New Retinoid Analogs from δ-Pyronene, a Natural Synthon

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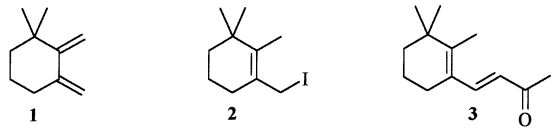
δ-Pyronene (**1**), a readily available terpenic synthon, is an excellent raw material for the preparation of numerous terpenic intermediates. Original retinoid analogs such as "*iso*"-retinyl acetate (**5**), "*iso*"-retinal (**6**) and ethyl "*iso*"-retinoate (**7**), in which the cyclogeranyl moiety is functionalized in an unusual position, were prepared from δ-pyronene.

Introduction

The authors have recently reported[1−5] on the efficient use of δ-pyronene (**1**), a terpenic synthon, in order to obtain new terpenoids with a cyclogeranyl skeleton bearing a functionalized side chain in an unusual position. Thus, for example, "*iso*"-β-ionone (**3**) has been prepared[5] using "*iso*"-β-cyclogeranyl iodide (**2**), which is itself derived from δ-pyronene (**1**) in an excellent yield (see Scheme 1).

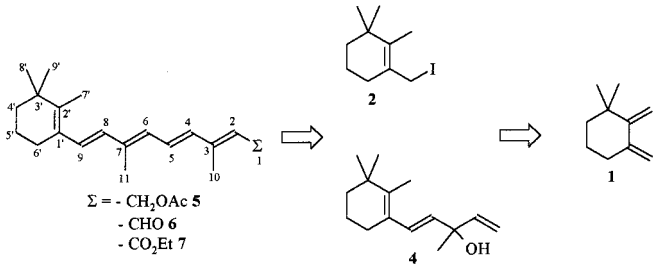


Scheme 1. δ-Pyronene (**1**), precursor of "*iso*"-β-cyclogeranyl derivatives **2** and **3**

Retinoids are the subject of much interest[6] due to their essential role in wide-ranging biological functions and therapies, e.g. the vision process, the treatment of skin disorders and more recently cancer prevention and therapy. Many natural or modified retinoids have also been synthesized and biologicaly evaluated for use in these applications (dermatology, oncology, etc.).

In this paper, the authors report on the use of δ-pyronene (**1**), as a precursor of the new retinoid analogs ("*iso*"-retinoids[7]) **5**−**7**, following coupling reactions via the C_{10} and C_{15} intermediates **2** and **4**, respectively (Scheme 2).

The homologation steps were based on the Wittig reaction[8] between the cyclic phosphonium salts **8** and **10** obtained from the same precursor, "*iso*"-β-cyclogeranyl iodide (**2**), and linear aldehydic units **16**, **17** and **19**, prepared from isoprene (**11**) (see Experimental Section, Scheme 6).



Scheme 2. Retrosynthetic analysis for the obtention of "*iso*"-retinoids **5**−**7**

C_{15} + C_5 Coupling

Coupling of "*iso*"-β-cyclogeranyl iodide (**2**) with the dianion prepared from the corresponding hydroxy sulfoxide, **13**,[9] afforded the C_{15} hydroxy sulfoxide **9** in a yield of 57%. This compound was refluxed in a toluene solution in the presence of potassium carbonate to give "*iso*"-vinyl-β-ionol (**4**) (83% yield), with an (*E*) configuration with respect to the newly formed double bond (see Scheme 3).

This new compound can be considered as an analog of vinyl-β-ionol, which is an important intermediate in the synthesis of retinoids.[10] Quantitative treatment of **4** with triphenylphosphane hydrobromide led to the phosphonium bromide **10**.

The aldehyde **17**, coupled (EtONa, 1 equiv.) with the phosphonium salt **10** gave "*iso*"-retinyl acetate (**5**) in a yield of 69%, corresponding to an approximately 1:1 mixture of (*E*) and (*Z*) isomers with respect to the C-4−C-5 double bond (see Scheme 4).

In a similar way, the coupling of the aldehyde **16** with the phosphorane derived from phosphonium bromide **10** with sodium ethoxide was realized. After acidic deprotection and the addition of hydroquinone, a yield of 64% of "*iso*"-retinal (**6**) as the only (all-*E*) isomer was obtained.

