Enantioselective Synthesis of Herbarumin III by Using a Chelation-Controlled Reduction

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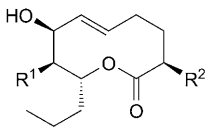
The total synthesis of herbarumin III (**1**) was achieved *via* an alkynide ion addition onto a chiral aldehyde and $LiAlH_4$/LiI reduction as key steps (*Scheme 2*).

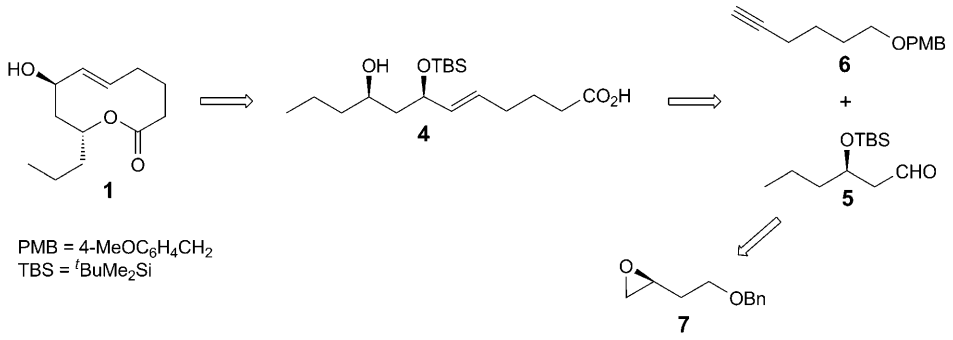
Introduction. – Natural lactones with a medium ring size between eight to eleven [1] are attracting the attention of several groups because of their significant biological importance, but their syntheses are challenging. The phytotoxic lactone herbarumin III (**1**) was isolated by *Mata* and co-workers from the fermentation broth and mycelium of the fungus *Phoma herbarum* along with herbarumin I (**2**) and II (**3**) [2]. The structure of **1** was elucidated by spectroscopic methods combined with molecular modeling. Herbarumin III showed significant phytotoxic effects when tested against seedlings of *A. hypochondriacus* [3]. The herbarumin macrolides **1**–**3** interact with bovine-brain calmodulin and inhibited the activation of the calmodulin-dependent enzyme camp phosphodiesterase. Considering its structure and selective biological profile, herbarumin III has attracted a great deal of interest among synthetic organic chemists. Consequently, the synthesis of **1** has been reported by various research groups [4]. Herein, we report a protocol for the synthesis of herbarumin III based on an alkynide ion addition onto a chiral aldehyde and reagent-controlled synthesis.



Herbarumin III (**1**) $R^1 = R^2 = H$
Herbarumin I (**2**) $R^1 = OH$, $R^2 = H$
Herbarumin II (**3**) $R^1 = R^2 = OH$

Retrosynthetically (*Scheme 1*), the macrolactone ring of **1** could be constructed by *Yamaguchi*'s lactonization method at the final stage, and the corresponding hydroxy acid **4** would be prepared from aldehyde **5** and PMB-protected 5-hexyn-1-ol **6** by alkynide ion addition onto the chiral aldehyde (PMB = 4-methoxybenzyl). Aldehyde **5** could be made from the known chiral oxirane **7**. The *syn*-1,3-diol moiety of **4** could be introduced by using a chelation-controlled reduction reaction.

