tions proceeded smoothly in the presence of a catalytic amount of **1** in water without using any organic co-solvents. To the best of our knowledge, this is the first example of the polymer-supported Lewis acid catalyst that can be used in this manner. It is noted that the reactions proceeded much faster in water than in other media including organic solvents. The simple procedures, easy recovery, reusable catalyst, and the use of water as a solvent are expected to contribute to development of benign chemical processes.

Experimental Section

A typical experimental procedure is described for the allylation reaction of 4-phenyl-2-butanone with tetraallyltin. 4-Phenyl-2-butanone (0.4 mmol), tetraallyltin (0.2 mmol), and **1** (0.0064 mmol, 1.6 mol%) were combined in water (3 mL). The mixture was stirred for 12 h at RT. Catalyst **1** was filtered and washed with ethyl acetate. The filtrate was extracted with ethyl acetate, and the combined organic layers were dried (Na_2SO_4). After filtration and concentration, the residue passed through a column packed with silica gel to afford the allylated adduct in 95% yield. The recovered **1** was reused several times without loss of activity.

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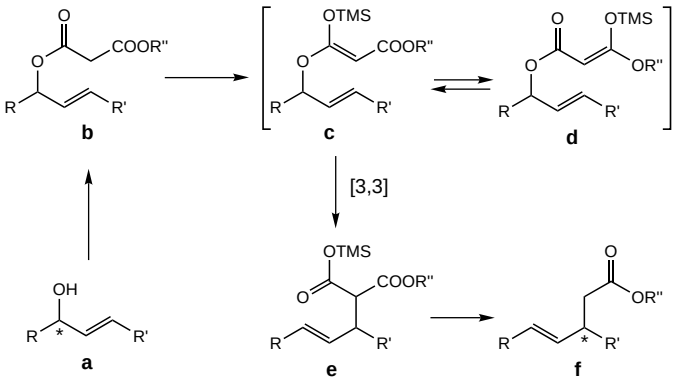
A New Variant of the Claisen Rearrangement from Malonate-Derived Allylic Trimethylsilyl Ketene Acetals: Efficient, Highly Enantio- and Diastereoselective Syntheses of (+)-Methyl Dihydroepijasmonate and (+)-Methyl Epijasmonate**

Charles Fehr* and José Galindo

Among the large variety of [3,3] sigmatropic rearrangements,[1] the Johnson ortho ester Claisen rearrangement[2] has proven to be particularly useful, owing to its facile and broad applicability. Nonetheless, it also suffers from some limitations: trimethyl orthoacetate is impractical, because the reaction temperature is limited by its low boiling point (105–110 °C) and therefore, triethyl orthoacetate (b.p. 142–145 °C) is commonly used. As the Johnson Claisen rearrangement requires excess ortho ester, its industrial application is unattractive in those cases that require ulterior transesterification (e.g. for the synthesis of methyl esters).

We now report an alternative methodology, which is based on the Claisen rearrangement of trimethylsilyl(TMS)-ketene acetals of type **c** (presumably in equilibrium with **d**) derived from malonates **b**, followed by desilylation/decarboxylation of malonates **e** to esters **f** (Scheme 1). The synthetic concept



Scheme 1. Claisen rearrangement from malonate-derived TMS ketene acetals.