C_{10} + C_{10} Coupling

"*iso*"-β-Cyclogeranyl iodide (**2**) was used as the precursor of cyclic C_{10} phosphonium iodide **8** (see Scheme 3). Genera-

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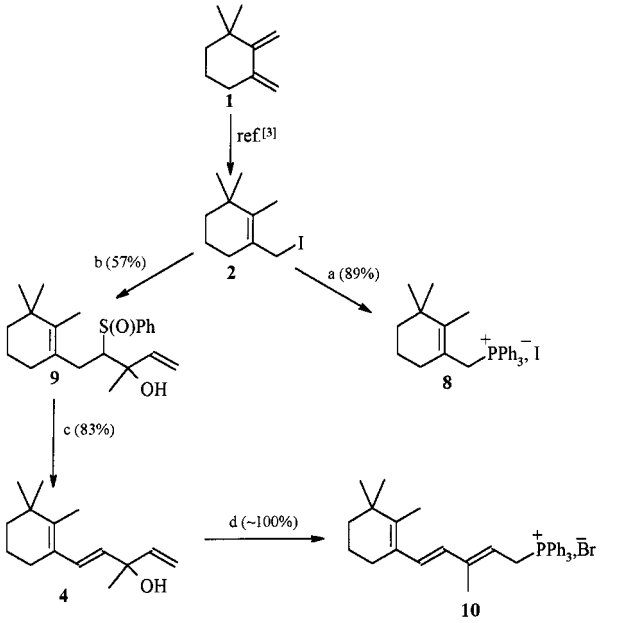
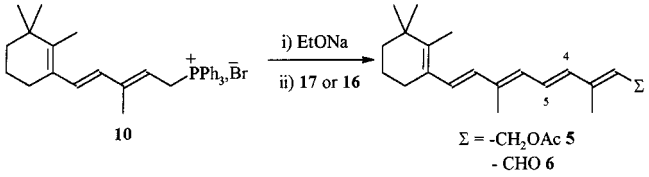
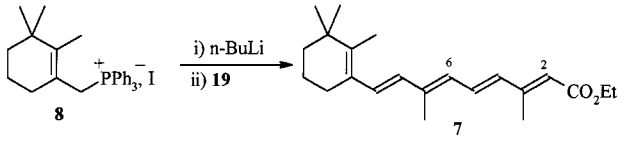


Scheme 3. Preparation of phosphonium salts **8** and **10**; reagents and conditions: (a) PPh_3, Et_2O; (b) **13**, *n*BuLi (2 equiv.), THF, −78°C; (c) K_2CO_3, toluene, reflux; (d) PPh_3/HBr, MeOH



Scheme 4. C_{15} + C_5 coupling

tion of the corresponding phosphorane with *n*BuLi at 0°C, followed by the addition of the linear C_{10} formyl ester **19** provided a 70% yield of polyene isomers. Treatment of this mixture with iodine gave ethyl "*iso*"-retinoate (**7**) as a mixture of four isomers, from which the two major components [(all-*E*) isomer (61%), (2*Z*,6*E*) isomer (31%)] were characterized by NMR analysis (see Scheme 5).



Scheme 5. C_{10} + C_{10} coupling

NMR Analysis

The complete ^{1}H- and ^{13}C-NMR chemical shift assignments of "*iso*"-retinyl acetate (**5**) [(all-*E*) and (4*Z*) isomers] and (all-*E*)-"*iso*"-retinal (**6**) were deduced from 2-D techniques such as COSY ^{1}H^{1}H,[11] ^{1}H-detected one-bond (CH) heteronuclear multiple quantum coherence (HMQC),[12] and long-range multi-bond (CH) heteronuclear connectivity (HMBC).[13]

"*iso*"-Retinyl Acetate (5) (Table 1)

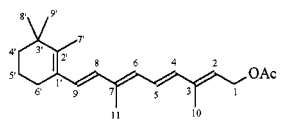
From the unambiguous assignment of the triplet signal at δ = 5.64 (2-H), we observed COSY crosspeaks with methyl singlets at δ = 1.91 and 1.94 that may be assigned to CH_3-10 methyl groups. The COSY spectrum revealed two three-spin systems, involving 4-H, 5-H and 6-H resonances. The signals (dd) at δ = 6.39 and 6.67 correspond to the 5-H proton for each isomer; the former is correlated with the protons resonating at δ = 5.88 and 6.59 and the latter with the protons resonating at δ = 6.18 and 6.27.

The HMBC spectrum showed a long-range correlation between CH_3-10 proton signals at δ = 1.91 and 1.94 and carbon (CH) resonances at δ = 136.1 and 132.3, respectively, which were therefore assigned to CH-4. Those latter carbon resonances can be associated, by a ^{1}H-^{13}C HMQC experiment, with the proton resonances at δ = 6.27 and 5.88; as a consequence, the assignments of 6-H vinylic proton at δ = 6.18 and 6.59 were straightforward. The δ = 1.99 and 1.96 signals were established for CH_3-11 methyl groups from the COSY spectrum, which exhibited correlation peaks with 6-H proton resonances at δ = 6.18 and 6.59.

