Total Synthesis of Halicholactone and Neohalicholactone

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Received 16 October 2009; revised 29 October 2009

Abstract: New total syntheses of the marine oxylipins halicholactone and neohalicholactone are presented. The key building blocks were synthesized utilizing chemoenzymatic methods.

Key words: natural product, total synthesis, enzymes, boron reagents, asymmetric synthesis

Introduction

Natural products are not only a rich source for active agents in general, but do also catalyze numerous synthetic efforts towards the total synthesis of the newly found targets, often triggering the development of new synthetic methods or the optimization of given protocols.[1] The seemingly not overly complex group of marine oxylipins bearing a cyclopropyl lactone moiety attracted considerable attention in recent years and en route to their total synthesis some elegant protocols were developed.[2] Our own endeavors focused on chemoenzymatic routes, applying enzymatic transformation[3] as well as developing a new boron reagent.[4] Here we describe the total synthesis of halicholactone (**1**) and neohalicholactone (**2**). Other representatives of the group of marine oxylipins are the constanolactones A–G[5] and solandelactones A–I[6] that differ in the ring size of the lactones and the configuration of the stereogenic units (Figure 1).

Halicholactone (**1**) and neohalicholactone (**2**) were isolated by the Yamada group from the marine sponge *Halichondria okadai* off the coast of Japan in 1989.[7] In 1994 Proteau et al. found another neohalicholactone from the brown alga *Laminaria sinclairii*, but structural analysis showed that the isolated natural product was the C_{15}-epimer of neohalicholactone (**2**).[8] Both target molecules were shown to be weak lipoxygenase inhibitors. For example, halicholactone (**1**) exhibits inhibitory activity against the 5-lipoxygenase of guinea pig polymorphonuclear leukocytes (IC_{50} = 630 μm).[7a] The first total synthesis of halicholactone (**1**) and neohalicholactone (**2**) was published in 1995 by Critcher and Wills.[9] They generated both natural products with a convergent synthetic strategy in 18 steps and 4% [halicholactone (**1**)] and 2% [neohalicholactone (**2**)] yield, respectively. Two more syntheses of halicholactone (**1**) were disclosed in 2000 (25 steps, 2% yield)[10] and in 2002 (13 steps, 12% yield),[11] and while preparing the manuscript, the Tang group reported another short synthesis (11% yield).[12]

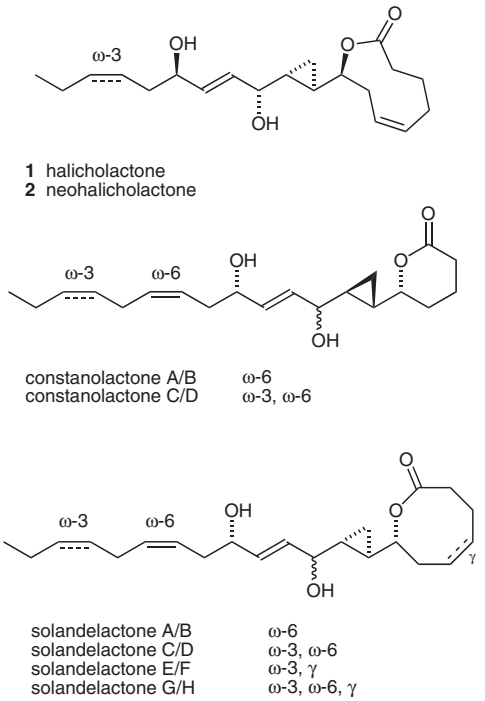


Figure 1 Members of the marine oxylipin family

Strategy

Based on our previous experience on the convergent synthesis of various members of the marine oxylipin family,[3,4] we followed a similar approach for generating halicholactone (**1**) and neohalicholactone (**2**). As a key step we chose the highly reliable chromium(II)-mediated coupling between aldehyde **3** and the corresponding iodides **4** and **5**,[13] respectively, that are derived from the corresponding propargylic alcohols **6** and **7** (Scheme 1). Obviously, the cyclopropyl lactone moiety is identical in both natural products **1** and **2**, while the aliphatic side chains are different. The additional *Z*-double bond at position C-17 (ω-3) of neohalicholactone (**2**) presents the special challenge that we envisaged to tackle with an allyl addition utilizing enantiomerically pure α-substituted allylboronic esters. Although (*R*)-oct-1-yn-3-ol (**6**) is commercially available, we found that its enantiomeric purity

SYNTHESIS 2010, No. 3, pp 0527–0537
Advanced online publication: 27.11.2009
DOI: 10.1055/s-0029-1217145; Art ID: E25809SS

Biographical Sketches

from left to right: Anja C. M. Nordschild, Diana Sandkuhl, Jörg Pietruszka, Verena Doum, Martina Bischop

Martina Bischop was born in Nordhorn, Germany in 1982. She received her diploma in chemistry at the Heinrich Heine University of Düsseldorf in 2007. She continued her doctoral thesis at the Institute of Bioorganic Chemistry, headed by Professor Pietruszka. Scientifically, her focus lies on the development of new synthetic methods (catalysis and boron reagents), which she is applying toward natural product synthesis. Since 2008 she is funded by a fellowship of the Jürgen-Manchot-Stiftung.

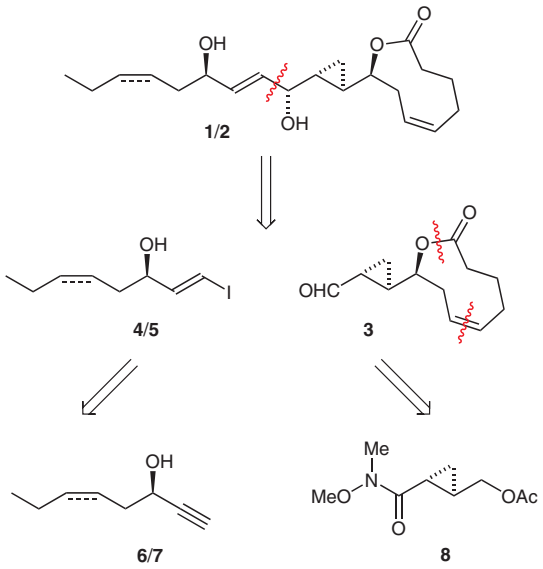
Verena Doum did her apprenticeship as laboratory assistant at the Forschungszentrum Jülich from 2005–2008. She joined the Institute of Bioorganic Chemistry in 2006 focusing on the synthesis of key building blocks and the development of the corresponding analytical tools, with the final year being dedicated to the marine oxylipin project. In September 2008 she started her undergraduate studies on applied chemistry at the FH Aachen.

Anja C. M. Nordschild (née Rieche) was born in Stuttgart, Germany in 1979. After her apprenticeship as chemical technical assistant, she started studying chemistry at the University of Stuttgart and spent half a year as ERASMUS student at the University of Edinburgh, UK. She received her diploma in 2003, which was rewarded with the Proctor & Gamble prize. She continued her endeavors on the total syntheses of marine oxylipins first at the University of Stuttgart and later at the Institute of Bioorganic Chemistry at the Heinrich Heine University of Düsseldorf where she obtained her doctorate (Dr. rer. nat.) in 2009. Her doctoral studies were funded by fellowships of the Degussa Foundation and the Heinrich Heine University of Düsseldorf. Meanwhile she gained industrial experience during internships with Bayer HealthCare and Evonik Industries.

Jörg Pietruszka studied chemistry at the University of Hamburg where he also obtained his doctorate (Dr. rer. nat.) in 1993 (Prof. W. A. König). After two postdoctoral years with Professor S. V. Ley (Cambridge, UK), he fulfilled the requirements for his 'Habilitation' – funded by a Liebig Fellowship and a DFG grant – at the University of Stuttgart in 2001. In 2000/2001 he was a visiting lecturer at the University of Freiburg (Germany), 2001/2002 a guest professor at the University of Cardiff (Wales), and 2002/2003 he held a substitute-professorship at the University of Tübingen (Germany). In 2004 an offer for a professorship at the University in Gießen was declined; since 2004 he holds the position as full professor and chair of Bioorganic Chemistry at the Heinrich Heine University of Düsseldorf. His research interests include the development of new chemoenzymatic methods and their application in the synthesis of natural products.

Diana Sandkuhl was born in Düsseldorf, Germany in 1981. She studied chemistry at the Heinrich Heine University of Düsseldorf, where she obtained her diploma in 2006. She continued her doctoral thesis at the Institute of Bioorganic Chemistry, headed by Professor Pietruszka, on chemoenzymatic syntheses and the application of enantiomerically pure propargylic alcohols.

is not highly reliable. Hence we pursued an enzymatic approach to generate enantiomerically pure starting material in high yield. The cyclopropyl lactone aldehyde **3** could be prepared from the Weinreb amide **8**, a building block readily available in our group.[3b] The *Z*-double bond of the unsaturated lactone could be introduced via ring-closing metathesis (RCM).



Scheme 1 Retrosynthesis of halicholactone (**1**)/neohalicholactone (**2**)

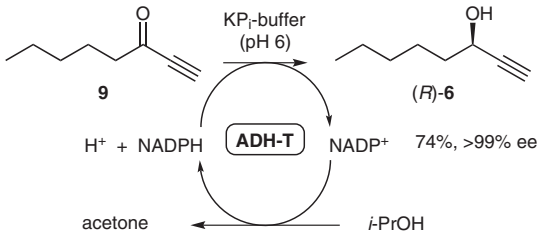
Syntheses of Aliphatic Side Chains

We started our endeavor with the syntheses of the required propargylic alcohols **6** and **7**. While successful enzymatic approaches towards propargylic alcohols using hydrolases[14] and especially alcohol dehydrogenases[15] have been previously reported, a high-yielding, highly *R*-selective protocol is still elusive: The enzymatic reduction of oct-1-yn-3-one (**9**) to the corresponding *R*-alcohol (*R*)-**6** (or related propargylic alcohols) has been reported, but these suffer from low yield and selectivity.[16] Screening several new enzymes showed that four of them transform ketone **9**, albeit also with either low conversion or selectivity [Table 1, entries 1–4: ADH-RS1,[17] 13% conv., 99% ee (*R*); ADH-RS2, 34% conv., 99% ee (*R*); ADH-CDX010, 17% conv., 99% ee (*R*); ADH-PF, 34% conv., 0% ee]. Moderate conversion, but very good selectivity was achieved with ADH-CP [entry 5: 70% conv., >99% ee (*R*)] and ADH-CDX013 [entry 6: 67% conv., 99% ee (*S*)]. The best results with an excellent enantiomeric excess showed ADH-LB [entry 7: *S*-selectivity, >99% conversion, >99% ee] and ADH-T [entry 8: *R*-selectivity >99% conversion, >99% ee] (Figure 2). The last entry proved to be the first convincing enzymatic approach towards alcohol (*R*)-**6** and when performing the transformation in preparative scale including cofactor recycling with isopropyl alcohol, 74% of the desired product was obtained in enantiomerically pure form (Scheme 2). The yield was not optimized, but on a larger scale the workup of the low-boiling product would surely allow improved results.