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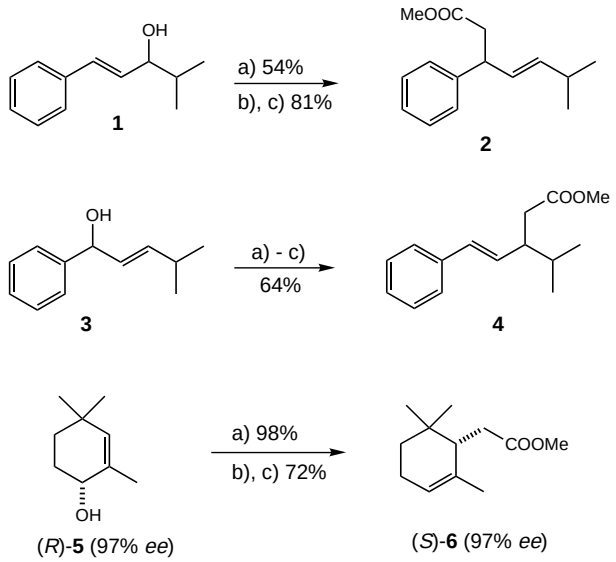
consists of linking any desired ester functionality (CO_2Me in this case) to the Claisen system, and then to discarding, after rearrangement, the ester unit that is involved in the rearrangement by desilylation/decarboxylation. Compared to an alkyl group, the TMS group allows the rearrangement to occur at lower temperature,[3] and following rearrangement, a selective desilylation/decarboxylation of the malonates **e** to the esters **f** is facilitated by the differentiated functionalities of the ester groups in **e** (Scheme 1). This new variant thus allows a perfect chirality transfer from **a** to **f** in both cyclic and acyclic systems.

Two literature precedents for rearrangements of allyl malonates should be mentioned: transesterification/rearrangement of an allylic alcohol and diethyl isopropyl malonate in the presence of $Ti(OEt)_4$ at 160–190 °C,[4] and the rearrangement of ethyl ketene acetals derived from allylic alcohols and ethyl β,β-diethoxyacrylate at 150–200 °C.[5] The first procedure turned out to be unsuitable for substrates that are prone to dehydration, and the second protocol, which also requires high reaction temperatures, additionally suffers from the difficulty of preparing ethyl β,β-diethoxyacrylates.

To demonstrate the feasibility of this new methodology, the two regioisomeric and relatively sensitive racemic allylic alcohols **1** and **3** were chosen as substrates. The corresponding allyl methyl malonates (Scheme 1: type **b**) were prepared from the alcohols and methyl malonyl chloride, and used without purification. Deprotonation (NaH (or KH)/THF) and silylation (TMSCl) afforded the labile silyl ketene acetals of type **c** (or **d**)[6] which, when heated in THF at 50–65 °C for 3 h, underwent smooth rearrangement to the rearranged malonates of type **e**.[7] These were desilylated and decarboxylated (*N*-methylpyrrolidone (NMP), H_2O, NaCl, 140 °C)[8] to afford the methyl esters **2** and **4**, respectively, in high yield (Scheme 2). Neither **2** nor **4** were contaminated with their regioisomeric esters (**4** and **2**, respectively), and no traces of isomeric (*Z*)-enoates could be detected, thus indicating that the reaction proceeds via a highly ordered transition state. As a consequence, this malonate rearrangement should be ideal for the transfer of chirality in nonracemic cyclic and acyclic systems.[9]

Indeed, as a test substrate, the known allylic alcohol (*R*)-**5**[10] was rearranged into the sterically constrained ester (*S*)-**6**[11] in 70% yield and without any loss in enantiomeric purity (GC: Megadex 5: peak 1).

In the context of our planned syntheses of (+)-methyl dihydroepijasmonate ((+)-**16a**) and (+)-methyl epijasmonate ((+)-**16b**), we next chose allylic alcohols (*R*)-**8a** and (*R*)-**8b** as substrates, whose conversion into the rearranged esters (*R*)-**10a** and (*R*)-**10b** (GC: Megadex 5: peak 1), respectively, also proceeded in good yield and without any racemization (Scheme 3). Allylic alcohols (*R*)-**8a** (93% *ee*, $[\alpha]_D^{20} = +28$ ($c = 2.7$ in $CHCl_3$)) and (*R*)-**8b** (92% *ee*; ($[\alpha]_D^{20} = +58$ ($c = 3.5$ in $CHCl_3$)) were prepared by oxazaborolidine-catalyzed highly enantioselective $BH_3 \cdot SMe_2$ reduction[12] of the readily accessible parent enones **7a** and **7b**.[13] The only moderate

