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Trienediolates of Hexadienoic Acids in Synthesis. Synthesis of Retinoic and nor-Retinoic Acids.

María J. Aurell, Ismael Carne, José E. Clar, Salvador Gil, Ramon Mestres*, Margarita Parra, and Amparo Tortajada.

Departament de Química Orgànica, Universitat de València, Burjassot, València, Spain.

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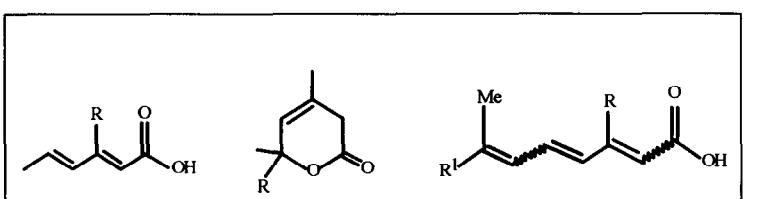
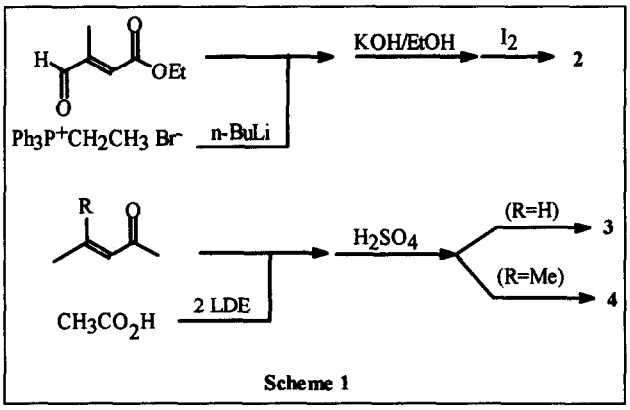
Abstract: Double deprotonation of either (*E,E*)-3-methyl-2,4-hexadienoic acid **2**, or 4,6-dimethyldihydro-2-pyrone **3** generates apparently the same lithium trienediolate, which affords ω-hydroxy acids **9** on reaction with ketones **7**. Hydroxy acids **9** are easily dehydrated to octatrienoic acids **5**, which are structurally related to retinoic acid. Similarly, sorbic acid **1** leads to nor-retinoic acid analogs **6**.

Synthetic utility of π delocalized carbanionic reagents mostly depends on the selectivity of their reactions with electrophiles. The trienediolate of sorbic acid **1** parallels the behaviour of the dienediolates of crotonic acid and other methyl substituted butenoic acids, and reacts with aldehydes and ketones at the α carbon atom at low temperature, but leads to all-*E* ω-adducts under equilibration conditions [1]. We were interested to find out whether 3-methylhexadienoic acid **2** could behave as a d^6 synthon as well. More particularly, we wanted to explore now the possibility of achieving a simple entry to retinoic and nor-retinoic acids, and to their analogs 7-aryloctatrienoic acids **5** and **6**, by reaction of 3-methyl-sorbic acid **2** and sorbic acid **1** with ketones [2]. In the course of the study we found 4,6-dimethyl-3,4-dihydropyrone **3** practically equivalent to 3-methylhexadienoic acid **2** for generation of the trienediolate, and most of the syntheses have been carried out with lactone **3**. Part of the present results have already been reported in a short com-munication [3], whereas application of the present method to the synthesis of retinoic acid from β-ionone and of an aryl retinoic acid from 4-(4-methoxy-2,3,6-trimethylphenyl)-but-3-enone, has been described elsewhere [4,5].



1: R = H **3**: R = H **5**: R = Me
2: R = Me **4**: R = Me **6**: R = H

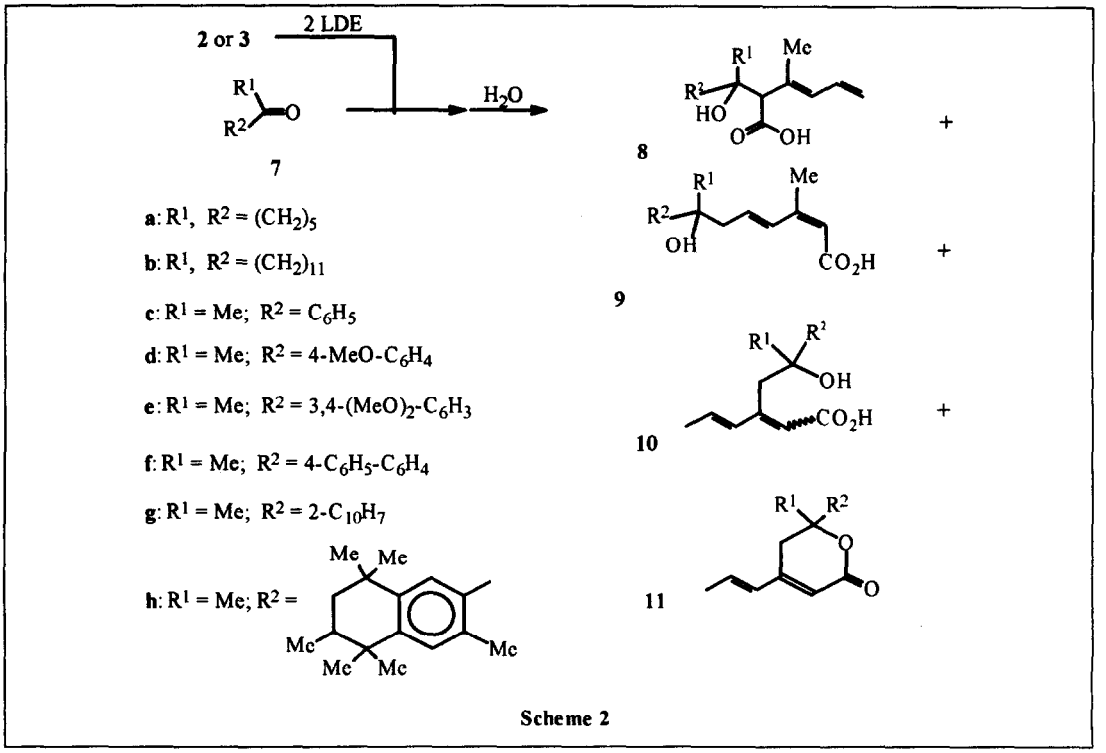
The (*E,E*)-3-methylhexadienoic acid **2** was easily prepared by a three step sequence (Scheme 1). Wittig reaction of the commercially available ethyl (*E*)-3-methyl-4-oxo-2-butenoate with ethyltriphenylphosphonium bromide, and alkaline saponification of the resulting ester gave a 2*E*,4*Z*/2*E*,4*E* mixture of 2-methylhexadienoic acid. Double bond isomerization with iodine led to the *E,E* acid, as its ^{1}H NMR spectrum clearly showed. Although a low yield (32%) was obtained for the whole sequence, this non optimized procedure resulted more convenient than previously described methods [6 to 10].



