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PATENT SPECIFICATION

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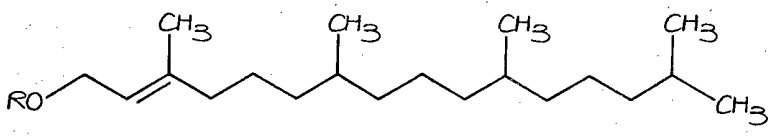
(19)

(54) PREPARATION OF TRANS-PHYTOL AND DERIVATIVES AND PRECURSORS THEREOF AND OF VITAMIN K_1

(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:—

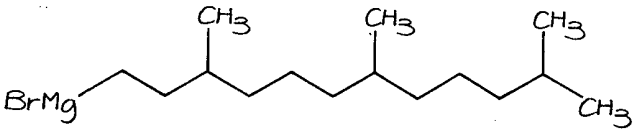
The present invention relates to the preparation of trans - phytol and derivatives and precursors thereof and of vitamin K_1.

According to the present invention, trans - phytol and derivatives thereof of the general formula



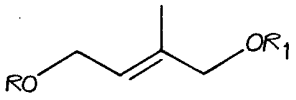
(I)

wherein R represents a hydrogen atom or a protecting group cleavable under acidic conditions, and vitamin K_1 are manufactured by condensing a Grignard compound of the formula



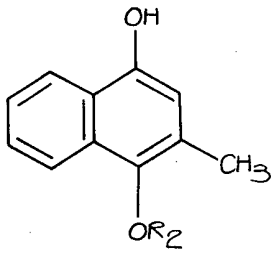
(II)

with a trans compound of the general formula



(III)

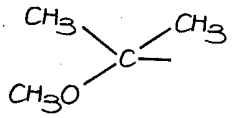
wherein R has the significance given earlier and R_1 represents an acyl group, in the presence of an organic solvent which is inert under the conditions of the condensation, and in the presence of a di - (alkali metal) - tetrahalocuprate, and, where vitamin K_1 is required, reacting a thus-obtained trans compound of formula I with a menadiol derivative of the general formula



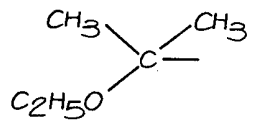
(IV)

wherein R_2 represents an acyl group, cleaving off the acyl group and oxidising the hydroxy groups.

The term "a protecting group cleavable under acidic conditions" used in this specification denotes, for example, a lower alkyl or phenyl - (lower alkyl) group, a group of the formula $R_3O—CHR_4—$ in which R_3 represents a $C_1—C_4$ alkyl group or a phenyl - ($C_1—C_3$ alkyl) group (e.g. benzyl, phenethyl or phenylpropyl) and R_4 represents a hydrogen atom or a $C_1—C_4$ alkyl group or R_3 and R_4 together represent a n-butylene group, especially the 2 - tetrahydropyranyl group; a group of the formula $(R_5)_3—A—$ in which R_5 represents a $C_1—C_4$ alkyl group and A represents a carbon or silicon atom (e.g. the tert. butyl or trimethylsilyl group); or a group of the formula



or



The term "acyl" denotes a straight-chain or branched-chain alkanoyl group containing up to 10 carbon atoms (e.g. formyl, acetyl, propionyl, butyryl, hexanoyl etc.) or an aroyl group containing up to 11 carbon atoms (e.g. benzoyl, phenylacetyl, naphthoyl etc.). The aromatic ring of the aroyl groups can be unsubstituted or substituted (e.g. by lower alkyl).

The term "lower alkyl" denotes a straight-chain or branched-chain alkyl group containing from 1 to 4 carbon atoms (e.g. methyl, ethyl, n - propyl, isopropyl, n - butyl, isobutyl, sec. butyl and tert. butyl).

The term "di - (alkali metal) - tetrahalocuprate" denotes, in particular, dilithium tetrachlorocuprate (Li_2CuCl_4).

In the present invention, in all chiral compounds the configuration at the asymmetric centres is (R) in the case of optically active compounds and (RS) in the case of the corresponding racemates.

The previous processes for the manufacture of vitamin K_1 are based on the condensation of a menadiol derivative of formula IV with isophytol or phytol. When isophytol or mixtures of trans - phytol and cis - phytol are used there are obtained relatively large amounts of cis-vitamin K_1 which exhibits only slight vitamin K_1 activity and which is accordingly undesirable. The amount of cis - vitamin K_1 has hitherto been smallest when pure trans - phytol is used, but pure trans - phytol has only been obtainable by relatively expensive synthetic methods and in an uneconomical manner.

The process provided by the present invention now offers a novel advantageous route to trans-phytol, or derivatives thereof, which can readily be converted in a manner known per se into vitamin K_1.

As specified above, the condensation of a Grignard compound of formula II with a trans compound of formula III is carried out in the presence of an organic solvent which is inert under the conditions of the condensation; thus use may be made of a solvent for Grignard compounds such as an ethereal solvent, for example, a di(lower alkyl) ether or a cyclic ether such as tetrahydrofuran, dioxan and the like. The condensation is carried out at a low temperature, i.e. at a temperature from about −80°C to about +50°C, preferably from about −70°C to about room temperature. The condensation should be conveniently be commenced at a low temperature (i.e. below about −60°C). The addition of the di - (alkali metal) - tetrahalocuprate used as the catalyst should also be carried out at this temperature. Subsequently, the temperature can be allowed to rise slowly up to

