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NEW SYNTHESES OF OPTICALLY ACTIVE VITAMIN E SIDE CHAIN BY CHEMICOENZYMATIC APPROACH†

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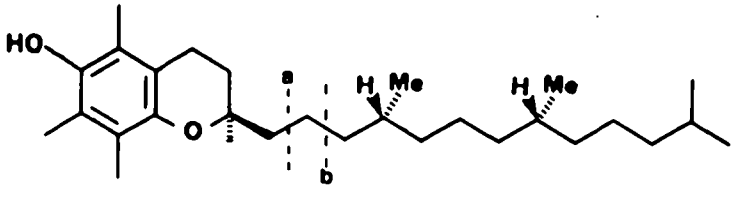
ABSTRACT . *Two independent syntheses of enantiomerically pure (3R,7R)-3,7,11-trimethyldodecan-1-ol (2a), the C_{15} tocopherol side chain, are described. Both reaction sequences start from (R)-citronellol, obtained by baker's yeast reduction of geraniol. One strategy is based on the coupling between (R)-citronellyl bromide and a C_5 optically active unit derived from chemical degradation of the common starting template; the other one uses an achiral isoprenic unit and a C_{10} building block containing two asymmetric carbon atoms generated by microbial reactions.*

In recent years much attention has been paid to the efficient synthesis of the natural form of vitamin E, i.e. (2R,4'R,8'R)-α-tocopherol (1), whose framework has been built up via the C-C bond formation between an optically active chroman moiety and a chiral acyclic terpene chain[1]. Retrosynthetically, the two strategies employed in the syntheses were based on the C-C bond disconnections "a" and "b" depicted in formula 1. In the former[2], a C_{14}-chromane unit[3] is coupled with a C_{15}-side chain synthon, while in the latter[2b,4], C_{15}-chromane[5] and a C_{14}-side chain building blocks are united. The homologous optically active alcohols 2a or 2b are key intermediates in all the above mentioned syntheses.



1

2a n=2 2b n=1

† Part 2 of the series "Microbial-mediated syntheses of EPC". For Part 1 see ref.8.

Although they can be obtained by degradation of naturally occurring (7R,11R)-phytol[2a,4a], both have been made accessible by synthesis as well. Many routes to 2a[6] and 2b[7] have been reported by various groups.

Because of continuing interest in the development of efficient stereocontrolled routes to 1,5-dimethylated acyclic chirons[6l,8,9], in the present paper we wish to describe two alternative methods for preparing (3R,7R)-3,7,11-trimethyldodecan-1-ol (hexahydrofarnesol, 2a) in enantiomerically pure form.

The first strategy stems from the possibility to use (R)-citronellol (8a, e.e.> 98%) produced by yeast reduction of geraniol (9)[8,10], as the only source of chirality centers (Scheme, path A); our plan envisaged the C-3 asymmetric carbon atom in 2a as arising from the five-carbon chiron 3f, which represents a versatile bifunctional C_5-building block for the synthesis of many natural products. Coupling between this C_5-unit, prepared by degradation of citronellol (8a), and the C_{10}-unit (4b), obtained by hydrogenation of the same starting material, would give 2a in diastereomerically and enantiomerically pure form.

3f was prepared from 8a by a seven step procedure: acetylation to 8b, oxidative ozonolysis (O_3; Jones reagent) to give the acid 3a, decarboxylation ($Pb(OAc)_4$, cat. $Cu(OAc)_2$) to the olefin 3b, changing of the protective group (MeONa/MeOH; ethyl vinyl ether in CF_3CO_2H), reductive ozonolysis (O_3; $NaBH_4$) of 3d and finally tosylation (overall yield 20% from 8a).

4b was prepared by catalytic hydrogenation of (R)-citronellol double bond and subsequent bromination of the dihydro derivative (4a) with N-bromosuccinimide and PPh_3. The corresponding Grignard reagent was treated in tetrahydrofuran with the tosylate 3f to give 2c, which, after acidic hydrolysis, afforded 2a in 75% yield. The diastereomeric purity (d.e.>95%) of 2a was checked by ^{13}C-NMR analysis at high field (75.47 MHz). (A 1:1 diastereomeric mixture of the product was used as reference†). Diastereomeric excess is indicative of enantiomeric excess in that they are equally dependent on the e.e. of starting 8a.

