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Chemoenzymatic Asymmetric Total Syntheses of Antitumor Agents (3*R*,9*R*,10*R*)- and (3*S*,9*R*,10*R*)-Panaxytriol and (*R*)- and (*S*)-Falcarinol from *Panax ginseng* Using an Enantioconvergent Enzyme-Triggered Cascade Reaction

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Total asymmetric synthesis of two components of *Panax ginseng* showing antitumor activity, i.e., (3*R*,9*R*,10*R*)- and (3*S*,9*R*,10*R*)-Panaxytriol and of both enantiomers of Falcarinol was accomplished. Due to the fact that the synthetic strategy was based on enantioconvergent biotransformations, the occurrence of any undesired stereoisomer was entirely avoided. The absolute configuration of naturally occurring Panaxytriol was confirmed to be (3*R*,9*R*,10*R*) on the basis of optical rotation values. It was shown that enzyme-triggered cascade reactions represent a valuable tool for the synthesis of natural products.

Introduction

The roots of *Panax ginseng* C. A. Meyer have been employed in Asia for many centuries, as an analeptic, stomachic, and erythropoietic agent.[1] The crude extract of *Panax ginseng* forms part of a traditional oriental medicine in Japan and is presently available as a commercial medicinal formulation.[2] Many types of polyacetylenic compounds, including Panaxytriol (**1**) and both enantiomers of Falcarinol [(*R*)-**3** and (*S*)-**3**] suppress the in vitro growth of cultured tumor cells (Figure 1).[3] These compounds also exhibit strong neurotoxicity, antifungal activity, and cytotoxic activity against leukemia cells (L-1210) in tissue cultures. Panaxytriol (**1**) also suppresses the growth of B-16 melanoma transplanted into mice and shows stimulative effects on the antitumor activity of mitomycin-C in cultured tumor cells. Both enantiomers of Falcarinol [(*R*)-**3** and (*S*)-**3**], also named Panaxynol, have been isolated from different plants. Until 1999, its absolute configuration was not clear, and conflicting data were reported, using CD exitation and Moshers method for its determination.[4,5] To confirm the absolute configuration, Cai et al. explored for the first time the enantioselective total synthesis of both enantiomers.[6] They confirmed that (+)-Falcarinol possesses the (3*S*)-configuration. Panaxytriol (**1**) was isolated as a characteristic

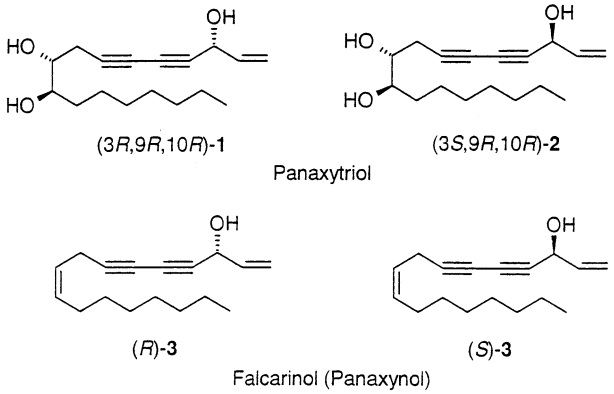

FIGURE 1. Antitumor components of *Panax ginseng*.

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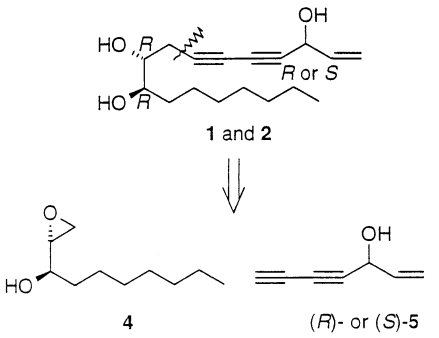
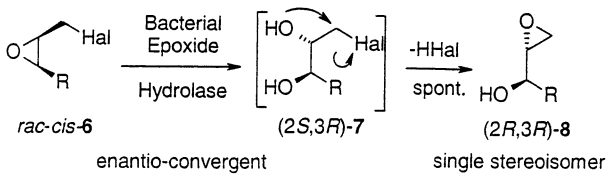


FIGURE 2. Retrosynthetic analysis of Panaxytriol.

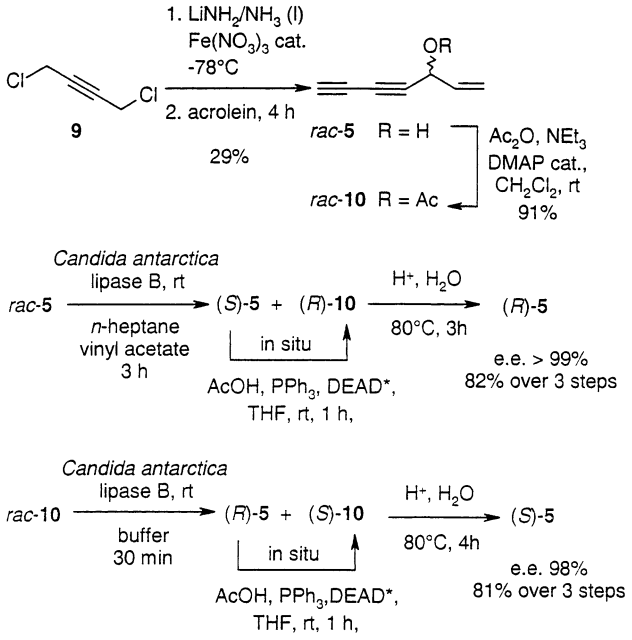
SCHEME 1. Enantioconvergent Enzyme-Triggered Cascade Reaction



constituent of red ginseng in 1983, and its chemical structure was elucidated in 1987.[7,8] Its absolute configuration was determined to be (3*R*,9*R*,10*R*).[9] To date, only three studies on the asymmetric synthesis of naturally occurring Panaxytriol have been published.[10−12] However, the absolute configuration is still unclear due to conflicting data. Furthermore, all syntheses suffer from long reaction sequences. In this report, we describe a concise short synthesis of (3*R*,9*R*,10*R*)- and (3*S*,9*R*,10*R*)-Panaxytriol (**1** and **2**) using a chemoenzymatic approach.

