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Trienediolates of Hexadienoic Acids in Synthesis. Addition to Unsaturated Ketones. A Convergent Approach to the Synthesis of Retinoic Acids.

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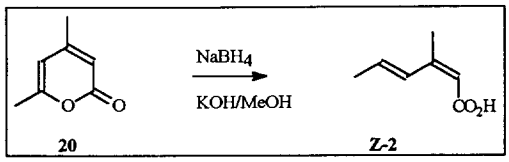
Abstract.- The regioselectivity of the addition of the lithium trienediolates generated from hexa-2,4-dienoic acids **1** and **2** or the dihydropyran-2-ones **4** and **5** to unsaturated ketones **6** is studied. Equilibration conditions favour reaction of the trienediolates through their ω carbon, and the ketones according to 1,2- and 1,4-additions. β-Ionone **6a** and the aryl-butenone **6b** lead to the 1,2-ω-adducts **8**, which undergo a facile acid catalyzed dehydration to retinoic acids **11**. On reaction with the unsaturated ketone **6b** or with the aryl ketones **21**, the trimethyldihydropyran-2-one **5** leads to γ'-adducts derived from deprotonation of the chain methyl substituent along with the 1,4-ω-adducts.

The outstanding biochemical and pharmacological features of retinoids have fostered the development of a great number of synthetic methods for prepa atural and modified retinoids.[1] In a former publication we described a two step synthesis of some aryl modified ration of both n nor-retinoic and retinoic acids based on the addition of lithium trienediolates of unsaturated carboxylic acids **1** and **2** to the carbonyl group of arylmethyl ketones.[2] The dihydropyran-2-one **4** was then found to be synthetically equivalent to (2*E*,4*E*) 3-methylhexa-2,4-dienoic acid **E-2**, as substantially the same addition products were obtained on reaction with the ketones. We now wish to describe our studies on the addition of the trienediolates of acids **1** and **2** to the α,β-unsaturated ketones β-ionone **6a** and 4-(4-methoxy-2,6,6-trimethylphenyl)but-3-en-2-one **6b**. The study has been extended to the reaction of the the latter unsaturated aryl ketone and the aryl ketones **21** with trimethyldihydropyran-2-one **5**, on the assumption that this dihydropyran-2-one should become equivalent to the 3,5-dimethylhexa-2,4-dienoic acid **3**, whose preparation has been obviated. Part of the present results have already been reported in a short communication.[3]

It has been established by some of us that 1,4-ω addition usually predominates on reaction of unsaturated carboxylic acids with unsaturated ketones under equilibration conditions [4]. However, when the trienediolate of hexa-2,4-dienoic acid **1** is added under the same conditions 1,2-ω-adducts are found as well [5]. This 1,2-ω

regioselectivity for the addition of the trienediolates of acids **1** to **3** to the unsaturated ketones **6** would now become a synthetically convenient course, as the resulting hydroxy acids **7** to **9** would afford acids **10** to **12** on dehydration. A short synthesis of these natural and aryl or chain modified retinoic acids would then be at hand, provided fairly high 1,2-ω regioselectivity and an easy separation of the resulting hydroxyacids from other regiochemical outcomes could be available.