Table 1 Enzyme Screening in the Reduction of Ketone **9**[a]

Entry	Enzyme	Cofactor	Conv. (%)	Config.	ee (%)
1	ADH RS1	NADH	13	*R*	99
2	ADH RS2	NADH	34	*R*	99
3	ADH CDX010	NADH	17	*R*	99
4	ADH PF	NADPH	34	–	–
5	ADH CP	NADH	70	*R*	>99
6	ADH CDX013	NADPH	67	*S*	99
7	ADH LB	NADPH	>99	*S*	>99
8	ADH T	NADPH	>99	*R*	>99

[a] Screening conditions: KP_i buffer (100 mM K_2HPO_4/KH_2PO_4, pH 6, 1 mM $MgCl_2$).



Scheme 2 Enzymatic reduction of ketone **9**

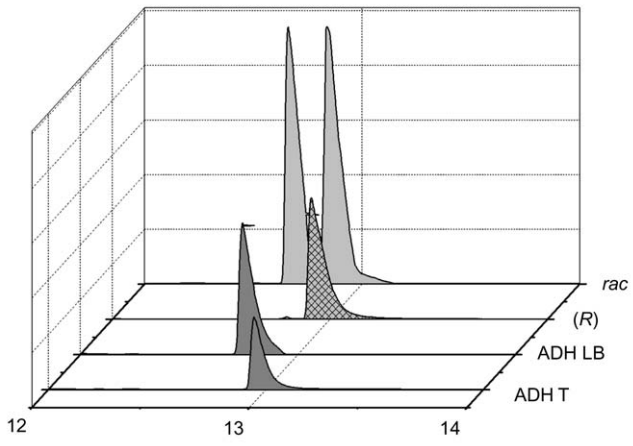
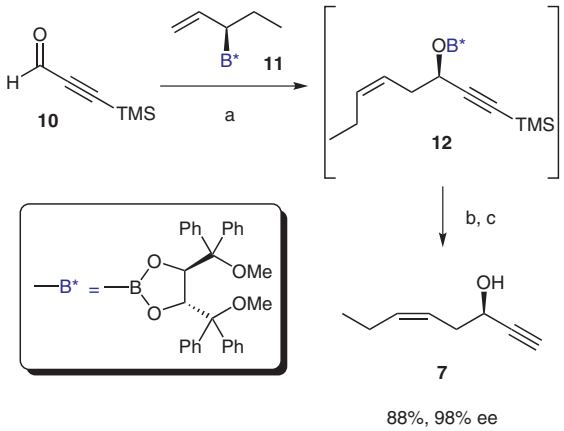


Figure 2 GLC profiles in the enzymatic reduction of ketone **9**. GLC conditions: Lipodex G, H_2 (0.6 bar), 90 °C.

Next, we focused on the second propargylic alcohol (*R*)-**7** required for the neohalicholactone (**2**) synthesis (Scheme 3). As discussed above, the homoallylic alcohol should be accessible via an allyl addition using the known

aldehyde **10**[18] and the recently established allyl boronate **11**,[4d,e] a reagent stabilized through the auxiliary.[19] Indeed, the NMR analysis of intermediate[4d] boric ester **12** showed only one diastereomer. The resulting *Z*-configured homoallylic alcohol, which was isolated after hydrolysis on silica gel (during column chromatography), manifested the assumption: The enantiomeric excess – as determined by GLC – was 98%, the intermediate (not shown) was isolated in 89% yield. It should be noted that the corresponding enantiomer could be obtained from the diastereomeric boron reagent in 96% yield (95% ee). Deprotection of the TMS group using tetrabutylammonium fluoride (TBAF) furnished the required *R*-configured propargylic alcohol **7** (99%).

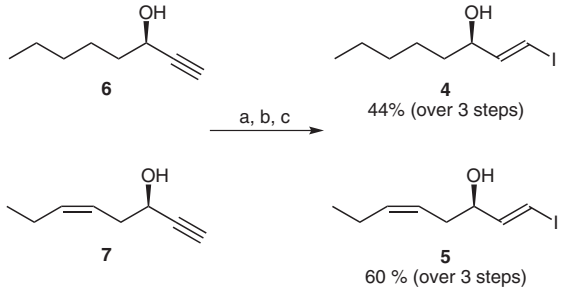


Scheme 3 Synthesis of propargylic alcohol **7**. *Reagents and conditions*: (a) allyl addition: boronate **11**, CH_2Cl_2, 0 °C → r.t.; (b) chromatography on SiO_2 (89%); (c) TBAF·$3H_2O$, THF, r.t. (99%).

For the following three-step sequence towards the final coupling partners **4** and **5** an established route was used (Scheme 4): Silyl protection of the propargylic alcohols **6** and **7** with TBSCl (TBS: *tert*-butyldimethylsilyl) yielded the corresponding ethers in 87% and 88%, respectively. Hydrozirconation with the Schwartz reagent was followed by quenching the intermediate with a solution of iodine in dichloromethane (yield: 70% and 79%). The final deprotection with TBAF in THF lead to the first coupling partners **4** (73%) and **5** (86%). Attempts to omit the protection-deprotection steps by a direct transformation of alcohols **6** and **7** to yield the iodides **4** and **5** failed,[20] because a number of side-products prevented the isolation of the pure target compounds. Concluding the first part, the acyclic side chains could be successfully synthesized: The overall yield for iodide **4** was 32% starting from ketone **9** (4 steps) and 35% (5 steps) when starting from allyl boronate **11**.

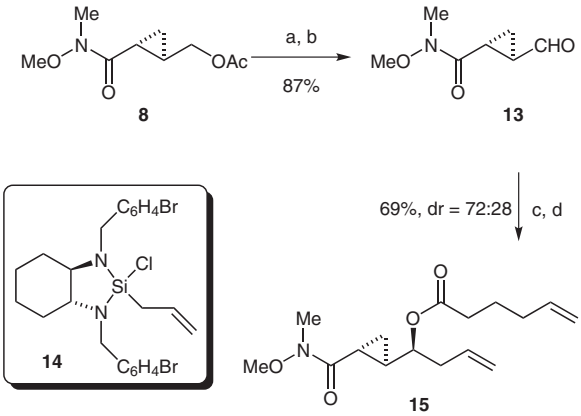
Syntheses of Natural Products

Next we focused on the synthesis of the cyclopropyl lactone moiety **3**. As previously reported,[3b] the enantiomerically pure cyclopropane **8** was obtained via a reliable



Scheme 4 Preparation of vinyl iodide **4** and **5**. *Reagents and conditions*: (a) imidazole, TBSCl, THF, r.t.; (b) *i*. $Cp_2Zr(H)Cl$, CH_2Cl_2, r.t., *ii*. I_2, r.t.; (c) TBAF·$3H_2O$, THF, 0 °C → r.t.

chemoenzymatic route starting from cinnamyl alcohol (58% yield over 5 steps). After deprotection under basic conditions (Schemes 5, 96%) the resulting alcohol was oxidized with Dess–Martin periodinane (DMP)[21] furnishing aldehyde **13**[4b] (91%). The next stereogenic unit was formed by an allyl addition with Leighton's reagent **14**:[22] The homoallylic alcohols (73%, dr 72:28) could be separated by chromatography. It should be noted that the obtained low *anti*-selectivity can be explained by a mismatched interaction while the enantiomeric Leighton's reagent *ent*-**14** – used for the synthesis of the solandelactones A–H[4b] – gave almost exclusively the *syn* diastereoisomer. Similar to the synthesis of constanolactones A–D[3a,4a] we envisaged an acylation/ring-closing metathesis sequence to finally synthesize the lactone. After esterification of the homoallylic alcohol with hex-5-enoic acid, we obtained the required diene **15** (94%).

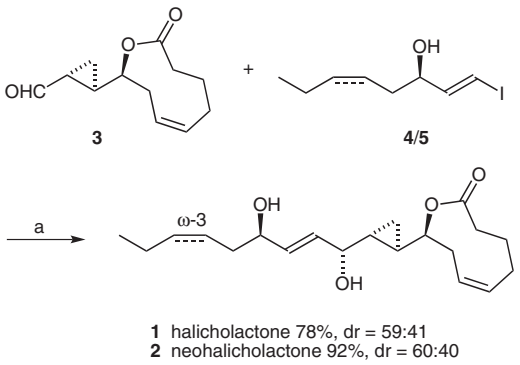


Scheme 5 Synthesis of diene **15**. *Reagents and conditions*: (a) MeOH, K_2CO_3, r.t.; (b) DMP, CH_2Cl_2, 4 h, r.t.; (c) Leighton's reagent (**14**), CH_2Cl_2, 96 h, –12 °C; (d) hex-5-enoic acid, EDC·HCl, DMAP, CH_2Cl_2, 20 h, r.t.

While the ring-closing metathesis was successfully applied for related substrates,[12] we observed difficulties when applying standard catalysts for the synthesis of eight- or nine-membered lactones:[4b] For this reason six catalysts **A**–**F** (Figure 3) were tested using the same diene concentration, albeit in different refluxing solvents (Table 2, entries 1–8). While in many cases the transformation was incomplete and resulted in considerable for-

mation of oligomers, in our hands the best result was achieved with the Neolyst M1 catalyst[23] **C** in toluene at higher temperature (entry 8, yield of lactone **16**: 61%). Only minor amounts of oligomers were detected. Chemoselective reduction of amide **16** with diisobutylaluminum hydride (DIBAL-H) yielded 75% of the desired aldehyde **3**. Starting material **16** was recovered (17%), since the reaction needed to be quenched before the lactone is reduced. The synthesis of the cyclopropyl lactone **3** was achieved in 11 steps starting from cinnamyl alcohol.

The final chromium(II)-mediated Nozaki–Hiyama–Kishi coupling proceeded smoothly for both natural products affording halicholactone (**1**) (78%, dr 59:41) and neohalicholactone (**2**) (92%, dr 60:40) (Scheme 6). The diastereoisomers could be successfully separated by preparative HPLC.



Scheme 6 Synthesis of halicholactone (**1**) and neohalicholactone (**2**). *Reagents and conditions:* (a) $NiCl_2$, $CrCl_2$, DMSO, r.t., 3 d.