Our synthetic strategy was based on two main building blocks, i.e., epoxy-alcohol (2*R*,3*R*)-**4** and the *sec*-alcohol **5** (Figure 2). We envisaged that the former could easily be prepared via a biocatalytic enantioconvergent cascade reaction recently developed by us (Scheme 1).[13] Thus, when *cis*-configured *rac*-halomethyl-oxiranes of type **6** were subjected to the action of a bacterial epoxide hydrolase, both enantiomers were transformed through opposite regioselective pathways in an enantioconvergent fashion to furnish a single enantiomeric *vic*-diol [(2*S*,3*R*-**7**)] as the sole product.[14] Due to the presence of a halohydrin moiety, the latter underwent spontaneous ring-closure to yield epoxy-alcohol (2*R*,3*R*)-**8** as the final product in excellent de and ee. This latter reaction shows some resemblance to a Payne-type rearrangement.[16]

SCHEME 2. Synthesis of Building Block 5 via Deracemization



* Diisopropyl azodicarboxylate

Overall, this sequence represented an enzyme-catalyzed cascade reaction.[13,15,16] Due to the enantioconvergence, chemical yields were markedly beyond the 50% limitation set for kinetic resolutions. Such 'deracemization' processes have recently gained considerably attention due to their improved economic balance.[17]

The synthetic elegance of this process prompted us to utilize it for a synthesis of Panaxytriol (**1** and **2**). For the second building block (**5**), the application of lipase technology was obvious to obtain nonracemic material. To circumvent the drawbacks of kinetic resolution, we employed an in situ inversion to obtain (*R*)- and (*S*)-**5** in an enantioconvergent fashion without loss of material.[18] In addition, an asymmetric synthesis of both enantiomers of Falcarinol [(*R*)-**3** and (*S*)-**3**] was accomplished by using this strategy.

Results and Discussion

Asymmetric Synthesis of the C(1)−C(7) Segment 5. Alcohol *rac*-**5** was prepared from 1,4-dichloro-2-butyne (**9**) (Scheme 2) by lithiation of the dichloro-acetylene **9** using *n*-BuLi in liquid ammonia and addition of acrolein to furnish *rac*-**5** in 29% yield (not optimized). Acetate *rac-cis*-**10** as reference material for the biotransformation was prepared according to literature procedures.[19] Both enantiomers of **5** were obtained in nonracemic form via *Candida antarctica* lipase B-catalyzed kinetic resolution via acyl-transfer [for (*R*)-**5**] or ester hydrolysis of *rac*-**10** [for (*S*)-**5**]. Both kinetic resolution processes were linked to an in situ inversion in order to avoid the occurrence of an undesired stereoisomer. Thus, (*R*)-**5** or (*S*)-**5** were obtained in >98% ee from the racemate in 82 and 80% yield, respectively.[20,21]

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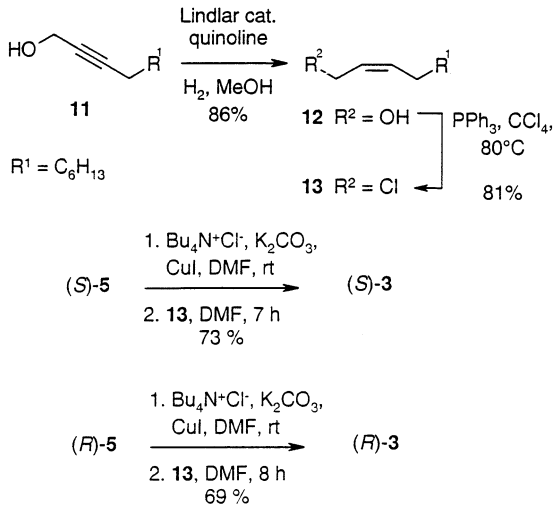
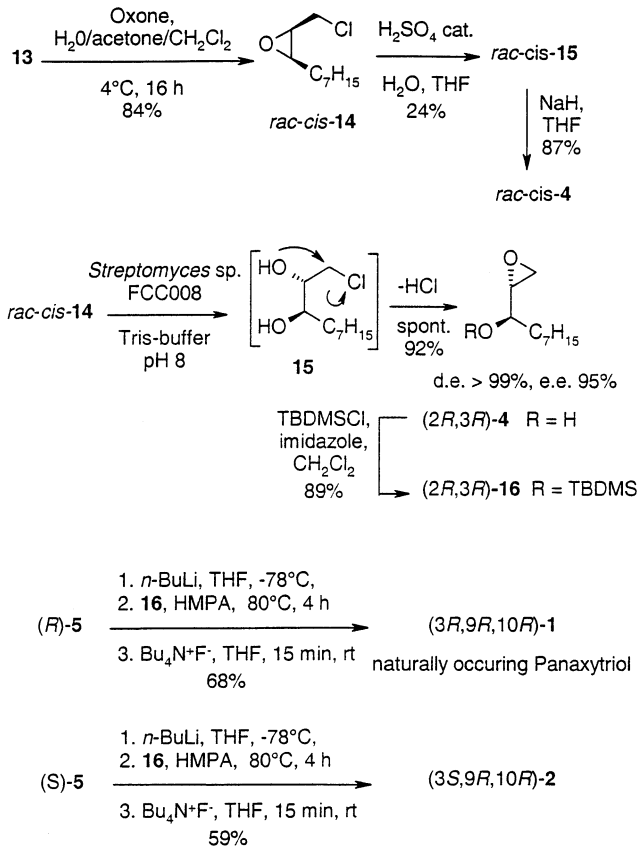
SCHEME 3. Synthesis of (*R*)- and (*S*)-Falcarinol



Synthesis of the C(8)−C(17) Segment 13 and Asymmetric Synthesis of Both Enantiomers of Falcarinol (3). Alcohol **11** was selectively hydrogenated with Lindlar catalyst to give the corresponding *cis*-alkene **12** in 86% yield (Scheme 3). To achieve absolute *cis*-selectivity, poisoning of the Lindlar catalyst with quinoline alone was not sufficient (*trans*/*cis*-isomer = 1:7), but required the addition of KOH. Halogenation of the hydroxyl group of **12** via Appel conditions (PPh_3/CCl_4) gave chloride **13** in 81% yield.[22] In the last step, **13** was coupled to alcohol (*R*)- or (*S*)-**5** using K_2CO_3, $Bu_4N^+Cl^-$, and CuI, furnishing Falcarinol (**3**) in both enantiomeric forms.[23] Thus, (*S*)-**3** and (*R*)-**3** were synthesized over five steps in an overall yield of 12 and 11%. The absolute configuration of **3** was confirmed by comparison with known optical rotation values.[6] The absolute configuration of (*R*)-**5** and (*S*)-**5** was deduced from that of the final products (*R*)-**3** and (*S*)-**3**, since the configuration at C-3 remained untouched. In addition, these results are in accordance with the 'Kazlauskas-rule', which predicts the stereopreference of lipases for *sec*-alcohols.[24]