Scheme 1

Addition of acetic acid lithium enediolate to 3-penten-2-one, and treatment of the intermediate hydroxy acid with cold concentrated sulfuric acid gave crude 4,6-dimethyl-3,4-dihydropyrone **3** [11,12] in 72% yield (Scheme 1). This crude material is in fact a 75/25 to 70/30 mixture of dimethyl lactone **3** and the lactone **4** derived from the mesityl oxide present in commercial 3-penten-2-one. This material was used without further purification. The smaller amounts of adducts derived from lactone **4** were hardly observed in the mixtures, and easily removed chromatographically. Resolution of either the commercial mixture of pentenone and mesityl oxide, the intermediate hydroxy acids or the lactones required chromatographic methods, and no substantial difference was observed (^{1}H NMR and TLC) between the crude mixtures obtained from either crude or pure samples of dihydropyrone **3** on reaction with ketone **7d**.

The regioselectivity of the reactions of (*E,E*)-3-methylhexa-2,4-dienoic acid **2** and lactone **3** with a variety of ketones **7** was first studied (Scheme 2). Kinetic and equilibration selectivity trends found now parallel those observed for sorbic acid; namely, α-attack at -70°C, and ω-attack at room temperature (^{1}H NMR spectra of aliquots).



Scheme 2

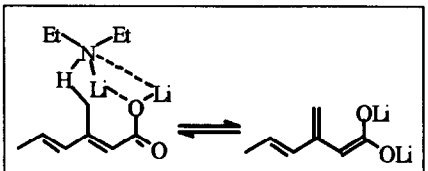
Table I. Reaction of 3-Methylhexadienoic Acid 2 and Dihydro-2-Pyrone 3 with Carbonyl Compounds.

Acid or Lactone	Carbonyl Compound	Reaction Time (h)[a]	Crude Yields(%)	Product Yields (%)[b] 8	9	10
2	**7a**	24	96	3	40	15[e]
	7b	72	85	-	31[c]	-
	7c	24	88	3	51	4
	7g	2	90	-	45	12
3	**7d**	2	84	-	43[d]	-
	7e	2	93 (46)	-	46[d]	-
	7f	2	83 (42)	-	42[d]	-
	7g	2	71	-	34[d]	-

a.- At room temperature; **b**.- Isolated chromatographically as ester; **c**.- Isolated by crystallization as acid; **d**.- Isolated chromatographically as acid; **e**.- Isolated as lactone **11**.

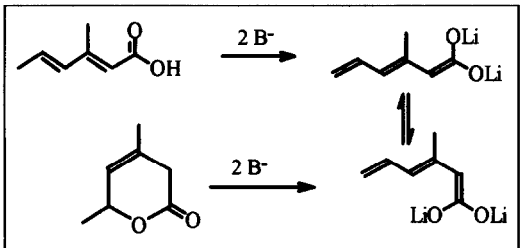
Yields for compounds isolated chromatographically or by crystallization are given in Table I. Hydroxy acids **9** were obtained chromatographically and spectroscopically above 95% pure, but good analyses were attained only for a limited number of them. Whenever comparable, the *E,E* dienoic acid **2** and the dimethyldihydropyrone **3** lead to roughly the same crude mixtures. Although the lactone affords lower crude yields than acid **2** for addition to 2-acetonaphtone **7g**, the resulting mixture is simpler, and isolation of the pure ω -adducts becomes easier for this and for other ketones. The higher complexity of additions of acid **2** to ketones is most probably due to occurrence of deprotonation at the substituent methyl group of the polyenic acid, in keeping with the carboxylate group assistance observed by Weiler in the deprotonation of the cis methyl group of dimethylacrylic acid lithium salt [13]. Such assistance would be possible here for the lithium salt of acid **2** (Scheme 3), but not for either lactone **3** or the likely intermediate lithium salt of the 2*Z* hexadienoic acid. Thus, hydroxy acids **10** or lactones **11** are generally observed (^{1}H NMR) as minor components in mixtures of adducts obtained from acid **2**, but not from lactone **3**.

The present ω-additions to ketones **7** lead to the same 2*Z*,4*E* stereoisomer for either acid **2** or lactone **3** as precursor of the trienediolate. Configurations for all isolated ω-adducts have been established through known chemical shift correlations, coupling constants, or by NOE experiments, and no other isomers have been observed in the crude mixtures (^{1}H NMR). It should be pointed out however, that stereoisomeric 2*Z*/2*E* mixtures were observed in some experiments with benzophenone as substrate. It is remarkable that 2*Z*,4*E* acids are obtained from the *E,E* acid **2**, as the present stereoselectivity no longer parallels that previously found for sorbic acid, which leads to 2*E*,4*E* ω-adducts [1]. For butenoic acids, a 2*E* to 2*Z* stereoselectivity change is observed as well when



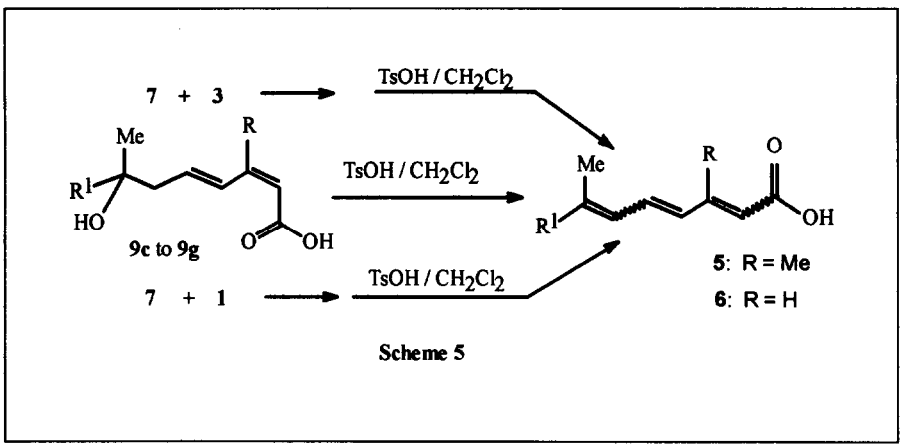
Scheme 3

similar γ-adducts of crotonic and dimethylacrylic acids are compared [14]. The 2*Z* selectivities observed for methyl substituted polyenediolates are most probably due to the relative stabilities of 2,3-s-cis and s-trans conformers, along with a low barrier for rotation around the 2,3 C-C bond of the dianion, and thus either acid **2** or lactone **3** should lead to the same trienediolate on deprotonation (Scheme 4).



Scheme 4

Dehydration of crudes of addition of dihydropyrone **3** to methyl ketones **7d** to **7g**, or of isolated hydroxy acid **9g** by *p*-toluenesulfonic acid in dichloromethane led to 3-methyl-7-aryl-octatrienoic acids **5** (Scheme 5), which were obtained as 2*E*/2*Z* stereoisomeric mixtures (Table II).



