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STEREOSELECTIVE TOTAL SYNTHESIS OF NATURAL PHYTOL VIA DOUBLE BOND REDUCTIONS BY BAKER'S YEAST†

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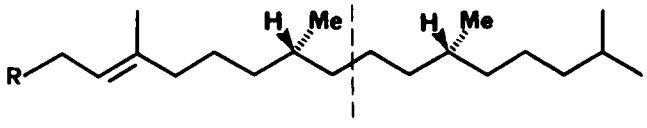
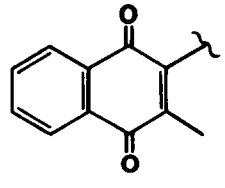
ABSTRACT.- *Natural (E)-(7R,11R)-phytol (1), a component of the chlorophyll molecule, vitamin K1 (2) and other natural compounds, was synthesized in enantiomerically and diastereomerically pure form by Li_2CuCl_4-induced coupling of two C_{10}-units (8, 12). Both these units were prepared from geraniol (3) via enzymatic enantioselective hydrogenation of activated double bonds.*

Phytol (1) is universally distributed in green plants as a component of the chlorophyll molecule, in which it is present in ester combination, and as a component part of phylloquinone (Vitamin K_1, 2) and tocopherols (Vitamin E, e.g. α-tocopherol). It is the lipophilic phytyl side-chain of chlorophyll a which renders the molecule biologically active[1]. In addition, the antihemorrhagic activity of vitamin K_1 is strictly dependent on the (E)-configuration of the double bond in the phytyl side-chain[2]. Natural phytol has (E)-(7R,11R)-configuration[3] and it has been largely used for the synthesis of tocopherols[4] and natural vitamin K_1[5]. Phytol can only be obtained in relatively small quantities from natural sources, and so, a synthetic substitute would be desirable. Many syntheses of phytol in its racemic form[6] as well as in the optically active one[3,7] have been published.



1 R = OH

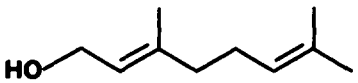


†Part 4 of the series "Microbial-mediated syntheses of EPC". For Part 3 see ref.11a.

In this paper we describe a new synthesis of (E)-(7R,11R)-phytol in its enantiomerically and diastereomerically pure form. This method is based on the coupling of two C_{10}-units, shown by the disconnection in formula 1. Both the stereogenic centers at the 11- and 7-position of 1 were obtained through baker's yeast hydrogenation of the "activated" double bond in geraniol (3) and in the C_{10}-intermediate 4 (Scheme). A sequence of reactions was devised to assure that the correct configuration (E) of the double bond in the starting geraniol was retained in 1.

(R)-Citronellol (5), prepared by enzymatic reduction of geraniol[8], was hydrogenated over platinum oxide to give dihydrocitronellol (6), which was transformed into the bromide 7 by reaction with N-bromosuccinimide and triphenylphosphine. The bromide 7, obtained in 85% yield from 5, was then converted with magnesium turnings in tetrahydrofuran into the Grignard derivative 8, which was used for the coupling reaction with the other C_{10}-unit (12).

To obtain 12, geraniol (3) was oxidized to methyl geraniate (*via* geranial) by the Corey's procedure[9], which gives a high yield without *cis-trans* isomerisation of the α,β-olefinic linkage. Methyl geraniate was functionalized by selenium dioxide oxidation using the Rapoport method[10], to produce 4. The double bond in α,β-position with respect to the aldehyde group was then hydrogenated *via* baker's yeast fermentation to afford the corresponding α-methyl saturated alcohol (9)[11] in enantiomerically pure form and (S)-configuration[11a] (35% yield). The double bond in α,β-position with respect to the ester group was retained in its original (E)-configuration during this reduction. In order to have the C_{10}-chiron properly functionalized for the subsequent coupling reaction, the alcoholic function of 9 was converted into the tosylate group, which is the best leaving group for the coupling[12]. The carbomethoxy group was reduced with lithium aluminum hydride and the resulting allylic alcohol was protected by reaction with ethyl vinyl ether in trifluoroacetic acid (54% yield of 12 from 9). Coupling of 8 and 12 to produce 13 was then performed with dilithium tetrachlorocuprate at -30°C. Pure (7R,11R)-phytol (1) was finally obtained by the deprotection of the alcoholic function of 13 by means of HCl 0.5N. No isomerisation of the double bond was found to occur when using this acid treatment, as demonstrated by ^{1}H- and ^{13}C-NMR data[7e,13a,b]. Concerning the C-7 and C-11 stereogenic centers, the diastereomeric purity of 1 was shown to be >90% by high field ^{13}C-NMR analysis[13c]. This diastereomeric excess of the target compound 1 is also indicative of its enantiomeric excess[14] (>99%), both being directly related to the e.e. of 5 (>98%) and 9 (>97%).



