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Enantiocomplementary Chemoenzymatic Asymmetric Synthesis of (*R*)- and (*S*)-Chromanemethanol

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A non-lipase-based, enantiocomplementary chemoenzymatic route towards enantiopure (*R*)- and (*S*)-chromanemethanol (**12**), which are the key building blocks for the synthesis of stereoisomerically pure α-tocopherols, has been achieved by the biocatalytic resolution of a racemic 2,2-disubstituted oxirane using an epoxide hydrolase and a halohydrin dehalogenase, which exhibit opposite enantiopreferences. The introduction of chirality at an early stage of the synthesis ensured a high efficiency, leading to total overall yields of 16 and 26 % for (*R*)- and (*S*)-chromanemethanol (**12**), respectively.

Introduction

The increase in human life expectancy during the last few decades is driving the research in the field of antioxidants and antiageing agents. In this context, studies on vitamin E and its homologues have proven that these compounds possess great potential with regard antioxidant, antiageing and pharmaceutical properties. These characteristics have made vitamin E a popular target for organic synthesis.

Vitamin E comprises a group of eight molecules that differ in the number and position of methyl groups on the aromatic part of the chromane system and the degree of unsaturation in the side-chain (Figure 1).[1]

In terms of bioavailability, α-tocopherol transfer proteins[2,3] show a preference for the naturally occurring (2*R*,4′*R*,8′*R*)-α-tocopherol resulting in a pronounced bio-

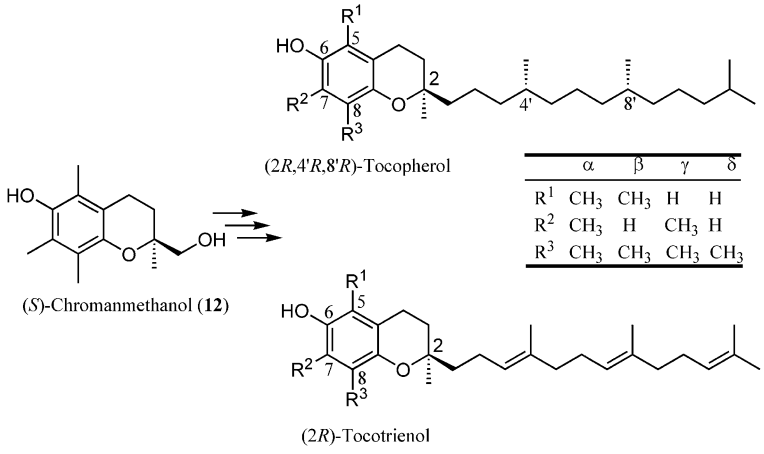

Figure 1. Tocopherol and tocotrienol derivatives.

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discrimination towards the other seven stereoisomers.[4,5] Competition studies of the binding to the transfer protein revealed that the unlabelled (2*R*,4′*R*,8′*R*)-α-tocopherol shows the highest competitive effect compared with deuterium-labelled (2*R*,4′*R*,8′*R*)-α-tocopherol. In contrast,

(2*S*,4′*R*,8′*R*)-α-tocopherol, which differs only in the stereoconfiguration at C-2, exhibits significantly lower competition.[2] These experiments reveal that the uptake of vitamin E is strongly dependent on its stereoconfiguration. However, although (2*R*,4′*R*,8′*R*)-α-tocopherol is the biologically most active stereoisomer, only 7% of the global market for vitamin E can be supplied in its desirable stereoform from natural sources, which is mainly derived from soya deodoriser distillates.[1a] As a consequence, efforts towards the asymmetric synthesis of (2*R*,4′*R*,8′*R*)-α-tocopherol and the corresponding building blocks have gained increasing attention.[1b] On the other hand, other stereoisomers of this important antioxidant are required for the evaluation of their bioavailability. In view of these facts, synthetic access to both stereoisomers of the chiral chromane building block, generally denoted as "chromanemethanol", represents a challenge for academic and industrial research.

The first asymmetric synthesis of vitamin E using racemate resolution was published by Mayer et al. in 1963.[6] In general, the large-scale industrial synthesis of (*all-rac*)-α-tocopherol can be divided into three major strategies, which have been reviewed by Baldenius et al.,[7] Mayer and Isler[8] and Netscher et al.[9] i) the synthesis of the chromane unit, ii) the synthesis of the side-chain and iii) the coupling of these two building blocks. The asymmetric synthesis of the chiral side-chain is well established on the laboratory and industrial scales and is accomplished by asymmetric hydrogenation using ruthenium complexes with chiral ligands.[9] In contrast, the synthesis of the chromane moiety in a nonracemic form remains problematic due to the general difficulty of generating the fully substituted chiral C-2 centre.

Several strategies have been applied to the synthesis of chromanemethanol, such as optical resolution, the use of chiral auxiliaries in stoichiometric or catalytic amounts[10–16] and biocatalysis. Two biocatalytic approaches have been reported. In the first, the racemic chromane unit was enzymatically resolved by lipase-catalysed ester hydrolysis involving the hydroxymethyl moiety at C-2[17–19] or the phenolic 6-hydroxy group,[20,21] or by using prochiral substrate analogues[19] or a suitable chiral building block.[22] The second approach employed a chiral building block (obtained by enzymatic desymmetrisation or kinetic resolution) for the synthesis of the chromane unit. The latter strategy, recently demonstrated by Breit and coworkers[23] based on the lipase-catalysed kinetic resolution of 2-methylglycerol derivatives,[24] is more economic because chirality is introduced at a very early stage of the multistep sequence.

