Synthesis of the Salicylihalamide Core Structure from Epichlorohydrin – Laying the Foundation to Macrolactone Collections

Christian Herb,[a] Frank Dettner,[a] and Martin E. Maier*[a]

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Starting from (*R*)-epichlorohydrin, two successive carbon–carbon bond formations, one with acetylide and the other with cyanide, led to the 3-hydroxynitrile **20**. This compound was further elaborated to the enynol **29** via an Evans aldol reaction of the derived aldehyde **22** with the pentenoyloxazolidinone **23** and conversion of the carboxyl to a methyl group after the aldol reaction. Mitsunobu esterification of the enynol **29** with the benzoic acid **5** gave rise to the ester **30** with two double bonds and one triple bond. After protection of the terminal triple bond with a TIPS group, the ring closing metathesis proceeded in good yield. The macrolactone ***E*-33** was converted into the vinyl iodide **34** and the pyridin containing salicylihalamide analog **36**. The described sequence, the two-sided elongation of epichlorohydrin appears as a general route to secondary alcohols that can be further elaborated to functionalized macrolactones.
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Introduction

Natural products still serve as sources of new drugs to a substantial degree.[1] Among them are many macrolactones which usually originate from the polyketide pathway. The macrocycle secures the appropriate orientation of polar and non-polar groups.[2] Natural products such as macrolactones also represent attractive starting points or lead structures for the preparation of compound libraries that can be used for chemical genetic studies.[3–6] Besides the macrolactone core, certain side chains can also be essential for biological activity. For example, in the benzolactone enamides it seems that the enamide side chain can form an acyliminium ion that is trapped by a nucleophilic amino acid side chain. This is most likely an important step in the reversible inhibition of mammalian V-ATPases.[7] Inhibition of these proton pumps eventually leads to cell death via apoptosis. Important representatives of the benzolactone enamides are the salicylihalamides (***E*-1**, ***Z*-1**) and apicularen A (**2**) (Figure 1). In addition, other related molecules are known.[8] The salicylihalamides were isolated from the sponge *Haliclona* sp.,[9] whereas apicularen A was found in various myxobacteria strains.[10]

The challenging structural features of these natural products combined with their novel mode of action have stimulated a number of synthesis programs. Thus, several total syntheses for the salicylihalamides[11] and apicularen A[12] were published. In addition, formal total syntheses[13,14] and

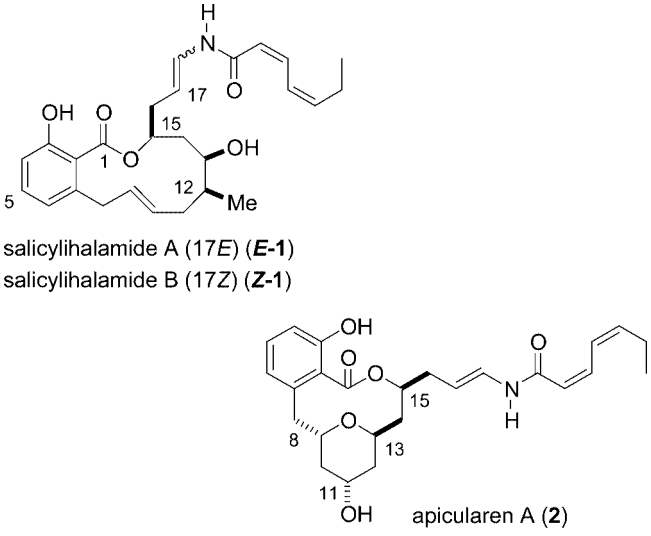

Figure 1. Structures of two important benzolactone enamides.

synthetic studies[15] are known in the literature. Finally, the synthesis of several simplified salicylihalamide analogs was described by ring closing metathesis of bisolefinic ester substrates.[16] In the case of the salicylihalamides, all syntheses first construct the macrocyclic core followed by attachment of the enamide side chain. The length and terminus of the side chain at C15 of the salicylihalamides depends very much on the way the enamide is established. Thus, the enamide was attached by nucleophilic addition to a vinyl isocyanate,[11d,11f,11g] by cross-coupling between a vinyl iodide and the unsaturated amide,[11b] or by reaction of the unsaturated amide with an aldehyde function.[11c] With the enamide side chain and the macrolactone core it might be specu-

[a] Institut für Organische Chemie, Universität Tübingen
Auf der Morgenstelle 18, 72076 Tübingen, Germany
Fax: (internat.) +49-(0)7071-295137
E-mail: martin.e.maier@uni-tuebingen.de
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lated that salicylihalamide consists of two binding domains. We reasoned that strong modifications on the C15 side chain might generate macrolactones with new modes of biological activity. For this purpose a terminating functional group was sought that has a high diversity potential[17] and at the same time is chemically quite robust. Therefore we chose a terminal alkyne function. With regard to library generation Sonogashira couplings or 1,3-dipolar cycloaddition reactions[18] appear ideal. Accordingly, the macrolactone **3** (Figure 2) became our target as a branching platform. Among the various strategies that have been used to fashion the macrolactone core of the salicylihalamides[11,13,15] the ring closing metathesis is probably the most general one with regard to functional group tolerance and potential for upscaling.[19] In addition, the high convergence, the avoidance of hydroxy acids, and the reliability of the reaction are advantageous. The retrosynthetic analysis, illustrated in Figure 2 leads to optically active epichlorohydrin, a compound that is easily available from the racemate by Jacobsen resolution.[20]

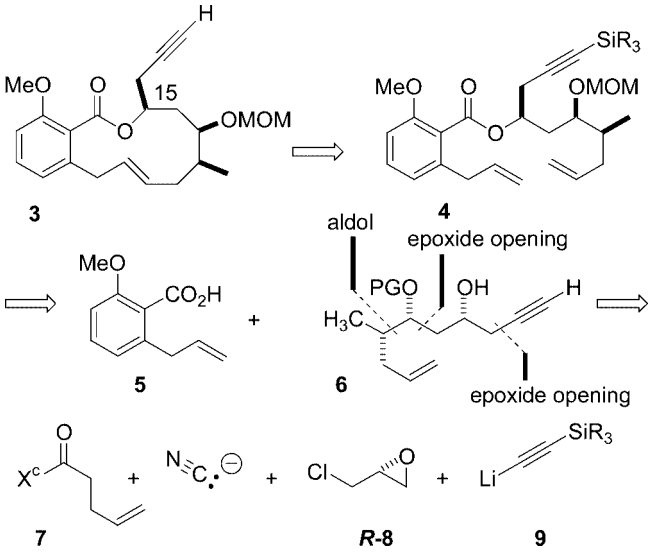
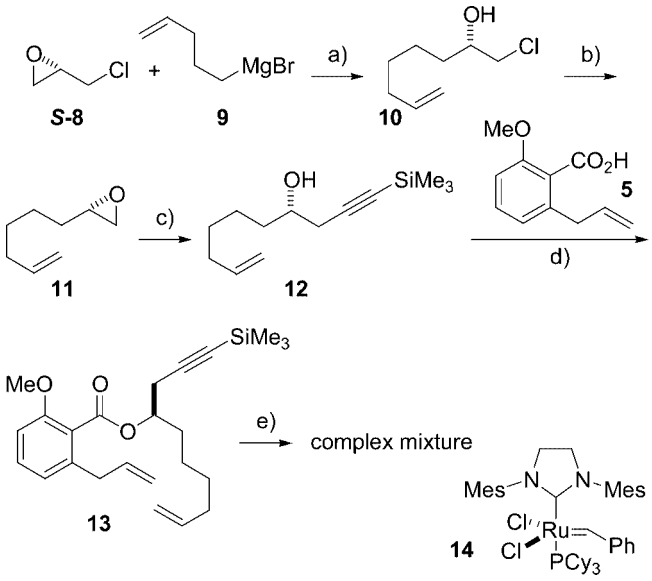


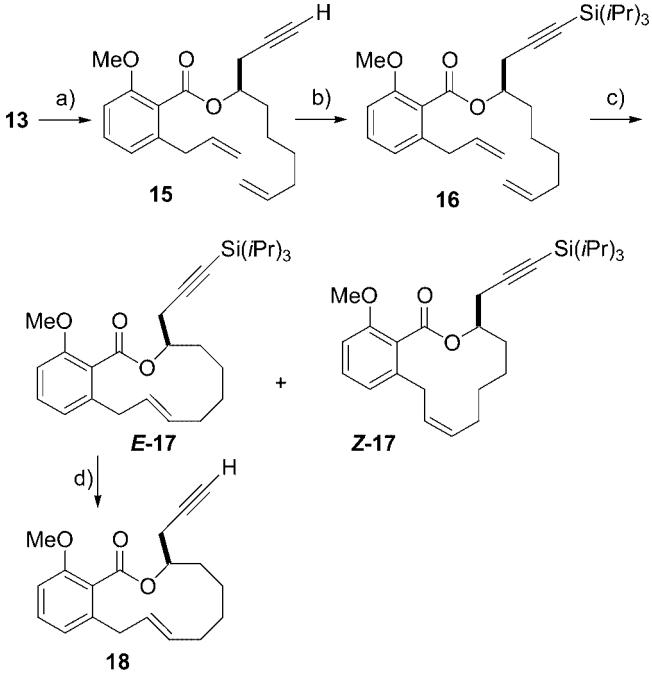
Figure 2. Retrosynthetic analysis of the propynyl-substituted macrolactone **3** leading to epichlorohydrin as starting material; R = alkyl, PG = non-silyl protecting group, X^c = chiral auxiliary.

Results

In order to probe the feasibility of this strategy and to test the compatibility of the alkyne with the metathesis condition, a model system was constructed (Scheme 1). Thus, opening of (*S*)-epichlorohydrin (***S*-8**) with 5-pentenylmagnesium bromide in the presence of copper cyanide (CuCN) gave a quantitative yield of the chlorohydrin **10**.[21] Treatment of **10** with sodium hydroxide generated the terminal epoxide **11**.[22] Now a second carbon–carbon bond formation was performed with lithium trimethylsilyl acetylide[23] in the presence of borontrifluoride–diethyl ether.[24] The resulting secondary alcohol **12** was then condensed with the benzoic acid **5** under Mitsunobu conditions[11b,25] leading to the dienyl ester **13**. However, treatment of the ynediene



Scheme 1. Synthesis of the benzoate **13** and its attempts to cyclize it to the corresponding macrolactone; a) bromopentene (1 equiv.), THF, Mg (1.38 equiv.), 50 °C, add to CuCN (0.04 equiv.), ***S*-8** (0.77 equiv.), THF, –50 °C, 2 h, 100 %; b) NaOH (2 equiv.), ethylene glycol, 0 to 23 °C, 1 h, 73 %; c) Me_3SiCCH (1 equiv.), *n*BuLi (0.93 equiv.), THF, –78 °C, 30 min, add $BF_3{\cdot}Et_2O$ (1 equiv.), 30 min, add **11** (0.64 equiv.), –78 °C, 3 h, 36 %; d) **12** (1 equiv.), Ph_3P (2.5 equiv.), acid **5** (5 equiv.), DIAD (2.5 equiv.), toluene, 23 °C, 3 h, 65 %. DIAD = diisopropylazodicarboxylate.



Scheme 2. Synthesis of the benzoate **16** with a TIPS-protected alkyne and its ring closing metathesis to the macrolactones **17**; a) K_2CO_3 (2 equiv.), MeOH, 23 °C, 4 h, 85 %; b) *n*BuLi (1.12 equiv.), THF, –78 to –20 °C, 30 min, then add $(iPr)_3SiCl$ (1.2 equiv.), THF, –78 to 23 °C, 15 h, 78 %; c) catalyst **14** (0.05 equiv.), toluene, 75 °C, 2 h, 99 % (*E*/*Z* = 4.21:1); d) TBAF (5 equiv.), THF, 0 to 23 °C, 5 h, (100 %).

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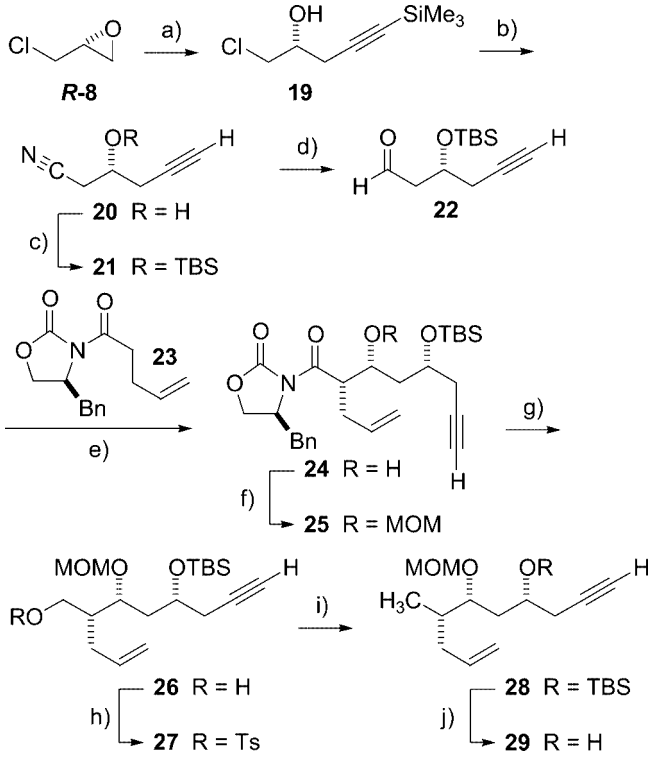
13 with the second generation Grubbs catalyst **14** in toluene (0.001 M of **13** in toluene, 0.1 equiv. of **14**, 70 °C, 2 h) led to a complex mixture of compounds that was not further characterized. This was attributed to the participation of the triple bond.

