Tetrahedron 65 (2009) 1902–1910

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Gold catalysis in stereoselective natural product synthesis: (+)-linalool oxide, (−)-isocyclocapitelline, and (−)-isochrysotricine

Frank Volz, Sipke H. Wadman, Anja Hoffmann-Röder, Norbert Krause *

Dortmund University of Technology, Organic Chemistry II, Otto-Hahn-Strasse 6, D-44227 Dortmund, Germany

ARTICLE INFO

Article history:
Received 18 September 2008
Received in revised form 4 November 2008
Accepted 5 November 2008
Available online 24 December 2008

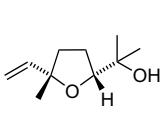
Keywords:
Allenes
Chirality transfer
Cycloisomerization
Gold catalysis
Heterocycles
Tetrahydrofurans

ABSTRACT

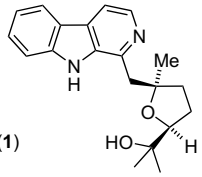
A stereoselective synthesis of the tetrahydrofuran-containing natural products (2*S*,5*R*)-(+)-linalool oxide (**1**), (−)-isocyclocapitelline (**2**), and (−)-isochrysotricine (**3**) is reported. Key steps are the copper-mediated S_N2'-substitution of propargyl oxiranes **7** and the gold-catalyzed cycloisomerization of dihydroxyallenes **8**/**17**, resulting in a highly efficient center-to-axis-to-center chirality transfer. The enantioselective total synthesis of (−)-isocyclocapitelline (**2**) and (−)-isochrysotricine (**3**) allowed the elucidation of the absolute configuration of these β-carboline natural products.

1. Introduction

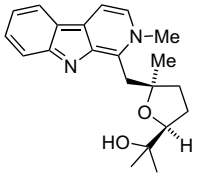
Due to their presence in many biologically active natural products, chiral tetrahydrofurans continue to be of high interest in preparative and medicinal chemistry.[1] Recently, 2,5-substituted tetrahydrofurans have attracted much attention since they occur in annonaceous acetogenins, which exhibit highly diverse biological properties.[2] Various other natural products also contain this heterocyclic system, including the terpenoid linalool oxide (**1**), the β-carboline alkaloids, (−)-isocyclocapitelline (**2**), and (−)-isochrysotricine (**3**).



(2*S*,5*R*)-(+)-Linalool Oxide (**1**)



(−)-Isocyclocapitelline (**2**)



(−)-Isochrysotricine (**3**)

Furanoid linalool oxide (**1**) is an important constituent of oolong, black and green tea and is also found in many essential oils[3] and fruit aromas (e.g., in papaya).[4] It is used in perfumery (e.g., for lavender notes) and for the reconstitution of essential oils.[5] For these applications, control of the stereochemistry is crucial since the fragrance properties of linalool oxide depend on the absolute configuration at C-2: the (2*R*)-isomers have a leafy earthy note whereas the (2*S*)-isomers exhibits a sweet floral creamy flavor.[6,7] Although many syntheses of linalool oxide have been reported,[8] most of them are not stereoselective; only two diastereo- and enantioselective routes have been disclosed so far.[9]

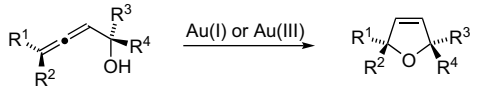
Isocyclocapitelline (**2**) and isochrysotricine (**3**) were isolated (together with their diastereomers cyclocapitelline and chrysotricine) in 1999 from the Rubiaceae plant *Hedyotis capitellata*, which has been widely used in traditional Chinese and Vietnamese herb medicine.[10] The constitution and relative configuration of these β-carboline alkaloids were confirmed by NMR data and an X-ray analysis; the absolute configuration was unknown at the beginning of our work. Studies of the biological activity of isochrysotricine and isocyclocapitelline were hampered by the minute amounts of the alkaloids available from natural sources; for chrysotricine, however, an interesting in vitro activity against the growth of HL-60 leukemia cells has been observed.[11] Previous synthetic studies were devoted to (+)-chrysotricine,[12] racemic isocyclocapitelline/isochrysotricine,[13] and norisocyclocapitelline.[8g]

Taking into account that all three natural products contain a chiral 2,5-trisubstituted tetrahydrofuran ring of the same relative configuration,[14] we reasoned that related synthetic routes should lead to these target molecules. Based on our experience with the gold-catalyzed[15] cycloisomerization of α-hydroxyallenes[16]

* Corresponding author. Tel.: +49 231 755 3882; fax: +49 231 755 3884.
E-mail address: norbert.krause@tu-dortmund.de (N. Krause).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.11.104

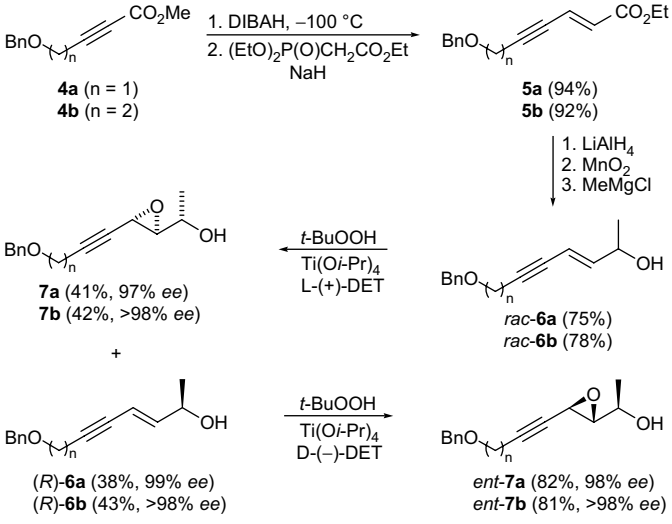
(Scheme 1) and other functionalized allenes[17] to five- or six-membered heterocycles, we planned to use this reaction (which takes place with efficient axis-to-center chirality transfer) as the key step for the synthesis of the natural products **1**–**3**. In this paper, we report on our synthesis of (2*S*,5*R*)-(+)-linalool oxide (**1**), as well as the first total syntheses of (−)-isocyclocapitelline (**2**) and (−)-isochrysotricine (**3**).[18]



Scheme 1. Gold-catalyzed cycloisomerization of α-hydroxyallenes to 2,5-dihydrofurans.

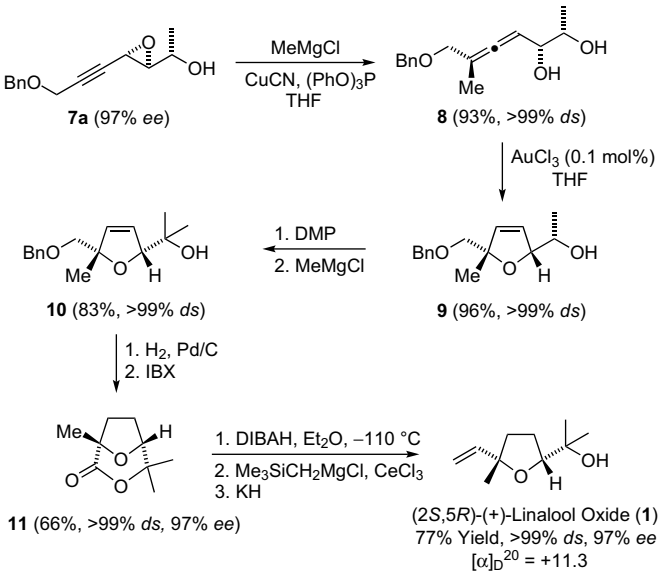
2. Results and discussion

Our approach started from the known esters **4a**[19] and **4b**,[20] which were converted into the enynoates **5** by a one-pot reduction–olefination sequence (Scheme 2).[21] Efficient transformation into the racemic secondary alcohols *rac*-**6** was achieved by standard reduction–oxidation–Grignard addition. Both enynes turned out to be excellent substrates for a kinetic resolution by Katsuki–Sharpless epoxidation;[22] with L-(+)-diethyl tartrate, both the epoxides **7** and the unreacted starting materials (*R*)-**6** (configuration assigned according to the Katsuki–Sharpless mnemonic device[22]) were obtained with high enantiomeric excess.[23] The enynes (*R*)-**6** were converted into oxiranes *ent*-**7**[23] by a matched Katsuki–Sharpless epoxidation using D-(−)-diethyl tartrate. It should be noted that the corresponding tertiary epoxyalcohols are not accessible by Katsuki–Sharpless epoxidation, due to the low reactivity of tertiary allylic alcohols.[22] With both enantiomers of the epoxyalcohols **7** at hand, either enantiomer of the target molecules **1**–**3** is accessible.



Scheme 2. Stereodivergent synthesis of propargyl oxiranes **7** by Katsuki–Sharpless epoxidation (DET=diethyl tartrate).

