Pyrylium salts in polyene natural product synthesis: organometallic additions to 4-methylpyrylium tetrafluoroborate

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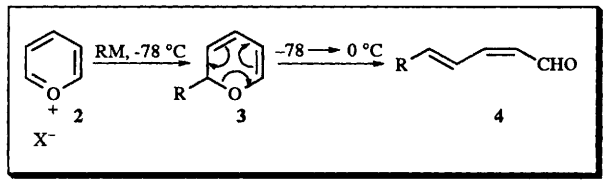
The synthetic utility of organometallic additions to pyrylium salts as a procedure for the stereocontrolled preparation of 2*Z*,4*E*-dienals, and the use of these compounds in polyene natural product synthesis, is summarised. The extension of this methodology to 4-methylpyrylium tetrafluoroborate to give a new route to 3-methyl-2*Z*,4*E*-dienals *via* a six-carbon organometallic homologation procedure is then described. Finally, the utilisation of this methodology to provide a concise synthetic approach to 13*Z*-retinal, retinal and a range of retinal analogues is then elaborated.

Overview and introduction

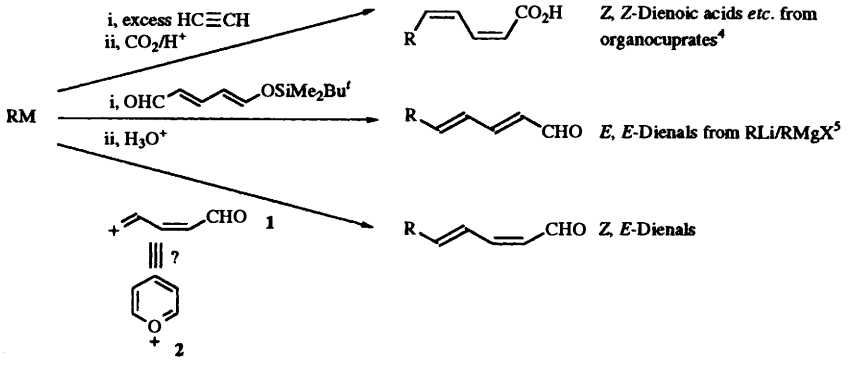
The biological importance of polyene-based natural products[1] such as antibiotics, insect pheromones, leukotrienes and related compounds has stimulated the search for versatile, stereocontrolled routes to these types of compounds.[2] We have established a programme in this area which has been concerned with the development of organometallic homologation processes (Scheme 1) in order to produce stereodefined dienals, or their precursors, that can be further elaborated to higher polyenes *via* Wittig-type processes if required. Thus, a 'double acetylene carbocupration' modification of the Normant reaction[3] has been developed to prepare a range of *Z*,*Z*-dienoic acids,[4] and *E*,*E*-dienals have been obtained by organometallic addition to silylated glutaconaldehyde derivatives followed by hydrolysis of the adducts.[5] As shown in Scheme 1, we were also interested in the preparation of *Z*,*E*-dienals by a related organometallic homologation procedure. We were intrigued by the idea that the required cationic pentadienal synthon **1** could be provided, in a stereoselective manner, by the pyrylium cation **2**. Thus, as shown in Scheme 2, organometallic addition at C-2 of the pyrylium cation to give the 2*H*-pyrans **3** followed by electrocyclic ring opening,[6-8] should give the required *Z*,*E*-dienals **4**.

The nucleophilic additions of substituted pyrylium salts had been described in the literature[6,7] and some examples using organometallic nucleophiles had been reported.[9] However, although unsubstituted pyrylium salts are known,[10] there had been no reports of their nucleophilic additions prior to our study. Indeed, it had been stated that unsubstituted pyrylium cations 'do not give clean reactions, even with the most common nucleophiles . . .'[7] Contrary to this statement, we found that

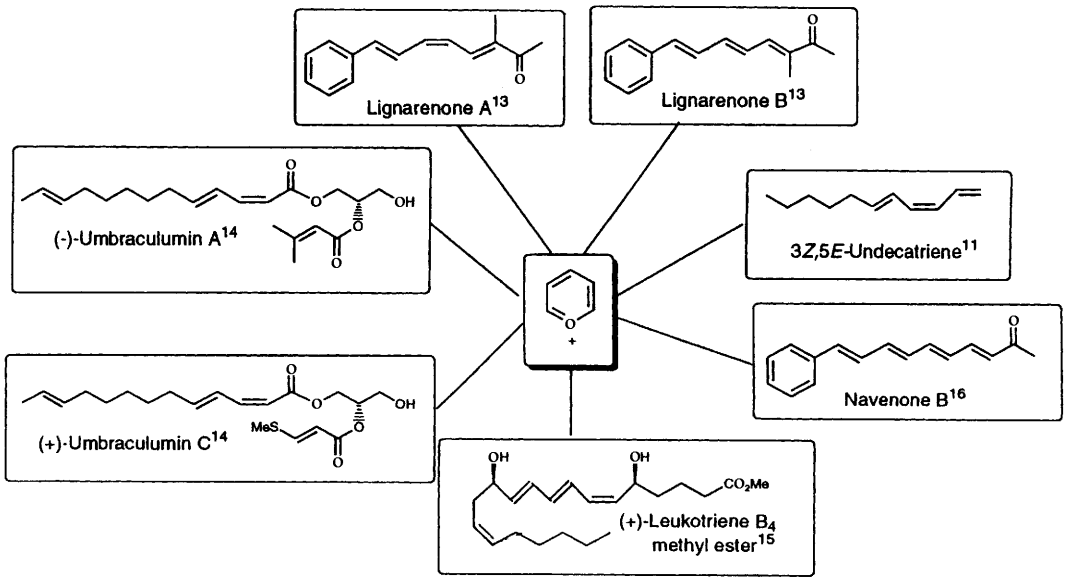


Scheme 2

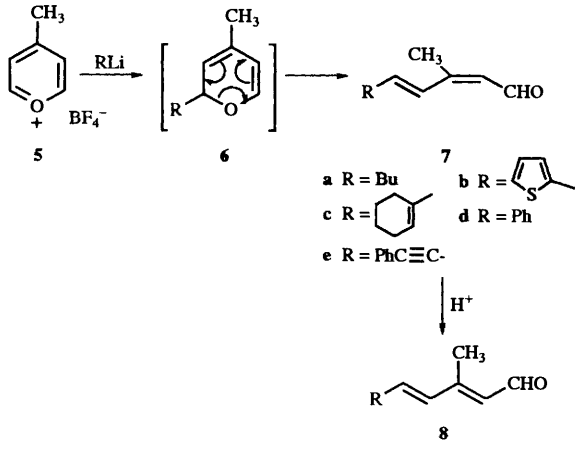
the organometallic addition–ring opening process occurred smoothly giving reasonable to high yields of the required dienals **4**, with excellent *Z*,*E*-stereoselectivity, when organolithium reagents were employed.[11,12] The only by-product observed in this reaction was the 4-substituted pyran resulting from organometallic addition to C-4 of the pyrylium salt: this adduct was normally present in low amounts but became more significant when softer organometallic reagents were employed.[11] The value of this new route to 2*Z*,4*E*-dienals was subsequently demonstrated by its use as the cornerstone in the synthesis of a range of polyunsaturated natural products as shown in Scheme 3.[11-16] These syntheses illustrate the synthetic potential of 2*Z*,4*E*-dienals: they can be employed, with retention of stereochemistry, to prepare trienes using Wittig homologation (3*Z*,5*E*-undecatriene[11] and lignarenone A[13]), dienoates *via* oxidation (umbraculumin A[14] and umbraculumin C[14]), and trienols by use of a vinyl organometallic followed by organometallic 1,2-addition (leukotriene B_4[15]). In addition, by isomerisation, all-*E* natural products can be prepared (lignarenone B[13] and navenone B[16]), and the latter example illustrates that tetraenes are also available using this methodology.



