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A Formal, One-Pot β-Chlorination of Primary Alcohols and Its Utilization in the Transformation of Terpene Feedstock and the Synthesis of a C_2-Symmetrical Terminal Bis-Epoxide

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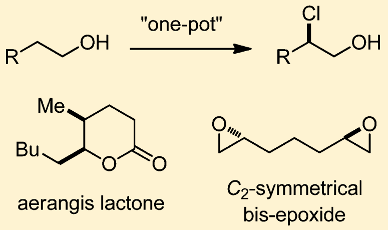
Supporting Information

ABSTRACT: A one-pot transformation of alkan-1-ols into 2-chloroalkan-1-ols is described. As a practical application, terpene-derived primary alcohols were converted into semiochemicals such as olfactory lactones (aerangis lactone, whisky lactone, and cognac lactone) and pheromones (cruentol and ferrugineol). Using heptane-1,7-diol as a bifunctional substrate, the corresponding bis-epoxide was synthesized by bidirectional synthesis in good yield and high enantioselectivity.



INTRODUCTION

The conversion of biomass into high-value chemicals[1] is a central goal in catalysis.[2] In recent years, terpenes have been utilized increasingly as feedstock[3] for the synthesis of biologically active natural products,[4] fragrance compounds,[5] and fine chemicals.[6] The key methodological challenge in this approach is to achieve site-selective functionalization of the terpene scaffold, thereby allowing for subsequent C−C coupling reactions. To this end, our group has developed protocols for the conversion of terpene aldehydes into the corresponding 1,2-epoxides[7] as well as an allylic substitution of terpene acetates with vinyl nucleophiles to give 1,4-dienes.[8] Taking advantage of both methods, we have assembled a major part of ripostatin B's polyketide backbone from two molecules of geranyl acetate.[9]

Herein, we describe the development of a telescoped oxidation−chlorination−reduction and its application to the conversion of primary alcohols into enantioenriched 1,2-epoxides and a C_2-symmetrical terminal bisepoxide via chlorohydrin intermediates. Using terpene-derived alcohols as substrates has allowed us to synthesize a range of semiochemicals while bisepoxides might prove useful in the bidirectional synthesis of polyols.

Halogen-bearing chiral centers[10] constitute a useful handle for subsequent transformations, and halogenation of carbonyl compounds[11] provides a highly stereoselective entry into this substrate class. In particular, α-haloaldehydes represent versatile building blocks for heterocyclic scaffolds[12] and for natural product synthesis.[13] For example, the Britton group has demonstrated the broad utility of α-chloroaldehydes in the synthesis of carbohydrates,[14] alkaloids,[15] and acetogenins.[16]

The merging of the oxidation and the chlorination step into a single reaction vessel (one-pot reaction)[17] obviates the need to isolate and purify possibly unstable aldehyde intermediates. For this purpose, a mild oxidation protocol was sought that would not interfere with the rather sensitive subsequent organocatalytic chlorination step. In this sense, harsh reaction conditions and reactive stoichiometric byproducts from the terminal oxidant were to be avoided. In 2011, Hoover and Stahl[18] reported a mild protocol for the Cu-catalyzed aerobic oxidation[19] of primary alcohols to aldehydes based on pioneering work by Semmelhack,[20] Markó,[21] Sheldon,[22] and Koskinen.[23] With water as the only stoichiometric byproduct, we envisioned this protocol to be an ideal starting point for telescoping an oxidation with subsequent organocatalytic transformations.[24] In a proof-of-concept study, we joined Stahl's oxidation conditions with a DMAP-catalyzed isomerization and an organocatalytic Diels−Alder reaction,[25] while Jang et al. reported a similar oxidation in conjunction with an organocatalytic Michael addition/oxyamination.[26]

RESULTS AND DISCUSSION

Before we investigated the one-pot reaction, the conditions for the organocatalytic α-chlorination[27] were optimized for citronellal (**1a**) as the substrate. Our previously described procedure is based on the work of Jørgensen[28,29] and MacMillan[30,31] and employs catalyst **2**[32] together with N-chlorosuccinimide (NCS) as an inexpensive chlorine source. The screening of the α-chlorination was carried out using (R)-citronellal with 96% *ee*, and the sensitive α-chloroaldehyde was converted to the corresponding alcohol by in situ reduction with sodium borohydride (Table 1). While the reaction exhibited high diastereoselectivity over a wide temperature range, between 23 and 0 °C the isolation of pure (2S,3R)-**3a** was hampered by the formation of unidentified side products.

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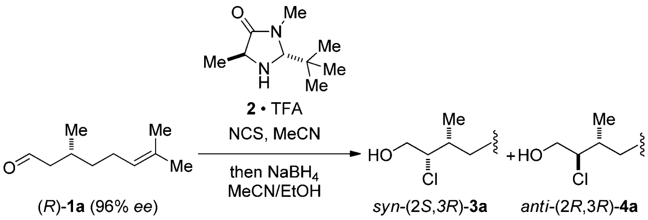
Table 1. Optimized Organocatalytic α-Chlorination of Citronellal[a]



(R)-**1a** (96% *ee*) syn-(2S,3R)-**3a** anti-(2R,3R)-**4a**

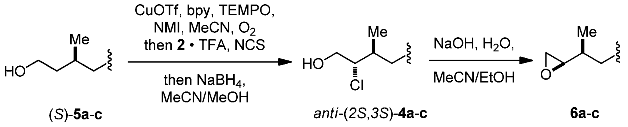
	T [°C]	*t* [h]	yield [%]	*syn*:*anti*	*ee* [%][b]
1	+23	1.5	65	98:2	99
2	0	1.5	68	97:3	99
3	−15	4	73	97:3	98
4	−28	8	82	2:98[c]	99

[a] 30 mol % **2**·TFA, 1.30 equiv of NCS, then 2.50 equiv of $NaBH_4$, 0 °C. [b] *ee* of the major diastereomer. [c] *ent*-**2** (30 mol %) was used.

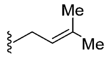
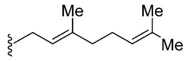
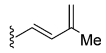
This problem was circumvented efficiently by lowering the temperature to −15 °C. Accordingly, the alcohol (2*S*,3*R*)- **3a** was isolated in 73% yield with >99% ee. The *syn*/*anti* ratio of 98:2 reflects the 96% *ee* of the starting material. Using the enantiomeric MacMillan catalyst *ent*-**2** at −28 °C afforded the *anti*-diastereomer (2*R*,3*R*)-**4a** in a 98:2 ratio in >99% *ee*. From these results we conclude that the α-chlorination appears to be catalyst-controlled.

We next turned our attention to the possibility of employing alcohols as substrates in a three-step one-pot sequence consisting of oxidation, α-chlorination, and reduction. Exploratory experiments indicated that reagents for the Cu-catalyzed aerobic oxidation do not interfere with chlorination. As shown in Table 2, the reactions using alcohols **5a**−**c** proceeded smoothly and were completely catalyst-controlled. The low *anti*/*syn* ratio of **4b** is a direct consequence of the low *ee* of the starting alcohol (**5b**). Treatment of the chlorohydrins **4a**−**c** with NaOH afforded the corresponding terminal epoxides **6a**−**c** in 93−97% yield.