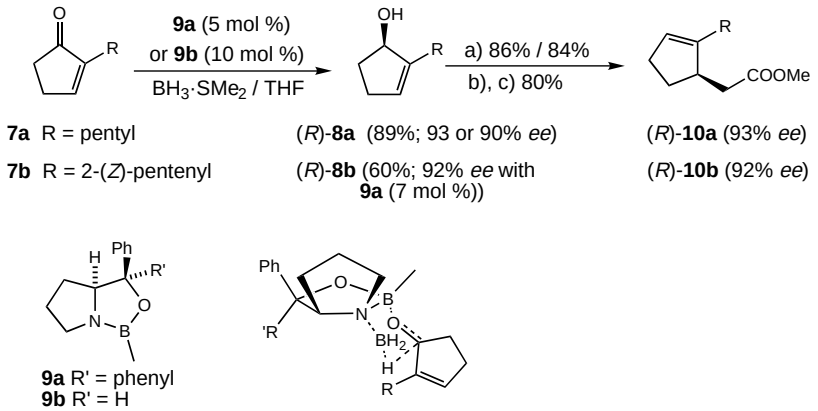


Scheme 2. Regiocontrol and chirality transfer in the Claisen rearrangement of malonate-derived TMS ketene acetals: a) methyl malonyl chloride (1.2 equiv), NEt_3 (1.3 equiv), CH_2Cl_2, 2–5 °C, 30 min; b) NaH (1.25 equiv), THF or DME, 55 °C, 1 h, then TMSCl (2.0 equiv), 50–65 °C, 3 h or DME, 85 °C, 8 h (for (*S*)-**6**); c) NMP, H_2O (1.8 equiv), NaCl (1.3 equiv), 140 °C, 30 min.

yield obtained in the reduction of **7b** to (*R*)-**8b** (60%) is due to competing hydroboration of the 2-(*Z*)-pentenyl double bond.

The diphenyl prolinol derived oxazaborolidine **9a** is thought to bind substrate and borane as shown in Scheme 3.[12] However, as the contribution of the α-phenyl group is not evident, we also examined the reduction of **7a** with the hitherto unknown monophenyl prolinol[14] derived oxazaborolidine **9b**. Its efficiency turned out to be slightly inferior to **9a**: whereas 5 mol% of **9a** affords (*R*)-**8a** of 93% *ee*, **9b** (5 or 10 mol%) gives rise to 86 or 90% *ee*.

As an alternative to this enantioselective reduction/esterification protocol for access to the enantiopure malonate intermediates, we have now developed a new procedure involving enzymatic kinetic resolution. This method achieves highly selective mono-transesterification of dimethyl malonate with one enantiomer of a racemic allylic alcohol substrate.[15] Thus, treatment of (±)-**8a** or (±)-**8b**[16] and



Scheme 3. Preparation of (*R*)-**10a** and (*R*)-**10b** by enantioselective reduction/Claisen rearrangement: a)–c) see Scheme 2.

