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Total Synthesis and Biological Evaluation of Amphidinolide V and Analogues

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Abstract: A sequence of ring-closing alkyne metathesis followed by an intermolecular enyne metathesis of the resulting cycloalkyne with ethene was used to forge the macrocyclic skeleton and to set the vicinal *exo*-methylene branches characteristic for the cytotoxic marine natural product amphidinolide V (**1**). Comparison of the synthetic material with an authentic sample of this extremely scarce metabolite isolated from a dinoflagellate of the *Amphidinium* sp. eliminated any doubts about its structure and allowed the absolute configuration of amphidinolide V to be determined as 8*R*,9*S*,10*S*,13*R*. Moreover, the flexibility inherent to the underlying synthesis blueprint also opened access to a comprehensive set of diastereomers of **1** as well as to synthetic analogues differing from the natural lead in the lipophilic chains appended to the macrocyclic core. This set of designed analogues gave first insights into structure–activity relationships, which revealed that the stereostructure of the macrolactone is a highly critical parameter, whereas the examined alterations of the side chain did not diminish the cytotoxicity of the compounds to any notable extent.

Keywords: anticancer agents · macrolides · metathesis · natural products · structure elucidation

Introduction

Marine microorganisms constitute rich sources of chemically novel and biologically significant secondary metabolites. This holds particularly true for the dinoflagellates of the genus *Amphidinium* sp., which are distinguished by an exceptional prolificacy, giving rise to a large number of highly diverse and strongly cytotoxic macrolides.[1] Low isolation yields, however, render the structure elucidation and in-depth biological assessment of these enticing natural products rather difficult.

One of the rarest members of this series is amphidinolide V extracted from the *Amphidinium* strain Y-5 (0.00005% of the wet weight).[2] Based on a sample of no more than 0.2 mg, structure **1** was proposed for this particular metabolite, but its absolute configuration could not be established. As evident from Scheme 1, amphidinolide V features a set of conspicuous structural elements, with the four *exo*-methylene groups decorating the 14-membered ring being particularly notable. The fact that two of them are vicinal to each other raises interesting questions as to the possible biosynthetic pathway leading to this uncommon marine natural product.

In preparative terms, this distinctive s-*trans*-diene unit provides a unique opportunity for chemical innovation. Rather than forming the macrocycle by standard lactonization techniques, one may envisage to forge the backbone at the C-4–C-5 bond by ring-closing alkyne metathesis (RCAM)[3,4] of a precursor diyne **B**; provided that the resulting cycloalkyne **A** could be engaged in a subsequent intermolecular enyne metathesis reaction with ethylene,[5–7] formation of the macrocyclic edifice and installation of the *vic*-methylene branches could be nicely synchronized (Scheme 1). From the conceptual standpoint, this application would help extend the scope of RCAM in general beyond the stereoselective generation of (*Z*)-configured cycloalkenes, which constituted the major application in the past upon Lindlar-type hydrogenation of the cycloalkynes primarily formed.[4,8] Moreover, the dense array of fragile functional groups in **1**, comprising a labile *trans*-configured vinyl epoxide flanked by a reactive allylic alcohol, represents a stringent test for the performance and tolerance of the available alkyne metathesis catalysts.[4,9–11] Finally, it

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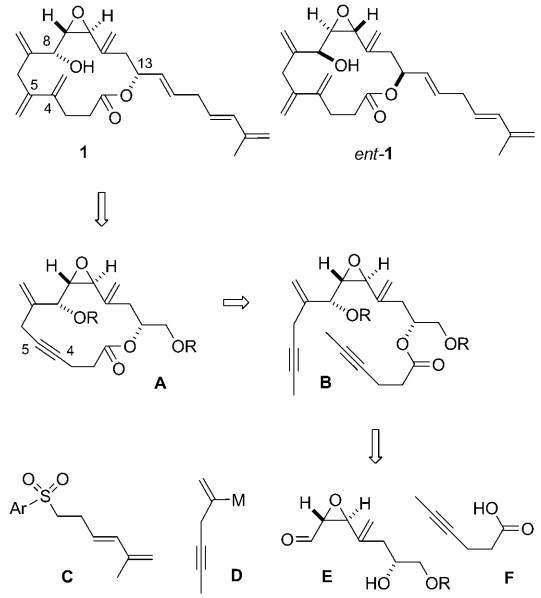


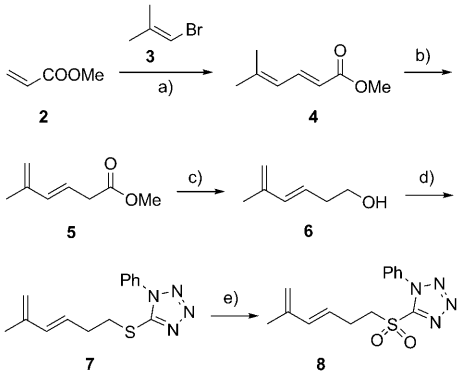
Scheme 1. Proposed structure and retrosynthetic analysis of amphidinolide V.

should be noticed that the envisaged late-stage enyne metathesis is not without risk either, as exposure of a compound of type **A** to a standard olefin metathesis catalyst might engender competing RCM or enyne metathesis events that would damage the integrity of the polyunsaturated framework.[12]

Outlined below is a full account of our work, which not only reduced the ambitious plan sketched in Scheme 1 to practice, but also clarified the remaining open questions concerning structure and stereochemistry of amphidinolide V.[13–17] In addition, this synthesis-driven approach made a set of designed analogues available, which allowed first insights into the structure–activity relationships (SAR) governing this series.

Results and Discussion

Preparation of the building blocks and assembly of the cyclization precursor: As outlined in Scheme 1, it was envisaged to assemble the target in a convergent fashion from four building blocks **C**–**F**. Specifically, synthon **C** representing the natural product's unsaturated appendix should be attached to the macrocyclic core by a Julia olefination, preferably in form of the particularly effective Kocienski variant.[18–20] The required *N*-phenyltetrazolyl sulfone **8** was prepared by a Heck reaction[21] between alkenyl bromide **3** and methyl acrylate, followed by base-mediated isomerisation of the resulting product **4** to compound **5**, wherein the diene is no longer conjugated with the ester (Scheme 2). Dibal-H reduction,[22] thioether formation under Mitsunobu conditions,[23] followed by standard oxidation of **7** with H_2O_2 under ammonium molybdate catalysis furnished the required sulfone **8** in excellent overall yield.

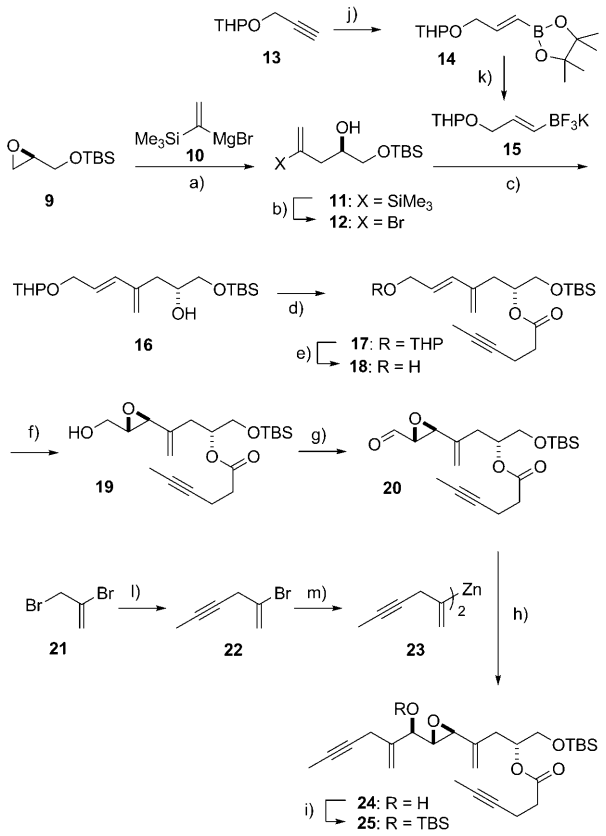


Scheme 2. a) $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), Et_3N, 100°C, 87%; b) LiHMDS, THF/DMPU, −35°C, 99%; c) Dibal-H, CH_2Cl_2, −78°C, 70%; d) PPh_3, DEAD, 1-phenyl-1*H*-tetrazol-5-thiol, THF, 63%; e) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2, EtOH, 76%; DEAD = diethyl azodicarboxylate; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone.

The preparation of the oxygenated sector of **1** commenced with epoxide **9**, which can be obtained in optically pure form (≥99% *ee*) by Jacobsen's convenient hydrolytic kinetic resolution (HKR) method.[24] Copper-catalyzed opening of this compound with the Grignard reagent **10** derived from commercial (1-bromovinyl)trimethylsilane afforded multigram quantities of alcohol **11**, which was transformed into alkenyl bromide **12** amenable to subsequent cross coupling.[25] This seemingly trivial *ipso*-substitution, however, required careful optimization. Thereby, it was essential to treat **11** with bromine at −78°C for ≤15 min prior to addition of a pre-cooled solution of NaOMe in MeOH at the same temperature to trigger elimination of TMSBr, and to quench the reaction with dilute HOAc at low temperature. Under these conditions, bromide **12** was reliably obtained in analytically pure form and good yield in batches of up to 12 g.

Bromide **12** was then subjected to a Suzuki reaction[26] with trifluoroborate **15**, which in turn derived from O-THP-protected propargyl alcohol **13** and pinacol borane as shown in Scheme 3.[27] In contrast to the recommended procedure, however, which emphasizes the importance of aqueous media for reactions of alkenyl trifluoroborates as Suzuki donors,[28] the cross coupling of **12** and **15** would not proceed well unless performed in anhydrous THF with *t*$BuNH_2$ as the base. Since the elaboration of **11** did not require protection of the secondary -OH group, the resulting product **16** could be directly esterified with 4-hexynoic acid with the aid of EDC. Unmasking of the terminus in **17**, Sharpless epoxidation[29] of the released allylic alcohol **18**, followed by oxidation of **19** with Dess–Martin periodinane[30] under buffered conditions provided the somewhat labile epoxy-aldehyde **20** in diastereomerically pure form and in high overall yield.

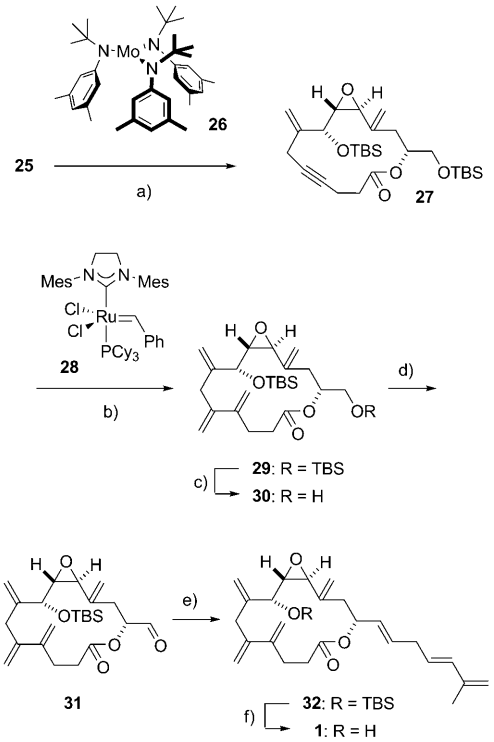
Initial attempts to subject this carbonyl derivative to chelation controlled additions of various organometallic reagents derived from bromide **22** were unrewarding. Gratifyingly, however, this sensitive skipped enyne derivative react-



Scheme 3. a) **10**, CuCN (10 mol%), THF, 0°C → RT, 99%; b) 1) Br_2, CH_2Cl_2, −78°C; 2) NaOMe, MeOH, −20°C; 3) HOAc, 72%; c) **15**, Pd(OAc)$_2$ (10 mol%), dppf (10 mol%), *t*BuNH$_2$, THF, reflux, 78%; d) 4-hexynoic acid, EDC·HCl, HOAt, (*i*Pr)$_2$NEt, DMAP, CH_2Cl_2/DMF, 97%; e) PPTS (cat.), *i*PrOH, 70°C, 97%; f) L-(+)-DET (20 mol%), Ti(O*i*Pr)$_4$ (20 mol%), *t*BuOOH, MS 4 Å, CH_2Cl_2, −20°C, 83%; g) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 87%; h) **23**, toluene, −50 → −25°C, 64%; i) TBSCl, imidazole, CH_2Cl_2, 10°C, 98%; j) pinacolborane, (cyclohexyl)$_2$BH cat., RT → 35°C, 81%; k) KHF_2, MeCN/H_2O, 40°C, 83%; l) MeC≡CMgBr, CuBr·Me_2S, Et_2O, 99%; m) Li, $ZnBr_2$, **22**, THF, 0°C, ultrasound; EDC = *N*-(3-dimethylaminopropyl)-*N*′-ethyl-carbodiimide; HOAt = 1-hydroxy-7-azabenzotriazole; DET = diethyl tartrate; DMAP = 4-dimethylaminopyridine; PPTS = pyridinium *p*-toluenesulfonate; TBS = *tert*-butyldimethylsilyl; THP = 2-tetrahydro-pyranyl.

ed cleanly with $ZnBr_2$ and Li sand under ultrasonication.[31] Slow addition of aldehyde **20** to a salt-free solution of the resulting bis(alkenyl)zinc reagent **23** in toluene at low temperature furnished alcohol **24** with appreciable levels of diastereocontrol (d.r. 7.5:1). Subsequent *O*-silylation of the major isomer provided diyne **25** as the substrate for the envisaged ring closure by RCAM.

Ring-closing alkyne metathesis and completion of the total synthesis: The formation of the strained 14-membered cycloalkyne **27** by RCAM of **25** was smoothly effected by a catalyst generated in situ from the molybdenum complex **26**[32] and CH_2Cl_2, as previously described by our group (Scheme 4).[33] Even though this catalyst system had already served well in various synthetic contexts,[34–39] it is remarkable that the active molybdenum species is compatible with the reactive vinyl epoxide, the allylic alcohol motif, as well as the rather sensitive skipped enyne function embedded into this particular substrate. Moreover, this example highlights again the striking abstinence of the alkyne metathesis catalyst from reacting with alkenes.[4,34,36,37,40–42] This rigorous and apparently general distinction between the different π-systems should have a positive impact on the logic of retrosynthetic planning and is therefore deemed important from the conceptual standpoint.



Scheme 4. a) **26** (30 mol%), CH_2Cl_2/toluene, 80°C, 84%; b) **28** (10 mol%), C_2H_4 (1.8 atm), toluene, 45°C, 70%; c) PPTS (cat.), MeOH, 78%; d) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 74%; e) **8**, KHMDS, DME/DMPU, −78°C → RT, 70% (*E*/*Z* 10:1); f) TASF, DMF, 0°C, 85%; KHMDS = potassium hexamethyldisilazide; DME = 1,2-dimethoxyethane; TASF = tris-(dimethylamino)sulfonium difluorotrimethylsilicate.

Equally rewarding was the outcome of the subsequent enyne metathesis between cycloalkyne **27** and ethylene gas (≈1.8 atm) effected by the "second-generation" Grubbs complex **28**,[43,44] which installed the vicinal methylene branches characteristic for amphidinolide V. The productivity of this transformation shows that other conceivable metathesis reactions invoking the preexisting olefins of the substrate did not interfere to any noticeable extent.

With a good supply of **29** secured, the total synthesis of **1** could be completed by routine protecting group and oxidation state management, followed by a Julia–Kocienski olefination[18–20] of aldehyde **31** with sulfone **8**. This reaction was best performed with KHMDS in DME/DMPU 50:1 as the reaction medium, which resulted in substantially higher *E*/*Z* ratios (ca. 10:1) than the use of pure THF (ca. 3:1). Because

the minor stereoisomer could be readily removed by flash chromatography, isomerically and analytically pure **1** was obtained after cleavage of the only remaining protecting group in **32** with the aid of TASF as a particularly mild fluoride source,[14,16,45–48] which does not compromise the resulting base-sensitive hydroxy-epoxide entity of the target.

Because the absolute configuration of amphidinolide V was unknown at the outset of this project, the opposite enantiomer *ent*-**1** was also prepared by following the exact same route, using *ent*-**9** as the starting material and D-(−)-DET as the ligand in the Sharpless epoxidation step (*ent*-**18** → *ent*-**19**). HPLC analysis using a Chiralpak OD column as chiral stationary phase showed that **1** co-elutes with an authentic sample, re-extracted from the natural source after completion of the total synthesis, whereas *ent*-**1** has a significantly different retention time (see Figure 3 in the Experimental Section). The identity of **1** with amphidinolide V was further confirmed by comparison of the CD spectra, thus allowing the absolute configuration of the natural product to be assigned as 8*R*,9*S*,10*S*,13*R* (Figure 1). This dual proof was

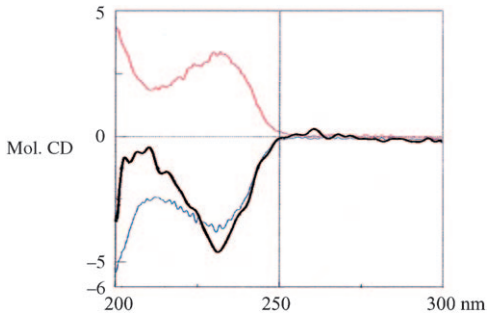
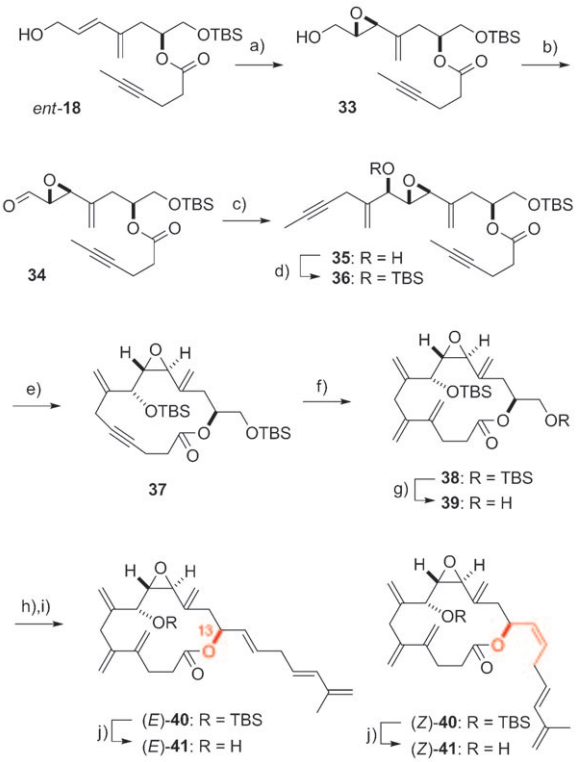


Figure 1. CD spectra of amphidinolide V (black) and products **1** (blue) and *ent*-**1** (red) in MeOH.

deemed necessary because of a singular mismatch between the recorded NMR data of **1** with those of the natural product tabulated in the original publication.[2,13] Whereas all ^{13}C NMR data of synthetic **1** in $CDCl_3$ as well as in [D_6]benzene were in excellent agreement with the reported spectra and the ^1H NMR in [D_6]benzene also matched exceedingly well, the ^1H NMR in $CDCl_3$ showed a discrepancy for the resonance assigned to H-8 of no less than 0.50 ppm, while all other shifts and coupling constants were again in good accord (see Tables 2 and 3 in the Experimental Section). However, the direct comparison of the synthetic samples with the re-extracted natural product by HPLC and CD unambiguously showed that this disparity was merely caused by a typographical error. The analytical and spectroscopic data of **1** compiled in the Experimental Section hence constitute the reference data set for amphidinolide V.

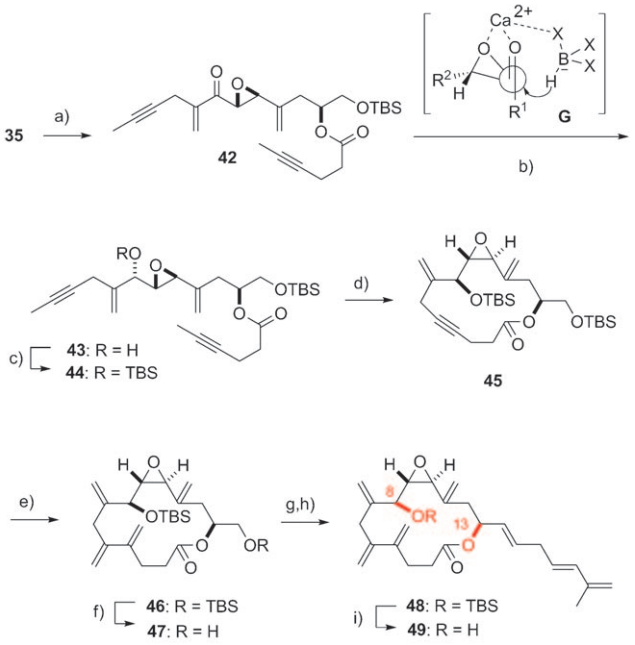
Stereoisomers and analogues: To further corroborate the identity of this structurally unique natural product and to gain first insights into pertinent structure–activity relationships, a set of designed analogues was prepared.[13] Rather than targeting product structures that might also be obtained by functionalization of the natural product itself, we were aiming at compounds incorporating deeper seated structural "mutations" that require a synthesis-driven editing of the molecular framework according to the logic of "diverted total synthesis".[49,50] In particular, we were keen on studying the effect of stereochemical permutations on the biological activity of the resulting "amphidinolide V-like" compounds.

Product **41** was targeted in the initial foray, which differs from **1** only in the configuration at C-13 carrying the lateral chain (Scheme 5). To this end, it sufficed to use *ent*-**18** as the substrate for the epoxidation reaction and to pursue the established route from there on without any major changes.[51] Particularly gratifying was the finding that the RCAM reaction of diyne **36** worked even better than that of its diastereomer **25**, furnishing cycloalkyne **37** in appreciable 89% yield. As expected, this product underwent the subsequent enyne metathesis with ethylene gas without incident. To further increase the diversity, the Julia–Kocienski olefination was deliberately carried out in THF rather than DME/DMPU, as this results in a lower *E*/*Z* ratio. The minor isomer could be separated by routine chromatography, thus furnishing (*Z*)-**41** as an additional analogue for testing after final deprotection.



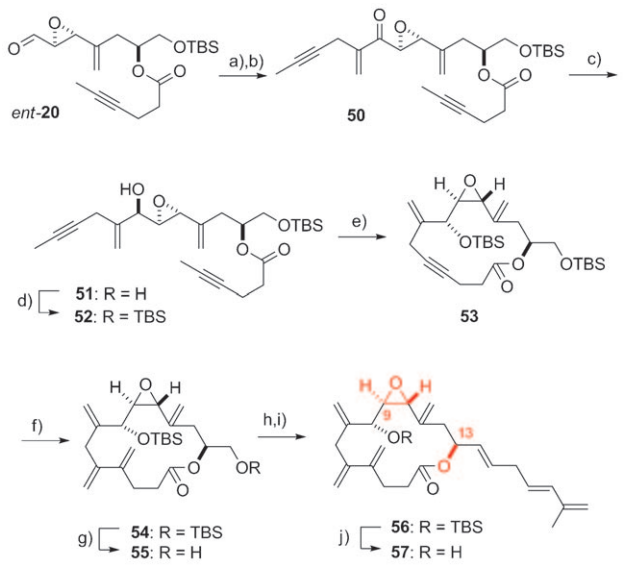
Scheme 5. a) L-(+)-DET (20 mol%), $Ti(OiPr)_4$ (20 mol%), *t*BuOOH, MS 4 Å, CH_2Cl_2, −20°C, 92%; b) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 90%; c) **23**, (+)-*N*-methylephedrine (60 mol%), toluene, −25°C, *syn*/*anti* 4:1, 70% (pure **35**); d) TBSCl, imidazole, CH_2Cl_2, 10°C, 99%; e) **26** (20 mol%), CH_2Cl_2/toluene, 80°C, 89%; f) **28** (5 mol%), C_2H_4 (1.8 atm), toluene, 45°C, 96%; g) PPTS (cat.), MeOH, 64%; h) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 86%; i) **8**, KHMDS, THF, −78°C → RT, 66% (*E*/*Z* 3:1); j) TASF, DMF, −5°C, 99%.

