Enantioselective transesterification of (±)-6-benzyloxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-1-benzopyran-2-ylmethanol catalyzed by the *Amano PS* lipase in the ionic liquid [bmim]PF_6

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(*S*)-(−)-6-Benzyloxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-1-benzopyran-2-ylmethanol, a synthon for the design of natural α-tocopherol, was obtained by kinetically selective acetylation of the corresponding racemic alcohol in the presence of the *Amano PS* lipase from *Burkholderia cepacia* in the ionic liquid 1-butyl-3-methylimidazolinium hexafluorophosphate ([bmim]PF_6).

Key words: (*S*)-(−)-6-benzyloxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-1-benzopyran-2-ylmethanol, α-tocopherol, enantioselective acetylation, *Amano PS* lipase, ionic liquid.

(*S*)-(−)-6-Benzyloxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-1-benzopyran-2-ylmethanol ((*S*)-chromanylmethanol, (*S*)-**1**) and debenzylated (*S*)-chromanylmethanol (*S*)-**2** are key synthons for the preparation of natural tocols: α-tocopherol and α-tocotrienol.[1—6] In early studies, chromanylmethanols (*S*)-**1** and (*S*)-**2** were obtained from (*S*)-chromane-2-carboxylic acid isolated in turn from the corresponding racemic acid with (*S*)-α-methylbenzylamine as an enantioselective agent.[7,8]

Various reported[9—15] synthetic routes to compounds (*S*)-**1** and (*S*)-**2** start from optically active acyclic compounds and chiral auxiliary reagents. In the last few decades, homochiral chromane building blocks for tocopherols and tocotrienols have been actively synthesized by asymmetric epoxidation of allylic alcohols and the Sharpless dihydroxylation of enynes in combination with cross-coupling reactions of iodoarenes with chiral diols in the presence of palladium complexes as catalysts.[16—19] An efficient and versatile synthetic strategy for the design of homochiral chromanes that involves palladium-catalyzed asymmetric allylic alkylation of phenols with allyl carbonates has been developed by various research teams.[20—22] With the chiral ligands and catalysts found, the target chromanes have been obtained with >97% *ee*.[23,24] However, despite their high enantioselectivity, the aforesaid asymmetric catalysis methods for the synthesis of homochiral chromanes are not used commercially so far. Biocatalytic transformations provide a promising alternative to chemical processes.[25] Immobilized hydrolytic enzymes (lipases) are known to be employed in commercial production of vitamins, drugs, and biologically active food supplements, with a total output over 10 000 tons per year.[26] Stereodivergent syntheses of (*S*)-chromanylmethanols **1** and **2** *via* biocatalytic transesterification of chromanylmethanols assisted by lipases has been studied.[3,4,27,28] However, the syntheses were carried out in organic ether-type solvents, which are undesirable for use in large-scale production. In the last few years, ionic liquids have attracted considerable attention as environmentally safe media for biocatalytic transformations.[29] For instance, it has been found that they enhance the catalytic activity, stereoselectivity, and stability of lipases in resolution of racemic alcohols.[30]

In the present work, we propose an efficient route to (*S*)-(−)-6-benzyloxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-1-benzopyran-2-ylmethanol (*S*)-**1** *via* lipase-catalyzed selective acetylation of the corresponding racemic alcohol **1** in the ionic liquid 1-butyl-3-methylimidazolinium hexafluorophosphate ([bmim]PF_6) containing the *Amano PS* lipase from *Burkholderia cepacia* (Scheme 1). Earlier, 2-methylchromane derivatives have never been subjected to transesterification in ionic liquids.