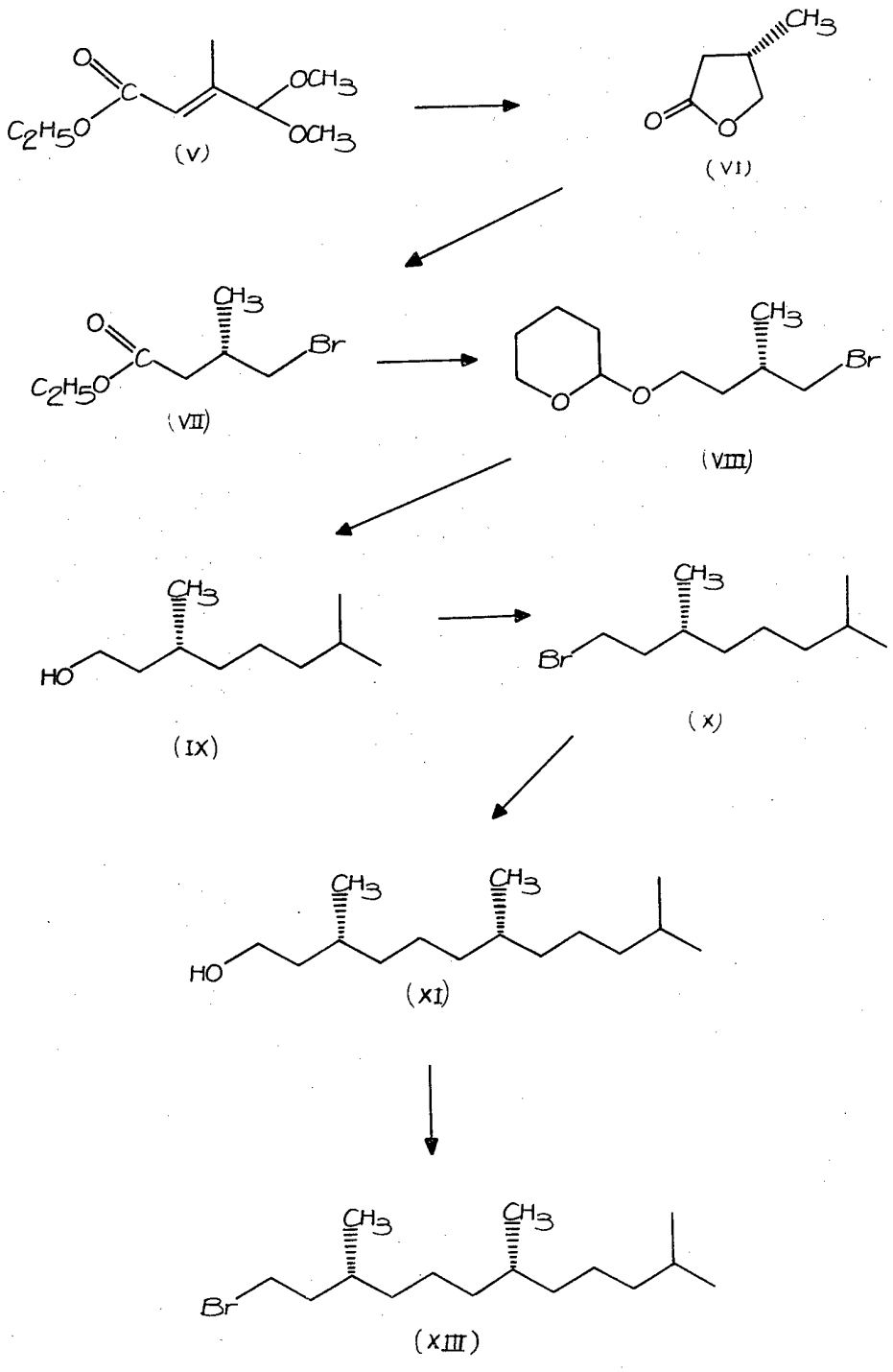
about room temperature. The condensation is conveniently also carried out under the atmosphere of an inert gas such as argon, nitrogen and the like.

A compound of formula I in which R represents not a hydrogen atom but a protecting group cleavable under acidic conditions can be converted into a compound of formula I in which R represents a hydrogen atom. As implied, this conversion can readily be carried out under acidic conditions; for example, by heating in alcoholic solution with p - toluenesulphonic acid or with an aqueous mineral acid such as hydrochloric acid, hydrobromic acid, sulphuric acid etc. or with a Lewis acid such as, for example, boron trifluoride, boron trichloride etc.

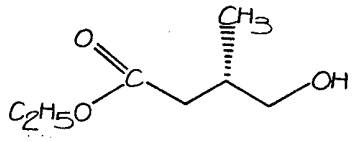
The conversion of a compound of formula I into vitamin K_1 is carried out by reaction with a menadiol derivative of formula IV in a manner known per se. The reaction is conveniently carried out in the presence of an acidic compound such as, for example, zinc chloride, sulphuric acid, trichloroacetic acid, acetic acid, oxalic acid or the like. Especially preferred are, however, sulphuric acid in small amounts, formic acid in large amounts as well as boron trifluoride, the latter especially in the form of its etherate. Conveniently, there is used as the solvent an open-chain or cyclic ether such as diethyl ether, diisopropyl ether, dibutyl ether, dioxan and the like. The temperature is not critical and the reaction is generally carried out at a temperature between about room temperature and the reflux temperature of the reaction mixture. When boron trifluoride ethyl etherate is used as the acidic compound, the reaction is advantageously carried out at, for example, about 50°—100°C.

Following the previously described reaction, the acyl group is cleaved and the hydroxy groups are oxidised, the cleavage and oxidation being carried out in a manner known per se. Thus, for example, the cleavage of the acyl group can be carried out by saponification in an aqueous organic solvent with an alkali metal hydroxide (e.g. sodium or potassium hydroxide), conveniently with the exclusion of air. The subsequent oxidation of the hydroxy groups can be carried out, for example, using silver oxide or also using atmospheric oxygen.