Compound **49** shows two stereochemical variations relative to the parent compound **1** (Scheme 6). The inversed configuration at C-8 was easily set by oxidation of adduct **35** followed by treatment of the resulting enone **42** with $NaBH_4/CaCl_2$. The particular reagent combination is thought to engender a chelation-controlled reduction via a transition state of type **G**, yet is mild enough not to damage the sensitive oxirane ring.[52] With compound **43** in hand, the previously successful strategy was pursued en route to **49**, with the RCAM- and enyne metathesis events being again remarkably productive.



Scheme 6. a) Dess–Martin periodinane, CH_2Cl_2; b) $NaBH_4$, $CaCl_2$, MeOH, 0 °C, 71 % (over both steps); c) TBSCl, imidazole, CH_2Cl_2, 10 °C, 87 %; d) **26** (20 mol %), CH_2Cl_2/toluene, 80 °C, 75 %; e) **28** (2 mol %), C_2H_4 (1.8 atm), toluene, 45 °C, 92 %; f) PPTS (cat.), MeOH, 61 %; g) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 97 %; h) **8**, KHMDS, DME/DMPU 50:1, −78 °C → RT, 98 % (*E*/*Z* >10:1); i) TASF, DMF, −5 °C, 78 %.

The only remaining diastereomeric format of the macrocyclic core required analogue **57** to be prepared, which retains the configuration of the natural product at C-8, but inverts that of the three other chiral centers (Scheme 7). Starting from aldehyde *ent*-**20**, addition of the Grignard reagent derived from **22** followed by oxidation of the resulting alcohol furnished enone **50**,[53] which was reduced with high selectivity to the *anti*-configured epoxy-alcohol **51**, again by recourse to the combination $NaBH_4/CaCl_2$.[52] *O*-Silylation followed by a remarkably effective ring-closing alkyne metathesis of diyne **52** afforded macrocycle **53**, which was processed in the usual way to the targeted compound **57** with high overall yield. This particular product, however, was found significantly less stable than the other stereoisomers prepared during this investigation.

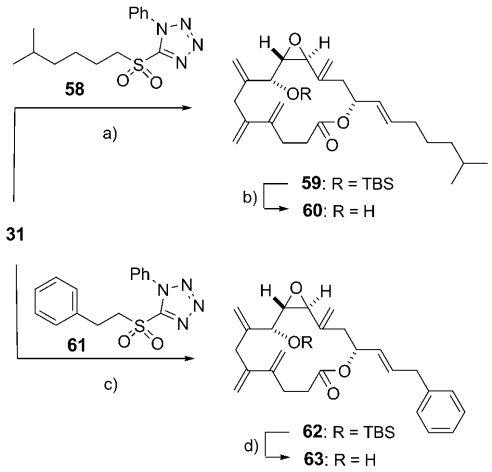


Scheme 7. a) **22**, Mg, THF, −10 °C, 70 % (d.r. 1:1); b) Dess–Martin periodinane, CH_2Cl_2; c) $NaBH_4$, $CaCl_2$, MeOH, 0 °C, 70 % (over both steps); d) TBSCl, imidazole, CH_2Cl_2, 10 °C, 93 %; e) **26** (20 mol %), CH_2Cl_2/toluene, 85 °C, 93 %; f) **28** (10 mol %), C_2H_4 (1.8 atm), toluene, 45 °C, 73 %; g) PPTS (cat.), MeOH, 85 %; h) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 60 %; i) **8**, KHMDS, THF, −78 °C → RT, 75 % (*E*/*Z* 3:1); j) TASF, DMF, −5 °C, 60 %.

It should be noticed that **1** and analogues **41**, **49** and **57** represent the complete set of conceivable diastereomers of amphidinolide V. Since it has already been demonstrated that **1** co-eludes with amphidinolide V and shows an identical CD spectrum, it came as no surprise that the high field NMR spectra of the other isomers are distinctly different from that of the natural product (Table 2 in the Experimental Section).[13] Yet, this comprehensive data set provides the ultimate proof that amphidinolide V is correctly described by the originally proposed structure **1** despite the singular discrepancy with the tabulated ^{1}H NMR data (see above and the data compiled in Table 3), and eliminates any possible doubt concerning constitution and stereochemistry of this particular marine natural product.

Finally, analogues **60** and **63** were prepared, which exhibit the macrocycle of **1** but terminate in altered side chains (Scheme 8). Although the Kocienski olefination of aldehyde **31** with either sulfone **58** or **61** remained un-optimized, enough material was secured for a first round of biological testing.

Evaluation of the cytotoxicity: As can be seen from the results compiled in Table 1, the IC_{50} of natural as well as synthetic amphidinolide V (**1**) against murine lymphoma P388 cells were found identical within the experimental error of the assay. Importantly, these data also show that analogues **60** and **63** carrying different side chains exhibit the same level of cytotoxicity as the natural product, whereas all isomers with altered stereostructures are essentially inactive, including enantiomeric *ent*-**1**. Therefore one must conclude that the 3D structure of the macrocycle is a very critical pa-



Scheme 8. a) **58**, KHMDS, DME/DMPU, −78 °C → RT, 46 % (*E*/*Z* >10:1); b) TASF, DMF, −10 °C, 80 %; c) **61**, KHMDS, DME/DMPU, −78 °C → RT, 28 % (*E*/*Z* >10:1); d) TASF, DMF, −10 °C, 91 %.

Table 1. Cytotoxicities of natural and synthetic amphidinolide V and analogues thereof against P388 murine lymphoma cells.

Compound	IC_{50} [μg mL^{-1}]
amphidinolide V (natural)	5.5
1	7.0
ent-**1**	>10
(*E*)-**41**	>10
(*Z*)-**41**	>10
49	>10
60	6.8
63	6.4

rameter, whereas the lateral chain constitutes a permissive site.

Conclusion

In comparison with alkene metathesis, the related metathesis of alkynes is still in its infancy. A growing number of applications to increasingly complex targets, however, highlights the remarkable potential of this transformation as well as the outstanding compatibility of the available catalysts with a host of sensitive functionalities, even when grouped in dense arrays.[4,8,33–39,42,54–63] The examples reported herein bear witness for this notion and provide compelling evidence for the fact that alkyne metathesis—and in particular ring-closing alkyne metathesis (RCAM)—offers more than an indirect entry into stereodefined (cyclo)alkenes by semi-reduction of the products primarily formed.[8] Specifically, it is demonstrated that RCAM in combination with a subsequent intermolecular enyne metathesis opens a convenient, flexible and high yielding entry into amphidinolide V (**1**) and a range of fully synthetic analogues of this rather unique metabolite of marine origin. At the same time, this approach eliminated the remaining doubts concerning the constitution of this natural product and established its absolute configuration as 8*R*,9*S*,10*S*,13*R*. Deviations from the route leading to **1** also allowed a set of designed analogues to be obtained, which revealed that the lateral chain is a permissive site for structural variation, whereas the relative and absolute stereochemistry of the macrocycle is a critical parameter with regard to the cytotoxicity profile. Together with the data reported in the accompanying paper,[64] this study constitutes the first synthesis-driven investigation into structure–activity relationships governing the amphidinolide macrolides.[65]

Experimental Section

General: All reactions were carried out under Ar. The solvents used were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O (Mg/anthracene), CH_2Cl_2 (P_4O_{10}), MeCN, Et_3N, pyridine, DMF (CaH_2), MeOH (Mg), hexanes, cyclohexane, toluene, benzene (Na/K), DME (Na). Flash chromatography: Merck silica gel 60 (230–400 mesh). NMR: Spectra were recorded on a DPX 300, AV 400 or DMX 600 spectrometer (Bruker) in the solvents indicated; chemical shifts (δ) are given in ppm relative to residual solvent peaks, coupling constants (J) in Hz. IR: Nicolet FT-7199 spectrometer, wavenumbers in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), (ESI) Finnigan MAT 95, accurate mass determination: Finnigan MAT 95, Bruker APEX III FT-ICR-MS (7 T magnet). Melting points: Büchi melting point apparatus (corrected). Elemental analyses: H. Kolbe, Mülheim/Ruhr. All commercially available compounds (Lancaster, Fluka, Aldrich, TCI Europe) were used as received unless stated otherwise. The catalyst **26** was prepared according to previously described procedure[32,33] and was stored (−20 °C) and handled in an argon glove box.

Building blocks

(*E*)-Methyl 5-methylhexa-2,4-dienoate (4):[66] A mixture of 2-methyl-1-bromopropene (15 mL, 146 mmol), methyl acrylate (16.48 mL, 183 mmol), triethylamine (30.62 mL, 219 mmol), $Pd(OAc)_2$ (1.64 g, 7.32 mmol) and PPh_3 (3.84 g, 14 mmol) was heated at 100 °C for 45 h in a sealed tube. After cooling to ambient temperature, the mixture was filtered through a plug of silica, which was carefully rinsed with Et_2O/pentanes 1:1. The combined filtrates were evaporated and the residue purified by distillation to afford ester **4** as a colorless liquid (17.64 g, 87 %). B.p. 85–87 °C (17 mbar); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.86 (s, 3H), 1.88 (s, 3H), 3.73 (s, 3H), 5.75 (d, J = 15.1 Hz, 1H), 5.97 (d, J = 11.6 Hz, 1H), 7.56 ppm (dd, J = 11.6, 15.1 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.5 (CH_3), 26.1 (CH_3), 50.9 (CH_3), 117.7 (CH_3), 123.3 (CH_3), 140.8 (CH), 146.0 (C), 167.7 ppm (C).

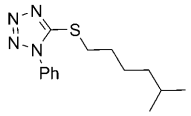
(*E*)-Methyl 5-methylhexa-3,5-dienoate (5):[22] A solution of LiHMDS (5.67 g, 33 mmol) in THF (100 mL) and DMPU (4.1 mL, 33 mmol) was stirred at −35 °C for 30 min before a solution of diene **4** (3.96 g, 28 mmol) in THF (14 mL) was added dropwise over a period of 45 min. Once the addition was complete, the mixture was stirred for 4 h at that temperature. For work up, the dark orange mixture was poured into aq. HOAc solution (10 % *w*/*w*, 52 mL). The aqueous phase was extracted with hexanes (3 × 20 mL), the combined extracts were washed with water (50 mL), dried over Na_2SO_4 and evaporated. The crude product was purified by distillation to yield ester **5** as a colorless oil (3.92 g, 99 %). B.p. 76–78 °C (24 mbar); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.84 (s, 3H), 3.14 (d, J = 7.1 Hz, 2H), 3.68 (s, 3H), 4.92 (s, 1H), 4.94 (s, 1H), 5.72 (dt, J = 7.1, 15.6 Hz, 1H), 6.21 ppm (d, 1H, J = 15.6 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.1 (CH_3), 37.5 (CH_2), 51.4 (CH_3), 115.8 (CH_2), 121.0 (CH), 136.0 (CH), 141.0 (C), 171.7 ppm (C).

(*E*)-5-Methylhexa-3,5-dien-1-ol (6):[22] Dibal-H (1 M in hexanes, 31.4 mL, 31.4 mmol) was slowly added to a solution of ester **5** (2.0 g, 14.26 mmol) in CH_2Cl_2 (14 mL) at −78 °C and the resulting mixture was stirred at that temperature for 30 min before it was poured into an ice-cold sat. aq. solution of Rochelle's salt (100 mL) and diluted with CH_2Cl_2 (100 mL). The

slurry was stirred overnight to ensure clean phase separation before the aqueous layer was extracted with CH_2Cl_2 (4×30 mL). The combined extracts were dried over Na_2SO_4 and evaporated (>500 mbar), and the residue was purified by flash chromatography (pentanes/Et_2O 10:1) to give alcohol **6** as a pale yellow oil (1.11 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.83 (s, 3H), 2.37 (q, J=6.5 Hz, 2H), 3.68 (t, J=6.0 Hz, 2H), 4.90 (s, 2H), 5.57 (dt, J=7.1, 15.6 Hz, 1H), 6.23 ppm (d, 1H, J=15.7 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=18.2 (CH_3), 35.7 (CH_2), 61.6 (CH_2), 115.0 (CH_2), 125.7 (CH), 135.4 (CH), 141.3 ppm (C).

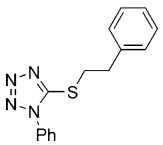
(*E*)-5-(5-Methylhexa-3,5-dienylthio)-1-phenyl-1*H*-tetrazole (7): DEAD (1.23 mL, 6.68 mmol) was slowly added at 0°C to a solution of the alcohol **6** (0.5 g, 4.46 mmol), PPh_3 (1.75 g, 6.69 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (1.19 g, 6.69 mmol) in THF (15 mL). The mixture was stirred at room temperature for 3 h before the solvent was evaporated. Flash chromatography (hexanes/ethyl acetate 10:1) of the residue gave compound **7** as a colorless oil (0.761 g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.79 (s, 3H), 2.64 (q, J=7.1 Hz, 2H), 3.47 (t, J=7.1 Hz, 2H), 4.89 (s, 1H), 4.91 (s, 1H), 5.62 (dt, J=7.0, 15.6 Hz, 1H), 6.20 (d, J=15.6 Hz, 1H), 7.50–7.56 ppm (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=18.4 (CH_3), 32.3 (CH_2), 33.0 (CH_2), 115.8 (CH_2), 123.8 (CH), 126.4 (CH), 129.7 (CH), 130.0 (CH), 133.6 (C), 135.4 (CH), 141.4 (C), 154.2 ppm (C); IR (film): $\tilde{\nu}$=3078, 3022, 2971, 2941, 2920, 2853, 1675, 1608, 1597, 1500, 1455, 1412, 1386, 1316, 1279, 1243, 1176, 1089, 1074, 1015, 969, 889, 761, 694, 551 cm^{-1}; MS (EI): m/z (%): 272 (15) [M^+], 135 (23), 117 (15), 95 (18), 94 (100), 93 (12), 91 (11), 81 (16), 79 (80), 77 (34), 65 (17), 55 (10); HRMS (ESI): m/z: calcd for $C_{14}H_{16}N_4S$ [M^+]: 272.1097, found: 272.1096; elemental analysis calcd (%) for $C_{14}H_{16}N_4S$ (272.37): C 61.74, H 5.92, N 20.57; found: C 61.70, H 6.05, N 20.36.

5-(5-Methylhexylthio)-1-phenyl-1*H*-tetrazole: Prepared analogously from 5-methyl-1-hexanol (0.6 mL, 4.25 mmol) as a colorless oil (1.02 g, 90%).



^{1}H NMR (400 MHz, $CDCl_3$): δ=0.85 (s, 3H), 0.87 (s, 3H), 1.17–1.23 (m, 2H), 1.39–1.47 (m, 2H), 1.52 (dq, J=6.6, 6.6 Hz, 1H), 1.80 (dt, J=7.5, 15.0 Hz, 2H), 3.39 (t, J=7.4 Hz, 2H), 7.50–7.60 ppm (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=22.5 (CH_3), 22.5 (CH_3), 26.4 (CH_2), 27.8 (CH), 29.3 (CH_2), 33.3 (CH_2), 38.2 (CH_2), 123.8 (CH), 129.7 (CH), 130.0 (CH), 133.7 (C), 154.4 ppm (C); IR (film): $\tilde{\nu}$=2953, 2926, 2867, 1597, 1499, 1462, 1410, 1384, 1278, 1240, 1087, 1074, 1014, 758, 693, 684 cm^{-1}; MS (EI): m/z (%): 276 (2) [M^+], 220 (13), 150 (17), 131 (10), 130 (12), 119 (16), 118 (100), 117 (19), 115 (22), 97 (22), 91 (16), 87 (53), 77 (24), 69 (11), 65 (11), 57 (18), 55 (54), 43 (30), 41 (26); HRMS (ESI): m/z: calcd for $C_{14}H_{20}N_4SNa$ [M^++Na]: 299.1299, found: 299.1300; elemental analysis calcd (%) for $C_{14}H_{20}N_4S$ (276.40): C 60.84, H 7.29, N 20.27; found: C 60.74, H 7.33, N 20.21.

5-(Phenethylthio)-1-phenyl-1*H*-tetrazole: Prepared analogously from 2-phenylethanol (0.5 mL, 4.17 mmol) as a colorless oil (1.07 g, 92%).



^{1}H NMR (400 MHz, $CDCl_3$): δ=3.13–3.17 (m, 2H), 3.62–3.66 (m, 2H), 7.22–7.26 (m, 2H), 7.29–7.33 (m, 3H), 7.50–7.56 ppm (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=34.4 (CH_2), 35.4 (CH_2), 123.8 (CH), 126.8 (CH), 128.6 (CH), 128.7 (CH), 129.7 (CH), 130.0 (CH), 133.6 (C), 138.9 (C), 154.1 ppm (C); IR (film): $\tilde{\nu}$=3062, 3027, 2935, 1596, 1497, 1454, 1410, 1384, 1316, 1276, 1240, 1088, 1073, 1014, 977, 913, 757, 692 cm^{-1}; MS (EI): m/z (%): 282 (6) [M^+], 178 (100), 137 (10), 136 (16), 135 (54), 117 (14), 105 (17), 104 (36), 91 (27), 77 (22), 65 (12); HRMS (ESI): m/z: calcd for $C_{15}H_{14}N_4SNa$ [M^++Na]: 305.0830, found: 305.0831; elemental analysis calcd (%) for $C_{15}H_{14}N_4S$ (282.36): C 63.80, H 5.00, N 19.84; found: C 63.72, H 4.95, N 19.77.

(*E*)-5-(5-Methylhexa-3,5-dienylsulfonyl)-1-phenyl-1*H*-tetrazole (8): A solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (2.49 g, 2.01 mmol) in aq. H_2O_2 (30% *w*/*w*, 11 mL) was stirred at 0°C for 15 min before it was added to a solution of thioether **7** (2.74 g, 10 mmol) in EtOH (167 mL). The resulting mixture was stirred for 2 h at ambient temperature before the reaction was quenched with phosphate buffer (0.4 M, pH 7, 20 mL) and extracted with CH_2Cl_2 (4×30 mL). The combined organic phases were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate 20:1) to give sulfone **8** as a colorless solid (2.31 g, 76%). The material should be stored at −20°C as a frozen solution in benzene. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.79 (s, 3H), 2.77 (dt, J=6.6, 8.3 Hz, 2H), 3.84 (t, J=7.6 Hz, 2H), 4.94 (s, 1H), 4.97 (s, 1H), 5.56 (dt, J=7.0, 15.5 Hz, 1H), 6.24 (d, J=15.6 Hz, 1H), 7.56–7.69 ppm (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=18.4 (CH_3), 25.6 (CH_2), 55.5 (CH_2), 116.8 (CH_2), 123.6 (CH), 125.0 (CH), 129.6 (CH), 131.4 (CH), 132.9 (C), 136.3 (CH), 141.0 (C), 153.4 ppm (C); IR (film): $\tilde{\nu}$=3080, 3027, 2973, 2944, 2920, 1609, 1595, 1498, 1460, 1438, 1348, 1233, 1156, 1076, 1015, 969, 893, 763, 689, 637, 536 cm^{-1}; MS (EI): m/z (%): 304 (1) [M^+], 212 (21), 183 (15), 169 (15), 118 (30), 117 (29), 95 (43), 94 (78), 93 (16), 91 (12), 80 (16), 79 (100), 77 (37), 67 (55), 65 (34), 55 (47); HRMS (ESI): m/z: calcd for $C_{14}H_{16}N_4O_2SNa$ [M^++Na]: 327.0886, found: 327.0886; elemental analysis calcd (%) for $C_{14}H_{16}N_4O_2S$ (304.37): C 55.25, H 5.30, N 18.41; found: C 55.11, H 5.21, N 18.30.

5-(5-Methylhexylsulfonyl)-1-phenyl-1*H*-tetrazole (58): Prepared analogously from 5-(5-methylhexylthio)-1-phenyl-1*H*-tetrazole (1.70 g, 6.15 mmol) as a colorless solid (1.20 g, 64%). M.p. 46–47°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.86 (s, 3H), 0.88 (s, 3H), 1.19–1.25 (m, 2H), 1.45–1.59 (m, 3H), 1.89–1.97 (m, 2H), 3.71–3.74 (m, 2H), 7.56–7.64 (m, 3H), 7.66–7.70 ppm (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=22.1 (CH_2), 22.4 (CH_3), 22.4 (CH_3), 25.9 (CH_2), 27.6 (CH), 38.0 (CH_2), 55.9 (CH_2), 125.0 (CH), 129.6 (CH), 131.4 (CH), 133.0 (C), 153.4 ppm (C); IR (film): $\tilde{\nu}$=2957, 2901, 2869, 1595, 1498, 1470, 1401, 1335, 1293, 1150, 1101, 1048, 1015, 763, 710, 687 cm^{-1}; MS (EI): m/z (%): 309 (<1) [M^+], 173 (10), 119 (13), 118 (100), 117 (30), 65 (11), 57 (42), 55 (13), 43 (29), 41 (18); HRMS (ESI): m/z: calcd for $C_{14}H_{20}N_4O_2SNa$ [M^++Na]: 331.1201, found: 331.1199; elemental analysis calcd (%) for $C_{14}H_{20}N_4O_2S$ (308.40): C 54.52, H 6.54, N 18.17; found: C 54.58, H 6.51, N 18.12.

5-(Phenethylsulfonyl)-1-phenyl-1*H*-tetrazole (61): Prepared analogously from 5-(phenethylthio)-1-phenyl-1*H*-tetrazole (1.30 g, 4.60 mmol) as a colorless solid (1.20 g, 83%). M.p. 97–98°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.23–3.29 (m, 2H), 3.97–4.02 (m, 2H), 7.24–7.35 (m, 5H), 7.57–7.70 ppm (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=28.4 (CH_2), 57.2 (CH_2), 125.0 (CH), 127.3 (CH), 128.4 (CH), 129.0 (CH), 129.7 (CH), 131.4 (CH), 132.9 (C), 136.2 (C), 153.3 ppm (C); IR (film): ν=3068, 3027, 2982, 2930, 1594, 1495, 1457, 1389, 1342, 1331, 1242, 1153, 1075, 1048, 1014, 967, 920, 833, 765, 743, 688 cm^{-1}; MS (EI): m/z (%): 250 (21), 131 (11), 118 (54), 117 (19), 105 (100), 104 (78), 103 (12), 79 (18), 77 (27), 65 (13); HRMS (ESI): m/z: calcd for $C_{15}H_{14}N_4O_2SNa$ [M^++Na]: 337.0732, found: 337.0729; elemental analysis calcd (%) for $C_{15}H_{14}N_4O_2S$ (314.36): C 57.31, H 4.49, N 17.82; found: C 57.25, H 4.43, N 17.74.

4,4,5,5-Tetramethyl-2-[3-(tetrahydro-2*H*-pyran-2-yloxy)prop-(1*E*)-enyl]-1,3,2-dioxa-borolane (14):[27] $BH_3\cdot(Me_2S)$ (10.64 g, 140 mmol) was slowly added to a solution of pinacol (16.54 g, 140 mmol) in THF (5 mL) at 0°C and the mixture was stirred at ambient temperature for 1.5 h and at 40°C for 1 h until the evolution of gas had ceased. Compound **13** (7.0 g, 50 mmol) was then introduced, followed by a suspension of *c*Hex_2BH (1 M in THF, 2.5 mL). The resulting mixture was stirred for 24 h and at 35°C for another 24 h until complete conversion (TLC) was reached. For work up, air was bubbled through the mixture for 2 h before hexanes (100 mL) were added. All insoluble materials were filtered off, the filtrate was evaporated and the residue purified by flash chromatography (hexanes/ethyl acetate 30:1 → 4:1) to give product **14** as a colorless oil (10.9 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.26 (s, 12H), 1.47–1.90 (m, 6H), 3.46–3.51 (m, 1H), 3.81–3.87 (m, 1H), 4.06 (ddd, J=1.7, 4.8, 15.0 Hz, 1H), 4.30 (ddd, J=1.9, 4.1, 15.0 Hz, 1H), 4.64 (t, J=3.4 Hz, 1H), 5.73 (dt, J=1.8, 18.1 Hz, 1H), 6.66 ppm (dt, J=4.4, 18.1 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=19.1 (CH_2), 24.7 (CH_3), 25.4 (CH_2), 30.4 (CH_2), 61.8 (CH_2), 68.2 (CH_2), 83.2 (C), 97.7 (CH), 149.2 ppm (CH).