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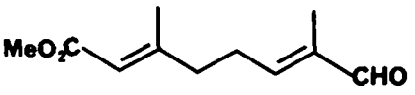

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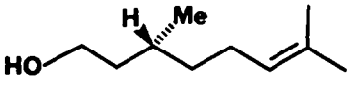

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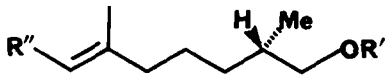
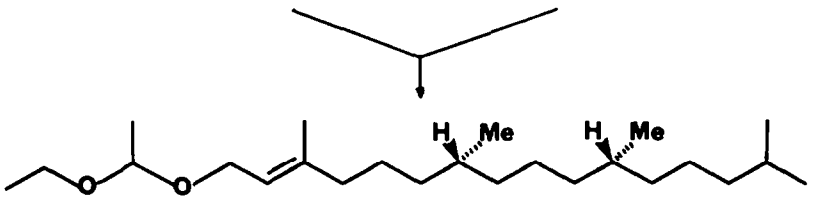


9	R'=H	R''=CO_2Me
10	R'=Ts	R''=CO_2Me
11	R'=Ts	R''=CH_2OH
12	R'=Ts	R''=$CH_2OCH(Me)OEt$

6	X=OH
7	X=Br
8	X=MgBr



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SCHEME

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 681 spectrophotometer. ^{1}H-NMR spectra were obtained on a Bruker WP80 SY and ^{13}C-NMR spectra on a Bruker CXP300 operating at 75.47 MHz. Chemical shifts are reported in δ from internal Me_4Si. Optical rotations were measured in a 1.0 dm cell on a Perkin-Elmer Model 241 polarimeter. MS spectra were recorded on a Varian MAT 112 mass spectrometer. Flash column chromatography was performed on silica gel Merck 60 (230-400 mesh). Baker's yeast was "Distillerie Italiane" brand from Eridania [S.Quirico-Trecasali (Parma)] . "Usual work up" means that the reaction mixture was treated with water and $CHCl_3$ or ether, the organic layer washed with water and brine, dried ($MgSO_4$), and evaporated under vacuum. Phytol (mixture of isomers, Fluka) was used as a reference product.

Methyl 3,7-Dimethyl-8-formyl-2,6-octadienoate (4). *Methyl geraniate (prepared by oxidation of geraniol via geranial according to E.Corey's procedure)[9](1.44g, 7.9mmol) in EtOH (20mL) was treated dropwise with a solution of SeO_2 (1.34g, 12mmol) in EtOH (30mL) at 50°C and refluxed for 5h. The reaction mixture was filtered and the solvent evaporated. Usual work up gave crude 4, which was flash chromatographed (hexane:ethyl acetate 2:1) to afford pure 4 (750mg, 48% yield): IR and NMR data as in ref.11a; MS m/e (relative intensity): 196 (M^+, 1), 167 (10), 163 (84), 137 (25), 136 (20), 135 (52), 124 (26), 108 (32), 106 (78), 82 (78), 81 (100), 40 (75). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.54; H, 8.19.*

Methyl (E)-(S)-(-)-3,7-Dimethyl-8-hydroxy-2-octenoate (9). *4 was reduced by baker's yeast fermentation as in ref. 11a (35% yield, e.e.>97%): $[\alpha]^{25}_D$ -10.40° (c 2.092, $CHCl_3$); IR and NMR data as in ref. 11a; MS m/e (relative intensity): 200 (M^+, 1), 182 (3), 169 (9), 123 (17), 110 (36), 82 (64), 67 (43), 59 (40), 55 (84), 41 (100). Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.06. Found: C, 66.18; H, 9.86.*