Results and Discussion

Racemic chromanylmethanol (±)-**1** was prepared in three steps from commercial chroman-2-ylcarboxylic acid (Trolox) (±)-**3** as described earlier.[4] Out of the tested accessible and relatively inexpensive enzymes (the lipases from *Burkholderia cepacia* (*Amano PS*), *Candida cylindracea* (*CCL*), and *Hog pancreas* (*PPL*)), we selected the *Amano PS* lipase for its highest catalytic activity and enantioselectivity in the ionic liquid [bmim]PF_6. Partial acylation of alcohol (±)-**1** with succinic anhydride in

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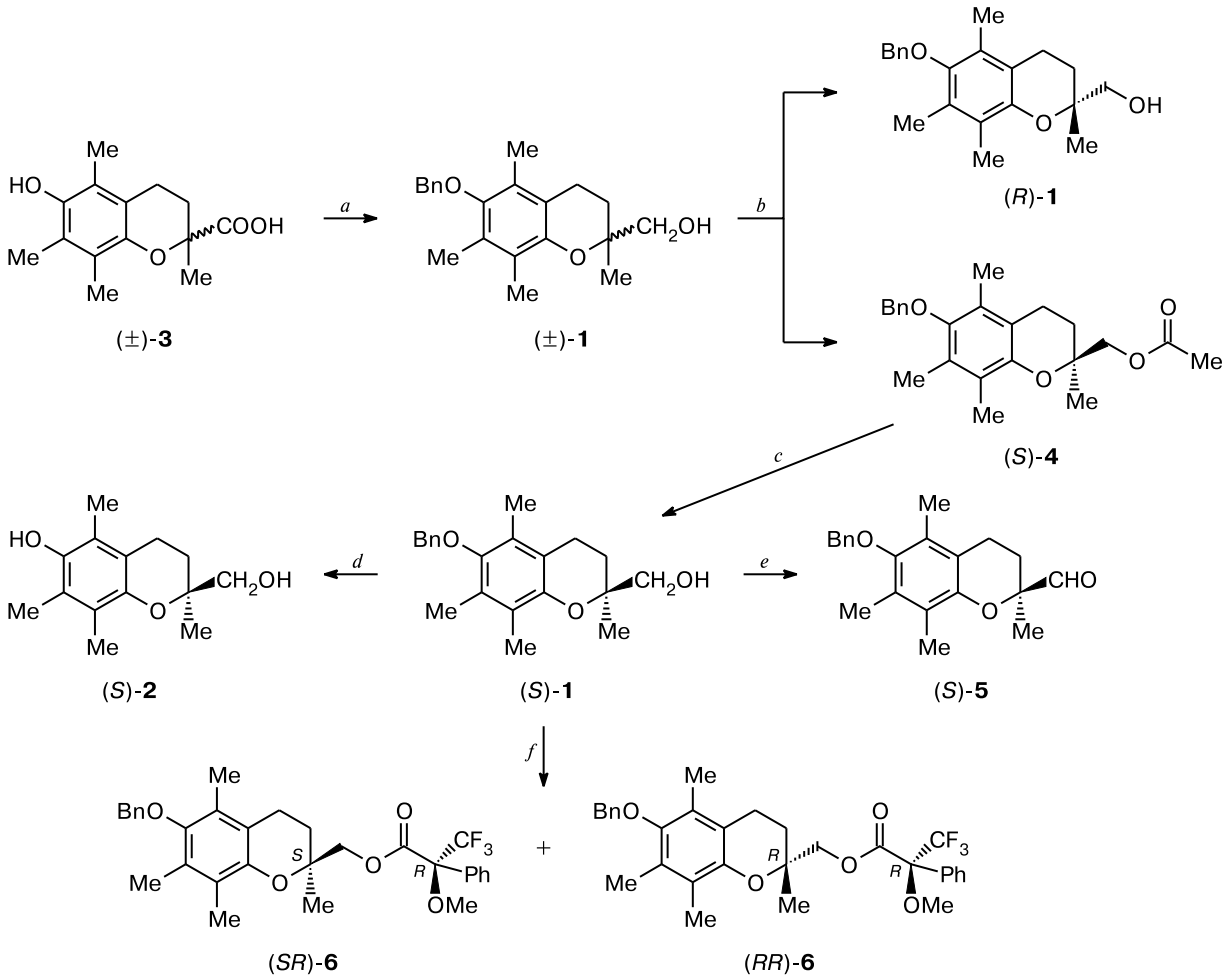
Scheme 1



Reagents and conditions: *a*. 1) TsOH, MeOH; 2) BnCl, K_2CO_3, DMF; 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, Pd(20%)—C, AcOEt; *e*. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −70 °C; *f*. (*R*)-(+)-α-Methoxy-α-phenyl-α-trifluoromethylacetyl chloride ((*R*)-MTPA-Cl), Py-d_5, $CDCl_3$, 24 h.

