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Stereoselective *anti*-S_N2'-Substitutions of Secondary Alkylcopper-Zinc Reagents with Allylic Epoxides: Total Synthesis of (3*S*,6*R*,7*S*)-Zingiberenol

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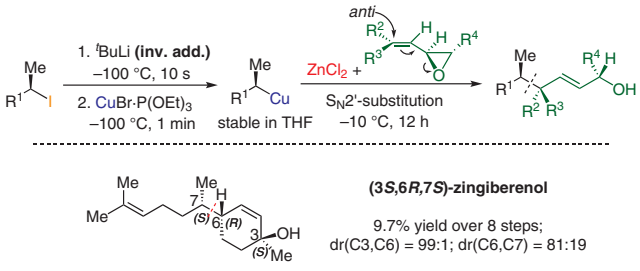

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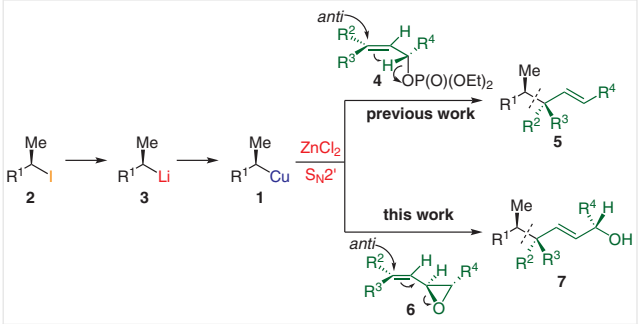
Abstract Chiral secondary mixed alkylcopper-zinc reagents were prepared from the corresponding alkyl iodides and reacted with allylic epoxides via an *anti*-S_N2'-substitution and retention of configuration of the chiral alkylorganometallic, leading to chiral allylic alcohols. This method was used in a total synthesis of the natural product (3*S*,6*R*,7*S*)-zingiberenol in 8 steps and 9.7% overall yield [dr (3*S*,6*R*) = 99:1; dr (6*R*,7*S*) = 81:19] starting from commercially available 3-methyl-2-cyclohexenone.

Key words lithium, stereoselective, copper, allylic epoxides, natural products

Metal-catalyzed S_N2- and S_N2'-substitutions of allylic substrates are common methods for the preparation of chiral molecules.[1,2] Thereby the chirality depends on the use of chiral ligands[1] or the use of chiral allylic substrates, which react according to an *anti*-S_N2'-substitution.[2] In addition, the control of regioselectivity of allylic substitutions is of high importance for organic synthesis and was intensively investigated.[3]

Recently, we have reported that chiral secondary alkylcopper reagents undergo highly selective S_N2- and S_N2'-substitution reactions with allylic halides and phosphates depending on the nature of the organometallic reagent.[4] Thus, secondary alkylcopper reagents of type **1** were prepared via a retentive I/Li-exchange reaction of secondary alkyl iodides **2** with ^{t}BuLi followed by a transmetalation with CuBr·P(OEt)$_3$ (see Scheme 1).[5] Compared to the corresponding alkyllithium reagents **3**, these organocopper reagents have a significantly higher configurational stability (up to –50 °C for several hours) in THF making them suitable for S_N2-substitutions with allylic bromides.[4] The addition of $ZnCl_2$ and the use of chiral allylic phosphates **4** switches the regioselectivity towards S_N2'-substitutions, leading to alkenes of type **5** with absolute control of two adjacent stereocenters (see Scheme 1). Furthermore, this methodology was used in the enantioselective total synthesis of several natural products, for example, the ant pheromones (+)-lasiol and (+)-faranal.[5]



Scheme 1 Stereoselective preparation of chiral alkylcopper reagents **1** and subsequent *anti*-S_N2'-substitutions with allylic electrophiles **4** and **6**

Herein, we report the stereoselective reaction of secondary alkylcopper-zinc reagents with allylic epoxides **6** leading to chiral allylic alcohols of type **7** (Scheme 1), which represent a common motif in organic synthesis and natural products. An example for a chiral cyclic allylic alcohol is the natural product zingiberenol (**8**) (see Figure 1).[6] Only two of 8 possible stereoisomers exist in nature, (3*S*,6*R*,7*S*)- and (3*S*,6*S*,7*S*)-zingiberenol. Retrosynthetic analysis showed that (3*S*,6*R*,7*S*)-zingiberenol (**8**) can be prepared via an *anti*-S_N2'-substitution reaction of the chiral allylic epoxide **9** and the copper reagent **10** (prepared from the corresponding alkyl iodide **11**, see Figure 1). Starting from zingiberenol, several other natural products can be prepared using literature known transformations. Reaction of zingiberenol with AD-mix-α and subsequent epoxidation leads to the pheromone of the brown marmorated stink bug, murgantiol (**12**).[7]

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Further dehydration using sulfuric acid leads to the β-sesquiphellandrene (**13**) and the monocyclic sesquiterpene zingiberene (**14**).[6a]

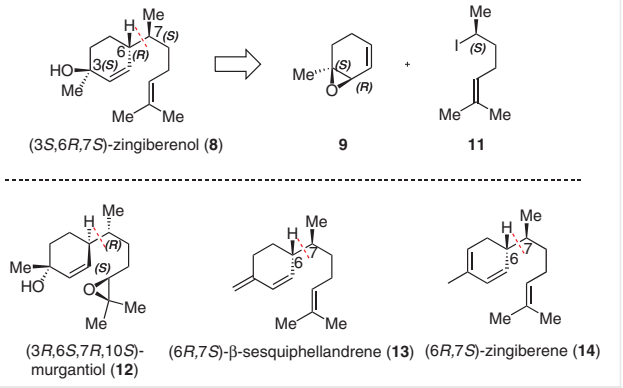
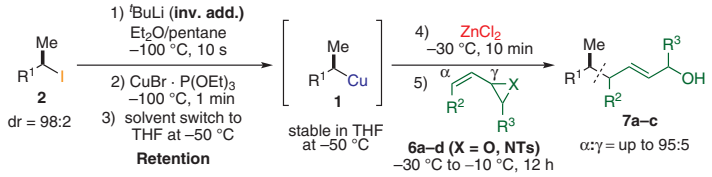