Table 2. Scope of the Telescoped Oxidation−Chlorination−Reduction Sequence[a]



(S)-**5a-c** anti-(2S,3S)-**4a-c** **6a-c**

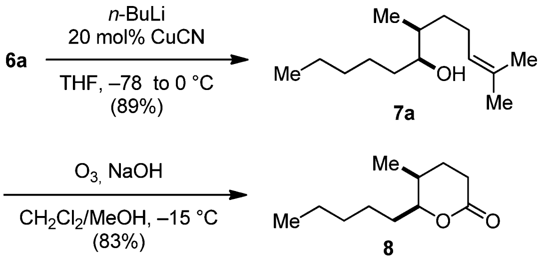
	substrate	yield 4 [%]	*anti*:*syn*	*ee* [%]	yield 6 [%]
1	 (S)-**5a** 97% *ee*	79	98:2	99	97
2	 (S)-**5b** 20% *ee*	86	58:42	90	98
3	 (S)-**5c** 97% *ee*	82	95:5	96	93

[a] 5.0 mol % CuOTf, 5.0 mol % 2,2′-bipyridine, 5.0 mol % TEMPO, 10 mol % NMI (1-methylimidazole), rt, then 30 mol % **2**·TFA, 1.30 equiv of NCS, −28 °C, then 2.50 equiv of $NaBH_4$, 0 °C; 22.3 equiv of NaOH, rt.

The epoxide function (a^2-synthon) is a useful handle for carbon chain extension. With the optimized procedure in hand, we next demonstrated the utility of monoterpene-derived 1,2-epoxides as chiral building blocks. Apart from the Roche ester,[33] citronellol is one of only a few viable resources for transferring methyl group bearing stereogenic centers from the chiral pool into target molecules and that is readily available in both enantiomeric forms. While citronellol's trisubstituted double bond represents a masked carbonyl group, the primary hydroxyl group can be transformed into a chiral 1,2-epoxide via one-pot oxidation−chlorination.

Thus, the citronellol-derived epoxide **6a** was converted into the main odor component of the African orchids *Aerangis kirkii* and *A. confusa*, (−)-*cis*-aerangis lactone **8**,[34] in just two synthetic steps.[35−40] As shown in Scheme 1, a Cu-catalyzed regioselective opening of **6a** with *n*-butyllithium using CuCN (20 mol %) as the catalyst afforded **7a** in 89% yield. Using Marshall's ozonolytic esterification[41]/lactonization[42] protocol, (−)-*cis*-aerangis lactone **8** was obtained in 83% yield.

Scheme 1. Synthesis of (−)-*cis*-Aerangis Lactone



7a

8

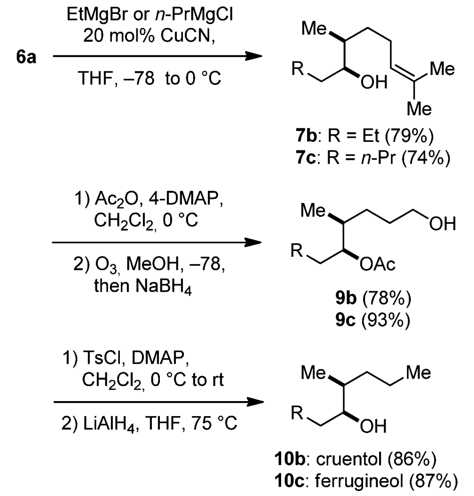
(−)-*cis*-aerangis lactone

Alternatively, **6a** can be converted into palm weevil pheromones.[43] Epoxide opening with Grignard reagent derived cuprates afforded the alcohols **7b** and **7c** in good yields. Acetylation of the hydroxyl group was followed by an ozonolysis with a reductive workup to give the primary alcohols **9b** and **9c**. Finally, tosylation and global reduction completed the synthesis of cruentol[44] **10b** and ferrugineol[45,46] **10c** (Scheme 2).

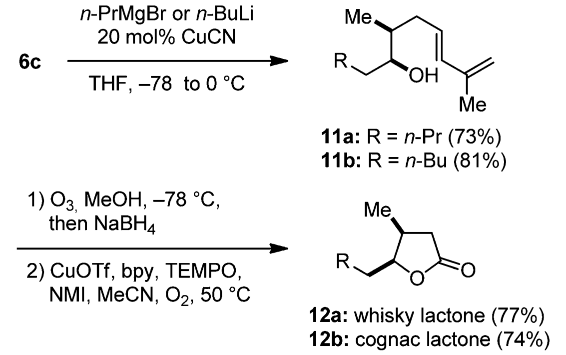
In a similar vein, 1,2-epoxydiene **6c** was subjected to a CuCN-catalyzed opening with *n*-BuLi and *n*-propylmagnesium bromide, respectively to afford the alcohols **11a** (81%) and **11b** (74%). A reductive ozonolysis was followed by an oxidative lactonization and yielded cognac lactone[47−52] (**12a**, R = *n*-Bu, 77%) and whisky lactone[53−57] (**12b**, R = *n*-Pr, 73%), two major flavor contributing constituents of most alcoholic beverages aged in smoked oak or other wooden casks.[58] Moreover, avoidance of the isolation of the labile and volatile aldehyde proved time-saving and led to satisfactory overall yields (Scheme 3).

Two-directional chain extension[59] is a multibond forming approach[60] to molecules with repeating functional group patterns. While this strategy has been applied to various achiral, prochiral,[61] *meso*- and C_2-symmetrical substrates,[62] examples of regioselective double opening of C_2-symmetrical terminal bis-epoxides with C-nucleophiles are scarce.[63] The currently established synthesis of C_2-symmetrical bis-epoxides involves peracid-mediated double epoxidation of two terminal

Scheme 2. Synthesis of Cruentol and Ferrugineol



Scheme 3. Synthesis of Whisky Lactone and Cognac Lactone

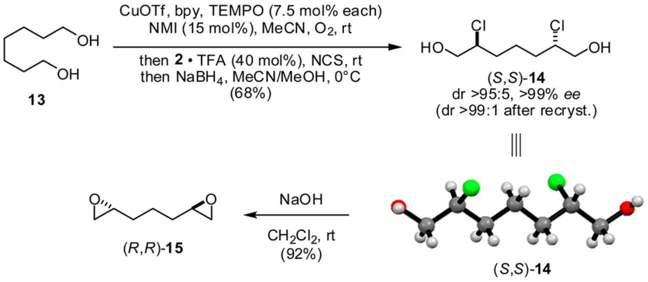


alkene moieties[64] followed by hydrolytic kinetic resolution[65] of the resulting *meso*/*rac*-mixture.[66,67] As a consequence, the theoretical yield is limited to 25% of either of the two enantiomeric C_2-symmetrical bis-epoxides and 50% of the *meso*-diastereomer. To test the hypothesis whether a formal double chlorination of symmetrical diols would serve as an entry into C_2-symmetrical bis-epoxides, we subjected 1,7-heptanediol (**13**) to the previously established conditions. Gratifyingly, the (2*S*,6*S*)-2,6-dichloroheptane-1,7-diol (**14**) was obtained as a crystalline solid in good yield and selectivity. The high enantiomeric excess of the C_2-symmetrical diastereomer is due to the fact that the minor enantiomer in the first chlorination is preferentially converted to the *meso*-diastereomer in the second chlorination (Horeau principle).[68] The minor *meso*-isomer can be removed efficiently by recrystallization. Treatment of **14** with NaOH in dichloromethane affords the desired bisepoxide **15** in 92% yield and >99% enantiomeric excess (Scheme 4).