Scheme 5

The course of the dehydration could be easily followed by a strong colour change of the reacting solution, and low 2*E*/2*Z* ratios were obtained by allowing short reaction times, but in no case stereoisomeric mixtures could be completely avoided. Attempts for attaining 2*E* compounds by prolonged acid treatment failed as well, due to occurrence of other side conversions. Crystallization of the isomeric mixtures gave the 2*Z* isomers for acids **5d** and **5g** and the 2*E* isomer for acid **5e**. The single isomers thus isolated enabled assignment of signals for both *E* and *Z* isomers for each acid **5** (Table III). The *E* configuration of the newly

Table II. Retinoic Acids 5 from Dihydropyrone 3 and Ketones 7

Ketone	yield(%)	Single Isolated acid
7d	70.5 (17.5)[a]	2*Z*
7e	41 [b]	2*E*
7f	41.6	-
7g	32 (22.5)	2*Z*

In parenthesis, yield for 2*E*/2*Z* mixture; **a**.- Purified chromatographically; **b**.- Obtained hydroxy acid 9 was purified before dehydration.

formed double bond at C-6 for all 7-aryl-octatrienoic acids was established through NOE experiments, whereas the *E* configuration at C-4 became evident from the coupling constants.

Table III. ^{1}H NMR of Retinoic Acids 5

Acid	Chemical Shifts[c,d]						Coupling Constants	
	H-2	**H-4**	**H-5**	**H-6**	**H-8**	**3-CH_3**	**$J_{4,5}$**	**$J_{5,6}$**
2E,4E,6E								
5a[a]	5.81	6.37	7.05	6.50	2.11	2.37	14.1	9.9
5e[b]	5.83	6.40	7.15-6.98	6.54	2.23	2.37	14.8	11.0
5f[a]	5.82	6.40	7.02	6.65	1.98	2.28	15.9	10.1
2Z,4E,6E								
5d[a]	5.67	7.87	7.03	6.66	2.21	2.07	14.1	9.9
5e[b]	5.69	7.82	7.15-6.98	6.65	2.23	2.13	15.3	11.4
5f[a]	5.68	7.88	7.02	6.78	2.30	2.10	15.9	11.0
5g[b]	5.72	7.95	7.14	6.90	2.40	2.20	15.5	12.1

a.- As methyl esters. CH_3OCO at δ 3.70; **b**.- As acids; **c**.- CH_3OAr at δ 3.80 for **5d** and 3.90 and 3.91 for **5e**; **d**.- Aromatic signals between δ 6.60 and 8.20.

Sorbic acid **1**, whose reaction with other ketones was known to give ω adducts [1], was added to aryl methyl ketones **7d** to **7h** under equilibration conditions, and the resulting crude hydroxy acids dehydrated without purification. The corresponding all-*E* nor-retinoic acids **6** were obtained now in good yields, except for ketone **7h** which afforded a moderated yield (Table IV). Configuration at C-6 for the octatrienoic acid **6g** was established by a differential NOE experiment. The all-*E* configuration for other acids **6** could be inferred from similarity of chemical shifts and coupling constants (Table V). Departure of chemical shifts of acid **6h** from those of other acids **6** is probably due to steric compression of the aromatic methyl group against the C-6 hydrogen atom which prevents coplanarity of the polyethylenic chain and the aromatic ring. MMX force field calculations (carried out with PCMODEL ver. 4.0) for conformational equilibria of either 7-phenyl- or 7-(2-naphtyl)-octatrienoic acids show a dihedral angle of 40-42° for the planes of polyenic chain and the aryl ring, whereas a dihedral angle of 67° is found for acid **6h**. The anomalous chemical shift could be assigned as well to a 6*Z* configuration. However, an exceptional dehydration leading to the 6*Z* double bond would be least likely to

Table IV. Nor-retinoic Acids Obtained from Sorbic Acid 1

Ketone	all-*E*-Octatrienoic acid **6** Isolated yield (%)[a]
7d	83 (60)
7e	84 (59)
7f	67 (60)
7g	77 (53)
7h	47.5 (13)[b]

a.- Yield for pure compound in parenthesis;
b.- Purified chromatographically as ester.

occur only for the one adduct bearing a methyl substituent, which should hinder those conformations of the C-C bond of the intermediate carbenium ion expected to lead to the 6*Z* double bond.

TABLE V. ^{1}H NMR Spectral Data of Nor-retinoic Acids 6.

Acid	Chemical Shifts (δ)						Coupling constants			
	H-2	**H-3**	**H-4**	**H-5**	**H-6**	**H-8**	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$
6d	5.87	7.48	6.41	7.01	6.52	2.21	15.1	11.4	14.5	11.4
6e	5.87	7.50	6.44	7.00	6.53	2.22	15.1	11.4	14.5	11.0
6f	5.91	7.60-7.30	6.40	7.01	6.64	2.15	15.2	11.4	14.6	11.4
6g	5.91	7.46	6.51	7.09	6.75	2.36	15.2	11.4	14.5	11.4
6h	5.78	7.20-6.80	6.20	6.63	6.20	2.10	15.3	-	-	-

As a conclusion, either 3-methylhexa-2,4-dienoic acid **2** or the dimethyldihydropyrone **3** may be very conveniently used as d^6 synthons, specially for preparation of modified retinoic acids **5** obtainable as 2*Z*/2*E* mixtures in a two step procedure. Similarly, sorbic acid **1** affords all-*E* nor-retinoic acids **6**. Better regioselectivity as d^6 synthon is achieved by dimethyldihydropyrone **3** than by 3-methylhexa-2,6-dienoic acid **2**.

EXPERIMENTAL

M.p.s were determined with a Reichert apparatus and are uncorrected. IR spectral data were obtained for liquid film or KBr discs, with a Perkin-Elmer 281 spectrophotometer. NMR spectra were recorded for $CDCl_3$ solutions, with a Bruker AC-200 spectrometer (200 MHz). For ^{1}H NMR delays between pulses were inserted in order to attain reliable integration of signals. For NOE experiments standard Brucker Aspect 3000 NOE difference routine with suitable decoupling powers was used. Elemental analyses were determined by "Servicio de Semimicroanálisis del Centro de Investigación y Desarrollo (CSIC) de Barcelona". Silica gel Merck 60 (0.06-0.20 mm) was used for column chromatography, and Silica gel Merck 60 (230-400 mesh) for flash column chromatography, in any case with elution with hexane/ether mixtures. Tetrahydrofuran (THF) was distilled from blue sodium diphenylketyl immediatelly before use. Diethylamine was dried over CaH_2 and distilled before use. Generation and reactions of the trienediolates were carried out under an argon atmosphere, using standard conditions for exclusion of moisture. The reaction temperature (-70°C) was achieved by cooling with a CO_2/acetone bath. Evaporation of solvents was carried out with a vacuum rotatory evaporator and a bath at 40°C. 3-Penten-2-one (containing up to 30% mesityl oxide) was purchased from Aldrich and distilled before use. Esterifications were performed by treatment of acids with diazomethane in ethyl ether or ethyl acetate.

