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Catalytic Asymmetric Claisen Rearrangement of Gosteli-Type Allyl Vinyl Ethers: Total Synthesis of (−)-9,10-Dihydroecklonialactone B

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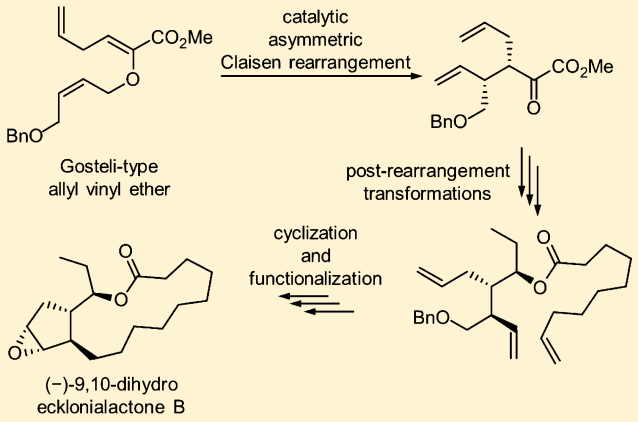
Supporting Information

ABSTRACT: The enantioselective synthesis of (−)-9,10-dihydroecklonialactone B is described. The catalytic asymmetric Claisen rearrangement of a Gosteli-type allyl vinyl ether was utilized to afford an acyclic α-keto ester building block endowed with functionality amenable to the preparation of the carbocyclic target molecule by suitable postrearrangement transformations: A highly diastereoselective Corey−Bakshi−Shibata reduction of a β-chiral α-keto ester and a reductive homologation of an α-hydroxy ester. A transprotection tactic by a chemoselective intramolecular 6-*exo*-trig iodoetherification enabled regioselective ring-closing alkene metatheses to afford the 5- as well as the 14-membered ring, however, with mixed success in terms of *E*/*Z* selectivity.



INTRODUCTION

The [3,3]-sigmatropic rearrangement of allyl vinyl ethers is generally known as the Claisen rearrangement.[1,2] The catalysis of the Claisen rearrangement requires matching combinations of electrophilic catalysts and specifically substituted allyl vinyl ethers.[3,4] Sufficient σ- or π-electrophilicity of the catalyst has to be carefully balanced against transition-state-structure chair/boat dichotomy, substrate decomposition by C/O bond heterolysis, and product inhibition of the catalyst. Hence, the known catalysts suffer from a rather narrow substrate specificity.[4] Furthermore, only a very limited number of chiral catalyst/allyl vinyl ether combinations that enable truly catalytic asymmetric Claisen rearrangements (CAC) are known, and the application of the CAC in target-oriented synthesis is still in a stage of infancy.[4]

During the past decade, it has been demonstrated that the Claisen rearrangement of Gosteli-type allyl vinyl ethers, the Gosteli−Claisen rearrangement,[5] can be catalyzed by chiral copper(II) bis(oxazoline) Lewis acids or guanidinium dual hydrogen-bond-donating organocatalysts.[6−8] The Cu(box)-catalyzed catalytic asymmetric Gosteli−Claisen rearrangement (CAGC) delivers branched and functionalized δ,ε-unsaturated α-keto esters in a synthetically useful selectivity.[9,10] Intending to demonstrate the utility of acyclic α-keto esters in the synthesis of carbocyclic target molecules as well, we considered the total synthesis of carbocyclic oxylipins as a rewarding challenge.[11]

The oxylipins ecklonialactone A (**1**) and B (**2**) have been isolated from the brown algae *Ecklonia stolonifera* by Kurata et al. (Figure 1).[12] The relative configuration of (−)-**1** was secured by crystallography, whereas the absolute configuration was deduced from the chiroptical properties of the levorotatory natural product.[13] The structure of (−)-**2** was initially deduced from the similarities of the spectroscopic properties of (−)-**1** and (−)-**2**.[12] Semisynthesis of the saturated 9,10-dihydro ecklonialactone B (+)-**3** from either (−)-**1** or (−)-**2** by hydrogenation corroborated the assignment.[12]

The first total synthesis of (−)-**1** or (−)-**2** was reported by Fürstner in 2010 and features a ring-closing alkyne metathesis and a subsequent hydrogenation for the construction of the Z-configured 9,10-double bond.[14] Following an initial report on the synthesis of a cyclopentanoid building block in 2007,[15] we achieved the first total synthesis of (+)-**3** via (−)-**2** in 2013.[16] Our route embarked from the enantiomerically pure building block (+)-**6** which is accessible from the Gosteli-type allyl vinyl ether (*E*,*Z*)-**5** by [Cu{(*S*,*S*)-*t*-Bu-box}(tfe)$_2$](SbF$_6$)$_2$[17] ((*S*,*S*)-**4**) catalyzed Claisen rearrangement (Figure 2). A ring-closing alkene metathesis was used for the formation of the cyclopentanoid segment; the 14-membered lactone was synthesized from the corresponding hydroxy acid.

Our laboratory was intrigued by the possibility of using (*Z*,*Z*)-**5**, on hand from the synthetic campaign that made available (*E*,*Z*)-**5**, to access *syn*-**6** and to explore opportunities to harvest the pseudodiastereotopic relationship between the vinyl and the benzyloxymethyl group (Figure 2). If successful, the diastereomeric rearrangement product *syn*-**6** could be

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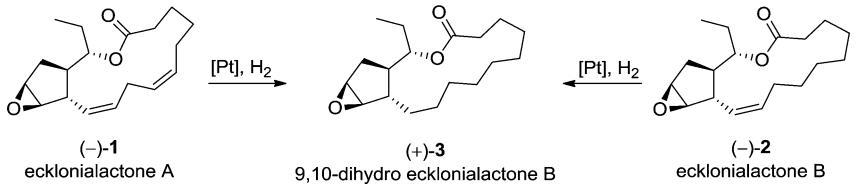

Figure 1. Ecklonialactones from the brown algae *Ecklonia stolonifera* and the semisynthetic saturated derivative 9,10-dihydroecklonialactone B.

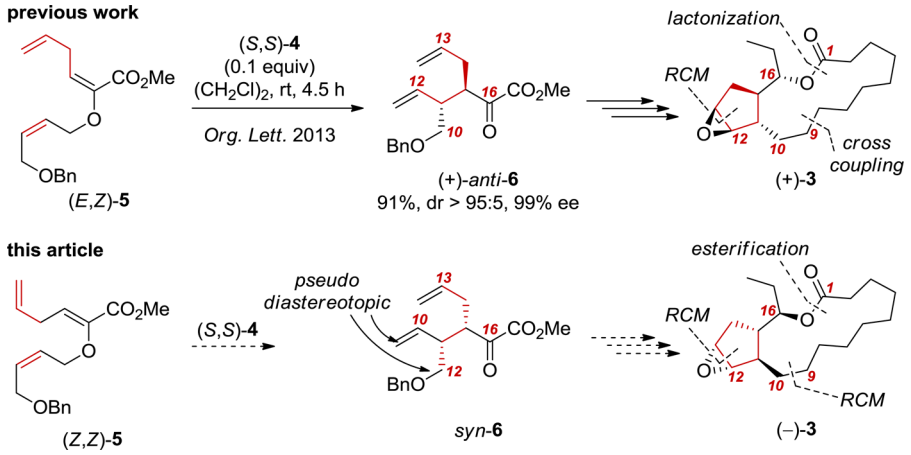

Figure 2. Assembling enantiomeric target molecules from diastereomeric building blocks.

converted to the enantiomeric target molecule (−)-3; in this paper, we describe in detail the results from this endeavor.

RESULTS AND DISCUSSION

In retrospective, our synthetic planning toward (−)-9,10-dihydroecklonialactone B ((−)-3) was guided by the possibility of a differentiation of the double bonds of 12,13-desepoxy-ecklonialactone B (7) by a regio- and diastereoselective epoxidation of the 12,13-double bond (Figure 3).[16] Further-

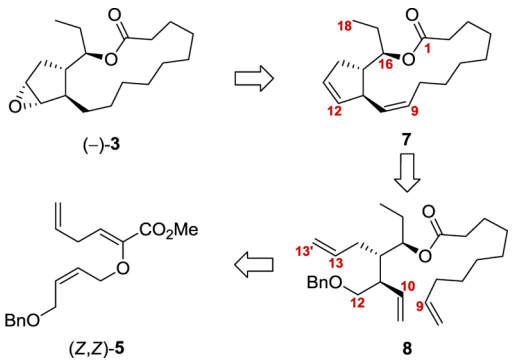

Figure 3. Synthesis of (−)-3 in retrospective.

more, we intended to make use of 9-decenoic acid, which is commercially available, for the assemblage of the C1−C9 segment of 7. The approach toward 7 then required three distinct stages. First, a robust scalable synthesis of the functionalized Gosteli-type allyl vinyl ether 5, containing a skipped dienoate, was in demand. Second, 5 needed to be converted into the elaborated chiral building block 8. Third, following the protection of the 13,13′-double bond in 8 against an untimely participation on a metathesis event, successive ring-closing olefin metatheses (RCM) were envisioned for formation of desepoxyecklonialactone (7).

Synthesis of the Gosteli-Type Allyl Vinyl Ether 5. The synthesis of the Gosteli-type allyl vinyl ether (*Z*,*Z*)-**5** commenced from commercial (*Z*)-butene-1,4-diol as outlined in Scheme 1. Two successive Williamson etherifications and a subsequent Fischer esterification delivered the ester **10**. Aldol reaction between the lithium enolate of **10** and (4-phenylselenyl)butanal **11**,[15] a synthetic equivalent for 3-butenal[18] for which, in our hands, double-bond isomerization was unavoidable, delivered the *β*-hydroxy ester **12** in a roughly 2:1 ratio of diastereomers. No attempts were made to assign the relative configuration of the diastereomeric *β*-hydroxy esters **12**. Synthesis of the aldehyde **11** was accomplished by reductive ring-opening of tetrahydrofuran[19] followed by Parikh−Doering oxidation.[20]

Mesylation of **12** followed by treatment of the crude mesylate with DBU at ambient temperature delivered the Gosteli-type allyl vinyl ether **13** as a mixture of vinyl ether double-bond isomers (*Z*/*E* = 3:2). Separation of the double-bond isomers was achieved by preparative HPLC. Oxidation of the separated selenides (*E*,*Z*)- and (*Z*,*Z*)-**13** triggered elimination[21] to afford the Gosteli-type allyl vinyl ethers (*E*,*Z*)- and (*Z*,*Z*)-**5**.

The uncatalyzed Gosteli−Claisen rearrangement of (*E*,*Z*)-**5** was briefly studied on preparative scale delivering the racemic *α*-keto ester *anti*-**6** in good yield and diastereoselectivity. The Claisen rearrangement was performed at 80 °C in 1,2-dichloroethane for several days to ensure complete conversion of the starting material. The relative configuration of *anti*-**6** was initially assigned assuming a chairlike transition-state structure. NOE analysis of a synthetic derivative provided evidence for the feasibility of the assignment.[15]

Our laboratory is interested in rate effects on pericyclic reactions in general and the Claisen rearrangement in particular.[22] Having gained access to the Gosteli-type allyl vinyl ethers **5** and **13**, we elected to pursue a kinetic study. Thus, temperature-dependent kinetics of the uncatalyzed

