

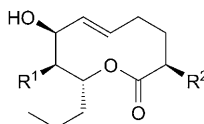
Enantioselective Synthesis of Herbarumin III by Using a Chelation-Controlled Reduction

by Gowravaram Sabitha*, Chitti Srinivas, Chittapragada Maruthi, and Jhillu Singh Yadav

Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500007, India
(phone: + 91-40-27160512; fax: + 91-40-27160512; e-mail: gowravaramsr@yahoo.com)

The total synthesis of herbarumin III (**1**) was achieved *via* an alkynide ion addition onto a chiral aldehyde and $\text{LiAlH}_4/\text{LiI}$ 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.



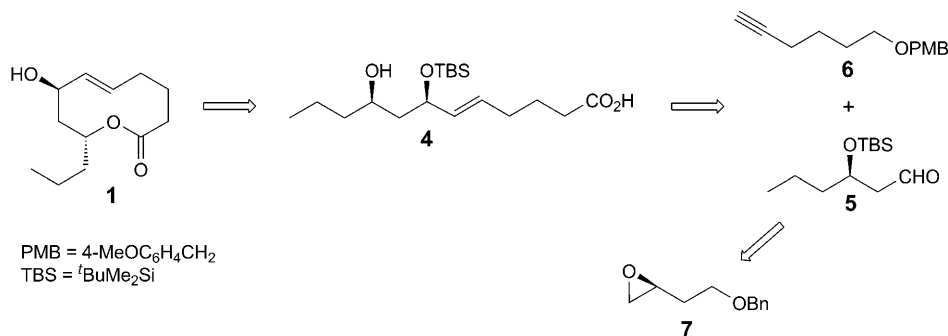
Herbarumin III (**1**) $\text{R}^1 = \text{R}^2 = \text{H}$

Herbarumin I (**2**) $\text{R}^1 = \text{OH}, \text{R}^2 = \text{H}$

Herbarumin II (**3**) $\text{R}^1 = \text{R}^2 = \text{OH}$

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.

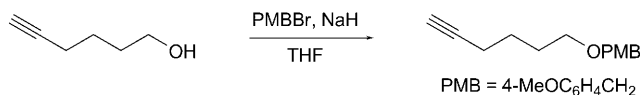
Scheme 1. Retrosynthetic Analysis



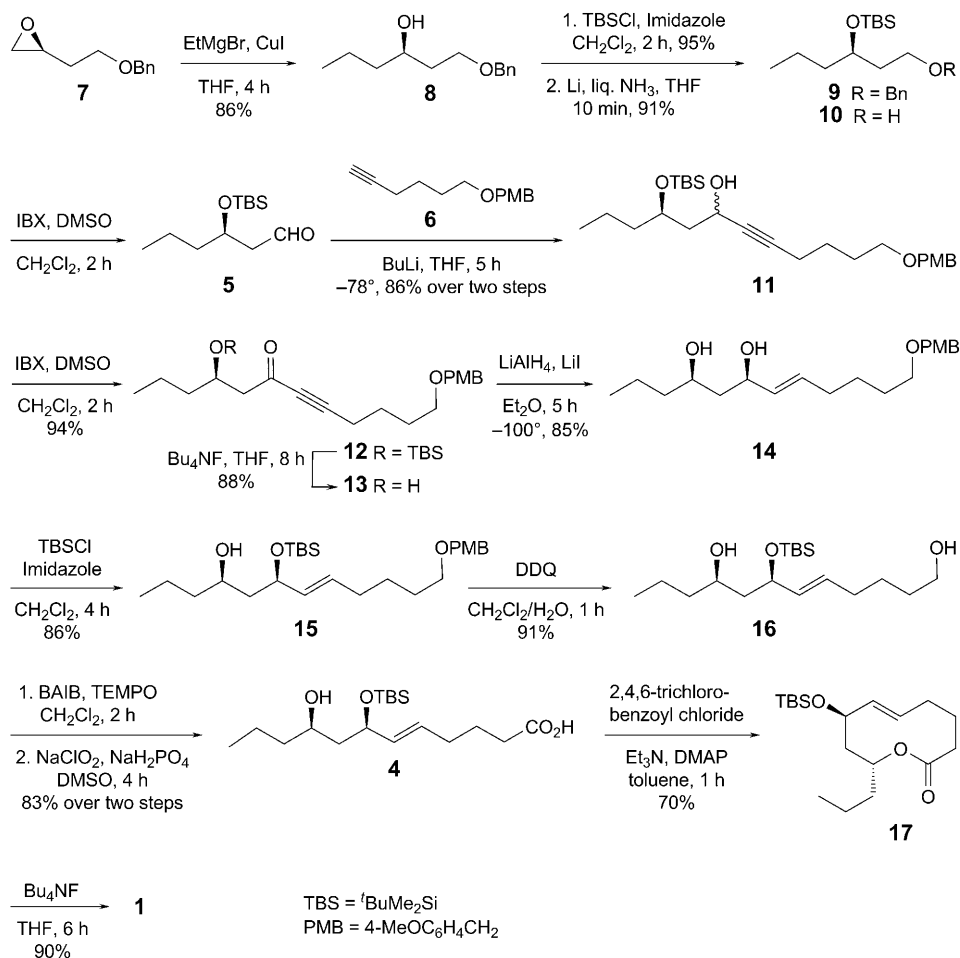
Results and Discussion. – Accordingly, the synthesis started with the known chiral oxirane **7** (Scheme 2). Ring opening of **7** with EtMgBr in the presence of CuI in THF gave alcohol **8**, which was protected as its ^tBuMe₂Si ether **9**, and subsequent debenzoylation with Li in liquid NH₃ afforded 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 LiAlH₄/LiI [5] in Et₂O at –100° to provide the desired *syn*-diol **14** in 85% yield (*syn/anti* 95:5). Alkenediol **14** was selectively protected as ^tBuMe₂Si 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], CH₂Cl₂/H₂O, 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 CH₂Cl₂, followed by further oxidation with perchlorite/dihydrogen orthophosphate (NaClO₂, NaH₂PO₄·2 H₂O, 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 Et₃N and *N,N*-dimethylpyridin-4-amine (DMAP), gave, the required lactone **17** in 70% yield.