(2*E*,4*E*)-3-methylhexa-2,4-dienoic acid, 2.- n-Butyllithium (80 mmol, 50 ml, 1.6 M in hexane) was concentrated and dissolved in dry ether (250 ml). Solid ethyltriphenylphosphonium (29.7 g, 80 mmol) was added portionwise for 5 min at 20°C, and the mixture stirred at room temperature for 1 h. Ethyl 3-methyl-4-oxobut-2-enoate (10.9 g, 77 mmol) in dry ether (90 ml) was added dropwise for 20 min, and the mixture stirred for 16 h and filtered. The solution was washed with water and dried, and the solvent evaporated. Distillation of the residue (42°C/3 mmHg) afforded an about 2:1 mixture of 2*E*,4*Z* and 2*E*,4*E* ethyl 3-methylhexa-2,4-dienoate (5.1 g); ν_{max} (liquid film) 1705 (C=O), 1635 and 1610 (C=C) cm^{-1}; δ_H (2*E*,4*E*) 6.2-6.0 (m, 4-H and 5-H), 5.8-5.6 (m, 2-H), 4.10 (q, J 7 Hz, $CO_2CH_2CH_3$), 2.22 (s, 3-CH_3), 1.8 (dd, J 6.9 and 1.5 Hz, 6-H), 1.22 (t, J 7 Hz, $CO_2CH_2CH_3$); δ_H (2*E*,4*Z*) 5.86 (d, J 12.1 Hz, 5-H), 5.8-5.6 (m, 2-H and 4-H), 4.11 (q, J 7 Hz, (2*E*,4*Z*) $CO_2CH_2CH_3$), 2.22 (s, 3-CH_3), 1.8 (dd, J 6.9 and 1.5 Hz, 6-H), 1.23 (t, J 7 Hz, $CO_2CH_2CH_3$).

Potasium hydroxide (4.6 g, 81.6 mmol) in 96% ethanol (100 ml) was added dropwise during 30 min to a stirred solution of the above ethyl 3-methylhexa-2,4-dienoate (4.5 g, 29 mmol) in ethanol (30 ml) in an ice-water bath. The mixture was heated at 50-60°C for 2 h and stirred at room temperature for 16 h. The solvent was partly evaporated, the residue poured into water (150 ml), and the resulting mixture washed with ethyl ether (4 X 25 ml). The aqueous layer was acidified and extracted with ethyl acetate (4 X 25 ml). Evaporation of the solvent gave a mixture of 2*E*,4*E* and 2*E*,4*Z* 3-methylhexa-2,4-dienoic and 3-methylhexa-3,5-dienoic acids obtained as a colorless oil (3.22 g).

The foregoing oil was dissolved in ether (250 ml), and iodine in benzene (0.5%, 10 ml) was added. The resulting solution was stirred for 1 h at room temperature under argon while illuminated with a 100 W standard bulb at 32 cm, and then washed with aqueous sodium thiosulphate and brine and dried. Evaporation of the solvent gave (2*E*,4*E*)-3-methylhexa-2,4-dienoic acid, **2** (3.1 g), as white crystalls, m.p. 117°C (lit.,[7] 119-120°C); ν_{max} (KBr) 3300-2800 (O-H), 1690 (C=O), 1645 and 1615 (C=C) cm^{-1}; δ_H 6.3-6.0 (2 H, m, 4-H and 5-H), 5.68 (1 H, s, 2-H), 2.25 (3 H, d, J 1.04 Hz, 3-CH_3), 1.84 (d, J 5.2 Hz, 6-H).

4,6-Dimethyl-3,6-dihydro-2H-pyran-2-one, 3.- Acetic acid (4.08 ml, 72 mmol) in THF (100 ml) was added dropwise, for 30 min, at -70°C to lithium diethylamide [from lithium (1.12 g, 160 mmol), naphtalene (10.2 g, 79.6 mmol) and diethylamine (17 ml, 160 mmol)] in THF (100 ml). After 30 min at -70°C, 3-penten-2-one (7.28 ml, 72 mmol) (containing 25% mesityl oxide) in THF (100 ml) was added dropwise over 30 min at -70°C and the mixture stirred for 1 h. The cooling bath was replaced for an ice-water bath and the mixture stirred for 1 h. Aqueous sodium hydroxide (100 ml, 1M) was added, the solvent was partially evaporated under reduced pressure, and the residue extracted with ether. The aqueous layer was cooled in an ice-water bath and acidified with stirring by slow addition of concentrated hydrochloric acid. The mixture was extracted with ether and the organic layer was dried. Evaporation of the solvent led to a mixture (about 75/25) of 3-hydroxy-3-methylhexa-4-enoic acid and 3,5-dimethyl-3-hydroxyhex-4-enoic acid as a yellow oil (7.5 g); ν_{max} (KBr) 3700-2440 (O-H), 1720 (C=O) cm^{-1};δ_H 5.73-5.4 (m, 5-H and 4-H), 2.54 (s, CH_2), 1.63 (d, J 5.7 Hz, 6-H) and 1.3 (s, CH_3).

Conc. H_2SO_4 (2.9 ml, 51.4 mmol) at 0°C was added with ice-water cooling for 10 min to the stirred foregoing oil, in an ice-bath. Ice was added to the mixture, the bath removed, the mixture stirred for other 10 min, and then extracted with ether. The combined extracts were washed with water, dried, and evaporated to give a 70/30 mixture of 4,6-dimethyl-3,6-dihydro-2H-pyran-2-one, **3** and 4,6,6-trimethyl-3,6-dihydro-2H-pyran-2-one **4** as a yellow oil (6.1 g); ν_{max} (KBr) 3600-3200 (O-H), 1730 (C=O) cm^{-1}; δ_H (4,6-dimethyl-3,6-dihydro-2H-pyran-2-one **3**) 5.5 (m, 5-H), 5.0 (m, 6-H), 2.92 (broad s, CH_2), 1.75 (s, 4-CH_3) and 1.38 (d, J 6.7 Hz, 6-CH_3) and δ_H (4,6,6-trimethyl-3,6-dihydro-2H-pyran-2-one **4**) 5.46 (1 H, s, 5-H), 2.90 (2 H, s, 3-H), 1.67 (3 H, s, 4-CH_3) and 1,40 (6 H, s, (6-CH_3)$_2$).

Column chromatography of that mixture (3.05 g) gave pure dihydropyrone **3** (1.2 g); δ_H 5.49 (1 H, m, 5-H), 4.98 (1 H, m broad, 6-H), 2.90 (2 H, m, 3-H), 1.74 (3 H, s 4-CH_3), and 1.39 (3 H, d J 8 Hz, 6-CH_3) ppm [11,12].