[bmim]PF_6 at both 0 and 20 °C was virtually non-stereoselective: the specific rotations of the products were within the measurement error. However, using vinyl acetate as an acylating reagent (substrate : enzyme = 1.5 : 1 (w/w), 20 °C, 24 h, 39% conversion), we obtained acetate (*S*)-**4** (35% yield, $[\alpha]_D^{20}$ 3.6° (*c* 1.3, $CHCl_3$)) and nonconsumed alcohol (*R*)-**1** (59% yield, $[\alpha]_D^{20}$ 1.1° (*c* 1.6, $CHCl_3$)); the signs and values of their specific rotations correspond to those of their optically pure samples.[3,4]

Hydrolysis of acetate (*S*)-**4** gave optically pure (*S*)-chromanylmethanol ($[\alpha]_D^{20}$ −2.2° (*c* 0.7, $CHCl_3$)).[4,5] The enantiomer excess (*ee*) of alcohol (*S*)-**1** was determined from the ^{1}H NMR spectra of diastereomeric Mosher esters (*SR*)-**6** and (*RR*)-**6** prepared from alcohol (*S*)-**1** and acid chloride (*R*)-MTPA-Cl. The ^{1}H NMR spectra of esters (*SR*)-**6** and (*RR*)-**6** were recorded in deuterated solvents (pyridine, chloroform, and toluene) in a narrow range from δ 2.5 to 5.0 to reduce the effect of intense signals. According to the signal intensity ratio for the protons of the oxymethylene group OCH_2 in esters (*SR*)-**6** (δ 4.02 or 4.27, ^2J = 11.2 Hz) and (*RR*)-**6** (4.08 or 4.18, ^2J = 11.2 Hz), the ratio of diastereomeric Mosher esters (*SR*)-**6** and (*RR*)-**6** in the final mixture is 96 : 4. Thus, the diastereomer excess *de* of ester (*SR*)-**6** and, consequently, the enantiomer excess *ee* of alcohol (*S*)-**1** are 92%. The absolute configuration and optical purity of compound (*S*)-**1** were confirmed by its Swern oxidation into aldehyde (*S*)-**5** ($[\alpha]_D^{20}$ 11.3° (*c* 0.9, $CHCl_3$)); data[5] for optically pure (*S*)-**5**: $[\alpha]_D^{25}$ 11.9° ($CHCl_3$). Hydrogenolysis of alcohol (*S*)-**1** with Pd(20%)—C in ethyl acetate gave compound (*S*)-**2** in 90% yield ($[\alpha]_D^{20}$ 1.5° (*c* 1.4, EtOH)); data[3] for optically pure (*S*)-**2**: $[\alpha]_D^{23}$ 1.6° (EtOH).

A study of the partial acetylation of chromanylmethanol (±)-**1** under the action of the *Amano PS* lipase in diisopro-

pyl ether or in its mixture with [bmim]PF_6 revealed a favorable effect of the ionic liquid on the stereoselectivity of the biocatalyst. For instance, the specific rotations of alcohol (*S*)-**1** obtained in [bmim]PF_6 and in Pr^i_2O are $[\alpha]_D^{20}$ −2.2° (*c* 0.7, $CHCl_3$) and $[\alpha]_D^{20}$ −1.4° (*c* 0.9, $CHCl_3$), respectively. In mixtures of these solvents for [bmim]PF_6—Pr^i_2O = 3 : 1, 1 : 1, and 1 : 3 (v/v), the specific rotations of compound (*S*)-**1** are −2.0, −1.9, and −1.5°, respectively (data[4] for optically pure (*S*)-**1**: $[\alpha]_D^{20}$ −2.36° ($CHCl_3$)).

In addition, the ionic liquid [bmim]PF_6 containing the *Amano PS* lipase can be reused at least three times with no noticeable reduction in the catalytic activity of the lipase or in the enantioselectivity of the reaction (*i.e.*, the biocatalyst is stable under these conditions).

