# PATENT SPECIFICATION (11) 1 563 732

1 563 732

(21) Application No. 47205/76 (22) Filed 12 Nov. 1976
(31) Convention Application No. 632 028
(32) Filed 14 Nov. 1975
(31) Convention Application No. 722 939
(32) Filed 13 Sept. 1976 in
(33) United States of America (US)
(44) Complete Specification published 26 March 1980
(51) INT CL³ C07C 69/76; A61K 31/035//C07C 43/164, 47/26, 49/84, 57/42; C07F 9/54
(52) Index at acceptance
C2C 200 201 202 204 21X 220 227 22Y 231 237 240 248 259 294 295 304 30Y 311 31Y 350 351 355 35Y 360 361 362 364 366 367 368 36Y 388 401 409 40Y 43X 46Y 47X 490 503 506 50Y 623 624 625 628 652 655 658 65X 662 695 776 778 779 802 80Y AA BW TB UN WP
C2P 1L2 3B11A 3B18B 3B18D 3B19B 8 9


(19)

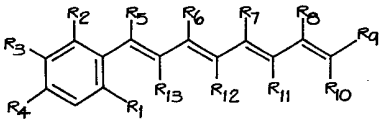

## (54) POLYENE COMPOUNDS


(71) We, F. HOFFMANN - LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company, of 124—184 Grenzacherstrasse, Basle, Switzerland, do

hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to polyene compounds. More particularly, the invention in concerned with fluorinated aromatic polyene compounds, a process for the manufacture thereof and pharmaceutical preparations containing same.

The polyene compounds provided by the present invention are compounds of the general formula

(I) 


wherein $R_1$, $R_2$ and $R_3$ each represent a lower alkyl group, $R_4$ represents a lower alkoxy group, $R_6$ and $R_8$ each represent a methyl or trifluoromethyl group, $R_9$ represents a formyl, hydroxymethyl, alkoxymethyl, alkanoyloxymethyy, carboxyl, alkoxycarbonyl, lower alkenoxycarbonyl, lower alkynoxycarbonyl, carbamoyl, mono-(lower alkyl)carbomyl, di(lower alkyl)-carbamoyl, or N-heterocyclylcarbonyl group and $R_5$, $R_7$, $R_{10}$, $R_{11}$, $R_{12}$ and $R_{13}$ each represent a hydrogen or fluorine atom, with the proviso that at least one of $R_5$, $R_7$, $R_{10}$, $R_{11}$, $R_{12}$ and $R_{13}$ reepresents a fluorine atom or at least one of $R_6$ and $R_8$ represents a trifluoromethyl group,

and pharmaceutically acceptable salts thereof.

The compounds of formula I can occur as *cis/trans* mixtures which can be separated into the *cis* and *trans* compounds or isomerised to the all-*trans* compound using conventional techniques.

As used in this specification, the term "lower alkyl" means alkyl groups which contain from 1 to 6 carbon atoms (e.g. methyl, ethyl, propyl, *iso*propyl and 2-methyl-propyl), the term "lower alkoxy" means alkoxy groups which contain from 1 to 6 carbon atoms (e.g. methoxy, ethoxy and *iso*propoxy and the terms "alkoxymethyl" and "alkoxycarbonyl" include straight-chain and branched-chain alkoxy groups which contain from 1 to 20 carbon atoms (e.g. methoxy, ethoxy, *iso*-propoxy and cetyloxy). Preferred, however, are those alkoxy groups which contain from 1 to 6 carbon atoms. The said alkoxy group can be unsubstituted or substituted by functional groups; for example, by nitrogen-containing groups such as by substituted or alkyl-substituted amino or morpholino groups or by a piperidyl or pyridyl group. The terms "lower alkenoxycarbonyl" and "lower alkynoxycarbonyl" mean alkenoxy and alkynoxy groups which contain from 2 to 6 carbon atoms, e.g. allyloxy and propargyloxy). The alkanoyloxy groups present in the alkanoyloxymethyl group are derived from alkanecarboxylic acids which contain from 1 to 20 carbon atoms (e.g. acetic acid, propionic acid, pivalic acid, palmitic acid and stearic acid). The preferred alkanecarboxylic acids are lower alkanecarboxylic acids which contain from 1 to 6 carbon atoms. The carbamoyl groups can be monosubstituted or disubstituted by

straight-chain or branched-chain lower alkyl groups (e.g. methyl, ethyl and *iso*propyl). Examples of such substituted-carbamoyl groups are the methylcarbamoyl, dimethylcarbamoyl and diethylcarbamoyl groups. The term "N-heterocyclyl" includes 5-membered and 6-membered heterocyclic groups which, in addition to the one nitrogen atom, may contain a second nitrogen atom or an oxygen or sulphur atom. Of the heterocyclic rings, the piperidino, morpholino, thiomorpholino and pyrrolidino rings are preferred. The term "pharmaceutically acceptable salts" means alkali metal salts (e.g. sodium and potassium) salts. All formulae given in this specification include *cis/trans* and all-*trans* isomers of the double-bonds on the polyene side-chains.

Examples of polyene compounds of formula I are:

9 - (4 - methoxy - 2,3,6 - trimethylphenyl)-2 - fluoro - 3,7 - dimethyl - (2(Z),4(E),6(E),8(E)-nonatetraenoic acid ethyl ester,

9 - (4 - methoxy - 2,3,6 - trimethylphenyl)-2 - fluoro - 3,7 - dimethyl - 2(Z),4(E), 6(Z),8(E) - nonatetraenoic acid ethyl ester,

9 - (4 - methoxy - 2,3,6 - trimethylphenyl)-6 - fluoro - 3,7 - dimethyl - 2(E),4(E),6(Z),8(E)- - nonatetraenoic acid methyl ester,

9 - (4 - methoxy - 2,3,6 - trimethylphenyl)-6 - fluoro - 3,7 - dimethyl - 2(Z),4(E),](Z),8(E) - nonatetraenoic acid methyl ester,

9 - (4 - methoxy - 2,3,6 - trimethylphenyl)-6 - fluoro - 3,7 - dimethyl - 2(E),4(E), 6(E),8(E) - nonatetraenoic acid methyl ester,

9 - (4 - methoxy - 2,3,6 - trimethylphenyl)-4 - fluoro - 3,7 - dimethyl - 2(E),4(E),6(E),8(E) - nonatetraenoic acid ethyl ester,

9 - (4 - methoxy - 2,3,6 - trimethylphenyl)-4 - fluoro - 3,7 - dimethyl - 2(E),4(Z),6(E)-8(E) - nonatetraenoic acid ethyl ester,

9 - (4 - methoxy - 2,3,6 - trimethylphenyl)-3 - methyl - 7 - trifluoromethyl - 2(E),4(E),6(E),8(E) - nonatetraenoic acid methyl ester,

9 - (4 - methoxy - 2,3,6 - trimethylphenyl)-3,7 - dimethyl - 5 - fluoro - 2,4,6,8 - nonatetraenoic acid ethyl ester,

9 - (4 - methoxy - 2,3,6 - trimethylphenyl)-3,7 - dimethyl - 8 - fluoro - 2,4,6,8 - nonatetraenoic acid methyl ester,

9 - (4 - methoxy - 2,3,6 - trimethylphenyl)-3 - trifluoromethyl - 7 - methyl - 2,4,6,8-nonatetraenoic acid ethyl ester,

9 - (4 - methoxy - 2,3,6 - trimethylphenyl)-8 - fluoro - 3,7 - dimethyl - 2(E),4(E),6(E),8(Z)-nonatetraenoic acid methyl ester,

9 - (4 - methoxy - 2,3,6 - trimethylphenyl)-3 - trifluoromethyl - 7 - methyl - 2(E),4(E),6(E),8(E) - nonatetraenoic acid ethyl ester.

The polyene compounds provided by this invention are pharmacodynamically valuable. They can be used for the topical and systemic therapy of benign and malignant neoplasia and of premalignant lesions as well as for the systemic and topical prophylaxis of these conditions.

The polyene compounds provided by this invention are relatively non-toxic. The tumour-inhibiting activity of the present polyene compounds is significant. In the papilloma test, tumours induced with dimethylbenzanthracene and croton oil regress.

The following Table illustrates the activity and toxicity of representative polyene compounds provided by this invention:

TABLE I

| Polyene compound of Example | Hypervitaminosis*) effective dosage mg/kg/day | Dosage administered mg/kg/wk | Decrease of papillomae in diameter % |
|---|---|---|---|
| 1 | 12.5 | 50 | –37 |
| 2 | 100 | 400 | –65 |
| 3A | 50 | 200 | –79 |
| | | 100 | –60 |
| | | 50 | –35 |
| | | 25 | –24 |
| 3B | | 200 | –28 |
| 4 | >200 | 400 | –20 |
| 5A | >200 | 400 | –51 |
| 5B, 7 | 75 | 400 | –82 |
| | | 100 | –61 |
| | | 25 | –41 |
| 6 | >200 | 400 | –25 |
| 8 | >200 | 400 | –34 |
| 9 | >200 | 400 | – 8 |

*) Bollag: Europ. J. Cancer Vol 10 (1974) 732–733.

The compounds of formula I and pharmaceutically acceptable salts thereof can be used as medicaments in the form of pharmaceutical preparations which contain them in association with a compatible carrier material.

Pharmaceutical preparations for systemic administration can be prepared, for example, by adding a compound of formula I or a pharmaceutically acceptable salt thereof as the active ingredient to pharmaceutically acceptable, non-toxic, inert, solid or liquid carriers which are usual in such preparations. The pharmaceutical preparations can be administered enterally, parenterally or topically. Suitable preparations for enteral administration are, for example, tablets, capsules, dragées, syrups, suspensions, solutions and suppositories. Suitable pharmaceutical preparations for parenteral administration are infusion solutions.

The dosages in which the compounds of formula I and pharmaceutically acceptable salts thereof are administered can be varied according to the mode and route of administration and according to the requirements of the patient. For example, from 25 mg to 100 mg can be administered daily in a single or divided dosages.

The pharmaceutical preparations can also contain pharmaceutically acceptable inert or pharmacodynamically active additives. Tablets or granules, for example, can contain a series of pharmaceutically acceptable binders, fillers, carrier materials or diluents. Liquid preparations can, for example, take the form of sterile water-miscible solutions. Capsules can contain a pharmaceutically acceptable filler or thickener. Furthermore, pharmaceutically acceptable flavour-improving additives and pharmaceutically acceptable substances commonly used as preservatives, stabilisers, moisture retainers or emulsifiers, salts for varying the osmotic pressure, buffers and other pharmaceutically acceptable additives can also be present in the pharmaceutical preparations.

The aforementioned pharmaceutically acceptable carrier materials and diluents are well-known in the pharmaceutical field and can be organic or inorganic substances such as water, gelatin, lactose, magnesium stearate, talc, gum arabic and polyalkyleneglycols. It

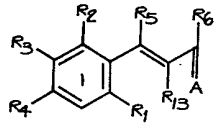
is, of course, a prerequisite that all adjuvants used in the preparation of the pharmaceutical preparations are non-toxic and pharmaceutically acceptable.