Methyl (E)-(S)-(+)-3,7-Dimethyl-8-[(p-tolylsulfonyl)oxyl-2-octenoate (10). *p-TsCl (700mg, 3.93mmol) was added to a stirred and ice-cooled solution of 9 (588mg, 2.94mmol) in dry pyridine (10mL). The mixture was stirred overnight at 0°C under nitrogen. Subsequent work up gave a crude product which was purified by flash chromatography (benzene: ethyl acetate 4:1) to afford 10 (837mg, 80% yield): $[\alpha]^{25}_D$ +0.90° (c 1.69, $CHCl_3$); IR (liquid film): 2920, 1700, 1635, 1585, 1420, 1345, 1210, 1175, 1160, 1140 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.9 (3 H, d, J=6.5 Hz, CH_3CH), 1.0-2.2 (7 H, m, $3CH_2$ and CH), 2.1 (3 H, d, J=1.5 Hz, CH_3C=), 2.4 (3 H, s, CH_3-Ar), 3.7 (3 H, s, OCH_3), 3.85 (2 H, d, J=5.5 Hz, CH_2OTs), 5.6 (1 H, q, J=1.5 Hz, CH=), 7.3 (2 H, d, J=8 Hz, 2Ar ortho to CH_3), 7.8 (2 H, d, J=8 Hz, 2Ar ortho to SO_3R); MS m/e (relative intensity): 354 (M^+, 1), 327 (31), 307 (6), 172 (6), 165 (100), 160 (66), 150 (72), 139 (24), 135 (45), 127 (72), 124 (93), 91 (97). Anal. Calcd for $C_{18}H_{26}SO_5$: C, 60.99; H, 7.39. Found: C, 61.20; H, 7.41.*

(E)-(S)-(+)-3,7-Dimethyl-8-[(p-tolylsulfonyl)oxyl-2-octen-1-ol (11). *10 (500mg, 1.41mmol) in dry THF (20mL) was treated portionwise with $LiAlH_4$ (104mg, 2.82mmol) and stirred under nitrogen at -5°/0°C for 2h. Subsequent work up gave an oil, which was purified by flash chromatography (benzene:ethyl acetate 4:1) to afford 11 (353mg, 77% yield): $[\alpha]^{25}_D$ +2.6° (c 1.78, $CHCl_3$); IR (liquid film): 3620-3160, 2940, 1360, 1190, 1180, 1100 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.9 (3 H, d, J=6.5 Hz, CH_3CH), 1.6 (3 H, s, CH_3C=), 1.0-2.2 (8 H, m, $3CH_2$, CH and OH), 2.4 (3 H, s, CH_3Ar), 3.85 (2 H, 2d, J=5.5 Hz, CH_2OTs), 4.15 (2 H, d, J=7 Hz, CH_2OH), 5.35 (1 H, broad t, J=7 Hz, =$CHCH_2OH$), 7.3 (2 H, d, J=8 Hz, 2Ar ortho to CH_3), 7.8 (2 H, d, J=8 Hz, 2Ar ortho to SO_3R); MS m/e (relative intensity): 326 (M^+, 1), 308 (3), 241 (2), 171 (88), 170 (24), 155 (15), 154 (55), 153 (39), 138 (44), 135 (38), 91 (58), 70 (100), 56 (72). Anal. Calcd for $C_{17}H_{26}SO_4$: C, 62.55; H, 8.03. Found: C, 62.33; H, 8.10.*