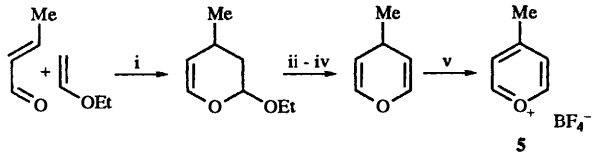
Scheme 1 Stereoselective organometallic homologation routes to functionalised dienes



Scheme 3



Scheme 4



Scheme 5 *Reagents and conditions:* i, 200 °C, 24 h[19]; ii, aq. HCl[20]; iii, HCl(g), −78 °C[18]; iv, $PhNMe_2$ 140 °C[18]; v, Ph_3CBF_4, MeCN (61–78%)

The synthesis and reactions of 4-methylpyrylium tetrafluoroborate

In an extension of this work (Scheme 4),[17] we envisaged using the 4-methylpyrylium salt **5** to provide a six-carbon homologation procedure leading, *via* the pyran **6**, to the methyl substituted dienals **7** with potential in isoprenoid natural product synthesis. A major attraction of this approach is that it would be expected to produce initially *Z,E*-dienals **7**, which should be easily isomerised to their all-*trans* isomers **8**, thereby making both systems readily accessible in a stereocontrolled manner. In addition, the presence of the 4-methyl substituent would be expected to hinder C-4 attack on the pyrylium salt.

We therefore investigated the viability of this synthetic sequence. 4-Methylpyrylium tetrafluoroborate **5** was obtained from crotonaldehyde and ethyl vinyl ether by modification of the procedure employed by Degani and Vincenzi[18–20] for the preparation of the corresponding perchlorate salt (Scheme 5). This sequence can be carried out on a large scale and allows access to multi-gram quantities of **5** and its precursor, 4-methyl-4*H*-pyran. In contrast to the unsubstituted pyrylium salt **2**, the 4-methyl substituted salt **5** darkened and appeared to decompose on storage and was therefore prepared immediately before use. We were aware that, on treatment with organometallic reagents, the pyrylium salt **5** might undergo deprotonation at the 4-Me group to give the corresponding anhydro base[21] but in the event this process was not detected. Thus, addition of the organolithium reagent to the freshly prepared pyrylium salt in tetrahydrofuran (THF) or diethyl ether at −70 °C under nitrogen, followed by quenching with aqueous ammonium chloride, gave a range of the dienals **7** in reasonable, unoptimised yields (Table 1). It should also be noted that 4*H*-pyrans, which result from C-4 addition and which are observed with the unsubstituted pyrylium cation **2**,

Table 1 Yields of compounds **7** and **8** (see Scheme 4)

R	7 (%)[a]	8 (%)[b]
(a) Bu	55	—[c]
(b) 2-Thienyl	49 (63[d])	81
(c) Cyclohexenyl	— (90[d])	—[c]
(d) Ph	57 (68[d])	86
(e) PhC≡C	54	68

[a] THF as solvent at −70 °C unless otherwise stated. [b] Yield from **7**; isomerisation using conc. HCl–EtOH–$CHCl_3$. [c] Dienal **7** decomposed under these reaction conditions. [d] Diethyl ether as solvent at −70 °C.

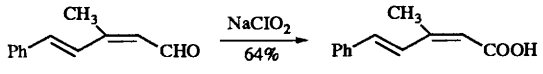
Table 2 Selected NMR data for the aldehydes **7** and **8**

	^{1}H NMR: δ_{CHO} (*J*/Hz)		^{13}C NMR: $\delta_{3\text{-}Me}$	
	Z,E-**7**	*E,E*-**8**	*Z,E*-**7**	*E,E*-**8**
(a) Bu	10.17 (8.2)	—	21.39	—
(b) 2-Thienyl	10.21 (7.9)	10.12 (7.9)	20.84	12.83
(c) Cyclohexenyl	10.25	—	20.90	—
(d) Ph	10.26 (7.6)[22a]	10.10 (8.15)[22b]	20.93	13.03
(e) PhC≡C	10.18 (7.9)	10.14 (8)	20.12	—

were present in negligible amounts according to an NMR analysis of the crude reaction product.

The *E,Z*-stereochemistries of compounds **7** were confirmed by highfield ^{1}H NMR spectroscopy ($J_{4,5}$ in the range 15.5–15.9 Hz) and NOE studies (irradiation of 2-H caused enhancement of the 3-Me signal but had no effect on 4-H; in the *E,E*-isomers irradiation of 2-H caused enhancement of 4-H but had no effect on the 3-Me signal). Isomerisation of the *E,Z*-dienals **7** into their *E,E*-isomers **8** proceeded smoothly in acid with three of the aldehydes examined (Table 1). As shown in Table 2, the formyl proton is deshielded in the *E,Z*-dienals as compared to their *E,E*-isomers but the difference is not so marked as in the non-methylated analogues (where the *E,Z*-formyl proton is usually > 0.5 ppm to lower field). However, as is also shown in Table 2, the ^{13}C resonance of the 3-methyl substituent is extremely diagnostic: in the *E,Z*-isomers the methyl resonates in the 20–22 ppm range whereas in the *E,E*-isomers, 12–13 ppm is the norm. This observation is supported by published data[22] and by examples described later in this paper.

The dienals **7** readily isomerise and/or decompose on storage at room temperature. The aromatic examples, **7b** and **7d**, were stable indefinitely when stored at −20 °C, whereas at this temperature **7c** and **7e** showed significant signs of isomerisation/decomposition after 1 week, and the butyl adduct **7a** deteriorated in hours, even when stored at low temperature. It is therefore advisable to carry out further modifications as soon as possible. For example, the aldehydes can be reduced (see later) or oxidised to the more stable carboxylic acid (*e.g.* **7d** to **9**) with retention of configuration.



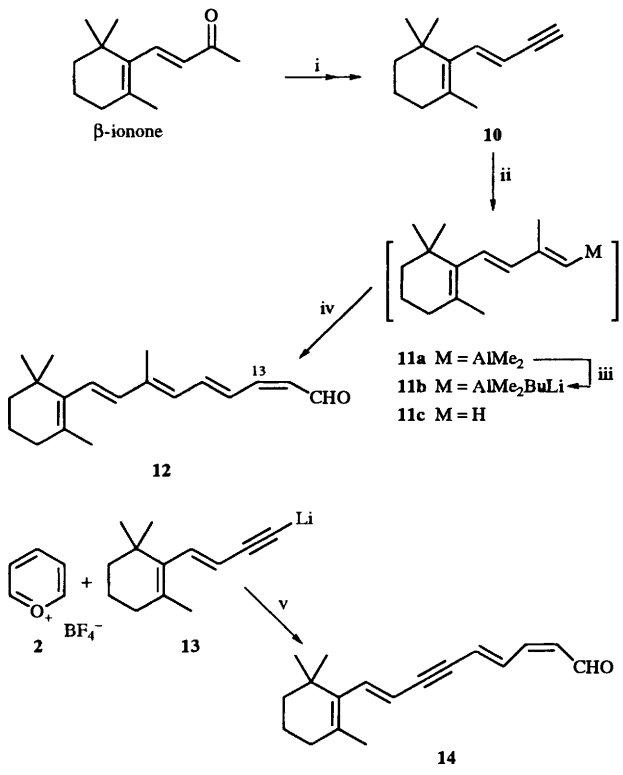
7d **9**

The use of pyrylium salts for the synthesis of retinoids and retinal

The approach shown in Scheme 4 seemed ideally suited to the synthesis of retinoids[23] which are of interest in studies of visual processes,[24] as devices,[25] and as anti-cancer agents,[26] in both 13*E*- and 13*Z*-forms.[27–29] In addition, retinoic acid analogues, which are of use in cell growth studies,[30] and retinol (vitamin A) analogues[31] would be readily available by such a route. The successful implementation of this strategy is illustrated in Schemes 6 and 7.[17]

The viability of the process was first tested using pyrylium tetrafluoroborate **2**[12] producing 13-demethyl-13*Z*-retinal **12**[27] as is shown in Scheme 6. β-Ionone was first converted into the alkyne **10** and then into vinylalane **11a** using the methodology devised by Negishi's group.[32,33] Addition of **11a** to the pyrylium salt **2** gave the retinal analogue **12** in 31% yield (along with **11c** in 62% yield). The use of the corresponding alanate **11b** raised the yield of **12** to 43%. In both cases, 4 equiv. of the organometallic reagent were required to obtain satisfactory yields (with 1 equiv. no reaction was observed, with 2 equiv. yields of 5–10% were obtained). The pyrylium salt **2** was also converted into the novel dehydro-demethyl-retinoid **14** in 56% yield by reaction with the acetylide **13**, prepared by deprotonation of **10**.

