New possibilities in a synthesis of (2*R*,4'*R*,8'*R*)-α-tocopherol (natural vitamin E)

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Dedicated to Professor Usein M. Dzemilev on the occasion of his 65th birthday

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Abstract

New methods for the synthesis of homochiral C_{14} and C_{15}-terpenoids desired as building blocks for phytilic side chain of natural α-tocopherol have been developed. A natural phytone resulted from the proposed effective method of chlorophyll ozonolysis was used in a synthesis of optically active terpenoids. Chiral chroman compound for vitamin E, namely, (*S*)-(-)-6-benzyloxy-3,4-dihydro-2,5,7,8-tetramethylchroman-2-methanol was obtained by enantioselective transesterification of the corresponding racemic alcohol catalysed by *Amano PS* lipase from *Burkholderia cepacia* in ionic liquid [bmim]PF_6.

Keywords: Natural α-tocopherol, chlorophyll, (6*R*,10*R*)-6,10,14-trimethylpentadecane-2-on (phytone), homochiral chroman compounds, enantioselective transesterification, ionic liquid [bmim]PF_6.

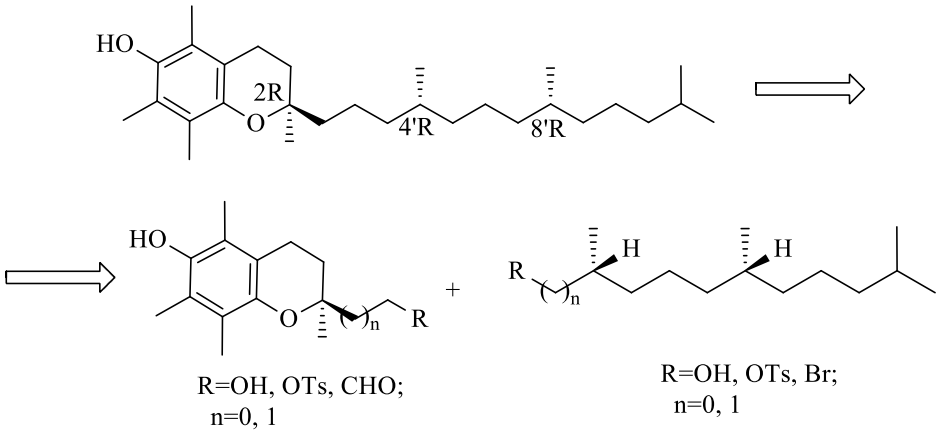
Introduction

(2*R*,4'*R*,8'*R*)-α-Tocopherol is the most studied principal component of vitamin E which defines its anti-oxidant properties.[1,2] In addition, (2*R*,4'*R*,8'*R*)-α-tocopherol participates in transmission of signals between cells, decreases activity of C proteinkinase, inhibits proliferation of the smooth muscle cells and governs the expression of α-tropomiosine gene.[3] The last decade studies showed that the specific liver transport protein (α-TTP) recognizes only the natural α-tocopherol out of all tocopherol isoforms and provides its transportation to plasma.[4]

At present a simple and economic overall synthesis of natural α-tocopherol does not exist. A semisynthetic isomerically pure (2*R*,4'*R*,8'*R*) - α-tocopherol is obtained from vegetable oils,

mainly from soya deodorizes distillates in a limited volume (~2000 tons per year) according to the complex technology.[5,6]

Methodology based on the combination of chiral trimethyllated 2-substituted chromanes with optically pure C_{14}- and C_{15}-terpenoids is widely used in the laboratory practice (Scheme 1).[6] For the building blocks of chromane and isoprenoid structure the various synthetic schemes were developed with the use of microbiological methods,[7] chemoenzymatic transformations,[8] chiral auxiliaries[9] or asymmetric metal complex catalysis.[10] As a rule, these methods were shown to be multistep, based on the use of atmosphere sensitive reagents and catalysts, and low perspective for practical application.



