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Total Synthesis of (+)-7,11-Helianane and (+)-5-Chloro-7,11-helianane through Stereoselective Aromatic Claisen Rearrangement

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The aromatic bisabolene sesquiterpene of marine origin (+)-7,11-helianane (**1**) and its moderately cytotoxic halogenated relative (+)-5-chloro-7,11-helianane (**3**) have been synthesized by a concise, stereoselective route. By capitalizing on a palladium-catalyzed asymmetric allylic alkylation (Pd-AAA) reaction, followed by a thermal (uncatalyzed) aromatic Claisen rearrangement, which allowed for the installation of the required benzylic stereocenter, the aforementioned natural products were secured in 80 % *ee*, with almost complete transfer of stereochemical information during the [3,3] sigmatropic process. The enantioselective total synthesis confirmed the recently proved (*S*) absolute configuration for (+)-7,11-helianane (**1**) and demonstrated the same configuration, for the first time, in the case of (+)-5-chloro-7,11-helianane (**3**).

Introduction

(+)-7,11-Helianane (**1**),[1] isolated from the marine sponges *Haliclona fascigera*[2] and *Spirastrella hartmani*,[3] and its halogenated derivatives (+)-5-bromo- (**2**) and (+)-5-chloro-7,11-helianane (**3**), both isolated from the sponge *Spirastrella hartmani*,[3] are aromatic bisabolene sesquiterpenes featuring a benzoxocane ring (Figure 1). This hitherto unprecedented molecular topology among marine natural products has its parallel in terrestrial plants, where a number of benzoxocane ring-containing sesquiterpenes, all at higher oxidation state compared to compounds **1**–**3**, has been identified as secondary metabolites of sunflowers (*Helianthus annus*).[4]

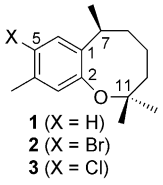

Figure 1. The helianane family.

Heliananes (**1**–**3**) contain a single stereogenic center, the absolute configuration of which was provisionally assigned as 7*S*, based upon the existing correlation between the absolute configuration and the optical rotation sign of their presumed biogenetic precursors.[2–4] However, despite the simple logic underpinning this designation, still some confusion is present in the literature, as testified by the large number of inconsistent drawings representing optically active heliananes.[5]

Whereas (+)-7,11-helianane (**1**) has not been subjected to any biological assay so far, (+)-5-chloro-7,11-helianane (**3**) showed double-digit micromolar in vitro activity on NSCL (A549, GI_{50} 37.2 μM), colon (HT29, GI_{50} 37.6 μM), and breast (MDA-MB-231, GI_{50} 37.6 μM) human cancer cell lines. (+)-5-Bromo-7,11-helianane (**2**), on the other hand, when tested on the same cell lines, proved to be inactive.[3]

The first total synthesis of racemic 7,11-helianane (**1**) was reported by Snieckus and Stefanovic in 1998.[6] Later, the group of Venkateswaran entered the field by publishing three communications[5a,5b,5e] and two full papers[5c,5d] on the subject. Remarkably, in their last communication, Venkateswaran et al.[5e] also accomplished the first synthesis of (±)-5-bromo- (**2**) and (±)-5-chloro-7,11-helianane (**3**). Very recently, Shishido and co-workers reported the first enantioselective total synthesis of (+)-helianane (**1**), confirming its provisionally assigned, biogenetically based, (*S*) absolute configuration.[7]

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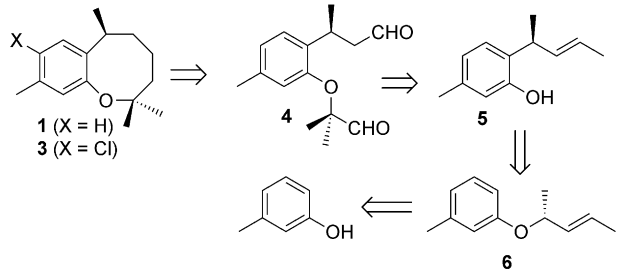
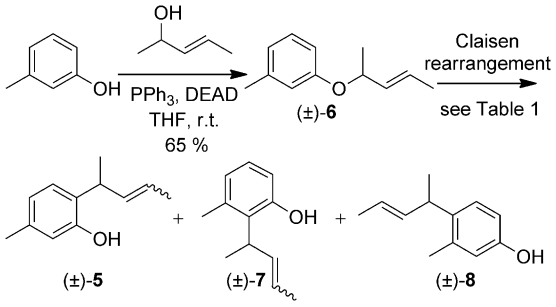
Results and Discussion

The envisioned retrosynthetic analysis of (*S*)-7,11-helianane (**1**) and (*S*)-5-chloro-7,11-helianane (**3**) starts with the well-documented (in its racemic form)[5b,5c] dialdehyde precursor **4** and entails Trost's palladium-catalyzed asymmetric allylic alkylation (Pd-AAA)[8,9] on *meta*-cresol, followed by a stereoselective aromatic Claisen rearrangement as the key steps to install the required stereogenic center (Scheme 1). Robust literature precedents, based upon the concept of dynamic kinetic asymmetric transformation (DYKAT),[8,9] support the feasibility of the planned asymmetric alkylation of the starting phenol.[10] In contrast, the challenge of accomplishing a stereoselective aromatic Claisen rearrangement can be appreciated by looking at the paucity of examples reported so far.[10–12] The asymmetric version of this [3,3] sigmatropic rearrangement is complicated by the coexistence of nonsynchronized concerted and ionic mechanisms (the latter often enhanced by Lewis acids), and by the potential presence (especially under the vigorous thermal conditions required for the reaction to occur) of competing chair-like and boat-like transition states;[13] *ortho*/*para* as well as *ortho*/*ortho′* (in the case of *meta*-substituted allyl aryl ethers) regioselectivity issues further complicate the picture, alongside abnormal Claisen rearrangement.[13a]



Scheme 1. Retrosynthetic approach to heliananes.

The search for optimal Claisen rearrangement conditions (in terms of conversion, regio- and stereoselectivity) was undertaken on racemic allyl phenyl ether (±)-**6**, which was prepared in moderate yield by reaction of *meta*-cresol with (*E*)-3-penten-2-ol using a standard Mitsunobu protocol (Scheme 2). Because the *E*/*Z* isomer ratio of (±)-**5** reflects the diastereoselectivity of the sigmatropic rearrangement process,[10,11,14,15] a ^{1}H NMR-based assessment of the composition of the crude reaction mixture allowed rapid comparison of the conditions, in terms of both regio- and stereoselectivity (Table 1).



Scheme 2. Synthesis of (±)-**6** and studies of the Claisen rearrangement.

Table 1. Claisen rearrangement of (±)-**6**; optimization of the reaction conditions.