■ CONCLUSION

In summary, we have demonstrated that alkan-1-ols can be converted to the corresponding 2-chloroalkan-1-ols in an efficient one-pot procedure involving a Cu-catalyzed oxidation and an enamine chlorination/reduction. Using terpene derived alcohols as feedstock, several chiral semiochemicals have been synthesized in an efficient manner via the corresponding 1,2-epoxides. Application of this telescoped sequence to bisepoxides in the bidirectional synthesis of more complex targets will be the subject of forthcoming reports from our laboratory.

Scheme 4. Synthesis of Terminal Bis-Epoxide 15



■ EXPERIMENTAL SECTION

(2*R*,3*R*)-2-Chloro-3,7-dimethyloct-6-en-1-ol 4a. To a solution of (*R*)-citronellal **1a** (135 mg, 0.88 mmol) in MeCN (1.75 mL) (2*S*,5*R*)-2-(*tert*-butyl)-3,5-dimethylimidazolidin-4-one-TFA-salt (74.8 mg, 0.30 mmol, 0.30 equiv) and NCS (152 mg, 0.65 mmol, 1.30 equiv) were added successively at −28 °C. The reaction was stirred for 8 h at −28 °C and warmed to 0 °C. After the addition of EtOH (1.0 mL) and $NaBH_4$ (82.8 mg, 2.50 mmol, 2.50 equiv) the reaction was stirred for 30 min at 0 °C, quenched by the addition of a saturated aqueous solution of NH_4Cl (2 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/Et_2O = 25:1), and **4a** was obtained as a colorless liquid (136 mg, 82%, 98:2 dr, >99:1 er). $[\alpha]_D^{20}$ = +16.7 (*c* 0.75, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 5.09 (t, J = 7.1 Hz, 1H), 3.98 (ddd, J = 8.3, 5.1, 3.8 Hz, 1H), 3.71−3.85 (m, 2H), 2.04−2.13 (m, 2H), 1.88−1.99 (m, 2H), 1.69 (s, 3H), 1.61 (s, 3H), 1.52−1.60 (m, 1H), 1.27−1.35 (m, 1H), 1.03 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.0, 123.9, 71.0, 64.9, 36.3, 32.7, 25.7, 25.3, 17.7, 16.3; IR 3375, 2965, 2928, 2877, 2858, 1455, 1379, 1259, 1199, 1071, 1031, 987, 953, 824, 669 cm^{-1}; HRMS (EI) m/z calcd for $C_{10}H_{19}OCl$ $[M]^{\bullet+}$ 190.11189, found 190.11225; calcd for $C_{10}H_{19}O^{37}Cl$ $[M]^{\bullet+}$ 192.10894, found 192.10772; GC (Hydrodex-β-TBDM, 130 °C isotherm, 1.1 mL/min He, 50:1 split) $\tau_{(2R,3R)}$ = 25.5 min, $\tau_{(2S,3R)}$ = 26.4 min, $\tau_{(2R,3S)}$ = 29.6 min, $\tau_{(2S,3S)}$ = 31.2 min, isomeric ratio = 70:1:1:0.

(2*S*,3*S*)-2-Chloro-3,7-dimethyloct-6-en-1-ol 4a (One-Pot Procedure). To a solution of (*S*)-citronellol **5a** (3.12 g, 20 mmol) in MeCN (20 mL) were added solutions of CuOTf·4MeCN (377 mg, 0.05 mmol, 0.05 equiv), 2,2′-bipyridine (156 mg, 0.05 mmol, 0.05 equiv), TEMPO (156 mg, 0.05 mmol, 0.05 equiv), and 1-methylimidazole (164 mg, 0.10 mmol, 0.10 equiv) each in 20 mL of MeCN. The reaction mixture was degassed for 5 min, the atmosphere in the reaction vessel was replaced by O_2, and the reaction mixture was stirred for 2 h at rt. After the reaction was cooled to −28 °C, (2*R*,5*S*)-2-(*tert*-butyl)-3,5-dimethylimidazolidin-4-one-TFA-salt (1.60 g, 6.00 mmol, 0.30 equiv) and NCS (3.47 g, 26.0 mmol, 1.30 equiv) were added successively, and the reaction was stirred 24 h at −28 °C and warmed to 0 °C. After the addition of EtOH (50 mL) and $NaBH_4$ (189 g, 50.0 mmol, 2.50 equiv) the reaction was stirred for 30 min at 0 °C, quenched by the addition of a saturated aqueous solution of NH_4Cl (100 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/Et_2O = 10:1), and **4a** was directly submitted to the following reaction conditions.

Alternatively after column chromatography on silica (*n*-pentane/Et_2O = 35:1−25:1−15:1), **4a** can be obtained as a colorless liquid (3.05 g, 79%, 98:2 dr, >99:1 er).

$[\alpha]_D^{20}$ = −13.5 (*c* 1.09, $CHCl_3$); GC (Hydrodex-β-TBDM, 130 °C isotherm, 1.1 mL/min He, 50:1 split) $\tau_{(2R,3R)}$ = 25.5 min, $\tau_{(2S,3R)}$ = 26.4 min, $\tau_{(2R,3S)}$ = 29.6 min, $\tau_{(2S,3S)}$ = 31.2 min, isomeric ratio = 0:1:1:83.

(2*S*,3*S*,*E*)-2-Chloro-3,7,11-trimethyldodeca-6,10-dien-1-ol 4b. The same procedure as above was applied to (*S*,*E*)-dihydrofarnesol **5b** (449 mg, 2.00 mmol). The crude product was purified by column chromatography on silica (*n*-pentane/Et_2O = 35:1), and **4b**

was obtained as a colorless liquid (444 mg, 86%, 58:42 dr, 90:10 er). $[\alpha]_D^{20} = -9.64°$ (*c* 1.03, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 5.10 (d, *J* = 6.0 Hz, 2H), 4.11–4.02 (m, 1H), 3.86–3.79 (m, 2H), 1.87–2.13 (m, 8H), 1.69 (s, 3H), 1.61 (m, 7H), 1.28–1.38 (m, 1H), 1.04 (d, *J* = 6.8 Hz, 1/2 3H), 0.98 (d, *J* = 6.7 Hz, 1/2 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.6, 135.6, 131.4, 131.3, 124.2, 124.2, 123.8, 123.7, 71.1, 70.2, 65.7, 64.9, 39.7 (2C), 36.3, 35.3, 34.2, 32.7, 26.6 (2C), 25.7 (2C), 25.2, 25.1, 17.7 (2C), 16.3, 16.0 (2C), 14.6; IR 3387, 2965, 2926, 2856, 1667, 1452, 1380, 1107, 1074, 1030, 831, 669 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{29}OCl$ $[M+H]^+$ 259.18232, found 259.18244; calcd for $C_{15}H_{29}O^{37}Cl$ $[M+H]^+$ 261.17937, found 261.17944; GC (Lipodex E, 130 °C isotherm, 1.1 mL/min He, 20:1 split) $\mathrm{T}_{(2R,3R)}$ = 83.0 min, $\mathrm{T}_{(2S,3R)}$ = 90.1 min, $\mathrm{T}_{(2R,3S)}$ = 97.6 min, $\mathrm{T}_{(2S,3S)}$ = 105.0 min, isomeric ratio = 1:1:20:14.