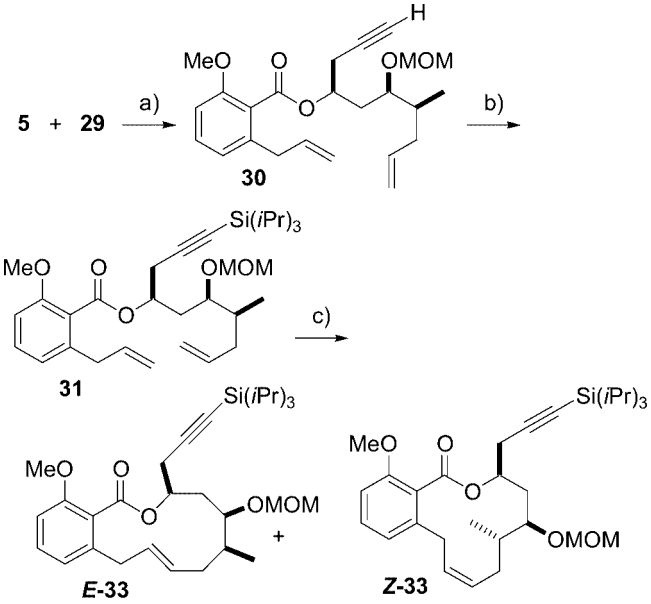
It was reasoned that a larger protecting group at the alkyne might prevent participation of the alkyne in the metathesis reaction.[26–29] Accordingly, the trimethylsilyl group was removed by stirring the ester **13** with potassium carbonate in methanol to give the alkynoate **15** (Scheme 2). In a rather remarkable reaction a selective deprotonation of the terminal alkyne **15** was achieved with *n*-butyllithium. Quenching of the intermediate acetylide with triisopropylsilyl chloride furnished the TIPS-protected alkyne **16** in 78 % yield. To our delight, ring closing metathesis of **16** with the Grubbs catalyst[30] **14** in toluene at 70 °C gave an excellent yield of the two macrolactones ***E*-17** (80 %) and ***Z*-17** (19 %) which could be separated by chromatography. Deprotection of ***E*-17** led to macrolactone **18**.

In order to reach macrolactone **3** with this strategy, the optically active (*R*)-epichlorohydrin was first opened with lithium trimethylsilylacetylide to the known chlorohydrin[24b,31] **19** (Scheme 3). As a second nucleophile, cyanide came to use. The best results were obtained with sodium cyanide in ethanol,[32] which gave the hydroxynitrile **20** in almost quantitative yield. This substitution reaction was accompanied with the cleavage of the trimethylsilyl group. Thereafter, the secondary hydroxy group of **20** was protected as *tert*-butyldimethylsilyl ether yielding the nitrile **21**. A chemoselective reduction of the cyano function to the aldehyde **22** was possible with DIBAL in dichloromethane. The crude aldehyde **22** was then utilized in an Evans aldol reaction[33–35] with the pentenoyloxazolidinone[36] **23**. This gave a good yield of the *syn*-product **24**. Continuing with the synthesis, the secondary hydroxy group was protected with methoxymethyl chloride to give the MOM ether **25**. Subsequent treatment of **25** with $LiBH_4$ led to the primary alcohol **26** and recovered (benzyl)oxazolidinone. The required methyl group was created from the hydroxymethyl group of **26** via the tosylate **27**. Substitution of the tosylate with hydride[37] in the form of $LiEt_3BH$ provided the enyne **28**. Finally, cleavage of the silyl ether with TBAF gave rise to the alcohol **29**.

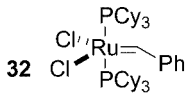
Esterification of the benzoic acid **5** with the secondary alcohol **29** using Mitsunobu conditions provided the benzoate **30** (Scheme 4). Like in the model system, the acetylene



Scheme 3. Synthesis of the enynol **29** from epichlorohydrin ***R*-8**; a) Me_3SiCCH (1 equiv.), *n*BuLi (0.93 equiv.), –78 °C, 30 min, then add BF_3 Et_2O (1 equiv.), –78 °C, 30 min, then add ***R*-8** (0.64 equiv.), –78 °C, 3 h, (98 %),[24b] b) NaCN (2.5 equiv.), EtOH, 23 °C, 3 d, 96 %; c) *t*$BuMe_2SiCl$ (1.5 equiv.), imidazole (2.5 equiv.), DMAP (0.05 equiv.), DMF, 23 °C, 3 d, 100 %; d) DIBAL (1.2 equiv.), CH_2Cl_2, –78 °C, 4 h, 96 %; e) compound **23** (1 equiv.), $TiCl_4$ (1.05 equiv.), (–)-sparteine (2.5 equiv.), CH_2Cl_2, 0 °C, 20 min, add aldehyde **22** (1.27 equiv.), 0 °C, 1 h, 89 %; f) *i*Pr_2NEt (10 equiv.), $MeOCH_2Cl$ (5 equiv.), Bu_4NI (0.2 equiv.), 0 to 23 °C, 24 h, 80 %; g) $LiBH_4$ (1.3 equiv.), EtOH (1.3 equiv.), Et_2O, 0 to 23 °C, 12 h, 68 %; h) *p*TsCl (3 equiv.), pyridine, 0 °C, 5 h, 100 %; i) Et_3BHLi (5 equiv.), THF, 0 to 23 °C, 93 %; j) TBAF (2 equiv.), THF, 0 to 23 °C, 84 %.



catalyst	*E*/*Z*-ratio	total yield
14	2.2 : 1	76%
32	30 : 1	94%



Scheme 4. Synthesis of the macrolactones ***E*-33** and ***Z*-33** by ring closing metathesis of the TIPS-protected ynediene **32**; a) alcohol **29** (1 equiv.), Ph_3P (1.5 equiv.), acid **5** (1.05 equiv.), DEAD (1.5 equiv.), toluene, 23 °C, 15 h, 69 %; b) *n*BuLi (1.1 equiv.), THF, –78 to –20 °C, 30 min, then add $(iPr)_3SiCl$ (1.2 equiv.), DMAP (0.01 equiv.), THF, –78 to 23 °C, 15 h, 89 %; c) add solutions of ester **31** and complex **32** (0.15 equiv.) slowly to CH_2Cl_2, 23 °C, 12 h, 93 % (*E*/*Z* = 30:1). DMAP = 4-Dimethylaminopyridine, DEAD = diethylazodicarboxylate.

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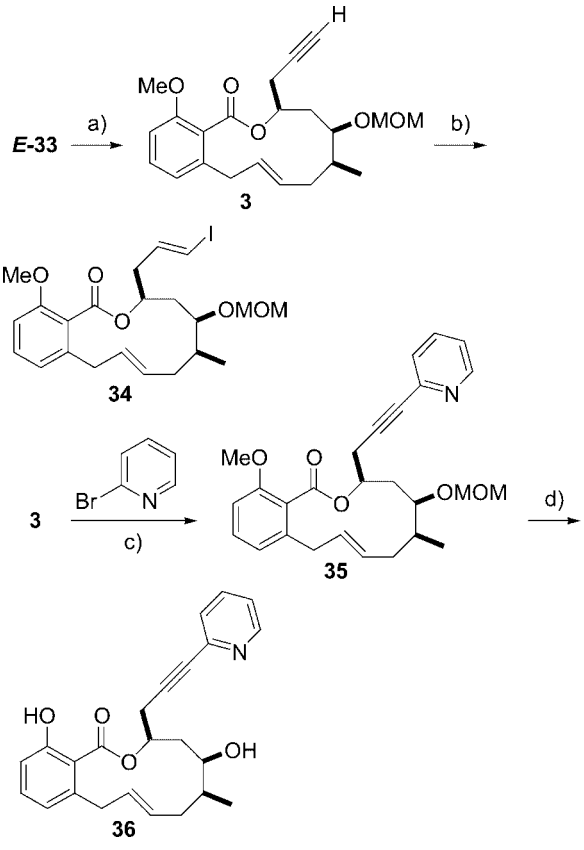
was protected by reacting the corresponding anion, which was generated with *n*-butyllithium, with TIPSCl leading to the metathesis substrate **31**. Both of the Grubbs catalysts **14** and **32** were able to induce the desired macrocyclization. With the second generation catalyst **14** the *E*/*Z* selectivity was moderate (*E*/*Z* = 2.2:1). Surprisingly the first generation catalyst **32** provided the macrolactones **33** in good chemical yield and excellent *E*/*Z* selectivity (*E*/*Z* = 30:1). The increase in selectivity for the ring closing metathesis using Grubb's first generation catalyst has actually been observed before.[8]

Removal of the TIPS group from the alkyne ***E*-33** with TBAF delivered the key compound **3**. The alkyne **3** could be converted into the vinyl iodide **34** by hydrostannylation followed by treatment of the intermediate vinyl stannane with iodine. Since **34** is an advanced intermediate in the Fürstner synthesis of salicylihalamide,[11b] our route to **34** represents a new formal total synthesis of salicylihalamide A. The utility of the macrolactone **3** as a platform for the generation of salicylihalamide analogs was demonstrated by its conversion to the pyridin-salicylihalamide derivative **36**. Thus, a Sonogashira coupling of alkyne **3** with 2-bromopyridine provided the substituted pyridine **35**. Finally, cleavage of the ether and acetal protecting groups with BBr_3 in dichloromethane furnished the macrolactone **36** with a 15-[3-(2-pyridinyl)-2-propynyl] side chain. The biological evaluation on L929 mouse fibroblast cells led to the following IC_{50} values: Salicylihalamide A (***E*-1**) 25 ng·mL^{-1}, salicylihalamide B (***Z*-1**) 500 ng·mL^{-1}, and analog **36** 2000 ng·mL^{-1}.[38] This result is of interest since **36** does not contain an enamide which is required for ATPase inhibition (Scheme 5).



Scheme 5. Synthesis of the vinyl iodide **34** and the salicylihalamide analog **36** from the macrolactone ***E*-33**; a) TBAF (4.8 equiv.), THF, 23 °C, 5 h, 94 %; b) Bu_3SnH (1.2 equiv.), AIBN (0.13 equiv.), toluene, reflux, 18 h, change solvent to Et_2O, add I_2 (1.2 equiv.), 0 °C, 1 h, 83 % (*E*/*Z* = 3.8:1); c) bromopyridine (0.92 equiv.), $[PdCl_2(PPh_3)_2]$ (0.022 equiv.), CuI (0.045 equiv.), Et_3N, 23 °C, 18 h, 90 %; d) 9-I-9-BBN (4 equiv.), CH_2Cl_2, 23 °C, 70 s, 88 %. 9-I-9-BBN = 9-Iodo-9-borabicyclo[3.3.1]nonane.

Conclusions

Starting from (*R*)-epichlorohydrin (***R*-8**) two carbon–carbon bond formations led to the 3-hydroxynitrile **20**. This compound was further elaborated to the enyne **29** via an Evans aldol reaction of the aldehyde **22** with the (pentenoyl)oxazolidinone **23** and conversion of the carboxyl to a methyl group of the aldol product **24**. Mitsunobu esterification of the alcohol **29** with the benzoic acid **5** gave rise to the ester **30** with two double bonds and one triple bond. After protection of the terminal triple bond with a sterically demanding TIPS group, the ring closing metathesis proceeded in good yield. The macrolactone ***E*-33** was converted into the vinyl iodide **34** and the pyridin containing salicylihalamide analog **36**. The described sequence, the two-sided elongation of epichlorohydrin, Mitsunobu esterification of the secondary alcohol, ring closing metathesis to a macrolactone, and side chain modification could be the foundation for the synthesis of macrolactone collections. Further sophistication could be introduced by using aldol reactions in the synthesis of the acid component.

