Biocatalytic Asymmetric Rearrangement of a Methylene-Interrupted Bis-epoxide: Simultaneous Control of Four Asymmetric Centers Through a Biomimetic Reaction Cascade

Silvia M. Glueck, Walter M. F. Fabian, Kurt Faber,* and Sandra F. Mayer[a]

Abstract: Asymmetric enzyme-catalyzed hydrolysis of methylene-interrupted bis-epoxides **1a** and **1b** catalyzed by bacterial epoxide hydrolases furnished tetrahydrofuran derivatives **2a** and **2b** through a hydrolysis–rearrangement cascade. Whereas racemic bis-oxiranes **1b–d** underwent kinetic resolution with moderate stereoselectivities to yield products with up to 92% *ee* and 66% *de*: *meso*-bis-oxirane *cis*,*cis*-**1a** was transformed into (6*R*,7*R*,9*S*,10*S*)-**2a** in 94% *ee* and 89% *de* at high conversion (85%) by *Rhodococcus* sp. CBS 717.73 as the major product. The reaction sequence resembles a biomimetic reaction cascade and provides an efficient entry into the structural core of annonaceous acetogenins with simultaneous control of four stereocenters.

Keywords: annonaceous acetogenins · biomimetic synthesis · cyclization · epoxide hydrolase · epoxides · rearrangement

Introduction

Annonaceous acetogenins are a subgroup of natural polyether products possessing an (oligo)-THF structure with diverse stereochemistry and are derived from the *Annonaceae* (custard-apple) plant family.[1] After the discovery of its first representative—the antileukemic agent uvaricin[2]—in 1982, they have attracted much interest on account of their diverse bioactivities, such as anthelmintic, antitumor, antimalarial, antimicrobial, antiprotozoal, and pesticidal activities. These last effects are generally exerted through suppression of ATP-driven resistance mechanisms, which in turn causes apoptosis (programmed cell death). For these reasons, annonaceous acetogenins became promising new chemotypes for the development of antitumor and pesticidal agents.

Biogenetically, annonaceous acetogenins are derived from the polyketide pathway.[3] The hypothesis that they are formed from (poly)unsaturated fatty acids by enzymatic epoxidation of the olefinic moieties followed by cascade cyclization of the epoxy fatty acids thus obtained[4] is supported by the identification of matching precursors, the location of double bonds in the appropriate positions within the fatty acid chain, and by the semisynthesis of additional THF rings from double-bond-containing acetogenins.[5,6] Most recently, the discovery of muridienins (presumed precursors of mono-THF acetogenins) and chatenaytrienins (precursors for bis-THF analogues) has provided evidence that acetogenins are most probably derived from lacceroic (C32) and ghedoic (C34) fatty acids after enzymatic combination with a three-carbon unit.[7]

The complex structure and the potent and diverse bioactivity of annonaceous acetogenins has prompted numerous efforts directed towards their total synthesis.[8] To achieve an economic sequence involving a minimum of protection groups, the occurrence of up to three THF units has suggested the use of reiterative methodology. It is interesting to note that the majority of synthetic strategies closely followed the (presumed) biosynthetic pathways: thus, an open-chain olefin bearing double bonds in the appropriate positions and a terminal nucleophile (usually OH) was epoxidized to the corresponding oligo-epoxy derivative, which was subjected to metal-catalyzed,[9] acid-catalyzed,[10–15,27] or base-catalyzed[16] cascade cyclization. This approach proved to be highly efficient as the stereochemical outcome of the cyclization cascade could be controlled to a high extent by the relative (or absolute) stereochemistry of the epoxy units.[17] Whenever access to nonracemic material was desired, asymmetry was usually introduced at the epoxide-stage intermediate by means of Sharpless asymmetric epoxidation or -dihydroxylation protocols.[16,14,9] To the best of our knowledge, no asymmetric catalytic variant of an epoxide cyclization cascade has been reported to date.

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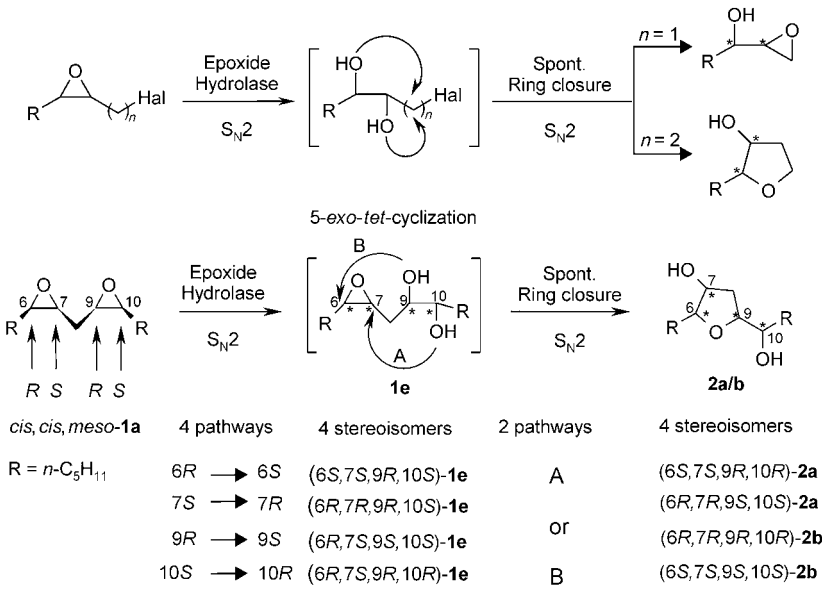
Results and Discussion

Recently, we discovered an enzyme-triggered cyclization cascade of haloalkyl-oxiranes catalyzed by bacterial epoxide hydrolases (Scheme 1).[18,19] Thus, asymmetric enzyme-catalyzed hydrolysis of halo*methyl* oxiranes ($n=1$) by bacterial epoxide hydrolases furnished the corresponding *vic*-diols, which spontaneously underwent an *exo-tet*-cyclization to form hydroxyepoxides as the final products. In contrast, halo*ethyl* derivatives ($n=2$) gave the corresponding THF derivatives. 5-*exo-tet*-Cyclization is favored over both 6- and 5-*endo-tet*-cyclization in nucleophilic substitution reactions involving sp^3 centers. The restriction is loosened for "sp^2-like" centers; however, it still applies to epoxide ring opening.[20]



Scheme 1. Stereochemical pathways of biocatalytic epoxide hydrolysis–cyclization cascade reactions.

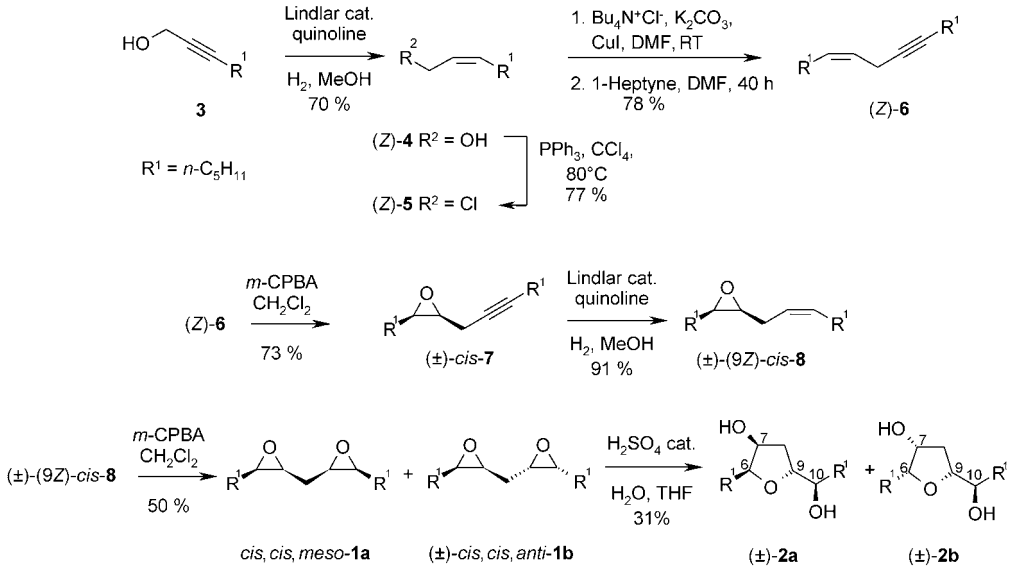
Because the enzymatic step proceeded in an enantioconvergent fashion,[21] the final products were predominantly obtained as single stereoisomers in high enantiomeric excess (*ee*) and diastereomeric excess (*de*) bearing two asymmetric centers. In order to demonstrate the synthetic elegance of this strategy, several natural products were synthesized by means of this strategy.[22]

Prompted by these encouraging results, we envisaged the application of this methodology to a stereochemically even more challenging task, that is, a biocatalytic hydrolysis–cyclization cascade of methylene-interrupted bis-epoxides. In this case, the number of possible pathways is even more complex (Scheme 1). Because both the enzyme-catalyzed hydrolysis[23] and the spontaneous cyclization[24] follow a "clean" S_N2-type mechanism, four positions of enzyme attack are possible in the first step, thus causing inversion of the carbon atom attacked by the epoxide hydrolase[25] to furnish four stereoisomeric *vic*-epoxydiols **1e** as intermediates. Each of these may undergo cyclization to the respective diastereomeric THF product **2a**,**b** following two different pathways (A, B as outlined in Scheme 1), again with chiral inversion of the carbon atom involved in the cyclization.

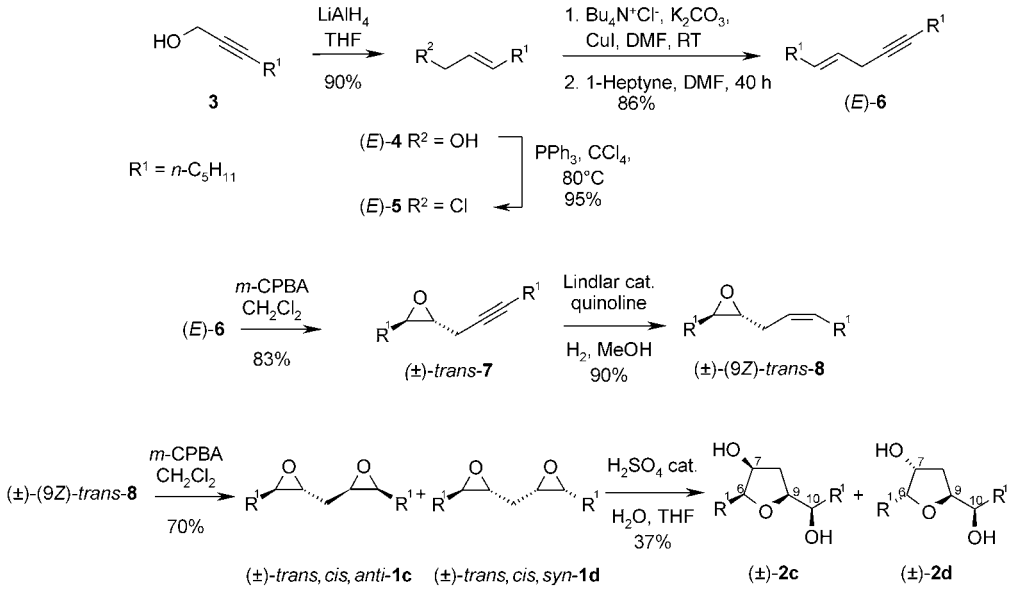
The overall cascade is composed of eight possible stereochemical pathways to furnish four (theoretically) possible stereoisomeric THF derivatives as final products (**2a**,**b**).[26]

