OH), 5.68 (1 H, s, 14-H), 6.08 (1 H, d, *J* 15.5, 12-H) and 6.27 (1 H, ddd, *J* 15.5, 8 and 6.5, 11-H) (Found: M^+ + H, 347.225. $C_{21}H_{31}O_4$ requires *M* + H, 347.222).

A mixture of the aldehyde **11** (2.74 g, 10.7 mmol), 3-methoxycarbonyl-2-methylprop-2-enylidene)triphenylphosphorane[15] (4.80 g, 12.8 mmol) and dry benzene (138 cm^3) was refluxed for 30 min. After cooling, evaporation of the solvent gave the residue which was purified by CC (Et_2O–hexane, 1:4) to afford the ester **12** (3.56 g, 96%) as an isomeric mixture.

Methyl (E,E,E/Z,E,E)-3-*Methyl*-7-(4,5,6,7-*tetrahydro*-4,4-*dimethyl*-1H-*inden*-2-*yl*)*octa*-2,4,6-*trienoate* **13a**, *Methyl* (E,E,E/Z,E,E)-3-*Methyl*-7-(4,5,6,7-*tetrahydro*-7,7-*dimethyl*-1H-*inden*-2-*yl*)*octa*-2,4,6-*trienoate* **13b**.—To a solution of the ester **12** (300 mg, 0.87 mmol) in THF (6 cm^3) was added $NaBH_4$ (92 mg, 4.18 mmol) and the mixture was stirred at room temp. for 2 h. The mixture was poured into water and extracted with Et_2O. The extracts were washed with brine, dried and evaporated to give an oil which was dissolved in light petroleum (b.p. 30–40 °C) (5 cm^3). To this solution was added iodine (13.5 mg, 0.053 mmol) and the mixture was refluxed for 30 min and then cooled and diluted with Et_2O. The organic layer was washed with 10% aqueous $Na_2S_2O_3$, followed by brine, dried and evaporated to give a residue which was purified by CC (Et_2O–hexane, 1:9) to afford the title compounds **13** (50 mg, 20%) as a mixture of geometrical isomers; $\nu_{max}(CHCl_3)/cm^{-1}$ 1700 (CO_2Me); λ_{max}(EtOH)/nm 398 and 282 (Found: M^+, 312.210. $C_{21}H_{28}O_2$ requires *M*, 312.209).

(E,E,E/Z,E,E)-3-*Methyl*-7-(4,5,6,7-*tetrahydro*-4,4/7,7-*dimethyl*-1H-*inden*-2-*yl*)*octa*-2,4,6-*trienal* **14** and **5**.—LAH (25 mg, 0.66 mmol) was added to a solution of the ester **13** (102 mg, 0.33 mmol) in dry Et_2O (4 cm^3) and the mixture was stirred at room temp. for 10 min. The reaction was quenched by EtOAc and the mixture was diluted with Et_2O. The diluted mixture was washed with brine, dried and evaporated to give the resulting hydroxy compound which was dissolved in acetone and shaken with active MnO_2 (1.56 g) at room temp. for 2 h. The mixture was filtered through Celite. Evaporation of the filtrate gave an oil which was purified by CC (Et_2O–hexane, 1:4) to provide an isomeric mixture of the title compounds **14** and **5** (48 mg, 52%) as an orange oil. Separation of the mixture by preparative HPLC [LiChromosorb Si-60 (5 μm), Et_2O–hexane, 8:92] gave the 13*Z*-isomers **14b**, **5b** and the all-*E*-isomers **14a**, **5a**, in a ratio *ca.* 1.0:1.4:1.2:1.7. 13*Z*-Isomer **14b**: λ_{max}(EtOH)/nm 420 (ε 20 000) and 297 (11 000); δ_H(200 MHz; $CDCl_3$) 1.14 (6 H, s, gem-Me), 2.07 (3 H, s, 9-Me), 2.15 (3 H, s, 13-Me), 3.18 (2 H, br s, 18-H_2), 5.83 (1 H, d, *J* 8, 14-H), 6.43 (1 H, d, *J* 11.5, 10-H), 6.45 (1 H, s, 7-H), 7.04 (1 H, dd, *J* 15 and 11.5, 11-H), 7.33 (1 H, d, *J* 15, 12-H) and 10.22 (1 H, d, *J* 8, CHO) (Found: M^+, 282.198. $C_{20}H_{26}O$ requires *M*, 282.198). 13*Z*-Isomer **5b**: ν_{max}(KBr)/cm^{-1} 1660 (C=O) and 1584 (C=C); λ_{max}(EtOH)/nm 420 (ε 19 000) and 297 (ε 13 000); δ_H(200 MHz; $CDCl_3$) 1.12 (6