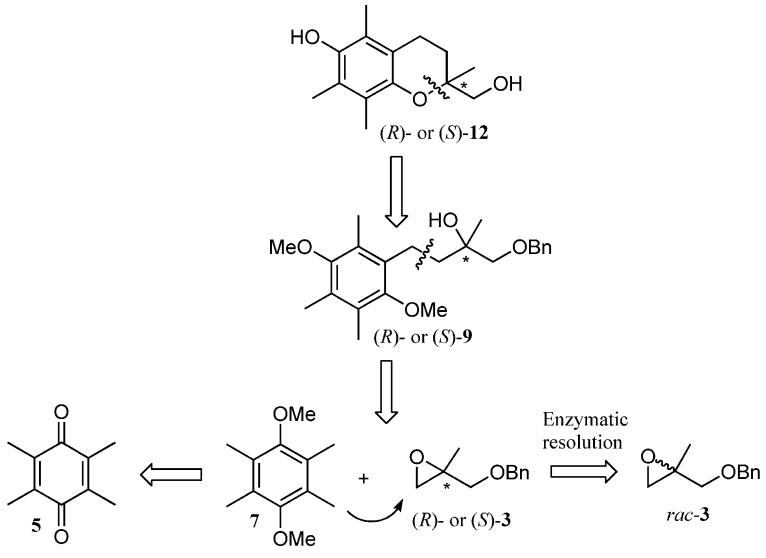
Herein we report the synthesis of both enantiomers of chromanemethanol by means of enzymatic kinetic resolution using two different classes of enantiocomplementary enzymes. (*S*)-Chromanemethanol **12** was obtained from *rac*-oxirane **3** in 26% overall yield and >99% *ee* by using epoxide hydrolases in the key step, whereas (*R*)-**12** was synthesised in 16% yield and >99% *ee* by using halohydrin dehalogenases.[25] This strategy is a successful example of the application of enzymes that act in an enantiocomplementary fashion.[26]

In principle, this strategy should also be applicable to the synthesis of structurally related bioactive 2-methylchromane derivatives such as clusifoliol (antitumour),[27,28] rhododaurichromaneic acid A (anti-HIV),[29] siccanin (antifungal)[30] and troglitazone (diabetes).[31]

Results and Discussion

Retrosynthetic Analysis

Our approach is based on the biocatalytic kinetic resolution of epoxide *rac*-**3**, which leads to the chiral centre at



Scheme 1. Retrosynthetic approach towards (*R*)- and (*S*)-chromanemethanol **12**.

C-2 of the chromane moiety (*R*)- or (*S*)-**12**, whose precursor **9** is obtained by coupling the appropriate epoxide enantiomer to the aromatic system **7**. After deprotection of the methoxy protecting groups, compound **9** undergoes cyclisation to yield (*R*)- or (*S*)-chromanemethanol **12** (Scheme 1).

Enantiocomplementary Biohydrolysis of *rac*-3

Racemic epoxide **3** was obtained by the *O*-benzylation of 2-methylprop-2-enol (**1**) to yield benzyl methallyl ether (**2**), which was subsequently epoxidised using *m*-chloroperbenzoic acid to yield *rac*-epoxide **3** in 85% yield over two steps (Scheme 2).[32]

In the search for enzymes capable of accomplishing the kinetic resolution of *rac*-**3** in an enantiocomplementary fashion, two types of biocatalysts were envisaged (Scheme 2). Epoxide hydrolases of (resting) whole cells of *Rhodococcus ruber* CBS 717.73 were recently shown by us to possess high enantioselectivity in the kinetic resolution of **3** by preferential hydrolysis of (*R*)-**3** with complete retention of configuration to furnish diol (*S*)-**8** and unreacted (*S*)-**3**.[33] Note the switch in Cahn–Ingold–Prelog (CIP) preference from epoxide **3** to diol **8**. Recent studies by Janssen and co-workers[34] on the biocatalytic regio- and stereoselective nucleophilic ring-opening of oxiranes catalysed by halohydrin dehalogenases (previously also termed haloalcohol dehalogenases or haloalcohol epoxidases) showed that these enzymes not only introduced the "natural" nucleophilic halide (Cl^-, Br^-, I^-) into the oxirane leading to vicinal haloalcohols, but also accepted an impressive range of non-natural nucleophiles, such as azide, cyanate, formate and nitrite. In the presence of nitrite, the corresponding mono-nitrite esters of *vic*-diols are obtained. In aqueous buffer solution, the latter are unstable and spontaneously hydrolyse to furnish the corresponding *vic*-diols as the final products.[35] This "promiscuous catalytic activity"[36] of halohydrin dehalogenases turns them into suitable substitutes for epoxide hydrolases. Substrate selectivity data on halohydrin dehalogenase HheC from *Agrobacterium radiobacter* AD1 suggest that the sterically demanding 2,2-disubstituted oxirane *rac*-**3** should be transformed with high enantioselectivity and analysis of the stereochemical course of the reaction showed that HheC might exhibit a stereopreference opposite to that of the epoxide hydrolase from *Rhodococcus ruber* CBS 717.73.