Scheme 1. *Retrosynthetic Analysis*



Results and Discussion. – Accordingly, the synthesis started with the known chiral oxirane **7** (*Scheme 2*). Ring opening of **7** with EtMgBr in the presence of CuI in THF gave alcohol **8**, which was protected as its ^{t}BuMe$_2$Si ether **9**, and subsequent debenzylation with Li in liquid NH_3 afforded compound **10**. Further oxidation of alcohol **10** with iodoxybenzoic acid (=1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide; IBX) in DMSO furnished aldehyde **5** which was taken to the next step without purification. To prepare alkynol **11**, alkyne **6**[1]) was treated with BuLi in THF at $-78°$, and the resulting alkynide was quenched with aldehyde **5** to furnish **11** as a diastereomer mixture. Oxidation of alkynol **11** with IBX in DMSO gave ketone **12**, which on subsequent removal of the silyl protecting group furnished compound **13**. A highly *syn*-stereoselective 1,3-asymmetric reduction was carried out with $LiAlH_4$/LiI [5] in Et_2O at $-100°$ to provide the desired *syn*-diol **14** in 85% yield (*syn*/*anti* 95:5). Alkenediol **14** was selectively protected as ^{t}BuMe$_2$Si ether at the allylic position leaving the other OH group intact (→**15**). The next task was to release the PMB group (4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (DDQ) [6], CH_2Cl_2/H_2O, room temp.; 91%) in order to oxidize the ensuing alcohol **16** into an acid. Accordingly, the primary alcohol **16** was oxidized to the corresponding acid by a two-step process, firstly to an aldehyde with 2,2,6,6-tetramethylpiperidin-1-yloxy (TEMPO) and bis(acetoxy)iodobenzene (BAIB) in CH_2Cl_2, followed by further oxidation with perchlorite/dihydrogen orthophosphate ($NaClO_2$, $NaH_2PO_4 \cdot 2\,H_2O$, DMSO) [7] to afford the acid **4** (83% over two steps). Lactonization was achieved by applying *Yamaguchi*'s protocol. The hydroxy acid **4** when treated with 2,4,6-trichlorobenzoyl chloride in refluxing toluene in the presence of Et_3N and *N*,*N*-dimethylpyridin-4-amine (DMAP), gave, the required lactone **17** in 70% yield.

Finally, ^{t}BuMe$_2$Si deprotection was carried out with Bu_4NF to furnish the target molecule **1** in 90% yield. The ^{1}H- and ^{13}C-NMR data and optical-rotation value of synthetic **1** were in good accordance with those of the natural product.

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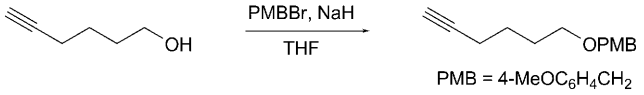
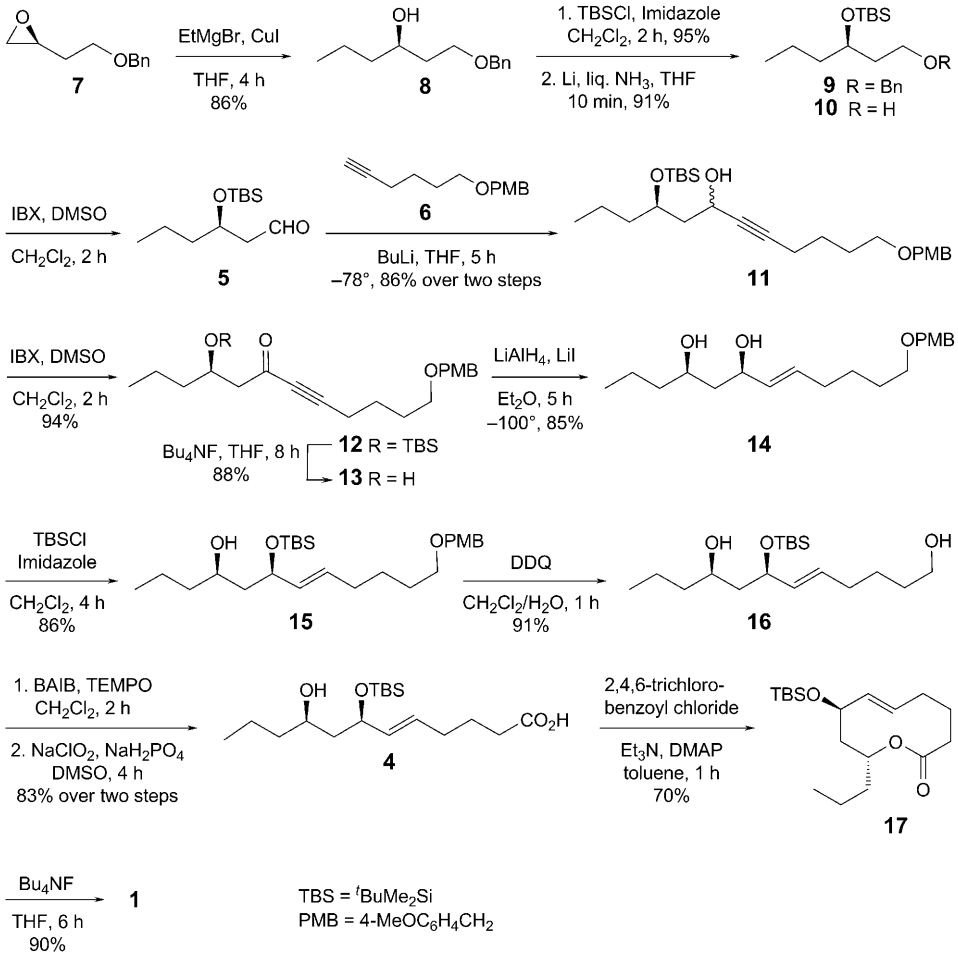
[1]) Hex-5-yn-1-ol was protected as its PMB ether by the standard procedure:



Scheme 2



Conclusions. – In conclusion, an enantioselective total synthesis of herbarumin III (**1**) was achieved *via* an alkynide ion addition onto a chiral aldehyde, a $LiAlH_4$/LiI reduction, and the *Yamaguchi*'s protocol as key steps.

C. S. thanks *UGC*, and *C. M.* thanks *CSIR*, New Delhi, for the award of fellowships.

Experimental Part

General. Reactions were conducted under N_2 in anh. solvents such as CH_2Cl_2, THF, and AcOEt (TLC monitoring). Light petroleum ether (b.p. 60–80°) was used. Yields refer to chromatographically and spectroscopically (^{1}H- and ^{13}C-NMR) homogeneous material. Air-sensitive reagents were transferred by syringe or double-ended needle. TLC: *Merck 60 F_{254}* SiO_2 plates; visualization under UV light. Column chromatography (CC): SiO_2 (60–120 mesh; *Acme Chemical Co.*, India). Optical rotations: *JASCO-DIP-370* polarimeter; at 25°. IR: *Thermo Nicolet Nexus-670* FT-IR spectrometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H-

and ^{13}C-NMR Spectra: *Varian-FT-200* (*Gemini*) and *Bruker-UXNMR-FT-300* (*Avance*) spectrometers; in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, J in Hz. MS: *LC-MSD* spectrometers (*Agilent Technologies*) under EI conditions at 70 eV; in *m/z* (rel. %). HR-MS: *QSTAR-XL* hybrid MS/MS system (*Applied Biosystems/MDS Sciex*, Foster City, CA, USA), equipped with an ESI source (*IICT*, Hyderabad).

*(3*R*)-1-(Benzyloxy)hexan-3-ol* (**8**). To a suspension of Mg (1.08 g, 44.88 mmol) in dry THF (30 ml), EtBr (3.46 ml, 44.88 mmol) was added dropwise under N_2 at 0°. The mixture was stirred for 1 h at r.t. A catalytic amount of CuI was then added at 0° to the suspension of *Grignard* reagent, and the mixture was stirred at 0° for 30 min. Oxirane **7** (4 g, 22.44 mmol) in dry THF (15 ml) was then added dropwise at 0° and stirred at r.t. for *ca.* 30 min. After completion of the reaction, the mixture was quenched with sat. aq. NH_4Cl soln. and extracted with AcOEt (3×50 ml). The org. layer was washed with brine, dried (Na_2SO_4), and concentrated. Purification by CC (SiO_2) afforded **8** (4.02 g, 86%). Viscous liquid. $[\alpha]_D^{25} = +3.88$ ($c = 6$, $CHCl_3$). IR (neat): 3433, 2946, 2866, 1715, 1454, 1275, 1099, 738, 699. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.24–7.35 (*m*, 5 H); 4.51 (*s*, 2 H); 3.73–3.82 (*m*, 1 H); 3.57–3.73 (*m*, 2 H); 2.69 (br. *s*, 1 H); 1.66–1.74 (*m*, 2 H); 1.32–1.50 (*m*, 4 H); 0.93 (*t*, $J = 7.5$, 3 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 137.8; 129.5; 128.3; 127.6; 73.2; 71.0; 69.1; 39.5; 36.3; 18.7; 14.1. ESI-MS: 209 ($[M + Na]^+$). HR-ESI-MS: 231.1349 ($[M + Na]^+$, $C_{13}H_{20}NaO_2^+$; calc. 231.1361).