Potassium trifluoro[3-(tetrahydro-2*H*-pyran-2-yloxy)prop-(1*E*)-enyl]borate (15): A mixture containing **14** (5.50 g, 0.021 mmol), MeCN (39 mL), water (12.7 mL) and ground KHF_2 (6.84 g) was vigorously stirred for 2 h at ambient temperature and for another 2 h at 50°C. All volatile materials were evaporated and the residue dried in vacuo before it was triturated with acetone (3×100 mL). The combined filtrates were evaporated, the residue dried in vacuo before it was dissolved in acetone (15 mL).

Et_2O (10 mL) was added and the mixture kept in the freezer overnight. The precipitated product was filtered off and dried in vacuo to give **15** as a colorless solid (4.2 g, 83%). ^{1}H NMR (400 MHz, CD_3COCD_3): $\delta =$ 1.45–1.85 (m, 6H), 3.39–3.44 (m, 1H), 3.76–3.82 (m, 1H), 3.83 (dddd, $J =$ 1.1, 1.2, 6.2, 11.6 Hz, 1H), 4.08 (dddd, $J = 1.3$, 1.4, 5.2, 11.8 Hz, 1H), 4.59 (t, $J = 3.6$ Hz, 1H), 5.57–5.64 (m, 1H), 5.77–5.85 ppm (ddd, $J = 5.2$, 6.2, 17.7 Hz, 1H); ^{13}C NMR (100.6 MHz, CD_3COCD_3): $\delta = 20.5$ (CH_2), 26.7 (CH_2), 31.9 (CH_2), 62.4 (CH_2), 71.7 (CH_2), 98.3 (CH), 133.0 (CH), 133.1 ppm (CH); IR (film): $\tilde{\nu} = 2940$, 2867, 1649, 1453, 1442, 1384, 1350, 1283, 1259, 1201, 1182, 1118, 1098, 1024, 1001, 951, 868, 813, 738 cm^{-1}; HRMS (ESI): m/z: calcd for $C_8H_{13}O_2BF_3$ [M^-−K]: 209.0968, found: 209.0966; elemental analysis calcd (%) for $C_8H_{13}BF_3KO_2$ (248.09): C 38.73, H 5.28; found: C 38.57, H 5.28.

Hex-4-ynoic acid:[67] Hex-5-ynoic acid (5.0 g, 44.6 mmol) was added to aq. KOH (15 M, 50 mL) and the mixture was heated at 170 °C for 3 h. The solution was then cooled to −20 °C and carefully acidified with ice-cold HCl (12 M, 150 mL). Dichloromethane (100 mL) was added and the slurry was stirred for 1 h before the precipitate was filtered off and the filtrate was extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried over Na_2SO_4 and evaporated, and the crude product was recrystallized from pentanes to give the title compound as a colorless solid (3.09 g, 62%). M.p. 96–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.69$ (t, $J = 2.5$ Hz, 3H), 2.35–2.40 (m, 2H), 2.47–2.51 (m, 2H), 11.79 ppm (br s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 3.0$ (CH_3), 14.0 (CH_2), 33.3 (CH_2), 76.2 (C), 76.5 (C), 178.1 ppm (C); IR (film): $\tilde{\nu} = 2924$, 2857, 2636, 2555, 1708, 1430, 1410, 1302, 1217, 947, 778, 659, 525 cm^{-1}.

2-Bromohex-1-en-4-yne (22): CuBr·Me_2S (3.08 g, 15 mmol) was added to a solution of 2-bromoallyl bromide (7.55 mL, 75 mmol) in Et_2O (234 mL) at 0 °C. The resulting mixture was stirred for 1 h before a solution of propyn-1-ylmagnesium bromide (0.5 M in Et_2O, 300 mL, 150 mmol) was introduced. After stirring overnight at room temperature, the excess of the Grignard reagent was quenched by careful addition of sat. aq. NH_4Cl (300 mL). The aqueous layer was extracted with Et_2O (3 × 100 mL), the combined organic fractions were dried over Na_2SO_4 and evaporated (> 200 mbar), and the residue purified by distillation to give bromide **22** as a pale yellow liquid (9.20 g, 99%). B.p. 47–50 °C (30 mbar); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.76$ (t, $J = 2.5$ Hz, 3H), 3.21–3.23 (m, 2H), 5.46 (dt, $J = 1.3$, 1.5 Hz, 1H), 5.91 ppm (dt, $J = 1.6$, 1.7 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 3.1$ (CH_3), 31.5 (CH_2), 73.8 (C), 79.2 (C), 117.1 (CH_2), 127.7 ppm (C); IR (film): $\tilde{\nu} = 2957$, 2919, 2895, 2855, 2226, 1635, 1418, 1109, 1082, 893, 643 cm^{-1}; MS (EI): m/z (%): 160 (17) [M^++H], 159 (1) [M^+], 158 (16), 79 (100), 78 (14), 77 (78), 53 (27), 51 (32); HRMS (ESI): m/z: calcd for C_6H_7Br [M^+]: 157.9731, found: 157.9731; elemental analysis calcd (%) for C_6H_7Br (159.02): C 45.32, H 4.44; found: C 45.43, H 4.41.

Preparation of the cyclization precursors

(*R*)-1-(*tert*-Butyldimethylsilyloxy)-4-(trimethylsilyl)pent-4-en-2-ol (11): A two-necked flask equipped with a reflux condenser was charged with Mg turnings (10.06 g, 0.41 mol) and THF (100 mL). The suspension was heated to reflux for 1 min before 1,2-dibromoethane (0.3 mL) was added and stirring continued for 5 min. (1-Bromovinyl)trimethylsilane (14.5 mL, 0.093 mol) was then added dropwise over 15 min at such a rate as to maintain gentle reflux but avoid strong foaming. Once the addition was complete, the mixture was stirred for 30 min at 60 °C.

A separate two-necked flask was charged with CuCN (0.66 g, 7.37 mmol, 10 mol%), glycidyl ether **9** (16.0 mL, 0.073 mol) and THF (185 mL). The mixture was cooled to −30 °C before the solution of the Grignard reagent **10** was added via cannula within 5 min. The resulting mixture was stirred at 0 °C for 1 h and at ambient temperature for 1 h. Sat. aq. NH_4Cl (3 mL) was added and the mixture stirred for 5 min before it was diluted with hexanes/EtOAc 1:1 (170 mL). Na_2SO_4 was added and the solid materials were filtered off, the filtrate was evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate 20:1) to give product **11** as a colorless oil (22.3 g, 99%). $[\alpha]_D^{20} = -2.2$ ($CHCl_3$, $c = 0.5$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.07$ (s, 6H), 0.10 (s, 9H), 0.90 (s, 9H), 2.27 (dd, $J = 7.7$, 14.1 Hz, 1H), 2.32–2.34 (m, 1H), 2.35 (dd, $J = 5.7$, 14.2 Hz, 1H), 3.46 (dd, $J = 6.8$, 9.9 Hz, 1H), 3.60 (dd, $J = 4.1$, 9.9 Hz, 1H), 3.72–3.78 (m, 1H), 5.45 (d, $J = 3.0$ Hz, 1H), 5.67 ppm (dt, $J = 1.2$, 2.7 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = -5.3$ (CH_3), −1.3 (CH_3), 18.2 (C), 25.8 (CH_3), 40.1 (CH_2), 66.7 (CH_2), 70.4 (CH), 127.0 (CH_2), 148.7 ppm (C); IR (film): $\tilde{\nu} = 3580$, 3472, 3049, 2955, 2930, 2897, 2858, 1472, 1463, 1390, 1362, 1250, 1116, 1037, 1006, 930, 837, 777, 759, 690, 668 cm^{-1}; MS (EI): m/z (%): 175 (8), 149 (11), 147 (36), 117 (73), 75 (43), 73 (100), 67 (62); HRMS (ESI): m/z: calcd for $C_{14}H_{32}O_2Si_2Na$ [M^++Na]: 311.1831, found: 311.1833.

(*R*)-4-Bromo-1-(*tert*-butyldimethylsilyloxy)pent-4-en-2-ol (12): A precooled (−78 °C) solution of Br_2 (0.02 mol, 1.02 mL) in CH_2Cl_2 (43 mL) was added via cannula within 1 min to a solution of **11** (4.44 g, 0.015 mol) in CH_2Cl_2 (88 mL) at −78 °C. The resulting mixture was stirred at that temperature for 5 min before a cold (−78 °C) solution of MeONa (3.86 g, 4.66 mol) in MeOH (180 mL) was added via cannula within 1 min. The mixture was then allowed to stir at −20 °C for 4 h before HOAc (80 mL) was introduced and stirring continued at ambient temperature for 2 h. After evaporation of the solvents under reduced pressure at a bath temperature of 35 °C, the residue was suspended in Sorensen buffer (0.4 M, pH 7, 400 mL). The mixture was extracted with CH_2Cl_2 (3 × 100 mL), the combined organic phases were dried over Na_2SO_4 and evaporated, and the crude product purified by flash chromatography (hexanes/ethyl acetate 40:1) to give bromide **12** as a colorless oil (3.25 g, 72%). $[\alpha]_D^{20} = +1.3$ ($CHCl_3$, $c = 0.65$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.08$ (s, 6H), 0.91 (s, 9H), 2.38 (br s, 1H), 2.56 (ddd, $J = 0.8$, 5.3, 14.6 Hz, 1H), 2.61 (ddd, $J =$ 0.7, 7.3, 14.3 Hz, 1H), 3.52 (dd, $J = 6.1$, 10.0 Hz, 1H), 3.67 (dd, $J = 3.8$, 10.0 Hz, 1H), 3.96–4.01 (m, 1H), 5.52 (d, $J = 1.6$ Hz, 1H), 5.69 ppm (dd, $J = 1.0$, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -5.4$ (CH_3), −5.3 (CH_3), 18.2 (C), 25.8 (CH_3), 45.1 (CH_2), 65.8 (CH_2), 69.4 (CH), 119.1 (CH_2), 130.1 ppm (C); IR (film): $\tilde{\nu} = 3431$, 2954, 2929, 2858, 1631, 1471, 1463, 1390, 1361, 1253, 1205, 1114, 1006, 938, 888, 838, 775, 668 cm^{-1}; MS (EI): m/z (%): 175 (5), 147 (9), 145 (10), 117 (100), 105 (12), 75 (87), 73 (21); HRMS (ESI): m/z: calcd for $C_{11}H_{23}O_2BrSiNa$ [M^++Na]: 317.0545, found: 317.0542.

(2*R*,*E*)-1-(*tert*-Butyldimethylsilyloxy)-4-methylene-7-(tetrahydro-2*H*-pyran-2-yloxy)hept-5-en-2-ol (16): A solution of $Pd(OAc)_2$ (0.38 g, 1.6 mmol), 1,1′-diphenylphosphinoferrocene (dppf) (0.93 g, 1.6 mmol) and THF (60 mL) was stirred for 2 min before trifluoroborate **15** (5.46 g, 22 mmol), bromide **12** (5.00 g, 16 mmol) and *tert*-butylamine (23 mL) were successively added. The flask was tightly stoppered and the mixture was stirred at 85 °C for 1.5 h. For work up, the mixture was allowed to reach ambient temperature before it was diluted with Sorensen buffer (0.4 M, pH 7, 105 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic fractions were dried over Na_2SO_4 and evaporated. The residue was taken up in Et_2O (130 mL) and hexanes (280 mL), remaining solid materials were filtered off, the filtrate was evaporated and the crude product was purified by flash chromatography (hexanes/ethyl acetate 20:1 → 10:1) to give compound **16** as a colorless oil (4.68 g, 78%). $[\alpha]_D^{20} = +0.8$ ($CHCl_3$, $c = 0.54$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.06$ (s, 6H), 0.89 (s, 9H), 1.50–1.63 (m, 4H), 1.68–1.75 (m, 1H), 1.78–1.89 (m, 1H), 2.32–2.37 (m, 2H), 2.43 (dd, $J = 5.7$, 14.2 Hz, 1H), 3.48 (dd, $J = 6.4$, 9.9 Hz, 1H), 3.48–3.53 (m, 1H), 3.60 (dd, $J = 4.1$, 9.9 Hz, 1H), 3.79–3.89 (m, 2H), 4.04 (ddd, $J = 0.9$, 6.4, 13.0 Hz, 1H), 4.29 (ddd, $J = 1.1$, 5.5, 13.0 Hz, 1H), 4.64 (t, $J = 3.5$ Hz, 1H), 5.05 (s, 1H), 5.10 (s, 1H), 5.84 (dt, $J = 6.0$, 15.9 Hz, 1H), 6.29 ppm (d, $J = 15.9$ Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = -5.4$ (CH_3), 18.2 (C), 19.3 (CH_2), 25.4 (CH_2), 25.8 (CH_3), 30.5 (CH_2), 36.1 (CH_2), 62.1 (CH_2), 66.5 (CH_2), 67.4 (CH_2), 69.9 (CH), 97.8 (CH), 117.9 (CH_2), 126.1 (CH), 133.8 (CH), 141.8 ppm (C); IR (film): $\tilde{\nu} = 3471$, 2928, 2856, 1607, 1463, 1388, 1360, 1323, 1253, 1116, 1076, 1023, 968, 904, 833, 813, 775, 668 cm^{-1}; MS (EI): m/z (%): 197 (6), 159 (2), 119 (2), 118 (6), 117 (58), 105 (14), 86 (6), 85 (100), 81 (10), 79 (8), 75 (25), 73 (18), 57 (12); HRMS (ESI): m/z: calcd for $C_{19}H_{36}O_4SiNa$ [M^++Na]: 379.2278, found: 379.2275.

(2*R*,*E*)-1-(*tert*-Butyldimethylsilyloxy)-4-methylene-7-(tetrahydro-2*H*-pyran-2-yloxy)hept-5-en-2-yl hex-4-ynoate (17): EDC·HCl (3.47 g, 0.018 mol) and DMAP (0.768 g, 0.006 mol) were successively added to a solution of 4-hexynoic acid (2.03 g, 0.018 mol) and (iPr)$_2$NEt (3.21 mL, 0.018 mol) in CH_2Cl_2 (36 mL). The mixture was stirred for 10 min before a solution of HOAt (2.73 g, 0.02 mol) in DMF (20 mL) was introduced. The mixture was cooled to 0 °C, a solution of **16** (3.87 g, 0.01 mol) in

CH_2Cl_2 (36 mL) was added, and the resulting mixture was stirred at ambient temperature for 14 h. The reaction was quenched with Sorensen buffer (0.4 M, pH 7, 60 mL), the aqueous phase was extracted with CH_2Cl_2 (4×20 mL), the combined organic layers were dried over Na_2SO_4 and evaporated, and residual DMF removed in high vacuum before the residue was purified by flash chromatography (hexanes/ethyl acetate 30:1) to give ester **17** as a colorless oil (4.72 g, 97%). $[\alpha]_D^{20}=+15.5$ ($CHCl_3$, $c=0.49$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.04$ (s, 6H), 0.88 (s, 9H), 1.50–1.64 (m, 4H), 1.68–1.74 (m, 1H), 1.75 (t, $J=2.4$ Hz, 3H), 1.80–1.90 (m, 1H), 2.38–2.49 (m, 5H), 2.60 (dd, $J=5.9$, 14.2 Hz, 1H), 3.48–3.53 (m, 1H), 3.61 (dd, $J=4.7$, 10.8 Hz, 1H), 3.65 (dd, $J=4.9$, 10.9 Hz, 1H), 3.87 (ddd, $J=3.3$, 8.4, 11.2 Hz, 1H), 4.01–4.07 (m, 1H), 4.30 (dddd, $J=1.3$, 5.5, 5.6, 12.6 Hz, 1H), 4.65 (t, $J=3.5$ Hz, 1H), 5.02 (s, 1H), 5.02–5.07 (m, 1H), 5.07 (s, 1H), 5.91 (dt, $J=5.9$, 15.9 Hz, 1H), 6.27 ppm (d, $J=15.9$ Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=-5.4$ (CH_3), 3.4 (CH_3), 14.6 (CH_2), 18.2 (C), 19.3 (CH_2), 25.4 (CH_2), 25.8 (CH_3), 30.5 (CH_2), 33.2 (CH_2), 34.1 (CH_2), 62.1 (CH_2), 63.6 (CH_2), 67.4 (CH_2), 73.2 (CH), 76.2 (C), 77.2 (C), 97.8 (CH), 118.2 (CH_2), 126.1 (CH), 133.6 (CH), 141.2 (C), 171.5 ppm (C); IR (film): $\tilde{\nu}=2929$, 2857, 1736, 1608, 1463, 1441, 1360, 1252, 1200, 1164, 1120, 1079, 1024, 1005, 971, 903, 834, 813, 775, 668 cm^{-1}; MS (EI): m/z (%): 197 (12), 169 (20), 159 (45), 117 (15), 105 (22), 85 (100), 75 (18), 73 (12), 67 (16), 57 (7), 41 (6); HRMS (ESI): m/z: calcd for $C_{25}H_{42}O_5SiNa$ [M^++Na]: 473.2691, found: 473.2693.

(*R*,*E*)-1-(*tert*-Butyldimethylsilyloxy)-7-hydroxy-4-methylenehept-5-en-2-yl hex-4-ynoate (18): PPTS (0.655 g) was added to a solution of **17** (4.52 g, 0.01 mol) in *i*PrOH (668 mL) and the mixture was stirred at 70 °C for 3.5 h. After reaching ambient temperature, triethylamine (6 mL) was introduced, all volatile materials were evaporated under reduced pressure at 35 °C, and the residue was purified by flash chromatography (hexanes/ethyl acetate 8:1) to give alcohol **18** as a colorless oil (3.55 g, 97%). $[\alpha]_D^{20}=+22.9$ ($CHCl_3$, $c=0.5$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.04$ (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 1.61 (brs, 1H), 1.75 (t, $J=2.4$ Hz, 3H), 2.38–2.49 (m, 5H), 2.60 (ddd, $J=0.6$, 6.0, 14.1 Hz, 1H), 3.63 (dd, $J=4.6$, 10.9 Hz, 1H), 3.66 (dd, $J=5.0$, 10.9 Hz, 1H), 4.22 (dd, $J=1.2$, 5.6 Hz, 2H), 5.02 (s, 1H), 5.02–5.08 (m, 1H), 5.08 (s, 1H), 5.99 (dt, $J=5.7$, 15.9 Hz, 1H), 6.26 ppm (d, $J=15.9$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-5.3$ (CH_3), 3.4 (CH_3), 14.6 (CH_2), 18.2 (C), 25.7 (CH_3), 33.4 (CH_2), 34.1 (CH_2), 63.5 (CH_2), 63.7 (CH_2), 73.1 (CH), 76.2 (C), 77.2 (C), 118.4 (CH_2), 128.8 (CH), 132.4 (CH), 141.1 (C), 171.6 ppm (C); IR (film): $\tilde{\nu}=3429$, 2954, 2928, 2857, 1733, 1607, 1463, 1361, 1252, 1167, 1128, 1087, 1048, 970, 833, 775, 667 cm^{-1}; MS (EI): m/z (%): 309 (13), 197 (25), 170 (14), 169 (100), 123 (21), 117 (51), 105 (93), 95 (25), 93 (11), 81 (17), 79 (42), 75 (71), 73 (32), 67 (46), 55 (15), 41 (16); HRMS (ESI): m/z: calcd for $C_{20}H_{34}O_4SiNa$ [M^++Na]: 389.2115, found: 389.2118.

(*R*)-1-(*tert*-Butyldimethylsilyloxy)-4-((2*S*,3*S*)-3-(hydroxymethyl)oxiran-2-yl)pent-4-en-2-yl hex-4-ynoate (19): A Schlenk flask was charged with CH_2Cl_2 (96 mL), 4 Å MS and L-(+)-DET (0.49 mL, 2.87 mmol) and the suspension stirred for 4 h. After cooling to −20 °C, Ti(O*i*Pr)$_4$ (0.85 mL, 2.87 mmol) was introduced and stirring continued at −20 °C for 1.5 h. A solution of *t*BuOOH (5.5 M in decane, 4.17 mL, pre-dried over MS 4 Å) was added and the suspension stirred for 30 min at −20 °C before a solution of **18** (3.51 g, 9.57 mmol, pre-dried over MS 4 Å for 4 h prior to use) in CH_2Cl_2 (19 mL) was introduced. The mixture was stirred at −20 °C for 14 h before it was poured into a cooled (0 °C) solution of $FeSO_4{\cdot}7H_2O$ (4.6 g) and citric acid (10 g) in water (200 mL). The suspension was stirred at 0 °C for 30 min, the phases were separated, the aqueous layer extracted with $CHCl_3$ (5×30 mL), the combined extracts were dried over Na_2SO_4 and evaporated, and the residue purified by flash chromatography (hexanes/ethyl acetate 7:1) to afford epoxide **19** as a colorless oil (3.05 g, 83%, d.r. >98%). $[\alpha]_D^{20}=+15.5$ ($CHCl_3$, $c=0.5$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.04$ (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 1.75 (t, $J=2.4$ Hz, 3H), 1.87 (brs, 1H), 2.24 (dd, $J=7.5$, 14.5 Hz, 1H), 2.36–2.50 (m, 5H), 3.10 (dt, $J=2.9$, 3.6 Hz, 1H), 3.40 (d, $J=2.1$ Hz, 1H), 3.62 (dd, $J=4.5$, 10.8 Hz, 1H), 3.65 (dd, $J=4.9$, 10.8 Hz, 1H), 3.69–3.75 (m, 1H), 3.90 (d, $J=12.6$ Hz, 1H), 4.99 (dq, $J=5.0$, 7.4 Hz, 1H), 5.05 (s, 1H), 5.24 ppm (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=-5.4$ (CH_3), 3.4 (CH_3), 14.6 (CH_2), 18.2 (C), 25.7 (CH_3), 32.7 (CH_2), 34.0 (CH_2), 56.9 (CH), 59.2 (CH), 61.4 (CH_2), 63.5 (CH_2), 73.2 (CH), 76.3 (C), 77.1 (C), 116.1 (CH_2), 140.3 (C), 171.7 ppm (C); IR (film): $\tilde{\nu}=3474$, 2954, 2928, 2857, 1735, 1644, 1463, 1440, 1361, 1252, 1166, 1129, 1085, 1048, 1004, 910, 833, 776, 668 cm^{-1}; MS (EI): m/z (%): 213 (18), 195 (21), 183 (41), 170 (14), 169 (100), 121 (29), 117 (32), 95 (29), 93 (14), 79 (11), 75 (80), 73 (36), 67 (53), 55 (14), 41 (15); HRMS (ESI): m/z: calcd for $C_{20}H_{34}O_5SiNa$ [M^++Na]: 405.2065, found: 405.2067.

(*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-((2*S*,3*S*)-3-(hydroxymethyl)oxiran-2-yl)pent-4-en-2-yl hex-4-ynoate (33): Prepared analogously from *ent*-**18** (2.0 g, 4.58 mmol) using L-(+)-DET (0.522 g, 2.61 mmol) as the chiral ligand. Colorless oil (1.9 g, 92%, d.r. >98%). $[\alpha]_D^{20}=-0.7$ ($CHCl_3$, $c=0.5$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.04$ (s, 6H), 0.88 (s, 9H), 1.74 (t, $J=2.4$ Hz, 3H), 1.87 (m, 1H), 2.28 (dd, $J=8.6$, 14.5 Hz, 1H), 2.34–2.48 (m, 5H), 3.02 (dd, $J=3.2$, 5.8 Hz, 1H), 3.36 (d, $J=1.9$ Hz, 1H), 3.62 (dd, $J=4.8$, 10.9 Hz, 1H), 3.65 (dd, $J=5.2$, 10.9 Hz, 1H), 3.74 (m, 1H), 3.89 (m, 1H), 5.02 (s, 1H), 5.07 (dq, $J=4.9$, 9.8 Hz, 1H), 5.20 ppm (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=-5.4$ (CH_3), 3.4 (CH_3), 14.6 (CH_2), 18.2 (C), 25.7 (CH_3), 33.4 (CH_2), 34.0 (CH_2), 56.5 (CH), 59.9 (CH), 61.3 (CH_2), 63.9 (CH_2), 72.8 (CH), 76.3 (C), 77.1 (C), 115.0 (CH_2), 140.3 (C), 171.6 ppm (C); IR (film): $\tilde{\nu}=3468$, 3088, 2954, 2929, 2885, 2857, 1737, 1645, 1472, 1463, 1440, 1388, 1376, 1362, 1254, 1168, 1131, 1087, 1049, 1005, 910, 838, 778, 669 cm^{-1}; MS (EI): m/z (%): 214 (3), 213 (17), 195 (21), 183 (21), 170 (14), 169 (100), 121 (28), 117 (27), 95 (25), 93 (15), 81 (10), 79 (11), 75 (83), 73 (36), 67 (53), 55 (15), 41 (18); HRMS (ESI): m/z: calcd for $C_{20}H_{34}O_5SiNa$ [M^++Na]: 405.2065, found: 405.2068; elemental analysis calcd (%) for $C_{20}H_{34}O_5Si$ (382.57): C 62.79, H 8.96; found: C 62.68, H 8.90.