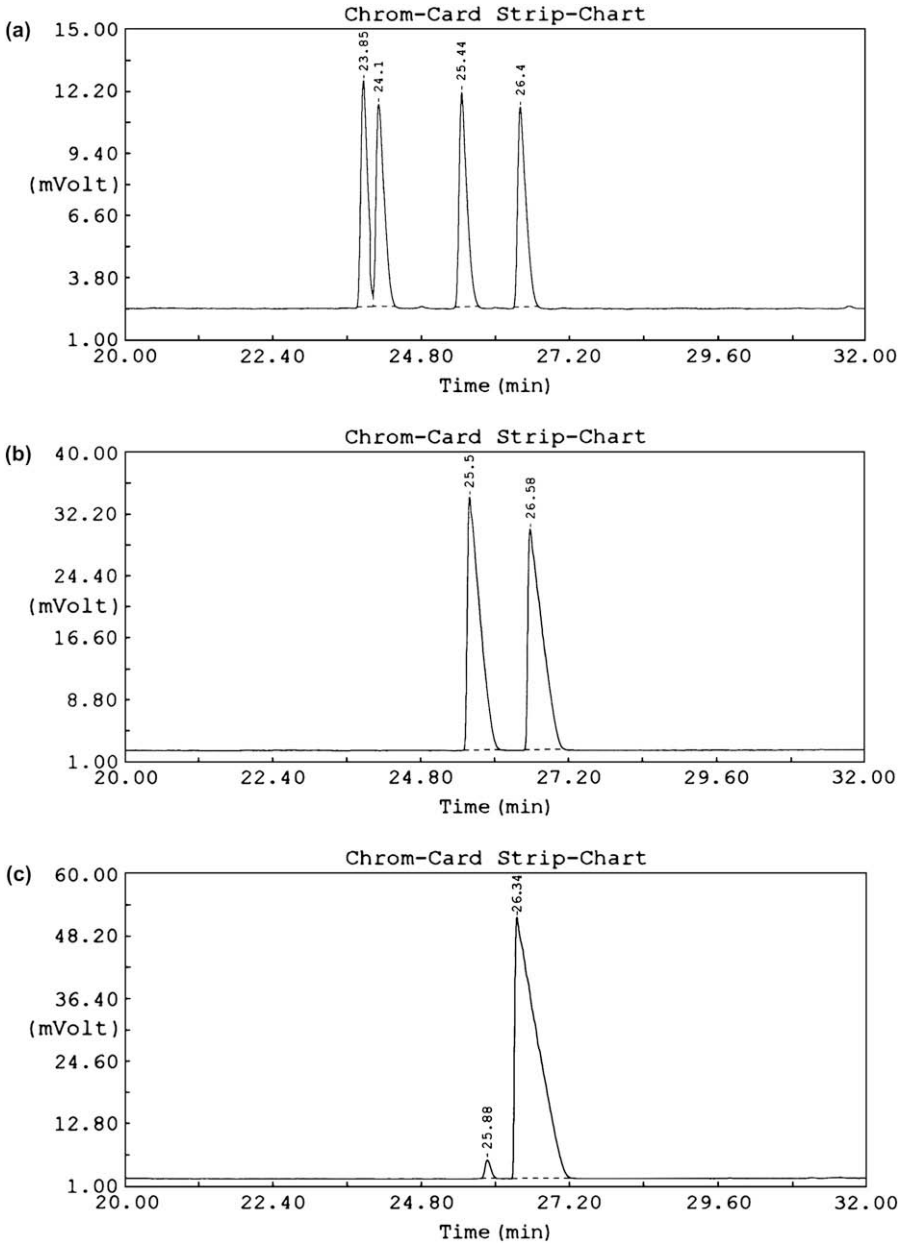
The key steps of the synthesis of (2*S*,5*R*)-(+)-linalool oxide (**1**) are the *anti*-selective copper-mediated S_N2'-substitution of propargyl oxirane **7a** and the gold-catalyzed cycloisomerization of the dihydroxyallene **8** thus formed (Scheme 3). Treatment of **7a** with a methylmagnesium cyanocuprate in the presence of triphenylphosphite as ligand to copper (in order to prevent epimerization of the allene[24]) afforded **8** with excellent chemical yield (93%) and diastereoselectivity (>99% ds).[25] The subsequent gold-catalyzed cycloisomerization was achieved in the presence of only 0.1 mol % $AuCl_3$ in THF, which gave the 2,5-dihydrofuran **9** with 96% yield (960 turnovers on a 2 g scale) as a single diastereomer, completing the key center-to-axis-to-center chirality transfer. As expected from previous results,[16,17e] only the hydroxy group in α-position participates in the cyclization.



Scheme 3. Stereoselective synthesis of (2*S*,5*R*)-(+)-linalool oxide (**1**) from propargyl oxirane **7a** (DMP=Dess–Martin periodinane; IBX=2-iodoxybenzoic acid).

Conversion of the secondary alcohol **9** into the tertiary alcohol **10** by oxidation with Dess–Martin periodinane (DMP; 94% yield)[26] or with 2-iodoxybenzoic acid (IBX) in DMSO[27] (63% yield) and subsequent Grignard addition proceeded smoothly. One-pot hydrogenation–debenzylation of **10** using palladium on charcoal as the catalyst furnished the desired diol with 81% yield; however, all attempts to selectively oxidize this to the corresponding lactol failed. Rather, we obtained mixture of the lactol and lactone **11**, regardless whether PCC, PDC, DMP, or IBX was used as the oxidizing agent. Therefore, we decided to completely oxidize the diol to lactone **11**, which was obtained with 66% yield over two steps when 2 equiv of IBX were used. For the final conversion of **11** into (2*S*,5*R*)-(+)-linalool oxide (**1**), we initially utilized a one-pot procedure consisting of the reduction of **11** with DIBAH at −110 °C and subsequent treatment of the lactol thus formed with freshly prepared $Ph_3P{=}CH_2$.[28] Since the yield of **1** was only 20% (33% for a stepwise process), we switched to a modified Peterson olefination using trimethylsilylmethylmagnesium chloride/cerium chloride and potassium hydride.[29] Under these conditions, the target molecule **1** was obtained with 77% overall yield for the reduction–olefination sequence. Gratifyingly, the high stereochemical purity was maintained overall steps, so that (2*S*,5*R*)-(+)-linalool oxide (**1**) was obtained with >99% ds and 97% ee (determined by GC; see Scheme 4). Comparison of the optical rotation of our product {$[\alpha]_D^{20}$ +11.3 (*c* 0.065, $CHCl_3$)} with the literature value[7] {$[\alpha]_D^{20}$ +4.0 (*c* 0.028, $CHCl_3$)} confirms the absolute configuration.

In contrast to linalool oxide, the absolute configuration of the other two target molecules, (−)-isocyclocapitelline (**2**) and (−)-isochrysotricine (**3**), was unknown at the onset of our study. We randomly selected epoxyalcohol *ent*-**7b** for our synthesis (Scheme 5). The first step matches with those used for linalool oxide: *anti*-selective copper-mediated S_N2'-substitution with MeMgCl/CuCN/$(PhO)_3P$ afforded the allenic diol **12** with high diastereoselectivity (>98% ds), and the chemo- and stereoselective gold-catalyzed cycloisomerization furnished the desired 2,5-dihydrofuran **13** with excellent yield and center-to-axis-to-center chirality transfer. With a catalyst loading of only 0.05 mol % $AuCl_3$ in

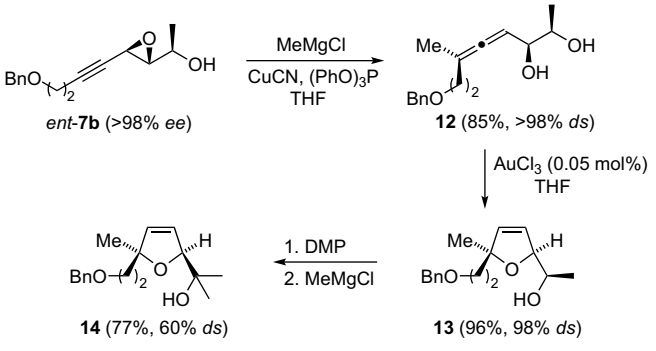


Scheme 4. Gas chromatograms of linalool oxide on Lipodex G: (a): racemic mixture of diastereomers (Sigma–Aldrich); (b): racemic *cis*-**1**; (c): (2*S*,5*R*)-(+)-**1** prepared in this work.

THF,[16] the cycloisomerization of **12** (over 1900 turnovers on a 2 g-scale!) belongs to the most efficient transformations reported so far in homogeneous gold catalysis.

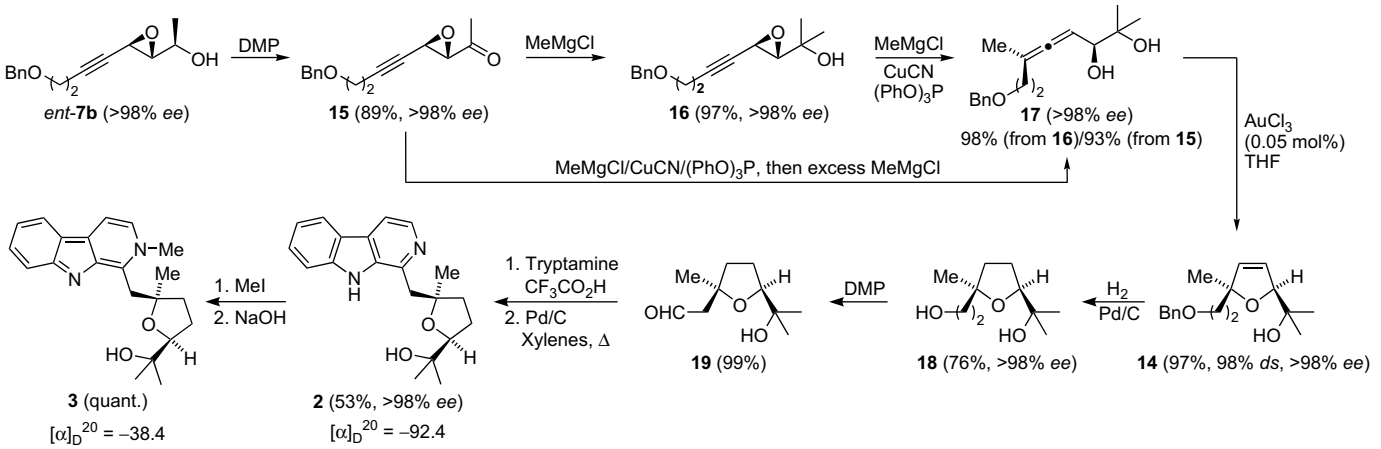
In contrast to these unproblematic steps, the conversion of the secondary alcohol **13** into the tertiary alcohol **14** turned out to be tricky. The oxidation of **11** to the corresponding ketone could be achieved with IBX in DMSO[27] (79% yield) or with Dess–Martin periodinane (DMP)[26] in CH_2Cl_2 (91% yield). Unfortunately, this ketone undergoes a very facile epimerization (probably via the corresponding enol), so that the subsequent Grignard addition afforded alcohol **14** only as a 60:40 mixture of diastereomers. The ease of this epimerization is surprising considering the fact that the analogous ketone obtained by oxidation of alcohol **9** shows no tendency to epimerize (Scheme 3). Possibly, the longer benzyloxyethyl side chain is stabilizing the enol by an intramolecular hydrogen bridge.