For topical administration, the pharmaceutical preparations are expediently made up in the form of salves, tinctures, creams, solutions, lotions, sprays, suspensions and the like. Ointments, creams and solutions are preferred. These pharmaceutical preparations for topical administration can be prepared by mixing a compound of formula I or a pharmaceutically acceptable salt thereeof as the active ingredient with pharmaceutically acceptable non-toxic, inert, solid or liquid carriers which are customary in such preparations and which are suitable for topical administration.

A conventional pharmaceutically acceptable antioxidant (e.g., tocopherol, N - methyl - γ-tocopheramine, butylated hydroxyanisole or butylated hydroxytoluene) can also be incorporated into the present pharmaceutical preparations.

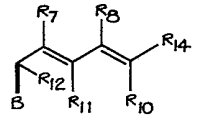
According to the process provided by the present invention, the polyene compounds of formula I hereinbefore and pharmaceutically acceptable salts thereof are manufactured by reacting a compound of the general formula

(IIa)



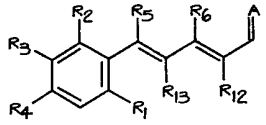
with a compound of the general formula

(IIIa)



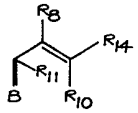
or by reacting a compound of the general formula

(IIb)



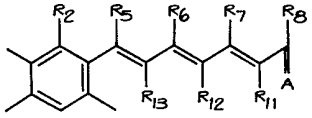
with a compound of the general formula

(IIIb)



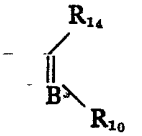
or by reacting a compound of the general formula

(IIc)



with a compound of the general formula

(IIIc)



wherein in formulae IIa, IIb, IIc and IIIa, IIIb, IIIc, one of A and B represents an oxo group and the other represents hydrogen and either a triarylphosphonium group of the formula

$$-P[Y]_3^{\oplus}\ Z^{\ominus},$$

in which Y represents an aryl group and Z represents the anion of an inorganic or organic acid, or a dialkoxyphosphinyl group of the formula

$$-P[X]_2 \downarrow O$$

in which X represents an alkoxy group, $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_{10}$, $R_{11}$, $R_{12}$ and $R_{13}$ have the significance given earlier, $R_{14}$ represents an alkoxymethyl, dialkoxymethyl, alkanoyloxymethyl, alkoxycarbonyl, alkenoxycarbonyl or alkynoxycarbonyl group when B represents an oxo group, or $R_{14}$ represents a formyl, hydroxymethyl, alkoxymethyl, dialkoxymethyl, carboxyl, alkoxycarbonyl, alkenoxycarbonyl or alkynoxycarbonyl group when B represents hydrogen and a triarylphosphonium or dialkoxy phosphinyl group,

and, in optional sequence and if desired, esterifying or amidating a carboxylic acid obtained, or hydrolysing or amidating a carboxylic acid ester obtained, or reducing a carboxylic acid or carboxylic acid ester to the corresponding alcohol and, if desired, etherifying or esterifying said alcohol, or saponifying an alcohol ester, or hydrolysing an acetal obtained, or oxidising an alcohol or alcohol ester obtained, and, if desired, converting an acid obtained into a pharmaceutically acceptable salt.

The aryl groups denoted by Y in the aforementioned triarylphosphonium groups include all known aryl groups, but preferably include mononuclear aryl groups such as the phenyl group, (lower alkyl)-phenyl or (lower alkoxy)-phenyl groups; for example, tolyl, xylyl, mesityl and *p*-methoxyphenyl. Of the inorganic acid anions denoted by Z in the triarylphosphonium groups aforesaid, the chlorine,

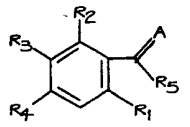
bromine, iodine and hydrosulphate ions are preferred. The preferred organic acid anion is the tosyloxy ion. The alkoxy groups denoted by X in the dialkoxyphosphinyl groups aforesaid are preferably lower alkoxy groups and most preferably the methoxy and ethoxy groups.

Compounds falling within formula II, some of which are novel, can be prepared, for example, by treating an appropriately-substituted benzene with a formylating agent in a conventional manner in the presence of a Lewis acid and condensing the resulting substituted benzaldehyde with acetone in a conventional manner. The resulting 4 - (substituted phenyl) - but - 3 - en - 2 - one (IIa) is subsequently converted into a 3 - methyl - 5 - (substituted phenyl) - penta - 2,4 - dien - 1 - oic acid ethyl ester or a 2 - fluoro - 3 - methyl - 5 - (substituted phenyl) - penta - 2,4 - dien - 1 - oic acid ethyl ester by condensation with (diethoxyphosphinyl)acetic acid ethyl ester or with (diethoxyphosphinyl) - fluoroacetic acid ester in a conventional manner. The carboxylic acid ester obtained is reduced in a conventional manner using di*iso*-butyl aluminium hydride or bis(2 - methoxyethoxy) - sodium aluminium hydride. The resulting 3 - methyl - (5 - substituted phenyl) - penta - 2,4 - dien - 1 - ol or 2 - fluoro - 3 - methyl - (5 - (substituted phenyl) - penta - 2,4 - dien - 1 - ol is treated with an oxidising agent (e.g. manganese dioxide in an organic solvent such as acetone or methylene chloride) to give a compound of formula IIb in which A represents an oxo group.

Compounds falling within formula IIb in which A represents hydrogen and a triarylphosphonium or dialkoxyphosphinyl group can be prepared by halogenating a 3 - methyl - 5 - (substituted phenyl) - penta - 2,4 - dien - 1 - ol or a 2 - fluoro - 3 - methyl - 5 - (substituted phenyl) - penta - 2,4 - dien - 1 - ol in a conventional manner (e.g. by treatment with a phosphorus trihalide or phosphorus pentahalide) and reacting the resulting halide with a triarylphosphine or with a trialkylphosphite.

Compounds falling within formula IIa carrying a trifluoromethyl group on the side-chain can be prepared, for example, by treating an appropriately substituted benzaldehyde with a propargyl Grignard reagent (e.g. $CF_3{\equiv}C{-}MgBr$) and rearranging the resulting propargyl compound by treatment with mercuric sulphate in an acidic medium according to the Meyer Schuster rearrangement reaction.

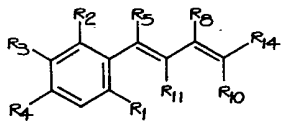
Compounds falling within formula IIb can also be prepared by reacting a compound of formula IIIb hereinbefore wherein $R_{14}$ is formyl with a compound of the general formula



(IV)

wherein A, $R_1$, $R_2$, $R_3$, $R_4$ and $R_5$ have the significance given earlier.

When A in formula IV represents an oxo group, such a compound can be reacted with a compound of formula IIIb in which B represents hydrogen and either a triarylphosphonium or dialkoxyphosphinyl group (as in formula III) to give a novel compound of the general formula



(V)

wherein $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_8$, $R_{10}$, $R_{11}$ and $R_{14}$ have the significance given earlier with the exception that the proviso of formula I does not apply since the compounds of formula V need not carry a fluorine atom or a trifluoromethyl group.

When B in formula IIIb represents an oxo group, then A in formula IV represents hydrogen and a triarylphosphonium or dialkyoxyphosphinyl group.

The preparation of the compounds of formula IIIb is documented in the literature.

The reaction of a compound of formula IIa, IIb or IIc with a compound of formula IIIa, IIIb or IIIc yields a compound of formula I. The reaction is carried out under the conditions of a Wittig or a Horner reaction.

According to the Wittig procedure, the respective starting materials are reacted together in the presence of an acid-binding agent (e.g. an alkali metal alcoholate such as sodium methylate or an alkylene oxide which may be alkyl-substituted, preferably ethylene oxide or 1,2-butylene oxide) in a solvent (e.g. a chlorinated hydrocarbon such as methylene chloride or dimethylformamide) or in the absence of a solvent at a temperature between room temperature and the boiling point of the reaction mixture.

According to the Horner procedure, the reaction is carried out with the aid of a base and preferably in the presence of an inert organic solvent (e.g., using sodium hydride in benzene, toluene, dimethylformamide, tetrahydrofuran, dioxane or 1,2-dimethoxyethane or using an alkali metal alcoholate in an alkanol such as sodium methylate in methanol) at a temperature between 0°C and the boiling point of the reaction mixture.

A carboxylic acid of formula I can be converted in a conventional manner (e.g. by treat-

ment with thionyl chloride, preferably in pyridine) into an acid chloride which then can be converted into an ester by reaction with an alkanol or into an amide by treatment with ammonia.

A carboxylic acid ester of formula I can be hydrolysed to a carboxylic acid in a conventional manner; for example, by treatment with alkali, especially aqueous-alcoholic sodium hydroxide or potassium hydroxide at a temperature between room temperature and the boiling point of the mixture. The resulting carboxylic acid can then be amidated via an acid halide as described earlier. Alternatively, a carboxylic acid ester can be directly amidated as described hereinafter.

A carboxylic acid ester of formula I can be converted directly into a corresponding amide by treatment with lithium amide. This treatment is advantageously carried out at room temperature.

A carboxylic acid or carboxylic acid ester of formula I can be reduced to a corresponding alcohol of formula I in a conventional manner. The reduction is advantageously carried out using a metal hydride or an alkyl metal hydride in an inert solvent. Examples of hydrides which have proved to be especially suitable are mixed metal hydrides such as lithium aluminium hydride and bis(2-methoxy-ethoxy)-sodium aluminium hydride. Suitable inert solvents are, *inter alia*, ether, tetrahydrofuran or dioxan when lithium aluminium hydride is used and ether, hexane, benzene or toluene when di*iso*butylaluminium hydride or bis(2 - methoxy - ethoxy) - sodium aluminium hydride is used.

An alcohol of formula I can be etherified with an alkyl halide such as ethyl iodide, such as etherification being carried out, for example, in the presence of a base, preferably sodium hydride, in an organic solvent such as dioxan, tetrahydrofuran, 1,2-dimethoxyethane or dimethylformamide at a temperature between 0°C and room temperature.

An alcohol of formula I can be esterified by treatment with an alkanoyl halide or anhydride, conveniently in the presence of a base (e.g. pyridine or triethylamine) at a temperature between room temperature and the boiling point of the mixturre.

An alcohol ester obtained as described earlier can be saponified in a conventional manner; for example, in the manner previously described in connection with the saponification of a carboxylic acid ester.

An acetal obtained as described earlier can be hydrolysed in a conventional manner by treatment with a proton donator in an inert solvent (e.g. using hydrochloric acid in tetrahydrofuran).