H, s, gem-Me), 2.09 (3 H, s, 9-Me), 2.15 (3 H, s, 13-Me), 3.14 (2 H, s, 18-H_2), 5.82 (1 H, d, *J* 8, 14-H), 6.40 (1 H, d, *J* 11.5, 10-H), 6.63 (1 H, s, 7-H), 7.03 (1 H, dd, *J* 15 and 11.5, 11-H), 7.30 (1 H, d, *J* 15, 12-H) and 10.21 (1 H, d, *J* 8, CHO); δ_H(200 MHz; C_6D_6) 1.13 (6 H, s, gem-Me), 1.65 (3 H, s, 13-Me), 1.89 (3 H, s, 9-Me), 2.84 (2 H, s, 18-H_2), 5.76 (1 H, d, *J* 7.5, 14-H), 6.30 (1 H, d, *J* 11.5, 10-H), 6.62 (1 H, s, 7-H), 6.84 (1 H, dd, *J* 15 and 11.5, 11-H), 7.27 (1 H, d, *J* 15, 12-H) and 10.21 (1 H, d, *J* 7.5, CHO) (Found: M^+, 282.197. $C_{20}H_{26}O$ requires *M*, 282.198). All-*E*-isomer **14a**: λ_{max}(EtOH)/nm 425 (ε 32 000) and 295 (ε 10 000); δ_H(200 MHz; $CDCl_3$) 1.14 (6 H, s, gem-Me), 2.07 (3 H, s, 9-Me), 2.33 (3 H, s, 13-Me), 3.16 (2 H, br s, 18-H_2), 5.97 (1 H, d, *J* 8.5, 14-H), 6.39 (1 H, d, *J* 16, 12-H), 6.40 (1 H, d, *J* 11.5, 10-H), 6.45 (1 H, s, 7-H), 7.15 (1 H, dd, *J* 16 and 11.5, 11-H) and 10.10 (1 H, d, *J* 8.5, CHO) (Found: M^+, 282.196. $C_{20}H_{26}O$ requires *M*, 282.198). All-*E*-isomer **5a** m.p. 113–116 °C; ν_{max}(KBr)/cm^{-1} 1660 (C=O) and 1582 (C=C); λ_{max}(EtOH)/nm 425 (ε 29 000) and 295 (ε 11 000); λ_{max}(hexane)/nm 429 (ε 36 000), 406 (ε 40 000), 386sh (ε 29 000) and 292 (ε 10 000); δ_H(200 MHz; $CDCl_3$) 1.12 (6 H, s, gem-Me), 2.09 (3 H, s, 9-Me), 2.33 (3 H, s, 13-Me), 3.12 (2 H, s, 18-H_2), 5.98 (1 H, d, *J* 8.5, 14-H), 6.36 (1 H, d, *J* 11.5, 10-H), 6.36 (1 H, d, *J* 15, 12-H), 6.63 (1 H, s, 7-H), 7.15 (1 H, dd, *J* 15 and 11.5, 11-H) and 10.10 (1 H, d, *J* 8.5, CHO); δ_H(200 MHz; C_6D_6) 1.13 (6 H, s, gem-Me), 1.79 (3 H, s, 13-Me), 1.89 (3 H, s, 9-Me), 2.83 (2 H, s, 18-H_2), 6.05 (1 H, d, *J* 8, 14-H), 6.12 (1 H, d, *J* 15.5, 12-H), 6.23 (1 H, d, *J* 11.5, 10-H), 6.62 (1 H, s, 7-H), 6.91 (1 H, dd, *J* 15.5 and 11.5, 11-H) and 10.07 (1 H, d, *J* 8, CHO) (Found: M^+, 282.199. $C_{20}H_{26}O$ requires *M*, 282.198).