Finally, ^tBuMe₂Si deprotection was carried out with Bu₄NF to furnish the target molecule **1** in 90% yield. The ¹H- and ¹³C-NMR data and optical-rotation value of synthetic **1** were in good accordance with those of the natural product.

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 $\text{LiAlH}_4/\text{LiI}$ 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. $60\text{--}80^\circ$) was used. Yields refer to chromatographically and spectroscopically (^1H - 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} . ^1H -

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).

(3R)-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. ^1H -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 ($[M + \text{Na}]^+$). HR-ESI-MS: 231.1349 ($[M + \text{Na}]^+$, $\text{C}_{13}\text{H}_{20}\text{NaO}_2^+$; calc. 231.1361).

{(1R)-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 BuMe_2SiCl (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. ^1H -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 ($[M + \text{Na}]^+$). HR-ESI-MS: 345.2213 ($[M + \text{Na}]^+$, $\text{C}_{19}\text{H}_{34}\text{NaO}_2\text{Si}^+$; calc. 345.2226).

(3R)-3-[(*tert*-Butyl)dimethylsilyloxy]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. ^1H -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 ($[M + \text{Na}]^+$, $\text{C}_{12}\text{H}_{28}\text{NaO}_2\text{Si}^+$; calc. 255.1756).

(3R)-3-[(*tert*-Butyl)dimethylsilyloxy]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.

(4R)-4-[(*tert*-Butyl)dimethylsilyloxy]-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 2.5*M* 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**.

(4R)-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 CH₂Cl₂ (40 ml). Washing with H₂O (50 ml) and brine (50 ml) and CC (SiO₂) afforded **12** (3.55 g, 94%). Viscous liquid. $[\alpha]_D^{25} = -8.7$ ($c = 3$, CHCl₃). IR (neat): 3453, 2955, 2931, 2856, 2211, 1673, 1612, 1512, 1463, 1248, 1101, 1038, 834, 755. ¹H-NMR (CDCl₃, 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). ¹³C-NMR (CDCl₃, 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 ($[M + Na]^+$, C₂₆H₄₂NaO₄Si⁺; calc. 469.2750).

(4R)-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 Bu₄NF in THF (11.41 ml, 11.41 mmol) at 0°. The mixture was stirred for 8 h and then diluted with H₂O and extracted with AcOEt (3 × 50 ml). The org. layer was washed with H₂O (50 ml) and brine (50 ml), dried (Na₂SO₄), and concentrated and the crude product purified by CC (SiO₂): **13** (2.22 g, 88%). Colorless oil. $[\alpha]_D^{25} = +29.9$ ($c = 3$, CHCl₃). IR (neat): 3445, 2956, 2869, 2211, 1717, 1665, 1602, 1512, 1250, 1168, 1101, 1030, 824, 769. ¹H-NMR (CDCl₃, 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). ¹³C-NMR (CDCl₃, 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 ($[M + Na]^+$, C₂₀H₂₈NaO₄⁺; calc. 355.1885).

(4R,6R,7E)-12-[(4-Methoxybenzyl)oxy]dodec-7-ene-4,6-diol (**14**). To a stirred soln. of **13** (2.1 g, 6.32 mmol) in Et₂O (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 LiAlH₄ (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 Et₂O (4 × 50 ml), the combined org. layer dried (Na₂SO₄) and concentrated, and the residue purified by CC (SiO₂): **14** (1.83 g, 85%). Colorless oil. $[\alpha]_D^{25} = +2.94$ ($c = 4$, CHCl₃). IR (neat): 3392, 2934, 2860, 1611, 1513, 1453, 1247, 1094, 1034, 825. ¹H-NMR (CDCl₃, 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). ¹³C-NMR (CDCl₃, 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 ($[M + Na]^+$, C₂₀H₃₂NaO₄⁺; calc. 359.2198).