Asymmetric Synthesis of the C(8)−C(17) Segment (2*R*,3*R*)-4 via Enzyme-Triggered Enantioconvergent Cascade Reaction and Synthesis of Two Diastereoisomers of Panaxytriol (3*R*,9*R*,10*R*)-1 and (3*S*,9*R*,10*R*)-2. The key substrate for the biocatalytic step with bacterial epoxide hydrolases (BEH) was epoxide *rac-cis*-**14** (Scheme 4), which was synthesized by epoxidation of alkene **13** with Oxone in 84% yield. For the identification of the expected biotransformation product, *rac*-**4** was synthesized as reference material. Acid-catalyzed epoxide opening of *rac-cis*-**14** gave *rac-cis*-**15**, which subjected to ring-closure by NaH to give epoxy-alcohol *rac-cis*-**4**.

SCHEME 4. Synthesis of (3*R*,9*R*,10*R*)- and (3*S*,9*R*,10*R*)-Panaxytriol



Substrate *rac-cis*-**14** was screened for biohydrolysis in Tris-buffer at pH 8.0 using resting cells of a range of bacteria known to possess strong secondary metabolic activity and epoxide hydrolase activity, in particular *Actinomyces* spp. Under screening conditions it was verified that in the absence of biocatalyst no spontaneous hydrolysis of *rac-cis*-**14** was observed within the anticipated reaction time of ~150 h. We were pleased to see that hydrolysis of *rac-cis*-**14** furnished the corresponding diol **15**, and that the latter intermediate (detected at low concentration <5%) underwent subsequent intramolecular cyclization to yield the epoxy-alcohol **4** as the final product.

Table 1 shows the stereoselectivities [given as conversion (*c*) and enantiomeric purities of substrate (ee_S), intermediate (ee_I), and product (ee_P)] obtained in the biohydrolysis of *rac-cis*-**14** using various biocatalysts. In general, substrate *rac-cis*-**14** was converted in moderate to good selectivities by several bacterial strains with the predominant formation of (2*R*,3*R*)-**4** in up to >99% ee, except for *Rhodococcus sp.* NCIMB 11216, which produced the mirror-image counterpart (2*S*,3*S*)-**4** albeit in low optical purity (entry 7). Several data sets of *c*, ee_S, ee_I, and ee_P clearly indicated that the transformation does not follow a kinetic resolution pathway, which is most striking for entry 1. Although *Streptomyces lavendulae* ATCC 55209 (entry 6) showed good stereoselectivity, but the conversion was too low for preparative applications.

To provide sufficient material of **4** for the asymmetric syntheses of **1** and **2**, *Streptomyces* sp. FCC008 was chosen for the preparative-scale biotransformation. Thus,

(20) Alternatively, a highly efficient dynamic resolution of *rac*-**5** was tested using combined *C. antarctica* lipase B-catalyzed acyl transfer (4-chlorophenyl acetate as acyl donor) with Ru-catalyzed in-situ racemization of the nonreacting substrate enantiomer to furnish (*R*)-**10**. However, this protocol failed since no racemization was observed due to the inactivity of the Ru catalyst [$Ru_2(CO)_4(\mu$-H)($C_4Ph_4COHOCC_4Ph_4$)] on this substrate.

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TABLE 1. Biocatalytic Enantioconvergent Transformation of Chloroalkyl-oxirane *rac-cis*-14

entry	biocatalyst	substrate[a] ee_S [%]	intermediate[b] ee_I [%]	product ee_P [%]	conversion[c,d] [%]
1	*Streptomyces* sp. FCC008	47	>99 (2*S*,3*R*)	>99 (2*R*,3*R*)	78
2	*Rhodococcus equi* IFO 3730	13	65 (2*S*,3*R*)	67 (2*R*,3*R*)	69
3	*Mycobacterium paraffinicum* NCIMB 10420	80	53 (2*S*,3*R*)	52 (2*R*,3*R*)	75
4	*Rhodococcus* sp. R 312 (CBS 717.73)	13	45 (2*S*,3*R*)	47 (2*R*,3*R*)	25
5	*Rhodococcus ruber* DSM 44540	90	30 (2*S*,3*R*)	32 (2*R*,3*R*)	79
6	*Streptomyces lavendulae* ATCC 55209	39	97 (2*S*,3*R*)	98 (2*R*,3*R*)	18
7	*Rhodococcus* sp. NCIMB 11216	21	28 (2*R*,3*S*)	31 (2*S*,3*S*)	35

[a] Absolute configuration of the oxirane was not determined due to its low concentration toward the end of the enantioconvergent biotransformation. [b] Absolute configuration of intermediate was deduced from that of the product based on the S_N2-type mechanism of ring closure.[13] [c] Conversion based on nonreacted substrate: c = [substrate] − ([intermediate] + [product]). [d] After 146 h.

conversion of substrate *rac-cis*-**14** (0.85 g) in Tris-buffer (pH 8.0) gave (2*R*,3*R*)-**4** in 92% yield, 99% de and 95% ee as the sole product (Scheme 4).

Protection of the free hydroxy moiety in substrate (2*R*,3*R*)-**4** with TBDMSCl afforded (2*R*,3*R*)-**16** in 89% yield. The last step in the synthesis of **1** and **2** consisted of the coupling of (2*R*,3*R*)-**16** and (*S*)- or (*R*)-**5**, respectively (Figure 2). This was accomplished by treatment of (*R*)- or (*S*)-**5**, respectively**,** with *n*-BuLi in THF at −78 °C and subsequent addition of HMPA and (2*R*,3*R*)-**16**, followed by deprotection of the silyl ether using $Bu_4N^+F^-$. Thus the synthesis of (3*R*,9*R*,10*R*)-**1** {$[\alpha]_D^{20}$ −19.5 (*c* 0.83, $CHCl_3$)} and (3*S*,9*R*,10*R*)-**2** {$[\alpha]_D^{20}$ +24.3 (*c* 1.10, $CHCl_3$)} was completed over eight steps in an overall yield of 8% and 7%, respectively.