In order to circumvent this pitfall, we changed the order of events (Scheme 6). Treatment of epoxyalcohol *ent*-**7b** with Dess–Martin periodinane[26] (or with IBX;[27] 88% yield) gave the ketone **15**, which turned out to be configurationally stable. Subsequent

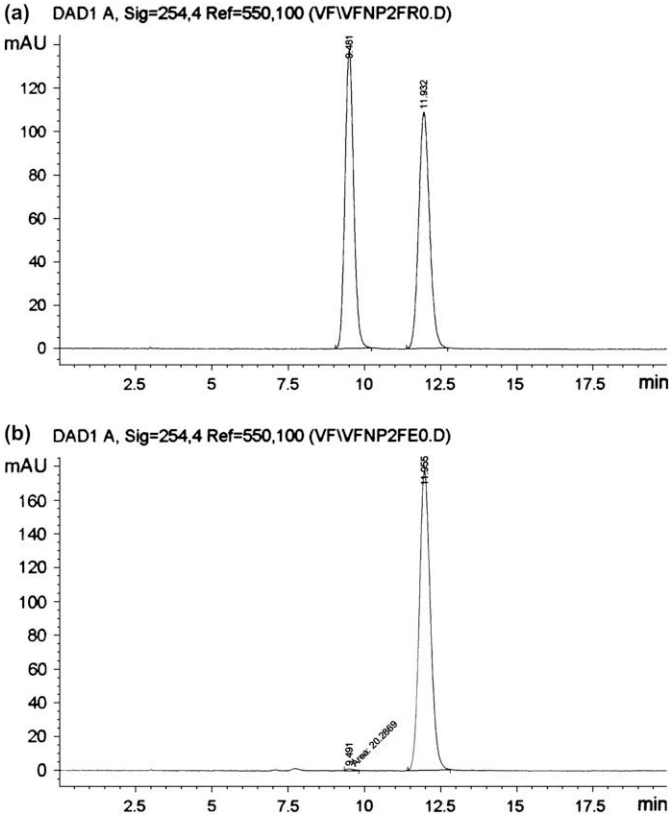


Scheme 5. Synthesis of 2,5-dihydrofuran **14** from propargyl oxirane *ent*-**7b** (DMP=Dess–Martin periodinane).

Grignard addition and S_N2'-substitution of tertiary alcohol **16** to allene **17** proceeded with excellent yield and without any loss of stereochemical information (>98% ee). Alternatively, the



Scheme 6. Stereoselective synthesis of (−)-isocyclocapitelline (**2**) and (−)-isochrysotricine (**3**) from propargyl oxirane *ent*-**7b** (DMP=Dess–Martin periodinane).



Scheme 7. HPLC chromatograms of isocyclocapitelline on Chiralpak AD: (a): racemic **2**; (b) (2*S*,5*R*)-(−)-**2** prepared in this work.

conversion of **15** to **17** can be carried out in a one-pot S_N2'-substitution/1,2-addition by treating the substrate first with the methylmagnesium cuprate and then with excess Grignard reagent. Also this sequence afforded allenic diol **17** with 93% yield and excellent stereocontrol (>98% ee). The subsequent axis-to-center chirality transfer by gold-catalyzed cycloisomerization (0.05 mol % $AuCl_3$ in THF) proceeded as for allene **12** to give the key intermediate **14** with excellent yield (97%) and high stereochemical purity (98% ds, >98% ee).

The next steps to the target molecules, hydrogenation/debenzylation of **14** using palladium on charcoal as the catalyst, as well as oxidation of **18** with Dess–Martin periodinane,[26] gave hydroxyaldehyde **19** with good yield. Interestingly, this does not show any tendency to form a lactol of the type **11** (Scheme 3). We then carried out a Pictet–Spengler cyclization[30] of **3** with tryptamine;[12,13] (−)-isocyclocapitelline (**2**) was obtained with 53% yield over two steps and >98% ds/ee (see Scheme 7) after aromatization of the crude tetrahydro-β-carboline with palladium on charcoal in refluxing xylenes. Comparison of the optical rotation of our product {$[\alpha]_D^{20}$ −92.4 (*c* 0.525, $CHCl_3$)} with that of the natural product[11] {$[\alpha]_D^{20}$ −75 (*c* 0.50, $CHCl_3$)} suggests that the latter was not isolated as an enantiomerically pure compound. More importantly, it confirms the absolute configuration of (−)-isocyclocapitelline (**2**) to be (2*S*,5*R*).[31] Finally, methylation of the β-carboline with MeI in refluxing acetone and deprotonation with aqueous NaOH[12,13] afforded (2*S*,5*R*)-(−)-isochrysotricine (**3**) with an optical rotation of $[\alpha]_D^{20}$ −38.4 (*c* 1.020; no literature value reported, MeOH). The spectroscopic data of synthetic **1** and **2** are in excellent agreement with those reported in the literature.[10]

3. Conclusion

In this paper, we describe a highly stereoselective synthesis of three natural products bearing a 2,5-trisubstituted tetrahydrofuran ring: (2*S*,5*R*)-(+)-linalool oxide (**1**), (−)-isocyclocapitelline (**2**), and (−)-isochrysotricine (**3**). The key feature of our synthetic approach is a center-to-axis-to-center chirality transfer by anti-selective copper-mediated S_N2'-substitution of propargyl oxiranes and subsequent chemo- and stereoselective gold-catalyzed cycloisomerization of dihydroxyallenes to 2,5-dihydrofurans. Due to the stereodivergent nature of our syntheses, both enantiomers of the target molecules are accessible via the same route. With extremely low catalyst loadings of 0.05–0.1 mol % $AuCl_3$, the cycloisomerizations of the allenic diols **8**, **12**, and **17** belong to the most efficient transformations reported so far in homogeneous gold catalysis. For the β-carboline alkaloids (−)-isocyclocapitelline and (−)-isochrysotricine, our synthesis confirms the hitherto unknown absolute configuration of these natural products. Our approach clearly demonstrates the power of combined coinage metal-catalysis for the synthesis of complex target molecules.

4. Experimental

4.1. General

Moisture and oxygen sensitive reactions were performed in oven-dried glassware under argon. Diethyl ether and THF were distilled from sodium/benzophenone. Dichloromethane, *n*-hexane, and acetonitrile were distilled from CaH_2. Column chromatography was carried out with Merck silica gel F 60 (70–230 mesh). Dess–Martin periodinane[26] and IBX[27] were synthesized according to the

literature. *n*-BuLi and MeMgCl were titrated with salicylaldehyde phenylhydrazone according to the procedure of Love and Jones.[32] Gold(III)-chloride was used as a stock solution in dry acetonitrile. ^{1}H and ^{13}C NMR spectra were recorded with Bruker DRX 400 and DRX 500 spectrometers at room temperature in $CDCl_3$ as solvent and internal standard (^{1}H NMR: δ=7.27; ^{13}C NMR: δ=77.0). The NMR spectra of α-hydroxyallenes were measured in K_2CO_3-doped $CDCl_3$ in order to prevent acid-promoted cyclization. The signals of the major component of a product mixture are marked with asterisks (*) and signals marked with ^{n} showed no separation in the NMR spectra. Enantiomeric ratios were determined by gas chromatography on a Carbo Erba 8000 TOP gas chromatograph with hydrogen as carrier gas and a Lipodex® G column, or with a Hewlett Packard HPLC system 1050 with a multi UV detector 1050 using Chiralcel OD, ODH or Chiralpak® AD columns and *n*-heptane/isopropanol as eluent. Diastereomeric ratios were determined by gas chromatography on a Carbo Erba 8000 TOP gas chromatograph with helium as carrier gas and a DB1 capillary column, as well as by NMR spectroscopy. IR spectra were measured with a Nicolet Avatar 320 FT-IR spectrometer as a liquid film between NaCl plates or as a KBr pellet. Optical rotations were determined with a Perkin–Elmer 341 polarimeter using a 10 cm cuvette. GC–MS spectra were recorded using a Thermoquest Finnigan Polaris GCQ spectrometer. Mass spectra and high resolution mass spectra (HRMS) were measured on a Jeol SX102A spectrometer.

4.2. Ethyl (*E*)-6-(benzyloxy)hex-2-en-4-ynoate (5a)

To a solution of ester **4a**[19] (20.0 g, 98.0 mmol) in dry diethyl ether (200 mL) was added slowly DIBAH (108 mL, 108 mmol, 1 M in *n*-hexane) at −100 °C. In a second flask ethyl (diethoxyphosphoryl) acetate (28.5 g, 127 mmol) dissolved in dry THF (60 mL) was added to a suspension of NaH (5.09 g, 127 mmol, 60% in paraffin oil) in THF (100 mL). The solution was warmed to room temperature, stirred for additional 30 min, then cooled to −80 °C and transferred via Teflon tube to the other flask. The mixture was warmed to room temperature and stirred for 18 h. After adding saturated aqueous citric acid/NaH_2PO_4, the layers were separated and extracted with diethyl ether; the combined organic layers were dried over $MgSO_4$. The solvents were removed in vacuo and the crude product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate, 10:1→7:3) to afford enynoate **5a** (22.6 g, 94%, *E*/*Z*=47:1 by GC and NMR analysis). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.38–7.31 (m, 5H), 6.81 (dt, *J*=16.1, 1.6 Hz, 1H), 6.26 (d, *J*=16.1 Hz, 1H), 4.62 (s, 2H), 4.35 (d, *J*=1.6 Hz, 2H), 4.23 (q, *J*=7.1 Hz, 2H), 1.31 (t, *J*=7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.7, 137.0, 130.9, 128.5, 128.1, 128.0, 124.4, 94.3, 83.3, 71.8, 60.8, 57.7, 14.2. IR (neat): ν=2287, 1720, 1622, 1354, 1304, 1267, 1181, 1091, 961 cm^{-1}. HRMS (FAB): calcd for $C_{15}H_{17}O_3$ $[M+H]^+$: *m*/*z*=245.1178; found: *m*/*z*=245.1179.

4.3. Ethyl (*E*)-7-(benzyloxy)hept-2-en-4-ynoate (5b)

Analogous to the synthesis of **5a**: ester **4b**[20] (15.8 g, 72.4 mmol), DIBAH (80 mL, 80 mmol, 1 M in *n*-hexane), diethyl ether (200 mL), ethyl (diethyloxyphosphoryl)acetate (18.9 mL, 94 mmol), NaH (3.77 g, 94 mmol, 60% in paraffin), and THF (150 mL) afforded enynoate **5b** (17.2 g, 92%, *E*/*Z*=99:1 by GC and NMR analysis) as a pale yellow oil. Spectroscopic data: see Supplementary data in Ref. 18.