Scheme 1

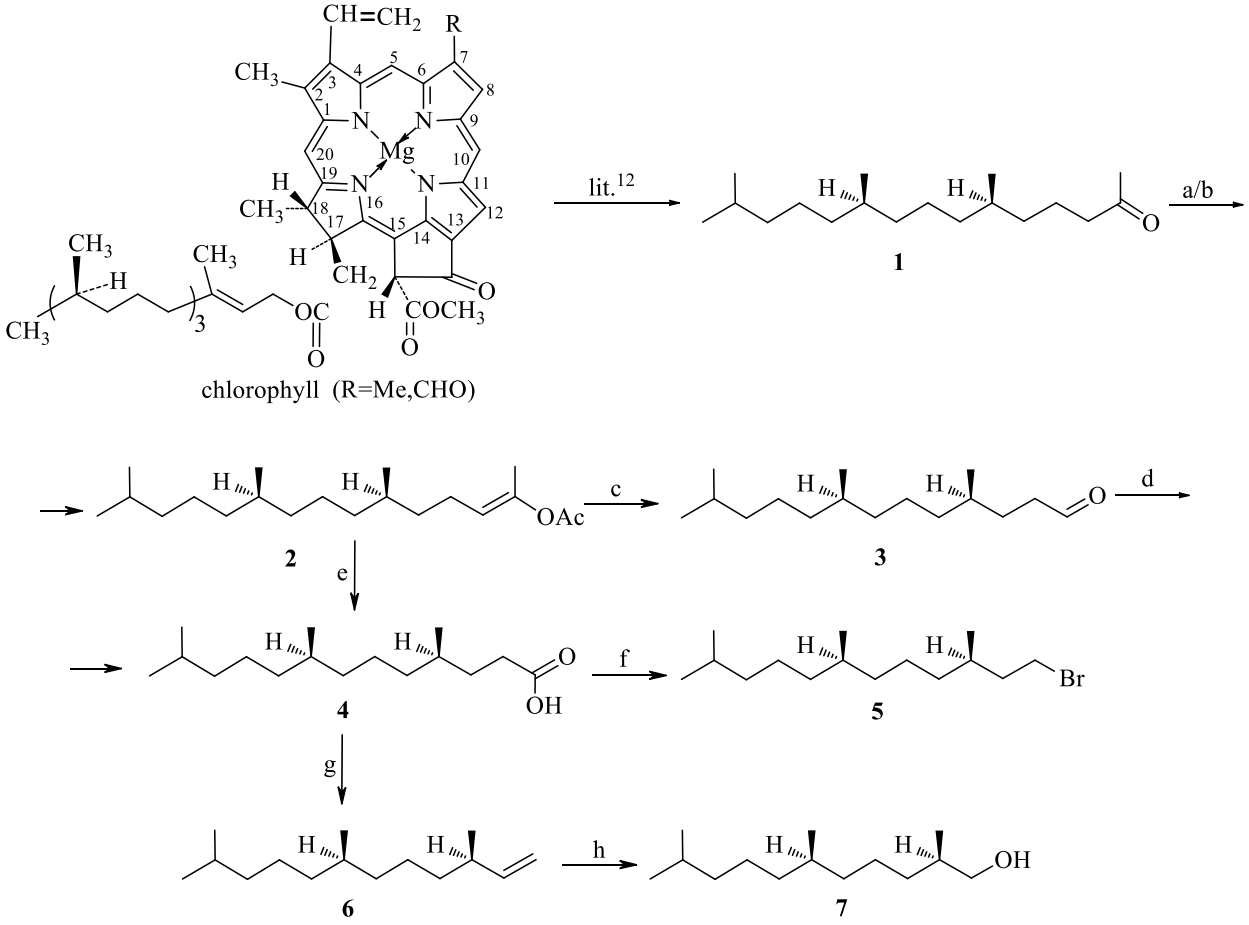
Results and Discussion

Synthesis of (3*R*,7*R*)-1-bromo-3,7,11-trimethyldodecane and (2*R*,6*R*)-2,6,10-trimethylundecan-1-ol

We proposed an original methods for the transformation of available homochiral (6*R*,10*R*)-6,10,14-trimethylpentadecan-2-on (phytone) **1,** obtained by ozonolysis of chlorophyll, to (2*R*,6*R*)-2,6,10-trimethylundecan-1-ol **7** and (3*R*,7*R*)-1-bromo-3,7,11-trimethyldodecane ((3*R*,7*R*)-hexahydrofarnesyl bromide) **5** – synthones for the side chain of (2*R*,4'*R*,8'*R*)-α-tocopherol (Scheme 2).