Table 1. ^{1}H- and ^{13}C-NMR chemical shifts assignments of (all-*E*)- and (4*Z*)-"*iso*"-retinyl acetate **5**

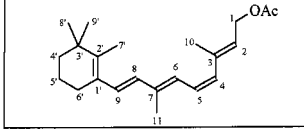
δ_H (ppm)	multiplicity, intégration	COSY HH' ($\delta_{H'}$)	^{1}H (n°)
1.07	s, 6H		*8', 9'*
1.51	m, 2H	1.68	*4'*
1.68	m, 2H	1.51 ; 2.20	*5'*
1.83	s, 3H	2.20	*7'*
1.91	s, 3H	4.75 ; 5.64	*10*
1.99	s, 3H	6.18	*11*
2.08	s, 3H		*13*
2.20	m, 2H	1.68 ; 1.83	*6'*
4.75	d, 2H	1.91 ; 5.64	*1*
5.64	t, 1H	1.91 ; 4.75	*2*
6.18	d, 1H	1.99 ; 6.67	*6*
6.25-6.33	m, 2H	6.75	*4,8*
6.67	dd, 1H	6.18 ; 6.27	*5*
6.75	d, 1H	~6.30	*9*

δ_C (ppm)	CH_n (n)	HMQC ($^1J_{CH}$)	selected HMBC ($^nJ_{CH}$)	^{13}C (n°)
12.8	3	1.91	4.75	*10*
13.3	3	1.99		*11*
14.2	3	1.83		*7'*
19.5	2	1.68		*5'*
21.4	3	2.08		*13*
27.0	2	2.20	6.75	*6'*
28.4	3	1.07		*8', 9'*
36.0	0			*3'*
39.6	2	1.51		*4'*
61.7	2	4.75		*1*
124.8	1	5.64	1.91 ; 4.75	*2*
126.4	1	6.67		*5*
128.0	1	6.75		*9*
128.2	0		6.30	*1'*
131.0	1	6.18	1.99	*6*
131.5	1	~6.30	1.99	*8*
136.1	1	6.27	1.91	*4*
137.5	0		1.99	*7*
139.6	0		1.91 ; 4.75	*3*
141.6	0		1.07 ; 6.75	*2'*
171.4	0			*12*



δ_H (ppm)	multiplicity, intégration	COSY HH' ($\delta_{H'}$)	^{1}H (n°)
1.07	s, 6H		*8', 9'*
1.51	m, 2H	1.68	*4'*
1.68	m, 2H	1.51 ; 2.20	*5'*
1.83	s, 3H	2.20	*7'*
1.94	s, 3H	4.75 ; 5.64	*10*
1.96	s, 3H	6.59	*11*
2.08	s, 3H		*13*
2.20	m, 2H	1.68 ; 1.83	*6'*
4.75	d, 2H	1.94	*1*
5.64	t, 1H	1.94	*2*
5.88	d, 1H	6.39	*4*
6.30	m, 1H	6.77	*8*
6.39	dd, 1H	5.88 ; 6.59	*5*
6.59	d, 1H	1.96 ; 6.39	*6*
6.77	d, 1H	6.30	*9*

δ_C (ppm)	CH_n (n)	HMQC ($^1J_{CH}$)	selected HMBC ($^nJ_{CH}$)	^{13}C (n°)
13.1	3	1.96		*11*
14.2	3	1.83		*7'*
17.7	3	1.94	4.75	*10*
19.5	2	1.68		*5'*
21.4	3	2.08		*13*
27.0	2	2.20	6.77	*6'*
28.4	3	1.07		*8', 9'*
36.0	0			*3'*
39.6	2	1.51		*4'*
61.7	2	4.75		*1*
125.2	1	5.64	1.94 ; 4.75	*2*
126.3	1	6.39		*5*
127.3	1	6.59	1.96	*6*
128.2	0		6.30	*1'*
128.3	1	6.77		*9*
131.7	1	6.30	1.96	*8*
132.3	1	5.88	1.94	*4*
138.5	0		1.96	*7*
139.0	0		1.94 ; 4.75	*3*
141.7	0		1.07 ; 6.77	*2'*
171.4	0			*12*



By means of an HMBC experiment, multi-bond correlations were also detected from CH_3-11 proton signals to carbon (CH) resonances at δ = 131.7 and 131.5, and thus assigned to C-8. Thereby, the remaining vinylic proton signals at δ = 6.75 and 6.77 were assigned to 9-H.

The assignments of sp^2 quaternary carbon atoms were obtained from the analysis of long-range-correlation responses over two and three bonds using the HMBC techniques. The quaternary carbon resonances at δ = 139.0 and 139.6 were assigned to C-3 from ^3J connectivities with a 1-H proton (δ = 4.75) and ^2J connectivities with CH_3-10 protons. The C-7 quaternary carbon atoms correspond to signals at δ = 137.5 and 138.5 which correlate long-range ($^2J_{CH}$) with CH_3-11 proton signals at δ = 1.99 and 1.96, respectively. Furthermore, the HMBC spectrum revealed $^3J_{CH}$ connectivities from the *gem*-dimethyl proton signals (δ = 1.07) to sp^2-quaternary carbon atoms at δ = 141.6 and 141.7(C-2′).