Our second synthetic plan to 2a was based on the use of an enantiomerically pure 1,5-dimethylated C_{10}-unit, i.e. 5b, as key intermediate. Really, this is readily available via enantioselective microbial hydrogenation of both the double bonds of geraniol (9), as outlined retrosynthetically in the Scheme (path B)[8]. Sequential reduction-activation-reduction of the methyl substituted C=C bonds of 9 (i.e. 9→8→7a→7b→5a) allows a C_{10} compound to be obtained having two easily distinguishable end functions. This feature makes it suitable for insertion in terpene skeleton.

Thus, 5a[8] was tosylated and then coupled with an achiral C_5-unit (6), i.e. $(i\text{-Am})_2CuLi$, giving rise to 2a (e.e.~100%) in 14% yield calculated from (R)-citronellol as starting material.

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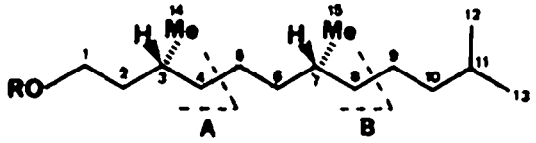
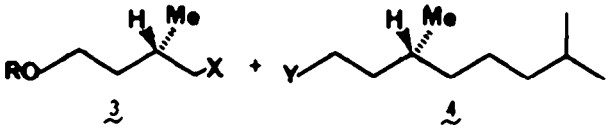
† A 1:1 diastereomeric mixture of (RS)- and (SR)-hexahydrofarnesol was prepared by coupling $(i\text{-Am})_2CuLi$ with the tosylate of (2RS,6RS)- and (2RS,6SR)-dimethyl-8-acetoxyoctan-1-ol (see formula 5b)[8] as described in the experimental part for the synthesis of optically active 2a (path B).



2a : R=H 2c : R=CH(Me)OEt

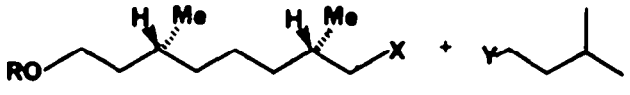


3

a R=Ac X=CH_2CO_2H
b R=Ac X= $=CH_2$
c R=H X= $=CH_2$
d R=CH(Me)OEt X= $=CH_2$
e R=CH(Me)OEt X=OH
f R=CH(Me)OEt X=OTs

4

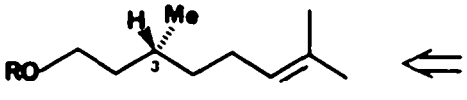
a Y=OH
b Y=Br



5

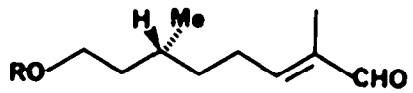
a R=Ac X=OH
b R=Ac X=OTs

6



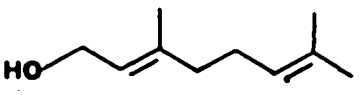
8

a R=H
b R=Ac



7

a R=H
b R=Ac



9

SCHEME

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 681 spectrophotometer. ^{1}H-NMR spectra were obtained on a Bruker WP80 SY. ^{13}C-NMR spectra were recorded on a Bruker CXP 300 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. TLC were carried out on silica gel Merck 60 F_{254} plates, normally using hexane-ethyl acetate as eluent. Flash column chromatography was performed on silica gel Merck 60 (230-400 mesh). Baker's yeast was "Distillerie Italiane" brand from Eridania (San Quirico-Trecasali (Parma, Italy)). "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.

(R)-(+)-Citronellol (8a). 8a was prepared as reported in ref.8 (25% yield): $[\alpha]_D^{25}$= +5.1° (c=3, $CHCl_3$); e.e.>98% by ^{1}H-NMR analysis with Eu(tfc)$_3$.

(R)-(+)-Citronellyl acetate (8b). 8a (2.3 g, 14.7 mmol) in dry pyridine (5 ml) was acetylated with Ac_2O (4.5 ml) at room temperature overnight. Usual work-up and distillation of the crude product gave pure 8b (1.78 g, 90% yield): $[\alpha]_D^{25}$= +5.5° (c=9.5, $CHCl_3$); IR and ^{1}H-NMR data as in ref.11. Anal. Calcd for $C_{11}H_{22}O_2$: C, 72.63; H, 11.10. Found: C, 72.54; H, 10.97.

(R)-(+)-6-Acetoxy-4-methylhexanoic acid (3a). 3a was prepared as reported in ref.11 (80% yield): $[\alpha]_D^{25}$= +2.72° (c=21.7, $CHCl_3$) lit.[11] +2.61° (c=3.52, $CHCl_3$). IR and ^{1}H-NMR data as in ref.11. MS m/e (relative intensity): 171 (M^+-OH, 1.4), 170 (M^+-H_2O, 1.5), 146 (2.1), 143 (2.8), 138 (34.3), 129 (44.8), 128 (98.3), 115 (46.9), 100 (71.3), 87 (100). Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.19; H, 8.67.