General Procedure for addition of acids 1 and 2 or lactone 3 to ketones 7. To Lithium diethylamide [from lithium (20 mmol), naphtalene and diethylamine (2.1 ml)] in THF (10 ml) acid **2** or lactone **3** (9 mmol) in THF (10 ml) was added dropwise for 30 min at -70°C. After 15 min the stirred solution was allowed to warm up to 0°C for 30 min, and cooled again at -70°C. The ketone (9 mmol) in THF (15 ml) was added dropwise over 20 min and the mixture stirred at the same temperature for other 30 min. The cooling bath was then removed and the solution stirred for the time stated in each case. Water (10 ml) was added, the solvent was partially

evaporated under reduced pressure, and the residue extracted with ether. The aqueous layer was acidified by slow addition of concentrated hydrochloric acid with stirring and ice-water cooling, and the hydroxy acids were either filtered off or extracted with ether. In the latter case the organic layer was dried, and the solvent evaporated.

General Procedure for dehydratation of hydroxy acids or hydroxy esters. *p*-Toluensulfonic acid (0.28 g, 1.5 mmol) and the hydroxy acid or (4,5 mmol) were heated in dichloromethane (60 ml) under reflux for the time stated in each case. The solution was then washed with water and dried, and the solvent evaporated.

Addition of (*E*,*E*)-3-methyl-2,4-hexadienoic acid 2 to cyclohexanone 7a.- When (*E*,*E*)-3-methyl-2,4-hexadienoic acid **2** (1.13 g) and cyclohexanone **7a** (0.86 ml) were allowed to react for 24 h at room temperature, a syrup (1.93 g) was obtained. Esterification and column chromatography led to isolation of fairly pure samples of each:

(3*E*)-2-(1-hydroxycyclohexyl)-3-methyl-3,5-hexadienoic acid (**8a**) methyl ester (0.08 g). ν_{max} 3600-3400 (OH), 1715 (CO_2), 990 and 910 ($CH=CH_2$) cm^{-1}. δ_H 6.58 (1 H, dt, J 16.8 and 10.6 Hz, 5-H), 6.02 (1 H, d, J 10.6 Hz, 4-H), 5.18 (1 H, dd, J 17.7 and 1.72 Hz, 6-H) 5.09 (1 H, dd, J 10.05 and 1.5, 6-H) 3.67 (3 H, s, CO_2CH_3), 3.02 (1 H, s, 2-H), 1.87 (3 H, s, 3-CH_3) and 1.8-1.1 (10 H, m, C_6H_{10}). Found: C, 66.19; H 8.53. $C_{14}H_{22}O_4$ requires: C, 66.12; H 8.72%.

4-(1-propenyl)-1-oxa-2-oxoespiro[5.5]undec-3-ene (**11a**) (0.28 g). ν_{max} 1700 (CO_2Me), 1640 ($CH=CH_2$) cm^{-1}. δ_H 6.19 (2 H, m, 1'-H and 2'-H), 5.73 (1 H, s, 3-H), 2.44 (2 H, s, 5-H), 1.87 (3 H, d, J 4.86 Hz, CH_3-2'-C) and 1.8-1.1 (10 H, m, C_6H_{10}). Found: C, 75.34; H 8.49. $C_{13}H_{18}O_2$ requires: C, 75.68; H 8.80%.

and (2*Z*,4*E*)-6-(1-hydroxycyclohexyl)-3-methyl-2,4-hexa-dienoic acid (**9a**) methyl ester (0.87 g) as a colourless oil. ν_{max} 3600-3300 (OH), 1700 (CO_2), 1635 and 1605 ($CH=CH_2$) cm^{-1}. δ_H 7.57 (1 H, d, J 14.6 Hz, 4-H), 6.2 (1 H, dt, J 14.5 and 7.3 Hz, 5-H), 5.6 (1 H, s, 2-H), 3.66 (3 H, s, CO_2CH_3), 2.35 (2 H, dd, J 7.3 and 0.91 Hz, 6-H), 1.98 (3 H, s, 3-CH_3) and 1.8-1.1 (10 H, m, C_6H_{10}). Found: C, 66.23; H 8.59. $C_{14}H_{22}O_4$ requires: C, 66.12; H 8.72%.

Addition of (*E*,*E*)-3-methyl-2,4-hexadienoic acid 2 to cyclododecanone 7b.- When (*E*,*E*)-3-methyl-2,4-hexadienoic acid **2** (1.13 g) and cyclododecanone **7b** (1.64 g) were allowed to react for 72 h at room temperature, a syrup (2.37 g) was obtained, which crystallized from diethyl ether to afford (2*Z*,4*E*)-6-(1-hydroxycyclododecyl)-3-methyl-2,4-hexadienoic acid (**9b**) (0.86 g) as white prisms, m.p. 156-158°C. ν_{max} 3600-3200 (OH), 1710 (CO_2), 1640 and 1600 (C=C) cm^{-1}.δ_H 7.56 (1 H, d, J 15.88 Hz, 4-H), 6.30 (1 H, dt, J 15.86 and 7.5 Hz, 5-H), 5.64 (1 H, s, 2-H), 2.32 (2 H, d, J 7.5 Hz, 6-H), 2.04 (3 H, d, J 0.85 Hz, 3-CH_3) and 1.6-1.1 (22 H, br s, $C_{12}H_{22}$). Found: C, 73.70; H 10.50. $C_{19}H_{32}O_3$ requires: C, 73.98; H 10.45%.

Addition of (*E*,*E*)-3-Methyl-2,4-hexadienoic acid 2 to acetophenone 7c.- (*E*,*E*)-3-Methyl-2,4-hexadienoic acid **2** (1.13 g) and acetophenone **7c** (1.09 g) were allowed to react according to the general method. After 1/2 h at -70°C and 24 h at room temperature, and usual work-up, led to a yellow oil (1.95 g). Esterification and column chromatography allowed isolation of:

(3*E*)-2-(1-phenyl-1-hydroxyethyl)-3-methyl-3,5-hexadienoic acid (**8c**) methyl ester (0.08 g) as a white oil. ν_{max} 3600-3400 (OH), 1710 (C=O), 750 and 690 (Ph) cm^{-1}. δ_H 7.5-7.0 (5 H, m, Ph), 6.64 (1 H, dt, J 16.7 and 10.5 Hz, 5-H), 6.16 (1 H, d, J 11 Hz, 4-H), 5.25 (1 H, dd, J 16.5 and 1.6 Hz, 6-H), 5.16 (1 H, dd, J 10.9 and 1.5 Hz, 6-H), 3.58 and 3.73 (2 H, 2s, 1'-H and OH), 3.46 (3 H, s, CO_2CH_3), 1.96 (3 H, s, 3-CH_3) and 1.37 (3 H, s, 2'-H). Found: C, 73.25; H 7.17. $C_{16}H_{20}O_3$ requires: C, 73.81; H 7.75%.