*{(1*R*)-1-[2-(Benzyloxy)ethyl]butoxy}(*tert*-butyl)dimethylsilane* (**9**). To a stirred soln. of **8** (3.8 g, 18.24 mmol) and 1*H*-imidazole (2.48 g, 36.48 mmol) in dry CH_2Cl_2 (50 ml) was added ^{t}BuMe$_2$SiCl (4.12 g, 27.36 mmol), portionwise at 0°. The mixture was stirred at 0° for 2 h and then quenched with sat. aq. NH_4Cl soln. and extracted with CH_2Cl_2 (3×50 ml). The extract was washed with H_2O (50 ml) and brine (50 ml), dried (Na_2SO_4), and concentrated and the residue purified by CC (SiO_2): **9** (5.58 g, 95%). Colorless liquid. $[\alpha]_D^{25} = -6.24$ ($c = 5$, $CHCl_3$). IR (neat): 2954, 2931, 2858, 1744, 1462, 1252, 1109, 1073, 835, 774, 697. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.24–7.31 (*m*, 5 H); 4.45 (*AB q*, $J = 12.1$, 18.1, 2 H); 3.79–3.86 (*m*, 1 H); 3.42–3.52 (*m*, 2 H); 1.63–1.77 (*m*, 2 H); 1.26–1.46 (*m*, 4 H); 0.90 (*t*, $J = 7.4$, 3 H); 0.86 (*s*, 9 H); 0.03 (*s*, 3 H); 0.02 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 138.6; 128.3; 127.6; 127.4; 72.9; 69.3; 67.2; 39.8; 36.9; 25.9; 18.3; 18.1; 14.3; −4.4; −4.6. ESI-MS: 345 ($[M + Na]^+$). HR-ESI-MS: 345.2213 ($[M + Na]^+$, $C_{19}H_{34}NaO_2Si^+$; calc. 345.2226).

*(3*R*)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}hexan-1-ol* (**10**). Lithium metal (0.325 g, 46.5 mmol) was added to a stirred soln. of freshly dist. NH_3 (50 ml) and **9** (5 g, 15.5 mmol) in dry THF (15 ml) (250 ml two-necked round-bottomed flask fitted with a cold-finger condenser at −33°). The mixture was then stirred for another 10 min at −33° and quenched by the addition of solid NH_4Cl, and NH_3 was then allowed to diffuse. The residue left was partitioned between H_2O (50 ml) and Et_2O (50 ml), and the aq. phase was extracted with Et_2O (2×50 ml). The combined org. layers were washed with H_2O (50 ml) and brine (50 ml), dried (Na_2SO_4), and concentrated. The residue was purified by CC (SiO_2): pure **10** (3.27 g, 91%). Clear colorless liquid. $[\alpha]_D^{25} = -11.27$ ($c = 5$, $CHCl_3$). IR (neat): 3362, 2948, 2863, 1464, 1474, 1253, 1051, 835, 755, 716, 699. ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.86–3.95 (*m*, 1 H); 3.74–3.85 (*m*, 1 H); 3.61–3.71 (*m*, 1 H); 2.15 (*t*, $J = 5.3$, 1 H); 1.73–1.85 (*m*, 1 H); 1.56–1.67 (*m*, 1 H); 1.45–1.55 (*m*, 2 H); 1.24–1.37 (*m*, 2 H); 0.92 (*t*, $J = 6.8$, 3 H); 0.90 (*s*, 9 H); 0.09 (*s*, 3 H); 0.07 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 71.7; 60.2; 39.1; 37.4; 25.8; 18.5; 17.93; 14.2; −4.5; −4.8. ESI-MS: 233 ($[M + 1]^+$). HR-ESI-MS: 255.1764 ($[M + Na]^+$, $C_{12}H_{28}NaO_2Si^+$; calc. 255.1756).

*(3*R*)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}hexanal* (**5**). To an ice-cooled soln. of 2-iodoxybenzoic acid (5.42 g, 19.36 mmol) in dry DMSO (5.5 ml, 77.44 mmol) was added a soln. of **10** (3 g, 12.90 mmol) in dry CH_2Cl_2 (50 ml). The mixture was stirred at r.t. for 2 h and then filtered through a *Celite* pad and washed with Et_2O. The combined org. filtrates were washed with H_2O (40 ml) and brine (40 ml), dried (Na_2SO_4), and concentrated. The unstable crude aldehyde **5** was immediately used for the next reaction.