The screening, optimisation and upscaling of the biocatalytic kinetic resolution employing epoxide hydrolase from *Rhodococcus ruber* CBS 717.73 has already been published by us.[33]

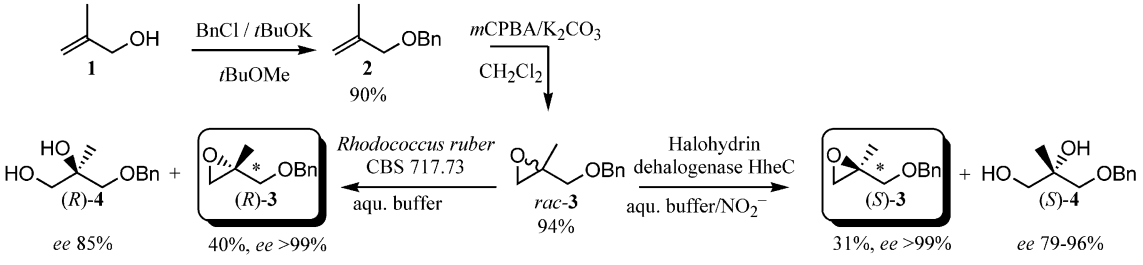
Initial small-scale tests on the kinetic resolution of *rac*-**3** using halohydrin dehalogenase HheC from *Agrobacterium radiobacter* AD1 (HheC) in the presence of nitrite showed perfect regio- and enantioselectivity of this enzyme with a matching stereopreference by rapidly converting (*R*)-**3** with strict retention of configuration into (*S*)-**4** (96% *ee*) and unreacted (*S*)-**3** (>99 *ee*), which corresponds to an *E* value of >200 (Table 1, entry 1). During scale-up, it was observed that the non-enzymatic hydrolysis of the intermediate nitrate ester was rather slow. To circumvent this limitation, sodium hydrogen carbonate was added during work-up, which led to a gradual decrease of the diol (*S*)-**4** [the *ee* of the product (ee_P) decreased from 96 to 79%, entries 2 and 3]. Because the *ee* of the substrate (ee_S) remained at a perfect level of >99%, the decrease in ee_P was attributed to the non-enzymatic hydrolysis of (*R*)-**3** in the basic medium with retention of configuration, which caused an apparent depletion in the *E* value. Because (*S*)-**3** was the desired enantiomer for further synthesis, this depletion was not significant. Finally, a preparative-scale experiment (entry 4) using 100 mg of *rac*-**3** gave (*S*)-**3** in 31% isolated yield and >99% *ee*.

Table 1. Biocatalytic kinetic resolution of *rac*-**3** using halohydrin dehalogenase HheC from *Agrobacterium radiobacter* AD1 in the presence of nitrite.

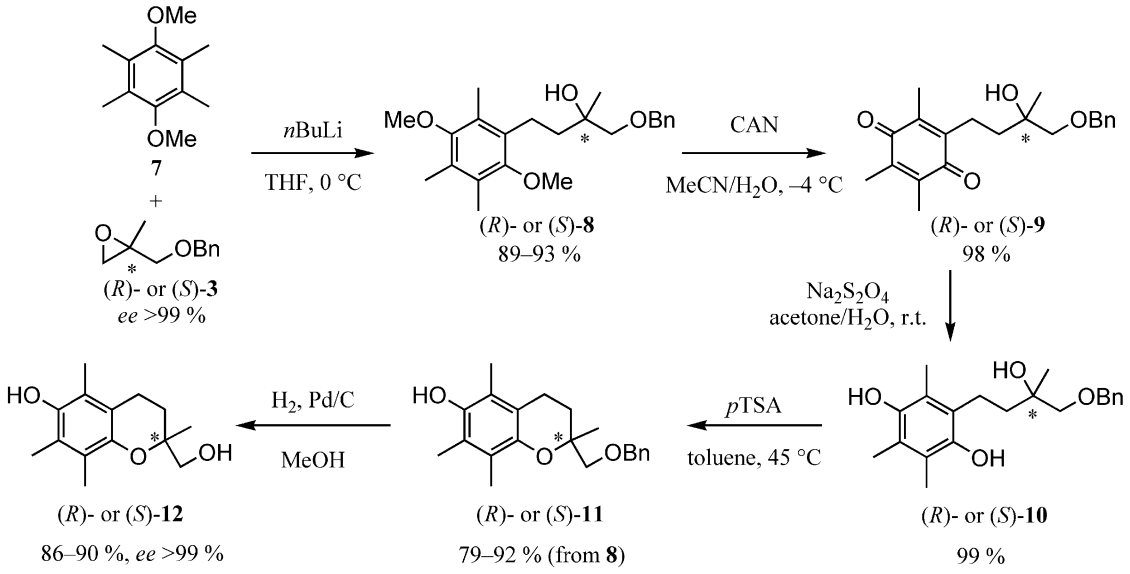
Entry	Time [h]	Conv. [%][a]	ee_S [%][b]	ee_P [%][b]	Enantioselectivity *E*[a]
1	6	51	>99 (*S*)	96 (*S*)	>200
2	12	52	>99 (*S*)	90 (*S*)	99
3	24	56	>99 (*S*)	79 (*S*)	43
4	16	31[c]	>99 (*S*)	88 (*S*)	81

[a] Calculated from the ee_S and ee_P values (see the Exp. Sect.), substrate concentration 168 mM. [b] Absolute configuration is denoted in parentheses; ee_S and ee_P refer to the enantiomeric excesses of the substrate and product, respectively. Note the switch in CIP preference from epoxide **3** to diol **8**. [c] Isolated yield from preparative-scale experiment.

Based on the successful enantiocomplementary biohydrolysis of oxirane **3** using an epoxide hydrolase and a halohydrin dehalogenase, (*R*)- and (*S*)-chromanemethanol (**12**), respectively, were synthesised as follows (Scheme 3).



Scheme 2. Enantiocomplementary biocatalytic kinetic resolution of (*rac*)-**3** using epoxide hydrolase and halohydrin dehalogenase.



Scheme 3. Asymmetric synthesis of (*R*)- and (*S*)-chromanemethanol (**12**).