Experimental Section

General: ^1H and ^{13}C NMR: Bruker Avance 400, spectra were recorded at 295 K either in $CDCl_3$, C_6D_6 or CD_3OD; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ (δ_H = 7.25 ppm, δ_C = 77.0 ppm), C_6D_6 (δ_H = 7.16, δ_C = 128.0 ppm) or CD_3OD (δ_H = 3.30, δ_C = 49.0 ppm). IR: Jasco FT/IR-430. Optical rotation: Jasco polarimeter P-1020, reported in $[\alpha]_D$ {*c* [g/100 mL], solvent}; recorded at 298 K. MS: Finnigan Triple-Stage-Quadrupol TSQ-70 (ionizing voltage of 70 eV) or Intectra AMD 402 mass spectrometer. HRMS: Intectra AMD MAT-711A (EI) or Bruker Daltonic APEX 2 (ESI). Flash chromatography: J. T. Baker silica gel 43–60 μm. Thin-layer chromatography Macherey–Nagel Polygram Sil G/UV_{254}. All solvents used in the reactions were distilled before use. Dry diethyl ether, tetrahydrofuran, and toluene were distilled from sodium and benzophenone, whereas dry dichloromethane, dimethylformamide, pyridine, and triethylamine were distilled from CaH_2. Petroleum ether with a boiling range of 40–60 °C was used. Reactions were generally run under argon. All commercially available compounds were used as received unless stated otherwise. NMR peaks were assigned according to IUPAC rules or the numbering by Boyd et al.[9]

(3*S*,5*R*,6*S*)-14-Methoxy-5-(methoxymethoxy)-6-methyl-3-(prop-2-ynyl)-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-1-one (3): To a solution of TIPS alkyne ***E*-33** (130 mg, 0.25 mmol) in THF (4.8 mL) was added TBAF (1.2 mL, 1.2 mmol, 1 M in THF) at 0 °C. After being stirred for 5 h at room temperature, the solution was

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treated with saturated aqueous $NaHCO_3$ solution (4 mL) and the mixture extracted with Et_2O (2 × 10 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 5:1) to provide 86 mg (94 %) of the desired alkyne **3** as a colorless wax. R_f = 0.41 (petroleum ether/ethyl acetate, 4:1). $[\alpha]_D$ = –49.3 (*c* = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1274, 1468, 1727, 2930, 2959, 3289 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.64–1.78 (m, 3 H, 14-H, 11-H), 2.04 (t, *J* = 2.7 Hz, 1 H, 18-H), 2.07–2.17 (m, 1 H, 12-H), 2.29 (br. d, *J* = 14.2 Hz, 1 H, 11-H), 2.49 (ddd, *J* = 16.7, 7.5, 2.7 Hz, 1 H, 16-H), 2.57 (ddd, *J* = 16.7, 5.5, 2.7 Hz, 1 H, 16-H) 3.29 (br. d, *J* = 16.3 Hz, 1 H, 8-H), 3.46 (s, 3 H, MOM-CH_3), 3.68 (dd, *J* = 16.3, 9.6 Hz, 1 H, 8-H), 3.78 (s, 3 H, Ph-OCH_3), 4.11 (br. dd, *J* = 8.2, 3.3 Hz, 1 H, 13-H), 4.80 (d, *J* = 6.8 Hz, 1 H, MOM-CH_2), 4.88 (d, *J* = 6.8 Hz, 1 H, MOM-CH_2), 5.32 (br. dd, *J* = 15.3, 9.6 Hz, 1 H, 9-H), 5.39–5.51 (m, 2 H, 15-H, 10-H), 6.74 (d, *J* = 7.6 Hz, 1 H, 6-H), 6.79 (d, *J* = 8.4 Hz, 1 H, 4-H), 7.22 (dd, *J* = 8.4, 7.6 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3 (CH_3), 25.6 (C-16), 34.4 (C-12), 34.5 (C-14), 37.5 (C-8), 37.6 (C-11), 55.5 (MOM-CH_3), 55.7 (Ph-OCH_3), 70.3 (C-18), 72.1 (C-15), 78.8 (C-13), 80.0 (C-17), 96.8 (MOM-CH_2), 109.3 (C-4), 122.6 (C-6), 124.4 (C-2), 128.7 (C-9), 130.0 (C-5), 131.2 (C-10), 138.8 (C-7) 156.7 (C-3), 167.9 (C-1) ppm. MS (EI): *m*/*z* (%) = 372 (3), 340 (10), 327 (19), 311 (21), 301 (10), 271 (10), 259 (62), 228 (26), 215 (33), 199 (36), 187 (100), 161 (38), 148 (24), 115 (30), 31 (13), 45 (48). HRMS (EI): $[M]^+$ calcd. for $C_{22}H_{28}O_5$ 372.19365, found 372.19547.

(2*S*)-1-Chlorooct-7-en-2-ol (10): To a suspension of magnesium (2.36 g, 97.2 mmol) in THF (40 mL) were added a few drops of 5-bromopent-1-ene (8.31 mL, 10.46 g, 70.2 mmol) in THF (40 mL) and some grains of iodine to start the reaction. After warming to 50 °C the remaining solution of the bromide was added slowly. Formation of the Grignard reagent **9** was completed by refluxing the mixture for 30 min. In a second flask copper(I) cyanide (0.24 g, 2.67 mmol) was suspended in THF (55 mL) and the slurry treated with (*S*)-epichlorohydrin (***S*-8**) (4.23 mL, 5.00 g, 54.0 mmol). To this solution the Grignard solution was transferred carefully at –50 °C and stirring was continued for 2 h while warming to room temperature. The reaction was quenched by addition of saturated NH_4Cl solution (100 mL), stirring was continued for 15 min, and the phases were separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the combined organic extracts were dried with Na_2SO_4. After filtration and evaporation of the solvent, the crude alcohol was purified by flash chromatography (petroleum ether/ethyl acetate, 4:1) to provide the pure product **10** (8.74 g, 100 %) as a light yellow oil. R_f = 0.62 (petroleum ether/ethyl acetate, 3:1). $[\alpha]_D$ = +0.2 (*c* = 1.30, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1436, 1640, 2859, 2933, 3393 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29–1.47 (m, 4 H, 5-H, 4-H), 1.47–1.54 (m, 2 H, 3-H), 2.03 (br. dt, *J* = 6.6, 5.6 Hz, 2 H, 6-H), 2.44 (br. s, 1 H, OH), 3.44 (dd, *J* = 11.1, 7.0 Hz, 1 H, 1-H), 3.59 (dd, *J* = 11.1, 3.3 Hz, 1 H, 1-H), 3.72–3.80 (m, 1 H, 2-H), 4.91 (br. d, *J* = 10.2 Hz, 1 H, 8-H), 4.97 (br. dd, *J* = 17.1, 1.5 Hz, 1 H, 8-H), 5.76 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1 H, 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.5 (C-6), 33.9 (C-3), 50.3 (C-1), 71.3 (C-2), 114.5 (C-8), 138.6 (C-7) ppm. MS (EI): *m*/*z* (%) = 239 (10), 219 (5), 169 (100), 151 (23), 139 (15), 127 (30), 111 (100), 109 (63), 95 (54), 83 (86), 69 (36), 55 (61), 43 (61). HRMS (ESI): $[M + Na]^+$ calcd. for $C_8H_{15}ClNaO$ 185.07036, found 185.06847.

(2*S*)-(2-Hex-5-enyl)oxirane (11): A cooled (0 °C) solution of chlorooctenol **10** (8.74 g, 54.0 mmol) in ethylene glycol (60 mL) was treated with grained sodium hydroxide (4.32 g, 108 mmol) and was stirred for 1 hour while warming to room temperature. The reaction was stopped by addition of ice-cold water (120 mL) and the mixture extracted with pentane (3 × 100 mL). The combined organic extracts were washed with water (100 mL), dried with $MgSO_4$, filtered and the solvents evaporated. Distillation of the crude epoxide **11** provided a colorless liquid (5.03 g, 73 %) boiling at 27 °C (1 mbar). R_f = 0.77 (petroleum ether/ethyl acetate, 3:1). $[\alpha]_D$ = –10.1 (*c* = 1.50, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1640, 2859, 2931, 2978, 3075 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.36–1.48 (m, 4 H, 3′-H, 2′-H), 1.48–1.55 (m, 2 H, 1′-H), 2.04 (br. dt, *J* = 6.5, 5.6 Hz, 2 H, 4′-H), 2.43 (dd, *J* = 5.0, 2.7 Hz, 1 H, 1-H), 2.72 (dd, *J* = 5.0, 3.9 Hz, 1 H, 1-H), 2.85–2.90 (m, 1 H, 2-H), 4.92 (br. d, *J* = 10.2 Hz, 1 H, 6′-H), 4.98 (br. dd, *J* = 17.1, 1.5 Hz, 1 H, 6′-H), 5.78 (ddt, *J* = 17.1, 10.2, 6.5 Hz, 1 H, 5′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4 (C-2′), 28.6 (C-3′), 32.3 (C-1′), 33.6 (C-4′), 47.0 (C-1), 52.2 (C-2), 114.5 (C-6′), 138.6 (C-5′) ppm. MS (EI): *m*/*z* (%) = 93 (49), 79 (46), 68 (47), 67 (100), 55 (55), 54 (76), 41 (52). HRMS (ESI): $[M + Na]^+$ calcd. for $C_8H_{14}NaO$ 149.09369, found 149.09467.

(4*S*)-1-(Trimethylsilyl)dec-9-en-1-yn-4-ol (12): A cooled (–78 °C) solution of TMS-acetylene[23] (1.70 mL, 1.21 g, 12.3 mmol) in THF (33 mL) was treated with *n*BuLi (4.60 mL, 11.5 mmol, 2.5 M in hexane) and the suspension was stirred for 30 min at that temperature. After addition of borontrifluoride–diethyl ether(1.55 mL, 1.75 g, 12.3 mmol) the mixture was stirred for 30 min and treated with a solution of epoxide **11** (1.00 g, 7.94 mmol) in THF (8 mL) slowly. Temperature was kept for 3 h and the reaction was quenched by addition of saturated NH_4Cl solution (1.6 mL). The mixture was poured into saturated NH_4Cl solution (50 mL) and extracted with diethyl ether (3 × 40 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (20 mL), brine (20 mL), and dried with $MgSO_4$. After filtration and evaporation of the solvent the crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 5:1). Hydroxyalkyne **12** (6.44 g, 36 %) was obtained as light yellow oil. R_f = 0.70 (petroleum ether/ethyl acetate, 3:1). $[\alpha]_D$ = +3.4 (*c* = 1.24, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1249, 2175, 2853, 2930, 3366 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.13 [s, 9 H, $Si(CH_3)_3$], 1.29–1.47 (m, 4 H, 7-H, 6-H), 1.47–1.54 (m, 2 H, 5-H), 2.00–2.07 (m, 3 H, OH, 8-H), 2.32 (dd, *J* = 16.8, 6.9 Hz, 1 H, 3-H), 2.43 (dd, *J* = 16.8, 4.7 Hz, 1 H, 3-H), 3.66–3.75 (m, 1 H, 4-H), 4.92 (br. d, *J* = 10.2 Hz, 1 H, 10-H), 4.98 (br. d, *J* = 17.2, 1.5 Hz, 1 H, 10-H), 5.78 (ddt, *J* = 17.2, 10.2, 6.7 Hz, 1 H, 9-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 0.0 [$Si(CH_3)_3$], 25.0 (C-6), 28.7 (C-7), 28.8 (C-3), 33.6 (C-8), 36.0 (C-5), 69.7 (C-4), 87.5 (C-1), 103.2 (C-2), 114.4 (C-10), 138.7 (C-9) ppm. MS (EI): *m*/*z* (%) = 185 (8), 141 (14), 112 (43), 95 (84), 73 (100), 41 (16). HRMS (ESI): $[M + Na]^+$ calcd. for $C_{13}H_{24}NaOSi$ 247.14886, found 247.14879.

(1*R*)-1-[3-(Trimethylsilyl)prop-2-ynyl]hept-6-enyl 2-Allyl-6-methoxybenzoate (13): To a solution of alcohol **12** (125 mg, 0.56 mmol) and triphenylphosphane (370 mg, 1.41 mmol) in toluene (6 mL) was added dropwise a solution of acid[11g] **5** (538 mg, 2.80 mmol) and DIAD (278 μL, 285 mg, 1.41 mmol) in toluene (6 mL). After 3 hours of stirring at room temperature, the solvent was removed and the residue purified by flash chromatography (petroleum ether/ethyl acetate, 10:1). Ester **13** (146 mg, 65 %) was isolated as a pale yellow oil. R_f = 0.58 (petroleum ether/ethyl acetate, 10:1). $[\alpha]_D$ = +29.3 (*c* = 0.95, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1266, 1470, 1585, 1729, 2928 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.14 [s, 9 H, $Si(CH_3)_3$], 1.37–1.52 (m, 4 H, 4′-H, 3′-H), 1.69–1.87 (m, 2 H, 2′-H), 2.07 (br. dt, *J* = 6.3, 6.3 Hz, 2 H, 5′-H), 2.58 (dd, *J* = 17.0, 6.9 Hz, 1 H, 1′′-H), 2.66 (dd, *J* = 17.0, 5.1 Hz, 1 H, 1′′-H), 3.37 (br. d, *J* = 6.6 Hz, 2 H, 7-H), 3.79 (s, 3 H, Ph-OCH_3), 4.93 (br. d, *J* = 10.1 Hz, 1 H, 7′-H), 5.00 (br. d, *J* = 17.1, 1 H, 7′-H), 5.05 (br. d, *J* = 10.4 Hz, 1 H, 9-H), 5.05 (br. d, *J* = 17.2 Hz, 1 H, 9-H), 5.13–5.20 (m, 1 H, 1′-H), 5.80 (ddt, *J* = 17.1, 10.1, 6.7 Hz, 1 H, 6′-H), 5.86–5.97 (m, 1

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H, 8-H), 6.77 (d, J = 8.3 Hz, 1 H, 5-H), 6.82 (d, J = 7.7 Hz, 1 H, 3-H), 7.27 (dd, J = 8.3, 7.7 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 0.0 [Si(CH_3)$_3$], 24.5 (C-3′), 25.4 (C-1′), 28.6 (C-4′), 32.8 (C-2′), 33.6 (C-5′), 37.4 (C-7), 55.8 (Ph-OCH_3), 70.5 (C-3′′), 73.0 (C-1′), 87.0 (C-3′′), 102.3 (C-2′′), 108.9 (C-5), 114.5 (C-7′), 116.4 (C-9), 121.6 (C-3), 123.8 (C-1), 130.3 (C-4), 136.4 (C-8), 138.3 (C-2), 138.7 (C-6′), 156.4 (C-6), 167.7 (Ph-CO_2) ppm. MS (EI): m/z (%) = 399 (14), 249 (28), 192 (78), 177 (92), 175 (92), 174 (100), 147 (76), 192 (50), 115 (39), 91 (26), 73 (43). HRMS (EI): $[M]^+$ calcd. for $C_{24}H_{34}SiO_3$ 398.2277, found 398.2257.