In order to gain insight into the stereochemistry of the spontaneous (nonenzymatic) cyclization reaction, the key parameters, such as the Gibbs free energy (ΔG_{react}), deprotonation enthalpies ($\Delta\Delta G$), and activation energies ($\Delta\Delta G^{\neq}$), were calculated by density functional theory [PB-SCRF-B3LYP/6-311++g(d,p)//B3LYP/+6-31 g(d)] on the basis of a structurally simplified analogue of epoxydiol **1e** in which both *n*-pentyl groups were "reduced" to methyl substituents (for computational details, see the Experimental Section). It was found that the Gibbs free energy ΔG_{react} for both cyclization pathways A and B was ≈ 17 kcal mol^{-1}. However, significant energetic discrimination was found between the deprotonation energies of the alcohol groups (OH at C10 versus OH at C9, $\Delta = 3$ kcal mol^{-1}) in favor of the less hindered OH group at C10. In addition, the difference in the Gibbs free energy of activation of pathways A ($\Delta G^{\neq} = 23$ kcal mol^{-1}) versus B ($\Delta G^{\neq} = 32$ kcal mol^{-1}) proved to be high ($\Delta\Delta G^{\neq} \approx 10$ kcal mol^{-1}). In other words, the regioselectivity for pathway A versus B is virtually "absolute", which is in agreement with Baldwin's rules for ring closure.[20,24] As may be deduced from the *de* values in Table 3 (see later), the calculations are in good agreement with the experimental data.

Bis-epoxides *cis,cis,meso*-**1a** and (±)-*cis,cis,anti*-**1b** were synthesized as follows (Scheme 2): Lindlar hydrogenation of alkynol **3** gave the allylic alcohol (*Z*)-**4**, which was chlorinated to the corresponding allyl chloride (*Z*)-**5** under Appel conditions. Compound **5** was then coupled to 1-heptyne to furnish enyne (*Z*)-**6**. Epoxidation of the olefinic bond gave epoxyalkyne (±)-*cis*-**7**. Stereoselective Lindlar reduction of the acetylenic bond furnished epoxyalkene (±)-(9*Z*)-*cis*-**8**, which was epoxidized to a (1:1.2) diastereomeric mixture of methylene-interrupted bis-epoxides *cis,cis,meso*-**1a** and (±)-*cis,cis,anti*-**1b**. Both diastereomers were separated by chromatography and stereochemically assigned by NMR spectroscopy.[27] In order to provide the complete stereochemical set of substrates, the corresponding diastereomeric *trans,cis,anti*- and *trans,cis,syn*-bis-epoxides (±)-*trans,cis,anti*-**1c** and (±)-*trans,cis,syn*-**1d** were synthesized following the same general strategy as outlined above, with the exception that the required *trans*-olefins were obtained by stereoselective reduction of the corresponding acetylenic bond of alkynol **3** with $LiAlH_4$ (Scheme 3). Reference material for the expected diastereomeric biotransformation products (±)-**2a** to (±)-**2d** was obtained in racemic form by acid-catalyzed hydrol-



Scheme 2. Synthesis of substrates *cis,cis,meso*-**1a** and (±)-*cis,cis,anti*-**1b**.



Scheme 3. Asymmetric synthesis of reference material for **2c**,**d**.

ysis rearrangement of bis-epoxides *cis,cis,meso*-**1a**, (±)-*cis,cis,anti*-**1b**, (±)-*trans,cis,anti*-**1c**, and (±)-*trans,cis,syn*-**1d** (see Schemes 2 and 3).[27]

To obtain rapid insight into the feasibility of the transformation, a diastereomeric (1:1.2) mixture of *cis,cis,meso*-**1a** and (±)-*cis,cis,anti*-**1b** was tested in a screening for biohydrolytic activity in Tris buffer at pH 8.0 using resting cells of a variety of 21 *Actinomyces* spp. known to possess strong secondary metabolic activity and epoxide hydrolase activity, in particular. The absence of any undesired spontaneous nonenzymatic hydrolysis/cyclization reaction was verified under standard conditions in the absence of biocatalyst within the anticipated reaction time of ≈49 h. We were pleased to see that the only products formed during enzyme-catalyzed hydrolysis were the expected corresponding THF products of type **2a,b**, neither the intermediate epoxy-diols **1e** nor any other side products were detected in measurable amounts.

The results of a careful stereochemical analysis of the products and the remaining nonconverted oxirane **1b** by co-injection with independently synthesized reference material of known relative and absolute configuration (see below) by means of chiral GC are presented in Table 1.

Both diastereomeric substrates were converted by a series of bacterial cells into the expected THF rearrangement products through the anticipated cascade cyclization at various rates. The stereochemical course of the sequence always followed a double S_N2 mechanism as expected (see above), since diastereomers **2a** and **2b** were formed exclusively. No trace of **2c** or **2d** was detected, because it would require

Table 1. Enzyme-catalyzed hydrolysis of a mixture of *cis,cis,meso*-**1a** and (±)-*cis,cis,anti*-**1b.**

	Biocatalyst	c[a] [%]	ee_S (**1b**) [%]	ee_P (**2a**) [%]	ee_P (**2b**) [%]	de_S[h] [%]	de_P [%]
1	*Rhodococcus ruber* DSM 44539	46	47[b]	77[e]	71[f]	52	24[i]
2	*Rhodococcus ruber* DSM 44541	14	8[b]	83[e]	67[f]	55	1[j]
3	*Rhodococcus equi* IFO 3730	76	84[c]	83[d]	3[g]	99	12[i]
4	*Mycobacterium paraffinicum* NCIMB 10420	62	58[c]	53[e]	56[g]	91	20[i]
5	*Rhodococcus ruber* DSM 43338	15	48[b]	46[e]	6[g]	74	48[i]
6	*Rhodoccoccus sp.* NCIMB 11216	35	48[b]	65[d]	49[g]	49	12[j]
7	*Rhodococcus* sp. CBS 717.73	70	86[b]	73[e]	72[f]	84	29[i]
8	*Streptomyces griseus* ATCC 10137	8	13[c]	35[e]	79[g]	66	85[i]
9	*Streptomyces griseus* DSM 40236	7	13[c]	58[d]	85[g]	46	86[i]

[a] Conversion after 49 h, calculated as the sum of the products formed versus the remaining bis-epoxide. [b] *ee* of *cis,cis,anti*-**1b**: excess of enantiomer eluting first on chiral GC analysis. [c] *ee* of *cis,cis,anti*-**1b**: excess of enantiomer eluting second on chiral GC analysis. [d] *ee* of (6*S*,7*S*,9*R*,10*R*)-**2a**. [e] *ee* of (6*R*,7*R*,9*S*,10*S*)-**2a**. [f] *ee* of (6*R*,7*R*,9*R*,10*R*)-**2b**. [g] *ee* of (6*S*,7*S*,9*S*,10*S*)-**2b**. [h] *de* of (**1a**/**1b**), diastereomer *cis,cis,anti*-**1b** in excess. [i] *de* of (**2a**/**2b**): diastereomer **2b** in excess. [j] *de* of (**2a**/**2b**): diastereomer **2a** in excess.

that one step proceeds with retention to form **2c** or **2d** from *cis,cis,meso*-**1a** or *cis,cis,anti*-**1b**, respectively.

The racemic *cis,cis,anti*-**1b** diastereomer underwent kinetic resolution, as may be deduced by the fact that the remaining (more slowly converted) oxirane enantiomer was detected with up to 86% *ee* (entry 7), depending on the strain. Overall, the enantioselectivities were low-to-moderate ($ee < 20$), while various biocatalysts exhibited an opposite enantiopreference (cf. entries 1,2,5–7 versus entries 3,4,8,9). Both diastereomers were converted at significantly different rates, with the *cis,cis,meso*-**1a** diastereomer being faster, as denoted by the *de* of the substrate (de_S). Remarkably, *Rhodococcus equi* IFO 3730 (entry 3) showed absolute selectivity for the *cis,cis,meso*-**1a** (de_S 99%).

Overall, all four possible stereoisomeric products (i.e., both enantiomers of diastereomers of **2a** and **2b**) were formed by the various strains with up to 86% *ee*.

Since low selectivities are often caused by the presence of parallel stereochemical pathways competing with each other, in particular when acting on (dia)stereomeric substrate mixtures, we anticipated that the product purity of the biotransformation of pure diastereomers would be higher. Thus, *cis,cis,meso*-**1a** and (±)-*cis,cis,anti*-**1b** were subjected to biotransformation separately.

Selected results for the separate biotransformation of (±)-*cis,cis,anti*-**1b** are gathered in Table 2. As may be deduced from the *ee*'s of **1b**, kinetic resolution of the racemate with opposite enantiopreference (entries 1, 2, and 5 versus 3 and 4) could be verified. Again, all four possible stereoisomers, that is, both enantiomers of **2a** and **2b**, were formed in varying amounts. Whereas diastereomer **2a** was generally formed with reduced enantiomeric excesses in comparison to the results obtained with the mixture (cf. entries 1 and 3 in Table 1, and entries 2 and 3 Table 2), the enantiomeric composition of isomer **2b** was significantly improved. Thus, diastereomer **2b** was formed in up to 90–92% *ee* (entries 1 and 5, Table 2), albeit at moderate *de* (54–66%). Despite its remarkable stereochemical aspects, these results were not considered to be of synthetic value. The results from an analogous biotransformation of diastereomeric bis-epoxides (±)-*trans,cis,anti*-**1c** and (±)-*trans,cis,syn*-**1d** (see Scheme 3 and the Experimental Section) were unsatisfactory in terms of activities and selectivities (data not shown).

In contrast to kinetic resolution with its complex underlying kinetics,[28] which cause the enantiomeric excess of the substrate (ee_S) and the product (ee_P) to become a function of the conversion (c), the stereochemical aspects of the desymmetrization of a *meso*-compound is considerably simpler, as the ee_P in this case is *independent* of c. Thus, better selectivities were expected from the bioconversion of *cis,cis,meso*-**1a**. The results, given in Table 3, prove that this assumption was correct: of the two possible diastereomers, only isomer **2a** was formed exclusively by four microorganisms (entries 1–4, $de > 99\%$) with up to 59% *ee*, except for entry 5, whereby diastereomer **2b** was detected in minor amounts (≈5%). Again, various strains exhibited opposite stereoselectivities (entries 1, 2, and 5 versus 3 and 4). Most remarkably, *Rhodococcus* sp. CBS 717.73 (entry 5) selectively formed (6*R*,7*R*,9*S*,10*S*)-**2a** in 94% *ee* in addition to minor amounts of the three other possible stereoisomers (each <5%) at high conversion ($c = 84\%$; Scheme 4).