Asymmetric Synthesis of (*R*)- and (*S*)-Chromanemethanol (12)

Owing to the propensity of hydroquinones to spontaneous oxidation in air, the hydroxy groups of the hydroquinone moiety had to be protected, which was achieved by employing a modified literature protocol.[37] Thus, reduction of 2,3,5,6-tetramethyl-*p*-benzoquinone (duroquinone, **5**) with zinc dust gave the corresponding hydroquinone **6**, which was immediately protected by methylation of the hydroxy groups using dimethyl sulfate in the presence of KOH to furnish dimethoxydurol (**7**) in 65% overall yield.

The regioselective C–C coupling between the epoxide (*R*)- or (*S*)-**3** and the aromatic moiety **7** was achieved by nucleophilic attack of the (soft) benzylic lithium species of **7** (obtained by deprotonation using *n*BuLi) on the less hindered carbon atom of the oxirane ring system.[11] To minimise undesired double-coupling of two epoxides onto one molecule of dimethoxydurol (**7**), an excess of 2 molar equivalents of the aromatic component was used. The excess **7** could be recycled during the purification step. Overall, excellent coupling yields of 89–93% of (*R*)- or (*S*)-**8** were obtained in various experiments.

For cyclisation to the chromane moiety, the methoxy groups had to be cleaved. This was achieved by the oxidation of **8** to the corresponding quinone **9** using cerium ammonium nitrate. The latter was immediately reduced to the hydroquinone system **10** by employing sodium dithionite.[38] Because both intermediates **9** and **10** are prone to decomposition, the oxidation/reduction sequence was carried out in a rapid fashion without isolation and/or purification steps, only washing and extraction. Both compounds were obtained in almost quantitative yields (crude yields of 98–99% for **9** and **10**). Compound **10** can be cyclised under Brønsted acid catalysis[38] to the desired chromane derivative at slightly elevated temperatures. After considerable experimentation involving the variation of the acid catalyst and reaction conditions, *p*-toluenesulfonic acid was used to form the desired chromane scaffold **11** in 79–92% overall yields from compound **8**. The cyclisation reaction proceeded with perfect retention of configuration, which corresponds nicely to the proposed mechanism postulated by Cohen et al.[38]

Finally, deprotection of the *O*-benzyl ether by palladium-catalysed hydrogenation gave (*R*)- and (*S*)-**12** in >99% *ee* and 86–90% yields.

Conclusions

An efficient, non-lipase based, chemoenzymatic route towards enantiopure (*R*)- and (*S*)-chromanemethanol (**12**), which are the key building blocks for the synthesis of stereoisomerically pure α-tocopherols and derivatives thereof, has been achieved by employing a novel enantiocomplementary biocatalytic resolution protocol of oxirane *rac*-**3** using the epoxide hydrolase activity of *Rhodococcus ruber* CBS 717.73 and halohydrin dehalogenase HheC from *Agrobacterium radiobacter* AD1. The introduction of chirality at an early stage of the synthesis ensured a high efficiency, demonstrated by the total overall yields of 16 and 26% for (*R*)- and (*S*)-chromanemethanol (**12**), respectively.

The extension of this chemoenzymatic protocol to the enantiocomplementary synthesis of bioactive compounds bearing a fully substituted chiral carbon centre derived from a tertiary alcohol is currently being explored.

Experimental Section

General: All chemicals from commercial sources were used as received. Anhydrous solvents were dried with 4-Å molecular sieves except for THF, which was distilled from sodium/benzophenone. All biocatalytic reactions were shaken with a HT Infors Unitron AJ shaker 260 at 120 rpm and 30 °C, Eppendorff vials were

mounted in a horizontal position and centrifugation was carried out at 13000 rpm in a Heraeus Biofuge pico. NMR spectra were recorded with a Bruker NMR spectrometer in $CDCl_3$ at 360 (^1H) and 90 MHz (^{13}C). Shifts are given in ppm and coupling constants in Hz. Chiral analysis was performed with a Shimadzu HPLC system on Daicel chiral columns as specified below. Optical rotation values were measured on a Perkin–Elmer Polarimeter 341 instrument. TLC analysis was performed on silica gel 60 F_{254} aluminium sheets (Merck). Detection was achieved by UV light (254 nm) by dipping the sheets into cerium ammonium molybdate/H_2SO_4 solution [$(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (100 g/L) and $Ce(SO_4)_2$ (4 g/L) in H_2SO_4 (10%)] or by spraying with vanillin/H_2SO_4 solution (5 g/L) in H_2SO_4 (80%). For flash chromatography Merck silica gel 60 (40–63 μm) was used. The petroleum ether employed had a boiling range of 60–95 °C.

Benzyl Methallyl Ether (2): Benzyl chloride (8.0 mL, 8.8 g, 69 mmol) and *t*BuOK (15.2 g, 135 mmol) were added to a solution of 2-methylprop-2-en-1-ol (**1**, 5.0 g, 69 mmol) in *t*BuOMe (75 mL) and the mixture was heated at reflux overnight. The reaction mixture was cooled and quenched with a semi-saturated NH_4Cl solution (50 mL). The organic layer was separated and dried with Na_2SO_4. The solvent was removed under reduced pressure and the remaining yellow oil was purified by distillation to obtain **2** as a yellow oil (10.2 g, 62.6 mmol, 90% yield), b.p. 53 °C (0.5 Torr), R_f = 0.80 (petroleum ether/EtOAc). The NMR spectroscopic data are in accordance with the literature.[39] ^1H NMR: δ = 7.38–7.29 (m, 5 H), 5.03 (s, 1 H), 4.95 (s, 1 H), 4.52 (s, 2 H), 3.96 (s, 2 H), 1.79 (s, 3 H) ppm. ^{13}C NMR: δ = 142.3, 138.6, 128.4, 128.3, 127.7, 127.6, 127.4, 112.4, 74.2, 71.9, 19.6 ppm.