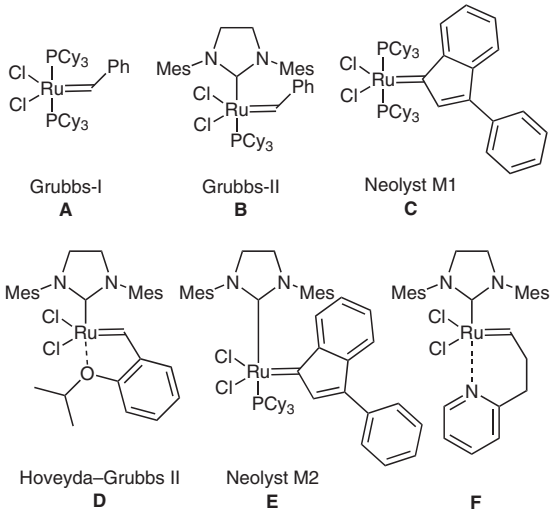
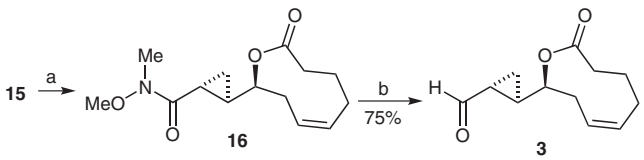


Figure 3 Catalysts used in the synthesis of aldehyde **3**

Table 2 Synthesis of Aldehyde **3**[a]



Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%) of **16**
1	**A**	CH_2Cl_2	37	12	37[b,c]
2	**B**	CH_2Cl_2	37	18	16[c]
3	**F**	CH_2Cl_2	37	30	–[b]
4	**D**	CH_2Cl_2	37	48	–[b,c]
5	**E**	CH_2Cl_2	37	24	52[b,c]
6	**C**	CH_2Cl_2	37	3	58[b,c]
7	**E**	toluene	105	18	44[c]
8	**C**	toluene	105	24	61[c]

[a] Reaction conditions: (a) catalyst **A**–**F**, solvent, temperature, $Ti(O\textit{i}\text{-}Pr)_4$; (b) DIBAL-H, THF, 1 h, –78 °C, 75% (92% brsm).
[b] Side-product: starting material.
[c] Side-product: oligomer.

Conclusion

In summary, with our convergent strategy for oxylipin syntheses we added to the already published approaches towards constanolactones A–D[3a,4a] and solandelactones A–H,[4b] two more completed syntheses. Halicholactone (**1**) and neohalicholactone (**2**) were synthesized from cinnamyl alcohol in 12 steps with an overall yield of 13% (dr 59:41) and 16% yield (dr 60:40), respectively. En route the enzymatic reduction towards propargylic alcohol (*R*)-**6** was established as well as a first application of boron reagent **11** in total synthesis given, thus demonstrating the potential for providing *Z*-homoallyl alcohols (such as the neohalicholactone intermediate **7**) in high selectivity.

Unless specified, the reactions were carried out by using standard Schlenk techniques under dry Ar/N_2 with magnetic stirring. Glassware was oven-dried overnight at 120 °C. Solvents were dried and purified by conventional methods or by a Solvent Purification System (MBRAUN). Common solvents for chromatography (petroleum ether, EtOAc) were distilled prior to use; petroleum ether (PE) refers to the fraction with a boiling point between 4060 °C. Column chromatography and flash column chromatography were performed on silica gel 60, 0.040–0.063 mm (230–400 mesh). TLC (monitoring the course of the reactions) was performed on precoated plastic sheets (Polygram® SIL G/UV254, Macherey-Nagel) with detection by UV (254 nm) or by coloration with cerium molybdenum solution [phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), concd H_2SO_4 (60 mL), H_2O (940 mL)]. ^1H and ^{13}C NMR spectra were recorded at r.t. in $CDCl_3$ with Bruker Avance DRX 600 spectrometer. Chemical shifts are given in ppm relative to TMS as internal standard [^1H: Me_4Si = 0.00 ppm] or relative to the resonance of the solvent (^{13}C: $CDCl_3$ = 77.0 ppm); coupling constants *J* are given in Hz. Higher order δ and *J* values are not corrected. ^{13}C signals were (re)assigned by means of H–H COSY and HSQC or HMBC spectroscopy. IR spectra were obtained on a PerkinElmer Spectrum One spectrophotometer. MS were recorded on a Finnigan MAT 95 [EI, CI], a Varian MAT 711 (EI), a Finnigan MAT LC-Q (ESI, LC-MS-MS), or a Applied Biosystems/MDS SCIEX 4000 Q TRAP (ESI, LC-MS-MS) spectrometer.

(*R*)-Oct-1-yn-3-ol (6)

Ketone **9** (124 mg, 1.00 mmol, 1.0 equiv) in *i*-PrOH (1.00 mL), NADPH (83.3 mg, 0.06 mmol, 0.06 equiv), and ADH-T-solution (~50% in glycerine, 100 μL, as supplied by Jülich Chiral Solutions, now Codexis) were added to KP_i-buffer (100 mM K_2HPO_4/KH_2PO_4, pH 6, 1 mM $MgCl_2$, 100 mL). The reaction mixture was stirred for 96 h (100% turnover as judged by GC) at r.t. After filtration, the aqueous solution was extracted with MTBE (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvents were removed under reduced pressure. Purification of the crude product by flash column chromatography on silica gel (PE–EtOAc, 90:10) yielded 93 mg (74%) of alcohol (*R*)-**6** as a colorless liquid; R_f = 0.18 (PE–EtOAc, 90:10); $[\alpha]_D^{20}$ +5.3 (*c* = 1.00, $CHCl_3$), 99% ee (*R*-enantiomer), as determined by GLC [Lipodex G, H_2 (0.6 bar), 150 °C iso: t_R = 13.50 min; *S*-enantiomer: t_R = 13.33 min].

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.89 (t, ^3J = 6.8 Hz, 3 H, 8-H), 1.26–1.32 (m, 4 H, 6-H and 7-H), 1.56–1.65 (m, 2 H, 5-H), 1.72 (m_c, 2 H, 4-H), 2.00 (br, 1 H, OH), 2.45 (d, ^4J = 2.1 Hz, 1 H, 1-H), 4.40 (dt, ^4J = 2.1 Hz, ^3J = 6.6 Hz, 1 H, 3-H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 13.9 (C-8), 22.5 (C-5), 24.7 (C-7), 31.4 (C-6), 37.6 (C-4), 62.4 (C-3), 72.8 (C-1), 85.0 (C-2).

The analytical and spectral data were in full agreement with those previously reported.[24]

(*R*)-*tert*-Butyldimethyl(oct-1-yn-3-yloxy)silane

To a stirred solution of (*R*)-oct-1-yn-3-ol (**6**; 950 mg, 7.53 mmol, 1.0 equiv) in anhyd CH_2Cl_2 (17 mL) was added imidazole (923 mg, 13.6 mmol, 1.8 equiv), followed by TBSCl (1.35 g, 8.96 mmol, 1.19 equiv) and the stirring was continued overnight at r.t. After hydrolysis with H_2O (10 mL), the layers were separated and the aqueous layer was extracted with *n*-pentane (3 × 50 mL). The combined organic layers were washed with H_2O (2 × 50 mL), dried ($MgSO_4$), filtered, and the solvents were removed under reduced pressure. The crude product was subjected to flash column chromatography (SiO_2; eluent: *n*-pentane–Et_2O, 98:2). The product was obtained as a colorless liquid (1.57 g, 87%); R_f = 0.32 (*n*-pentane); $[\alpha]_D^{20}$ +47.3 (*c* = 1.30, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.11, 0.14 [2 s, 6 H, $Si(CH_3)_2$], 0.89 (t, ^3J = 7.2 Hz, 3 H, 8-H), 0.90 [s, 9 H, $SiC(CH_3)_3$], 1.26–1.34 (m, 4 H, 6-H, 7-H), 1.38–1.47 (m, 2 H, 5-H), 1.62–1.71 (m, ^3J = 6.5 Hz, 2 H, 4-H), 2.37 (d, ^3J = 2.1 Hz, 1 H, 1-H), 4.33 (td, ^3J = 6.5 Hz, ^4J = 2.1 Hz, 1 H, 3-H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = –5.1, –4.6 (CH_3), 14.0 (C-8), 18.2 [*C*$(CH_3)_3$], 22.6 (C-6), 24.8 (C-5), 25.7 [C(*C*$H_3)_3$], 31.4 (C-7), 38.6 (C-4), 62.8 (C-3), 71.8 (C-1), 85.8 (C-2).

The analytical and spectral data were in full agreement with those previously reported.[25,26]

(*R*,*E*)-*tert*-Butyl(1-iodooct-1-en-3-yloxy)dimethylsilane

The Schwartz reagent (3.10 g, 12.0 mmol, 2.2 equiv) in anhyd CH_2Cl_2 (24 mL) was placed in a 250 mL Schlenk flask under dry N_2. A solution of (*R*)-*tert*-butyldimethyl(oct-1-yn-3-yloxy)silane (1.31 g, 5.45 mmol, 1.0 equiv) in anhyd CH_2Cl_2 (34 mL) was added and the mixture stirred for 15 min at r.t. The mixture was cooled with an ice bath and then a solution of I_2 (1.52 g, 5.99 mmol, 1.1 equiv) in CH_2Cl_2 (34 mL) was added. The mixture was allowed to warm to r.t. and stirring was continued for 15 min. The reaction was quenched by pouring it into 10% aq $Na_2S_2O_3$ (150 mL). The resulting white precipitate was filtered. The organic layer was separated and the aqueous layer was extracted with *n*-pentane (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered, and the solvents were removed under reduced pressure. The crude product was subjected to flash column chromatography (SiO_2; eluent: *n*-pentane) to give a yellow liquid (1.35 g, 70%); R_f = 0.63 (*n*-pentane); $[\alpha]_D^{20}$ +33.9 (*c* = 0.83, $CHCl_3$).

IR (film): 2955, 2929, 2857, 1607, 1463, 1361, 1254, 1203, 1164, 1118, 1086, 1005, 942, 919, 834, 810, 789, 698 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.03, 0.04 [2 s, 6 H, $Si(CH_3)_2$], 0.88 (t, ^3J = 7.3 Hz, 3 H, 8-H), 0.89 [s, 9 H, $SiC(CH_3)_3$], 1.22–1.36 (m, 6 H, 5-H, 6-H, 7-H), 1.41–1.50 (m, 2 H, 4-H), 4.07 (tdd, ^3J = 6.1 Hz, ^3J = 6.0 Hz, ^4J = 1.3 Hz, 1 H, 3-H), 6.19 (dd, ^3J = 14.4 Hz, ^4J = 1.3 Hz, 1 H, 1-H), 6.52 (dd, ^3J = 14.4 Hz, ^3J = 6.0 Hz, 1 H, 2-H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = –4.9, –4.5 (CH_3), 14.0 (C-8), 18.2 [*C*$(CH_3)_3$], 22.6 (C-6), 24.6 (C-5), 25.8 [C(*C*$H_3)_3$], 31.8 (C-7), 37.5 (C-4), 75.2 (C-3), 75.4 (C-1), 149.4 (C-2).

MS (EI, 70 eV): *m*/*z* (%) = 367 (<1, $[(M - H)^+]$), 311 (100, $[(M - C_4H_9)^+]$), 297 (26, $[(M - C_5H_{11})^+]$).

Anal. Calcd for $C_{14}H_{29}IOSi$ (368.37): C, 45.65; H, 7.94. Found: C, 45.50; H, 7.93.

