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Hydroxyl-Assisted *trans*-Reduction of 1,3-Enynes: Application to the Formal Synthesis of (+)-Aspicilin

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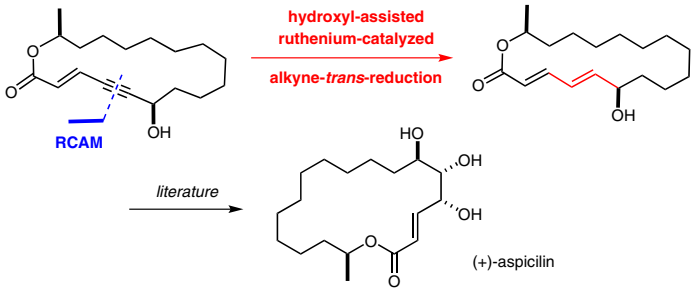
Dedicated to Prof. Dieter Enders on the occasion of his 70th birthday



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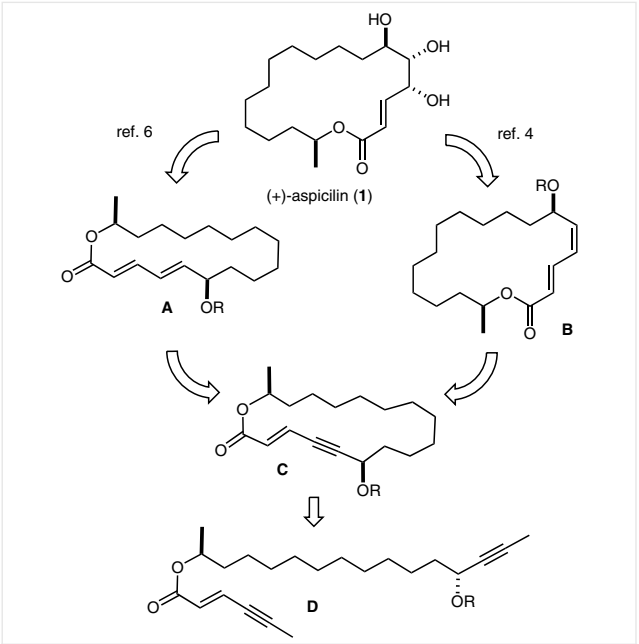
Abstract 1,3-Enynes are hardly amenable to *trans*-hydrometalation reactions, because they tend to bind the standard ruthenium catalysts too tightly. However, catalysts comprising a [Cp*Ru–Cl] unit allow such compounds to be used, provided they contain an OH group next to the triple bond. This aspect is illustrated by a formal synthesis of the lichen-derived macrolide aspicilin. The required macrocyclic enyne precursor was formed by an efficient ring-closing alkyne metathesis reaction.

Key words alkyne metathesis, enynes, hydrostannation, molybdenum alkylidynes, natural products, ruthenium, *trans*-reduction

Ever since the structure of (+)-aspicilin (**1**) has been elucidated,[1,2] this lichen-derived macrolide[3] serves as a popular testing ground for methodological innovations.[4–21] In line with this tradition, we saw an opportunity to scrutinize two catalytic transformations under investigation in our laboratory by implementing them into a formal synthesis of this prominent target.

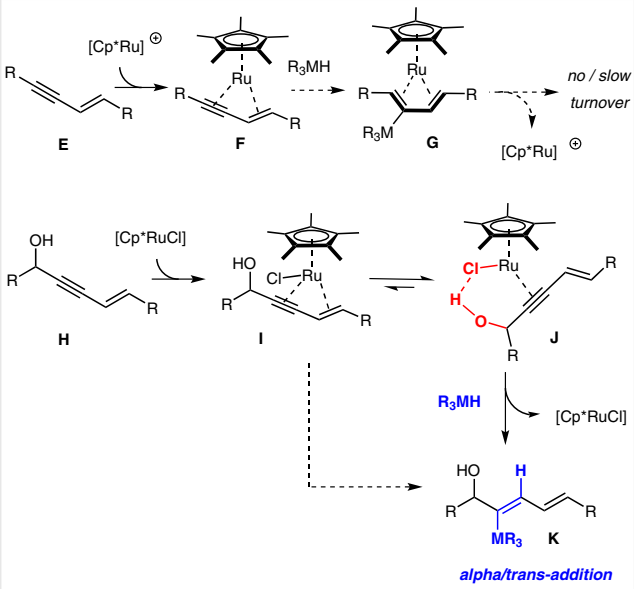
Of particular interest to us was the question whether a diene of type **A** can be reached by *trans*-reduction of an enyne precursor **C**,[22] which in turn could be made by ring-closing alkyne metathesis (RCAM)[23,24] of a readily available substrate of type **D** (Scheme 1). If successful, this approach intercepts the total synthesis of **1** reported by Oppolzer and co-workers, who showed that diene **A** (R = H) can be efficiently converted into the final target by a sequence of hydroxyl-directed epoxidation followed by acetate-assisted epoxide opening.[6] Interestingly, the more conventional *cis*-reduction of **C** to diene **B** also provides access to **1**, as the historically first total synthesis of aspicilin by Quinkert et al. passed through this particular intermediate: however, the osmylation of **B** had proven only modestly effective.[4,20,25]