(*rac*)-2-Benzyloxymethyl-2-methyloxirane [(*rac*)-3]: Compound **2** (8.5 g, 53 mmol) was dissolved in CH_2Cl_2 (15 mL) and K_2CO_3 (1.45 g, 10.5 mmol) was added. The mixture was cooled to 0 °C, *m*CPBA (70%, 1.55 g, 6.27 mmol) was added and the mixture was stirred overnight at room temperature. After washing with sodium pyrosulfite solution (10%, 3 × 25 mL), the organic phase was dried with Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by chromatography (petroleum ether/EtOAc, 15:1) to obtain (*rac*)-**3** as a colourless oil (9.0 g, 50 mmol, 94% yield), R_f = 0.52 (petroleum ether/EtOAc, 4:1). The NMR spectroscopic data are in accordance with the literature.[40] ^1H NMR: δ = 7.36–7.28 (m, 5 H), 4.58 (dd, J_1 = 7.0, J_2 = 12.0 Hz, 2 H), 3.52 (dd, J_1 = 38.5, J_2 = 11.0 Hz, 2 H), 2.70 (dd, J_1 = 39.0, J_2 = 4.8 Hz, 2 H), 1.41 (s, 3 H) ppm. ^{13}C NMR: δ = 138.9, 128.4, 127.7, 73.5, 73.2, 56.0, 51.5, 18.5 ppm.

Analytical Procedures: The enantiomeric excesses were determined by chiral HPLC analysis. The sample was dissolved in the appropriate eluent mixture. Enantiomers were separated by using a 250 × 4 mm Diacel Chiralpak AD column. The enantiomers of epoxide **3** were separated with *n*-heptane as eluent, 0.4 mL/min flow, detection at 215 and 254 nm, 12 °C oven temperature; t_{ret}[(*R*)-**3**] = 24.9 min, t_{ret}[(*S*)-**3**] = 28.0 min. The enantiomers of diol **4** were separated with *n*-heptane/*i*PrOH (90:10) as eluent, 0.5 mL/min flow, detection at 215 and 254 nm, 18 °C oven temperature; t_{ret}[(*R*)-**4**] = 18.2 min, t_{ret}[(*S*)-**4**] = 19.7 min. Conversion was calculated from the obtained *ee* values according to the literature.[41] Lyophilised whole cells of *Rhodoccocus ruber* sp. CBS 717.73 were prepared as described previously[42] and haloalcohol dehalogenase HheC from *Agrobacterium radiobacter* was obtained from Juelich, a Codexis company.

***Agrobacterium radiobacter* AD1 Halohydrin Dehalogenase (HheC) Mediated Hydrolysis of 3:** $NaNO_2$ (105 mg, 1.52 mmol) was dissolved in Tris/H_2SO_4 buffer (1.0 mL, 0.1 M, pH = 7.5). Substrate (*rac*)-**3** (30 μL, 30 mg, 0.168 mmol) and HheC (180 μL, stock solution of 65 U/mL) were added and the suspension was shaken automatically. After 6, 12 and 24 h, samples (500 μL of the suspension) were taken. Five drops of saturated Na_2CO_3 solution were added to each sample followed by extraction with Et_2O (2 × 500 μL). The organic phase was separated from the enzyme by centrifugation. The combined organic phases were dried with Na_2SO_4, the solvent was evaporated and the crude product obtained was purified by chromatography with petroleum ether/EtOAc (2:1) to give (*S*)-**3**. A change in the eluent to pure EtOAc gave (*S*)-**4**.

(*R*)-2-Benzyloxymethyl-2-methyloxirane [(*R*)-3]: Lyophilised cells of *Rhodoccocus ruber* sp. CBS 717.73 (1.0 g) were rehydrated in a mixture of Tris/HCl buffer (20 mL, 0.05 M, pH = 8) and isooctane (4 mL) by shaking. After 1 h, (*rac*)-**3** (100 μL, 100 mg, 0.56 mmol) was added and the suspension was shaken for 24 h. EtOAc (20 mL) was added, the mixture was stirred for 5 min and the solid cells were removed by filtration. The organic phase of the filtrate was separated, the aqueous layer was extracted with EtOAc (2 × 20 mL) and the combined organic phases were dried with Na_2SO_4. The solvent was removed under reduced pressure to give a brown oily crude product, which was purified by chromatography (petroleum ether/EtOAc, 15:1) to give the epoxide as a red oil (39.7 mg, 0.22 mmol, 40% yield), R_f = 0.49 (petroleum ether/EtOAc, 3:1), *ee* >99% {HPLC, Daicel Chiralpak AD, *n*-heptane, 0.4 mL/min, 10 °C, UV: 215 and 254 nm, t_{ret}[(*R*)-**3**] = 24.9 min, t_{ret}[(*S*)-**3**] = 28.0 min}. $[\alpha]_D^{20}$ = –11.5 (*c* = 1.1, MeOH) {ref.[40] $[\alpha]_D^{23}$ = –10.1 (*c* = 1.26, MeOH)}. The NMR spectroscopic data are in accordance with the literature.[40] ^1H NMR: δ = 7.36–7.28 (m, 5 H), 4.61 (d, *J* = 12.0 Hz, 1 H), 4.56 (d, *J* = 12.0 Hz, 1 H), 3.59 (d, *J* = 11.0 Hz, 1 H), 3.45 (d, *J* = 11.0 Hz, 1 H), 2.76 (d, *J* = 4.8 Hz, 1 H), 2.64 (d, *J* = 4.8 Hz, 1 H), 1.41 (s, 3 H) ppm. ^{13}C NMR: δ = 138.9, 128.4, 127.7, 73.5, 73.2, 56.0, 51.5, 18.5 ppm.