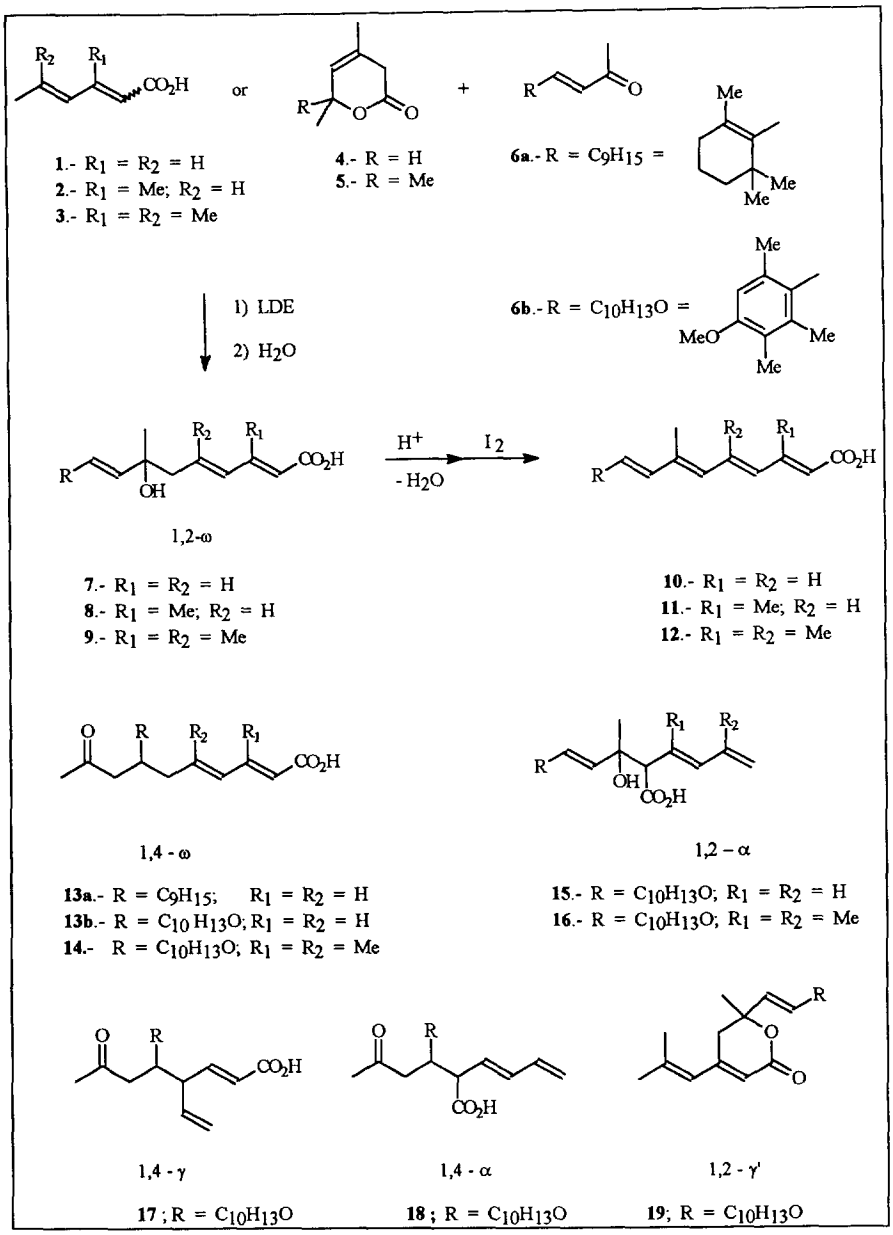
20 **Z-2**

2,4-Dimethyl-2H-pyran-2-one **20** is easily obtained from ethyl acetoacetate [6] and its reduction with methanolic sodium borohydride under alkaline conditions [7] has been used for preparation of (2*Z*,4*E*)-3-methylhexa-2,4-dienoic acid **Z-2**. The 4,6,6-trimethyl-3,6-dihydro-2H-pyran-2-one **5** has been prepared by addition of acetic acid lithium enediolate to mesityl oxide, followed by dehydration with cold sulfuric acid. In fact, the 4,6-dimethyl-3,6-dihydro-2H-pyran-2-one **4** used now and in the former work, is contaminated by the trimethyldihydropyran-2-one **5**, which is derived from the mesityl oxide present in the starting commercial pent-3-en-2-one.[2]

Results observed for addition of hexa-2,4-dienoic acid **1** to the ketones **6** were in agreement with the behaviour observed in related additions of the same acid to other unsaturated ketones [5] Thus, when the reaction mixtures were allowed to equilibrate at room temperature 1,2-ω- and 1,4-ω-adducts **7** and **13** became predominant, and were isolated in low yields (see Table), although HPLC allowed estimation of higher amounts in the crude mixtures. On addition to the arylbutenone **6b**, aliquot samples taken after short times at -70° or at room temperature allowed isolation of partially purified samples whose ^{1}H NMR were in agreement with the 1,2-α- 1,4-γ-, and 1,4-α- adducts **15**, **17**, and **18**, respectively. The hydroxyacid **7a** obtained from β-ionone **6a** was especially unstable, and very low recovery was observed when purified by a second chromatography. Dehydration of this hydroxyacid with p-toluensulfonic acid in methylene dichloride led to the also unstable 7-methyl-9-trimethylcyclohexenylnonatetrenoic acid **10a**, which was characterized through its ^{1}H NMR spectrum as a mixture of all-E and 2*E*,4*E*,6*Z*,8*E* isomers.[8] Dehydration of the methyl ester of the 1,2-ω addition hydroxyacid **7b** gave a 23% yield of the ester of acid **10b**, whose ^{1}H NMR spectrum showed it to constitute a mixture of the all-E and 2,*E*,4*E*,6*Z*,8*E* isomers.

The 3-methyl substituent in the trienediolate apparently simplifies the regiochemistry of the addition. Small amounts of 1,2-α- and 1,4-ω-adducts as well as the γ'adducts derived from deprotonation of the methyl

substituent, were spectrocopically observed in the reaction crudes obtained for both unsaturated ketones **6** on reaction with methylhexadienoic acids **2** or with the dimethyldihydropyranone **4**. However, only the 1,2-ω-adducts **8** were found in significant amounts. Thus, β-ionone **6a** on reaction with the (2*E*,4*E*)-3-methylhexa-2,4-dienoic acid **E-2** and with the dihydropyranone **4** gave 35% and 30%, respectively of a chromatographically



and spectroscopically (^{1}H NMR) pure hydroxyacid **8a**, which on dehydration with p-toluensulfonic acid in refluxing mehylene dichloride gave a 2-*E*/*Z*-6-*E*/*Z* stereoisomeric mixture of retinoic acid **11b**. Isomerization of this mixture with iodine led to an *all-E* retinoic acid, which showed identical ^{1}H and, ^{13}C NMR spectra as an commercial sample (although a lower mp than reported [9])was determined.

Table. Addition of Lithium Trienediolates to Unsaturated Ketones.

Ketone	Trienediolate Precursor	Reaction Conditions Temp °C	Time h	Crude Yield %	Isolated Adducts (%) [a]	Adducts Observed in Aliquots (%) [b]
6a	**1**	25	0.5	90	**7a** (20), **13a** (7)[c]	
	***E*-2**	25	0.5	88	**8a** (35)	
	4	25	0.5	93	**8a** (30)	
6b	**1**	-70	0.5	56		**7b** (13), **15** (23)[c], **17** (52)[c]
		25	1	61		**7b** (13), **18** (28)[c], **17** (37)[c]
		25	24	65	**7b** (22), **13b** (10)	
	***E*-2**	25	18	87	**8b** (18)	
	***Z*-2**	25	18	80	**8b** (39)	
	5	-70	0.5	63		**16** (62)[c], **19** (9)
		25	2	70	**9b** (32), [c]**14** (11) [c], **19** (5)	

a.- Yields in brackets for purified compounds. Isolated as acids, unless otherwise stated; b.- Chromatographic yields in brackets; c.- Isolated as methyl ester; d.- Not fully purified or characterized material. Structure established through IR and ^{1}H NMR spectra.

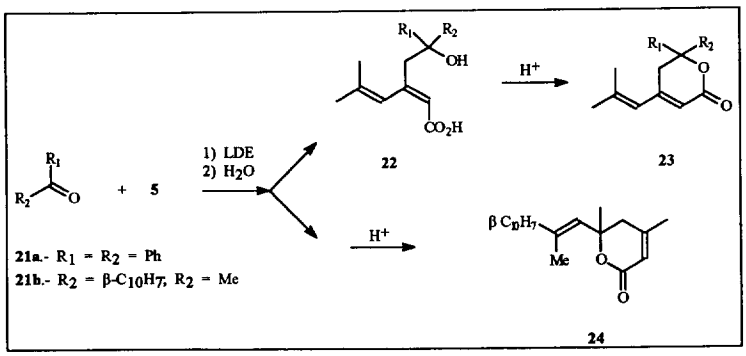
Similarly (methoxytrimethylphenyl)butenone **6b** and (2*Z*,4*E*)-3-methylhexa-2,4-dienoic acid **Z-2** gave the corresponding 1,2-ω-adduct **8b** in 39% yield after purification. This acid underwent dehydration to give an stereoisomeric mixture which, on iodine isomerization, afforded the *all-E* 9-(methoxytrimethylphenyl)-3 methylnonatetraenoic acid **11b**, whose ^{1}H and ^{13}C NMR spectra were in agreement with those reported.[10] Reaction of the same ketone with the (*E*,*E*)-methylhexadienoic acid **E-2** gave substantially the same result, although the 1,2-ω-adduct **8b** was isolated in lower purified yield (18%), probably due to occurrance of 1,2-γ'

addition, in keeping with former results, which showed that the (*E,E*)-methylhexadienoic acid **E-2** is more easily deprotonated at the methyl substituent than the related dihydropyran-2-one **4**.[2]

Improvement of the 1,2-ω addition by protection of the double bond conjugated to the carbonyl group was attempted for β-ionone by conversion into its π- tricarbonyliron complex,[11] or its phenylthiol Michael adduct [12]. However, no satisfactory results were obtained in both occasions, due to low conversion (40%) in the first instance, and instability of the thiol adduct under trienediolate addition conditions in the second one.