(E)-(S)-(+)-8-(1'-Ethoxy)ethoxy-2,6-Dimethyl-6-octenyl p-Toluene-sulfonate (12). *11 (230mg, 0.7mmol) was treated with ethyl vinyl ether (6.5mL) and CF_3COOH (2ml) and stirred at room temperature for 30min. After addition of triethylamine (0.1mL) the reaction mixture was stirred for 45'. Subsequent work up gave a crude product, which was purified by flash chromatography (benzene:ethyl acetate 4:1) to afford pure 12 (246mg, 88% yield): $[\alpha]^{25}_D$ +1.95° (c 1.44, $CHCl_3$); IR (liquid film): 2980, 2940, 1605, 1470, 1370, 1195, 1180, 1140 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.9 (3 H, d, J=6.5 Hz, CH_3CH), 1.2 (3 H, t, J=7 Hz, CH_3CH_2O), 1.3 (3 H, d, J=5.5 Hz, $OCH(CH_3)O$, 1.6 (3 H, broad s, CH_3C=), 1.0-2.2 (7 H, m, $3CH_2$ and CH), 2.45 (3 H, s, CH_3Ar), 3.5 (2 H, 2q, J=7 Hz, OCH_2CH_3), 3.85(2 H, 2d, J=5.5 Hz, CH_2OTs), 4.05 (2 H, 2d, J=7 Hz, =$CHCH_2O$), 4.7 (1 H, q, J=5.5 Hz, $OCH(CH_3)O$), 5.3 (1 H, tq, J=7 Hz, J'=1.5 Hz, =$CHCH_2O$), 7.3 (2 H, d, J=8 Hz, 2 Ar ortho to CH_3), 7.8 (2 H, d, J=8 Hz, 2 Ar ortho to SO_3R); MS m/e (relative intensity): 398 (M^+,1), 341 (7), 325 (40), 309 (11), 213 (9), 185 (12), 155 (68), 91 (100), 89 (26), 73 (91), 57 (80). Anal. Calcd for $C_{21}H_{34}SO_5$: C, 63.28; H, 8.60. Found: C, 62.60; H, 8.58.*

(R)-(+)-Citronellol (5). *5 was prepared as in ref. 8 (30% yield, e.e.>98%): $[\alpha]^{25}_D$ +5.1° (c 3, $CHCl_3$).*

(R)-(+)-3,7-Dimethyl-octan-1-ol (6). *5 (550mg, 3.55mmol) in ethyl acetate (40mL) was hydrogenated over PtO_2 Adams (84mg) with stirring for 2h. Pt was filtered off and the solvent evaporated in vacuo; distillation (108°C, 20mmHg) gave pure 6 (510mg, 90% yield): $[\alpha]^{25}_D$ +4.81° (c 1.48, $CHCl_3$) [lit. +4.20 (c 5, $CHCl_3$)][15]; IR (liquid film): 3600-3100, 2960 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.87 and 0.90 (9 H, 2d, J=6 Hz, $3CH_3$), 1.45 (11 H, m, $4CH_2$, 2CH and OH), 3.68 (2 H, d, J=6.2 Hz, CH_2O-); MS m/e (relative intensity): 140 (M^+-H_2O, 1), 41 (100). Anal. Calcd for $C_{10}H_{22}O$: C, 75.88; H, 14.01. Found: C, 75.62; H, 13.88.*

(R)-(-)-1-Bromo-3,7-dimethyloctane (7). *7 was prepared as in ref.15 (85% yield): $[\alpha]^{25}_D$ -5.5° (c 1.4, $CHCl_3$) [lit. -5.7° (neat)][15]; IR (liquid film): 2960, 2870, 2850, 600-500 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.88-0.89 (9 H, 2d, J=6 Hz, $3CH_3$), 1.1-1.4 (6 H, m, $3CH_2$), 1.5-2.2 (4 H, m, CH_2 and 2CH), 3.54 (2 H, 2t, J=7.2 Hz, CH_2Br). Anal. Calcd for $C_{10}H_{21}Br$: C, 54.30; H, 9.57. Found: C, 54.57; H, 9.32.*