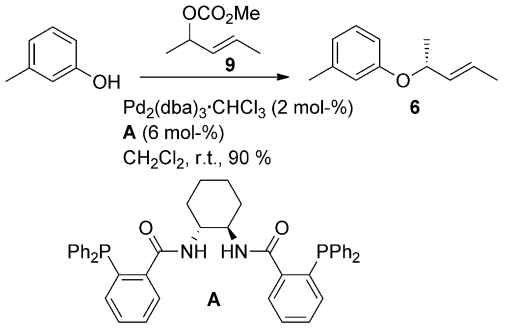
Entry	Reagents and conditions	Time [h]	Regioisomers;[a] yield [%] (*E*/*Z*)[b]
1	$[Eu(fod)_3]$, $CHCl_3$, reflux	48	**5**; 59 (3:1) **7**; 18 (3:1) **8**; 14
2	$[Eu(fod)_3]$, DCE, 80 °C	48	**5**; 64 (4:1) **7**; 25 (4:1) **8**; 8
3	$[Eu(hfc)_3]$, DCE, 80 °C	72	**5**; 62 (3:1) **7**; 32 (3:1) **8**; 3
4	$SnCl_4$, CH_2Cl_2, 0 °C to r.t.	2	extensive decomposition
5	*N*,*N*-diethylaniline, 190 °C	4	**5**; 67 (7:1) **7**; 17 (7:1) **8**; 13

[a] All regioisomers are racemic. [b] Yields and *E*/*Z* ratios were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

The shift reagent $[Eu(fod)_3]$ was initially used as a catalyst in an attempt to promote the Claisen rearrangement of allyl phenyl ether (±)-**6**, due to the mild reaction conditions and high diastereoselectivity reported by Trost and Toste with a similar substrate.[10] Unfortunately, modest yield and diastereoselectivity [(±)-**5**; 59%, *E*/*Z* = 3:1] were observed in this case (Table 1, Entry 1). A slight increase in conversion and diastereoselectivity [(±)-**5**; 64%, *E*/*Z* = 4:1] was obtained by working at higher temperature, as suggested for less electron-rich substrates[10] (Table 1, Entry 2). Attempts to further improve these results by using a more sterically demanding europium salt proved unsuccessful (Table 1, Entry 3). Tin tetrachloride, which was recently claimed to be effective in catalyzing some Claisen rearrangements[16] and also influencing the regioselective course of the reaction,[5d] unfortunately delivered a complex mixture containing negligible amounts of phenol (±)-**5** (Table 1, Entry 4).[17] Gratifyingly, the more conventional thermal process, performed in a polar solvent such as *N*,*N*-diethylaniline (Table 1, Entry 5), resulted in a significant improvement in the diastereoselectivity [(±)-**5**; *E*/*Z* = 7:1] with a yield (67%) comparable to that obtained in the europium-catalyzed reaction (cf. Table 1, Entries 2 and 5). As expected, the same levels of diastereoselectivity were observed in allylphenol (±)-**5** and its *ortho′* regioisomer (±)-**7** (Table 1, Entries 1–3 and 5). The effect of the branched (and thus more sterically demanding) allylic chain on the equilibrium population of the ground-state conformers[18] reasonably accounts for the pleasingly good *ortho*/*ortho′* regioselectivity that was experimentally observed in the thermal [3,3] sigmatropic rearrangement [(±)-**5**/(±)-**7** = ca. 4:1; Table 1, Entry 5].

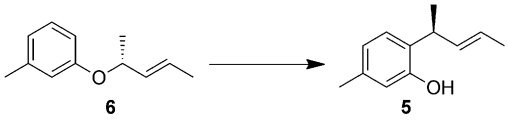
Having identified suitable reaction conditions for the aromatic Claisen rearrangement of (±)-**6**, their application to the corresponding optically active substrate was then investigated. To this end, *meta*-cresol was submitted to a Pd-

AAA reaction in the presence of allyl carbonate **9**, catalytic [Pd_2dba_3·$CHCl_3$] and (*R*,*R*)-Trost ligand (**A**), delivering **6**[19] in excellent isolated yield (90%) and good enantiomeric excess (82%), as determined by chiral HPLC analysis (Scheme 3). Attempts to shorten the reaction time (20 h), by performing the asymmetric allylation under microwave irradiation, resulted in a comparable yield (88%) but reduced enantiomeric excess (75%). The enantiomerically enriched allyl phenyl ether **6** was then subjected to a Claisen rearrangement (Table 2) according to the optimized reaction conditions (Table 1). Bearing in mind the possible stereochemical erosion that could arise from such a vigorous thermal process (Table 1, Entry 5), we decided to run the reaction under both the optimized thermal conditions and under the milder Trost–Toste catalytic conditions[10] (Table 1, Entry 2), in order to compare the resulting enantiopurities of **5**.



Scheme 3. Pd-AAA reaction to give enantiomerically enriched **6** (82%*ee*).

Table 2. Claisen rearrangement of ether **6** (82%*ee*) to phenol **5**.



Entry	Reagents and conditions	Time [h]	Isolated yield [%]	*ee* [%]
1	[Eu(fod)$_3$], DCE, 80 °C	48	14	76
2	*N*,*N*-diethylaniline, 190 °C	4	32	80

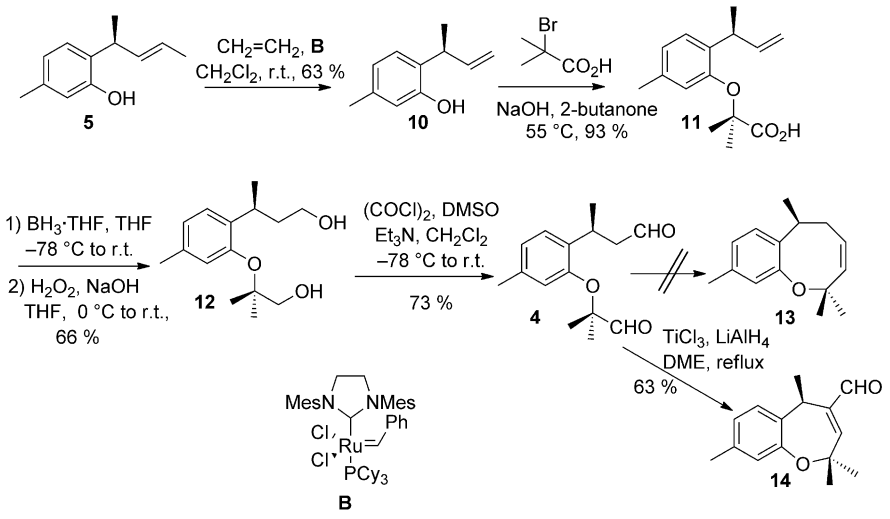
Isolation of the desired (*E*)-isomer of **5** required, in addition to classical flash chromatography, a second purification step with a silver nitrate-impregnated silica gel stationary phase[20] to separate the *E*/*Z* mixture. Despite the separation efficiency demonstrated by this venerable technique, unfortunately, the recovery proved to be lower than expected, probably due to some silver-mediated phenol oxidation.[20] However, with the pure (*E*)-isomer in hand, the enantiomeric excess of **5** was then assessed through ^{1}H NMR analysis of the corresponding diastereomeric Mosher esters.[21] Notably, in addition to a slightly higher enantiomeric excess (80 vs. 76%*ee*; cf. Table 2, Entries 2 and 1), a doubling of the isolated yield of **5** (32 vs. 14%; cf. Table 2, Entries 2 and 1) was observed in the case of the thermal (uncatalyzed) Claisen rearrangement as a logical consequence of the better diastereoselectivity. Furthermore, the thermal reaction required significantly shorter reaction time to go to completion.

From these results, it is clear that, regardless of the reaction conditions employed, excellent transfer of stereochemical information took place during the rearrangement (compare the 76–80%*ee* of phenol **5** with the 82%*ee* of the starting ether **6**). However, a greater diastereoselectivity was achieved under thermal conditions. Success in scaling up (up to 10 mmol) the palladium-catalyzed asymmetric allylic alkylation/aromatic Claisen rearrangement sequence, provided enough phenol **5** to complete the synthesis of (*S*)-7,11-helianane (**1**) and (*S*)-5-chloro-7,11-helianane (**3**) (see below).