With this success in hand, we turned our attention to the use of the 4-methylpyrylium salt **5** as is shown in Scheme 7. Thus, treatment of **5** with the previously described alanate **11b** gave 13*Z*-retinal **15**[28] in 48% yield. This route enables a range of retinal analogues to be prepared extremely easily as both organometallic reagent and pyrylium salt can be varied. Thus, the use of the alkynyllithium reagent **13** with the 4-methylpyrylium salt **5** gave the known[29] retinoid **16** in 57%



Scheme 6 *Reagents and conditions:* i, see ref. 32; ii, Me_3Al, $[Zr(Cl)_2]Cl_2$, $(CH_2Cl)_2$, 0 °C to room temp.[33] (then replace solvent by THF); iii, BuLi, THF, −78 to 0 °C; iv, pyrylium tetrafluoroborate **2**, THF, −78 °C (31–43%, see text); v, THF, −78 °C (56%)

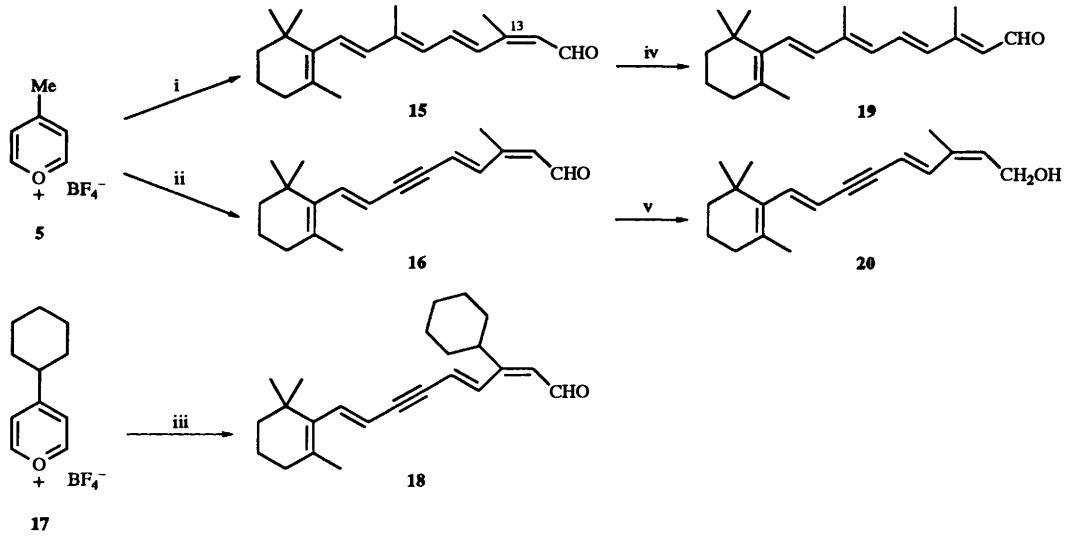
yield and treatment of the 4-cyclohexylpyrylium tetrafluoroborate **17**[34] with the same organometallic reagent gave the novel retinal analogue **18** in 52% yield. In agreement with the generalisations drawn from the data in Table 2, the ^{13}C NMR spectra of the *Z*-unsaturated aldehydes **15** and **16** show the methyl substituents resonating at δ 20.12 and 19.63 ppm, respectively.

These 'initial adducts' can be further modified. Thus, **15** was efficiently isomerised,[35] thereby completing a new synthesis of retinal **19**. In addition, **16** was reduced with DibalH to give the novel retinol analogue **20** in 81% yield. Highfield NMR and NOE studies confirmed that the 2*Z*,4*E*-stereochemistry had been retained.

To summarise, the preparation and organometallic additions of 4-methylpyrylium tetrafluoroborate **5** have been described and shown to provide a new, stereoselective route for the preparation of 3-methyl-2*Z*,4*E*-dienals *via* a six-carbon homologation procedure. Examples have been provided to demonstrate that corresponding 3-methyl-2*Z*,4*E*-dienols and dienoic acids are also available by this route, as are the corresponding *E,E*-isomers. This new methodology has been utilised to prepare a number of known and novel retinal analogues, and we feel that these examples illustrate the potential of this new route to retinoids and related isoprenoids.

Experimental

^{1}H NMR spectra (δ_H) were recorded using JEOL PMX 60, JEOL EX 270 and JEOL GSX 400 NMR spectrometers referencing to TMS as internal standard or to the deuteriochloroform lock and were assigned using homonuclear decoupling experiments or COSY-45 at 270 or 400 MHz and DIFNOE experiments at 270 MHz where necessary. ^{13}C NMR spectra (δ_C) were recorded using JEOL EX 90, JEOL EX 270 or



Scheme 7 *Reagents:* i, **11b** (4 equiv.), THF, −78 °C, 48%; ii, **13**, THF, −78 °C, 58%; iii, **13**, THF, −78 °C, 52%; iv, I_2, Et_2O, PhH, room temp., 48 h, 91%; v, DibalH, −78 to 0 °C, 81%

JEOL GSX 400 NMR spectrometers at 22.5, 67.5 or 100 MHz, respectively, referencing to the deuteriochloroform lock and were assigned using DEPT or heteronuclear correlation experiments. Samples were run as solutions in $CDCl_3$ unless otherwise stated. *J* Values are in Hz. IR spectra were recorded on a Perkin-Elmer FTIR 1720X spectrometer or an ATI Mattson Genesis Series FTIR and were run as neat liquid or deposited solid films. Mass spectra were recorded on a Kratos MS25 (low resolution EI only) or a Fisons Instruments VG Analytical Autospec Spectrometer system (low and high resolution EI and CI spectra). Light petroleum refers to the fraction of boiling range 40–60 °C and was redistilled before use. THF and diethyl ether were dried over sodium–benzophenone ketyl and distilled immediately before use; triethylamine, acetonitrile, dichloromethane and dichloroethane were dried by boiling over calcium hydride and distilled immediately before use. Ethyl acetate refers to HPLC grade solvent and was used as purchased. Solutions of organolithium compounds were regularly titrated using diphenylacetic acid.[36] Other starting materials were used as purchased or prepared according to established literature procedures using references given in the text. Low temperature reactions were carried out in a Cryocool C80 immersion bath. Analytical TLC was performed on Merck 5554 aluminium-backed silica gel plates and were visualised using UV, $KMnO_4$–acetone solutions or acidic ethanolic vanillin solutions. Column chromatography was carried out under flash conditions[37] unless otherwise stated using silica gel (Phase Separations Ltd Sorbsil C60 40/60H or ICN Biomedicals GmbH silica 32-63, 60A) and the specified eluent. Preparative centrifugal chromatography was carried out on Chromatotron Model 7924T using silica gel (Merck 7749) plates. Melting points were recorded on a Kofler hot-stage melting point apparatus or an Electrothermal IA9100 digital melting point apparatus and are uncorrected. Boiling points refer to oven temperatures (Kugelrohr) or distillation temperatures. Microanalyses were performed by Mr A. W. Saunders at The University of East Anglia.