Photoisomerization of **5a**.—All-*E*-bicyclic retinal **5a** (33 mg) in MeOH (33 cm^3) was irradiated with a daylight fluorescent lamp (30 W, without filter) for 1 h at room temp. to give a mixture of geometrical isomers. Evaporation of MeOH and subsequent preparative HPLC [LiChrosorb Si-60 (5 μm), THF–hexane, 3:97] of the residue in the dark gave the 13*Z*-isomer **5b**, the 11*Z*-isomer **5c**, the 9*Z*-isomer **5d** and the all-*E*-isomer **5a** in a ratio of *ca.* 4:9:15:17. 11*Z*-Isomer **5c**: ν_{max}(KBr)/cm^{-1} 1660 (C=O) and 1581 (C=C); λ_{max}(EtOH)/nm 422, 299 and 229; λ_{max}(hexane)/nm 407 (ε 14 000), 295 (ε 8000) and 229 (ε 9000); δ_H(200 MHz; C_6D_6) 1.11 (6 H, s, gem-Me), 1.85 (6 H, s, 9 and 13-Me), 2.84 (2 H, s, 18-H_2), 5.61 (1 H, d, *J* 12, 12-H), 6.22 (1 H, d, *J* 8, 14-H), 6.47 (1 H, t-like, *J* 12, 11-H), 6.60 (1 H, s, 7-H), 6.77 (1 H, d, *J* 12, 10-H) and 10.07 (1 H, d, *J* 8, CHO) (Found: M^+, 282.199. $C_{20}H_{26}O$ requires *M*, 282.198). 9*Z*-Isomer **5d**: ν_{max}(KBr)/cm^{-1} 1660 (C=O) and 1582 (C=C); λ_{max}(EtOH)/nm 416 (ε 21 000) and 295 (ε 14 000); δ_H(200 MHz; $CDCl_3$) 1.13 (6 H, s, gem-Me), 2.07 (3 H, s, 9-Me), 2.30 (3 H, s, 13-Me), 3.17 (2 H, s, 18-H_2), 5.97 (1 H, d, *J* 8.5, 14-H), 6.06 (1 H, d, *J* 12, 10-H), 6.32 (1 H, d, *J* 16, 12-H), 6.63 (1 H, s, 7-H), 7.36 (1 H, dd, *J* 16 and 12, 11-H) and 10.10 (1 H, d, *J* 8.5, CHO); δ_H(200 MHz; C_6D_6) 1.12 (6 H, s, gem-Me), 1.78 (3 H, s, 13-Me), 1.91 (3 H, s, 9-Me), 2.83 (2 H, s, 18-H_2), 5.90 (1 H, d, *J* 12, 10-H), 5.97 (1 H, d, *J* 8, 14-H), 6.08 (1 H, d, *J* 15.5, 12-H), 6.63 (1 H, s, 7-H), 7.21 (1 H, dd, *J* 15.5 and 12, 11-H) and 10.03 (1 H, d, *J* 8, CHO) (Found: M^+, 282.199. $C_{20}H_{26}O$ requires *M*, 282.198).

Synthesis of 6*s*-trans-*Locked Bicyclic Retinal* **6**: 3-(1-*Hydroxy*-2,6-*dimethylcyclohexyl*)-1-(*tetrahydro*-2H-*pyran*-2-*yl*)*prop*-2-*yne* **16**.—To a stirred solution of the tetrahydropyranyl ether of prop-2-yn-1-ol (33 g, 240 mmol) in dry Et_2O (150 cm^3) was added a solution of BuLi (10% w/v; 152 cm^3, 240 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min and a solution of 2,6-dimethylcyclohexanone (15 g, 120 mmol) in dry Et_2O (150 cm^3) was then added dropwise at 0 °C. After being stirred for 30 min at room temp., the reaction mixture was quenched by addition of saturated aqueous NH_4Cl. The organic layer was separated, washed with brine, dried and evaporated to give an oil which was distilled (b.p. 153–156 °C/0.2 mmHg) to afford the title compound **16** (32 g, 100%) as a mixture of diastereoisomers; ν_{max}($CHCl_3$)/cm^{-1} 3610 and 3450 (OH); δ_H(200 MHz; $CDCl_3$) 1.09 (6 H, d, *J* 7, 1- and 5-Me), 3.53 and 3.84 (each 1 H, each m, OCHOCH_2), 4.31 (2 H, s, 9-H_2) and 4.84 (1 H, m, OCHO) (Found: M^+, 266.186. $C_{16}H_{26}O_3$ requires *M*, 266.188).