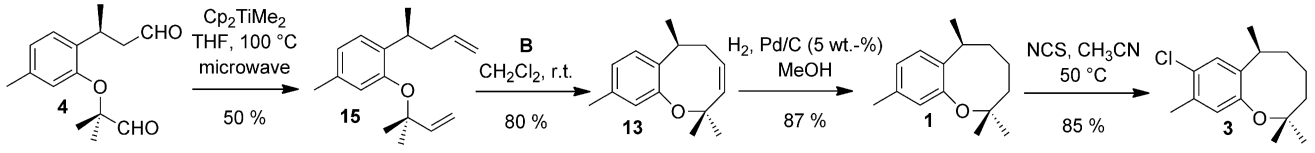
For this purpose, access to key intermediate dialdehyde **4** (Scheme 1) required, first, the preparation of alkene **10** (Scheme 4). Deletion of the redundant terminal carbon atom of **5** was achieved in moderate yield through cross metathesis, by exposing **5** to an atmosphere of ethylene in the presence of Grubbs second generation ruthenium catalyst (**B**). Subsequent straightforward alkylation of the phenol moiety with 2-bromo-2-methylpropanoic acid allowed the installation of the quaternary carbon in nearly quantitative yield. With the aim of verifying the integrity of the benzylic stereocenter at this stage, diastereomeric amides were prepared by coupling acid **11** with (*R*)-(–)-2-phenylglycine methyl ester, and the resulting crude reaction was analyzed by ^{1}H NMR spectroscopy. Gratifyingly, despite the strongly alkaline medium required for the alkylation reaction, no stereochemical erosion was observed (80%*ee* based upon the relative intensity of the diastereomeric protons).[21] Alkene hydroboration with simultaneous carboxylic acid reduction, followed by treatment with hydrogen peroxide, secured the desired diol **12** (the only solid compound along the synthetic sequence), which was subsequently oxidized to the corresponding dialdehyde **4** using a standard Swern protocol (Scheme 4).

At this point, an intramolecular pinacol-type McMurry coupling[22a] of the carbonyl functionalities present in **4** was envisioned as a promising shortcut to benzooxocene **13**. Unfortunately, reaction of **4** with Ti^0, which was generated in situ, delivered either a complex reaction mixture (with $TiCl_3$ and freshly prepared Zn/Cu alloy),[22b,22c] or the benzooxepine derivative **14** arising from an intramolecular aldol condensation (with $TiCl_3$ and $LiAlH_4$)[22d] (Scheme 4).

Failure to synthesize the benzooxocene intermediate **13** through McMurry coupling prompted us to retrace the final synthetic steps reported by Venkateswaran et al.[5b,5c] to access (*S*)-7,11-helianane (**1**). Accordingly, double Wittig olefination of dialdehyde **4** would set the stage for the subsequent ring-closing metathesis, delivering **13**. Unexpectedly, attempts to reproduce the Wittig olefination[5b,5c] proved to be exceedingly troublesome, affording the desired alkene **15** in an unacceptable 17% yield at best. Similar frustrating outcomes were encountered by employing commercially available Tebbe reagent. Finally, microwave-assisted[23] Petasis (Cp_2TiMe_2) olefination[24] secured alkene



Scheme 4. Synthesis of the key precursor dialdehyde **4** and attempts at McMurry coupling.



Scheme 5. (*S*)-(+)-7,11-Helianane (**1**) and (*S*)-(+)-5-chloro-7,11-helianane (**3**) syntheses completion.

15 in moderate yield (Scheme 5). Ring-closing metathesis with Grubbs second generation ruthenium catalyst (**B**), followed by catalytic hydrogenation of the benzooxocene double bond proceeded uneventfully, delivering (*S*)-7,11-helianane (**1**) as a colorless oil, the spectroscopic data of which matched those reported for both natural and synthetic **1** (Scheme 5). Chiral HPLC analysis (80%*ee*; see the Experimental Section) of synthetic (*S*)-7,11-helianane (**1**) demonstrated that no stereochemical erosion had occurred during the last five steps of the synthesis. Furthermore, optical rotation measurements proved **1** to be dextrorotatory, thus confirming the recently proved (*S*) absolute configuration for this marine sesquiterpene.[7] In agreement with the data reported by Shishido and co-workers,[7] the absolute value of the optical rotation of the enantioenriched (80%*ee*) synthetic (*S*)-(+)-7,11-helianane (**1**) {$[a]_D$ = +18.9 (c = 0.59, CH_2Cl_2)} turned out to be dramatically higher than that reported for the supposed optically pure natural compound {$[a]_D$ = +8.0 (c = 1.01, CH_2Cl_2)}.[2] (*S*)-(+)-7,11-Helianane (**1**) was then brought forward to the biologically more appealing (*S*)-5-chloro-7,11-helianane (**3**). Thus, halogenation of **1** with *N*-chlorosuccinimide (NCS) in acetonitrile at 50 °C gave **3** in 85% yield. The conservation of enantiopurity of **3** was assessed by chiral HPLC analysis (80%*ee*; see the Experimental Section), whereas the proposed (*S*) absolute configuration was confirmed by optical rotation measurements. Quite surprisingly, the absolute value of the optical rotation of the enantioenriched (80%*ee*) (*S*)-(+)-5-chloro-7,11-helianane (**3**) {$[a]_D$ = +33.4 (c = 0.36, $CHCl_3$)} proved to be discordantly lower than that reported for the supposed optically pure natural material {$[a]_D$ = +80.0 (c = 0.01, $CHCl_3$)}.[3]

Accurate biological profiling of (*S*)-(+)-5-chloro-7,11-helianane (**3**) on a number of different cancer cell lines, as well as investigation of its mechanism of action are underway, and will be reported in due course.

Conclusions

A palladium-catalyzed, asymmetric allylic alkylation (Pd-AAA) on *meta*-cresol, followed by a stereoselective aromatic Claisen rearrangement were the key reactions of a nine-step synthetic sequence that secured the marine sesquiterpene (*S*)-(+)-7,11-helianane (**1**) in good enantiomeric excess. The reported moderately cytotoxic (*S*)-(+)-5-chloro-7,11-helianane (**3**) was also attained, with the same enantiomeric excess, by simple halogenation of the parent compound (**1**). Dynamic kinetic asymmetric transformation (DYKAT) provided the initial enantioenrichment, which was faithfully transferred during the [3,3] sigmatropic process and preserved throughout the whole synthetic pathway. The enantioselective total synthesis confirmed the recently proved (*S*) absolute configuration for (+)-7,11-helianane (**1**) and demonstrated it for the first time in the case of (+)-5-chloro-7,11-helianane (**3**), despite discrepancies between the absolute values of the optical rotation of the natural and synthetic materials. Furthermore, the present work underlines the power of the diastereoselective aromatic Claisen rearrangement in generating benzylic stereocenters from a

given chiral allyl phenyl ether precursor. Despite a number of potential setbacks and the lack of a full comprehension of the mechanistic details, which has probably contributed to its limited use in wider applications, this functional group compatible [3,3] sigmatropic rearrangement is one of the least expensive, experimentally simplest, and efficient strategies for the transfer of stereochemical information.

Experimental Section

General: All solvents were reagent grade and all reagents were used as supplied. Flash chromatography was performed with silica gel 60 Å (particle size 230–400 mesh) supplied by Aldrich. Melting points were recorded with a Buchi 535 instrument. NMR spectra were recorded at 25, 28, and 50 °C in [D$_6$]DMSO and $CDCl_3$ with a Varian Inova 500 spectrometer equipped with 5 mm ^{1}H{^{13}C,^{15}N} *z*-axis-PFG indirect detection cold probe and with a Varian Inova 400 spectrometer equipped with 5 mm ^{1}H{^{15}N-^{31}P} *z*-axis-PFG indirect detection probe. Residual solvent signal was used as reference (δ = 2.50 and 7.24 ppm for ^{1}H and δ = 39.5 and 77.2 ppm for ^{13}C). Standard two-dimensional sequences provided by Varian (COSY, gradient-enhanced HSQC and HMBC) were used to assign proton and carbon resonances. Exact mass data ESI(+) high-resolution mass spectra (HRMS) were obtained with a Waters Q-Tof Ultima spectrometer directly connected to a micro HPLC 1100 Agilent instrument, as described previously.[25] Optical rotation measurements were performed with a Perkin–Elmer 241 polarimeter.