4.4. (*E*)-7-(Benzyloxy)hept-3-en-5-yn-2-ol (*rac*-6a)

4.4.1. (*E*)-6-(Benzyloxy)hex-2-en-4-yn-1-ol

A suspension of $LiAlH_4$ (4.66 g, 123 mmol) in dry diethyl ether (200 mL) was cooled to −80 °C and enynoate **5a** (15.0 g, 61.4 mmol) was added dropwise. The solution was warmed to −20 °C for 5 h and saturated NH_4Cl was added slowly. The mixture was stirred for an additional hour by warming to room temperature. The mixture was filtered through a pad of Celite® and the layers were separated, dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate, 7:3) to afford (*E*)-6-(benzyloxy)hex-2-en-4-yn-1-ol (11.2 g, 90%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.37–7.29 (m, 5H), 6.28 (dt, *J*=16.0, 5.0 Hz, 1H), 5.80 (dt, *J*=16.0, 1.6 Hz, 1H), 4.62 (s, 2H), 4.30 (d, *J*=1.6 Hz, 2H), 4.20 (d, *J*=5.0 Hz, 2H), 2.20 (s, 1H, OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ=142.5, 137.3, 128.4, 128.0, 127.8, 109.5, 85.6, 84.4, 71.5, 62.6, 57.8. IR (neat): ν=3408, 2214, 1159, 1026, 952 cm^{-1}. HRMS (FAB): calcd for $C_{13}H_{13}O_2$ $[M-H]^+$: *m*/*z*=201.0916; found: *m*/*z*=201.0929; calcd for $C_{13}H_{15}O_2$ $[M+H]^+$: *m*/*z*=203.1072; found: *m*/*z*=203.1094.

4.4.2. (*E*)-6-(Benzyloxy)hex-2-en-4-ynal

To a suspension of activated MnO_2 (129 g, 1.48 mol) in CH_2Cl_2 (400 mL) was added (*E*)-6-(benzyloxy)hex-2-en-4-yn-1-ol (10.0 g, 49.4 mmol) in one portion, and the mixture was stirred for 18 h. The reaction mixture was filtered through a Celite®/silica gel pad, the solvent was removed in vacuo and the crude product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate, 7:3) to afford (*E*)-6-(benzyloxy)hex-2-en-4-ynal (8.95 g, 90%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.58 (d, *J*=7.5 Hz, 1H), 7.38–7.31 (m, 5H), 6.65 (dt, *J*=16.0, 1.0 Hz, 1H), 6.48 (dd, *J*=16.0, 7.5 Hz, 1H), 4.63 (s, 2H), 4.40 (d, *J*=1.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=192.9, 139.8, 136.9, 131.7, 128.5, 128.0, 100.3, 82.8, 72.0, 57.7. IR (neat): ν=2848, 2734, 2210, 1686, 1605, 961 cm^{-1}. HRMS (FAB): calcd for $C_{13}H_{12}O_2$ $[M]^+$: *m*/*z*=200.0837; found: *m*/*z*=200.0845; calcd for $C_{13}H_{13}O_2$ $[M+H]^+$: *m*/*z*=201.0916; found: *m*/*z*=201.0913.

4.4.3. (*E*)-7-(Benzyloxy)hept-3-en-5-yn-2-ol (*rac*-**6a**)

A solution of (*E*)-6-(benzyloxy)hex-2-en-4-ynal (3.65 g, 18.2 mmol) in dry THF (150 mL) was cooled to −80 °C and MeMgCl (9.1 mL, 27.3 mmol, 3 M in THF) was added dropwise. The reaction mixture was warmed for 3 h to 0 °C and saturated NH_4Cl solution was added. The layers were separated, the aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried over $MgSO_4$. The solvents were removed in vacuo and the crude product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate, 8:2→6:4) to afford alcohol *rac*-**6a** (3.67 g, 93%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.37–7.30 (m, 5H), 6.21 (dd, *J*=15.9, 5.6 Hz, 1H), 5.75 (dd, *J*=15.9, 1.5 Hz, 1H), 4.62 (s, 2H), 4.36 (m, 1H), 4.30 (d, *J*=1.5 Hz, 1H), 1.94 (s, 1H, OH), 1.29 (d, *J*=6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=147.2, 137.3, 128.4, 128.0, 127.8, 108.4, 85.7, 84.3, 71.5, 68.0, 57.8, 22.9. IR (neat): ν=3385, 2858, 2214, 1454, 1354, 1071, 958 cm^{-1}. HRMS (FAB): calcd for $C_{14}H_{15}O_2$ $[M-H]^+$: *m*/*z*=215.1072; found: *m*/*z*=215.1047.

4.5. (*E*)-8-(Benzyloxy)oct-3-en-5-yn-2-ol (*rac*-6b)

4.5.1. (*E*)-7-(Benzyloxy)hept-2-en-4-yn-1-ol

Analogous to the synthesis of (*E*)-6-(benzyloxy)hex-2-en-4-yn-1-ol, $LiAlH_4$ (3.80 g, 100 mmol), diethyl ether (200 mL), and enynoate **5b** (12.9 g, 50 mmol) afforded (*E*)-7-(benzyloxy)hept-2-en-4-yn-1-ol (9.80 g, 91%) as colorless solid. Mp 34 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.37–7.28 (m, 5H), 6.18 (dt, *J*=15.8, 5.3 Hz, 1H), 5.72 (dt, *J*=15.8, 1.8 Hz, 1H), 4.57 (s, 2H), 4.15 (d, *J*=4.8 Hz, 2H), 3.61 (t, *J*=7.0 Hz, 2H), 2.64 (dt, *J*=7.0, 1.5 Hz, 2H), 2.07 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=140.9, 137.9, 128.3, 127.6, 127.6, 110.6, 87.5, 79.3, 72.9, 68.2, 62.7, 20.7. IR (KBr): ν=3358, 2216, 1408, 1089, 953 cm^{-1}. HRMS (FAB): calcd for $C_{14}H_{15}O_2$ $[M-H]^+$: *m*/*z*=215.1072; found: *m*/*z*=215.1106; calcd for $C_{14}H_{16}O_2$ $[M]^+$: *m*/*z*=216.1150; found: *m*/*z*=216.1125.

4.5.2. (E)-7-(Benzyloxy)hept-2-en-4-ynal

Analogous to the synthesis of (*E*)-6-(benzyloxy)hex-2-en-4-ynal, MnO_2 (91.9 g, 1.06 mol), CH_2Cl_2 (300 mL), and (*E*)-7-(benzyloxy)hept-2-en-4-yn-1-ol (7.62 g, 35.3 mmol) afforded (*E*)-7-(benzyloxy)hept-2-en-4-ynal (6.67 g, 88%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.54 (d, $^3J_{HH}$=7.8 Hz, 1H, 1-H), 7.39–7.29 (m, 5H), 6.60 (dt, *J*=15.8, 2.3 Hz, 1H), 6.41 (dd, *J*=15.8, 7.8 Hz, 1H), 4.58 (s, 2H), 3.65 (t, *J*=6.8 Hz, 2H), 2.76 (dt, *J*=6.8, 2.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=193.4, 139.2, 137.7, 133.4, 128.4, 127.7, 127.6, 103.5, 78.5, 73.0, 67.5, 21.4. IR (neat): ν=2864, 2734, 2217, 1685, 1605, 1454, 1122, 961 cm^{-1}. HRMS (FAB): calcd for $C_{14}H_{15}O_2$ $[M+H]^+$: *m*/*z*=215.1072; found: *m*/*z*=215.1101.

*4.5.3. (E)-8-(Benzyloxy)oct-3-en-5-yn-2-ol (rac-**6b**)*

Analogous to the synthesis of *rac*-**6a**, MeMgCl (12 mL, 36.4 mmol, 3 M in THF), THF (200 mL), and (*E*)-7-(benzyloxy)hept-2-en-4-ynal (5.20 g, 24.3 mmol) afforded *rac*-**6b** (5.42 g, 97%) as colorless oil. Spectroscopic data: see Supplementary data in Ref. 18.

4.6. (*R*,*E*)-7-(Benzyloxy)hept-3-en-5-yn-2-ol ((*R*)-6a) and (*S*,*S*,*S*)-1-(3-(3-(benzyloxy)prop-1-ynyl)oxiran-2-yl)-ethanol (7a)

A solution of Ti(O*i*-Pr)$_4$ (6.88 mL, 23.1 mmol) in dry CH_2Cl_2 (40 mL) was cooled to −30 °C and L-(+)-DET (4.75 mL, 27.7 mmol) was added dropwise. After 30 min a solution of alcohol *rac*-**6a** (5.0 g, 23.1 mmol) in CH_2Cl_2 (5 mL) was added dropwise, the reaction mixture was stirred for additional 30 min, and subsequently TBHP (4.22 mL, 12.0 mmol, 2.85 M in PhMe) was added. The reaction mixture was left in the freezer for 14 days at −20 °C and then a solution of tartaric acid (10.4 g, 69.4 mmol) and $FeSO_4 \cdot 7H_2O$ (12.0 g, 43.3 mmol) in H_2O (37 mL) was added. The mixture was stirred with gradual warming from −30 °C to room temperature over 1 h. The layers were separated, the aqueous layer extracted with CH_2Cl_2, and the combined layers were concentrated in vacuo. The crude product was dissolved in diethyl ether (100 mL), the solution was cooled to 0 °C and aqueous 0.75 M NaOH (110 mL) was added with vigorously stirring. After 1.5 h the layers were separated, the aqueous layer was extracted with diethyl ether, and the combined layers were concentrated in vacuo. The crude product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate, 8:2→6:4→2:1) to afford alcohol (*R*)-**6a** (1.88 g, 38%) and epoxide **7a** (2.18 g, 41%), both as a colorless oils. Compound (*R*)-**6a**: $[\alpha]_D^{20}$ +7.8 (*c* 1.215, $CHCl_3$). HPLC assay: Chiralcel OD-H, *n*-heptane/isopropanol 95:5, flow 1 mL min^{-1}, detection by UV at 220, 230 nm, t_R=22.0 min (*S*-enantiomer, minor), t_R=23.9 min (*R*-enantiomer, major), 99% ee. Compound **7**: $[\alpha]_D^{20}$ +5.3 (*c* 1.340, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.37–7.30 (m, 5H), 4.59 (s, 2H), 4.21 (d, *J*=1.3 Hz, 2H), 4.01 (dq, *J*=6.3, 2.5 Hz, 1H), 3.51 (d, *J*=1.0 Hz, 1H), 3.21 (t, *J*=2.5 Hz, 1H), 2.05 (s, 1H, OH), 1.29 (d, *J*=2.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=137.1, 128.4, 128.0, 127.9, 82.5, 80.3, 71.8, 63.9, 63.1, 57.2, 41.6, 18.4. IR (neat): ν=3424, 2864, 2360, 1354, 1264, 882 cm^{-1}. HRMS (FAB): calcd for $C_{14}H_{15}O_3$ $[M-H]^+$: *m*/*z*=231.1021; found: *m*/*z*=231.0996.