The relative configuration of THF products **2a**–**2d** was determined by a comparison of the ^{1}H and ^{13}C NMR data with reference samples obtained from acid-catalyzed hydrolysis/cyclization of diastereomeric mixtures of bis-epoxides *cis,cis,meso*-**1a**/(±)-*cis,cis,anti*-**1b** and (±)-*trans,cis,anti*-**1c**/(±)-*trans,cis,syn*-**1d** with the literature data.[27]

The absolute configuration of the products was proven by co-injection with independently synthesized reference compounds **2a**–**2d** on GC with a chiral stationary phase. The latter materials were obtained as shown in Schemes 5 and 6.

Table 2. Bioconversion of (±)-*cis,cis,anti*-**1b**.

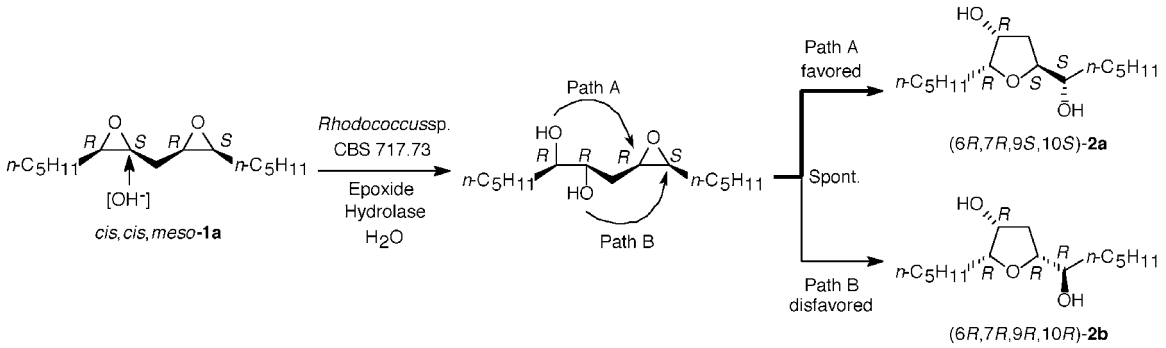
	Biocatalyst	c[a] [%]	ee_S (**1b**) [%]	ee_P (**2a**)[d] [%]	ee_P (**2b**) [%]	de_P [%]
1	*Rhodococcus ruber* DSM 44540	4	2[b]	17	90[e]	54[g]
2	*Rhodococcus ruber* DSM 44539	77	82[b]	19	56[e]	22[g]
3	*Rhodococcus equi* IFO 3730	21	37[c]	47	9[e]	24[g]
4	*Mycobacterium paraffinicum* NCIMB 10420	28	12[c]	28	37[f]	42[h]
5	*Rhodococcus* sp. CBS 717.73	59	18[b]	75	92[e]	66[g]

[a] Conversion after 91 h, calculated as the sum of the products formed versus the remaining bis-epoxide. [b] *ee* of *cis,cis,anti*-**1b**: excess of enantiomer eluting first on chiral GC analysis. [c] *ee* of *cis,cis,anti*-**1b**: excess of enantiomer eluting second on chiral GC analysis. [d] *ee* of (6*S*,7*S*,9*R*,10*R*)-**2a**. [e] *ee* of **2b**: (6*R*,7*R*,9*R*,10*R*)-**2b**. [f] *ee* of **2b**: (6*S*,7*S*,9*S*,10*S*)-**2b**. [g] *de* of (**2a**/**2b**): diastereomer **2b** in excess. [h] *de* of (**2a**/**2b**): diastereomer **2a** in excess.

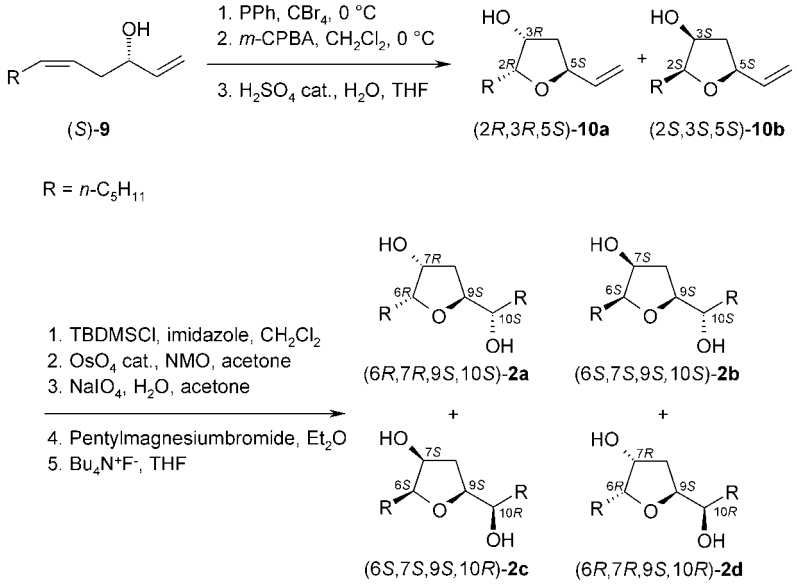
Table 3. Enzyme-catalyzed hydrolysis of *cis,cis,meso*-**1a.**

Entry	Biocatalyst	c[a] [%]	ee_P (**2a**) [%]	ee_P (**2b**)[d] [%]	de_P[e] [%]
1	*Rhodococcus ruber* DSM 44540	87	51[b]	<1	>99
2	*Rhodococcus ruber* DSM 44539	56	24[b]	<1	>99
3	*Rhodococcus equi* IFO 3730	40	59[c]	<1	>99
4	*Mycobacterium paraffinicum* NCIMB 10420	38	37[c]	<1	>99
5	*Rhodococcus* sp. CBS 717.73	84	94[b]	65	89

[a] Conversion after 49 h, calculated as the sum of the products formed versus the remaining bis-epoxide. [b] *ee* of **2a**: (6*R*,7*R*,9*S*,10*S*)-**2a**. [c] *ee* of **2a**: (6*S*,7*S*,9*R*,10*R*)-**2a**. [d] *ee* of (6*R*,7*R*,9*R*,10*R*)-**2b**. [e] *de* of (**2a**/**2b**), diastereomer **2a** is in excess.



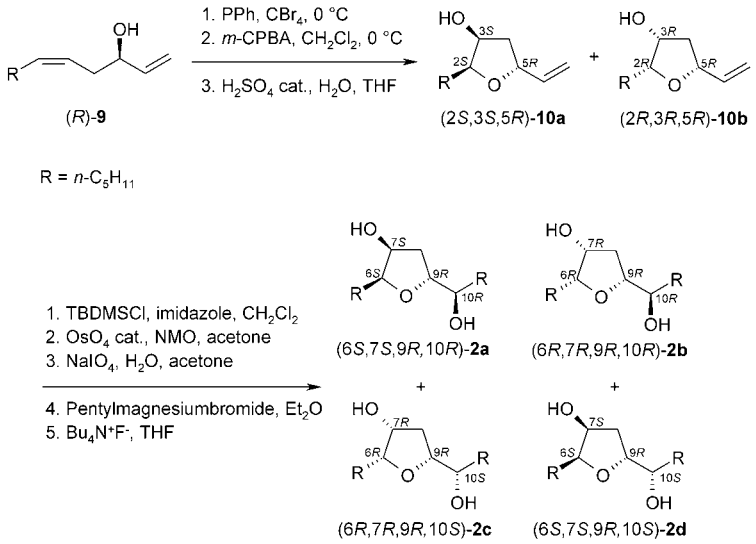
Scheme 4. Stereochemical course of enzyme-catalyzed hydrolysis–cyclization cascade of *cis,cis,meso*-**1a**.



Scheme 5. Asymmetric synthesis of reference material for **2a**–**d**.

Allylic alcohol (*S*)-**9**, which was obtained from a lipase-catalyzed kinetic resolution–stereoinversion sequence[29] was halogenated under Appel conditions to furnish the corresponding allylic bromide with inversion of the configuration. Epoxidation of the *Z*-configured and more active homoallylic olefin moiety gave the diastereomeric homoallylic epoxybromides, which were subjected to acid-catalyzed hydrolysis–cyclization to furnish the diastereomeric THF products (2*R*,3*R*,5*S*)-**10a** and (2*S*,3*S*,5*S*)-**10b**. Because of the double inversion involved in this last sequence, the absolute configuration at C5 is *S*. The relative configuration of the chiral centers at C2 and C3 are *R*,*R* and *S*,*S*, respectively, as predetermined by the *Z*-configuration of the internal olefin of (*S*)-**9**. The diastereomeric mixture of (2*R*,3*R*,5*S*)-**10a** and (2*S*,3*S*,5*S*)-**10b** was then transformed into the stereoisomeric products (6*R*,7*R*,9*S*,10*S*)-**2a**, (6*S*,7*S*,9*S*,10*S*)-**2b**, (6*S*,7*S*,9*S*,10*R*)-**2c**, and (6*R*,7*R*,9*S*,10*R*)-**2d**, by means of the following one-pot sequence without isolation of intermediates: protection of the hydroxyl-group in the 3-position, followed by a two-step oxidative degradation of the vinyl moiety (OsO_4-catalyzed dihydroxylation followed by glycol cleavage with $NaIO_4$) led to the formation of THF-carbaldehydes, which were trapped in situ by a Grignard reagent prepared from *n*-pentyl bromide. Finally, F^--mediated desilylation of the hydroxyl group gave reference samples for THF products (6*R*,7*R*,9*S*,10*S*)-**2a**, (6*S*,7*S*,9*S*,10*S*)-**2b**, (6*S*,7*S*,9*S*,10*R*)-**2c**, and (6*R*,7*R*,9*S*,10*R*)-**2d**.

An analogous sequence leading to the enantiomeric series (6*S*,7*S*,9*R*,10*R*)-**2a**, (6*R*,7*R*,9*R*,10*R*)-**2b**, (6*R*,7*R*,9*R*,10*S*)-**2c**, and (6*S*,7*S*,9*R*,10*S*)-**2d** was accomplished by means of the same protocol starting from alcohol (*R*)-**9**[29] (Scheme 6).



Scheme 6. Asymmetric synthesis of reference material for **2a**–**d**.

Conclusion

The following trends for the enzyme-initiated hydrolysis–cyclization cascade of methylene-interrupted bis-epoxides *cis,cis,meso*-**1a** and (±)-*cis,cis,anti*-**1b** can be summarized as follows:

1) The *meso*-compound *cis,cis,meso*-**1a** was converted faster and more selectively than the diastereomeric bis-epoxide (±)-*cis,cis,anti*-**1b**.
2) Bacterial epoxide hydrolases from different origin exhibit opposite enantiopreferences for the enantiomeric bis-epoxide (±)-*cis,cis,anti*-**1b**.
3) Enzyme-catalyzed hydrolysis of *cis,cis,meso*-**1a** with *Rhodoccoccus* sp. CBS 717.73 predominantly formed a single enantiomer in 94% *ee* and 89% *de* (Scheme 4).
4) The enzyme-triggered hydrolysis–cyclization cascade of methylene-interrupted bis-epoxides allows the simultaneous creation of a THF unit containing four stereocenters in a single reaction.