The analytical and spectral data were in full agreement with those previously reported.[26,27]

(*R*,*E*)-1-Iodooct-1-en-3-ol (4)

(*R*,*E*)-*tert*-Butyl(1-iodooct-1-en-3-yloxy)dimethylsilane (270 mg, 762 μmol, 1.0 equiv) in anhyd THF (8 mL) was cooled to 0 °C and solid TBAF·3H_2O (268 mg, 848 μmol, 1.1 equiv) was added. The mixture was warmed to r.t. and stirred for 3 h; TLC indicated the complete conversion of the starting material. After hydrolysis with H_2O (4 mL), the aqueous layer was separated and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with H_2O (2 × 20 mL), dried ($MgSO_4$), and filtered. The solvents were removed under reduced pressure and the crude product subjected to flash column chromatography (SiO_2; eluent: CH_2Cl_2). Product **4** (141 μg, 73%) was obtained as a colorless liquid; R_f = 0.53 (CH_2Cl_2); $[\alpha]_D^{24}$ –7.5 (*c* = 0.59, MeOH).

IR (film): 3333 (OH), 2955, 2928, 2858, 1607, 1465, 1378, 1269, 1169, 1126, 1052, 1023, 941, 777, 725, 673 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.89 (t, ^3J = 7.1 Hz, 3 H, 8-H), 1.14–1.33 (m, 6 H, 5-H, 6-H, 7-H), 1.38–1.46 (m, 2 H, 4-H), 1.49 (d, ^3J = 4.4 Hz, 1 H, OH), 4.00 (dddd, ^3J = 11.9 Hz, ^3J = 6.3 Hz, ^3J = 4.4 Hz, ^3J = 1.2 Hz, 1 H, 3-H), 6.25 (dd, ^3J = 14.4 Hz, ^4J = 1.2 Hz, 1 H, 1-H), 6.58 (dd, ^3J = 14.4 Hz, ^3J = 6.3 Hz, 1 H, 2-H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 14.0 (C-8), 22.6 (C-6), 24.8 (C-5), 31.7 (C-7), 36.6 (C-4), 74.8 (C-3), 77.1 (C-1), 148.7 (C-2).

MS (EI, 70 eV): *m*/*z* (%) = 254 (<1, $[M^+]$), 236 (4, $[M - H_2O^+]$), 183 (100, $[(M - C_5H_{11})^+]$).

The analytical and spectral data were in full agreement with those previously reported.[28,29]

(*R*,*Z*)-1-Trimethylsilyloct-5-en-1-yn-3-ol

Allylboronic ester **11**[4d,e] (515 mg, 970 μmol, 1.0 equiv) was dissolved in anhyd (0.5 mL) CH_2Cl_2 (0.5 mL/mmol allyl boronic ester **11**) and cooled to 0 °C. Freshly prepared 3-(trimethylsilyl)propiolaldehyde (**10**;[18] 150 mg, 1.16 mmol, 1.2 equiv) was slowly added to the stirred solution. The cooling bath was removed and the reaction mixture warmed to r.t. Complete conversion of the starting material – as judged by TLC – was detected after 3 d. The solvent was evaporated and the crude product evaluated by NMR spectroscopy and purified by flash column chromatography (SiO_2; eluent: PE–EtOAc, 98:2). The product was obtained as a colorless liquid (170 mg, 89%); R_f = 0.39 (PE–EtOAc, 85:15); $[\alpha]_D^{20}$ +4.2 (*c* = 0.15, $CHCl_3$); 98% ee, as determined by GLC [Hydrodex-β-TBDAc, H_2 (0.6 bar), 150 °C iso, t_R = 77.6 min].

IR (film): 3341 (OH), 2963, 1472, 1407, 1334, 1250, 1124, 1042, 959, 886, 842, 759, 699 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.17 [s, 9 H, $Si(CH_3)_3$], 0.98 (t, ^3J = 7.5 Hz, 3 H, 8-H), 1.85 (d, ^3J = 6.0 Hz, 1 H, OH), 2.09 (qdd, ^3J = 7.5 Hz, ^3J = 7.5 Hz, ^4J = 1.6 Hz, 2 H, 7-H), 2.48 (m_c, 2 H, 4-H), 4.38 (q, ^3J = 6.0 Hz, 1 H, 3-H), 5.43 (dtt, ^3J = 10.6 Hz, ^3J = 7.5 Hz, ^4J = 1.6 Hz, 1 H, 5-H), 5.63 (dtt, ^3J = 10.6 Hz, ^3J = 7.5 Hz, ^4J = 1.6 Hz, 1 H, 6-H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 0.1 [$Si(CH_3)_3$], 14.4 (C-8), 20.9 (C-7), 35.7 (C-4), 62.5 (C-3), 89.6 (C-1 or C-2), 106.4 (C-1 or C-2), 122.9 (C-5), 136.0 (C-6).

MS (EI, 70 eV): *m*/*z* (%) = 195 (<1, [(M – H)$^+$]), 181 (11, [(M – CH_3)$^+$]), 127 (61, [(M – C_5H_9)$^+$]), 99 (100, [($C_6H_{11}O$)$^+$]).

Anal. Calcd for $C_{11}H_{20}OSi$ (196.36): C, 67.28; H, 10.27. Found: C, 67.07; H, 10.20.

(*R*,*Z*)-Oct-5-en-1-yn-3-ol (7)

TBAF·3H_2O (2.24 g, 7.1 mmol, 1.5 equiv) in anhyd THF (12 mL) was placed in a 100 mL Schlenk flask. A solution of (*R*,*Z*)-1-trimethylsilyloct-5-en-1-yn-3-ol (928 mg, 4.72 mmol, 1.0 equiv) in anhyd THF (19 mL) was slowly added. Stirring was continued for 1 h until the desilylation was complete (as judged by TLC). After hydrolysis with brine (50 mL), the aqueous layer was extracted with Et_2O (3 × 60 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvents were removed under reduced pressure. The crude propargylic alcohol was subjected to flash column chromatography (SiO_2; eluent: *n*-pentane-Et_2O, 95:5). The product **7** (582 mg, 99%) was obtained as a colorless liquid; R_f = 0.34 (PE–EtOAc, 85:15); $[\alpha]_D^{20}$ +33.6 (*c* = 0.25, $CHCl_3$).

IR (film): 3298 (OH), 3014, 2964, 2934, 2876, 1457, 1304, 1123, 1037, 955, 867, 793, 628 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.98 (t, ^3J = 7.5 Hz, 3 H, 8-H), 1.93 (d, ^3J = 6.1 Hz, 1 H, OH), 2.10 (qdd, ^3J = 7.5 Hz, ^3J = 7.3 Hz, ^4J = 1.7 Hz, 2 H, 7-H), 2.47 (d, ^4J = 2.1 Hz, 1 H, 1-H), 2.46–2.54 (m, 2 H, 4-H), 4.40 (dddd, ^3J = 6.2 Hz, ^3J = 6.2 Hz, ^3J = 6.1 Hz, ^4J = 2.1 Hz, 1 H, 3-H), 5.45 (dddt, ^3J = 10.6 Hz, ^3J = 7.4 Hz, ^3J = 7.4 Hz, ^4J = 1.7 Hz, 1 H, 5-H), 5.64 (dddt, ^3J = 10.6 Hz, ^3J = 7.3 Hz, ^3J = 7.3 Hz, ^4J = 1.7 Hz, 1 H, 6-H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 14.2 (C-8), 20.8 (C-7), 35.4 (C-4), 61.8 (C-3), 73.0 (C-2), 84.5 (C-1), 122.3 (C-5), 136.2 (C-6).

MS (EI, 70 eV): *m*/*z* (%) = 123 [3, (M – H)$^+$], 109 (29, [(M – CH_3)$^+$]), 95 (49, [(M – C_2H_5)$^+$]).

The analytical and spectral data were in full agreement with those previously reported.[30,31]

(*R*,*Z*)-*tert*-Butyl(oct-5-en-1-yn-3-yloxy)dimethylsilane

To a stirred solution of **7** (585 mg, 4.71 mmol, 1.0 equiv) in anhyd CH_2Cl_2 (11 mL) were added imidazole (578 mg, 8.49 mmol, 1.8 equiv) and TBSCl (847 mg, 5.62 mmol, 1.19 equiv) and the mixture was stirred overnight. After hydrolysis with H_2O (10 mL), the layers were separated, and the aqueous layer was extracted with *n*-pentane (3 × 50 mL). The combined organic layers were washed with H_2O (2 × 50 mL), dried ($MgSO_4$), filtered, and the solvents were removed under reduced pressure. The crude product was subjected to flash column chromatography (SiO_2; eluent: *n*-pentane–Et_2O, 99:1). The pure product (992 mg, 88%) was obtained as a colorless liquid; R_f = 0.53 (*n*-pentane–Et_2O, 99:1); $[\alpha]_D^{20}$ +34.0 (*c* = 0.07, $CHCl_3$).

IR (film): 3312, 2959, 2931, 2858, 1473, 1464, 1390, 1362, 1342, 1252, 1086, 1006, 939, 874, 835, 786 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.11, 0.13 [2 s, 6 H, $Si(CH_3)_2$], 0.91 [s, 9 H, $SiC(CH_3)_3$], 0.97 (t, ^3J = 7.5 Hz, 3 H, 8-H), 2.07 (qd, ^3J = 7.5 Hz, ^3J = 7.5 Hz, 2 H, 7-H), 2.39 (d, ^4J = 2.1 Hz, 1 H, 1-H), 2.45 (dd, ^3J = 7.0 Hz, ^3J = 7.0 Hz, 2 H, 4-H), 4.34 (td, ^3J = 7.0 Hz, ^4J = 2.1 Hz, 1 H, 3-H), 5.41 (m_c, 1 H, 5-H), 5.53 (m_c, 1 H, 6-H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = –5.0, –4.6 (CH_3), 14.2 (C-8), 18.3 [$C(CH_3)_3$], 20.8 (C-7), 25.7 [$C(CH_3)_3$], 36.5 (C-4), 62.8 (C-3), 72.1 (C-1), 85.4 (C-2), 123.6 (C-5), 134.5 (C-6).

MS (EI, 70 eV): *m*/*z* (%) = 238 (<1%, M$^+$), 223 (4, [(M – CH_3)$^+$]), 209 (3), 181 (52), 169 (53), 153 (10), 139 (10), 115 (8), 113 (49), 107 (9), 99 (9), 91 (7), 83 (38).

Anal. Calcd for $C_{14}H_{26}OSi$ (238.44): C, 70.52; H, 10.99. Found: C, 69.03; H, 10.85.

The analytical and spectral data were in full agreement with those previously reported.[30]

(*R*,1*E*,5*Z*)-*tert*-Butyl[1-iodoocta-1,5-dien-3-yloxy]dimethylsilane

The Schwartz reagent (744 mg, 2.89 mmol, 2.2 equiv) in anhyd CH_2Cl_2 (6 mL) was placed in a 50 mL Schlenk flask under dry N_2. A solution of (*R*,*Z*)-*tert*-butyl(oct-5-en-1-yn-3-yloxy)dimethylsilane (313 mg, 1.31 mmol, 1.0 equiv) in anhyd CH_2Cl_2 (8 mL) was added and stirred for 20 min at r.t. The mixture was cooled with an ice bath and then a solution of I_2 (366 mg, 1.44 mmol, 1.1 equiv) in CH_2Cl_2 (8 mL) was added. The mixture was allowed to warm to r.t. and stirring was continued for 1 h. The reaction was quenched by pouring the mixture into 10% aq $Na_2S_2O_3$ (150 mL). The resulting white precipitate was filtered. The organic layer was separated and the aqueous layer was extracted with *n*-pentane (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered, and the solvents were removed under reduced pressure. The crude product was subjected to flash column chromatography (SiO_2; eluent: *n*-pentane). The pure vinyl iodide product was obtained as a yellow liquid (382 mg, 79%), which was directly used in the next step; R_f = 0.49 (*n*-pentane); $[\alpha]_D^{20}$ +12.3 (*c* = 0.20, $CHCl_3$).