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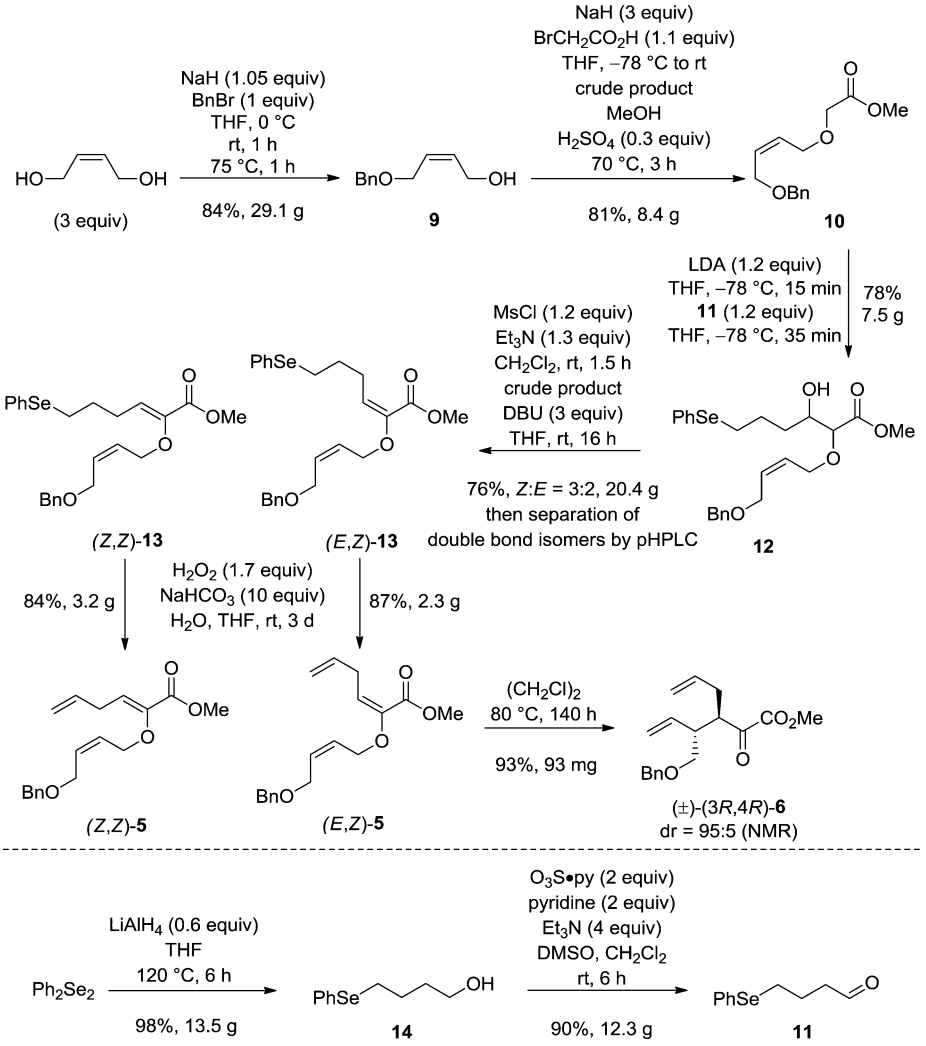
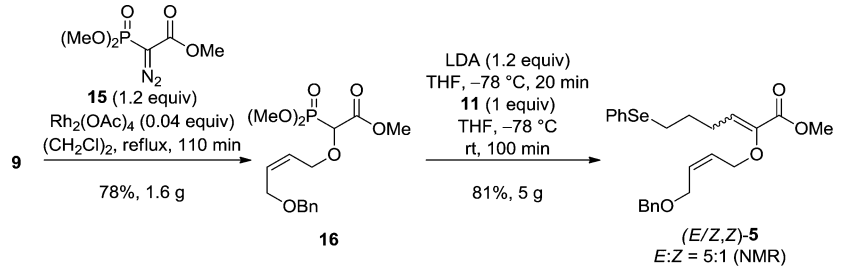
Scheme 1. Synthesis of the Gosteli-Type Allyl Vinyl Ether 5 by Aldol Condensation



Scheme 2. Synthesis of the Gosteli-Type Allyl Vinyl Ether 5 by Horner–Wadsworth–Emmons Olefination



Gosteli–Claisen rearrangement of (*Z*,*Z*)-**5** and (Z,Z)-**13** were measured, and Eyring analyses of the obtained data provided activation parameters for the rearrangement of the two allyl vinyl ethers. From the Eyring plot, we determined for (*Z*,*Z*)-**5** in 1,2-dichloroethane at 80 °C a $\Delta G^{\ddagger}$ = 28.7 kcal/mol. This value compares well with free energies of activation previously determined by our laboratory for structurally related Gosteli-type allyl vinyl ethers.[22] The Gosteli-type allyl vinyl ethers **13** ($PhSeCH_2CH_2CH_2$) and **5** ($H_2C{=}CHCH_2$) are distinguished by the nature of the substituent at the terminal carbon atom of the vinyl ether double bond. The question surfaced whether the two substituents would exert a significant substituent-rate effect on the uncatalyzed rearrangement. Judging from the comparable steric and electronic bias of the two substituents, we expected, if any, a rather small substituent rate effect. Indeed, (*Z*,*Z*)-**13** in 1,2-dichloroethane at 80 °C was found to be only slightly less reactive ($\Delta G^{\ddagger}$ = 29.2 kcal/mol) than (*Z*,*Z*)-**5** ($\Delta G^{\ddagger}$ = 28.7 kcal/mol). From the Eyring plot we found that in comparison to 1,2-dichloroethane, the solvent 2,2,2-trifluoroethanol (*Z*,*Z*)-**5** at 80 °C has a small barrier-lowering bias ($\Delta G^{\ddagger}$ = 28.2 kcal/mol) which is also measurable for (*Z*,*Z*)-**13** in trifluoroethanol at 80 °C ($\Delta G^{\ddagger}$ = 28.4 kcal/mol). Notably, our Eyring analyses indicate a negative $\Delta S^{\ddagger}$ in all cases (between −21 and −30 cal/K mol) as would be expected for a concerted rearrangement.[23]

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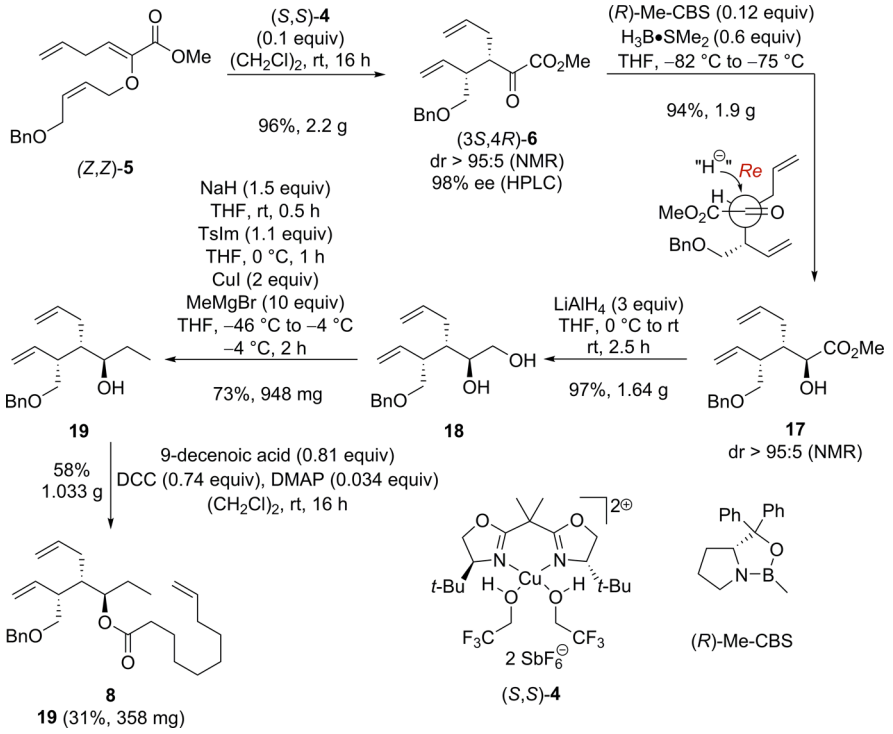
Scheme 3. Successive Catalytic Asymmetric Transformations Are Key to the Synthesis of the Triene 8



Turning back to synthesis, we investigated an alternative to the aldol condensation route to the allyl vinyl ether **5** with the aim of improving our control over the vinyl ether double-bond configuration. From previous experience, we expected that an *E*-selective olefination route using a functionalized trimethyl phosphonoacetate would be a viable alternative (Scheme 2).[9] To access the required phosphonate **16**, the diazo phosphonate **15**[24] and the allylic alcohol **9** were subjected to a Rh(II)-catalyzed O–H insertion.[25] As anticipated, subsequent Horner–Wadsworth–Emmons olefination between the resulting phosphonate **16** and the aldehyde **11** delivered **5** with an *E*/*Z* = 5:1 selectivity.[26,27] However, despite being more *E*-selective, the olefination route is less attractive for our laboratory because of the cost of the catalyst for the O–H-insertion reaction and, in our hands, its limited scalability.

Catalytic Asymmetric Synthesis of the Triene 8. With a robust and scalable synthesis of the Gosteli-type allyl vinyl ether (*Z*,*Z*)-**5** developed, we turned our attention to the stereoselective synthesis of the triene **8** (Scheme 3). (*S*,*S*)-**4** catalyzed Claisen rearrangement of (*Z*,*Z*)-**5** afforded the α-keto ester **6** in high yield and synthetically useful diastereo- and enantioselectivity.[28] Catalysis performed on a preparative scale in 1,2-dichloroethane at room temperature required a liberal loading of (*S*,*S*)-**4** (0.1 equiv) to ensure complete conversion. The copper(II) bis(oxazoline) precatalyst (*S*,*S*)-**4** was found to be particularly effective for the CAGC enabling an even faster turnover than the related bis(aqua) complex [Cu{(*S*,*S*)-*t*-Bu-box}$(H_2O)_2$]$(SbF_6)_2$[29] originally reported by Evans. The bis(trifluoroethanol) complex (*S*,*S*)-**4** can be synthesized as a stock solution from the commercial *t*-Bu-BOX ligand and shows a characteristic UV–vis spectrum.[17] The proposed catalytic cycle is depicted in Figure 4 for the generic Gosteli-type allyl vinyl ether (*Z*,*Z*)-**20**.[4] Substrates containing a (*Z*)-configured allylic ether double bond are required to alleviate the propensity for a chair/boat dichotomy. The σ-electrophilic

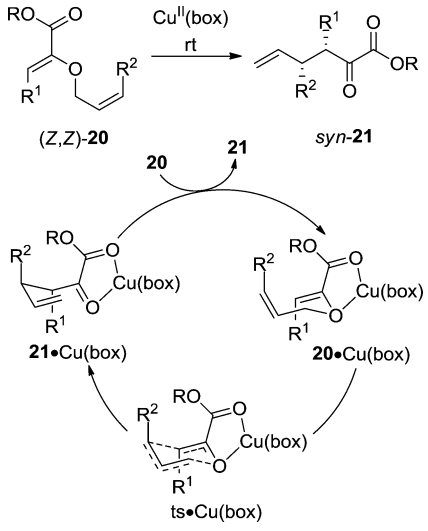


Figure 4. Schematized catalytic cycle for the catalytic asymmetric Gosteli–Claisen rearrangement. Formal charges on Cu(II) and counterions are omitted for clarity.

catalyst decreases the rearrangement barrier by a peak-affinity transition-state (ts) complexation. In comparison to the uncatalyzed rearrangement, an increased "looseness" of the Cu(box)-complexed transition-state structure is predicted by calculation.[30] The C_2 dissymmetric *t*-Bu-BOX ligand is responsible for the enantioface differentiation with respect to the vinyl ether double bond.[31] A direct substrate (**20**)/product (**21**) exchange at the catalyst without the assistance of auxiliary ligands is assumed.[32]

Our next objective was to investigate the diastereoselective reduction of the α-keto ester **6**. In order to exploit the anticipated intrinsic substrate-induced diastereoselectivity in favor of the desired diastereomer of **17**,[33] we initially selected

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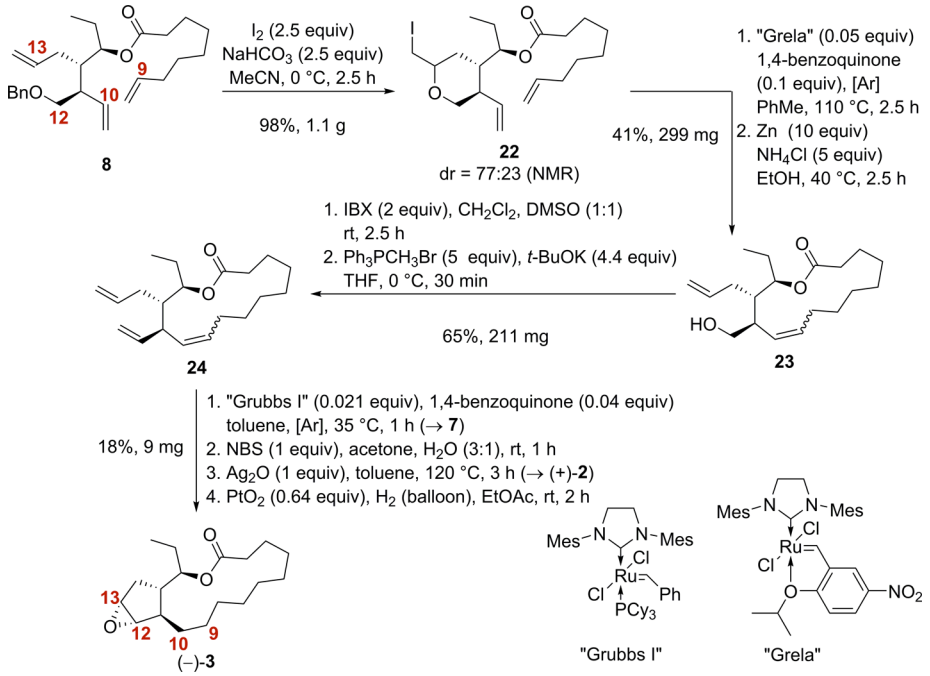
Scheme 4. Successive Ring-Closure by Alkene Metathesis



K-Selectride as a bulky reducing agent.[6] In the event, and as expected, the reduction (THF, below −90 °C) proceeded highly diastereoselectively (dr >95:5) in favor of (2*S*)-**17**. However, and despite being a spot-to-spot reaction judging from TLC, the yield of the K-Selectride reduction never exceeded 80% in a reliable and scalable fashion. Fortunately, our laboratory had previously observed encouraging results applying the Corey−Bakshi−Shibata protocol for the diastereoselective reduction of β-chiral α-keto esters from the Gosteli−Claisen rearrangement.[34,35] Accordingly, application of the (*R*)-MeCBS catalyst afforded the (2*S*)-configured α-hydroxy ester **17** as a single diastereomer (NMR) in high yield on gram scale.[36] Notably, application of the (*S*)-MeCBS catalyst also delivered (2*S*)-**17** albeit in slightly lower yield (dr >95:5, 81%). This result illustrates the dominance of the substrate-induced 2*Re*-diastereoface-differentiation for (3*S*,4*R*)-**6**.