(2*S*,3*S*,*E*)-2-Chloro-3,7-dimethylocta-5,7-dien-1-ol 4c. The same procedure as above was applied to (*S*,*E*)-3,7-dimethylocta-5,7-dien-1-ol **5c** (425 mg, 2.75 mmol) with a reaction temperature of 50 °C for the oxidation. The crude product was purified by column chromatography on silica (*n*-pentane/Et_2O = 15:1), and **4c** was obtained as a colorless liquid (422 mg, 82%, 95:5 dr, 98:2 er). $[\alpha]_D^{20} = -20.8°$ (*c* 1.12, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 6.19 (d, *J* = 15.4 Hz, 1H), 5.59 (dt, *J* = 15.4, 7.4 Hz, 1H), 4.90 (s, 2H), 3.97 (ddd, *J* = 7.4, 6.2, 3.5 Hz, 1H), 3.74–3.89 (m, 2H), 2.36–2.43 (m, 1H), 2.01–2.17 (m, 3H), 1.84 (d, *J* = 0.8 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.7, 135.3, 127.2, 115.1, 70.1, 64.9, 37.1, 36.2, 18.6, 16.5; IR 3382, 3080, 3019, 2967, 2937, 1646, 1608, 1454, 1378, 1310, 1136, 1073, 967, 885 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{10}H_{17}OCl$ $[M]^{\bullet+}$ 188.09624, found 188.09702; calcd for $C_{10}H_{17}O^{37}Cl$ $[M]^{\bullet+}$ 190.09329, found 190.09356; GC (Lipodex E, 100 °C isotherm, 1.1 mL/min He, 20:1 split) $\mathrm{T}_{(2R,3R)}$ = 42.7 min, $\mathrm{T}_{(2S,3R)}$ = 44.7 min, $\mathrm{T}_{(2R,3S)}$ = 63.5 min, $\mathrm{T}_{(2S,3S)}$ = 71.7 min, isomeric ratio = 1:2:357:20.

(*S*,*E*)-3,7-Dimethylocta-5,7-dien-1-ol 5c. To a solution of SeO_2 (140 mg, 1.26 mmol, 0.05 equiv) and salicylic acid (348 mg, 2.52 mmol, 0.10 equiv) in CH_2Cl_2 (12 mL) at rt, *t*-BuOOH (70% in H_2O, 15.6 mL, 114 mmol, 4.50 equiv) was added slowly. After 15 min (*S*)-citronellol **5a** (5.00 g, 25.2 mmol) was added and stirred 48 h at rt. SeO_2 (140 mg, 1.26 mmol, 0.05 equiv) was added and stirred for another 72 h at rt. The reaction was quenched by the addition of MeOH (25 mL) and a saturated aqueous solution of $Na_2S_2O_3$ (40 mL). After 1 h of stirring at rt the reaction was filtered and extracted with Et_2O (3 × 50 mL), the combined organic layers were washed with an aqueous solution of NaOH (1 M, 200 mL), and the basic aqueous layer was washed with Et_2O (1 × 100 mL). The combined organic layers were washed with a saturated aqueous solution of NH_4Cl (1 × 150 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was solved in dry MeOH (25 mL) and cooled to 0 °C, and $NaBH_4$ (2.39 g, 63.0 mmol, 2.5 equiv) was added successively. After stirring for 1 h at 0 °C the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (25 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc = 3:1–2:1–1:1–0:1), and (*S*,*E*)-2,6-dimethyloct-2-en-1,8-diol was obtained as a colorless liquid (3.69 g, 66%).

To a solution of (*S*,*E*)-2,6-dimethyloct-2-en-1,8-diol (2.88 g, 16.7 mmol) in dry CH_2Cl_2 (17 mL) at 0 °C were added Et_3N (6.13 mL, 44.2 mmol, 2.64 equiv), DMAP (205 mg, 1.67 mmol, 0.10 equiv), and Ac_2O (3.80 mL, 40.18 mmol, 2.40 equiv) and stirred for 1.5 h at 0 °C. The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc = 30:1), and (*S*,*E*)-2,6-dimethyloct-2-en-1,8-diyldiacetate was obtained as a colorless liquid (4.20 g, 98%).

To a solution of (*S*,*E*)-2,6-dimethyloct-2-en-1,8-diyldiacetate (1.28 g, 5.00 mmol) in dry THF (15 mL) at rt were added $ZnCl_2$ (682 mg, 5.00 mmol, 1.00 equiv) and $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol, 0.01 equiv). Over 30 min AllylMgCl (1.7 M in Et_2O, 5.88 mL, 10.0 mmol, 2.00 equiv) was added, and the reaction was stirred 1.5 h at rt. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl-Lsg. (10 mL) and H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 35 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was solved in MeOH (5 mL) at rt, and K_2CO_3 (1.83 g, 12.5 mmol, 2.50 equiv) was added and stirred 17 h at rt. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl-Lsg. (2.5 mL) and extracted with Et_2O (3 × 15 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc = 25:1), and **5c** was obtained as a colorless liquid (612 mg, 80%). (*S*,*E*)-2,6-Dimethyloct-2-en-1,8-diol: $[\alpha]_D^{20} = -4.25°$ (*c* 0.91, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 5.35 (td, *J* = 7.2, 1.1 Hz, 1H), 3.92 (s, 2H), 3.54–3.65 (m, 2H), 2.72 (br. s., 2H), 1.94–2.09 (m, 2H), 1.62 (s, 3H), 1.51–1.59 (m, 2H), 1.29–1.38 (m, 2H), 1.12–1.23 (m, 1H), 0.87 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.5, 126.0, 68.5, 60.6, 39.6, 36.6, 28.8, 24.9, 19.4, 13.5; IR 3320, 2923, 1455, 1377, 1219, 1057, 1011, 848, 667 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{10}H_{17}$ $[M + H - 2H_2O]^+$ 137.13248, found 137.13219; calcd for $C_{10}H_{19}O$ $[M + H - H_2O]^+$ 155.14304, found 155.14290, calcd for $C_{10}H_{21}O_2$ $[M + H]^+$ 173.15361, found 173.15347. (*S*,*E*)-2,6-Dimethyloct-2-en-1,8-diyldiacetate: $[\alpha]_D^{20} = -2.01°$ (*c* 1.89, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 5.38 (t, *J* = 7.1 Hz, 1H), 4.38 (s, 2H), 3.98–4.08 (m, 2H), 1.92–2.07 (m, 8H), 1.56–1.66 (m, 4H), 1.45–1.54 (m, 1H), 1.29–1.42 (m, 2H), 1.12–1.21 (m, 2H), 0.86 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 170.6, 129.9, 129.4, 70.0, 62.6, 36.2, 35.2, 29.3, 24.9, 20.8, 20.7, 19.2, 13.7; IR 2959, 2927, 2873, 1743, 1458, 1369, 1241, 1147, 1024, 957, 850, 639, 608 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{25}O_4$ $[M + H]^+$ 257.17474, found 257.17506; calcd for $C_{14}H_{25}O_4Na$ $[M + Na]^+$ 279.15668, found 279.15701. **5c**: $[\alpha]_D^{20} = -8.62°$ (*c* 1.39, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 6.13 (d, *J* = 15.6 Hz, 1H), 5.59–5.66 (m, 1H), 4.86 (s, 2H), 3.60–3.72 (m, 2H), 2.13 (dt, *J* = 13.9, 7.0 Hz, 1H), 1.95–2.02 (m, 1H), 1.82–1.84 (m, 3H), 1.79 (br. s., 1H), 1.59–1.73 (m, 2H), 1.35–1.42 (m, 1H), 0.91 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 134.3, 128.8, 114.3, 60.9, 40.2, 39.3, 29.9, 19.5, 18.6; IR 3337, 3080, 2925, 1741, 1644, 1608, 1455, 1376, 1242, 1055, 1003, 966, 882 cm^{-1}; HRMS *m*/*z* calcd for $C_{10}H_{17}$ $[M + H - H_2O]^+$ 137.13248, found 137.13227.