Phytone **1** is usually obtained by the ozonolysis of (2*E*,7*R*,11*R*)-phytol isolated from green plants by alkaline treatment of acetone extract of chlorophyll. This method requires a pre-purification of the chlorophyll from lipids. In addition, an alkaline saponification of chlorophyll in acetone gives sodium salts of high fat acids, and products of acetone self-condensation, that impedes the isolation of phytoll in pure form.[11] The method for the preparation of phytone **1** proposed by us is simple and includes ozonolytic oxidation of acetone extract of chlorophyll from great nettle without pre-purification of extract from related impurities. The reaction in the

presence of $Ba(OH)_2$ (acceptor of peroxide oxygen) led to phytone **1** in ~90% yield (in calculation on a chlorophyll content in the acetone extract).[12]



Scheme 2. *Reagents and conditions:* a. Ac_2O, $TsOH\cdot H_2O$, microvawe irradiation, 750 W, 10 min.; b. Ac_2O, $TsOH\cdot H_2O$, 150 ºC, 7 h.; c. O_3 (1 eq.) /$Ba(OH)_2$, Me_2CO; d. CrO_3//H_2SO_4, Me_2CO; e. O_3 (2 eq.)/$Ba(OH)_2$, Me_2CO; f. KOH/$AgNO_3$; Br_2/CCl_4; g. $Pb(OAc)_4/Cu(OAc)_2$, C_6H_6, 70 ºC; h. 1) O_3 (2 eq.), $Ba(OH)_2$, Me_2CO; 2) $NaBH_4$, MeOH.

The main problem in the transformation of phytone **1** to **5** or **7** compounds concludes in the shortening of the starting C_{18}-isoprenoid chain by three or four C atoms respectively. The pathway based on the enolization of ketone **1** to $\Delta^{2,3}$-enol esters and its ozonolitic oxidation to C_{16}-acid **4** seems to be the most rational. The desired $\Delta^{2,3}$-enol acetates **2** (mixture of *E*- and *Z*-isomers) were successfully obtained by the reflux (7h) of ketone **1** with acetic anhydride in the presence of $TsOH\cdot H_2O$ under conditions of thermodynamic control.[13] The other $\Delta^{1,2}$ –izomer was not formed. Conversion of ketone **1** was 49%. The use of microwave irradiation allowed us to considerably decrease the reaction time with complete retention of regeoselectivity reaction. Conversion of starting ketone **1** to the mixture of $\Delta^{2,3}$-enol acetates **2** consisted of 57% after irradiation for 10 min (power 750W). Enol acetates **2** can be easily separated from the unreacted

phytone **1** by column chromatography on silica gel, and the recovered phytone **1** can be repeatedly involved into the enolysation reaction.