IR (film): 2957, 2930, 2857, 1607, 1472, 1463, 1405, 1389, 1361, 1253, 1212, 1163, 1086, 1006, 941, 894, 832, 811, 785 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.04, 0.05 [2 s, 6 H, $Si(CH_3)_2$], 0.89 [s, 9 H, $SiC(CH_3)_3$], 0.96 (t, ^3J = 7.5 Hz, 3 H, 8-H), 2.03 (m_c, 2 H, 7-H), 2.24 (m_c, 2 H, 4-H), 4.09 (tdd, ^3J = 6.1 Hz, ^3J = 5.8 Hz, ^4J = 1.4 Hz, 1 H, 3-H), 5.31 (dddt, ^3J = 10.6 Hz, ^3J = 7.5 Hz, ^3J = 7.5 Hz, ^4J = 1.6 Hz, 1 H, 5-H), 5.48 (dddt, ^3J = 10.6 Hz, ^3J = 7.3 Hz, ^3J = 7.3 Hz, ^4J = 1.6 Hz, 1 H, 6-H), 6.21 (dd, ^3J = 14.3 Hz, ^4J = 1.4 Hz, 1 H, 1-H), 6.54 (dd, ^3J = 14.3 Hz, ^3J = 5.8 Hz, 1 H, 2-H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = –5.0, –4.5 (CH_3), 14.2 (C-8), 18.4 [$C(CH_3)_3$], 20.8 (C-7), 25.8 [$C(CH_3)_3$], 35.6 (C-4), 73.7 (C-3), 75.3 (C-1), 123.6 (C-5), 134.3 (C-6), 148.7 (C-2).

MS (EI, 70 eV): *m*/*z* (%) = 351 (2, [(M – CH_3)$^+$]), 309 (29, [(M – C_4H_9)$^+$]), 297 (100, [(M – C_5H_9)$^+$]).

(*R*,1*E*,5*Z*)-1-Iodoocta-1,5-dien-3-ol (5)

(*R*,1*E*,5*Z*)-*tert*-Butyl[1-iodoocta-1,5-dien-3-yloxy]dimethylsilane (339 mg, 925 μmol, 1.0 equiv) in anhyd THF (10 mL) was cooled to 0 °C and solid TBAF·3H_2O (328 mg, 1.04 mmol, 1.12 equiv) was added. The mixture was warmed to r.t. and stirred for 2 h; TLC indicated the complete conversion of the starting material. After hydrolysis with H_2O (10 mL), the aqueous layer was separated and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with H_2O (2 × 30 mL), dried ($MgSO_4$), and filtered. The solvents were removed under reduced pressure and the crude product subjected to flash column chromatography (SiO_2; eluent: *n*-pentane–Et_2O, 99:1). Product **5** (200 mg, 86%) was obtained as a yellow slightly impure liquid; R_f = 0.06 (*n*-pentane–Et_2O, 95:5); $[\alpha]_D^{20}$ +16.4 (*c* = 1.2, $CHCl_3$).

IR (film): 3332 (OH), 3011, 2960, 2930, 2856, 1607, 1463, 1254, 1208, 1165, 1038, 944, 863, 837, 774, 706, 669 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.98 (t, ^3J = 7.6 Hz, 3 H, 8-H), 1.72 (br, 1 H, OH), 2.07 (qddd, ^3J = 7.6 Hz, ^3J = 7.6 Hz, ^4J = 1.5 Hz, ^5J = 0.8 Hz, 2 H, 7-H), 2.31 (m_c, 2 H, 4-H), 4.13 (m_c, 1 H, 3-H), 5.33 (dddt, ^3J = 11.1 Hz, ^3J = 7.6 Hz, ^3J = 7.2 Hz, ^4J = 1.5 Hz, 1 H, 5-H), 5.61 (dddt, ^3J = 11.1 Hz, ^3J = 7.6 Hz, ^3J = 7.2 Hz, ^4J = 1.5 Hz, 1 H, 6-H), 6.37 (dd, ^3J = 14.4 Hz, ^4J = 1.5 Hz, 1 H, 1-H), 6.60 (dd, ^3J = 14.4 Hz, ^3J = 5.7 Hz, 1 H, 2-H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 14.2 (C-8), 20.8 (C-7), 34.6 (C-4), 73.9 (C-3), 77.3 (C-1), 122.7 (C-5), 136.2 (C-6), 147.8 (C-2).

MS (EI, 70 eV): *m*/*z* (%) = 234 [4, $(M - H_2O)^+$], 183 (100, $[(M - C_5H_9)^+]$).

(1*R*,2*R*,1′*S*)-2-(1′-Hydroxybut-3-enyl)-*N*-methoxy-*N*-methylcyclopropanecarboxamide

Under dry N_2, the Leighton reagent **14**[21,22] (3.13 g, 5.66 mmol, 2.0 equiv) in CH_2Cl_2 (30 mL) was placed in a 100 mL Schlenk flask and cooled to –12 °C. Aldehyde **13**[4b] (445 mg, 2.83 mmol, 1.0 equiv) in CH_2Cl_2 (8 mL) was slowly added and the temperature was kept constant for 72 h. The mixture was diluted and quenched with EtOAc (10 mL) and aq 1 M HCl (10 mL); stirring was continued for ~10 min at –12 °C and at r.t. until the layers separated. The aqueous layer was extracted with EtOAc (5 × 20 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure. The crude product was subjected to flash column chromatography (SiO_2; eluent: PE–EtOAc, 50:50); to give a colorless oil; yield: 413 mg (73%, dr 96:4, ee >98%). The separation of diastereoisomers was not possible; R_f = 0.22 (PE–EtOAc, 50:50); $[\alpha]_D^{20}$ –27.5 (*c* = 0.70, $CHCl_3$, dr 96:4, ee >98%).

IR (film): 3412 (OH), 3184, 3159, 3075, 3006, 2973, 2936, 2900, 1730 (C=O), 1630, 1558, 1465, 1422, 1386, 1260, 1177, 1149, 1107, 1046, 993, 961, 913, 821, 763, 647 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.85 (ddd, ^3J = 8.4 Hz, ^3J = 6.2 Hz, ^2J = 4.1 Hz, 1 H, 3-H_a), 1.24 (ddd, ^3J = 9.0 Hz, ^3J = 5.0 Hz, ^2J = 4.1 Hz, 1 H, 3-H_b), 1.54 (dddd, ^3J = 9.0 Hz, ^3J = 7.6 Hz, ^3J = 6.2 Hz, ^3J = 4.2 Hz, 1 H, 2-H), 1.64 (br, 1 H, OH), 2.22 (br, 1 H, 1-H), 2.32 (dddt, ^2J = 13.9 Hz, ^3J = 7.8 Hz, ^3J = 7.7 Hz, ^4J = 1.1 Hz, 1 H, 2′-H_a), 2.44 (dddt, ^2J = 13.9 Hz, ^3J = 6.5 Hz, ^3J = 4.5 Hz, ^4J = 1.1 Hz, 1 H, 2′-$_b$), 3.21 (s, 3 H, NCH_3), 3.24 (br ddd, ^3J = 7.7 Hz, ^3J = 7.6 Hz, ^3J = 4.5 Hz, 1 H, 1′-H), 3.79 (s, 3 H, OCH_3), 5.15 (ddt, ^3J = 10.2, ^2J = 2.0, ^4J = 1.1 Hz, 1 H, 4′-H_a), 5.17 (ddt, ^3J = 16.9 Hz, ^2J = 2.0 Hz, ^3J = 1.1 Hz, 1 H, 4′-H_b), 5.86 (dddd, ^3J = 16.9 Hz, ^3J = 10.2 Hz, ^3J = 7.8 Hz, ^3J = 6.5 Hz, 1 H, 3′-H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 12.0 (C-3), 15.2 (C-1), 27.7 (C-2), 32.5 (NCH_3), 41.8 (C-2′), 61.6 (OCH_3), 72.9 (C-1′), 118.5 (C-4′), 134.2 (C-3′), 171.8 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 199 (5, $[M^+]$), 158 (50, $[M - C_3H_5^+]$), 139 (85, $[M - C_2H_6NO^+]$).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{10}H_{17}NO_3$: 199.1208; found: 199.1208.

Ester 15

To a stirred solution of (1*R*,2*R*,1′*S*)-2-(1′-hydroxybut-3-enyl)-*N*-methoxy-*N*-methylcyclopropanecarboxamide (404 mg, 2.03 mmol, 1.0 equiv) in anhyd CH_2Cl_2 (31 mL) were added *N*-3-diethylaminopropyl-*N*′-ethylcarbodiimide hydrochloride (EDC-hydrochloride) (572 mg, 2.98 mmol, 1.5 equiv), DMAP (126 mg, 1.10 mmol, 0.5 equiv) and hex-5-enoic acid (364 μL, 3.10 mmol, 1.5 equiv) at 0 °C. The stirring was continued for 20 h at r.t. After hydrolysis with sat. aq NH_4Cl (30 mL), the aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The crude product was subjected to flash column chromatography (SiO_2; eluent: PE–EtOAc, 70:30). The slightly impure product **15** (562 mg, 94%) was obtained as a colorless oil; R_f = 0.63 (PE–EtOAc, 50:50); $[\alpha]_D^{20}$ –49.9 (*c* = 0.7, $CHCl_3$, dr 96:4, ee >98%).