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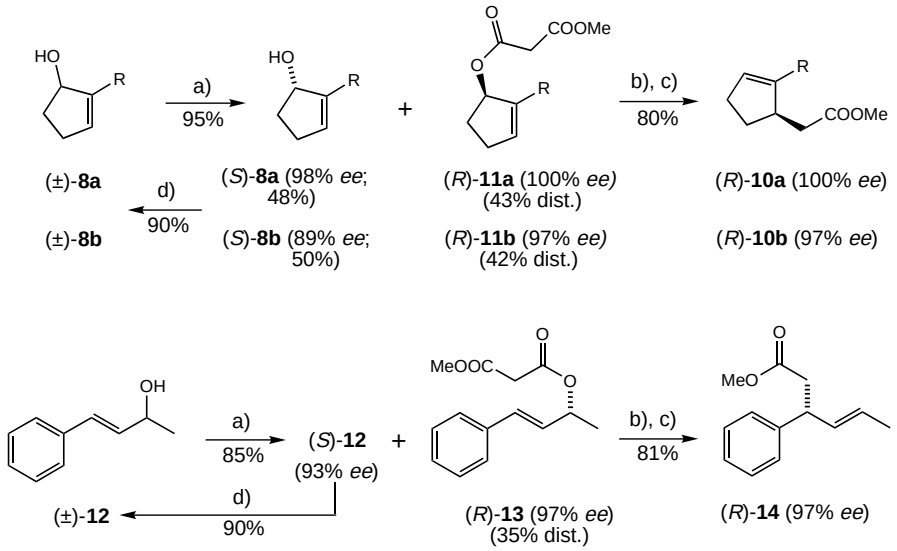
dimethyl malonate at 40 °C and reduced pressure with catalytic amounts of Novozym 435 (immobilized *Candida antarctica* from *Novo Nordisk*) in the presence of $KHCO_3$ (5 mol %)[17] affords the corresponding malonates (*R*)-**11a** or (*R*)-**11b** with excellent enantioselectivity (97 – 100 % *ee*) and almost 50 % conversion (Scheme 4). Conversion to the



Scheme 4. Enzymatic transesterification of dimethyl malonate and allylic alcohols, followed by Claisen rearrangement of the malonate-derived TMS ketene acetals: a) dimethyl malonate (1.15 molar equivalents), $KHCO_3$ (0.05 equivalents), Novozym 435 (10 wt %), 40 °C, 8 Torr, 80 min; b) and c) see Scheme 2; d) aqueous H_2SO_4, THF, 20 °C, 24 h.

rearranged methyl esters (*R*)-**10a** and (*R*)-**10b** was subsequently effected as described above.[18] The unconverted alcohols, (*S*)-**8a** and (*S*)-**8b**, could be racemized under acidic conditions and recycled, thus further improving the efficiency of this process.

Another example, the transformation of (±)-**12** to (*R*)-**14** (97 % *ee*) demonstrates the superiority of this methodology in comparison with the related Pd-catalyzed malonate allylation reaction, where, starting from (*S*)-**12** (39 % *ee*), ester (*S*)-**14** (30 % *ee*) is obtained only as a very minor regioisomer (8 % of mixture).[19]

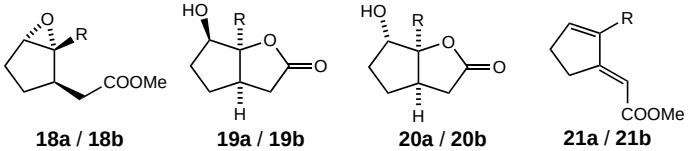
With (*R*)-**10a** and (*R*)-**10b** in hand, we were now ready to accomplish very efficient syntheses of (+)-methyl dihydroepijasmonate ((+)-**16a**) and (+)-methyl epijasmonate ((+)-**16b**).

Ever since the isolation of (−)-methyl jasmonate ((−)-**15b**), which possesses an elegant jasmine odor, from *Jasmine oil* in 1962,[20] racemic methyl jasmonate ((±)-**15b**) has engendered intense research activity culminating in two industrial syntheses of (±)-**15b**.[21] Later on, isolation of the enantiomers of **15b**, as well as those of its diastereomer **16b**, revealed that solely (1*R*,2*S*)-(+)-**16b**, the primary product of biosynthesis, was organoleptically active.[22] Thus, although all stereoisomers of **15b** may exert synergic effects or improve a perfume composition as fixatives or enhancers, under equilibrating conditions racemic **15b** contains as little as 3 % of the olfactively active (+)-methyl epijasmonate ((+)-**16b**). In addition, (+)-**16b** displays several other biological activities such as regulation of plant growth[23] and plant defense,[24] as well as signal transmission in interplant communication.[25] Therefore, renewed recent synthetic activity has centered around methyl epijasmonate (**16b**) in its racemic[26, 27] or nonracemic form.[26, 28]

In close analogy, (+)-methyl dihydroepijasmonate ((+)-**16a**)[29] represents the organoleptically active stereoisomer of methyl dihydrojasmonate (Hedione: ((±)-**15a** (93 %) + (±)-**16a** (7 %)).