An alcohol of formula I or an ester thereof can be oxidised in a conventional manner to give a corresponding carboxylic acid of formula I. The oxidation is advantageously carried out using silver (I) oxide and an alkali in water or in a water-miscible organic solvent at a temperature between room temperature and the boiling point of the oxidation mixture.

A carboxylic acid of formula I forms salts with bases, especially with alkali metal hydroxides and particularly with sodium hydroxide and potassium hydroxide.

The following Examples illustrate the process provided by the present invention:

Example 1.

9 - (4 - Methovy - 2,3,6 - trimethylphenyl)-2 - fluoro - 3,7 - dimethyl - 2(Z),4(E),6(E),8(E) - nonatetraenoic acid ethyl ester.

5.05 g (0.0179 mol) of 4 - (diethoxyphosphinyl) - 2(Z,E) - fluoro - 3 - methylcrotonic acid ethyl ester in 10 ml. of 1,2-dimethoxyethane were added dropwise to a cold (0°—5°C) suspension of 0.83 g (0.0173 mol) of sodium hydride (50% oil dispersion), which had been washed with pentane to remove the oil, in 50 ml of 1,2-dimethoxyethane. The resulting mixture was stirred at 23°C for 1 hour. To this dark brown mixture were then added 4.35 g (0.0178 mol) of 5 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 3 - methyl-2(E),4(E) - pentadien - 1 - al in 20 ml of 1,2-dimethoxyethane. The resulting mixture was stirred at 23°C under argon for 2 hours. It was then poured into 250 ml of ice-water, acidified to pH 4 with 1-*N* hydrochloric acid and extracted with three 200 ml portions of methylene chloride. The methylene chloride extracts were combined, washed with two 200 ml portions of water and two 150 ml portions of saturated brine and then dried over magnesium sulphate. Evaporation to dryness *in vacuo* yielded crude crystalline material which was purified by column chromatography on 250 g of silica gel. Elution with ether/petroleum ether (5:95) gave a crystalline substance which, on recrystallisation from methylene chloride/petroleum ether, yielded pure 9 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 2 - fluoro - 3,7 - dimethyl - 2(Z),4(E),6(E),8(E) - nonatetraenoic acid ethyl ester as yellow crystals of melting point 140°—143°C.

Example 2.

9 - (4 - Methoxy - 2,3,6 - trimethylphenyl)-2 - fluoro - 3,7 - dimethyl - 2(Z),4(E),6(Z),8(E) - nonatetraenoic acid ethyl ester.

5.52 g (0.0196 mol) of 4 - (diethoxyphosphinyl) - 2(Z,E) - fluoro - 3 - methyl crotonic acid ethyl ester in 10 ml of 1,2-dimethoxyethane were added dropwise to a cold (0°—5°C) suspension of 0.984 g (0.0205 mol) of sodium hydride (50% oil dispersion), which had been washed with pentane to re-

move the oil, in 50 ml of 1,2-dimethoxyethane. The resulting mixture was stirred at 23°C for 1 hour. 4.80 g (0.0196 mol) of 5 - (4 - methoxy - 2,3,6 - trimethylphenyl)-3 - methyl - 2(Z),4(E) - pentadien - 1 - al in 20 ml of 1,2-dimethoxyethane were then addeed to the resulting dark brown suspension. The resulting mixture was stirred at 23°C under argon for 2 hours and then poured into 250 ml of ice-water. The mixture was worked-up as described in Example 1 to yield a crude oily product which was quickly chromatographed on 250 g of silica gel. Elution with ether/petroleum ether (5:95) yielded an oily substance which, upon further purification by five recrystallisations from petroleum ether, yielded 9 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 2 - fluoro - 3,7 - dimethyl - 2(Z),(4E),6(E),8(E) - nonatetraenoic acid ethyl ester as yellow crystals of melting point 103°—113°C. High-pressure liquid chromatographic analysis of this ester indicated a purity of approximately 90%.

The 5 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 3 - methyl - 2(E),4(E) - pentadien-1 - al used as the starting material in Example 1 and the 5 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 3 - methyl - 2(Z),4(E) - pentadien - 1 - al used as starting material in this Example can be prepared, for example, as follows:

a) 5 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 3 - methyl - 2(Z,E),4(E) - pentadienoic acid methyl ester.

4.92 g of sodium hydride (50% oil dispersion; 0.103 mol), which had been washed with three 50 ml portions of pentane, were added to a 1 litre 3-necked round-bottomed flask. 330 ml of 1,2-dimethoxyethane (distilled over lithium aluminium hydride) were added, the mixture was cooled to 0°C and 20.08 g (0.111 mol) of (dimethoxyphosphinyl)acetic acid methyl ester were slowly added. The resulting mixture was allowed to warm to 23°C and mechanically stirred at this temperature for 2 hours under argon. 20.0 g (0.092 mol) of 4 - (4 - methoxy - 2,3,6 - trimethylphenyl)-3 - buten - 2 - one in 50 ml of 1,2-dimethoxyethane were added dropwise to the resulting thick white paste. The resulting mixture was stirred at 23°C for 45 minutes and then refluxed for 2.5 hours. The mixture was then cooled in an ice-bath and then poured portionwise on to 1.2 litres of ice-water. The resulting solution was neutralised to pH 6—7 with 2-*N* hydrochloric acid and then extracted with three 300 ml portions of methylene chloride. The combined methylene chloride extracts were washed with three 300 ml portions of water and 300 ml of brine and then dried over anhydrous sodium sulphate. The solvent was evaporated *in vacuo* to give an orange-yellow oil which was quickly chromatographed on 250 g of silica gel. Elution with chloroform afforded 5 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 3 - methyl - 2(ZE),4(E) - pentadienoic acid methyl ester as a light orange coloured oil. The ratio of isomers was approximately 2:3 (2Z:2E) as determined by nuclear magnetic resonance analysis.

b) 5 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 3 - methyl - 2(Z,E),4(E) - pentadien - 1 - ol.

40.0 g (0.146 mol) of 5 - (4 - methoxy-2,3,6 - trimethylphenyl) - 3 - methyl - 2-(Z,E),4(E) - pentadienoic acid methyl ester in 500 ml of dry ether were added to a 2 litre three-necked round-bottom flask. The resulting solution was cooled to −73°C and, under argon, 106 ml of di*iso*butylaluminium hydride (1.5 molar in hexane; 0.160 mol) were added. The resulting mixture was stirred at −73°C for 0.5 hour and monitored by thin-layer chromatography. A further 100 ml (0.15 mol) of di*iso*butylaluminium hydride were added in three portions every 0.5 hour while stirring at −13°C. Thin-layer chromatography showed the presence of only a trace of starting material. The mixture was gradually warmed to −30°C and 250 ml of methanol/water (1:1) were slowly added while stirring. 500 ml of water were then added slowly and the temperature was maintained at *ca* 10°C until the formation of precipitate ceased. The mixture was filtered over Celite and washed several times with ether. The ethereal phase was separated and washed with three 100 ml portions of hydrochloric acid and three 100 ml portions of saturated brine and then dried over anhydrous magnesium sulphate. The solvent was evaporated *in vacuo* to give 5 - (4 - methoxy-2,3,6 - trimethylphenyl) - 3 - methyl - 2(Z,E),4(E) - pentadien - 1 - ol as a yellow oil. An analytical sample showed that the isomeric ratio of 2E to 2Z was *ca* 2:1.

c) 5 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 3 - methyl - 2(E),4(E) - pentadien-1 - al and 5 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 3 - methyl - 2(Z),4(E) - pentadien-1 - al.

306 g (3.5 mol) of manganese dioxide and 750 ml of methylene chloride were added to a 2 litre three-necked round-bottomed flask. The flask was flushed with argon. To the foregoing well-stirred mixture were added 66 g (0.268 mol) of 5 - (4 - methoxy - 2,3,6-trimethylphenyl) - 3 - methyl - 2(Z,E),4(E)-pentadien - 1 ol in 500 ml of methylene chloride. The resulting mixture was mechanically stirred at 23°C under argon for 4 days. The resulting mixture was filtered over Celite and the filter cake was washed with 2 litres of methylene chloride. The solvent was evaporated *in vacuo* to yield a crude oil. This oil was purified, initially by column chromatography on 800 g of silica gel and then by preparative high - pressure chromatography. This procedure led to the isolation of 5 - (4-

methoxy - 2,3,6 - trimethylphenyl) - 3-methyl - 2(Z),4(E) - pentadiene - 1 al as the less polar component which, on recrystallisation from ether/petroleum ether, gave light yelow crystals of melting point 82°—85°C. Further elution of the column gave 5 - (4-methoxy - 2,3,6 - trimethylphenyl) - 3-methyl - 2(E),4(E) - pentadien - 1 - al as light yellow crystals of melting point 61°—63°—C from ether-petroleum ether.

Example 3.

a) 9 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 6 - fluoro - 3,7 - dimethyl - 2(E),4(E),6(Z),8(E) - nonatetraenoic acid methyl ester.

1.152 g of sodium hydride (50% oil dispersion; 0.024 mol) were placed in a 250 ml three-necked flask and washed with two 50 ml portions of pentane. 25 ml of 1,2 - dimethoxyethane (distilled from lithium aluminium hydride) were added. 5.328 g (0.024 mol) of 4 - (dimethoxyphosphinyl) - 3 - methylcrotonic acid methyl ester in 25 ml of 1,2-dimethoxyethane were added dropwise to the mixture under argon with mechanical stirring over a period of 20 minutes. The resulting mixture was stirred under argon at 23°C for a further 2 hours. 6.288 g (0.024 mol) of 5 - (4 - methoxy - 2,3,6 - trimethylphenyl)-2 - fluoro - 3 - methyl - 2(Z),4(E) - pentadien - 1 al in 55 ml of 1,2-dimethoxyethane were added dropwise over a period of 35 minutes to the dark brown solution. A dark brown syrup appeared. The mixture was again stirred under argon at 23°C for 2.5 hours. The mixture was cooled in an ice-bath, 500 ml of ice-water were added and the solution was neutralised with 1-*N* hydrochloric acid to pH 5—6. 200 ml of methylene chloride were added and stirring was continued for a few minutes. The layers were separated and the aqueous phase was extracted with three 200 ml portions of methylene chloride. The combined methylene chloride extracts were washed with three 100 ml portions of water and dried over anhydrous magnesium sulphate. The solvent was removed in a rotary evaporator at 40°C/30 mm to yield a crude product which was chromatographed on 300 g of silica gel and eluted with ether/petroleum ether (30°—60°C) (1:9) to yield a yellow-orange crystalline substance. Fractional crystallisations of the yellow-orange crystalline substance from methylene chloride/petroleum ether (1:4) or acetone yielded pure 9 - (4 - methoxy - 2,3,6-trimethylphenyl) - 6 - fluoro - 3,7 - dimethyl-2(E),4(E),6(Z),8(E) - nonatetraenoic acid methyl ester as yellow-orange crystals of melting point 119°—121.5°C.

b) 9 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 6 - fluoro - 3,7 - dimethyl - 2(Z),4(E),6(Z),8(E) - nonatetraenoic acid methyl ester.