The Grignard compound of formula II used as the starting materials in the present process can be prepared in various ways depending on whether the racemate or the optically active form is desired. Thus, the optically active Grignard compound can be prepared, for example, as illustrated in the following Formula Scheme:

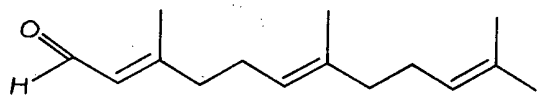

(V)
(VI)
(VII)
(VIII)
(IX)
(X)
(XI)
(XIII)

Having regard to the foregoing Formula Scheme, the compound of formula V (ethyl trans - 4,4 - dimethoxy - 3 - methylcrotonate) can be converted into the compound of formula VI by fermentation with a microorganism of the genus Saccharomyces cerevisiae and subsequent cyclisation of the thus-obtained compound of the formula



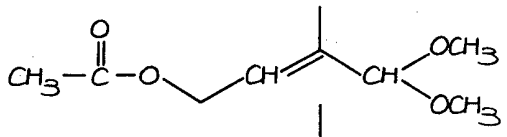
The cyclisation can be carried out using an acid such as, for example, dilute p - toluenesulphonic acid. The compound of formula VI can be converted into the compound of formula VII by treatment with alcoholic hydrogen bromide solution. This compound of formula VII can, in turn, be converted into the compound of formula VIII by reduction of the ester group with diisobutylaluminium hydride at a temperature of from about –20°C to about 0°C and subsequent reaction with 3,4 - dihydro - 2H - pyran. The conversion of the compound of formula VIII into the compound of formula IX is conveniently carried out by treatment with isoamyl - magnesium bromide in the presence of dilithium tetrachlorocuprate in an ethereal solvent at a temperature from about 0°C to about room temperature and subsequent cleavage of the 2 - tetrahydropyranyl group by acidic hydrolysis. The compound of formula IX can be converted into the bromide of formula X by treatment with N - bromosuccinimide and triphenylphosphine in a manner known per se. The conversion of the bromide of formula X into the compound of formula XI is carried out by reaction with activated magnesium in an ethereal solvent and coupling with the compound of formula VIII in the presence of dilithium tetrachlorocuprate in an ethereal solvent at a temperature from about 0°C to about room temperature. The bromination of the compound of formula XI can be carried out in an analogous manner to the bromination of the compound of formula IX. The conversion of the bromide of formula XII into the Grignard compound of formula II can be carried out by reaction with activated magnesium in an ethereal solvent in a manner known per se.

The racemic Grignard compound of formula II can be prepared, for example, from a compound of the formula

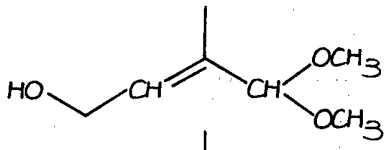


The compound of formula A is known and can be converted by reduction with hydrogen in the presence of basic Raney-nickel into the corresponding saturated alcohol. This alcohol can be converted by treatment with N - bromosuccinimide and triphenylphosphine in a manner known per se into the corresponding bromide. This bromide can, in turn, be converted in a manner known per se (e.g. by treatment with activated magnesium in an ethereal solvent) into the racemic Grignard compound of formula II.

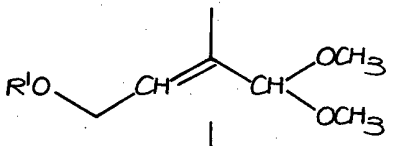
The trans compounds of formula III hereinbefore in which R represents not a hydrogen atom but a protecting group cleavable under acidic conditions are novel compounds, and also form part of the present invention. Those trans compounds in which R represents a lower alkyl or phenyl - (lower alkyl) group can be prepared as illustrated in the following Formula Scheme, wherein R′ represents a lower alkyl or phenyl - (lower alkyl) group and R_1 has the significance given earlier:



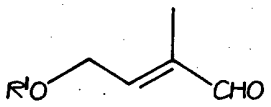
(XIII)



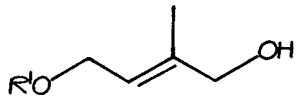
(XIV)



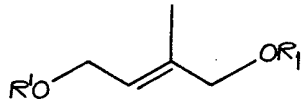
(XV)



(XVI)



(XVII)

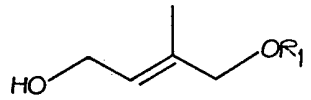


(XVIII)

Having regard to this Formula Scheme, the compound of formula XIII is known and can be saponified to the compound of formula XIV in a manner known per se by treatment with a base (e.g. an alkali metal hydroxide such as sodium hydroxide or potassium hydroxide or an alkaline earth metal hydroxide such as barium hydroxide). The thus-obtained compound of formula XIV can then be etherified using a lower alkyl halide, a phenyl - (lower alkyl) halide or di(lower alkyl) sulphate in the presence of a base (e.g. sodium hydride, phenyl lithium and the like). The resulting ether of formula XV is then converted into the aldehyde of formula XVI by hydrolysis with p - toluenesulphonic acid in a cyclic ether (e.g. dioxan or tetrahydrofuran), containing about 8—12% water, at about room temperature. Under these hydrolysis conditions, the quantitative isomerisation of the double bond from cis to trans is also brought about. The trans aldehyde of formula XVI is then reduced in a manner known per se (e.g. using sodium

borohydride) to give the alcohol of formula XVII. This alcohol of formula XVII is subsequently reacted with a compound yielding the acyl group denoted by R_1 e.g. an acid anhydride with pyridine, an acid halide with pyridine or a chloroformic acid ester with pyridine etc.) to give a trans compound of formula XVIII.