(1*R*)-1-(Prop-2-ynyl)hept-6-enyl 2-Allyl-6-methoxybenzoate (15): A solution of TMS-alkyne **13** (1.18 g, 2.95 mmol) in methanol (10 mL) was treated with potassium carbonate (0.82 g, 5.90 mmol) and stirred for 4 h at room temperature. The mixture was diluted with diethyl ether (200 mL) and washed with water (50 mL) and saturated NH_4Cl solution (50 mL). After filtration and evaporation of the solvent the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 5:1) to provide the unprotected alkyne **15** (0.82 mg, 85 %) as a colorless oil. R_f = 0.56 (petroleum ether/ethyl acetate, 5:1). $[\alpha]_D$ = +30.4 (c = 1.40, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1072, 1113, 1267, 1438, 1471, 1585, 1640, 1726, 2858, 2931, 3296 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34–1.49 (m, 4 H, 4′-H, 3′-H), 1.71–1.81 (m, 2 H, 2′-H), 1.97 (t, J = 2.6 Hz, 1 H, 3′′-H), 2.00–2.06 (m, 2 H, 5′-H), 2.56 (dd, J = 5.9, 2.6 Hz, 2 H, 1′′-H), 3.35 (d, J = 6.6 Hz, 2 H, 7-H), 3.76 (s, 3 H, Ph-OCH_3), 4.90 (d, J = 10.4 Hz, 1 H, 7′-H), 4.96 (dd, J = 17.2, 1.8 Hz, 1 H, 7′-H), 5.01 (br. d, J = 10.4 Hz, 1 H, 9-H), 5.02 (br. d, J = 17.2 Hz, 1 H, 9-H), 5.16 (tt, J = 5.9, 5.6 Hz, 1 H, 1′-H), 5.76 (ddt, J = 17.2, 10.4, 6.7 Hz, 1 H, 6′-H), 5.83–5.95 (m, 1 H, 8-H), 6.73 (d, J = 8.3 Hz, 1H, 5-H), 6.78 (d, J = 7.8 Hz, 1H, 3-H), 7.23 (dd, J = 8.3, 7.8 Hz, 1H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9 (C-1′′), 24.5 (C-3′), 28.6 (C-4′), 32.7 (C-2′), 33.6 (C-5′), 37.3 (C-7), 55.7 (Ph-OCH_3), 70.5 (C-3′′), 72.6 (C-1′), 79.8 (C-2′′), 108.8 (C-5), 114.5 (C-7′), 116.3 (C-9), 121.5 (C-3), 123.7 (C-1), 130.3 (C-4), 136.3 (C-8), 138.3 (C-2), 138.6 (C-6′), 156.4 (C-6), 167.7 (Ph-CO_2) ppm. MS (EI): m/z (%) = 326 (4), 192 (54), 177 (100), 175 (92), 147 (34), 129 (45), 115 (27), 91 (15), 77 (7). HRMS (ESI): $[M + Na]^+$ calcd. for $C_{21}H_{26}NaO_3$ 349.17742, found 349.17664.

(1*R*)-1-[3-(Triisopropylsilyl)prop-2-ynyl]hept-6-enyl 2-Allyl-6-methoxybenzoate (16): To alkyne **15** (0.74 g, 2.27 mmol) in THF (23 mL) was added at –78 °C *n*BuLi (1.02 mL, 2.55 mmol, 2.5 M in hexane) dropwise and the resulting solution was stirred 30 min while warming to –20 °C. After recooling to –78 °C the solution was treated with TIPS chloride (0.58 mL, 0.53 g, 2.72 mmol) in THF (13 mL) and warmed to room temperature within 15 h. The reaction was quenched by addition of saturated NH_4Cl solution (30 mL) at 0 °C. After separation of the phases the aqueous layer was extracted with diethyl ether (2 × 30 mL) and the combined organic extracts were dried with Na_2SO_4. The solid was filtered off, the solution was concentrated in vacuo, and the residue purified by flash chromatography (petroleum ether/ethyl acetate, 10:1) to provide the TIPS-alkyne **16** (0.85 g, 78 %) as a colorless oil. R_f = 0.61 (petroleum ether/ethyl acetate, 10:1). $[\alpha]_D$ = 31.8 (c = 1.30, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1071, 1113, 1267, 1438, 1470, 1585, 1729, 2175, 2865, 2942 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90–1.08 (m, 21 H, TIPS-CH, TIPS-CH_3), 1.35–1.51 (m, 4 H, 4′-H, 3′-H), 1.71–1.81 (m, 1 H, 2′-H), 1.85–1.95 (m, 1 H, 2′-H), 2.04 (dt, J = 6.7, 6.5 Hz, 2 H, 5′-H), 2.56 (dd, J = 16.7, 7.9 Hz, 1 H, 1′′-H), 2.71 (dd, J = 16.7, 4.3 Hz, 1 H, 1′′-H), 3.33 (d, J = 6.5 Hz, 2 H, 7-H), 3.75 (s, 3 H, Ph-OCH_3), 4.90 (br. d, J = 10.3 Hz, 1 H, 7′-H), 4.93–5.06 (m, 1 H, 7′-H, 9-H), 5.15 (ddt, J = 7.9, 4.3, 4.0 Hz, 1 H, 1′-H), 5.77 (ddt, J = 17.1, 10.3, 6.7 Hz, 1 H, 6′-H), 5.88 (ddt, J = 17.6, 9.5, 6.6 Hz, 1 H, 8-H), 6.73 (d, J = 8.3 Hz, 1 H, 5-H), 6.78 (d, J = 7.7 Hz, 1 H, 3-H), 7.23 (dd, J = 8.3, 7.7 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.2 (TIPS-CH), 18.5 (TIPS-CH_3), 24.4 (C-3′), 25.3 (C-1′′), 28.7 (C-4′), 32.5 (C-2′), 33.6 (C-5′), 37.3 (C-7), 55.7 (Ph-OCH_3), 73.0 (C-1′), 83.1 (C-3′′), 103.7 (C-2′′), 108.8 (C-5), 114.4 (C-7′), 116.3 (C-9), 121.6 (C-3), 123.8 (C-1), 130.3 (C-4), 136.3 (C-8), 138.2 (C-2), 138.7 (C-6′), 156.4 (C-6), 167.6 (Ph-CO_2) ppm. MS (EI): m/z (%) = 439 (4), 306 (23), 305 (100), 272 (8), 175 (42), 147 (23). HRMS (EI): $[M - i\text{Pr}]^+$ calcd. for $C_{27}H_{39}SiO_3$ 439.2668, found 439.2655.

14-Methoxy-3-[3-(triisopropylsilyl)prop-2-ynyl]-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-1-one (17): Grubbs 2nd generation catalyst **14** (54.3 mg, 64.1 μmol) was added to a solution of diene **16** (0.62 g, 1.28 mmol) in toluene (1280 mL) and the light purple solution was heated to 75 °C for 2 h. After completion of the reaction (checked by ^{1}H NMR), ethoxyethylene (5.76 mL, 7.97 g, 110 mmol) was added and the solution cooled to room temperature. The solvent was removed in vacuo and the residue purified by flash chromatography (petroleum ether/ethyl acetate, 10:1). The two isomers, (*E*)-macrolactone (***E*-17**, 0.46 g, 80 %) and (*Z*) derivative (***Z*-17**, 0.11 g, 19 %), could be separated by HPLC as color-?oas [jy?>less viscous oils. HPLC: t_R (*E* isomer) = 13.3 min, t_R (*Z* isomer) = 16.8 min on GROM-SIL 120 column, Si NP-2, 10 μm, 250 × 20 mm with *n*-heptane/ethyl acetate, 90:10, flow 10 mL/min.

***E*-17** (main product): M. p. 88 °C. R_f = 0.65 (petroleum ether/ethyl acetate, 10:1). $[\alpha]_D$ = –28.3 (c = 1.00, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 1069, 1117, 1256, 1275, 1470, 1726, 2864, 2941 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94–1.16 (m, 22 H, TIPS-CH, TIPS-CH_3, 13-H), 1.22–1.34 (m, 1 H, 12-H), 1.44–1.55 (m, 1 H, 12-H), 1.58–1.70 (m, 2 H, 13-H, 11-H), 1.72–1.80 (m, 1 H, 16-H), 1.81–1.91 (m, 1 H, 16-H), 2.13–2.22 (m, 1 H, 11-H), 2.53 (dd, J = 16.4, 9.4 Hz, 1 H, 14-H), 2.83 (dd, J = 16.4, 4.1 Hz, 1 H, 14-H), 3.15 (d, J = 14.3 Hz, 1 H, 8-H), 3.72 (dd, J = 14.3, 10.3 Hz, 1 H, 8-H), 3.77 (s, 3 H, Ph-OCH_3), 5.05–5.14 (m, 1 H, 15-H), 5.24–5.34 (m, 1 H, 9-H), 5.36–5.47 (m, 1 H, 10-H), 6.78 (d, J = 7.3 Hz, 1H, 6-H), 6.78 (d, J = 8.7 Hz, 1H, 4-H), 7.24 (dd, J = 8.7, 7.3 Hz, 1H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.2 (TIPS-CH), 18.6 (TIPS-CH_3), 19.8 (C-12), 24.4 (C-13), 25.3 (C-14), 31.3 (C-16), 32.7 (C-11), 37.8 (C-8), 55.9 (Ph-OCH_3), 70.6 (C-15), 82.9 (C-18), 104.0 (C-17), 109.6 (C-4), 122.4 (C-6), 124.0 (C-2), 128.9 (C-9), 130.3 (C-5), 132.6 (C-10), 139.4 (C-7), 156.9 (C-3), 167.8 (C-1) ppm. MS (EI): m/z (%) = 412 (34), 411 (100), 393 (8), 378 (9), 305 (33), 263 (23), 175 (31), 131 (33), 103 (51), 75 (32). HRMS (EI): $[M - i\text{Pr}]^+$ calcd. for $C_{25}H_{35}SiO_3$ 411.2355, found 411.2383.

***Z*-17** (minor product): R_f = 0.61 (petroleum ether/ethyl acetate, 10:1). $[\alpha]_D$ = –4.8 (c = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1114, 1243, 1267, 1469, 1587, 1728, 2864, 2941 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (br. s, 21 H, TIPS-CH, TIPS-CH_3), 1.37–1.53 (m, 4 H, 13-H, 12-H), 1.85–2.09 (m, 3 H, 16-H, 11-H), 2.31–2.42 (m, 1 H, 11-H), 2.57–2.63 (m, 2 H, 14-H), 3.20 (br. d, J = 15.0 Hz, 1 H, 8-H), 3.51 (dd, J = 15.0, 10.2 Hz, 1 H, 8-H), 3.79 (s, 3 H, Ph-OCH_3), 5.13–5.22 (m, 1 H, 10-H), 5.29–5.36 (m, 1 H, 15-H), 5.43–5.51 (m, 1 H, 9-H), 6.75 (d, J = 8.3 Hz, 1 H, 4-H), 6.89 (d, J = 7.7 Hz, 1 H, 6-H), 7.28 (dd, J = 8.3, 7.7 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.2 (TIPS-CH), 17.8 (C-12), 18.6 (TIPS-CH_3), 23.6 (C-14), 24.4 (C-11), 26.3 (C-13), 28.5 (C-16), 31.6 (C-8), 55.8 (Ph-OCH_3), 73.3 (C-15), 82.9 (C-18), 103.6 (C-17), 108.6 (C-4), 121.9 (C-6), 123.9 (C-2), 129.5 (C-10), 130.0 (C-9), 130.4 (C-5), 139.4 (C-7), 156.2 (C-3), 167.7 (C-1) ppm. MS (EI): m/z (%) = 412 (30), 411 (100), 393 (4), 378 (5), 263 (12), 175 (13), 131 (19), 103 (23), 75 (12). HRMS (EI): $[M - i\text{Pr}]^+$ calcd. for $C_{25}H_{35}O_3Si$ 411.23554, found 411.23212.

(3*R*)-14-Methoxy-3-(prop-2-ynyl)-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-1-one (18): To a solution of TIPS alkyne ***E*-17**

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(105 mg, 0.23 mmol) in THF (2.3 mL) was added TBAF (1 M in THF, 1.15 mL, 1.15 mmol) at 0 °C. The solution was stirred at room temperature for 5 h , then treated with saturated aqueous $NaHCO_3$ solution (3 mL) and the mixture extracted with Et_2O (2 × 3 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (petroleum ether/ethyl acetate, 5:1) of the residue gave 80 mg (100 %) of the desired alkyne **18** as a colorless wax. R_f = 0.63 (petroleum ether/ethyl acetate, 5:1). $[\alpha]_D$ = –21.9 (*c* = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1069, 1118, 1278, 1470, 1584, 1723, 2864, 2939, 3291, 3547 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.01–1.13 (m, 1 H, 13-H), 1.22–1.33 (m, 1 H, 12-H), 1.43–1.54 (m, 1 H, 12-H), 1.56–1.73 (m, 3 H, 13-H, 16-H, 11-H), 1.78–1.88 (m, 1 H, *H*-16), 2.01 (t, *J* = 2.7 Hz, 1 H, *H*-18), 2.12–2.21 (m, 1 H, *H*-11), 2.55–2.67 (m, 2 H, 14-H), 3.14 (d, *J* = 14.2 Hz, 1 H, 8-H), 3.71 (dd, *J* = 14.2, 10.5 Hz, 1 H, 8-H), 3.79 (s, 1 H, Ph-OCH_3), 5.07–5.14 (m, 3 H, 15-H), 5.24–5.32 (m, 1 H, 9-H), 5.35–5.45 (m, 1 H, 10-H), 6.77 (d, *J* = 7.0 Hz, 1 H, 6-H), 6.79 (d, *J* = 7.7 Hz, 1 H, 4-H), 7.23 (dd, *J* = 7.7, 7.0 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7 (C-12), 23.9 (C-14), 24.6 (C-13), 31.4 (C-16), 32.7 (C-11), 37.8 (C-8), 55.8 (Ph-OCH_3), 69.7 (C-15), 70.2 (C-18), 80.1 (C-17), 109.6 (C-4), 122.4 (C-6), 123.9 (C-2), 128.9 (C-9), 130.3 (C-5), 132.6 (C-10), 139.4 (C-7), 156.9 (C-3), 167.9 (C-1) ppm. MS (EI): *m*/*z* (%) = 298 (15), 177 (20), 131 (91), 103 (100), 75 (89), 61 (38). HRMS (EI): $[M]^+$ calcd. for $C_{19}H_{22}O_3$ 298.1569, found 298.1557.