1-Methyl-3-[(3*E*)-pent-3-en-2-yloxy]benzene [(±)-6]: To a solution of (3*E*)-pent-3-en-2-ol (5 g, 0.058 mol), *m*-cresol (12.4 g, 0.115 mol), and PPh_3 (30.45 g, 0.116 mol) in THF (70 mL), cooled to 0 °C, DEAD (18 mL, 0.116 mol) in THF (15 mL), was added dropwise. The reaction, which was monitored by TLC (hexane/AcOEt = 98:2), was stirred at room temperature overnight. The precipitate was filtered off and thoroughly washed with ethyl acetate. Purification by flash chromatography (hexane/AcOEt = 98:2) afforded (±)-**6** (6.64 g, 65%) as a colorless oil. IR (film): $\tilde{\nu}$ = 963 cm^{-1} (absence of signals at 720, 953, 1006 cm^{-1} indicated that no *Z* isomer was present).[11] ^{1}H NMR (400.5 MHz, [D$_6$]DMSO, 28 °C): δ = 1.30 (d, *J* = 6.2 Hz, 3 H, C*H*$_3$CH), 1.63 (ddd, *J* = 6.5, 1.5, 0.7 Hz, 3 H, C*H*$_3$CH=), 2.24 (s, 3 H, CH_3Ar), 4.81–4.88 (m, 1 H, C*H*CH$_3$), 5.46–5.53 (m, 1 H, C*H*=CHCH$_3$), 5.65–5.76 (m, 1 H, CH=C*H*CH$_3$), 6.63–6.74 (m, 3 H, Ar*H*), 7.11 (m, 1 H, Ar*H*) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 25 °C): δ = 16.8 (*C*H$_3$CH=), 20.5 (*C*H$_3$Ar), 20.9 (*C*H$_3$CH), 72.0 (*C*HCH$_3$), 112.8 (Ar*C*H), 116.2 (Ar*C*H), 120.7 (Ar*C*H), 126.4 (CH=*C*HCH$_3$), 129.1 (Ar*C*H), 131.3 (CH=*C*HCH$_3$), 139.0 (Ar*C*CH$_3$), 158.0 (Ar*C*O) ppm. HRMS (ESI+): calcd for $C_{12}H_{17}O$ [M + H]$^+$ 177.1274; found 177.1280.

Methyl (3*E*)-Pent-3-en-2-yl Carbonate (9): (3*E*)-Pent-3-en-2-ol (5 g, 0.058 mol) was dissolved in anhydrous Et_2O (130 mL) under an inert atmosphere and cooled to –78 °C. LiHMDS (1 M in THF, 70 mL, 0.07 mol) and, after 30 min, methylchloroformate (6.7 mL, 0.087 mol) were added. The disappearance of the starting material was monitored by TLC (hexane/AcOEt = 95:5). After 40 min, the reaction was quenched with water (130 mL) and then washed with 1 N HCl and water. The organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo. Crude **9** was purified on silica gel (CH_2Cl_2) and isolated as a colorless oil (6.37 g, 76%). ^{1}H NMR (400.5 MHz, [D$_6$]DMSO, 28 °C): δ = 1.27 (d, *J* = 6.5 Hz, 3 H, C*H*$_3$CH), 1.66 (ddd, *J* = 6.5, 1.6, 0.7 Hz, 3 H, C*H*$_3$CH=), 3.67 (s, 3 H, OCH$_3$), 5.04–5.10 (m, 1 H, C*H*CH$_3$), 5.46–5.56 (m, 1 H, C*H*=CHCH$_3$), 5.67–5.79 (m, 1 H, CH=C*H*CH$_3$) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 25 °C): δ = 16.9 (*C*H$_3$CH=), 19.7 (*C*H$_3$CH), 53.8 (OCH$_3$), 74.0 (*C*HCH$_3$), 128.3 (CH=*C*HCH$_3$), 130.4 (*C*H=CHCH$_3$), 154.8 (O*C*O$_2$CH$_3$) ppm.

1-Methyl-3-[(2*R*,3*E*)-pent-3-en-2-yloxy]benzene (6): Carbonate **9** (3 g, 20.8 mmol) was dissolved in anhydrous CH_2Cl_2 (40 mL) under an inert atmosphere, then [$Pd_2(dba)_3$·$CHCl_3$] (220 mg, 0.212 mmol) and (*R*,*R*)-Trost ligand (**A**; 440 mg, 0.637 mmol) were subsequently added at room temperature. As soon as the obtained red mixture turned yellow (nearly 40 min), a solution of *m*-cresol (3.35 mL, 32 mmol) in anhydrous CH_2Cl_2 (40 mL) was added dropwise. The reaction was monitored by TLC (hexane/AcOEt = 98:2). After 4 h, further [$Pd_2(dba)_3$·$CHCl_3$] (220 mg, 0.212 mmol) and ligand **A** (440 mg, 0.637 mmol) were added. The reaction was stirred at room temperature overnight, then filtered through a pad of Celite and the volatiles were removed under reduced pressure. Compound **6** was isolated by flash column chromatography (hexane) as a colorless oil (3.28 g, 90%). 82%*ee* (Chiral HPLC, column: Daicel Chiralpak AD, 4.6 × 250 mm, 10 µm; eluent: 100% hexane; flow: 0.2 mL/min; detector: UV 254 nm). For ^{1}H, ^{13}C NMR, and HRMS, see (±)-**6**.

5-Methyl-2-[(2*S*,3*E*)-pent-3-en-2-yl]phenol (5)