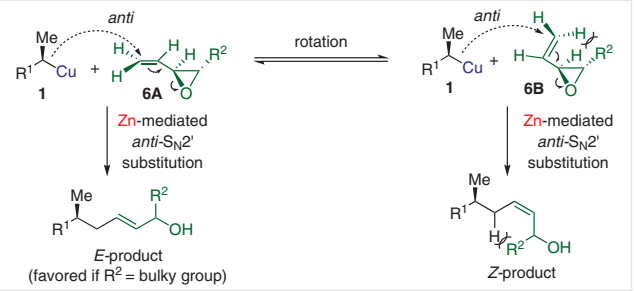
Figure 1 Retrosynthetic analysis of (3*S*,6*R*,7*S*)-zingiberenol (**8**). Structures of murgantiol (**12**), β-sesquiphellandrene (**13**), and zingiberene (**14**)

In preliminary experiments, the regioselectivity of S_N2'-substitution reactions of various allylic epoxides with chiral alkylcopper reagents was examined. Therefore, the diastereomerically enriched alkyl iodide *syn*-**2a** (dr = 98:2) was treated with ^{t}BuLi (2.2 equiv) at –100 °C in pentane/diethyl ether affording the corresponding alkyllithium reagent *syn*-**3a**. Subsequent treatment with CuBr·P(OEt)$_3$ (1.5 equiv) led to the organocopper reagent *syn*-**1a** (see Table 1). This alkylcopper reagent is configurationally stable in THF and thus, a solvent switch was performed at –50 °C.[5] The addition of $ZnCl_2$ (1.5 equiv, –30 °C, 10 min) and subsequent treatment with the allylic epoxide **6a** (3.0 equiv, –30 °C to –10 °C, 12 h) furnished the allylic alcohol *syn*-**7a** in 46% yield with retention of configuration (dr = 94:6; *E*/*Z* = 86:14; Table 1, entry 1). Interestingly, the ratio of S_N2'-substitution (α-position) to S_N2-substitution (γ-position) was higher than 95:5. In the same way, the corresponding *anti*-allylic alcohol (*anti*-**7a**) was prepared with retention of configuration and high S_N2'-selectivity (54% yield; dr = 9:91; α:γ = 95:5; *E*/*Z* = 88:12; entry 2).

Table 1 Optimization Reactions for the Opening of Allylic Substrates **6**



Entry	Alkylcopper	Electrophile	Product of type **7**
1	*syn*-**1a**	**6a**	*syn*-**7a**, 46%, dr = 94:6, α:γ = 95:5, *E*/*Z* = 86:14
2	*anti*-**1a**	**6a**	*anti*-**7a**, 54%, dr = 9:91, α:γ = 95:5, *E*/*Z* = 88:12
3	**1b**	**6b**	**7b**, 43%, α:γ = 80:20, *E*/*Z* = 99:1
4	**1b**	**6c**	**7c**, 51%, α:γ = 95:5
5	**1b**	**6d**	**7d**, trace, α:γ = n.a.

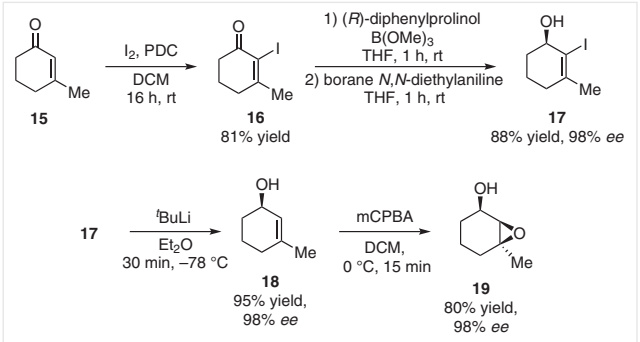


Scheme 2 S_N2'-substitution reaction via two different conformers **6A** or **6B** leading to the *E*- or the *Z*-product

To further investigate the stereo- and regioselectivity, the *anti*-S_N2'-substitution was performed with higher substituted allylic substrates **6b–d**. Thus, 2-phenyl-3-vinyloxirane (**6b**) was prepared and reaction with the chiral secondary alkylcopper reagent **1b** led to the racemic allylic alcohol **7b** in moderate yield (43%) and S_N2'-selectivity (α:γ = 80:20), but with excellent *E*/*Z* ratio (99:1; Table 1, entry 3). The observed *E*/Z-ratios by using **6a** or **6b** as electrophiles are rationalized in Scheme 2. The *anti*-substitution via conformer **6A** affords the *E*-product, whereas the substitution of conformer **6B** results in the *Z*-product. Depending on the 1,3-allylic strain, one conformer is more favored. If the residue R^2 of the allylic epoxide is bulky, such as the phenyl group of electrophile **6b**, the substitution proceeds via conformer **6A** due to steric reasons. Thus, the reaction of alkylcopper *anti*-**1a** with **6a** led to a mixture of *E*- and *Z*-products (*E*/*Z* = 88:12, see Table 1), whereas the reaction of **1b** with **6b** led exclusively to the *E*-product (*E*/*Z* = 99:1).

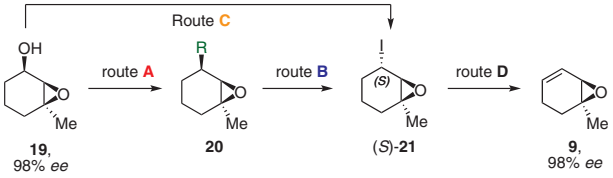
Switching to the cyclic allylic epoxide **6c** increased the regioselectivity significantly (**7c**, 51% yield, α:γ = 95:5; see Table 1, entry 4). We assume that the S_N2'-substitution of **6c** proceeds in an *anti*-S_N2'-fashion leading to **7c** as shown in Table 1 (hydroxyl group and hydrogen atom have a *syn*-orientation). Furthermore, the cyclic allylic aziridine **6d** was prepared according to literature from cyclohexadiene.[8] However, all attempts to open this allylic aziridine were unsuccessful. These preliminary experiments showed, that the *anti*-S_N2'-substitution of allylic epoxides is regioselective (α:γ = 95:5) and proceeds with retention of configuration of the secondary alkylcopper reagent.