From the measured H,H coupling constants $J_{4,5}$ the presence of an (all-*E*) isomer ($J_{4,5}$ = 15.6 Hz) and a (4*Z*) isomer ($J_{4,5}$ = 12 Hz) were unambiguously identified. Taking into account the observed values for C-11 methyl carbon resonances (δ ≈ 13), the C-6−C-7 double bond in each isomer can be assigned to an (*E*) configuration.

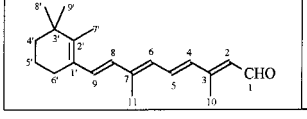
"*iso*"-Retinal (6) (Table 2)

The ethylenic proton area of the ^{1}H-NMR spectrum of "*iso*"-retinal (**6**) exhibited five doublets and a multiplet at δ = 7.13, corresponding to the 5-H proton. From the COSY spectrum, the aldehyde proton 1-H (δ = 10.08) showed a correlation peak with the proton resonance at δ = 5.96 which can be assigned to 2-H.

After associating proton and carbon resonances by an HMQC experiment, the CH_3-proton resonance at δ = 2.31 was assigned to CH_3-10 from a long-range correlation peak in the HMBC spectrum with the C-2 carbon resonance (δ = 128.8). The 10-H proton resonance also exhibited a correlation with a carbon resonance at δ = 154.9 (C) and 134.3 (CH), which were therefore assigned to C-3 and C-4, respectively.

Table 2. ^{1}H- and ^{13}C-NMR chemical shift assignments of (all-*E*)-"*iso*"-retinal **6**

δ_H (ppm)	multiplicity, intégration	COSY HH′ ($\delta_{H'}$)	^{1}H (n°)	δ_C (ppm)	CH_n (n)	HMQC ($^1J_{CH}$)	selected HMBC ($^nJ_{CH}$)	^{13}C (n°)
1.04	s, 6H		*8′, 9′*	13.0	3	2.03		*11*
1.47	m, 2H	1.66	*4′*	13.1	3	2.31		*10*
1.66	m, 2H	1.47 ; 2.18	*5′*	13.9	3	1.82		*7′*
1.82	s, 3H		*7′*	19.0	2	1.66		*5′*
2.03	s, 3H	6.23	*11*	26.4	2	2.18	6.86	*6′*
2.18	m, 2H	1.66	*6′*	27.8	3	1.04		*8′, 9′*
2.31	s, 3H	5.96	*10*	35.8	0		1.04 ; 1.82	*3′*
5.96	d, 1H	2.31 ; 10.08	*2*	39.0	2	1.47	1.04	*4′*
6.23	d, 1H	2.03 ; 7.13	*6*	127.9	0		1.82 ; 6.30	*1′*
6.30	d, 1H	6.86	*8*	128.8	1	5.96	2.31	*2*
6.35	d, 1H	7.13	*4*	129.8	1	6.86		*9*
6.86	d, 1H	6.30	*9*	130.0	1	6.23	2.03	*6*
7.13	dd, 1H	6.23 ; 6.35	*5*	130.5	1	6.30	2.03	*8*
10.08	d, 1H	5.96	*1*	132.6	1	7.13		*5*
				134.3	1	6.35	2.31	*4*
				141.9	0		2.03	*7*
				143.2	0		1.04 ; 1.82	*2′*
				154.9	0		2.31	*3*
				191.1	1	10.08		*1*



At this stage, the assignments of CH-6 (δ_H = 6.23, δ_C = 130.0) became unambiguous. In a similar approach, the CH_3 proton resonance at δ = 2.03 was assigned to CH_3-11 from the observed correlation peaks with three carbon resonances at δ = 130.0 (CH-6), 141.9 (C) and 130.5 (CH). As a consequence, these two latter carbon resonances may be assigned to C-7 and CH-8, respectively.

Conclusion

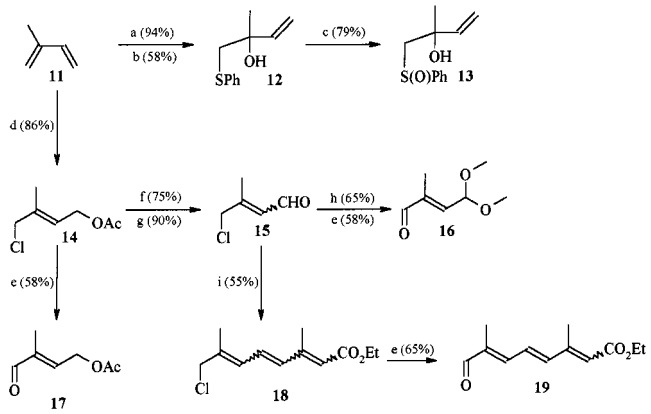
These results showed that δ-pyronene, easily available from myrcene, is a particularly efficient new terpenic synthon, allowing a synthetic approach to retinoid analogs. These compounds, having a skeleton in which the polyenic side-chain was linked to the cyclogeranyl moiety in an unusual position, represent a new type of retinoid with potential for biological uses.