Those novel trans compounds of formula III in which R represents a protecting group cleavable under acidic conditions other than a lower alkyl or phenyl - (lower alkyl) group can be prepared from a trans compound of the general formula



wherein R_1 has the significance given earlier, by introduction of the relevant protecting group which is cleavable under acidic conditions. Thus introduction can be carried out in a manner known per se; for example, by treatment with the corresponding olefinic compound such as 3,4 - dihydro - 2H - pyran, methyl vinyl ether or 2 - methyl - propene or with the corresponding halide such as chloromethyl ether or trimethylsilyl chloride and the like.

The following Examples illustrate the present invention:

Example 1

(E) - 2 - Methyl - 4 - [(Tetrahydro - 2H - Pyran - 2 - yl)oxy] - 2 - Butenyl Acetate

To 11.5 g (80 mmol) of (E) - 4 - hydroxy - 2 - methyl - 2 - butenyl acetate is added dropwise at 0°C with the exclusion of moisture 1 drop of phosphorus oxychloride and then 7 g (83.2 mmol) of freshly distilled 3,4 - dihydro - 2H - pyran. After completion of the addition of the 3,4 - dihydro - 2H - pyran, the mixture is stirred for 30 minutes at room temperature. The crude mixture is subsequently distilled through a Vigreux column. The yield of (E) - 2 - methyl - 4 [(tetrahydro - 2H - pyran - 2 - yl)oxy] - 2 - butenyl acetate amounts to 17.0 g (94%); boiling point 98°C/0.4 mmHG.

Example 2

(E) - 4 - Methoxy - 2 - Methyl - 2 - Butenyl Acetate

To a mixture of 2.3 g (20 mmol) of (E) - 4 - methoxy - 2 - methyl - 2 - buten - 1 - ol and 2.5 g (36 mmol) of pyridine are added dropwise at −10°C 3 ml of acetic anhydride. The mixture is stirred at room temperature for 3 hours and then neutralised with saturated sodium bicarbonate solution. After extraction with ether, drying of the organic phase over sodium sulphate and removal of the solvent, the residue is freed from pyridine by standing over concentrated sulphuric acid in a desiccator. After distillation at 45°C/1 Torr, there are obtained 2.1 g (67%) of (E) - 4 - methoxy - 2 - methyl - 2 - butenyl acetate which contains less than 0.4% of the (Z) isomer according to gas chromatography.

The (E) - 4 - methoxy - 2 - methyl - 2 - buten - 1 - ol used as the starting material can be prepared as follows:

a) To 188.2 g (1 mol) of (E/Z) - 4,4 - dimethoxy - 1 - acetoxy - 3 - methyl - 2 - butene is added while cooling with ice and with vigorous stirring a solution of 56.1 g (1 mol) of potassium hydroxide in 60 ml of water. 30 ml of methanol are then added dropwise to the mixture with good cooling. The saponification is complete after ca 30 minutes at room temperature. The mixture is diluted with water and extracted three times with ether. The combined ether phases are washed neutral with saturated sodium chloride solution and dried over sodium sulphate/potassium carbonate. After removal of the solvent on a rotary evaporator and distillation of the residue through a Vigreux column at 68°—69°C/0.5 Torr, the yield of (E/Z) - 4,4 - dimethoxy - 3 - methoxy - 3 - methyl - 2 - buten - 1 - ol amounts to 107.3 g (73%).

b) To a suspension of 9.6 g (0.4 mol) of sodium hydride in 50 ml of absolute ether is added dropwise at 0°C a solution of 58.4 g (0.4 mol) of (E/Z) - 4,4 - dimethoxy - 3 - methyl - 2 - buten - 1 - ol in 50 ml of absolute ether and the mixture is stirred at room temperature for 3 hours. To the resulting alcoholate are added 900 ml of absolute ether and 71 g (0.5 mol) of methyl iodide and the mixture is stirred for ca 14 hours. After filtration of the precipitated sodium iodide, removal of the solvent on a rotary eveporator and distillation of the residue, there are obtained 39.5 g

(62%) of (E/Z) - 4 - methoxy - 2 - methylcrotonaldehyde dimethylacetal of boiling point 74°C/13 Torr.

c) 5 g (31 mmol) of (E/Z) - 4 - methoxy - 2 - methylcrotonaldehyde dimethylacetal and 70 mg of p - toluenesulphonic acid in a mixture of 7 ml of tetrahydrofuran and 0.7 ml of water are stirred at room temperature in a nitrogen atmosphere. After ca 13 to 16 hours, the hydrolysis of the acetal is complete with cis to trans isomerisation. The mixture is diluted with methylene chloride and neutralised by shaking with saturated sodium bicarbonate solution. After drying the organic phase over sodium sulphate, the solvent is distilled off at normal pressure. After distillation of the residue at 68°C/20 Torr, there are obtained 3.27 g (92%) of (E) - 4 - methoxy - 2 - methyl - 2 - crotonaldehyde which contains less than 0.4% of the (Z) isomer according to gas chromatography and nuclear magnetic resonance spectroscopy.

d) A solution of 2.14 g (18.8 mmol) of (E) - 4 - methoxy - 2 - methyl - 2 - crotonaldehyde in 20 ml of ethanol is treated portionwise at 0°C with 0.38 g (10 mmol) of sodium borohydride and the mixture is subsequently stirred for 1 hour. After removal of the ethanol on a rotary evaporator, the residue is taken up in water and extracted twice with ether. The combined ether phases are washed with saturated sodium chloride solution and then dried over sodium sulphate. After removal of the ether and distillation of the residue, there are obtained 1.96 g (90%) of (E) - 4 - methoxy - 2 - methyl - 2 - buten - 1 - ol (boiling point 89°—90°C/11 Torr) which contains less than 0.4% of the (Z) isomer according to gas chromatography and nuclear magnetic resonance spectroscopy.