4-Methylpyrylium tetrafluoroborate 5

(a)[18] HCl gas was passed for 50 min through a stirred solution of freshly distilled β-methylglutaric dialdehyde[19,20] (53.2 g, 0.466 mol) in CH_2Cl_2 (300 cm^3) the internal temperature of which was kept at *ca.* −40 °C. The reaction mixture was stirred at −78 °C for 8 h, warmed to room temperature over 4 h and stirred at this temperature for a further 4 h. The resulting aqueous phase was removed and the organic phase was stirred for 1 h in the presence of Na_2SO_4. The mixture was filtered and the filtrate was evaporated under reduced pressure at room temperature, the residual CH_2Cl_2 being removed using high vacuum (2 mmHg) for 4 h to give the crude 2,6-dichloro-4-methyltetrahydropyran (70.76 g) as a pale tan oil.

(b)[18] The α,α′-dichlorotetrahydropyran (70.76 g) was placed in a flask containing *N*,*N*-diethylaniline (330 cm^3) and equipped with a Vigreux column and a distillation apparatus. The mixture was then heated for 1 h in an oil bath pre-heated to 140 °C at atmospheric pressure; it was noted that when the internal temperature of the solution reached 110 °C, a strong evolution of gas took place and the solution darkened significantly. The pressure was now slowly reduced to 55 mmHg and the fraction distilling up to 90 °C was collected in a cooled (−78 °C) receiver flask. This fraction was redistilled at lower pressure (1.5 mmHg) using a cold-finger condenser and a cooled (−78 °C) receiver flask. The fraction distilling at 8–13 °C/1.5 mmHg consisted of the first batch of pure 4-methyl-4*H*-pyran (*ca.* 15 g). The residue of the redistillation was recharged into the *N*,*N*-diethylaniline flask and reheated as before to afford a second batch of crude 4-methyl-4*H*-pyran, which was redistilled as above to give a second batch of pure 4-methyl-4*H*-pyran. The combined batches of 4-methyl-4*H*-pyran[18] (23.08 g, 51%), obtained as a colourless liquid, decomposed rapidly when stored at RT and at a slower rate when kept at −20 °C. A 10 g batch stored at −20 °C for 1 month yielded 7.4 g of 4-methyl-4*H*-pyran on redistillation.

(c) A suspension of trityl tetrafluoroborate [Fluka (other brands gave lower yields) 19.62 g, 59.4 mmol] in dry MeCN (100 cm^3) was added over 30 min to a stirred solution of freshly prepared 4-methyl-4*H*-pyran (5.69 g, 59.2 mmol) in dry MeCN (10 cm^3) held at −40 °C. The resulting mixture was stirred at 0 °C for 1 h, after which it was diluted with dry ether (250 cm^3) to precipitate a white sand-like solid. The solid was filtered off under N_2, washed with dry ether (2 × 50 cm^3) and dried under high vacuum (0.5 mmHg) for 1 h to give *4-methylpyrylium tetrafluoroborate* **5** (7.87 g, 73%) as a pale tan solid, which rapidly darkened to give a dark brown solid, mp 111–114 °C (decomp.) (Found: C, 39.8; H, 3.7. $C_6H_7BF_4O$ requires C, 39.6; H, 3.9%); δ_H(60 MHz, CF_3CO_2D/TMS) 3.0 (3 H, s, Me), 8.3–8.4 (2 H, m, 3-H and 5-H) and 9.3–9.4 (2 H, m, 2-H and 6-H); δ_C(67.5 MHz, CF_3CO_2D) 27.06, 131.19, 169.34 and 182.87. The pyrylium salt **5** was usually prepared fresh from freshly distilled pyran and used immediately.

Organolithium additions to 4-methylpyrylium tetrafluoroborate 5

Typical procedure. The organolithium reagent (1.1 mol equiv.) in the specified solvent was added dropwise over 10 min to a suspension of freshly prepared 4-methylpyrylium tetrafluoroborate **5** (~0.2–0.5 g) in dry diethyl ether or dry THF (5–20 cm^3) held at −70 °C under an atmosphere of dry nitrogen. The dark reaction mixture was stirred at −78 °C for 30 min to 24 h (longer times sometimes gave a small increase in yield) and then quenched with sat. aq. NH_4Cl (10–20 cm^3) and diluted with water (20 cm^3). The resulting mixture was extracted with ether (5 × 25 cm^3) and the combined extracts were washed with water (3 × 25 cm^3) and brine (3 × 25 cm^3), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude product was purified either by flash silica column chromatography or by preparative centrifugal chromatography using the eluent specified to give the aldehyde **7**.

(2*Z*,4*E*)-3-Methylnona-2,4-dienal 7a. This compound was prepared from butyllithium (1.52 mol dm^{-3} in hexane; 0.7 cm^3, 1.06 mmol), 4-methylpyrylium tetrafluoroborate **5** (178 mg, 0.978 mmol) in dry THF (5.0 cm^3) following the typical procedure above. ^1H NMR (60 MHz) spectroscopic analysis of the crude product showed the presence of a single isomeric aldehyde (formyl proton at δ 10.17) together with neglible amount (<5%) of 4-butyl-4-methylpyran as indicated by a signal at δ 4.5. Purification by preparative centrifugal chromatography [light petroleum–CH_2Cl_2 (1:1)] gave the *title compound* **7a** (82 mg, 55%) as a pale yellow oil {Found (CI): $[M + H^+]$, 153.1281. $C_{10}H_{16}O$ requires $[M + H^+]$, 153.1279}; R_F 0.19 [light petroleum–CH_2Cl_2 (1:1)]; ν_{max}/cm^{-1} 1668, 1634 and 963; δ_H(400 MHz) 0.93 (3 H, t, *J* 7.3, 9-H), 1.31–1.49 (4 H, m, 8-H and 7-H), 2.07 (3 H, d, *J* 1.2, Me), 2.22–2.27 [2 H, m (appt. q), 6-H], 5.81 (1 H, br d, *J* 8.2, 2-H), 6.21 (1 H, dt, *J* 15.6 and *J* 7.0, 5-H), 7.07 (1 H, d, *J* 15.6, 4-H) and 10.17 (1 H, d, *J* 8.2, 1-H); δ_C(22.4 MHz) 13.84, 21.39, 22.30, 30.99, 33.11, 125.44, 127.30, 140.87, 155.26 and 190.25; *m/z* (EI) 152 (M^+, 2%), 151 (1) and 95 (100). A sample of the aldehyde stored at −20 °C showed major decomposition and isomerisation products (TLC analysis) after 1 day.

(2*Z*,4*E*)-3-Methyl-5-(2-thienyl)penta-2,4-dienal 7b. This compound was prepared from 2-thienyllithium [prepared from BuLi (2.51 mol dm^{-3} in hexanes; 2.39 cm^3, 6.0 mmol) and thiophene (510 mg, 6.05 mmol) in THF (10 cm^3) stirred at −78 °C for 3 h] and 4-methylpyrylium tetrafluoroborate **5** (1000 mg, 5.50 mmol) in diethyl ether (10 cm^3) using the typical procedure given previously. Purification by flash column chromatography [light petroleum–EtOAc–triethylamine (90:10:0.1)] gave the *title compound* **7b** (617 mg, 63%) as a yellow solid, mp 58.1–61.2 °C (Found: C, 67.2; H, 5.45; S, 17.9. $C_{10}H_{10}OS$ requires C, 67.4; H, 5.65; S, 18.0%); R_F 0.18 [light petroleum–EtOAc (9:1)]; ν_{max}/cm^{-1} 3088, 3075, 3065, 1653, 1601, 945 and 710; δ_H(400 MHz) 2.10 (3 H, d, *J* 1.2, Me), 5.86 (1 H, br d, *J* 7.9, 2-H), 6.98–7.02 (1 H, m, 3′-H thioph.), 7.06 (1 H, d, *J* 15.6, 4-H‡), 7.13–7.18 (1 H, m, 4′-H thioph.), 7.26–7.29 (1 H, m, 5′-H thioph.), 7.57 (1 H, d, *J* 15.6, 5-H‡) and 10.21 (1 H, d, *J* 7.9, 1-H); δ_C(22.4 MHz) 20.84, 122.64, 126.88, 127.95, 128.21, 128.73, 129.38, 141.43, 153.38 and 189.48; *m/z* (EI) 180 (8%), 179 (12), 178 (M^+, 100) and 135 (62). (‡ These assignments may be interchanged.)