In view of the fact that there is no counterpart in chemocatalytic methodology available to date for such an asymmetric, catalytic cascade reaction, this biotransformation holds great potential for the short and efficient synthesis of the THF core to give annonaceous acetogenins. The scaleup, as well as scope and limitations of this protocol are under investigation in our laboratories.

Experimental Section

Computational methods: As simplified models for epoxydiol (6*R*,7*R*,9*R*,10*S*)-**1e** and the two diasteromeric products (6*R*,7*R*,9*S*,10*S*)-**2a** (pathway A) and (6*R*,7*R*,9*R*,10*R*)-**2b** (pathway B), analogous structures bearing a methyl group instead of *n*-pentyl were used. The starting structures of these models were created by the SYBYL molecular modeling package.[30] The random search procedure[31] as implemented in SYBYL (Merck molecular mechanics force-field MMFF94s[32,33]) was used for a conformational analysis of the reactant as well as the products. Conformations generated thereby were then first minimized by the semi-empirical AM1[34] method (program AMPAC[35]) followed by complete geometry optimization with Becke's three-parameter hybrid HF-DFT functional[36] and the Lee–Yang–Parr correlation functional[37] (B3LYP), as implemented in Gaussian.[38] The 6-31G(d) basis set was used throughout for neutral molecules and 6-31+G(d) for anionic species. All stationary points were characterized as true minima or transition states by frequency calculations. Transition states were further characterized by intrinsic reaction co-ordinate calculations (IRC) along both directions of the normal mode corresponding to the imaginary frequency. Zero-point energy corrections (ZPE) are unscaled. Solvent effects (aqueous solution) were modeled with the aid of the Poisson–Boltzmann selfconsistent reaction field (PB-SCRF B3LYP/6-311++G(d,p) single-point calculations) approximation[39,40] as implemented in the Jaguar program package.[41]

The formation of the two possible diastereomeric products (6*R*,7*R*,9*S*,10*S*)-**2a** and (6*R*,7*R*,9*R*,10*R*)-**2b** was calculated to be strongly exothermic and exergonic (with inclusion of bulk solvent effects (PB-SCRF (H_2O) B3LYP/6-311++G(d,p) + B3LYP/6-31G(d) thermal ΔG corrections, $\Delta G_{react} = 17$ kcal mol^{-1} with respect to the most stable conformation of the substrate **1e**). Notably, both products are predicted to have an almost equal Gibbs free energy of reaction, ΔG_{react}. Formation of tetrahydrofuran derivatives (6*R*,7*R*,9*S*,10*S*)-**2a** versus (6*R*,7*R*,9*R*,10*R*)-**2b** through pathways A and B requires either intramolecular nucleophilic attack of the OH at C10 with a concomitant opening of the epoxide ring at C7 accompanied by proton transfer (pathway A) or, alternatively, attack of the OH at C9, opening of the epoxide ring at C6 (pathway B). To locate the two respective transition states, either one of the three distances *r*(O10−C2), *r*(O8−C2), and *r*(O8−H11) for pathway A and *r*(O9−C3), *r*(O8−C3), and *r*(O8−H12) for pathway B (for atom numbering, see Figure 1) were used as reaction coordinates. Unfortunately, none of these reaction path calculations were successful. Direct proton-transfer reactions, for example, additions of neutral nucleophiles to carbonyl compounds, are generally quite high energy processes and require catalysis (water-assisted hydration or hydrolysis[42]) or the involvement of anionic nucleophiles. Consequently, calculations were performed for the anionic species resulting from deprotonation of the OH group at C19 and C10. Deprotonation of the C9 hydroxy group is less favorable by ≈ 3 kcal mol^{-1} than deprotonation of the C10 hydroxy group (PB-SCRF (H_2O)B3LYP/6-311++G(d,p) + B3LYP/6-31+G(d) thermal ΔG corrections). Analogous reaction path calculations (*r*(O10−C2) and *r*(O8−C2) for pathway A; *r*(O9−C3) and *r*(O8−C3) for pathway B) followed by transition-state optimizations led to the two transitions states **TS1** and **TS2** for the formation of furans (6*R*,7*R*,9*S*,10*S*)-**2a** and (6*R*,7*R*,9*R*,10*R*)-**2b** from the corresponding deprotonated reactants. With respect to the most stable deprotonated reactant conformer/isomer, the Gibbs free energy barriers (PB-SCRF (H_2O) B3LYP/6-31++G(d,p) + B3LYP/6-31+G(d) thermal ΔG corrections) for the formation of (6*R*,7*R*,9*S*,10*S*)-**2a** and (6*R*,7*R*,9*R*,10*R*)-**2b** are $\Delta G^{\neq} = 23$ and 32 kcal mol^{-1}, respectively. Thus, although the Gibbs free energy barrier differences appear somewhat exaggerated, the modeling results clearly support a strong preference for formation of the (6*R*,7*R*,9*S*,10*S*)-furan product **2a** according to pathway A.

General: NMR spectra were recorded in $CDCl_3$ with a Bruker AMX 360 spectrometer at 360 MHz(^{1}H) and 90 MHz (^{13}C), and a Bruker DMX Avance 500 at 500 MHz (^{1}H) and 125 MHz(^{13}C), respectively. Chemical shifts are reported relative to TMS ($\delta = 0.00$) with $CHCl_3$ as the internal

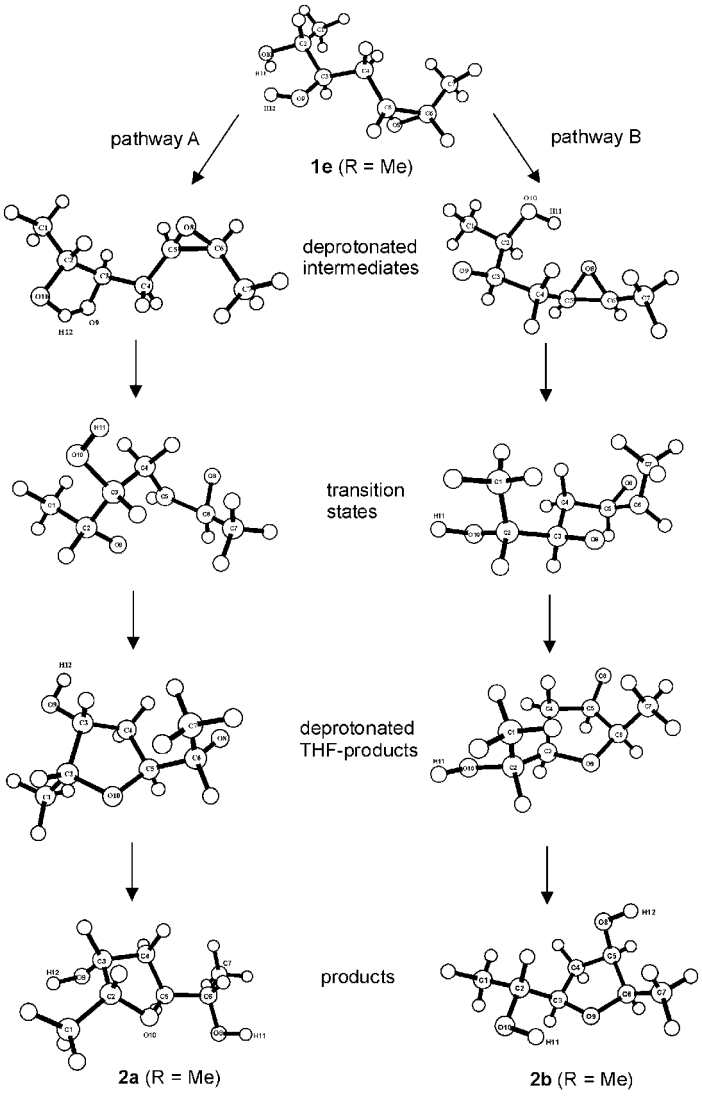


Figure 1. Calculated structures of reactants, transition states and products for cyclization pathways A and B. The structures correspond to compounds depicted in Scheme 1 (R = methyl).

standard [$\delta = 7.23$ (^{1}H) and 76.90 (^{13}C)], coupling constants (J) are given in Hz.

TLC was performed on silica gel Merck 60 (F_{254}), and compounds were visualized by spraying with Mo reagent [$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (100 g L^{-1}), $Ce(SO_4)_2\cdot 4H_2O$(4 g L^{-1}) in H_2SO_4 (10%); detection I] or by dipping into a $KMnO_4$ solution (2.5 g L^{-1} in H_2O; detection II). Compounds were purified by flash chromatography on silica gel (Merck 60, 230—400 mesh). Petroleum ether had a boiling range of 60–90 °C. GC analyses were carried out on a Varian 3800 gas chromatograph equipped with FID and a HP1301 (column C) capillary column (30 m, 0.25 mm, 0.25 μm film, N_2). Enantiomeric purities were analyzed with a CP-Chirasil DEX CB column (column A, 25 m, 0.32 mm, 0.25 μm film) or a Astec Chiraldex B-TA (column B, 30 m, 0.25 mm). H_2 was used as the carrier gas. Reactions were monitored by GC analysis on an achiral stationary phase, for analytical data see Table 4. Chiral materials were analyzed either directly or as the corresponding trifluoroacetate esters by GC on a chiral stationary phase, for analytical data see Table 5.

High-resolution mass spectra were recorded on a double-focusing Kratos Profile Mass Spectrometer with electron impact ionization (EI, +70 eV).

Solvents were dried and freshly distilled. All reactions were performed under an 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, Aldrich] was used as received. Substrate **3** and 1-heptyne were purchased from Aldrich. *m*-Chloroperbenzoic acid (*m*-CPBA, Fluka, 70%) was used. Bacteria were obtained from culture collections. Growth and maintenance of bacterial strains, as well as the preparation of lyophilized cultures was performed as previously described.[43]

General procedure for the enzyme-catalyzed hydrolysis of *cis,cis,meso*-1a and (±)-*cis,cis,anti*-1b: Epoxides *cis,cis,meso*-**1a** and (±)-*cis,cis,anti*-**1b** (5 μL) were hydrolyzed with lyophilized cells (50 mg) rehydrated in Tris buffer for 0.5 h (1 mL, 0.05 M, pH 8.0) by shaking the mixture at 30 °C at 120 rpm. The reactions were monitored by TLC and GC. After 49 h, the cells were removed by centrifugation, and the products were extracted with EtOAc (2×1 mL). The combined organic layers were dried (Na_2SO_4) and analyzed. The same procedure was also used for the conversion of the diasteromeric mixture of *cis,cis,meso*-**1a** and (±)-*cis,cis,anti*-**1b**.

General procedure for the synthesis of (*Z*)-4, (9*Z*)-*rac,cis*-8 and (9*Z*)-*rac,trans*-8: Compounds (*Z*)-**4**, (9*Z*)-*rac,cis*-**8** and (9*Z*)-*rac,trans*-**8** were obtained by selective hydrogenation of alkynes **3**, *rac,cis*-**7**, and *rac,trans*-**7** with the Lindlar catalyst according to Method A.