(*R*)-1-(*tert*-Butyldimethylsilyloxy)-4-((2*S*,3*R*)-3-formyloxiran-2-yl)pent-4-en-2-yl hex-4-ynoate (20): Solid $NaHCO_3$ (6.21 g, 0.073 mol) was added to a solution of **19** (2.83 g, 7.39 mmol) in CH_2Cl_2 (92 mL) and the resulting suspension was stirred for 30 min. The mixture was cooled to 0 °C before Dess–Martin periodinane (5.02 g, 0.011 mol) was introduced. Stirring was continued for 2.5 h at ambient temperature before cold (0 °C) sat. aq. $NaHCO_3$ (37 mL) and sat. aq. $Na_2S_2O_3$ (37 mL) were added. The aqueous phase was extracted with CH_2Cl_2 (3×30 mL), the combined organic fractions were dried over Na_2SO_4 and evaporated, and the residue purified by flash chromatography (hexanes/ethyl acetate 10:1) to give aldehyde **20** as a colorless oil (2.44 g, 87%). $[\alpha]_D^{20}=+73$ ($CHCl_3$, $c=0.52$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.04$ (s, 6H), 0.88 (s, 9H), 1.74 (t, $J=2.4$ Hz, 3H), 2.26 (ddd, $J=0.7$, 7.8, 14.7 Hz, 1H), 2.36–2.48 (m, 5H), 3.34 (dd, $J=1.9$, 6.1 Hz, 1H), 3.61 (dd, $J=4.8$, 10.9 Hz, 1H), 3.66 (dd, $J=4.7$, 10.9 Hz, 1H), 3.68 (d, $J=2.0$ Hz, 1H), 4.99 (dq, $J=4.8$, 7.8 Hz, 1H), 5.17 (s, 1H), 5.34 (s, 1H), 9.09 ppm (d, $J=6.1$ Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=-5.4$ (CH_3), 3.4 (CH_3), 14.6 (CH_2), 18.2 (C), 25.7 (CH_3), 32.1 (CH_2), 34.0 (CH_2), 57.6 (CH), 59.7 (CH), 63.3 (CH_2), 72.8 (CH), 76.3 (C), 77.1 (C), 117.9 (CH_2), 138.3 (C), 171.5 (C), 197.2 ppm (CH); IR (film): $\tilde{\nu}=2954$, 2929, 2857, 1730, 1472, 1440, 1361, 1252, 1165, 1134, 1090, 1049, 1005, 916, 833, 776, 669 cm^{-1}; MS (EI): m/z (%): 323 (2), 212 (4), 211 (22), 207 (8), 184 (9), 183 (57), 170 (14), 169 (100), 95 (42), 75 (61), 73 (33), 67 (57), 55 (12), 41 (17); HRMS (ESI): m/z: calcd for $C_{20}H_{32}O_5SiNa$ [M^++Na]: 403.1912, found: 403.1911.

(*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-((2*S*,3*R*)-3-formyloxiran-2-yl)pent-4-en-2-yl hex-4-ynoate (34): Prepared analogously from **33** (1.4 g, 3.66 mmol) as a colorless oil (1.26 g, 90%). $[\alpha]_D^{20}=+54.3$ ($CHCl_3$, $c=0.5$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.05$ (s, 6H), 0.88 (s, 9H), 1.75 (t, $J=2.3$ Hz, 3H), 2.25 (dd, $J=8.1$, 14.7 Hz, 1H), 2.34 (dd, $J=4.6$, 14.7 Hz, 1H), 2.40–2.49 (m, 4H), 3.36 (dd, $J=5.9$, 1.8 Hz, 1H), 3.59–3.67 (m, 3H), 5.02 (dq, $J=4.9$, 9.8 Hz, 1H), 5.17 (s, 1H), 5.33 (s, 1H), 9.11 ppm (d, $J=5.8$ Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=-5.4$ (CH_3), 3.4 (CH_3), 14.6 (CH_2), 18.2 (C), 25.7 (CH_3), 32.1 (CH_2), 34.0 (CH_2), 57.6 (CH), 59.8 (CH), 63.5 (CH_2), 72.9 (CH), 76.3 (C), 77.1 (C), 117.1 (CH_2), 138.4 (C), 171.5 (C), 197.3 ppm (CH); IR (film): $\tilde{\nu}=3088$, 2955, 2929, 2885, 2857, 1733, 1645, 1472, 1463, 1440, 1376, 1361, 1254, 1167, 1134, 1092, 1049, 1006, 915, 838, 778, 669 cm^{-1}; MS (EI): m/z (%): 323 (2), 212 (6), 211 (39), 207 (7), 183 (23), 181 (7), 170 (14), 169 (100), 95 (37), 75 (60), 73 (30), 67 (51), 55 (11), 41 (16); HRMS (ESI): m/z: calcd for $C_{20}H_{32}O_5SiNa$ [M^++Na]: 403.1914, found: 403.1911; elemental analysis calcd (%) for $C_{20}H_{32}O_5Si$ (380.55): C 63.12, H 8.48; found: C 63.06, H 8.40.

(*R*)-1-(*tert*-Butyldimethylsilyloxy)-4-((2*S*,3*S*)-3-((*R*)-1-hydroxy-2-methylenehex-4-ynyl)oxiran-2-yl)pent-4-en-2-yl hex-4-ynoate (24): Bromide **22**

(3.01 g, 18.92 mmol) was added to a solution of $ZnBr_2$ (2.13 g, 9.459 mmol) in THF (9.4 mL) at 0 °C. The solution was then transferred via cannula to a suspension of Li sand (0.131 g, 18.92 mmol) in THF (16 mL) at −5 °C and the resulting mixture was ultrasonicated (Sonorex RK SIOH cleaning bath) for 2 h at 0 °C. The solvent was distilled off from the stirred suspension under high vacuum and the brown residue was dried for 2 h at ambient temperature (10^{-3} Torr) to ensure complete removal of the THF. The remaining product was covered with toluene (45 mL), the suspension was stirred for 5 min, before all insoluble materials were allowed to settle during 5 min. The supernatant brown solution was then carefully filtered and transferred via a cannula to a second Schlenk tube.

A solution of aldehyde **20** (0.90 g, 2.36 mmol) in toluene (9 mL) was added to the solution of the zinc reagent **23** thus formed at −50 °C and the resulting mixture was stirred at −40 °C for 16 h and at −25 °C for 2 h. The reaction was quenched with sat. aq. NH_4Cl (20 mL), the mixture was extracted with CH_2Cl_2 (3×20 mL), the combined organic phases were dried over Na_2SO_4 and carefully evaporated (30 °C), and the crude product (*syn*/*anti* 7.5:1, NMR) was purified by flash chromatography (hexanes/ethyl acetate 10:1) to give compound **24** as a single diastereomer in form of a colorless oil (695 mg, 64 %). $[\alpha]_D^{20} = +11.5$ ($CHCl_3$, $c = 0.54$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.04$ (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 1.75 (t, $J = 2.4$ Hz, 3H), 1.81 (t, $J = 2.5$ Hz, 3H), 2.16 (d, $J = 6.3$ Hz, 1H), 2.24 (dd, $J = 7.7$, 14.5 Hz, 1H), 2.36 (dd, $J = 5.5$, 14.7 Hz, 1H), 2.39–2.49 (m, 4H), 3.00–3.05 (m, 2H), 3.07 (dd, $J = 2.2$, 4.4 Hz, 1H), 3.44 (d, $J = 2.1$ Hz, 1H), 3.61 (dd, $J = 4.7$, 10.9 Hz, 1H), 3.65 (dd, $J = 5.0$, 10.9 Hz, 1H), 4.15 (t, $J = 4.9$ Hz, 1H), 5.01 (dq, $J = 4.9$, 7.9 Hz, 1H), 5.07 (s, 1H), 5.24 (s, 1H), 5.25 (s, 1H), 5.30 ppm (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = -5.4$ (CH_3), 3.4 (CH_3), 3.5 (CH_3), 14.6 (CH_2), 18.2 (C), 23.1 (CH_2), 25.7 (CH_3), 32.4 (CH_2), 34.0 (CH_2), 57.3 (CH), 61.0 (CH), 63.5 (CH_2), 72.7 (CH), 72.9 (CH), 75.3 (C), 76.3 (C), 77.1 (C), 78.7 (C), 113.1 (CH_2), 116.3 (CH_2), 140.0 (C), 143.7 (C), 171.5 ppm (C); IR (film): $\tilde{\nu} =$ 3481, 2955, 2927, 2858, 1734, 1651, 1463, 1422, 1361, 1252, 1166, 1129, 1086, 1048, 1004, 909, 834, 776, 736 cm^{-1}; MS (EI): *m*/*z* (%): 291 (6), 273 (11), 227 (6), 207 (8), 199 (11), 183 (59), 170 (15), 169 (100), 117 (37), 109 (21), 107 (11), 95 (29), 81 (19), 79 (20), 77 (12), 75 (83), 73 (50), 67 (55), 55 (18), 53 (13), 41 (20); HRMS (ESI): *m*/*z*: calcd for $C_{26}H_{40}O_5SiNa$ [M^+ +Na]: 483.2534, found: 483.2537.

(*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-((2*S*,3*S*)-3-((*R*)-1-hydroxy-2-methylenehex-4-ynyl)oxiran-2-yl)pent-4-en-2-yl hex-4-ynoate (35): Prepared analogously from aldehyde **34** (1.2 g, 3.15 mmol) as a colorless oil (1.01 g, 70 %). $[\alpha]_D^{20} = +6.9$ ($CHCl_3$, $c = 0.57$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 0.04 (s, 6H), 0.88 (s, 9H), 1.74 (t, $J = 2.5$ Hz, 3H), 1.81 (t, $J = 2.6$ Hz, 3H), 2.17 (d, $J = 6.5$ Hz, 1H), 2.23 (dd, $J = 8.5$, 14.6 Hz, 1H), 2.31 (dd, $J = 4.5$, 14.6 Hz, 1H), 2.41 (m, 2H), 2.45–2.48 (m, 2H), 2.93–2.99 (m, 1H), 3.03 (dd, $J = 2.2$, 4.1 Hz, 1H), 3.06–3.11 (m, 1H), 3.41 (d, $J = 2.1$ Hz, 1H), 3.61 (dd, $J = 4.8$, 10.9 Hz, 1H), 3.65 (dd, $J = 5.2$, 10.9 Hz, 1H), 4.19 (dd, $J = 4.2$, 6.1 Hz, 1H), 5.04 (dq, $J = 4.8$, 8.7 Hz, 1H), 5.05 (s, 1H), 5.22 (s, 1H), 5.24 (s, 1H), 5.31 ppm (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = -5.4$ (CH_3), 3.4 (CH_3), 3.5 (CH_3), 14.6 (CH_2), 18.2 (C), 23.0 (CH_2), 25.7 (CH_3), 32.7 (CH_2), 34.0 (CH_2), 57.0 (CH), 61.0 (CH), 63.9 (CH_2), 72.4 (CH), 73.0 (CH), 75.3 (C), 76.3 (C), 77.2 (C), 78.7 (C), 113.0 (CH_2), 115.6 (CH_2), 140.2 (C), 143.8 (C), 171.5 ppm (C); IR (film): $\tilde{\nu} =$3489, 3086, 2955, 2928, 2885, 2857, 1737, 1652, 1472, 1463, 1423, 1376, 1362, 1254, 1167, 1131, 1090, 1049, 1005, 909, 838, 778, 669 cm^{-1}; MS (EI): *m*/*z* (%): 291 (7), 273 (14), 227 (6), 207 (8), 199 (11), 184 (6), 183 (36), 173 (7), 171 (10), 170 (14), 169 (100), 145 (7), 117 (30), 109 (16), 107 (10), 95 (25), 89 (9), 81 (15), 79 (18), 75 (70), 73 (44), 67 (44), 55 (15), 41 (15); HRMS (ESI): *m*/*z*: calcd for $C_{26}H_{40}O_5SiNa$ [M^++Na]: 483.2540, found: 483.2537; elemental analysis calcd (%) for $C_{26}H_{40}O_5Si$ (460.68): C 67.79, H 8.75; found: C 67.71, H 8.79.

(*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-((2*S*,3*S*)-3-((*S*)-1-hydroxy-2-methylenehex-4-ynyl)oxiran-2-yl)pent-4-en-2-yl hex-4-ynoate (43): Dess–Martin periodinane (0.764 g, 1.80 mmol) was added to a solution of alcohol **35** (0.67 g, 1.45 mmol) in CH_2Cl_2 (47 mL). The mixture was stirred for 1 h before the reaction was quenched with sat. aq. $Na_2S_2O_3$ (10 mL) and sat. aq. $NaHCO_3$ (10 mL). After stirring for 10 min, the aqueous phase was extracted with CH_2Cl_2 (3×10 mL), the combined extracts were dried over Na_2SO_4 and concentrated, and the remaining solution was rapidly passed through a plug of silica (hexanes/ethyl acetate 10:1). The resulting ketone **42** was dissolved in a freshly prepared solution of $CaCl_2$ (0.31 g, 2.75 mmol) in MeOH (25 mL). $NaBH_4$ (0.10 g, 2.63 mmol) was added in two portions at 0 °C and the resulting mixture was stirred at that temperature for 10 min, before the reaction was quenched with a small amount of ice. All volatile materials were evaporated, the residue was triturated with CH_2Cl_2 (10 mL), the organic phase was dried over Na_2SO_4 and evaporated, and the residue (*syn*/*anti* 1:11, NMR) was purified by flash chromatography (hexanes/ethyl acetate 10:1) to give alcohol **43** as a colorless oil (0.474 g, 71 % over two steps). $[\alpha]_D^{20} = -6.1$ ($CHCl_3$, $c = 0.57$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.04$ (s, 6H), 0.88 (s, 9H), 1.73–1.76 (m, 3H), 1.81–1.82 (m, 3H), 2.22–2.36 (m, 3H), 2.41–2.48 (m, 4H), 2.93–3.11 (m, 3H), 3.42–3.43 (m, 1H), 3.63–3.65 (m, 2H), 4.26 (m, 1H), 5.03–5.09 (m, 2H), 5.20 (s, 1H), 5.24 (s, 1H), 5.35 ppm (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = -5.4$ (CH_3), 3.4 (CH_3), 3.5 (CH_3), 14.6 (CH_2), 18.2 (C), 22.4 (CH_2), 25.7 (CH_3), 33.1 (CH_2), 34.0 (CH_2), 56.4 (CH), 60.8 (CH), 63.9 (CH_2), 72.0 (CH), 73.0 (CH), 75.4 (C), 76.3 (C), 77.2 (C), 78.6 (C), 113.3 (CH_2), 115.4 (CH_2), 140.2 (C), 143.3 (C), 171.7 ppm (C); IR (film): $\tilde{\nu} =$3489, 3086, 2955, 2928, 2885, 2857, 1737, 1652, 1472, 1463, 1423, 1376, 1362, 1254, 1167, 1131, 1090, 1049, 1005, 909, 838, 778, 669 cm^{-1}; MS (EI): *m*/*z* (%): 291 (7), 273 (14), 227 (6), 207 (8), 199 (11), 184 (6), 183 (36), 173 (7), 171 (10), 170 (14), 169 (100), 145 (7), 117 (30), 109 (16), 107 (10), 95 (25), 89 (9), 81 (15), 79 (18), 75 (70), 73 (44), 67 (44), 55 (15), 41 (15); HRMS (ESI): *m*/*z*: calcd for $C_{26}H_{40}O_5SiNa$ [M^+ +Na]: 483.2540, found: 483.2537; elemental analysis calcd (%) for $C_{26}H_{40}O_5Si$ (460.68): C 67.79, H 8.75; found: C 67.71, H 8.79.

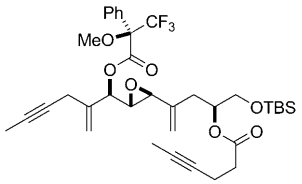
(*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-((2*R*,3*R*)-3-((*R*)-1-hydroxy-2-methylenehex-4-ynyl)oxiran-2-yl)pent-4-en-2-yl hex-4-ynoate (51): 1,2-Dibromoethane (3 drops) was added to a stirred suspension of Mg turnings (2.04 g, 84.09 mmol) in THF (4.5 mL) and the mixture was heated at 50 °C for 5 min. Bromide **22** (1.34 g, 8.41 mmol) was then added at such a rate as to maintain gentle reflux and the mixture was stirred at ambient temperature for 1.5 h once the addition was complete. The resulting green cloudy solution of the Grignard reagent was diluted with THF (5 mL), transferred via cannula into another flask and cooled to −10 °C. A solution of aldehyde *ent*-**20** (0.80 g, 2.10 mmol) in THF (1.6 mL) was introduced and the mixture was stirred at −10 °C for 3 h. The reaction was quenched with sat. aq. NH_4Cl (6 mL), the aqueous phase was extracted with CH_2Cl_2 (4×5 mL), the combined organic layers were dried over Na_2SO_4 and evaporated (30 °C), and the residue was purified by flash chromatography (hexanes/ethyl acetate 10:1) to give the corresponding alcohol as a colorless oil (*syn*/*anti* 1:1, 0.68 g, 70 %).

Dess–Martin periodinane (0.78 g, 1.83 mmol) was added to a solution of this alcohol (0.68 g, 1.47 mmol) in CH_2Cl_2 (50 mL) and the resulting mixture was stirred for 1 h. The reaction was quenched with sat. aq. $Na_2S_2O_3$ (20 mL) and sat. aq. $NaHCO_3$ (20 mL) and the slurry was stirred for 10 min. The aqueous phase was extracted with CH_2Cl_2 (3×20 mL), the combined organic layers were dried over Na_2SO_4 and concentrated to ca. $^1/_4$ of the original volume (30 °C). The solution of crude ketone **50** was filtered through a plug of silica, which was rinsed with hexanes/ethyl acetate 10:1. The filtrate was evaporated and the resulting ketone **50** dissolved in a freshly prepared solution of $CaCl_2$ (0.41 g, 3.67 mmol) in MeOH (25 mL). $NaBH_4$ (0.069 g, 1.85 mmol) was added at 0 °C and stirring continued at this temperature for 10 min before the reaction was quenched with a small amount of ice and concentrated under reduced pressure. The residue was triturated with CH_2Cl_2 (10 mL), the organic phase was dried over Na_2SO_4 and evaporated, and the residue (*anti*/*syn* = 10:1, NMR) purified by flash chromatography (hexanes/ethyl acetate 10:1) to give alcohol **51** as a colorless oil (0.47 g, 70 %). $[\alpha]_D^{20} = -35.1$ ($CHCl_3$, $c = 0.6$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.04$ (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 1.75 (t, $J = 2.4$ Hz, 3H), 1.81 (t, $J = 2.5$ Hz, 3H), 2.23 (dd, $J = 7.1$, 14.3 Hz, 1H), 2.32 (d, $J = 2.5$ Hz, 1H), 2.36–2.49 (m, 5H), 2.93–2.98 (m, 1H), 3.00–3.09 (m, 1H), 3.06 (dd, $J = 2.2$, 4.0 Hz, 1H), 3.45 (d, $J = 2.0$ Hz, 1H), 3.62 (dd, $J = 4.5$, 10.9 Hz, 1H), 3.65 (dd, $J = 4.9$, 10.9 Hz, 1H), 4.30 (s, 1H), 5.00 (dq, $J = 4.8$, 6.1 Hz, 1H), 5.05 (s, 1H), 5.24 (s, 2H), 5.34 ppm (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = -5.4$ (CH_3), 3.4 (CH_3), 3.4 (CH_3), 14.6 (CH_2), 18.2 (C), 22.5 (CH_2), 25.7 (CH_3), 32.7 (CH_2), 34.1 (CH_2), 56.5 (CH), 60.7 (CH), 63.4 (CH_2), 71.7 (CH), 73.1

(CH), 75.4 (C), 76.3 (C), 77.1 (C), 78.6 (C), 113.5 (CH_2), 116.1 (CH_2), 140.1 (C), 143.1 (C), 171.7 ppm (C); IR (film): $\tilde{\nu}$ = 3493, 2955, 2928, 2857, 1735, 1651, 1463, 1422, 1361, 1252, 1166, 1129, 1087, 1048, 1003, 909, 834, 776, 755, 667 cm^{-1}; MS (EI): *m/z* (%): 291 (8), 273 (19), 227 (6), 199 (13), 183 (48), 169 (100), 117 (34), 95 (23), 75 (71), 73 (41), 67 (44); HRMS (ESI): *m/z*: calcd for $C_{26}H_{40}O_5SiNa$ [M^++Na]: 483.2541, found: 483.2537; elemental analysis calcd (%) for $C_{26}H_{40}O_5Si$ (460.68): C 67.79, H 8.75; found: C 68.00, H 8.70.

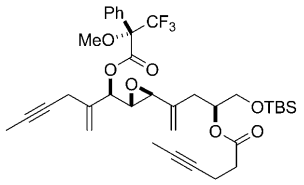
Representative analysis of a pair of Mosher esters

(*S*)-1-(tert-Butyldimethylsilyloxy)-4-((2*S*,3*R*)-3-((*R*)-2-methylene-1-((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy)hex-4-ynyl)oxiran-2-yl)pent-4-en-2-yl hex-4-ynoate: DMAP (6 mg, 0.052 mmol) und (*S*)-α-



methoxy-α-(trifluoromethyl)phenylacetic acid chloride (8.4 μL, 0.045 mmol) were added to a solution of alcohol **35** (16 mg, 0.034 mmol) in CH_2Cl_2 (2 mL) at −20 °C and the resulting mixture was stirred for 1 h at 0 °C. A standard extractive work up followed by flash chromatography (hexanes/ethyl acetate 20:1) gave the Mosher ester as a colorless oil (23 mg, 98 %). $[\alpha]_D^{20}$ = +13.7 ($CHCl_3$, *c* = 0.4); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.04 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 1.73 (t, *J* = 2.4 Hz, 3H), 1.81 (t, *J* = 2.5 Hz, 3H), 2.18 (dd, *J* = 8.6, 14.7 Hz, 1H), 2.27 (dd, *J* = 4.6, 14.8 Hz, 1H), 2.40 (m, 2H), 2.44 (m, 2H), 2.87 (m, 1H), 2.94 (m, 1H), 3.15 (dd, *J* = 2.0, 7.2 Hz, 1H), 3.41 (d, *J* = 1.9 Hz, 1H), 3.60 (dd, *J* = 4.8, 10.8 Hz, 1H), 3.62 (s, 3H), 3.64 (dd, *J* = 5.1, 10.9 Hz, 1H), 4.99 (dq, *J* = 4.8, 9.5 Hz, 1H), 5.08 (s, 1H), 5.10 (s, 1H), 5.24 (s, 1H), 5.26 (d, *J* = 7.1 Hz, 1H), 5.34 (s, 1H), 7.41 (m, 4H), 7.55 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = −5.4, −5.4, 3.3, 3.4, 14.6, 18.2, 23.3, 25.7, 32.0, 34.0, 55.7, 58.3, 58.3, 63.8, 73.0, 74.3, 76.3, 77.1, 70.2, 79.3, 84.6, 115.7, 116.6, 123.3, 127.2, 128.4, 129.6, 132.1, 139.1, 139.6, 165.4, 171.5 ppm; IR (film): $\tilde{\nu}$ = 3065, 2954, 2929, 2857, 1751, 1653, 1496, 1472, 1463, 1451, 1362, 1252, 1170, 1124, 1083, 1018, 916, 838, 814, 779, 720, 698, 669 cm^{-1}; MS (EI): *m/z* (%): 385 (7), 291 (8), 281 (6), 274 (7), 273 (33), 227 (11), 207 (9), 199 (15), 190 (10), 189 (100), 170 (10), 169 (70), 117 (11), 95 (13), 75 (26), 73 (21), 67 (21); HRMS (ESI): *m/z*: calcd for $C_{36}H_{47}O_7SiF_3Na$ [M^++Na]: 699.2936, found: 699.2935; elemental analysis calcd (%) for $C_{36}H_{47}O_7SiF_3$ (676.83): C 63.88, H 7.00; found: C 63.96, H 6.89.