Having these results in hand, the enantioselective synthesis of the chiral epoxide **19** was performed (see Scheme 3). Thus, the commercially available 3-methylcyclohex-2-en-1-one (**15**) was converted to the iodo derivative **16** (81% yield) using a pyridinium dichromate (PDC)-mediated



Scheme 3 Enantioselective synthesis of the precursor **19**

Table 2 Enantioselective Elimination of the Alcohol Leading to the Chiral Allylic Epoxide **9**



Route	Entry	Reagents and conditions	Product; yield (%)
A	1	MsCl (4.5 equiv), NEt_3 (6.0 equiv), DCM, –10 °C	**20a**, R = OMs; 80
	2	TsCl (4.5 equiv), NEt_3 (2.2 equiv), DCM, –10 °C	**20b**, R = OTs; 49
	3	$(PhSe)_2$ (4.0 equiv), $NaHBH_4$ (4.0 equiv), AcOH (1.8 equiv), DMF, rt, 24 h	**20a** to **20c**, R = SePh; 42
B	1	NaI (10 equiv), $NaHCO_3$ (20 equiv), THF, 65 °C	**20a** to **21**; 62
	2	NaI (10 equiv), $NaHCO_3$ (20 equiv), THF, 65 °C	**20b** to **21**; 48
	3	H_2O_2 (2.0 equiv), DCM, 0 °C to rt	**20c** direct to **9**; trace
C	1	I_2 (1.6 equiv), PPh_3 (1.6 equiv), NMI (1.6 equiv), DCM, –10 °C, 1 h	**21**; trace
	2	CI_4 (1.1 equiv), PPh_3 (1.1 equiv), NMI (1.1 equiv), DCM, 0 °C, 1 h	**21**; trace
D	1	DBU (5.0 equiv), THF, 60 °C, 12 h	**9**; 60
	2	NaOEt (1.5 equiv), EtOH, 60 °C, 12 h	**9**; trace
	3	TBD (5.0 equiv), THF, 60 °C, 12 h	**9**; trace

iodination.[9] The bulky iodo substituent allowed an enantioselective CBS-reduction of **16**, furnishing the chiral alcohol **17** in 88% yield and 98% *ee*.[9] Removal of the iodine via I/Li-exchange and subsequent protonolysis afforded the chiral allylic alcohol **18** in almost quantitative yield (95% yield) and 98% *ee*. Stereoselective directed epoxidation of **18** using mCPBA afforded the chiral epoxyalcohol **19** in 80% yield (98% *ee*).[10]

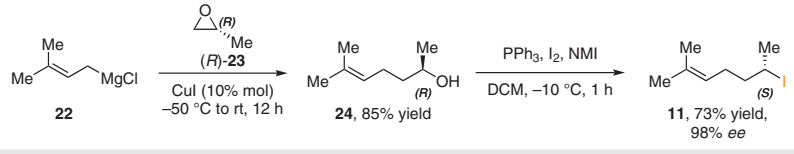
The elimination of the hydroxyl containing epoxide **19** to the desired allylic epoxide **9** proved to be rather challenging (see Table 2). Direct elimination using the Burgess reaction[11] or elimination via the corresponding phenylselenide[12] was unsuccessful. Thus, we envisioned a synthetic route, in which the hydroxyl group is converted into a good leaving group R (route A) followed by S_N2-substitution to the iodide **21** (routes B and C) and subsequent elimination leading to the allylic epoxide **9** (route D). After intensive screening of various leaving groups, the preparation of the mesylate **20a** (80% yield, R = OMs) followed by a Finkelstein reaction led to the desired iodide **21** (62% yield) with inversion of configuration (*S*/*R* = 80:20).[13] Subsequent elimination reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base furnished the desired epoxide **9** in 60% yield and with excellent enantiomeric excess (98% *ee*).[14]

Next, the optically enriched iodide **11** was prepared (Scheme 4). Insertion of magnesium into commercially available 1-chloro-3-methyl-2-butene led to **22**. Subsequent copper-catalyzed epoxide opening of (*R*)-**23** led to chiral alcohol **24** in 85% yield. After inversion of the configuration via an Appel reaction, the enantiomerically pure iodide **11** was obtained in 73% yield.[5b]

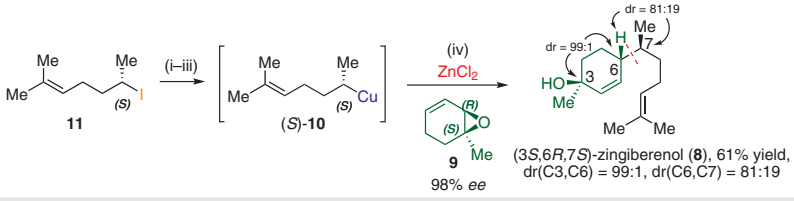
Finally, the secondary alkyl iodide **11** was converted to the corresponding alkylcopper reagent (*S*)-**10** under the above mentioned conditions (see Scheme 5). Subsequent zinc-mediated *anti*-S_N2'-substitution with allylic epoxide **9** led to (3*S*,6*R*,7*S*)-zingiberenol (**8**) in 61% yield [dr (C3,C6) = 99:1; and dr (C6,C7) = 81:19] with moderate selectivity at the C7-stereocenter.[15] All attempts to improve the stereoselectivity during the reaction by variation of conditions or additives, like $BF_3{\cdot}OEt_2$ were unsuccessful.[16] However, the substitution of allylic epoxide **9** proceeded in a highly *anti*-S_N2'-fashion leading to the *syn*-orientation of the hydroxyl group and the proton (3*S*,6*R*) of zingiberenol (dr = 99:1; see Scheme 5). This emphasizes the previous assumption that opening of allylic epoxides proceeds via an *anti*-S_N2'-substitution reaction.

In summary, we have shown that secondary alkylcopper-zinc reagents react regioselectively with allylic epoxides leading to chiral allylic alcohols (α:γ >95:5). This method was used in the total synthesis of the naturally occurring (3*S*,6*R*,7*S*)-zingiberenol (8 steps; 9.7% overall yield) starting from commercially available chemicals. Further mechanistical and computational studies are currently under investigation in our laboratories.

All reactions were carried out under argon atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon prior to use. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H NMR (25 °C) and capillary GC analysis. Column chromatographic purification was performed by using silica gel (0.040–0.063 mm, 230–400 mesh ASTM) from Merck. NMR spectra were recorded on Varian Mercury 200, Bruker AXR 300, Varian VXR 400 S, and Bruker AMX 600 instruments. Chemical shifts are reported as δ values in ppm relative to the deuterated solvent peak: $CDCl_3$ (δ_H = 7.26; δ_C = 77.16). High-resolution mass spectra by electron impact ionization (EI) and low-resolution mass spectra were recorded on a Finnigan MAT 95Q instrument. EI was conducted with an electron energy of 70 eV. For the combination of gas chromatography with mass spectroscopic detection, a GC/MS from Hewlett-Packard HP 6890/MSD 5973 was used. IR spectra were recorded from 4500 cm^{-1} to 650 cm^{-1} on a PerkinElmer Spectrum BX-59343 instrument. For detection, a Smiths Detection Dura SamplIR II Diamond ATR sensor was used. The absorption bands were reported in wavenumbers (cm^{-1}). GC-spectra were recorded on Hewlett-Packard 6890 or 5890 Series II



Scheme 4 Enantioselective synthesis of the iodide **11**



Scheme 5 Synthesis of zingiberenol. *Reagents and conditions*: i) ^{t}BuLi (2.2 equiv), inverse addition, pentane/Et_2O (3:2), –100 °C, 1 min; (ii) $CuBr{\cdot}P(OEt)_3$ (1.5 equiv), pentane/Et_2O, –100 °C, 1 min; (iii) solvent switch to THF at –50 °C; (iv) $ZnCl_2$ (1.5 equiv), –30 °C, 10 min; then **9** (3.0 equiv), –30 °C to –10 °C, 12 h.

instruments (Hewlett Packard, 5% phenylmethylpolysiloxane; length: 10 m, diameter: 0.25 mm; film thickness: 0.25 µm). All reagents not listed in the Supporting Information were obtained from commercial suppliers.