(E)-(7R,11R)-1-(1'-Ethoxy)ethoxy-3,7,11,15-tetramethyl-2-hexadecene (13). *A solution of the Grignard reagent was prepared from 7 (368mg, 1.66mmol) and magnesium turnings (51mg, 2.13mmol) in dry THF (2mL) according standard procedure[15]. To a stirring solution of the tosylate 12 (167.2mg, 0.42mmol) in dry THF (1.2mL), cooled at -35°C and under nitrogen, the Grignard solution (1mL, 0.78M) was added dropwise, followed by a 0.1M solution of Li_2CuCl_4 in dry THF (0.4mL). The resulting mixture was stirred for 10min at -35°C, then at 2°C for 18h and finally at room temperature for 30min. The reaction mixture was treated with a saturated solution of NH_4Cl (10mL) and the product isolated by extraction with ether in the usual manner. Flash chromatography of the crude product (hexane:ethyl acetate 3:1) afforded pure 13 (125mg, 72% yield): $[\alpha]^{25}_D$ -0.45°, $[\alpha]^{25}_{546}$ -0.52°, $[\alpha]^{25}_{436}$ -0.9° (c=2.3, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 0.87 (12 H, d, J=7 Hz, $4CH_3CH$), 1.2 (3 H, t, J=7 Hz, CH_3CH_2O), 1.3 (3 H, d, J=5.5 Hz, $OCH(CH_3)O$), 1.68 (3 H, s, CH_3C=), 1.0-1.8 (19 H, m, $8CH_2$ and 3CH), 2.0 (2 H, broad t, J=7 Hz, CH_2C=), 3.5 (2 H, 2q, J=7 Hz, OCH_2CH_3), 4.05 (2 H, 2d, J=7 Hz, =$CHCH_2OR$), 4.72 (1 H, q, J=5.5 Hz, $OCH(CH_3)O$), 5.35 (1 H, tq, J=7 Hz, J'=1.5 Hz, =$CHCH_2OR$) ; MS m/e (relative intensity): 325 (M^+-43, 3), 323 (5), 322 (14), 280 (13), 170 (5), 140 (10), 125 (30), 112 (29), 111 (40), 98 (16), 97 (100), 89 (20), 85 (45), 83 (59), 74 (67), 73 (100). Anal. Calcd for $C_{24}H_{48}O_2$: C, 78.19; H, 13.12. Found: C, 78.53; H, 12.96.*

(E)-(7R,11R)-3,7,11,15-Tetramethyl-2-hexadecen-1-ol (Phytol) (1). *A solution of HCl 0.5N (2.5mL) was slowly added to a solution of 13 (97mg, 0.263mmol) in THF (2.5mL) at 0°C. The reaction mixture was then stirred for 3h at room temperature. After addition of a solution of $NaHCO_3$ (5%, 2mL) the usual work up gave crude 1 which was flash chromatographed (hexane:ethyl acetate 1:1) to give pure phytol (67mg, 86% yield). Parallel deprotection experiments on protected geraniol and nerol afforded pure geraniol and nerol respectively without double bond isomerisation.*
IR (liquid film): 3300, 1665 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.9 (12 H, d, J=7 Hz, $4CH_3CH$), 1.52 (1 H, s, OH), 1.68 (3 H, s, CH_3C=), 1.0-1.8 (19 H, $8CH_2$ and 3CH), 2.0 (2 H, t, J=7 Hz, CH_2C=), 4.15 (2 H, d, J=7 Hz, =$CHCH_2OH$), 5.4 (1H, broad t, J=7 Hz, =$CHCH_2OH$); ^{13}C-NMR ($CDCl_3$) δ 16.16 (q, 20-CH_3 on (E)-double bond), 19.73 (q, 18-CH_3), 19.76* (q, 19-CH_3), 22.60 and 22.69 (2q, 16-CH_3 and 17-CH_3), 24.51 (t, C-9), 24.80 (t, C-13), 25.23 (t, C-5), 28.0 (d, C-15), 32.76* (d, C-11), 32.86* (d, C-7) , 36.75* (t, C-6), 37.37 (t, C-12), 37.44 (t, C-8), 37.50* (t, C-10), 39.46 (t, C-14), 39.91 (t, C-4), 59.44 (t, C-1), 123.36 (d, C-2), 140.12 (s, C-3); MS (m/e, relative intensity): 296 (M^+, 70), 278 (M^+-H_2O, 58), 263 (18), 253 (16), 219 (22), 207 (100). Anal.Calcd for $C_{20}H_{40}O$: C, 81.08; H, 13.51. Found: C, 81.18; H, 13.45. It was shown to be identical with an authentic sample by direct comparison.*

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