(3*R*)-3-Hydroxyhex-5-ynenitrile (20): To a solution of chlorohydrin[24b,31] **19** (5.13 g, 26.9 mmol) in ethanol (130 mL) was added sodium cyanide (3.30 g, 67.3 mmol) and potassium carbonate (3.90 g, 28.2 mmol) and the resulting suspension was stirred 3 days at room temperature. After complete consumption (TLC control) the mixture was diluted with petroleum ether (20 mL) and filtered through celite. The filter cake was washed with diethyl ether (150 mL) and the combined organic solutions were evaporated in vacuo. Flash chromatography (petroleum ether/ethyl acetate, 3:2) of the residue afforded the pure nitrile **20** (2.82 g, 96 %) as a colorless liquid. R_f = 0.55 (petroleum ether/ethyl acetate, 1:1). $[\alpha]_D$ = –21.1 (*c* = 1.58, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1080, 1416, 2254, 3291, 3444 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.13 (t, *J* = 2.6 Hz, 1 H, 6-H), 2.53 (dd, *J* = 6.0, 2.6 Hz, 2 H, 4-H), 2.64 (dd, *J* = 16.7, 6.6 Hz, 1 H, 2-H), 2.70 (dd, *J* = 16.7, 5.1 Hz, 1 H, 2-H), 2.81 (br. s, 1 H, OH), 4.08–4.15 (m, 1 H, 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.7 (C-2), 26.5 (C-4), 66.0 (C-3), 72.3 (C-6), 78.5 (C-5), 117.2 (C-1) ppm. MS (EI): *m*/*z* (%) = 130 (5), 110 (42), 93 (14), 82 (48), 70 (96), 69 (80), 68 (38), 65 (14), 42 (98), 41 (79), 40 (100), 39 (94). HRMS (EI): $[M]^+$ calcd. for C_6H_7ON 109.052755, found 109.053331.

(3*R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}hex-5-ynenitrile (21): TBDMS-Cl (8.28 g, 54.8 mmol) was added to a stirred solution of alcohol **20** (3.98 g, 36.5 mmol), imidazole (6.21 g, 91.3 mmol), and DMAP (224 mg, 1.83 mmol) in dry DMF (370 mL). The resulting solution was stirred at ambient temperature for 3 days, then diluted with water (370 mL) and extracted with diethyl ether (3 × 300 mL). The combined extracts were washed with 0.1 N HCl (200 mL), brine (200 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Volatile side products and unreacted starting material were removed by distillation at 70 °C (1 mbar) to leave the pure TBDMS ether **21** (8.13 g, 100 %) as slightly yellow oil. R_f = 0.70 (petroleum ether/ethyl acetate, 5:1). $[\alpha]_D$ = –16.2 (*c* = 1.32, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1112, 1257, 1364, 1472, 2858, 2931, 2955, 3310 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.11 [s, 3 H, $Si(CH_3)_2$], 0.13 [s, 3 H, $Si(CH_3)_2$], 0.90 [s, 9 H, $SiC(CH_3)_3$], 2.06 (dd, *J* = 2.7, 2.6 Hz, 1 H, 6-H), 2.42 (ddd, *J* = 16.9, 7.5, 2.6 Hz, 1 H, 4-H), 2.48 (ddd, *J* = 16.9, 5.0, 2.7 Hz, 1 H, 4-H), 2.60 (dd, *J* = 16.6, 6.4 Hz, 1 H, 2-H), 2.69 (dd, *J* = 16.6, 4.4 Hz, 1 H, 2-H), 4.04–4.12 (m, 1 H, 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.9 [$Si(CH_3)_2$], –4.8 [$Si(CH_3)_2$], 17.9 (SiC), 25.5 (C-2), 25.6 [$SiC(CH_3)_3$], 27.2 (C-4), 67.3 (C-3), 71.7 (C-6), 79.1 (C-5), 117.4 (C-1) ppm. MS (EI): *m*/*z* (%) = 208 (6), 184 (24), 166 (100), 147 (6), 125 (13), 101 (68), 98 (23), 97 (86), 73 (34). HRMS (ESI): $[M + Na]^+$ calcd. for $C_{12}H_{21}NNaOSi$ 246.12846, found 246.12838.

(3*R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}hex-5-ynal (22): To a stirred solution of the nitrile **21** (1.32 g, 4.47 mmol) in dry CH_2Cl_2 (45 mL) was added DIBAL (5.36 mL, 5.36 mmol, 1.0 M in hexane) dropwise over 10 min at –78 °C. After being stirred for 4 h at –78 °C, methanol (1.3 mL) was added, the cooling bath removed, and the mixture warmed to room temperature. Then water (13 mL) and diethyl ether (45 mL) were added, the phases were separated, and the cloudy aqueous layer extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude aldehyde **22** (1.33 g, 96 %) was obtained as a pale yellow oil and could be used without further purification in the next step. R_f = 0.71 (petroleum ether/ethyl acetate, 5:1). $[\alpha]_D$ = –22.8 (*c* = 1.19, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1107, 1256, 1728, 2857, 2929, 2953, 3312 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.06 [s, 3 H, $Si(CH_3)_2$], 0.09 [s, 3 H, $Si(CH_3)_2$], 0.85 [s, 9 H, $SiC(CH_3)_3$], 2.02 (t, *J* = 2.7 Hz, 1 H, 6-H), 2.38 (ddd, *J* = 16.7, 7.4, 2.7 Hz, 1 H, 4-H), 2.44 (ddd, *J* = 16.7, 5.0, 2.7 Hz, 1 H, 4-H), 2.65 (ddd, *J* = 16.2, 7.1, 2.5 Hz, 1 H, 2-H), 2.74 (ddd, *J* = 16.2, 4.5, 1.6 Hz, 1 H, 2-H), 4.34 (dddd, *J* = 7.4, 7.1, 5.0, 4.5 Hz, 1 H, 3-H), 9.80 (dd, *J* = 2.5, 1.6 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.9 [$Si(CH_3)_2$], –4.6 [$Si(CH_3)_2$], 17.9 (SiC), 25.6 [$SiC(CH_3)_3$], 27.7 (C-4), 50.2 (C-2), 66.7 (C-3), 71.1 (C-6), 80.2 (C-5), 201.2 (C-1) ppm. MS (EI): *m*/*z* (%) = 203 (4), 187 (19), 169 (32), 151 (16), 141 (27), 129 (36), 125 (64), 101 (100), 95 (56), 75 (70), 73 (49), 59 (25).

(4*S*)-3-[(2*S*,3*R*,5*R*)-2-Allyl-5-{[*tert*-butyl(dimethyl)silyl]oxy}-3-hydroxy-7-octynoyl]-4-benzyl-1,3-oxazolidin-2-one (24): To a stirred, cooled (0 °C) solution of (4*S*)-4-benzyl-3-pent-4-enoyl-1,3-oxazolidin-2-one[34] (**23**) (3.63 g, 14.0 mmol) in CH_2Cl_2 (140 mL) was added dropwise titanium(IV) chloride (1.62 mL, 2.79 g, 14.7 mmol) and the resulting mixture was stirred for 5 min. Subsequently, (–)-sparteine (8.04 mL, 8.20 g, 35.0 mmol) was added to the yellow slurry. The dark red enolate solution was stirred for 20 min at 0 °C before a solution of aldehyde **22** (4.00 g, 17.9 mmol) in CH_2Cl_2 (35 mL) was added dropwise and the mixture stirred for 1 h at 0 °C. The reaction was quenched with half-saturated NH_4Cl solution (70 mL) and allowed to reach room temperature. After separation of the layers, the aqueous layer was extracted with CH_2Cl_2 (2 × 70 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/diethyl ether, 1:1) afforded 6.66 g (89 %) of the desired aldol product **24** as a colorless viscous oil and 0.40 g (10 %) of unreacted aldehyde **22**. R_f = 0.51 (petroleum ether/diethyl ether, 1:1). $[\alpha]_D$ = +32.5 (*c* = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1105, 1208, 1248, 1290, 1386, 1695, 1779, 2857, 2889, 2929, 2951, 3308, 3521 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.10 [s, 3 H, $Si(CH_3)_2$], 0.11 [s, 3 H, $Si(CH_3)_2$], 0.88 [s, 9 H, $SiC(CH_3)_3$], 1.80 (ddd, *J* = 14.3, 8.8, 7.8 Hz, 1 H, 4′-H), 1.87 (ddd, *J* = 14.3, 4.9, 2.7 Hz, 1 H, 4′-H), 1.99 (t, *J* = 2.6 Hz, 1 H, 8′-H), 2.38 (d, *J* = 2.6 Hz, 1 H, 6′-H), 2.39 (d, *J* = 2.6 Hz, 1 H, 6′-H), 2.48 (ddd, *J* = 14.2, 6.0, 4.8 Hz, 1 H, C*H*$_2$CH=CH_2), 2.58–2.67 (m, 1 H, C*H*$_2$-CH=CH_2), 2.63 (dd, *J* = 13.3, 10.2 Hz, 1 H, Bn-CH_2), 3.19 (d, *J* = 1.7 Hz, 1 H, OH), 3.28 (dd, *J* = 13.3, 3.1 Hz, 1 H, Bn-CH_2), 4.00–4.17 (m, 5 H, 3′-H, 5′-H, 5-H, 2′-H), 4.64–4.71 (m, 1 H, 4-H), 5.03 (br. d, *J* = 10.2 Hz, 1 H, CH_2CH=C*H*$_2$), 5.11 (br. d, *J* = 17.1 Hz, 1 H, CH_2CH=C*H*$_2$), 5.86 (dddd, *J* = 17.1, 10.2, 7.6,

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6.6 Hz, 1 H, CH_2CH=CH_2), 7.19–7.34 (m, 5 H, Bn-H-2,6, Bn-H-4, Bn-H-3,5) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8 [$Si(CH_3)_2$], –4.4 [$Si(CH_3)_2$], 17.9 (SiC), 25.7 [$SiC(CH_3)_3$], 27.5 (C-6′), 31.9 (CH_2CH=CH_2), 37.9 (Bn-CH_2), 40.0 (C-4′), 47.4 (C-2′), 55.5 (C-4), 65.9 (C-5), 70.3 (C-5′), 70.5 (C-3′), 70.7 (C-8′), 80.6 (C-7′), 117.2 (CH_2CH=CH_2), 127.3 (Bn-C-4), 128.9 (Bn-C-3,5), 129.3 (Bn-C-2,6), 135.2 (CH_2 CH=CH_2), 135.3 (Bn-C-1), 153.2 (C-2), 174.5 (C-1′) ppm. MS (EI): *m*/*z* (%) = 490 (3), 432 (5), 411 (6), 402 (9), 384 (16), 355 (14), 310 (4), 270 (15), 255 (22), 253 (20), 252 (100), 237 (10), 196 (13), 152 (19), 171 (29), 91 (53), 75 (42), 73 (33). HRMS (ESI): $[M + Na]^+$ calcd. for $C_{27}H_{39}NNaO_5Si$ 508.24897, found 508.24921.