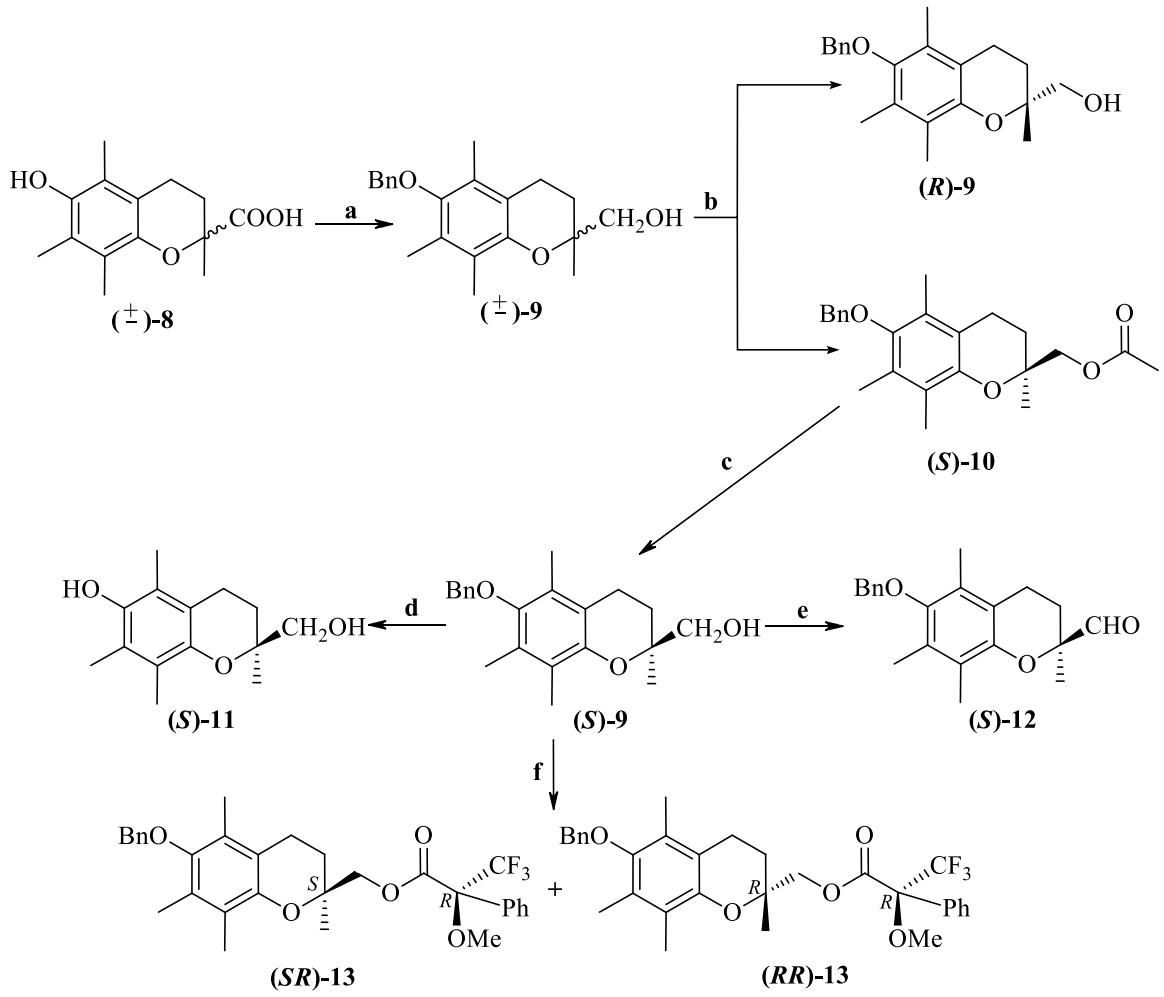
Aldehyde **3** was obtained by the ozonolysis of mixture of enol acetates **2** in acetone in the presence of $Ba(OH)_2$ and was oxidized by the Jones reagent to acid **4**. When enol acetates **2** are treated with excess ozone, they are converted to acid **4** in a single step. The Hunsdiecker reaction was used for the transformation of C_{16}-acid **4** to the target C_{15}-bromide **5**. The interaction between the silver salt of C_{16}-acid **4** and Br_2 in CCl_4 afforded the target bromide **5** in 46% yield. The oxidative decarboxylation of acid **4** led to (3*R*,7*R*)-3,7,11-trimethyl-1-dodocene **6**. Ozonolysis of the latter gave alcohol **7**.[14]

Synthesis of (*S*)-(-)-6-benzyloxy-3,4-dihydro-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-methanol

(*S*)-(-)-6-Benzyloxy-3,4-dihydro-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-methanol (*S*)-**9** and debenzylated (*S*)-chromanmethanol (*S*)-**11** are the important intermediates for the synthesis of the natural tocolls such as of α-tocopherol and α-tocotrienol.[6,8,15] A stereodivergent synthesis of (*S*)-cromanmethanols **9** and **11** with the use of lipases were described in papers.[8,15b,16] As a rull the ethereal solvents were used in reactions of biocatalytic transestherification of (R,S)-chromanmethanols that is a sufficient shortcoming for the application of hydrolytic enzymes (lipases) to the large-scale syntheses. In quest of the new possibilities to optimize the synthesis of chromanmethanols **9** and **11** our attention was turned to ionic liquids, which in recent years were used as the perfect reaction media for the biocatalytic transformations.[17]

We have proposed an effective method for the synthesis of (*S*)-(-)-6-benzyloxy-3,4-dihydro-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-methanol (*S*)-**9** by kinetically selective acylation with vinyl acetate of the corresponding racemic alcohol in the presence of *Amano PS* lipase (from *Burkholderia cepacia*) in ionic liquid (1-butyl-3-methylimidazolium hexafluorophosphate [bmim]PF_6) (Scheme 3). Earlier, the transesterification reaction of the derivatives of 2-methylchromanes was not conducted in ionic liquids.