(*S*)-1-(tert-Butyldimethylsilyloxy)-4-((2*S*,3*R*)-3-((*R*)-2-methylene-1-((*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy)hex-4-ynyl)oxiran-2-yl)pent-4-en-2-yl hex-4-ynoate (see Figure 2): Prepared analogously from



alcohol **35** (19 mg, 0.041 mmol) and (*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid chloride (10.0 μL, 0.053 mmol) as a colorless oil (27 mg, 97 %). $[\alpha]_D^{20}$ = −28.7 ($CHCl_3$, *c* = 0.545); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.03 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 1.73 (t, *J* = 2.4 Hz, 3H), 1.81 (t, *J* = 2.5 Hz, 3H), 2.16 (dd, *J* = 8.5, 14.7 Hz, 1H), 2.23 (dd, *J* = 4.7, 14.8 Hz, 1H), 2.40 (m, 2H), 2.44 (m, 2H), 3.01 (m, 1H), 3.05 (m, 1H), 3.11 (dd, *J* = 2.1, 6.2 Hz, 1H), 3.28 (d, *J* = 1.9 Hz, 1H), 3.54 (s, 3H), 3.60 (dd, *J* = 4.8, 10.9 Hz, 1H), 3.63 (dd, *J* = 5.1, 10.9 Hz, 1H), 4.97 (dq, *J* = 4.8, 9.6 Hz, 1H), 5.05 (s, 1H), 5.18 (s, 1H), 5.27 (s, 1H), 5.41 (d, *J* = 6.0 Hz, 1H), 5.44 (s, 1H), 7.41 (m, 4H), 7.54 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = −5.4, −5.4, 3.3, 3.4, 14.6, 18.2, 23.4, 25.7, 32.1, 34.0, 55.5, 57.5, 58.5, 63.8, 73.0, 74.4, 76.3, 77.2, 77.3, 79.4, 84.8, 116.1, 116.3, 123.2, 127.6, 128.4, 129.6, 132.0, 139.5, 139.7, 165.5, 171.4 ppm; IR (film): $\tilde{\nu}$ = 3065, 2954, 2929, 2857, 1751, 1653, 1496, 1472, 1463, 1451, 1362, 1252, 1170, 1124, 1083, 1018, 916, 838, 814, 779, 720, 698, 669 cm^{-1}; MS (EI): *m/z* (%): 385 (7), 291 (8), 281 (6), 274 (7), 273 (33), 227 (11), 207 (9), 199 (15), 190 (10), 189 (100), 170 (10), 169 (70), 117 (11), 95 (13), 75 (26), 73 (21), 67 (21); HRMS (ESI): *m/z*: calcd for $C_{36}H_{47}O_7SiF_3Na$ [M^++Na]: 699.2936, found: 699.2935; elemental analysis calcd (%) for $C_{36}H_{47}O_7SiF_3$ (676.83): C 63.88, H 7.00; found: C 63.96, H 6.89.

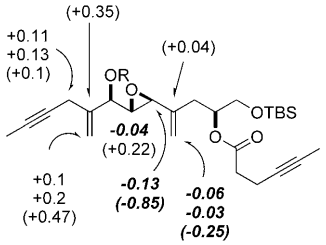


Figure 2. Analysis of the Mosher esters derived from alcohol **35**. The $\Delta\delta^{SR}$ values of ^{1}H (and ^{13}C) NMR signals are given in ppm.

(*R*)-1-(*tert*-Butyldimethylsilyloxy)-4-((2*S*,3*R*)-3-((*R*)-1-(*tert*-butyldimethylsilyloxy)-2-methylenehex-4-ynyl)oxiran-2-yl)pent-4-en-2-yl hex-4-ynoate (25): A solution containing **24** (595 mg, 1.291 mmol), imidazole (967 mg, 14.207 mmol) and TBSCl (1.090 g, 7.232 mmol) in CH_2Cl_2 (26 mL) was stirred at 10 °C for 16 h before the reaction was quenched with water (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), the combined extracts were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate 30:1) to give product **25** as a colorless oil (730 mg, 98 %). $[\alpha]_D^{20}$ = +18.7 ($CHCl_3$, *c* = 0.59); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 3H), 0.04 (s, 3H), 0.06 (s, 3H), 0.11 (s, 3H), 0.88 (s, 9H), 0.91 (s, 9H), 1.75 (t, *J* = 2.3 Hz, 3H), 1.81 (t, *J* = 2.5 Hz, 3H), 2.20 (dd, *J* = 8.0, 14.6 Hz, 1H), 2.32 (dd, *J* = 5.1, 14.7 Hz, 1H), 2.38–2.48 (m, 4H), 2.93 (dd, *J* = 2.2, 6.1 Hz, 1H), 2.88–2.95 (m, 1H), 2.98–3.05 (m, 1H), 3.31 (d, *J* = 2.0 Hz, 1H), 3.60 (dd, *J* = 4.6, 10.6 Hz, 1H), 3.64 (dd, *J* = 4.6, 10.6 Hz, 1H), 3.99 (d, *J* = 6.1 Hz, 1H), 5.00 (ddd, *J* = 5.0, 8.1, 10.3 Hz, 1H), 5.03 (s, 1H), 5.18 (s, 1H), 5.22 (s, 1H), 5.24 ppm (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = −5.4 (CH_3), −5.4 (CH_3), −5.1 (CH_3), −4.8 (CH_3), 3.4 (CH_3), 3.4 (CH_3), 14.6 (CH_2), 18.2 (C), 18.2 (C), 22.6 (CH_2), 25.8 (CH_3), 25.8 (CH_3), 32.0 (CH_2), 34.0 (CH_2), 57.7 (CH), 62.0 (CH), 63.5 (CH_2), 72.8 (CH), 75.9 (CH), 75.6 (C), 76.2 (C), 77.2 (C), 78.4 (C), 112.6 (CH_2), 115.8 (CH_2), 140.3 (C), 144.1 (C), 171.4 ppm (C); IR (film): $\tilde{\nu}$ = 2954, 2928, 2857, 1738, 1652, 1472, 1463, 1439, 1361, 1252, 1165, 1092, 1052, 1005, 907, 834, 775, 670 cm^{-1}; MS (EI): *m/z* (%): 405 (13), 277 (18), 273 (17), 223 (37), 170 (14), 169 (100), 75 (35), 73 (53), 67 (13); HRMS (ESI): *m/z*: calcd for $C_{32}H_{54}O_5Si_2Na$ [M^++Na]: 597.3405; found: 597.3402.

(*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-((2*S*,3*R*)-3-((*R*)-1-(*tert*-butyldimethylsilyloxy)-2-methylenehex-4-ynyl)oxiran-2-yl)pent-4-en-2-yl hex-4-ynoate (36): Prepared analogously from **35** (0.90 g, 1.96 mmol) as a colorless oil (1.12 g, 99 %). $[\alpha]_D^{20}$ = +0.6 ($CHCl_3$, *c* = 1.5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 3H), 0.06 (s, 3H), 0.11 (s, 6H), 0.88 (s, 9H), 0.91 (s, 9H), 1.74 (t, *J* = 2.3 Hz, 3H), 1.81 (t, *J* = 2.5 Hz, 3H), 2.17 (dd, *J* = 8.4, 14.7 Hz, 1H), 2.26 (dd, *J* = 4.7, 14.7 Hz, 1H), 2.38–2.50 (m, 4H), 2.90 (dd, *J* = 2.1, 5.8 Hz, 1H), 2.87–3.08 (m, 2H), 3.29 (d, *J* = 2.0 Hz, 1H), 3.61 (dd, *J* = 4.8, 10.8 Hz, 1H), 3.64 (dd, *J* = 5.0, 10.8 Hz, 1H), 4.01 (d, *J* = 5.8 Hz, 1H), 4.99–5.05 (m, 1H), 5.02 (s, 1H), 5.18 (s, 1H), 5.20 (s, 1H), 5.25 ppm (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = −5.3 (CH_3), −5.0 (CH_3), −4.8 (CH_3), 3.4 (CH_3), 3.4 (CH_3), 14.7 (CH_2), 18.2 (C), 22.5 (CH_2), 25.7 (CH_3), 25.8 (CH_3), 32.1 (CH_2), 34.0 (CH_2), 57.5 (CH), 61.8 (CH), 63.9 (CH_2), 73.2 (CH), 75.6 (CH), 75.7 (C), 76.2 (C), 77.2 (C), 78.5 (C), 112.6 (CH_2), 115.3 (CH_2), 140.7 (C), 144.3 (C), 171.4 ppm (C); IR (film): $\tilde{\nu}$ = 3084, 2955, 2929, 2886, 2857, 1740, 1652, 1472, 1463, 1440, 1389, 1361, 1254,

1166, 1126, 1096, 1058, 1005, 908, 838, 778, 670 cm^{-1}; MS (EI): *m/z* (%): 517 (1), 406 (4), 405 (13), 351 (1), 277 (19), 273 (20), 223 (31), 170 (14), 169 (100), 95 (7), 75 (33), 73 (47), 67 (11); HRMS (ESI): *m/z*: calcd for $C_{32}H_{55}O_5Si_2$ [M^++H]: 575.3592, found: 575.3588; elemental analysis calcd (%) for $C_{32}H_{54}O_5Si_2$ (574.94): C 66.85, H 9.47; found: C 66.80, H 9.43.

(*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-((2*S*,3*R*)-3-((*S*)-1-(*tert*-butyldimethylsilyloxy)-2-methylenehex-4-ynyl)oxiran-2-yl)pent-4-en-2-yl hex-4-ynoate (44): Prepared analogously from **43** (0.47 g, 1.01 mmol) as a colorless oil (0.51 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 6H), 0.06 (s, 6H), 0.88 (s, 18H), 1.75 (t, *J* = 2.3 Hz, 3H), 1.82 (t, *J* = 2.5 Hz, 3H), 2.17 (dd, *J* = 8.3, 14.7 Hz, 1H), 2.26 (dd, *J* = 4.8, 14.7 Hz, 1H), 2.38–2.48 (m, 4H), 2.88 (dd, *J* = 2.0, 3.5 Hz, 1H), 2.86–3.08 (m, 2H), 3.36 (d, *J* = 1.7 Hz, 1H), 3.61 (dd, *J* = 4.7, 10.9 Hz, 1H), 3.64 (dd, *J* = 5.8, 10.9 Hz, 1H), 4.26 (d, *J* = 3.5 Hz, 1H), 4.97–5.02 (m, 1H), 5.02 (s, 1H), 5.16 (s, 1H), 5.21 (s, 1H), 5.31 ppm (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = −5.4 (CH_3), −5.0 (CH_3), −4.9 (CH_3), 3.4 (CH_3), 3.5 (CH_3), 14.6 (CH_2), 18.2 (C), 21.6 (CH_2), 25.7 (CH_3), 25.8 (CH_3), 31.9 (CH_2), 34.1 (CH_2), 56.7 (CH), 60.8 (CH), 63.8 (CH_2), 73.4 (CH), 73.6 (CH), 75.6 (C), 76.2 (C), 77.2 (C), 78.5 (C), 112.9 (CH_2), 115.2 (CH_2), 141.0 (C), 144.6 (C), 171.4 ppm (C); IR (film): $\tilde{\nu}$ = 3084, 2955, 2929, 2886, 2857, 1740, 1652, 1472, 1463, 1440, 1389, 1361, 1254, 1166, 1126, 1096, 1058, 1005, 908, 838, 778, 670 cm^{-1}; MS (EI): *m/z* (%): 517 (1), 406 (4), 405 (13), 351 (1), 277 (19), 273 (20), 223 (31), 170 (14), 169 (100), 95 (7), 75 (33), 73 (47), 67 (11); HRMS (ESI): *m/z*: calcd for $C_{32}H_{55}O_5Si_2$ [M^++H]: 575.3592, found: 575.3588; elemental analysis calcd (%) for $C_{32}H_{54}O_5Si_2$ (574.94): C 66.85, H 9.47; found: C 66.80, H 9.43.

(*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-((2*R*,3*S*)-3-((*R*)-1-(*tert*-butyldimethylsilyloxy)-2-methylenehex-4-ynyl)oxiran-2-yl)pent-4-en-2-yl hex-4-ynoate (52): Prepared analogously from **51** (0.31 g, 0.66 mmol) as a colorless oil (0.36 g, 93%). $[\alpha]_D^{20}$ = −22.3 ($CHCl_3$, *c* = 0.55); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 6H), 0.06 (s, 6H), 0.87 (s, 9H), 0.88 (s, 9H), 1.75 (t, *J* = 2.3 Hz, 3H), 1.82 (t, *J* = 2.5 Hz, 3H), 2.22 (dd, *J* = 7.6, 14.7 Hz, 1H), 2.33 (dd, *J* = 5.7, 14.8 Hz, 1H), 2.38–2.49 (m, 4H), 2.88 (dd, *J* = 2.1, 3.6 Hz, 1H), 2.89 (d, *J* = 19.7 Hz, 1H), 3.05 (d, *J* = 19.7 Hz, 1H), 3.38 (d, *J* = 1.9 Hz, 1H), 3.61 (dd, *J* = 4.6, 10.8 Hz, 1H), 3.65 (dd, *J* = 4.9, 10.8 Hz, 1H), 4.25 (d, *J* = 3.5 Hz, 1H), 4.99–5.05 (m, 1H), 5.03 (s, 1H), 5.16 (s, 1H), 5.22 (s, 1H), 5.31 ppm (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = −5.4 (CH_3), −5.4 (CH_3), −5.0 (CH_3), −4.9 (CH_3), 3.4 (CH_3), 3.5 (CH_3), 14.6 (CH_2), 18.2 (C), 21.6 (CH_2), 25.7 (CH_3), 25.8 (CH_3), 32.1 (CH_2), 34.1 (CH_2), 56.7 (CH), 61.1 (CH), 63.4 (CH_2), 73.0 (CH), 73.6 (CH), 75.6 (C), 76.2 (C), 77.2 (C), 78.5 (C), 113.0 (CH_2), 115.5 (CH_2), 140.6 (C), 144.5 (C), 171.4 ppm (C); IR (film): $\tilde{\nu}$ = 2954, 2929, 2857, 1738, 1649, 1472, 1463, 1422, 1361, 1252, 1165, 1124, 1099, 1050, 1005, 960, 938, 908, 833, 775, 670 cm^{-1}; MS (EI): *m/z* (%): 405 (21), 273 (31), 247 (11), 223 (43), 169 (100), 75 (49), 73 (75); HRMS (ESI): *m/z*: calcd for $C_{32}H_{54}O_5Si_2Na$ [M^++Na]: 597.3300, found: 597.3402; elemental analysis calcd (%) for $C_{32}H_{54}O_5Si_2$ (574.94): C 66.85, H 9.47; found: C 66.73, H 9.39.

Ring-closing alkyne metathesis reactions

(1*S*,4*R*,13*R*,14*R*)-13-(*tert*-Butyldimethylsilyloxy)-4-((*tert*-butyldimethylsilyloxy)methyl)-2,12-dimethylene-5,15-dioxabicyclo[12.1.0]pentadec-9-yn-6-one (27): CH_2Cl_2 (19 mL) was added to a solution of complex **26** (104 mg, 0.169 mmol, 30 mol%) in toluene (560 mL) and the resulting mixture stirred for 15 min before a solution of diyne **25** (322 mg, 0.560 mmol) in toluene (20 mL) was introduced. The flask was tightly sealed and stirred at 80–85 °C for 14 h. The mixture was then cooled to room temperature before it was filtered through a short plug of silica, the filtrate was evaporated and the residue purified by flash chromatography (hexanes/ethyl acetate 70:1) to give cycloalkyne **27** (244 mg, 84%) as a colorless oil. $[\alpha]_D^{20}$ = +41.2 ($CHCl_3$, *c* = 0.38); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 3H), 0.04 (s, 3H), 0.07 (s, 3H), 0.14 (s, 3H), 0.88 (s, 9H), 0.92 (s, 9H), 2.41–2.58 (m, 6H), 2.83 (dd, *J* = 2.1, 7.0 Hz, 1H), 2.97 (d, *J* = 17.6, 1H), 3.12 (d, *J* = 17.6 Hz, 1H), 3.64 (d, *J* = 1.4 Hz, 1H), 3.65 (d, *J* = 6.0 Hz, 2H), 3.97 (d, *J* = 7.0 Hz, 1H), 4.98 (s, 1H), 5.01 (s, 1H), 5.12 (dq, *J* = 3.7, 6.1 Hz, 1H), 5.19 (s, 1H), 5.21 ppm (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = −5.3 (CH_3), −5.1 (CH_3), −4.6 (CH_3), 15.6 (CH_2), 18.1 (C), 18.3 (C), 23.5 (CH_2), 25.7 (CH_3), 25.8 (CH_3), 34.4 (CH_2), 34.6 (CH_2), 57.6 (CH), 63.0 (CH_2), 64.0 (CH), 73.1 (CH), 75.9 (CH), 78.8 (C), 79.8 (C), 113.7 (CH_2), 114.6 (CH_2), 140.4 (C), 143.2 (C), 171.5 ppm (C); IR (film): $\tilde{\nu}$ = 2955, 2929, 2857, 1740, 1649, 1472, 1463, 1432, 1389, 1361, 1251, 1152, 1102, 1055, 1005, 971, 906, 833, 775, 669 cm^{-1}; MS (EI): *m/z* (%): 463 (12), 331 (22), 169 (11), 147 (10), 117 (11), 89 (11), 75 (53), 73 (100); HRMS (ESI): *m/z*: calcd for $C_{28}H_{48}O_5Si_2Na$ [M^++Na]: 543.2934, found: 543.2932.

(1*S*,4*S*,13*R*,14*R*)-13-(*tert*-Butyldimethylsilyloxy)-4-((*tert*-butyldimethylsilyloxy)methyl)-2,12-dimethylene-5,15-dioxabicyclo[12.1.0]pentadec-9-yn-6-one (37): Prepared analogously from diyne **36** (94 mg, 0.163 mmol) as a colorless oil (76 mg, 89%). $[\alpha]_D^{20}$ = +15.8 ($CHCl_3$, *c* = 0.5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 6H), 0.13 (s, 6H), 0.88 (s, 9H), 0.91 (s, 9H), 2.30–2.49 (m, 6H), 2.92 (d, *J* = 17.5 Hz, 1H), 3.13 (dd, *J* = 1.9, 4.7 Hz, 1H), 3.18 (d, *J* = 17.6 Hz, 1H), 3.30 (d, *J* = 1.7 Hz, 1H), 3.60 (dd, *J* = 5.6, 10.4 Hz, 1H), 3.71 (dd, *J* = 4.9, 10.4 Hz, 1H), 4.11 (d, *J* = 4.7 Hz, 1H), 5.06–5.10 (m, 1H), 5.00 (s, 1H), 5.04 (s, 1H), 5.13 (s, 1H), 5.19 ppm (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = −5.4 (CH_3), −5.0 (CH_3), −4.8 (CH_3), 15.1 (CH_2), 18.1 (C), 18.2 (C), 22.4 (CH_2), 25.7 (CH_3), 25.8 (CH_3), 33.9 (CH_2), 34.1 (CH_2), 56.8 (CH), 62.5 (CH), 64.3 (CH_2), 72.5 (CH), 74.9 (CH), 78.6 (C), 80.1 (C), 113.9 (CH_2), 114.0 (CH_2), 141.0 (C), 143.8 (C), 171.5 ppm (C); IR (film): $\tilde{\nu}$ = 3082, 2955, 2929, 2886, 2857, 1739, 1650, 1472, 1463, 1430, 1389, 1361, 1255, 1205, 1164, 1129, 1096, 1060, 1006, 906, 838, 778, 670 cm^{-1}; MS (EI): *m/z* (%): 464 (10), 463 (27), 331 (27), 223 (13), 169 (13), 147 (12), 117 (11), 89 (11), 75 (44), 73 (100); HRMS (ESI): *m/z*: calcd for $C_{28}H_{48}O_5Si_2Na$ [M^++Na]: 543.2934, found: 543.2939; elemental analysis calcd (%) for $C_{28}H_{48}O_5Si_2$ (520.85): C 64.57, H 9.29; found: C 64.43, H 9.22.

(1*S*,4*S*,13*S*,14*R*)-13-(*tert*-Butyldimethylsilyloxy)-4-((*tert*-butyldimethylsilyloxy)methyl)-2,12-dimethylene-5,15-dioxabicyclo[12.1.0]pentadec-9-yn-6-one (45): Prepared analogously from diyne **44** (660 mg, 1.147 mmol) as a colorless oil (450 mg, 75%). $[\alpha]_D^{20}$ = −4.8 ($CHCl_3$, *c* = 1.7); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.87 (s, 9H), 0.87 (s, 9H), 2.17 (dd, *J* = 9.9, 15.4 Hz, 1H), 2.33–2.47 (m, 5H), 2.75 (d, *J* = 16.6 Hz, 1H), 3.06 (d, *J* = 16.5 Hz, 1H), 3.25 (dd, *J* = 1.9, 2.7 Hz, 1H), 3.48 (d, *J* = 1.9 Hz, 1H), 3.62 (dd, *J* = 5.6, 10.5 Hz, 1H), 3.70 (dd, *J* = 5.3, 10.4 Hz, 1H), 4.24 (d, *J* = 2.7 Hz, 1H), 5.01–5.09 (m, 1H), 5.07 (s, 1H), 5.13 (s, 1H), 5.16 (s, 1H), 5.31 ppm (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = −5.4 (CH_3), −5.3 (CH_3), −5.1 (CH_3), −5.0 (CH_3), 15.3 (CH_2), 18.1 (C), 18.2 (C), 21.2 (CH_2), 25.6 (CH_3), 25.7 (CH_3), 31.5 (CH_2), 34.4 (CH_2), 56.7 (CH), 59.7 (CH), 64.1 (CH_2), 72.9 (CH), 74.3 (CH), 79.0 (C), 79.3 (C), 115.3 (CH_2), 116.2 (CH_2), 144.1 (C), 144.7 (C), 171.3 ppm (C); IR (film): $\tilde{\nu}$ = 3082, 2955, 2929, 2886, 2857, 1739, 1650, 1472, 1463, 1430, 1389, 1361, 1255, 1205, 1164, 1129, 1096, 1060, 1006, 906, 838, 778, 670 cm^{-1}; MS (EI): *m/z* (%): 464 (10), 463 (27), 331 (27), 223 (13), 169 (13), 147(12), 117 (11), 89 (11), 75 (44), 73 (100); HRMS (ESI): *m/z*: calcd for $C_{28}H_{48}O_5Si_2Na$ [M^++Na]: 543.2934, found: 543.2930; elemental analysis calcd (%) for $C_{28}H_{48}O_5Si_2$ (520.85): C 64.57, H 9.29; found: C 64.43, H 9.22.

(1*R*,4*S*,13*R*,14*S*)-13-(*tert*-Butyldimethylsilyloxy)-4-((*tert*-butyldimethylsilyloxy)methyl)-2,12-dimethylene-5,15-dioxabicyclo[12.1.0]pentadec-9-yn-6-one (53): Prepared analogously from diyne **52** (0.323 g, 0.56 mmol) as a colorless oil (0.272 g, 93%). $[\alpha]_D^{20}$ = −25.5 ($CHCl_3$, *c* = 0.53); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 3H), 0.03 (s, 3H), 0.06 (s, 6H), 0.87 (s, 9H), 0.88 (s, 9H), 2.32–2.52 (m, 6H), 2.80 (d, *J* = 16.7 Hz, 1H), 3.06 (d, *J* = 16.7 Hz, 1H), 3.12 (t, *J* = 2.3 Hz t,), 3.61 (d, *J* = 1.9 Hz, 1H), 3.64 (s, 1H), 3.65 (s, 1H), 4.34 (d, *J* = 2.2 Hz, 1H), 4.89–4.95 (m, 1H), 5.06 (s, 1H), 5.10 (s, 1H), 5.11 (s, 1H), 5.29 ppm (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = −5.3 (CH_3), −5.1 (CH_3), −4.9 (CH_3), 15.8 (CH_2), 18.2 (C), 21.0 (CH_2), 25.7 (CH_3), 25.8 (CH_3), 33.6 (CH_2), 34.5 (CH_2), 56.5 (CH), 61.1 (CH), 64.2 (CH_2), 72.3 (CH), 73.9 (CH), 78.6 (C), 79.6 (C), 115.9 (CH_2), 117.3 (CH_2), 140.8 (C), 144.3 (C), 171.4 ppm (C); IR (film): $\tilde{\nu}$ = 2951, 2928, 2856, 1732, 1637, 1470, 1431, 1360, 1341, 1249, 1212, 1149, 1138, 1128, 1100, 1048, 1011, 988, 960, 932, 921, 900, 832, 777, 722, 673 cm^{-1}; MS (EI): *m/z* (%): 463 (11), 331 (26), 289 (11), 197 (12), 169 (11), 147 (11), 117 (13), 89 (11), 75 (49), 73 (100); HRMS (ESI): *m/z*: calcd for $C_{28}H_{48}O_5Si_2Na$ [M^++Na]: 543.2934, found: 543.2933; elemental analysis calcd (%) for $C_{28}H_{48}O_5Si_2$ (520.85): C 64.57, H 9.29; found: C 64.95, H 9.34.