(S)-(+)-3-Methyl-4-pentenyl acetate (3b). 3b was prepared as reported in ref.11 (65% yield): $[\alpha]_D^{25}$= +19.6° (c=5.3, $CHCl_3$) lit.[11] +19.9° (c=1.18, $CHCl_3$); IR and ^{1}H-NMR data as in ref.11. Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.38; H, 9.83.

(S)-(+)-3-Methyl-4-penten-1-ol (3c). 3c was prepared as reported in ref.11 (85% yield): $[\alpha]_D^{25}$= +24.33° (c=3.39, $CHCl_3$) lit.[11] +29.22° (c=1.54, $CHCl_3$); IR and ^{1}H-NMR data as in ref.11. Anal. Calcd for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 71.68; H, 11.85.

(S)-(+)-1-(1'-Ethoxy)ethoxy-3-methyl-4-pentene (3d). 3c (151 mg, 1.51 mmol) in ethyl vinyl ether (distilled over K_2CO_3, 5 ml) was stirred overnight under nitrogen with CF_3CO_2H (0.01 ml) at 0°C. After 30' at room temperature triethylamine (0.01 ml) was added and the mixture stirred for 30'. Usual work-up and purification by flash chromatography (hexane:ethyl acetate 9:1) gave pure 3d (182 mg, 70% yield): $[\alpha]_D^{25}$= +11.5° (c=0.63, $CHCl_3$); IR (liquid film): 3080, 2980, 1840, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.03 (3H, d, J=7 Hz, CH_3CH), 1.21 (3H, t, J=7 Hz, CH_3CH_2O), 1.30 (3H, d, J=5.5 Hz, OCH(CH_3)O), 1.60 (2H, dt, J=J'=7 Hz, $CHCH_2CH_2O$), 2.66 (1H, m, $CH_2CH(CH_3)CH$=), 3.65 (2H, m, CH_2CH_2O), 3.65 (2H, q, J=7 Hz, CH_2CH_3), 4.70 (1H, q, J=5.5 Hz, OCH(CH_3)O), 4.95 (2H, m, CH_2=), 5.70 (1H, m, CH=). Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.38; H, 11.58.

(S)-(+)-4-(1'-Ethoxy)ethoxy-2-methylbutan-1-ol (3e). O_3 in oxygen was bubbled into a cooled solution of 3d (100 mg, 0.59 mmol) in dry methanol (9 ml) at -50°C until saturation (blue color). To this solution of the ozonide, purged with a stream of nitrogen to remove the excess ozone, $NaBH_4$ (150 mg, 3.97 mmol) was added portionwise at -5°C with stirring. After 4h the solvent was distilled in vacuo, the residue was treated with a saturated NH_4Cl solution and extracted with ether. Usual work-up gave a crude product which was purified by flash chromatography (hexane:ethyl acetate 4:1) (3e, 81 mg, 80% yield): $[\alpha]_D^{25}$= +3.2° (c=2.19, $CHCl_3$); IR (liquid film): 3600-3000 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.92 (3H, d, J=7 Hz, CH_3CH), 1.20 (3H, t, J=7 Hz, CH_3CH_2O), 1.30 (3H, d, J=5.5 Hz, OCH(CH_3)O), 1.65 (3H, m, $CH_2CH(CH_3)CH_2$ and OCH_2CH_2CH), 2.35 (1H, s, OH), 3.60 (6H, m, 3 CH_2O), 4.71 (1H, q, J=5.5 Hz, OCH(CH_3)O). Anal. Calcd for $C_9H_{20}O_3$: C, 61.33; H, 11.44. Found: C, 61.02; H, 11.29.