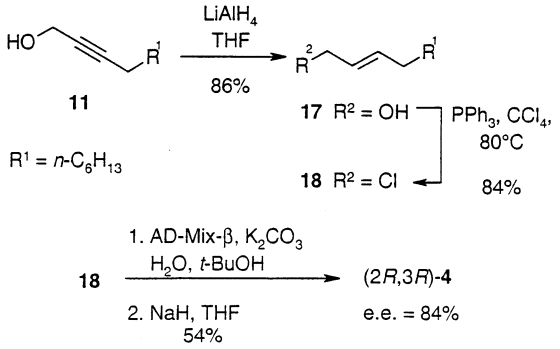
Due to the fact that conflicting data for the optical rotation of the key building block **4** were published, the determination of its absolute configuration was a difficult task. The optical rotation of the biotransformation product was in good accordance with one of the published values for the (2*R*,3*R*)-enantiomer {$[\alpha]_D^{20}$ −5.2 (*c* 0.67, $CHCl_3$), $[\alpha]_D^{20}$ −5.6 (*c* 1.8, $CHCl_3$)[12]},[25] which is in accordance with $[\alpha]^{20}_D$ +1.7 (*c* 1.2, CH_2Cl_2) for the (2*S*,3*S*)-enantiomer.[26] In contrast, somewhat dubious data—inasmuch both enantiomers show almost the same positive rotation ($[\alpha]_D^{20}$ +3.4 (*c* 1.0, $CHCl_3$) for the (2*R*,3*R*)- and $[\alpha]_D^{20}$ +3.5 (*c* 1.0, $CHCl_3$) for the (2*S*,3*S*)-enantiomer)—were reported.[11] Overall, it seems clear that the (2*S*,3*S*)-**4** has a positive[12] and the (2*R*,3*R*)-**4** a negative sign of optical rotation. To obtain an unambiguous proof, (2*R*,3*R*)-**4** was independently synthesized by following a known procedure (Scheme 5).[27]

Thus, reduction of alkyne **11** with $LiAlH_4$ gave (*E*)-hydroxyalkene **17**, which was halogenated using Appel conditions to furnish compound **18**. Asymmetric dihydroxylation of the latter using AD-Mix-β and treatment of the halodiol with NaH afforded (2*R*,3*R*)-**4** in 84% ee. This material showed an expected value of $[\alpha]_D^{20}$ −4.5 (*c* 1.25, $CHCl_3$). These data unambiguously prove that the absolute configuration of the biotransformation product using *Streptomyces* sp. FCC008 is (2*R*,3*R*)-**4**.

Conclusion

In summary, we have demonstrated that enzyme-triggered cascade reactions represent a valuable tool for the synthesis of natural products. Thus, the total synthesis of components of *Panax ginseng* showing antitumor activity, such as (3*R*,9*R*,10*R*)- and (3*S*,9*R*,10*R*)-Panaxytriol, as well as both enantiomers of Falcarinol, was accomplished. On the basis of the employment of enantioconvergent biocatalytic synthetic strategies, the occurrence of any undesired stereoisomer was entirely avoided. Since for naturally occurring Panaxytriol reported optical rotation values range from $[\alpha]_D^{20}$ −18 to −25.4, we can confirm its (3*R*,9*R*,10*R*)-configuration on the basis of our data {$[\alpha]_D^{20}$ −19.5}.

SCHEME 5. Synthesis of Reference Material (2*R*,3*R*)-4



Experimental Section

General. ^1H NMR (500, 360 or 200 MHz) and ^{13}C NMR (125, 90 or 50 MHz) spectra were obtained from solutions in $CDCl_3$, and chemical shifts are reported in parts per million (ppm, δ) downfield from the internal standard (TMS).

TLC plates were run on silica gel 60 (F_{254}), and compounds were visualized by spraying with Mo reagent [$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (100 g/L), $Ce(SO_4)_2\cdot 4H_2O$(4 g/L) in H_2SO_4 (10%)] (detection I) or by dipping into a $KMnO_4$ reagent [2.5 g/L $KMnO_4$ in H_2O] (detection II). Compounds were purified either by flash chromatography on silica gel or, for volatile substances, by Kugelrohr distillation. Enantioselective gas chromatography was conducted using a permethylated β-cyclodextrin column (column A, 25 m, 0.32 mm, 0.25 μm film) or propionated γ-cyclodextrin column (column B, 30 m, 0.25 mm). H_2 was used as carrier gas. For detailed analytical data vide infra. High resolution mass spectra and optical rotation values were obtained as previously reported.[15,19]

Solvents were dried and freshly distilled by common practice. All reactions were performed under argon atmosphere, unless otherwise stated. Organic extracts were dried over Na_2SO_4, and then the solvent was evaporated under reduced pressure. Lindlar catalyst [Pd on $CaCO_3$ (5% w/w)] poisoned with Pb was used. For biotransformations, lyophilized bacterial cells were used. The bacteria were obtained from culture collections; FCC numbers refer to the Fab-Crew-Collection at

(25) In the same paper, the rotation of the (2*S*,3*S*)-enantiomer was reported to be $[\alpha]_D^{20}$ +3.9 (*c* 1.42, $CHCl_3$).

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this institute. All strains were grown as previously described.[15] Lipase from *C. antarctica* B (SP 525, Batch: PPW 5328) was kindly donated by Novo (DK), and Ru-catalyst [$Ru_2(CO)_4(\mu$-H)($C_4Ph_4COHOCC_4Ph_4$)] was obtained through courtesy of J.-E. Bäckvall (Stockholm University).

Syntheses of Substrates and Reference Materials. *rac*-Hept-1-ene-4,6-diyn-3-ol (*rac*-5). To a vigorously stirred suspension of $LiNH_2$ (5.62 g, 245 mmol) in liquid ammonia (350 mL) at −50 °C was added a catalytic amount of $Fe(NO_3)_3$, which was followed by dropwise addition of 1,4-dichloro-2-butyne **9** (10 g, 81.3 mmol) over a period of 1 h. Subsequently, acrolein (5 g, 89.2 mmol, used as received) was added. After 2 h, stirring was stopped, and the reaction was quenched by addition of H_2O (150 mL), solid NH_4Cl (20 g), and Et_2O (200 mL). Ammonia was allowed to evaporate over a period of 16 h. The phases were separated, and the aqueous layer was extracted with Et_2O. The combined organic phases were washed with sat. $NaHCO_3$ (100 mL), dried, and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give *rac*-**5** (2.5 g, 29%) as a pale yellow liquid. GC-data: Column B [10 psi, H_2, 65 °C (iso), t_{R1} = 59.2 min (3*S*), t_{R2} = 60.3 min (3*R*)]. R_f (petroleum ether/EtOAc, 1:1) = 0.74, (detection I); ^{1}H NMR (360.13 MHz, $CDCl_3$): δ = 2.25 (1H, s), 2.51 (1H, s), 4.93 (1H, d, J = 4.2), 5.28 (1H, d, J = 10.5), 5.49 (1H, d, J = 17.4), 5.89−5.98 (1H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 63.7, 67.7, 69.5, 70.8, 75.2, 117.9, 136.1.[28]