(2*Z*,4*E*)-5-Cyclohex-1-enyl-3-methylpenta-2,4-dienal 7c. This compound was prepared from cyclohex-1-enyllithium[38] (0.56 mol dm^{-3} in diethyl ether; 7.08 cm^3, 3.96 mmol) and 4-methylpyrylium tetrafluoroborate **5** (601 mg, 3.30 mmol) in diethyl ether (10 cm^3) according to the typical procedure given above. Purification of the crude mixture by flash column chromatography [light petroleum–EtOAc–triethylamine (80:10:0.1)] gave the *title aldehyde* **7c** (526 mg, 90%) as an orange-coloured oil {Found (EI): $[M^+]$, 176.1200. $C_{12}H_{16}O$ requires $[M^+]$, 176.1201}; R_F 0.4 [light petroleum–EtOAc (4:1)]; ν_{max}/cm^{-1} 2933, 2884, 1665, 1605, 1118 and 958; δ_H(270 MHz) 1.62–1.84 (4 H, m, cyclohexyl methylenes), 2.15 (3 H, s, Me), 2.22–2.33 (4 H, m, cyclohexyl allylics), 5.87 (1 H, br d, *J* 7.9, 2-H), 6.09 (1 H, br s, 2′-H), 6.67 (1 H, d, *J* 15.6, 4-H†), 7.18 (1 H, d, *J* 15.6, 5-H†), 10.25 (1 H, d, *J* 7.9, 1-H); DIFNOE experiments showed enhancement at Me on irradiation at 2-H; δ_C(67.5 MHz) 20.90, 21.93, 24.06, 26.15, 119.21, 127.24, 135.51, 135.89, 140.36, 154.82 and 189.51; *m/z* (EI) 176 (M^+, 40%), 161 (21), 147 (48), 105 (100), 95 (58) and 79 (29). A sample of the aldehyde stored at −20 °C showed major decomposition products (TLC analysis) after 1 week. († These assignments may be interchanged.)

(2*Z*,4*E*)-3-Methyl-5-phenylpenta-2,4-dienal 7d. This compound was prepared from phenyllithium (1.8 mol dm^{-3} in hexane; 1.42 cm^3, 2.56 mmol), 4-methylpyrylium tetrafluoroborate **5** (387 mg, 2.13 mmol) and diethyl ether (10 cm^3) following the typical procedure above. ^1H NMR (60 MHz) spectroscopic analysis of the crude reaction mixture showed the presence of a single isomeric aldehyde (formyl proton at δ 10.2) and complete absence of the 4-methyl-4-phenylpyran by-product. Purification by flash column chromatography [light petroleum–EtOAc–triethylamine (100:10:0.1)] gave the *title aldehyde* **7d** (249 mg, 68%) as a gummy oil {Found (EI): $[M^+]$, 172.0892. $C_{12}H_{12}O$ requires $[M^+]$, 172.0888}; R_F 0.22 [light petroleum–EtOAc (9:1)]; ν_{max}/cm^{-1} 3057, 3024, 1661, 1615, 1449, 1199, 1118, 957, 750 and 691; δ_H(270 MHz) 2.16 (3 H, d, *J* 1.2, 3-Me), 5.92 (1 H, br d, *J* 7.6, 2-H), 6.96 (1 H, d, *J* 15.9, 5-H), 7.29–7.50 (5 H, m, PhH), 7.79 (1 H, d, *J* 15.9, 4-H) and 10.26 (1 H, d, *J* 7.6, 1-H) (in agreement with published[22a] data); DIFNOE experiments showed enhancement at 3-Me and no enhancement at 4-H on irradiation at 2-H; δ_C(67.5 MHz) 20.95, 123.03, 127.16, 128.43, 128.66, 129.03, 135.74, 136.56, 153.86 and 189.65; *m/z* (EI) 172 (M^+, 100%), 171 (28), 157 (46), 143 (24), 129 (67) and 128 (64).

(2*Z*,4*E*)-3-Methyl-7-phenylhepta-2,4-dien-6-ynal 7e. This compound was prepared from lithium phenylacetylide [prepared in turn from BuLi (1.6 mol dm^{-3} in hexanes; 1.4 cm^3, 2.24 mmol) and phenylacetylene (222 mg, 2.17 mmol) in dry THF (2 cm^3) at −78 °C for 2 h] and 4-methylpyrylium tetrafluoroborate **5** (362 mg, 1.99 mmol) in dry THF (10 cm^3) following the typical procedure given above. ^1H NMR spectroscopic analysis of the crude material indicated the presence of a single isomeric aldehyde (formyl proton δ 10.18) and the absence of any 4-methyl-4-substituted pyran by-product. Purification by preparative centrifugal chromatography [light petroleum–EtOAc (95:5)] gave the title aldehyde **7e** (210 mg, 54%) as a yellow solid, mp 46.2–48.5 °C; R_F 0.14 [light petroleum–EtOAc (95:5)]; ν_{max}/cm^{-1} 2190, 1653, 1603, 939, 763 and 693; δ_H(400 MHz) 2.06 (3 H, d, *J* 1.2, 3-Me), 5.88 (1 H, br d, *J* 7.9, 2-H), 6.24 (1 H, d, *J* 15.9, 4-H), 7.32–7.34 (3 H, m, PhH), 7.46–7.49 (2 H, m, PhH), 7.66 (1 H, d, *J* 15.9, 5-H) and 10.18 (1 H, d, *J* 7.9, 1-H); δ_C(22.4 MHz) 20.12, 88.13 and 96.24, 116.36, 122.42, 128.73, 129.09, 130.20, 131.53, 135.24, 152.95 and 189.35; *m/z* (EI) 196 (M^+, 59%), 195 (34), 181 (100), 167 (62) and 152 (64). A sample of the aldehyde stored at −20 °C showed decomposition products (TLC analysis) after 1 week.

Isomerisation of the *Z,E*-dienals 7 into the *E,E*-dienals 8

General procedure. To a solution of the *Z,E*-dienal (50–200 mg) in chloroform (5–10 cm^3) and ethanol (5–10 cm^3) was added 2 or 3 drops of concentrated hydrochloric acid. The mixture was then stirred whilst the progress of the reaction was monitored by TLC. Upon completion of the reaction (usually 24 h) the mixture was concentrated under reduced pressure and the crude product was purified either by flash column chromatography or by preparative centrifugal chromatography using the eluent specified.