(*R*)-2-((*S*)-6-Methylhept-5-en-2-yl)oxirane 6a. To a solution of **4a** (3.23 g, 17.0 mmol) in MeCN (20 mL) was added a solution of NaOH (17.8 g, 0.45 mmol, 22.3 equiv) in EtOH (24 mL) and H_2O (50 mL). After the reaction was stirred for 2 h at rt, *n*-pentane (50 mL) was added, the layers were separated, and the aqueous layer was extracted with *n*-pentane (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/Et_2O = 20:1), and **6a** obtained as a colorless liquid (2.53 g, 97%, 94:6 dr). $[\alpha]_D^{20} = -3.97$ (*c* 0.92, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 5.07 (td, *J* = 6.4, 1.3 Hz, 1H), 2.71–2.76 (m, 1H), 2.65–2.70 (m, 1H), 2.51 (dd, *J* = 5.0, 2.7 Hz, 1H), 1.95–2.08 (m, 2H), 1.67 (s, 3H), 1.59 (s, 3H), 1.38–1.47 (m, 1H), 1.24–1.33 (m, 2H), 1.02 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.6, 124.2, 56.9, 46.8, 35.7, 33.6, 25.6, 25.5, 17.6 16.9; IR 3043, 2966, 2919, 2856, 1483, 1455, 1376, 1257, 1114, 1088, 929, 916, 892, 856, 823 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{19}O$ $[M+H]^+$ 155.14304, found 155.14289.

(*R*)-2-((*S*,*E*)-6,10-Dimethylundeca-5,9-dien-2-yl)oxirane 6b. The same procedure as above was applied to (2*S*,3*S*,*E*)-**4b** (597 mg, 2.31 mmol). The crude product was purified by column chromatography on silica (*n*-pentane/Et_2O = 100:1), and **6b** was obtained as a colorless liquid (480 mg, 93%, 56:44 dr). ^1H NMR (400 MHz, $CDCl_3$): δ 5.05–5.16 (m, 2H), 2.66–2.77 (m, 2H), 2.46–2.53 (m, 1H), 2.02–2.10 (m, 4H), 1.96–2.01 (m, 2H), 1.68 (d, *J* = 0.9 Hz, 3H), 1.59–1.62 (m, 6H), 1.43 (s, 4H), 1.26–1.38 (m, 2H), 1.03 (d, *J* = 6.4 Hz, 1/2 3H), 0.93 (d, *J* = 6.5 Hz, 1/2 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.2, 135.1, 131.3, 131.2, 124.3, 124.3, 124.2, 124.1, 56.9, 56.9, 46.8, 45.5, 39.7, 39.7, 35.7, 35.6, 34.5, 33.6, 26.9 (2C), 26.7, 26.6, 25.6, 25.3, 25.2, 17.6, 17.0, 15.9, 15.9, 15.4; HRMS (ESI) calcd for $C_{15}H_{27}O$ $[M + H]^+$ 223.20578, found 223.20564.

(*R*)-2-((*S*,*E*)-6-Methylhepta-4,6-dien-2-yl)oxirane 6c. The same procedure as above was applied to (2*S*,3*S*,*E*)-**4c** (422 mg, 2.24 mmol). The crude product was purified by column chromatography on silica (*n*-pentane/Et_2O = 20:1), and **6c** was obtained as a colorless liquid (317 mg, 93%, 96:4 dr). $[\alpha]_D^{20}$ = +15.8° (*c* 1.25, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 6.18 (d, *J* = 15.4 Hz, 1H), 5.63 (dt, *J* = 15.6, 7.4 Hz, 1H), 4.89 (s, 2H), 2.73−2.77 (m, 2H), 2.54 (t, *J* = 4.4 Hz, 1H), 2.21−2.28 (m, *J* = 7.5, 6.5 Hz, 1H), 2.06−2.13 (m, 1H), 1.84 (s, 3H), 1.39−1.48 (m, 1H), 1.04 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.8, 134.6, 127.8, 114.8, 56.6, 46.7, 36.9, 36.5, 18.7, 16.7; IR: 2968, 2921, 1608, 1456, 1375, 966, 883, 756 cm^{-1}; HRMS *m*/*z* calcd for $C_{10}H_{17}O$ $[M + H]^+$ 153.12739, found 153.12722.

(6*S*,7*S*)-7,11-Dimethyldodec-10-en-6-ol 7a. To a solution of CuCN (254 mg, 2.84 mmol, 0.20 equiv) in THF (25 mL) at −78 °C were added **6a** (2.20 g, 14.2 mmol) and, after 20 min of stirring, dropwise *n*-BuLi (1.6 M in *n*-hexane, 28 mL, 2.00 equiv). The reaction was stirred for 7 h at −78 °C, warmed to 0 °C, quenched by the addition of a saturated aqueous solution of NH_4Cl (25 mL), and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc = 220:1−150:1−100:1), and **7a** was obtained as a colorless liquid (2.66 g, 89%, 92:8 dr). $[\alpha]_D^{20}$ = −5.9 (*c* 1.04, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 5.07−5.12 (m, 1H), 3.47−3.51 (m, 1H), 1.91−2.08 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.37−1.53 (m, 6H), 1.25−1.36 (m, 5H), 1.16−1.25 (m, 1H), 0.85−0.92 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.3, 124.6, 75.0, 37.7, 34.4, 33.4, 31.9, 25.9, 25.7, 25.6, 22.6, 17.6, 14.0, 13.5; IR 3377, 2959, 2928, 2857, 1458, 1378, 1118, 1082, 1013, 983, 943, 828 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{29}O$ $[M+H]^+$ 213.22129, found 213.22134.

(4*S*,5*S*)-5,9-Dimethyldec-8-en-4-ol 7b. The same procedure as above was applied to **6a** (849 mg, 5.50 mmol), using EtMgBr (1.0 M in THF, 16.5 mL, 3.00 equiv). The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc = 250:1), and **7b** was obtained as a colorless liquid (803 mg, 79%, 93:7 dr). $[\alpha]_D^{20}$ = −22.7 (*c* 1.33, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 5.10 (t, *J* = 7.1 Hz, 1H), 3.51 (dt, *J* = 7.5, 4.0 Hz, 1H), 1.91−2.09 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.27−1.53 (m, 7H), 1.16−1.25 (m, 1H), 0.93 (t, *J* = 7.1 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.3, 124.6, 74.8, 37.7, 36.6, 33.4, 25.7, 25.6, 19.4, 17.6, 14.1, 13.5; IR 2280, 2960, 2938, 2872, 1457, 1378, 1113, 974 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{25}O$ $[M + H]^+$ 185.18999, found 185.18994.