(*S*)-2-Benzyloxymethyl-2-methyloxirane [(*S*)-3]: $NaNO_2$ (61.9 mg, 0.90 mmol) was dissolved in Tris/H_2SO_4 buffer (20 mL, 0.1 M, pH = 7.35). Racemic epoxide (*rac*)-**3** (100 μL, 100 mg, 0.56 mmol) was added and the mixture was vortexed until an emulsion was formed. HheC solution (250 μL, 65 U/mL) was added and the mixture was shaken for 14 h, after which a second portion of HheC solution (100 μL, 65 U/mL) was added and the emulsion was shaken for another 2 h. The mixture was extracted with Et_2O (3 × 20 mL). During the first extraction, denatured enzyme was removed by filtration through a Celite pad. The combined organic phases were dried with Na_2SO_4, the solvent was removed under reduced pressure and the remaining yellow oil was purified by chromatography (petroleum ether/EtOAc, 15:1) to give (*S*)-**3** as a yellow oil (30.5 mg, 0.17 mmol, 31% yield). The TLC and spectroscopic data were identical to those of (*R*)-**3**, *ee* >99% {HPLC, Diacel Chiralpak AD, *n*-heptane/*i*PrOH, 99:1, 0.3 mL/min, 18 °C, UV: 215 nm, t_{ret}[(*R*)-**3**] = 21.6 min, t_{ret}[(*S*)-**3**] = 22.5 min}. The HPLC method had to be adapted to avoid peak collison with a side-product possessing the same retention time as one of the product enantiomers. $[\alpha]_D^{20}$ = +8.3 (*c* = 1.0, MeOH) {ref.[40] $[\alpha]_D^{23}$ = +10.9 (*c* = 1.20, MeOH)}.

2,3,5,6-Tetramethylbenzene-1,4-diol (6): 2,3,5,6-Tetramethyl-1,4-benzoquinone (**5**, 5.0 g, 30.4 mmol) was suspended in acetic acid (100 mL) and the mixture was heated to reflux. Zinc dust (12.0 g, 183.5 mmol, <325 mesh) was slowly added and the mixture was heated at reflux for 4 h until the yellow solution decolourised. The hot reaction mixture was filtered and the filter cake (white powder) was washed with hot acetic acid. The filtrate was cooled in an ice bath, filtered and washed with a small amount of acetic acid. The white powder obtained was dried overnight in a desiccator over

$CaCl_2$ to give **6** as a white powder (3.9 g, 24 mmol, 77% yield), m.p. 230–233 °C (ref.[43] 231–232 °C). No further analysis was performed because the compound easily reoxidises in solution.

1,4-Dimethoxy-2,3,5,6-tetramethylbenzene (7): An aqueous solution of 1.3 M KOH (100 mL) was slowly added to a suspension of compound **6** (3.9 g, 23.5 mmol) in 1,4-dioxane (40 mL) under argon. The mixture was stirred for 10 min, which resulted in a red solution. Dimethyl sulfate (10 mL, 13.3 g, 105 mmol) was added dropwise and the mixture was heated at reflux. After 1 h, further dimethyl sulfate (5.0 mL, 6.7 g, 53 mmol) was added. After a further 2 h of reflux, the reaction mixture was cooled. A white solid formed which was dissolved by addition of CH_2Cl_2 (30 mL). The organic layer was separated, the aqueous phase was washed with CH_2Cl_2 and the combined organic phases were dried with Na_2SO_4. The solvent was removed under vacuum and the solid obtained was recrystallised from CH_2Cl_2/EtOH and dried in a desiccator over $CaCl_2$ to give **7** as white crystals (3.9 g, 20 mmol, 85% yield), m.p. 113–116 °C (ref.[11] 113–114 °C), R_f = 0.63 (toluene/EtOAc, 10:1). The NMR spectroscopic data are in accordance with the literature.[11] ^{1}H NMR: δ = 3.66 (s, 6 H), 2.20 (s, 12 H) ppm. ^{13}C NMR: δ = 152.9, 127.7, 60.2, 12.6 ppm.

General Procedure for the Synthesis of 1-Benzyloxy-4-(2,5-dimethoxy-3,4,6-trimethylphenyl)-2-methylbutan-2-ol (8): *n*BuLi solution (2.5 M hexane solution, 1.8 equiv.) was added to a 0.5 M solution of compound **7** (2.0 equiv.) in dry THF at 0 °C. After 30 min of stirring at this temperature, a 0.5 M solution of epoxide (*R*)- or (*S*)-**3** in dry THF was added dropwise. The mixture was stirred for 15 min and was then quenched by the addition of a saturated NH_4Cl solution (20 mL). The white slurry was stirred for 15 min and then extracted with EtOAc (3 × 15 mL). The combined organic phases were dried with Na_2SO_4, the solvent was removed under reduced pressure and the colourless solid was purified by chromatography (petroleum ether/EtOAc, 10:1) to give (*R*)- or (*S*)-**8** as a pale-yellow oil.