(*E,E*)-3-(2-phenyl-2-hydroxypropyl)-hexa-2,4-dienoic acid (**10c**) methyl ester (0.10 g) as an oil. ν_{max} 3600-3300 (OH), 1680 (C=O), 1630 and 1600 (C=C), 760 and 690 (Ph) cm^{-1}. δ_H 7.5-7.1 (5 H, m, Ph), 5.93 (2 H, m, 4-H and 5-H), 5.54 (1 H, s, 2-H), 3.71 (3 H, s, CO_2CH_3), 3.12 (2 H, m, 1'-H), 1.68 (3 H, d, J 5.4 Hz, 6-H) and 1.54 (3 H, s, 3'-H). Found: C, 74.12; H 7.82. $C_{16}H_{20}O_3$ requires: C, 73.81; H 7.75%.

and (2*Z*,4*E*)-7-phenyl-7-hydroxy-3-methylocta-2,4-dienoic acid (**9c**) methyl ester (1.19 g) as an oil. ν_{max} 3600-3200 (OH), 1680 (C=O), 1630 and 1590 (C=C), 760 and 690 (Ph) cm^{-1}; δ_H 7.60 (1 H, d, J 15.6 Hz, 4-H), 7.5-7.1 (5 H, m, Ph), 5.93 (1 H, dt, J 15.8 and 7.7 Hz, 5-H), 5.60 (1 H, s, 2-H), 3.67 (3 H, s, CO_2CH_3), 2.8-2.6 (2 H, m, 6-H), 1.88 (3 H, s, 3-CH_3) and 1.55 (3 H, s, 8-H). Found: C, 73.60; H 7.50. $C_{16}H_{20}O_3$ requires: C, 73.81; H 7.75%.

Addition of (*E,E*)-3-methyl-hexa-2,4-dienoic acid 2 to 2-acetonaphtone 7g.- The reaction of acid **2** (1.13 g) and 2-acetonaphtone **7g** (1.53 g) for 0.5 h at -70°C and 2 h at 25°C as usual led to a syrup (2.39 g) which was esterified. Column chromatography led to isolation of:

(2*E*,4*E*)-3-(2-hydroxy-2-naphtylpropyl)-2,4-hexadienoic acid (**10g**) methyl ester (0.35 g) as an oil; ν_{max} 3600-3300 (OH), 1685 (C=O), 1630 and 1600 (C=C), 820 and 745 (naphtyl) cm^{-1}; δ_H 7.81-7.4 (7 H, m, C_8H_7), 5.94 (2 H, m, 4-H and 5-H), 4.84 (1 H, s, 2-H), 3.72 (3 H, s, CO_2CH_3), 3.32 (1 H, d, J 13.32 Hz, 1'-H), 3.18 (1 H, d, J 13.24 Hz, 1'-H), 1.63 (3 H, s, 3'-H) and 1.57 (3 H, s, 6-CH_3).

(2*E*,4*E*)-7-hydroxy-3-methyl-7-naphtyl-2,4-octadienoic acid (**9g**) methyl ester (1.27 g); ν_{max} 3600-3200 (OH), 1700 (C=O), 1630 and 1600 (C=C), 820 and 745 (naphtyl) cm^{-1}; δ_H 7.6 (1 H, d, J 14.9 Hz, 4-H), 8-7.3 (7 H, m, C_8H_7), 5.93 (1 H, ddd, J 15.6, 8.4 and 7 Hz, 5-H), 5.6 (1 H, s, 2-H), 3.7 (3 H, s, CO_2CH_3), 2.89 (1 H, dd, J 14.3 and 7 Hz, 6-H), 2.74 (1 H, dd, J 14.2 and 8.2 Hz, 6-H), 2.1 (1 H, s, OH), 1.84 (3 H, s, 3-CH_3) and 1.64 (3 H, s, 8-H). Found: C, 77.78, H 7.45. $C_{20}H_{22}O_3$ requires C, 77.39 and H, 7.14%.

Reaction of 4,6-Dimethyl-3,6-dihydropyran-2-one 3 with 4-methoxyacetophenone 7d.- 4,6-Dimethyl-3,6-dihydropyran-2-one **3** (1.13 g, 9 mmol) and 4-methoxyacetophenone **7d** (1.35 g, 9 mmol) as usual for 2 h at 25°C led to a crude hydroxy acid as a yellow waxy material (2.09 g). Column chromatography led to isolation of (2*Z*,4*E*)-7-(4-methoxyphenyl)-7-hydroxy-3-methylocta-2,4-dienoic acid **9d** as a yellow solid (1.07 g), m.p. 154-155°C; ν_{max} 3600-2800 (OH), 1680 (C=O) and 1600 (C=C) cm^{-1}; δ_H 7.51 (1 H, d, J 15.7 Hz, 4-H), 7.33-6.79 (4 H, m, Ar-H), 6.10 (1 H, m, 5-H), 5.57 (1 H, s, 2-H), 3.80 (3 H, s, OCH_3), 2.70 (1 H, d, J 6.8 Hz, 6-H), 2.62 (1 H, d, J 8.2 Hz, 6-H), 1.95 (3 H, s, 3-CH_3) and 1.80 (3 H, s, 8-H).

(2*Z*,4*E*,6*E*) 3-methyl-7-(4-methoxyphenyl)-octa-2,4,6-trienoic acid 5d.- 4,6-Dimethyl-3,6-dihydropyran-2-one **3** (1.13 g, 9 mmol) and 4-methoxyacetophenone **7d** (1.35 g, 9 mmol) as above led to a crude hydroxyacid that was dehydrated for 15 min at room temperature with *p*-toluensulfonic acid (0.25 equivalents) in dichloromethane to give a yellow solid material (1.64 g). Column chromatography led to isolation of (2*E*/2*Z*,4*E*,6*E*) 3-methyl-7-(4-methoxyphenyl)-octa-2,4,6-trienoic acid **5d** (410 mg) as a solid, which on crystallization from hexane-ether gave yelow prisms of (2*Z*,4*E*,6*E*)-3-methyl-7-(4-methoxyphenyl)-octa-2,4,6-trienoic acid, m.p. 173-174°C; ν_{max} 3600-2500 (OH), 1700 (C=O) and 1610 (C=C) cm^{-1}. NOE: Irradiation at 2.13 ppm (3-CH_3) enhanced the signals at 5.68 (2-H) and 7.06 (5-H) ppm; irradiation at 2.24 ppm (8-H) enhanced the signals at 7.06 ppm (5-H) and the signals of aromatic protons. $\delta 13_C$ 171.61, 159.40, 153.73, 140.32, 134.76, 133.39, 129.15, 126.95, 125.81, 115.67, 113.74, 55.29, 21.21, 16.19. Found: C, 74.36; H, 7.17. $C_{16}H_{18}O_3$ requires C, 74.40 and H, 7.02%.