IR (film): 3079, 2977, 2939, 1731 (C=O), 1658 (C=O), 1462, 1423, 1385, 1226, 1245, 1174, 1107, 1049, 990, 916 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.82 (ddd, ^3J = 8.5 Hz, ^3J = 6.0 Hz, ^2J = 4.2 Hz, 1 H, 3″-H_a), 1.24 (ddd, ^3J = 9.0 Hz, ^3J = 5.0 Hz, ^2J = 4.2 Hz, 1 H, 3″-H_b), 1.64 (dddd, ^3J = 9.0 Hz, ^3J = 8.9 Hz, ^3J = 6.0 Hz, ^3J = 4.1 Hz, 1 H, 1″-H), 1.65–1.78 (m, 2 H, 3-H), 2.08 (tddd, ^3J = 7.4 Hz, ^3J = 7.2 Hz, ^4J = 1.3 Hz, ^4J = 1.3 Hz, 1 H, 4-H), 2.29 (br m_c, 3 H, 2″-H, 2-H), 2.42 (ddddd, ^2J = 14.3 Hz, ^3J = 7.2 Hz, ^3J = 7.0 Hz, ^4J = 1.2 Hz, ^4J = 1.2 Hz, 1 H, 2′-H_a), 2.47 (ddddd, ^2J = 14.3 Hz, ^3J = 6.7 Hz, ^3J = 5.5 Hz, ^4J = 1.2 Hz, ^4J = 1.2 Hz, 1 H, 2′-H_b), 3.18 (s, 3 H, NCH_3), 3.71 (s, 3 H, OCH_3), 4.47 (ddd, ^3J = 8.9 Hz, ^3J = 7.0 Hz, ^3J = 5.5 Hz, 1 H, 1′-H), 4.99 (ddt, ^3J = 10.2 Hz, ^2J = 2.0 Hz, ^4J = 1.3 Hz, 1 H, 6-H_a), 5.02 (ddt, ^3J = 17.1 Hz, ^2J = 2.0 Hz, ^4J = 1.3 Hz, 1 H, 6-H_b), 5.07 (dddd, ^3J = 10.2 Hz, ^2J = 2.1 Hz, ^4J = 1.2 Hz, ^4J = 1.2 Hz, 1 H, 4-H_a), 5.11 (dddd, ^3J = 17.1 Hz, ^2J = 2.1 Hz, ^4J = 1.2 Hz, ^4J = 1.2 Hz, 1 H, 4-H_b), 5.73–5.81 (m, 2 H, 3′-H, 5-H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 12.7 (C-3″), 16.1 (C-2″), 24.2 (C-3), 25.3 (C-1″), 32.5 (NCH_3), 33.0 (C-4), 33.8 (C-2), 39.0 (C-2'), 61.6 (OCH_3), 74.3 (C-1′), 115.4 (C-6), 118.0 (C-4), 133.2 (C-5), 137.7 (C-3), 173.0 (NCO), 173.1 (C-1).

MS (EI, 70 eV): *m*/*z* (%) = 295 (<5, $[M^+]$), 254 (<5, $[M - C_3H_5^+]$).

Conversion of Ester 15 to (1*R*,2*R*,2′*S*,*Z*)-*N*-Methoxy-*N*-methyl-2-(9′-oxo-2′,3′,6′,7′,8′,9′-hexahydrooxonin-2′-yl)cyclopropanecarboxamide (16) by Ring-Closing Metathesis; General Procedure (Table 2, Entries 1–8)

Under an atmosphere of dry argon, in an oven-dried 2 L-three-neck flask, diene **15** (1.0 equiv) was dissolved in the desired anhyd solvent and Ti(O*i*-Pr)$_4$ (0.3 equiv) was added. The mixture was refluxed for 1 h. Then the catalyst was dissolved in of the same solvent (ca. 2 mL) and added to the reaction mixture. The mixture was stirred at a higher temperature (see Table 2). TLC indicated complete conversion of the starting material. The solvent was removed under reduced pressure (the bath temperature should not exceed 30 °C) until about 1 mL volume was left. The crude product was purified by flash column chromatography (SiO_2, eluent: PE–EtOAc, 70:30). For exact conditions and yield, see Table 2. The product **16** was obtained as a colorless oil; R_f = 0.46 (PE–EtOAc, 50:50); $[\alpha]_D^{20}$ –136 (*c* = 0.90, $CHCl_3$, dr 91:9).

IR (film): 3010, 2941, 2864, 1737 (C=O), 1653 (C=O), 1449, 1426, 1385, 1353, 1331, 1258, 1224, 1209, 1177, 1134, 1111, 1087, 1051, 1015, 985, 964, 917, 899, 876, 861, 840, 790, 767, 730 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.89 (ddd, ^3J = 8.5 Hz, ^3J = 6.0 Hz, ^2J = 4.2 Hz, 1 H, 3-H_a), 1.29 (ddd, ^3J = 8.9 Hz, ^3J = 5.0 Hz, ^2J = 4.2 Hz, 1 H, 3-H_b), 1.70 (dddd, ^3J = 8.9 Hz, ^3J = 8.8 Hz, ^3J = 6.0 Hz, ^3J = 4.1 Hz, 1 H, 2-H), 1.78 (m_c, 1 H, 7-H_a), 2.04–2.10 (m, 2 H, 7-H_b, 8′-H_a), 2.19–2.33 (m, 2 H, 6′-H), 2.20 (ddd, ^2J = 13.7 Hz, ^3J = 7.4 Hz, ^3J = 1.6 Hz, 1 H, 3′-H_a), 2.26 (br, 1 H, 1-H), 2.47–2.56 (m, 1 H, 8-H_b), 2.54 (dddd, ^2J = 13.7 Hz, ^3J = 10.6 Hz, ^3J = 7.2 Hz, ^5J = 0.9 Hz, 1 H, 3′-H_b), 3.21 (s, 3 H, NCH_3), 3.72 (s, 3 H, OCH_3), 4.25 (ddd, ^3J = 10.6 Hz, ^3J = 8.8 Hz, ^3J = 1.6 Hz, 1 H, 2′-H), 5.45–5.51 (m, 2 H, 4′-H, 5′-H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 12.7 (C-3), 16.1 (C-1), 25.0 (C-2), 25.3 (C-8′), 26.4 (C-7′), 32.5 (NCH_3), 33.5 (C-6′), 33.8 (C-3′), 61.5 (OCH_3), 75.8 (C-2′), 124.5 (C-4), 134.9 (C-5), 173.7 (N*C*O), 174.0 (C-8′).

MS (EI, 70 eV): *m*/*z* (%) = 268 (53, $(M + H)^+$]), 250 (24, $[(M - OH)^+]$).

HRMS (ESI, positive ion): *m*/*z* calcd for $C_{14}H_{21}NO_4$: 268.1543; found: 268.1534.

(1*R*,2*R*,2′*S*,*Z*)-2-[9′-Oxo-2′,3′,6′,7′,8′,9′-hexahydrooxonin-2′-yl)cyclopropanecarbaldehyde (3)

Under an atmosphere of dry argon, in a Schlenk flask Weinreb amide **16** (36 mg, 135 μmol, 1.0 equiv) was dissolved in anhyd THF (225 μL, *c* = 0.6) and cooled to –78 °C. A solution of DIBAL-H (135 μL, 135 μmol, 1 M solution in hexane) was slowly added and stirring was continued for an additional 50 min at this temperature. The reaction mixture was hydrolyzed with two drops of H_2O, one drop of aq NaOH (15%), and two drops of H_2O. The two phase mixture was warmed to r.t. and directly subjected to flash column chromatography (SiO_2; eluent: PE–EtOAc, 70:30). First the aldehyde **3** (21 mg, 75%) was eluted, and then the Weinreb amide **16** was recovered (7 mg, 17%). The product **3** was obtained as a colorless oil; R_f = 0.69 (PE–EtOAc, 50:50); $[\alpha]_D^{20}$ –240 (*c* = 0.5, $CHCl_3$, ee >98%, dr 91:9).

IR (film): 3011, 2948, 2858, 2733, 1737 (C=O), 1708 (C=O), 1449, 1353, 1259, 1224, 1208, 1167, 1134, 1088, 1058, 1015, 985, 938, 882, 855, 728 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.12 (ddd, ^3J = 8.4 Hz, ^3J = 6.4 Hz, ^2J = 4.9 Hz, 1 H, 3-H_a), 1.38 (ddd, ^3J = 9.0 Hz, ^3J = 4.9 Hz, ^2J = 4.9 Hz, 1 H, 3-H_b), 1.74–1.79 (m, 1 H, 7′-H_a), 1.80 (dddd, ^3J = 9.0 Hz, ^3J = 7.9 Hz, ^3J = 6.4 Hz, ^3J = 4.0 Hz, 1 H, 2-H), 2.02 (dddd, ^3J = 8.4 Hz, ^3J = 4.9 Hz, ^3J = 4.6 Hz, ^3J = 4.0 Hz, 1 H, 1-H), 2.04–2.11 (m, 2 H, 7′−H_b, 6′-H_a), 2.17 (ddd, ^2J = 13.6 Hz, ^3J = 7.3 Hz, ^3J = 1.6 Hz, 1 H, 3′-H_a), 2.24–2.33 (m, 2 H, 8′-H), 2.44–2.53 (m, 1 H, 6′-H_b), 2.52 (dddd, ^2J = 13.6 Hz, ^3J = 10.9 Hz, ^3J = 7.8 Hz, ^4J = 0.8 Hz, 1 H, 3′-H_b), 4.39 (ddd, ^3J = 10.9 Hz, ^3J = 7.9 Hz, ^3J = 1.6 Hz, 1 H, 2′-H), 5.46 (dddd, ^3J = 11.2 Hz, ^3J = 7.8 Hz, ^3J = 7.3 Hz, ^4J = 1.2 Hz, 1 H, 4′-H), 5.46–5.22 (m, 1 H, 5′-H), 9.24 (d, ^3J = 4.6 Hz, 1 H, CHO).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 12.7 (C-3), 25.3 (C-6′), 25.6 (C-2), 26.4 (C-7′), 27.9 (C-1), 33.5 (C-3′), 33.8 (C-8′), 74.1(C-2′), 124.1 (C-4′), 135.1 (C-5′), 173.8 (C-8′), 200.0 (CHO).

MS (EI, 70 eV): *m*/*z* (%) = 208 (47, $[M^+]$), 191 (23, $[(M - OH)^+]$), 110 (100, $[(M - C_5H_6O_2)^+]$).

HRMS (ESI, positive ion): *m*/*z* calcd for $C_{12}H_{16}O_3$: 209.1172; found: 209.1163.

Halicholactone (1)

Freshly prepared aldehyde **3** (27 mg, 130 μmol, 1.0 equiv) and vinyl iodide **4** (100 mg, 389 μmol, 3.0 equiv) in DMSO (7.6 mL) were placed in a 25 mL Schlenk flask and the mixture was degassed three times (at –78 °C/<10^{-2} mbar). $CrCl_2$ (104 mg, 843 μmol, 6.5 equiv) and $NiCl_2$ (4 mg, 33 μmol, 0.25 equiv) were added to the stirred solution under dry argon. After 2 d, no aldehyde **3** was detected by TLC. The mixture was poured into a separating funnel containing sat. aq NH_4Cl (15 mL). The aqueous layer was extracted with EtOAc (5 × 20 mL). The combined organic layers were washed with H_2O (50 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure (the bath temperature should not exceed 25 °C). In cases where traces of DMSO were still present, extraction with EtOAc and washing the organic layer with H_2O were repeated. The crude product was subjected to flash column chromatography (SiO_2; eluent: first PE–EtOAc, 60:40, then PE–EtOAc, 50:50, and pure EtOAc). Halicholactone (**1**) and its C_{12}-epimer were obtained as a mixture (34 mg, 78%, dr 59:41). Separation of the epimers by semi-preparative HPLC [Maxsil, 5 μ Si 250 mm × 4.6 mm; *n*-heptane–*i*-PrOH (90:10), 3 mL/min, 24 bar, t_R = 53.2 min; C_{12}-epimer: t_R = 49.8 min] yielded halicholactone (**1**) (dr 93:7) as a colorless oil; R_f = 0.55 (EtOAc); $[\alpha]_D^{15}$ –79.7 (*c* = 0.75, $CHCl_3$); $[\alpha]_D^{23}$ –79.0 (*c* = 0.75, $CHCl_3$).