The major synthetic challenge comprises the elaboration of the *cis*-relationship in these *cis*-2,3-disubstituted cyclopentanones which are known to readily undergo epimerization. Indeed, all reported syntheses pass through the corresponding secondary alcohol and necessitate a careful oxidation in the final step.[26] Based on our recent findings[30] that the preference for peracid attack on the more electron-rich π-face of a C−C double bond is increased by the use of strong peracids (electrostatic interactions), we envisaged the diastereoselective epoxidation of **10a** and **10b**. *syn*-Epoxides **17a** and **17b** would then be expected to undergo a Lewis acid catalyzed stereocontrolled suprafacial 1,2-H migration[31] leading to the *cis*-jasmonates **16a** and **16b** (Scheme 5).

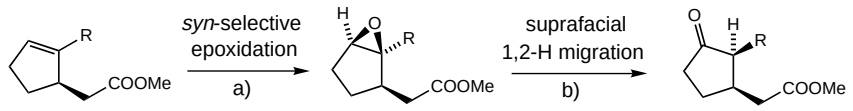
Indeed, epoxidation of (*R*)-**10a** with the strongest commonly used peracid, trifluoroperacetic acid, afforded the *syn*-epoxide **17a** with an excellent 99:1 diastereoselectivity.[32] Permaleic acid and *m*-chloroperbenzoic acid (*m*CPBA) showed decreased *syn*/*anti* selectivities of 89:11 and 86:14 and afforded lactones **19a** and **20a** in trace amounts.[33]



18a / 18b **19a / 19b** **20a / 20b** **21a / 21b**

The rearrangement of epoxide **17a** could be effected with a variety of Lewis acids, but in addition to **16a**, variable amounts of lactone **19a** and diene ester **21a** were produced. For instance, both $LiClO_4$ in diethyl ether,[31b] often used for acid-sensitive substrates, and trimethylsilyl triflate[31c] afford-

(–)-**15a**) (R = pentyl)
(+)-**16a**) (R = pentyl)
(–)-**15b**) (R = 2-(*Z*)-pentenyl)
(+)-**16b**) (R = 2-(*Z*)-pentenyl)



(*R*)-**10a** R = pentyl (+)-**17a** (+)-**16a**
(*R*)-**10b** R = 2-(*Z*)-pentenyl (+)-**17b** (+)-**16b**

Scheme 5. Synthesis of (+)-methyl dihydroepijasmonate and (+)-methyl epijasmonate. a) $(CF_3CO)_2O$ (2.0 equiv), H_2O_2 (1.35 equiv), Na_2CO_3 (2.7 equiv), CH_2Cl_2, $-50\,^\circ C$; b) $BF_3 \cdot OEt_2$ (0.25 – 0.32 equiv), CH_2Cl_2, 2 – 13 °C, 30 min.

ed large quantities of **19a** (30%) and **21a** (35 and 48% respectively) and only minor amounts of **16a** (28 and 10%, respectively).

The highest yields and selectivities in favor of **16a** were obtained with catalytic amounts of $AlCl_3$ (86%; containing 3% of **15a**), $BF_3 \cdot OEt_2$[31d] (83%; containing 2% of **15a**), or by using the dried, acidic clay Filtrol G-24 (75%; containing 5% of **15a**). Interestingly, no examples of $AlCl_3$-promoted epoxide rearrangements of this type have been reported.[31a]

These conditions were next successfully applied to the synthesis of (+)-methyl epijasmonate ((+)-**16b**). The *syn*-selective epoxidation of (*R*)-**10b** using trifluoroperacetic acid at $-50\,^\circ C$ afforded exclusively *syn*-epoxide (+)-**17b** (83%). Notably, the trisubstituted double bond in **10b** is epoxidized much faster than the disubstituted one; only 5% of di-epoxidation products are generated. Finally, stereocontrolled rearrangement of epoxide (+)-**17b** using catalytic amounts of $BF_3 \cdot OEt_2$ or $AlCl_3$ gave (+)-**16b** (97% *ee*) in 80% yield, accompanied by 6% of (−)-**15b**.