***rac*-3-Acetoxyhept-1-ene-4,6-diyne (*rac*-10).** To a stirred solution of alcohol *rac*-**5** (0.5 g, 4.7 mmol) in Ac_2O (10 mL) were added NEt_3 (0.7 g, 7.1 mmol) and DMAP (15 mg, cat.). The resulting solution was stirred at room temperature for 2 h. After the reaction was complete, it was quenched by addition of water (10 mL) and Et_2O (50 mL). After phase separation, the organic phase was dried and concentrated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give *rac*-**10** (0.6 g, 91%) as a pale yellow liquid. GC-data: column A [10 psi, H_2, 75 °C (iso), t_{R1} = 6.6 min (3*R*), t_{R2} = 6.8 min (3*S*)]. R_f (petroleum ether/EtOAc, 1:1) = 0.91, (detection I); ^{1}H NMR (360.13 MHz, $CDCl_3$): δ = 2.12 (3H, s), 2.24 (1H, s), 5.37 (1H, d, J = 9.7), 5.56 (1H, d, J = 16.1), 5.82−5.92 (2H, m). ^{13}C NMR (90 MHz, $CDCl_3$): δ = 20.8, 64.2, 67.2, 69.2, 71.0, 71.4, 119,9, 131.9, 169.4. HRMS ($C_9H_7O_2$): calcd 147.0446 $[M - H]^+$; found 147.0432 $[M - H]^+$.

(*R*)-Hept-1-ene-4,6-diyn-3-ol [(*R*)-5] via Biocatalytic In Situ Inversion. Lipase from *C. antarctica* B (150 mg) was dispersed in hexane (25 mL), and after addition of *rac*-**5** (0.9 g, 8.5 mmol) and vinyl acetate (2.0 g, 23.2 mmol), the mixture was agitated on an orbit shaker (rt, 120 rpm). The reaction was monitored by GC on a chiral stationary phase. When the conversion had reached ∼50% (3 h), the biocatalyst was filtered, and the solution was concentrated in vacuo. The residue was dissolved in anhydrous THF (100 mL), and AcOH (1.1 g, 18.6 mmol), PPh_3 (4.0 g, 15.2 mmol), and diisopropyl azodicarboxylate (2.6 g, 12.9 mmol) were added. The solution was stirred at room temperature for 1 h to yield crude (*R*)-**10** (ee > 99%). Without further isolation, the reaction mixture was diluted with H_2SO_4 (5%, 80 mL) and heated to 80 °C for 3 h. After neutralization with a sat. $NaHCO_3$ solution (150 mL) and extraction with Et_2O (3 × 60 mL), the organic phase was dried and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give (*R*)-**5** (0.74 g, 82%) ee >99%. $[\alpha]_D^{20}$ −58.5 (*c* 0.65, $CHCl_3$).

(*S*)-Hept-1-ene-4,6-diyn-3-ol [(*S*)-5] via Biocatalytic In Situ Inversion. *C. antarctica* B lipase (90 mg) was dissolved in Na_2HPO_4 buffer (70 mL, 50 mM, pH 7.5), and *rac*-**10** (0.85 g, 5.7 mmol) was added. The reaction was monitored by GC on a chiral stationary phase. When the conversion had reached ∼50% (30 min), the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL), and the organic phase was dried and concentrated in vacuo. The residue was treated with AcOH (6.1 g, 11.4 mmol), PPh_3 (2.4 g, 9.1 mmol), and diisopropyl azodicarboxylate (1.7 g, 8.5 mmol) in anhydrous THF (50 mL) as described above to yield (*S*)-**10** in ee = 98% after 1 h. Acid-catalyzed hydrolysis was complete after 4 h and workup was performed as described above. Flash chromatography (petroleum ether/EtOAc, 5:1) gave (*S*)-**5** (0.49 g, 81%) ee = 98%. $[\alpha]_D^{20}$ +56.4 (*c* 1.14, $CHCl_3$).

(*Z*)-2-Decen-1-ol 12. To a solution of alkyne **11** (10 g, 64.8 mmol) in EtOH (50 mL), quinoline (2 mL)were added a cat. amount of KOH and Lindlar catalyst (2 g), and the resulting mixture was vigorously stirred under H_2 for 16 h at atmospheric pressure. Then the solids were removed by filtration through a plug of Celite-545, and the solvent was evaporated. Flash chromatography (petroleum ether/EtOAc, 7:1) gave **12** as a colorless liquid (8.7 g, 86%). R_f (petroleum ether/EtOAc, 1:1) = 0.75, (detection I); ^{1}H NMR (360.13 MHz, $CDCl_3$): δ = 0.87 (3H, t, J = 6.7), 1.27−1.37 (10H, m), 1.64 (1H, m), 2.06 (2H, q, J = 6.6), 4.20 (2H, d, J = 10.4), 5.51−5.60 (2H, m). ^{13}C NMR (90 MHz, $CDCl_3$): δ = 14.1, 22.7, 27.5, 29.2, 29.3, 29.7, 31.9, 58.6, 128.4, 133.2.

(*Z*)-1-Chloro-2-decene 13. PPh_3 (16 g, 61.0 mmol) and alcohol **12** (8.5 g, 54.4 mmol) were dissolved in CCl_4 (50 mL) without Ar atmosphere. The reaction was complete after stirring for 16 h at 80 °C. The solution was concentrated, and pentane (50 mL) was added. The mixture was filtered, and the filtrate was concentrated in vacuo. After flash chromatography (petroleum ether) chloroalkene **13** (7.7 g, 81%) was isolated as a colorless liquid. R_f (petroleum ether/EtOAc, 1:1) = 0.95, (detection II); ^{1}H NMR (360.13 MHz, $CDCl_3$): δ = 0.90 (3H, t, J = 6.6), 1.29−1.44 (10H, m), 2.12 (2H, q, J = 6.7), 4.10 (2H, d, J = 6.8), 5.59−5.68 (2H, m). ^{13}C NMR (90 MHz, $CDCl_3$): δ = 14.3, 22.8, 27.3, 29.3, 29.4, 29.5, 32.0, 39.7, 125.4, 135.7.