4.7. (*R*,*E*)-8-(Benzyloxy)oct-3-en-5-yn-2-ol ((*R*)-6b) and (*S*,*S*,*S*)-1-(3-(4-(benzyloxy)but-1-ynyl)oxiran-2-yl)ethanol (7b)

Analogous to the synthesis of (*R*)-**6a** and **7a**, Ti(O*i*-Pr)$_4$ (7.8 mL, 26.1 mmol), L-(+)-DET (5.4 mL, 31.3 mmol), TBHP (5.0 mL, 14.3 mmol, 2.85 M in PhMe), CH_2Cl_2 (45 mL), and alcohol *rac*-**6b** (6.0 g, 26.1 mmol) afforded alcohol (*R*)-**6b** (2.61 g, 43%) and epoxide **7b** (2.71 g, 42%) both as colorless oils. Compound (*R*)-**6b**: $[\alpha]_D^{20}$ +6.6 (*c* 1.440, $CHCl_3$). Compound **7b**: $[\alpha]_D^{20}$ +4.0 (*c* 1.295, $CHCl_3$). Spectroscopic data: see Supplementary data in Ref. 18.

4.8. (*R*,*R*,*R*)-1-(3-(3-(Benzyloxy)prop-1-ynyl)oxiran-2-yl)ethanol (*ent*-7a)

Analogous to the synthesis of (*R*)-**6a** and **7a**, Ti(O*i*-Pr)$_4$ (0.40 mL, 1.34 mmol), D-(−)-DET (0.28 mL, 1.61 mmol), TBHP (0.71 mL, 2.01 mmol, 2.85 M in PhMe), CH_2Cl_2 (10 mL), and alcohol (*R*)-**6a** (290 mg, 1.34 mmol) afforded after 4 days reaction time at −20 °C and purification by column chromatography on silica gel (cyclohexane/ethyl acetate, 6:4) epoxide *ent*-**7a** (255 mg, 82%) as colorless oil. $[\alpha]_D^{20}$ −4.2 (*c* 1.345, $CHCl_3$).

4.9. (*R*,*R*,*R*)-1-(3-(4-(Benzyloxy)but-1-ynyl)oxiran-2-yl)ethanol (*ent*-7b)

Analogous to the synthesis of (*R*)-**6a** and **7a**, Ti(O*i*-Pr)$_4$ (1.81 mL, 6.1 mmol), D-(−)-DET (1.25 mL, 7.3 mmol), TBHP (3.2 mL, 9.1 mmol, 2.85 M in PhMe), CH_2Cl_2 (15 mL), and alcohol (*R*)-**6b** (1.40 g, 6.1 mmol) afforded after 6 days at −20 °C and purification by column chromatography on silica gel epoxide (cyclohexane/ethyl acetate, 6:4) *ent*-**7b** (1.22 g, 81%) as colorless oil. $[\alpha]_D^{20}$ −5.1 (*c* 1.315, $CHCl_3$).

4.10. (2*S*,3*R*,5*R*)-7-(Benzyloxy)-6-methylhepta-4,5-dien-2,3-diol (8)

To a suspension of CuCN (2.69 g, 30 mmol) in dry THF (100 mL) was added dropwise a solution of $(PhO)_3P$ (7.84 mL, 30 mmol) in THF (10 mL). The mixture was stirred at room temperature until the solution was homogeneous and then cooled to −80 °C. MeMgCl (10 mL, 30 mmol, 3 M in THF) was added dropwise, the mixture was warmed to −30 °C for 30 min and then recooled to −80 °C. A solution of propargyl oxirane **7a** (2.33 g, 10 mmol) in THF (10 mL) was added and the reaction mixture was warmed up gradually within 4 h to −20 °C. Saturated aqueous NH_4Cl solution was added and the mixture was stirred vigorously. After 1 h 10% aqueous NH_3 (10 mL) was added in one portion and the mixture was stirred until the color of the reaction mixture turned dark blue (2 h). The layers were separated, the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate, 1:1) to afford dihydroxyallene **8** (2.31 g, 93%) as colorless oil. $[\alpha]_D^{20}$ +11.4 (*c* 1.345, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.36–7.30 (m, 5H), 5.33 (m, *J*=6.1, 2.6 Hz, 1H), 4.54 (d, *J*=2.7 Hz, 2H), 4.03 (dd, *J*=6.1 Hz, 1H), 3.98 (d, *J*=2.4 Hz, 2H), 3.84 (m, 1H), 2.50 (s, 2H, OH), 1.75 (d, *J*=2.7 Hz, 3H), 1.14 (d, *J*=6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=201.3, 137.7, 128.4, 127.9, 127.8, 100.1, 91.5, 73.3, 72.2, 70.9, 70.2, 18.1, 15.8. IR (neat): ν=3405, 1969, 1072, 1028 cm^{-1}. HRMS (FAB): calcd for $C_{15}H_{21}O_3$ $[M+H]^+$: *m*/*z*=249.1491; found: *m*/*z*=249.1469.

4.11. (1*S*,2′*R*,5′*S*)-1-(5-((Benzyloxy)methyl)-2,5-dihydro-5-methylfuran-2-yl)ethanol (9)

To a solution of dihydroxyallene **8** (2.31 g, 9.3 mmol) in dry THF (93 mL) was added at room temperature $AuCl_3$ (56 μL, 9.3 μmol, 0.1664 M in MeCN). After 30 min the solvent was removed in vacuo and the crude product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate, 8:2→7:3) to afford dihydrofuran **9** (2.23 g, 96%, dr >99:1 by GC and NMR analysis) as colorless oil. $[\alpha]_D^{20}$ +71.5 (*c* 1.430, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.37–7.28 (m, 5H), 5.87 (d, *J*=6.2 Hz, 1H), 5.80 (dd, *J*=6.2, 1.4 Hz, 1H), 4.82 (d, *J*=1.4 Hz, 1H), 4.60 (dd, *J*=12.5 Hz, 2H), 4.02 (dq, *J*=6.8, 1.4 Hz, 1H), 3.47 (dd, *J*=10.0 Hz, 2H), 1.19 (s, 3H), 1.17 (d, *J*=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=137.0, 133.9, 128.4, 127.9, 127.8, 125.3, 90.3, 89.1, 74.5, 73.2, 68.6, 23.8, 18.1. IR (neat): ν=3439, 2972, 2864, 1453, 1367, 1102, 1054, 1026, 915 cm^{-1}. HRMS (FAB): calcd for $C_{15}H_{21}O_3$ $[M+H]^+$: *m*/*z*=249.1491; found: *m*/*z*=249.1479.

4.12. (2*R*,5*S*)-2-(5-((Benzyloxy)methyl)-2,5-dihydro-5-methylfuran-2-yl)propan-2-ol (10)

4.12.1. (2R,5S)-(5-((Benzyloxy)methyl)-2,5-dihydro-5-methylfuran-2-yl)ethanone

Dess–Martin periodinane (4.52 g, 10.7 mmol) was dissolved in CH_2Cl_2 (50 mL). $NaHCO_3$ (896 mg, 10.7 mmol) was added, followed by dihydrofuran **9** (1.32 g, 5.33 mmol). The mixture was stirred at room temperature for 9 h. Ethyl acetate (10 mL) was added and the mixture was filtered through a Celite®/silica gel pad. Saturated aqueous $NaHCO_3$ was added, the layers were separated and the organic layer was concentrated in vacuo. The crude product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate, 8:2) to afford (2*R*,5*S*)-(5-((benzyloxy)methyl)-2,5-dihydro-5-methylfuran-2-yl)-ethanone (1.24 g, 94%) as colorless oil. $[\alpha]_D^{20}$ +183.2 (*c* 1.080, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.37–7.29 (m, 5H), 5.91 (dd, *J*=6.0, 2.8 Hz, 1H), 5.83 (dd, *J*=6.0, 1.5 Hz, 1H), 5.13 (pt, *J*=2.1 Hz, 1H), 4.58 (s, 2H), 3.53 (dd, *J*=9.7 Hz, 2H), 2.22 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=209.5, 138.0, 134.2, 128.3, 127.6, 127.5, 125.3, 91.8, 91.0, 75.9, 73.4, 25.7, 23.3. IR (neat): ν=2858, 1716, 1095, 910 cm^{-1}. HRMS (FAB): calcd for $C_{15}H_{19}O_3$ $[M+H]^+$: *m*/*z*=247.1334; found: *m*/*z*=247.1320.