*(4*R*)-4-{[(*tert*-Butyl)dimethylsilyl]oxy}-12-[(4-methoxybenzyl)oxy]dodec-7-yn-6-ol* (**11**). To a soln. of **6** (2.7 g, 12.36 mmol) in dry THF (40 ml) was slowly added 2.5M BuLi in hexanes (5.44 ml, 13.59 mmol) at −78° under N_2. The mixture was stirred for 30 min at −78°, and a soln. (2.85 g, 12.36 mmol) of **5** in THF (10 ml) was added dropwise under stirring. The mixture was kept at −78° for 2 h and then allowed to warm to r.t. for 2 h. The reaction was quenched with sat. aq. NH_4Cl soln., the mixture extracted with AcOEt (3×50 ml), the extract dried (Na_2SO_4) and concentrated, and the crude product purified by CC (SiO_2): 4.98 g (86% over two steps) of **11**.

*(4*R*)-4-[[(*tert*-Butyl)dimethylsilyl]oxy}-12-[(4-methoxybenzyl)oxy]dodec-7-yn-6-one* (**12**). As described for **5**, with 2-iodoxybenzoic acid (3.55 g, 12.70 mmol), DMSO (3.6 ml, 50.81 mmol), **11** (3.8 g, 8.47 mmol), and CH_2Cl_2 (40 ml). Washing with H_2O (50 ml) and brine (50 ml) and CC (SiO_2) afforded **12** (3.55 g, 94%). Viscous liquid. $[\alpha]_D^{25} = -8.7$ ($c = 3$, $CHCl_3$). IR (neat): 3453, 2955, 2931, 2856, 2211, 1673, 1612, 1512, 1463, 1248, 1101, 1038, 834, 755. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.19 (*d*, *J* = 9.1, 2 H); 6.82 (*d*, *J* = 9.1, 2 H); 4.40 (*s*, 2 H); 4.18–4.26 (*m*, 1 H); 3.80 (*s*, 3 H); 3.43 (*t*, *J* = 6.0, 2 H); 2.67 (*dd*, *J* = 6.8, 15.1, 1 H); 2.55 (*dd*, *J* = 5.3, 15.1, 1 H); 2.39 (*t*, *J* = 6.8, 2 H); 1.66–1.73 (*m*, 4 H); 1.27–1.51 (*m*, 4 H); 0.92 (*t*, *J* = 7.5, 3 H); 0.87 (*s*, 9 H); 0.06 (*s*, 3 H); 0.04 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 186.5; 159.1; 130.5; 129.2; 113.7; 94.1; 81.6; 72.6; 69.1; 68.8; 55.2; 53.3; 39.9; 28.9; 25.7; 24.6; 18.7; 18.2; 18.0; 14.1; −4.5; −4.7. ESI-MS: 469 ($[M + Na]^+$). HR-ESI-MS: 469.2738 ($[M + Na]^+$, $C_{26}H_{42}NaO_4Si^+$; calc. 469.2750).

*(4*R*)-4-Hydroxy-12-[(4-methoxybenzyl)oxy]dodec-7-yn-6-one* (**13**). To a soln. of **12** (3.4 g, 7.61 mmol) in THF (30 ml) was added 1.0M Bu_4NF in THF (11.41 ml, 11.41 mmol) at 0°. The mixture was stirred for 8 h and then diluted with H_2O and extracted with AcOEt (3 × 50 ml). The org. layer was washed with H_2O (50 ml) and brine (50 ml), dried (Na_2SO_4), and concentrated and the crude product purified by CC (SiO_2): **13** (2.22 g, 88%). Colorless oil. $[\alpha]_D^{25} = +29.9$ ($c = 3$, $CHCl_3$). IR (neat): 3445, 2956, 2869, 2211, 1717, 1665, 1602, 1512, 1250, 1168, 1101, 1030, 824, 769. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.19 (*d*, *J* = 8.3, 2 H); 6.82 (*d*, *J* = 8.3, 2 H); 4.39 (*s*, 2 H); 4.25–4.36 (*m*, 1 H); 3.79 (*s*, 3 H); 3.40 (*t*, *J* = 6.1, 2 H); 2.55–2.72 (*m*, 1 H); 2.18–2.43 (*m*, 3 H); 1.24–1.82 (*m*, 8 H); 0.97 (*t*, *J* = 6.8, 3 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 193.4; 159.1; 131.9; 129.2; 113.7; 95.1; 81.1; 78.9; 72.5; 69.3; 55.2; 52.3; 40.9; 34.5; 29.0; 18.7; 18.1; 13.7. HR-ESI-MS: 355.1875 ($[M + Na]^+$, $C_{20}H_{28}NaO_4^+$; calc. 355.1885).