Method A: Quinoline (8 mL), KOH (0.8 g, 14.2 mmol), and Lindlar catalyst (1.2 g) were added to a solution of alkyne (10 g, 79.2 mmol) in EtOH (40 mL). The resulting mixture was vigorously stirred under H_2 for 18 h at atmospheric pressure. The solids were removed by filtration through a plug of Celite-545, and the solvent was evaporated. Flash chromatography afforded stereoisomerically pure alkynes **4** and **8**.

(E)-2-Octene-1-ol ((E)-4): A solution of alkyne **3** (30 g, 233 mmol) in anhydrous THF (30 mL) at 0 °C was added dropwise to a stirred solution of $LiAlH_4$ (9.73 g, 256.3 mmol) in anhydrous THF (100 mL) under an argon atmosphere. The cooling bath was removed, and the mixture was stirred for 16 h at room temperature and then cooled to 0 °C. Aqueous HCl (5%, 30 mL) was slowly added. After filtration, the product was extracted with Et_2O (2×50 mL), and the organic phase was dried and concentrated. The residue was purified by flash chromatography (pentane/Et_2O, 5:1) to afford (*E*)-**4** (26.86 g, 90%) as a colorless liquid. R_f (petroleum ether/EtOAc, 1:1) = 0.66 (detection II); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.86–0.90 (m, 3H; CH_3), 1.25–1.37 (br m, 6H; $3CH_2$), 1.69 (br s, 1H; OH), 2.00–2.04 (m, 2H; CH_2), 4.09 (d, J = 6.5 Hz, 2H; CH_2), 5.63–5.69 ppm (m, 2H; 2CH); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 14.1, 22.6, 28.9, 31.4, 32.2, 63.8, 128.9, 133.5 ppm.

(Z)-2-Octene-1-ol ((Z)-4): Method A was employed with alkyne **3** (10 g, 79.2 mmol). Flash chromatography (pentane/Et_2O, 5:1) gave *cis*-2-octen-1-ol (*Z*)-**4** as a colorless liquid (7.1 g, 70%). R_f (petroleum ether/EtOAc, 5:1) = 0.25, (detection II); ^{1}H NMR (360.13 MHz, $CDCl_3$): δ = 0.86–0.91 (m, 3H), 1.27–1.37 (m, 6H), 1.55 (br s, 1H), 2.07 (dt, J = 7.4, 6.5 Hz, 2H), 4.19 (d, J = 6.0 Hz, 2H;), 5.52–5.61 ppm (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 14.1, 22.7, 27.4, 29.3, 31.5, 58.6, 128.4, 133.3 ppm.

(6R,7S*,9Z)-6,7-Epoxy-9-pentadecene ((9Z)-rac,cis-8)*: Method A was employed with alkyne *rac,cis*-**7** (8.7 g, 39.1 mmol), but without addition of KOH. Flash chromatography (pentane/Et_2O, 10:1) gave alkene (9*Z*)-*rac,cis*-**8** as a colorless liquid (7.9 g, 91%). R_f (petroleum ether/EtOAc, 5:1) = 0.67, (detection I); ^{1}H NMR (360.13 MHz, $CDCl_3$): δ = 0.84–0.91 (m, 6H), 1.27–1.65 (br m, 14H), 2.04 (dt, J = 7.0, 7.2 Hz, 2H), 2.17–2.19 (m, 1H), 2.37–2.41 (m, 1H), 2.93 (t, J = 7.8 Hz, 2H), 5.40–5.46 (m, 1H), 5.50–5.55 ppm (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 14.1, 22.6, 22.7, 26.3, 26.4, 27.5, 27.8, 29.3, 31.6, 31.9, 56.6, 57.3, 123.9, 132.8 ppm.

(6R,7R*,9Z)-6,7-Epoxy-9-pentadecene ((9Z)-rac,trans-8)*: Method A was employed with alkyne *rac,trans*-**7** (2.6 g, 11.7 mmol), but without addition of KOH. Flash chromatography (pentane/Et_2O, 10:1) gave alkyne (9*Z*)-*rac,trans*-**8** as a colorless liquid (2.35 g, 90%). R_f (petroleum ether/EtOAc, 5:1) = 0.70, (detection I); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.87–0.90 (t, J = 7.0 Hz, 6H; $2CH_3$), 1.27–1.55 (br m, 14H; $7CH_2$), 2.03 (dt, J = 6.8, 7.0, Hz, 2H; CH_2), 2.24 (m, 1H; CH), 2.41 (m, 1H; CH), 2.68–2.71 (m, 2H; 2CH), 5.38–5.42 (m, 1H; CH), 5.48–5.54 ppm (m, 1H; CH); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 14.0, 14.1, 22.6, 22.6, 30.0, 25.7, 27.4, 29.3, 31.5, 31.7, 32.0, 58.1, 58.6, 123.4, 133.0 ppm.

General procedure for the synthesis of allylic chlorides (*E*)-5 and (*Z*)-5: Compounds (*Z*)-**5** and (*E*)-**5** were obtained by chlorination of alcohols (*Z*)-**4** and (*E*)-**4** according to Method B.

Method B: PPh_3 (31.4 g, 120.0 mmol) and allylic alcohol (13.3 g, 103.6 mmol) were dissolved in CCl_4 (80 mL). The reaction was complete

Table 4. GC data on an achiral stationary phase.

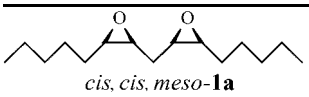
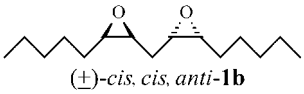
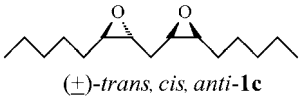
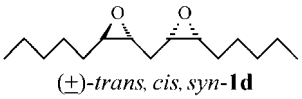
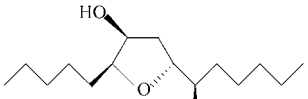
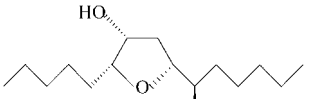
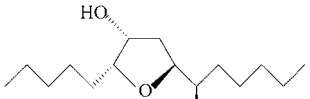
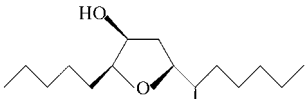
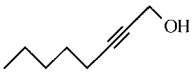
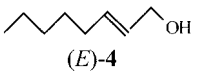
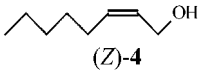
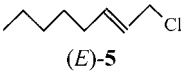
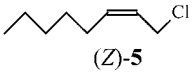
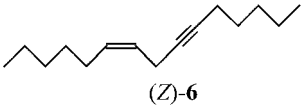
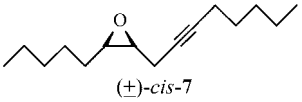
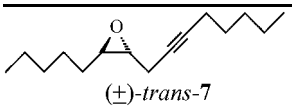
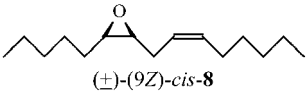
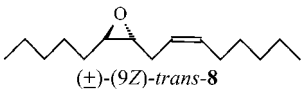
Compound	Column	Conditions[a]	t_R [min]
 *cis, cis, meso*-**1a**	C	A	14.11
 (±)-*cis, cis, anti*-**1b**	C	A	13.95
 (±)-*trans, cis, anti*-**1c**	C	A	13.97
 (±)-*trans, cis, syn*-**1d**	C	A	13.90
 (±)-**2a**	C	A	15.50
 (±)-**2b**	C	A	15.84
 (±)-**2c**	C	A	15.16
 (±)-**2d**	C	A	15.31
 **3**	C	B	10.38
 (*E*)-**4**	C	B	9.53
 (*Z*)-**4**	C	B	9.44
 (*E*)-**5**	C	B	8.79
 (*Z*)-**5**	C	B	8.66
 (*E*)-**6**	C	A	10.92
 (*Z*)-**6**	C	A	10.47
 (±)-*cis*-**7**	C	A	12.93

Table 4. (Continued)

Compound	Column	Conditions[a]	t_R [min]
 (±)-*trans*-**7**	C	A	12.69
 (±)-(9*Z*)-*cis*-**8**	C	A	12.57
 (±)-(9*Z*)-*trans*-**8**	C	A	12.26

[a] Conditions: A) 14.5 psi; held at 140 °C for 8 min; heat rate 15 °C min^{-1} up to 200 °C, then 50 °C min^{-1} up to 250 °C; held at 250 °C for 30 min; B) 14.5 psi; held at 60 °C for 2 min; heat rate 8 °C min^{-1} up to 150 °C, then 30 °C min^{-1} up to 250 °C; held at 250 °C for 20 min.

after stirring for 12 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. Flash chromatography afforded the allylic chlorides (*E*)-**5** and (*Z*)-**5**.

*(E)-1-Chloro-2-octene ((E)-**5**)*: Method B was employed with PPh_3 (73.9 g, 281.7 mmol) and alcohol (*E*)-**4** (25.8 g, 201.2 mmol). Flash chromatography (pentane/Et_2O, 10:1) gave chloroalkene (*E*)-**5** (28.0 g, 95 %) as a colorless liquid. R_f (petroleum ether/EtOAc, 5:1) = 0.87, (detection II); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.85–0.92 (m, 3H; CH_3), 1.28–1.42 (br m, 6H; 3CH_2), 2.06 (dt, J = 7.2, 6.9 Hz, 2H; CH_2), 4.02 (d, J = 7.0 Hz, 2H; CH_2), 5.60–5.64 (m, 1H; CH), 5.75–5.81 ppm (m, 1H; CH); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 14.1, 22.5, 28.6, 31.4, 32.1, 45.6, 125.9, 136.3 ppm.

*(Z)-1-Chloro-2-octene ((Z)-**5**)*: Method B was employed with PPh_3 (31.4 g, 120.0 mmol) and alcohol (*Z*)-**4** (13.3 g, 103.6 mmol). Flash chromatography (petroleum ether) gave chloroalkene (*Z*)-**5** (10.17 g, 77 %) as a colorless liquid. R_f (petroleum ether/EtOAc, 5:1) = 0.84, (detection II); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.90 (t, J = 6.8 Hz, 3H), 1.21–1.42 (m, 6H), 2.12 (dt, J = 7.2, 6.7 Hz, 2H), 4.11 (d, J = 6.6 Hz, 2H), 5.62–5.65 ppm (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 14.0, 22.5, 27.1, 29.0, 31.4, 39.6, 125.2, 135.6 ppm.