Double deprotonation of the trimethyldihydropyranone **5** should generate the trienediolate of the dimethylhexadienoic acid **3**. However the introduction of the second methyl group as substituent results in further complexity in the reaction. Thus, on reaction of dihydropyran-2-one **5** with the (methoxy-trimethylphenyl)butenone **6b**, an aliquot of the reacting mixture taken after short time at -70°C mostly constituted the *R/S* diatereoisomeric mixture of the 1,2-α adduct **16**. In agreement with previous experience by some of us,[5] this 1,2-α-adduct could not be isolated in pure form due to its instability and was only spectroscopically characterized (^{1} HNMR). When the reaction was allowed to equilibrate for 2 h at room temperature, 1,4-ω- and **14** and **9**, along with the minor 1,2-γ'-adduct **19** were isolated. Dehydration of the 1,2-ω-adduct **9** was expected to afford the 5-methyl-retinoic acid **12b**, but led to complex mixtures.

Adducts derived from deprotonation of the methyl group located at the carbon 4 of the trimethyldihydropyranone **5** were again observed on reaction with the aryl ketones benzophenone and β-acetonaphthone **21a** and **21b**, when the γ'-adducts **22a** and **22b** were obtained in 28% and 25% yields, respectively as purified materials. Acid treatment of these adducts led to the corresponding dihydropyranones **23**. The ω-adducts were observed for both ketones as *E/Z* mixtures, and a 19% yield of the dihydropyranone **24b** was obtained for acetonaphtone. These additions were not simple in any case, and mixtures of α-, ω-, and ω'-adducts could be observed in the crude mixtures.



In spite of the fact that reaction of both unsaturated and aryl ketones **6** and **21** with the trienediolates derived from hexadienoic acids or from their equivalent dihydropyrones do not afford a well defined regiochemical trend, in the particular case of of 3-methylhexa-2,4-dienoic acids **2** or the dihydropyran-2-one **4** simpler mixtures are obtained, from which the 1,2-ω-adducts are isolated in a sufficiently high amount to provide an easy route to retinoic acids **11**.

EXPERIMENTAL PART

M.p.s were determined with a Reichert apparatus and are uncorrected. IR spectroscopic 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) or 300 Varian Unity (300 MHz). Mass spectra were determined with a VG Autospec Spectrometer. 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. Lithium diethylamide (LDE) has been generated from lithium, naphthalene, and diethylamine, as previously described.[13] Generation and reactions of the trienediolates were carried out under 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. Esterifications were performed by treatment of acids with diazomethane in ethyl ether or ethyl acetate.

The starting unsaturated ketone (4-methoxy-2,3,6-trimethylphenyl)but-3-en-2-one **6b** was prepared from commercial 2,3,5-trimethylphenol by conventional methods. β-Ionone **6a** was purchased from Aldrich and distilled before use. (2E,4E)-Methylhexa-2,4-dienoic acid **E-2** and 4,6-dimethyl-3,6-dihydro-2H-pyran-2-one **4** were previously prepared [2].

4,6,6-Trimethyl-3,6-dihydro-2H-pyran-2-one 5.- Acetic acid (5,1 ml; 90 mmol) in THF (90 ml) was added dropwise for 0.5 h to stirred LDE (200 mmol) in THF (100ml) at -70°C. The solution was stirred for 1 h at 0°C, cooled again at -70°C, and mesityl oxide (12.3 ml; 90 mmol) in THF (100) ml was added dropwise for 20 min. The mixture was stirred for 1 h at the same temperature and for 1 h at rt. Water (250 ml) was added, the solvent was partly evaporated, and the residue extracted with diethyl ether (3 x 100 ml). The aqueous layer was cooled with an ice-water bath, acidified with conc hydrochloric acid, and extracted. with ethyl acetate (4 x

100 ml). The joint organic layers were washed with water and brine, and dried. Evaporation of the solvent gave a colourless oil (14.2 g), which was cooled with an ice water bath. Conc. sulfuric acid was added dropwise and with stirring. Ice (200 g) was added slowly, and the mixture stirred for 30 min and then extracted with diethyl ether. The ether layer was washed with water and dried, and the solvent evaporated to give the title dihydropyran-2-one **5** as a colourless oil (8.9 g) which was distilled under vacuum, bp 3_{mmHg} 72° C (lit. [14] $bp_{7\ mmHg}$ 89° C); ν_{max} 1720 (C=O) cm^{-1}; δ_H 5.46 (1 H, s, C5-H), 2.90 (2 H, s, C3-H), 1.67 (3 H, s, C4-Me), and 1,40 (6 H, s, C6-Me) ppm.

(2*Z*,4*E*)-Hexa-2,4-dienoic acid Z-2.- A mixture of 4,6-dimethyl-2H-pyran-2-one (1 g; 8 mmol), $NaBH_4$ (1,8 g, 48 mmol) and KOH (0,45 g, 80 mmol) in methanol (100 ml) was stirred for 14 h under reflux. Water (50 ml) was added, and the mixture heated under reflux for 5 min. The solvent was partly evaporated, and the residue poored into 20% acetic acid (30 ml). Acetic acid was added up to slight acid character of the solution, and extracted with ethyl acetate. The joint organic layers were washed with water and dried, and the solvent evaporated, affording an orange oil (0,90 g; 7,16 mmol, 89,5%) of crude acid **Z-2**. Crystallization from hexane gave coluorless prisms (0,28 g; 2,25 mmol, 28,2%) of (2*Z*,4*E*)-3-methylhexa-2,4-dienoic acid **Z-2** mp. 96-98° C (lit.[15] mp 97-98°C). ν_{max} 3600-2300 (OH), 1700 (C=O), and 1635 (C=C) cm^{-1}, δ_H 7.54 (1 H, d, J 16.3 Hz, C4-H), 6.21 (1 H, dq, J 15.75 and 6.76 Hz, C5-H), 5.61 (1 H, s, C2-H), 2.00 (3 H, s, C3-CH_3), and 1.89 (3 H, d, J 6.64 Hz, C6-H) ppm.