Thermal Claisen Rearrangement: A solution of 1-methyl-3-[(2*R*,3*E*)-pent-3-en-2-yloxy]benzene (**6**; 1.65 g, 9.36 mmol) in *N*,*N*-diethylaniline (1.6 mL) was heated at 190 °C for 4 h. The mixture was then diluted with Et_2O, washed with 1 N HCl and water. The organic layer was dried with Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Initial flash chromatography (hexane/AcOEt = 99:1) allowed **5** (0.875 g, mixture of *E*/*Z* isomers) to be separated from **7** (0.22 g, 13%) and **8** (0.18 g, 11%). A second purification, using hexane as the eluent, on silica gel 60 (230–400 mesh), previously impregnated with a solution of 10 wt./vol.-% $AgNO_3$ in water and dried in an oven at 70 °C, afforded pure (*E*)-**5** (0.53 g, 32%) and (*Z*)-**5** (0.06 g, 3.5%). Data for (*E*)-**5**: ^{1}H NMR (400.5 MHz, [D$_6$]DMSO, 28 °C): δ = 1.17 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$CH), 1.59–1.64 (m, 3 H, C*H*$_3$CH=), 2.16 (s, 3 H, CH_3Ar), 3.64–3.71 (m, 1 H, C*H*CH$_3$), 5.33–5.41 (m, 1 H, CH=C*H*CH$_3$), 5.57–5.65 (m, 1 H, C*H*=CHCH$_3$), 6.53 (dd, *J* = 7.7, 1.6 Hz, 1 H, ArC*H*), 6.57 (d, *J* = 1.6 Hz, 1 H, ArC*H*), 6.89 (d, *J* = 7.7 Hz, 1 H, ArC*H*), 9.07 (s, 1 H, OH) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]-DMSO, 25 °C): δ = 17.6 (*C*H$_3$CH=), 20.3 (*C*H$_3$CH), 20.6 (*C*H$_3$Ar), 34.1 (*C*HCH$_3$), 115.4 (Ar*C*H), 119.3 (Ar*C*H), 122.5 (CH=*C*HCH$_3$), 127.0 (Ar*C*H), 130.0 (Ar*C*CH), 135.5 (Ar*C*CH$_3$), 136.0 (*C*H=CHCH$_3$), 154.2 (Ar*C*OH) ppm. HRMS (ESI+): calcd for $C_{12}H_{17}O$ [M + H]$^+$ 177.1274; found 177.1271. Data for (*Z*)-**5**: ^{1}H NMR (400.5 MHz, [D$_6$]DMSO, 28 °C): δ = 1.16 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$CH), 1.58 (dd, *J* = 6.7, 1.7 Hz, 3 H, C*H*$_3$CH=), 2.16 (s, 3 H, CH_3Ar), 3.97–4.04 (m, 1 H, C*H*CH$_3$), 5.26–5.37 (m, 1 H, CH=C*H*CH$_3$), 5.56 (m, 1 H, C*H*=CHCH$_3$), 6.53 (dd, *J* = 7.7, 1.6 Hz, 1 H, ArC*H*), 6.56 (d, *J* = 1.6 Hz, 1 H, ArC*H*), 6.97 (d, *J* = 7.7 Hz, 1 H, ArC*H*), 9.08 (s, 1 H, OH) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 25 °C): δ = 17.4 (*C*H$_3$CH=), 20.5 (*C*H$_3$Ar), 21.6 (*C*H$_3$CH), 29.4 (*C*HCH$_3$), 115.3 (Ar*C*H), 119.2 (Ar*C*H), 121.4 (CH$_3$*C*H=CH), 126.5 (Ar*C*H), 129.4 (Ar*C*CH), 135.4 (CH$_3$CH=*C*H), 135.4 (Ar*C*CH$_3$), 150.1 (Ar*C*OH) ppm. Data for (*E*)-**7**: ^{1}H NMR (400.5 MHz, [D$_6$]DMSO, 28 °C): δ = 1.30 (d, *J* = 7.1 Hz, 3 H, C*H*$_3$CH), 1.59 (ddd, *J* = 6.5, 1.3, 1.0 Hz, 3 H, C*H*$_3$CH=), 2.22 (s, 3 H, CH_3Ar), 3.74–3.82 (m, 1 H, C*H*CH$_3$), 5.33–5.42 (m, 1 H, CH=C*H*CH$_3$), 5.87–5.93 (m, 1 H, C*H*=CHCH$_3$), 6.54 (d, *J* = 7.8 Hz, 1 H, ArC*H*), 6.60 (d, *J* = 7.6 Hz, 1 H, ArC*H*), 6.83 (dd, *J* = 7.8, 7.6 Hz, 1 H, ArC*H*), 9.03 (s, 1 H, OH) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 25 °C): δ = 17.5 (*C*H$_3$CH=), 18.6 (*C*H$_3$CH), 20.3 (*C*H$_3$Ar), 35.6 (*C*HCH$_3$),

113.5 (ArCH), 120.6 (ArCH), 121.8 (CH_3CH=CH), 125.8 (ArCH), 130.0 (ArCCH), 135.1 (CH_3CH=CH), 136.3 (ArCCH_3), 155.5 (ArCOH) ppm. Data for Compound **8**: ^{1}H NMR (400.5 MHz, [D$_6$]-DMSO, 28 °C): δ = 1.19 (d, J = 7.1 Hz, 3 H, CH_3CH), 1.61 (dt, J = 6.3, 1.2 Hz, 3 H, CH_3CH=), 2.17 (s, 3 H, CH_3Ar), 3.45–3.51 (m, 1 H, CHCH$_3$), 5.22–5.39 (m, 1 H, CH=CHCH$_3$), 5.42–5.56 (m, 1 H, CH=CHCH$_3$), 6.49–6.56 (m, 2 H, ArCH), 6.92 (m, 1 H, ArCH), 8.99 (s, 1 H, OH) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 25 °C): δ = 17.9 (CH_3CH=), 19.5 (CH_3Ar), 20.7 (CH_3CH), 36.4 (CHCH$_3$), 112.4 (ArCH), 116.5 (ArCH), 121.7 (CH_3CH=CH), 126.1 (ArCH), 134.1 (ArCCH), 136.0 (ArCCH_3), 136.4 (CH_3CH=CH), 155.0 (ArCOH) ppm.

Lewis Acid Catalyzed Claisen Rearrangement: A solution of **6** (100 mg, 0.567 mmol) and Eu(fod)$_3$ (13.3 mg, 0.013 mmol) in DCE (0.1 mL) was heated at 80 °C under an inert atmosphere for 48 h. After removal of the solvent under reduced pressure, the crude material was dissolved in Et$_2$O and washed with water. The organic layer was then dried with Na_2SO_4, filtered, and taken to dryness under vacuum. Initial flash chromatography (hexane/AcOEt = 99:1) allowed **5** (48 mg) to be isolated as a mixture of *E*/*Z* isomers. A second purification, using hexane as the eluent, on silica gel 60 (230–400 mesh), previously impregnated with a solution of 10 wt./vol.-% $AgNO_3$ in water and dried in an oven at 70 °C, afforded pure (*E*)-**5** (14 mg, 14%).

2-[(2*S*)-But-3-en-2-yl]-5-methylphenol (10): Gaseous ethylene was bubbled for 15 min through a solution of **5** (420 mg, 2.38 mmol) in degassed anhydrous CH_2Cl_2 (40 mL). In a separate flask, a solution of second generation Grubbs catalyst (**B**; 222 mg, 0.261 mmol) in the same solvent (26 mL), was bubbled with ethylene for 15 min. The contents of the first flask was then added via cannula to the catalyst solution, and the reaction was aged at room temperature under an ethylene atmosphere overnight. Disappearance of starting material was judged by TLC (hexane/AcOEt = 95:5). Volatiles were removed under vacuum, the crude material was dissolved in Et$_2$O, and the suspension was filtered through a pad of Celite. Compound **10** was finally purified by flash chromatography (hexane/AcOEt = 99:1) and isolated as a colorless oil (244 mg, 63%). IR (neat): $\tilde{\nu}$ = 3457, 1634, 911 cm^{-1}. ^{1}H NMR (400.5 MHz, [D$_6$]DMSO, 28 °C): δ = 1.20 (d, J = 7.1 Hz, 3 H, CH_3CH), 2.17 (s, 3 H, CH_3Ar), 3.69–3.76 (m, 1 H, CHCH$_3$), 4.92–5.03 (m, 2 H, CH$_2$=), 6.00 (ddd, J = 17.2, 10.2, 6.2 Hz, 1 H, CH=CH$_2$), 6.54 (br. d, J = 7.7 Hz, 1 H, ArCH), 6.59 (br. s, 1 H, ArCH), 6.88 (d, J = 7.7 Hz, 1 H, ArCH), 9.14 (s, 1 H, OH) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 25 °C): δ = 19.7 (CH_3CH), 20.9 (CH_3Ar), 35.5 (CHCH$_3$), 113.0 (CH$_2$=), 116.1 (ArCH), 120.3 (ArCH), 127.8 (ArCH), 128.6 (ArCCH), 135.9 (ArCCH_3), 143.7 (CH=CH$_2$), 154.7 (ArCOH) ppm. HRMS (ESI+): calcd. for $C_{11}H_{15}O$ [M + H]$^+$ 163.1117; found 163.1120.