Scheme 1 Retrosynthetic analysis of (+)-aspicilin (**1**) involving a RCAM/semi-reduction sequence

The envisaged key step **C** → **A**, however, bore considerable risk. Classical methods for the *trans*-reduction of alkynes using dissolving metal conditions are obviously inadequate in this case. Ruthenium-catalyzed *trans*-hydrometalation[22,26–32] and *trans*-hydrogenation[33] reactions, as the best current alternatives, show a broad scope, but invariably encounter limitations when applied to substrates capable of serving as potential 4- or 6-electron donors. 1,3-Enynes **E** and related compounds, as well as the derived 1,3-diene products, fall into this category and have therefore proven problematic in the past (Scheme 2). Their inertia is

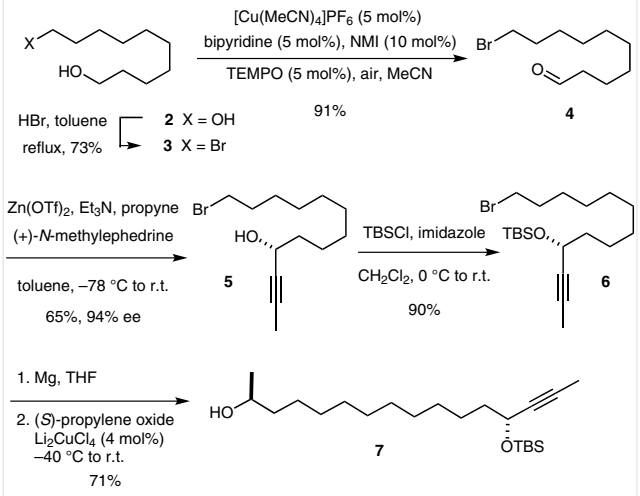
most likely caused by the formation of stable adducts of type **F** and/or **G**, which trap the catalyst,[34,35] especially when working with [Cp*Ru(MeCN)]PF_6 or related cationic complexes that have dominated the field until recently.[27]



Scheme 2 Top: 1,3-enynes and 1,3-dienes interfere with catalyst turnover, especially when using cationic $[Cp^*Ru]^+$ fragments; bottom: interligand hydrogen bonding between a 1,3-enyne flanked by a hydroxyl group and the polarized bond [Ru–Cl] might provide access to a reactive coordination mode and hence allow catalytic *trans*-hydrometalation to proceed; M = Si, Ge, Sn

In this context, our recent discovery might prove relevant that substrates bearing protic substituents synergize with catalysts comprising an intact [Ru–Cl] bond.[31] Experimental evidence suggests that this effect is due to an ensuing interligand hydrogen bonding, which imposes directionality on the actual hydrometalation step. In the case of 1,3-enyne substrates **H** with a flanking OH group, this favorable interaction might help to avoid the unproductive chelate **I**, but rather enforce a reactive coordination mode **J** and hence allow *trans*-addition with formation of products **K** to proceed. As the envisaged key intermediate **C** en route to **1** contains this exact substructure, it provides a stringent test to probe this aspect.

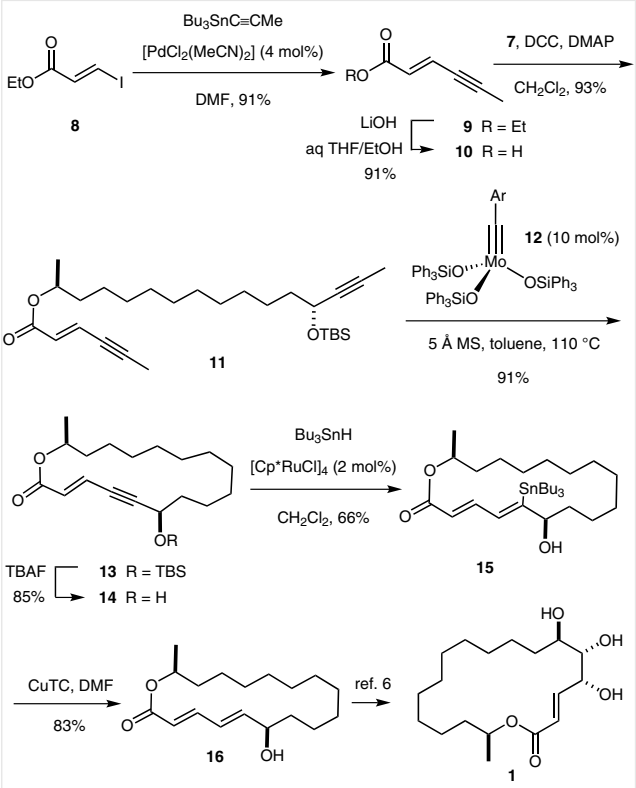
The synthesis started from the cheap decane-1,10-diol (**2**), which was transformed on multigram scale into 10-bromodecanal (**4**) in two straightforward steps; it is emphasized that the copper-catalyzed Stahl oxidation of **3** proved highly effective and convenient on scale (Scheme 3).[36] Although only few cases are documented in the literature in which propyne had been used as nucleophile in asymmetric Carreira alkynylation reactions,[32a,37,38] this transformation proceeded well to afford product **5** with high optical purity (94% ee). As this transformation relies on the use of (+)-*N*-methylephedrine, the compatibility of substrate **4** comprising a primary alkyl bromide is noteworthy; yet, one might suspect that the yield of only 65% indicates some material loss by competing *N*-alkylation of this chiral ligand.