Experimental Section

General: All reactions were performed under nitrogen; air- and moisture-sensitive compounds were introduced by syringe or cannula through a rubber septum to the reaction vessel. Solvents were freshly distilled prior to use. − ^{1}H and ^{13}C NMR: Bruker AC 250 (250 MHz for ^{1}H and 62.89 MHz for ^{13}C) or Bruker DPX 400 (400 MHz for ^{1}H and 100.61 MHz for ^{13}C), CD_3Cl solution, chemical shifts expressed downfield from tetramethylsilane (TMS), multiplicities in ^{13}C NMR of the different carbon atoms were determined using the DEPT sequences and *J*-Mod experiments. − IR: Perkin−Elmer 683, either neat or as a film on sodium chloride plates. − High-resolution mass spectra (HRMS): VG Micromass 16F (10000 resolution), 70 eV. − Flash chromatography: Merck alumina and Kieselgel 60, 60−200 μm. The standard workup means that the organic layers were washed with satd. sodium chloride aqueous solution (brine), dried with anhydrous magnesium sulfate, filtered and concentrated in vacuo.

Preparation of the Linear Aldehyde Units 16, 17, and 19 (Scheme 6)

2-Methyl-1-(phenylsulfinyl)-3-buten-2-ol (13): Isoprene (**11**) (12.5 mL, 0.125 mol) was added to a suspension of *N*-bromosuccinimide[14] (25.5 g, 0.14 mol) in a mixture of acetone/water (50:10, 120 mL) at 0°C. The reaction mixture was stirred for 15 h at room temp., then extracted with Et_2O. The combined organic layers were washed with satd. aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated under vacuo to give 19.4 g (94% yield) of a mixture of bromhydrines which was used without purification. Thiophenol (7.2 mL, 70 mmol) was added to a suspension of 95% sodium hydride (1.77 g, 70 mmol) in DMF (70 mL) at 0°C. After 1 h of stirring at ambient temp., bromohydrines (10.7 g, 65 mmol) were added at 0°C. The reaction was allowed to warm to room temp., then stirred for 15 h. after which it was poured into ice/water, extracted with $CHCl_3$, and treated by the standard workup. The residue was purified by chromatography on silica gel (petroleum ether/ether, 90:10) to give **12** (7.36 g, 58% yield).[15] − Sodium metaperiodate (4.41 g, 21 mmol) in water (40 mL) was added to a solution of hydroxy sulfide **12** (4 g, 21 mmol) in *tert*-butyl alcohol (100 mL), After 15 h of stirring at room temp., the reaction was quenched by the addition of water, and extracted with $CHCl_3$ followed by the standard workup. The white solid obtained was puri-



Scheme 6. Preparation of linear aldehydic units **16**, **17** and **18**; reagents and conditions: (a) NBS, acetone/H_2O; (b) PhSNa, DMF; (c) $NaIO_4$, *t*BuOH/H_2O; (d) *t*BuOCl, AcOH then $CuSO_4$, H_2SO_4; (e) DMSO, K_2HPO_4/KH_2PO_4, NaBr, 80°C; (f) Na_2CO_3, MeOH/H_2O; (g) PCC, CH_2Cl_2; (h) $HC(OCH_3)_3$, MeOH, APTS; (i) $Ph_3P{=}CHC(CH_3){=}CHCO_2Et$ then I_2

fied by chromatography (silica gel, petroleum ether/ether, 20:80) and gave **13** (3.41 g, 79% yield).[16]