With the key stereotriad in place, we turned our attention to the reductive homologation of the α-hydroxy ester **17** to afford the secondary alcohol **19** with retention of configuration. Thus, exposing **17** to LAH afforded the diol **18** in high yield on a gram scale. We then opted for a telescoped transformation consisting of oxirane formation by S_Ni and position-selective oxirane ring-opening by a methyl nucleophile. Formation of the epoxide from **18** was conducted using an excess of NaH and stoichiometric amounts of *N*-tosylimidazole (TsIm).[37] Subsequent addition of superstoichiometric amounts of CuI (2 equiv) and MeMgBr (10 equiv) afforded the secondary alcohol **19** in a just acceptable yield.[38] Attempts to lower the copper load or to improve the yield by varying the copper source ($CuBr{\cdot}SMe_2$, CuCN) were ineffective.

To conclude the assemblage of the triene **8** a seemingly straightforward esterification between the alcohol **19** and the commercially available 9-decenoic acid was required. Application of the protocol according to Steglich[39] indeed yielded the desired ester **8** along with the unconsumed alcohol **19**, which could be separated and reused. Using an excess of the alcohol **19** to enforce complete conversion of the acid was a tribute to avoid the cumbersome separation of unconsumed acid and the ester **8**.

Synthesis of (−)-Dihydroecklonialactone B (3). With the desired acyclic triene **8** in hand, we proceeded to investigate the formation of the 14-membered lactone by ring-closing alkene metathesis (RCM) with a particular interest in the expectable *E*/*Z* selectivity.[40] At first glance, we presumed, but never established experimentally, an unselective initiation of the RCM at the C13/C13′ and C9/C9′ terminal monosubstituted double bonds of **8**. Hence, we shied away from subjecting **8** to the conditions of the RCM and, instead, opted for a tactic which combines the mandatory cleavage of the benzyl ether protecting group with a protection of the C13/C13′ double bond by iodoetherification. The thus envisioned trans-protection could be complicated by regioselectivity and chemoselectivity (iodo lactonization) issues. However, we were hopeful that the desired 6-*exo*-*trig* iodoetherification would prevail over the 4-*exo*-, 5-*endo*-, 7-*endo*-*trig* alternatives.[41] The participation of the C9/C9′ double bond in a macrocyclization event was considered improbable.[42] To our delight, subjecting the benzyl ether **8** to an excess of iodine and $NaHCO_3$ in dry MeCN[43] at low temperature indeed delivered the desired product **22** of a 6-*exo*-*trig* iodoetherification as a mixture of diastereomers (dr = 77:23);[44] no attempt was made to separate the diastereomers or to assign the configuration of the labile compound.

Having masked the C13/C13′ double bond by iodo etherification, we proceeded to realize the envisioned lactone formation by RCM. Unfortunately, in our hands, this endeavor turned out to be much more challenging than desired because intermediate compounds proved to be labile and/or difficult to purify. After screening commercial catalyst and conditions for the ring-closing event, in our hands the Grela catalyst[45] (0.05 equiv) in the presence of 1,4-benzoquinone[46] (0.1 equiv) at elevated temperature was best performing and delivered the corresponding labile bicyclic lactone. In order to avoid extensive decomposition, particularly in solution, this bicyclic

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lactone was immediately subjected to Zn-mediated β-elimination to deliver the lactone **23** in a low yield (41%) and, unfortunately, as an inseparable mixture of double bond isomers (*Z*/*E* = 2:1).[47]

Nevertheless, having closed the lactone, reinstated the C13/C13′ double bond, and exposed the C12 hydroxyl group, we proceeded to introduce the C12/C12′ double bond in preparation for the final RCM event (Scheme 4). Hence, the alcohol **23** was oxidized with IBX[48] and subjected to a Wittig methylenation which delivered the diene **24** as a mixture of double bond isomers. Diene **24** was then subjected to a RCM employing "Grubbs I"[49] at slightly elevated temperature to deliver the 12,13-desepoxy ecklonialactone B (**7**) as a mixture of C9/C10 double-bond isomers. The mixture of C9/C10 double bond isomers was inconsequential at this stage as the double bond would need to be hydrogenated for the completion of the synthesis of (−)-**3**. However, we were thus denied access to a pure sample of (+)-ecklonialactone B (**2**), the enantiomer of the actual natural product. The regio- and diastereoselective epoxidation of the C12/C13 double bond was accomplished by employing our previously discovered two-step procedure.[16] Thus, subjecting **7** to NBS (1 equiv) in aqueous acetone delivered a bromohydrin which upon treatment with Ag_2O at elevated temperature underwent an S_Ni to deliver (+)-**2** still as a mixture of C9/C10 double-bond isomers and contaminated with an inseparable impurity. Interestingly, ^{1}H NMR data suggest the formation of single constitutional isomer of the intermediate bromohydrin; however, no attempts were made to unambiguously assign its structure. To complete the synthesis of (−)-dihydroecklonialactone B (**3**), hydrogenation of the remaining C9/C10 double bond was required. Thus, subjecting (+)-**2** to a hydrogen atmosphere in the presence of Adams' catalyst[50] delivered (−)-**3** having proton and carbon NMR spectra in very good accordance with those reported for (+)-**3** by Kurata[12] and by our laboratory.[16] However, our synthetic (−)-**3** was contaminated by an NMR-visible inseparable minor impurity, which judging from our experience,[16] is not the (12*S*,13*R*)-configured diastereomer of (−)-**3**. Under these circumstances, the measured specific rotation for (−)-**3** [$[\alpha]^{23}_D$ −16.5 (*c* 0.58, $CHCl_3$)] compared well to those reported for (+)-**3** [$[\alpha]^{23}_D$ +14.5 (*c* 0.55, $CHCl_3$)] by Kurata[12] and by our laboratory[16] [$[\alpha]^{25}_D$ +12.6 (*c* 1.0, $CHCl_3$)].

CONCLUSION

We have outlined herein the total synthesis of (−)-9,10-dihydroecklonialactone B (**3**). This endeavor was accomplished in three stages. First, a robust scalable synthesis of the functionalized Gosteli-type allyl vinyl ethers (*E*,*Z*)- and (*Z*,*Z*)-**5** was established using either a *Z*-selective aldol condensation or an *E*-selective olefination route; the separation of the vinyl ether double-bond isomers was accomplished by automated preparative HPLC. Second, key to the conversion of (*Z*,*Z*)-**5** into the elaborated chiral building block **8** was a sequence of two successive catalytic asymmetric transformations: a highly diastereo- and enantioselective Gosteli−Claisen rearrangement and a highly diastereoselective Corey−Bakshi−Shibata reduction. Third, an interesting transprotection tactic enabled successive ring-closing olefin metatheses (RCM) to provide the bicyclic core of the target molecule. Although we were unable to achieve the ring-closing metathesis to form the 14-membered macrolacatone with complete *Z*-selectivity, subsequent hydrogenation provided access to (−)-9,10-dihydroecklonialactone B (**3**). Thus, we have demonstrated that the catalytic asymmetric Claisen rearrangement of Gosteli-type allyl vinyl ethers delivers acyclic α-keto ester building blocks endowed with functionality amenable to the preparation of carbocyclic natural products by suitable postrearrangement transformations.

EXPERIMENTAL SECTION

Materials and Methods. Unless otherwise stated, commercially available reagents were used as purchased. Solvents (tetrahydrofuran, dichloromethane, 1,2-dichloroethane, acetonitrile, *N*,*N*-dimethylformamide, and toluene) were dried deploying a commercially available solvent purification system. Diisopropylamine and triethylamine were dried (CaH_2, rt, 12 h; distillation) and stored over activated 4 Å molecular sieves. DMSO was used as purchased (99.5% purity). $CDCl_3$ was stored under argon over activated 4 Å molecular sieves. Moisture-sensitive reactions were performed in flame-dried septum-sealed glassware under an atmosphere of argon. Reagents were transferred by means of syringe. Analytical TLC was performed using precoated silica gel foils (4 cm height). Visualization was achieved using 254 nm ultraviolet irradiation followed by staining (Kägi−Miescher reagent: *p*-anisaldehyde 2.53% v/v, acetic acid 0.96% v/v, ethanol 93.06% v/v, concd H_2SO_4 3.45% v/v; $KMnO_4$ reagent: $KMnO_4$ (3 g), K_2CO_3 (20 g), NaOH (0.25 g in 5 mL H_2O), H_2O (300 mL).[51] Chromatographic purification was performed on silica gel (particle size 0.040−0.063 mm) using mixtures of cyclohexane and ethyl acetate, heptane and ethyl acetate, or *n*-pentane and diethyl ether. ^{1}H NMR spectra were recorded at 400 or 500 MHz. Chemical shifts (δ) are reported in ppm relative to chloroform (7.26 ppm).[52] Signal splitting patterns are reported as they appear and are labeled accordingly: s = singlet, d = doublet, t = triplet, q = quartet, quintet = quint, m = multiplet or overlap of nonequivalent signals. ^{13}C NMR spectra were recorded at 101 or 126 MHz. Chemical shifts are reported in ppm relative to $CDCl_3$ (77.16 ppm); the total number of reported ^{13}C atom signals may fall short of the expected number because of coincidental chemical shifts, even for constitutopic or diastereotopic carbon atoms. HSQC and/or HMBC experiments were used to confirm the NMR signal assignments. Unless stated otherwise, IR spectra were recorded as a thin film on a KBr disk. Infrared absorptions are reported in reciprocal wavelength ν (cm^{-1}) and are adjusted down- or upward to 0 or 5 cm^{-1}. Relative intensities are indicated as they appear using the following abbreviations: s = strong, m = middle, w = weak, br = broad. Molecular formula assignment was confirmed by combustion elemental analysis and copies of reports are given in the Supporting Information. High-resolution mass spectra were recorded on a commercial spectrometer by electrospray ionization (ESI) using an Orbitrap mass analyzer. Optical rotations were measured deploying a commercial polarimeter operating on the sodium D line (589 nm) and using a 1 mL cuvette and are reported as: $[\alpha]^T_D$ (concentration in g/100 mL, solvent). Kinetic measurements for each substrate at each temperature were performed in double-parallel experiments. A sealable glass pressure tube was charged with a homogeneous solution of the corresponding allyl vinyl ether (60 mg) in the respective solvent (5 mL). The tube was sealed with a Teflon screw cap and placed in a preheated oil bath at the indicated temperature (60−85 °C). At the specified time, an aliquot (0.7 mL) was sampled and immediately chilled to 0 °C. The solvent was removed under reduced pressure at room temperature. The percentage of conversion was determined by integration of representative ^{1}H NMR ($CDCl_3$) signals. In order to probe for deviations in the mass balance of the uncatalyzed rearrangement, two experiments were performed in the presence of an internal standard.

[Cu{(*S*,*S*)-*t*-Bu-box}(tfe)$_2$](SbF$_6$)$_2$ ((*S*,*S*)-4. The synthesis of (*S*,*S*)-**4** was accomplished from (*S*,*S*)-*t*-Bu-bis(oxazoline); this ligand was prepared from (*S*)-*tert*-leucine following the procedures reported by Evans.[53−55] **[Cu[(S,S)-*t*-Bu-box]Cl$_2$]·(CH$_2$Cl)$_2$.** To a solution of 2,2′-isopropylidene bis[(4*S*)-4-*tert*-butyl-2-oxazoline] (294.43 g/mol, 4.0 g, 13.59 mmol, 1 equiv) in $(CH_2Cl)_2$ (50 mL) at room temperature was added dried (0.1 mbar, 70 °C, 1 h) $CuCl_2$ (99.999%, 134.45 g/mol,

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1.83 g, 13.59 mmol, 1 equiv). The mixture was stirred for 3 h in the dark. The resulting light green solution was filtered through a plug of cotton, and the filtrate was concentrated at reduced pressure and dried in vacuo. The title compound (7.09 g, 13.43 mmol, 99%) was isolated as a light green solid. $C_{19}H_{34}Cl_4CuN_2O_2$, 527.84 g/mol. **[Cu{(*S*,*S*)-*t*-Bu-box}(tfe)$_2$](SbF$_6$)$_2$ (*S*,*S*)-4**. To the light green solution of the [Cu[(*S*,*S*)-*t*-Bu-box]Cl$_2$]·(CH$_2$Cl)$_2$ complex (527.84 g/mol, 1372 mg, 2.6 mmol, 1 equiv) in (CH$_2$Cl)$_2$ (26 mL) at 0 °C under the exclusion of light was added $AgSbF_6$ (343.62 g/mol, 1787 mg, 5.2 mmol, 2 equiv). The reaction mixture was stirred for 2 h at 0 °C in the dark. The resulting dark green solution was filtered through a syringe filter (PTFE, 0.45 μm) in order to remove the precipitated AgCl. To the filtrate was added CF_3CH_2OH (100.04 g/mol, 1.39 g/mL, 0.74 mL, 10.32 mmol, 4 equiv), and the resulting green stock solution (0.1 M) of the title compound was used for the catalytic asymmetric Gosteli–Claisen rearrangement.