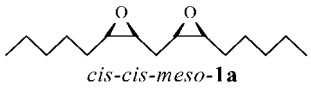
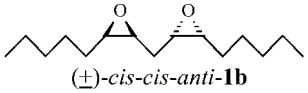
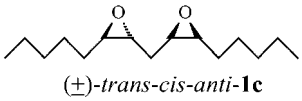
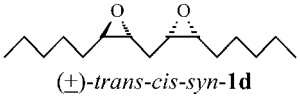
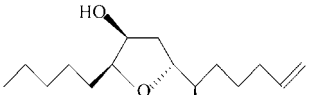
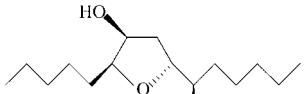
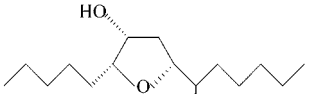
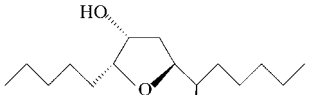
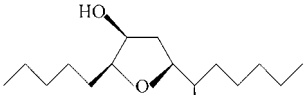
General procedure for the synthesis of enynes (*E*)-6 and (*Z*)-6: Compounds (*Z*)-**6** and (*E*)-**6** were obtained by coupling 1-heptyne onto allylic chlorides (*E*)-**5** and (*Z*)-**5** according to Method C.

Method C: $Bu_4N^+Cl^-$ (1 g, 3.56 mmol), K_2CO_3 (5.17 g, 37.41 mmol), and CuI (0.25 g, 1.29 mmol) were added to a stirred solution of 1-heptyne (2.92 g, 30.32 mmol) in anhydrous DMF (25 mL). After the mixture was stirred for 15 min at room temperature, a solution of allylic chloride (*E*)-**5** or (*Z*)-**5** (3.87 g, 26.38 mmol) in DMF (8 mL) was added dropwise within 15 min. The resulting solution was stirred at room temperature for a further 7 h. After the reaction was complete, the mixture was quenched by addition of water (15 mL) and Et_2O (50 mL). After phase separation, the organic phase was dried and concentrated. Flash chromatography afforded stereoisomerically pure enynes (*Z*)-**6** and (*E*)-**6**.

*(Z)-6-Pentadecen-9-yne ((Z)-**6**)*: Method C was employed with (*Z*)-**5** (3.87 g, 26.38 mmol). Flash chromatography (petroleum ether) gave (*Z*)-**6** (4.25 g, 78 %) as a colorless liquid. R_f (petroleum ether/EtOAc, 10:1) = 0.86, (detection II); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.88–0.93 (m, 6H), 1.25–1.55 (m, 12H), 2.03 (dt, J = 6.6, 7.6 HZ, 2H), 2.13–2.16 (m, 2H), 2.90 (dt, J = 5.1, 2.4 Hz, 2H), 5.40–5.44 ppm (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 14.0, 14.1, 17.2, 18.8, 22.3, 22.5, 27.2, 28.7, 29.1, 31.2, 31.5, 78.5, 80.2, 125.0, 131.4 ppm.

*(E)-6-Pentadecen-9-yne ((E)-**6**)*: Method C was employed with (*E*)-**5** (20.0 g, 136.3 mmol). Flash chromatography (petroleum ether) gave (*E*)-**6** (24.1 g, 86 %) as a colorless liquid. R_f (petroleum ether/EtOAc, 10:1) = 0.85, (detection II); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.88–0.93 (m, 6H; 2CH_3), 1.27–1.56 (br m, 12H; 6CH_2), 2.03 (dt, J = 6.8, 6.6 HZ, 2H; CH_2), 2.17–2.20 (m, 2H; CH_2), 2.89 (br s, 2H; CH_2), 5.38–5.45 (m, 1H; CH), 5.64–5.72 ppm (m, 1H; CH); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 14.0, 14.1,

Table 5. GC data on a chiral stationary phase.

Compound	Column	Conditions[a]	t_R [min]
 *cis-cis-meso*-**1a**	A	A	34.41
 (±)-*cis-cis-anti*-**1b**	A	A	29.48/30.31
 (±)-*trans-cis-anti*-**1c**	A	A	30.95/31.51
 (±)-*trans-cis-syn*-**1d**	A	A	30.18/30.50
 (6*S*,7*S*,9*R*,10*R*)-**2a**	B	A	23.51
 (6*R*,7*R*,9*S*,10*S*)-**2a**	B	A	25.02
 (±)-**2b**	A	B	15.10/15.50
 (±)-**2c**	A	C	17.71/18.34
 (±)-**2d**	A	C	16.47/16.89
(6*S*,7*S*,9*R*,10*R*)-**2a**-bis-trifluoroacetate	B	D	4.26
(6*R*,7*R*,9*S*,10*S*)-**2a**-bis-trifluoroacetate	B	D	4.44
(6*S*,7*S*,9*S*,10*S*)-**2b**-bis-trifluoroacetate	B	D	5.32
(6*R*,7*R*,9*R*,10*R*)-**2b**-bis-trifluoroacetate	B	D	5.40
(+)-**2c**-bis-trifluoroacetate	B	D	5.19
(6*S*,7*S*,9*R*,10*R*)-**2d**-bis-trifluoroacetate	B	D	3.57
(6*R*,7*R*,9*S*,10*S*)-**2d**-bis-trifluoroacetate	B	D	3.73

[a] Conditions: A) 5.0 psi, held at 140 °C for 30 min, heat rate 20 °C min^{-1} up to 170 °C; held at 170 °C for 10 min. B) 6.0 psi, 170 °C (isothermal). C) 7.0 psi, 170 °C (isothermal). D) 10.0 psi, 160 °C (isothermal).

18.9, 22.1, 22.3, 22.6, 28.9, 29.1, 31.2, 31.5, 32.3, 77.7, 82.2, 124.7, 131.9 ppm.

General procedure for the synthesis of *rac,cis*-7, *rac,trans*-7, *cis,cis,meso*-1a, (±)-*cis,cis,anti*-1b, (±)-*trans,cis,anti*-1c and (±)-*trans,cis,syn*-1d: These substrates were prepared by epoxidation of alkenes (*Z*)-**6**, (*E*)-**6**, (9*Z*)-*rac,cis*-**8**, and (9*Z*)-*rac,trans*-**8** with *m*-chloroperbenzoic acid (*m*-CPBA) following Method D. The relative configuration of substrates **1a**–**1d** was determined by a comparison of ^{1}H and ^{13}C NMR spectra with literature data.[27]

Method D: Finely powdered Na_2HPO_4 (≈2.6 equiv) was added to a vigorously stirred solution of alkene (40 mmol) in anhydrous CH_2Cl_2 (400 mL). The mixture was stirred for 15 min at room temperature and was then cooled to 0 °C. *m*-CPBA (1.05 equiv) was added slowly. The mixture was allowed to warm to room temperature and was stirred for an additional 18 h. The white suspension was filtered. The resulting solution was treated with 10% aqueous $Na_2S_2O_5$ (100 mL) to destroy excess peracid. The two-phase system was stirred for 30 min, the layers were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ (50 mL). The organic phase was dried and evaporated. Flash chromatography afforded oxiranes *rac,cis*-**7**, *rac,trans*-**7**, *cis,cis,meso*-**1a**, (±)-*cis,cis,anti*-**1b**, (±)-*trans,cis,anti*-**1c**, and (±)-*trans,cis,syn*-**1d**.

(6R*,7S*)-6,7-Epoxypentadec-9-yne (rac,cis-7): Method D was employed with alkene (*Z*)-**6** (4.0 g, 19.38 mmol). Flash chromatography (pentane/Et_2O, 20:1) gave oxirane *rac,cis*-**7** as a colorless liquid (2.9 g, 73%). R_f (petroleum ether/EtOAc, 5:1) = 0.67, (detection I); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.81–0.92 (m, 6H), 1.27–1.64 (br m, 14H), 2.13–2.18 (m, 2H), 2.27 (m, 1H), 2.59–2.60 (m, 1H), 2.96–2.98 (m, 1H), 3.09–3.12 ppm (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 14.0, 18.8, 18.8, 22.3, 22.6, 26.2, 27.5, 28.7, 31.1, 31.7, 55.5, 57.2, 74.9, 82.0 ppm.

(6R*,7R*)-6,7-Epoxypentadec-9-yne (rac,trans-7): Method D was employed with alkene (*E*)-**6** (0.3 g, 1.45 mmol). Flash chromatography (pentane/Et_2O, 20:1) gave oxirane *rac,trans*-**7** as a colorless liquid (0.25 g, 83%). R_f (petroleum ether/EtOAc, 5:1) = 0.61, (detection I); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.88–0.92 (t, J = 7.0 Hz, 6H; $2CH_3$), 1.32–1.55 (br m, 14H; $7CH_2$), 2.13–2.17 (m, 2H; CH_2), 2.36 (m, 1H; CH), 2.57 (m, 1H; CH), 2.82–2.85 ppm (m, 2H; 2CH); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 14.0, 18.8, 22.4, 22.3, 22.6, 25.7, 28.7, 31.1, 31.6, 31.7, 56.6, 58.5, 74.5, 82.7 ppm.

(6R*,7S*,9R*,10S*)-6,7:9,10-Bis(epoxy)pentadecane (cis,cis,meso-1a) and (6R*,7S*,9S*,10R*)-6,7:9,10-bis(epoxy)pentadecane ((±)-cis,cis,anti-1b): Method D was employed with alkene (9*Z*)-*rac,cis*-**8** (5.72 g, 25.5 mmol). Because the separation of the diastereomers was incomplete, repeated flash chromatography (pentane/Et_2O, 20:1) with GC analysis of the fractions was required to obtain bis-epoxides *cis,cis,meso*-**1a** (1.35 g, 23.7%, elutes first) and (±)-*cis,cis,anti*-**1b** (1.5 g, 26.3%, elutes second) as white crystals.

(6R*,7S*,9R*,10S*)-6,7:9,10-Bis(epoxy)pentadecane (cis,cis,meso-1a): R_f (petroleum ether/EtOAc, 5:1) = 0.28, (detection I); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 0.84–0.92 (m, 6H), 1.26–1.46 (m, 12H), 1.52–1.55 (m, 4H), 1.72–1.75 (m, 1H), 1.79–1.84 (m, 1H), 2.97 (dt, J = 5.5, 6.1 Hz, 2H), 3.06–3.09 ppm (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9, 22.5, 26.1, 26.8, 27.7, 31.6, 54.1, 56.6 ppm; HRMS ($C_{15}H_{26}O$) *m/z* calcd: 222.1984 $[M-H_2O]^+$; found: 222.1963 $[M-H_2O]^+$.

(6R*,7S*,9S*,10R*)-6,7:9,10-Bis(epoxy)pentadecane ((±)-cis,cis,anti-1b): R_f (petroleum ether/EtOAc, 5:1) = 0.23, (detection I); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 0.85–0.91 (m, 6H), 1.27–1.57 (m, 16H), 1.74 (t, J = 6.2 Hz, 2H), 2.99 (dt, J = 5.1, 6.4 Hz, 2H), 3.13 ppm (t, J = 4.3, 6.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0, 22.5, 26.1, 27.1, 27.8, 31.6, 54.3, 57.0 ppm; HRMS ($C_{15}H_{26}O$) *m/z* calcd: 222.1984 $[M-H_2O]^+$; found: 222.1959 $[M-H_2O]^+$.