Enyne metathesis reactions and elaboration of the macrocyclic cores

(1*S*,4*R*,13*R*,14*R*)-13-(*tert*-Butyldimethylsilyloxy)-4-((*tert*-butyldimethylsilyloxy)methyl)-2,9,10,12-tetramethylene-5,15-dioxabicyclo-[12.1.0]pentadecan-6-one (29): A solution of **27** (484 mg, 0.929 mmol) and catalyst **28** (79 mg, 0.092 mmol) in toluene (16 mL) was stirred at 45 °C under an atmosphere of ethylene (1.8 atm) for 14 h. Ethyl vinyl ether (4 drops) was added and the mixture stirred for 10 min before the solvent was evaporated. Purification of the residue by flash chromatography (hexanes/ethyl acetate 70:1) furnished product **29** as a colorless oil (356 mg, 70 %). $[\alpha]_D^{20} = +5$ ($CHCl_3$, $c = 0.27$); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.02$ (s, 3H), 0.03 (s, 3H), 0.09 (s, 3H), 0.16 (s, 3H), 0.87 (s, 9H), 0.96 (s, 9H), 2.34 (dd, $J = 2.8$, 14.4 Hz, 1H), 2.43–2.46 (m, 2H), 2.52 (dd, $J = 6.1$, 14.6 Hz, 1H), 2.56–2.63 (m, 1H), 2.71–2.77 (m, 1H), 2.75 (dd, $J = 2.1$, 7.5 Hz, 1H), 3.03 (d, $J = 16.6$ Hz, 1H), 3.21 (d, $J = 16.6$ Hz, 1H), 3.34 (d, $J = 1.3$ Hz, 1H), 3.55 (dd, $J = 6.6$, 10.4 Hz, 1H), 3.62 (dd, $J = 5.9$, 10.3 Hz, 1H), 3.88 (d, $J = 7.5$ Hz, 1H), 4.94 (s, 1H), 4.98 (s, 1H), 5.00–5.05 (m, 1H), 5.03 (s, 1H), 5.10 (s, 1H), 5.12 (s, 1H), 5.13 (s, 1H), 5.21 (s, 1H), 5.48 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = -5.4$ (CH_3), -5.4 (CH_3), -4.9 (CH_3), -4.4 (CH_3), 18.1 (C), 18.3 (C), 25.7 (CH_3), 25.8 (CH_3), 30.7 (CH_2), 33.7 (CH_2), 35.5 (CH_2), 38.7 (CH_2), 57.3 (CH), 62.5 (CH_2), 64.1 (CH), 73.6 (CH), 74.8 (CH), 112.7 (CH_2), 114.2 (CH_2), 114.6 (CH_2), 115.4 (CH_2), 140.7 (C), 142.7 (C), 144.6 (C), 145.0 (C), 172.1 ppm (C); IR (film): $\tilde{\nu} = 2954$, 2929, 2857, 1741, 1648, 1598, 1472, 1463, 1436, 1389, 1361, 1251, 1156, 1102, 1059, 1004, 910, 834, 775, 669 cm^{-1}; MS (EI): m/z (%): 548 (2) [M^+], 491 (18), 359 (17), 267 (10), 251 (17), 233 (12), 227 (11), 207 (14), 183 (28), 159 (18), 147 (10), 131 (26), 117 (16), 91 (10), 89 (15), 75 (64), 73 (100); HRMS (ESI): m/z: calcd for $C_{30}H_{52}O_5Si_2Na$ [M^++Na]: 571.3246, found: 571.3245.

(1*S*,4*S*,13*R*,14*R*)-13-(*tert*-Butyldimethylsilyloxy)-4-((*tert*-butyldimethylsilyloxy)methyl)-2,9,10,12-tetramethylene-5,15-dioxabicyclo-[12.1.0]pentadecan-6-one (38): Prepared analogously from **37** (0.13 g, 0.25 mmol) as a colorless oil (0.132 g, 96 %). $[\alpha]_D^{20} = -55$ ($CHCl_3$, $c = 0.65$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.03$ (s, 3H), 0.04 (s, 3H), 0.07 (s, 3H), 0.12 (s, 3H), 0.88 (s, 9H), 0.93 (s, 9H), 2.01 (dd, $J = 11.7$, 15.3 Hz, 1H), 2.14 (d, $J = 15.3$ Hz, 1H), 2.27–2.38 (m, 4H), 3.04 (s, 2H), 3.16 (dd, $J = 2.0$, 7.3 Hz, 1H), 3.21 (d, $J = 2.0$ Hz, 1H), 3.57–3.65 (m, 2H), 3.73 (d, $J = 7.3$ Hz, 1H), 4.81 (s, 1H), 4.88 (s, 1H), 4.99 (s, 1H), 5.04–5.10 (m, 1H), 5.07 (s, 1H), 5.18 (s, 1H), 5.24 (s, 1H), 5.33 ppm (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = -5.4$ (CH_3), -5.0 (CH_3), -4.7 (CH_3), 18.1 (C), 18.2 (C), 25.7 (CH_3), 25.7 (CH_3), 27.7 (CH_2), 30.5 (CH_2), 34.5 (CH_2), 36.7 (CH_2), 59.5 (CH), 59.7 (CH), 64.1 (CH_2), 74.1 (CH), 80.1 (CH), 112.4 (CH_2), 113.0 (CH_2), 115.8 (CH_2), 117.4 (CH_2), 141.1 (C), 144.4 (C), 146.5 (C), 146.7 (C), 172.4 ppm (C); IR (film): $\tilde{\nu} = 3083$, 2955, 2929, 2895, 2857, 1739, 1643, 1598, 1472, 1463, 1443, 1389, 1361, 1257, 1129, 1092, 1061, 902, 838, 778, 669 cm^{-1}; MS (EI): m/z (%): 548 (2) [M^+], 492 (12), 491 (30), 359 (18), 279 (11), 267 (11), 251 (20), 233 (15), 207 (13), 183 (27), 159 (19), 131 (24), 117 (14), 89 (15), 75 (58), 73 (100); HRMS (ESI): m/z: calcd for $C_{30}H_{52}O_5Si_2Na$ [M^++Na]: 571.3246, found: 571.3246; elemental analysis calcd (%) for $C_{30}H_{52}O_5Si_2$ (548.90): C 65.64, H 9.55; found: C 65.48, H 9.47.

(1*S*,4*S*,13*S*,14*R*)-13-(*tert*-Butyldimethylsilyloxy)-4-((*tert*-butyldimethylsilyloxy)methyl)-2,9,10,12-tetramethylene-5,15-dioxabicyclo-[12.1.0]pentadecan-6-one (46): Prepared analogously from **45** (0.170 g, 0.33 mmol) as a colorless oil (0.166 g, 92 %). $[\alpha]_D^{20} = +19.2$ ($CHCl_3$, $c = 0.6$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.02$ (s, 3H), 0.03 (s, 3H), 0.05 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 0.89 (s, 9H), 1.99 (ddd, $J = 1.5$, 11.7, 15.3 Hz, 1H), 2.16 (ddt, $J = 2.0$, 3.0, 15.3 Hz, 1H), 2.28–2.35 (m, 4H), 2.93 (s, 2H), 3.03 (dd, $J = 2.0$, 1.6 Hz, 1H), 3.57 (dd, $J = 5.4$, 10.5 Hz, 1H), 3.58 (d, $J = 2.1$ Hz, 1H), 3.63 (dd, $J = 4.6$, 10.5 Hz, 1H), 4.53 (s, 1H), 4.78 (s, 1H), 4.91 (s, 1H), 4.94 (s, 1H), 5.02–5.07 (m, 1H), 5.13 (s, 1H), 5.19 (s, 1H), 5.24 (s, 1H), 5.32 (s, 1H), 5.40 ppm (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = -5.4$ (CH_3), -5.4 (CH_3), -5.1 (CH_3), -5.0 (CH_3), 18.1 (C), 18.3 (C), 25.7 (CH_3), 25.7 (CH_3), 27.7 (CH_2), 29.9 (CH_2), 34.0 (CH_2), 36.1 (CH_2), 56.1 (CH), 58.2 (CH), 64.2 (CH_2), 73.4 (CH), 74.4 (CH), 111.7 (CH_2), 113.1 (CH_2), 115.5 (CH_2), 117.3 (CH_2), 141.8 (C), 145.1 (C), 146.3 (C), 146.9 (C), 172.4 ppm (C); IR (film): $\tilde{\nu} = 3083$, 2955, 2929, 2895, 2857, 1739, 1643, 1598, 1472, 1463, 1443, 1389, 1361, 1257, 1129, 1092, 1061, 902, 838, 778, 669 cm^{-1}; MS (EI): m/z (%): 548 (2) [M^+], 492 (12), 491 (30), 359 (18), 279 (11), 267 (11), 251 (20), 233 (15), 207 (13), 183 (27), 159 (19), 131 (24), 117 (14), 89 (15), 75 (58), 73 (100); HRMS (ESI): m/z: calcd for $C_{30}H_{52}O_5Si_2Na$ [M^++Na]: 571.3249, found: 571.3246; elemental analysis calcd (%) for $C_{30}H_{52}O_5Si_2$ (548.90): C 65.64, H 9.55; found: C 65.48, H 9.60.

(1*R*,4*S*,13*R*,14*S*)-13-(*tert*-Butyldimethylsilyloxy)-4-((*tert*-butyldimethylsilyloxy)methyl)-2,9,10,12-tetramethylene-5,15-dioxabicyclo-[12.1.0]pentadecan-6-one (54): Prepared analogously from **53** (0.252 g, 0.483 mmol) as a colorless oil (0.193 g, 73 %). $[\alpha]_D^{20} = -56$ ($CHCl_3$, $c = 0.5$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.03$ (s, 3H), 0.03 (s, 3H), 0.04 (s, 3H), 0.06 (s, 3H), 0.87 (s, 9H), 0.88 (s, 9H), 2.30–2.49 (m, 6H), 2.85 (t, $J = 2.0$ Hz, 1H), 2.93 (d, $J = 17.2$ Hz, 1H), 3.08 (d, $J = 16.8$ Hz, 1H), 3.45 (d, $J = 1.8$ Hz, 1H), 3.57 (dd, $J = 6.1$, 10.4 Hz, 1H), 3.65 (dd, $J = 5.2$, 10.5 Hz, 1H), 4.33 (m, 1H), 4.89–4.97 (m, 1H), 4.89 (s, 2H), 4.97 (s, 1H), 4.98 (s, 1H), 5.03 (s, 1H), 5.15 (s, 1H), 5.20 (s, 1H), 5.24 ppm (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = -5.4$ (CH_3), -5.3 (CH_3), -5.0 (CH_3), 18.1 (C), 18.2 (C), 25.7 (CH_3), 25.7 (CH_3), 30.3 (CH_2), 33.5 (CH_2), 33.8 (CH_2), 36.7 (CH_2), 55.9 (CH), 63.2 (CH_2), 63.2 (CH), 74.0 (CH), 74.2 (CH), 112.9 (CH_2), 114.7 (CH_2), 114.9 (CH_2), 115.2 (CH_2), 141.4 (C), 144.9 (C), 146.1 (C), 147.2 (C), 172.3 ppm (C); IR (film): $\tilde{\nu} = 2954$, 2929, 2857, 1739, 1646, 1472, 1463, 1361, 1251, 1122, 1101, 1005, 902, 833, 774, 671 cm^{-1}; MS (EI): m/z (%): 548 (2) [M^+], 491 (14), 359 (11), 207 (12), 183 (20), 159 (12), 131 (16), 117 (16), 89 (15), 75 (60), 73 (100); HRMS (ESI): m/z: calcd for $C_{30}H_{52}O_5Si_2Na$ [M^++Na]: 571.3246; found: 571.3252; elemental analysis calcd (%) for $C_{30}H_{52}O_5Si_2$ (548.3): C 65.64, H 9.55; found: C 65.56, H 9.50.

(1*S*,4*R*,13*R*,14*R*)-13-(*tert*-Butyldimethylsilyloxy)-4-(hydroxymethyl)-2,9,10,12-tetramethylene-5,15-dioxabicyclo[12.1.0]pentadecan-6-one (30): PPTS (91 mg, 0.364 mmol) was added to a solution of **29** (100 mg, 0.182 mmol) in MeOH (9 mL) at 0 °C and the resulting mixture was stirred for 20 h. Triethylamine (4 drops) was introduced before all volatile materials were evaporated (30 °C) and the residue was purified by flash chromatography (hexanes/ethyl acetate 8:1) to give alcohol **30** as a colorless oil (62 mg, 78 %) as well as a second fraction consisting of unreacted started material **30** (9 mg). $[\alpha]_D^{20} = -10$ ($CHCl_3$, $c = 0.26$); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.09$ (s, 3H), 0.15 (s, 3H), 0.95 (s, 9H), 1.90 (brs, 1H), 2.38 (dd, $J = 2.7$, 14.6 Hz, 1H), 2.46–2.64 (m, 4H), 2.74–2.79 (m, 1H), 2.75 (dd, $J = 2.1$, 7.6 Hz, 1H), 3.02 (d, $J = 16.6$ Hz, 1H), 3.21 (d, $J = 16.6$ Hz, 1H), 3.36 (d, $J = 1.3$ Hz, 1H), 3.67 (brs, 2H), 3.87 (d, $J = 7.6$ Hz, 1H), 4.94 (s, 1H), 4.99 (s, 1H), 5.02 (s, 1H), 5.05–5.11 (m, 1H), 5.11 (s, 1H), 5.13 (s, 1H), 5.14 (s, 1H), 5.22 (s, 1H), 5.49 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = -4.9$ (CH_3), -4.4 (CH_3), 18.3 (C), 25.8 (CH_3), 30.7 (CH_2), 33.7 (CH_2), 36.0 (CH_2), 38.6 (CH_2), 57.1 (CH), 63.8 (CH_2), 64.1 (CH), 74.4 (CH), 75.0 (CH), 112.8 (CH_2), 114.1 (CH_2), 114.7 (CH_2), 115.6 (CH_2), 140.9 (C), 142.5 (C), 144.5 (C), 145.0 (C), 173.1 ppm (C); IR (film): $\tilde{\nu} = 3456$, 2954, 2929, 2857, 1735, 1648, 1597, 1471, 1463, 1388, 1361, 1249, 1157, 1111, 1057, 1005, 906, 835, 776, 671 cm^{-1}; MS (EI): m/z (%): 434 (<1) [M^+], 251 (17), 233 (15), 207 (12), 183 (31), 177 (19), 159 (22), 131 (41), 117 (15), 113 (12), 109 (13), 105 (13), 91 (19), 81 (16), 79 (12), 75 (100), 73 (50), 59 (10), 57 (15), 55 (11), 43 (11); HRMS (ESI): m/z: calcd for $C_{24}H_{38}O_5SiNa$ [M^++Na]: 457.2382, found: 457.2380.

(1*S*,4*S*,13*R*,14*R*)-13-(*tert*-Butyldimethylsilyloxy)-4-(hydroxymethyl)-2,9,10,12-tetramethylene-5,15-dioxabicyclo[12.1.0]pentadecan-6-one (39): Prepared analogously from **38** (85 mg, 0.155 mmol) as a colorless oil (43 mg, 64 %). $[\alpha]_D^{20} = -35.2$ ($CHCl_3$, $c = 0.7$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.07$ (s, 3H), 0.12 (s, 3H), 0.93 (s, 9H), 1.98 (dd, $J = 11.6$, 15.4 Hz, 1H), 2.13 (d, $J = 15.6$ Hz, 1H), 2.29–2.43 (m, 4H), 3.04 (s, 2H), 3.14 (dd, $J = 2.1$, 7.3 Hz, 1H), 3.23 (d, $J = 2.1$ Hz, 1H), 3.60–3.65 (m, 1H), 3.70–3.75 (m, 1H), 3.74 (d, $J = 7.3$ Hz, 1H), 4.82 (s, 1H), 4.89 (s, 1H), 5.00 (s, 1H), 5.09–5.15 (m, 1H), 5.10 (s, 1H), 5.19 (s, 1H), 5.25 (s, 1H), 5.33 (s, 1H), 5.36 ppm (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = -5.0$ (CH_3), -4.6 (CH_3), 18.3 (C), 25.8 (CH_3), 28.2 (CH_2), 30.5 (CH_2), 34.4 (CH_2), 36.8 (CH_2), 59.5 (CH), 59.6 (CH), 65.1 (CH_2), 75.4 (CH), 79.8 (CH), 112.5 (CH_2), 113.2 (CH_2), 115.9 (CH_2), 117.6 (CH_2), 140.7 (C), 144.3 (C), 146.3 (C), 146.5 (C), 173.4 ppm (C); IR (film): $\tilde{\nu} = 3456$, 3082, 2954, 2929, 2895, 2857, 1736, 1641, 1598, 1472, 1462, 1443, 1389, 1361, 1252, 1093, 1060, 901, 838, 779, 670 cm^{-1}; MS (EI): m/z (%): 377 (5), 279

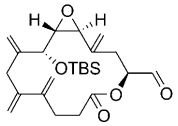
(7), 267 (5), 251 (14), 233 (13), 207 (10), 183 (26), 177 (15), 159 (18), 131 (35), 117 (15), 109 (11), 105 (13), 91 (19), 81 (15), 79 (12), 75 (100), 73 (56), 59 (11), 57 (15), 55 (11), 41 (11); HRMS (ESI): *m/z*: calcd for $C_{24}H_{38}O_5SiNa$ [M^++Na]: 457.2382, found: 457.2381; elemental analysis calcd (%) for $C_{24}H_{38}O_5Si$ (434.64): C 66.32, H 8.81; found: C 66.15, H 8.73.

(1*S*,4*S*,13*S*,14*R*)-13-(*tert*-Butyldimethylsilyloxy)-4-(hydroxymethyl)-2,9,10,12-tetra-methylene-5,15-dioxabicyclo[12.1.0]pentadecan-6-one (47): Prepared analogously from **46** (0.150 g, 0.273 mmol) as a colorless oil (73 mg, 61%). $[\alpha]_D^{20}=+48.8$ ($CHCl_3$, $c=0.75$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.05$ (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 1.99–2.16 (m, 3H), 2.29–2.42 (m, 4H), 2.93 (s, 2H), 3.02 (dd, $J=1.7$, 2.0 Hz, 1H), 3.58 (d, $J=1.9$ Hz, 1H), 3.57–3.63 (m, 1H), 3.69–3.74 (m, 1H), 4.53 (s, 1H), 4.78 (s, 1H), 4.91 (s, 1H), 4.94 (s, 1H), 5.07–5.12 (m, 1H), 5.14 (s, 1H), 5.20 (s, 1H), 5.24 (s, 1H), 5.32 (s, 1H), 5.43 ppm (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=-5.1$ (CH_3), -5.0 (CH_3), 18.3 (C), 25.7 (CH_3), 27.8 (CH_2), 29.8 (CH_2), 33.9 (CH_2), 36.1 (CH_2), 55.9 (CH), 58.3 (CH), 65.1 (CH_2), 73.4 (CH), 75.6 (CH), 111.8 (CH_2), 113.8 (CH_2), 115.5 (CH_2), 117.4 (CH_2), 141.4 (C), 145.1 (C), 146.2 (C), 146.8 (C), 173.4 ppm (C); IR (film): $\tilde{\nu}=3456$, 3082, 2954, 2929, 2895, 2857, 1736, 1641, 1598, 1472, 1462, 1443, 1389, 1361, 1252, 1093, 1060, 901, 838, 779, 670 cm^{-1}; MS (EI): *m/z* (%): 377 (5), 279 (7), 267 (5), 251 (14), 233 (13), 207 (10), 183 (26), 177 (15), 159 (18), 131 (35), 117 (15), 109 (11), 105 (13), 91 (19), 81 (15), 79 (12), 75 (100), 73 (56), 59 (11), 57 (15), 55 (11), 41 (11); HRMS (ESI): *m/z*: calcd for $C_{24}H_{38}O_5SiNa$ [M^++Na]: 457.2382, found: 457.2388; elemental analysis calcd (%) for $C_{24}H_{38}O_5Si$ (434.64): C 66.32, H 8.81; found: C 66.15, H 8.76.

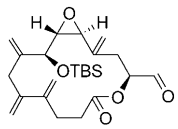
(1*R*,4*S*,13*R*,14*S*)-13-(*tert*-Butyldimethylsilyloxy)-4-(hydroxymethyl)-2,9,10,12-tetramethylene-5,15-dioxabicyclo[12.1.0]pentadecan-6-one (55): Prepared analogously from **54** (11 mg, 0.02 mmol) as a colorless oil (7.4 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.05$ (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 2.01–2.09 (m, 1H), 2.23 (dd, $J=4.8$, 14.7 Hz, 1H), 2.34–2.67 (m, 5H), 2.82–2.85 (m, 1H), 2.96–3.01 (m, 1H), 3.13–3.21 (m, 1H), 3.45–3.50 (m, 1H), 3.78–3.84 (m, 1H), 3.98 (dd, $J=5.7$, 11.1 Hz, 1H), 4.19–4.23 (m, 1H), 5.29–5.35 (m, 1H), 5.01 (s, 1H), 5.04 (s, 1H), 5.11 (s, 1H), 5.14 (s, 1H), 5.21 (s, 1H), 5.28 (s, 1H), 5.31 (s, 1H), 5.33 ppm (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=-5.0$ (CH_3), 18.3 (C), 25.7 (CH_3), 30.1 (CH_2), 33.5 (CH_2), 34.0 (CH_2), 36.9 (CH_2), 55.9 (CH), 63.1 (CH_2), 64.6 (CH), 74.1 (CH), 75.3 (CH), 112.9 (CH_2), 115.2 (CH_2), 115.2 (CH_2), 115.4 (CH_2), 141.2 (C), 144.7 (C), 146.1 (C), 146.9 (C), 172.4 ppm (C); IR (film): $\tilde{\nu}=3459$, 3085, 2954, 3000, 2856, 1737, 1471, 1439, 1388, 1256, 1106, 1007, 906, 836, 778, 673 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{24}H_{38}NaO_5Si$ [M^++Na]: 457.2381, found: 457.2372.

(1*S*,4*R*,13*R*,14*R*)-13-(*tert*-Butyldimethylsilyloxy)-2,9,10,12-tetramethylene-6-oxo-5,15-dioxabicyclo[12.1.0]pentadecane-4-carbaldehyde (31): $NaHCO_3$ (0.119 g, 1.426 mmol) was added to a solution of alcohol **30** (62 mg, 0.142 mmol) in CH_2Cl_2 (4 mL) and the resulting suspension was stirred for 30 min. After cooling to 0°C, Dess–Martin periodinane (0.108 g, 0.256 mmol) was introduced and the mixture was allowed to stir at ambient temperature for 3 h. The reaction was quenched with sat. aq. $NaHCO_3$ (1 mL) and sat. aq. $Na_2S_2O_3$ (1 mL), the aqueous phase was extracted with CH_2Cl_2 (5×1 mL), the combined organic phases were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate 10:1) to give aldehyde **31** as a colorless oil (45 mg, 74%). $[\alpha]_D^{20}=+13.5$ ($CHCl_3$, $c=0.35$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.08$ (s, 3H), 0.14 (s, 3H), 0.95 (s, 9H), 2.51–2.79 (m, 6H), 2.85 (dd, $J=2.1$, 7.4 Hz, 1H), 3.08 (d, $J=16.5$ Hz, 1H), 3.20 (d, $J=16.5$ Hz, 1H), 3.30 (d, $J=1.4$ Hz, 1H), 3.87 (d, $J=7.4$ Hz, 1H), 4.98 (s, 1H), 5.00 (s, 1H), 5.04 (s, 1H), 5.08 (s, 1H), 5.09–5.14 (m, 1H), 5.17 (s, 1H), 5.20 (s, 1H), 5.26 (s, 1H), 5.40 (s, 1H), 9.47 ppm (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=-5.0$ (CH_3), -4.5 (CH_3), 18.3 (C), 25.8 (CH_3), 30.5 (CH_2), 32.9 (CH_2), 33.4 (CH_2), 38.0 (CH_2), 57.6 (CH), 63.1 (CH), 75.8 (CH), 77.9 (CH), 113.7 (CH_2), 113.7 (CH_2), 115.4 (CH_2), 116.6 (CH_2), 139.7 (C), 143.0 (C), 144.9 (C), 145.2 (C), 172.1 (C), 197.8 ppm (CH); IR (film): $\tilde{\nu}=2955$, 2929, 2857, 1738, 1647, 1597, 1462, 1437, 1360, 1249, 1153, 1102, 1061, 1005, 907, 835, 777, 732, 671 cm^{-1}; MS (EI): *m/z* (%): 375 (16), 233 (12), 223 (10), 199 (11), 181 (20), 177 (11), 171 (16), 159 (17), 131 (33), 117 (12), 111 (14), 105 (12), 95 (10), 91 (18), 79 (15), 75 (100), 73 (54), 59 (11), 57 (19), 55 (15), 43 (14), 41 (12); HRMS (ESI): *m/z*: calcd for $C_{24}H_{36}O_5SiNa$ [M^++Na]: 455.2227, found: 455.2224.