The mother liquor from part a) was evaporated to dryness and the resulting oily residue was crystallised from ether/petroleum ether (ca 1:1) at 23°C to yield 9 - (4 - methoxy-2,3,6 - trimethylphenyl) - 6 - fluoro - 3,7-dimethyl - 2(Z),4(E),6(Z),8(E) - nonatetraenoic acid methyl ester as yellow crystals of melting point 134°—139.5°C.

Example 4.

9 - (4 - Methoxy - 2,3,6 - trimethylphenyl)-6 - fluoro - 3,7 - dimethyl - 2(E),4(E),6(E),8(E) - nonatetraenoic acid methyl ester.

5.32 g (0.024 mol) of 4 - (dimethoxyphosphinyl )- 3 - methylcrotonic acid methyl ester in 25 ml of dry 1,2 - dimethoxyethane were added dropwise to a suspension of sodium hydride (1.152 g; 0.024 mol; 50% dispersion), which has been washed with petroleum ether to remove the oil, in 25 ml of dry 1,2-dimethoxyethane. The resulting mixture was stirred under argon at 25°C for 1.5 hours. 6.288 g (0.024 mol) of 5 - (4 - methoxy-2,3,6 - trimethylphenyl) - 2 - fluoro - 3-methyl - 2(E),4(E) - pentadien - 1 - ol in 50 ml of 1,2-dimethoxyethane were added dropwise. The resulting mixture was then stirred at 25°C for 17 hours and refluxed for 1 hour under argon. The mixture was then cooled in an ice-bath. 500 ml of ice-water were and the resulting solution was acidified with 1-*N* aqueous hydrochloric acid to *ca* pH 3—4. The mixture was then extracted with three 200 ml portions of methylene chloride. The combined methylene chloride extracts were washed with three 100 ml portions of water, dried over anhydrous magnesium sulphate and concentrated *in vacuo* to yield an orange crystalline substance which was purified by chromatography on 200 g of silica gel. Elution with 5—10% ether in petroleum ether yielded yellow crystals which, upon two recrystallisations from methylene chloride/petroleum ether (1:4), gave 9 - (4-methoxy - 2,3,6 - trimethylphenyl) - 6-fluoro - 3,7 - dimethyl - 2(E),4(E),6(E),8(E) - nonatetraenoic acid methyl ester as yellow needles of melting point 133°—141°C. An analytical sample was obtained by one recrystallisation; melting point 139°—143°C.

The 5 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 2 - fluoro - 3 - methyl - 2(Z),4(E)-pentadien - 1 - al used as the starting material in Example 3 and the 5 - (4 - methoxy-2,3,6 - trimethylphenyl) - 2 - fluoro - 3-methyl - 2(E),4(E) - pentadien - 1 - al used as the starting material in this Example can be prepared, for example, as follows:

a) Ethyl 5 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 2(Z,E) - fluoro - 3 - methyl-2,4(E) - pentadienoate.

14.4 g of sodium hydride (50% oil dispersion; 0.30 mol) were placed in a 2 litre three-

necked flask under argon and washed with 100 ml of pentane. 250 ml of 1,2-dimethoxyethane (distilled from lithium aluminium hydride) were then added and the flask was cooled in an ice-bath. The resulting mixture was stirred well and 72.7 g (0.30 mol) of (diethoxyphosphinyl)fluoroacetic acid ethyl ester in 80 ml of 1,2-dimethoxyethane were added dropwise under argon over a period of 30 minutes. The resulting mixture was again stirred at 23°C under argon for 2 hours and the colour became brown. A further 70 ml of 1,2-dimethoxyethane were added. While stirring vigorously 65.4 g (0.30 mol) of 4 - (4-methoxy - 2,3,6 - trimethylphenyl) - 3 - buten-2 - one in 200 ml of 1,2-dimethoxyethane were then added dropwise at 23°C over a period of 40 minutes. An exothermic reaction was observed and a brown coloured syrupy precipitate began to appear. The mixture was stirred at 23°C for a further 1 hour and at 52°—55°C for 4 hours. The flask was then cooled in an ice-bath and 1 litre of ice-water was added. The solution was adjusted to pH *ca* 4—5 with 1-*N* hydrochloric acid and extracted with three 250 ml portions of methylene chloride. The combined methylene chloride extracts were washed with three 200 ml portions of water and dried over anhydrous magnesium sulphate. Evaporation of the solvent to dryness in a rotary evaporator under reduced pressure yielded a brown coloured oil which was purified by column chromatography on 800 g of silica gel. Elution with ether/petroleum ether (30°—60°C) (5:95) yielded pure ethyl 5 - (4 - methoxy - 2,3,6-trimethylphenyl) - 2(Z,E) - fluoro - 3-methyl - 2,4(E) - pentadienoate as a mixture of isomers in a 2(Z) to 2(E) ratio of approximately 3:2.

b) 5 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 2(Z,E) - fluoro - 3 - methyl-2,4(E) - pentadien - 1 - ol.

57.5 g (0.188 mol) of ethyl 5 - (4-methoxy - 2,3,6 - trimethylphenyl) - 2(Z,E)-fluoro - 3 - methyl - 2,4(E) - pentadienoate were dissolved in 1.2 litres of absolute ether and cooled in a dry ice/acetone bath to −70°C under argon while stirring (crystallisation occurred). 250 ml of di*iso*butylaluminium hydride (1.5 molar in hexane) were then added dropwise over a period of 30 minutes at such a rate that the internal temperature was maintained at −65°C to −70°C. The reaction was monitored by thin-layer chromatography which indicated the presence of ester starting material. A further 125 ml of di*iso*butylaluminium hydride were then added over a period of 2 hours and thin-layer chromatography showed that no more starting material was present. 500 ml of methanol/water (1:1) were added slowly and the mixture was stirred at 5°—10°C for a few minutes until the formulation of precipitates stopped in an exothermic reaction. The precipitate was filtered off through Celite and washed with four 800 ml portions of ether. The combined filtrates (*ca* 4.5 litres) were transferred to a separating funnel and the layers were separated. The aqueous phase was extracted with 500 ml of ether. The combined ether extracts were washed with three 800 ml portions of water and dried over anhydrous magnesium sulphate. Evaporation of the ether to dryness in a rotary evaporator yielded a crude material which, on crystallization from ether/petroleum ether (30°—60°C) (*ca* 1:30), yielded 5 - (4 - methoxy-2,3,6 - trimethylphenyl) - 2(Z,E) - fluoro-3 - methyl - 2,4(E) - pentadien - 1 - ol as yellow crystals of melting point 48°—80°C.

c) 5 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 2 - fluoro - 3 - methyl - 2(Z),4(E)-pentadien - 1 - al and 5 - (4 - methoxy-2,3,6 - trimethylphenyl) - 2 - fluoro - 3-methyl - 2(E),4(E) - pentadien - 1 - al.

53.5 g of 5 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 2(Z,E) - fluoro - 3 - methyl-2,4(E) - pentadien - 1 - ol were dissolved in 300 ml of methylene chloride and added in several portions to a mechanically stirred mixture of 200 g of manganese dioxide in 800 ml of methylene chloride under argon. The mixture was stirred in the dark for 3 days. A further 100 g of manganese dioxide were added and stirring was continued under argon for a further 4 days. The mixture was filtered through Celite and the filter cake was washed well with *ca* 1.5 litres of methylene chloride. (The word "Celite" is a registered Trade Mark). The solvent was evaporated to dryness in a rotary evaporator to yield a light brown coloured oil which was chromatographed on 1.4 kg of silica gel. Elution with diethyl ether/hexane (1:9) yielded a crystalline substance which was recrystallised once from ether/petroleum ether (1:1) to yield pure 5 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 2 - fluoro - 3 - methyl - 2(E),4(E)-pentadien - 1 - al as light yellow crystals of melting point 79°—84°C. The column was further eluted with diethyl ether/hexane (1:4) to yield 5 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 2 - fluoro - 3 - methyl - 2(Z),4(E)-pentadien - 1 - al as light yellow crystals of melting point 87°—91°C. An analytical sample had a melting point of 89°—93°C after two recrystallisations from ether.

Example 5.

a) A - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 4 - fluoro - 3,7 - dimethyl - 2(E), 4(E),6(E),8(E) - nonatetraenoic acid ethyl ester and

b) 9 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 4 - fluoro - 3,7 - dimethyl - 2(E), 4(Z),6(E),8(E) - nonatetraenoic acid ethyl ester.

4.88 g (0.0173 (mol) of 4 - (diethoxyphosphinyl) - 4 - fluoro - 3 - methyl - crotonic acid ethyl ester in 20 ml of 1,2-dimethoxyethane were added dropwise at 23°C under argon to a suspension of 1.25 g (0.025 mol; 50% oil dispersion) of sodium hydride, which had been washed with petroleum ether to remove the oil, in 60 ml of dry 1,2-dimethoxyethane (distilled from lithium aluminium hydride). The resulting mixture was stirred at 23°C for 10 minutes and then refluxed for 1.25 hours while stirring under argon. The mixture was then cooled to 35°—40°C over a period of 1 hour. 4.23 g (0.0173 mol) of 5 - (4 - methoxy - 2,3,6 - trimethylphenyl)-3 - methyl - 2(E),4(E) - pentadien - 1 - al in 20 ml of 1,2-dimethoxyethane were then added dropwise to the resulting light brown mixture over a period of 0.5 hour. The resulting mixture was stirred at 23°C for 1.5 hours and then refluxed for 45 minutes under argon. The mixture was then cooled in an ice-bath and *ca* 400 ml of crushed ice/water were added. The resulting solution was then adjusted to pH *ca* 2 with 1-N aqueous hydrochloric acid. 250 ml of methylene chloride were added and the resulting mixture was stirred for about 10 minutes. The aqueous phase was then separated from the methylene chloride phase and was extracted with three 150 ml portions of methylene chloride. The combined methylene chloride extracts were washed with two 100 ml portions of water, dried over anhydrous magnesium sulphate, filtered and evaporated *in vacuo* to give a brown oily product which was purified by column chromatography in 700 g of silica gel. Elution with 5% ether in petroleum ether yielded yellow crystalline 9 - (4 - methoxy - 2,3,6 - trimethylphenyl)-4 - fluoro - 3,7 - dimethyl - 2(E),4(E),6(E),8(E) - nonatetraenoic acid ethyl ester as the less polar isomer of melting point 76°—83°C which, upon recrystallisation from petroleum ether, yielded the pure ester of melting point 78°—84°C. The column was further eluted with 5—10% ether in petroleum ether to give the more polar isomer of melting point 84°—93°C which, upon recrystallisation from ether, yielded pure 9 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 4 - fluoro - 3,7 - dimethyl-2(E),4(Z),6(E),8(E) - nonatetraenoic acid ethyl ester as yellow crystals of melting point 92.5°—96.5°C.