Scheme 3 Preparation of the alcohol building block

The derived TBS-ether **6** was converted into the corresponding functionalized Grignard reagent, which served well in the subsequent copper-catalyzed opening of (*S*)-propylene oxide. Esterification of the resulting alcohol **7** with the readily available acid **10** furnished product **11** in readiness for macrocyclization (Scheme 4).

Alkyne metathesis in general and ring-closing alkyne metathesis (RCAM) in particular have witnessed considerable progress in recent years.[23] Molybdenum alkylidyne complexes endowed with triarylsilanolate ligands have a significant share for their high activity and remarkable functional group tolerance;[39,40] at the same time, they allowed the substrate scope to be considerably increased.[41] In this context, it is noteworthy that earlier catalyst generations had failed with propargyl alcohol derivatives as well as with electron-deficient alkyne substrates,[42] whereas complex **12** and relatives proved effective in a number of exigent cases.[43] Compound **11**, however, is the first substrate to comprise both of these demanding structural elements. Therefore, it is deemed rewarding that cyclization of **11** proceeded quantitatively within 10 minutes reaction time[44] on treatment with catalytic amounts of **12** in refluxing toluene to give the 18-membered lactone **13** in 91% yield on a 500 mg scale. This favorable result, however, is critically dependent on the proper reaction conditions: while the chosen catalyst is fully operative at ambient temperature, only the corresponding cyclic head-to-tail dimer was formed. This divergent outcome is thought to reflect the entropic component of the cyclization process and has precedent in previous work from our laboratory.[45]



Scheme 4 Completion of the formal synthesis of (+)-aspicilin (**1**); Ar = *p*-MeOC$_6$H$_4$

With the cyclic enyne **13** in hand, the stage was set to probe the critical *trans*-reduction manifold. In line with our expectation, an effective *trans*-hydrostannation took place only after deprotection of the propargylic alcohol group. Thus, reaction of **14** with Bu_3SnH in the presence of catalytic amounts of $[Cp^*RuCl]_4$ in CH_2Cl_2 cleanly furnished the desired product **15**; only traces of an undesired isomer were detected. The high fidelity with which the tin residue is delivered to the proximal C-atom of the reacting triple bond is confidently ascribed to the steering effect of the free OH group, which has precedent in our earlier work on ruthenium-catalyzed *trans*-hydrometalation reactions;[31] more importantly, the current example advocates the notion that the protic substituent can render otherwise unreactive substrates amenable to *trans*-addition. This aspect is deemed relevant for the further advancement of this field and is therefore subject to detailed investigations.

Treatment of **15** with CuTC [copper(I) thiophene-2-carboxylate] in DMF led to the *E*,*E*-configured dienoate **16** that intercepts the efficient total synthesis of (+)-aspicilin (**1**) described by Oppolzer and co-workers.[6] In concord with a rapidly growing number of examples from the literature, this application shows that RCAM in combination with alkyne semi-reduction provides a selective and predictable access to alkenes, dienes, and polyenes of all stereochemical formats.[46–48] This includes conjugated dienes as present in **16**, which are often subject to ring contraction and/or isomerization when approached by olefin metathesis.[49] The ability of complex **12** to rigorously distinguish between alkenes and alkynes precludes any such complication.[50]

All reactions using anhyd solvents were carried out under argon in flame-dried glassware. The solvents were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O (Mg/anthracene), CH_2Cl_2, toluene (Na/K), MeOH (Mg, stored over MS 3Å); DMF, MeCN, and Et_3N were dried by an adsorption solvent purification system based on molecular sieves. TLC: Macherey-Nagel precoated plates (POLYGRAM® SIL/UV254); Flash chromatography: Merck silica gel 60 (40–63 µm) with predistilled or HPLC grade solvents. Analytic HPLC: Shimadzu LC-2020, Column: 50 mm Eclipse Plus C8, 3.0 mm. NMR: Spectra were recorded on a Bruker AV 400 spectrometer in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δ_C = 77.16; residual $CHCl_3$ in $CDCl_3$: δ_H = 7.26). IR: Spectrum One (PerkinElmer) spectrometer, wavenumbers in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: ESQ3000 (Bruker), accurate mass determinations: Bruker APEX III FT-MS (7 T magnet) or Mat 95 (Finnigan). Optical rotations $[\alpha]_D^{20}$ were measured with a Perkin-Elmer Model 343 polarimeter. Unless stated otherwise, all commercially available compounds (Alfa Aesar, Aldrich, Fluka, TCI) were used as received.