IR (film): 3398 (OH), 3008, 2929, 2858, 1738 (C=O), 1714, 1448, 1401, 1354, 1328, 1261, 1224, 1204, 1135, 1085, 1013, 971, 915, 727 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 0.62 (ddd, ^3J = 8.5 Hz, ^3J = 5.1 Hz, ^2J = 5.1 Hz, 1 H, 10-H_a), 0.72 (ddd, ^3J = 8.7 Hz, ^3J = 5.2 Hz, ^2J = 5.1 Hz, 1 H, 10-H_b), 0.89 (t, ^3J = 7.0 Hz, 3 H, 20-H), 1.03 (dddd, ^3J = 8.7 Hz, ^3J = 8.3 Hz, ^3J = 5.1 Hz, ^3J = 4.8 Hz, 1 H, 9-H), 1.10 (dddd, ^3J = 8.5 Hz, ^3J = 7.4 Hz, ^3J = 5.2 Hz, ^3J = 4.8 Hz, 1 H, 11-H), 1.26–1.43 (m, 6 H, 17-H, 18-H, 19-H), 1.48-1.58 (m, 3 H, 16-H_a, 16-H_b, $OH_{C\text{-}15}$), 1.65 (br, 1 H, $OH_{C\text{-}12}$), 1.78 (m_c, 1 H, 3-H_a), 2.03–2.09 (m, 2 H, 3-H_b, 4-H_a), 2.15 (ddd, ^2J = 13.5 Hz, ^3J = 7.2 Hz, ^3J = 1.7 Hz, 1 H, 7-H_a), 2.23–2.32 (m, 2 H, 2-H), 2.44–2.52 (m, 2 H, 4-H_b, 7-H_b), 3.70 (br ddd, ^3J = 7.4 Hz, ^3J = 3.8 Hz, ^3J = 3.7 Hz, 1 H, 12-H), 4.11 (br m_c, 1 H, 15-H), 4.23 (ddd, ^3J = 10.9 Hz, ^3J = 8.3 Hz, ^3J = 1.7 Hz, 1 H, 8-H), 5.44–5.49 (m, 2 H, 5-H, 6-H), 5.75–5.77 (m, 2 H, 13-H, 14-H).

^1H NMR (600 MHz, C_6D_6): δ = 0.34 (ddd, ^3J = 8.5 Hz, ^3J = 5.0 Hz, ^2J = 5.0 Hz, 1 H, 10-H_a), 0.53 (ddd, ^3J = 8.7 Hz, ^3J = 5.2 Hz, ^2J = 5.1 Hz, 1 H, 10-H_b), 0.89 (t, ^3J = 7.1 Hz, 3 H, 20-H), 0.90 (dddd, ^3J = 8.7 Hz, ^3J = 8.4 Hz, ^3J = 5.0 Hz, ^3J = 4.4 Hz, 1 H, 9-H), 1.10 (dddd, ^3J = 8.5 Hz, ^3J = 7.0 Hz, ^3J = 5.2 Hz, ^3J = 4.4 Hz, 1 H, 11-H), 1.21–1.60 (m, 11 H, 3-H_a, 16-H_a, 16-H_b, 17-H, 18-H, 19-H, $OH_{C\text{-}12}$, $OH_{C\text{-}15}$), 1.73–1.89 (m, 2 H, 3-H_b, 4-H_a), 1.92 (ddd, ^2J = 13.4 Hz, ^3J = 7.3 Hz, ^3J = 1.6 Hz, 1 H, 7-H_a), 2.05–2.14 (m, 2 H, 2-H), 2.33–2.39 (m, 2 H, 4-H_b, 7-H_b), 3.60 (m_c, 1 H, 12-H), 3.99–4.02 (br m, 1 H, 15-H), 4.33 (ddd, ^3J = 10.8 Hz, ^3J = 8.4 Hz, ^3J = 1.6 Hz, 1 H, 8-H), 5.34–5.44 (m, 2 H, 5-H, 6-H), 5.71–5.76 (m, 2 H, 13-H, 14-H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 8.3 (C-10), 14.1 (C-20), 19.5 (C-9), 22.6 (C-17 or C-18 or C-19), 23.4 (C-11), 25.1 (C-17 or C-18 or C-19), 25.3 (C-4), 26.5 (C-3), 31.7 (C-17 or C-18 or C-19), 33.6 (C-2), 33.9 (C-7), 37.2 (C-16), 72.3 (C-15), 74.2 (C-12), 76.2 (C-8), 124.7 (C-5 or C-6), 131.6 (C-13 or C-14), 134.6 (C-13 or C-14), 134.7 (C-5 or C-6), 174.1 (C-1).

^{13}C NMR (151 MHz, C_6D_6): δ = 7.9 (C-10), 14.3 (C-20), 19.7 (C-9), 22.6 (C-17 or C-18 or C-19), 23.4 (C-11), 25.6 (C-17 or C-18 or C-19), 25.6 (C-4), 26.6 (C-3), 32.2 (C-17 or C-18 or C-19), 33.7 (C-2), 34.1 (C-7), 37.9 (C-16), 72.2 (C-15), 72.4 (C-12), 76.3 (C-8), 125.0 (C-5 or C-6), 132.1 (C-13 or C-14), 134.1 (C-13 or C-14), 134.7 (C-5 or C-6), 173.2 (C-1).

HRMS (ESI, positive ion): *m*/*z* calcd for $C_{20}H_{32}O_4$ + Na: 359.21928; found: 359.21965.

HRMS (ESI, positive ion): *m*/*z* calcd for $C_{20}H_{31}O_3$: 319.22677; found: 319.22707.

C_{12}-*epi*-Halicholactone

dr 93:7; $[\alpha]_D^{15}$ –73.6 (*c* = 0.55, $CHCl_3$); $[\alpha]_D^{23}$ –73.3 (*c* = 0.55, $CHCl_3$).

^1H NMR (600 MHz, $CDCl_3$): δ = 0.60 (ddd, ^3J = 8.6 Hz, ^3J = 5.2 Hz, ^2J = 5.2 Hz, 1 H, 10-H_a), 0.63 (ddd, ^3J = 8.1 Hz, ^3J = 5.3 Hz, ^2J = 5.2 Hz, 1 H, 10-H_b), 0.89 (t, ^3J = 7.0 Hz, 3 H, 20-H), 1.08 (dddd, ^3J = 8.6 Hz, ^3J = 7.6 Hz, ^3J = 5.3 Hz, ^3J = 4.4 Hz, 1 H, 11-H), 1.11 (dddd, ^3J = 8.3 Hz, ^3J = 8.1 Hz, ^3J = 5.2 Hz, ^3J = 4.4 Hz, 1 H, 9-H), 1.26–1.42 (m, 6 H, 17-H, 18-H, 19-H), 1.47–1.59 (m, 3 H, 16-H_a, 16-H_b, $OH_{C\text{-}15}$), 1.65 (br, 1 H, $OH_{C\text{-}12}$), 1.78 (m_c, 1 H, 3-H_a), 2.03–2.09 (m, 2 H, 3-H_b, 4-H_a), 2.18 (ddd, ^2J = 15.0 Hz, ^3J = 7.3 Hz, ^3J = 1.6 Hz, 1 H, 7-H_a), 2.23–2.26 (m, 1 H, 2-H_a), 2.33 (m_c, 1 H, 2-H_b), 2.47–2.53 (m, 2 H, 4-H_b, 7-H_b), 3.60 (br dd, ^3J = 7.6 Hz, ^3J = 4.4 Hz, 1 H, 12-H), 4.10–4.13 (br m, 1 H, 15-H), 4.19 (ddd, ^3J = 10.8 Hz, ^3J = 8.3 Hz, ^3J = 1.6 Hz, 1 H, 8-H), 5.44–5.50 (m, 2 H, 5-H, 6-H), 5.73–5.74 (m, 2 H, 13-H, 14-H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 7.9 (C-10), 14.0 (C-20), 20.6 (C-9), 22.6 (C-17 or C-18 or C-19), 23.8 (C-11), 25.1 (C-17 or C-18 or C-19), 25.3 (C-4), 26.5 (C-3), 31.7 (C-17 or C-18 or C-19), 33.7 (C-2), 33.9 (C-7), 37.2 (C-16), 72.4 (C-15), 74.7 (C-12), 76.1 (C-8), 124.6 (C-5 or C-6), 131.6 (C-13 or C-14), 134.0 (C-13 or C-14), 134.7 (C-5 or C-6), 174.1 (C-1).

Neohalicholactone (2)

Freshly prepared aldehyde **3** (27 mg, 130 μmol, 1.0 equiv) and vinyl iodide **5** (78 mg, 347 μmol, 2.67 equiv) in DMSO (7.6 mL) were placed in a 25 mL Schlenk flask and the mixture was degassed three times (at –78 °C/<10^{-2} mbar). $CrCl_2$ (104 mg, 843 μmol, 6.5 equiv) and $NiCl_2$ (4 mg, 33 μmol, 0.25 equiv) were added to the stirred solution under dry argon. After 3 d, no aldehyde **3** was detected by TLC. The mixture was poured into a separating funnel containing sat. aq NH_4Cl (15 mL). The aqueous layer was extracted with EtOAc (5 × 20 mL). The combined organic layers were washed with H_2O (50 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure (the bath temperature should not exceed 25 °C). In cases where traces of DMSO were still present, extraction with EtOAc and washing the organic layer with H_2O were repeated. The crude product was subjected to flash column chromatography (SiO_2; eluent: first PE–EtOAc, 60:40, then PE–EtOAc, 50:50, and pure EtOAc). Neohalicholactone (**2**) and its C_{12}-epimer was obtained as a mixture (40 mg, 92%, dr 60:40). Separation of the epimers by semi-preparative HPLC [Maxsil, 5 μ Si 250 mm × 4.6 mm; *n*-hexane–*i*-PrOH (90:10), 3 mL/min, 24 bar, t_R = 58.5 min; C_{12}-epimer: t_R = 52.3 min] yielded neohalicholactone (**2**) (dr 98:2) as a colorless oil; R_f = 0.6 (EtOAc); $[\alpha]_D^{18}$ –89.9 (*c* = 0.25, $CHCl_3$).