Example 6.

9 - (4 - Methoxy - 2,3,6 - trimethylphenyl)-3 - methyl - 7 - trifluoromethyl - (2E), 4(E),6(E),8(E) - nonatetraenoic acid methyl ester.

745 mg (3.35 mmol) of 4 - (diethoxyphosphinyl) - 3 - methylcrotonic acid methyl ester in 5 ml of 1,2-dimethoxyethane were added at 0°C to a suspension of 116 mg (3.35 mmol) of sodium hydride (50% oil dispersion; the oil was removed by washing three times with pentane) in 5 ml of dry 1,2-dimethoxyethane. The resulting mixture was first stirred at 0°C for 10 minutes and then at 23°C for 1 hour under argon. To the foregoing mixture was then added 1.0 g (3.35 mmol) of 5 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 3 - trifluoromethyl - 2(E),4(E)-pentadien - 1 - al in 5 ml of 1,2-dimethoxyethane over a period of 15 minutes. The resulting mixture was stirred at 23°C for 3 hours and refluxed for 0.5 hour. The mixture was cooled in an ice-bath and 250 ml of water were added. The solution was adjusted to pH 4 with aqueous 1-*N* hydrochloric acid and then extracted with four 50 ml portions of methylene chloride. The combined methylene chloride extracts were washed with water and brine and dried over magnesium sulphate. Evaporation of the methylene chloride *in vacuo* yielded a crude product which was purified by column chromatography on 25 g of silica gel. Elution with 5% ether in petroleum ether gave 5 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 3 - trifluoromethyl - 2(E),4(E)-pentadien - 1 - al. Further elution with 5% ether in petroleum ether yielded 9 - (4-methoxy - 2,3,6 - trimethylphenyl) - 3-methyl - 7 - trifluoromethyl - 2(E),4(E), 6(E) - nonatetraenoic acid methyl ester as yellow crystals of melting point 112°—113.5°C upon recrystallisation from petroleum ether.

The 5 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 3 - trifluoromethyl - 2(E),4(E)-pentadien - 1 - al used as the starting material can be prepared, for example, as follows:

a) 4 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 1,1,1 - trifluoro - 2 - butyn - 4 - ol.

43.4 g (0.40 mol) of ethyl bromide were added dropwise over a period of 1 hour under argon to a refluxing mixture of 10.6 g (0.436 mol) of magnesium metal in 1 litre of dry ether. The resulting mixture was refluxed while stirring for a further 1.5 hours and then cooled to 23°C. To this mixture of ethylmagnesium bromide were added through a gas dispersion tube 41.0 g (0.436 mol) of 1,1,1-trifluoro-2-propyne. The resulting mixture was stirred at 23°C under argon while the 1,1,1-trifluoro-2-propyne was recycled three times. A brown coloured viscous oil of 1,1,1-trifluoro-2-propynyl magnesium bromide was formed. 50 g (0.281 mol) of 2,3,6 - trimethyl-4 - methoxy - benzaldehyde were added to this mixture under argon while stirring vigorously at 23°C over a period of 30 minutes. The mixture was stirred at 23°—30°C for a further 2 hours. A further 10 g (0.056 mol) of 2,3,6-trimethyl - 4 - methoxy - benzaldehyde in 100 ml of ether were added and the mixture was stirred for a further 1 hour. The mixture was cooled in an ice-bath and a saturated aqueous solution of ammonia chloride was

added slowly while stirring. The layers were separated and the aqueous phase was extracted three times with ether. The combined ether extracts were washed with water and dried over anhydrous magnesium sulphate. Evaporation of the ether to dryness under reduced pressure gave a crude product which was recrystallised twice from chloroform/hexane to yield 4 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 1,1,1 - trifluoro - 2 - butyn - 4 - ol as white crystals of melting point 126°—130°C. An analytical sample melted at 127°—129.5°C.

b) 4 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 1,1,1 - trifluoro - 3(E) - buten-2 - one.

92 mg (0.233 mol) of mercuric sulphate and 0.05 ml of concentrated sulphuric acid in 5 ml of acetic acid were added to a solution of 277 mg (1.02 mmol) of 4 - (4 - methoxy-2,3,6 - trimethylphenyl) - 1,1,1 - trifluoro-2 - butyn - 4 - ol in 10 ml of glacial acetic acid. The resulting mixture was refluxed while stirring for 2 hours. The mixture was then diluted with 150 ml of ice-water and extracted with three 40 ml portions of ether. The combined ether extracts were washed with water and dried over anhydrous magnesium sulphate. Evaporation of the solvent to dryness *in vacuo* (45°—50°C/20 mm) yielded a yellow crystalline substance which was recrystallised twice from petroleum ether to give 4 - (4 - methoxy-2,3,6 - trimethylphenyl) - 1,1,1 - trifluoro-3(E) - buten - 2 - one as yellow crystals of melting point 79°—82°C.

In a similar manner, this crystalline substance was prepared from 60 g of 4 - (4-methoxy - 2,3,6 - trimethylphenyl) - 1,1,1-trifluoro 1 2 - butyn - 4 - ol.

c) Methyl - 5 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 3 - trifluoromethyl - 2(E), 4(E) - pentadienoate.

20.08 g (0.111 mol) of (dimethoxyphosphinyl)-acetic acid methyl ester in 50 ml of 1,2-dimethoxyethane were added dropwise at 0°C to a suspension of 4.92 g (0.103 mol) of sodium hydride (50% oil dispersion), which had been washed with pentane to remove the oil, in 200 ml of 1,2-dimethoxyethane. The resulting mixture was stirred at 23°C under argon for 2 hours. 25 g of 4 - (4 - methoxy-2,3,6 - trimethylphenyl) - 1,1,1 - trifluoro-3(E) - buten - 2 - one in 200 ml of 1,2-dimethoxyethane were then added dropwise to the resulting white paste-like mixture. The resulting mixture was stirred at 23°C for 0.5 hour and then refluxed for 2 hours. The mixture was then cooled in an ice-bath and the contents were poured into 1 litre of ice-water. The resulting solution was neutralised to pH 7 with aqueous 2-*N* hydrochloric acid and then extracted with three 200 ml portions of methylene chloride. The combined methylene chloride extracts were washed with water and brine and dried over anhydrous magnesium sulphate. Evaporation of the methylene chloride solution to dryness *in vacuo* gave a crude product which was purified by column chromatography on 700 g of silica gel. Elution with 3% ether in petroleum ether yielded methyl 5 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 3 - trifluoromethyl - 2(E),4(E)-pentadienoate which, upon crystallisation from pentane at −72°C, gave yellow crystals of melting point 42°—48°C.

d) 5 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 3 - trifluoromethyl - 2(E),4(E)-pentadien - 1 - ol.

69.5 ml of di*iso*butylaluminium hydride (1.53 molar in hexane; 0.106 mol) were added dropwise to a solution of 17.44 g (0.0531 mol) of methyl 5 - (4 - methoxy - 2,3,6-trimethylphenyl) - 3 - trifluoromethyl - 2(E), 4(E) - pentadienoate in 500 ml of dry ether at 72°C over a period of 0.5 hour. The resulting solution was stirred at −72°C for 20 minutes under argon. A further 25 ml (38.25 mmol) of di*iso*butylaluminium hydride were added and the mixture was stirred for a further 30 minutes at −72°C. To the resulting yellow solution were then added 100 ml of methanol/water (1:1) at −72°C while stirring. The resulting mixture was stirred and warmed slowly to 23°C. The precipitate which formed was removed by filtration and washed well with ether. The ether phase of the filtrate was separated and washed with water and brine and dried over magnesium sulphate. Evaporation of the ether solution to dryness *in vacuo* yielded a yellow crude crystalline substance which, upon recrystallisation from petroleum ether, gave 5 - (4 - methoxy - 2,3,6-trimethylphenyl) - 3 - trifluoromethyl - 2(E), 4(E) - pentadien - 1 - ol of melting point 69°—71°C.

e) 5 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 3 - trifluoromethyl - 2(E),4(E)-pentadien - 1 - al.

A mixture of 78 g (0.896 mol) of manganese dioxide and 13 g (0.0434 mol) of 5 - (4 - methoxy - 2,3,6 - trimethylphenyl)-3 - trifluoromethyl - 2(E),4(E) - pentadien-1 - ol in 750 ml of dry methylene chloride was stirred at 23°C under argon for 15 hours. The resulting mixture was filtered through Celite and the precipitate was washed well with 1 litre of methylene chloride. The methylene chloride was evaporated to dryness *in vacuo* to give an oily crude product which was purified by column chromatography on 600 g of silica gel. Elution with 5% ether in petroleum ether gave 5 - (4 - methoxy - 2,3,6-trimethylphenyl) - 3 - trifluoromethyl - 2(E), 4(E) - pentadien - 1 - al as a yellow oil. An analytical sample was obtained in the form of yellow crystals of melting point 55°—58°C

by crystallisation from pentane.

Example 7.

9 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 4 - fluoro - 3,7 - dimethyl - 2(E),4(Z), 6(E),8(E) - nonatetraenoic acid ethyl ester. The words "Florisil" and "Norit" in this Example are registered Trade Marks.

2.37 g (0.0494 mol) of a 50% sodium hydride oil dispersion were added to a flame-dried 500 ml three-necked flask under argon and then washed three times with 10 ml of pentane to remove the oil. After the addition of 10 ml of dry dimethoxy ethane [distilled from di(methoxymethylenemethoxy)-sodium aluminium hydride], 11.08 g (0.0494 mol) of (diethoxyphosphinyl)-acetic acid ethyl ester in 30 ml of dry dimethoxyethane were added dropwise while stirring at 23°C. The mixture was stirred at 23°C until no more hydrogen was evolved (*ca* 1 hour). 10 g (0.033 mol) of 8 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 3 - fluoro - 6 - methyl - 3(Z),5(E),7(E) - octatrien - 2 - one in 75 ml of dimethoxymethane were then added dropwise to the resulting brown mixture at 23°C while stirring under argon. After completion of the addition, the mixture was stirred at 23°C for 0.5 hour and then at 50°C for 2 hours under argon. Thin-layer chromatography [silica gel; ethyl acetate/hexane (15:85)] showed that no more starting material was present. The mixture was then cooled to *ca* 20°C and poured on to 200 ml of cold water containing crushed ice. The resulting mixture was acidified to pH 4 by the dropwise addition, while stirring, of concentrated hydrochloric acid. The mixture was then extracted three times with 200 ml of ether. The combined ether extracts were washed three times with 200 ml of water and dried over anhydrous magnesium sulphate. After evaporation of the ether to dryness, the resulting crude product was quickly passed through 200 g of Florisil and eluted with 10% ether/petroleum ether. The eluant was collected and concentrated almost to dryness at aspirator pressure at *ca* 40°C. The resulting residue was added to 300 ml of methylene chloride, treated with 10 g of Norit A on a steam-bath for *ca* 2 minutes, then filtered and washed with 400 ml of methylene chloride. A yellow crystalline material formed on evaporation of the methylene chloride to dryness at 35°—40°C/20—30 mm. The crystalline material was dissolved in 25 ml of ether containing 1 ml of methylene chloride and diluted with 50 ml of petroleum ether (30°—60°C). The resulting solution was kept at 23°C for several hours and crystallisation then occurred. After further cooling at 0°—4°C for 18 hours, the crystals were collected, washed with 50 ml of petroleum ether and dried to yield pure 9 - (4 - methoxy-2,3,6 - trimethylphenyl) - 4 - fluoro - 3,7-dimethyl - 2(E),4(Z),6(E),8(E) - nonatetraenoic acid ethyl ester.