10-Bromodecan-1-ol (3)[51,52]

HBr (48% in H_2O, w/w, 16.3 mL, 138 mmol) was added to a mixture of decane-1,10-diol (**2**; 20 g, 115 mmol) and toluene (250 mL). The resulting mixture was stirred at reflux temperature for 16 h. After reaching r.t. and careful addition of sat. aq $Na_2S_2O_3$ (50 mL), the aqueous layer was extracted with EtOAc (3 × 200 mL). The combined extracts were dried ($MgSO_4$), filtered, and the solvent was evaporated. Purification of the residue by flash chromatography (silica gel, hexanes/EtOAc, 4:1 to 2:1) afforded the title compound as a colorless oil (19.8 g, 73%).

IR (ATR): 3328, 2924, 2853, 1463, 1437, 1371, 1352, 1256, 1242, 1129, 1055, 899, 756, 722, 644, 562, 505, 465, 445, 428, 417 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.63 (t, *J* = 6.6 Hz, 2 H), 3.40 (t, *J* = 6.9 Hz, 2 H), 1.88–1.80 (m, 2 H), 1.60–1.51 (m, 2 H), 1.46–1.24 (m, 13 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 63.2, 34.2, 32.92, 32.89, 29.6, 29.49, 29.48, 28.9, 28.3, 25.8.

HRMS-ESI: *m*/*z* calcd for $[C_{10}H_{21}BrO + Na]^+$: 259.0669; found: 259.0668.

10-Bromodecanal (4)[53]

10-Bromodecan-1-ol (**3**; 10.0 g, 42 mmol) and TEMPO (312 mg, 2.0 mmol) were added to a mixture of $[Cu(MeCN)_4]PF_6$ (744 mg, 2.0 mmol), 2,2′-bipyridine (312 mg, 2.0 mmol), and 1-methylimidazole (328 mg, 4.0 mmol) in MeCN (200 mL). The resulting red brown mixture was stirred for 14 h at r.t. under air, causing a color change to blue. The mixture was filtered through a pad of silica gel and the filtrate was evaporated. Purification of the residue by flash chromatography (silica gel, hexanes/EtOAc, 20:1 to 10:1) afforded the title compound as a pale red oil (9.0 g, 91%).

IR (ATR): 2926, 2854, 2716, 1723, 1463, 1409, 1390, 1245, 1111, 846, 723, 643, 560 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.77 (t, *J* = 1.8 Hz, 1 H), 3.42 (t, *J* = 6.8 Hz, 2 H), 2.44 (td, *J* = 7.4, 1.8 Hz, 2 H), 1.90–1.81 (m, 2 H), 1.68–1.59 (m, 2 H), 1.47–1.37 (m, 2 H), 1.36–1.27 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.7, 43.9, 33.9, 32.8, 29.21, 29.18, 29.1, 28.7, 28.1, 22.1.

HRMS-ESI: *m*/*z* calcd for $[C_{10}H_{19}BrO + Na]^+$: 257.0510; found: 257.0512.

(*R*)-13-Bromotridec-2-yn-4-ol (5)

Et_3N (3.90 mL, 27.9 mmol) was added dropwise to a suspension of $Zn(OTf)_2$ (10.1 g, 27.9 mmol) and (+)-*N*-methylephedrine (5.0 g, 27.9 mmol) in toluene (120 mL). The colorless suspension was stirred for 2 h at r.t. before the mixture was cooled to –78 °C and liquid propyne (ca. 4 mL) was added via cannula from a Schlenk tube at –78 °C. The mixture was allowed to reach r.t. over the course of 1 h. A solution of aldehyde **4** (5.48 g, 23.3 mmol) in toluene (10 mL) was added dropwise over 4 h and stirring continued for 14 h at r.t. before the reaction was quenched with sat. aq NH_4Cl (20 mL). The aqueous layer was extracted with EtOAc (3 × 150 mL). The remaining aqueous layer was acidified to pH 2 by the addition of aq 2 M HCl and extracted with EtOAc (150 mL). The combined extracts were dried ($MgSO_4$), filtered, and the solvent was evaporated. Purification of the residue by flash chromatography (silica gel, hexanes/EtOAc, 10:1) afforded the title compound as a colorless oil (4.15 g, 65%, 94% ee); $[\alpha]_D^{20}$ –0.8 (*c* = 1, $CHCl_3$).