Reaction of 4,6-Dimethyl-3,6-dihydropyran-2-one 3 with 3,4-dimethoxyacetophenone 7e.- 4,6-Dimethyl-3,6-dihydropyran-2-one **3** (1.13 g, 9 mmol) and 3,4-dimethoxyacetophenone **7e** (1.62 g, 9 mmol) for 2 h at 25°C led to crude hydroxy acid as a yellow oil (2.56 g). Column chromatography led to isolation of (2*Z*,4*E*)-

7-(3,4-dimethoxyphenyl)-7-hydroxy-3-metylocta-2,4-dienoic acid **9e** as a yellow solid (1.27 g), m.p. 124-125°C; ν_{max} 3600-2600 (OH), 1680 (C=O) and 1600 (C=C) cm^{-1}; δ_H 7.56 (1 H, d, J 15.9 Hz, 4-H), 7.25-6.80 (3 H, m, Ar-H), 6.01 (1 H, m, 5-H), 5.62 (1 H, s, 2-H), 3.71 (3 H, s, OCH_3), 3.66 (3 H, s, OCH_3), 2.73 (1 H, dd, J 14.0 and 6.9 Hz, 6-H), 2.68 (1 H, dd, J 14.1 and 8.1 Hz, 6-H), 1.9 (3 H, s, 3-CH_3) and 1.52 (3 H, s, 8-H).

(2*E*/2*Z*,4*E*,6*E*)-7-(3,4-dimethoxy-phenyl)-3-methylocta-2,4,6-trienoic acid 5e.- 4,6-Dimethyl-3,6-dihydropyran-2-one **3** (1.13 g, 9 mmol) and 3,4-dimethoxyacetophenone **7e** (1.62 g, 9 mmol) as above gave a crude hydroxy acid, which was dehydrated according to the general method for 15 min to give (2*E*/2*Z*,4*E*,6*E*)-7-(3,4-dimethoxyphenyl)-3-methylocta-2,4,6-trienoic acid **5e** (1.07 g) which on crystallization from hexane-ether gave (2*E*,4*E*,6*E*)-7-(3,4-dimethoxyphenyl)-3-methylocta-2,4,6-trienoic acid as yellow crystals, m.p. 176-178°C; ν_{max} 3600-2600 (OH), 1670 (C=O) and 1600 and 1580 (C=C) cm^{-1}. NOE: Irradiation at 7.10 ppm (5-H, 2'-H and 6'-H) enhanced the signals of 4-H and those corresponding to both methyl and methoxyl groups. NOE: Irradiation at 2.23 ppm (8-H) enhanced the signal at 7.15-6.98 ppm (5-H and aromatic protons); δ_{13C} 170.62, 155.22, 149.08, 148.74, 140.43, 136.61, 135.27, 135.20, 132.05, 125.37, 118.54, 117.31, 110.89, 108.88, 55.93, 16.47, 14.05. Found: C, 70.98, H 7.10. $C_{17}H_{20}O_4$ requires C, 70.81 and H, 6.99%.

(2*Z*,4*E*)-7-(4-biphenyl)-7-hydroxy-3-methylocta-2,4-dienoic acid 9f.- 4,6-Dimethyl-3,6-dihydropyran-2-one **3** (1.13 g, 9 mmol) and 4-phenylacetophenone **7f** (1.75 g, 9 mmol) as usual for 2 h at 25°C led to a crude hydroxy acid as a yellow oil (2.41 g). Column chromatography led to isolation of (2*Z*,4*E*)-7-(4-biphenyl)-7-hydroxy-3-metylocta-2,4-dienoic acid **9f** as white prisms (1.22 g), m.p. 163-164°C; ν_{max} 3500-2300 (OH), 1660 (C=O), 1590 (C=C), 760 and 690 (Ph) cm^{-1}. δ_H (methyl ester) 7.65-7.25 (10 H, m, Ar-H and 4-H), 5.99 (1 H, m, 5-H), 5.62 (1 H, s, 2-H), 3.69 (3 H, s, CO_2CH_3), 2.78 (1 H, dd, J 14.0 and 6.7 Hz, 6-H), 2.72 (1 H, dd, J 14.0 and 8.2 Hz, 6-H), 1.92 (3 H, s, 3-CH_3), and 1.63 (3 H, s, 8-H).

(2*E*/2*Z*,4*E*,6*E*)-7-biphenyl-3-methylocta-2,4,6-trienoic acid 5f.- 4,6-Dimethyl-3,6-dihydropyran-2-one **3** (1.13 g, 9 mmol) and 4-phenylacetophenone **7f** (1.75 g, 9 mmol) as above gave a crude hydroxy acid, which was dehydrated according to the general procedure for 15 min to give (2*E*/2*Z*,4*E*,6*E*)-7-(4-biphenyl)-3-methylocta-2,4,6-trienoic acid **5f** (1.14 g) as yellow solid; ν_{max} 3300-2800 (OH), 1680 (C=O) 1600 and 1580 (C=C), 760 and 690 (Ph) cm^{-1}; NOE: Irradiation at 6.78 ppm (6-H), enhanced only the signal at 7.88 ppm (4-H) and the signals of aromatic protons. Found: C, 82.67; H, 6.68. $C_{21}H_{20}O_2$ requires C, 82.72 and H, 6.26%)

Reaction of 4,6-Dimethyl-3,6-dihydropyran-2-one 3 with 2-acetonaphtone 7g.- 4,6-Dimethyl-3,6-dihydropyran-2-one **3** (0.63 g; 5 mmol) and 2-acetonaphtone **7g** (0.85 g; 5 mmol), for 2 h at 25°, led to an orange oil (1.05 g). Column chromatography of the crude product gave pure (2*E*,4*E*)-7-hydroxy-3-methyl-7-(2-naphtyl)-2,4-octadienoic acid (**9g**) (0.50 g) as an orange oil; ν_{max} 3600-2800 (OH), 1700 (C=O), 1670 and 1600 (C=C), 815 and 745 (naphtyl) cm^{-1}. δ_H 7.90-7.40 (7 H, m, naphtyl), 7.62 (1 H, d, J 16.0 Hz, 4-H), 6.00 (1 H, m, 5-H), 5.63 (1 H, s, 2-H), 2.87 (1 H, d, J 6.5, 6-H), 2.80 (1 H, dd, J 8.2 Hz, 6-H), 1.87 (3 H, s, 3-CH_3) and 1.66 (3 H, s, 8-H).

(2*Z*,4*E*,6*E*)-3-methyl-7-(2-naphtyl-)-2,4,6-octa-trienoic acid 5g.- (2*E*,4*E*)-7-hydroxy-3-methyl-7-(2-naphtyl)-2,4-octadienoic acid **9g** (0.50 g) was dehydrated according to the general method for 15 min to give (2*E*/2*Z*,4*E*,6*E*)-3-methyl-7-(2-naphtyl)-2,4,6-octatrienoic acid (**5g**) (0.45 g) which on crystallization from methanol gave (2*Z*,4*E*,6*E*)-3-methyl-7-(2-naphtyl)-2,4,6-octatrienoic acid (**5g**) as yellow prisms (0.31 g), m.p. 207-209°C; ν_{max} 3500-2500 (OH), 1670 (C=O), 1590 (C=C), 815 and 745 (naphtyl) cm^{-1}; NOE: Irradiation at 2.12 ppm (3-CH_3) enhanced only the signals at 5.69 ppm (2-H) and at 7.14 ppm (5-H). Found: C, 81.75; H, 6.63. $C_{19}H_{18}O_2$ requires C, 81.98 and H, 6.52%.