(4R,6R,7E)-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), 1H-imidazole (0.667 g, 9.51 mmol), CH₂Cl₂ (20 ml), and ^tBuMe₂SiCl (1.07 g, 7.13 mmol); for 4 h. Extraction with CH₂Cl₂ (3 × 40 ml and then 2 × 30 ml), washing with H₂O (30 ml) and brine (30 ml), and purification by CC (SiO₂) afforded **15** (1.84 g, 86%). Colorless liquid. $[\alpha]_D^{25} = +12.56$ ($c = 5$, CHCl₃). IR (neat): 3472, 2929, 2856, 1743, 1613, 1513, 1463, 1249, 1092, 1039, 835. ¹H-NMR (CDCl₃, 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). ¹³C-NMR (CDCl₃, 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 ($[M + Na]^+$, C₂₆H₄₆NaO₄Si⁺; calc. 473.3063).

(5E,7R,9R)-7-[[*tert*-Butyl]dimethylsilyl]oxy]dodec-5-ene-1,9-diol (**16**). To a soln. of **15** (1.6 g, 3.55 mmol) in CH₂Cl₂/H₂O 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% NaHCO₃ soln. and brine (30 ml), dried (Na₂SO₄), and concentrated. Purification by CC gave **16** (1.06 g, 91%). $[\alpha]_D^{25} = +0.7$ ($c = 1.8$, CHCl₃). IR (neat): 3396, 2930, 2854, 1740, 1612, 1515, 1455, 1246, 1093, 1035, 829. ¹H-NMR (CDCl₃, 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). ¹³C-NMR (CDCl₃, 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).

(5E,7R,9R)-7-[[*tert*-Butyl]dimethylsilyloxy]-9-hydroxydodec-5-enoic Acid (**4**). BAIB (0.847 g, 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. 1H -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).

(6E,8R,10R)-8-[[*tert*-Butyl]dimethylsilyloxy]-3,4,5,8,9,10-hexahydro-10-propyl-2H-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. 1H -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).

(6E,8R,10R)-3,4,5,8,9,10-Hexahydro-8-hydroxy-10-propyl-2H-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. 1H -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).

REFERENCES

- [1] H. C. Brown, R. S. Fletcher, R. B. Johannesen, *J. Am. Chem. Soc.* **1951**, 73, 212; E. Eliel, in 'Stereochemistry of Carbon Compounds', McGraw-Hill, New York, 1962, p. 189.
- [2] J. F. Rivero-Cruz, M. Macías, C. M. Cerda-García-Rojas, R. Mata, *J. Nat. Prod.* **2003**, 66, 511.
- [3] R. Mata, M. L. Macías, I. S. Rojas, B. Lotina-Hennsen, R. A. Toscano, A. L. Anaya, *Phytochemistry* **1998**, 49, 441.
- [4] M. K. Gurjar, S. Karmakar, D. K. Mohapatra, *Tetrahedron Lett.* **2004**, 45, 4525; M. K. Gurjar, R. Nagaprasad, C. V. Ramanna, S. Karmakar, D. K. Mohapatra, *ARKIVOC* **2005**, 237; S. Nanda,

- Tetrahedron Lett.* **2005**, *46*, 3661; A. Salaskar, A. Sharma, S. Chattopadhyay, *Tetrahedron: Asymmetry* **2006**, *17*, 325; J. Boruwa, N. Gogoi, N. C. Barua, *Org. Biomol. Chem.* **2006**, *4*, 3521; X. S. Chen, S. J. Da, L. H. Yang, B. Y. Xu, Z. X. Xie, Y. Li, *Chin. Chem. Lett.* **2007**, *18*, 255; J. Lee, Y.-H. Jung, J. Tae, *Bull. Korean Chem. Soc.* **2007**, *28*, 513; J. S. Yadav, V. N. Kumar, R. S. Rao, P. Srihari, *Synthesis* **2008**, 1938; J. S. Yadav, H. Atter, K. U. Gayathri, N. V. Rao, A. R. Prasad, *Synthesis* **2008**, 3945.
- [5] A. K. Ghosh, H. Lei, *J. Org. Chem.* **2002**, *67*, 8783.
- [6] K. Horita, T. Yoshioka, T. Tanaka, Y. Oikawa, O. Yonemitsu, *Tetrahedron* **1986**, *42*, 3021.
- [7] B. S. Bal, W. E. Childers Jr., H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091.

Received December 1, 2009