(5*S*,6*S*)-6,10-Dimethylundec-9-en-5-ol 7c. The same procedure as above was applied to **6a** (849 mg, 5.50 mmol), using *n*PrMgCl (2.0 M in Et_2O, 5.5 mL, 2.00 equiv). The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc = 250:1), and **7c** was obtained as a colorless liquid (803 mg, 74%, 93:7 dr). $[\alpha]_D^{20}$ = −23.1 (*c* 1.18, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 5.10 (tt, *J* = 7.1, 1.3 Hz, 1H), 3.49 (dt, *J* = 7.6, 4.0 Hz, 1H), 1.91−2.09 (m, 2H), 1.68 (d, *J* = 0.7 Hz, 3H), 1.60 (s, 3H), 1.16−1.53 (m, 11H), 0.91 (t, *J* = 7.1 Hz, 3), 0.87 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.3, 124.6, 75.0, 37.7, 34.1, 33.4, 28.4, 25.7, 25.6, 22.8, 17.6, 14.0, 13.5; IR 3380, 2959, 2928, 2859, 1457, 1378, 1116, 1079, 978 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{27}O$ $[M + H]^+$ 199.20564, found 199.20565.

(5*S*,6*S*)-5-Methyl-6-pentyltetrahydro-2*H*-pyran-2-one 8, (−)-*cis*-Aerangis Lactone. A solution of **7a** (106 mg, 0.50 mmol) and NaOH (200 mg, 5.00 mmol, 10.0 equiv) in MeOH−CH_2Cl_2 (1:1, 5 mL) was cooled to −78 °C, and ozone enriched O_2 was bubbled through the solution until the color changed from red to yellow and finally to blue with a yellowish precipitate. Air was bubbled through the solution until the blue color disappeared. The precipitate was dissolved by the addition of water (5 mL). After extraction with CH_2Cl_2 (3 × 10 mL) the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/Et_2O = 5:1), and **8** was obtained as a colorless liquid (75.6 mg, 83%, 95:5 dr). $[\alpha]_D^{20}$ = −57.8 (*c* 1.01, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 4.25 (ddd, *J* = 8.6, 4.4, 3.1 Hz, 1H), 2.50 (t, *J* = 7.3 Hz, 2H), 1.94−2.05 (m, 2H), 1.58−1.68 (m, 2H), 1.41−1.55 (m, 2H), 1.22−1.34 (m, 5H), 0.93 (d, *J* = 6.9, 3H), 0.86 (t, *J* = 6.7, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 82.9, 31.8, 31.5, 29.2, 26.6, 25.9, 25.1, 22.4, 13.9, 12.3; IR 3465, 2934, 2872, 1735, 1462, 1380, 1344, 1244, 1204, 1123, 1097, 1070, 994, 909, 732 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{21}O_2$ $[M + H]^+$ 185.15361, found 185.15422.

(4*S*,5*S*)-8-Hydroxy-5-methyloctan-4-yl Acetate 9b. To a solution of **7b** (777 mg, 4.21 mmol) in dry CH_2Cl_2 (21 mL) at 0 °C were added Et_3N (1.54 mL, 11.2 mmol, 2.64 equiv), DMAP (102 mg, 0.84 mmol, 0.20 equiv), Ac_2O (0.96 mL, 10.1 mmol, 2.40 equiv) and stirred for 2.5 h at 0 °C. The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/Et_2O = 25:1) and (4*S*,5*S*)-5,9-dimethyldec-8-en-4-yl acetate was obtained as a colorless liquid (914 mg, 96%, 97:3 dr). A solution of (4*S*,5*S*)-5,9-dimethyldec-8-en-4-yl acetate (869 g, 3.84 mmol) in MeOH (20 mL) was cooled to −78 °C, ozone enriched O_2 was bubbled through the solution until it turned blue, followed by stirring for 5 min, and air was bubbled through the solution until the blue color disappeared. The reaction was quenched by the addition of $NaBH_4$ (348 mg, 9.20 mmol, 2.40 equiv), stirred for 1 h while warming to rt, and extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/Et_2O = 2:1−1:1), and **9b** was obtained as a colorless liquid (632 mg, 80%, 96:4 dr). (4*S*,5*S*)-5,9-Dimethyldec-8-en-4-yl acetate: $[\alpha]_D^{20}$ = −21.2 (*c* 1.46, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 5.06 (tt, *J* = 6.5, 1.5 Hz, 1H), 4.86 (dt, *J* = 8.7, 4.3 Hz, 1H), 1.89−2.06 (m, 5H), 1.57−1.69 (m, 7H), 1.53 (dd, *J* = 9.6, 5.0 Hz, 1H), 1.21−1.48 (m, 4H), 1.09−1.17 (m, 1H), 0.87−0.92 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 131.4, 124.4, 76.8, 35.8, 33.5, 33.0, 25.6, 25.6, 21.0, 18.9, 17.6, 14.3, 13.9; IR 2962, 2930, 2874, 1736, 1456, 1375, 1241, 1019 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{27}O_2$ $[M + H]^+$ 227.20056, found 227.20060. **9b**: $[\alpha]_D^{20}$ = −27.4 (*c* 1.52, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 4.85−4.90 (m, 1H), 3.60 (t, *J* = 6.5 Hz, 2H), 2.03 (d, *J* = 0.8 Hz, 3H), 1.11−1.69 (m, 10H), 0.86−0.93 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 76.7, 63.0, 36.2, 33.5, 30.4, 29.1, 21.1, 19.0, 14.4, 13.9; IR 3397, 2960, 2937, 2874, 1733, 1458, 1373, 1247, 1056, 1022, 756, 406 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{23}O_3$ [M + H] 203.16417, found 203.16423.

(4*S*,5*S*)-1-Hydroxy-4-methylnonan-5-yl Acetate 9c. The same procedure as above was applied to **7c** (771 mg, 3.89 mmol). The crude products were purified by column chromatography on silica as above. (5*S*,6*S*)-6,10-Dimethylundec-9-en-5-yl acetate (916 mg, 98%, 93:7 dr) and **9c** (761 mg, 97%, 97:3 dr) were obtained as colorless liquids. (5*S*,6*S*)-6,10-Dimethylundec-9-en-5-yl acetate: $[\alpha]_D^{20}$ = −16.6 (*c* 1.12, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 5.04−5.09 (m, 1H), 4.84 (dt, *J* = 8.5, 4.4 Hz, 1H), 1.89−2.06 (m, 5H), 1.58−1.68 (m, 7H), 1.43−1.57 (m, 2H), 1.17−1.42 (m, 5H), 1.08−1.17 (m, 1H), 0.84−0.91 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 131.4, 124.4, 77.0, 35.7, 33.0, 31.0, 27.9, 25.6, 25.6, 22.6, 21.1, 17.6, 14.2, 13.9; IR 2960, 2929, 2860, 1736, 1456, 1375, 1241, 1018 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{29}O_2$ $[M + H]^+$ 241.21621, found 241.21622. **9c**: $[\alpha]_D^{20}$ = −19.4 (*c* 1.36, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 4.86 (dt, *J* = 8.7, 4.3 Hz, 1H), 3.61 (t, *J* = 6.5 Hz, 2H), 2.04 (s, 3H), 1.12−1.68 (m, 12H), 0.85−0.92 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 77.0, 76.7, 63.0, 36.2, 31.0, 30.5, 29.1, 27.9, 22.6, 21.1, 14.3, 13.9; IR 3397, 2957, 2936, 2872, 1735, 1716, 1458, 1373, 1242, 1057, 1021, 406 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{25}O_3$ $[M + H]^+$ 217.17982, found 217.18003.