We have developed a concise, highly stereocontrolled synthesis of (+)-methyl dihydroepijasmonate ((+)-**16a**) and (+)-methyl epijasmonate ((+)-**16b**) based on an original methodology, comprising an enzyme-catalyzed enantioselective mono-esterification with dimethyl malonate, a novel Claisen rearrangement of the malonate-derived allylic silyl ketene acetal, and a highly stereoselective epoxidation – rearrangement sequence.

Experimental Section

(*R*)-**11a**: A homogeneous mixture of (±)-**8a** (27.5 g, 181 mmol) and dimethyl malonate (27.5 g, 208 mmol, 2.30 molar equivalents with respect to (*R*)-**8a**) was treated with ground $KHCO_3$ (0.89 g, 8.9 mmol) and then with Novozym 435 (immobilized *Candida antarctica* from *Novo Nordisk*, 1.80 g) and gently swirled in a 100-mL flask connected to a Büchi rotavapor at 40 °C and 8 Torr.[34] After 80 min, the reaction mixture was filtered and rinsed (Et_2O), washed (saturated $NaHCO_3$, saturated NaCl), dried (Na_2SO_4), and concentrated (48.4 g). Distillation under vacuum afforded a fraction (26.5 g; b.p. 35 – 90 °C/0.8 Torr) containing (*S*)-**8a** (98% *ee*), dimethyl malonate, and some (*R*)-**11a** and (*R*)-**11a** (19.95 g; b.p. 93 – 105 °C; yield: 43%; 100% *ee*, as determined by conversion into (*R*)-**10a**). For determining the yield of recovered (*S*)-**8a**, the mixed fractions (26.5 g) were hydrolyzed (KOH, MeOH, H_2O) to afford distilled (*S*)-**8a** (yield: 13.31 g; 48%; 89% *ee*).

Racemization of (*S*)-**8a**: The above distillation fraction was dissolved in THF (160 mL) and treated with 2% aqueous H_2SO_4 (100 mL). The slightly turbid mixture was stirred at 24 °C for 24 h, poured into a stirred 5% aqueous NaOH solution, and extracted twice with Et_2O. The organic phase was washed (H_2O, then saturated NaCl), dried (Na_2SO_4), concentrated, and distilled (bulb-to-bulb) to afford (±)-**8a** (12.2 g; containing 2% of dehydration products; yield: 90%).

(*R*)-**10a**: Malonate (*R*)-**11a** (9.90 g, 39.0 mmol) was added at 55 °C within 15 min to a mechanically stirred suspension of washed (3 × pentane) NaH (55% in oil; 2.14 g (1.18 g pure NaH), 49.0 mmol) in THF (100 mL) (350 mL three-necked flask, N_2), whereby immediate gas evolution (H_2) was observed. After 30 min, trimethylchlorosilane (8.50 g (9.80 mL); 78.0 mmol) was added rapidly. After the milky reaction mixture had been heated at 55 °C for 3 h, the product mixture containing the desired silyl methyl malonate of type **e** (Scheme 1) was concentrated at reduced pressure, dissolved in pentane, filtered through Celite, and concentrated (13.81 g; yield: 84% (GC); ^1H NMR (360 MHz, $CDCl_3$): $\delta = 3.72$ and 3.66 (83:17 (COOMe))). The crude product was dissolved in NMP (30 mL) and added slowly (90 min) to a hot (140 °C) mixture of NMP (60 mL (58.1 g)), H_2O (1.2 mL, 67 mmol), and NaCl (2.90 g, 49 mmol). After 15 min, the cooled reaction mixture was poured into water, and the ester was extracted (Et_2O, 2 ×), washed (H_2O, 3 ×, saturated aqueous NaCl), dried (Na_2SO_4), filtered, and concentrated. Bulb-to-bulb distillation of the residue (8.89 g) at 70 – 80 °C (oven temperature)/0.07 Torr afforded ester (*R*)-**10a** (7.10 g, 92% pure (80% yield; 100% *ee* (Megadex 5: peak 1)). A sample was further purified by chromatography (SiO_2; cyclohexane/AcOEt 98/2): $[\alpha]_D^{20} = +27$ ($c = 2.1$ in $CHCl_3$).