The 8 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 3 - fluoro - 6 - methyl - 3(Z), 5(E),7(E) - octatrien - 2 - one used as the starting material can be prepared, for example, as follows:

a) Ethyl 7 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 2 - fluoro - 5 - methyl - 2-(Z,E),4(E),6(E) - heptatrienoate.

20.16 g (0.42 mol) of 50% sodium hydride were added to a 3 litre three-necked flask under argon and washed with three 50 ml portions of pentane. The flask was then charged with 250 ml of dry dimethoxyethane. 79.92 g (0.33 mol) of (diethoxyphosphinyl)-fluoroacetic acid ethyl ester were added dropwise to the resulting mixture while stirring over a period of 0.5 hour at 23°C. The mixture was stirred and heated at 40°C for a further 1 hour under argon and then cooled to room temperature. 75 g (0.306 mol) of 5 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 3 - methyl - 2(E),4(E) - pentadien - 1 - al in 500 ml of dry dimethoxyethane were added dropwise to the resulting yellow-orange mixture while stirring under argon. The resulting mixture was stirred at 23°C for 2 hours and at 40°C for a further 2 hours. The resulting mixture was cooled to *ca* 20°C, poured on to 500 ml of crushed ice-water and then adjusted to pH *ca* 4 by the addition of portions of 1-*N* hydrochloric acid while stirring. The solution was extracted four times with 500 ml of ether. The combined ether extracts were washed four times with 500 ml of water and 500 ml of brine and dried over anhydrous magnesium sulphate. Evaporation of the ether to dryness at aspirator pressure yielded a dark orange oil which was quickly filtered through 2.2 kg of silica gel. Elution with 10—20% by volume ether in petroleum ether (30°—60°C) yielded an oily ester as a mixture of isomers (E:Z *ca* 3:2). The column was further eluted with 40% ether to remove unreacted starting material. The resulting mixture of isomeric esters was converted directly into ethyl 7 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 2 - fluoro - 5 - methyl - 2(Z), 4(E),6(E) - heptatrienoate.

b) Ethyl 7 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 2 - fluoro - 5 - methyl-2(Z),4(E),6(E) - heptatrienoate.

66.1 g (0.199 mol) of ethyl 7 - (4-methoxy - 2,3,6 - trimethylphenyl) - 2-fluoro - 5 - methyl - 2(Z,E),4(E),6(E)-heptatrienoate (E:Z *ca* 3:2) were dissolved in 600 ml of dry ether and 1.4 g of crystalline iodine were added portionwise to the solution. The resulting solution was stirred under argon at 23°C for 48 hours and then washed three times with 200 ml of 5% sodium thiosulphate solution and twice with 200 ml of water and

then dried over anhydrous magnesium sulphate. Evaporation of most of the ether in a rotary evaporator under reduced pressure yielded a concentrated solution which was quickly passed through 100 g of Florisil. The column was washed with 1.5 litres of ether and the residue obtained after evaporation of the ether to dryness was then redissolved in 100 ml of ether and diluted with 600 ml of petroleum ether (30°—60°C). This solution was kept at 23°C for 1 hour and at 0°C for 3 hours. The resulting crystals were collected, washed with cold petroleum ether and dried to yield yellow crystals of 7 - (4 - methoxy-2,3,6 - trimethylphenyl) - 2 - fluoro - 5-methyl - 2(Z),4(E),6(E) - heptatrienoic acid ethyl ester of melting point 106°110°C. The mother liquor was evaporated to dryness to yield an oil which was dissolved in 750 ml of ether. 0.83 g of iodine crystals was added to the resulting solution which was then stirred under argon at 23°C for 70 hours and worked-up as described earlier to yield yellow crystals of 7 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 2 - fluoro - 5 - methyl-2(Z),4(E),6(E) - heptatrienoic acid ethyl ester of melting point 109°—111°C.

c) 7 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 2 - fluoro - 5 - methyl - 2(Z), 4(E),6(E) - heptatrienoic acid.

150 ml of methanol and 40 ml of 6-*N* sodium hydroxide were added to 41.5 g (0.125 mol) of 7 - (4 - methoxy - 2,3,6-trimethylphenyl) - 2 - fluoro - 5 - methyl-(Z),4(E),6(E) - heptatrienoic acid ethyl ester dissolved in 450 ml of tetrahydrofuran. The resulting solution was stirred at 23°C for 15 minutes. A white precipitate formed. 500 ml of water were added to dissolve the precipitate. The resulting solution was then stirred for 1 hour at 23°C and most of the tetrahydrofuran and methanol were evaporated off at 50°C and at aspirator pressure. 150 ml of water were then added and the solution was extracted twice with 200 ml of ether. The resulting alkaline-aqueous phase was cooled to 0°—4°C, acidified to pH *ca* 3—4 with concentrated hydrochloric acid and then extracted three times with 300 ml of ether. The combined ether extracts were washed twice with 200 ml of water and once with 200 ml of brine and dried over anhydrous magnesium sulphate. The solvent was evaporated to dryness under reduced pressure to yield yellow crystals of 7 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 2 - fluoro - 5 - methyl-2(Z),4(E),6(E) - heptatrienoic acid of melting point 203°—210°C.

d) 8 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 3 - fluoro - 6 - methyl - 3(Z),5(E), 7(E) - octatrien - 2 - one.

37.82 g (0.124 mol) of 7 - (4 - methoxy-2,3,6 - trimethylphenyl) - 2 - fluoro - 5-methyl - 2(Z),4(E),6(E) - heptatrienoic acid, which had been dried in a desiccator containing phosphorus pentoxide at *ca* 0.5 mm for 24 hours, were dissolved in 400 ml of dry tetrahydrofuran and cooled in a dry ice-acetone bath. 154 ml (0.248 mol) of methyl lithium (1.61 molar in ether) were added dropwise to the resulting solution at −72°C under argon from a syringe while stirring. After completion of the addition, the mixture was stirred at −75°C under argon for 15 minutes. Thin-layer chromatography [silica gel; ethyl acetate/hexane (3:7)] indicated that some acid was still present. A further 15.4 ml (0.025 mol) of methyl lithium were then added in the same manner as described earlier. The resulting mixture was stirred at −75°C for 1 hour. Thin-layer chromatography showed that some acid was still present. However, no more methyl lithium was added since an excess of this reagent produced a *ter*-alcohol as a byproduct. The cooling bath was removed and 150 ml of water were carefully added. Most of the tetrahydrofuran was removed at 50°C/30—50 mm. The aqueous solution was extracted three times with 300 ml of ether. The combined ether extracts were washed three times with 300 ml of water and dried over anhydrous magnesium sulphate. Evaporation of the ether to dryness under reduced pressure yielded a crude product which was dissolved in 50 ml of methylene chloride and diluted with 300 ml of hexane. The resulting solution was kept at 23°C for 1 hour, crystallisation occurring. After further refrigeration for 18 hours, the resulting crystals were collected, washed with 200 ml of cold hexane and dried to yield orange crystals of the product, 8 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 3 - fluoro - 6 - methyl - 3(Z), 5(E),7(E) - octatrien - 2 - one of melting point 108°—110°C. From the mother liquor there was obtained, as a second crop, orange crystals of the product of melting point 107°—110°C.

Example 8.

9 - (4 - Methoxy - 2,3,6 - trimethylphenyl)-8 - fluoro - 3,7 - dimethyl - 2(Z),4(E), 6(E),8(Z) - nonatetraenoic acid methyl ester.

1.31 g (0.027 mol) of a 50% sodium hydride oil dispersion were placed in a dry flask and washed with 40 ml of petroleum ether under argon. The petroleum ether was replaced by 60 ml of dry dimethoxyethane. 6.06 g (0.027 mol) of 4 - (dimethoxyphosphinyl) - 3 - methyl - crotonic acid methyl ester in 30 ml of dimethoxyethane were then added dropwise while stirring to the resulting slurry. The mixture was stirred at 23°C until evolution of hydrogen stopped. 6.0 g (0.0229 mol) of 5 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 3 - methyl - 4 - fluoro - 2(E),4(Z)-pentadien - 1 - al in 30 ml of dimethoxyethane were then added over a period of 10 minutes

to the resulting dark brown mixture. The resulting mixture was stirred at 23°C under argon for 1.6 hours. *Ca* 500 ml of crushed ice/water were then slowly added. The solution was adjusted to pH ca 1 with 6-*N* hydrochloric acid and then immediately extracted with ether. The extract was then worked-up in the usual manner to yield a crude product which was purified by column chromatography on 500 g (4.5 cm × 84 cm column) of silica gel. Elution with ether/petroleum ether (1:9) yielded a yellow crystalline substance containing mainly two isomers. This yellow crystalline substance was crystallised from methylene chloride/ether (1:3) to yield 9 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 8 - fluoro - 3,7 - dimethyl - 2(E), 4(E),6(E),8(Z) -nonatetraenoic acid methyl ester as yellow crystals of melting point 121.5° —130°C.

The 5 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 3 - methyl - 4 - fluoro - 2(E), 4(Z), pentadien - 1 - al used as the starting material can be prepared, for example, as follows:

a) 3 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 2 - fluoro - 2(Z,E) - propenoic acid ethyl ester.

60 g (0.248 mol) of (diethoxyphosphinyl)-fluoroacetic acid ethyl ester in 50 ml of dimethoxyethane were added dropwise at 23°C over a period of two hours to a suspension of 17.8 g (0.37 mol) of a 50% sodium hydride oil dispersion, which had been washed with petroleum ether to remove the oil, in 150 ml of dry dimethoxyethane. The resulting mixture was stirred at 23°C for 3 hours. When evolution of hydrogen could no longer be observed, 44 g (0.247 mol) of 2,3,6-trimethylanisaldehyde in 50 ml of dry dimethoxyethane were added over a period of 15 minutes. The mixture was stirred at 23°C under argon for 20 hours. A further 20 g (0.0825 mol) of (diethoxyphosphinyl)-fluoroacetic acid ethyl ester in 20 ml of dimethoxyethane were then added in several portions. The mixture was refluxed while stirring for 1.5 hours under argon. After the mixture had been cooled to *ca* 30°C, 1.92 g (0.04 mol) of 50% sodium hydride and 5.0 g (0.0206 mol) of (diethoxyphosphinyl)-fluoroacetic acid ethyl ester in 10 ml of dimethoxyethane were added. After refluxing for a further 0.5 hour, thin-layer chromatography indicated that the reaction did not proceed any further. The resulting mixture was cooled to *ca* 4°C and poured on to 1 litre of crushed ice/water. The solution which formed was acidified to pH 2 by the portionwise addition of 150 ml of 1-*N* hydrochloric acid. The resulting solution was extracted three times with 400 ml of methylene chloride. The combined methylene chloride extracts were washed five times with 500 ml of water and once with 250 ml of brine and dried over anhydrous sodium sulphate. Evaporation of solvent to dryness under reduced pressure yielded a brown oily material which was shown to contain approximately 90—95% product by thin-layer chromaotgraphy.