In a manner analogous to the foregoing, there can be prepared (E) - 4 - ethoxy - 2 - methyl - 2 - butenyl acetate of boiling point 105°C/12 mmHg in a bulb-tube.

Example 3

(E) - 4 - Methoxy - 2 - Methyl - 2 - Butenyl Benzoate

To a stirred solution of 580 mg (5 mmol) of (E) - 4 - methoxy - 2 - methyl - 2 - buten - 1 - ol in 3 ml of absolute pyridine are added dropwise while cooling with ice 775 mg (5.5 mmol) of benzoyl chloride. The mixture is stirred for 5 minutes at room temperature and then for 15 minutes at 70°C. The mixture is then poured on to ice-water and extracted twice with n - hexane. The hexane phases are combined, washed with brine and dried over sodium sulphate. After evaporation of the solvents on a rotary evaporator and distillation of the residue in a bulb-tube at 100°C/0.01 Torr, there is obtained 1 g (91%) of pure product.

In a manner analogous to the foregoing, from 580 mg (5 mmol) of (E) - 4 - methoxy - 2 - methyl - 2 - buten - 1 - ol and 740 mg (5.5 mmol) of caproic acid there is obtained 0.93 g (87%) of (E) - 4 - methoxy - 2 - methyl - 2 - butenyl hexanoate of boiling point 65°C/0.01 Torr (bulb-tube).

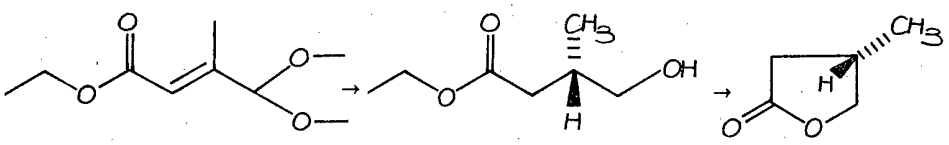
Example 4

Tetrahydro - 2 - [(7R,11R) - trans - Phytyloxyl - 2H - Pyran

250 mg (10.3 mmol) of magnesium shavings in 5 ml of absolute tetrahydrofuran in a three-necked flask under an argon atmosphere and provided with a reflux condenser and drying tube are activated by the addition of 2—3 drops of methyl iodide. After standing for 5 minutes, the solution is removed and the magnesium washed several times with absolute tetrahydrofuran. After the additon of 10 ml of absolute tetrahydrofuran to the activated magnesium, 2.3 g (7.85 mmol) of (3R,7R) - (—) - 1 - bromo - 3,7,11 - trimethyldodecane, the mixture is stirred at rate such that the solution just boils. After completion of the addition of the (3R,7R) - (— - 1 - bromo - 3,7,11 - trimethyldodecane, the mixture is stirred at 85°C for a further ca 10—15 minutes until (3R,7R) - (—) - 1 - bromo - 3,7,11 - trimethyldodecane is no longer present according to gas chromatography. The Grignard solution is filtered through a glass frit into a two-necked flask while flushing with argon and cooled down to −78°C with magnetic stirring. Through a dropping funnel there are added slowly 1.8 g (7.85 mmol) of (E) - 2 - methyl - 4 - [(tetrahydro - 2H - pyran - 2 - yl)oxy] - 2 - butenyl acetate (prepared as described in Example 1), followed by 0.3 ml of a 0.1 M solution of dilithium tetrachlorocuprate in absolute tetrahydrofuran. The mixture is stirred at −78°C for 10 minutes, then at 0°C for 2 hours and subsequently at room temperature for a further 15 hours. The formation of (7R,11R) - trans - phytyl tetrahydropyranyl ether can be followed by means of thin-layer chromatograms [hexane/ether (4:1); Rf=0.5]. The mixture is poured on to ice and acidified weakly (pH 5—6 with 1N sulphuric acid. This mixture

is extracted three times with ether and the combined organic phases are washed with saturated sodium bicarbonate solution and then with saturated sodium chloride solution. After drying the organic phase over sodium sulphate/sodium carbonate and removal of the solvent on a rotary evaporator, there are obtained 3.1 g of crude product which is purified by chromatography on 90 g of silica gel with hexane/ether (4:1). After bulb-tube distillation at 150°C/0.1 Torr, the yield of pure tetrahydro - 2 - [(7R,11R) - trans - phytyloxy] - 2H - pyran amounts to 2.14 g (72%); $[\alpha]_D^{20}=-0.56°$ (c=10 in chloroform).

The (3R,7R) - (–) - 1 - bromo - 3,7,11 - trimethyldodecane used as the starting material can be prepared by a procedure whose first two stages are as follows:



(b) (c) (d)

A clean, but not sterilised, fermenter having a total volume of 31 litres is charged with the following ingredients:

Deionised water	9.9 l
Pressed yeast	1.1 kg
Sugar	0.55 kg
Ethyl 4,4 - dimethoxy - 3 - methylcrotonate, i.e. compound "(b)" above	135 g
Polypropyleneglycol monobutyl ether	10 ml

The fermentation is carried out under the following conditions:

Temperature	30°C (thermostatically regulated)
Stirring frequency	1000 revolutions/minute
Air-flow rate	600 litres/hour
pH	3.4—3.8 (no pH regulation)
Fermentation time	56 hours

The fermentation is interrupted after 56 hours and the desired fermentation product isolated as follows:

The fermentation broth is saturated with sodium chloride and extracted continuously with diethyl ether for 4 days. The solvent is separated, dried over sodium sulphate and removed under reduced pressure. There are obtained 122 g of crude extract which for the most part contains ethyl (S) - 3 - methyl - 4 - hydroxy - butyrate, i.e. compound "(c)" above. This ester can be purified chromatographically (over silica gel deactivated with 0.5% ammonia).