General procedure for reaction of acids 1 and 2 or dihydropyran-2-ones 4 and 5 with ketones. The acid **1** or **2** or lactone **4** or **5** (9 mmol) in THF (10 ml) was added dropwise for 30 min to lithium diethylamide [from lithium (20 mmol), naphthalene and diethylamine (2.1 ml)] in THF (10 ml) at -70°C. The solution was stirred for15 min at the same temperature, and then allowed to warm 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 partly evaporated under reduced pressure, and the residue extracted with ether. The aqueous layer was acidified by slow addition of conc hydrochloric acid with stirring and ice-water cooling, and the hydroxy acids were extracted with ether, the organic layer 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 ester (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 hexa-2,4-dienoic acid 1 to β-ionone 6a.- According to the general method, hexa-2,4-dienoic acid (1,01 g; 9 mmol), and β-ionone (1.83 g; 9 mmol), on reaction for 40 min at 25°C, and usual work-

up gave a crude yellow oil (2,47 g; 90%). Flash column chromatography of an aliquot (1.0 g) allowed isolation of 7-hydroxy-7-methyl-9-(2,6,6-trimethyl-1-cyclohexenyl)nona-2,4,8-trienoic acid **7a** as a yellow oil (200 mg; 20%); ν_{max} 37000-2400 (O-H), 1690 (C=O), and 1640 and 1620 (C=C) cm^{-1}; δ_H 7.32 (1 H, dd, J 15.3 and 10 Hz, C3-H), 6.33-6.1 (2 H, m, C4-H and C5-H), 6.03 (1 H, d, J 16.2 Hz, C9-H), 5.78 (1 H, d, J 15.4 Hz, C2-H), 5.46 (1 H, d, J 16.2 Hz, C8-H), 2.45 (2 H, d, J 6.1 Hz, C7-H), 1.94 (2 H, t, J 6.2 Hz, C3'-H), 1.62 (3 H, s, C2'-CH_3), 1.56 (2 H, m, C4'-H), 1.42 (2 H, m, C5'-H), 1.34 (3 H, s, C7-CH_3), and 0.95 (6 H, s, 2 C6'-CH_3) ppm; δ^{13}_C 172.06 (CO_2H), 146.71 (C3), 136.8 (C1'), 128.42 (C2'), 139.47, 131.55, and 125.88 (C=C), 119.3 (C2), 73.27 (C7), 46.48 (C6), 39.32 (C5'), 34.0 (C6'). 32.63 (C7-CH_3), 28.74 (2 x C6'-CH_3), 28.38 (C3'), 21.4 (C2'-CH_3) and 19.25 (C4') ppm.

Methyl esters: The remaining above crude oil was esterified. Flash column chromatography of an aliquot (0.87 g) allowed isolation of the **methyl ester of 8-oxo-7-(2,6,6-trimethyl-1-cyclohexenyl)deca-2,4-dienoic acid 13a** (65 mg; 7%). Found, C, 75.39; H, 9.66. $C_{20}H_{30}O_3$ requires C, 75.43; H, 9.5 %; ν_{max} 1715 (C=O) and 1640 cm^{-1} δ_H 7.16 (1 H, dd, J 15.4 and 9.8 Hz, C3-H), 6.85-6.15 (2 H, m, C4-H and C5-H), 5.72 (1 H, d, J 15.4 Hz, C2-H), 3.67 (3 H, CO_2CH_3), 2.78 (1 H, J 17.5 and 8.9 Hz, C8-H), 2.60-2,28 (3 H, m, C6-H and C7-H), 2.02 (3 H, s, C10-H), 1.85 (2 H, t, J 6 Hz, C3'-H), 1.60 (3 H, s, C2'-CH_3), 1.50-1.25 (4 H, m, C4'-H and C5'-H), and 0.94 and 0.88 (6 H, 2 s, 2 C6'-CH_3).

7-Methyl-9-(2,6,6-trimethyl-1-cyclohexenyl)nona-2,4,6,8-tetraenoic acid 10a.- Dehydration of acid **7a** (200 mg) according to the general method gave a *2E,4E,6E,8E/ 2E,4E,6Z,8E* mixture of the title acid, as a yellow oil (177 mg; 94%) δ_H 7.5 and 7.43 (1 H, 2 dd, J15.1 and 11.4 Hz each, C3-H), 7.25 and 7.06 (1 H, 2 dd, 14.4 and 11.8 Hz each, C5-H), 6.64 1 H, d J 16 Hz, C9-H), 6.34-6.0 (3 H, C4-H, C8-H, and C6-H), 5.82 (1 H, d, J 15.1 Hz, C2-H), 2.03 (2 H, m, C3'-H), 1.99 and 1.98 (3 H, 2 s, C2'-CH_3), 1.73 and 1.69 (3 H, 2 s, C7-CH_3), 1.6 (2 H, m, C4'-H), 1.46 (2 H, C5'-H), and 1.02 and 1.01 (6 H, 2 s, 2 C6'-CH_3).

Addition of hexa-2,4-dienoic acid 1 to 4-(4-methoxy-2,3,6-trimethylphenyl)but-3-en-2-one 6b.- Hexa-2,4-dienoic acid (2,01 g; 18 mmol), and 4-(4-methoxy-2,3,6-trimethylphenyl)but-3-en-2-one (3.92 g; 18 mmol) were allowed to react according to the general method for 24 h at rt. On work-up an oil (3.59 g; 60.5%) was obtained. Esterification of an aliquot (1.9 g) and column chromatography allowed isolation of the methyl ester of **(2E,4E)-7-(4-methoxy-2,3,6-trimethylphenyl)-9-oxodeca-2,4-dienoic acid 13b** as colouless prisms (344 mg; 10 %), mp 121-126°C; %. Found: C, 73.15; H, 8.27. $C_{21}H_{28}O_4$ requires C, 73.21; H, 8.20 %. ν_{max} 1720 (C=O), and 1650 (C=C), cm^{-1}; δ_H 7.18 (1 H, dd, J 15.4 and 10.7 Hz, C3-H), 6.5 (1 H, s, Ar-H), 6.2 (1 H, dd, J 15.4 and 10.5 Hz, C4-H), 5.9 (1 H, dt, J 15.4 and 7.5 Hz, C5-H), 5.73 (1 H, d, J 15.4 Hz, C2-H) 4.0-3.7 (1 H, m, C7-H), 3.73 (3 H, s, Ar-OCH_3), 3.69 (3 H, s, CO_2CH_3), 2.85 (2 H, d, J 6.1 Hz, C8-H), 2.53 (2 H, dd, J 11.5 and 7.5 Hz, C6-H) 2.38, 2.24 2.08 (9 H, 3s, 3 Ar-CH_3), and 2.02 (3 H, s, C10-H) ppm.