(1*S*,4*S*,13*R*,14*R*)-13-(*tert*-Butyldimethylsilyloxy)-2,9,10,12-tetramethylene-6-oxo-5,15-dioxabicyclo[12.1.0]pentadecane-4-carbaldehyde: Prepared analogously from alcohol **39** (42 mg, 0.097 mmol) as a colorless oil (37 mg, 86%). $[\alpha]_D^{20}=-63.4$ ($CHCl_3$, $c=0.75$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.07$ (s, 3H), 0.12 (s, 3H), 0.93 (s, 9H), 2.09 (dd, $J=11.6$, 15.1 Hz, 1H), 2.43–2.57 (m, 5H), 3.09 (s, 2H), 3.11 (dd, $J=2.0$, 7.4 Hz, 1H), 3.25 (d, $J=1.9$ Hz, 1H), 3.78 (d, $J=7.3$ Hz, 1H), 4.87 (s, 1H), 4.94 (s, 1H), 5.04 (s, 1H), 5.09 (dd, $J=3.1$, 11.6 Hz, 1H), 5.12 (s, 1H), 5.19 (s, 1H), 5.25 (s, 1H), 5.33 (s, 1H), 5.37 (s, 1H), 9.50 ppm (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=-5.0$ (CH_3), -4.6 (CH_3), 18.3 (C), 25.8 (CH_3), 27.3 (CH_2), 30.3 (CH_2), 33.6 (CH_2), 36.9 (CH_2), 58.9 (CH), 60.2 (CH), 78.4 (CH), 79.1 (CH), 112.9 (CH_2), 113.6 (CH_2), 115.8 (CH_2), 117.8 (CH_2), 139.8 (C), 144.0 (C), 146.1 (C), 146.2 (C), 172.3 (C), 197.2 ppm (CH); IR (film): $\tilde{\nu}=3083$, 2952, 2930, 2857, 1741, 1647, 1463, 1442, 1360, 1257, 1092, 1023, 1005, 971, 905, 838, 779, 670 cm^{-1}; MS (EI): *m/z* (%): 375 (6), 219 (7), 181 (17), 171 (13), 159 (12), 131 (26), 117 (12), 111 (12), 105 (11), 91 (19), 79 (14), 75 (100), 73 (50), 59 (11), 57 (16), 55 (14), 41 (10); HRMS (ESI): *m/z*: calcd for $C_{24}H_{36}O_5SiNa$ [M^++Na]: 455.2228, found: 455.2234; elemental analysis calcd (%) for $C_{24}H_{36}O_5Si$ (432.63): C 66.63, H 8.39; found: C 66.80, H 8.39.



(1*S*,4*S*,13*S*,14*R*)-13-(*tert*-Butyldimethylsilyloxy)-2,9,10,12-tetramethylene-6-oxo-5,15-dioxabicyclo[12.1.0]pentadecane-4-carbaldehyde: Prepared analogously from alcohol **47** (70 mg, 0.160 mmol) as a colorless oil (67 mg, 97%). $[\alpha]_D^{20}=+24.9$ ($CHCl_3$, $c=0.45$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.05$ (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 2.08 (dd, $J=11.8$, 15.4 Hz, 1H), 2.41–2.55 (m, 5H), 2.97 (s, 2H), 3.01 (dd, $J=1.6$, 1.8 Hz, 1H), 3.58 (d, $J=1.8$ Hz, 1H), 4.48 (s, 1H), 4.84 (s, 1H), 4.97 (s, 1H), 4.98 (s, 1H), 5.09 (dd, $J=3.2$, 11.8 Hz, 1H), 5.18 (s, 1H), 5.22 (s, 1H), 5.25 (s, 1H), 5.32 (s, 1H), 5.45 (s, 1H), 9.49 ppm (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=-5.1$ (CH_3), -5.1 (CH_3), 18.3 (C), 25.7 (CH_3), 26.5 (CH_2), 29.8 (CH_2), 33.4 (CH_2), 36.8 (CH_2), 55.5 (CH), 59.1 (CH), 73.1 (CH), 78.7 (CH), 112.5 (CH_2), 113.7 (CH_2), 115.7 (CH_2), 117.9 (CH_2), 140.5 (C), 144.7 (C), 146.2 (C), 146.4 (C), 172.3 (C), 197.1 ppm (CH); IR (film): $\tilde{\nu}=3083$, 2952, 2930, 2857, 1741, 1647, 1463, 1442, 1360, 1257, 1092, 1023, 1005, 971, 905, 838, 779, 670 cm^{-1}; MS (EI): *m/z* (%): 375 (6), 219 (7), 181 (17), 171 (13), 159 (12), 131 (26), 117 (12), 111 (12), 105 (11), 91 (19), 79 (14), 75 (100), 73 (50), 59 (11), 57 (16), 55 (14), 41 (10); HRMS (ESI): *m/z*: calcd for $C_{24}H_{36}O_5SiNa$ [M^++Na]: 455.2228, found: 455.2234; elemental analysis calcd (%) for $C_{24}H_{36}O_5Si$ (432.63): C 66.63, H 8.39; found: C 66.80, H 8.39.



Completion of the carbon framework and final deprotections

(1*S*,4*R*,13*R*,14*R*)-13-(*tert*-Butyldimethylsilyloxy)-2,9,10,12-tetramethylene-4-((1*E*,4*E*)-6-methylhepta-1,4,6-trienyl)-5,15-dioxabicyclo-[12.1.0]pentadecan-6-one (32): KHMDS (0.5 M in toluene, 0.4 mL, 0.20 mmol) was added at −78°C to a solution of sulfone **8** (61 mg, 0.20 mmol) in DME (4.4 mL) and DMPU (0.13 mL). The resulting mixture was stirred at −78°C for 30 min before a solution of aldehyde **31** (31 mg, 0.071 mmol) in DME (2.2 mL) was added dropwise. Stirring was continued at −78°C for 3 h before the cooling bath was removed and the mixture was stirred for additional 30 min. The reaction was quenched with sat. aq. NH_4Cl (2 mL), the aqueous layer was extracted with EtOAc (2×2 mL) and CH_2Cl_2 (3×2 mL), the combined organic phases were dried over Na_2SO_4 and evaporated, and the crude material purified by flash chromatography (hexanes/ethyl acetate 40:1) to give product **32** as a colorless oil (25 mg, 70%). $[\alpha]_D^{20}=+8$ ($CHCl_3$, $c=0.2$); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=0.10$ (s, 3H), 0.16 (s, 3H), 0.96 (s, 9H), 1.82 (s, 3H), 2.36–2.48 (m, 4H), 2.55–2.63 (m, 1H), 2.72–2.75 (m, 1H), 2.78 (dd, $J=2.1$, 7.6 Hz, 1H), 2.82 (t, $J=6.5$ Hz, 2H), 3.03 (d, $J=16.7$ Hz, 1H), 3.22 (d, $J=16.6$ Hz, 1H), 3.37 (d, $J=1.3$ Hz, 1H), 3.89 (d, $J=7.6$ Hz, 1H), 4.89 (s, 2H), 4.90 (s, 1H), 4.98 (s, 1H), 5.02 (s, 1H), 5.11 (s, 1H), 5.12 (s, 1H), 5.14 (s, 1H), 5.22 (s, 1H), 5.50 (s, 1H), 5.39–5.48 (m, 2H),

5.59 (dt, $J=6.6$, 15.5 Hz, 1H), 5.73 (dt, $J=6.5$ Hz, 14.2 Hz, 1H), 6.12 ppm (d, 1H, $J=15.7$ Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta=-4.9$ (CH_3), -4.4 (CH_3), 18.3 (C), 18.6 (CH_3), 25.9 (CH_3), 30.8 (CH_2), 33.9 (CH_2), 35.1 (CH_2), 38.6 (CH_2), 39.5 (CH_2), 57.6 (CH), 63.8 (CH), 74.3 (CH), 75.0 (CH), 112.7 (CH_2), 114.1 (CH_2), 115.0 (CH_2), 115.1 (CH_2), 115.4 (CH_2), 127.5 (CH), 128.0 (CH), 132.1 (CH), 134.0 (CH), 141.0 (C), 141.8 (C), 142.7 (C), 144.7 (C), 145.1 (C), 171.8 ppm (C); IR (film): $\tilde{\nu}=2951$, 2928, 2855, 1737, 1646, 1600, 1461, 1433, 1357, 1258, 1155, 1111, 1059, 967, 911, 837, 778 cm^{-1}; MS (EI): m/z (%): 510 (< 1) [M^+], 453 (19), 279 (12), 251 (28), 235 (12), 233 (25), 221 (12), 207 (11), 185 (13), 177 (25), 159 (32), 157 (10), 145 (12), 143 (18), 133 (13), 131 (58), 129 (17), 119 (22), 117 (26), 107 (16), 105 (33), 95 (13), 93 (30), 91 (36), 81 (41), 79 (27), 75 (100), 73 (63), 55 (14); HRMS (ESI): m/z: calcd for $C_{31}H_{46}O_4SiNa$ [M^++Na]: 533.3057, found: 533.3057.

Compound 40: Prepared analogously as a mixture of isomers (*E*/*Z* 3:1) which could be separated by flash chromatography (hexanes/ethyl acetate 40:1) to give pure (*E*)-**40** (24 mg) and pure (*Z*)-**40** (8 mg) in 66% combined yield. Analytical and spectroscopic data of (*E*)-**40**: $[\alpha]_D^{20}=-14.6$ ($CHCl_3$, $c=1$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.08$ (s, 3H), 0.13 (s, 3H), 0.93 (s, 9H), 1.84 (s, 3H), 1.96 (dd, $J=11.2$, 15.3 Hz, 1H), 2.13 (d, $J=15.3$ Hz, 1H), 2.26–2.37 (m, 4H), 2.83 (t, $J=6.4$ Hz, 2H), 3.05 (s, 2H), 3.20 (dd, $J=2.0$, 7.3 Hz, 1H), 3.23 (d, $J=2.0$ Hz, 1H), 3.74 (d, $J=7.3$ Hz, 1H), 4.80 (s, 1H), 4.89 (brs, 3H), 4.99 (s, 1H), 5.09 (s, 1H), 5.19 (s, 1H), 5.24 (s, 1H), 5.34 (brs, 2H), 5.40–5.46 (m, 2H), 5.60 (dt, $J=6.7$, 15.4 Hz, 1H), 5.73–5.80 (m, 1H), 6.13 ppm (d, $J=15.7$ Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=-5.0$ (CH_3), -4.7 (CH_3), 18.3 (C), 18.6 (CH_3), 25.8 (CH_3), 30.6 (CH_2), 31.8 (CH_2), 34.6 (CH_2), 35.1 (CH_2), 36.6 (CH_2), 59.5 (CH), 59.7 (CH), 74.1 (CH), 80.0 (CH), 112.4 (CH_2), 113.0 (CH_2), 115.1 (CH_2), 115.8 (CH_2), 117.5 (CH_2), 127.3 (CH), 128.9 (CH), 131.9 (CH), 134.2 (CH), 141.0 (C), 141.8 (C), 144.4 (C), 146.3 (C), 146.7 (C), 172.2 ppm (C); IR (film): $\tilde{\nu}=3082$, 2955, 2928, 2895, 2856, 1736, 1642, 1608, 1462, 1361, 1251, 1213, 1156, 1087, 1052, 1012, 966, 899, 835, 803, 777, 669 cm^{-1}; MS (EI): m/z (%): 510 (<1) [M^+], 453 (8), 361 (4), 321 (5), 309 (7), 233 (15), 177 (16), 171 (10), 159 (21), 157 (10), 145 (15), 143 (18), 133 (13), 131 (45), 129 (19), 119 (26), 117 (25), 105 (34), 91 (42), 75 (100); HRMS (ESI): m/z: calcd for $C_{31}H_{46}O_4SiNa$ [M^++Na]: 533.3057, found: 533.3053.

Analytical and spectroscopic data of (*Z*)-**40**: $[\alpha]_D^{20}=+36$ ($CHCl_3$, $c=0.3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.08$ (s, 3H), 0.13 (s, 3H), 0.94 (s, 9H), 1.82 (s, 3H), 1.99 (dd, $J=11.5$, 15.4 Hz, 1H), 2.06 (ddt, $J=1.5$, 3.2, 15.4 Hz, 1H), 2.25–2.38 (m, 4H), 3.04 (m, 2H), 3.06 (s, 2H), 3.20 (dd, $J=2.0$, 7.4 Hz, 1H), 3.24 (d, $J=2.0$ Hz, 1H), 3.75 (d, $J=7.4$ Hz, 1H), 4.81 (s, 1H), 4.89 (s, 2H), 4.90 (s, 1H), 4.99 (s, 1H), 5.10 (s, 1H), 5.20 (s, 1H), 5.24 (s, 1H), 5.33 (s, 1H), 5.34 (s, 1H), 5.35 (s, 1H), 5.57 (dt, $J=7.6$, 10.8 Hz, 1H), 5.64 (dt, $J=6.6$, 15.6 Hz, 1H), 5.70 (ddd, $J=3.2$, 9.4, 11.3 Hz, 1H), 6.17 ppm (d, $J=15.6$ Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=-5.0$ (CH_3), -4.6 (CH_3), 18.3 (C), 18.6 (CH_3), 25.8 (CH_3), 30.6 (CH_2), 31.0 (CH_2), 32.3 (CH_2), 34.5 (CH_2), 36.7 (CH_2), 59.6 (CH), 59.7 (CH), 70.3 (CH), 79.8 (CH), 112.4 (CH_2), 113.1 (CH_2), 115.0 (CH_2), 115.7 (CH_2), 117.7 (CH_2), 127.6 (CH), 128.7 (CH), 131.1 (CH), 133.7 (CH), 140.9 (C), 141.8 (C), 144.4 (C), 146.3 (C), 146.7 (C), 172.1 ppm (C); IR (film): $\tilde{\nu}=3082$, 2955, 2929, 2857, 1736, 1646, 1608, 1462, 1360, 1256, 1213, 1092, 1051, 1012, 969, 902, 837, 778, 669 cm^{-1}; MS (EI): m/z (%): 510 (2) [M^+], 453 (11), 361 (6), 322 (10), 309 (21), 233 (17), 177 (28), 131 (47), 75 (100); HRMS (ESI): m/z: calcd for $C_{31}H_{46}O_4SiNa$ [M^++Na]: 533.3057, found: 533.3058.

(1*S*,4*S*,13*S*,14*R*)-13-(*tert*-Butyldimethylsilyloxy)-2,9,10,12-tetramethylene-4-((1*E*,4*E*)-6-methylhepta-1,4,6-trienyl)-5,15-dioxabicyclo-[12.1.0]pentadecan-6-one (48): Prepared analogously as a colorless oil (8 mg, 98%). $[\alpha]_D^{20}=+26.5$ ($CHCl_3$, $c=0.46$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.05$ (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 1.83 (s, 3H), 1.95–2.04 (m, 1H), 2.14 (d, $J=15.0$ Hz, 2H), 2.26–2.38 (m, 4H), 2.82 (t, $J=6.5$ Hz, 2H), 2.92 (brs, 2H), 3.07 (dd, $J=1.6$, 1.8 Hz, 1H), 3.59 (d, $J=1.9$ Hz, 1H), 4.54 (s, 1H), 4.77 (s, 1H), 4.89 (s, 2H), 4.91 (s, 1H), 4.93 (s, 1H), 5.14 (s, 1H), 5.21 (s, 1H), 5.23 (s, 1H), 5.33 (s, 1H), 5.39–5.45 (m, 2H), 5.42 (s, 1H), 5.60 (dt, $J=6.8$, 15.6 Hz, 1H), 5.71–5.80 (m, 1H), 6.13 ppm (d, $J=15.6$ Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=-5.1$ (CH_3), -5.0 (CH_3), 18.3 (C), 18.6 (CH_3), 25.7 (CH_3), 29.9 (CH_2), 31.6 (CH_2), 34.2 (CH_2), 35.1 (CH_2), 36.0 (CH_2), 56.0 (CH), 58.3 (CH), 73.4 (CH), 74.2 (CH), 111.7 (CH_2), 113.1 (CH_2), 115.1 (CH_2), 115.5 (CH_2), 117.3 (CH_2), 127.3 (CH), 129.0 (CH), 131.7 (CH), 134.2 (CH), 141.7 (C), 141.8 (C), 145.2 (C), 146.3 (C), 147.1 (C), 172.2 ppm (C); IR (film): $\tilde{\nu}=3081$, 2953, 2928, 2894, 2856, 1738, 1668, 1608, 1471, 1462, 1436, 1361, 1342, 1256, 1125, 1109, 1011, 966, 905, 836, 779, 675 cm^{-1}; MS (EI): m/z (%): 309 (19), 233 (13), 177 (31), 171 (11), 159 (22), 157 (10), 145 (15), 143 (18), 131 (48), 119 (32), 117 (28), 105 (35), 91 (43), 75 (100), 73 (89); HRMS (ESI): m/z: calcd for $C_{31}H_{46}O_4SiNa$ [M^++Na]: 533.3057, found: 533.3054.

(1*R*,4*S*,13*R*,14*S*)-13-(*tert*-Butyldimethylsilyloxy)-2,9,10,12-tetramethylene-4-((1*E*,4*E*)-6-methylhepta-1,4,6-trienyl)-5,15-dioxabicyclo-[12.1.0]pentadecan-6-one (56): Prepared analogously from alcohol **55** (15 mg, 0.035 mmol) by Dess–Martin periodinane oxidation followed by Julia–Kocienski olefination of the resulting aldehyde (9 mg, 60%) with sulfone **8** (13 mg, 0.04 mmol). Colorless oil (8 mg, 75%, *E*/*Z* 3:1). Analytical and spectroscopic data of pure (*E*)-**56**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.06$ (s, 3H), 0.07 (s, 3H), 0.81 (s, 9H), 1.83 (s, 3H), 2.26–2.52 (m, 6H), 2.83 (t, $J=6.5$ Hz, 2H), 2.88 (t, $J=1.8$ Hz, 1H), 2.95 (d, $J=16.8$ Hz, 1H), 3.10 (d, $J=16.8$ Hz, 1H), 3.49 (d, $J=1.6$ Hz, 1H), 4.39 (s, 1H), 4.90

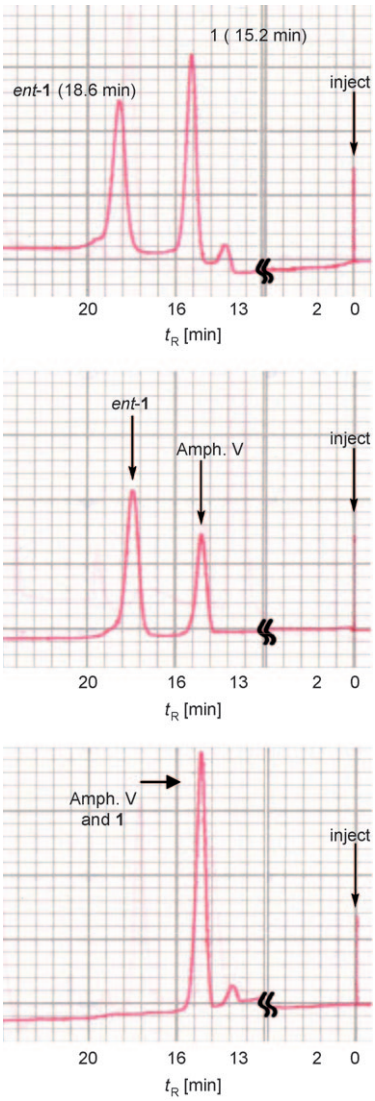


Figure 3. HPLC traces (Chiralpak OD column) of natural amphidinolide V, synthetic **1** and *ent*-**1**: Top: retention times of **1** and *ent*-**1**; middle: HPLC trace after co-injection of natural amphidinolide and *ent*-**1**; bottom: HPLC trace after co-injection of natural amphidinolide and **1**.

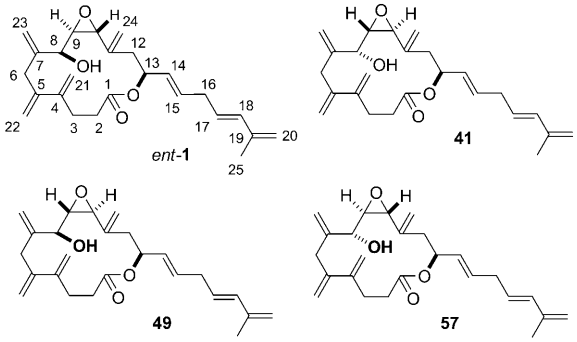
(s, 2H), 4.99 (d, J=4.3 Hz, 2H), 5.02 (s, 1H), 5.18 (d, J=1 Hz, 1H), 5.21 (s, 2H), 5.26 (s, 1H), 5.30 (s, 1H), 5.31–5.37 (m, 1H), 5.45 (dd, J=6.7, 15.5 Hz, 1H), 5.61 (dt, J=6.7, 15.5 Hz, 1H), 5.73 (dt, J=6.7, 15.5 Hz, 1H), 6.13 ppm (d, J=15.5 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= −5.0 (CH_3), 18.3 (C), 18.6 (CH_3), 25.8 (CH_3), 30.5 (CH_2), 34.0 (CH_2), 35.1 (CH_2), 36.7 (CH_2), 37.6 (CH_2), 55.7 (CH), 63.4 (CH), 74.2 (CH), 77.2 (CH), 113.0 (CH_2), 115.0 (CH_2), 115.1 (CH_2), 115.1 (CH_2), 115.4 (CH_2), 127.5 (CH), 128.9 (CH), 131.5 (CH), 134.1 (CH), 140.5 (C), 141.4 (C), 146.2 (C), 174.1 ppm (C); IR (film): $\tilde{\nu}$=2927, 2855, 1731, 1422, 1264, 1125, 969, 896, 837, 703 cm^{-1}; MS (EI): m/z (%): 414 (2), 323 (1), 159 (26), 105 (67), 91 (100), 79 (87), 67 (34); HRMS (ESI): m/z: calcd for $C_{31}H_{46}O_4SiNa$ [M^++Na]: 533.3057, found: 533.3058.