(*E*)-4,4-Dimethoxy-2-methyl-2-butenal (16): ***tert*-**Butyl hypochlorite (17.3 g, 0.16 mol) was added at 0°C to a solution of isoprene (**11**) (13.6 g, 0.2 mol) in acetic acid (58 g, 0.96 mol).[17] The reaction mixture was stirred for 1 h, hydrolyzed and extracted with petroleum ether. The combined extracts were successively washed with satd. $NaHCO_3$ and satd. NaCl, and dried ($MgSO_4$). The filtrate was concentrated under reduced pressure, dissolved in acetic acid (60 mL), and treated with both copper sulfate (0.4 g, 2 mmol) and sulfuric acid (0.4 g, 4 mmol). The resultant mixture was stirred for 4 d at ambient temp., quenched by the addition of water and extracted with ether. The standard workup gave (*E*)-4-chloro-3-methyl-2-buten-1-ol acetate (**14**) (14.8 g, 86% yield).[18] Without further purification this residue was dissolved in methanol (240 mL) and stirred for 5 h at 0°C in the presence of an aqueous solution (80 mL) of sodium carbonate (14.3 g, 135 mmol). The mixture was filtered, concentrated and poured onto ice/water. The extraction with chloroform followed by a standard workup afforded a crude product which was purified by chromatography (silica gel, petroleum ether/ether, 60:40) to provide the chloro alcohol (9.05 g, 75% yield). The chloro alcohol (900 mg, 6.6 mmol) in dichloromethane (10 mL) was added at 0°C to a suspension of pyridinium chlorochromate (2.2 g, 10.5 mmol) in dichloromethane (20 mL). The resultant reaction was kept at 0°C for an additional 90 min, then filtered through a short alumina column. Elution with ether gave 4-chloro-3-methyl-2-butenal (**15**) (800 mg, 90% yield)[19] as a mixture of (*E*)/(*Z*) stereoisomers. Trimethyl orthoformate (8 mL) and *p*-toluenesulfonic acid (160 mg, 0.9 mmol) were added to the chloro aldehyde **15** (1.072 g, 9 mmol) in a solution of methanol (8 mL). After stirring for 18 h at room temp., the solution was hydrolyzed with satd. $NaHCO_3$, extracted with ether and treated by the standard workup. Further purification by chromatography on silica gel, eluting with petroleum ether/ether (90:10) gave the chloro acetal (968 mg, 65% yield). K_2HPO_4 (845 mg, 4.86 mmol), KH_2PO_4 (177 mg, 1.31 mmol) and sodium bromide (50 mg, 0.49 mmol) were added to a solution of the chloro acetal (628 mg, 3.8 mmol) in DMSO (20 mL). This mixture was stirred at 80°C for 20 h, poured into water (100 mL) and extracted with chloroform. The standard workup afforded a residue which was purified by chromatography (silica gel, petroleum ether/ether, 80:20) to yield **16** (323 mg, 58% yield). − ^{1}H NMR: δ = 1.79 (s, 3 H), 3.32 (s, 6 H), 5.21 (d, 1 H, 4-H), 6.32 (d, 1 H, 3-H), 9.50 (s, 1 H, C*H*O). − ^{13}C NMR: δ = 18.3 (*C*H$_3$), 52.7 (O*C*H$_3$), 99.3 (C-4), 142.4 (C-2), 146.9 (C-3), 194.8 (C-1).

(*E*)-4-Acetoxy-2-methyl-2-butenal (17): K_2HPO_4 (1.32 g, 7.7 mmol), KH_2PO_4 (276 mg, 2 mmol) and sodium bromide (80 mg, 0.77 mmol) were added to a solution of chloro acetate **14** (1.07 g, 6.5 mmol) in DMSO (8 mL). After stirring for 16 h at 80°C, the reaction mixture was poured into water (100 mL) and extracted with $CHCl_3$. The organic layers were washed with satd. sodium chloride and dried ($MgSO_4$). The evaporation of solvents under reduced pressure provided a crude product which was purified by chromatography (silica gel). The elution with petroleum ether/ether (60:40) gave **17** (532 mg, 58% yield).[18]

Ethyl 3,7-Dimethyl-8-oxo-2,4,6-octatrienoate (19):[20] The chloro aldehyde **15** (1.44 g, 1 mmol) was added at 0°C to an ethanol solution (5 mL) of the phosphonium salt (400 mg, 0.85 mmol) prepared from ethyl 4-bromo-3-methyl-2-butenoate (EtONa/EtOH, 0°C). The reaction mixture was stirred for 2 h and extracted with Et_2O. The combined organic layers were washed with 10% aqueous HCl, satd. $NaHCO_3$, satd. NaCl, dried ($MgSO_4$) and concentrated to give the C_{10} chloro ester **18** (120 mg, 55% yield) after chromatography (silica gel, petroleum ether/ether, 92:8). K_2HPO_4 (201 mg, 1.15 mmol), KH_2PO_4 (42 mg, 0.31 mmol) and NaBr (12 mg, 0.115 mmol) were added to a solution of **18** (229 mg, 1 mmol) in DMSO (8 mL) The solution was stirred for 18 h at 80°C, poured into water (100 mL) and extracted with chloroform followed by the standard workup. The residue purified by chromatography (silica gel, petroleum ether/ether, 70:30) gave **19** (135 mg, 65% yield) as a 1:1 mixture of (2*E*)/(2*Z*) isomers. − ^{1}H NMR [(2*E*)]: δ = 1.28 (t, 3 H, C*H*$_3$CH$_2$), 1.90 (s, 3 H, 9-H), 2.35 (s, 3 H, 10-H), 4.18 (q, 2 H, CH$_3$C*H*$_2$), 5.93 (s, 1 H, 2-H), 6.65 (d, 1 H, $J_{4,5}$ = 15.6 Hz, 4-H), 6.92−6.99 (m, 2 H, 5-H and 6-H), 9.48 (s, 1 H, C*H*O). − ^{13}C NMR: δ = 9.7 (C-9), 13.7 (C-10), 14.2(*C*H$_3$CH$_2$), 60.1 (CH$_3$*C*H$_2$), 123.3 (C-2), 128.3 (C-5), 139.9 (C-7), 143.6 (C-4), 147.9 (C-6), 150.5 (C-3), 166.4 (C-1), 194.7 (C-8). − ^{1}H NMR [(2*Z*)]: δ = 1.28 (t, 3 H, C*H*$_3$CH$_2$), 1.90 (s, 3 H, 9-H), 2.09 (s, 3 H, 10-H), 4.18 (q, 2 H, CH$_3$C*H*$_2$), 5.84 (s, 1 H, 2-H), 8.16 (d, 1 H, $J_{4,5}$ = 15.6 Hz, 4-H), 6.92−6.96 (m, 2 H, H-5 and 6-H), 9.48 (s, 1 H, C*H*O). − ^{13}C NMR: δ = 9.8 (C-9), 14.2 (*C*H$_3$CH$_2$), 20.6 (C-10), 60.1 (CH$_3$*C*H$_2$), 121.1 (C-2), 129.2 (C-5), 137.3 (C-4), 139.8 (C-7), 147.1 (C-6), 149.0 (C-3), 165.8 (C-1), 194.5 (C-8).