*(4*R*,6*R*,7*E*)-12-[(4-Methoxybenzyl)oxy]dodec-7-ene-4,6-diol* (**14**). To a stirred soln. of **13** (2.1 g, 6.32 mmol) in Et_2O (100 ml) was added LiI (8.45 g, 63.16 mmol), and the resulting mixture was stirred at −40° for 30 min. Then, the mixture was cooled to −100°, and $LiAlH_4$ (2.87 g, 75.80 mmol) was added. The mixture was stirred for 1 h at −100° and then for 3 h at r.t. After quenching with 10% aq. potassium sodium tartrate soln., the aq. layer was extracted with Et_2O (4 × 50 ml), the combined org. layer dried (Na_2SO_4) and concentrated, and the residue purified by CC (SiO_2): **14** (1.83 g, 85%). Colorless oil. $[\alpha]_D^{25} = +2.94$ ($c = 4$, $CHCl_3$). IR (neat): 3392, 2934, 2860, 1611, 1513, 1453, 1247, 1094, 1034, 825. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.19 (*d*, *J* = 8.3, 2 H); 6.82 (*d*, *J* = 8.3, 2 H); 5.61 (*dt*, *J* = 6.8, 15.5, 1 H); 5.45 (*dd*, *J* = 6.8, 15.5, 1 H); 4.39 (*s*, 2 H); 4.24–4.30 (*m*, 1 H); 3.78–3.86 (*m*, 1 H); 3.79 (*s*, 3 H); 3.39 (*t*, *J* = 6.8, 2 H); 2.04 (*t*, *J* = 6.8, 2 H); 1.52–1.66 (*m*, 2 H); 1.25–1.50 (*m*, 8 H); 0.93 (*t*, *J* = 6.8, 3 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 157.9; 154.8; 132.8; 131.4; 129.2; 113.7; 73.7; 72.5; 72.1; 69.9; 55.3; 43.4; 40.2; 31.8; 29.1; 25.6; 18.5; 14.1. ESI-MS: 355 ($[M + Na]^+$). HR-ESI-MS: 359.2187 ($[M + Na]^+$, $C_{20}H_{32}NaO_4^+$; calc. 359.2198).

*(4*R*,6*R*,7*E*)-6-[[(*tert*-Butyl)dimethylsilyl]oxy}-12-[(4-methoxybenzyl)oxy]dodec-7-en-4-ol* (**15**). As described for **9**, with **14** (1.6 g, 4.75 mmol), 1*H*-imidazole (0.667 g, 9.51 mmol), CH_2Cl_2 (20 ml), and ^{t}BuMe$_2$SiCl (1.07 g, 7.13 mmol); for 4 h. Extraction with CH_2Cl_2 (3 × 40 ml and then 2 × 30 ml), washing with H_2O (30 ml) and brine (30 ml), and purification by CC (SiO_2) afforded **15** (1.84 g, 86%). Colorless liquid. $[\alpha]_D^{25} = +12.56$ ($c = 5$, $CHCl_3$). IR (neat): 3472, 2929, 2856, 1743, 1613, 1513, 1463, 1249, 1092, 1039, 835. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.18 (*d*, *J* = 8.3, 2 H); 6.81 (*d*, *J* = 8.3, 2 H); 5.52 (*dt*, *J* = 7.3, 15.6, 1 H); 5.39 (*dd*, *J* = 7.3, 15.6, 1 H); 4.38 (*s*, 2 H); 4.24–4.30 (*m*, 1 H); 3.78 (*s*, 3 H); 3.69–3.75 (*m*, 1 H); 3.39 (*t*, *J* = 6.2, 2 H); 1.98–2.07 (*m*, 2 H); 1.54–1.62 (*m*, 3 H); 1.40–1.49 (*m*, 3 H); 1.31–1.39 (*m*, 4 H); 0.92 (*t*, *J* = 7.3, 3 H); 0.89 (*s*, 9 H); 0.08 (*s*, 3 H); 0.03 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 159.1; 133.5; 132.1; 130.9; 129.2; 113.7; 75.3; 72.5; 70.8; 69.8; 55.2; 44.7; 39.8; 31.8; 29.3; 25.8; 25.7; 18.5; 18.0; 14.1; −3.6; −4.7. ESI-MS: 473 ($[M + Na]^+$). HR-ESI-MS: 473.3052 ($[M + Na]^+$, $C_{26}H_{46}NaO_4Si^+$; calc. 473.3063).