*4.12.2. (2R,5S)-2-(5-((Benzyloxy)methyl)-2,5-dihydro-5-methylfuran-2-yl)propan-2-ol (**10**)*

A solution of (2*R*,5*S*)-(5-((benzyloxy)methyl)-2,5-dihydro-5-methylfuran-2-yl)-ethanone (1.16 g, 4.70 mmol) in dry THF (50 mL) was cooled to −80 °C and MeMgCl (2.35 mL, 7.05 mmol, 3 M in THF) was added dropwise. The reaction mixture was warmed gradually to room temperature for 6 h. Saturated aqueous NH_4Cl was added, the layers were separated, the aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried over $MgSO_4$. The solvents were removed in vacuo and the crude product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate, 7:3) to afford tertiary alcohol **10** (1.09 g, 88%, dr >99:1 by GC and NMR analysis) as colorless oil. $[\alpha]_D^{20}$ +25.1 (*c* 1.230, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.37–7.28 (m, 5H), 5.91 (dd, *J*=6.0, 1.0 Hz, 1H), 5.79 (dd, *J*=6.3, 2.3 Hz, 1H), 4.68 (dd, *J*=2.3, 1.5 Hz, 1H), 4.59 (s, 2H), 3.45 (dd, *J*=9.9 Hz, 2H), 1.31 (s, 3H), 1.20 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=137.2, 133.3, 128.4, 128.0, 127.8, 127.0, 92.5, 89.2, 74.6, 73.2, 71.3, 27.5, 25.5, 23.9. IR (neat): ν=3438, 1454, 1370, 1162, 1089, 1041 cm^{-1}. HRMS (FAB): calcd for $C_{16}H_{23}O_3$ $[M+H]^+$: *m*/*z*=263.1647; found: *m*/*z*=263.1631.

4.13. (1*S*,5*R*)-1,4,4-Trimethyl-3,8-dioxabicyclo[3.2.1]-octan-2-one (11)

4.13.1. (2R,5S)-2-(Tetrahydro-5-(hydroxymethyl)-5-methylfuran-2-yl)propan-2-ol

A mixture of dihydrofuran **10** (970 mg, 3.70 mmol) and 10% Pd/C (776 mg) in ethyl acetate (80 mL) was equipped with an H_2-ballon and stirred vigorously for 18 h. The reaction mixture was filtered through a Celite® pad and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate, 7:3) to afford (2*R*,5*S*)-2-(tetrahydro-5-(hydroxymethyl)-5-methylfuran-2-yl)propan-2-ol (525 mg, 81%) as colorless oil. $[\alpha]_D^{20}$ +1.3 (*c* 1.150, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.86 (t, *J*=7.4 Hz, 1H), 3.51 (dd, *J*=11.2 Hz, 2H), 2.47 (s, 1H, OH), 2.11–2.04 (m, 1H), 2.02–1.87 (m, 2H), 1.71–1.64 (m, 1H), 1.28 (s, 3H), 1.20 (s, 3H), 1.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=85.4, 83.6, 71.8, 69.5, 34.1, 27.7, 27.0, 25.1, 23.9. IR (neat): ν=3385, 1266, 1110, 1063 cm^{-1}. HRMS (FAB): calcd for $C_9H_{17}O_3$ $[M-H]^+$: *m*/*z*=173.1178; found: *m*/*z*=173.1204; calcd for $C_9H_{18}O_3$ $[M]^+$: *m*/*z*=174.1256; found: *m*/*z*=174.1246.

*4.13.2. (1S,5R)-1,4,4-Trimethyl-3,8-dioxabicyclo[3.2.1]-octan-2-one (**11**)*

IBX (3.57 g, 12.7 mmol) was dissolved in DMSO (15 mL) and the mixture was stirred until the solution was homogenous. (2*R*,5*S*)-2-(Tetrahydro-5-(hydroxymethyl)-5-methylfuran-2-yl)propan-2-ol (1.11 g, 6.37 mmol) was added and the reaction mixture was stirred for 18 h at room temperature. Ethyl acetate (20 mL) and saturated $NaHCO_3$ solution were added, the layers were separated, the aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over $MgSO_4$. The solvents were removed in vacuo and the crude product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate, 8:2) to lactone **11** (885 mg, 82%) as colorless solid. Mp 84 °C. $[\alpha]_D^{20}$ −22.9 (*c* 1.215, $CHCl_3$); literature value for the (1*R*,5*S*)-enantiomer:[8c] $[\alpha]_D^{20}$ +40 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.09 (d, *J*=7.3 Hz, 1H), 2.23–2.04 (m, 3H), 1.84–1.74 (m, 1H), 1.55 (s, 3H), 1.52 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.8, 84.9, 80.6, 79.7, 36.5, 27.1, 23.9, 23.8, 19.6. IR (KBr): ν=2988, 1728, 1391, 1376, 1347, 1332, 1171, 1154, 1129, 1082, 1026 cm^{-1}. HRMS (FAB): calcd for $C_9H_{15}O_3$ $[M+H]^+$: *m*/*z*=171.1021; found: *m*/*z*=171.1049. HPLC assay: Chiralpak AD, *n*-heptane/isopropanol 98.5:1.5, flow 1 mL min^{-1}, detection by UV at 230 nm, t_R=9.0 min (1*R*,5*S*-enantiomer, minor), t_R=9.8 min (1*S*,5*R*-enantiomer, major), 97% ee.

4.14. (2*S*,5*R*)-5-(1-Hydroxy-1-methylethyl)-2-methyl-2-vinyltetrahydrofuran ((2*S*,5*R*)-(+)-linalool oxide, 1)

4.14.1. (1S,5R)-1,4,4-Trimethyl-3,8-dioxabicyclo[3.2.1]-octan-2-ol

A solution of lactone **11** (600 mg, 3.5 mmol) in dry diethyl ether (50 mL) was cooled to −110 °C and DIBAH (3.5 mL, 3.5 mmol, 1 M in *n*-hexane) was added in one portion. After 5 min saturated NH_4Cl solution was added and the mixture was warmed to room temperature. The layers were separated, the aqueous layer was extracted with diethyl ether and the combined organic layers were dried over $MgSO_4$. The solvent was removed in vacuo and the crude product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate, 8:2) to afford (1*S*,5*R*)-1,4,4-trimethyl-3,8-dioxabicyclo[3.2.1]-octan-2-ol (519 mg, 85%, dr=83:17 by NMR analysis) as colorless solid. Mp 74 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=4.81*, 4.55 (s, 1H), 3.92, 3.76* (d, *J*=7.0 Hz, 1H), 3.26*, 3.09 (s, 1H, OH), 2.16–1.98[n] (m, 3H), 1.90–1.84[n] (m, 1H), 1.52, 1.40* (s, 3H), 1.33, 1.29* (s, 3H), 1.12*, 1.07 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=96.0, 94.4*, 82.8, 81.5*, 80.9[n], 80.3, 77.5*, 33.6, 27.6*, 27.3, 25.3*, 26.1, 23.0*, 25.6*, 24.7, 21.0, 20.3*. IR (KBr): ν=3327, 2945, 1372, 1135, 1123, 1102, 989 cm^{-1}. HRMS (FAB): calcd for $C_9H_{15}O_3$ $[M-H]^+$: *m*/*z*=171.1021; found: *m*/*z*=171.1003; calcd for $C_9H_{17}O_3$ $[M+H]^+$: *m*/*z*=173.1178; found: *m*/*z*=173.1150.

4.14.2. (2S,5R)-5-(1-Hydroxy-1-methylethyl)-2-methyl-2-vinyltetrahydrofuran ((2S,5R)-(+)-linalool oxide, 1)

To a solution of $CeCl_3$ (385 mg, 1.56 mmol) in dry THF (4 mL) was added dropwise at room temperature trimethylsilylmethylmagnesium chloride (8.5 mL, 9.4 mmol, 1.1 M in THF). After 1 h (1*S*,5*R*)-1,4,4-trimethyl-3,8-dioxabicyclo[3.2.1]-octan-2-ol (90 mg, 0.52 mmol) was added and the reaction mixture was stirred for 18 h at room temperature. Saturated NH_4Cl solution was added, the layers were separated, the aqueous layer was extracted with diethyl ether, the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was dissolved in dry THF (1 mL) and added with stirring to a cooled suspension (0 °C) of KH (31 mg, 0.78 mmol; the commercially available suspension of KH was washed with hexane before use to remove the paraffin oil) in THF (1 mL). After 10 min saturated NH_4Cl was added slowly. The layers were separated, the organic layer was extracted with diethyl ether, and the combined organic layers were dried over $MgSO_4$. The solvents were removed in vacuo and the crude product was

purified by column chromatography on silica gel (pentane/diethyl ether, 8:2) to afford **1** (81 mg, 91%) as a colorless oil. $[\alpha]_D^{20}$ +11.3 (*c* 0.065, $CHCl_3$); literature value:[7] $[\alpha]_D^{20}$ +4.0 (*c* 0.028, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ=5.97 (dd, *J*=17.5, 10.8 Hz, 1H), 5.19 (dd, *J*=17.5, 1.3 Hz, 1H), 5.00 (dd, *J*=10.8, 1.3 Hz, 1H), 3.85 (m, 1H), 2.09 (s, 1H, OH), 1.95–1.75 (m, 4H), 1.31 (s, 3H), 1.23 (s, 3H), 1.12 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=144.2, 111.5, 85.5, 82.7, 71.1, 37.8, 27.4, 26.4, 25.9, 24.3. IR (neat): ν=3454, 3086, 2974, 1643, 1173, 1058, 1033, 992, 889 cm^{-1}. GC–MS: 171 (1) $[M+H]^+$, 155 (5), 137 (10), 119 (3), 109 (2), 97 (9), 94 (10), 93 (32), 91 (80), 81 (7), 79 (100), 77 (44), 67 (55), 65 (20), 59 (13), 55 (23). GC assay: Lipodex G: start temperature: 50 °C for 1 min, then 1 °C/min to 140 °C, 60 kPa H_2, t_R=25.9 (2*R*,5*S*-enantiomer, minor), t_R=26.3 (2*S*,5*R*-enantiomer, major), 97% ee.

4.15. (2*S*,3*R*)-(3-(4-(Benzyloxy)but-1-ynyl)oxiran-2-yl)ethanone (15)

Analogous to the synthesis of **10**, DMP (2.07 g, 4.9 mmol), $NaHCO_3$ (410 mg, 4.9 mmol), CH_2Cl_2 (25 mL), and *ent*-**7b** (600 mg, 2.4 mmol) afforded after 5 h at room temperature and purification by column chromatography on silica gel (cyclohexane/ethyl acetate, 7:3) ketoepoxide **15** (533 mg, 89%) as colorless oil. $[\alpha]_D^{20}$ +10.8 (*c* 1.205, $CHCl_3$). HPLC assay: Chiralpak AD, *n*-heptane/isopropanol 95:5, flow 1 mL min^{-1}, detection by UV at 215 nm, t_R=10.6 min (2*R*,3*S*-enantiomer, minor), t_R=11.9 min (2*S*,3*R*-enantiomer, major), >98% ee. Spectroscopic data: see Supplementary data in Ref. 18.