Chroman-2-methanol (±)-**9** was obtained by the three-step transformation of commercially available (±)-chroman-2-carboxylic acid (±)-**8** according to the described methods.[8] From commercially available and inexpensive enzymes, such as lipases from *Burkholderia cepacia* (*Amano PS*), *Candida cylindracea* (*CCL*) and *Hog pancreas* (*PPL*) tested, the lipase *Amano PS* has been chosen. It was found, that *Amano PS* lipase showed a high catalytic activity and enantioselectivity. Kinetic resolution of alcohol (±)-**9** through selective acylation with succinic anhydride in [bmim]PF_6 proceeded (at 0º or 20ºC) with low stereoselectivity to afford the products with an optical rotation within the measurement error. When, vinyl acetate was employed as the acyl donor (substrate : enzyme weight ratio of 1.5:1, 20ºC, 24 h, 39% conversion), (*S*)-acetate (*S*)-**10** ($[\alpha]_D^{20}$ 3.6º, 35%) and the unchanged alcohol (*R*)-**9** ($[\alpha]_D^{20}$ 1.1º, 59%) were obtained. The signs of $[\alpha]_D$ and values of optically rotation were identical to those as described for optically pure compounds.[8,15b]



Scheme 3. *Reagents and conditions:* a: 1) TsOH, MeOH; 2) BnCl, K_2CO_3, DMFA; 3) $LiAlH_4$, Et_2O. b: $AcOCH=CH_2$/*Amano PS*, $[bmim]PF_6$, 20 °C, 24 h. c: MeONa/MeOH; 0.5 h. d: H_2, 20% Pd-C, AcOEt. e: $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -70 °C. f: (*R*)-MTPA-Cl, d-Py, $CDCl_3$, 24 h.

The saponification of (*S*)-**10** led to optically pure chromanmethanol of *S*-configuration (*S*)-**9**,[8,15b] in accordance with a sign and value of optical rotation [$[\alpha]_D^{20}$ -2.2° (*c* 0.7, $CHCl_3$)]. An enantiomeric excess (*ee*) for alcohol (*S*)-**9** was determined on the basic of analysis of ^{1}H NMR spectra of diastereomeric esters (Mosher esters – (*SR*)-**13** and (*RR*)-**13**, obtained by the interaction between alcohol (*S*)-**9** and (*R*)-(+)-α-methoxy-α-trifluoromethyl-α-phenylacetic acid chloride (MTPA-Cl). ^{1}H NMR spectra were recorded in $CDCl_3$ or C_6D_5N with in a narrow interval of chemical shifts from 2.5 to 5 ppm. The ratio of the obtained Mosher diastereomeric esters (*SR*)-**13** and (*RR*)-**13** (96:4) were determined from the intensity ratio of the signals (^{1}H NMR) attributable to protons of the isolated methylene group OCH_2 in esters (*SR*)-**13** (δ 4.02 or 4.27 ppm, ^2J = 11.2 Hz) and (*RR*)-**13** (δ 4.08 or 4.18 ppm, ^2J = 11.2 Hz). Thus, an diastereomeric excess (*de*) of ester (*SR*)-**13** and enantiomeric excess (*ee*) of alcohol (*S*)-**9** are equal to 92%

respectively. An absolute configuration and optically purity of compound (*S*)-**9** were confirmed by its Swern oxidation to aldehyde (*S*)-**12** ($[\alpha]_D^{20}$ 11.3º (0.9, $CHCl_3$)) (lit[15c] $[\alpha]_D^{25}$ 11.9º ($CHCl_3$). Hydrogenolysis of alcohol (*S*)-**9** 20% Pd-C in ethylacetate led to compound (*S*)-**11** (90% yield) with a specific rotation $[\alpha]_D^{20}$ 1.5º (*c* 1.4, EtOH) (lit[15b] $[\alpha]_D^{23}$ 1.6º (*c* 1.2, EtOH)).

We have studied the reaction of partial acetyllation of chromanmethanols (±)-**9** in the presence of *Amano PS* lipase in diisopropylether or in a mixture of organic solvent and [bmim]PF_6 and established a sufficient influence of ionic liquid upon the stereoselectivity of the biocatalyst. Thus, this reaction in [bmim]PF_6 afforded alcohol (*S*)-**9** with $[\alpha]_D^{20}$ -2.2º (*c* 0.7 $CHCl_3$) and in $(Pr^i)_2O$ - (S)-**9** with $[\alpha]_D^{20}$ -1.4º (*c* 0.9 $CHCl_3$). In the mixture of solvents at volume ratio [bmim]PF_6 and $(Pr^i)_2O$ equal to 3:1, 1:1 or 1:3 the value of optical rotation of (*S*)-**9** consisted of -2.0º, -1.9º and -1.5º respectively (lit[8] $[\alpha]_D^{20}$ -2.36º ($CHCl_3$)). In addition we found that *Amano PS* lipase containing in the ionic liquid [bmim]PF_6 retaines its initial activity and enantioselectivity reaction even after the third catalytic cycle, that evidences for the stability of biocatalyst under the reaction conditions.