The foregoing crude extract is treated with 100 mg of p - toluene sulphonic acid and distilled under reduced pressure in a nitrogen atmosphere. The (S) - dihydro - 4 - methyl - 2(3H) - furanone, i.e. compound "(d)" above, which forms during the distillation distills at 86°—88°C/14 Torr (bath temperature 125°—140°C). There are obtained 26.2 g of product which contains 93% of (S) - dihydro - 4 - methyl - 2(3H) - furanone according to gas chromatography and which shows an optical rotation of –21° (4% in methanol).

The yield of isolated optically pure (S) - dihydro - 4 - methyl - 2 - (3H) - furanone is 34.4% of theory.

To 110 ml of a freshly prepared ethanolic hydrogen bromide solution (about 8-N) are added dropwise while stirring at 0°C within 10 minutes 11.0 g (0.11 mol) of (S) - dihydro - 4 - methyl - 2 - (3H) - furanone. The mixture is then stirred at room temperature for 2 hours. For the working-up, the mixture is poured on to ice, diluted with water to about 1 litre and extracted twice with chloroform. The combined organic phases are washed neutral, first with water and then with saturated sodium bicarbonate solution, and dried over sodium sulphate. After

removal of the chloroform on a rotary evaporator, the colourless ethyl (S) - 4 - bromo - 3 - methylbutyrate distils in a water-jet vacuum at 90°—92°C in a yield of 18.5 g (80%); $[\alpha]_D^{20}=-2.3°$ (c=4.0 in chloroform).

204 ml (0.204 mol) of a 1-M solution of diisobutylaluminium hydride are treated dropwise in an argon atmosphere at 0°C while stirring within 15 minutes with 17.8 g (0.085 mol) of ethyl (S) - 4 - bromo - 3 - methylbutyrate. The excess reducing agent is decomposed by the dropwise addition of methanol at 0°C. Subsequently, the mixture is poured on to ice and acidified by the addition of 2-N aqueous sulphuric acid, the precipitated aluminium hydroxide goes partially into solution. The (S) - 4 - bromo - 3 - methyl - 1 - butanol formed is taken up in ether by repeated extraction. The combined ether phases are washed neutral, first with saturated sodium bicarbonate solution and then with saturated sodium chloride solution, and dried over sodium sulphate. After removal of the solvent on a rotary evaporator, the yield amounts to 14.0 g (98%). The product can be used in the next step without distillation. For analytical purposes, a sample is distilled in a bulb-tube at 60°C/0.04 Torr; $[\alpha]_D^{20}=-2.0°$ (c=3.3 in chloroform).

14 g (0.084 mol) of (S) - 4 - bromo - 3 - methyl - 1 - butanol are treated dropwise at 0°C with 50 ml of freshly distilled 3,4 - dihydro - 2H - pyran. The mixture is subsequently stirred at 0°C for 1 hour. Excess 3,4 - dihydro - 2H - pyran is removed on a rotary evaporator at 35°C. For the removal of the 3,4 - dihydro - 2H - pyran as completely as possible, chloroform is repeatedly added and distillation on a rotary evaporator is carried out after each addition. The crude product, [(S) - 4 - bromo - 3 - methylbutoxy] - tetrahydro - 2H - pyran, is distilled at 75°C/0.03 Torr in a yield of 17.5 g (83%); $[\alpha]_D^{20}=+3.4°$ (c=4.0 in chloroform).

To a Grignard solution prepared (in a manner analogous to that described earlier) from 0.3 g (12.4 mmol) of magnesium and 1.15 g (10 mmol) of 1 - bromo - 3 - methylbutane in 25 ml of absolute tetrahydrofuran are added dropwise within 1 minute at 0°C in an argon atmosphere and while stirring 1.26 g (5 mmol) of 2 - [(S) - 4 - bromo - 3 - methylbutoxy] - tetrahydro - 2H - pyran. There is then added 0.3 ml of a 0.1-M solution of dilithium tetrachlorocuprate in tetrahydrofuran and the mixture is stirred at 0°C for 3 hours. The working-up as well as the hydrolysis of 2 - [(R) - 3,7 - dimethyloctanoxy] - tetrahydro - 2H - pyran to (R) - 3,7 - dimethyl - 1 - octanol is carried out in the same manner as described earlier. After bulb-type distillation at 95°/14 Torr, the yield of (R) - 3,7 - dimethyl - 1 - octanol amounts to 0.56 g (71%); $[\alpha]_D^{20}=+4.0$ (c=1.03 in chloroform).

To a solution of 5 g (31.6 mmol) of (R) - 3,7 - dimethyl - 1 - octanol and 9.05 g (34.5 mmol) of triphenylphosphine in 20 ml of methylene chloride are added portionwise while stirring 5.65 g (31.8 mmol) of N - bromosuccinimide. The temperature is held below 25°C by occasional cooling of the reaction vessel. After stirring at room temperature for 30 minutes, the solvent is removed on a rotary evaporator. The residue is extracted several times with n - hexane, filtered and again rinsed with n - hexane. The combined n - hexane phases are concentrated on a rotary evaporator and the crude product is chromatographed on 200 g of silica gel with n - hexane. Distillation in a bulb-tube at 105°C/15 Torr gives 6.1 g (87%) of (R) - 1 - bromo - 3,7 - dimethyloctane; $[\alpha]_D^{20}=-5.0$ (c=0.82 in chloroform).