Methyl ester $\delta 13_C$ 169.96, 153.49, 140.51, 139.47, 133.37, 133.09, 132.98, 130.08, 128.28, 127.86, 127.47, 126.24, 126.04, 124.81, 123.84, 115.78, 21.19, 16.27.

(2*E*,4*E*,6*E*)-7-(4-methoxyphenyl)-octa-2,4,6-trienoic acid 6d.- Addition of (2*E*,4*E*)-hexadienoic acid **1** (1.01 g, 9 mmol) to 4-methoxyacetophenone **7d** (1.35 g, 9 mmol) by the general procedure at room temperature for 2 h led to a yellow oil (2.03 g). This was dehydrated with *p*-toluensulfonic acid (0.98 g; 5.2 mmol) in CH_2Cl_2 (200 ml) for 20 min, and (2*E*,4*E*,6*E*)-7-(4-methoxyphenyl)-octa-2,4,6-trienoic acid **6d** was obtained (1.83 g) that crystallized (1.32 g) from hexane-ether as yellow prisms, m.p. 208°C; ν_{max} 3400-2500 (OH), 1720 (C=O), 1590 (C=C) cm^{-1}; λ_{max} (log ε) 353.5 (2.375), and 265.3 (2.422) nm. Found: C, 73.83; H, 6.64. $C_{15}H_{16}O_3$ requires C, 73.75 and H, 6.60%.

Methyl ester $\delta 13_C$ 167.62, 159.49, 145.17, 140.81, 137.66, 134.59, 129.43, 126.90, 119.30, 113.76, 56.25, 51.39 and 16.16.

(2*E*,4*E*,6*E*)-7-(3,4-dimethoxyphenyl)-octa-2,4,6-trienoic acid 6e.- Addition of sorbic acid **1** (1.01 g, 9 mmol) to 3,4-dimethoxyacetophenone **7e** (1.62 g, 9 mmol) by the general procedure, at room temperature for 2 h led to a yellow oil (2.14 g). This was dehydrated with *p*-toluensoulfonic acid (0.93 g, 4.9 mmol) in CH_2Cl_2 (200 ml) for 20 min as usual. Evaporation of the solvent gave crude (2*E*,4*E*,6*E*)-7-(3,4-dimethoxy-phenyl)-octa-2,4,6-trienoic acid **6e** (2.07 g), which crystallized from hexane-ether as yellow prisms (1.45 g), m.p. 125-126°C; ν_{max} 3500-2600 (OH), 1695 (C=O), 1640 (C=C) cm^{-1}. NOE: Irradiation at 2.22 ppm (8-H) enhances the signals correponding at 7.00 (5-H) and at 6.70 ppm (2'-H). $\delta 13_C$ 172.08, 149.32, 148.80, 147.25, 141.64, 138.57, 135.04, 129.43, , 125.01, 118.82, 118.72, 110.96, 109.00, 55.95 and 16.40. Found: C, 70.01; H, 6.70. $C_{16}H_{18}O_4$ requires C, 70.60 and H, 6.61%.

(2*E*,4*E*,6*E*)-7-biphenyl-octa-2,4,6-trienoic acid 6f.- Addition of sorbic acid **1** (1.01 g, 9 mmol) to 4-phenylacetonaphtone **7f** (1.75 g, 9 mmol) by the general procedure, at room temperature for 2 h, led to a yellow oil (1.89 g) which was dehydrated with *p*-toluensulfonic acid (780 mg, 4.10 mmol) in CH_2Cl_2 (200 ml) for 20 min as usual, to give (2*E*,4*E*,6*E*)-7-biphenyl-octa-2,4,6-trienoic acid **6f** (1.76 g) which crystallized from ethyl acetate as orange prisms (1.56 g), m.p. 220-222°C; ν_{max} 3600-2600 (OH), 1700 (C=O), 1600 (C=C), 760 and 690 (Ph) cm^{-1}; Methyl ester ^{13}C-NMR δ 167.62, 145.02, 137.39, 130.35, 128.81, 127.43, 127.06, 126.93, 126.28, 126.16, 119.90, 51.52, 29.69, 16.21. Found: C, 82.53; H, 6.36. $C_{20}H_{18}O_2$ requires C, 82.73 and H, 6.25%.

(2*E*,4*E*,6*E*)-7-(2-naphtyl)-octa-2,4,6-trienoic acid 6g.- Addition of sorbic acid **1** (1.01 g, 9 mmol) and acetonaphtone **7g** (1.53 g, 9 mmol) at 25°C for 2 h according to the general method led to a yellow oil (2.18 g) which was dehydrated with *p*-toluensulfonic acid (0.94 g) in CH_2Cl_2 (200 ml) for 20 min as usual. A pale yellow solid (1.83 g) was obtained which crystallized from methanol to give yellow prisms of (2*E*,4*E*,6*E*)-7-(2-naphtyl)-octa-2,4,6-trienoic acid **6g**, m.p. 214-215°C; ν_{max} 3600-2800 (OH), 1670 (C=O), 1595 (C=C), 850 and 760 (naphtyl) cm^{-1}. NOE: Irradiation at 2.36 ppm (8-H) enhances the signal at 7.09 ppm (5-H) and the signals of aromatic protons. Found: C, 81.79; H, 5.99. $C_{18}H_{16}O_2$ requires C, 81.79 and H, 6.10.

Methyl ester $\delta 13_C$ 167.53, 144.94, 140.98, 139.31, 137.32, 133.31, 132.91, 130.42, 128.23, 127.86, 127.46, 126.77, 126.27, 126.10, 124.86, 123.66, 119.93, 51.45 and 16.20.

Methyl (2*E*,4*E*,6*Z*)-7-{7-(1,1,3,4,4,6-hexamethyl-tetra-linyl)}-octa-2,4,6-trienoate 6h.- Addition of sorbic acid **1** (1.01 g, 9 mmol) to 7-acetyl-1,1,3,4,4,6-hexamethyltetraline **7h** (2.33 g, 9 mmol) by the general procedure, at room temperature for 2 h, led to a yellow oil (1.73 g) which was dehydrated with *p*-toluensulfonic acid (0.59 g, 3.11 mmol) in CH_2Cl_2 (125 ml) for 20 min as usual. Evaporation of the solvent led to a yellow oil

(1.50 g) that was esterified and purified by column chromatography to give methyl (2*E*,4*E*,6*E*)-7-{7-(1,1,3,4,4,6-hexamethyltetralinyl)}-octa-2,4,6-trienoate **6h** (0.43 g); ν_{max} 2980 and 2930 (C-H), 1730 (C=O), 1615 (C=C) and 1440 (C-H) cm^{-1}.

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