(2*E*,4*E*)-3-Methyl-5-(2-thienyl)penta-2,4-dienal 8b. This compound was prepared according to the general procedure from (2*Z*,4*E*)-3-methyl-5-(2-thienyl)penta-2,4-dienal **7b** (150 mg), the crude mixture being purified by preparative centrifugal chromatography [light petroleum–EtOAc (9:1)] to give the *title* (E,E)-*dienal* **8b** (121 mg, 81%) as a yellow gummy solid {Found (EI): [M^+], 178.0458. $C_{10}H_{10}OS$ requires [M^+], 178.0452}; R_F 0.11 [light petroleum–EtOAc (9:1)]; ν_{max}/cm^{-1} 3088, 3075 and 3065, 1653, 1601, 956 and 710; δ_H(400 MHz) 2.33 (3 H, d, *J* 0.9, Me), 6.03 (1 H, br d, *J* 7.9, 2-H), 6.69 (1 H, d, *J* 15.9, 4-H†), 7.03 (1 H, dd, *J* 3.7 and 5.2, 4′-H thioph.), 7.15–7.17 (1 H, m, 3′-H thioph.), 7.19 (1 H, d, *J* 15.9, 5-H†), 7.31 (1 H, d, *J* 5.2, 5′-H) and 10.12 (1 H, d, *J* 7.9, 1-H); δ_C(22.4 MHz) 12.83, 126.84, 127.89, 128.31, 128.60, 129.41, 130.55, 141.43, 153.57 and 190.75; *m/z* 178 (M^+, 100%), 163 (49), 149 (52) and 135 (74). († These assignments may be interchanged.)

(2*E*,4*E*)-3-Methyl-5-phenylpenta-2,4-dienal 8d. This compound was prepared according to the general procedure from (2*Z*,4*E*)-3-methyl-5-phenylpenta-2,4-dienal **7d** (100 mg), with the crude product purified by preparative centrifugal chromatography [light petroleum–EtOAc (10:1)] to give the title compound **8d** as an orange-coloured oil (86 mg, 86%), which was fully characterised and which displayed data consistent with those published.[22b]

(2*E*,4*E*)-3-Methyl-7-phenylhepta-2,4-dien-6-ynal 8e. This compound was prepared according to the general procedure from the (*Z*,*E*)-aldehyde **7e** (100 mg) which was purified by preparative centrifugal chromatography [light petroleum–EtOAc (95:5)] to give the title compound **8e** (68 mg, 68%) as an orange-coloured oil; R_F 0.10 [light petroleum–EtOAc (95:5)]; δ_H(400 MHz) 2.29 (3 H, s, 3-Me), 6.01 (1 H, d, *J* 8.0, 2-H), 6.36 (1 H, d, *J* 15.9, 5-H), 6.79 (1 H, d, *J* 15.9, 4-H), 7.34–7.37 (3 H, m, PhH), 7.46–7.50 (2 H, m, PhH) and 10.14 (1 H, d, *J* 8.0, 1-H).

(2*Z*,4*E*)-3-Methyl-5-phenylpenta-2,4-dienoic acid 9. To a solution of (2*Z*,4*E*)-3-methyl-5-phenylpenta-2,4-dienal **7d** (313 mg, 1.82 mmol) and 2-methylbut-2-ene (11 cm^3) in *tert*-butyl alcohol (50 cm^3) was added, with vigorous stirring at room temperature, a solution of sodium chlorite (2.3 g)[39] and potassium dihydrogen phosphate (2.3 g) in distilled water (20 cm^3). The reaction was monitored by TLC for disappearance of the aldehyde. After 48 h the volatile components were removed on the rotary evaporator at room temperature and the residue extracted with diethyl ether (5 × 20 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure and the residue purified by flash chromatography [light petroleum–EtOAc–AcOH (400:100:1)] to give the title acid **9** (219 mg, 64%) as a white solid, mp 128.9–131.4 °C (lit.,[40] 125 °C) which was fully characterised and gave spectroscopic data in accord with the assigned structure. DIFNOE experiments showed enhancement at 3-Me on irradiation at 2-H and no enhancement at 4-H.

(2*Z*,4*E*,6*E*,8*E*)-7-Methyl-9-(2′,6′,6′-trimethylcyclohex-1-enyl)nona-2,4,6,8-tetraenal 12 (13-*cis*-13-demethylretinal). (i) *Via the alanate* **11b**.[33]—To a solution of zirconocene dichloride (1.250 g, 4.28 mmol) in freshly distilled dichloroethane (20 cm^3) at 0 °C, under an atmosphere of dry nitrogen, was added trimethylaluminium (2.0 mol dm^{-3} in hexanes; 4.28 cm^3, 9.56 mmol) dropwise over 15 min. The resultant lemon-yellow solution was warmed to room temperature and treated with a solution of 1-(*trans*-but-1′-en-3′-ynyl)-2,6,6-trimethylcyclohex-1-ene **10** (700 mg, 4.30 mmol) in dichloroethane (5 cm^3) added dropwise over 15 min. The resulting clear brown solution was stirred at room temperature for 24 h, after which the solvent was removed under reduced pressure and replaced with THF (10 cm^3); the THF solution of the alane **11a** was then cooled to −78 °C and treated with butyllithium (2.50 mol dm^{-3} in hexanes; 1.72 cm^3, 4.30 mmol). The resulting solution of the alanate **11b** was allowed to warm to 0 °C over 3 h after which it was recooled to −78 °C and added *via* a cannula to a stirred suspension of pyrylium tetrafluoroborate **2** (180 mg, 1.07 mmol) in THF (10 cm^3) at −78 °C, over 10 min. The mixture was stirred for 40 h at this temperature and worked up as described in the typical procedure. The crude mixture showed the presence of a single retinal isomer in its ^1H NMR spectrum (270 MHz). Purification by flash column chromatography [light petroleum–EtOAc–triethylamine (100:0:0.1 to 160:10:0.1) (gradient elution)] in a darkened room gave 1-(3′-methyl-*trans*-but-1′,3′-dienyl)-2,6,6-trimethylcyclohex-1-ene **11c** (515 mg, 62%) as a yellow oil; R_F 0.5 (light petroleum); δ_H(60 MHz) 1.0 (6 H, s, 2 × 6 Me), 1.1–2.1 (6 H, m, 3-H, 4-H, 5-H), 1.7 (3 H, s, 2-Me), 1.9 (3 H, br s, 3′-Me), 4.9 (2 H, br s, 4′-H), 6.1 (2 H, br s, 1′-H and 2′-H) in accord with published values.[41] Next to be eluted was the title compound **12** (124 mg, 43%) as an intense orange oil which was stored and handled in the dark; {Found (EI): [M^+], 270.1981. Calc. for $C_{19}H_{26}O$, 270.1984}; R_F 0.40 [light petroleum–EtOAc (8:1)]; ν_{max}/cm^{-1} 2943, 1672 and 1594; δ_H(270 MHz) 1.03 (6 H, s, 2 × 6′-Me), 1.45–1.50 (2 H, m, 4′-H), 1.53–1.59 (2 H, m, 5′-H), 1.77 (3 H, s, 2′-Me), 1.97–2.02 (2 H, m, 3′-H), 2.03 (3 H, s, 7-Me), 5.81 (1 H, dd, *J* 7.9, 11.2, 2-H), 6.09 (1 H, d, *J* 15.9, 8-H), 6.20 (1 H, d, *J* 11.9, 6-H), 6.35 (1 H, d, *J* 15.9, 9-H), 6.94 (1 H, dd, *J* 14.1, 11.9, 5-H), 7.04 (1 H, dd, *J* 11.8, 11.2, 3-H), 7.20 (1 H, dd, *J* 14.1, 11.8, 4-H) and 10.19 (1 H, d, *J* 7.9, 1-H); δ_C(67.5 MHz) 12.81, 19.43, 22.11, 29.77, 33.24, 34.53, 39.70, 124.89, 126.13, 128.76, 130.35, 130.59, 136.59, 137.82, 138.80, 142.54, 147.38 and 190.07; *m/z* (EI) 270 (40%), 253 (12), 225 (77), 171 (60), 105 (57), 91 (75) and 41 (100). All spectroscopic data were in accord with those reported in the literature.[27]

(ii) *Via the alane* **11a**.[33]—Procedure (i) was followed exactly to obtain a THF solution of alane **11a** which was then added *via* a cannula to a stirred suspension of pyrylium tetrafluoroborate **2** (180 mg, 1.07 mmol) in THF (5 cm^3). The mixture was stirred at −78 °C for 36 h after which work-up and purification as above gave **11c**[41] (460 mg, 60%) and the title compound **12** (91 mg, 31%).