(6R*,7R*,9R*,10S*)-6,7:9,10-Bis(epoxy)pentadecane ((±)-trans,cis,anti-1c) and (6R*,7R*,9S*,10R*)-6,7:9,10-bis(epoxy)pentadecane ((±)-trans,cis,syn-1d): Method D was employed with alkene (9*Z*)-*rac,trans*-**8** (0.2 g, 9.05 mmol). Because the separation of the diastereomers was incomplete, repeated flash chromatography (pentane/Et_2O, 20:1) with GC analysis of the fractions was required to obtain bis-epoxides (±)-*trans,cis,anti*-**1c** (0.06 g, 30%, elutes first) and (±)-*trans,cis,syn*-**1d** (0.07 g, 35%, elutes second) as colorless liquids.

(6R*,7R*,9R*,10S*)-6,7:9,10-Bis(epoxy)pentadecane ((±)-trans,cis,anti-1c): R_f (petroleum ether/EtOAc, 5:1) = 0.45, (detection I); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87–0.90 (m, 6H; $2CH_3$), 1.31–1.57 (br m, 16H; $8CH_2$), 1.82 (t, J = 5.5 Hz, 2H; CH_2), 2.80–2.85 (m, 2H; 2CH), 2.93 (dt, J = 4.4, 6.0, 1H; CH), 2.99–3.02 ppm (m, 1H; CH); ^{13}C NMR (500 MHz, $CDCl_3$): δ = 13.9, 22.5, 25.6, 26.1, 27.8, 31.5, 31.6, 31.8, 30.3, 53.2, 55.7, 56.4, 58.1 ppm.

(6R*,7R*,9S*,10R*)-6,7:9,10-Bis(epoxy)pentadecane ((±)-trans,cis,syn-1d): R_f (petroleum ether/EtOAc, 5:1) = 0.45, (detection I); ^{1}H NMR

(500 MHz, $CDCl_3$) $\delta = 0.88$–0.91 (m, 6H; $2CH_3$), 1.26–1.62 (br m, 16H; $8CH_2$), 1.71–1.76 (m, 2H; CH_2), 2.74 (dt, $J = 2.2$, 5.6 Hz, 1H; CH), 2.84–2.86 (m, 1H; CH), 2.96–2.97 (m, 1H; CH), 3.08–3.10 ppm (m, 1H; CH); ^{13}C NMR (500 MHz, $CDCl_3$) $\delta = 13.9$, 22.5, 25.5, 26.0, 27.7, 31.5, 31.5, 31.8, 31.2, 53.9, 55.9, 56.8, 58.7 ppm.

General procedure for the synthesis of reference material for (±)-2a, (±)-2b, (±)-2c, and (±)-2d: Substrates (±)-**2a–d** were prepared by acid-catalyzed hydrolysis followed by rearrangement of mixtures of the corresponding diastereomeric bis-epoxides *cis,cis,meso*-**1a**/(±)-*cis,cis,anti*-**1b**, and (±)-*trans,cis,anti*-**1c**/(±)-*trans,cis,syn*-**1d** following a previously reported procedure[27] (Method E, see Schemes 2 and 3).

Method E: A mixture of bis-epoxides (0.2 g, 0.83 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 an argon atmosphere. The reaction was complete after 24 h. The solution was extracted with EtOAc (2×20 mL). The combined organic layers were dried and evaporated to afford (±)-**2a** and (±)-**2b**, or (±)-**2c** and (±)-**2d**, respectively, which were separated by flash chromatography (petroleum ether/ethyl acetate 10:1). Details and spectroscopic data are given below.

(6R,7R*,9S*,10S*)-6,9-Epoxypentadecane-7,10-diol ((±)-**2a**) and (6R*,7R*,9R*,10R*)-6,9-epoxypentadecane-7,10-diol ((±)-**2b**)*: Method E was employed with a mixture of bis-epoxides *cis,cis,meso*-**1a** and (±)-*cis,cis,anti*-**1b** (0.2 g, 0.83 mmol). Flash chromatography (petroleum ether/EtOAc, 10:1) afforded (±)-**2a** (0.07 g, 31%) and (±)-**2b** (0.13 g, 59%).

(6R,7R*,9S*,10S*)-6,9-Epoxypentadecane-7,10-diol ((±)-**2a**)*: R_f (petroleum ether/EtOAc, 1:1) = 0.46, (detection I); ^1H NMR (500.13 MHz, $CDCl_3$): $\delta = 0.85$–0.90 (m, 6H), 1.29–1.65 (m, 16H), 1.85–1.90 (m, 1H), 2.00–2.04 (m, 1H), 3.36–3.40 (m, 1H), 3.73–3.77 (m, 1H), 4.00–4.04 (m, 1H), 4.25 ppm (t, $J = 3.4$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 13.9$, 14.0, 22.5, 22.5, 25.2, 25.9, 28.7, 31.0, 31.8, 33.0, 37.8, 73.4, 74.0, 80.1, 82.4 ppm; HRMS ($C_{15}H_{30}O_3$) *m/z* calcd: 258.2195 $[M]^+$; found: 258.2227 $[M]^+$.

(6R,7R*,9R*,10R*)-6,9-Epoxypentadecane-7,10-diol ((±)-**2b**)*: R_f (petroleum ether/EtOAc, 1:1) = 0.54, (detection I); ^1H NMR (500.13 MHz, $CDCl_3$): $\delta = 0.88$–0.90 (t, $J = 6.3$ Hz, 6H), 1.31–1.66 (m, 16H), 1.84 (dd, $J = 14.1$, 3.5 Hz, 1H), 2.36–2.41 (m, 1H), 3.46–3.48 (m, 1H), 3.63–3.68 (m, 1H), 3.94–3.97 (m, 1H), 4.04 ppm (dd, $J = 5.4$ Hz, 1H; 2.7); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 14.0$, 22.5, 25.6, 25.8, 28.7, 31.6, 32.0, 34.3, 38.7, 71.5, 73.9, 79.0, 84.3 ppm; HRMS ($C_{15}H_{30}O_3$) *m/z* calcd: 258.2195 $[M]^+$; found: 258.2198 $[M]^+$.

(6R,7R*,9R*,10S*)-6,9-Epoxypentadecane-7,10-diol ((±)-**2c**) and (6R*,7R*,9S*,10R*)-6,9-epoxypentadecane-7,10-diol ((±)-**2d**)*: Method E was employed with a mixture of bis-epoxides (±)-*trans,cis,anti*-**1c** and (±)-*trans,cis,syn*-**1d** (0.2 g, 0.83 mmol). Flash chromatography (petroleum ether/EtOAc, 10:1) afforded (±)-**2c** (0.08 g, 35%) and (±)-**2d** (0.10 g, 45%).

(6R,7R*,9R*,10S*)-6,9-Epoxypentadecane-7,10-diol ((±)-**2c**)*: R_f (petroleum ether/EtOAc, 1:1) = 0.54 (detection I); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.87$–0.89 (t, $J = 6.7$ Hz, 6H; $2CH_3$), 1.28–1.68 (br m, 16H; $8CH_2$), 1.90 (dd, $J = 14.1$, 3.3 Hz, 1H; CH), 2.14–2.19 (m, 1H; CH), 3.56–3.60 (m, 1H; CH), 3.80–3.83 (m, 1H; CH), 3.98–4.01 (m, 1H; CH); ^{13}C NMR (500 MHz, $CDCl_3$): $\delta = 13.9$, 13.9, 22.4, 22.5, 25.5, 25.9, 28.7, 31.6, 32.0, 33.3, 34.2, 71.0, 71.9, 79.9, 83.8 ppm; HRMS ($C_{15}H_{30}O_3$) *m/z* calcd: 258.2195 $[M]^+$; found: 258.2209 $[M]^+$.

(6R,7R*,9S*,10R*)-6,9-Epoxypentadecane-7,10-diol ((±)-**2d**)*: R_f (petroleum ether/EtOAc, 1:1) = 0.34 (detection I); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.86$–0.89 (t, $J = 5.3$ Hz, 6H; $2CH_3$), 1.29–1.59 (br m, 16H; $8CH_2$), 1.84 (dd, $J = 13.2$, 6.1 Hz, 1H; CH), 2.08–2.13 (m, 1H; CH), 3.82–3.86 (m, 2H; 2CH), 4.13–4.17 (m, 1H; CH), 4.27 ppm (br s, 1H; CH); ^{13}C NMR (500 MHz, $CDCl_3$): $\delta = 13.9$, 22.5, 22.5, 25.5, 25.9, 29.1, 31.8, 32.1, 32.4, 34.1, 72.0, 73.1, 79.9, 83.5 ppm; HRMS ($C_{15}H_{30}O_3$) *m/z* calcd: 258.2195 $[M]^+$; found: 258.2205 $[M]^+$.

(2*R*,3*R*,5*S*)-2-Pentyl-5-vinyl-tetrahydrofuran-3-ol ((2*R*,3*R*,5*S*)-10a) and (2*S*,3*S*,5*S*)-2-pentyl-5-vinyl-tetrahydrofuran-3-ol ((2*S*,3*S*,5*S*)-10b): PPh_3 (2.13 g, 8.12 mmol) and CBr_4 (2.41 g, 7.26 mmol) were dissolved in anhydrous CH_2Cl_2 (30 mL). The stirred solution was cooled to 0 °C, and (*S*)-**9** (650 mg, 3.86 mmol) was added dropwise. After stirring for 5 h, the solution was concentrated, and pentane (30 mL) was added. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue (381 mg) was epoxidized according to Method D. The residue (122 mg) of the diastereomeric mixture of the epoxy bromide was hydrolyzed–rearranged in a mixture of water (6 mL) and THF (4 mL) under acidic conditions (conc. H_2SO_4, 10 drops) at room temperature overnight. The solution was extracted with EtOAc (2×10 mL). The combined organic layers were dried and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to afford the diastereomeric mixture of the cyclization products (2*R*,3*R*,5*S*)-**10a** and (2*S*,3*S*,5*S*)-**10b** (85 mg). R_{f1}, R_{f2} (petroleum ether/EtOAc, 1:1) = 0.66, 0.61 (detection I).

First diastereomer: ^1H NMR (360 MHz,$CDCl_3$): $\delta = 0.89$–0.91 (t, $J = 6.7$ Hz, 3H; CH_3), 1.25–1.34 (m, 4H; CH_2), 1.41–1.47 (m, 2H; CH_2), 1.64–1.68 (m, 2H; CH_2), 1.74–1.80 (m, 1H; CH_2), 2.39–2.45 (m, 1H; CH_2), 3.62–3.67 (m, 1H; CH), 4.18 (m, 1H; CH), 4.30–4.36 (m, 1H; CH), 5.10–5.13 (dd, $J = 10.4$, 1.5 Hz, 1H; CH_2), 5.28–5.33 (dd, $J = 17.2$, 1.7 Hz, 1H; CH_2), 5.92–6.02 ppm (ddd, $J = 17.2$, 10.7, 6.5 Hz, 1H; CH); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 14.0$, 22.5, 25.9, 28.8, 32.0, 41.7, 73.1, 77.9, 83.6, 115.1, 140.1 ppm.