A Grignard solution from 0.3 g (12.4 mmol) of magnesium and 2.54 g (11.5 mmol) of (R) - 1 - bromo - 3,7 - dimethyloctane in 10 ml of absolute tetrahydrofuran is prepared in a manner analogous to that described earlier. To this solution are added dropwise at 0°C 1.45 g (5.57 mmol) of 2 - [(S) - 4 - bromo - 3 - methylbutoxy] - tetrahydro - 2H - pyran and then 0.3 ml of a 0.1-M solution of dilithium tetrachlorocuprate in tetrahydrofuran. The resulting mixture is stirred at 0°C for 3 hours. The working-up as well as the hydrolysis of the resulting tetrahydro - 2 - {[(3R,7R) - 3,7,11 - trimethyldodecyl]oxy} - 2H - pyran to (3R,7R) - 3,7,11 - trimethyl - 1 - dodecanol is carried out in a manner analogous to that described earlier. After bulb-tube distillation at 90°—95°C/0.05 Torr, the yield of (3R,7R) - 3,7,11 - trimethyl - 1 - dodecanol amounts to 0.5 g {43% based on 2 - [(S) - 4 - bromo - 3 - methylbutoxy] - tetrahydro - 2H - pyran}; $[\alpha]_D^{20}=+3.9°$ (c=1.05 in n - octane).

3.1 g (13.6 mmol) of (3R,7R) - 3,7,11 - trimethyl - 1 - dodecanol are treated with 4.02 g (15.3 mmol) of N - bromosuccinimide and 2.62 g (14.7 mmol) of triphenylphosphine in 13 ml of methylene chloride according to the procedure described earlier. After chromatography and distillation, there are obtained 3.54 g (90%) of (3R,7R) - bromo - 3,7,11 - trimethyldodecane of boiling point 90°C/0.05 Torr; $[\alpha]_D^{20}=-3.6°$ (c=1.005 in n - octane).

Example 5

(7R,11R) - trans - Phytol

1.32 g of tetrahydro - 2 - [(7R,11R) - trans - phytyloxy] - 2H - pyran (prepared as described in Example 4) are heated at 60°C for 10 minutes in 15 ml of ethanol together with 20 mg of p - toluenesulphonic acid. The cooled mixture is diluted with 150 ml of water and extracted three times with ether. The combined organic phases are washed neutral by repeated shaking with saturated sodium bicarbonate solution and subsequently dried over sodium sulphate. After removal of the solvent on a rotary evaporator, the residue is distilled in a bulb-tube at 140°C/0.64 Torr. The yield of (7R,11R) - trans - phytol amounts to 0.8 g (80%).

Example 6

Methyl (7R,11R) - (E) - Phytyl Ether

In a manner analogous to that described in Example 4, from 620 mg (2.13 mmol) of (3R,7R) - (–) - 1 - bromo - 3,7,11 - trimethyldodecane and 60 mg (2.5 mmol) of magnesium there is prepared the corresponding Grignard compound which is reacted with 256 mg (1.14 mmol) of (E) - 4 - methoxy - 2 - methyl - 2 - butenyl acetate (prepared as described in Example 2) with the use of 0.1 ml of a 0.1-M solution of dilithium tetrachlorocuprate in tetrahydrofuran. After chromatography on silica gel with pentane/ether (4:1) and bulb-tube distillation at 110°C/0.04 Torr, the yield of methyl (7R,11R) - (E) - phytyl ether (less than 0.3% of the cis isomer) amounts to 399 mg [80% based on (E) - 4 - methoxy - 2 - methoxy - 2 - methyl - 2 - butenyl acetate]; $[\alpha]_D^{20}=-0.48°$ (c=5.35% in chloroform).

In a manner analogous to the foregoing there can be prepared ethyl (7R,11R) - (E) - phytyl ether of boiling point 125°C/0.03 mmHg in a bulb-tube.

In a manner analogous to the foregoing, methyl (7R,11R) - (E) - phytyl ether can also be prepared by reacting the Grignard compound with (E) - 4 - methoxy - 2 - methyl - 2 - butenyl benzoate or with (E) - 4 - methoxy - 2 - methyl - 2 - butenyl - hexanoate.

Example 7

1 - (O - Benzoyl) - trans - (7'R,11'R) - Phyllohydroquinone

1.67 g (6 mmol) of 1 - (O - benzoyl) - menadiol are suspended, with the exclusion of moisture, in 25 ml of absolute di(n - butyl)ether in a three-necked flask provided with a reflux condenser and the suspension is warmed to 85°C under an argon atmosphere. After the addition of 0.3 ml (3 mmol) of boron trifluoride ethyl etherate, there are added dropwise within 2—3 minutes with vigorous stirring 1.13 g (3mmol) of tetrahydro - 2 - [(7R,11R) - trans - phytyloxy] - 2H - pyran (prepared as described in Example 4) in 2 ml of absolute di(n - butyl ether. The mixture is stirred at 85°C for a further 10 minutes, then cooled rapidly and washed neutral several times with warm water. The organic phase is subsequently dried over sodium sulphate and the di(n - butyl) ether removed on a rotary evaporator at 50°C. The last residues of the solvent are removed in a high vacuum at room temperature. The solid residue is treated with 20 ml of hexane and stirred vigorously, the 1 - (O - benzoyl) - (7'R,11'R) - phyllohydroquinone preferentially going into solution. This solution is filtered through Hyflo, there being obtained after removal of the hexane on a rotary evaporator 1.69 g of crude product containing the 1 - (O - benzoyl) - (7'R,11'R) - phyllohydroquinone in a trans:cis ratio of 88%:12% according to high pressure liquid chromatography. (The word "Hyflow" is a Registered Trade Mark). By chromatography on silica gel with benzene/methylene chloride (1:1), there are obtained 1.25 g (77%) of 1 - (O - benzoyl) - trans - (7'R,11'R) - phyllohydroquinone of melting point 88°C after recrystallisation from methanol/toluene; $[\alpha]_D^{20}=-0.8°$ (c=1.0 in chloroform).