IR (film): 3391 (OH), 3009, 2957, 2868, 1737 (C=O), 1448, 1354, 1332, 1263, 1224, 1208, 1136, 1089, 1014, 973, 917, 873, 790, 728 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.61 (ddd, ^3J = 8.5 Hz, ^3J = 5.1 Hz, ^2J = 5.1 Hz, 1 H, 10-H_a), 0.72 (ddd, ^3J = 8.5 Hz, ^3J = 5.1 Hz, ^2J = 5.1 Hz, 1 H, 10-H_b), 0.97 (t, ^3J = 7.5 Hz, 3 H, 20-H), 1.03 (dddd, ^3J = 8.5 Hz, ^3J = 8.4 Hz, ^3J = 5.1 Hz, ^3J = 4.4 Hz, 1 H, 9-H), 1.10 (dddd, ^3J = 8.5 Hz, ^3J = 7.3 Hz, ^3J = 5.1 Hz, ^3J = 4.4 Hz, 1 H, 11-H), 1.55 (d, ^3J = 3.7 Hz, 1 H, $OH_{C\text{-}12}$), 1.65 (d, ^3J = 3.8 Hz, 1 H, $OH_{C\text{-}15}$), 1.78 (m_c, 1 H, 3-H_a), 2.02–2.09 (m, 2 H, 3-H_b, 4-H_a), 2.07 (qdddd, ^3J = 7.5 Hz, ^3J = 7.4 Hz, ^4J = 1.6 Hz, ^5J = 0.7 Hz, ^5J = 0.7 Hz, 2 H, 19-H), 2.15 (ddd, ^2J = 13.5 Hz, ^3J = 7.3 Hz, ^3J = 1.6 Hz, 1 H, 7-H_a), 2.22–2.30 (m, 2 H, 2-H), 2.31 (ddddt, ^2J = 14.1 Hz, ^3J = 7.3 Hz, ^3J = 5.1 Hz, ^4J = 1.8 Hz, ^5J = 0.7 Hz, 1 H, 16-H_a), 2.33 (ddddt, ^2J = 14.1 Hz, ^3J = 7.6 Hz, ^3J = 7.0 Hz, ^4J = 1.5 Hz, ^5J = 0.7 Hz, 1 H, 16-H_b), 2.44–2.48 (m, 1 H, 4-H_b), 2.50 (ddd, ^2J = 13.5 Hz, ^3J = 10.9 Hz, ^3J = 7.2 Hz, 1 H, 7-H_b), 3.70 (br ddd, ^3J = 7.3 Hz, ^3J = 3.7 Hz, ^3J = 3.7 Hz, 1 H, 12-H), 4.17 (br m_c, 1 H, 15-H), 4.23 (ddd, ^3J = 10.9 Hz, ^3J = 8.4 Hz, ^3J = 1.6 Hz, 1 H, 8-H), 5.35 (dddt, ^3J = 10.6 Hz, ^3J = 7.6 Hz, ^3J = 7.3 Hz, ^4J = 1.6 Hz, 1 H, 17-H), 5.44–5.55 (m, 2 H, 5-H, 6-H), 5.58 (dtdd, ^3J = 10.6 Hz, ^3J = 7.4 Hz, ^4J = 1.8 Hz, ^4J = 1.6 Hz, 1 H, 18-H), 5.75–5.82 (m, 2 H, 13-H, 14-H).

^{1}H NMR (600 MHz, C_6D_6): δ = 0.27 (ddd, ^3J = 8.5 Hz, ^3J = 5.0 Hz, ^2J = 5.0 Hz, 1 H, 10-H_a), 0.46 (ddd, ^3J = 8.6 Hz, ^3J = 5.0 Hz, ^2J = 5.0 Hz, 1 H, 10-H_b), 0.86 (dddd, ^3J = 8.6 Hz, ^3J = 8.4 Hz, ^3J = 5.0 Hz, ^3J = 4.5 Hz, 1 H, 9-H), 0.89 (t, ^3J = 7.5 Hz, 3 H, 20-H), 1.04 (dddd, ^3J = 8.5 Hz, ^3J = 6.9 Hz, ^3J = 5.1 Hz, ^3J = 4.5 Hz, 1 H, 11-H), 1.23 (br, 1 H, $OH_{C\text{-}12}$), 1.41 (br, 1 H, $OH_{C\text{-}15}$), 1.49–1.58 (m, 2 H, 3-H), 1.72–1.77 (m, 1 H, 4-H_a), 1.86 (ddd, ^2J = 13.4 Hz, ^3J = 7.3 Hz, ^3J = 1.6 Hz, 1 H, 7-H_a), 1.97 (qdddd, ^3J = 7.5 Hz, ^3J = 7.4 Hz, ^4J = 1.6 Hz, ^5J = 0.8 Hz, ^5J = 0.8 Hz, 2 H, 19-H), 2.05–2.12 (m, 2 H, 2-H), 2.22 (ddddt, ^2J = 14.1 Hz, ^3J = 7.3 Hz, ^3J = 5.9 Hz, ^4J = 1.6 Hz, ^5J = 0.8 Hz, 1 H, 16-H_a), 2.27 (ddddt, ^2J = 14.1 Hz, ^3J = 8.4 Hz, ^3J = 6.9 Hz, ^4J = 1.6 Hz, ^5J = 0.8 Hz, 1 H, 16-H_b), 2.32–2.38 (m, 2 H, 4-H_b, 7-H_b), 3.54 (br m_c, 1 H, 12-H), 4.00 (m_c, 1 H, 15-H), 4.32 (ddd, ^3J = 10.8 Hz, ^3J = 8.4 Hz, ^3J = 1.6 Hz, 1 H, 8-H), 5.34–5.43 (m, 3 H, 5-H, 6-H, 17-H), 5.50 (dtdd, ^3J = 10.8 Hz, ^3J = 7.4 Hz, ^4J = 1.6 Hz, ^4J = 1.6 Hz, 1 H, 18-H), 5.73 (m_c, 2 H, 13-H, 14-H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 8.2 (C-10), 14.2 (C-20), 19.5 (C-9), 20.8 (C-19), 23.4 (C-11), 25.3 (C-4), 26.5 (C-3), 33.6 (C-2), 33.7 (C-7), 35.2 (C-16), 71.5 (C-15), 74.2 (C-12), 76.1 (C-8), 123.6 (C-17), 124.7 (C-5 or C-6), 131.8 (C-14), 133.2 (C-13), 134.7 (C-5 or C-6), 135.4 (C-18), 174.1 (C-1).

^{13}C NMR (151 MHz, C_6D_6): δ = 7.8 (C-10), 14.4 (C-20), 19.6 (C-9), 21.0 (C-19), 23.8 (C-11), 25.6 (C-4), 26.6 (C-3), 33.7 (C-2), 34.1 (C-7), 35.8 (C-16), 71.7 (C-15), 73.4 (C-12), 76.1 (C-8), 124.7 (C-17 or C-7), 125.1 (C-17 or C-7), 132.2 (C-13 or C-14), 133.2 (C-13 or C-14), 134.6 (C-6 or C-18), 134.7 (C-18 or C-6), 173.0 (C-1).

HRMS (ESI, positive ion): *m*/*z* calcd for $C_{40}H_{60}O_8$ + Na: 691.41823; found: 691.41824.

HRMS (ESI, positive ion): *m*/*z* calcd for $C_{20}H_{30}O_4$ + Na: 357.20387; found: 357.20388.

C_{12}-*epi*-Neohalicholactone

$[\alpha]_D^{18}$ 69.1 (*c* = 0.49, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.60 (ddd, ^3J = 8.7 Hz, ^3J = 5.2 Hz, ^2J = 5.2 Hz, 1 H, 10-H_a), 0.63 (ddd, ^3J = 8.4 Hz, ^3J = 5.2 Hz, ^2J = 5.2 Hz, 1 H, 10-H_b), 0.97 (t, ^3J = 7.5 Hz, 3 H, 20-H), 1.08 (dddd, ^3J = 8.7 Hz, ^3J = 7.6 Hz, ^3J = 5.2 Hz, ^3J = 4.4 Hz, 1 H, 11-H), 1.12 (dddd, ^3J = 8.4 Hz, ^3J = 8.3 Hz, ^3J = 5.2 Hz, ^3J = 4.4 Hz, 1 H, 9-H), 1.66 (br, 1 H, $OH_{C\text{-}12}$), 1.71 (d, ^3J = 3.4 Hz, $OH_{C\text{-}15}$), 1.77 (m_c, 1 H, 3-H_a), 2.03–2.08 (m, 2 H, 3-H_b, 4-H_a), 2.07 (qdddd, ^3J = 7.5 Hz, ^3J = 7.4 Hz, ^4J = 1.6 Hz, ^5J = 0.8 Hz, ^5J = 0.8 Hz, 2 H, 19-H), 2.16 (ddd, ^2J = 13.6 Hz, ^3J = 7.3 Hz, ^3J = 1.6 Hz, 1 H, 7-H_a), 2.23–2.26 (m_c, 1 H, 2-H_a), 2.28–2.35 (m, 1 H, 2-H_b), 2.29 (ddddt, ^2J = 14.3 Hz, ^3J = 7.7 Hz, ^3J = 5.8 Hz, ^4J = 1.8 Hz, ^5J = 0.8 Hz, 1 H, 16-H_a), 2.34 (ddddt, ^2J = 14.3 Hz, ^3J = 8.6 Hz, ^3J = 7.1 Hz, ^4J = 1.5 Hz, ^5J = 0.8 Hz, 1 H, 16-H_b), 2.47–2.53 (m, 1 H, 4-H_b), 2.51 (ddd, ^2J = 13.6 Hz, ^3J = 10.7 Hz, ^3J = 3.7 Hz, 1 H, 7-H_b), 3.61 (br dd, ^3J = 7.6 Hz, ^3J = 3.6 Hz, 1 H, 12-H), 4.17 (m_c, 1 H, 15-H), 4.19 (ddd, ^3J = 10.7 Hz, ^3J = 8.3 Hz, ^3J = 1.6 Hz, 1 H, 8-H), 5.35 (dddt, ^3J = 10.9 Hz, ^3J = 7.7 Hz, ^3J = 7.1 Hz, ^4J = 1.6 Hz, 1 H, 17-H), 5.44–5.50 (m, 2 H, 5-H, 6-H), 5.58 (dtdd, ^3J = 10.9 Hz, ^3J = 7.4 Hz, ^4J = 1.5 Hz, ^4J = 1.5 Hz, 1 H, 18-H), 5.74–5.80 (m, 2 H, 14-H, 13-H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 7.8 (C-10), 14.2 (C-20), 20.5 (C-9), 20.7 (C-19), 23.7 (C-11), 25.3 (C-4), 26.5 (C-3), 33.7 (C-2), 33.8 (C-7), 35.2 (C-16), 71.6 (C-15), 74.6 (C-12), 76.4 (C-8), 123.6 (C-17), 124.7 (C-6 or C-5), 131.7 (C-13), 133.1 (C-14), 134.7 (C-5 or C-6), 135.4 (C-18), 174.2 (C-1).

Acknowledgment

We gratefully acknowledge the Deutsche Forschungsgemeinschaft and the Ministry of Innovation, Science, Research and Technology of the German federal state of North Rhine-Westphalia for the generous support of our projects. Donations from the Umicore AG & Co KG, the Jülich Chiral Solutions GmbH (now Codexis), the Wakker AG, and the Forschungszentrum Jülich (Prof. Dr. H. Sahm, Prof. Dr. Wandrey) are greatly appreciated. This work was generously supported through grants from the Jürgen Manchot Stiftung (for M.B.), the Degussa Stiftung and the Heinrich-Heine-Universität Düsseldorf (scholarships for A.C.M.N.). Furthermore, we thank the analytical departments at the University of Stuttgart and the FZ Jülich as well as Rainer Goldbaum, Monika Gehsing, Birgit Henßen, Christoph Lorenz, Erik Kranz, David Müller, Vera Ophoven, Bea Paschold, and Truc Pham for their ongoing support.

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