2-{2-[(2*S*)-But-3-en-2-yl]-5-methylphenoxy}-2-methylpropanoic Acid (11): Under an inert atmosphere, **10** (193 mg, 1.19 mmol) was dissolved in 2-butanone (4 mL) and NaOH (261 mg, 6.52 mmol) was added. The mixture was stirred at 55 °C for 70 min, then a solution of 2-bromo-2-methylpropanoic acid (302 mg, 1.81 mmol) in 2-butanone (1 mL) was added dropwise, and the mixture was kept at 55 °C for a further 3 h (TLC: hexane/AcOEt = 90:10 + 2 vol.-% of 4 M HCl in dioxane). After removal of the volatiles, the crude material was treated with AcOEt and washed with 0.5 M HCl and water. The organic layer was dried with Na_2SO_4, filtered, and taken to dryness under reduced pressure. Flash chromatography (hexane/AcOEt = 95:5 + 2 vol.-% of 4 M HCl in dioxane) yielded **11** as a yellow oil (274 mg, 93%). IR (film): $\tilde{\nu}$ = 2966, 1711, 1411, 1254, 909 cm^{-1}. ^{1}H NMR (400.5 MHz, [D$_6$]DMSO, 28 °C): δ = 1.22 (d, J = 7.0 Hz, 3 H, CH_3CH), 1.49 and 1.51 [2 s, 6 H, (CH$_3$)$_2$C], 2.20 (s, 3 H, CH_3Ar), 3.76–3.84 (m, 1 H, CHCH$_3$), 4.93–5.04 (m, 2 H, CH$_2$=), 5.98 (ddd, J = 17.1, 10.4, 6.3 Hz, 1 H, CH=CH$_2$), 6.51 (br. s, 1 H, ArCH), 6.73 (br. d, J = 7.8 Hz, 1 H, ArCH), 7.00 (d, J = 7.8 Hz, 1 H, ArCH), 12.99 (br. s, 1 H, COOH) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 25 °C): δ = 19.4 (CH_3CH), 21.0 (CH_3Ar), 25.3 [(CH$_3$)$_2$C], 35.5 (CHCH$_3$), 78.5 [(CH$_3$)$_2$C], 113.1 (CH$_2$=), 117.2 (ArCH), 121.6 (ArCH), 127.4 (ArCH), 132.7 (ArCCH), 135.6 (ArCCH_3), 143.3 (CH=CH$_2$), 152.9 (ArCO), 176.0 (COOH) ppm. HRMS (ESI+): calcd. for $C_{15}H_{21}O_3$ [M + H]$^+$ 249.1485; found 249.1480.

(3*S*)-3-{2-[(1-Hydroxy-2-methylpropan-2-yl)oxy]-4-methylphenyl}-butan-1-ol (12): To a solution of **11** (570 mg, 2.29 mmol) in anhydrous THF (20 mL), cooled to –78 °C, BH_3·THF (14 mL, 14 mmol) was slowly added dropwise. The mixture was allowed to reach room temperature, and stirred overnight. The reaction mixture was then cooled to 0 °C, and water (7 mL), H_2O_2 (2.1 mL, 30 wt.-% in water), and 0.1 N NaOH (1.4 mL) were subsequently added. The mixture was then allowed to reach room temperature and stirred for 2.5 h, then diluted with AcOEt and washed with an aqueous saturated solution of $Na_2S_2O_3$ and water. The organic phase was dried with Na_2SO_4, filtered, and the solvents evaporated to dryness. Diol **12** was isolated by flash chromatography (hexane/AcOEt = 65:35) as a white solid (380 mg, 66%). M.p. 90–93 °C. IR (film): $\tilde{\nu}$ = 3303 cm^{-1}. ^{1}H NMR (400.5 MHz, [D$_6$]DMSO, 28 °C): δ = 1.08 (d, J = 7.0 Hz, 3 H, CH_3CH), 1.20 and 1.23 [2 s, 6 H, (CH$_3$)$_2$C], 1.59 (q, J = 7.0 Hz, 2 H, CHCH_2), 2.23 (s, 3 H, CH_3Ar), 3.25–3.36 (m overlapped by water signal, 3 H, CHCH$_2$CH$_2$OH), 3.43–3.49 (m, 2 H, CCH_2OH), 4.32 (t, J = 5.2 Hz, 1 H, CH$_2$CH$_2$O*H*), 4.92 (t, J = 5.9 Hz, 1 H, CCH$_2$O*H*), 6.78 (br. d, J = 7.8 Hz, 1 H, ArCH), 6.85 (br. s, 1 H, ArCH), 7.05 (d, J = 7.8 Hz, 1 H, ArCH) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 25 °C): δ = 20.6 (CH_3Ar), 21.0 (CH_3CH), 23.2 [(CH$_3$)$_2$C], 27.2 (CHCH$_3$), 40.5 (CHCH$_2$), 59.2 (CH$_2$CH$_2$OH), 68.7 (CCH$_2$OH), 80.2 [(CH$_3$)$_2$C], 122.2 (ArCH), 123.3 (ArCH), 126.4 (ArCH), 135.0 (ArCCH$_3$), 137.1 (ArCCH), 152.5 (ArCO) ppm. HRMS (ESI+): calcd. for $C_{15}H_{25}O_3$ [M + H]$^+$ 253.1798; found 253.1798.

(3*S*)-3-{4-Methyl-2-[(2-methyl-1-oxopropan-2-yl)oxy]phenyl}butanal (4): To a solution of oxalyl chloride (0.5 mL, 5.9 mmol) in anhydrous CH_2Cl_2 (11 mL), cooled to –78 °C, a solution of DMSO (0.8 mL, 11.3 mmol) in anhydrous CH_2Cl_2 (3 mL) was carefully added under an argon atmosphere. After 25 min, a solution of **12** (363 mg, 1.44 mmol) in CH_2Cl_2 (7 mL) was added and the mixture was stirred at –78 °C for 1 h, then treated dropwise with Et_3N (2 mL, 14.3 mmol). After 2 h, the mixture was allowed to reach room temperature and stirred for an additional 2 h. Disappearance of the starting material was judged by TLC (hexane/AcOEt = 80:20). The mixture was then washed with an aqueous saturated solution of Na_2CO_3 and water. The organic layer was dried with Na_2SO_4, filtered, and taken to dryness under reduced pressure. Compound **4** was finally purified on silica gel by flash chromatography (hexane/AcOEt = 98:2), and isolated as a yellow oil (260 mg, 73%). IR (film): $\tilde{\nu}$ = 1722 cm^{-1}. ^{1}H NMR (400.5 MHz, [D$_6$]DMSO, 28 °C): δ = 1.19 (d, J = 7.0 Hz, 1 H, CH_3CH), 1.40 [s, 6 H, (CH$_3$)$_2$C], 2.20 (s, 3 H, CH_3Ar), 2.64–2.67 (m, 2 H, CHCH_2), 3.60–3.72 (m, 1 H, CHCH$_3$), 6.44 (br. s, 1 H, ArCH), 6.78 (d, J = 7.6, 1 Hz, ArCH), 7.12 (d, J = 7.6 Hz, 1 H, ArCH), 9.62 (t, J = 2.1 Hz, 1 H, CHOCH$_2$), 9.82 (s, 1 H, CHOC) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 25 °C): δ = 20.5 (CH_3Ar), 20.7 (CH_3CH), 21.3 [(CH$_3$)$_2$C], 26.4 (CHCH$_3$), 50.2 (CHCH$_2$), 82.6 [(CH$_3$)$_2$C], 117.6 (ArCH), 123.3 (ArCH), 127.3 (ArCH), 133.0 (ArCCH), 136.5 (ArCCH$_3$), 152.2 (ArCO), 203.3 (CHOCH$_2$), 204.3 (CHOC) ppm. HRMS (ESI+): calcd. for $C_{15}H_{21}O_3$ [M + H]$^+$ 249.1485; found 249.1483.