(2*Z*,4*E*,8*E*)-9-(2′,6′,6′-Trimethylcyclohex-1-enyl)nona-2,4,8-trien-6-ynal 14. This compound was prepared from the organolithium reagent **13** [from 1-(*trans*-but-1′-en-3′-ynyl)-2,6,6-trimethylcyclohex-1-ene **10**[32] (560 mg, 3.21 mmol) and BuLi (2.61 mol dm^{-3} in hexanes; 1.23 cm^3, 3.21 mmol) in dry THF (5 cm^3), −78 to 0 °C over 2 h] and pyrylium tetrafluoroborate (500 mg, 2.98 mmol) in THF (5 cm^3) according to the typical procedure given previously. Work-up according to the typical procedure and purification by flash chromatography [light petroleum–EtOAc–triethylamine (550:25:0.5)] gave the *title compound* **14** (462 mg, 56%) as an orange-coloured syrup {Found (EI): [M^+], 254.1667. $C_{18}H_{22}O$ requires [M^+], 254.1671}; R_F 0.29 [light petroleum–EtOAc (16:1)]; ν_{max}/cm^{-1} 2956, 2930, 2864, 2171, 1737, 1681, 1607, 1457, 1373, 1157, 1144, 1133, 1109, 1009 and 955; δ_H(270 MHz) 1.05 (6 H, s, 6′-Me), 1.44–1.47 (2 H, m, 5′-H), 1.58–1.61 (2 H, m, 4′-H), 1.75 (3 H, s, 2′-Me), 2.02–2.05 (2 H, m, 3′-H), 5.67 (1 H, dd, *J* 16.45, 2.44, 8-H), 5.88 (1 H, dd, *J* 10.99, 7.65, 2-H), 6.16 (1 H, dd, *J* 14.95, 2.44, 5-H), 6.72 (1 H, d, *J* 16.48, 9-H), 6.95 (1 H, t, *J* 11.75, 3-H), 7.51 (1 H, dd, *J* 15.11, 12.36, 4-H) and 10.18 (1 H, d, *J* 7.81, 1-H); δ_C(67.5 MHz) 19.28, 21.96, 29.09, 33.62, 34.36, 39.91, 89.11, 98.64, 111.50, 122.21, 128.01, 133.53, 133.60, 137.30, 143.50, 146.00 and 190.15; *m/z* (EI) 254 (M^+, 57%), 239 (23), 211 (100), 185 (20), 171 (20), 157 (38), 141 (28), 129 (28), 115 (28), 91 (26) and 41 (25).

(2*Z*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2′,6′,6′-trimethylcyclohex-1-enyl)nona-2,4,6,8-tetraenal 15 (13-*cis*-retinal, 13-*cis*-vitamin A aldehyde). A solution of the alanate **11b**[33] (4.30 mmol) in THF (25 cm^3), prepared as in experiment (i) for compound **12**, was

added *via* a cannula to a stirred suspension of 4-methylpyrylium tetrafluoroborate **5** (195 mg, 1.07 mmol) in THF (10 cm^3) at −78 °C over 10 min. The mixture was stirred for 40 h at this temperature and worked up as described above in the typical procedure. The crude mixture showed a single retinal isomer in the ^1H NMR spectrum (270 MHz). Purification by flash column chromatography [light petroleum–EtOAc–triethylamine (300:10:0.1 to 200:10:0.1) (gradient elution)] in a darkened room gave 1-(3′-methyl-*trans*-but-1′,3′-dienyl)-2,6,6-trimethylcyclohex-1-ene **11c** (487 mg, 59%) as a yellow oil.[41] Next to be eluted was the title compound **15** (146 mg, 48%) as an intense orange-coloured oil which was stored and handled in the dark; R_F 0.25 [light petroleum–EtOAc (16:1)]; ν_{max}/cm^{-1} 2927, 1660, 1581, 1452, 1379, 1115 and 968; δ_H(270 MHz) 0.97 (6 H, s, 2 × 6′-Me), 1.32–1.43 (2 H, m, 4′-H), 1.46–1.62 (2 H, m, 5′-H), 1.64 (3 H, s, 7-Me), 1.90–2.00 (5 H, br s, 3′-H and 2′-Me), 2.14 (3 H, d, *J* 1.2, 3-Me), 5.76 (1 H, br d, *J* 7.91, 2-H), 6.03–6.35 (3 H, m, 6-H, 8-H, 9-H), 6.98 (1 H, dd, *J* 11.2, 15.2, 5-H), 7.25 (1 H, d, *J* 14.8, 4-H) and 10.21 (1 H, d, *J* 7.91, 1-H); δ_C(67.5 MHz) 13.10, 19.16, 20.12, 21.75, 28.95, 33.11, 34.25, 39.57, 126.25, 127.66, 129.36, 129.67, 130.49, 133.42, 137.02, 137.57, 141.47, 154.66 and 189.88; *m/z* (EI) 284 (M^+, 100%), 269 (18), 187 (19), 173 (61), 147 (40), 133 (48), 119 (70), 105 (65), 95 (71), 77 (42), 69 (56), 55 (54) and 41 (84). All spectroscopic data were in accord with those reported in the literature.[28]

(2*Z*,4*E*,8*E*)-3-Methyl-9-(2′,6′,6′-trimethylcyclohex-1-enyl)-nona-2,4,8-trien-6-ynal 16. Butyllithium (2.61 mol dm^{-3} in hexane; 2.2 cm^3, 5.74 mmol) was added dropwise to a solution of 1-(*trans*-but-1′-en-3′-ynyl)-2,6,6-trimethylcyclohex-1-ene **10**[32] (1000 mg, 5.74 mmol) in dry THF (10.0 cm^3) under an atmosphere of dry nitrogen at −78 °C and the resulting solution was stirred and allowed to warm to 0 °C over 2 h whereupon it was stirred for a further 2 h. Addition of this solution of compound **13** to 4-methylpyrylium tetrafluoroborate **5** (1000 mg, 5.50 mmol) in THF (10.0 cm^3) following the typical procedure with purification by flash silica column chromatography [light petroleum–EtOAc–triethylamine (200:10:0.1)] gave the title compound **16** (907 mg, 58%) as a yellow oil {Found (EI): [M^+], 268.1826. Calc. for $C_{19}H_{24}O$; [M^+], 268.1827}; R_F 0.25 [light petroleum–EtOAc (16:1)]; ν_{max}/cm^{-1} 2928, 2174, 1668, 1593, 1445, 1378, 1203, 1114, 953 and 732; δ_H(270 MHz) 1.04 (6 H, s, gem CH_3), 1.43–1.47 (2 H, m, CH_2), 1.56–1.62 (2 H, m, CH_2), 1.75 (3 H, s, 2′-Me), 2.01–2.06 (2 H, m, 3′-H), 2.08 (3 H, d, *J* 1.32, 3-Me), 5.66 (1 H, dd, *J* 16.31, 2.47, 8-H), 5.87 (1 H, br d, *J* 7.9, 2-H), 6.21 (1 H, dd, *J* 15.51, 2.31, 5-H), 6.70 (1 H, d, *J* 16.16, 9-H), 7.59 (1 H, d, *J* 15.51, 4-H) and 10.19 (1 H, d, *J* 7.9, 1-H); DIFNOE experiments showed enhancement of 3-Me on irradiation of 2-H and no enhancement of 4-H; δ_C(67.5 MHz) 18.91, 20.33, 21.55, 28.68, 33.19, 33.95, 39.50, 88.81, 96.89, 111.25, 116.93, 128.84, 132.85, 134.38, 136.91, 142.71, 152.40 and 189.52; *m/z* (EI) 268 (M^+, 14%), 253 (15), 241 (7), 225 (79), 199 (33), 171 (72), 128 (48), 115 (60), 105 (40), 91 (66), 77 (54) and 41 (100). The spectroscopic data were in full agreement with published data.[29]