IR (ATR): 3434, 2924, 2854, 2219, 1734, 1674, 1454, 1441, 1352, 1323, 1260, 1200, 1135, 1119, 1076, 1022, 988, 904, 868, 811, 723, 543, 428 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.35–4.29 (m, 1 H), 3.42 (t, *J* = 6.9 Hz, 2 H), 1.85 (d, *J* = 2.1 Hz, 3 H), 1.89–1.80 (m, 2 H), 1.72–1.60 (m, 3 H), 1.47–1.36 (m, 4 H), 1.35–1.25 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 81.1, 80.6, 62.9, 38.3, 34.2, 33.0, 29.6, 29.5, 29.4, 28.9, 28.3, 25.3, 3.7.

HRMS-ESI: *m*/*z* calcd for $[C_{13}H_{23}BrO + Na]^+$: 297.0825; found: 297.0826.

(*R*)-[(13-Bromotridec-2-yn-4-yl)oxy](*tert*-butyl)dimethylsilane (6)

TBSCl (2.86 g, 19.0 mmol) was added to a solution of alcohol **5** (3.6 g, 13.1 mmol) and imidazole (2.66 g, 39.0 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The cooling bath was removed and the mixture stirred for 2 h at r.t. before the reaction was quenched with sat. aq NH_4Cl (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), the combined extracts were dried ($MgSO_4$), filtered, and the solvent was evaporated. Purification of the residue by flash chromatography (silica gel, hexanes/EtOAc, 50:1) afforded the title compound as a colorless oil (4.57 g, 90%); $[\alpha]_D^{20}$ +24.5 (*c* = 1, $CHCl_3$).

IR (ATR): 2927, 2855, 2238, 1716, 1586, 1463, 1389, 1360, 1341, 1250, 1154, 1075, 1005, 939, 834, 775, 723, 666, 647, 563 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.36–4.28 (m, 1 H), 3.40 (t, *J* = 6.9 Hz, 2 H), 1.82 (d, *J* = 21.0 Hz, 3 H), 1.88–1.81 (m, 2 H), 1.65–1.55 (m, 2 H), 1.46–1.34 (m, 4 H), 1.33–1.24 (m, 8 H), 0.90 (s, 9 H), 0.11 (s, 3 H), 0.09 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 81.3, 79.9, 63.3, 39.1, 34.2, 33.0, 29.6, 29.5, 29.4, 28.9, 28.3, 26.0, 25.4, 18.4, 3.7, –4.3, –4.9.

HRMS-ESI: *m*/*z* calcd for $[C_{19}H_{37}BrOSi + Na]^+$: 411.1691; found: 411.1689.

(2*S*,13*R*)-13-(*tert*-Butyldimethylsilyloxy)hexadec-14-yn-2-ol (7)

Mg turnings (250 mg, 10.3 mmol) and I_2 (20 mg) were vigorously stirred under argon atmosphere for 14 h at 90 °C. After reaching r.t., the activated Mg powder was suspended in THF (5 mL) and the suspension stirred at reflux temperature for 1 h. A solution of bromide **6** (2.0 g, 5.14 mmol) in THF (2 mL) was added over 2 min and stirring continued at reflux temperature for 1 h. The resulting mixture was cooled to –40 °C and Li_2CuCl_4 (0.1 M in THF, 2 mL, 0.2 mmol, 4 mol%) was introduced. (*S*)-Propylene oxide (407 mg, 7.0 mmol, 0.49 mL) was added dropwise over 5 min and the mixture was allowed to reach r.t. over 14 h. The reaction was quenched with sat. aq NH_4Cl (5 mL), the aqueous layer was extracted with EtOAc (3 × 50 mL), the combined extracts were dried ($MgSO_4$), filtered, and the solvent was evaporated. Purification of the residue by flash chromatography (silica gel, hexanes/EtOAc, 50:1 to 20:1) afforded the title compound as a colorless oil (1.35 g, 71%); $[\alpha]_D^{20}$ +32.6 (*c* = 1, $CHCl_3$).

IR (ATR): 3355, 2925, 2854, 1744, 1463, 1407, 1389, 1361, 1341, 1250, 1083, 1005, 939, 834, 775, 721, 666, 559 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.32–4.25 (m, 1 H), 3.84–3.74 (m, 1 H), 1.82 (d, *J* = 2.1 Hz, 3 H), 1.65–1.55 (m, 2 H), 1.49–1.33 (m, 5 H), 1.32–1.23 (m, 14 H), 1.18 (d, *J* = 6.2 Hz, 3 H), 0.90 (s, 9 H), 0.11 (s, 3 H), 0.09 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 81.3, 79.9, 68.4, 63.4, 39.5, 39.1, 29.8, 29.7, 29.4, 26.0, 26.0, 25.9, 25.4, 23.6, 18.5, 3.7, –4.3, –4.9.

HRMS-ESI: *m*/*z* calcd for $[C_{22}H_{44}O_2Si + Na]^+$: 391.3000; found: 391.3003.