Reductive Selenation: Phenyl Selenide 14.[56] The synthesis of the title compound was performed in parallel using three commercially available glass pressure tubes with Teflon screw cap. To three solutions of diphenyl diselenide ($C_{12}H_{10}Se_2$, 312.13 g/mol, 3 × 3.121 g, 3 × 9.99 mmol, 3 × 1 equiv) in THF (3 × 20 mL) at 0 °C was added LAH (37.95 g/mol, 3 × 228 mg, 3 × 6.0 mmol, 3 × 0.6 equiv). The pressure tubes were sealed, and the reaction mixtures were subsequently heated to 120 °C in an oil bath for 6 h. The reaction mixtures were cooled to ambient temperature and combined. The combined reaction mixtures were diluted with H_2O and aqueous HCl (1 M). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 ×). The combined organic phases were dried ($MgSO_4$) and concentrated. Purification of the residue by chromatography (cyclohexane/ethyl acetate 20/1 to 5/1) afforded the phenyl selenide **14** (13.469 g, 58.77 mmol, 99%): R_f 0.31 (cyclohexane/ethyl acetate 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (br s, 1H), 1.69–1.76 (m, 2H), 1.80–1.87 (m, 2H), 2.99 (t, J = 7.3 Hz, 2H), 3.69 (t, J = 6.5 Hz, 2H), 7.27–7.33 (m, 3H), 7.51–7.55 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 26.6 (CH_2), 27.8 (CH_2), 32.9 (CH_2), 62.5 (CH_2), 126.9 (CH), 129.2 (CH), 130.4 (C), 132.7 (CH); IR ν 3350 (br s), 2930 (s), 2865 (m), 1580 (m), 1480 (s), 1440 (m), 1385 (w), 1070 (m), 1025 (m), 735 (s), 690 (m), 670 (w). Anal. Calcd for $C_{10}H_{14}OSe$: C, 52.4; H, 6.1. Found: C, 52.4; H, 6.2; 229.18 g/mol.

Parikh–Doering Oxidation:[20] **Aldehyde 11.**[15] To a suspension of O_3S·pyridine ($C_5H_5NO_3S$, 159.16 g/mol, 17.1 g, 107.3 mmol, 2 equiv) and pyridine (C_5H_5N, 79.1 g/mol, 0.982 g/mL, 8.64 mL, 107.3 mmol, 2 equiv) in DMSO (53 mL) at 0 °C was added a chilled solution (0 °C) of the alcohol **14** (229.18 g/mol, 12.292 g, 53.63 mmol, 1 equiv) and Et_3N (101.19 g/mol, 0.73 g/mL, 29.7 mL, 214.52 mmol, 4 equiv) in CH_2Cl_2 (214 mL). After being stirred for 6 h at room temperature, the reaction mixture was diluted with H_2O. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic phases were dried ($MgSO_4$) and concentrated. Purification of the residue by chromatography (cyclohexane/ethyl acetate 50/1 to 10/1) delivered the aldehyde **11** (10.907 g, 48.01 mmol, 90%): R_f 0.45 (cyclohexane/ethyl acetate 5/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.05 (t, J = 7.0 Hz, 2H), 2.64 (t, J = 7.0 Hz, 2H), 2.98 (t, J = 7.0 Hz, 2H), 7.29–7.33 (m, 3H), 7.52–7.54 (m, 2H), 9.80 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 22.6, 27.2, 43.6, 127.2, 129.3, 129.7, 132.9, 201.6; IR ν 3425 (m), 3070 (m), 2940 (m), 2825 (w), 1715 (s), 1580 (m), 1480 (m), 1435 (m), 1390 (w), 1070 (w), 1020 (w), 735 (s), 690 (s), 670 (w). Anal. Calcd for $C_{10}H_{12}OSe$: C, 52.9; H, 5.3. Found: C, 52.9; H, 5.7; 227.16 g/mol.

Protecting Group Transformation: Benzyl Ether 9.[57] To a stirred solution of *cis*-2-butene-1,4-diol ($C_4H_8O_2$, 88.11 g/mol, 50.0 g, 567.5 mmol, 2.93 equiv) in THF (200 mL) was added sodium hydride (24.0 g/mol, 60% m/m dispersion in mineral oil, 7.8 g, 195 mmol, 1.01 equiv) at 0 °C. After being stirred for 30 min at room temperature, benzyl bromide (used as purchased, C_7H_7Br, 171.03 g/mol, 1.44 g/mL, 23.0 mL, 193.7 mmol, 1 equiv) was added, and the resulting mixture was stirred at reflux for 1 h. The reaction mixture was diluted at room temperature by the addition of saturated aqueous NH_4Cl solution at 0 °C. Water was added until the white solid was dissolved. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatographic purification of the residue (cyclohexane/ethyl acetate 10/1 to 5/1 to 1/1) afforded the alcohol **9** (29.107 g, 163.3 mmol, 84% from benzyl bromide) as pale yellow oil: R_f 0.48 (cyclohexane/ethyl acetate 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.86 (br s, 1H), 4.10 (d, J = 6.0 Hz, 2H), 4.18 (d, J = 6.5 Hz, 2H), 4.53 (s, 2H), 5.72–5.78 (m, 1H), 5.80–5.86 (m, 1H), 7.29–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 58.9, 65.8, 72.6, 128.0, 128.5, 128.1, 128.6, 132.5, 130.0; $C_{11}H_{14}O_2$, 178.23 g/mol.

Synthesis of α-Allyloxy Acetate 10. Williamson Etherification. To a stirred solution of bromoacetic acid (138.94 g/mol, 6.343 g, 45.65 mmol, 1.1 equiv) in THF (75 mL) at −78 °C was added sodium hydride (24.0 g/mol, 60% m/m dispersion in mineral oil, 4.98 g, 124.5 mmol, 3 equiv). After being stirred at −78 °C for 0.5 h, a solution of the alcohol **9** (178.23 g/mol, 7.355 g, 41.27 mmol, 1 equiv) in THF (20 mL) was added at −78 °C, and the resulting mixture was allowed to warm to ambient temperature overnight. The reaction mixture was diluted with aqueous KOH (1 M, 60 mL), and the layers were separated. The aqueous phase was acidified by the addition of concentrated HCl (pH < 4) and extracted with CH_2Cl_2 (3×). The combined organic layers were dried ($MgSO_4$) and concentrated. After removing all volatiles in vacuo, the crude product was used without further purification. **Fischer Esterification.** To a solution of the crude acid in MeOH (41 mL) at 0 °C was added concentrated (98% v/v) sulfuric acid (98.08 g/mol, 1.84 g/mL, 0.66 mL, 12.45 mmol, 0.3 equiv). After being stirred at reflux for 5 h, the reaction mixture was diluted with H_2O and brine at room temperature. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic layers were dried ($MgSO_4$) and concentrated. Purification of the residue by chromatography (cyclohexane/ethyl acetate 10/1 to 5/1) afforded the ester **10** (8.4 g, 33.56 mmol, 81%) as a colorless oil: R_f 0.47 (cyclohexane/ethyl acetate 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.75 (s, 3H), 4.07 (s, 2H), 4.09 (d, J = 5.9 Hz, 2H), 4.15 (d, J = 6.2 Hz, 2H), 4.51 (s, 2H), 5.72–5.78 (m, 1H), 5.80–5.86 (m, 1H), 7.27–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 51.9, 65.7, 66.9, 67.2, 72.4, 127.7, 127.8, 128.4, 130.5, 138.1, 170.7; IR ν 3030 (w), 2855 (w), 1755 (s), 1455 (m), 1440 (m), 1280 (w), 1210 (s), 1135 (s), 1075 (m), 1005 (w), 945 (w), 740 (m), 700 (m), 580 (w); $C_{14}H_{18}O_4$; 250.29 g/mol.

Ester Enolate Aldol Addition: β-Hydroxy Ester 12. LDA was prepared in situ from diisopropylamine (101.19 g/mol, 0.72 g/mL, 3.65 mL, 26.0 mmol, 1.3 equiv) and *n*-BuLi (10 mL, 24.0 mmol, 1.2 equiv, 2.4 M in *n*-hexanes) in THF (60 mL) at 0 °C. To this THF solution of LDA (1.2 equiv) at −78 °C was added the ester **10** (250.29 g/mol, 5.0 g, 20.0 mmol, 1 equiv) in THF (60 mL). The reaction mixture was stirred for 15 min at −78 °C. A solution of the aldehyde **11** (227.16 g/mol 5.446 g, 24.0 mmol, 1.2 equiv) in THF (20 mL) was then added. After being stirred for 35 min at −78 °C, the reaction mixture was diluted by the addition of saturated aqueous NH_4Cl solution and the mixture was allowed to warm to room temperature. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic layers were dried ($MgSO_4$) and concentrated. Purification of the residue by chromatography (cyclohexane/ethyl acetate 50/1 to 5/1) provided the β-hydroxy ester **12** as a mixture of diastereomers (7.483 g, 15.67 mmol, 78%, dr ∼2:1). The diastereomeric ratio was difficult to quantify because of overlapping NMR signals. Characterization data are reported for the mixture of *syn*/*anti* diastereomers: R_f 0.37 (cyclohexane/ethyl acetate 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60–1.68 (m, 2H), 1.75–1.85 (m, 1H), 1.90–1.97 (m, 1H), 2.27–2.31 (m, 1H), 2.92–2.97 (m, 2H), 3.76 (s, 3H), 3.79–3.90 (m, 1H), 3.92–3.93 (m, 1H), 4.03–4.10 (m, 3H), 4.25–4.30 (m, 1H), 4.53 (s, 2H), 5.71–5.80 (m, 1H), 5.81–5.88 (m, 1H), 7.26–7.39 (m, 8H), 7.49–7.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 26.3, 26.5, 27.7, 32.4, 33.3, 52.2, 52.3, 65.8, 66.6, 66.7, 71.8, 72.0, 72.6, 80.9, 81.4, 126.9, 127.9, 128.4, 128.5, 128.6, 129.2, 130.4, 130.6, 130.7, 132.7, 138.1, 171.1, 171.5; IR ν 3470 (br m), 2950 (m), 2925 (m), 2860 (m), 1745 (s), 1480 (m), 1440 (m), 1265 (w), 1205 (m), 1075 (s), 1025 (m), 910 (s), 735 (s), 700 (m), 650 (w). Anal.

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Calcd for $C_{24}H_{30}O_5Se$: C, 60.4; H, 6.3. Found: C, 60.5; H, 6.4; 477.45 g/mol.

Gosteli-Type Allyl Vinyl Ether (*E,Z*)-13 and (*Z,Z*)-13. Mesylation. To a solution of the alcohol **12** (477.45 g/mol 27.8 g, 58.23 mmol, 1 equiv) in CH_2Cl_2 (175 mL) were successively added Et_3N (101.19 g/mol, 0.726 g/mL, 10.55 mL, 75.69 mmol, 1.3 equiv) and methanesulfonyl chloride (114.55 g/mol, 1.478 g/mL, 5.4 mL, 69.67 mmol, 1.2 equiv) at 0 °C. After being stirred for 1.5 h at room temperature, the reaction mixture was diluted by the addition of saturated aqueous $NaHCO_3$ solution. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic phases were dried ($MgSO_4$) and concentrated. Volatiles were removed in vacuo, and the crude product was used without further purification. **Elimination.** To a solution of the crude mesylate in THF (175 mL) at 0 °C was added DBU ($C_9H_{16}N_2$, 152.24 g/mol, 1.02 g/mL, 26.3 mL, 176.21 mmol, 3 equiv). The reaction mixture was allowed to warm to room temperature and stirred for 16 h at ambient temperature. H_2O was then added, and the layers were separated. The aqueous layer was extracted with ethyl acetate (3×). The combined organic phases were dried ($MgSO_4$) and concentrated. Purification by chromatography (cyclohexane/ethyl acetate 50/1 to 10/1) afforded the allyl vinyl ether **13** (20.4 g, 44.40 mmol, 76%) as mixture of double-bond isomers (*E,Z*):(*Z,Z*) = 40:60; the ratio was determined by integration of the ^{1}H NMR signals at 2.34 ppm {(*Z,Z*)-**13**} and 2.56 ppm {(*E,Z*)-**13**}, 3.74 ppm {(*Z,Z*)-**13**} and 3.78 ppm (*E,Z*)-**13**}, 4.31 ppm {(*E,Z*)-**13**} and 4.41 ppm {(*Z,Z*)-**13**}, 5.17 {(*E,Z*)-**13**} and 6.23 {(*Z,Z*)-**13**}. The double-bond isomers were separated by preparative HPLC: Nucleosil 50-5, 32 × 250 mm, heptane/ethyl acetate 8/1, 25 mL/min, (*Z,Z*)-**13** at 19 min (10.17 g, 22.13 mmol, 38%), (*E,Z*)-**13** at 22 min (6.55 g, 14.26 mmol, 25%); R_f 0.39 (cyclohexane/ethyl acetate 5/1). (*Z,Z*)-**13**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.76−1.83 (m, 2H), 2.34 (q, J = 7.5 Hz, 2H), 2.90 (t, J = 7.4 Hz, 2H), 3.74 (s, 3H), 4.09 (d, J = 4.5 Hz, 2H), 4.41 (d, J = 4.8 Hz, 2H), 4.50 (s, 2H), 5.79−5.81 (m, 2H), 6.23 (t, J = 7.6 Hz, 1H), 7.23−7.37 (m, 8H), 7.47−7.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 26.0, 27.4, 29.2, 52.1, 65.8, 67.8, 72.5, 127.0, 127.8, 127.9, 128.3, 128.5, 128.6, 129.2, 130.1, 130.5, 132.8, 138.2, 145.0, 164.3; IR ν 2950 (w), 2860 (w), 1725 (s), 1650 (w), 1440 (w), 1455 (w), 1325 (w), 1270 (m), 1280 (m), 1215 (m), 1095 (s), 1030 (m), 1000 (m), 915 (w), 780 (w), 740 (w), 700 (w). Anal. Calcd for $C_{24}H_{28}O_4Se$: C, 62.7; H, 6.1. Found: C, 63.0; H, 6.4. (*E,Z*)-**13**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.81 (quint, J = 7.4 Hz, 2H), 2.56 (dt, J_1 = 7.6 Hz, J_2 = 7.6 Hz, 2H), 2.91 (t, J = 7.4 Hz, 2H), 3.78 (s, 3H), 4.09 (d, J = 4.5 Hz, 2H), 4.30 (d, J = 4.5 Hz, 2H), 4.51 (s, 2H), 5.17 (t, J = 7.8 Hz, 1H), 5.80 (dt, J_1 = J_2 = 4.6 Hz, 2H), 7.22−7.34 (m, 8H), 7.49 (dd, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 27.1, 27.3, 30.7, 52.1, 64.9, 65.9, 72.5, 116.0, 126.8, 127.9, 128.6, 129.1, 129.9, 130.5, 132.6, 138.1, 144.8, 164.0; IR ν 2950 (m), 2860 (m), 1725 (s), 1635 (m), 1480 (w), 1455 (m), 1440 (s), 1095 (m), 1075 (m), 1025 (w), 910 (s), 735 (s), 695(m). Anal. Calcd for $C_{24}H_{28}O_4Se$: C, 62.7; H, 6.1. Found: C, 62.4; H, 6.0; 459.44 g/mol.