(5*S*)-2,2,8-Trimethyl-2,5-dihydro-1-benzoxepine-5-carbaldehyde (14): $TiCl_3$ (57.5 mg, 0.373 mmol) was dissolved in DME (2.5 mL) under an inert atmosphere, $LiAlH_4$ (7 mg, 0.184 mmol) was added and the suspension was heated to reflux for 20 min. A solution of **4** (20 mg, 0.081 mmol) in DME (3 mL) was then added by syringe-pump (flow: 0.009 mL/ min) under reflux. The reaction was monitored by TLC (hexane/AcOEt = 95:5). When the addition of **4** was complete, the reaction mixture was heated to reflux for a further 17 h before being filtered through a pad of Celite and concentrated to dryness. Flash chromatography (hexane/AcOEt = 98:2) allowed the isolation of pure **14** as a colorless oil (11 mg, 63%). ^{1}H NMR (400.5 MHz, [D$_6$]DMSO, 28 °C): δ = 1.23 (s, 3 H, CH_3CCH_3), 1.30 (d, J = 7.1 Hz, 3 H, CH_3CH), 1.59 (s, 3 H, CH_3CCH_3), 2.24 (s, 3 H, $ArCH_3$), 3.72 (q, J = 7.1 Hz, 1 H, $CHCH_3$), 6.63 (s, 1 H, CH=), 6.80 (br. s, 1 H, ArC*H*), 6.83 (br. d, J = 7.9 Hz, 1 H, ArC*H*), 7.03 (d, J = 7.9 Hz, 1 H, ArC*H*), 9.34 (s, 1 H, CHO) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 25 °C): δ = 19.8 (CH_3Ar), 21.1 (CH_3CH), 24.6 (CH_3CCH_3), 28.6 (CH_3CCH_3), 33.0 ($CHCH_3$), 77.8 [$(CH_3)_2C$], 124.1 (Ar*C*H), 124.1 (Ar*C*H), 128.5 (Ar*C*H), 135.3 (Ar*C*CH), 136.8 (Ar*C*CH_3), 141.3, (CH=*C*), 152.9 (Ar*C*O), 157.3 (*C*H=), 193.7 (*C*HO) ppm. HRMS (ESI+): calcd. for $C_{14}H_{17}O_2$ [M + H]$^+$ 217.1223; found 217.1218.

2-Methylbut-3-en-2-yl 5-Methyl-2-[(2*S*)-pent-4-en-2-yl]phenyl Ether (15): A solution of **4** (91 mg, 0.367 mmol) and Petasis reagent (Cp_2TiMe_2; 10.7 wt.-% in THF/toluene, 4.26 g, 2.19 mmol) in anhydrous THF (1.5 mL) was irradiated in a microwave reactor at 100 °C for 15 min. Hexane was then added and the mixture was stirred for 1 h. The resulting white precipitate was filtered off and the mother liquor was taken to dryness under reduce pressure. Diene **15** was purified by flash chromatography (hexane/AcOEt = 100:1) and isolated as a colorless oil (44 mg, 50%). ^{1}H NMR (499.7 MHz, [D$_6$]DMSO, 25 °C): δ = 1.10 (d, J = 6.9 Hz, 3 H, CH_3CH), 1.41 [s, 6 H, $(CH_3)_2C$], 2.18 (s, 3 H, $ArCH_3$), 2.16–2.31 (m, 2 H, CH_2CH), 3.12–3.20 (m, 1 H, $CHCH_3$), 4.90–4.93 (m, 1 H, $CH_2CH{=}CH_{cis}$), 4.94–5.00 (m, 1 H, $CH_2CH{=}CH_{trans}$), 5.15 (dd, J = 10.8, 1.1 Hz, 1 H, $CCH{=}CH_{cis}$), 5.22 (dd, J = 17.6, 1.1 Hz, 1 H, $CCH{=}CH_{trans}$), 5.62–5.75 (m, 1 H, $CH_2CH{=}CH$), 6.12 (dd, J = 17.66, 10.8 Hz, 1 H, $CCH{=}CH$), 6.71 (br. d, J = 7.6 Hz, 1 H, ArC*H*), 6.80 (s, 1 H, ArC*H*), 7.03 (d, J = 7.6 Hz, 1 H, ArC*H*) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 25 °C): δ = 20.1 (CH_3CH), 20.7 (CH_3Ar), 27.1 [$(CH_3)_2C$], 31.3 ($CHCH_3$), 40.9 (CH_2CH), 79.0 [$(CH_3)_2C$], 112.7 ($CCH{=}CH_2$), 115.6 ($CH_2CH{=}CH_2$), 119.1 (Ar*C*H), 121.7 (Ar*C*H), 126.2 (Ar*C*H), 134.9 (Ar*C*CH), 135.3 (Ar*C*CH_3), 137.4 ($CH_2CH{=}CH_2$), 144.2 ($CCH{=}CH_2$), 153.2 (Ar*C*O) ppm. HRMS (ESI+): calcd. for $C_{17}H_{25}O$ [M + H]$^+$ 245.1900; found 245.1896.

(3*Z*,6*S*)-2,2,6,9-Tetramethyl-5,6-dihydro-2*H*-1-benzoxocine (13): The second generation Grubbs catalyst (**B**; 8.8 mg, 0.01 mmol) was charged in a two-necked round-bottomed flask under an inert atmosphere. A solution of **15** (24 mg, 0.098 mmol) in anhydrous degassed CH_2Cl_2 (8 mL) was then added and the mixture was stirred for 6 h [reaction monitored by TLC (hexane)]. After the disappearance of the starting material, the solvent was removed in vacuo and **13** was isolated by flash chromatography on silica gel (hexane/AcOEt = 100:1) as a light-yellow oil (17 mg, 80%). ^{1}H NMR (499.7 MHz, [D$_6$]DMSO, 25 °C): δ = 1.13 (d, J = 6.7 Hz, 3 H, CH_3CH), 1.31 (s, 3 H, CH_3CCH_3), 1.51 (s, 3 H, CH_3CCH_3), 2.09 (br. s, 1 H, $CHHCH$), 2.21 (s, 3 H, $ArCH_3$), 2.89 (br. s, 1 H, $CHCH_3$), 3.13 (br. s, 1 H, $CHHCH$), 5.22 (d, J = 10.8 Hz, 1 H, $CCH{=}CHCH_2$), 5.57–5.66 (m, 1 H, $CCH{=}CHCH_2$), 6.68 (s, 1 H, ArC*H*), 6.83 (br. d, J = 7.3 Hz, 1 H, ArC*H*), 6.96 (d, J = 7.3 Hz, 1 H, ArC*H*) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 25 °C): δ = 20.6 (CH_3Ar), 25.2 (CH_3CH), 28.2 (CH_3CCH_3), 29.3 (CH_3CCH_3), 33.7 (CH_2CH), 39.3 (CH_3CH), 80.2 [$(CH_3)_2C$], 125.0 (Ar*C*H), 126.6 (Ar*C*H), 129.8 ($CCH{=}CHCH_2$), 130.5 (Ar*C*H), 134.8 (Ar*C*CH_3), 134.9 ($CCH{=}CHCH_2$), 136.5 (Ar*C*CH), 152.3 (Ar*C*O) ppm. HRMS (ESI+): calcd. for $C_{15}H_{21}O$ [M + H]$^+$ 217.1587; found 217.1580.