3-(1-*Hydroxy*-2,6-*dimethylcyclohexyl*)*prop*-2-*yn*-1-*ol* **17**.—A solution of the alcohol **16** (21 g, 80 mmol) in acetone (194 cm^3) was added to 5% H_2SO_4 (194 cm^3). The mixture was stirred at room temp. for 18 h and then neutralized with $NaHCO_3$. After evaporation of the acetone, the residue was extracted twice with Et_2O. The combined extracts were washed with brine, dried and evaporated to give an oil which was purified by CC (Et_2O–hexane, 1:1) to provide the title compound **17** (15 g, 100%) as a mixture of diastereoisomers; ν_{max}($CHCl_3$)/cm^{-1} 3612 and 3422 (OH); δ_H(200 MHz; $CDCl_3$) 1.09 (6 H, d, *J* 7, 1- and 5-Me) and 4.31 (2 H, d, *J* 4, 9-H_2) (Found: M^+, 182.131. $C_{11}H_{16}O_2$ requires *M*, 182.131).

2,3,3a,4,5,6-*Hexahydro*-3a,7-*dimethylinden*-1-*one* **18**.—A mixture of phosphorus pentoxide (4 g) and methanesulfonic acid (30 cm^3) was stirred at 80 °C until a homogeneous solution was obtained. The solution was then cooled to −15 °C and the diol **17** (5 g, 27 mmol) was added to it over 10 min. The cooling bath was then removed and stirring continued for 15 min. The solution was poured into ice–water and extracted twice with Et_2O. The extracts were washed sequentially with aqueous $NaHCO_3$ and brine. The dried extracts were evaporated to give a dark brown oil which was purified by CC (Et_2O–hexane, 1:4) to afford the ketone **18** (1.97 g, 44%). Distillation (b.p. 72 °C/1 mmHg) gave a colourless oil which solidified to a crystalline mass in a refrigerator; ν_{max}($CHCl_3$)/cm^{-1} 1697 (C=O) and 1631 (C=C); λ_{max}(EtOH)/nm 253; δ_H(200 MHz; $CDCl_3$) 1.05 (3 H, s, 1-Me) and 2.07 (3 H, s, 5-Me); δ_C(125 MHz; $CDCl_3$) 18.76 (CH_2), 18.80 (C-17), 25.2 (C-18), 33.1, 35.9, 36.0 and 36.5 (CH_2 × 4), 39.3 (C-1), 137.9 (C-6), 145.9 (C-5) and 208.1 (C=O) (Found: M^+, 164.121. $C_{11}H_{16}O$ requires *M*, 164.120).

Methyl 2,3,3a,4,5,6-*Hexahydro*-3a,7-*dimethyl*-1-*oxo*-1H-*indene*-2-*carboxylate* **19**.—To a suspension of NaH (60% oil dispersion; 0.26 g, 18.3 mmol) in dry benzene (10 cm^3) was added dimethyl carbonate (1.03 cm^3, 12.2 mmol). The mixture was heated to reflux, and a solution of the bicyclic ketone **18** (1.0 g, 6.10 mmol) in dry benzene (10 cm^3) was then added to it. The reaction mixture was refluxed for 20 h and after cooling to room temp., was treated with glacial acetic acid. The mixture was extracted with Et_2O, and the combined extracts were washed with brine, dried and evaporated to give an oil which was purified by CC (Et_2O–hexane, 1:3) to afford the keto ester **19** (1.25 g, 92%) as a colourless oil; ν_{max}($CHCl_3$)/cm^{-1} 1738 (CO_2Me), 1698 (C=O) and 1633 (C=C); λ_{max}(EtOH)/nm 301 and 255; δ_H(200 MHz; $CDCl_3$) 1.07 (3 H, s, 1-Me), 2.08 (3 H, s, 5-Me), 3.47 (1 H, m, 8-H) and 3.77 (3 H, s, CO_2Me) (Found: M^+, 222.125. $C_{13}H_{18}O_3$ requires *M*, 222.125).