Further elution gave the **methyl ester of (2E,4E,8E)-7-hydroxy-7-methyl-9-(4-methoxy-2,3,6-trimethylphenyl)nona-2,4-8-trienoic acid 7b** as a yellow oil (732 mg; 22 %). Found: 73.45; H, 8.35. $C_{21}H_{28}O_4$ requires C, 73.21; H, 8.20 %. ν_{max}, 3600-3300 (O-H), and 1700 (C=O) cm^{-1}; δ_H 7.24 (dd, J 15.1 and 10.7 Hz, 1H, C3-H), 6.57 (1 H, d, J 16.2 Hz, C9-H), 6.56 (1 H, s, Ar-H), 6.2-5.9 (2 H, m, C4-H and C5-H), 5.82 (1 H, d, J 15.4 Hz, C2-H), 5.63 (1 H, d, J 16.3 Hz, C8-H), 3.78 (3 H, s, CO_2CH_3), 3.73 (3 H, s, $ArOCH_3$), 2.50 (2 H, d, J 8.42 Hz, CH_2), 2.20 , 2.15 and 2.12 (9 H, 3s, 3 Ar-CH_3), and 1.41 (3 H, s, C7-CH_3) ppm.

Methyl ester of 7-methyl-9-(4-methoxy-2,3,6-trimethylphenyl)nona-2,4,6,8-tetraenoic acid 10b.- Dehydration of the methyl ester of acid **7b** (99 mg) with p-toluensulfonic acid in refluxing methylene dichloride, work-up, and column chromatography of the resulting crude oil led to a 2*E*,4*E*,6*E*,8*E*/2*E*,4*E*,6*Z*,8*E* mixture of the **methyl ester of 7-methyl-9-(4-methoxy-2,3,6-trimethylphenyl)nona-2,4,6,8-tetraenoic acid 10b** as a yellow oil (21,9 mg. 31%).; Found: C, 77.12; H, 8.12. $C_{21}H_{26}O_3$ requires C, 77.26; H, 8.03 %.ν_{max} 1700 (C=O), 1120 ($ArOCH_3$), 840 and 710 (Ph) cm^{-1}; δ_H (2*E*,4*E*,6*Z*,8*E*) 7.39 (1 H, dd, J 15.4 and 11.4 Hz, C3-H), 6.96 (1 H, dd, J 14.5 and 11.7 Hz, C5-H), 6.74 (1 H, s, Ar-H), 6.65 (1 H, d, J 11.7 Hz, C6-H), 6.62 (1 H, d, J 16.3 Hz, C9-H), 6.35 (1 H, dd, J 14.4 and 11.8 Hz, C4-H), 6.22 (1 H, d, J 16.3 Hz, C8-H), 5.86 (1 H, d, J 15.2 Hz, C2-H), 3.80 (3 H, s, CO_2CH_3), 3.73 (3 H, s, Ar-OCH_3), 2.29, 2.23, 2.14 and 2.08 (12 H, 4s, 4 CH_3) ppm; δ_H (2*E*,4*E*,6*E*,8*E*) 7.39 (1 H, dd, J 15.4 and 11.4 Hz, C3-H), 6.99 (1 H, dd, J 14.5 and 11.7 Hz, C5-H), 6.74 (1 H, s, Ar-H), 6.65 (1 H, d, J 16.2 Hz, C6-H), 6.62 (1 H, d, J 16.3 Hz, C9-H), 6.35 (1 H, dd, J 14.4 and 11.8 Hz, C4-H), 6.22 (1 H, d, J 16.3 Hz, C8-H), 5.86 (1 H, d, J 15.2 Hz, C2-H), 3.82 (3 H, s, CO_2CH_3), 3.74 (3 H, s, Ar-OCH_3), 2.30, 2.25, 2.15 and 2.10 (12 H, 4s, 4 CH_3) ppm.

Addition of (2*E*,4*E*)-3-Methylhexa-2,4-dienoic acid E-2 to β-ionone 6a.- (2*E*,4*E*)-3-methylhexa-2,4-dienoic acid (1.13 g; 9 mmol), LDE (20 mmol) and β-ionone (1.83 ml; 9 mmol) on reaction first at -70°C and for 40 min at rt led to a yellow oil (2.52 g; 88 %). Flash column chromatography of part of this mixture (2.41 g) allowed isolation of a 2*E*,4*E*,8*E*/2*Z*,4*E*,8*E* mixture of 7-hydroxy-7-methyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-nona-2,4,8-trienoic acid **8a** (966 mg; 35 %) as an oil.

Methyl ester ν_{max} 3600-3300 (OH), 1720 (C=O), and 1635 and 1605 cm^{-1}; δ_H 7.58 (d, J 15.8 Hz, 2Z C4-H), 6.27-6.12 (m, 2E C4-H and C5-H), 6.04 (d, J 16.3 Hz, C9-H), 5.71 (s, 2E C2-H), 5.63 (s, 2Z C2-H), 5.48 (d, J 16.1 Hz, 2Z C8-H), 5.47 (d, 16.1 Hz, 2E C8-H), 2.5 (2 H, d, J 7.5 Hz, C6-H), 1.99 (3 H, s C2'-CH_3), 1.97 (2 H, t, J 7.3 Hz, C3'-H), 1.62 (3 H, s, C7-CH_3), 1.6 (2 H, m, C4'-H), 1.4 (2 H, m, C5'-H), 1.35 (3 H, s, C3-CH_3), and 0.95 (6 H, s, 2 C6'-CH_3) ppm.