(*S*)-1-Benzyloxy-4-(2,5-dimethoxy-3,4,6-trimethylphenyl)-2-methylbutan-2-ol [(*S*)-8]: Compound **7** (132.1 mg, 0.68 mmol) in dry THF (1.5 mL) was treated with an *n*BuLi solution (240 μL, 2.5 M in hexane, 0.6 mmol) and epoxide (*R*)-**3** (60.0 mg, 0.34 mmol) in dry THF (750 μL) to yield (*S*)-**8** (117.1 mg, 0.31 mmol, 93% yield), R_f = 0.35 (petroleum ether/EtOAc, 3:1). ^{1}H NMR: δ = 7.37–7.31 (m, 5 H), 4.60 (s, 2 H), 3.70 (s, 3 H), 3.66 (s, 3 H), 3.42 (m, 2 H), 2.74–2.69 (m, 2 H), 2.28 (s, 3 H), 2.20 (s, 6 H), 1.76–1.68 (m, 2 H), 1.31 (s, 3 H) ppm. ^{13}C NMR: δ = 153.1, 152.8, 138.2, 132.2, 128.4, 128.2, 127.9, 127.6, 127.2, 76.7, 73.5, 72.2, 60.9, 60.1, 39.2, 23.7, 21.6, 12.8, 12.7, 11.9 ppm.

(*R*)-1-Benzyloxy-4-(2,5-dimethoxy-3,4,6-trimethylphenyl)-2-methylbutan-2-ol [(*R*)-8]: Compound **7** (63.7 mg, 0.33 mmol) in dry THF (0.7 mL) was treated with an *n*BuLi solution (120 μL, 2.5 M in hexane, 0.3 mmol) and epoxide (*S*)-**3** (28.5 mg, 0.16 mmol) in dry THF (350 μL) to yield (*R*)-**8** (53.3 mg, 0.14 mmol, 89% yield). The TLC and spectroscopic data are identical to those of (*S*)-**8**.

General Procedure for the Synthesis of 2-(4-Benzyloxy-3-hydroxy-3-methylbutyl)-3,5,6-trimethyl-1,4-benzoquinone (9): A solution of cerium(IV) ammonium nitrate (260 mM in MeCN/H_2O, 1:1, 10 equiv.) was cooled to –4 °C and a solution of compound **8** (26 mM in MeCN) was added. The solution was stirred for 1.5 h at this temperature. CH_2Cl_2 (30 mL) was added, the mixture was stirred for 5 min and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic phases were dried with Na_2SO_4. Filtration through a pad of Celite and evaporation of the solvent under reduced pressure gave (*R*)- or (*S*)-**9** as a yellow oil. The residue was used without further purification or analysis in the subsequent reaction.

(*S*)-2-(4-Benzyloxy-3-hydroxy-3-methylbutyl)-3,5,6-trimethyl-1,4-benzoquinone [(*S*)-9]: Cerium ammonium nitrate (1.42 g, 2.6 mmol) in H_2O/MeCN (1:1, 10 mL) was treated with (*S*)-**8** (105.6 mg, 0.28 mmol) in MeCN (10 mL) to yield (*S*)-**9** (93.9 mg, 0.27 mmol, 98% yield), R_f = 0.33 (petroleum ether/EtOAc, 3:1).

(*R*)-2-(4-Benzyloxy-3-hydroxy-3-methylbutyl)-3,5,6-trimethyl-1,4-benzoquinone [(*R*)-9]: Cerium ammonium nitrate (730 mg, 1.3 mmol) in H_2O/MeCN (1:1, 5 mL) was treated with (*R*)-**8** (53.3 mg, 0.14 mmol) in MeCN (5 mL) to yield (*R*)-**9** (47 mg, 0.14 mmol, 98% yield). The TLC analysis was identical to that of (*S*)-**9**.

General Procedure for the Synthesis of 2-(4-Benzyloxy-3-hydroxy-3-methylbutyl)-3,5,6-trimethylbenzene-1,4-diol (10): Compound **9** was dissolved in acetone (6.8 mM) and an aqueous solution of $Na_2S_2O_4$ (635 mM) was poured into the solution. The mixture was stirred for 30 min at room temperature. CH_2Cl_2 (20 mL) was added to the solution, the organic phase was separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic phases were dried with Na_2SO_4. Filtration through a pad of Celite and evaporation of the solvent under reduced pressure gave (*R*)- or (*S*)-**10** as a pale-yellow oil, which was used without further purification in the subsequent reaction.

(*S*)-2-(4-Benzyloxy-3-hydroxy-3-methylbutyl)-3,5,6-trimethylbenzene-1,4-diol [(*S*)-10]: Compound (*S*)-**9** (93.9 mg, 0.27 mmol) in acetone (40 mL) was treated with $Na_2S_2O_4$ (2.204 g, 12.7 mmol) in distilled H_2O (20 mL) to yield (*S*)-**10** (94.4 mg, 0.27 mmol, 99% yield), R_f = 0.17 (petroleum ether/EtOAc, 3:1).

(*R*)-2-(4-Benzyloxy-3-hydroxy-3-methylbutyl)-3,5,6-trimethylbenzene-1,4-diol [(*R*)-10]: Compound (*R*)-**9** (47 mg, 0.14 mmol) in acetone (20 mL) was treated with $Na_2S_2O_4$ (1.167 g, 6.7 mmol) in distilled H_2O (10 mL) to yield (*R*)-**10** (47 mg, 0.14 mmol, 99% yield). The TLC analysis was identical to that of compound (*S*)-**10**.