To sum up, enantioselective transesterification of (±)-6-benzyloxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-1-benzopyran-2-ylmethanol catalyzed by the *Amano PS* lipase in the ionic liquid [bmim]PF_6 affords the target (*S*)-(−)-enantiomer with high *ee*; both the biocatalyst and the solvent can be reused.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance-400 instrument (400.13 (^1H) and 100.62 MHz (^{13}C)) in $CDCl_3$. Chemical shifts δ are referenced to Me_4Si. The reaction products were analyzed by HPLC on a Hewlett—Packard 1050 chromatograph (C-18 column (250×4.6 mm, Zorbax), elution rate 1 mL min^{-1}, CH_3COCN—H_2O (80 : 20) + 1% Et_3N) fitted with a UV detector at a wavelength of 254 nm). IR spectra were recorded on a Specord 75 IR spectrophotometer (Carl Zeiss, Jena) in KBr pellets. The specific rotations measured on a Perkin—Elmer-141 polarimeter are expressed in deg mL g^{-1} dm^{-1}; the concentration of the solution is cited in g (100 mL)$^{-1}$. Melting points were determined on a Boetius hot stage. TLC was carried out on SiO_2 plates (Silufol); spots were visualized in a solution of anisaldehyde in ethanol acidified with H_2SO_4.

The specific activities of the lipases from *Candida cylindracea* (*CCL*, Fluka) and *Hog pancreas (PPL*, Fluka) were 3.85 and 20.6 unit mg^{-1}, respectively. The *Amano PS* lipase from *Burkholderia cepacia* (Aldrich) was used. Racemic chromanylmethanol (±)-**1** was prepared from commercial chroman-2-ylcarboxylic acid (Trolox) (±)-**3** as described earlier.[4] The synthesis of the ionic liquid [bmim]PF_6 followed a known procedure.[31]

(*S*)-(+)-2-Acetoxymethyl-6-benzyloxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-1-benzopyran (*S*)-4 and (*R*)-(+)-6-benzyloxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-1-benzopyran-2-ylmethanol (*R*)-1. Equimolar amounts of vinyl acetate (0.05 mL) and the *Amano PS* lipase (120 mg) were added to a solution of chromanylmethanol (±)-**1** (180 mg, 0.55 mmol) in [bmim]PF_6 (2.8 mL). The reaction mixture was stirred with a magnetic stirring bar at 20 °C. The course of the reaction was monitored by TLC (hexane—ethyl acetate, 3 : 1) and HPLC. After the given conversion (39%) was achieved, the products were extracted with Et_2O (3×10 mL) and the combined extracts were concentrated *in vacuo* at 40 °C. The residue was chromatographed on SiO_2 (8 g) with light petroleum as an eluent. The yield of acetate (*S*)-**4** was 70 mg (35%), R_f 0.74 (hexane—ethyl acetate, 3 : 1), m.p. 38—40 °C, $[\alpha]_D^{20}$ 3.6° (*c* 1.3, $CHCl_3$) (for optically pure acetate (*S*)-**4**, *cf.* Ref. 4: m.p. 39 °C, $[\alpha]_D^{22}$ 4.0° ($CHCl_3$)). The yield of residual alcohol (*R*)-**1** was 107 mg (59%), R_f 0.61 (hexane—ethyl acetate, 3 : 1), m.p. 67—69 °C, $[\alpha]_D^{20}$ 1.1° (*c* 1.6, $CHCl_3$) (for (*R*)-**1**, *cf.* Ref. 3: m.p. 72—74 °C, $[\alpha]_D^{22}$ 1.1° ($CHCl_3$)). The IR and ^1H and ^{13}C NMR spectra of compounds (*S*)-**4** and (*R*)-**1** are identical with those reported earlier.[3] The suspension of the *Amano PS* lipase in [bmim]PF_6 was separated and reused three times.