Phosphonate 16. To each of the three solutions of the alcohol **9** (178.23 g/mol, 3 × 341 mg, 3 × 1.91 mmol, 3 × 1 equiv) and $Rh_2(OAc)_4$ (441.99 g/mol, 3 × 33.8 mg, 3 × 0.0765 mmol, 3 × 0.04 equiv) in 1,2-dichloroethane (3 × 20 mL) under reflux was slowly added a solution of methyl 2-diazo-2-(dimethoxyphosphoryl)acetate **15** ($C_5H_9N_2O_5P$, 208.11 g/mol, 3 × 477 mg, 3 × 2.29 mmol, 3 × 1.2 equiv) in 1,2-dichloroethane (3 × 20 mL) over a period of 110 min. The three reaction mixtures were then cooled to ambient temperature and combined, and the solvent was removed at reduced pressure. The residue was filtered through a short plug of silica (cyclohexane/ethyl acetate 1/1), and the eluent was concentrated at reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL), and the solution was successively washed with water (2 × 30 mL) and saturated aqueous NH_4Cl (4 × 30 mL). The combined aqueous phases were extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were then dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (cyclohexane/ethyl acetate 1/1 to 0/1) to deliver the phosphonate **16** (1.6 g, 4.47 mmol, 78%) as a pale grayish oil: R_f = 0.35 (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.8 (s, 3H), 3.82 (d, J = 4.2 Hz, 3H), 3.84 (d, J = 4.0 Hz, 3H), 4.07 (d, J = 6.2 Hz, 2H), 4.18 (dd, J_1 = 12.2 Hz, J_2 = 7.0 Hz, 1H), 4.30 (dd, J_1 = 12.5 Hz, J_2 = 6.0 Hz, 1H), 4.40 (d, J = 18.9 Hz, 1H), 4.50 (s, 2H), 5.71−5.76 (m, 1H), 5.84−5.89 (m, 1H), 7.28−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 52.8, 54.2, 65.6, 67.8, 67.9, 72.5, 74.1, 75.7, 127.3, 127.4, 127.7, 128.4, 131.6, 137.9, 167.7; IR ν 3030 (w), 2955 (m), 2855 (m), 1750 (s), 1455 (m), 1265 (s), 1035 (s), 915 (s), 735 (s), 700 (m); HRMS (ESI) calcd for $C_{16}H_{24}O_7P$ ($[M + H]^+$) 359.1254, found 359.1260; calcd for $C_{16}H_{23}NaO_7P$ ($[M + Na]^+$) 381.1074, found 381.1076; $C_{16}H_{23}O_7P$, 358.32 g/mol.

Synthesis of Gosteli-Type Allyl Vinyl Ethers by Horner−Wadsworth−Emmons Reaction: Allyl Vinyl Ether (*E,Z*)-13 and (*Z,Z*)-13. LDA was prepared in situ from diisopropylamine (101.19 g/mol, 0.72 g/mL, 2.4 mL, 17.2 mmol, 1.3 equiv) and *n*-BuLi (7.2 mL, 15.8 mmol, 1.2 equiv, 2.2 M in *n*-hexanes) in THF (53 mL) at 0 °C. To this THF solution of LDA (1.1 equiv) at −78 °C was added the phosphonate **16** (358.32 g/mol, 4.73 g, 13.2 mmol, 1 equiv) in THF (53 mL), and the mixture was stirred for 20 min at −78 °C. A solution of the aldehyde **11** (227.16 g/mol, 3.0 g, 13.2 mmol, 1 equiv) in THF was slowly added at −78 °C. The cooling bath was immediately removed, the reaction mixture was allowed to stir at ambient temperature for 100 min, and saturated aqueous NH_4Cl solution was added. The layers were separated, and the organic phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (cyclohexane/ethyl acetate 50/1 to 10/1) to deliver the Gosteli-type allyl vinyl ether **13** (5 g, 10.9 mmol, 81%) as a mixture of double bond isomers {(*E,Z*):(*Z,Z*) = 5:1}. The double-bond isomers were separated as described above.

Selenide Oxidation and Elimination: Gosteli-Type Allyl Vinyl Ether (*E,Z*)-5. To a solution of the selenide (*E,Z*)-**13** (459.44 g/mol, 3.997 g, 8.70 mmol, 1 equiv) in THF (87 mL) at 0 °C were added $NaHCO_3$ (84.01 g/mol, 7.309 g, 87.0 mmol, 10 equiv) and H_2O_2 (34.02 g/mol, 1.5 mL of a 30% m/v H_2O, 1.11 g/mL, 495 mg, 14.55 mmol, 1.7 equiv). The reaction mixture was stirred at room temperature for 3 days. H_2O was subsequently added, and the layers were separated. The aqueous phase was extracted with ethyl acetate (3×), and the combined organic phases were dried ($MgSO_4$). The solvents were removed, and the residue was purified by chromatography (cyclohexane/ethyl acetate 100/1 to 20/1) to afford (*E,Z*)-**5** (2.291 g, 7.58 mmol, 87%): R_f 0.49 (cyclohexane/ethyl acetate 5/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.21 (m, 2H), 3.79 (s, 3H), 4.11 (d, J = 4.0 Hz, 2H), 4.35 (d, J = 4.5 Hz, 2H), 4.52 (s, 2H), 5.00−5.09 (m, 2H), 5.23 (t, J = 7.8 Hz, 1H), 5.77−5.89 (m, 3H), 7.27−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 31.1, 52.1, 64.9, 66.0, 72.5, 114.2, 115.3, 127.8, 127.9, 128.6, 130.0, 136.7, 138.1, 144.8, 164.0; IR ν 2950 (w), 2860 (w), 1730 (s), 1640 (m), 1455 (w), 1435 (m), 1370 (m), 1290 (w), 1225 (s), 1155 (s), 1115 (m), 1075 (m), 990 (w), 915 (w), 735 (m), 700 (m). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.5; H, 7.3. Found: C, 71.7; H, 7.3; 302.37 g/mol.

Selenide Oxidation and Elimination: Gosteli-Type Allyl Vinyl Ether (*Z,Z*)-5. To a solution of the selenide (*Z,Z*)-**13** (459.44 g/mol, 5.867 g, 12.79 mmol, 1 equiv) in THF (64 mL) were added $NaHCO_3$ (84.01 g/mol, 10.745 g, 127.90 mmol, 10 equiv) and H_2O_2 (34.02 g/mol, 2.2 mL of a 30% m/v H_2O, 1.11 g/mL, 733 mg, 21.53 mmol, 1.7 equiv). The reaction mixture was stirred at room temperature for 3 days. Water was added, the layers were separated, and the aqueous phase was extracted with ethyl acetate (3×). The combined organic layers were dried ($MgSO_4$) and concentrated. Purification of the residue by chromatography (cyclohexane/ethyl acetate 100/1 to 20/1) afforded (*Z,Z*)-**5** (3.243 g, 10.78 mmol, 84%): R_f 0.52 (cyclohexane/ethyl acetate 5/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.96−3.00 (ddt, J_1 = 7.7 Hz, J_2 = 6.2 Hz, J_3 = 1.6 Hz, 2H), 3.75 (s, 3H), 4.10 (m, 2H), 4.44 (d, J = 5.0 Hz, 2H), 4.50 (s, 2H), 5.02−5.10 (m, 2H), 5.74 (m, 3H), 6.30 (t, J = 7.5 Hz, 1H), 7.27−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 30.0, 52.1, 65.8, 67.8, 72.5, 116.2, 126.9, 127.8, 127.9, 128.3, 128.5, 130.5, 134.9, 138.2, 144.9, 164.3; IR ν 3030 (m), 2950 (m), 2860 (m), 1730 (s), 1650 (s), 1435 (m), 1455 (m), 1370 (m), 1325 (m), 1280 (m), 1210 (m), 1095 (m), 1025 (m), 915 (m), 780

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(m), 740 (m), 700 (m). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.5; H, 7.3. Found: C, 71.3; H, 7.4; 302.37 g/mol.

Catalytic Asymmetric Gosteli–Claisen Rearrangement: α-Keto Ester (+)-(3*S*,4*R*)-6. To a solution of (*Z*,*Z*)-**5** (302.37 g/mol, 2.30 g, 7.61 mmol, 1 equiv) in $(CH_2Cl)_2$ (40 mL) was added $[Cu\{(S,S)$-*t*-Bu-box$\}(tfe)_2](SbF_6)_2$ (*S*,*S*)-**4** (7.6 mL, 0.1 M in 1,2-dichloroethane, 0.76 mmol, 0.1 equiv). The reaction mixture was stirred for 18 h at ambient temperature. The solvent was removed under reduced pressure, and the residue was purified by chromatography (cyclohexane/ethyl acetate 100/1 to 50/1) to afford (3*S*,4*R*)-**6** (2.197 g, 7.27 mmol, 96%, dr >95/5, 98% ee). Only one diastereomer was detectable by NMR. The enantiomeric excess was determined by HPLC: Chiracel IA, 4.6 × 250 mm, *n*-heptane/ethyl acetate, 99.5/0.5, 1 mL/min, (3*S*,4*R*)-**6** 22.5 min, (3*R*,4*S*)-**6** 19.5 min; R_f 0.34 (cyclohexane/ethyl acetate 10/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.21–2.27 (m, 1H), 2.40–2.46 (m, 1H), 2.72–2.77 (m, 1H), 3.45 (dd, J_1 = 9.2 Hz, J_2 = 5.4 Hz, 1H), 3.57 (dd, J_1 = 9.2 Hz, J_2 = 4.2 Hz, 1H), 3.65 (s, 3H), 3.71 (dd, J_1 = 8.7, J_2 = 5.4 Hz, 1H), 4.37–4.43 (m, 2H), 4.98–5.15 (m, 4H), 5.66–5.75 (m, 1H), 5.85–5.92 (m, 1H), 7.25–7.28 (m, 2H), 7.31–7.34 (m, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 33.4, 46.9, 47.2, 52.8, 72.0, 73.0, 117.5, 118.0, 127.5, 127.7, 128.4, 135.2, 135.7, 137.8, 161.8, 195.1; IR ν 3080 (m), 3030 (m), 2950 (m), 2860 (m), 1730 (s), 1640 (s), 1495 (w), 1450 (m), 1435 (m), 1360 (m), 1275 (s), 1225 (m), 1105 (m), 1030 (w), 995 (m), 920 (m), 740 (m), 700 (m). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.5; H, 7.3. Found: C, 71.4; H, 7.3; $[\alpha]_D^{20}$ +23.3 (c 1.03, $CHCl_3$); 302.37 g/mol.