General Procedure for the Synthesis of 2-Benzyloxymethyl-2,5,7,8-tetramethylchroman-6-ol (11): Compound **10** was dissolved in dry toluene (11 mM) and purged with argon. The solution was heated to 45 °C and *p*-toluenesulfonic acid monohydrate (0.45 equiv.) was added. The solution was stirred for 3.5–4.5 h at this temperature. The solvent was removed under vacuum and the brown residue obtained was purified by chromatography (petroleum ether/EtOAc, 10:1) to give (*R*)- or (*S*)-**11** as a yellow oil. The *ee* value was determined by chiral HPLC analysis {Daicel Chiralcel OD-H, *n*-heptane/EtOH, 99:1, 1.0 mL/ min, 18 °C, UV: 215 nm, t_{ret}[(*R*)-**11**] = 21.6 min, t_{ret}[(*S*)-**11**] = 26.1 min}.

(*S*)-2-Benzyloxymethyl-2,5,7,8-tetramethylchroman-6-ol [(*S*)-11]: Compound (*S*)-**10** (94.4 mg, 0.27 mmol) in dry toluene (25 mL) was treated with *p*-toluenesulfonic acid monohydrate (21.2 mg, 0.11 mmol) to yield (*S*)-**11** (80.7 mg, 0.25 mmol, 92% yield), *ee* >99% (t_{ret} = 32.8 min), R_f = 0.70 (petroleum ether/EtOAc, 1:1). The NMR spectroscopic data are in accordance with the literature.[44] ^{1}H NMR: δ = 7.37–7.29 (m, 5 H), 4.65 (d, *J* = 12.2 Hz, 1 H), 4.60 (d, *J* = 12.2 Hz, 1 H), 3.55 (d, *J* = 9.7 Hz, 1 H), 3.47 (d, *J* = 9.7 Hz, 1 H), 2.62 (t, *J* = 6.7 Hz, 2 H), 2.18 (s, 3 H), 2.14 (s, 3 H), 2.13 (s, 3 H), 2.04 (t, *J* = 6.7 Hz, 1 H), 1.80 (t, *J* = 6.7 Hz, 1 H), 1.33 (s, 3 H) ppm. ^{13}C NMR: δ = 145.3, 144.8, 138.7, 128.3, 127.5, 122.5, 121.1, 118.5, 117.4, 75.4, 74.8, 73.5, 28.7, 22.3, 20.4, 12.2, 11.9, 11.3 ppm.

(*R*)-2-Benzyloxymethyl-2,5,7,8-tetramethylchroman-6-ol [(*R*)-11]: Compound (*R*)-**10** (47 mg, 0.14 mmol) in dry toluene (12.5 mL)

was treated with *p*-toluenesulfonic acid monohydrate (12.4 mg, 0.07 mmol) to yield (*R*)-**11** (34.4 mg, 0.11 mmol, 79% yield). The TLC and spectroscopic data are identical to those of (*S*)-**11**; *ee* >99% (t_{ret} = 21.2 min).

General Procedure for the Synthesis of 2-Hydroxymethyl-2,5,7,8-tetramethylchroman-6-ol (12): A catalytic amount of Pd on C (10%) was added to a solution of compound **11** (8 mM) in MeOH and the mixture was purged with H_2 for 5 h. The reaction mixture was filtered through a pad of Celite, the solvent was evaporated under reduced pressure and the white solid obtained was purified by chromatography (petroleum ether/EtOAc, 5:1) to give (*R*)- or (*S*)-**12** as a white solid. The *ee* was determined by chiral HPLC analysis {Diacel Chiralcel OD-H, *n*-heptane/EtOH, 95:5, 1.0 mL/min, 18 °C, UV: 215 nm, t_{ret}[(*R*)-**12**] = 16.0 min, t_{ret}[(*S*)-**12**] = 20.0 min}.

(*S*)-2-Hydroxymethyl-2,5,7,8-tetramethylchroman-6-ol [(*S*)-12]: Compound (*S*)-**11** (65.6 mg, 0.20 mmol) in MeOH (25 mL) was treated as described above to yield (*S*)-**12** (42.3 mg, 0.18 mmol, 90% yield), m.p. 128–129 °C (ref.[23] 129.5–131.5 °C), R_f = 0.34 (petroleum ether/EtOAc, 2:1), *ee* >99% (t_{ret} = 20.0 min). $[\alpha]_D^{20}$ = +1.6 (*c* = 0.9, EtOH) {ref.[23] $[\alpha]_D^{23}$ = +1.61 (*c* = 2.25, EtOH)}. The NMR spectroscopic data are in accordance with the literature.[23] ^{1}H NMR: δ = 3.64 (dd, J_1 = 9.5, J_2 = 11.3 Hz, 2 H), 2.71–2.66 (m, 2 H), 2.19 (s, 3 H), 2.14 (s, 3 H), 2.13 (s, 3 H), 2.06–1.98 (m, 1 H), 1.78–1.71 (m, 1 H), 1.24 (s, 3 H) ppm. ^{13}C NMR: δ = 145.1, 144.9, 122.6, 121.4, 118.8, 117.3, 75.1, 69.4, 27.8, 20.4, 20.3, 12.2, 11.9, 11.3 ppm.

(*R*)-2-Hydroxymethyl-2,5,7,8-tetramethylchroman-6-ol [(*R*)-12]: Compound (*R*)-**11** (34.4 mg, 0.11 mmol) in MeOH (12.5 mL). was treated as described above to yield (*R*)-**12** (22.4 mg, 0.09 mmol, 86% yield). The m.p., TLC and spectroscopic data are identical to those of (*S*)-**12**, *ee* >99% (t_{ret} = 16.0 min). $[\alpha]_D^{20}$ = –1.5 (*c* = 1.0, EtOH) {ref.[23] $[\alpha]_D^{23}$ = –1.8 (*c* = 1.45, EtOH)}.

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