$CuBr·P(OEt)_3$

A dry and argon-flushed 100 mL Schlenk flask was charged with a magnetic stirring bar, freshly distilled $P(OEt)_3$ (4.98 g, 30 mmol, 5.14 mL) and toluene (30 mL). CuBr (4.30 g, 30 mmol) was added portionwise and the mixture was stirred for 1 h at rt. The light green solution was stirred 30 min at 80 °C. The cooled solution was filtered to obtain a clear solution of $CuBr·P(OEt)_3$. To the solution was added *i*-hexane (20 mL) and the solvent was removed under high vacuum. This step was repeated three times affording the purified complex without traces of toluene.

$ZnCl_2$

A 1 L Schlenk flask, equipped with a magnetic stirring bar, was charged with $ZnCl_2$ (68.2 g, 500 mmol). The mixture was heated under vacuum at 140 °C for 5 h. After cooling the mixture to 25 °C, anhyd THF (500 mL) was added and stirring was continued until the salt was dissolved, providing a 1.0 M solution.

I/Li-Exchange Reaction Using ᵗBuLi and Subsequent S_N2'-Substitution Reaction of Secondary Alkylcopper Reagents 3 with Allylic Electrophiles 6a–d; General Procedure 1 (GP1)

3,4-Epoxy-1-butene (**6a**) and 3,4-epoxy-1-cyclohexene (**6c**) are commercially available (Sigma Aldrich). The alkyl iodides **2a**[5c] and **2b**[5b] as well as the electrophiles 2-phenyl-3-vinyloxirane (**6b**)[2g] and 7-tosyl-7-azabicyclo[4.1.0]hept-2-ene (**6d**)[8] were prepared according to literature.

A dry and argon-flushed Schlenk tube was cooled to –100 °C and charged with a solution of ᵗBuLi (0.22 mmol, 2.2 equiv) together with a mixture of Et_2O (1.00 mL) and *n*-pentane (1.50 mL). A solution of alkyl iodide **2** (0.10 mmol, 1.0 equiv) in Et_2O (0.40 mL) was added dropwise over 1 min. After stirring for 10 s, a solution of $CuBr·P(OEt)_3$ (0.05 mL, 3 M in Et_2O, 0.15 mmol, 1.5 equiv) was added and the reaction mixture was stirred for 1 min at –100 °C to observe the color change from yellow to green. The Schlenk tube was transferred to a cooling bath (–50 °C) and the solvent was pumped away under high vacuum (10 min). Precooled THF (2 mL) was added and after 10 s, $ZnCl_2$ (0.15 mmol, 0.15 mL, 1.0 M in THF, 1.5 equiv) was added dropwise. The mixture was warmed to –30 °C and stirred for 10 min. The allylic epoxide **6** (0.3 mmol, dissolved in 0.60 mL THF) was added and the mixture was warmed to –10 °C. After 12 h, the mixture was quenched with aq NH_3 solution and extracted with Et_2O (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and the solvents were evaporated. The obtained crude product was purified by flash column chromatography on silica gel to afford products of type **7**.

syn-(*E*)-5-Methyl-7-phenyloct-2-en-1-ol (*syn*-7a)

The allylic alcohol *syn*-**7a** was prepared according to GP1 from the alkyl iodide *syn*-**2a** (0.1 mmol, 27 mg) and 3,4-epoxy-1-butene (**6a**; 0.3 mmol, 0.024 mL). The crude product was purified by flash column chromatography on silica gel with *n*-pentane/Et_2O (4:1) to afford *syn*-**7a** as a colorless oil; yield: 10 mg (0.046 mmol, 46%).

IR (diamond-ATR, neat): 3344 (m), 3026 (m), 2957 (s), 2916 (s), 2869 (m), 2142 (vw), 2010 (vw), 1603 (w), 1493 (m), 1452 (m), 1378 (m), 1084 (m), 1003 (m), 971 (s), 762 (s), 671 cm^{-1} (vs).

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.32–7.26 (m, 2 H), 7.21–7.14 (m, 3 H), 5.69–5.48 (m, 2 H), 4.18–3.99 (m, 2 H), 2.85–2.67 (m, 1 H), 2.04–1.93 (m, 1 H), 1.90–1.79 (m, 1 H), 1.72–1.60 (m, 1 H), 1.37–1.27 (m, 2 H), 1.22 (d, *J* = 6.9 Hz, 3 H), 0.86 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 147.5, 131.8, 130.4, 128.5, 127.2, 126.0, 64.0, 45.3, 40.2, 37.5, 30.5, 23.6, 19.4.

MS (EI, 70 eV): *m*/*z* (%) = 157 (6), 145 (100), 131 (10), 118 (47), 106 (34), 105 (47), 91 (62), 79 (19), 77 (21), 55 (6), 41 (13).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{22}O$: 218.1671; found: 218.1673.

anti-(*E*)-5-Methyl-7-phenyloct-2-en-1-ol (*anti*-7a)

The allylic alcohol *anti*-**7a** was prepared according to GP1 from the alkyl iodide *anti*-**2a** (0.1 mmol, 27 mg) and 3,4-epoxy-1-butene (**6a**; 0.3 mmol, 0.024 mL). The crude product was purified by flash column chromatography on silica gel with *n*-pentane/Et_2O (4:1) to afford *anti*-**7a** as a colorless oil; yield: 11.8 mg (0.054 mmol, 54%).

IR (diamond-ATR, neat): 3344 (m), 3026 (m), 2957 (s), 2912 (s), 2870 (m), 2141 (vw), 2009 (vw), 1603 (w), 1493 (m), 1452 (m), 1377 (m), 1084 (m), 1024 (m), 970 (s), 908 (m), 762 (s), 733 (m), 671 cm^{-1} (vs).