Second diastereomer: ^1H NMR (360 MHz,$CDCl_3$): $\delta = 0.89$–0.90 (t, $J = 6.4$ Hz, 3H; CH_3), 1.32–1.33 (m, 4H; CH_2), 1.54–1.66 (m, 4H; CH_2), 1.88–1.91 (m, 1H; CH_2), 2.14–2.20 (m, 1H; CH_2), 3.82–3.85 (m, 1H; CH), 4.26 (m, 1H; CH), 4.60–4.66 (m, 1H; CH), 5.08–5.11 (dd, $J = 9.3$, 1.0 Hz, 1H; CH_2), 5.22–5.27 (dd, $J = 16.0$, 1.1 Hz, 1H; CH_2), 5.79–5.89 ppm (ddd, $J = 15.2$, 8.7, 3.7 Hz, 1H; CH); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 14.0$, 22.5, 26.0, 29.0, 31.8, 41.9, 73.3, 77.6, 82.4, 114.9, 139.1 ppm.

(6*R*,7*R*,9*S*,10*S*)-6,9-Epoxypentadecane-7,10-diol ((6*R*,7*R*,9*S*,10*S*)-2a), (6*S*,7*S*,9*S*,10*S*)-6,9-epoxypentadecane-7,10-diol ((6*S*,7*S*,9*S*,10*S*)-2b), (6*S*,7*S*,9*S*,10*R*)-6,9-epoxypentadecane-7,10-diol ((6*S*,7*S*,9*S*,10*R*)-2c), and (6*R*,7*R*,9*S*,10*R*)-6,9-epoxypenta-decane-7,10-diol ((6*R*,7*R*,9*S*,10*R*)-2d): A solution of the diasteromeric mixture of (2*R*,3*R*,5*S*)-**10a** and (2*S*,3*S*,5*S*)-**10b** (85 mg, 0.46 mmol), TBDMSCl (90.3 mg, 0.60 mmol), and imidazole (40.4 mg, 0.60 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature overnight and then poured into a mixture of saturated $NaHCO_3$ and CH_2Cl_2. The resulting 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. *N*-Methylmorpholine-*N*-oxide (124.0 mg, 1.1 mmol) and one crystal of OsO_4 were added to a solution of the crude residue (158 mg) in acetone (10 mL). This mixture was stirred for 1.5 h at room temperature. Sodium sulfite (196 mg, 3.14 mmol) was added and stirring was continued for 30 min. The solution was extracted with EtOAc (2×10 mL). The combined organic phases were washed with water and concentrated under reduced pressure. Acetone (10 mL) followed by $NaIO_4$ (198.8 mg, 0.93 mmol) were added to a suspension of the residue (182 mg) in water (4 mL). The mixture was stirred for 30 min at room temperature. The solution was extracted with EtOAc (2×10 mL), and the combined organic layers were dried and evaporated. The residue (141 mg) was dissolved in Et_2O (10 mL). Pentylmagnesium bromide (0.5 mL of a 2 M solution in THF, 1 mmol) was added to the vigorously stirred solution and stirring was continued for 5 h at room temperature. The reaction was quenched by addition of H_2O (5 mL) and Et_2O (10 mL). The phases were separated, and the aqueous layer was extracted with Et_2O (2×10 mL). The combined organic phases were dried and evaporated. The residue (130 mg) was dissolved in THF (10 mL), and $Bu_4N^+F^-$ (161 mg, 0.51 mmol) was added. The reaction was stirred overnight at room temperature. The mixture was quenched by addition of water (5 mL) and Et_2O (10 mL). The phases were separated, and the aqueous layer was extracted with Et_2O (2×10 mL). The combined organic phases were dried and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to afford a diasteromeric mixture of the cyclization products (6*R*,7*R*,9*S*,10*S*)-**2a**, (6*S*,7*S*,9*S*,10*S*)-**2b**, (6*S*,7*S*,9*S*,10*R*)-**2c**, and (6*R*,7*R*,9*S*,10*R*)-**2d** (17 mg). R_f (petroleum ether/EtOAc, 1:1; detection I) = 0.46 (**2a**), 0.51 (**2b**), 0.54 (**2c**), 0.34 (**2d**).

(6R,7R,9S,10S)-2a: ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.85$–0.90 (m, 6H; $2CH_3$), 1.29–1.65 (br m, 16H; $8CH_2$), 1.85–1.90 (m, 1H; CH), 2.00–2.04 (m, 1H; CH), 3.36–3.40 (m, 1H; CH), 3.73–3.77 (m, 1H; CH), 4.0–4.04 (m, 1H; CH), 4.25 ppm (t, $J = 3.4$ Hz, 1H; CH); ^{13}C NMR (500 MHz, $CDCl_3$): $\delta = 13.93$, 13.96, 22.47, 22.52, 25.19, 25.89, 28.73, 31.81, 31.89, 33.02, 37.81, 73.35, 74.0, 80.11, 82.36 ppm.

(6S,7S,9S,10S)-2b: ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.88$–0.90 (t, $J = 6.3$ Hz, 6H; $2CH_3$), 1.31–1.66 (br m, 16H; $8CH_2$), 1.84 (dd, $J = 14.1$,

3.5 Hz, 1H; CH), 2.36–2.41 (m, 1H; CH), 3.46–3.48 (m, 1H; CH), 3.63 (m, 1H; CH), 3.94–3.97 (m, 1H; CH), 4.04 ppm (dd, J = 5.4, 2.7 Hz, 1H; CH); ^{13}C NMR (500 MHz, $CDCl_3$): δ = 13.94, 22.51, 25.59, 25.82, 28.67, 31.64, 31.95, 43.29, 38.68, 71.46, 73.88, 78.96, 84.26 ppm.

*(6S,7S,9S,10R)-**2c***: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87–0.89 (t, J = 6.7 Hz, 6H; $2CH_3$), 1.28–1.68 (br m, 16H; $8CH_2$), 1.90 (dd, J = 14.1, 3.3 Hz, 1H; CH), 2.14–2.19 (m, 1H; CH), 3.56–3.60 (m, 1H; CH), 3.80–3.83 (m, 1H; CH), 3.98–4.01 ppm (m, 1H; CH); ^{13}C NMR (500 MHz, $CDCl_3$): δ = 13.90, 13.93, 22.43, 22.52, 25.48, 25.89, 28.69, 31.63, 31.96, 33.29, 34.17, 70.98, 71.86, 79.89, 83.75 ppm.

*(6R,7R,9S,10R)-**2d***: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86–0.89 (t, 6H; J = 5.3, $2CH_3$), 1.29.1.59 (br m, 16H; $8CH_2$), 1.84 (dd, J = 13.2, 6.1 Hz, 1H; CH), 2.08–2.13 (m, 1H; CH), 3.82–3.86 (m, 2H; 2CH), 4.13–4.17 (m, 1H; CH), 4.27 ppm (br s, 1H; CH); ^{13}C NMR (500 MHz, $CDCl_3$): δ = 13.93, 22.47, 22.50, 25.51, 25.90, 29.10, 31.83, 32.13, 32.35, 34.10, 71.98, 73.08, 79.94, 83.49 ppm.

(2*R*,3*R*,5*R*)-2-Pentyl-5-vinyl-tetrahydrofuran-3-ol ((2*R*,3*R*,5*R*)-10b) and (2*S*,3*S*,5*R*)-2-pentyl-5-vinyl-tetrahydrofuran-3-ol ((2*S*,3*S*,5*R*)-10a): PPh_3 (3.0 g, 11.44 mmol) and CBr_4 (3.41 g, 10.28 mmol) were dissolved in anhydrous CH_2Cl_2 (30 mL). The stirred solution was cooled to 0 °C and (*R*)-**9** (919 mg, 5.46 mmol) was added dropwise. After stirring for 5 h, the solution was concentrated, and pentane (30 mL) was added. The mixture was filtered, and the filtrate was concentrated in vacuo. The crude residue (370 mg) was epoxidized according to Method D. The residue (128 mg) of the diastereomeric mixture of the epoxy-bromide was hydrolyzed in a mixture of water (6 mL) and THF (4 mL) under acidic conditions (conc. H_2SO_4, 10 drops) at room temperature overnight. The solution was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to afford the diasteromeric mixture of the cyclization products (2*S*,3*S*,5*R*)-**10a** and (2*R*,3*R*,5*R*)-**10b** (57 mg). R_{f1}, R_{f2} (petroleum ether/EtOAc, 1:1) = 0.66, 0.61 (detection I). Spectroscopic data were in accordance to those previously reported.

(6*S*,7*S*,9*R*,10*R*)-6,9-Epoxypentadecane-7,10-diol ((6*S*,7*S*,9*R*,10*R*)-2a), (6*R*,7*R*,9*R*,10*R*)-6,9-epoxypentadecane-7,10-diol ((6*R*,7*R*,9*R*,10*R*)-2b), (6*R*,7*R*,9*R*,10*S*)-6,9-epoxypenta-decane-7,10-diol ((6*R*,7*R*,9*R*,10*S*)-2c), and (6*S*,7*S*,9*R*,10*S*)-6,9-epoxypentadecane-7,10-diol ((6*S*,7*S*,9*R*,10*S*)-2d): A solution of the diasteromeric mixture of (2*R*,3*R*,5*R*)-**10b** and (2*S*,3*S*,5*R*)-**10a** (57 mg, 0.31 mmol), TBDMSCl (60.3 mg, 0.40 mmol), and imidazole (27.2 mg, 0.40 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature overnight and then poured into a mixture of saturated $NaHCO_3$ 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. *N*-Methylmorpholine-*N*-oxide (70.6 mg, 0.60 mmol) and one crystal of OsO_4 were added to a solution of the crude residue (91 mg) in acetone (10 mL). The mixture was stirred for 1.5 h at room temperature. Sodium sulfite (230 mg, 1.83 mmol) was added and stirring was continued for 30 min. The solution was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with water and concentrated under reduced pressure. The residue (90 mg) was suspended in water (4 mL) to which was added acetone (10 mL) followed by $NaIO_4$ (98.2 mg, 0.46 mmol). The mixture was stirred for 30 min at room temperature. Then the solution was extracted with EtOAc (2 × 10 mL), and the combined organic layers were dried and evaporated. The residue (70 mg) was dissolved in Et_2O (10 mL). Pentylmagnesium bromide (0.5 mL of a 2 M solution in THF, 1 mmol) was added to the vigorously stirred solution and stirring was continued for 5 h at room temperature. The reaction was quenched by addition of H_2O (5 mL) and Et_2O (10 mL). The phases were separated, and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic phases were dried and evaporated. The residue (122 mg) was dissolved in THF (10 mL), and $Bu_4N^+F^-$ (107 mg, 0.34 mmol) was added. The reaction was stirred overnight at room temperature. The mixture was quenched by addition of water (5 mL) and Et_2O (10 mL). The phases were separated, and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic phases were dried and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to afford the diasteromeric mixture of the cyclization products (6*S*,7*S*,9*R*,10*R*)-**2a**, (6*R*,7*R*,9*R*,10*R*)-**2b**, (6*R*,7*R*,9*R*,10*S*)-**2c** and (6*S*,7*S*,9*R*,10*S*)-**2d** (10 mg). R_f (petroleum ether/EtOAc, 1:1; detection I) = 0.46 (**2a**), 0.51 (**2b**), 0.54 (**2c**), 0.34 (**2d**). Spectroscopic data were in accordance to those described above.

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