(S)-4-(1'-Ethoxy)ethoxy-2-methylbutyl tosylate (3f). 3e (183 mg, 1.04 mmol) in dry pyridine (1 ml) and 4-N,N-dimethylaminopyridine (0.5 ml) was slowly added to a solution of p-TsCl (250 mg, 1.3 mmol) in dry CH_2Cl_2 (10 ml) at -5°C. The mixture was stirred at -5°C for 2h and at room temperature overnight. Usual work-up gave crude 3f which was directly used for the next step (308 mg, 90% yield): IR (liquid film): 2000, 1660, 1600, 1360, 1170 cm^{-1}; ^{1}H-NMR (CDCl) δ 0.96 (3H, d, J=7 Hz, CH_3CH), 1.18 (3H, t, J=7 Hz, CH_3CH_2O), 1.25 (3H, d, J=5.5 Hz, OCH(CH_3)O), 1.55 (2H, 2q, $CHCH_2CH_2O$), 1.96 (1H, m, $CH_2CH(CH_3)CH_2$), 2.45 (3H, s, CHAr), 3.5 (2H, m, CH_2CH_2O), 3.5 (2H, q, J=7 Hz, CH_2CH_3), 3.9 (2H, 2d, J=5.5 Hz, CH_2OTs), 4.7 (1H, q, J=5.5 Hz, OCH(CH_3)O), 7.2 (2H, d, J=8.2 Hz, 2 Ar ortho to CH_3), 7.8 (2H, d, J=8.2 Hz, 2 Ar ortho to SO_3R).

(R)-(+)-3,7-Dimethyl-octan-1-ol (4a). (R)-Citronellol (5.55 g, 0.0356 mol) in ethyl acetate (390 ml) was hydrogenated over PtO_2 Adams (840 mg) with stirring for 2h. Pt was filtered and the solvent evaporated in vacuo; distillation (108°C, 20 mmHg) gave pure 4a (5.1 g, 90% yield): $[\alpha]_D^{25}$= +4.81° (c=1.48, $CHCl_3$) lit. +4.20° (c=5, $CHCl_3$)[4b], +4.0° (c=1.6, $CHCl_3$)[6c]; IR (liquid film): 3600-3100, 2960 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.87 and 0.90 (9H, 2d, J=6 Hz, 3 CH_3), 1.45 (11H, m, 4 CH_2, 2 CH and OH),

3.68 (2H, 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 (4b). 4b was prepared as reported in ref. 4b (85% yield): $[\alpha]_D^{25}$= -5.5° (c=1.4, $CHCl_3$) lit.: -5.0° (c=0.82, $CHCl_3$)[6c], -5.7° (neat)[4b] ; IR (liquid film): 2960, 2870, 2850, 600-500 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.88-0.89 (9H, 2d, J=6 Hz, $3CH_3$), 1.1-1.4 (6H, m, $3CH_2$), 1.5-2.2 (4H, m, CH_2 and 2CH), 3.54 (2H, 2t, J=7.2 Hz, CH_2Br). Anal. Calcd for $C_{10}H_{21}Br$: C, 54.30; H, 9.54. Found: C, 54.57; H, 9.32.

(3R,7R)-(+)-1-(1'-Ethoxy)ethoxy-3,7,11-trimethyldodecane (2c). A solution of the Grignard reagent was prepared from 1b (1.33 g, 6.03 mmol) and magnesium turnings (177.8 mg, 7.31 mmol) in dry THF (12 ml) according standard procedure[4b] . To a stirring solution of 3f (698.3 mg, 2.11 mmol) in dry THF (15 ml), cooled at -78°C and under nitrogen, the Grignard solution (5.5 ml, 0.5 M) was added dropwise followed by a 0.1 M solution of Li_2CuCl_4 in dry THF (0.3 ml). The resulting mixture was stirred at -78°C for 10', then at 0°C for 2h, and finally at room temperature for 18h. The reaction mixture was treated with a saturated solution of NH_4Cl (80 ml) and the product isolated by extraction with ether in the usual manner. Flash chromatography of the crude product (hexane:ethyl acetate 95:5) afforded pure 2c (476 mg 75% yield): $[\alpha]_D^{25}$= +2.6° (c=3.32, $CHCl_3$); IR (liquid film): 2960, 2925, 2870, 2850 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.85 (12H, d, J=7 Hz, $4CH_3$), 1.20 (3H, t, J=7 Hz, CH_3CH_2O), 1.30 (3H, d, J=5.5 Hz, $OCH(CH_3)O$), 1.10-1.60 (m, $7CH_2$ and 3CH), 3.50 (4H, m, $2CH_2O$), 4.66 (1H, q, J=5.5 Hz, $OCH(CH_3)O$). Anal. Calcd for $C_{19}H_{40}O_2$: C, 75.94; H, 13.42. Found: C, 76.21; H, 13.31.