C_{15} + C_5 Coupling

"*iso*"-Vinyl-β-ionol (4): **n**-Butyllithium (4.9 mL of a 2.5 M solution in hexane) was added at −78°C to a solution of **13** (1.28 g, 6.1 mmol) in THF (50 mL). After the solution was stirred for 15 min, a solution of "*iso*"-β-cyclogeranyl iodide (**2**) (1.45 g, 5.5 mmol) in THF (10 mL) was added. The reaction mixture was kept at −78°C for 15 h, poured in ice/water, acidified with 10% aqueous HCl and extracted with ether, followed by the standard workup. Purification by chromatography (silica gel, petroleum ether/ether, 50:50) provided C_{15} hydroxy sulfoxide **9** (1.05 g, 57% yield). A solution of **9** (660 mg, 1.91 mmol) in toluene (10 mL) was refluxed in the presence of potassium carbonate (905 mg) for 72 h. After stirring and evaporation of toluene, the mixture was purified by chromatography on deactivated alumina. Elution with petroleum ether/ether (90:10) gave **4** (350 mg, 83% yield). − IR: $\tilde{\nu}$ = 3384 cm^{-1} (OH). − ^{1}H NMR: δ = 1.02 (s, 6 H), 1.41 (s, 3 H, 6-H), 1.76 (s, 3 H, 7′-H), 5.07−5.26 (m, 2 H, C*H*$_2$=), 5.68 (m, 1 H, $J_{4,5}$ = 15.9 Hz, 4-H), 6.68 (m, 1 H, $J_{4,5}$ = 15.9 Hz, 5-H), 5.94−6.05 (m, 1 H, C*H*=). − ^{13}C NMR: δ = 13.6

(C-7′), 19.0 (C-5′), 26.6 (C-6′), 27.9 (C-8′ and C-9′), 28.3 (C-6), 35.4 (C-3′), 39.2 (C-4′), 73.6 (C-3), 111.9 (C-1), 126.5 (C-1′), 127.2 (C-5), 132.5 (C-4), 140.8 (C-2′), 144.3 (C-2). − HRMS ($C_{15}H_{24}O$): calcd. 220.1827; found 220.1824.

"*iso*"-Retinyl Acetate (5): A solution of triphenylphosphane hydrobromide (587 mg, 1.82 mmol) in methanol (5 mL) was added to "*iso*"-vinyl-β-ionol (**4**) (400 mg, 1.82 mmol) in a methanol solution (10 mL). The mixture was stirred for 48 h at room temp., concentrated under vacuo and washed with ether to afford the phosphonium salt **10** (950 mg, 99% yield). Sodium ethoxide (88 mg, 1.14 mmol) in ethanol (2 mL), was added at −15°C to a solution of **10** (725 mg, 1.14 mmol) in dry ethanol (10 mL). After the mixture was stirred for 15 min at this temp., it was treated with the aldehyde acetate **17** (263 mg, 1.85 mmol). The resultant reaction was kept at −15°C for 1 additional h. The reaction mixture was allowed to warm to ambient temp. and hydrolyzed. Extraction with ether was followed by a standard workup. Further purification of the residue by chromatography (silica gel, petroleum ether/ether, 95:5) gave a 50:50 mixture [(4*E*)/(4*Z*)] of **5** (260 mg, 69% yield). − ^{1}H and ^{13}C NMR: see Table 1. − HRMS ($C_{22}H_{32}O_2$): calcd. 328.2402; found 328.2407.

"*iso*"-Retinal (6): Sodium ethoxide (68 mg, 1 mmol) in ethanol solution was added at 0°C to a solution of the phosphonium salt **10** (627 mg, 1 mmol) in dry ethanol (8 mL), and the mixture was stirred at −10°C for 15 min. The reaction mixture was treated with the aldehyde acetal **16** (173 mg, 1.2 mmol) at −10°C for 1 h, hydrolyzed with 10% HCl and extracted with ether. The combined organic layers were washed with satd. $NaHCO_3$, satd. NaCl, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by chromatography on silica gel, eluting with petroleum ether/ether (80:20) to give the (all-*E*) isomer of **6** (183 mg, 64% yield) which, to be stabilized, was kept in ether solution with hydroquinone (0.5 equiv.). − ^{1}H and ^{13}C NMR: see Table 2. − HRMS ($C_{20}H_{28}O$): calcd. 285.2218; found 285.2208.