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.32–7.26 (m, 2 H), 7.21–7.11 (m, 3 H), 5.69–5.52 (m, 2 H), 4.13–4.02 (m, 2 H), 2.80 (q, *J* = 7.0 Hz, 1 H), 2.14–2.02 (m, 1 H), 1.94–1.81 (m, 1 H), 1.54–1.38 (m, 3 H), 1.21 (d, *J* = 6.9 Hz, 3 H), 0.85 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.2, 131.8, 130.5, 128.5, 127.1, 126.0, 64.0, 45.7, 39.6, 37.3, 30.7, 22.2, 19.8.

MS (EI, 70 eV): *m*/*z* (%) = 218 (1), 185 (2), 145 (32), 106 (11), 105 (100), 91 (14), 77 (6), 41 (4).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{22}O$: 218.1671; found: 218.1666.

(*E*)-5-Methyl-1,7-diphenylhept-2-en-1-ol (7b)

The allylic alcohol **7b** was prepared according to GP1 from the alkyl iodide **2b** (0.1 mmol, 26 mg) and 2-phenyl-3-vinyloxirane (**6b**; 0.3 mmol, 44 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane/Et_2O (4:1) to afford **7b** as a colorless oil and a mixture of two diastereoisomers, which could not be separated; yield: 12.1 mg (0.043 mmol, 43%).

Analytic data refer to the two diastereoisomers of the α-substitution product.

IR (diamond-ATR, neat): 3354 (w), 3061 (w), 3026 (w), 2953 (w), 2921 (w), 2869 (w), 2361 (vw), 1667 (vw), 1603 (w), 1493 (m), 1453 (m), 1377 (w), 1243 (w), 1192 (w), 1068 (w), 1029 (m), 969 (m), 915 (w), 842 (w), 745 (m), 723 (m), 697 cm^{-1} (vs).

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.40–7.31 (m, 8 H), 7.31–7.25 (m, 6 H), 7.21–7.09 (m, 6 H), 5.80–5.60 (m, 4 H), 5.20–5.16 (m, 2 H), 2.70–2.60 (m, 2 H), 2.60–2.49 (m, 2 H), 2.20–2.04 (m, 2 H), 2.02–1.90 (m, 2 H), 1.85 (s, 1 H), 1.85 (s, 1 H), 1.74–1.51 (m, 4 H), 1.51–1.40 (m, 2 H), 0.99–0.91 (m, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 143.5, 143.0, 133.9, 131.0, 131.0, 128.7, 128.6, 128.5, 128.4, 127.7, 127.7, 126.3, 126.3, 125.8, 75.3, 75.3, 39.6, 39.6, 38.5, 38.5, 33.5, 33.5, 32.7, 32.7, 19.7, 19.6.

MS (EI, 70 eV): *m*/*z* (%) = 280 (8), 262 (25), 173 (12), 171 (12), 158 (29), 157 (22), 133 (26), 129 (19), 120 (25), 117 (114), 115 (17), 105 (33), 92 (11), 91 (100), 77 (22).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{24}O$: 280.1827; found: 280.1817.

4-Phenylbutan-2-ylcyclohex-2-en-1-ol (7c)

The allylic alcohol **7c** was prepared according to GP1 from the alkyl iodide **2b** (0.1 mmol, 26 mg) and 3,4-epoxy-1-cyclohexene (**6c**; 0.3 mmol, 0.020 mL). The crude product was purified by flash column chromatography on silica gel with *n*-pentane/Et_2O (4:1) to afford **7c** as a colorless oil and a mixture of diastereoisomers, which could not be separated; yield: 11.7 mg (0.051 mmol, 51%).

Analytic data refer to the diastereoisomers of the α-substitution product.

IR (diamond-ATR, neat): 3340 (m), 3025 (m), 2930 (s), 2860 (s), 1603 (w), 1496 (m), 1453 (m), 1379 (m), 1055 (s), 1040 (s), 747 (s), 735 (s), 698 cm^{-1} (vs).

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.31–7.27 (m, 4 H), 7.21–7.15 (m, 6 H), 5.74–5.67 (m, 2 H), 5.61 (tq, *J* = 10.0, 1.8 Hz, 2 H), 4.28–4.16 (m, 2 H), 2.75–2.61 (m, 2 H), 2.61–2.43 (m, 2 H), 2.25–2.00 (m, 4 H), 1.78–1.62 (m, 4 H), 1.58–1.32 (m, 10 H), 0.92 (d, *J* = 6.5 Hz, 3 H), 0.87 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 142.9, 133.8, 132.7, 131.9, 131.6, 128.5, 128.5, 125.8, 67.8, 40.9, 40.3, 36.7, 36.6, 36.1, 35.6, 34.1, 34.0, 33.02, 32.9, 24.1, 22.4, 16.5, 15.8.

MS (EI, 70 eV): *m*/*z* (%) = 212 (7), 183 (8), 131 (15), 117 (10), 108 (13), 104 (14), 93 (11), 91 (100), 79 (27).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{22}O$: 230.1671; found: 230.1656.

Preparation of the Allylic Epoxide 9

2-Iodo-3-methylcyclohex-2-en-1-one (16)

According to literature,[9] PDC (3.38 g, 9 mmol, 0.3 equiv) and I_2 (12.9 g, 51.0 mmol, 1.7 equiv) were added in one portion to a solution of 3-methyl-2-cyclohexenone (**15**; 3.40 mL, 30 mmol, 1.0 equiv) in DCM (250 mL). The reaction mixture was covered with aluminum foil and stirred at rt overnight. The mixture was filtered and the filtrate was extracted with *n*-pentane. The combined organic phases were washed with aq 2 M HCl, aq $NaHCO_3$, sat. aq $Na_2S_2O_3$, and brine, dried ($MgSO_4$), and concentrated. The crude product was purified by flash column chromatography on silica gel with *n*-pentane/Et_2O (7:3) to afford **16** as a slightly yellow oil; yield: 5.72 g (24.3 mmol, 81%).

IR (diamond-ATR, neat): 2938 (w), 2883 (w), 2866 (w), 1672 (vs), 1589 (s), 1423 (m), 1369 (m), 1261 (s), 1190 (m), 1167 (s), 1131 (m), 968 (s), 908 (m), 781 cm^{-1} (vs).

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.63–2.47 (m, 4 H), 2.28–2.20 (m, 3 H), 2.03–1.94 (m, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 192.3, 166.8, 107.0, 36.4, 34.3, 32.0, 22.2.