(4*S*)-3-[(2*S*,3*R*,5*R*)-2-Allyl-5-{[*tert*-butyl(dimethyl)silyl]oxy}-3-(methoxymethoxy)oct-7-ynoyl]-4-benzyl-1,3-oxazolidin-2-one (25): To astirred, cooled (0 °C) solution of alcohol 24 (3.24 g, 6.67#160;mmol) in CH_2Cl_2 (67 mL) were added *N*,*N*-diisopropylethylamine (11.4 mL, 8.64 g, 66.7 mmol), chloromethylmethyl ether (2.55 mL, 2.68 g, 33.4 mmol) and TBAI (0.49 g, 1.33 mmol). The reaction mixture was protected from light and allowed to reach room temperature within 24 h whilst stirring before it was treated with saturated aqueous $NaHCO_3$ solution (35 mL) and the phases were separated. After extraction of the aqueous layer with diethyl ether (2 × 60 mL) the combined extracts were washed with 1 N HCl (35 mL) and brine (35 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/ethyl acetate, 3:1) of the residue provided MOM ether 25 as a colorless viscous oil; yield 2.81 g (80 %). R_f = 0.58 (petroleum ether/ethyl acetate, 3:1). $[\alpha]_D$ = +76.3 (*c* = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1025, 1101, 1208, 1251, 1384, 1698, 1781, 2929, 2953 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.08 [s, 3 H, $Si(CH_3)_2$], 0.09 [s, 3 H, $Si(CH_3)_2$], 0.88 [s, 9 H, $SiC(CH_3)_3$], 1.82 (ddd, *J* = 14.4, 8.7, 4.6 Hz, 1 H, 4′-H), 1.96 (t, br, *J* = 2.5 Hz, 1 H, 8′-H), 1.97 (ddd, *J* = 14.4, 7.8, 3.5 Hz, 1 H, 4′-H), 2.36 (ddd, *J* = 16.7, 5.1, 2.5 Hz, 1 H, 6′-H), 2.36 (d, *J* = 14.1 Hz, 1 H, CH_2-CH=CH_2), 2.45 (ddd, *J* = 16.7, 5.0, 2.5 Hz, 1 H, 6′-H), 2.59 (ddd, *J* = 14.1, 8.6, 8.6 Hz, 1 H, CH $_2CH$=CH_2), 2.67 (dd, *J* = 13.3, 10.0 Hz, 1 H, Bn-CH_2), 3.27 (dd, *J* = 13.3, 3.0 Hz, 1 H, Bn-CH_2), 3.35 (s, 3 H, MOM-CH_3), 3.82–3.87 (m, 1 H, 3′-H), 3.93–4.00 (m, 1 H, 5′-H), 4.08–4.16 (m, 2 H, 5-H), 4.33 (ddd, *J* = 9.6, 4.7, 4.7 Hz, 1 H, 2′-H), 4.54 (d, *J* = 7.2 Hz, 1 H, MOM-CH_2), 4.61–4.67 (m, 1 H, 4-H), 4.66 (d, *J* = 7.2 Hz, 1 H, MOM-CH_2), 5.04 (br. d, *J* = 10.1 Hz, 1 H, CH_2CH=CH $_2$), 5.12 (br. d, *J* = 17.1 Hz, 1 H, CH_2CH=CH $_2$), 5.82 (dddd, *J* = 17.1, 10.1, 6.9, 6.9 Hz, 1 H, CH_2CH=CH_2), 7.18–7.34 (m, 5 H, Bn-H-2,6, Bn-H-4, Bn-H-3,5) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.7 [$Si(CH_3)_2$], 18.0 (SiC), 25.7 [$SiC(CH_3)_3$], 26.4 (C-6′), 32.5 (CH_2CH=CH_2), 37.8 (Bn-CH_2), 39.2 (C-4′), 45.6 (C-2′), 55.8 (C-4), 56.2 (MOM-CH_3), 65.7 (C-5), 67.9 (C-5′), 70.0 (C-8′), 75.4 (C-3′), 81.4 (C-7′), 95.9 (MOM-CH_2), 117.1 (CH_2CH=CH_2), 127.2 (Bn-C-4), 128.8 (Bn-C-3,5), 129.4 (Bn-C-2,6), 135.1 (CH_2 CH=CH_2), 135.3 (Bn-C-1), 153.2 (C-2), 173.3 (C-1′) ppm. MS (EI): *m*/*z* (%) = 472 (38), 428 (30), 410 (19), 370 (9), 296 (11), 265 (21), 258 (44), 251 (62), 235 (28), 211 (30), 190 (100), 169 (36), 159 (16), 117 (25), 91 (28), 86 (48), 84 (63), 49 (55). HRMS (ESI): $[M + Na]^+$ calcd. for $C_{29}H_{43}NNaO_6Si$ 552.27519, found 552.27534.

(2*R*,3*R*,5*R*)-2-Allyl-5-{[*tert*-butyl(dimethyl)silyl]oxy}-3-(methoxymethoxy)oct-7-yn-1-ol (26): Lithium borohydride (2.45 mL, 4.91 mmol, 2 M in THF) was added dropwise to a cooled (0 °C) solution of amide **25** (2.00 g, 3.78 mmol) and ethanol (0.29 mL, 0.23 g, 4.91 mmol) in dry diethyl ether (40 mL). Stirring was continued for 12 h with concomitant warming of the mixture to room temperature. The solution was treated with saturated NH_4Cl solution (10 mL), stirred for 1 h, and transferred into a separation funnel. After extraction with CH_2Cl_2 (3 × 15 mL) the combined organic layers were washed with brine (5 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/ethyl acetate, 3:2) of the residue provided alcohol **26** (0.91 g, 68 %) as a colorless oil. R_f = 0.64 (petroleum ether/ethyl acetate, 1:1). $[\alpha]_D$ = –14.9 (*c* = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1036, 1100, 1151, 1256, 2857, 2888, 2929, 2954, 3467 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 [s, 3 H, $Si(CH_3)_2$], 0.05 [s, 3 H, $Si(CH_3)_2$], 0.85 [s, 9 H, $SiC(CH_3)_3$], 1.77 (ddd, *J* = 14.3, 7.4, 6.1 Hz, 1 H, 4-H), 1.87 (ddd, *J* = 14.3, 6.0, 6.0 Hz, 1 H, 4-H), 1.87–1.94 (m, 1 H, 2-H), 1.94–2.02 (m, 1 H, CH $_2CH$=CH_2), 1.96 (dd, *J* = 2.6, 2.6 Hz, 1 H, 8-H), 2.07 (br. ddd, *J* = 14.2, 6.1, 6.1 Hz, 1 H, CH $_2$-CH=CH_2), 2.31 (ddd, *J* = 16.9, 5.1, 2.6 Hz, 1 H, 6-H), 2.37 (ddd, *J* = 16.9, 6.0, 2.6 Hz, 1 H, 6-H), 2.71 (br. dd, *J* = 5.7, 5.7 Hz, 1 H, OH), 3.36 (s, 3 H, MOM-CH_3), 3.54–3.68 (m, 2 H, 1-H), 3.81–3.91 (m, 2 H, 3-H, 5-H), 4.60 (s, 2 H, MOM-CH_2), 4.97 (br. d, *J* = 10.1 Hz, 1 H, CH_2CH=CH $_2$), 5.02 (br. d, *J* = 17.1 Hz, 1 H, CH_2CH=CH $_2$), 5.75 (br. dddd, *J* = 17.1, 10.1, 7.0, 7.0 Hz, 1 H, CH_2CH=CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.7 [$Si(CH_3)_2$], –4.6 [$Si(CH_3)_2$], 17.9 (SiC), 25.7 [$SiC(CH_3)_3$], 27.0 (C-6), 31.2 (CH_2CH=CH_2), 37.5 (C-4), 42.6 (C-2), 55.9 (MOM-CH_3), 63.1 (C-1), 68.0 (C-5), 70.3 (C-8), 76.1 (C-3), 81.1 (C-7), 95.9 (MOM-CH_2), 116.3 (CH_2CH=CH_2), 136.8 (CH_2 CH=CH_2) ppm. MS (EI): *m*/*z* (%) = 267 (10), 237 (23), 199 (13), 183 (15), 169 (52), 145 (40), 131 (63), 123 (100), 105 (30), 89 (42), 75 (61), 45 (38). HRMS (FAB): $[M + Na]^+$ calcd. for $C_{19}H_{36}NaO_4Si$ 379.22807, found 379.22608.

(2*R*,3*R*,5*R*)-2-Allyl-5-{[*tert*-butyl(dimethyl)silyl]oxy}-3-(methoxymethoxy)oct-7-ynyl 4-Methylbenzenesulfonate (27): To a stirred solution of alcohol **26** (0.88 g, 2.47 mmol) in pyridine (5 mL) was added *p*-toluenesulfonyl chloride (1.42 g, 7.41 mmol) at 0 °C. After being stirred for 5 h, the reaction was quenched by addition of ice (2.5 g) and H_2O (12 mL). The mixture was diluted with Et_2O (50 mL) and washed with saturated $NaHCO_3$ solution (10 mL), 1 N HCl (10 mL), and brine (10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Filtration (petroleum ether/ethyl acetate, 3:1) of the residue over a short pad of silica gel and evaporation of the solvent gave the pure tosylate **27** as a colorless viscous oil, yield 1.26 g (100 %). R_f = 0.56 (petroleum ether/ethyl acetate, 3:1). $[\alpha]_D$ = –4.1 (*c* = 1.42, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1036, 1098, 1178, 1189, 1253, 1366, 2857, 2894, 2929, 2953 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 [s, 3 H, $Si(CH_3)_2$], 0.05 [s, 3 H, $Si(CH_3)_2$], 0.85 [s, 9 H, $SiC(CH_3)_3$], 1.67 (ddd, *J* = 14.3, 6.9, 6.2 Hz, 1 H, 4-H), 1.85 (ddd, *J* = 14.3, 5.8, 5.8 Hz, 1 H, 4-H), 1.96 (t, *J* = 2.6 Hz, 1 H, 8-H), 1.97–2.08 (m, 2 H, 2-H, CH_2-CH=CH_2), 2.10–2.20 (m, 1 H, CH $_2CH$=CH_2), 2.31 (dd, *J* = 5.7, 2.6 Hz, 2 H, 6-H), 2.43 (s, 3 H, Ts-CH_3), 3.27 (s, 3 H, MOM-CH_3), 3.69–3.74 (m, 1 H, 3-H), 3.80–3.88 (m, 1 H, 5-H), 4.01 (dd, *J* = 9.4, 5.3 Hz, 1 H, 1-H), 4.08 (dd, *J* = 9.4, 6.1 Hz, 1 H, 1-H), 4.48 (d, *J* = 6.8 Hz, 1 H, MOM-CH_2), 4.52 (d, *J* = 6.8 Hz, 1 H, MOM-CH_2), 4.95–5.02 (m, 2 H, CH_2CH=CH $_2$), 5.67 (dddd, *J* = 17.1, 10.1, 7.1, 7.1 Hz, 1 H, CH_2CH=CH_2), 7.33 (d, *J* = 8.2 Hz, 2 H, Ts-H-3,5), 7.77 (d, *J* = 8.2 Hz, 2 H, Ts-H-2,6) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.7 [$Si(CH_3)_2$], –4.5 [$Si(CH_3)_2$], 18.0 (SiC), 21.6 (Ts-CH_3), 25.8 [$SiC(CH_3)_3$], 27.0 (C-6), 30.7 (CH_2CH=CH_2), 37.8 (C-4), 41.1 (C-2), 55.8 (MOM-CH_3), 67.9 (C-5), 69.7 (C-1), 70.4 (C-8), 74.2 (C-3), 81.1 (C-7), 96.1 (MOM-CH_2), 117.2 (CH_2CH=CH_2), 128.0 (Ts-C-2,6), 129.8 (Ts-C-3,5), 133.0 (Ts-C-1), 135.7 (CH_2 CH=CH_2), 144.7 (Ts-C-4) ppm. MS (EI): *m*/*z* (%) = 409 (8), 309 (4), 287 (5), 237 (32), 229 (100), 197 (11), 169 (24), 155 (32), 145 (50), 117 (21), 91 (62), 89 (28), 73 (22), 45 (22). HRMS (FAB): $[M + Na]^+$ calcd. for $C_{26}H_{42}NaO_6SSi$ 533.23691, found 533.23997.

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(4*S*,5*R*,7*R*)-7-{[*tert*-Butyl(dimethyl)silyl]oxy}-5-(methoxymethoxy)-4-methyldec-1-en-9-yne (28): A cooled (0 °C) solution of tosylate **27** (915 mg, 1.79 mmol) in THF (18 mL) was treated dropwise with lithium triethylboronhydride (8.96 mL, 8.96 mmol, 1 M in THF). After being stirred for 15 h and warming up to room temperature, the reaction was quenched by careful addition of a 1:1 mixture of THF and water (total 3 mL) at 0 °C. Saturated NH_4Cl solution (10 mL) was added and the mixture stirred 1 h. After extraction with diethyl ether (3 × 10 mL) the combined organic extracts were dried with Na_2SO_4, filtered and the solvents evaporated. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 3:1) provided the methyl derivative **28** (567 mg, 93 %) as a colorless oil. R_f = 0.79 (petroleum ether/ethyl acetate, 3:1). $[\alpha]_D$ = +18.1 (*c* = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1038, 1092, 1150, 1257, 2857, 2887, 2930, 2957 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.06 [s, 3 H, $Si(CH_3)_2$], 0.08 [s, 3 H, $Si(CH_3)_2$], 0.88 [s, 9 H, $SiC(CH_3)_3$], 0.88–0.90 (m, 3 H, CH_3), 1.64–1.90 (m, 4 H, 5-H, 7-H, 8-H), 1.95 (t, *J* = 2.6 Hz, 1 H, 1-H), 2.06–2.15 (m, 1 H, 8-H), 2.33 (ddd, *J* = 16.7, 5.4, 2.6 Hz, 1 H, 3-H), 2.41 (ddd, *J* = 16.7, 5.4, 2.6 Hz, 1 H, 3-H), 3.36 (s, 3 H, MOM-C*H* $_3$), 3.51 (ddd, *J* = 8.1, 4.0, 4.0 Hz, 1 H, 6-H), 3.92–3.98 (m, 1 H, 4-H), 4.58 (d, *J* = 6.9 Hz, 1 H, MOM-CH_2), 4.61 (d, *J* = 6.9 Hz, 1 H, MOM-CH_2), 4.97 (br. d, *J* = 10.1 Hz, 1 H, 10-H), 5.01 (br. d, *J* = 17.1 Hz, 1 H, 10-H), 5.74 (dddd, *J* = 17.1, 10.1, 6.9, 6.9 Hz, 1 H, 9-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.6 [$Si(CH_3)_2$], –4.6 [$Si(CH_3)_2$], 14.4 (CH_3), 18.1 (SiC), 25.8 [$SiC(CH_3)_3$], 26.8 (C-3), 35.8 (C-7), 36.9 (C-8), 37.0 (C-5), 55.8 (MOM-CH_3), 68.3 (C-4), 70.0 (C-1), 77.9 (C-6), 81.5 (C-2), 95.6 (MOM-CH_2), 115.9 (C-10), 137.3 (C-9) ppm. MS (EI): *m*/*z* (%) = 240 (11), 239 (60), 203 (19), 183 (20), 157 (41), 147 (36), 119 (63), 107 (75), 105 (100), 89 (70), 73 (45), 59 (19), 45 (82). HRMS (ESI): $[M + Na]^+$ calcd. for $C_{19}H_{36}NaO_3Si$ 363.23259, found 363.23226.