Ethyl (*E*)-Hex-2-en-4-ynoate (9)[54]

$[PdCl_2(MeCN)_2]$ (60.8 mg, 0.21 mmol) was added to a solution of ethyl (*E*)-3-iodoacrylate (**8**;[55] 1.20 g, 5.0 mmol) and tributyl(prop-1-yn-1-yl)stannane (1.71 g, 5.2 mmol) in DMF (10 mL) and the resulting mixture was stirred for 14 h at r.t.. Aq KF (0.5 M, 20 mL) and EtOAc (20 mL) were added and stirring was continued for 2 h. After filtration, the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined extracts were dried ($MgSO_4$), filtered, and the solvent was evaporated. Purification of the residue by flash chromatography (silica gel, hexanes/EtOAc, 50:1 to 20:1) afforded the title compound as a colorless oil (630 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.72 (dq, *J* = 15.8, 2.5 Hz, 1 H), 6.13 (dd, *J* = 15.8, 0.6 Hz, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 2.02 (dd, *J* = 2.5, 0.6 Hz, 3 H), 1.29 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 129.4, 126.2, 96.3, 77.2, 60.8, 14.3, 4.9.

HRMS-ESI: *m*/*z* calcd for $[C_8H_{10}O_2 + Na]^+$: 161.0575; found: 161.0573.

(*E*)-Hex-2-en-4-ynoic Acid (10)

LiOH (479 mg, 20.0 mmol) was suspended in a mixture of THF (10 mL), H_2O (10 mL) and EtOH (2 mL). Ester **9** (950 mg, 6.88 mmol) was added and the mixture was stirred for 1 h at r.t. After the addition of sat. aq NH_4Cl (10 mL), the pH was adjusted to 2 by addition of aq 2 M HCl. The aqueous layer was extracted with EtOAc (3 × 50 mL), the combined extracts were dried ($MgSO_4$), filtered, and the solvent was evaporated. The title compound was isolated as a colorless solid (690 mg, 91%); mp 175–177 °C.

IR (ATR): 2925, 2582, 2216, 1674, 1614, 1452, 1421, 1310, 1279, 1210, 1172, 1033, 962, 921, 865, 677, 539, 422 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.92 (br s, 1 H), 6.82 (dq, *J* = 15.8, 2.5 Hz, 1 H), 6.14 (d, *J* = 15.8 Hz, 1 H), 2.05 (d, *J* = 2.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 129.0, 128.6, 98.6, 77.1, 5.1.

HRMS-ESI: *m*/*z* calcd for $[C_6H_5O_2]^-$: 109.0295; found: 109.0295.

(2*S*,13*R*)-13-[(*tert*-Butyldimethylsilyl)oxy]hexadec-14-yn-2-yl (*E*)-Hex-2-en-4-ynoate (11)

Alcohol **7** (1.50 g, 4.07 mmol), DCC (887 mg, 4.3 mmol), and DMAP (10 mg, 0.82 mmol) were successively added at 0 °C to a solution of acid **10** (473 mg, 4.07 mmol) in CH_2Cl_2 (10 mL). After stirring for 2 h at 0 °C, the mixture was filtered through a pad of silica gel. Sat. aq NH_4Cl (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined extracts were dried ($MgSO_4$), filtered, and the solvent was evaporated. Purification of the residue by flash chromatography (silica gel, hexanes/EtOAc, 100:1 to 50:1) afforded the title compound as a colorless oil (1.75 g, 93%); $[\alpha]_D^{20}$ +35.9 (*c* = 1, $CHCl_3$).

IR (ATR): 2926, 2854, 2222, 2120, 1712, 1463, 1359, 1300, 1256, 1180, 1164, 1078, 1005, 961, 835, 776, 720, 667, 516 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.71 (dq, *J* = 15.8, 2.4 Hz, 1 H), 6.12 (d, *J* = 15.8 Hz, 1 H), 5.00–4.90 (m, 1 H), 4.32–4.25 (m, 1 H), 2.02 (d, *J* = 2.4 Hz, 3 H), 1.81 (d, *J* = 2.1 Hz, 3 H), 1.66–1.54 (m, 3 H), 1.54–1.24 (m, 17 H), 1.23 (d, *J* = 6.3 Hz, 3 H), 0.90 (s, 9 H), 0.11 (s, 3 H), 0.09 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 130.1, 125.9, 96.1, 81.3, 79.9, 77.3, 71.6, 63.4, 39.1, 36.1, 29.70, 29.66, 29.59, 29.4, 26.0, 25.5, 25.4, 20.1, 18.4, 4.9, 3.7, –4.4, –4.9.

HRMS-ESI: *m*/*z* calcd for $[C_{28}H_{48}O_3Si + Na]^+$: 483.3266; found: 483.3265.