The oily material was purified by column chromatography on 1.50 kg of silica gel. Elution with ether/petroleum ether (30°—60°C) (1:19 to 1:9) yielded 3 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 2 - fluoro-2(Z,E) - propenoic acid ethyl ester as a light yellow oil.

b) 3 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 2 - fluoro - 2(Z,E) - propenoic acid.

97.7 ml (0.586 mol) of aqueous 6-*N* sodium hydroxide were added dropwise to a stirred solution of 78.10 g (0.293 mol) of 3 - (4 - methoxy - 2,3,6 - trimethylphenyl)-2 - fluoro - 2(Z,E) - propenoic acid ethyl ester in 150 of methanol. A white precipitate appeared and became very thick. The resulting mixture was stirred rapidly for 0.5 hour at 23°C and then diluted with 1 litre of ice-water. *Ca* 50 ml of concentrated hydrochloric acid were added dropwise to the well-stirred mixture until it reached pH 1. The white solid which precipitated was extracted three times into 400 ml of ether. The combined ether extracts were washed once with 500 ml of brine and dried over anhydrous sodium sulphate. Evaporation of the ether to dryness under reduced pressure yielded a white solid of melting point 157°—184°C which was dried over phosphorus pentoxide in a high vacuum at 23°C for several days to yield 3-(4 - methoxy - 2,3,6 - trimethylphenyl) - 2-fluoro - 2(Z,E) - propenoic acid of melting point 163°—181°C.

c) 4 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 3 - fluoro - 3(Z) - buten - 2 - one.

A solution of 25 g (0.105 mol) of 3 - (4-methoxy - 2,3,6 - trimethylphenyl) - 2-fluoro - 2(Z,E) - propenoic acid in 35 ml of dry tetrahydrofuran and 215 ml of anhydrous ether was cooled to −70°C in a dry ice/acetone bath. 47.5 ml (0.105 mol) of methyl lithium (2.23-*M* in ether) were then injected slowly into this cooled solution from a hypodermic syringe while stirring under argon at such a rate that the internal temperature was maintained at −60°C to −70°C. The mixture was stirred under argon at −70°C for 10 minutes. A further 47.5 ml of methyl lithium were then injected into the solution in the same manner. The resulting solution was stirred at −70°C under argon for 1 hour. An additional 5 ml (0.0115 mol) of methyl lithium were added as before and stirring was continued for 10 minutes. The resulting mixture was then poured cautiously on to 500 ml of crushed ice/water, acidified with concentrated hydrochloric acid to pH *ca*

1 and extracted with ether. This was separated into neutral and acidic fractions to yield the crude product, 4 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 3 - fluoro - 3(Z) - buten-2 - one, as a light yellow oil and a small amount of unchanged starting material as a white solid. The crude product was then purified by column chromatography on 1.6 kg of silica gel (8.6 × 86 cm column). Elution with ether/petroleum ether (1:9 yielded a low melting crystalline substance. Upon further elution with ether/petroleum ether (1:9) a crystalline E-isomeric keto compound of melting point 56°—59°C was isolated. Further elution with the same eluant yielded the Z-isomer which was crystallised from petroleum ether (30°—60°C) to yield 4 - (4 - methoxy-2,3,6 - trimethylphenyl) - 3 - fluoro - 3(Z)-buten - 2 - one of melting point 34°—43.5°C.

d) 5 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 3 - methyl - 4 - fluoro - 2(E),4(Z)-pentadienoic acid ethyl ester.

26.84 g (0.12 mol) of (diethoxyphosphinyl)acetic acid ethyl ester were added dropwise over a period of 25 minutes to a suspension of 5.75 g (0.12 mol) of a 50% sodium hydride oil dispersion, which had been washed with petroleum ether to remove the oil, in 200 ml of dry dimethoxyethane. The mixture was stirred at 23°C for 1 hour and then 23.53 g (0.0997 mol) of unsaturated 4 - (4 - methoxy - 2,3,6 - trimethylphenyl)-3 - fluoro - 3(Z) - buten - 2 - one in 10 ml of dimethoxyethane were added dropwise. The mixture was stirred at 23°C under argon for 1.25 hours. *Ca* 1 litre of crushed ice/water were slowly added and the solution was acidified to pH 2 with 6-*N* hydrochloric acid. The mixture was extracted with ether and worked-up in the usual manner to yield a brown oily crude product which was purified by column chromatography on 600 g of silica gel. Elution with ether/petroleum ether (30°—60°C) (1:19 to 1:9) yielded a white crystalline powder, 5 - (4 - methoxy - 2,3,6-trimethylphenyl) - 3 - methyl - 4 - fluoro-2(E),4(Z) - pentadienoic acid ethyl ester, of melting point 50°—51°C.

e) 5 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 3 - methyl - - 4 - fluoro - 2(E), 4(Z) - pentadien - 1 - ol.

86.5 ml (0.13 mol) of di*iso*butylaluminium hydride (1.5-*M* in hexane) were added dropwise to a solution of 14.48 g (0.065 mol) of 5 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 3 - methyl - 4 - fluoro - 2(E),4(Z)-pentadienoic acid ethyl ester dissolved in 400 ml of anhydrous ether and cooled to —65°C under argon. The resulting mixture was stirred under argon at —65°C for 5 minutes. A further 17 ml (0.0255 mol) of di*iso*butylaluminium hydride were added in two portions. The mixture was stirred at —65°C for approximately 20 minutes and the excess hydride was destroyed by the dropwise addition of 85 ml of methanol/water (1:1) at such a rate that the internal temperature did not exceed —30°C. 100 ml of water were then added and the mixture was stirred at 10°C for approximately 40 minutes. The precipitate which formed was filtered off and washed well with ether. The resulting layers were separated and the aqueous phase was further extracted with ether. The combined ether phases were washed with water and brine and dried over anhydrous sodium sulphate. Evaporation of the ether to dryness under reduced pressure yielded a crude product which was dissolved in 215 ml of ether, diluted with 60 ml of petroleum ether (30°—60°C) and kept at —10°C for 20 hours. The crystals which formed were collected, washed with 50 ml of petroleum ether and dried to yield pure 5 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 3 - methyl - 4 - fluoro-2(E),4(Z) - pentadien - 1 - ol as pale yellow crystals of melting point 71°—73.5°C.

f) 5 - 4 - Methoxy - 2,3,6 - trimethylphenyl) - 3 - methyl - 4 - fluoro - 2(E),4(Z)-pentadienal.

13.84 g (0.0524 mol) of 5 - ( 4 - methoxy-2,3,6 - trimethylphenyl) - 3 - methyl - 4-fluoro - 2(E),4(Z) - pentadien - 1 - ol in 55 ml of methylene chloride were added to a stirred mixture of 54.66 g (0.629 mol) of manganese dioxide in 60 ml of methylene chloride. The resulting mixture was stirred in the dark under argon for 65 hours and worked-up as usual to yield a yellow crystalline substance which was recrystallised from methylene chloride/petroleum ether (*ca* 1:4) to yield 5-(4 - methoxy - 2,3,6 - trimethylphenyl) - 3-methyl - 4 - fluoro - 2(E),4(Z) - pentadienal as yellow crystals of melting point 85°—88.5°C. A sample was recrystallised once for analysis and had a melting point of 86.5°—88.5°C.

Example 9.

9 - ( 4 - Methoxy - 2,3,6 - trimethylphenyl)-3 - trifluoromethyl - 7 - methyl - 2(E), 4(E),6(E),8(E) - nonatetraenoic acid ethyl ester.

9. 44 g (29.7 mmol) of 4 - (diethoxyphosphinyl) - 2(Z,E) - 3 - trifluoromethylcrotonic acid ethyl ester in 50 ml of dimethoxyethane were added dropwise to a suspension of 1.42 g (29.7 mmol) of a 50% sodium hydride oil dispersion (the oil was removed by washing with pentane) in 25 ml of dimethoxyethane at 0°C. The resulting mixture was stirred at 23°C until no more hydrogen gas was evolved (approximately 1 hour). 6.59 g (27 mmol) of 5 - (4 - methoxy - 2,3,6-trimethylphenyl) - 3 - methyl - 2(E),4(E)-pentadien - 1 al in 50 ml of dimethoxyethane were added dropwise to the resulting brown mixture under argon. The resulting mixture was stirred at 23°C under argon for 5 hours,

then poured on to crushed ice/water, adjusted to pH 3 with 2-N hydrochloric acid and then extracted three times with 250 ml of ether. The combined ether extracts were washed with water and dried over anhydrous magnesium sulphate. Evaporation of the ether to dryness *in vacuo* yielded a brown oily material which was purified by column chromatography on 300 g of silica gel. Elution with ether/petroleum ether (1:19) yielded a crystalline substance which was further recrystallised from petroleum ether to yield pure 9 - (4-methoxy - 2,3,6 - trimethylphenyl) - 3 - trifluoromethyl - 7 - methyl - 2(E),4(E),6(E),8(E) - nonatetraenoic acid ethyl ester as bright yellow crystals of melting point 72°—75°C.

The 4 - (diethoxyphosphinyl) - 2(Z,E)-3 - trifluoromethylcrotonic acid ethyl ester used as the starting material can be prepared, for example, as follows:

18.48 g (70.7 mmol) of ethyl 3 - trifluoromethyl - 4 - bromo - 2(Z,E) - butenoate and 12.95 g (78 mmol) of triethylphosphite were heated at 140°C for 3 hours while the ethyl bromide formed during the reaction was distilled off. The resulting crude product was distilled using a Vigreux column at 1 mm to yield a colourless liquid of boiling point 105°—110°C, containing a 1:1 mixture of isomers including 4 - diethoxyphosphinyl) - 2(Z-E)-3 - trifluoromethyl ) - crotonic acid ethyl ester, and a mixture (boiling point (110°—113°C) of the same isomers.