(4*R*,6*R*,7*S*)-6-(Methoxymethoxy)-7-methyldec-9-en-1-yn-4-ol (29): To a solution of silyl ether **28** (875 mg, 2.57 mmol) in THF (20 mL) was added TBAF (5.14 mL, 5.14 mmol, 1 M in THF) at 0 °C and the mixture stirred for 12 h with concomitant warming to room temperature. After addition of saturated $NaHCO_3$ solution (20 mL) the phases were separated and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/diethyl ether, 1:4) provided alcohol **29** (487 mg, 84 %) as a pale yellow oil. R_f = 0.59 (petroleum ether/ethyl acetate, 1:1). $[\alpha]_D$ = +56.6 (*c* = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1034, 1097, 1150, 2932, 2959, 3455 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.62 (ddd, *J* = 14.6, 9.7, 8.7 Hz, 1 H, 5-H), 1.73 (ddd, *J* = 14.6, 3.3, 3.3 Hz, 1 H, 5-H), 1.83–1.96 (m, 2 H, 8-H, 7-H), 1.97–2.04 (m, 1 H, 8-H), 2.00 (dd, *J* = 2.7, 2.6 Hz, 1 H, 1-H), 2.34 (ddd, *J* = 16.7, 6.4, 2.7 Hz, 1 H, 3-H), 2.39 (ddd, *J* = 16.7, 5.7, 2.6 Hz, 1 H, 3-H), 3.37 (s, 3 H, MOM-CH_3), 3.45 (br. s, 1 H, OH), 3.70 (ddd, *J* = 9.7, 3.8, 3.3 Hz, 1 H, 6-H), 3.85–3.93 (m, 1 H, 4-H), 4.60 (d, *J* = 6.8 Hz, 1 H, MOM-CH_2), 4.69 (d, *J* = 6.9 Hz, 1 H, MOM-CH_2), 4.95–5.02 (m, 2 H, 10-H), 5.71 (dddd, *J* = 17.0, 10.2, 6.9, 6.9 Hz, 1 H, 9-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5 (CH_3), 27.0 (C-3), 34.8 (C-5), 35.2 (C-7), 37.5 (C-8), 56.0 (MOM-CH_3), 69.6 (C-4), 70.3 (C-1), 80.7 (C-6), 80.9 (C-2), 95.3 (MOM-CH_2), 116.1 (C-10), 136.7 (C-9) ppm. MS (EI): *m*/*z* (%) = 155 (4), 127 (10), 125 (100), 107 (13), 95 (43), 81 (19), 55 (18), 45 (61). HRMS (FAB): $[M + Na]^+$ calcd. for $C_{13}H_{22}NaO_3$ 249.14667, found 249.14613.

(1*S*,3*R*,4*S*)-3-(Methoxymethoxy)-4-methyl-1-(prop-2-ynyl)hept-6-enyl 2-Allyl-6-methoxybenzoate (30): To a solution of alcohol **29** (285 mg, 1.26 mmol) and triphenylphosphane (495 mg, 1.89 mmol) in toluene (13 mL) was added a solution of salicylic acid[11g] **5** (254 mg, 1.32 mmol) and DEAD (955 mg, 1.89 mmol, of a 40 % in toluene) in toluene (13 mL) at room temperature. The mixture was stirred for 15 h and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 4:1) provided the ester **30** (350 mg, 69 %) as a colorless oil. R_f = 0.55 (petroleum ether/ethyl acetate, 4:1). $[\alpha]_D$ = +39.4 (*c* = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1038, 1072, 1111, 1245, 1267, 1471, 1585, 1730, 2932, 2962 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.71–1.85 (m, 3 H, 2′-H, 5′-H), 1.85–1.94 (m, 1 H, 4′-H), 1.98 (t, *J* = 2.7 Hz, 1 H, CH_2CCH), 1.99–2.06 (m, 1 H, 5′-H), 2.57 (ddd, *J* = 16.9, 4.6, 2.7 Hz, 1 H, C*H* $_2$CCH), 2.65 (ddd, *J* = 16.9, 6.2, 2.7 Hz, 1 H, C*H*$_2$-CCH), 3.36 (s, 3 H, MOM-CH_3), 3.68 (ddd, *J* = 9.4, 3.7, 2.9 Hz, 1 H, 3′-H), 3.77 (s, 3 H, Ph-OCH_3), 4.67 (s, 2 H, MOM-CH_2), 4.87 (br. d, *J* = 10.1 Hz, 1 H, 7′-H), 4.92 (br. d, *J* = 17.0 Hz, 1 H, 7′-H), 4.98–5.04 (m, 2 H, 9-H), 5.29–5.35 (m, 1 H, 1′-H), 5.69 (dddd, *J* = 17.0, 10.1, 7.3, 6.7 Hz, 1 H, 6′-H), 5.90 (dddd, *J* = 17.3, 9.6, 6.6, 6.6 Hz, 1 H, 8-H), 6.72 (d, *J* = 8.4 Hz, 1 H, 3-H), 6.77 (d, *J* = 7.7 Hz, 1 H, 5-H), 7.23 (dd, *J* = 8.4, 7.7 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6 (CH_3), 24.6 (*C*H_2CCH), 33.9 (C-2′), 36.5 (C-4′), 37.2 (C-7), 37.6 (C-5′), 55.5 (Ph-OCH_3), 55.7 (MOM-CH_3), 69.8 (CH_2C*C*H), 70.9 (C-1′), 77.9 (C-3′), 79.6 (CH_2 *C*CH), 96.9 (MOM-CH_2), 108.6 (C-3), 115.9 (C-7′), 116.3 (C-9), 121.5 (C-5), 123.6 (C-1), 130.3 (C-4), 136.4 (C-8), 137.0 (C-6′) 138.3 (C-6), 156.3 (C-2), 167.7 (Ph-CO_2) ppm. MS (EI): *m*/*z* (%) = 331 (13), 237 (10), 219 (8), 187 (15), 175 (100), 174 (52), 156 (30), 129 (34), 123 (18), 115 (18), 91 (13), 84 (19), 45 (18). HRMS (FAB): $[M + Na]^+$ calcd. for $C_{24}H_{32}NaO_5$ 423.21475, found 423.21227.

(1*S*,3*R*,4*S*)-3-(Methoxymethoxy)-4-methyl-1-[3-(triisopropylsilyl)-prop-2-ynyl]hept-6-enyl 2-Allyl-6-methoxybenzoate (31): To a solution of the alkyne **30** (470 mg, 1.17 mmol) in THF (12 mL) was added at –78 °C *n*BuLi (516 μL, 1.29 mmol, 2.5 M in hexane) dropwise and the resulting solution stirred 30 min while warming up to –20 °C. After recooling to –78 °C, the solution was treated with TIPS-chloride (298 μL, 272 mg, 1.41 mmol) and DMAP (1.4 mg, 11 μmol) in THF (0.5 mL) and warmed to room temperature within 15 h. The reaction was quenched by addition of saturated NH_4Cl solution (10 mL) at 0 °C. After separation of the phases the aqueous layer was extracted with diethyl ether (2 × 15 mL) and the combined organic extracts were dried with Na_2SO_4. Filtration and evaporation led to the crude TIPS alkyne **31**, which was purified by flash chromatography (petroleum ether/diethyl ether, 3:1) yielding 581 mg (89 %) of a colorless oil. R_f = 0.41 (petroleum ether/ethyl acetate, 5:1). $[\alpha]_D$ = +51.3 (*c* = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1038, 1071, 1111, 1243, 1267, 1471, 1585, 1730, 2865, 2889, 2942, 2959 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.04 (br. s, 21 H, TIPS-CH, TIPS-CH_3), 1.82 (br. ddd, *J* = 13.2, 8.0, 8.0 Hz, 1 H, 5′-H), 1.85–1.97 (m, 3 H, 2′-H, 4′-H), 2.03 (br. ddd, *J* = 13.2, 5.9, 5.9 Hz, 1 H, 5′-H), 2.70–2.73 (m, 2 H, CH_2CCTIPS), 3.37 (br. d, *J* = 6.6 Hz, 2 H, 7-H), 3.39 (s, 3 H, MOM-CH_3), 3.68–3.72 (m, 1 H, 3′-H), 3.80 (s, 3 H, Ph-OCH_3), 4.69 (s, 2 H, MOM-CH_2), 4.88 (br. d, *J* = 10.2 Hz, 1 H, 7′-H), 4.93 (br. d, *J* = 17.1 Hz, 1 H, 7′-H), 5.01–5.07 (m, 2 H, 9-H), 5.30–5.38 (m, 1 H, 1′-H), 5.72 (dddd, *J* = 17.1, 10.2, 7.4, 6.7 Hz, 1 H, 6′-H), 5.87–5.98 (m, 1 H, 8-H), 6.76 (d, *J* = 8.3 Hz, 1 H, 3-H), 6.80 (d, *J* = 7.7 Hz, 1 H, 5-H), 7.27 (dd, *J* = 8.3, 7.7 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.2 (TIPS-CH), 13.5 (*C*H_3), 18.6 (TIPS-CH_3), 26.0 (*C*H_2CCTIPS), 33.5 (C-2′), 36.4 (C-4′), 37.3 (C-7), 37.7 (C-5′), 55.6 (Ph-OCH_3), 55.7 (MOM-CH_3), 70.1 (C-1′), 77.6 (C-3′), 83.4 (CH_2C*C*TIPS), 96.8 (MOM-CH_2), 103.6 (CH_2 *C*CTIPS), 108.6 (C-3), 115.8 (C-7′), 116.3 (C-9), 121.5 (C-5), 123.8 (C-1), 130.3 (C-4), 136.4 (C-8), 137.0 (C-6′) 138.3 (C-6), 156.3 (C-

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2), 167.8 (Ph-CO_2) ppm. MS (EI): *m*/*z* (%) = 513 (3), 451 (2), 306 (22), 305 (100), 175 (88), 148 (21), 131 (22), 103 (18), 75 (15), 45 (8). HRMS (EI): $[M - iPr]^+$ calcd. for $C_{30}H_{45}O_5Si$ 513.303595, found 513.310648.

(3*S*,5*R*,6*S*)-14-Methoxy-5-(methoxymethoxy)-6-methyl-3-[3-(triisopropylsilyl)prop-2-ynyl]-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-1-one (33): To a flask charged with absolute CH_2Cl_2 (42.5 mL) was added simultaneously a solution of $[\{(Cy)_3P\}_3Ru{=}CHPhCl_2]$ (**32**) (33 mg, 0.04 mmol) in CH_2Cl_2 (7.1 mL) and a solution of ester 31 (150 mg, 0.27 mmol) in CH_2Cl_2 (12 mL) over a 4 h period via syringe pumps. After the addition was complete, the solvent was evaporated and the residue purified by flash chromatography (petroleum ether/ethyl acetate, 10:1) to give benzolactone ***E*-33** (130 mg, 91 %) and the corresponding Z-isomer ***Z*-33** (4.3 mg, 3 %) as colorless waxes.

***E*-33** (main product): R_f = 0.56 (petroleum ether/ethyl acetate, 5:1). $[\alpha]_D$ = –31.1 (*c* = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1047, 1116, 1154, 1274, 1468, 1585, 1733, 2176, 2866, 2887, 2942 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.04 (br. s, 21 H, TIPS-CH, TIPS-CH_3), 1.63–1.74 (m, 1 H, 11-H), 1.75 (br. dd, *J* = 15.3, 8.6 Hz, 1 H, 14-H), 1.83 (br. dd, *J* = 15.3, 8.4 Hz, 1 H, 14-H), 2.29 (br. d, *J* = 13.7 Hz, 1 H, 11-H), 2.57 (br. s, 1 H, 16-H), 2.58 (d, *J* = 3.1 Hz, 1 H, 16-H) 3.28 (br. d, *J* = 16.3 Hz, 1 H, 8-H), 3.43 (s, 3 H, MOM-CH_3), 3.68 (dd, *J* = 16.3, 9.5 Hz, 1 H, 8-H), 3.78 (s, 3 H, Ph-OCH_3), 4.07–4.12 (m, 1 H, 13-H), 4.76 (d, *J* = 6.8 Hz, 1 H, MOM-CH_2), 4.85 (d, *J* = 6.8 Hz, 1 H, MOM-CH_2), 5.29 (br. dd, *J* = 15.3, 9.6 Hz, 1 H, 9-H), 5.37- 5.43 (m, 1 H, 15-H), 5.47 (br. dd, *J* = 15.3, 10.9 Hz, 1 H, 10-H), 6.74 (d, *J* = 7.6 Hz, 1 H, 6-H), 6.78 (d, *J* = 8.4 Hz, 1 H, 4-H), 7.21 (dd, *J* = 8.4, 7.6 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.2 (TIPS-CH), 13.2 (CH_3), 18.5 (TIPS-CH_3), 26.9 (C-16), 34.1 (C-14), 34.2 (C-12), 37.5 (C-11), 37.6 (C-8), 55.4 (MOM-CH_3), 55.8 (Ph-OCH_3), 72.2 (C-15), 78.7 (C-13), 83.2 (C-18), 96.7 (MOM-CH_2), 103.9 (C-17), 109.4 (C-4), 122.6 (C-6), 124.6 (C-2), 128.7 (C-9), 129.9 (C-5), 131.2 (C-10), 138.7 (C-7) 156.7 (C-3), 167.9 (C-1) ppm. MS (EI): *m*/*z* (%) = 485 (85), 455 (54), 423 (52), 390 (13), 375 (10), 317 (43), 275 (49), 259 (61), 199 (50), 187 (100), 145 (82), 131 (51), 84 (47), 45 (75). HRMS (EI): $[M]^+$ calcd. for $C_{28}H_{41}SiO_5$ 485.27231, found 485.27382.