(+)-**16a** (using $AlCl_3$): A solution of (+)-**17a** (28.2 g, 124 mmol) in toluene (60 mL) was added between 4 and 7 °C (ice bath) in 45 min to a mechanically stirred solution of $AlCl_3$ (2.50 g, 19.0 mmol) in toluene (800 mL), to which had been added a trace amount of Na_2CO_3 (31 mg). Fifteen minutes after complete addition, the clear reaction mixture was hydrolyzed by adding a saturated $NaHCO_3$ solution (125 mL) at such a rate that the temperature did not exceed 15 °C. After the mixture was stirred for 15 h at room temperature, the organic layer was separated, washed (10% H_2SO_4, then H_2O, then saturated NaCl), dried (Na_2SO_4), and concentrated. The crude product (29.7 g; **16a**/**15a** = 97:3) was mixed with Primol 352 (Esso (heavy hydrocarbon), 100 g) and $CaCO_3$ (820 mg) and distilled at 85 – 90 °C/0.01 Torr to afford (+)-**16a** (25.9 g, 93% pure[35] (86%; **16a**/**15a** = 95:5; 100% *ee*, as determined by chiral GC (Megadex 5 or CD-Chirasil-DEX CB)).

(+)-**16a** (using $BF_3 \cdot OEt_2$): Compound (+)-**17a** (100 g, 442 mmol) was added between 2 and 5 °C in 35 min to a mechanically stirred solution of $BF_3 \cdot OEt_2$ (15.7 g, 110 mmol) in CH_2Cl_2 (800 mL). Two minutes after complete addition, the orange-brown reaction mixture was hydrolyzed by adding quickly a saturated $NaHCO_3$ solution (280 mL) (CO_2 evolution). After the mixture had been stirred for 2 h at room temperature, the organic layer was separated, washed with H_2O (50 mL), and concentrated. Leybold distillation at 82 °C/0.08 Torr afforded (+)-**16a** (89.5 g, 92% pure[35] (containing **21a** (7%)), 83%; **16a**/**15a** = 98:2; 100% *ee*).

(+)-**16b** (using $BF_3 \cdot OEt_2$): A solution of (+)-**17b** (2.0 g, 94% pure (containing diepoxides (5%)); 8.40 mmol) in CH_2Cl_2 was added between 11 and 13 °C in 25 min to a stirred solution of $BF_3 \cdot OEt_2$ (0.38 g (0.34 mL), 2.68 mmol) in CH_2Cl_2 (20 mL). Two minutes after complete addition, the dark reaction mixture was hydrolyzed and isolated as above. Yield after bulb-to-bulb distillation: 1.65 g (92% pure[35] (containing **21b** (6%)), 80%; **16b**/**15b** = 94:6; 97% *ee*, as determined by chiral GC (Megadex 5 or CD-Chirasil-DEX CB)).

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[34] The reaction was followed by quenching samples with $NaHCO_3$/Et_2O, followed by silylation of the unconverted alcohol with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) in toluene at 100 °C for 5 min and chiral GC analysis (Megadex 5). Normal GC analysis did not always give reproducible results (thermal instability of **11a**).

[35] The product can be further purified by flash column chromatography (SiO_2 F 60, 35–70 μ), using CH_2Cl_2 as solvent.