(*S*)-(+)-7,11-Helianane (1): Alkene **13** (16 mg, 0.074 mmol), dissolved in MeOH (11 mL), was hydrogenated in the presence of 5 wt.-% Pd/C (10 mg) at 30 psi for 5 h. The catalyst was filtered through a pad of Celite, and (*S*)-(+)-7,11-helianane (**1**; 14 mg, 87%) was recovered as a colorless oil after flash chromatography (hexane/AcOEt = 100:1). $[\alpha]_D$ = +18.9 (c = 0.59, CH_2Cl_2). 80%*ee* (Chiral HPLC; column: Phenomenex Lux Amylose-2, 4.6 × 250 mm, 5 μm; eluent: H_2O/CH_3CN = 60:40 isocratic; flow: 0.8 mL/min; detector: UV 220 nm). ^{1}H NMR (499.7 MHz, $CDCl_3$, 50 °C): δ = 1.25 (d, J = 7.1 Hz, 3 H, CH_3CH), 1.28 (s, 3 H, CH_3CCH_3), 1.40 (s, 3 H, CH_3CCH_3), 1.35–1.39 (m, 1 H, $CHCH_2CH_2CHHC$), 1.40–1.46 (m, 2 H, $CHCHHCHCH_2C$), 1.50–1.55 (m, 1 H, $CHCH_2CH_2CHHC$), 1.56–1.63 (m, 1 H, $CHCH_2CHHCH_2C$), 1.70–1.78 (m, 1 H, $CHCHHCH_2CH_2C$), 2.27 (s, 3 H, $ArCH_3$), 3.14–3.21 (m, 1 H, $CHCH_3$), 6.70 (br. s, 1 H, ArC*H*), 6.87 (d, J = 7.0 Hz, 1 H, ArC*H*), 7.05 (d, J = 7.0 Hz, 1 H, ArC*H*) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 50 °C): δ = 21.0 (CH_3Ar), 21.3 (CH_3CH), 21.9 ($CHCH_2CH_2CH_2C$), 26.9 (CH_3CCH_3), 29.3 (CH_3CCH_3), 31.7 ($CHCH_3$), 38.2 ($CHCH_2CH_2CH_2C$), 39.5 ($CHCH_2CH_2CH_2C$), 80.8 [$(CH_3)_2C$], 124.7 (Ar*C*H), 126.1 (Ar*C*H), 126.1 (Ar*C*H), 134.9 (Ar*C*CH_3), 138.5 (Ar*C*CH), 152.7 (Ar*C*O) ppm. HRMS (ESI+): calcd. for $C_{15}H_{22}ONa$ [M + Na]$^+$ 241.1568; found 241.1571.

(*S*)-(+)-5-Chloro-7,11-helianane (3): A solution of (*S*)-(+)-7,11-helianane (**1**; 8 mg, 0.0366 mmol) and NCS (5.7 mg, 0.0366 mmol) in anhydrous CH_3CN (1 mL) was heated at 50 °C for 3.5 h [the reaction was monitored by TLC (hexane)]. After removal of the solvent under reduced pressure, purification by flash chromatography (hexane/AcOEt = 100:1) afforded **3** as a colorless oil (7.9 mg, 85%). $[\alpha]_D$ = +33.4 (c = 0.36, $CHCl_3$). 80%*ee* (Chiral HPLC; column: Phenomenex Lux Amylose-2, 4.6 × 250 mm, 5 μm; eluent: H_2O/CH_3CN = 50:50 isocratic; flow: 1 mL/min; detector: UV 220 nm). ^{1}H NMR (499.7 MHz, $CDCl_3$, 25 °C): δ = 1.24 (d, J = 7.1 Hz, 3 H, CH_3CH), 1.27 (s, 3 H, CH_3CCH_3), 1.39 (s, 3 H, CH_3CCH_3), 1.35–1.39 (m, 1 H, $CHCH_2CH_2CHHC$), 1.40–1.46 (m, 2 H, $CHCHHCHCH_2C$), 1.50–1.55 (m, 1 H, $CHCH_2CH_2CHHC$), 1.56–1.63 (m, 1 H, $CHCH_2CHHCH_2C$), 1.72–1.77 (m, 1 H, $CHCHHCH_2CH_2C$), 2.28 (s, 3 H, $ArCH_3$), 3.11–3.17 (m, 1 H, $CHCH_3$), 6.74 (br. s, 1 H, ArC*H*), 7.11 (s, 1 H, ArC*H*) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 25 °C): δ = 19.3 (CH_3Ar), 20.8 (CH_3CH), 21.6 ($CHCH_2CH_2CH_2C$), 26.3 (CH_3CCH_3), 29.2 (CH_3CCH_3), 31.9 ($CHCH_3$), 37.9 ($CHCH_2CH_2CH_2C$), 39.2 ($CHCH_2CH_2CH_2C$), 81.5 [$(CH_3)_2C$], 126.6 (Ar*C*H), 127.1 (Ar*C*H), 129.5 (Ar*C*Cl), 132.9 (Ar*C*CH_3), 141.3 (Ar*C*CH), 151.7 (Ar*C*O) ppm. HRMS (ESI+): calcd. for $C_{15}H_{21}ClONa$ [M + Na]$^+$ 275.1173; found 275.1790.

Supporting Information (see footnote on the first page of this article): Copies of the NMR spectra (^{1}H, COSY, TROESY, gradient-enhanced HSQC, and HMBC experiments) for compounds **1**, **3**, **5**, **6**, **11**, **12**, **13**, and **14** described in this paper. Copies of chiral HPLC spectra of compounds **1**, **3**, and **6**. Experimental procedures for the synthesis of Mosher's esters of **5**, diastereomeric amides of **11** (**21**), and compound **20**.

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Chemistry, Department Head) for support, encouragement, and valuable suggestions. F. Q. is profoundly indebted to Dr. Maurizio Pulici for helpful suggestions.

[1] As the numbering system proposed by Macías et al. (see ref.[4]) for this sesquiterpene family faithfully reflects that reported for the basic bisabolane skeleton, it has been adopted throughout this paper. However, the original name of "helianane" coined by Crews and Harrison (see ref.[2]) was maintained.
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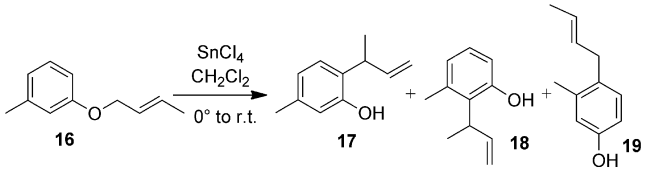
[17] According to the results reported by Venkateswaran et al. (see ref.[5e]), the disappointingly poor performance of tin tetrachloride in catalyzing the Claisen rearrangement of (±)-**6** can be attributed to the presence of a secondary carbon atom in the 1-position of the allylic chain. In fact, by exposing the simpler 2-(*E*)-butenyl-derivative **16** to a freshly prepared 1 M $SnCl_4$ solution in CH_2Cl_2 (see ref.[16]), a smooth Claisen rearrangement occurred (Scheme 6). However, ^1H NMR analysis of the crude reaction mixture (**17**: 40%, **18**: 23%, and **19**: 37%) showed profound discrepancies with the published data (80% isolated yield of **17**, see ref.[5e]). The formation of competitive amounts of the domino Claisen–Cope rearrangement product **19** in the Lewis acid-catalyzed aromatic Claisen rearrangement has been already documented (see ref.[15]).



Scheme 6. $SnCl_4$-mediated Claisen rearrangement of allyl phenyl ether **16**.

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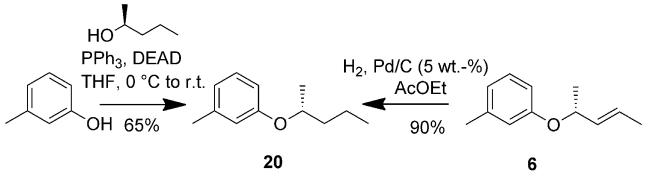
[19] The absolute stereochemistry of **6** was demonstrated to be (*R*) by comparison of the specific rotation of its saturated derivative **20** with a sample synthesized from *meta*-cresol through Mitsunobu etherification with (*S*)-2-pentanol (Scheme 7). See the Supporting Information for the detailed experimental procedure.



Scheme 7. Determination of the absolute configuration of **6**.

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