***Z*-33** (minor product): R_f = 0.39 (petroleum ether/ethyl acetate, 5:1). $[\alpha]_D$ = +10.8 (*c* = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1037, 1111, 1266, 1470, 1733, 2865, 2889, 2942 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.1 Hz, 3 H, CH_3), 1.04 (br. s, 21 H, TIPS-CH, TIPS-CH_3), 1.82–1.89 (m, 2 H, 14-H, 11-H), 2.00–2.11 (m, 3 H, 14-H, 12-H, 11-H), 2.59 (dd, *J* = 17.0, 4.2 Hz, 1 H, 16-H), 2.68 (dd, *J* = 17.0, 7.2 Hz, 1 H, 16-H) 2.99 (br. d, *J* = 15.9 Hz, 1 H, 8-H), 3.38 (s, 3 H, MOM-CH_3), 3.77 (br. d, *J* = 9.3 Hz, 1 H, 13-H), 3.81 (s, 3 H, Ph-OCH_3), 3.99 (dd, *J* = 15.9, 8.9 Hz, 1 H, 8-H), 4.71 (d, *J* = 6.8 Hz, 1 H, MOM-CH_2), 4.77 (d, *J* = 6.8 Hz, 1 H, MOM-CH_2), 5.24–5.36 (m, 2 H, 9-H, 10-H), 5.49–5.56 (m, 1 H, 15-H), 6.79 (d, *J* = 7.7 Hz, 1 H, 6-H), 6.80 (d, *J* = 8.4 Hz, 1 H, 4-H), 7.27 (dd, *J* = 8.4, 7.7 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.2 (TIPS-CH), 13.4 (CH_3), 18.6 (TIPS-CH_3), 26.9 (C-16), 32.0 (C-11), 32.5 (C-8), 35.0 (C-14), 36.5 (C-12), 55.5 (MOM-CH_3), 55.9 (Ph-OCH_3), 71.2 (C-15), 77.3 (C-13), 83.3 (C-18), 97.3 (MOM-CH_2), 103.7 (C-17), 109.4 (C-4), 122.7 (C-6), 122.7 (C-2), 128.6 (C-10), 129.4 (C-9), 131.0 (C-5), 140.5 (C-7) 157.3 (C-3), 166.6 (C-1) ppm. MS (EI): *m*/*z* (%) = 499 (6), 485 (42), 455 (9), 423 (11), 315 (20), 275 (34), 260 (29), 199 (36), 187 (65), 162 (88), 161 (100), 145 (79), 131 (46), 105 (39), 77 (57), 45 (78). HRMS (EI): $[M]^+$ calcd. for $C_{28}H_{41}SiO_5$ 485.27231, found 485.27288.

(3*S*,5*R*,6*S*)-3-[(2*E*)-3-Iodoprop-2-enyl]-14-methoxy-5-(methoxymethoxy)-6-methyl-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-1-one (34): A solution of the alkyne **3** (30 mg, 0.081 mmol), Bu_3SnH (28 mg, 0.097 mmol) and AIBN (1.9 mg, 0.011 mmol) in toluene (0.5 mL) was heated under reflux for 18 h. After cooling to room temperature, the solvent was evaporated, Et_2O (0.1 mL) was added and the mixture was treated with I_2 (25 mg, 0.097 mmol) at 0 °C. The solution was stirred for 1 h at room temperature and then quenched with a saturated aqueous solution of KF (1 mL). After extraction of the aqueous layer twice with Et_2O (1 mL), the combined organic phases were washed with a saturated aqueous solution of $Na_2S_2O_4$ (1 mL), then dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (toluene/ethyl acetate, 10:1) to afford vinyl iodide ***E*-34** (27.1 mg, 68 %) and the corresponding *Z*-isomer ***Z*-34** (5.9 mg, 15 %) as colorless syrups.

***E*-34** (main product): R_f = 0.45 (toluene/ethyl acetate, 10:1). $[\alpha]_D$ = –37.5 (*c* = 1.00, benzene). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.79 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.33 (dd, *J* = 15.5, 9.5 Hz, 1 H, 14-H), 1.61–1.67 (m, 2 H, 14-H, 11-H), 2.01–2.12 (m, 1 H, 12-H), 2.21–2.28 (m, 2 H, 11-H, 16-H), 2.36–2.44 (m, 1 H, 16-H), 3.26 (br. d, *J* = 16.3 Hz, 1 H, 8-H), 3.38 (s, 3 H, MOM-CH_3), 3.64 (dd, *J* = 16.4, 9.4 Hz, 1 H, 8-H), 3.83 (s, 3 H, Ph-OCH_3), 4.07 (br. dd, *J* = 9.2, 3.7 Hz, 1 H, 13-H), 4.73 (d, *J* = 6.6 Hz, 1 H, MOM-CH_2), 4.82 (d, *J* = 6.8 Hz, 1 H, MOM-CH_2), 5.22–5.31 (m, 2 H, 9-H, 15-H), 5.38–5.44 (m, 1 H, 10-H), 6.06 (d, *J* = 14.4 Hz, 1 H, 18-H), 6.70–6.78 (m, 1 H, 17-H), 6.76 (d, *J* = 8.1 Hz, 1 H, 6-H), 6.82 (d, *J* = 8.6 Hz, 1 H, 4-H), 7.24 (dd, *J* = 7.8 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3 (CH_3), 25.6 (C-16), 34.1 (C-12), 35.4 (C-14), 37.7 (C-8, C-11), 42.5 (C-16), 55.6 (MOM-CH_3), 56.0 (Ph-OCH_3), 73.3 (C-15), 77.1 (C-18), 79.3 (C-13), 97.1 (MOM-CH_2), 109.3 (C-4), 122.8 (C-6), 124.3 (C-2), 128.5 (C-9), 130.1 (C-5), 131.3 (C-10), 139.0 (C-7), 142.2 (C-17), 156.6 (C-3), 168.2 (C-1) ppm. MS (EI): *m*/*z* (%) = 468 (10), 455 (30), 439 (50), 301 (15), 275 (48), 259 (100), 215 (50), 201 (54), 187 (87), 163 (43), 45 (46). HRMS (EI): $[M]^+$ calcd. for $C_{22}H_{29}O_5I$ 500.1060, found 500.1021.

(3*S*,5*R*,6*S*)-14-Methoxy-5-(methoxymethoxy)-6-methyl-3-[3-(pyridin-2-yl)prop-2-ynyl]-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-1-one (35): To a mixture of 2-bromopyridine (19.2 mg, 0.122 mmol) and the alkyne **3** (50 mg, 0.133 mmol) in triethylamine (0.61 mL) were added $[PdCl_2(PPh_3)_2]$ (2.2 mg, 0.003 mmol) and CuI (0.83 mg, 0.006 mmol). The reaction mixture was then stirred at room temperature under nitrogen for 18 h. After removal of the solvent in vacuo, the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 4:1) to afford the substituted pyridine **35** (48.8 mg, 90 %) as a light yellowish wax. R_f = 0.12 (petroleum ether/ethyl acetate, 4:1). $[\alpha]_D$ = –79.9 (*c* = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1116, 1274, 1428, 1466, 1583, 1727, 2929, 2954 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.66–1.82 (m, 2 H, 14-H, 11-H), 2.06–2.16 (m, 1 H, 12-H), 2.28 (d, *J* = 14.2 Hz, 1 H, 11-H), 2.79 (dd, *J* = 16.4, 6.3 Hz, 2 H, 16-H), 3.28 (d, *J* = 16.4 Hz, 1 H, 8-H), 3.43 (s, 3 H, MOM-CH_3), 3.67 (dd, *J* = 16.3, 9.5 Hz, 1 H, 8-H), 3.72 (s, 3 H, Ph-OCH_3), 4.12 (br. d, *J* = 6.3 Hz, 1 H, 13-H), 4.80 (d, *J* = 6.6 Hz, MOM-CH_2), 4.87 (d, *J* = 6.8 Hz, MOM-CH_2), 5.29–5.35 (m, 1 H, 9-H), 5.42–5.55 (m, 2 H, 15-H, 10-H), 6.72 (d, *J* = 7.6 Hz, 1 H, 6-H), 6.76 (d, *J* = 8.3 Hz, 1 H, 4-H), 7.15–7.22 (m, 2 H, 5-H, 21-H), 7.38 (d, *J* = 7.8 Hz, 1 H, 23-H), 7.59 (td, *J* = 7.8, 1.8 Hz, 1 H, 22-H), 8.52 (d, *J* = 4.8 Hz, 1 H, 20-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4 (CH_3), 26.5 (C-16), 34.5 (C-14), 34.8 (C-12), 37.6 (C-8, C-11), 55.5 (MOM-CH_3), 55.8 (Ph-OCH_3), 72.2 (C-15), 78.9 (C-13), 81.8 (C-18), 86.3 (C-17), 96.8 (MOM-CH_2), 109.4 (C-4), 122.5 (C-6, C-21), 124.3 (C-2), 127.1 (C-23), 128.7 (C-9), 130 (C-5), 131.2 (C-10),

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136 (C-22), 138.8 (C-7), 143.5 (C-19), 149.7 (C-20), 156.7 (C-3), 167.9 (C-1) ppm. MS (EI): *m*/*z* (%) = 449 (15), 418 (18), 404 (71), 388 (41), 244 (10), 216 (23), 187 (24), 172 (80), 144 (100), 131 (52), 117 (48), 93 (18). HRMS (EI): $[M]^+$ calcd. for $C_{27}H_{31}NO_5$ 449.22020, found 449.22360.

(3*S*,5*R*,6*S*)-5,14-Dihydroxy-6-methyl-3-[3-(pyridin-2-yl)prop-2-ynyl]-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-1-one (36): To a stirred solution of compound **35** (45 mg, 0.1 mmol) in CH_2Cl_2 (2.1 mL) was quickly added 9-iodo-9-BBN (99.3 mg, 0.4 mmol) at 23 °C. After 70 s, the reaction was stopped by adding methanol (2.1 mL) and then stirred for 1 h at room temperature. The solvent and the formed boronic acid ester was removed under reduced pressure. This procedure, addition of methanol and solvent evaporation was repeated twice. Pure product **36** (37.7 mg, 88 %) was obtained after flash chromatography (petroleum ether/ethyl acetate, 1:1) as a colorless wax. R_f = 0.26 (petroleum ether/ethyl acetate, 1:1). $[\alpha]_D$ = –6.3 (*c* = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1116, 1247, 1292, 1465, 1587, 1723, 2235, 2925, 2958, 3060, 3166, 3491 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.25 (s, 1 H, OH), 1.53 (dd, *J* = 14.9, 8.8 Hz, 1 H, 14-H), 1.80–1.88 (m, 1 H, 11-H), 1.91–1.97 (m, 1 H, 12-H), 2.19 (dd, *J* = 15.0, 10.7 Hz, 1 H, 14-H), 2.31–2.36 (m, 1 H, 11-H), 2.88 (dd, *J* = 5.7, 5.7 Hz, 2 H, 16-H), 3.43 (br. dd, *J* = 16.7, 3.3 Hz, 1 H, 8-H), 3.77 (br. dd, *J* = 16.4, 5.1 Hz, 1 H, 8-H), 3.83 (dd, *J* = 8.6, 3.0 Hz, 1 H, 13-H), 5.16–5.23 (m, 1 H, 10-H), 5.50 (dt, *J* = 15.4, 4.6 Hz, 1 H, 9-H), 5.65 (dt, *J* = 10.5, 5.7 Hz, 1 H, 15-H), 6.70 (d, *J* = 7.3, 1 H, 6-H), 6.88 (d, *J* = 7.8 Hz, 1 H, 4-H), 7.24–7.29 (m, 2 H, 21-H, 5-H), 7.42 (d, *J* = 7.8 Hz, 1 H, 23-H), 7.68 (td, *J* = 7.8, 1.6 Hz, 1 H, 22-H), 8.56 (d, *J* = 4.3 Hz, 1 H, 20-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6 (CH_3), 26.1 (C-16), 35.7 (C-14), 37.4 (C-12), 38.3 (C-11), 38.9 (C-8), 70.4 (C-13), 72.2 (C-15), 81.9 (C-18), 86.6 (C-17), 116.5 (C-4), 122.9 (C-6), 123.2 (C-21), 127.1 (C-10), 127.3 (C-23), 132.2 (C-9), 133.4 (C-5), 136.7 (C-22), 141.8 (C-7), 142.8 (C-19), 149.3 (C-20), 161.1 (C-3), 170.3 (C-1) ppm. MS (EI): *m*/*z* (%) = 391 (78), 184 (15), 173 (22), 172 (43), 144 (85), 117 (100), 115 (25), 91 (12), 55 (10) ppm. HRMS (EI): $[M]^+$ calcd. for $C_{24}H_{25}NO_4$ 391.17834, found 391.18067.

Supporting Information Available: Copies of ^1H- and ^{13}C NMR spectra for all new compounds reported. For Supporting Informations see also the footnote on the first page of this article.

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