Gosteli–Claisen Rearrangement: α-Keto Ester (±)-(3*R*,4*R*)-6. A solution of (*E*,*Z*)-**5** (302.37 g/mol, 0.1 g, 0.33 mmol) in 1,2-dichloroethane (5 mL) was stirred at 80 °C for 140 h. The solvent was removed in vacuo, and the residue was purified by chromatography (hexanes/ethyl acetate 100/1 to 50/1) to deliver the title compound (93 mg, 0.31 mmol, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.30–2.37 (m, 3H), 2.77–2.88 (m, 1H), 3.33 (m, 1H), 3.37–3.46 (m, 1H), 3.55 (s, 3H), 4.30 (m, 2H), 4.88–4.99 (m, 2H), 5.10–5.20 (m, 2H), 5.43–5.59 (m, 1H), 5.59–5.70 (m, 1H), 7.16–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 34.7, 48.2, 48.3, 52.5, 72.6, 117.2, 118.9, 127.5, 128.2, 134.7, 135.4, 137.3, 161.2, 194.8.

Diastereoselective Reduction: α-Hydroxy Ester 17. To a solution of the α-ketoester **6** (302.37 g/mol, 1.977 g, 6.54 mmol, 1 equiv) in THF (65 mL) at −82 °C was added (*R*)-(+)-2-methyl-CBS-oxazaborolidine ($C_{18}H_{20}BNO$, 277.17 g/mol, 1 M in CH_2Cl_2, 0.78 mL, 0.78 mmol, 0.12 equiv). After 20 min of stirring, borane dimethyl sulfide complex (75.97 g/mol, 0.801 g/mL, 0.37 mL, 3.90 mmol, 0.6 equiv) was added, and the reaction mixture was allowed to warm to −75 °C over a period 35 min. The reaction mixture was diluted with MeOH (65 mL), warmed to ambient temperature, and further diluted by the addition of saturated aqueous NH_4Cl solution. The phases were separated, the aqueous layer was extracted with CH_2Cl_2 (3×), and the combined organic phases were dried ($MgSO_4$) and concentrated. Purification of the residue by chromatography (cyclohexane/ethyl acetate 50/1 to 10/1) provided the α-hydroxy ester **17** (1.867 g, 6.13 mmol, 94%, dr >95:5) as a clear oil: R_f 0.35 (cyclohexane/ethyl acetate 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15–2.22 (m, 3H), 2.51–2.54 (m, 1H), 3.42–3.51 (m, 2H), 3.74 (s, 3H), 4.17 (d, J = 8.4 Hz, 1H), 4.26 (dd, J_1 = 8.4 Hz, J_2 = 2.9 Hz, 1H), 4.52 (d, J = 12.0 Hz, 1H), 4.59 (d, J = 12.1 Hz, 1H), 5.01–5.12 (m, 4H), 5.68–5.83(m, 2H), 7.27–7.39 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 31.1, 43.5, 44.4, 52.1, 70.0, 71.6, 73.5, 116.6, 117.5, 128.0, 128.6, 136.5, 137.4, 138.2, 175.5; IR ν 3445 (s), 1730 (s), 1640 (s), 1455 (w), 1220 (w), 1095 (m), 915 (w), 735 (w), 700 (m). Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.0; H, 8.0. Found: C, 70.9; H, 7.8; $[\alpha]^{20}_D$ +45.6 (*c* 1.065, $CHCl_3$); 304.38 g/mol.

Reductive Homologation of α-Hydroxy Esters: Diol 18. To a solution of the α-hydroxy ester **17** (304.38 g/mol, 1.867 g, 6.13 mmol, 1 equiv) in THF (62 mL) at 0 °C was added $LiAlH_4$ (37.95 g/mol, 697 mg, 18.37 mmol, 3 equiv). After being stirred for 30 min at 0 °C, the suspension was allowed to warm to ambient temperature and was stirred for an additional 2.5 h at room temperature. The reaction mixture was diluted with HCl (1 M) and H_2O at 0 °C. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (6×). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by chromatography (cyclohexane/ethyl acetate 5/1 to 2/1) afforded the diol **18** (1.64 g, 5.93 mmol, 97%): R_f 0.41 (cyclohexane/ethyl acetate 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80 (qd, J_1 = 6.7 Hz, J_2 = 2.3 Hz, 1H), 2.02–2.13 (m, 2H), 2.14–2.18(m, 1H), 2.73–2.77 (m, 1H), 3.49–3.59 (m, 3H), 3.61–3.66 (m, 2H), 4.08 (d, J = 5.7 Hz, 1H), 4.53–4.59 (m, 2H), 5.02–5.13 (m, 4H), 5.67–5.76 (m, 1H), 5.78–5.87 (m, 1H), 7.29–7.39 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 32.2, 43.0, 44.0, 65.8, 71.4, 72.2, 73.7, 116.8, 116.9, 128.1, 128.2, 128.7, 137.2, 137.3, 137.6; IR ν 3435 (s), 2920 (m), 2870 (m), 1640 (m), 1455 (w), 1095 (m), 1030 (w), 915 (w), 735 (m), 700 (m). Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.9; H, 8.8. Found: C, 73.8; H, 9.1. $[\alpha]^{20}_D$ +31.9 (c 1.64, $CHCl_3$); 276.37 g/mol.

Reductive Homologation of α-Hydroxy Esters: Alcohol 19. To a suspension of sodium hydride (24.00 g/mol, 280 mg of a 60% m/m dispersion in mineral oil, 168 mg, 7.0 mmol, 1.5 equiv) in THF (48 mL) at 0 °C was added the diol **18** (276.37 g/mol, 1.302 g, 4.71 mmol, 1 equiv) in THF (5 mL). The suspension was stirred for 30 min at room temperature. 1-(*p*-Toluenesulfonyl)imidazole (TsIm, $C_{10}H_{10}N_2O_2S$, 222.26 g/mol, 1.15 g, 5.17 mmol, 1.1 equiv) was added, and the reaction mixture was stirred for 1 h at room temperature. CuI (190.45 g/mol, 1.79 g, 9.40 mmol, 2 equiv) was added. The reaction mixture was chilled to −46 °C, and MeMgBr (47 mL, 47.04 mmol, 10 equiv, 1 M in THF) was added dropwise. The solution was allowed to warm to −4 °C and stirred for an additional 2 h at this temperature. The reaction mixture was then diluted by the addition of saturated aqueous NH_4Cl solution. The aqueous phase was extracted with CH_2Cl_2 (4×). The combined organic phases were dried ($MgSO_4$) and concentrated. Purification of the residue by chromatography (cyclohexane/ethyl acetate 50/1 to 20/1) delivered the alcohol **19** (0.948 g, 3.45 mmol, 73%): R_f 0.48 (cyclohexane/ethyl acetate 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, J = 7.4 Hz, 3H), 1.48–1.55 (m, 2H), 1.68–1.73 (m, 1H), 2.03–2.09 (m, 1H), 2.16–2.24 (m, 1H), 2.75–2.78 (m, 1H), 3.41–3.55 (m, 4H), 4.51–4.58 (m, 2H), 4.99–5.12 (m, 4H), 5.72–5.84 (m, 2H), 7.28–7.38 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.7, 28.5, 31.7, 42.4, 46.3, 70.8, 73.0, 73.6, 115.9, 116.3, 128.0, 128.6, 137.5, 138.0, 139.0; IR ν 3440 (s), 3075 (w), 2960 (w), 2930 (w), 2875 (w), 1640 (m), 1455 (w), 1095 (m), 1075 (w), 910 (w), 735 (m), 670 (w). Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.8; H, 9.6. Found: C, 78.6; H, 9.4. $[\alpha]^{20}_D$ = +39.6 (*c* 1.06, $CHCl_3$); 274.40 g/mol.

Alternative Procedure. To a suspension of sodium hydride (24.00 g/mol, 181 mg of a 60% m/m dispersion in mineral oil, 109 mg, 4.54 mmol, 2.5 equiv) in THF (18 mL) at 0 °C was added the diol **18** (276.37 g/mol, 500 mg, 1.81 mmol, 1 equiv) in THF (1.8 mL). The suspension was stirred for 30 min at room temperature. TsIm (222.26 g/mol, 442 mg, 1.95 mmol, 1.1 equiv) was added, and the reaction mixture was stirred for 1 h at room temperature. $CuBr{\cdot}SMe_2$ (C_2H_6BrCuS, 205.58 g/mol, 744 mg, 3.62 mmol, 2 equiv) was added. The reaction mixture was chilled to −46 °C, and MeMgBr (1 M in THF, 18.1 mL, 18.1 mmol, 10 equiv) was added dropwise. The solution was allowed to warm to −4 °C and stirred for an additional 2 h at this temperature. The reaction mixture was then diluted with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with CH_2Cl_2 (4×), and the combined organic phases were dried ($MgSO_4$). After evaporation of the solvents, purification by chromatography (cyclohexane/ethyl acetate 50/1 to 20/1) delivered the alcohol **19** (277.40 g/mol, 376 mg, 1.36 mmol, 75%).

Steglich Esterification: Ester 8. To a solution of 9-decenoic acid (170.25 g/mol, ≥90% purity, used as purchased, 527 mg, 3.36 mmol, 0.81 equiv) in 1,2-dichloroethane (3 mL) at 0 °C was added a solution of DCC (206.33 g/mol, 633 mg, 3.07 mmol, 0.73 equiv) in 1,2-dichloroethane (4 mL). DMAP (122.17 g/mol, 17 mg, 0.14 mmol, 0.03 equiv) and alcohol **19** (274.40 g/mol, 1.148 g, 4.18 mmol, 1.0 equiv) were successively added at ambient temperature. After being stirred for 16 h, the reaction mixture was filtered through a plug of Celite on silica gel. The plug was rinsed with CH_2Cl_2. The solvents were evaporated, and subsequent purification of the residue by chromatography (cyclohexane/ethyl acetate 200/1) afforded the ester **8** (1.033 g, 2.42 mmol, 58% from **19**) along with recovered **19** (274.40 g/mol, 358 mg, 1.29 mmol, 31%): R_f 0.53 (cyclohexane/ethyl acetate

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5/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78 (t, J = 7.4 Hz, 3H), 1.23 (s, 6H), 1.29−1.34 (m, 2H), 1.46−1.57 (m, 4H), 1.84−1.89 (m, 1H), 1.98 (q, J = 6.9 Hz, 2H), 2.04 (q, J = 6.7 Hz, 2H), 2.13−2.17 (m, 2H), 2.45−2.50 (m, 1H), 3.43 (dd, J_1 = 9.1 Hz, J_2 = 7.9 Hz, 1H), 3.54 (dd, J_1 = 9.3 Hz, J_2 = 4.8 Hz, 1H), 4.41−4.46 (m, 2H), 4.82−4.85 (m, 1H), 4.86−4.88 (m, 1H), 4.91−4.92 (m, 1H), 4.94−4.95 (m, 2H), 5.01−5.08 (m, 2H), 5.64−5.79 (m, 3H), 7.19−7.22 (m, 2H), 7.25−7.29 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.1, 23.9, 25.2, 29.0, 29.1, 29.3, 32.5, 33.9, 34.8, 42.5, 45.0, 71.9, 73.1, 76.1, 114.3, 116.3, 116.8, 127.6, 127.7, 128.4, 137.8, 138.7, 139.3, 173.4; IR ν 3465 (w), 3075 (w), 2970 (m), 2925 (s), 2855 (m), 1730 (s), 1635 (w), 1455 (w), 1370 (w), 1245 (w), 1175 (m), 1105 (s), 910 (s). Anal. Calcd for $C_{28}H_{42}O_3$: C, 78.8; H, 9.9. Found: C, 78.5; H, 9.8. $[\alpha]^{20}_D$ +15.5 (c 1.18, $CHCl_3$); 426.63 g/mol.

Transprotection by Intramolecular Iodo Etherification: Tetrahydropyran 22. To a solution of the triene **8** (426.63 g/mol, 1.033 g, 2.42 mmol, 1 equiv) in MeCN (25 mL) were successively added $NaHCO_3$ (84.01 g/mol, 508 mg, 6.05 mmol, 2.5 equiv) and I_2 (253.81 g/mol, 1.54 g, 6.07 mmol, 2.5 equiv) at 0 °C. The solution was allowed to warm to ambient temperature and stirred for 2.5 h. The reaction mixture was subsequently diluted by the addition of saturated aqueous $Na_2S_2O_3$ solution. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic phases were dried ($MgSO_4$) and concentrated. Purification of the residue by chromatography (cyclohexane/ethyl acetate 200/1 to 20/1) delivered the labile tetrahydropyrane **22** (1.096 g, 2.37 mmol, 98%, dr = 77:23) as a mixture of diastereomers. The dr was determined by integration of the ^{1}H NMR signals at 5.51−5.60 ppm and 5.75−5.89 ppm. The relative configuration was not assigned. Characterization data are reported for the mixture of diastereomers. Isolated signals that are related to the minor diastereomer are labeled accordingly: R_f 0.70 (cyclohexane/ethyl acetate 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (q, J = 7.5 Hz, 3H), 1.15−1.24 (m, 1H), 1.31 (s, 6H), 1.33−1.39 (m, 2H), 1.44−1.56 (m, 1H), 1.58−1.68 (m, 3H), 1.80−1.95 (m, 2H), 2.02 (q, J = 6.6 Hz, 2H), 2.08−2.19 (m, 1H), 2.27−2.33 (m, 2H), 3.18−3.30 (m, 3H), 3.55 (m, 2H), 4.85−4.90 (m, 2H^{minor}), 4.93 (dd, J_1 =10.2 Hz, J_2 = 1.1 Hz, 1H), 4.99 (dd, J_1 = 17.1 Hz, J_2 = 1.5 Hz, 1H), 5.06−5.17 (m, 3H), 5.51−5.60 (m, 2H^{minor}), 5.75−5.89 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 7.8, 9.6, 9.8, 10.7, 21.6, 23.3, 25.2, 27.8, 29.0, 29.1, 29.3, 31.1, 33.9, 34.7, 38.4, 40.7, 42.7, 43.9, 66.2, 72.5, 74.7, 76.1, 76.7, 114.4, 116.9, 118.3, 136.1, 138.3, 139.2, 173.7, 173.8; IR ν 3075 (w), 2925 (m), 2855 (m), 1730 (s), 1640 (s), 1460 (s), 1380 (s), 1245 (s), 1180 (s), 1090 (s), 995 (s), 915 (s); $C_{21}H_{35}IO_3$, 462.41 g/mol.