Amphidinolide V (1) (see Figure 3 for HPLC diagrams and Tables 2 and 3 for comparison of the NMR data): A freshly prepared solution of TASF (52 mg, 0.189 mmol) in DMF (0.9 mL) was added to a solution of **32** (17 mg, 0.033 mmol) in DMF (1.7 mL) at 0 °C and the resulting mixture was stirred at this temperature for 20 h. The reaction was quenched with pH 7 phosphate buffer (2 mL) and extracted with CH_2Cl_2 (5×1 mL), the combined extracts were dried over Na_2SO_4 and evaporated, and the residue purified by flash chromatography (hexanes/ethyl acetate 20:1) to give **1** as a colorless oil (11 mg, 85 %) as well as a second fraction consisting of unreacted started material **32** (1 mg). $[\alpha]_D^{20}$=+3.5 ($CHCl_3$, c= 0.45); $[\alpha]_D^{20}$=−12 (MeOH, c=0.29); ^{1}H NMR ($CDCl_3$, 400 MHz): δ=1.82 (s, 3H), 2.16 (brs, 1H), 2.35–2.50 (m, 4H), 2.59–2.67 (m, 1H), 2.73 (dt, J=4.7, 13.8 Hz, 1H), 2.80–2.84 (m, 3H), 3.11 (d, J=16.2 Hz, 1H), 3.25 (d, J=16.2 Hz, 1H), 3.46 (d, J=1.1 Hz, 1H), 4.01 (d, J=5.7 Hz, 1H), 4.89 (s, 2H), 4.93 (s, 1H), 5.07 (s, 1H), 5.10 (s, 1H), 5.12 (s, 1H), 5.15 (s, 1H), 5.19 (s, 1H), 5.23 (s, 1H), 5.38–5.45 (m, 2H), 5.46 (s, 1H), 5.59 (dt, J=6.7, 15.6 Hz, 1H), 5.72 (ddq, J=3.9, 6.4, 13.1 Hz, 1H), 6.12 ppm (d, J=15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=18.6 (CH_3), 30.5 (CH_2), 33.7 (CH_2), 35.0 (CH_2), 39.0 (CH_2), 39.1 (CH_2), 57.9 (CH), 63.2 (CH), 71.4 (CH), 74.3 (CH), 114.0 (CH_2), 114.8 (CH_2), 114.8 (CH_2), 115.1 (CH_2), 115.1 (CH_2), 127.4 (CH), 128.0 (CH), 132.0 (CH), 134.1 (CH), 140.7 (C), 141.8 (C), 142.1 (C), 144.5 (C), 144.9 (C), 171.8 ppm (C); IR (film): $\tilde{\nu}$=3451, 3083, 2987, 2941, 2918, 1735, 1647, 1597, 1434, 1359, 1224, 1156, 1120, 968, 902 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{25}H_{32}O_4Na$ [M^++Na]: 419.2194, found: 419.2192.

(1*S*,4*S*,13*R*,14*S*)-13-Hydroxy-2,9,10,12-tetramethylene-4-((1*E*,4*Z*)-6-methylhepta-1,4,6-trienyl)-5,15-dioxabicyclo[12.1.0]pentadecan-6-one [(*Z*)-41]: Prepared analogously from (*Z*)-**40** (10 mg, 0.020 mmol) as a colorless oil (8 mg, 99 %). $[\alpha]_D^{20}$=+34.7 ($CHCl_3$, c=0.4); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.81 (s, 3H), 2.06 (dd, J=10.5, 15.1 Hz, 1H), 2.14 (dd, J=1.5, 15.1 Hz, 1H), 2.19 (d, J=4.0 Hz, 1H), 2.31–2.43 (m, 4H), 3.01–3.04 (m, 2H), 3.08 (s, 2H), 3.17 (dd, J=1.8, 6.8 Hz, 1H), 3.34 (d, J=1.9 Hz, 1H), 3.90 (dd, J=4.0, 6.4 Hz, 1H), 4.86 (s, 1H), 4.87 (s, 2H), 5.01 (s, 1H), 5.02 (s, 1H), 5.16 (s, 1H), 5.21 (s, 1H), 5.27 (s, 1H), 5.29 (s, 1H), 5.30 (s, 1H), 5.35 (s, 1H), 5.54–5.68 (s, 3H), 6.15 (d, J=15.6 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=18.6 (CH_3), 30.4 (CH_2), 31.0 (CH_2), 33.5 (CH_2), 34.2 (CH_2), 37.3 (CH_2), 59.7 (CH), 59.9 (CH), 70.4 (CH), 75.9 (CH), 113.2 (CH_2), 114.0 (CH_2), 115.1 (CH_2), 115.7 (CH_2), 117.9 (CH_2), 127.6 (CH), 128.6 (CH), 131.1 (CH), 133.7 (CH), 140.5 (C), 141.8 (C), 144.0 (C), 145.0 (C), 146.4 (C), 172.0 ppm (C); IR (film): $\tilde{\nu}$=3456, 3082, 2924, 2859, 1734, 1647, 1607, 1438, 1362, 1341, 1262, 1235, 1157, 1133, 1033, 987, 969, 896, 800 cm^{-1}; MS (EI): m/z (%): 396 (<1) [M^+], 202 (13), 201 (14), 177, (23), 173 (14), 159 (21), 131 (50), 119 (53), 105 (65), 93 (64), 91 (100), 81 (52), 79 (85), 77 (54), 55 (64), 41 (64); HRMS (ESI): m/z: calcd for $C_{25}H_{32}O_4Na$ [M^++Na]: 419.2194, found: 419.2193.

(1*S*,4*S*,13*R*,14*S*)-13-Hydroxy-2,9,10,12-tetramethylene-4-((1*E*,4*E*)-6-methylhepta-1,4,6-trienyl)-5,15-dioxabicyclo[12.1.0]pentadecan-6-one [(*E*)-41]: Prepared analogously from (*E*)-**40** (15 mg, 0.029 mmol) as a colorless oil **62** (12 mg, 99 %). $[\alpha]_D^{20}$= −46.5 ($CHCl_3$, c=0.31); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.82 (s, 3H), 2.04 (dd, J=10.5, 15.1 Hz, 1H), 2.19–2.25 (m, 2H), 2.29–2.41 (m, 4H), 2.81 (t, J=6.4 Hz, 2H), 3.07 (s, 2H), 3.16 (dd, J=2.0, 6.9 Hz, 1H), 3.33 (d, J= 2.0 Hz, 1H), 3.88 (dd, J=2.8, 6.4 Hz, 1H), 4.85 (s, 1H), 4.87 (s, 1H), 4.88 (s, 1H), 5.00 (s, 1H), 5.02 (s, 1H), 5.16 (s, 1H), 5.21 (s, 1H), 5.25 (s, 1H), 5.31 (s, 1H), 5.34 (s, 1H), 5.37–5.43 (m, 2H), 5.58 (dt, J=6.8, 15.6 Hz, 1H), 5.75 (dt, J=6.4, 14.5 Hz, 1H), 6.11 ppm (d, J= 15.6 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=18.6 (CH_3), 30.4 (CH_2), 33.2 (CH_2), 34.3 (CH_2), 35.1 (CH_2),

Table 2. Comparison of the ^{13}C NMR ($CDCl_3$) data of compounds *ent*-**1**, **41**, **49** and **57** with those of amphidinolide V reported in the literature;[2] numbering scheme as shown in the insert.



No.	Lit.[2]	*ent*-**1**	Δδ[a]	**41**	Δδ[a]	**49**	Δδ[a]	**57**	Δδ[a]
1	171.3	171.8	0.5	172.1	0.8	172.1	0.8	172.0	0.7
2	33.5	33.7	0.2	34.3	0.8	34.1	0.6	36.5	**3.0**
3	30.2	30.5	0.3	30.4	0.2	29.8	−0.4	29.7	−0.5
4	144.5	144.6	0.1	146.5	**2.0**	146.0	**1.5**	144.2	−0.3
5	141.4	142.1	0.7	144.0	**2.6**	144.4	**3.0**	140.6	−0.8
6	39.0	39.1	0.1	37.2	**−1.8**	37.7	**−1.3**	37.9	**−1.1**
7	144.7	144.9	0.2	145.0	0.3	144.4	−0.3	146.6	1.9
8	71.1	71.4	0.3	76.2	**5.1**	70.4	−0.7	71.8	0.7
9	63.2	63.2	0.0	59.8	**−3.4**	57.8	**−5.4**	62.3	−0.9
10	57.7	57.9	0.2	59.7	**2.0**	56.4	**−1.3**	55.6	**−2.1**
11	n.o.[b]	140.7		140.6		140.8		n.o.[b]	
12	38.9	39.0	0.1	33.2	**−5.7**	31.7	**−7.2**	35.1	**−3.8**
13	74.3	74.3	0.0	74.2	−0.1	74.3	0.0	74.1	−0.2
14	127.6	128.0	0.4	128.7	**1.1**	128.9	**1.3**	129.6	**2.0**
15	131.2	132.0	0.8	132.1	0.9	131.9	0.7	131.6	0.4
16	34.9	35.0	0.1	35.1	0.2	35.1	0.2	33.9	**−1.0**
17	127.1	127.4	0.3	127.2	0.1	127.3	0.2	127.4	0.3
18	133.3	134.1	0.8	134.2	0.9	134.3	**1.0**	134.2	0.9
19	141.5	141.8	0.3	141.8	0.3	141.8	0.3	141.1	−0.4
20	114.8	115.1	0.3	115.1	0.3	115.1	0.3	115.1	0.3
21	114.4	114.8	0.4	113.1	**-1.3**	112.6	**-1.8**	115.0	0.6
22	113.6	114.0	0.4	115.8	**2.2**	115.7	**2.1**	113.5	−0.1
23	114.4	114.8	0.4	114.0	−0.4	113.8	−0.6	115.8	**1.4**
24	114.8	115.0	0.2	117.7	**2.9**	117.9	**3.1**	116.5	**1.7**
25	18.3	18.6	0.3	18.6	0.3	18.6	0.3	18.6	0.3

[a] Δδ=δ(synthetic isomer)−δ (ref. [2]); [b] n.o.=not observed; shift differences $\Delta\delta_C$=1.0 ppm in bold.

Table 3. Comparison of the ^{1}H NMR data of synthetic **1** with those of amphidinolide V reported in the literature;[2] numbering scheme as shown in the previous Table. For a discussion of the single discrepancy, see main text.

No.	C_6D_6		$CDCl_3$	
	Lit.	**1**	Lit.	**1**
2	2.17 (m), 2.05 (ddd, J = 14.4, 4.7, 3.8 Hz)	2.08–2.18 (m), 2.01 (ddd, J = 14.4, 5.6, 4.0 Hz)	2.45 (m)	2.43–2.47 (m)
3	2.57 (ddd, J = 14.1, 12.1, 3.8 Hz), 2.38 (dt, J = 14.1, 4.7 Hz)	2.52 (ddd, J = 14.1, 12.1, 4.0 Hz), 2.34 (dt, J = 14.1, 4.2 Hz)	2.73 (m), 2.63 (m)	2.70–2.77 (m), 2.50–2.67 (m)
6	3.05 (d, J = 16.3 Hz), 2.88 (d, J = 16.3 Hz)	3.01 (d, J = 16.1 Hz), 2.86 (d, J = 16.1 Hz)	3.25 (d, J = 16.4 Hz), 3.11 (d, J = 16.4)	3.25 (d, J = 16.4 Hz), 3.11 (d, J = 16.4 Hz)
8	3.97 (m)	3.93 (brs)	**4.50 (m)**	**4.00 (dd, J = 5.8, 5.4)**
9	2.82 (dd, J = 6.5, 2.2 Hz)	2.77 (dd, J = 6.5, 2.1 Hz)	2.80 (m)	2.79–2.82 (m)
10	3.55 (d, 2.2)	3.50 (brs)	3.46 (brs)	3.46 (brs)
12	2.29 (dd, J = 14.5, 3.3 Hz), 2.18 (m)	2.24 (dd, J = 14.1, 2.6 Hz), 2.08–2.18 (m)	2.41 (m)	2.39–2.41 (m)
13	5.62 (dt, J = 7.1, 3.3 Hz)	5.53–5.59 (m)	5.43 (m)	5.43–5.45 (m)
14	5.47 (dd, J = 15.5, 7.1 Hz)	5.42 (dd, J = 15.4, 6.6 Hz)	5.42 (m)	5.40–5.43 (m)
15	5.74 (dt, J = 15.5, 6.6 Hz)	5.69 (dt, J = 15.4, 6.6 Hz)	5.72 (m)	5.67–5.77 (m)
16	2.70 (t, J = 6.6 Hz)	2.64 (t, J = 6.5 Hz)	2.83 (m)	2.82–2.85 (m)
17	5.57 (dt, J = 15.6, 6.6 Hz)	5.52 (dd, J = 15.6, 6.6 Hz)	5.60 (dt, J = 15.6, 6.7 Hz)	5.60 (dt, J = 15.6, 6.7 Hz)
18	6.21 (d, J = 15.6 Hz)	6.15 (d, J = 15.6 Hz)	6.12 (d, 15.6 Hz)	6.12 (d, J = 15.6 Hz)
20	5.01 (s), 4.94 (s)	4.95 (s), 4.89 (s)	4.89 (s)	4.89 (s)
21	5.03 (s), 4.97 (s)	4.98 (s), 4.92 (s)	5.13 (s), 5.08 (s)	5.13 (s), 5.08 (s)
22	4.97 (s), 4.92 (s)	4.92 (s), 4.89 (s)	5.26 (s), 5.10 (s)	5.24 (s), 5.10 (s)
23	5.68 (s), 5.34 (s)	5.62 (s), 5.28 (s)	5.46 (s), 5.14 (s)	5.46 (s), 5.16 (s)
24	5.10 (s), 4.76 (s)	5.04 (s), 4.71 (s)	5.19 (s), 4.93 (s)	5.19 (s), 4.93 (s)
25	1.78 (s)	1.73 (s)	1.83 (s)	1.83 (s)

37.2 (CH_2), 59.7 (CH), 59.8 (CH), 74.2 (CH), 76.2 (CH), 113.1 (CH_2), 114.0 (CH_2), 115.1 (CH_2), 115.8 (CH_2), 117.7 (CH_2), 127.2 (CH), 128.7 (CH), 132.1 (CH), 134.2 (CH), 140.6 (C), 141.8 (C), 144.0 (C), 145.0 (C), 146.5 (C), 172.1 ppm (C); IR (film): $\tilde{\nu}$ = 3450, 3080, 2920, 1732, 1644, 1607, 1435, 1263, 1234, 1157, 1131, 1032, 967, 891 cm^{-1}; MS (EI): m/z (%): 396 (< 1) [M^+], 201 (8), 177, (21), 173 (12), 159 (21), 157 (13), 147 (17), 145 (18), 143 (19), 135 (18), 131 (44), 129 (21), 121 (34), 119 (46), 117 (31), 105 (65), 93 (66), 91 (100), 81 (55), 79 (86), 55 (60), 41 (58); HRMS (ESI): m/z: calcd for $C_{25}H_{32}O_4Na$ [M^++Na]: 419.2194, found: 419.2193.

(1*S*,4*S*,13*S*,14*S*)-13-Hydroxy-2,9,10,12-tetramethylene-4-((1*E*,4*E*)-6-methylhepta-1,4,6-trienyl)-5,15-dioxabicyclo[12.1.0]pentadecan-6-one (49): Prepared analogously from **48** (20 mg, 0.039 mmol) as a colorless oil (12 mg, 78%). $[\alpha]_D^{20}$ = +6.9 ($CHCl_3$, c = 0.35); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.83 (s, 3H), 1.92–2.19 (m, 2H), 2.20 (brs, 1H), 2.27–2.45 (m, 2H), 2.33–2.45 (m, 2H), 2.83 (dd, J = 6.5, 6.5 Hz, 2H), 3.04 (brs, 2H), 3.22 (dd, J = 2.2, 2.2 Hz, 1H), 3.59 (d, J = 2.2 Hz, 1H), 4.57 (s, 1H), 4.82 (s, 1H), 4.89 (brs, 2H), 5.02 (brs, 2H), 5.14 (s, 1H), 5.24 (s, 1H), 5.26 (s, 1H), 5.29 (s, 1H), 5.33 (s, 1H), 5.40 (brs, 1H), 5.40–5.45 (m, 1H), 5.60 (dt, J = 15.6, 6.8 Hz, 1H), 5.77 (dt, J = 14.2, 6.3 Hz, 1H), 6.13 ppm (d, J = 15.7 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.6 (CH_3), 29.8 (CH_2), 31.7 (CH_2), 34.1 (CH_2), 35.1 (CH_2), 37.7 (CH_2), 56.4 (CH), 57.8 (CH), 70.4 (CH), 74.3 (CH), 112.6 (CH_2), 113.8 (CH_2), 115.1 (CH_2), 115.7 (CH_2), 117.9 (CH_2), 127.3 (CH), 128.9 (CH), 131.9 (CH), 134.3 (CH), 140.8 (C), 141.8 (C), 144.4 (C), 144.4 (C), 146.0 (C), 172.1 ppm (C); IR (film): $\tilde{\nu}$ = 3480, 3081, 3018, 2985, 2921, 1735, 1640, 1608, 1435, 1374, 1262, 1239, 1155, 1089, 969, 896 cm^{-1}; MS (EI): m/z (%): 159 (27), 131 (58), 105 (70), 91 (100), 79 (84), 55 (52); HRMS (ESI): m/z: calcd for $C_{25}H_{32}O_4Na$ [M^++Na]: 419.2196, found: 419.2193.

(1*R*,4*S*,13*R*,14*R*)-13-Hydroxy-2,9,10,12-tetramethylene-4-((1*E*,4*E*)-6-methylhepta-1,4,6-trienyl)-5,15-dioxabicyclo[12.1.0]pentadecan-6-one (57): Prepared analogously from **56** (6 mg, 11.8 μmol) as a colorless oil (3 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.83 (s, 3H), 2.20–2.57 (m, 2H), 2.27–2.57 (m, 2H), 2.39–2.56 (m, 2H), 2.83 (dd, J = 6.4 Hz, 2H), 3.01 (d, J = 16.4 Hz, 1H), 3.02 (dd, J = 2.1, 2.1 Hz, 1H), 3.18 (d, J = 16.4 Hz, 1H), 3.59 (d, J = 1.7 Hz, 1H), 4.51 (brs, 1H), 4.90 (s, 2H), 4.94 (s, 1H), 5.04 (s, 1H), 5.08 (s, 1H), 5.12 (s, 1H), 5.18 (s, 1H), 5.24 (s, 1H), 5.26 (s, 1H), 5.29 (m, 1H), 5.36 (s, 1H), 5.42 (m, 1H), 5.60 (dt, J = 14.0, 6.7 Hz, 1H), 5.74 (dt, J = 6.7, 14.7 Hz, 1H), 6.13 ppm (d, J = 15.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.6 (CH_3), 29.7 (CH_2), 33.9 (CH_2), 35.1 (CH_2), 36.5 (CH_2), 37.9 (CH_2), 55.6 (CH), 62.3 (CH), 71.8 (CH), 74.1 (CH), 113.5 (CH_2), 115.0 (CH_2), 115.1 (CH_2), 115.8 (CH_2), 116.5 (CH_2), 127.4 (CH), 129.6 (CH), 131.6 (CH), 134.2 (CH), 140.6 (C), 141.1 (C), 144.2 (C), 146.6 (C), 172.0 ppm (C); IR (film): $\tilde{\nu}$ = 3444, 2922, 1732, 1438, 1259, 1156, 900 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{25}H_{32}NaO_4$ [M^++Na]: 419.2196, found: 419.2195.

(1*S*,4*R*,13*R*,14*S*)-13-Hydroxy-2,9,10,12-tetramethylene-4-((*E*)-6-methylhept-1-enyl)-5,15-dioxabicyclo-[12.1.0]pentadecan-6-one (60): KHMDS (0.5 M in toluene, 0.36 mL, 0.180 mmol) was added to a solution of sulfone **58** (55.6 mg, 0.180 mmol) in DME (3.7 mL) and DMPU (0.116 mL) at −78 °C and the mixture was stirred at that temperature for 30 min. A solution of the aldehyde **31** (26 mg, 0.06 mmol) in DME (1.8 mL) was then added dropwise and stirring continued at −78 °C for 3 h before the cooling bath was removed and the mixture was stirred for additional 30 min. The reaction was quenched with sat. aq. NH_4Cl (2 mL), the aqueous layer was extracted with EtOAc (2×2 mL) and CH_2Cl_2 (3×2 mL), the combined organic phases were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate 60:1) to give **59** as a colorless oil (14 mg, 46%) which was used in the next step without further characterization. To this end, a fresh solution of TASF (36.6 mg, 0.132 mmol) in DMF (0.6 mL) was added dropwise to a solution of **59** (12 mg, 0.023 mmol) at −10 °C and the resulting mixture stirred at this temperature for 20 h. The reaction was quenched with phosphate buffer (pH 7, 2 mL) and extracted with CH_2Cl_2 (5×2 mL), the combined extracts were dried over Na_2SO_4 and evaporated, and the residue purified by flash chromatography (hexanes/ethyl acetate 20:1) to give product **60** as a colorless oil (7.4 mg, 80%) and a second fraction consisting of unreacted **59** (1 mg). $[\alpha]_D^{20}$ = +1.8 ($CHCl_3$, c = 0.74); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.84 (s, 3H), 0.86 (s, 3H), 1.10–1.21 (m, 2H), 1.30–1.37 (m, 2H), 1.51 (dq, J = 6.6, 6.6 Hz, 1H), 1.98 (dd, J = 7.1, 14.3 Hz, 2H), 2.16 (d, J = 5.1 Hz, 1H), 2.34–2.45 (m, 4H), 2.59–2.66 (m, 1H), 2.70–2.76 (m, 1H), 2.81 (dd, J = 1.7, 6.1 Hz, 1H), 3.10 (d, J = 16.2 Hz, 1H), 3.25 (d, J = 16.2 Hz, 1H), 3.46 (brs, 1H), 4.01 (dd, J = 4.7, 4.7 Hz, 1H), 4.92 (s, 1H), 5.07 (s, 1H), 5.09 (s, 1H), 5.12 (s, 1H), 5.15 (s, 1H), 5.18 (s, 1H), 5.23 (s, 1H), 5.31–5.42 (m, 2H), 5.46 (s, 1H), 5.65–5.75 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 22.5 (CH_3), 22.5 (CH_3), 26.6 (CH_2), 27.7 (CH), 30.5 (CH_2), 32.3 (CH_2), 33.7 (CH_2), 38.3 (CH_2), 39.1 (CH_2), 39.2 (CH_2), 57.9 (CH), 63.3 (CH), 71.4 (CH), 74.6 (CH), 113.9 (CH_2), 114.8 (CH_2), 114.8 (CH_2), 115.0 (CH_2), 126.7 (CH), 134.8 (CH), 140.7 (C), 142.0 (C), 144.5 (C), 144.9 (C), 171.8 ppm (C); IR (film): $\tilde{\nu}$ = 3465, 2953, 2926, 2869, 1736, 1648, 1597, 1460, 1434, 1364, 1225, 1156, 1120, 1025, 978, 902 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{25}H_{36}O_4Na$ [M^++Na]: 423.2505, found: 423.2505.

(1*S*,4*R*,13*R*,14*S*)-13-Hydroxy-2,9,10,12-tetramethylene-4-((*E*)-3-phenylprop-1-enyl)-5,15-dioxabicyclo[12.1.0]pentadecan-6-one (63): Prepared analogously from sulfone **61** (66 mg, 0.210 mmol) and aldehyde **31**

(30.4 mg, 0.07 mmol) as a colorless oil (4.9 mg, 25% over both steps). $[\alpha]_D^{20} = +10.3$ ($CHCl_3$, $c = 0.49$); ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 2.15$ (d, $J = 4.4$ Hz, 1H), 2.36–2.50 (m, 4H), 2.59–2.66 (m, 1H), 2.74 (dt, $J = 4.7$, 13.8 Hz, 1H), 2.81 (dd, $J = 2.0$, 6.2 Hz, 1H), 3.10 (d, $J = 16.2$ Hz, 1H), 3.25 (d, $J = 16.3$ Hz, 1H), 3.36 (d, $J = 6.1$ Hz, 2H), 3.45 (brs, 1H), 3.99 (brs, 1H), 4.92 (s, 1H), 5.07 (s, 1H), 5.09 (s, 1H), 5.12 (s, 1H), 5.15 (s, 1H), 5.19 (s, 1H), 5.23 (s, 1H), 5.42–5.50 (m, 2H), 5.46 (s, 1H), 5.79–5.88 (m, 1H), 7.13–7.21 (m, 3H), 7.26–7.30 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 30.5$ (CH_2), 33.6 (CH_2), 38.4 (CH_2), 39.1 (CH_2), 57.9 (CH), 63.3 (CH), 71.4 (CH), 74.1 (CH), 113.9 (CH_2), 114.8 (CH_2), 115.1 (CH_2), 126.1 (CH), 128.4 (CH), 128.4 (CH), 128.5 (CH), 132.5 (CH), 139.5 (C), 140.6 (C), 142.0 (C), 144.4 (C), 144.9 (C), 171.8 ppm (C); IR (film): $\tilde{\nu} = 3484$, 3083, 3017, 2917, 1734, 1647, 1597, 1495, 1453, 1433, 1399, 1359, 1225, 1156, 1120, 1027, 975, 904, 748, 699 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{26}H_{30}O_4Na$ [M^++Na]: 429.2038, found: 429.2036.

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