(7*R*,18*S*,*E*)-7-[(*tert*-Butyldimethylsilyl)oxy]-18-methyloxacyclooctadec-3-en-5-yn-2-one (13)

Diyne **11** (500 mg, 1.09 mmol) was added to a suspension of molecular sieves 5Å (flame dried, 8 g) in toluene (800 mL) and the resulting mixture was stirred for 1 h at r.t. The mixture was then warmed to 110 °C before a solution of complex **12** (110 mg, 0.106 mmol, 10 mol%) in toluene (2 mL) was added over 2 min. After stirring for 10 min at this temperature, the suspension was filtered through a plug of Celite, which was carefully rinsed with EtOAc (50 mL). The combined filtrates were evaporated and the residue was purified by flash chromatography (silica gel, hexanes/EtOAc, 100:1 to 50:1) to give the title compound as a colorless oil (400 mg, 91%); the product contained ca. 8% of the dimeric macrocycle and was used without further purification for the next step.

IR (ATR): 2927, 2855, 1715, 1619, 1462, 1360, 1299, 1254, 1178, 1153, 1125, 1083, 1006, 982, 960, 940, 835, 777, 717, 669 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.75 (dd, *J* = 15.8, 2.1 Hz, 1 H), 6.21 (d, *J* = 15.8 Hz, 1 H), 5.06–4.93 (m, 1 H), 4.54 (ddd, *J* = 7.5, 4.8, 2.1 Hz, 1 H), 1.77–1.62 (m, 3 H), 1.61–1.17 (m, 17 H), 1.23 (d, *J* = 6.3 Hz, 3 H), 0.92 (s, 9 H), 0.12 (s, 3 H), 0.10 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 131.8, 124.9, 101.2, 82.1, 72.8, 63.6, 37.6, 34.2, 29.9, 29.8, 29.5, 29.2, 28.6, 25.9, 25.8, 25.5, 23.8, 20.3, –4.5, –4.8.

HRMS-ESI: *m*/*z* calcd for $[C_{24}H_{42}O_3Si + Na]^+$: 429.2799; found: 429.2795.

(7*R*,18*S*,*E*)-7-Hydroxy-18-methyloxacyclooctadec-3-en-5-yn-2-one (14)

TBAF (1 M in THF, 2 mL, 2 mmol) was added at 0 °C to a solution of compound **13** (400 mg, 0.98 mmol) in THF (5 mL) and the mixture was stirred for 2 h till r.t. was reached The reaction was quenched with sat. aq NH_4Cl (1 mL) and H_2O (1 mL) and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined extracts were dried ($MgSO_4$), filtered, and the filtrate was evaporated. Purification of the residue by flash chromatography (silica gel, hexanes/EtOAc, 20:1 to 4:1) afforded the title compound as a colorless solid (243 mg, 85%); mp 62–63 °C; $[\alpha]_D^{20}$ +61.1 (*c* = 1, $CHCl_3$).

IR (ATR): 3266, 2922, 2850, 2215, 1702, 1622, 1611, 1460, 1378, 1351, 1302, 1271, 1188, 1155, 1128, 1107, 1077, 1021, 979, 871, 755, 719, 585, 499, 410 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.75 (dd, *J* = 15.9, 2.1 Hz, 1 H), 6.24 (d, *J* = 15.9 Hz, 1 H), 5.04–4.94 (m, 1 H), 4.61–4.54 (m, 1 H), 2.05–1.16 (m, 24 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 132.3, 124.4, 99.9, 82.8, 72.9, 63.1, 36.6, 34.2, 29.8, 29.7, 29.5, 29.2, 29.1, 28.5, 25.4, 23.9, 20.2.

HRMS-ESI: *m*/*z* calcd for $[C_{18}H_{28}O_3]^-$: 291.1668; found: 291.1966.

(3*E*,5*E*,7*R*,18*S*)-7-Hydroxy-18-methyl-6-(tributylstannyl)oxacyclooctadeca-3,5-dien-2-one (15)

[{Cp*RuCl}$_4$] (10 mg, 9.0 µmol, 2 mol%) was added to a solution of compound **14** (150 mg, 0.51 mmol) in CH_2Cl_2 (2.5 mL). A solution of Bu_3SnH (163 mg, 0.56 mmol) in CH_2Cl_2 (1 mL) was then added dropwise over 5 min. After stirring for 2 h at r.t., the solvent was evaporated. Purification of the residue by flash chromatography (silica gel, hexanes/EtOAc, 20:1 to 10:1) afforded the title compound as a pale yellow oil (196 mg, 66%). A second fraction containing the *cis*-isomer was also isolated and purified by preparative HPLC (8 mg, 3%); $[\alpha]_D^{20}$ –31.7 (*c* = 1, $CHCl_3$).