Conclusions

The short and efficient synthesis of C_{14}- and C_{15}-terpenoids as synthones for the natural α-tocopherol has been developed using a microwave-activated regioselective enolization of homochiral phytone. The method for the synthesis of (*S*)-(-)-6-benzyloxy-3,4-dihydro-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-methanol (*S*)-**9** has been proposed by kinetically selective acylation with vinyl acetate of the corresponding racemic alcohol in the presence of *Amano PS* lipase in [bmim]PF_6. The ionic liquid is an efficient recyclable solvent in this reaction allowing to give a target (*S*)-(-)-enantiomer of high enantiomeric purity.

Experimental Section

General. ^1H- and ^{13}C-NMR spectra were recorded on a Bruker Avance-400 spectrometer (400.13 and 100.62 MHz for ^1H and ^{13}C respectively) in $CDCl_3$. Chemical shifts are on the δ scale, relative to internal Me_4Si. HPLC analysis used a Helwett Packard 1050 chromatograph with 250×4.6 mm columns C-18 ”zorbax”, the rate of elution was 1 ml/min, CH_3COCN:H_2O – 80:20 + 1% Et_3N with UV-detector under wavelength 254 nm. IR spectra were recorded on a Specord IR-75 spectrometer by CARL ZEISS JENA in tablet of KBr. Specific angles of rotation was determined using a Perkin-Elmer-141 polarimeter.

The specific activity of lipase from *Candida cylindracea* (CCL, Fluka) was 3.85 ед·мг$^{-1}$ and from *Hog pancreas* (PPL, Fluka) – 20.6 ед.мг$^{-1}$ *Amano* lipase *PS from Burkholderia cepacia* of Aldrich firm. Racemic chromanmethanol (±)-**9** was obtained by three-step transformation from commercial accessible 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (“Trolox” acid)

(±)-1 according. [8] Ionic liquid [bmim]PF_6 was obtained according. [18] (6*R*, 10*R*)-Phytone **1** ($[\alpha]_D^{20}$ 1.1º (c 1.78, $CHCl_3$)) was synthesized according to the our method, described earlier.[12] Methods of synthesis, spectral data (HNMR, IR, elemental analysis) and specific angles of rotation of compounds **2-7** described in our manuscripts. [13,14]

(*S*)-(+)-2-Acetoxymethyl-6-benzyloxy-2,5,7,8-tetramethylchromane ((*S*)-10) and (*R*)-(+)-6-benzyloxy-2,5,7,8-tetramethylchroman-2-methanol ((*R*)-9). To a solution of (±)-**9** (0.18 g, 0.55 mmol) in [bmim]PF_6 (2.8 ml) was added equimolar amount of vinyl acetate (0.05 ml) and of *Amano PS* lipase (0.12 g). The reaction mixture was stirred at a temperature of 20˚C and was controlled by TLC (hexane-ethyl acetate, 3:1) and HPLC analysis. When given conversion was achieved the reaction mixture was extracted by Et_2O (3×10 ml) and combined extracts were concentrated *in vacuo* at a temperature of 40˚C. Column chromatography on Si_2O (8 g, eluent – petroleum ether) gave acetate (*S*)-**10** (0.07 g, 35%), R_f 0.74 (hexane-ethyl acetate, 3:1), m.p. 38-40˚C, $[\alpha]_D^{20}$ 3.6˚ (c 1.3, $CHCl_3$) (lit.[8] m.p. 39˚C, $[\alpha]_D^{22}$ 4.0˚ ($CHCl_3$)] and of residual alcohol (*R*)-**9** (0.11 g, 59%) [R_f 0.61 (hexane-ethyl acetate, 3:1), m.p. 67-69˚C, $[\alpha]_D^{20}$ 1.1˚ (c 1.6, $CHCl_3$) (lit. [15b] m.p. 72-74˚C, $[\alpha]_D^{22}$ 1.1˚ ($CHCl_3$)). IR-, NMR ^{1}H- and ^{13}C-spectra of compounds (*S*)-**10** and (*R*)-**9** in agreement with those described.[15b] Separated suspension of lipase *Amano PS* in [bmim]PF_6 was used threefold.