Methyl 1-tert-*Butyldimethylsilyloxy*-2,3,3a,4,5,6-*hexahydro*-3a,7-*dimethyl*-1H-*indene*-2-*carboxylate* **20**.—To a stirred solution of the keto ester **19** (0.95 g, 4.28 mmol) in MeOH (12 cm^3) was added $NaBH_4$ (163 mg, 4.28 mmol) at 0 °C and the mixture was stirred at 0 °C for 10 min and then at room temp. for 20 min. The reaction mixture was then twice extracted with Et_2O and the extracts were washed with brine, dried and evaporated to give an oil which was dissolved in CH_2Cl_2 (13 cm^3). To this solution were added Et_3N (1.46 cm^3, 5.14 mmol), 4-dimethylaminopyridine (1.88 g, 8.56 mmol) and *tert*-butyldimethylsilyl chloride (2.63 g, 8.56 mmol). The mixture was stirred at room temp. overnight and then quenched

with water and extracted twice with Et_2O. The combined extracts were washed with 5% HCl, aqueous $NaHCO_3$ and brine, dried and evaporated to give an oil. This was purified by CC (Et_2O–hexane, 1:9) to provide the title compound **20** (0.84 g, 55%) as a colourless oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1727 (CO_2Me); δ_H(200 MHz; $CDCl_3$) 0.05 and 0.09 (each 3 H, each s, Me_2Si), 0.86 (9 H, s, Me_3C), 1.12 (3 H, s, 1-Me), 1.64 (3 H, s, 5-Me), 2.96 (1 H, m, 8-H), 3.70 (3 H, s, CO_2Me) and 4.97 (1 H, d, *J* 4, 7-H) (Found: M^+, 338.226. $C_{19}H_{34}O_2Si$ requires *M*, 338.227).

1-tert-*Butyldimethylsilyloxy*-2,3,3a,4,5,6-*hexahydro*-3a,7-*dimethyl*-1H-*indene*-2-*carbaldehyde* **21**.—To a stirred suspension of LAH (68 mg, 1.78 mmol) in dry Et_2O (5 cm^3) was added a solution of the ester **20** (300 mg, 0.89 mmol) in dry Et_2O (5 cm^3) at 0 °C. The mixture was stirred at 0 °C for 10 min after which the excess of LAH was destroyed by the addition of moist Et_2O and water. The reaction mixture was then twice extracted with Et_2O and the combined extracts were washed with brine, dried and evaporated to give the crude alcohol (280 mg). This was dissolved in dry CH_2Cl_2 (3 cm^3) and the solution was treated with the Swern oxidation reagent prepared from dimethyl sulfoxide (0.22 cm^3, 2.70 mmol) and oxalyl chloride (0.11 cm^3, 1.35 mmol) in CH_2Cl_2 at −60 °C. Stirring was continued at −60 °C for 15 min after which Et_3N was added to the mixture. After continued stirring at −60 °C for 15 min and at room temp. for 5 min, saturated aqueous citric acid was added to the reaction mixture and the whole solution was twice extracted with Et_2O. The extracts were washed with brine, dried and evaporated to give an oil which was purified by CC (Et_2O–hexane, 1:19) to provide the aldehyde **21** (210 mg, 77%) as a colourless oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 (CHO); δ_H(200 MHz; $CDCl_3$) 0.07 and 0.10 (each 3 H, each s, Me_2Si), 0.87 (9 H, s, Me_3C), 1.17 (3 H, s, 1-Me), 1.66 (3 H, s, 5-Me), 2.99 (1 H, m, 8-H), 4.98 (1 H, d, *J* 4, 7-H) and 9.73 (1 H, d, *J* 3, CHO).

1-(1-tert-*Butyldimethylsilyloxy*-2,3,3a,4,5,6-*hexahydro*-3a,7-*dimethyl*-1H-*inden*-2-*yl*)*ethanone* **22**.—To a solution of the aldehyde **21** (879 mg, 2.85 mmol) in dry THF (22 cm^3) was added a solution of MeMgBr (2.5 mol dm^{-3}; 3.0 cm^3, 7.13 mmol) in THF at 0 °C. After being stirred at 0 °C for 30 min, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl and twice extracted with Et_2O. The combined extracts were washed with brine, dried and evaporated to give a crude alcohol (924 mg). Swern oxidation as above, using the following quantities, dimethyl sulfoxide (0.66 cm^3, 9.0 mmol), oxalyl chloride (0.36 cm^3, 4.5 mmol), CH_2Cl_2 (9 cm^3) and alcohol (924 mg) in dry CH_2Cl_2 (7 cm^3) and then Et_3N (3.3 cm^3) afforded a crude oil which was purified by CC (Et_2O–hexane, 1:19) to afford **22** (783 mg, 85%) as a colourless oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1700 (C=O); δ_H(200 MHz; $CDCl_3$) 0.01 and 0.09 (each 3 H, each s, Me_2Si), 0.86 (9 H, s, Me_3C), 1.16 (3 H, s, 1-Me), 1.65 (3 H, s, 5-Me), 2.17 (3 H, s, 9-Me), 3.11 (1 H, m, 8-H) and 5.04 (1 H, d, *J* 4, 7-H).