(3R,7R)-(+)-3,7,11-Trimethyldodecan-1-ol (2a) (Path A). A stirred solution of 2c (266 mg, 0.87 mmol) in dry THF (10 ml) was treated with 0.5 N HCl (20 ml) at room temperature for 6h. Usual work-up (washing with 5% $NaHCO_3$ solution) gave pure 2a (195 mg, 98% yield): $[\alpha]_D^{25}$= +3.55° (c=1.075, $CHCl_3$) lit. +3.49° (c=0.98, $CHCl_3$)[6n], +3.50° (c=2.19, octan)[6o] ; IR (liquid film): 3340, 2960, 2870 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 0.83, 0.86 and 0.90 (12H, 3d, J=5.3 Hz, $4CH_3$), 1.0-1.8 (18H, m, $7CH_2$, 3CH and OH), 3.65 (2H, t, J=6.6 Hz, CH_2O); ^{13}C-NMR ($CDCl_3$) δ 19.76* (q, CH_3(14,15)), 22.61 (q) and 22.69 (q) (CH_3(12,13)), 24.42 (t) and 24.81 (t) (CH_2(5,9)), 28.01 (d, CH(11)), 29.70* (d) and 32.86* (d) (CH(3,7)), 37.36* (t), 37.45 (t) and 37.59* (t) (CH_2 (4, 6,8)), 39.46 (t, CH_2(10)), 40.13* (t, CH_2(2)), 61.29 (t, CH_2(1)). The ^{13}C-NMR peaks with an asterisk indicate those diagnostic for diastereomeric distinction: diastereomeric purity > 95%. MS m/e (relative intensity): 210 (M^+-H_2O, 4.04), 182 (11.1), 140 (39.4), 112 (100), 70 (96.9). Anal. Calcd for $C_{15}H_{32}O$: C, 78.95; H, 14.04. Found: C, 78.80; H, 13.95.

(2S,6R)-(-)-2,6-Dimethyl-8-acetoxyoctan-1-ol (5a). 5a was prepared as reported in ref. 8 (19% yield from (R)-citronellol) (d.e.>95%, e.e.~100%).

(2S,6R)-(+)-2,6-Dimethyl-8-acetoxyoctyl tosylate (5b). 5a (1.9 g, 8.86 mmol) was treated with p-TsCl (2.33 g, 12.27 mmol) in dry Py (50 ml) at 0°C overnight. Usual work-up with acidic washings (dil. HCl) gave a crude product which was flash chromatographed (benzene:ethyl acetate 3:1) to afford pure 5b (3.02 g, 92% yield): $[\alpha]_D^{25}$= +3.85° (c=4.36, $CHCl_3$); IR (liquid film): 2960, 2870, 1740, 1600, 1450, 1360 1170 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.9 (6H, d, J=5.3 Hz, $2CH_3$), 1.0-1.8 (10 H, m, $4CH_2$ and 2CH), 2.0 (3H, s, CH_3CO), 2.4 (3H, s, CH_3Ar), 3.8 (2H, dd, J=5.3 Hz, J'=1.3 Hz, CH_2OTs), 4.05 (2H, t, J=6.6 Hz, CH_2OAc), 7.30 (2H, dd, J=7.9 Hz, J'=2.6 Hz, 2 Ar ortho to CH_3), 7.80 (2H, d, J=7.9 Hz, 2 Ar ortho to SO_3R); MS m/e (relative intensity): 370 (M^+, 43.3), 328 (1.7), 215 (10), 199 (46.7), 173 (96.7), 155 (100). Anal. Calcd for $C_{19}H_{30}O_5S$: C, 61.62; H, 8.11. Found: C, 61.87; H, 7.97.

(3R,7R)-(+)-3,7,11-Trimethyldodecan-1-ol (2a) (Path B). A solution of *i*-AmLi in dry ether (25 ml) was prepared from *i*-AmBr (3.8 g) and Li (537 mg) at -15°C. 15 ml of this solution (7.1 mmol) was added to a vigorously stirred and cooled suspension of CuI (335 mg, 1.76 mmol) in dry ether (10 ml) at -35°C under nitrogen till dark solution. 5b (137.4 mg, 0.37 mmol) in dry ether (10 ml) was then added dropwise to the *i*-Am_2CuLi solution at -35°C. The temperature was raised to -15°C for 2h. The reaction was quenched by addition of saturated NH_4Cl aqueous solution and the product extracted with ether. Usual work-up gave a residue, which was flash chromatographed (hexane:ethyl acetate 4:1) to afford pure 2a (67.7 mg, 80% yield): $[\alpha]_D^{25}$= +3.58° (c=3.075, $CHCl_3$); diastereomeric purity > 95% by ^{13}C-NMR analysis.

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