MS (EI, 70 eV): *m*/*z* (%) = 236 (100), 208 (68), 81 (10), 79 (8), 53 (48), 41 (10).

HRMS (EI): *m*/*z* calcd for C_7H_9IO: 235.9698; found: 235.9688.

(*R*)-2-Iodo-3-methylcyclohex-2-en-1-ol (17)

A dry and argon-flushed round-bottomed flask was charged with a solution of (*R*)-diphenylprolinol (232 mg, 0.91 mmol, 0.05 equiv) and $B(OMe)_3$ (0.095 mL, 0.91 mmol, 0.05 equiv) in THF (18 mL). The mixture was stirred for 1 h at rt. Borane *N*,*N*-diethylaniline (3.35 mL, 18.3 mmol, 1.00 equiv) and 2-iodo-3-methylcyclohex-2-en-1-one (**16**; 4.31 g, 18.3 mmol, 1.00 equiv; dissolved in 18 mL THF) were added dropwise. The reaction mixture was stirred for 1 h and then quenched with MeOH (20 mL). The solvent was removed under reduced pressure and the obtained crude product was diluted with Et_2O. The organic phase was washed with 7% aq Na_2CO_3, 10% aq $KHSO_4$, and brine. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel with *n*-pentane/Et_2O (3:1) to afford **17** as a white solid; yield: 3.86 g (16.2 mmol, 88%); 98% *ee*; mp 39–40 °C; $[\alpha]_D^{20}$ +54.1 (*c* 4.9, $CHCl_3$).

IR (diamond-ATR, neat): 3249 (m), 2937 (m), 2916 (m), 2907 (m), 2859 (m), 2820 (w), 1639 (m), 1420 (m), 1290 (m), 1165 (m), 1076 (m), 1065 (m), 1033 (m), 1019 (m), 999 (m), 959 (vs), 898 (m), 880 (s), 783 (s), 730 cm^{-1} (m).

^1H NMR ($CDCl_3$, 400 MHz): δ = 4.37–4.20 (m, 1 H), 2.27–2.02 (m, 3 H), 1.88 (s, 3 H), 1.87–1.74 (m, 2 H), 1.71–1.60 (m, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 143.1, 104.2, 74.0, 33.4, 31.9, 29.6, 18.6.

MS (EI, 70 eV): *m*/*z* (%) = 238 (13), 210 (10), 111 (100), 93 (19), 91 (15), 77 (7).

HRMS (EI): *m*/*z* calcd for $C_7H_{11}IO$: 237.9855; found: 237.9845.

(*R*)-3-Methylcyclohex-2-en-1-ol (18)

A dry and argon-flushed round-bottomed flask was charged with a solution of **17** (2.38 g, 10.0 mmol, 1.0 equiv) in Et_2O (92 mL). After cooling to –78 °C, ^{t}BuLi (23.9 mL, 45.0 mL, 4.5 equiv) was added dropwise. The mixture was stirred for 30 min and then quenched with sat. aq $NaHCO_3$ (30 mL). The solution was poured into sat. aq $NaHCO_3$ (200 mL) and extracted with Et_2O (3 ×). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel with *n*-pentane/Et_2O (2:1) to afford **18** as a white solid; yield: 1.06 g (9.5 mmol, 95%); 98% *ee*; mp 34–36 °C; $[\alpha]_D^{20}$ +86.3 (*c* 1.4, $CHCl_3$).

IR (diamond-ATR, neat): 3320 (br), 2930 (s), 2910 (m), 2859 (m), 2358 (vw), 2333 (vw), 1671 (w), 1447 (m), 1436 (m), 1376 (m), 1343 (m), 1277 (m), 1164 (m), 1074 (m), 1059 (s), 1032 (s), 1013 (m), 992 (s), 956 (vs), 905 (m), 814 (m), 706 cm^{-1} (m).

^1H NMR ($CDCl_3$, 400 MHz): δ = 5.51–5.44 (m, 1 H), 4.22–4.11(m, 1 H), 2.01–1.82 (m, 2 H), 1.81–1.70 (m, 2 H), 1.70–1.66 (m, 3 H), 1.63–1.51 (m, 2 H), 1.40–1.34 (m, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 138.9, 124.4, 66.0, 31.8, 30.2, 23.8, 19.1.

MS (EI, 70 eV): *m*/*z* (%) = 98 (11), 97 (100), 83 (16), 79 (23).

HRMS (EI): *m*/*z* calcd for $C_7H_{11}O$ [M – H^+]: 111.0810; found: 111.0803.

(1*R*,2*R*,6*S*)-6-Methyl-7-oxabicyclo[4.1.0]heptan-2-ol (19)

A dry and argon-flushed round-bottomed flask was charged with a solution of **18** (1.12 g, 10.0 mmol, 1.0 equiv) in DCM (70 mL) and cooled to 0 °C. mCPBA was added dropwise as a solution in DCM (50 mL). After stirring for 15 min, the reaction mixture was quenched with a 10% aq Na_2CO_3 and extracted with DCM (3 × 20 mL). The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel with *n*-pentane/Et_2O (2:1) to afford **19** as a colorless oil; yield: 1.02 g (8.0 mmol, 80%); 98% *ee*; $[\alpha]_D^{20}$ +26.9 (*c* 3.0, $CHCl_3$).

IR (diamond-ATR, neat): 3387 (m), 2976 (m), 2937 (m), 2862 (m), 1708 (m), 1423 (m), 1264 (m), 1074 (s), 1063 (s), 1037 (s), 1018 (s), 990 (s), 894 (s), 843 (vs), 766 (s), 669 (s), 654 cm^{-1} (s).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.01 (td, *J* = 5.5, 3.3 Hz, 1 H), 3.15 (d, *J* = 3.3 Hz, 1 H), 1.93–1.79 (m, 1 H), 1.68–1.59 (m, 1 H), 1.57–1.43 (m, 3 H), 1.34 (s, 3 H), 1.32–1.23 (m, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 66.5, 62.3, 61.7, 29.3, 28.9, 23.8, 17.6.

MS (EI, 70 eV): *m*/*z* (%) = 111 (100), 93 (68), 84 (38), 81 (19), 70 (12), 67 (46), 43 (24).

HRMS (EI): *m*/*z* calcd for $C_7H_{12}O_2$: 128.0837; found: 128.0830.