1-(3a,4,5,6-*Tetrahydro*-3a,7-*dimethyl*-3H-*inden*-2-*yl*)*ethanone* **23**.—To a stirred solution of the ketone **22** (140 mg, 0.43 mmol) in dry THF was added a solution of TBAF (1.0 mol dm^{-3}; 1.88 cm^3, 1.88 mmol) in THF at 0 °C. After being stirred at room temp. for 1 h, the reaction mixture was quenched by the addition of water and then twice extracted with Et_2O. The combined extracts were washed with brine, dried and evaporated to give an oil which was purified by CC (Et_2O–hexane, 3:17) to afford the dienone **23** (68 mg, 83%) as a pale yellow oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1640 (C=O) and 1568 (C=C); λ_{max}(EtOH)/nm 312; δ_H(200 MHz; $CDCl_3$) 1.03 (3 H, s, 1-Me), 1.79 (3 H, s, 5-Me), 2.36 (1 H, s, 9-Me), 2.37 (2 H, s, 16-H_2) and 7.16 (1 H, s, 7-H) (Found: M^+, 190.137. $C_{13}H_{18}O$ requires *M*, 190.136).

(E)-*Ethyl* 3-(3a,4,5,6-*Tetrahydro*-3a,7-*dimethyl*-3H-*inden*-2-*yl*)*but*-2-*enoate* **24**.—To a stirred solution of diethyl ethoxycarbonylmethylphosphonate (1.36 g, 6.10 mmol) in dry THF (5 cm^3) was added a solution of BuLi (1.58 mol dm^{-3}; 3.85 cm^3, 6.08 mmol) at 0 °C. After this mixture had been stirred at room temp. for 30 min, a solution of the dienone **23** (231 mg, 1.22 mmol) in dry THF (5 cm^3) was added to it at 0 °C and the mixture was refluxed for 3 h. After cooling, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl and twice extracted with Et_2O. The combined extracts were washed with brine, dried and evaporated to give an oil which was purified by CC (Et_2O–hexane, 1:19) to provide the ester **24** (198 mg, 63%) as a pale yellow oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1703 (CO_2Et) and 1603 (C=C); λ_{max}(EtOH)/nm 331 and 266; δ_H(200 MHz; $CDCl_3$) 1.04 (3 H, s, 1-Me), 1.29 (3 H, t, *J* 7, $CO_2CH_2CH_3$), 1.74 (3 H, s, 5-Me), 2.40 (3 H, s, 9-Me), 4.18 (2 H, q, *J* 7, $CO_2CH_2CH_3$), 5.75 (1 H, s, 10-H) and 6.75 (1 H, s, 7-H) (Found: M^+, 260.176. $C_{17}H_{24}O_2$ requires *M*, 260.177).

Methyl 3-*Methyl*-7-(3a,4,5,6-*tetrahydro*-3a,7-*dimethyl*-3H-*inden*-2-*yl*)*octa*-2,4,6-*trienoate* **26**.—A solution of the ester **24** (332 mg, 1.28 mmol) in dry Et_2O (5 cm^3) was added dropwise to a stirred suspension of LAH (97 mg, 2.56 mmol) in dry Et_2O (5 cm^3) at 0 °C. The mixture was stirred at 0 °C for 15 min after which the excess of LAH was destroyed by the addition of moist Et_2O and water and the whole twice extracted with Et_2O. The extracts were washed with brine, dried and evaporated to give an oil which was dissolved in MeOH (5 cm^3). This was added to a solution of Ph_3P·HBr (442 mg, 1.28 mmol) in MeOH (5 cm^3) and the mixture was stirred at room temp. for 20 h. Evaporation of the MeOH gave a residue which was washed with Et_2O to provide a Wittig salt. To this salt and (*E*)-methyl 3-formylbut-2-enoate (164 mg, 1.28 mmol) dissolved in dry CH_2Cl_2 (5 cm^3) was added a solution of NaOMe (90 mg, 1.66 mmol) in MeOH (1 cm^3) at 0 °C. The mixture was stirred at 0 °C for 1 h and then poured into water and twice extracted with Et_2O. The combined extracts were washed with brine, dried and evaporated to give a yellow oil which was purified by CC (Et_2O–hexane, 1:9) to yield the ester **26** (168 mg, 42%) as a mixture of geometrical isomers; $\nu_{max}(CHCl_3)/cm^{-1}$ 1697 (CO_2Et) and 1588 (C=C) (Found: M^+, 312.207. $C_{21}H_{28}O_2$ requires *M*, 312.209).