(*S*)-Falcarinol (*S*)-3. To a stirred solution of (*S*)-**5** (0. 16 g, 1.51 mmol) in anhydrous DMF (10 mL) were added $Bu_4N^+Cl^-$ (0.05 g, 0.18 mmol), K_2CO_3 (0.26 g, 1.88 mmol), and CuI (0.02 g, 0.11 mmol). After the mixture was stirred for 15 min at room temperature, chloroalkene **13** (0.28 g, 1.60 mmol), dissolved in DMF (2 mL), was added dropwise within 15 min. The resulting solution was stirred at room temperature for further 7 h. After the reaction was complete, it was quenched with water (15 mL) and Et_2O (50 mL). After phase separation, the organic phase was dried and concentrated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 7:1) to give (*S*)-**3** (0.27 g, 73%) as a colorless liquid. $[\alpha]_D^{20}$ +31.4 (*c* 1.12, $CHCl_3$), which is in good agreement with literature data $[\alpha]_D^{20}$ +33.8 (*c* 0.53, $CHCl_3$).[6] R_f (petroleum ether/EtOAc, 5:1) = 0.37 (detection I); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 0.89 (3H, t, J = 6.7), 1.28−1.36 (10H, m), 1.93 (1H, d, J = 6.6), 2.02 (2H, q, J = 7.1), 3.03 (2H, d, J = 6.9), 4.91 (1H, t, J = 5.6), 5.24 (1H, d, J = 5.1), 5.35−5.52 (3H, m), 5.91−5.98 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0, 17.6, 22.5, 27.1, 29.04, 29.08, 29.13, 31.7, 63.3, 63.9, 71.2, 74.1, 80.2, 116.9, 121.9, 133.0, 136.1. NMR data match those previously reported.[9] HRMS ($C_{17}H_{24}O_1$): calcd. 244.1827 $[M]^+$; found 244.1824 $[M]^+$.

(*R*)-Falcarinol (*R*)-3. Following the procedure described above for (*S*)-**3**, alcohol (*R*)-**5** (0. 19 g, 1.8 mmol) was treated with anhydrous DMF (15 mL), $Bu_4N^+Cl^-$ (0.06 g, 0.22 mmol), K_2CO_3 (0.3 g, 2.2 mmol), CuI (0.02 g, 0.11 mmol), and chloroalkene **13** (0.33 g, 1.89 mmol) to afford (*R*)-**3** (0.30 g, 69%) as a colorless liquid after flash chromatography (petroleum ether/EtOAc, 10:1). $[\alpha]_D^{20}$ −35.3 (*c* 1.45, $CHCl_3$) is in good agreement with literature data $[\alpha]_D^{20}$ −36.6 (*c* 0.92, $CHCl_3$).[6] The ^{1}H and ^{13}C NMR spectra and mass spectra matched those described above for (*S*)-**3**.

***cis*-1-Chloro-2,3-epoxydecane *rac-cis*-14.** To a solution of alkene **13** (3 g, 17.2 mmol) in CH_2Cl_2 (80 mL), acetone (80 mL), and H_2O (20 mL) were added a cat. amount of 18-crown-6 and a solution of Oxone (15.9 g, 25.9 mmol) in H_2O (60 mL) at 4 °C without argon atmosphere. After 16 h the reaction was complete, and the organic phase was separated from the

(28) HRMS and elemental analysis data could not be obtained due to polymerization.

aqueous phase. After extraction of the aqueous layer with CH_2Cl_2 (3 × 50 mL), the combined organic phase was dried and evaporated. Kugelrohr distillation gave *rac-cis*-**14** (2.75 g, 84%) as a colorless liquid. GC-data: Column A [10 psi, H_2, 135 °C (iso), $t_{R1} = 3.2$ min, $t_{R2} = 3.3$ min]. R_f (petroleum ether/EtOAc, 2:1) = 0.83, (detection I); bp_{20mbar} (Kugelrohr): 130−135 °C; ^{1}H NMR (360.13 MHz, $CDCl_3$): δ = 0.89 (3H, s), 1.29−1.54 (12H, m), 3.06 (1H, s), 3.21−3.25 (1H, m), 3.45−3.51 (1H, m), 3.65−3.70 (1H, m). ^{13}C NMR (90 MHz, $CDCl_3$): δ = 14.2, 22.8, 26.6, 27.6, 29.3, 29.5, 31.9, 41.7, 55.9, 58,2. HRMS ($C_{10}H_{19}O_1$-Cl): calcd 191.1124 $[M]^+$; found 190.1147 $[M]^+$ and HRMS ($C_{10}H_{19}O_1$): calcd 155.1436 $[M - Cl]^+$; found 155.1427 $[M - Cl]^{+\cdot}$.

***threo*-1-Chloro-2,3-decanediol *rac-cis*-15.** Epoxide *rac-cis*-**14** (0.5 g, 2.6 mmol) was hydrolyzed in a mixture of water (5 mL) and THF (5 mL) under acidic conditions (6 N H_2SO_4, 20 drops) without argon atmosphere. After 5 h the reaction was complete. The solution was extracted twice with EtOAc (20 mL). The combined organic layers were dried and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to afford *rac-cis*-**15** (0.13 g, 87%). GC-data: Column A [10 psi, H_2, 135 °C (iso), t_{R1} = 22.2 min (2*R*,3*S*), t_{R2} = 24.0 min (2*S*,3*R*)]. R_f (petroleum ether/EtOAc, 5:1) = 0.16, (detection I); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 0.88 (3H, t, J = 6.6), 1.24−1.55 (12H, m), 3.60−3.68 (3H, m), 4.12 (1H, q, J = 7.1). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.3, 21.9, 24.8, 28.5, 28.7, 31.0, 33.0, 46.1, 70.8, 73.0. HRMS ($C_{10}H_{20}O_2Cl$): calcd 207.1152 $[M - H]^+$; found 207.1157 $[M - H]^{+\cdot}$.