In a manner analogous to the foregoing, 1 - O - benzoyl - trans - (7'R,11'R) - phyllohydroquinone can also be prepared by condensing 1 - (O - benzoyl) - menadiol with methyl (7R,11R - (E) - phytyl ether or with trans - (7R,11R) - phytol.

Example 8

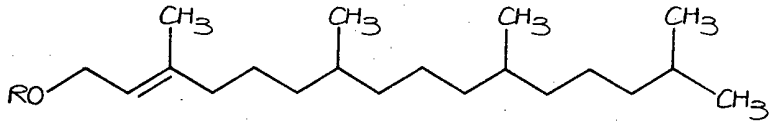
Trans - (7'R,11'R) - Phylloquinone

0.9 g (1.62 mmol) of 1 - (O - benzoyl) - trans - (7'R,11'R) - phyllohydroquinone (prepared as described in Example 7) is saponified at room temperature with the exclusion of air for 2 hours in a mixture of 20 ml of hexane, 2.6 g of potassium hydroxide, 13 ml of chloroform and 2.3 ml of water. After

removal of the organic phase, the aqueous mixture is washed with hexane. After addition of 10 ml of hexane to the aqueous phase, oxidation is carried out by introducing air into the mixture. For the working-up, the organic phase is separated and washed neutral with saturated sodium chloride solution. After removal of the solvent on a rotary evaporator, there is obtained 0.76 g of crude trans - (7'R,11'R) - phylloquinone which, for purification, is chromatographed on aluminium oxide neutral (activity IV) with hexane. The yield of (7'R,11'R) - phylloquinone amounts to 0.473 g (66%), which shows a purity of 100% and a trans:cis ratio of 96.5%:3.5% according to high pressure liquid chromatography with internal standard; $[\alpha]_D^{20}=-0.26°$ (c=10.0 in dioxan).

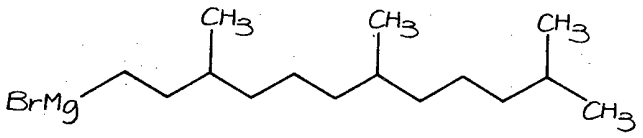
WHAT WE CLAIM IS:—

1. A process for the manufacture of trans - phytol and derivatives thereof of the general formula



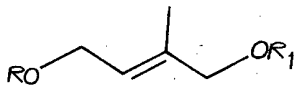
(I)

wherein R represents a hydrogen atom or a protecting group cleavable under acidic conditions, and of vitamin K_1, which process comprises condensing a Grignard compound of the formula



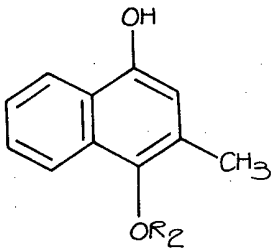
(II)

with a trans compound of the general formula



(III)

wherein R has the significance given earlier in this claim and R_1 represents an acyl group, in the presence of an organic solvent which is inert under the conditions of the condensation, and in the presence of a di - (alkali metal) - tetrahalocuprate, and, where vitamin K_1 is required, reaction a thus-obtained trans compound of formula I with a menadiol derivative of the general formula



(IV)

wherein R_2 represents an acyl group, cleaving off the acyl group and oxidising the hydroxy groups.

2. A process according to Claim 1, wherein there is used a trans compound of formula III in which R represents other than a hydrogen atom.

3. A process according to Claim 2, wherein there is used a trans compound of formula III in which R represents the 2 - tetrahydropyranyl group or the methyl group.

4. A process according to Claim 1, Claim 2 or Claim 3, wherein there is used a starting material of formula III in which R_1 represents the acetyl group.

5. A process according to any one of Claims 1 to 4 inclusive, wherein dilithium

tetrachlorocuprate is used as the di - (alkali metal) - tetrahalocuprate.

6. A process according to any one of Claims 1 to 5 inclusive, wherein the condensation of a Grignard compound of formula II with a trans compound of formula III is carried out at a temperature from about −80°C to about +50°C.

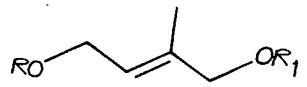
7. A process according to Claim 6, wherein the condensation is carried out at a temperature from about −70°C to about room temperature.

8. A process for the manufacture of trans - phytol and derivatives thereof of formula I given in Claim 1 and of vitamin K_1, substantially as hereinbefore described with reference to the foregoing Examples.

9. Trans - phytol and derivatives thereof of formula I given in Claim 1, when manufactured by the process claimed in any one of Claims 1 to 8 inclusive or by an obvious chemical equivalent thereof.

10. Vitamin K_1, when manufactured by the process claimed in any one of Claims 1 to 8 inclusive or by an obvious chemical equivalent thereof.

11. Trans compounds of the general formula



(III)

wherein R represents a protecting group cleavable under acidic conditions and R_1 represents an acyl group.

12. (E) - 2 - methyl - 4 - [(tetrahydro - 2H - pyran - 2 - yl)oxy] - 2 - butenyl acetate.

13. (E) - 4 - methoxy - 2 - methyl - 2 - butenyl acetate.

14. (E) - 4 - ethoxy - 2 - methyl - 2 - butenyl acetate.

15. (E) - 4 - methoxy - 2 - methyl - 2 - butenyl benzoate.

16. (E) - 4 - methoxy - 2 - methyl - 2 - butenyl hexanoate.

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