(Z,E,E/E,Z,E/E,E,E)-3-*Methyl*-7-(3a,4,5,6-*tetrahydro*-3a,7-*dimethyl*-3H-*inden*-2-*yl*)*octa*-2,4,6-*trienal* **6**.—A solution of the ester **26** (168 mg, 0.54 mmol) in dry Et_2O (5 cm^3) was added to a stirred suspension of LAH (41 mg, 1.08 mmol) in dry Et_2O at 0 °C. After the mixture had been stirred at 0 °C for 10 min, the excess of LAH was destroyed by the addition of moist Et_2O and water and the whole twice extracted by Et_2O. The combined extracts were washed with brine, dried and evaporated to give the hydroxy compound as a pale yellow amorphous product. A mixture of the resulting hydroxy compound and active MnO_2 (1.6 g) in dry CH_2Cl_2 was shaken at room temp. for 3 h and then filtered through Celite. Evaporation of the filtrate gave an oil which was purified by CC (Et_2O–hexane, 1:9) to yield an isomeric mixture of the aldehydes **6** (58 mg, 38%) as an orange oil. Separation of the isomers by preparative HPLC [Li-Chrosorb Si-60 (5 μm) 1 × 30 cm, THF–hexane, 3:97, 1.5–3.0 cm^3 min^{-1}, 350 nm] gave 13*Z*, 11*Z* and all-*E*-isomer in a pure state, respectively, in a ratio of 1.4:1:4. 13*Z*-Isomer **6b**: ν_{max}(KBr)/cm^{-1} 1664, 1660 (CHO) and 1593 (C=C); λ_{max}(EtOH)/nm 407 and 280; δ_H(200 MHz; $CDCl_3$) 1.06 (3 H, s, 1-Me), 1.75 (3 H, s, 5-Me), 2.10 (3 H, s, 9-Me), 2.15 (3 H, s, 13-Me), 5.84 (1 H, d, *J* 8, 14-H), 6.29 (1 H, d, *J* 12, 10-H), 6.56 (1 H, s, 7-H), 7.04 (1 H, dd, *J* 15 and 12, 11-H), 7.32 (1 H, d, *J* 15, 12-H) and 10.22 (1 H, d, *J* 8, CHO) (Found: M^+, 282.197. $C_{20}H_{26}O$ requires *M*, 282.198). 11*Z*-Isomer **6c**: ν_{max}(KBr)/cm^{-1} 1663, 1660 (CHO) and 1592 (C=C); λ_{max}(EtOH)/nm 405, 310,

258 and 227sh; λ_{max}(MeOH)/nm 405; δ_H(200 MHz; $CDCl_3$) 1.05 (3 H, s, 1-Me), 1.74 (3 H, s, 5-Me), 2.06 (3 H, s, 9-Me), 2.39 (3 H, s, 13-Me), 5.95 (1 H, d, *J* 10, 12-H), 6.08 (1 H, d, *J* 8, 14-H), 6.55 (1 H, s, 7-H), 6.61 (1 H, d, *J* 10, 10-H), 6.70 (1 H, t-like, *J* 10, 11-H) and 10.10 (1 H, d, *J* 8, CHO) (Found: M^+, 282.197. $C_{20}H_{26}O$ requires *M*, 282.198). All-*E*-isomer **6a**: ν_{max}(KBr)/cm^{-1} 1663, 1660 (CHO) and 1593 (C=C); λ_{max}(EtOH)/nm 413; λ_{max}(MeOH)/nm 410; δ_H(200 MHz; $CDCl_3$) 1.05 (3 H, s, 1-Me), 1.74 (3 H, s, 5-Me), 2.10 (3 H, s, 9-Me), 2.33 (3 H, s, 13-Me), 5.98 (1 H, d, *J* 8.5, 14-H), 6.26 (1 H, d, *J* 12, 10-H), 6.40 (1 H, d, *J* 15, 12-H), 6.56 (1 H, s, 7-H), 7.15 (1 H, dd, *J* 15 and 12, 11-H) and 10.12 (1 H, d, *J* 8.5, CHO) (Found: M^+, 282.199. $C_{20}H_{26}O$ requires *M*, 282.198).