(*S*)-(-)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-methanol ((*S*)-9). To a solution of (*S*)-**10** (0.07 g, 0.19 mmol) in methanol (4 ml) was added of natrium (0.004 g, 0.17 mmol). The reaction mixture was stirred for 0.5 h then was added 5% solution of HCl (until neutral reaction) and the mixture was extracted with EtOAc (3×7 ml), evaporated. Column chromatography on Si_2O (4 g , eluent – petroleum ether) gave (*S*)-**9** (0.06 g, 93%) as a colourless oil, R_f 0.61 (hexane-ethyl acetate, 3:1), $[\alpha]_D^{20}$ -2.2˚ (c 0.7, $CHCl_3$) (lit.[8] $[\alpha]_D^{23}$ -2.36˚ ($CHCl_3$)). IR- and NMR ^{1}H-spectra are in agreement with those described.[8]

(*S*)-(+)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-methanol ((*S*)-11). To a solution of (*S*)-**9** (0.09 g, 0.26 mmol) in anhydrous AcOEt (5 ml) was added 20% Pd-C (0.04 g) and stirred under H_2 for 6 h. When the reaction was over (control by TLC in mixture hexane-ethyl acetate = 3:1) the catalyst was filtered off and the filtrate evaporated. The residue was chromatographed on Si_2O column (4 g, eluent – petroleum ether) to obtain of (*S*)-**11** (0.06 g, 90%) R_f 0.42 (hexane-ethyl acetate, 3:1), $[\alpha]_D^{20}$ 1.5˚ (c 1.4, EtOH) (lit.[15b] $[\alpha]_D^{23}$ 1.6˚ (EtOH)). IR- and NMR ^{1}H- and ^{13}C-spectra are in agreement with those described.[15b]

(*S*)-(+)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-carboxaldehyde ((*S*)-12). To a solution of DMSO (0.2 g, 2.54 mmol) in dichloromethane (2 ml) at a temperature of -70˚C was added oxalylcholoride (0.11 ml, 1.32 mmol) and stirred for 0.5 h. A solution of (*S*)-**9** (0.05 g, 0.16 mmol) in dichloromethane (2 ml) was added and stirred for 1 h at -70˚C. Then triethylamine (0.7 ml) was added and stirred at -70˚C for 0.5 h. Temperature was raised to 0˚C and the mixture was stirred over again for 0.5 h. The reaction mixture was diluted of water (10 ml) and extracted with ethyl acetate (3×10 ml). Combined organic layers were dried ($MgSO_4$) and concentrated under low pressure. The residue was chromatographed on Si_2O column (5 g, eluent – hexane) to give of

(*S*)-**12** (0.05 g, 93%) R_f 0.67 (hexane-ethyl acetate, 3:1), m.p. 57-59˚C, $[\alpha]_D^{20}$ 11.3˚ (c 0.7, $CHCl_3$) (lit.[15c] m. p. 56˚C, $[\alpha]_D^{23}$ 11.9˚ ($CHCl_3$)). IR- and NMR ^{1}H-spectra are in agreement with those described.[8]

[(*S*)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-methanol] ether (*R*)-α-methoxy-α-trifluoromethyl-α-phenylacetic acid ((*SR*)-13). To a solution of (*S*)-**9** (0.002 g, 0.006 mmol) in C_6D_5N (0.1 ml) and $CDCl_3$ (0.1 ml) was added of (+)-α-methoxy-α-trifluoromethyl-α-phenylacetic acid chloride (MTPA-Cl) (0.003 g, 0.012 mmol) and stirred for 24h at room temperature. Then the reaction maxture was diluted of toluene (0.6 ml) and $C_6D_5CD_3$ (0.1 ml) and recorded NMR ^{1}H-spectra. The enantiomeric purity of ester (*SR*)-**6** 92% *ee* were obtained from ratio intensities of signals, CH_2-O (96:4) diastereomeric esters (SR)-**13** (δ 4.02 or 4.27 ppm ^2J = 11.2 Hz) and (RR)-**13** (δ 4.08 or 4.18 ppm ^2J = 11.2 Hz).

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