(4*S*,5*S*)-5-Methyloctan-4-ol 10b, Cruentol. To a solution of **9b** (405 mg, 2.00 mmol) in dry CH_2Cl_2 (1.4 mL) at 0 °C were added DMAP (48.9 mg, 0.40 mmol, 0.20 equiv), Et_3N (360 μL, 2.60 mmol, 1.30 equiv), and TsCl (458 mg, 2.40 mmol, 1.20 equiv) and stirred for 4 h while warming to rt. The reaction was quenched by the addition of H_2O (2 mL) and extracted with EtOAc (3 × 5 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/Et_2O = 5:1) and (4*S*,5*S*)-5-methyl-8-(tosyloxy)octan-4-yl acetate obtained as a yellowish liquid (639 mg, 90%, 94:6 dr). To a solution of $LiAlH_4$ (171 mg, 4.53 mmol, 3.00 equiv) in dry THF (4.53 mL) at 0 °C a solution of (4*S*,5*S*)-5-methyl-8-(tosyloxy)octan-4-yl acetate (538 mg, 1.51 mmol) in dry THF (2.16 mL) was added and heated to 75 °C for 5 h. After cooling to 0 °C the reaction was quenched by the addition of MeOH (5 mL) and a saturated aqueous solution of NaK-tatrate (10 mL) and extracted with EtOAc (3 × 25 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/Et_2O = 10:1), and **10b** was obtained as a colorless liquid (210 mg, 96%, 97:3 dr). (4*S*,5*S*)-5-Methyl-8-(tosyloxy)octan-4-yl acetate: $[\alpha]_D^{20}$ = −17.9° (*c* 1.30, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 4.79 (dt, J = 8.8, 4.0 Hz, 1H), 3.94−4.03 (m, 2H), 2.44 (s, 3H), 2.01 (s, 3H), 1.07−1.74 (m, 9H), 0.88 (t, J = 7.3 Hz, 3H), 0.83 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 144.6, 133.1, 129.7 (2C), 127.8 (2C), 76.3, 70.6, 35.8, 33.2, 28.6, 26.6, 21.5, 21.0, 18.9, 14.2, 13.8; IR 2960, 2874, 1731, 1598, 1462, 1360, 1244, 1188, 1177, 1120, 1097, 1020, 964, 917, 815, 664 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{32}O_5NS$ $[M + NH_4]^+$ 374.19957, found 374.20048, calcd for $C_{18}H_{28}O_5NaS$ $[M + Na]^+$ 379.15497, found 379.15546. **10b**: $[\alpha]_D^{20}$ = −31.9 (*c* 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.51 (dt, J = 7.5, 4.3 Hz, 1H), 1.24−1.54 (m, 9H), 1.12−1.20 (m, 1H), 0.93 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 6.9 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 74.9, 37.9, 36.7, 35.6, 20.4, 19.4, 14.3, 14.1, 13.5; IR 3374, 2958, 2931, 2872, 1465, 1378, 1286, 1220, 1148, 1114, 1062, 1012, 970 cm^{-1}; HRMS (ESI): *m*/*z* calcd for C_9H_{19} $[M + H - H_2O]^+$ 127.14813, found 127.14775.

(4*S*,5*S*)-4-Methylnonan-5-ol 10c, Ferrugineol. The same procedure as above was applied to **9c** (432 mg, 2.00 mmol). The crude products were purified by column chromatography on silica as above. (4*S*,5*S*)-4-Methyl-1-(tosyloxy)nonan-5-yl acetate (639 mg, 90%, 97:3 dr) and **10c** (261 mg, 93%, 98:2 dr) were obtained as yellowish or colorless liquids, respectively. (4*S*,5*S*)-4-Methyl-1-(tosyloxy)nonan-5-yl acetate: $[\alpha]_D^{20}$ = −14.7 (*c* 1.39, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 4.78 (dt, J = 8.5, 4.4 Hz, 1H), 3.95−4.04 (m, 2H), 2.44 (s, 3H), 2.02 (s, 3H), 1.08−1.73 (m, 12H), 0.87 (t, J = 7.3 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 144.6, 133.2, 129.7 (2C), 127.8 (2C), 76.5, 70.6, 35.8, 30.8, 28.6, 27.9, 26.6, 22.5, 21.5, 21.0, 14.2, 13.9; IR 2958, 2870, 1732, 1598, 1461, 1363, 1242, 1177, 1097, 1020, 955, 890, 815, 765 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{30}O_5NaS$ $[M + Na]^+$ 393.17062, found 393.17096. **10c**: $[\alpha]_D^{20}$ = −27.2 (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.48 (dt, J = 7.9, 4.1 Hz, 1H), 1.23−1.52 (m, 11H), 1.11−1.19 (m, 1H), 0.91 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 7.1 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H); ^{13}C NMR 75.1, 37.9, 35.6, 34.2, 28.5, 22.8, 20.4, 14.3, 14.0, 13.5; IR 3379, 2958, 2930, 2870, 1462, 1379, 1145, 1114, 1015, 974 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{21}$ $[M + H - H_2O]^+$ 141.16378, found 141.16351.

(5*S*,6*S*,*E*)-6,10-Dimethylundeca-8,10-dien-5-ol 11a. The same procedure to synthesize **7a** was applied to **6c** (256 mg, 1.68 mmol), using *n*PrMgCl (2.0 M in Et_2O, 1.68 mL, 2.00 equiv). The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc = 250:1−100:1), and **11a** (244 mg, 74%, 94:6 dr) was obtained as a colorless liquid. $[\alpha]_D^{20}$ = −13.3 (*c* 1.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.17 (d, J = 15.6 Hz, 1H), 5.61−5.69 (m, 1H), 4.87 (s, 2H), 3.54 (td, J = 6.1, 3.7 Hz, 1H), 2.27 (dt, J = 13.7, 6.6 Hz, 1H), 1.98−2.06 (m, 1H), 1.84 (s, 3H), 1.57−1.66 (m, 1H), 1.24−1.48 (m, 7H), 0.87−0.94 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 134.2, 129.2, 114.4, 74.6, 38.5, 36.9, 34.2, 28.4, 22.7, 18.7, 14.0, 13.3; IR 3380, 3080, 2958, 2930, 2871, 1646, 1608, 1457, 1378, 1312, 1123, 1004, 966, 881 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{25}O$ $[M + H]^+$ 197.18999, found 197.18996.

(6*S*,7*S*,*E*)-7,11-Dimethyldodeca-9,11-dien-6-ol 11b. The same procedure to synthesize **7a** was applied to **6c** (158 mg, 1.04 mmol). The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc = 250:1), and **11b** (178 mg, 81%, 96:4 dr) was obtained as a colorless liquid. $[\alpha]_D^{20}$ = −12.7 (*c* 1.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.17 (d, J = 15.6 Hz, 1H), 5.61−5.68 (m, 1H), 4.87 (s, 2H), 3.53 (td, J = 6.1, 3.7 Hz, 1H), 2.23−2.30 (m, 1H), 2.02 (dt, J = 14.5, 7.5 Hz, 1H), 1.84 (s, 3H), 1.57−1.66 (m, 1H), 1.40−1.47 (m, 4H), 1.26−1.35 (m, 6H), 0.87−0.92 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.9, 134.2, 129.2, 114.4, 74.6, 38.5, 36.9, 34.5, 31.9, 25.9, 22.6, 18.7, 14.0, 13.3; IR 3379, 2958, 2929, 2860, 1608, 1457, 1377, 1124, 1017, 965, 881 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{27}O$ $[M + H]^+$ 211.20564, found 211.20571.