Reaction of 4,6-dimethyl-3,6-dihydro-2H-pyran-2-one 4 with β-ionone 6a.- 4,6-Dimethyl-3,6-dihydro-2H-pyran-2-one (1.13 g; 9 mmol), and β-ionone (1.83 ml; 9 mmol) as above gave a yellow oil (2.67 g; 93

%). Flash column chromatography allowed isolation of circa 4:6 stereoisomeric 2*E*,4*E*,8*E*/2*Z*,4*E*,8*E* mixture of 7-hydroxy-7-methyl-9-(2,6,6-trimethyl-1-cyclohexenyl)nona-2,4,8-trienoic acid **8a** as a yellow oil (541 mg; 29.5 %); δ_H 7.58 (d, J 15.8 Hz, 2Z C4-H), 6.27-6.12 (m, 2E C4-H and C5-H), 6.04 (d, J 16.3 Hz, C9-H), 5.71 (s, 2E C2-H), 5.63 (s, 2Z C2-H), 5.48 (d, J 16.1 Hz, 2E C8-H), 5.47 (d, J 16.1 Hz, 2E C8-H), 2.5 (2 H, d, J 7.5 Hz, C6-H), 1.99 (3 H, s, C2'-CH_3), 1.97 (2 H, t, J 7.3 Hz, C3'-H), 1.62 (3 H, s, C7-CH_3), 1.60 (2 H, m, C4'-H), 1.4 (2 H, m, C5'-H), 1.35 (3 H, s, C3-CH_3), and 0.95 (6 H, s, 2 C6'-CH_3) ppm.

(2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-nona-2,4,6,8-tetraenoic acid 11a.

Dehydration of the above acid **8a** (407 mg) with p-toluensulfonic acid (197 mg) in refluxing methylene dichloride, according to the general procedure led to a yellow oil (372 mg; 95 %). A solution of this oil in diethyl ether (4 ml) and 0.1 % iodine in benzene was allowed to stand for 7 h at rt. The solution was poured into water and extracted with diethyl ether. The organic layer was washed with sodium bisulfite and water, and dried. Evaporation gave a thick yellow oil, which crystallized from methanol/water as yellow prisms of the title acid, mp 166-68°C (lit [9] mp 179-80°C); ν_{max} 3300-2500 (OH), 1685 (C=O), 1605 and 1575 (C=C) cm^{-1}; δ_H 7.04 (1 H, dd, J 14.9 and 11.5 Hz, C5-H), 6.3 (1 H, d, J 15.5 Hz C4-H), 6.22 (1 H, d, J 16.2 Hz C9-H), 6.15 (1 H, d, J 10.5 Hz, C6-H), 6.13 (1 H, d, J 16.2, C8-H), 2.35 (3 H, s, C3-CH_3), 2.0 (5 H, s, C7-CH_3, and m, C3'-H), 1.7 (3 H, s, C2'-CH_3), 1.62 (2 H, m, C4'-H), 1.47 (2 H, m, C5'-H), and 1.02 (6 H, s, 2 x C6'-CH_3); $\delta^{13}C$ 171.6 (CO_2H), 155.28 (C3), 140.27 (C4), 137.67 (C7), 137.2 (C1'), 134.86 (C8), 131.84 (C5), 130.16 (C6), 129.38 (C2'), 129.04 (C9), 117.41 (C2), 39.61 (C5'), 34.26 (C6'), 33.12 (C3'), 28.95 (C6'-CH_3), 21.72 (C2'-CH_3), 19.2 (C4'), 14.04 (C3-CH_3), and 12.93 (C7-CH_3).[16]

Addition of (2*E*,4*E*)-3-methylhexa-2,4-dienoic acid E-2 to 4-(4-methoxy-2,3,6-trimethylphenyl)-but-3-en-2-one 6b.- (2*E*,4*E*)-3-Methylhexa-2,4-dienoic acid (1,13 g; 9 mmol), and 4-(4-methoxy-2,3,6-trimethylphenyl)but-3-en-2-one (1,96 g; 9 mmol on reaction as usual for 1 h at -70°C and 18 h at rt, led to a yellow oil (2,68 g; 87 %). Separation by flash column chromatography allowed isolation of a 2*E*,4*E*,8*E*/2*Z*,4*E*,8*E* mixture of **3,7-dimethyl-7-hydroxy-9-(4-methoxy-2,3,6-trimethylphenyl)nona-2,4-8-trienoic acid 8b** as an oil which crystallized as yellow prisms, mp 132-139°C. Found: C, 73.32; H, 8.05. $C_{21}H_{28}O_4$ requires C, 73.21; H, 8.20 %. ν_{max} 3600-3300 (O-H), 1715 (C=O), and 1600 (C=C) cm^{-1}; δ_H (2*Z*), 7.63 (1 H, d, J 15.8 Hz, C4-H), 6.58 (1 H, s, Ar-H), 6.57 (1 H, d, J 16.3 Hz, C9-H), 6.4-6.1 (1 H, m, C5-H), 5.67 (1 H, s, C2-H), 5.66 (1 H, d, J 16.3 Hz, C8-H), 3.79 (3 H, s, Ar-OCH_3), 2.58 (2 H, d, J 7,2 Hz, CH_2), 2.25, 2.18 and 2.13 (9 H, 3s, 3 Ar-CH_3), and 2.04 (3 H, s, C3-CH_3) 1.44 (3 H, s, C7-CH_3) ppm; δ_H (2*E*), 6.58 (1 H s, ArH), 6.57 (1 H, d, J 16.3 Hz, C9-H), 6.4-6.1 (1 H, m, C5-H), 6.26 (1 H, d, J 15.2 Hz, C4-H), 5.75 (1 H, s, C2-H), 5.65 (1 H, d, J 16.3 Hz, C8-H), 3.79 (3 H, s, Ar-OCH_3), 2.56 (2 H, d, J 7.3 Hz, CH_2), 2.27 (3 H, s, C3-CH_3), 2.25, 2.18 and 2.13 (9 H, 3s, 3 Ar-CH_3), and 1.44 (3 H, s, C7-CH_3) ppm.

Addition of (2*Z*,4*E*)-3-methylhexa-2,4-dienoic acid Z-2 to 4-(4-methoxy-2,3,6-trimethylphenyl)but-3-en-2-one 6b.- (2*Z*,4*E*)-3-Methylhexa-2,4-dienoic acid (1,13 g; 9 mmol) and 4-(4-methoxy-2,3,6-trimethylphenyl)but-3-en-2-one (1,96 g; 9 mmol), on reaction as usual for 1 h at -70°C and 18 h at rt led to a yellow oil (2,79 g; 90 %). Purification by flash column chromatography allowed isolation of a yellow oil (1,21 g; 39 %) of the same mixture of acids **8b** as above.