Alcohol 23. Ring-Closing Metathesis. The RCM was performed in three parallel reactions. To three solutions of the diene **22** (462.41 g/mol, 3 × 365 mg, 3 × 0.79 mmol, 3 × 1 equiv) in toluene (3 × 158 mL) at ambient temperature were successively added 1,4-benzoquinone (108.09 g/mol, 3 × 8 mg, 3 × 0.074 mmol, 3 × 0.1 equiv) and the Grela metathesis catalyst ($C_{31}H_{37}Cl_2N_3O_3$, 671.62 g/mol, 3 × 26 mg, 3 × 0.039 mmol, 3 × 0.05 equiv). The reaction mixtures were refluxed for 2.5 h while a constant stream of argon was maintained. After being cooled to ambient temperature, the reaction mixtures were combined and the solvent was removed under reduced pressure. Purification of the residue by chromatography (cyclohexane/ethyl acetate 200/1) afforded the labile RCM product ($C_{19}H_{31}IO_3$, 434.35 g/mol, 544 mg, 1.25 mmol) as a mixture of diastereomers, R_f 0.64 (cyclohexane/ethyl acetate 5/1). **Reductive Cleavage of the Tetrahydropyran.** To a solution of the purified RCM product (544 mg, 1.25 mmol, 1 equiv) in EtOH (25 mL) were added NH_4Cl (53.49 g/mol, 335 mg, 6.26 mmol, 5 equiv) and zinc powder (purity >95%, particle size <45 μm, 65.39 g/mol, 819 mg, 12.52 mmol, 10 equiv). After being stirred for 2.5 h at 40 °C, the reaction mixture was filtered through Celite and the solvent was removed under reduced pressure. Purification of the residue by chromatography (cyclohexane/ethyl acetate 50/1 to 20/1 to 10/1) afforded the alcohol **23** (299 mg, 0.97 mmol, 41% from **22**) as an (apparent) mixture of double bond isomers. The E/Z ratio (~1/2) was determined by integration of the ^{1}H NMR signals at 5.61 ppm and 5.49−5.55 ppm. Characterization data are reported for the mixture of double-bond isomers, R_f 0.59 (cyclohexane/ethyl acetate 2/1). NMR assignments of selected ^{1}H and ^{13}C signals rests on ^{1}H/^{1}H COSY and ^{1}H/^{13}C HSQC experiments and are provided for the major compound only. Signals that refer to the minor diastereomer are labeled accordingly: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83−0.89 (m, 3H), 1.31−1.56 (m, 10H), 1.56−1.65 (m, 2H), 1.67−1.73 (m, 2H), 1.73−1.82 (m, 1H, 15-CH), 1.83−1.90 (m), 2.04−2.14 (m, 1H), 2.16−2.20 (m, 2H), 2.25−2.36 (m, 1H), 2.40−2.54 (m, 2H), 2.78−2.84 (m, 1H, 11-CH), 3.51 (dd, J_1 = 10.2 Hz, J_2 = 8.4 Hz, 1H, 12-CH_2), 3.62 (dd, J_1 = 10.0 Hz, J_2 = 9.8 Hz, 1H^{minor}), 3.69−3.74 (m, 1H^{minor}), 3.78 (dd, J_1 = 10.8 Hz, J_2 = 6.8 Hz, 1H, 12-CH_2), 4.99−5.07 (m, 2H, 13′-CH_2), 5.08−5.12 (m, 1H, 16-CH), 5.34−5.43 (m, 1H^{minor}), 5.49−5.55 (m, 1H^{minor}), 5.61 (dt, J_1 = 10.3 Hz, J_2 = 8.0 Hz, 1H, 9-CH), 5.71−5.85 (m, 1H, 13-CH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 9.8, 10.9, 24.1, 24.4, 24.5, 25.2, 25.5, 25.9, 26.2, 26.3, 26.5, 26.8, 27.1, 27.7, 30.6, 32.1, 33.1, 33.2, 37.3, 39.1 (C11), 42.2, 45.1 (C15), 50.1, 63.5 (C12), 65.9, 78.0 (C16), 78.2, 116.1 (C13′), 117.2, 129.8, 131.1 (C9), 132.6 (C10), 134.2, 137.0, 138.1 (C13), 173.9, 174.8 (C1); IR ν 3470 (m), 2930 (s), 2860 (s), 1730 (s), 1640 (m), 1460 (m), 1365 (m), 1225 (s), 1175 (m), 1055 (m), 910 (m), 735 (w). Anal. Calcd for $C_{19}H_{32}O_3$: C, 74.0; H, 10.5. Found: C, 73.8; H, 10.4; 308.46 g/mol.

Synthesis of the Triene 24. Oxidation. To a solution of the alcohol **24** (308.46 g/mol, 326 mg, 1.06 mmol, 1 equiv) in CH_2Cl_2 (10.5 mL) and DMSO (10.5 mL) was added 2-iodoxybenzoic acid ($C_7H_5IO_4$, 280.02 g/mol, 592 mg, 2.11 mmol, 2 equiv). After being stirred for 2.5 h, the reaction mixture was diluted by the addition of water. The aqueous phase was separated and extracted with CH_2Cl_2 (3×). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (cyclohexane/ethyl acetate 100/1 to 50/1) to afford the corresponding aldehyde ($C_{19}H_{30}O_3$, 306.44 g/mol, 274 mg, 0.894 mmol) as a mixture of double-bond isomers. Characterization data are reported for the mixture of isomers; signals that refer to the 9E-configured lactone are labeled accordingly: R_f 0.59 (cyclohexane/ethyl acetate 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83−0.91 (m, 3H), 1.25−1.86 (series of m, 12H), 1.97−2.51 (series of m, 6H), 3.02 (dd, J_1 = 9.5 Hz, J_2 = 2.8 Hz, 1H^E), 3.61−3.65 (m, 1H), 4.96−5.12 (m, 3H), 5.19−5.31 (m, 1H^E), 5.43−5.49 (m, 1H), 5.56−5.63 (m, 2H^E), 5.67−5.81 (m, 2H), 9.56 (d, J = 2.5 Hz, 1H), 9.75 (s, 1H^E), 29 proton signals reported for the major compound. **Methylenation.** To a stirred solution of methyltriphenylphosphonium bromide (357.22 g/mol, 1.596 g, 4.47 mmol, 5 equiv) in THF (15 mL) at 0 °C was added t-BuOK (112.21 g/mol, 2.185 g of a 20% w/w (1.7 M) solution in THF, 437 mg, 3.89 mmol, 4.4 equiv). After being stirred for 20 min at 0 °C, a solution of the aldehyde just prepared (306.44 g/mol, 274 mg, 0.894 mmol, 1 equiv) in THF (15 mL) at 0 °C was added. After being stirred for 30 min at 0 °C, the reaction mixture was diluted by the addition of saturated aqueous NH_4Cl solution. The aqueous layer was separated and extracted with CH_2Cl_2 (3×). The organic extracts were combined, dried ($MgSO_4$), and concentrated. Purification of the residue by chromatography (cyclohexane/ethyl acetate 200/1) delivered the triene **24** (211 mg, 0.69 mmol, 65%) as an inseparable mixture of double bond isomers. Characterization data are reported for the mixture of isomers; signals that refer to the 9E-configured lactone are labeled accordingly: R_f 0.80 (cyclohexane/ethyl acetate 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, J = 7.4 Hz, 3H), 1.30−1.43 (m, 7H), 1.48−1.55 (m, 2H), 1.59−1.65 (m, 1H), 1.72−1.79 (m, 2H), 1.82−1.89 (m, 2H), 1.91−1.99 (m, 1H), 2.06−2.12 (m, 1H), 2.18−2.25 (m, 1H), 2.27−2.36 (m, 2H^E), 2.43−2.48 (m, 2H), 2.93−3.00 (m, 1H^E), 3.28 (td, J_1 = 7.9 Hz, J_2 = 4.0 Hz, 1H), 4.95−5.08 (m, 5H), 5.20−5.32 (m, 5H^E), 5.46−5.56 (m, 2H), 5.61−5.67 (m, 2H^E), 5.74−5.87 (m, 2H), 5.97−6.05 (m, 2H^E); ^{13}C NMR (101 MHz, $CDCl_3$) δ 9.6, 11.1^E, 23.8^E, 24.5^E, 24.6, 24.9, 25.0, 25.7, 25.8, 26.1^E, 26.4^E, 26.6, 26.7, 27.2^E, 27.7^E, 30.6^E, 32.4, 33.0^E, 33.3, 37.0^E, 41.2, 45.8^E, 46.0, 49.5^E, 76.3, 78.7^E, 113.6 ^{E}, 115.8, 116.3, 117.0^E, 129.7, 130.5^E, 131.7^E, 131.8, 137.3^E, 137.8, 138.5, 143.5^E, 173.8, 174.1^E; IR ν 3075 (w), 2930 (s), 2860 (s), 1730 (s), 1640 (m), 1455 (s), 1370 (m), 1220 (s), 1150 (s), 995 (s), 745 (w). Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.9; H, 10.6. Found: C, 79.1; H, 10.7; 304.47 g/mol.