C_{10} + C_{10} Coupling

Ethyl "*iso*"-Retinoate (7): A solution of triphenylphosphane (19.3 g, 73 mmol) in anhydrous ether (50 mL) was added to "*iso*"-β-cyclogeranyl iodide (**2**) (12 g, 58 mmol). After 4 h of stirring at room temp., filtration and washing with ether, the Wittig salt **8** was afforded (27.2 g, 87% yield). *n*-Butyllithium (0.35 mL of a 2.5 M solution in hexane) was added at 0°C to **8** (416 mg, 0.8 mmol) in a THF solution (20 mL). After the mixture had been stirred for 15 min, it was treated with the aldehyde ester **19** (165 mg, 0.8 mmol) in THF solution (5 mL). The resultant reaction mixture was kept 12 h at ambient temp., quenched with 10% HCl and extracted with Et_2O. The organic layers were washed with satd. $NaHCO_3$, satd. NaCl and dried ($MgSO_4$). The solvent was evaporated to give a residue which was chromatographed (silica gel, petroleum ether/ether, 92:8). The crude product was dissolved in petroleum ether (5 mL) and stirred at room temp. for 2 h with iodine (1 mg) in the dark. The reaction mixture was washed with sodium thiosulfate and dried ($MgSO_4$). The solvent was removed in vacuo to give **7** as a mixture of two major isomers: − ^{1}H NMR [(all-*E*)]: δ = 0.97 (s, 6 H), 1.21 (t, 3 H, CH_3CH$_2$), 1.41 (m, 2 H, 4′-H), 1.59 (m, 2 H, 5′-H), 1.75 (s, 3 H, 7′-H), 1.93 (s, 3 H, 11-H), 2.11 (m, 2 H, 6′-H), 2.28 (s, 3 H, 10-H), 4.09 (q, 2 H, CH$_3$CH_2), 5.69 (s, 1 H, 2-H), 5.96 (d, 1 H, 6-H), 6.08 (d, 1 H, 8-H), 6.30 (d, 1 H, 4-H), 6.73 (d, 1 H, $J_{8,9}$ = 15 Hz, 9-H), 6.92 (dd, 1 H, $J_{4,5}$ = 16 Hz, $J_{5,6}$ = 12 Hz, 5-H). − ^{1}H NMR (2*Z*): δ = 0.97 (s, 6 H), 1.21 (t, 3 H, CH_3CH$_2$), 1.41 (m, 2 H, 4′-H), 1.59 (m, 2 H, 5′-H), 1.75 (s, 3 H, 7′-H), 1.93 (s, 3 H, 11-H), 1.98 (s, 3 H, 10-H), 2.11 (m, 2 H, 6′-H), 4.09 (q, 2 H, CH$_3$CH_2−), 5.55 (s, 1 H, 2-H), 6.11 (d, 1 H, 8-H), 6.35 (d, 1 H, 6-H), 6.73 (d, 1 H, $J_{8,9}$ = 15 Hz), 6.90 (dd, 1 H, $J_{4,5}$ = 16 Hz; $J_{5,6}$ = 12 Hz, 5-H), 7.71 (d, 1 H, $J_{4,5}$ = 16 Hz, 4-H). − ^{13}C NMR [(all-*E*)]: δ = 13.1 (C-11), 13.8 (C-10), 13.9 (C-7′), 14.4 (*C*H$_3$CH$_2$−), 19.1 (C-5′), 26.5 (C-6′), 28.0 (C-8′ and C-9′), 35.8 (C-3′), 39.2 (C-4′), 59.7 (CH$_3$*C*H$_2$), 118.6 (C-2), 127.9 (C-1′), 129.1 (C-9), 130.1 (C-6), 131.0 (C-8), 131.1 (C-5), 135.1 (C-4), 140.2 (C-7), 142.3 (C-2′), 152.8 (C-3), 167.2 (*C*O$_2$Et). − ^{13}C NMR (2*Z*): δ = 13.1 (C-11), 13.9 (C-7′), 14.4 (*C*H$_3$CH$_2$), 19.1 (C-5′), 21.0 (C-10), 26.5 (C-6′), 28.0 (C-8′ and C-9′), 35.8 (C-3′), 39.2 (C-4′), 59.7 (CH$_3$*C*H$_2$), 116.5 (C-2), 128.0 (C-1′), 129.1 (C-9), 129.3 (C-4), 130.1 (C-6), 131.0 (C-8), 132.3 (C-5), 140.4 (C-4), 142.4 (C-2′), 151.1 (C-3), 166.5 (*C*O$_2$Et).

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