(*S*)-(−)-6-Benzyloxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-1-benzopyran-2-ylmethanol (*S*)-1. Metallic sodium (4 mg, 0.17 mmol) was added to a solution of compound (*S*)-**4** (70 mg, 0.19 mmol) in MeOH (4 mL). The reaction mixture was stirred for 0.5 h and then neutralized with 5% HCl. The product was extracted with EtOAc (3×7 mL) and the combined extracts were concentrated. The residue was chromatographed on SiO_2 (4 g) with light petroleum as an eluent. The yield of compound (*S*)-**1** was 58 mg (93%), colorless oil, R_f 0.61 (hexane—ethyl acetate, 3 : 1), $[\alpha]_D^{20}$ −2.2° (*c* 0.7, $CHCl_3$) (for optically pure alcohol (*S*)-**1**, *cf.* Ref. 4: $[\alpha]_D^{23}$ −2.36° ($CHCl_3$)). The IR and ^1H NMR spectra of compound (*S*)-**1** are identical with those reported earlier.[4]

(*S*)-(+)-6-Hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-1-benzopyran-2-ylmethanol (*S*)-2. The catalyst Pd(20%)—C (40 mg) was added to a solution of compound (*S*)-**1** (85 mg, 0.26 mmol) in anhydrous AcOEt (5 mL). The mixture was stirred under hydrogen for 6 h. After the reaction was completed (monitoring by TLC in hexane—ethyl acetate, 3 : 1), the catalyst was filtered off and washed with AcOEt. The filtrate was concentrated and the residue was chromatographed on SiO_2 (4 g) with light petroleum as an eluent. The yield of compound (*S*)-**2** was 55 mg (90%), R_f 0.42 (hexane—ethyl acetate, 3 : 1), $[\alpha]_D^{20}$ 1.5° (*c* 1.4, EtOH) (for optically pure alcohol (*S*)-**2**, *cf.* Ref. 3: $[\alpha]_D^{23}$ 1.6° (EtOH)). The IR and ^1H and ^{13}C NMR spectra of compound (*S*)-**2** are identical with those reported earlier.[3]

(*S*)-6-Benzyloxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-1-benzopyran-2-carbaldehyde (*S*)-5. Oxalyl chloride (0.11 mL, 1.32 mmol) was added at −70 °C to a solution of DMSO (198 mg, 2.54 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred for 0.5 h. Then a solution of compound (*S*)-**1** (50 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) was added and stirring was continued at −70 °C for 1 h. Triethylamine was added and the mixture was stirred at −70 °C for 0.5 h and then at 0 °C for 0.5 h. The reaction mixture was diluted with water (10 mL) and the product was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on SiO_2 (5 g) with hexane as an eluent. The yield of compound (*S*)-**5** was 46 mg (93%), R_f 0.67 (hexane—ethyl acetate, 3 : 1), m.p. 57—59 °C, $[\alpha]_D^{20}$ 11.3° (*c* 0.7, $CHCl_3$) (for optically pure aldehyde (*S*)-**5**, *cf.* Ref. 5: m.p. 56 °C, $[\alpha]_D^{25}$ 11.9° ($CHCl_3$)). The IR and ^1H NMR spectra of compound (*S*)-**5** are identical with those reported earlier.[4]

(*S*)-6-Benzyloxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-1-benzopyran-2-ylmethyl (*R*)-α-methoxy-α-phenyl-α-trifluoromethylacetate (*SR*)-6. (*R*)-α-Methoxy-α-phenyl-α-trifluoromethylacetyl chloride (3 mg, 0.012 mmol) was added to a solution of alcohol (*S*)-**1** (2 mg, 0.006 mmol) in C_6D_5N (0.1 mL) and $CDCl_3$ (0.1 mL). The reaction mixture was stirred at ~20 °C for 24 h and then diluted with toluene (0.6 mL) and $C_6D_5CD_3$ (0.1 mL) for recording ^1H NMR spectra. It follows from the signal intensity

ratio for CH_2—O (96 : 4) in diastereomers (*SR*)-**6** (δ 4.01 (d) or 4.27 (d), ^2J = 11.2 Hz) and (*RR*)-**6** (δ 4.07 (d) or 4.18 (d), ^2J = 11.2 Hz) that the diastereomer excess *de* and optical purity of (*SR*)-**6** is 92%.

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