The following Examples illustrate typical pharmaceutical preparations provided by the present invention:

Example A.
Wet Granulation Formulation
(25 mg Tablets).

| Ingredients | Per tablet |
|---|---|
| Active compound (2% excess) | 25.5 mg |
| Modified starch | 2.5 mg |
| Pregelatinised starch | 2.5 mg |
| Microcrystalline cellulose | 3.5 mg |
| Lactose, anhydrous | 3.0 mg |
| Magnesium stearate | .3 mg |
| Talc | .7 mg |
| Total weight | 38.0 mg |

*Procedure:*

1. Mix all ingredients, except magnesium stearate and talc, in a suitable mixer. Mill and mix.
2. Granulate with water to a uniform wet consistency. Mill and spread on trays.
3. Dry overnight in a suitable dryer.
4. Mill and prepare a premix with magnesium stearate and talc. Mix for 5 minutes.
5. Compress on a suitable press.

Example B.
Direct Compression Formulation
(25 mg Tablets).

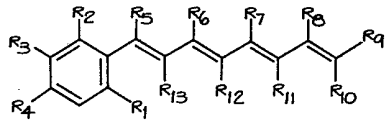
| Ingredients | Per tablet |
|---|---|
| Active compound (2% excess) | 25.5 mg |
| Lactose, anhydrous | 172.5 mg |
| Microcrystalline cellulose (pH 101) | 25.0 mg |
| Starch | 25.0 mg |
| Magnesium stearate | 2.0 mg |
| Total weight | 250 mg |

*Procedure:*

1. Mix all ingredients, except magnesium stearate, in a suitable mixer.
2. Make a premix with magnesium stearate and add to the mix in Step 1. Mix for 5 minutes.
3. Compress on a suitable press.

WHAT WE CLAIM IS:—

1. Polyene compounds of the general formula




(I)

wherein $R_1$, $R_2$ and $R_3$ each represent a lower alkyl group, $R_4$ represents a lower alkoxy group, $R_6$ and $R_8$ each represent a methyl or trifluoromethyl group, $R_9$ represents a formyl, hydroxymethyl, alkoxymethyl, alkanoyloxymethyl, carboxyl, alkoxycarbonyl, lower alkenoxycarbonyl, lower alkynoxycarbonyl, carbamoyl, mono-(lower alkyl)carbamoyl, di(lower alkyl)-carbamoyl, or N-heterocyclylcarbonyl group and $R_5$, $R_7$, $R_{10}$, $R_{11}$, $R_{12}$ and $R_{13}$ each represent a hydrogen or fluorine atom, with the proviso that at least one of $R_5$, $R_7$, $R_{10}$, $R_{11}$, $R_{12}$ and $R_{13}$ represents a fluorine atom or at least one of $R_6$ and $R_8$ represents a trifluoromethyl group,
and pharmaceutically acceptable salts thereof.

2. 9 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 2 - fluoro - 3,7 - dimethyl - 2(Z), 4(E),6(E),8(E) - nonatetraenoic acid ethyl ester.

3. 9 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 2 - fluoro - 3,7 - dimethyl - 2(Z), 4(E),6(Z),8(E) - nonatetraenoic acid ethyl ester.

4. 9 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 6 - fluoro - 3,7 - dimethyl - 2(E), 4(E),6(Z),8(E) - nonatetraenoic acid methyl ester.

5. 9 - (4 - Methoxy - 2,3,6 - trimethylphenyl) 6 - fluoro - 3,7 - dimethyl - 2(Z)-4(E),6(Z),8(E) - nonatetraenoic acid methyl ester.

6. 9 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 6 - fluoro - 3,7 - dimethyl - 2(E), 4(E),6(E),8(E) - nonatetraenoic acid methyl ester.

7. 9 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 4 - fluoro - 3,7 - dimethyl - 2(E), 4(E),6(E),8(E) - nonatetraenoic acid ethyl ester.

8. 9 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 4 - fluoro - 3,7 - dimethyl - 2(E), 4(Z),6(E),8(E) - nonatetraenoic acid ethyl ester.

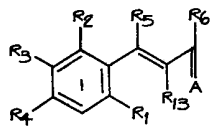
9. 9 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 3 - methyl - 7 - trifluoromethyl-2(E),4(E),6(E),8(E) - nonatetraenoic acid methyl ester.

10. 9 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 8 - fluoro - 3,7 - dimethyl - 2(E), 4(E),6(E),8(Z) - nonatetraenoic acid methyl ester.

11. 9 - (4 - Methoxy - 2,3,6 - trimethylphenyl) - 3 - trifluoromethyl - 7 - methyl-2(E),4(E),6(E),8(E) - nonatetraenoic acid ethyl ester.

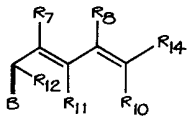
12. A process for the manufacture of the polyene compounds of formula I given in claim 1 and of pharmaceutically acceptable salts thereof, which process comprises reacting a compound of the general formula

(IIa)



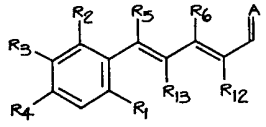
with a compound of the general formula

(IIIa)



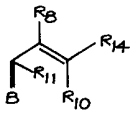
or reacting a compound of the general formula

(IIb)

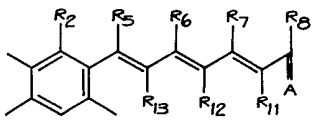


with a compound of the general formula

(IIIb)

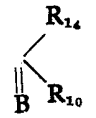


or reacting a compound of the general formula



(IIc)

with a compound of the general formula

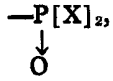


(IIIc)

wherein in formulae IIa, IIb, IIc and IIIa, IIIb, IIIc, one of A and B represents an oxo group and the other represents hydrogen and either a triarylphosphonium group of the formula

$$-P[Y]_3^{\oplus}\ Z^{\ominus},$$

in which Y represents an aryl group and Z represents the anion of an inorganic or organic acid, or a dialkoxyphosphinyl group of the formula



in which X represents an alkoxy group $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_{10}$, $R_{11}$, $R_{12}$ and $R_{13}$ have the significance given in claim 1, $R_{14}$ represents an alkoxymethyl, dialkoxymethyl, alkanoyloxymethyl, alkoxycarbonyl, alkenoxycarbonyl or alkynoxycarbonyl group when B represents an oxo group, or $R_{14}$ represents a formyl, hydroxymethyl, alkoxymethyl, dialkoxymethyl, carboxyl, alkoxycarbonyl, alkenoxycarbonyl or alkynoxycarbonyl group when B represents hydrogen and a triarylphosphonium or dialkoxyphosphinyl group,

and, in optional sequence and if desired, esterifying or amidating a carboxylic acid obtained, or hydrolysing or amidating a carboxylic acid ester obtained, or reducing a carboxylic acid or carboxylic acid ester obtained to the corresponding alcohol and, if desired, etherifying or esterifying said alcohol, or saponifying an alcohol ester, or hydrolysing an acetal obtained, or oxidising an alcohol or alcohol ester obtained, and, if desired, converting an acid into a pharmaceutically acceptable salt.

13. A process according to claim 12, wherein the reaction is carried out under the conditions of a Wittig reaction in the presence of an alkali metal alcoholate or in the presence of an alkylene oxide which may be alkyl-substituted.

14. A process according to claim 13, wherein said alkali metal alcoholate is sodium methylate.

15. A process according to claim 13, wherein said alkylene oxide which may be alkyl-substituted is ethylene oxide or 1,2-butylene oxide.

16. A process according to claim 13, claim 14 or claim 15, wherein the reaction is carried out in an inert organic solvent.

17. A process according to claim 16, wherein said inert organic solvent is a chlorinated hydrocarbon.

18. A process according to claim 17, wherein said chlorinated hydrocarbon is methylene chloride.

19. A process according to claim 16, wherein said inert organic solvent is dimethylformamide.

20. A process according to claim 12, wherein the reaction is carried out under the conditions of a Horner reaction using a base in the presence of an inert organic solvent.

21. A process according to claim 20, wherein the reaction is carried out using sodium hydride in 1,2-dimethoxyethane.

22. A process according to claim 20, wherein the reaction is carried out using an alkali metal alcoholate in an alkanol.

23. A process according to any one of claims 12 to 22 inclusive, wherein 5 - (4-methoxy - 2,3,6 - trimethylphenyl) - 3-methyl - penta - 2,4 - dien - 1 - al is reacted with 4 - (diethoxyphosphinyl) - 2 - fluoro-3 - methyl - crotonic acid ethyl ester.

24. A process according to any one of claims 12 to 22 inclusive, wherein 5 - (4-methoxy - 2,3,6 - trimethylphenyl) - 2-fluoro - 3 - methyl - penta - 2,4 - dien - 1-al is reacted with 4 - (dimethoxyphosphinyl)-3 - methyl - crotonic acid methyl ester.

25. A process according to any one of claims 12 to 22 inclusive, wherein 5 - (4-methoxy - 2,3,6 - trimethylphenyl) - 3-trifluoromethyl - penta - 2,4 - dien - 1 - al is reacted with 4 - (dimethoxyphosphinyl) - 3-methyl - crotonic acid methyl ester.

26. A process according to any one of claims 12 to 22 inclusive, wherein 8 - (4-methoxy - 2,3,6 - trimethylphenyl) - 3-fluoro - 6 - methyl - 3,5,7 - octatrien - 2-one is reacted with (diethoxyphosphinyl)-acetic acid ethyl ester.

27. A process according to any one of claims 12 to 22 inclusive, wherein 5 - (4-methoxy - 2,3,6 - trimethylphenyl) - 3-methyl - 4 - fluoro - 2,4 - pentadien - 1 - al is reacted with 4 - (dimethoxyphosphinyl)-3 - methyl - crotonic acid methyl ester.

28. A process according to any one of claims 12 to 22 inclusive, wherein 5 - (4-methoxy - 2,3,6 - trimethylphenyl) - 3-methyl - 2,4 - pentadien - 1 - al is reacted with 4 - (diethoxyphosphinyl) - 3 - trifluoromethyl - crotonic acid ethyl ester.

29. A process according to claim 12 for the manufacture of the polyene compounds of formula I given in claim 1 and of pharmaceutically acceptable salts thereof, substantially as hereinbefore described with reference to any one of Examples 1 to 9.

30. Polyene compounds of formula I given in claim 1 and pharmaceutically acceptable salts thereof, when manufactured by the process claimed in any one of claims 12 to 29 inclusive.

31. A pharmaceutical preparation containing a polyene compound of formula I given in claim 1 or a pharmaceutically acceptable salt thereof in association with a compatible carrier material.

32. A pharmaceutical preparation according to claim 31, wherein said polyene compound is 9 - (4 - methoxy - 2,3,6 - trimethylphenyl)-6 - fluoro - 3,7 - dimethyl - 2(E),4(E),6(Z), 8(E) - nonatetraenoic acid methyl ester.

For the Applicants,
CARPMAELS & RANSFORD,
Chartered Patent Agents,
43 Bloomsbury Square, London, WC1A 2RA.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1980.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.