(2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(4-methoxy-2,3,6-trimethylphenyl)nona-2,4,6,8-tetraenoic acid 11b .- Dehydration of a stereoisomeric mixture of acid **8b** (1.2 g; 3.48 mmol) with p-toluensulfonic acid (445 mg; 2.3 mmol) in refluxing methylene dichloride 200 ml for 15 min, and usual work-up gave the title acid as a mixture of stereoisomers. A solution of 0.1 % iodine in benzene was added to the above acid in diethyl ether (15 ml), and the solution allowed to stand for 7 h. The solution was poured into water, extracted with diethyl ether. The organic layer was washed with sodium bisulfite and water and dried. Evaporation of the solvent gave a thick oil of the title acid (1.13 g; 94 %), which crystallized from ethanol as yellow prisms, mp. 220-225° C (lit [17], mp 228-230° C). Found: M^+ 326.187841. $C_{21}H_{26}O_3$ requires 326.188141. ν_{max} 3600-3300 (O-H), 1700 (C=O), 1600 (C=C) cm^{-1}. δ_H 7,09 (1 H, dd, J 15.02 and 11,4 Hz, C5-H), 6.7 (1 H, d, J 16.3 Hz, C9-H), 6.6 (1 H, s, Ar-H), 6.4 (1 H, d, J 15.04 Hz, C4-H), 6.24 (1 H, d, J 16.3 Hz, C8-H), 6.2 (1 H, d, J 11.4 Hz, C6-H), 5.8 (1 H, s, C2-H), 3.8 (3 H, s, Ar-OCH_3), 2.37 (3 H, s, C3-CH_3), 2.28, 2.24 and 2.14 (9 H, 3s, 3 Ar-CH_3), and 2.10 (3 H, s, C7-CH_3) ppm;[10] δ^{13}_C 166.85 (CO_2H), 156,25 (C4'), 152.3 (C3), 138.95 (C7), 138.2 (C8), 135.85 (C4), 135.8 (C2') 133.85 (C1' or C6'), 130.55 (C5), 130.4 (C6), 130.0 (C6' or C1'), 128.65 (C9), 122.85 (C3) 119.1 (C2), 110.25 (C5'), 55.4 (CH_3O), 21.36 (C6'-CH_3), 17.35 (C2'-CH_3), 13.85 (C3-CH_3), 12.85 (C7-CH_3), and 11.8 (C3'-CH_3) ppm.[10]

Reaction of 4,6,6-trimethyl-3,6-dihydro-2H-pyran-2-one 5 with 4-(4-methoxy-2,3,6-trimethylphenyl)but-3-en-2-one 6b.- The trimethyldihydropyran-2-one **5** (1.26 g; 9 mmol) and the arylbut-3-2-one **6b** (1.96 g; 9 mmol) were allowed to react under the usual conditions for 2 h at rt. On work-up an oil (2.332 g; 72 %) was obtained. Esterification of an aliquot (0.51 g) and purification by flash column chromatography allowed isolation of **6-[2-(4-methoxy-2,3,6-trimethylphenyl)ethenyl]-6-methyl- 4-(2-methyl-1-propenyl-5,6-dihydropyran-2-one 19** as colourless prisms (46 mg; 5.7 %), mp 67-71°C. Found: M^+ 340.203967. $C_{22}H_{28}O_3$ requires 340.203845. ν_{max} 1700 (C=O) cm^{-1}; δ_H 6.55 (1 H, s, Ar-H) 6.53 (1 H, d, J 16.3 Hz, Ar-CH=), 5.88 (1 H, s, (Me_2C=CH), 5.7 (1 H, s, C=CHCO), 5.55 (1 H, d, J 16.5 Hz, Ar-C=CH), 3.78 (3 H, s, Ar-OCH_3), 2.7 (1 H, d, J 15.4 Hz, C5-H), 2,57(1 H, d, J 15.5 Hz, C5-H), 2.18, 2.12 and 2.10 (9 H, 3 s, 3 Ar-CH_3), 1.91 and 1.88 (6 H, 2 s, $(CH_3)_2$C=C), and 1.62 (3 H, s, C6-CH_3) ppm; δ^{13}_C 165.75, 156.2, 151.9, 144.55, 136.55, 133.65, 133,55, 127.8, 128.5, 123.7, 122.6, 116.25, 109.8, 80.8, 55.55, 39.4, 27.95, 27.9, 21.1, 20.85, 17.2, and 11.75 ppm.

Further elution gave a 2*Z*/2*E* mixture of the **methyl ester of 3,5-dimethyl-7-(4-methoxy-2,3,6-**

trimethylphenyl)-9-oxodeca-2,4-dienoic acid 14 as colourless prisms (82.3 mg; 11 %), mp 186-192°C: Found: M^+ 372.228715. $C_{23}H_{32}O_4$ requires 372.230059. ν_{max} 1710 (C=O), 1640(C=C) cm^{-1}; δ_H, (2Z) 6,48 (1 H, s, Ar-H), 5,92 (1 H, s, C4-H), 4,67 (1 H, s, C2-H), 4,35-4,1 (1 H, m, C7-H), 3.76 (3 H, s, CO_2CH_3), 3.71 (3 H, s, Ar-OCH_3), 3.42 (2 H, d, J 11.8 Hz, C8-CH_2), 2.8 (2 H, m, C6-CH_2), 2.46, 2.27 and 2.16 (9 H, 3s, 3 Ar-CH_3), 2.37 (3 H, s, CH_3-C=O), 1.94 (3 H, s, C3-CH_3), and 1.46 (3 H, s, C5-CH_3) ppm; δ_H, (2E) 6.45 (1 H, s, Ar-H), 4.69 (1 H, s, C4-H), 4.67 (1 H, s, C2-H), 4.35-4.1 (1 H, m, C7-H), 3.76 (3 H, s, CO_2CH_3), 3.71 (3 H, s, Ar-OCH_3), 3.42 (2 H, d, J 11.8 Hz, C8-CH_2), 2.8 (2 H, m, C6-CH_2), 2.46, 2.27 and 2.16 (9 H, 3s, 3 Ar-CH_3), 2.41 (3 H, s, CH_3-C=O), 2.08 (3 H, s, C3-CH_3), and 1.43 (3 H, s, C5-CH_3) ppm.