IR (ATR): 3464, 2953, 2922, 2852, 1707, 1688, 1619, 1565, 1460, 1376, 1354, 1258, 1186, 1125, 1072, 1019, 976, 903, 863, 757, 716, 666, 595, 536, 504 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (dd, *J* = 15.1, 11.5 Hz, 1 H), 6.81 (d, *J* = 11.6 Hz, J_{Sn-H} = 54.8 Hz, 1 H), 5.78 (d, *J* = 15.0 Hz, 1 H), 5.05 (dqd, *J* = 9.3, 6.3, 2.9 Hz, 1 H), 4.31 (dt, *J* = 9.3, 3.4 Hz, J_{Sn-H} = 26.1 Hz, 1 H), 1.71–1.58 (m, 2 H), 1.54–1.38 (m, 9 H), 1.35–1.06 (m, 22 H), 1.05–0.91 (m, 9 H), 0.84 (t, *J* = 7.3 Hz, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 166.8, 144.5, 137.0, 123.2, 80.3, 71.3, 36.1, 35.2, 29.9, 29.8, 29.5, 29.28, 29.25, 29.01, 28.96, 27.6, 25.2, 23.9, 20.6, 13.8, 11.8.

^{119}Sn NMR (186 MHz, $CDCl_3$): δ = –56.0.

HRMS-ESI: *m*/*z* calcd for $[C_{30}H_{56}O_3Sn + H]^+$: 585.3329; found: 585.3324.

(3*E*,5*Z*,7*R*,18*S*)-7-Hydroxy-18-methyl-6-(tributylstannyl)oxacyclooctadeca-3,5-dien-2-one [(5*Z*)-15]

Minor isomer formed in the reaction described above, which was isolated and purified by preparative HPLC (8 mg, 3%).

IR (ATR): 3500, 2953, 2923, 2854, 1710, 1691, 1569, 1460, 1419, 1376, 1357, 1337, 1268, 1186, 1125, 1072, 1021, 979, 893, 876, 845, 804, 769, 722, 665, 596, 548, 505, 435, 408 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.51 (ddt, *J* = 15.2, 11.0, 3.3 Hz, 1 H), 6.33 (dd, *J* = 11.2, 1.6 Hz, J_{Sn-H} = 30.8 Hz, 1 H), 5.81 (d, *J* = 15.0 Hz, 1 H), 5.18 (ddp, *J* = 9.5, 6.3, 3.1 Hz, 1 H), 5.03 (t, *J* = 7.3 Hz, J_{Sn-H} = 32.0 Hz, 1 H), 1.65–1.11 (m, 37 H), 0.99–0.92 (m, 5 H), 0.89 (t, *J* = 7.3 Hz, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.5, 166.5, 138.7, 134.6, 121.2, 72.2, 69.6, 37.8, 36.0, 29.8, 29.2, 28.7, 28.4, 27.7, 27.6, 26.6, 25.3, 24.2, 21.0, 13.9, 10.9.

^{119}Sn NMR (186 MHz, $CDCl_3$): δ = –40.2.

HRMS-ESI: *m*/*z* calcd for $[C_{30}H_{56}O_3Sn + Na]^+$: 607.3148; found: 607.3143.

(3*E*,5*E*,7*R*,18*S*)-7-Hydroxy-18-methyloxacyclooctadeca-3,5-dien-2-one (16)

CuTC (65 mg, 0.34 mmol) was added to a solution of stannane **15** (100 mg, 0.17 mmol) in DMF (2 mL) and the resulting mixture was stirred for 1 h at r.t. before H_2O (5 mL) was added. The aqueous layer was extracted with EtOAc (3 × 10 mL), the combined extracts were dried ($MgSO_4$), filtered, and the solvent was evaporated. Purification of the residue by flash chromatography (silica gel, hexanes/EtOAc, 10:1 to 4:1) afforded the title compound as a colorless oil (42 mg, 83%); $[\alpha]_D^{20}$ +14.2 (*c* = 1, $CHCl_3$).

IR (ATR): 3412, 2925, 2854, 1701, 1644, 1618, 1460, 1355, 1296, 1260, 1178, 1124, 999, 910, 883, 730, 647, 411 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.24 (dd, *J* = 15.4, 10.9 Hz, 1 H), 6.32 (dd, *J* = 15.2, 10.9 Hz, 1 H), 6.07 (dd, *J* = 15.2, 7.9 Hz, 1 H), 5.85 (d, *J* = 15.4 Hz, 1 H), 5.02 (dqd, *J* = 9.4, 6.3, 3.2 Hz, 1 H), 4.27 (td, *J* = 8.3, 3.7 Hz, 1 H), 1.82–1.73 (m, 1 H), 1.69–1.54 (m, 4 H), 1.50–1.37 (m, 2 H), 1.28 (d, *J* = 6.3 Hz, 3 H), 1.33–1.12 (m, 14 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 145.1, 143.6, 128.4, 122.6, 73.3, 71.5, 35.5, 35.4, 29.7, 29.14, 29.10, 29.05, 28.8, 24.8, 23.4, 20.6.

HRMS-ESI: *m*/*z* calcd for $[C_{18}H_{30}O_3 + Na]^+$: 317.2087; found: 317.2087.

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Supporting Information

Copies of spectra of new compounds for this article is available online at http://dx.doi.org/10.1055/s-0035-1562381.

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