(1*R*,2*R*,6*S*)-6-Methyl-7-oxabicyclo[4.1.0]heptan-2-yl Methanesulfonate (20a)

A dry and argon-flushed round-bottomed flask was charged with a solution of **19** (0.64 g, 5.0 mmol, 1.0 equiv) and NEt_3 (2.58 mL, 30.0 mmol, 6.0 equiv) in DCM (30 mL). After cooling to –10 °C, MsCl (1.48 mL, 22.5 mmol, 4.5 equiv) was added dropwise. The reaction mixture was stirred for 1 h and then diluted with EtOAc (10 mL). The organic phase was washed with aq 1 M HCl, sat. aq $NaHCO_3$, and brine. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel with *n*-pentane/Et_2O (1:2) to afford **20a** as a colorless oil; yield: 0.84 g (4.0 mmol, 80%); 98% *ee*; $[\alpha]_D^{20}$ –7.0 (*c* 1.5, $CHCl_3$).

IR (diamond-ATR, neat): 3519 (w), 2940 (w), 2361 (w), 2332 (w), 1452 (w), 1333 (s), 1170 (vs), 1131 (w), 1057 (m), 1006 (w), 952 (s), 933 (vs), 894 (m), 858 (m), 831 cm^{-1} (m).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.13–5.01 (m, 1 H), 3.25 (d, *J* = 2.4 Hz, 1 H), 3.09 (s, 3 H), 1.93–1.79 (m, 1 H), 1.78–1.60 (m, 4 H), 1.36 (s, 3 H), 1.34–1.26 (m, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 78.2, 61.5, 59.4, 39.2, 27.8, 25.7, 23.9, 19.1.

MS (EI, 70 eV): *m*/*z* (%) = 111 (29), 110 (32), 95 (19), 93 (21), 84 (22), 81 (45), 79 (20), 71 (50), 70 (57), 69 (11), 67 (32), 55 (35), 53 (13), 43 (100), 41 (43).

HRMS (EI): *m*/*z* calcd for $C_8H_{14}O_4S$: 206.0613; found: 206.0609.

(1*S*,5*S*,6*S*)-5-Iodo-1-methyl-7-oxabicyclo[4.1.0]heptane (21)

A dry and argon-flushed round-bottomed flask was charged with a solution of **20a** (0.84 g, 4.0 mmol, 1.0 equiv), $NaHCO_3$ (6.7 g, 80.0 mmol, 20 equiv), and NaI (6.0 g, 40.0 mmol, 10 equiv) in THF (10 mL). The mixture was stirred for 10 h at 65 °C, then diluted with H_2O (50 mL), and extracted with Et_2O (3 ×). The combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel with *n*-pentane/Et_2O (16:1) to afford **21** as a yellow oil; yield: 590 mg (2.5 mmol, 62%); 98% *ee*; $[\alpha]_D^{20}$ +0.3 (*c* 1.9, $CHCl_3$).

IR (diamond-ATR, neat): 3503 (br), 2935 (s), 2857 (w), 2538 (w), 1652 (w), 1441 (m), 1413 (w), 1376 (m), 1355 (w), 1295 (w), 1263 (w), 1219 (w), 1199 (w), 1135 (s), 1098 (s), 1050 (vs), 1002 (m), 962 (m), 929 (w), 890 (s), 848 (m), 766 (m), 668 (m), 656 cm^{-1} (m).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.50 (ddd, *J* = 8.3, 5.9, 2.6 Hz, 1 H), 3.22 (d, *J* = 2.7 Hz, 1 H), 2.07–1.89 (m, 3 H), 1.82–1.69 (m, 1 H), 1.62–1.47 (m, 1 H), 1.29 (s, 3 H), 1.27–1.25 (m, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 66.3, 64.1, 32.8, 28.6, 27.8, 24.4, 21.7.

MS (EI, 70 eV): *m*/*z* (%) = 127 (67), 111 (93), 93 (100), 91 (60), 81 (17), 79 (16), 77 (23), 67 (67), 55 (9), 43 (46).

HRMS (EI): *m*/*z* calcd for $C_7H_{11}IO$: 237.9855; found: 237.9843.

(1*R*,6*S*)-6-Methyl-7-oxabicyclo[4.1.0]hept-2-ene (9)

A dry and argon-flushed pressure tube was charged with a solution of **21** (590 mg, 2.5 mmol, 1.0 equiv) in THF (25 mL). After the addition of DBU (0.56 mL, 3.75 mmol, 1.5 equiv), the reaction mixture was stirred for 12 h at 60 °C. The crude reaction mixture was purified by Kugelrohr distillation (45–55 °C/atmospheric pressure) to afford **9** as a colorless oil with small impurities of THF; yield: 165 mg (1.5 mmol, 60%); 98% *ee*; $[\alpha]_D^{20}$ –8.3 (*c* 1.0, THF).

IR (diamond-ATR, neat): 3430 (m), 2964 (m), 2931 (s), 2927 (s), 2359 (m), 2328 (m), 1374 (m), 1260 (s), 1123 (s), 1103 (vs), 1091 (vs), 1087 (vs), 1071 (vs), 1058 (vs), 1042 (s), 1038 (s), 1034 (s), 1024 (s), 798 (s), 668 cm^{-1} (s).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.97–5.84 (m, 2 H), 3.04 (dd, *J* = 3.5, 1.8 Hz, 1 H), 2.21–1.86 (m, 2 H), 1.72–1.53 (m, 2 H), 1.42 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 132.9, 123.7, 61.2, 54.7, 26.6, 22.3, 22.0.

MS (EI, 70 eV): *m*/*z* (%) = 95 (13), 91 (19), 82 (100), 81 (28), 79 (16), 69 (14).

HRMS (EI): *m*/*z* calcd for $C_7H_{10}O$: 110.0732; found: 110.0724.

Preparation of the Iodide 11

(*R*)-6-Methylhept-5-en-2-ol (24)

A dry and argon-flushed Schlenk flask was charged with Mg turnings (0.52 g, 21.0 mmol) and THF (20 mL). After addition of I_2 (ca. 5 mg), the mixture was stirred and warmed until the color of I_2 disappeared. The allylmagnesium chloride **22** (1.94 mL, 20.0 mmol) was added in such a rate to keep a mild reflux. After the addition, the reaction mixture was stirred for 1 h at rt to obtain the corresponding Grignard reagent (67% yield, 0.67 M in THF). To a solution of the Grignard reagent (15.4 mL, 0.67 M in THF, 10.0 mmol), CuI (186 mg, 1.0 mmol) was added in one portion at 0 °C and the resulting black suspension was stirred for 5 min at 0 °C. Then (*R*)-propylene oxide [(*R*)-**23**; 0.70 mL, 10.0 mmol] in THF (10 mL) was added dropwise at 0 °C. The reaction mixture was warmed to rt and stirred for 12 h. The mixture was quenched with sat. aq NH_4Cl and extracted with Et_2O (3 × 20 mL). The combined organic phases were dried over $NaSO_4$ and the solvents were evaporated. The crude product was purified by flash column chromatography on silica gel with *n*-pentane/Et_2O (2:1) to afford **24** as a colorless oil; yield: 1.08 g (8.5 mmol, 85%); 98% *ee*; $[\alpha]_D^{23}$ –14.0 (*c* 0.9, $CHCl_3$).