*(5*E*,7*R*,9*R*)-7-[[(*tert*-Butyl)dimethylsilyl]oxy}dodec-5-ene-1,9-diol* (**16**). To a soln. of **15** (1.6 g, 3.55 mmol) in CH_2Cl_2/H_2O 19:1 (30 ml), DDQ (1.208 g, 5.32 mmol) was added and the soln. stirred for 1 h at r.t. The mixture was filtered off and the filtrate washed with 5% $NaHCO_3$ soln. (30 ml) and brine (30 ml), dried (Na_2SO_4), and concentrated. Purification by CC gave **16** (1.06 g, 91%). $[\alpha]_D^{25} = +0.7$ ($c = 1.8$, $CHCl_3$). IR (neat): 3396, 2930, 2854, 1740, 1612, 1515, 1455, 1246, 1093, 1035, 829. ^{1}H-NMR ($CDCl_3$, 500 MHz): 5.55 (*dt*, *J* = 6.8, 15.6, 1 H); 5.41 (*dd*, *J* = 6.8, 15.6, 1 H); 4.26–4.32 (*m*, 1 H); 3.71–3.77 (*m*, 1 H); 3.62 (*t*, *J* = 6.8, 2 H); 2.02–2.11 (*m*, 2 H); 1.24–1.70 (*m*, 10 H); 0.92 (*t*, *J* = 6.8, 3 H); 0.90 (*s*, 9 H); 0.09 (*s*, 3 H); 0.04 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 133.6; 130.8; 75.2; 70.8; 62.7; 44.7; 39.8; 32.3;

31.8; 25.8; 25.2; 18.5; 18.0; 14.1; −3.6; −4.7. ESI-MS: 353 ($[M+Na]^+$). HR-ESI-MS: 353.2475 ($[M+Na]^+$, $C_{18}H_{38}NaO_3Si^+$; calc. 353.2488).

*(5*E*,7*R*,9*R*)-7-{[(*tert*-Butyl)dimethylsilyl]oxy}-9-hydroxydodec-5-enoic Acid* (**4**). BAIB (0.847g, 2.66 mmol) was added to a soln. of **16** (0.8 g, 2.42 mmol) and TEMPO (0.038 g, 0.242 mmol) in CH_2Cl_2 (1 ml). The mixture was stirred until **16** was no longer detectable (TLC). Then the mixture was diluted with CH_2Cl_2 (20 ml), washed with sat. aq. $Na_2S_2O_3$ soln. (20 ml), and extracted with CH_2Cl_2 (4 × 20 ml). The combined org. extracts were washed with aq. $NaHCO_3$ soln. (30 ml) and brine (30 ml), dried (Na_2SO_4), and concentrated. The unstable crude aldehyde was immediately used for the next reaction.

A soln. of $NaClO_2$ (0.33 g, 3.65 mmol) in H_2O (2 ml) was added dropwise within 5 min at r.t. to a stirred soln. of the above crude aldehyde (0.8 g, 2.43 mmol) in DMSO (5 ml) and NaH_2PO_4 (0.759 g, 4.869 mmol) in H_2O (5 ml). The mixture was left overnight at r.t., and then 5% aq. $NaHCO_3$ soln. was added. The aq. phase was extracted with CH_2Cl_2 (3 × 30 ml), the extract washed with brine (30 ml), dried (Na_2SO_4), and concentrated, and the residue purified by CC (SiO_2). **4** (0.692 g, 83% over two steps). Yellowish liquid. $[\alpha]_D^{25} = +14.0$ ($c = 5$, $CHCl_3$). IR (neat): 3397, 2956, 2930, 2858, 1711, 1613, 1460, 1251, 1074, 977, 837. ^{1}H-NMR ($CDCl_3$, 500 MHz): 5.53 (*dt*, $J = 6.8, 15.6$, 1 H); 5.44 (*dd*, $J = 6.8, 15.6$, 1 H); 4.27–4.33 (*m*, 1 H); 3.70–3.78 (*m*, 1 H); 2.35 (*t*, $J = 6.8$, 2 H); 2.06–2.18 (*m*, 2 H); 1.69–1.78 (*m*, 2 H); 1.25–1.64 (*m*, 6 H); 0.93 (*t*, $J = 5.8$, 3 H); 0.90 (*s*, 9 H); 0.10 (*s*, 3 H); 0.04 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 178.9; 134.4; 129.7; 75.1; 70.9; 44.6; 39.7; 33.3; 31.3; 25.8; 24.0; 18.5; 18.1; 14.1; −3.6; −4.7. ESI-MS: 367 ($[M+Na]^+$). HR-ESI-MS: 367.2272 ($[M+Na]^+$, $C_{18}H_{36}NaO_4Si^+$; calc. 367.2281).