(2*Z*,4*E*,8*E*)-3-Cyclohexyl-9-(2′,6′,6′-trimethylcyclohex-1-enyl)nona-2,4,8-trien-6-ynal 18. This compound was prepared from the organolithium reagent **13** [prepared from 1-(*trans*-but-1′-en-3′-ynyl)-2,6,6-trimethylcyclohex-1-ene **10**[32] (320 mg, 1.82 mmol) and BuLi (2.84 mol dm^{-3} in hexanes; 0.65 cm^3, 1.85 mmol) in dry THF (5 cm^3), −78 to 0 °C over 2 h] and 4-cyclohexylpyrylium tetrafluoroborate[34] (412 mg, 1.65 mmol) in THF (5 cm^3) according to the typical procedure. Purification of the crude material by silica column chromatography [light petroleum–EtOAc–triethylamine (200:10:0.1)] gave the alkyne starting material **10** (82 mg) and the *title compound* **18** (235 mg, 52%) as an orange-coloured oil {Found (EI): [M^+], 336.2453. $C_{24}H_{32}O$ requires [M^+], 336.2453}; R_F 0.41 [light petroleum–EtOAc (16:1)]; ν_{max}/cm^{-1} 2925, 2854, 2174, 1664, 1626, 1588, 1450, 1199, 1174, 1133, 1115 and 953; δ_H(270 MHz) 1.12 (6 H, s, 2 × Me), 1.25–1.45 (4 H, m, cyclohexyl), 1.52–1.56 (2 H, m, 5′-H), 1.66–1.71 (2 H, m, 4′-H), 1.83 (3 H, s, Me), 1.85–1.91 (6 H, m, cyclohexyl), 2.12 (2 H, t, *J* 5.94, 3′-H), 2.45 (1 H, t, *J* 11.21, (3-cyclohexyl) 1-H), 5.73 (1 H, d, *J* 7.92, 2-H), 6.26 (1 H, dd, *J* 2.31, 15.83, 8-H), 6.77 (1 H, d, *J* 16.5, 4-H), 7.34 (1 H, d, *J* 15.84, 9-H) and 10.18 (1 H, d, *J* 7.25, 1-H); DIFNOE experiments showed enhancement at the 3-cyclohexyl 1-H proton and enhancement in the other 3-cyclohexyl ring protons and no enhancement at 4-H on irradiation at 2-H; δ_C(67.5 MHz) 18.96, 21.60, 25.95, 26.45, 28.74, 32.46, 33.23, 34.02, 39.53, 41.69, 88.63, 95.71, 111.30, 116.41, 126.18, 132.78, 134.27, 136.98, 142.64, 163.12 and 191.10; *m/z* (EI) 336 (M^+, 15%), 308 (52), 293 (100), 239 (26), 211 (25), 145 (24), 131 (21), 105 (20), 91 (26) and 41 (27).

(2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2′,6′,6′-trimethylcyclohex-1-enyl)nona-2,4,6,8-tetraenal 19 (vitamin A aldehyde, retinal). To a stirred solution of 13-*cis*-retinal **15** (120 mg) in diethyl ether (5 cm^3) at room temperature was added dropwise a solution of iodine (5 mg) in benzene (5 cm^3). The mixture was stirred at room temperature for 48 h,[35] after which the solvent was removed under reduced pressure and the residue purified by preparative centrifugal chromatography [light petroleum–EtOAc (20:1)] to yield the title aldehyde **19** as an orange-coloured oil (109 mg, 91%); R_F 0.21 [light petroleum–EtOAc (16:1)]; ν_{max}/cm^{-1} 2956, 1660, 1579, 1447, 1381, 1361, 1162, 1131, 1121 and 970; δ_H(270 MHz) 1.12 (6 H, s, 2 × 6′-Me), 1.54–1.58 (2 H, m, 4′-H), 1.67–1.76 (2 H, s, 5′-H), 1.81 (3 H, s, 5′-Me), 2.12 (5 H, br s, 4′-H and 7-Me), 2.26 (3 H, d, *J* 1.2, 3-Me), 6.06 (1 H, br d, *J* 8.25, 2-H), 6.22–6.33 (2 H, m, 6-H and 8-H), 6.41–6.49 (2 H, m, 4-H and 9-H), 7.23 (1 H, dd, *J* 15.18, 11.55, 5-H) and 10.10 (1 H, d, *J* 8.24); δ_C(67.5 MHz) 13.01, 13.12, 19.18, 21.76, 28.69, 33.14, 34.27, 39.59, 129.00, 129.38, 129.72, 130.53, 132.54, 134.50, 137.07, 137.61, 141.29, 154.84 and 191.12. The spectroscopic data were in full accord with published data.[28]

(2*Z*,4*E*,8*E*)-3-Methyl-9-(2′,6′,6′-trimethylcyclohex-1-enyl)-nona-2,4,8-trien-6-yn-1-ol 20. To a solution of the aldehyde **16** (252 mg, 0.94 mmol) in dry diethyl ether (10 cm^3), stirred at −78 °C under an atmosphere of dry nitrogen, was added DibalH (1.0 mol dm^{-3} in hexanes; 0.94 cm^{-3}, 0.94 mmol) and the mixture was stirred at this temperature for 14 h; it was then allowed to warm to 0 °C over 2 h and held at this temperature for a further 1 h. The mixture was then quenched by the addition to it of saturated aqueous sodium hydrogen carbonate (10 cm^3), after which it was extracted with ethyl acetate (5 × 10 cm^3). The combined extracts were dried ($NaSO_4$) and concentrated under reduced pressure and the residue was purified by flash column chromatography [light petroleum–EtOAc–triethylamine (450:100:5)] to give the *title alcohol* **20** as a pale yellow–orange oil (205 mg, 81%) {Found (EI): [M^+], 270.198 05. $C_{19}H_{26}O$ requires [M^+], 270.1984}; R_F 0.23 [light petroleum–EtOAc (4:1)]; ν_{max}/cm^{-1} 3342, 2928, 2176, 1626, 1456, 1379, 1361, 1294, 1022 and 953; δ_H(270 MHz) 1.11 (6 H, s, 2 × 6′-Me), 1.51–1.55 (2 H, m, 4′-H), 1.66–1.71 (2 H, m, 5′-H), 1.82 (3 H, s, 2′-Me), 1.95 (3 H, d, *J* 0.99, 3-Me), 2.04 (1 H, br s, OH), 2.08–2.13 (2 H, m, 3′-H), 4.40 (2 H, d, *J* 6.93, 1-H), 5.67–5.74 (2 H, dd overlapped with t, *J* 16.17, 2.31, 7.16, 2-H and 8-H), 5.93 (1 H, dd, *J* 2.31, 15.83, 5-H), 6.68 (1 H, d, *J* 16.16, 9-H) and 7.05 (1 H, d, *J* 15.84, 4-H); DIFNOE experiments showed clear enhancement at 3-Me on irradiation of 2-H with no enhancement at 4-H; δ_C(67.5 MHz) 18.99, 19.63, 21.57, 28.72, 33.14, 33.98, 39.52, 58.24, 89.31 and 92.49, 109.96, 111.84, 130.39, 131.90, 134.41, 136.55, 137.04 and 141.06; *m/z* (EI) 270 (M^+, 100%), 255 (21), 237 (27), 183 (33), 165 (32), 155 (29), 141 (33), 128 (52), 115 (47), 105 (34), 109 (66), 77 (36), 55 (30) and 39 (62).

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