IR (diamond-ATR, neat): 2967 (m), 2917 (m), 2859 (w), 1742 (s), 1728 (m), 1448 (w), 1395 (w), 1374 (s), 1300 (w), 1238 (vs), 1126 (m), 1113 (m), 1071 (m), 1046 (s), 952 (w), 935 cm^{-1} (w).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.18–5.05 (m, 1 H), 3.93–3.72 (m, 1 H), 2.17–1.94 (m, 2 H), 1.69 (s, 3 H), 1.62 (s, 3 H), 1.54–1.39 (m, 2 H), 1.19 (d, *J* = 6.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 132.3, 124.2, 68.1, 39.3, 25.9, 24.6, 23.6, 17.8.

MS (EI, 70 eV): *m*/*z* (%) = 128 (1), 113 (9), 110 (13), 96 (8), 95 (100), 85 (10), 79 (5), 71 (5), 57 (36), 41 (6).

HRMS (EI): *m*/*z* calcd for $C_8H_{16}O$: 128.1201; found: 128.1194.

(*S*)-6-Iodo-2-methylhept-2-ene (11)

A dry and argon-flushed Schlenk flask was charged with a solution of I_2 (1.65 g, 6.5 mmol, 1.3 equiv) in DCM (50 mL) and cooled to –10 °C. PPh_3 (1.70 g, 6.5 mmol, 1.3 equiv) was added at –10 °C and the resulting yellow suspension was stirred for 1 h at –10 °C. Then *N*-methyl-

imidazole (0.52 mL, 0.53 g, 6.5 mmol, 1.3 equiv) was added. After 10 min of further stirring, the alcohol **24** (0.64 g, 5.0 mmol, 1.0 equiv) dissolved in DCM (5 mL) was added and the reaction mixture was stirred for 1 h at –10 °C. The mixture was quenched with freshly prepared sat. aq $NaHSO_3$·$Na_2S_2O_5$ solution and extracted with DCM (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and the solvents were evaporated at 30 °C. The residue was triturated three times with a mixture of Et_2O/*n*-pentane (1:4). The precipitate was filtered off and all organic phases were combined. The solvents were evaporated at 30 °C. The crude product was purified by flash column chromatography on silica gel with *n*-pentane to obtain **11**as a colorless oil; yield: 833 mg (3.5 mmol, 73%); 98% *ee*; $[\alpha]_D^{20}$ +89.0 (*c* 0.9, $CHCl_3$).

IR (diamond-ATR, neat): 2979 (m), 2964 (s), 2914 (s), 2883 (m), 2858 (m), 1443 (s), 1376 (vs), 1231 (m), 1194 (m), 1181 (s), 1142 (s), 1136 (s), 1113 (s), 1080 (m), 843 (m), 824 (m), 805 (m), 744 cm^{-1} (m).

^1H NMR ($CDCl_3$, 400 MHz): δ = 5.14–4.98 (m, 1 H), 4.26–4.02 (m, 1 H), 2.23–1.99 (m, 2 H), 1.93 (d, *J* = 6.8 Hz, 3 H), 1.92–1.82 (m, 1 H), 1.69 (s, 3 H), 1.65 (s, 3 H), 1.64–1.56 (m, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 133.1, 122.7, 43.1, 30.6, 29.1, 28.4, 25.9, 18.1.

MS (EI, 70 eV): *m*/*z* (%) = 238 (3), 127 (5), 111 (29), 95 (5), 70 (6), 69 (100), 67 (6), 41 (14).

HRMS (EI): *m*/*z* calcd for $C_8H_{15}I$: 238.0218; found: 238.0213.

All analytical data were in accordance with literature values for the *R*-enantiomer.[5b]

(3*S*,6*R*,7*S*)-Zingiberenol (8)

The natural product **8** was prepared according to GP1 from **11** (98% *ee*, 0.20 mmol, 48 mg) and electrophile **9** (0.60 mmol, 66 mg, 98% *ee*). The crude product was purified by flash column chromatography on silica gel with *n*-pentane/Et_2O (3:1) to afford **8** as a colorless oil; yield: 26.7 mg (0.12 mmol, 61%); 98% *ee*; dr (3*S*,6*R*) = 99:1; dr (6*R*,7*S*) = 81:19; $[\alpha]_D^{20}$ –32.9 (*c* 0.8, CH_2Cl_2) {Lit.[7a] $[\alpha]_D$ –37.7 (*c* 2.0, CH_2Cl_2)}.

The NMR data refer to the major diastereoisomer (3*S*,6*R*,7*S*)-zingiberenol (**8**).

IR (diamond-ATR, neat): 3381 (br), 2962 (vs), 2928 (vs), 2859 (s), 2363 (w), 2338 (w), 1715 (w), 1669 (w), 1456 (m), 1450 (m), 1376 (s), 1367 (m), 1120 (s), 978 (m), 916 (m), 743 cm^{-1} (m).

^1H NMR (CD_2Cl_2, 400 MHz): δ = 5.59–5.53 (m, 1 H), 5.54–5.45 (m, 1 H), 5.10 (t, *J* = 7.1 Hz, 1 H), 2.16–2.06 (m, 1 H), 2.04–1.78 (m, 4 H), 1.67 (s, 3 H), 1.60 (s, 3 H), 1.52–1.44 (m, 2 H), 1.42–1.31 (m, 2 H), 1.22 (s, 3 H), 1.20–1.08 (m, 1 H), 0.81 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (CD_2Cl_2, 100 MHz): δ = 135.4, 132.3, 131.7, 125.2, 70.0, 40.7, 38.9, 36.8, 34.7, 28.8, 26.5, 26.0, 22.9, 17.9, 16.0.

MS (EI, 70 eV): *m*/*z* (%) = 207 (20), 189 (11), 161 (28), 138 (15), 137 (38), 123 (33), 119 (100), 105 (30), 93 (35), 79 (18), 67 (17).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{26}O$: 222.1984; found: 222.1975.

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Supporting Information

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