*(6*E*,8*R*,10*R*)-8-{[(*tert*-Butyl)dimethylsilyl]oxy}-3,4,5,8,9,10-hexahydro-10-propyl-2 H-oxecin-2-one* (**17**). The 2,4,6-trichlorobenzoyl chloride (0.272 ml, 1.74 mmol) was added to a soln. of **4** (0.4 g, 1.16 mmol) and Et_3N (0.245 mg, 1.74 mmol) in THF (3 ml). The soln. was stirred at r.t. for 3 h, diluted with toluene (6 ml), and added into a refluxing soln. of DMAP (0.709 g, 5.80 mmol) and toluene (50 ml). The mixture was refluxed for 6 h and cooled to r.t. Sat. aq. $NaHCO_3$ soln. was added, the aq. layer further extracted with AcOEt (3 × 20 ml), the combined org. layer washed with H_2O (20 ml) and brine (20 ml), dried (Na_2SO_4), and concentrated, and the crude product purified by CC: **17** (0.265 g, 70%). Colorless oil. $[\alpha]_D^{25} = +5.0$ ($c = 5$, $CHCl_3$). IR (neat): 2956, 2929, 2856, 1732, 1485, 1341, 1252, 1199, 1100, 940, 836. ^{1}H-NMR ($CDCl_3$, 500 MHz): 5.45–5.52 (*m*, 2 H); 5.24–5.32 (*m*, 1 H); 4.35–4.41 (*m*, 1 H); 2.20–2.38 (*m*, 2 H); 1.89–2.02 (*m*, 2 H); 1.67–1.79 (*m*, 2 H); 1.23–1.48 (*m*, 6 H); 0.94 (*s*, 9 H); 0.92 (*t*, $J = 6.9$, 3 H); 0.03 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 178.9; 134.4; 129.7; 75.1; 70.9; 44.6; 39.7; 33.3; 31.3; 25.8; 24.0; 18.5; 18.1; 14.1; −3.6; −4.7. ESI-MS: 349 ($[M+Na]^+$). HR-ESI-MS: 349.2159 ($[M+Na]^+$, $C_{18}H_{34}NaO_3Si^+$; calc. 349.2175).

*(6*E*,8*R*,10*R*)-3,4,5,8,9,10-Hexahydro-8-hydroxy-10-propyl-2*H*-oxecin-2-one* (**1**). As described for **13**, with **17** (0.15 g, 0.459 mmol), THF (10 ml), and 1M Bu_4NF in THF (0.689 ml, 0.689 mmol); for 6 h. Workup with AcOEt (3 × 10 ml), H_2O (20 ml), and brine (20 ml). CC (SiO_2) gave **1** (0.087 g, 90%). Colorless oil. $[\alpha]_D^{25} = +20.9$ ($c = 2.5$, EtOH). IR (neat): 3443, 2930, 2859, 1731, 1636, 1452, 1253, 1205, 1094, 770. ^{1}H-NMR ($CDCl_3$, 500 MHz): 5.57 (*d*, $J = 16.1$, 1 H); 5.38–5.48 (*m*, 1 H); 5.19–5.27 (*m*, 1 H); 4.33–4.40 (*m*, 1 H); 2.34–2.44 (*m*, 1 H); 2.22–2.31 (*m*, 1 H); 1.88–2.03 (*m*, 3 H); 1.84–1.87 (*m*, 1 H); 1.80–1.84 (*m*, 1 H); 1.72–1.79 (*m*, 1 H); 1.49–1.58 (*m*, 1 H); 1.37–1.47 (*m*, 1 H); 1.28–1.36 (*m*, 2 H); 0.91 (*t*, $J = 7.2$, 3 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 176.8; 134.5; 124.8; 67.9; 67.8; 40.5; 37.4; 34.6; 33.6; 25.9; 18.4; 13.8. ESI-MS: 235 ($[M+Na]^+$). HR-ESI-MS: 235.1309 ($[M+Na]^+$, $C_{12}H_{20}NaO_3^+$; calc. 235.1310).

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