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(−)-9,10-Dihydroecklonialactone B (3). RCM. To a solution of the triene **24** (304.47 g/mol, 53 mg, 0.174 mmol, 1 equiv) in toluene (14 mL) were successively added 1,4-benzoquinone (108.09 g/mol, 0.7 mg, 0.0648 mmol, 0.04 equiv) and Grubbs catalyst, first generation ($C_{43}H_{72}Cl_2P_2Ru$, 822.96 g/mol, 3 mg, 0.00365 mmol, 0.021 equiv). Under a constant stream of argon, the reaction mixture was stirred for 1.5 h at 35 °C. The solvent was then evaporated at reduced pressure, and the residue was purified by chromatography (cyclohexane/ethyl acetate 200/1) to deliver the corresponding bicyclic lactone ($C_{18}H_{28}O_2$, 276.41 g/mol, 43 mg, 0.156 mmol) as a mixture of double-bond isomers. Characterization data are reported for the mixture of isomers; signals that refer to the 9*E*-configured lactone are accordingly: R_f 0.73 (cyclohexane/ethyl acetate 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 7.4 Hz, 3H), 1.22−1.50 (m, 8H), 1.53−1.62 (m, 2H), 1.64−1.69 (m, 2H^E), 1.70−1.77 (m, 1H), 1.78−1.84 (m, 1H), 1.94−2.02 (m, 1H), 2.04−2.10 (m, 1H), 2.15−2.23 (m, 1H), 2.25−2.32 (m, 2H), 2.34−2.43 (m, 1H), 2.44−2.52 (m, 1H), 3.15−3.21 (m, 1H^E), 3.49−3.57 (m, 1H), 4.7−4.76 (m, 1H^E), 4.84 (ddd, J_1 = 8.2 Hz, J_2 = 6.7 Hz, J_3 = 4.8 Hz, 1H), 4.90−4.97 (m, 1H^E), 5.10−5.15 (m, 1H^E), 5.24−5.29 (m, 1H), 5.35−5.39 (m, 1H), 5.42−5.44 (m, 1H), 5.61−5.66 (m, 1H + 1H^E), 28 proton signals reported for the major compound. **Bromohydrin.** To solution of the RCM product (43 mg, 0.156 mmol, 1 equiv) in acetone (6.5 mL) and H_2O (2.2 mL) was added NBS (177.99 g/mol, 28 mg, 0.157 mmol, 1 equiv) at 0 °C. After being stirred at ambient temperature for 1 h, the reaction mixture was diluted with water. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography (cyclohexane/ethyl acetate 50/1 to 20/1) to deliver the bromohydrin ($C_{18}H_{29}BrO_3$, 373.33 g/mol, 26 mg, 0.070 mmol): R_f 0.53 (cyclohexane/ethyl acetate 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82−0.90 (m, 3H), 1.20−2.25 (m, 2H), 1.32−1.41 (m, 4H), 1.42−1.48 (m, 2H), 1.52−1.62 (m, 2H), 1.65−1.75 (m, 3H), 1.88−1.96 (m, 1H), 2.28−2.37 (m, 2H), 2.43−2.55 (m, 2H), 2.62 (ddd, J_1 = 14.4 Hz, J_2 = 10.4 Hz, J_3 = 6.3 Hz, 1H), 3.47 (dd, J_1 = 8.7 Hz, J_2 = 4.9 Hz, 1H), 4.15 (d, J = 4.5 Hz, 1H), 4.43 (d, J = 6.3 Hz, 1H), 4.82 (dt, J_1 = 6.7 Hz, J_2 = 3.4 Hz, 1H), 5.43−5.48 (m, 1H), 5.52−5.59 (m, 1H). **(+)-Ecklonialactone B.** To a solution of the bromohydrin (26 mg, 0.07 mmol, 1 equiv) in toluene (3 mL) was added Ag_2O (231.74 g/mol, 16 mg, 0.07 mmol, 1 equiv). The reaction mixture was heated to 120 °C for 3 h. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified by chromatography (cyclohexane/ethyl acetate 200/1 to 100/1) to afford ecklonialactone B ($C_{18}H_{28}O_3$, 292.41 g/mol, 12 mg, 0.041 mmol) as a mixture of $\Delta^{9,10}$-double bond isomers and contaminated with an inseparable impurity. Characterization data are reported for the major compound from the mixture of isomers: R_f 0.77 (cyclohexane/ethyl acetate 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, J = 7.3 Hz, 3H), 1.25−1.49 (m, 12H), 1.55−1.62 (m, 1H), 1.67−1.77 (m, 1H), 1.80−1.95 (m, 2H), 2.05−2.11 (m, 2H), 2.36−2.43 (m, 1H), 3.03 (d, J = 9.5 Hz, 1H), 3.25 (d, J = 2.5 Hz, 1H), 3.50 (d, J = 2.0 Hz, 1H), 4.97 (ddd, J_1 = 12.7 Hz, J_2 = 7.6 Hz, J_3 = 2.7 Hz, 1H), 5.11 (dd, J_1 = J_2 = 10.2 Hz, 1H), 5.48 (dddd, J_1 = 10.4 Hz, J_2 = J_3 = J_4 = 8.0 Hz, 1H). **Hydrogenation.** To a solution of synthetic ecklonialactone B as a mixture of $\Delta^{9,10}$-double-bond isomers and contaminated by the inseparable impurity (12 mg, 0.041 mmol, 1 equiv) in EtOAc (8 mL) was added PtO_2 (227.08 g/mol, 6 mg, 0.026 mmol, 0.64 equiv). The vacuum degassed (3×) reaction mixture was flushed with Ar (2×) and finally with H_2 (balloon). The reaction mixture was then stirred for 3 h at ambient temperature under an atmosphere of H_2 (balloon). The reaction mixture was subsequently filtered through Celite, and the solvent was removed under reduced pressure. Purification of the residue by chromatography (cyclohexane/ethyl acetate 100/1 to 50/1) afforded (−)-9,10-dihydroecklonialactone B [(−)-**3**] (9 mg, 0.031 mmol, 18%) contaminated with an NMR-visible but inseparable minor impurity. NMR signal assignment rests on ^{1}H/^{1}H COSY and ^{1}H/^{13}C HSQC experiments. For copies of NMR spectra see the Supporting Information: R_f 0.71 (cyclohexane/ethyl acetate 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, J = 7.4 Hz, 3H, H-18), 1.23−1.49 (m, 15H), 1.58−1.63 (m, 1H), 1.69−1.82 (m, 2H), 1.83−1.90 (m, 3H, H-14 and H-15), 2.13 (t, J = 7.9 Hz, 1H, H-11), 2.35−2.38 (m, 2H), 3.31 (d, J = 2.5 Hz, 1H, H-12), 3.44 (d, J = 2.0 Hz, 1H, H-13), 4.87 (ddd, J_1 = 10.2 Hz, J_2 = 7.1 Hz, J_3 = 2.9 Hz, 1H, H-16); ^{13}C NMR (101 MHz, $CDCl_3$) δ 8.9, 24.40, 24.43, 24.90, 24.93, 25.06, 25.40, 25.88, 26.12, 28.7, 29.1, 33.8, 39.2, 44.4, 57.2, 61.5, 79.2, 174.0; IR ν 2930 (s), 2860 (s), 1730 (s), 1455 (m), 1360 (w), 1260 (m), 1220 (m), 1175 (m), 1045 (m), 1085 (w), 945 (w), 840 (s); HRMS (ESI) calcd for $C_{18}H_{31}O_3$ ([M + H]$^+$) 295.22677, found 295.22734; $[\alpha]^{23}_D$ −16.5 (*c* 0.58, $CHCl_3$); $C_{18}H_{30}O_3$, M = 294.43 g/mol; for comparison, (+)-**3**: $[\alpha]^{23}_D$ = +14.5 (*c* 0.55, $CHCl_3$).[12,16]

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H NMR, ^{13}C NMR, and IR spectra. Experimental details for kinetic measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Claisen, L. *Chem. Ber.* **1912**, *45*, 3157−3167.
(2) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423−1452.
(3) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205−247.
(4) Rehbein, J.; Hiersemann, M. *Synthesis* **2013**, *45*, 1121−1159.
(5) Gosteli-type allyl vinyl ethers refers to 2-alkoxycarbonyl-substituted allyl vinyl ethers; the [3,3]-sigmatropic rearrangement of Gosteli-type allyl vinyl ethers is denoted as the Gosteli−Claisen rearrangement. Gosteli, J. *Helv. Chim. Acta* **1972**, *55*, 451−460.
(6) Abraham, L.; Körner, M.; Schwab, P.; Hiersemann, M. *Adv. Synth. Catal.* **2004**, *346*, 1281−1294.
(7) (a) Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 9228−9229. (b) Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 5062−5075. See also: Kirsten, M.; Rehbein, J.; Hiersemann, M.; Strassner, T. *J. Org. Chem.* **2007**, *72*, 4001−4011.
(8) For conceptually related work, see: (a) Helmboldt, H.; Hiersemann, M. *Tetrahedron* **2003**, *59*, 4031−4038. (b) Tan, J.; Cheon, C.-H.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 8264−8267.
(9) Pollex, A.; Hiersemann, M. *Org. Lett.* **2005**, *7*, 5705−5708.
(10) Körner, M.; Hiersemann, M. *Org. Lett.* **2007**, *9*, 4979−4982.
(11) Gerwick, W. H. *Chem. Rev.* **1993**, *93*, 1807−1823.
(12) Kurata, K.; Taniguchi, K.; Shiraishi, K.; Hayama, N.; Tanaka, I.; Suzuki, M. *Chem. Lett.* **1989**, 267−270. Only incomplete ^{1}H NMR data have been reported for compound (+)-**3**, and ^{13}C NMR data have not been provided.
(13) Todd, J. S.; Proteau, P. J.; Gerwick, W. H. *J. Nat. Prod.* **1994**, *57*, 171−174.
(14) (a) Hickmann, V.; Alcarazo, M.; Fürstner, A. *J. Am. Chem. Soc.* **2010**, *132*, 11042−11044. (b) Hickmann, V.; Kondoh, A.; Gabor, B.; Alcarazo, M.; Fürstner, A. *J. Am. Chem. Soc.* **2011**, *133*, 13471−13480.
(15) Wang, Q.; Millet, A.; Hiersemann, M. *Synlett* **2007**, 1683−1686.
(16) Becker, J.; Butt, L.; von Kiedrowski, V.; Mischler, E.; Quentin, F.; Hiersemann, M. *Org. Lett.* **2013**, *15*, 5982−5985.
(17) Jaschinski, T.; Hiersemann, M. *Org. Lett.* **2012**, *14*, 4114−4117.
(18) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653−5660.
(19) Modified conditions, based on: Haraguchi, K.; Tanaka, H.; Miyasaka, T. *Synthesis* **1989**, 434−436.

(20) (a) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507. (b) Chen, L.; Lee, S.; Renner, M.; Tian, Q.; Nayyar, N. *Org. Process Res. Dev.* **2005**, *10*, 16−164.
(21) (a) Jones, D. N.; Mundy, D.; Whitehouse, R. D. *J. Chem. Soc.* **1970**, 86−87. (b) Sharpless, K. B.; Young, M. W.; Lauer, R. F. *Tetrahedron Lett.* **1973**, *14*, 1979−1982.
(22) (a) Rehbein, J.; Leick, S.; Hiersemann, M. *J. Org. Chem.* **2009**, *74*, 1531−1540. (b) Rehbein, J.; Hiersemann, M. *J. Org. Chem.* **2009**, *74*, 4336−4342.
(23) Schuler, F. W.; Murphy, G. W. *J. Am. Chem. Soc.* **1950**, *72*, 3155−3159.
(24) Regitz, M.; Anschütz, W.; Liedhegener, A. *Chem. Ber.* **1968**, *101*, 3734−3743.
(25) Miller, D. J.; Moody, C. J. *Tetrahedron* **1995**, *51*, 10811−10843.
(26) (a) Paquet, F.; Sinaÿ, P. *J. Am. Chem. Soc.* **1984**, *106*, 8313−8315. (b) Pawlak, J. L.; Berchtold, G. A. *J. Org. Chem.* **1987**, *52*, 1765−1771. (c) Lesuisse, D.; Berchtold, G. A. *J. Org. Chem.* **1988**, *53*, 4992−4997.
(27) Initial experiments indicate a noticeable dependence of the yield and the *E*/*Z* selectivity on the nature of the base and the reaction temperature profile. Most significantly, using the diethyl phosphonate and/or NaH, NaHMDS, LiHMDS as the Brønsted base led to decreased *E*/*Z* selectivity.
(28) In our hands, allyl vinyl ether **13** refused to undergo the catalytic asymmetric Gosteli−Claisen rearrangement; instead, **13** was reisolated as a mixture of double bond isomers, and we assume a Lewis acid catalyzed intramolecular conjugate addition of the nucleophilic selenium atom is likely responsible for the unusual lack of reactivity and the double-bond isomerization as well.
(29) Evans, D. A.; Miller, S. J.; Lectka, T.; Matt, P. v. *J. Am. Chem. Soc.* **1999**, *121*, 7559−7573.
(30) Balta, B.; Öztürk, C.; Aviyente, V.; Vincent, M. A.; Hillier, I. H. *J. Org. Chem.* **2008**, *73*, 4800−4809.
(31) Application of $[Cu\{(R,R)\text{-Ph-box}\}(tfe)_2](SbF_6)_2$ enables a faster conversion (87% after 1 h) at a lower catalyst loading (0.025 equiv). However, the Ph-BOX ligand is far less effectively enantioface-differentiating (dr > 95:5, 65% ee).
(32) Control experiments have demonstrated that complexes like **21**·Cu(box) are catalytically active even in the absence of auxiliary ligands like H_2O or CF_3CH_2OH.
(33) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191−1224.
(34) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553.
(35) Gille, A.; Hiersemann, M. *Org. Lett.* **2010**, *12*, 5258−5261.
(36) The assignment of the absolute configuration is in accordance with the stereochemical model for the doubly diastereoselective (*R*)-Me-CBS reduction of α-keto esters as described in: Harb, W.; Ruiz-López, M. F.; Coutrot, F.; Grison, C.; Coutrot, P. *J. Am. Chem. Soc.* **2004**, *126*, 6996−7008.
(37) Hicks, D. R.; Fraser-Reid, B. *Synthesis* **1974**, 203.
(38) Cink, R. D.; Forsyth, C. J. *J. Org. Chem.* **1995**, *60*, 8122−8123.
(39) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522−524.
(40) (a) Wang, C.; Yu, M.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Chem.—Eur. J.* **2013**, *19*, 2726−2740. (b) Marx, V. M.; Herbert, M. B.; Keitz, B. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2012**, *135*, 94−97.
(41) Favored 6-*exo*-*trig* versus disfavored 5-*endo*-*trig* iodoetherification; see: Gao, X.; Woo, S. K.; Krische, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 4223−4226.
(42) Simonot, B.; Rousseau, G. *J. Org. Chem.* **1993**, *58*, 4−5.
(43) (a) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963−3964. (b) Bennett, F.; Bedford, S. B.; Bell, K. E.; Fenton, G.; Knight, D. W.; Shaw, D. *Tetrahedron Lett.* **1992**, *33*, 6507−6510.
(44) The ^{13}C NMR spectrum shows two (new) signals at 7.8 and 9.6 ppm which we consider as evidence for the presence of the RCH_2I carbon atoms of the two diastereomers of **22**.
(45) Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4038−4040.
(46) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160−17161.
(47) $^1H/^1H$ COSY and $^1H/^{13}C$ HSQC experiments support our structural assignment.
(48) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019−8022.
(49) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039−2041.
(50) Voorhees, V.; Adams, R. *J. Am. Chem. Soc.* **1922**, *44*, 1397−1405.
(51) (a) Miescher, K. *Helv. Chim. Acta* **1946**, *29*, 743−752. (b) Stahl, E.; Kaltenbach, U. *J. Chromatogr.* **1961**, *5*, 351−355.
(52) Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. *Organometallics* **2010**, *29*, 2176−2179.
(53) McKennon, M. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 3568−3571.
(54) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824−5825.
(55) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726−728.
(56) Haraguchi, K.; Tanaka, H.; Hayakawa, H.; Miyasaka, T. *Chem. Lett.* **1988**, *6*, 931−934.
(57) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.