Photoisomerization of **6a**.—All-*E*-bicyclic retinal **6a** (8 mg) in MeOH (8 cm^3) was irradiated with a daylight fluorescent lamp (30 W, without filter) at room temp. for 2 h to give a geometrical mixture. The MeOH was then evaporated and the residue was separated by preparative HPLC [LiChrosorb Si-60 (5 μm), THF–hexane, 3:97] in the dark to afford the 13*Z*-isomer **6b**, 11*Z*-isomer **6c**, 9*Z*-isomer **6d** and all-*E*-isomer **6a**. 9*Z*-Isomer **6d**: ν_{max}(KBr)/cm^{-1} 1663, 1660 (CHO) and 1593 (C=C); λ_{max}(EtOH)/nm 402, 301sh, 257 and 222; λ_{max}(MeOH)/nm 401; δ_H(200 MHz; $CDCl_3$) 1.10 (3 H, s, 1-Me), 1.73 (3 H, s, 5-Me), 2.03 (3 H, s, 9-Me), 2.28 (3 H, s, 13-Me), 5.98 (1 H, d, *J* 8, 14-H), 6.14 (1 H, d, *J* 11.5, 10-H), 6.28 (1 H, d, *J* 15, 12-H), 6.46 (1 H, s, 7-H), 7.27 (1 H, dd, *J* 15 and 11.5, 11-H) and 10.10 (1 H, d, *J* 8, CHO) (Found: M^+, 282.199. $C_{20}H_{26}O$ requires *M*, 282.198).

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References

1 Part 14, M. Ito, Y. Katsuta, Y. Yamano and K. Tsukida, *J. Chem. Soc., Perkin Trans. 1*, 1993, 987.
2 M. Ottolenghi, *Adv. Photochem.*, 1980, **12**, 97.
3 R. R. Birge, *Annu. Rev. Biophys. Bioeng.*, 1981, **10**, 315.
4 T. G. Ebrey and T. Yoshizawa, *Exp. Eye Res.*, 1973, **17**, 545.
5 S. Horiuchi, F. Tokunaga and T. Yoshizawa, *Biochim. Biophys. Acta*, 1980, **591**, 445.
6 T. Yoshizawa and Y. Shichida, *Methods Enzymol.*, 1982, **81**, 634.
7 M. Ito, A. Kodama, K. Tsukida, Y. Fukada, Y. Shichida and T. Yoshizawa, *Chem. Pharm. Bull.*, 1982, **30**, 1913.
8 Y. Fukada, Y. Shichida, T. Yoshizawa, M. Ito, A. Kodama and K. Tsukida, *Biochemistry*, 1984, **23**, 5826.
9 M. Ito, A. Kodama, T. Hiroshima and K. Tsukida, *J. Chem. Soc., Perkin Trans. 1*, 1986, 905.
10 M. Ito, Y. Katsuta, Y. Imamoto, Y. Shichida and T. Yoshizawa, *Photochem. Photobiol.*, 1992, **56**, 915.
11 M. Ito, Y. Mantani, K. Tsukida, Y. Shichida, S. Ioshida, Y. Fukada and T. Yoshizawa, *J. Nutr. Sci., Vitaminol*, 1988, **34**, 641.
12 G. A. MacAlpine, R. A. Raphael, A. Shaw, A. W. Taylor and H.-J. Wild, *J. Chem. Soc., Perkin Trans. 1*, 1976, 410.
13 M. Ito, T. Hiroshima, K. Tsukida, Y. Shichida and T. Yoshizawa, *J. Chem. Soc., Chem. Commun.*, 1985, 1443.
14 R. S. H. Liu and A. Asato, *Tetrahedron*, 1984, **40**, 1931.
15 R. N. Gedye, K. C. Westaway, P. Arora, R. Bisson and A. K. Khalil, *Can. J. Chem.*, 1977, **55**, 1218.

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