***cis*-1,2-Epoxy-3-decanol *rac-cis*-4.** Diol *rac-cis*-**15** (0.11 g, 0.53 mmol) was dissolved in dry THF (5 mL), and NaH (1 mmol) was added. After 30 min, water (10 mL) was added carefully. The solution was extracted three times with Et_2O (20 mL). The combined organic layers were dried and concentrated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 8:1) to afford *rac-cis*-**4** (0.079 g, 87%) as a colorless liquid. GC-data: Column A [10 psi, H_2, 135 °C (iso), t_{R1} = 4.2 min (2*S*,3*S*), t_{R2} = 4.3 min (2*R*,3*R*)]. R_f (petroleum ether/EtOAc, 1:1) = 0.74, (detection I); ^{1}H NMR (360.13 MHz, $CDCl_3$): δ = 0.89 (3H, t, J = 6.6), 1.29−1.63 (12H, m), 1.87 (1H, d, J = 5.7), 2.71−2.74 (1H, m), 2.83 (1H, t, J = 4.9), 2.99 (1H, q, J = 4), 3.42−3.48 (1H, m). ^{13}C NMR (90 MHz, $CDCl_3$): δ = 14.1, 22.7, 25.3, 29.2, 29.6, 31.8, 34.5, 45.2, 55.4, 71.7. HRMS ($C_{10}H_{19}O_2$): calcd 171.1385 $[M - H]^+$; found 171.1381 $[M - H]^{+\cdot}$.

(2*R*,3*R*)-1,2-Epoxy-3-decanol (2*R*,3*R*)-4 via Biotransformation. Lyophilized whole cells of *Streptomyces* sp. FCC008 (7 g) were rehydrated in Tris buffer (350 mL, pH 8.0, 50 mM) for 1 h, and epoxide *rac-cis*-**14** (0.85 g, 4.46 mmol) was added in one portion. The reaction was monitored by GC on a chiral stationary phase. After shaking the mixture at 30 °C for 156 h, the reaction was complete, and the product was continuously extracted with CH_2Cl_2 (400 mL) for 24 h. The organic phase was dried and concentrated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 8:1) to give (2*R*,3*R*)-**4** (0.71 g, 92%, ee = 95%) as a colorless liquid. $[\alpha]_D^{20}$ −5.2 (*c* 0.67, $CHCl_3$), which is consistent with literature data $[\alpha]_D^{20}$ −5.6 (*c* 1.8, $CHCl_3$)[12]

(2*R*,3*R*)-3-*tert*-Butyldimethylsilyloxy-1,2-epoxydecane (2*R*,3*R*)-16. A solution of alcohol (2*R*,3*R*)-**4** (0.68 g, 4.0 mmol), TBDMSCl (0.9 g, 5.9 mmol), and imidazole (0.4 g, 5.9 mmol) in CH_2Cl_2 (30 mL) was stirred at room temperature overnight and poured into a mixture of sat. $NaHCO_3$ and CH_2Cl_2. The mixture was stirred vigorously for 30 min, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried and concentrated. The residue was purified by flash chromatography (petroleum ether) to afford (2*R*,3*R*)-**16** (1.01 g, 89%). $[\alpha]_D^{20}$ +5.9 (*c* 1.38, $CHCl_3$). R_f (petroleum ether/EtOAc, 3:1) = 0.89, (detection I); ^{1}H NMR (360.13 MHz, $CDCl_3$): δ = 0.07 (3H, s), 0.13 (3H, s), 0.90 (3H, t, J = 7.1), 0.92 (9H, s), 1.29−1.56 (12H, m), 2.56 (1H, dd, J = 4.9, 2.7), 2.79 (1H, t, J = 4.9), 2.91−2.94 (1H, m), 3.27 (1H, q, J = 6.5).[11] ^{13}C NMR (90 MHz, $CDCl_3$): δ = −5.0, −4.3, 14.1, 18.2, 22.7, 25.3, 25.9, 29.3, 29.7, 31.9, 34,8, 44.9, 56.0, 74.7. HRMS ($C_{15}H_{31}O_2Si$): calcd 271.2093 $[M - CH_3]^+$; found 271.2093 $[M - CH_3]^+$.

(3*R*,9*R*,10*R*)-Heptadec-1-ene-4,6-diyne-3,9,10-triol, (3*R*,9*R*,10*R*)-Panaxytriol, (3*R*,9*R*,10*R*)-1. To a stirred solution of (*R*)-**5** (0.11 g, 1.04 mmol) in dry THF (10 mL) was added *n*-BuLi (0.85 mL of a 2.5 M solution in hexane, 2.08 mmol) at −78 °C. After 30 min, HMPA (3 mL) and a solution of (2*R*,3*R*)-**16** (0.33 g, 1.14 mmol) in THF (5 mL) were added dropwise at −78 °C, and the reaction was stirred for 3 h at 80 °C. The reaction was quenched by addition of H_2O (30 mL) and Et_2O (40 mL). The phases were separated, and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic phases were dried and evaporated. The residue was dissolved in THF (10 mL), and $Bu_4N^+F^-$ (0.36 g, 1.14 mmol) was added. After 30 min, the reaction was quenched with water (10 mL) and Et_2O (20 mL). The phases were separated, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic phases were dried and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to afford (3*R*,9*R*,10*R*)-**1** (0.19 g, 68%). $[\alpha]_D^{20}$ −19.5 (*c* 0.83, $CHCl_3$). R_f (petroleum ether/EtOAc, 1:1) = 0.35, (detection I); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 0.90 (3H, t, J = 7.1), 1.27−1.54 (12H, m), 2.02 (2H, s), 2.38 (1H, s), 2.58−2.64 (2H, m), 3.56−3.65 (2H, m), 4.94 (1H, d, J = 4.5), 5.27 (1H, d, J = 10.2), 5.46 (1H, d, J = 17.1), 5.96 (1H, ddd, J = 17.0, 10.1, 5.5). ^{13}C NMR (90 MHz, $CDCl_3$): δ = 14.1, 22.6, 25.0, 25.5, 29.2, 29.5, 31.7, 33.6, 63.5, 66.5, 70.9, 72.1, 73.0, 74.7, 78.1, 117.2, 136.0.[12] HRMS ($C_{17}H_{24}O_2$): calcd 260.1776 $[M - H_2O]^+$; found 260.1775 $[M - H_2O]^+$.