4.16. (2*S*,3*R*)-2-(3-(4-(Benzyloxy)but-1-ynyl)oxiran-2-yl)propan-2-ol (16)

A solution of **15** (2.54 g, 10.4 mmol) in dry THF (200 mL) was cooled to −80 °C and MeMgCl (5.2 mL, 15.6 mmol, 3 M in THF) was added dropwise. The reaction mixture was warmed to −20 °C for 7 h and saturated NH_4Cl solution was added slowly. The layers were separated, the aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried over $MgSO_4$. The solvent was removed in vacuo and the crude product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate, 8:2→6:4) to afford tertiary alcohol **16** (2.63 g, 97%) as colorless oil. $[\alpha]_D^{20}$ −1.2 (*c* 1.250, $CHCl_3$). HPLC assay: Chiralcel OD-H, *n*-heptane/isopropanol 95:5, flow 1 mL min^{-1}, detection by UV at 210 nm, t_R=19.3 min (2*S*,3*R*-enantiomer), t_R=23.9 min (2*R*,3*S*-enantiomer), >98% ee. Spectroscopic data: see Supplementary data in Ref. 18.

4.17. (3*S*,5*S*)-8-(Benzyloxy)-2,6-dimethylocta-4,5-diene-2,3-diol (17)

*4.17.1. From (2S,3R)-2-(3-(4-(Benzyloxy)but-1-ynyl)-oxiran-2-yl)propan-2-ol (**16**)*

Analogous to the synthesis of **8**, CuCN (1.46 g, 16.3 mmol), $(PhO)_3P$ (4.3 mL, 16.3 mmol), THF (200 mL), MeMgCl (5.4 mL, 16.3 mmol, 3 M in THF), and propargyl oxirane **16** (1.42 g, 5.4 mmol) afforded dihydroxyallene **17** (1.48 g, 98%) as colorless oil.

*4.17.2. From (2S,3R)-(3-(4-(Benzyloxy)but-1-ynyl)-oxiran-2-yl)ethanone (**15**)*

To a suspension of CuCN (213 mg, 2.4 mmol) in dry THF (50 mL) was added dropwise $(PhO)_3P$ (0.62 mL, 2.4 mmol) dissolved in dry THF (2 mL). The mixture was stirred until the solution was homogenous and cooled to −80 °C. MeMgCl (0.79 mL, 2.4 mmol, 3 M in THF) was added dropwise, the mixture was warmed to −30 °C for 30 min and then recooled to −80 °C. Ketoepoxide **15** (194 mg, 0.8 mmol) dissolved in THF (3 mL) was added and the reaction mixture was warmed gradually to −20 °C over 3 h. MeMgCl (1.6 mL, 4.8 mmol, 3 M in THF) was added at this temperature and the reaction mixture was warmed to 0 °C for 3 h. Saturated aqueous NH_4Cl solution was added and the mixture was stirred vigorously. After 1 h 10% aqueous NH_3 solution (10 mL) was added and the mixture was stirred until the color of the reaction mixture turned dark blue (2 h). The layers were separated, the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over $MgSO_4$ and the solvents were removed in vacuo. The crude product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate, 1:1) to afford dihydroxyallene **17** (205 mg, 93%) as colorless oil. $[\alpha]_D^{20}$ −79.1 (*c* 1.530, $CHCl_3$). HPLC assay: Chiralpak AD, *n*-heptane/isopropanol 95:5, flow 1 mL min^{-1}, detection by UV at 210 nm, t_R=18.1 min (*R*,*R*-enantiomer, minor), t_R=20.8 min (*S*,*S*-enantiomer, major), >98% ee. Spectroscopic data: see Supplementary data in Ref. 18.

4.18. (2*S*,5*S*)-2-(5-(2-(Benzyloxy)ethyl)-2,5-dihydro-5-methylfuran-2-yl)propan-2-ol (14)

Analogous to the synthesis of **9**, $AuCl_3$ (15 μl, 2.54 μmol, 0.1664 M in MeCN), THF (51 mL), and dihydroxyallene **31** (1.40 g, 5.1 mmol) afforded after 10 min at room temperature and purification by column chromatography on silica gel (cyclohexane/ethyl acetate, 7:3) dihydrofuran **14** (1.36 g, 97%, dr=98:2 by GC and NMR analysis) as colorless oil. $[\alpha]_D^{20}$ −61.8 (*c* 1.545, $CHCl_3$). HPLC assay: Chiralpak AD, *n*-heptane/isopropanol 95:5, flow 1 mL min^{-1}, detection by UV at 215 nm, t_R=8.2 min (*R*,*R*-enantiomer, minor), t_R=10.6 min (*S*,*S*-enantiomer, major), >98% ee. Spectroscopic data: see Supplementary data in Ref. 18.

4.19. (2*S*,5*R*)-2-(Tetrahydro-5-(2-hydroxyethyl)-5-methylfuran-2-yl)propan-2-ol (18)

Analogous to the synthesis of **11**, 10% Pd/C (600 mg), ethyl acetate (70 mL), and dihydrofuran **14** (800 mg, 2.9 mmol) afforded after 18 h at room temperature and purification by column chromatography (ethyl acetate) tetrahydrofuran **18** (416 mg, 76%) as colorless oil. $[\alpha]_D^{20}$ −7.4 (*c* 1.325, $CHCl_3$). GC assay: Lipodex G: start temperature: 100 °C for 1 min, then 2 °C/min to 200 °C, 60 kPa H_2, t_R=16.1 (2*S*,5*R*-enantiomer, major), t_R=16.3 (2*R*,5*S*-enantiomer, minor), >98% ee. Spectroscopic data: see Supplementary data in Ref. 18.

4.20. (2*R*,5*S*)-(Tetrahydro-5-(2-hydroxypropan-2-yl)-2-methylfuran-2-yl)acetaldehyde (19)

Analogous to the synthesis of **10**, DMP (900 mg, 2.1 mmol), $NaHCO_3$ (179 mg, 2.1 mmol), CH_2Cl_2 (20 mL), and tetrahydrofuran **18** (200 mg, 1.1 mmol) afforded after 12 h at room temperature and purification by chromatography on silica gel (cyclohexane/ethyl acetate, 9:1→8:2) aldehyde **19** (197 mg, 99%) as colorless oil. $[\alpha]_D^{20}$ −15.8 (*c* 1.335, $CHCl_3$). Spectroscopic data: see Supplementary data in Ref. 18.

4.21. (2*S*,5*R*)-2-(-5-((9*H*-Pyrido[3,4-*b*]indol-1-yl)-methyl)-tetrahydro-5-methylfuran-2-yl)propan-2-ol ((−)-isocyclocapitelline, 2)

A solution of tryptamine (103 mg, 0.64 mmol) and aldehyde **19** (120 mg, 0.64 mmol) in dry CH_2Cl_2 (15 mL) was cooled to −80 °C and trifluoroacetic acid (0.95 mL, 1.28 mmol) was added dropwise. With stirring, the reaction mixture was warmed to room temperature within 3 h, and saturated $NaHCO_3$ solution was added. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$. The solvent was removed in vacuo and the crude product was dissolved in xylenes (15 mL). 10% Pd/C (300 mg) was added and the reaction

mixture was refluxed for 7 h. It was filtered through a Celite® pad, which was rinsed with CH_2Cl_2. The solvents were removed in vacuo and the crude product was purified by column chromatography (ethyl acetate) on silica gel to afford **2** (110 mg, 53%) as a pale yellow solid. Mp 197 °C. $[\alpha]_D^{20}$ −92.4 (*c* 0.525, $CHCl_3$); literature value:[10] $[\alpha]_D^{20}$ −75 (*c* 0.50, $CHCl_3$). HPLC assay: Chiralpak AD, *n*-heptane/isopropanol 92:8, flow 1 mL min^{-1}, detection by UV at 254 nm, t_R=9.5 min (2*R*,5*S*-enantiomer, minor), t_R=11.9 min (2*S*,5*R*-enantiomer, major), >98% ee. Spectroscopic data: see Supplementary data in Ref. 18.

4.22. (2*S*,5*R*)-2-(Tetrahydro-5-methyl-5-((2-methyl-2*H*-pyrido[3,4-*b*]indol-1-yl)methyl)furan-2-yl)propan-2-ol ((−)-isochrysotricine, 3)

A solution of **2** (33 mg, 0.10 mmol) and MeI (9.4 μl, 0.15 mmol) in acetone (5 mL) was refluxed for 6 h. The solvent was removed in vacuo and the crude product was dissolved in $CHCl_3$ (10 mL). Aqueous 2 M NaOH (5 mL) was added and the mixture was stirred for 1 h at room temperature. The layers were separated, the aqueous layer was extracted with $CHCl_3$, the combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product was filtered through a short Celite®/silica gel column (eluation with CH_2Cl_2) to afford **3** (34 mg, quant.) as a pale yellow solid. Mp 159 °C. $[\alpha]_D^{20}$ −38.4 (*c* 1.020, MeOH), no literature value reported. Spectroscopic data: see Supplementary data in Ref. 18.

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft and the European Community for financial support of our work.