(4*S*,5*S*)-5-Butyl-4-methyldihydrofuran-2(3*H*)-one 12a, (−)-*cis*-Whisky Lactone. A solution of **11a** (80.0 mg, 0.40 mmol) in MeOH (5 mL) was cooled to −78 °C, ozone enriched O_2 was bubbled through the solution until it turned blue, following by stirring for 5 min, and air was bubbled through the solution until the blue color disappeared. The reaction was quenched by the addition of $NaBH_4$ (36.3 mg, 0.96 mmol, 2.40 equiv), stirred for 1 h while warming up to rt, and extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was solved in MeCN (1 mL), and solutions of CuOTf·4MeCN (7.54 mg, 0.02 mmol, 0.05 equiv), 2,2′-bipyridine (3.13 mg, 0.02 mmol, 0.05 equiv), TEMPO (3.13 mg, 0.02 mmol, 0.05 equiv), and 1-methylimidazole (3.29 mg, 0.04 mmol, 0.10 equiv) each in MeCN (1 mL) were added. The reaction mixture was degassed for 5 min, the atmosphere in the reaction vessel was replaced by O_2, and the reaction was stirred for 2 h at 50 °C, quenched by the addition of H_2O (1 mL), and extracted with CH_2Cl_2 (3 × 5 mL); the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/Et_2O = 5:1), and **12a** was obtained as a colorless liquid (50.0 mg, 73%, 98:2 dr). $[\alpha]_D^{20}$ = −59.2° (*c* 1.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.39−4.44 (m, 1H), 2.68 (dd, J = 17.0, 7.8 Hz, 1H), 2.53−2.61 (m, 1H), 2.18 (dd, J = 17.0, 4.0 Hz, 1H), 1.59−1.69 (m, 1H), 1.43−1.55 (m, 2H), 1.29−1.40 (m, 3H), 1.00 (d, J = 7.1 Hz, 3H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 83.6, 37.5, 32.9, 29.5, 28.0, 22.4, 13.8, 13.8; IR 3523, 2958, 2873, 1774, 1465, 1422, 1383, 1336, 1293, 1209, 1170, 1092, 1080, 994, 974, 940, 928 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_9H_{17}O_2$ $[M + H]^+$ 157.12231, found 157.12216.

(4*S*,5*S*)-4-Methyl-5-pentyldihydrofuran-2(3*H*)-one 12b, (−)-*cis*-Cognac Lactone. The same procedure as above was applied to **11b** (127 mg, 0.60 mmol). The crude product was purified by column chromatography on silica as above, and **12b** (78.8 mg, 77%, 98:2 dr) was obtained as a colorless liquid. $[\alpha]_D^{20}$ = −64.8 (*c* 1.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.41 (ddd, J = 9.4, 5.4, 4.4 Hz, 1H), 2.67 (dd, J = 17.0, 7.8 Hz, 1H), 2.52−2.60 (m, 1H), 2.17 (dd, J = 17.0, 4.0 Hz, 1H), 1.63 (q, J = 9.3 Hz, 1H), 1.45−1.53 (m, 2H), 1.26−1.39 (m, 5H), 0.99 (d, J = 7.3 Hz, 3H), 0.85−0.91 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 83.6, 37.5, 32.9, 31.5, 29.8, 25.5, 22.4, 13.9, 13.7; IR 2956, 2865, 1779, 1462, 1423, 1383, 1335, 1294, 1212, 1168, 1079, 1006, 978, 932 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{19}O_2$ $[M + H]^+$ 171.13796, found 171.13783.

(2*S*,6*S*)-2,6-Dichloroheptane-1,7-diol 14. To a solution of freshly distilled 1,7-heptandiol **13** (512 mg, 4.00 mmol) in MeCN (40 mL) were added CuOTf·4MeCN (149 mg, 0.30 mmol, 0.075 equiv), 2,2′-bipyridine (46.8 mg, 0.30 mmol, 0.075 equiv), TEMPO (46.8 mg, 0.30 mmol, 0.075 equiv), and 1-methylimidazole (49.7 mg, 0.60 mmol, 0.15 equiv). The reaction mixture was degassed for 5 min, and the atmosphere in the reaction vessel was replaced by O_2. The reaction mixture was stirred for 3 h at rt, and (2*R*,5*S*)-2-(*tert*-butyl)-3,5-dimethylimidazolidin-4-one-TFA-salt (457 mg, 1.60 mmol, 0.40 equiv) and NCS (1.33 g, 10.0 mmol, 2.50 equiv) were added successively. The reaction was stirred for 18 h at rt, cooled to 0 °C, and diluted with EtOH (40 mL). After successive addition of $NaBH_4$ (756 mg, 20 mmol, 5.00 equiv) the reaction was stirred for 30 min at 0 °C, quenched by the addition of a saturated aqueous solution of NH_4Cl (20 mL), and extracted with EtOAc (3 × 60 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica (n-pentane/Et_2O = 1:5), and **14** was obtained as a white solid (547 mg, 68%, 95:5 dr, >99:1 er). After recrystallization from $CHCl_3$, the dr can be enriched to >99:1. Mp: 79.3 °C; $[\alpha]_D^{20}$ = +51.1° (c 1.18, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 4.00–4.06 (m, 2H), 3.78–3.83 (m, 2H), 3.68–3.73 (m, 2H), 1.90 (br. s, 2H), 1.76–1.86 (m, 4H) 1.67–1.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 66.9 (2C), 64.6 (2C), 33.6 (2C), 23.3; IR 3324, 2962, 2866, 1455, 1391, 1286, 1073, 1020, 998, 745, 611, 568, 510, 455 cm^{-1}; HRMS (ESI): m/z calcd for $C_7H_{15}O_2Cl_2$ $[M + H]^+$ 201.04436, found 201.04433, calcd for $C_7H_{15}O_2Cl^{37}Cl$ $[M + H]^+$ 203.04141, found 203.04138, calcd for $C_7H_{15}O^{37}Cl_2$ $[M + H]^+$ 205.03846, found 205.03825; GC (Hydrodex-β-TBDAC, 170 °C isotherm, 1.1 mL/min He, 50:1 split) $\tau_{(2R,6R)}$ = 60.6 min, $\tau_{(meso)}$ = 63.6 min, $\tau_{(2R,6S)}$ = 70.5 min, isomeric ratio = 0:1:351.

1,3-Di-((*R*)-oxiran-2-yl)propane 15. To a solution of **14** (1.60 g, 7.69 mmol) in CH_2Cl_2 (27 mL) was added an aqueous solution of NaOH (1 M, 100 mL). After the reaction was stirred for 15 h at rt, the layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica (Et_2O), and **15** was obtained as a colorless liquid (937 mg, 92%, 99:1 dr). $[\alpha]_D^{20}$ = +23.0 (c 1.1, EtOH); ^1H NMR (400 MHz, $CDCl_3$): δ 2.89–2.95 (m, 2H), 2.71–2.79 (m, 2H), 2.48 (dd, J = 5.0, 2.7 Hz, 2H), 1.62–1.68 (m, 4H), 1.52–1.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.0 (2C), 47.0 (2C), 32.2 (2C), 22.5; IR 2985, 2929, 2862, 1410, 1258, 1133, 911, 831, 764, 512 cm^{-1}; HRMS (ESI): m/z calcd for $C_7H_{13}O_2$ $[M + H]^+$ 129.09101, found 129.09072.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental, ^1H and ^{13}C NMR spectra, GC chromatograms, and crystal data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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