(3*S*,9*R*,10*R*)-Heptadec-1-ene-4,6-diyne-3,9,10-triol, (3*S*,9*R*,10*R*)-Panaxytriol, (3*S*,9*R*,10*R*)-2. According to the procedure described above for (3*R*,9*R*,10*R*)-**1**, alcohol (*S*)-**5** (0.09 g, 0.85 mmol) in dry THF (10 mL) was treated with *n*-BuLi (0.70 mL of a 2.5 M solution in hexane, 1.7 mmol), with HMPA (2 mL) and a solution of (2*R*,3*R*)-**16** (0.27 g, 0.94 mmol) in THF (4 mL), and finally with $Bu_4N^+F^-$ (0.30 g, 0.94 mmol) to afford (3*S*,9*R*,10*R*)-**2** (0.14 g, 59%) after flash chromatography (petroleum ether/EtOAc, 10:1). $[\alpha]_D^{20}$ +24.3 (*c* 1.10, $CHCl_3$), which is consistent with literature $[\alpha]_D^{20}$ +25.3 (*c* 3.9, $CHCl_3$).[12] R_f (petroleum ether/EtOAc, 1:1) = 0.38, (detection I); ^{1}H NMR (360.13 MHz, $CDCl_3$): δ = 0.89 (3H, t, J = 6.9), 1.20−1.50 (12H, m), 2.18 (3H, bs), 2.57−2.61 (2H, m), 3.72−3.78 (2H, m), 4.93 (1H, d, J = 5.5), 5.27 (1H, d, J = 10.1), 5.48 (1H, d, J = 16.5), 5.95 (1H, ddd, J = 17.0, 10.0, 5.4). ^{13}C NMR (90 MHz, $CDCl_3$): δ = 14.1, 22.6, 25.0, 25.5, 29.2, 29.5, 31.7, 33.6, 63.5, 66.5, 70.9, 72.1, 73.0, 74.7, 78.1, 117.2, 136.0. HRMS ($C_{17}H_{24}O_2$): calcd. 260.1776 $[M - H_2O]^+$; found 260.1775 $[M-H_2O]^+$.

General Procedure for the Screening for Biocatalytic Activity of *rac-cis*-14. Epoxide *rac-cis*-**14** (5 μL) was hydrolyzed using rehydrated lyophilized cells (50 mg) in Tris-buffer (1 mL, 0.05 M, pH 8.0) by shaking the mixture at 30 °C with 120 rpm. The reactions were monitored by TLC and GC. After 146 h, the cells were removed by centrifugation, and products were extracted with EtOAc (2 × 1 mL). The combined organic layers were dried (Na_2SO_4) and analyzed.

Syntheses of Nonracemic Reference Material and Determination of Absolute Configuration. The absolute configuration of (*R*)-Falcarinol (*R*)-**3** and (*S*)-Falcarinol (*S*)-**3** was confirmed by comparison with known optical rotation values.[6]

The absolute configuration of compound (2*R*,3*R*)-**4** was confirmed by comparison with a known optical rotation value. Since conflicting values have been reported,[11,12] the absolute configuration of (2*R*,3*R*)-**4** was elucidated by GC analysis on a chiral stationary phase by coinjection with the independently synthesized (2*R*,3*R*)-enantiomer following a known procedure.[27]

(*E*)-2-Decen-1-ol 17. To a stirred solution of $LiAlH_4$ (4.5 g, 39.5 mmol) in dry THF (80 mL) was added a solution of alkyne

11 (6 g, 39 mmol) in dry THF (30 mL) dropwise at 0 °C. Then the cooling bath was removed, the mixture was refluxed for 16 h and cooled to 0 °C, and 5% aq HCl (30 mL) was slowly added. The product was extracted with Et_2O (2 × 50 mL), and the organic phase was dried and concentrated. Flash chromatography (petroleum ether/EtOAc, 7:1) gave **17** as a colorless liquid (5.2 g, 86%). R_f (petroleum ether/EtOAc, 1:1) = 0.75, (detection I); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 0.87 (3H, t, J = 6.6), 1.22−1.37 (10H, m), 1.88, (1H, s), 2.02 (2H, q, J = 6.8), 4.06 (2H, d, J = 5.6), 5.58−5.69 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0, 22.5, 29.0 (3×), 31.7, 32.1, 63.6, 128.7, 133.3.

(*E*)-1-Chloro-2-decene 18. According to the procedure described for **13**, alcohol **17** (5 g, 32.0 mmol) in CCl_4 (50 mL) was treated with PPh_3 (12.5 g, 47.5 mmol) without argon atmosphere to afford **18** (4.70 g, 84%) as a colorless liquid after flash chromatography (petroleum ether). R_f (petroleum ether/EtOAc, 1:1) = 0.95, (detection II); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 0.90 (3H, t, J = 6.8), 1.24−1.42 (10H, m), 2.06 (2H, q, J = 7.1), 4.04 (2H, d, J = 7.0), 5.60−5.64 (1H, m), 5.75−5.80 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0, 22.6, 28.8, 29.00, 29.03, 31.8, 32.0, 45.4, 125.8, 136.1.

(2*R*,3*R*)-1,2-Epoxy-3-decanol (2*R*,3*R*)-4 via Asymmetric Dihydroxylation Using AD-Mix-*β*. To a stirred solution of methanesulfonamide (0.16 g, 1.7 mmol), K_2CO_3 (0.7 g, 5.13 mmol), and AD-mix-β (1 g) in *t*-BuOH (13 mL) and H_2O (13 mL) was added chloroalkene **18** (0.3 g, 1.7 mmol) at 0 °C. The solution was stirred for 124 h at room temperature. The phases were separated, and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic phases were dried and evaporated. The residue was dissolved in dry THF (30 mL), and NaH (2 mmol) was added. After 30 min, water (15 mL) was added carefully. The solution was extracted three times with Et_2O (20 mL). The combined organic layers were dried and concentrated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to afford (2*R*,3*R*)-**4** (0.16 g, 54%) ee = 84%. $[\alpha]_D^{20}$ −4.5 (*c* 1.25, $CHCl_3$). The optical rotation of this material is in accordance to that of the biotransformation product with *Streptomyces* sp. FCC008. The ^{1}H and ^{13}C NMR spectra matched those described above for *rac-cis*-**4**.

The absolute configuration of (3*R*,9*R*,10*R*)-Panaxytriol (3*R*,9*R*,10*R*)-**1** and (3*S*,9*R*,10*R*)-Panaxytriol (3*S*,9*R*,10*R*)-**2** was confirmed by comparison with known optical rotation values.[11,12]

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Supporting Information Available: ^{1}H NMR spectra of all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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