References and notes

1. Marine toxins: (a) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897–1909; (b) Kobayashi, J.; Kubota, T. *J. Nat. Prod.* **2007**, *70*, 451–460; Lignans: (c) Ward, D. S. *Nat. Prod. Rep.* **1999**, *16*, 75–96.
2. (a) McLaughlin, J. L. *J. Nat. Prod.* **2008**, *71*, 1311–1321; (b) Makabe, H. *Biosci. Biotechnol. Biochem.* **2007**, *71*, 2367–2374; (c) Maezaki, N.; Kojima, N.; Tanaka, T. *Synlett* **2006**, 993–1003; (d) Bermejo, A.; Figadère, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estomell, E.; Cortes, B. L. *Nat. Prod. Rep.* **2005**, *22*, 269–303.
3. (a) Naves, Y. R.; Bachmann, P. *Helv. Chim. Acta* **1945**, *28*, 1227–1230; (b) Naves, Y. R. *Helv. Chim. Acta* **1945**, *28*, 1231–1233; (c) Kirchner, J. G.; Miller, J. M.; Rice, R. G.; Keller, G. J.; Fox, M. M. *J. Agric. Food Chem.* **1953**, *1*, 510–512; (d) Naves, Y. R.; Ochsner, P.; Tullen, P. *Helv. Chim. Acta* **1960**, *43*, 1616–1619; (e) Naves, Y. R.; Magalhães Alves, H.; Arndt, V. H.; Gottlieb, O. R.; Magalhães, M. T. *Helv. Chim. Acta* **1963**, *46*, 1056–1059; (f) Kreis, P.; Mosandl, A. *Flavour Fragrance J.* **1992**, *7*, 187–193; (g) Kawakami, M.; Ganguly, S. N.; Banerjee, J.; Kobayashi, A. *J. Agric. Food Chem.* **1995**, *43*, 200–207; (h) Wüst, M.; Mosandl, A. *Eur. Food Res. Technol.* **1999**, *209*, 3–11.
4. (a) Flath, R. A.; Forrey, R. R. *J. Agric. Food Chem.* **1977**, *25*, 103–109; (b) Winterhalter, P.; Katzenberger, D.; Schreier, P. *Phytochemistry* **1986**, *25*, 1347–1350.
5. (a) *Common Fragrance and Flavor Materials. Preparation, Properties and Uses*, 2nd ed.; Bauer, K., Garbe, D., Surburg, H., Eds.; VCH: New York, NY, 1990; (b) *Perspectives in Flavor and Fragrance Research*; Kraft, P., Swift, K. A. D., Eds.; Helvetica Chimica Acta: Zürich, 2005.
6. (a) Wang, D.; Ando, K.; Morita, K.; Kubota, K.; Kobayashi, A. *Biosci. Biotechnol. Biochem.* **1994**, *58*, 2050–2053; (b) Ito, Y.; Sugimoto, A.; Kakuda, T.; Kubota, K. *J. Agric. Food Chem.* **2002**, *50*, 4878–4884; (c) Bentley, R. *Chem. Rev.* **2006**, *106*, 4099–4112.
7. The direction of the optical rotation of linalool oxide depends on the solvent and is opposite for MeOH and $CHCl_3$ (David, L.; Veschambre, H. *Tetrahedron Lett.* **1984**, *25*, 543–546). In this paper, rotations measured in $CHCl_3$ are used.
8. (a) Prileschajew, N. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 4811–4815; (b) Felix, D.; Melera, A.; Seibl, J.; Kovats, E. *Helv. Chim. Acta* **1963**, *46*, 1513–1536; (c) Klein, E.; Farnow, H.; Rojahn, W. *Liebigs Ann. Chem.* **1964**, *675*, 73–82; (d) Corma, A.; Iglesias, M.; Sanchez, F. *J. Chem. Soc., Chem. Commun.* **1995**, 1635–1636; (e) Schofield, L. J.; Kerton, O. J.; McMorn, P.; Bethell, D.; Ellwood, S.; Hutchings, G. J. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1475–1481; (f) De Villa, A. L. P.; De Vos, D. E.; De Montes, C. C.; Jacobs, P. A. *Tetrahedron Lett.* **1998**, *39*, 8521–8524; (g) Hartung, J.; Drees, S.; Geiss, B.; Schmidt, P. *Synlett* **2003**, 223–226; (h) Rychnovsky, S.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963–3964; (i) Méou, A.; Bouanah, N.; Archelas, A.; Zhang, X. M.; Guglielmetti, R.; Furstoss, R. *Synthesis* **1990**, 752–753; (j) Méou, A.; Bouanah, N.; Archelas, A.; Zhang, X. M.; Guglielmetti, R.; Furstoss, R. *Synthesis* **1991**, 681–682; (k) Garcia, M.-A.; Méou, A.; Brun, P. *Synlett* **1994**, 911–912; (l) Fournier-Nguefack, C.; Lhoste, P.; Sinou, D. *Tetrahedron* **1997**, *53*, 4353–4362; (m) Demyttenaere, J. C. R.; Willemen, H. M. *Phytochemistry* **1998**, *47*, 1029–1036; (n) Demyttenaere, J. C. R.; Adams, A.; Vanoverschelde, J.; De Kimpe, N. *J. Agric. Food Chem.* **2001**, *49*, 5895–5901.
9. (a) Mischitz, M.; Faber, K. *Synlett* **1996**, 978–980; (b) Duan, S.; Moeller, K. D. *Org. Lett.* **2001**, *3*, 2685–2688.
10. Phuong, N. M.; Sung, T. V.; Porzel, A.; Schmidt, J.; Merzweiler, K.; Adam, G. *Phytochemistry* **1999**, *52*, 1725–1729.
11. Peng, J. N.; Feng, X. Z.; Zheng, Q. T.; Liang, X. T. *Phytochemistry* **1997**, *56*, 1119–1121.
12. Zhang, J. X.; Wang, G. X.; Xie, P.; Chen, S. F.; Liang, X. T. *Tetrahedron Lett.* **2000**, *41*, 2211–2213.
13. (a) Wang, G. X.; Chen, S. F.; Liang, X. T. *Chin. Chem. Lett.* **1998**, *9*, 357–360; (b) Mahboobi, S.; Koller, M.; Schollmeyer, D. *Monatsh. Chem.* **2000**, *131*, 383–392; (c) Wang, G. X.; Zhang, J. X.; Chen, S. F.; Liang, X. T. *Chin. Chem. Lett.* **2001**, *12*, 199–202.
14. A stereoisomeric tetrahydrofuran is found in the natural product glaciapyrrole A: Macherla, V. R.; Liu, J.; Bellows, C.; Teisan, S.; Nicholson, B.; Lam, K. S.; Potts, B. C. M. *J. Nat. Prod.* **2005**, *68*, 780–783.
15. Reviews: (a) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387–391; (b) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555–4563; (c) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem.* **2006**, *118*, 8064–8105; *Angew. Chem., Int. Ed.* **2006**, *45*, 7896–7936; (d) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333–346; (e) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395–403; (f) Fürstner, A.; Davis, P. W. *Angew. Chem.* **2007**, *119*, 3478–3519; *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449; (g) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211; (h) Bongers, N.; Krause, N. *Angew. Chem.* **2008**, *120*, 2208–2211; *Angew. Chem., Int. Ed.* **2008**, *47*, 2178–2181; (i) Widenhoefer, R. A. *Chem.—Eur. J.* **2008**, *14*, 5382–5391; (j) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885–3903; (k) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917–4938; (l) Muzart, J. *Tetrahedron* **2008**, *64*, 5816–5849; (m) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239–3265; (n) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266–3325; (o) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350; (p) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378.
16. (a) Hoffmann-Röder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537–2538; (b) Krause, N.; Hoffmann-Röder, A.; Canisius, J. *Synthesis* **2002**, 1759–1774; (c) Deutsch, C.; Gockel, B.; Hoffmann-Röder, A.; Krause, N. *Synlett* **2007**, 1790–1794; (d) Erdsack, J.; Krause, N. *Synthesis* **2007**, 3741–3750.
17. Review: (a) Krause, N.; Belting, V.; Deutsch, C.; Erdsack, J.; Fan, H.-T.; Gockel, B.; Hoffmann-Röder, A.; Morita, N.; Volz, F. *Pure Appl. Chem.* **2008**, *80*, 1063–1069; α-Aminoallenes: (b) Morita, N.; Krause, N. *Org. Lett.* **2004**, *6*, 4121–4123; (c) Morita, N.; Krause, N. *Eur. J. Org. Chem.* **2006**, 4634–4641; α-Thioallenes: (d) Morita, N.; Krause, N. *Angew. Chem.* **2006**, *118*, 1930–1933; *Angew. Chem., Int. Ed.* **2006**, *45*, 1897–1899; β-Aminoallenes, β-hydroxyallenes: (e) Gockel, B.; Krause, N. *Org. Lett.* **2006**, *8*, 4485–4488; (f) Sawama, Y.; Sawama, Y.; Krause, N. *Org. Biomol. Chem.* **2008**, *6*, 3573–3579.
18. For a preliminary account, see: Volz, F.; Krause, N. *Org. Biomol. Chem.* **2007**, *5*, 1519–1521.
19. (a) Ren, X. F.; Turos, E.; Lake, C. H.; Churchill, M. R. *J. Org. Chem.* **1995**, *60*, 6468–6483; (b) Sparks, S. M.; Gutierrez, A. J.; Shea, K. J. *J. Org. Chem.* **2003**, *68*, 5274–5285.
20. Qin, D.-G.; Zha, H.-Y.; Yao, Z.-J. *J. Org. Chem.* **2002**, *67*, 1038–1040.
21. Koop, U.; Handke, G.; Krause, N. *Liebigs Ann.* **1996**, 1487–1499.
22. (a) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237–6240; (b) Pfenninger, A. *Synthesis* **1986**, 89–116; (c) Sharpless, K. B. *Tetrahedron* **1994**, *50*, 4235–4258; (d) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1–299.
23. The enantiomeric excess of the epoxyalcohols **7** and *ent*-**7** was determined after oxidation to the corresponding epoxyketone.
24. Review: Krause, N.; Hoffmann-Röder, A. *Tetrahedron* **2004**, *60*, 11671–11694.
25. Yield/diastereoselectivity (%) for the transformation of **7a** to **8** with MeMgCl/CuCN/THF in the presence of other additives: 81:96 (*n*-Bu_3P), 80:97 (Bn_3P), 82:97 [$(EtO)_3P$], 74:>95 (no additive).
26. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156; (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287; (c) Boeckman, R. K., Jr.; Shao, P.; Mullins, J. J. *Org. Synth.* **2000**, *77*, 141–152.
27. Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019–8022.
28. Boland, W.; Ney, P.; Jaenicke, L. *Synth. Commun.* **1980**, 1015–1017.
29. (a) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780–784; (b) Harmata, M.; Jones, D. E. *J. Org. Chem.* **1997**, *62*, 1578–1579; (c) Van Staden, L. F.; Gravestock, D.; Ager, D. J. *Chem. Soc. Rev.* **2002**, *31*, 195–200.
30. Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797–1842.
31. Opposite numbering is used for the tetrahydrofuran rings of **1** and **2**/**3**.
32. Love, B. E.; Jones, E. G. *J. Org. Chem.* **1999**, *64*, 3755–3756.