Further elution gave the **methyl ester of (2*Z*,4*E*,8*E*)-7-hydroxy-3,5,7-trimethy-9-(4-methoxy-2,3,6-trimethylphenyl) nona-2,4,8-trienoic acid 9b** as a yellow oil (231 mg. 32.5 %). Found: C,74.32; H, 8.53. $C_{23}H_{32}O_4$ requires C, 74.15; H, 8.66 %. ν_{max} 3600 (O-H), and 1710 (C=O) cm^{-1}; δ_H 6.58 (1 H, d, J 16.7 Hz, C9-H), 6.57 (1 H, s, Ar-H), 5.86 (1 H, s, C4-H), 5.75 (1 H, s, C2-H), 5.68 (1 H, d, J 16,3 Hz, C8-H), 3.79 (3 H, s, CO_2CH_3), 3.72 (3 H, s, Ar-OCH_3), 3.09 (1 H, d, J 12.8 Hz, CH_2), 2.80 (1 H, d, J 12.7 Hz, CH_2), 2.27 2.20 and 2.13 (9 H, 3s, 3 Ar-CH_3), 1.86 (3 H, s, C3-CH_3), 1.80 (3 H, s, C5-CH_3), and 1.37 (3 H, s, C7-CH_3) ppm.

Reaction of 4,6,6-trimethyl-3,6-dihydro-2H-pyran-2-one 5 with benzophenone 21a.- The trimethyldihydropyran-2-one **5** (1.26 g) and benzophenone (1.64 g) were allowed to react according to the general method for 2 h at rt, leading to a solid material (2.5 g; 86 %). Esterification and purification of an aliquot (0.56 g) by column chromatography gave the methyl ester of acid (2Z)-3-(2-hydroxy-2,2-diphenylethyl)-5-methylhexa-2,4-dienoic acid **22a** as colourless prisms (153 mg; 23.5 %), mp 79-81°C. ν_{max} 3500-3300 (O-H), 1670 (C=O), and 1590 (C=C) cm^{-1}; δ_H 7.5-7.1 (10 H, m, 2 Ph), 5.75 (1 H, s, C4-H), 5.02 and 4.97 (2 H, 2 s, C2-H and OH), 3.71 (3 H, s, CO_2CH_3), 3.60 (2 H, s, CH_2), 1.56 (3 H, s, CH_3) and 1,36 (3 H, s, CH_3) ppm.

When the above methyl ester was heated with p-toluensulfonic acid (52 mg) under the conditions for dehydration, colourless prisms of 4-(2-methyl- 2-propenyl)-6,6-diphenyl-5,6-dihydropyran-2-one **23a**. Found: M^+ 304.145812. $C_{21}H_{20}O_2$ requires 304.146330. ν_{max} 1660 (C=O), 870 and 635 (Ph) cm^{-1}; δ_H 7.38-7.22 (10 m, 2 Ph), 5.76 (2 H, s, C3-H and C1'-H), 3.2 (2 H, s, C5-H), 1,90 (3 H, s, CH_3), and 1,63 (3 H, s, CH_3) ppm; δ_{13C} 165.15, 152.55, 144.9, 143.19, 128.38, 127.65, 125.8, 123.4, 117.28, 85.6, 39.5, 27.8, and 20.7 ppm.

Reaction of 4,6,6-trimethyl-3,6-dihydro-2H-pyran-2-one 5 with 2-acetonaphthone 21b.- a) When the trimethyldihydropyran-2-one **5** (1.26 g) and 2-acetonaphthone (1.53 g) were allowed to react according to the general method for 2 h at rt, leading to an oil (2.36 g; 85 %) was obtained, which was dehydrated according to the general procedure, to give a solid material (2.04 g). An aliquot of this was purified by column chromatography to give colourless needles (389 mg; 25 %) of **4,6-dimethyl-6-[2-(2-naphthyl)prop-1-enyl]-5,6-dihydropyran-2-one 24**, mp 147-148°C. Found: C, 81.75; H, 6.88. $C_{20}H_{20}O_2$ requires C, 82.16; H, 6.89

%. ν_{max} 1705 (C=O) cm^{-1}; δ_H 7.82.7.26 (7 H, m, $C_{10}H_7$), 5.85 (1 H, s, C1'-H), 5.81 (1 H, s, C=$CHCO_2$), 2.62 and 2.51 (2 H, 2d, CH_2), 2.38 (3 H, s, $C_{10}H_7$-C-CH_3), 2.00 (3 H, s, C4-CH_3), and 1.72 (3 H, s, C6-CH_3) ppm; $\delta^{13}C$ 164.75, 155.35, 141.15, 140.6, 133.2, 132, 65, 131.05, 128,05, 127.75, 127.45, 126.2, 125.85, 124.6, 124.35, 116.85, 80.95, 42.15, 26.95, 23.3, and 17.25 ppm.

b) When the reacting mixture was stirred for 24 h a syrup (1.21 g; 87%) was obtained. Esterification and column chromatography allowed isolation of the methyl ester of (2*Z*)-3-[2 hydroxy-2-(2-naphthyl)propyl]-5-methylhexa-2,4-dienoic acid **22b** as a colourless oil; ν_{max} 3600-3400 (OH) and 1710 (C=O) cm^{-1}; δ_H 8.0-7.4 (7 H, m, C_8H_7) 5.75 (1 H, s, C4-H), 5.22 (1 H, s, C2-H), 4.72 (1 H, s, OH), 3.74 (3 H, s, CO_2CH_3), 3.32 (1 H, d, J 12.8 Hz, C3-CH_2), 2.95 (1 H, d, 12.8 Hz, C3-CH_2), 1.66 and 1.57 (6 H, 2 s, C5-CH_3 and C6-CH_3), and 1.31 (3 H, s, C3-C-CH3).

4-(2-Methylprop-1-enyl)-6-methyl-6-(2-naphthyl)-5,6-dihydropyran-2-one 23b.- When the above methyl ester of acid **22b** (104 mg) was heated with p-toluensulfonic acid in refluxing methylene dichloride, the title dihydropyran-2-one **23b** was obtained as a colourless solid (75 mg; 72 %), mp 132-137° C. Found: C, 81.9; H, 6.92. $C_{20}H_{20}O_2$ requires C, 82.16; H, 6.89 %. ν_{max} 1700 (C=O) cm^{-1}; δ_H 7.9-7.3 (7 H, m, $C_{10}H_7$), 5.78 (1 H, s, C1'-H), 5.69 (1 H, s, C2-H), 3.07 and 2.91 (2 H, 2 d J 17.4 Hz, C5-H), and 1.86, 1.82 and 1.78 (9 H, 3 s, 3 CH_3) ppm; $\delta^{13}C$ 165.51, 152.14, 144.54, 141.13, 132.85, 132.37, 128.31, 128.10, 127.35, 126.29, 126.10, 123.51, 123.32, 122.53, 116.25, 82.42, 39.78, 29.81, 27.68, and 20.59 ppm.

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