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Sodium borohydride / methoxydiethylborane mediated *syn*-1,3-stereoselective total synthesis of Herbarumin-III

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A simple and efficient stereoselective total synthesis of 10-membered macrolide, herbarumin-III is described. The key steps involved in this synthesis are the selective terminal alkylation of ethyl acetoacetate with ethyl bromide, Sharpless epoxidation, $NaBH_4$/Et_2BOMe mediated stereoselective *syn*-1,3-asymmetric reduction, esterification and olefin metathesis.

Keywords: Macrolactone, alkylation, Sharpless epoxidation, $NaBH_4$, Et_2BOMe, stereoselective *syn*-1,3-reduction, ring-closing metathesis (RCM)

8- or 10-membered ring lactones are frequently found in a large number of natural products. Many of them exhibit a wide range of biological activities. In particular, 10-membered macrolides such as pinolidoxin and lethaloxin have received considerable attention[1]. The nonenolide, Herbarumin-III **1** was isolated along with Herbarumin-I **2** and Herbarumin-II **3** from the fermentation broth and mycelium of the fungus *Phoma herbarum*[2]. Structurally, these natural products constitute 10-membered lactone ring systems. The herbarumin macrolides **1**-**3** (**Figure 1**) are found to exhibit significant phytotoxic effects tested at low concentration against seedlings of *Amaranthus hypochondriacus*. They interact with bovine-brain calmodulin and inhibit the activation of calmodulin-dependent enzyme cAMP-phosphodiesterase[2a]. The phytotoxic activity of herbarumin-III **1** was equal to herbarumin-I **2** and higher than that of herbarumin-II **3** and also exhibits higher potency than 2,4-dichlorophenoxy acetic acid[2b]. Considering its potent herbicidal activity and fascinating structural features, several approaches have been reported for the synthesis of herbarumin-III **1** (Ref. 3).

Construction of substituted phytotoxic nonenolide ring and the stereoselective synthesis of *syn*-1,3-diol unit are the main two targets in the synthesis of herbarumin-III **1**. The strategy for construction of herbarumin-III **1** is outlined in **Scheme I**. The key intermediate *syn*-1,3-diol **14** could be prepared by stereoselective *syn*-1,3-asymetric reduction of hydroxyl ketone **13**. The 10-membered lactonization could be achieved *via* esterification followed by ring closing metathesis (**Scheme II**).

Results and Discussion

Accordingly, synthesis of the natural product **1** began with ethyl acetoacetate **4** (**Scheme II**). Alkylation of **4** with ethyl bromide *via* the formation of ethyl acetoacetate dianion using NaH and *n*-BuLi in THF at 0°C to RT gave the terminal alkylated β-ketoester **5** in 85% yield[4]. The selective protection of keto group of **5** with ethylene glycol using 10 mol% PTSA afforded the ester **6** in 98% yield[5]. Reduction of ester **6** with LAH in THF gave a saturated primary alcohol **7** in 88% yield. The compound **7** was converted into the corresponding aldehyde under Swern oxidation conditions[6] and then homologated by a two-carbon Wittig ylide, (ethoxycarbonyl-methelene)triphenyl phosphorane in benzene under reflux conditions for 3 hr to furnish the corresponding α, β-unsaturated ester **8** in 90% yield. Reduction of **8** with DIBAL-H in CH_2Cl_2 at □78°C to 0°C gave the allyl alcohol **9** in 87% yield[7]. The Sharpless epoxidation of allylic alcohol **9** with (-)-DET, $Ti(O^iPr)_4$ and *tert*-butyl hydroperoxide in CH_2Cl_2 gave the epoxide **10** in 89% yield[7]. The epoxy alcohol **10** was then converted

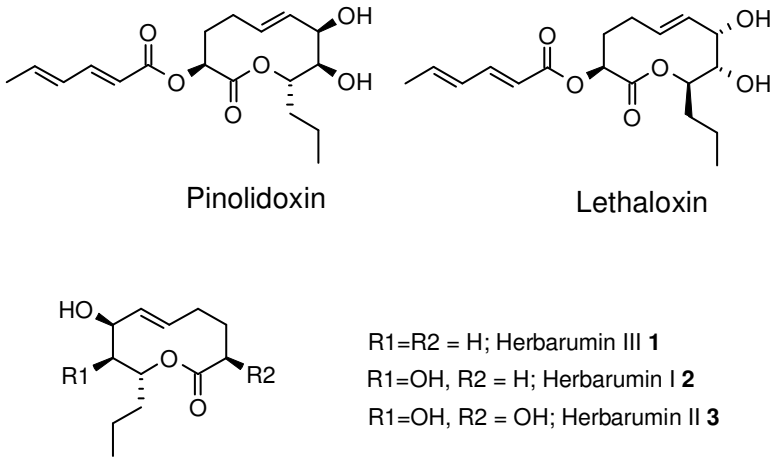
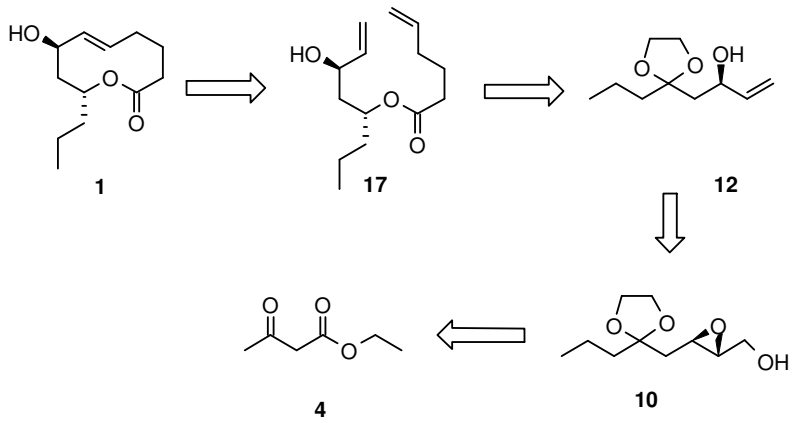


Figure 1 — Structures of nonenolides

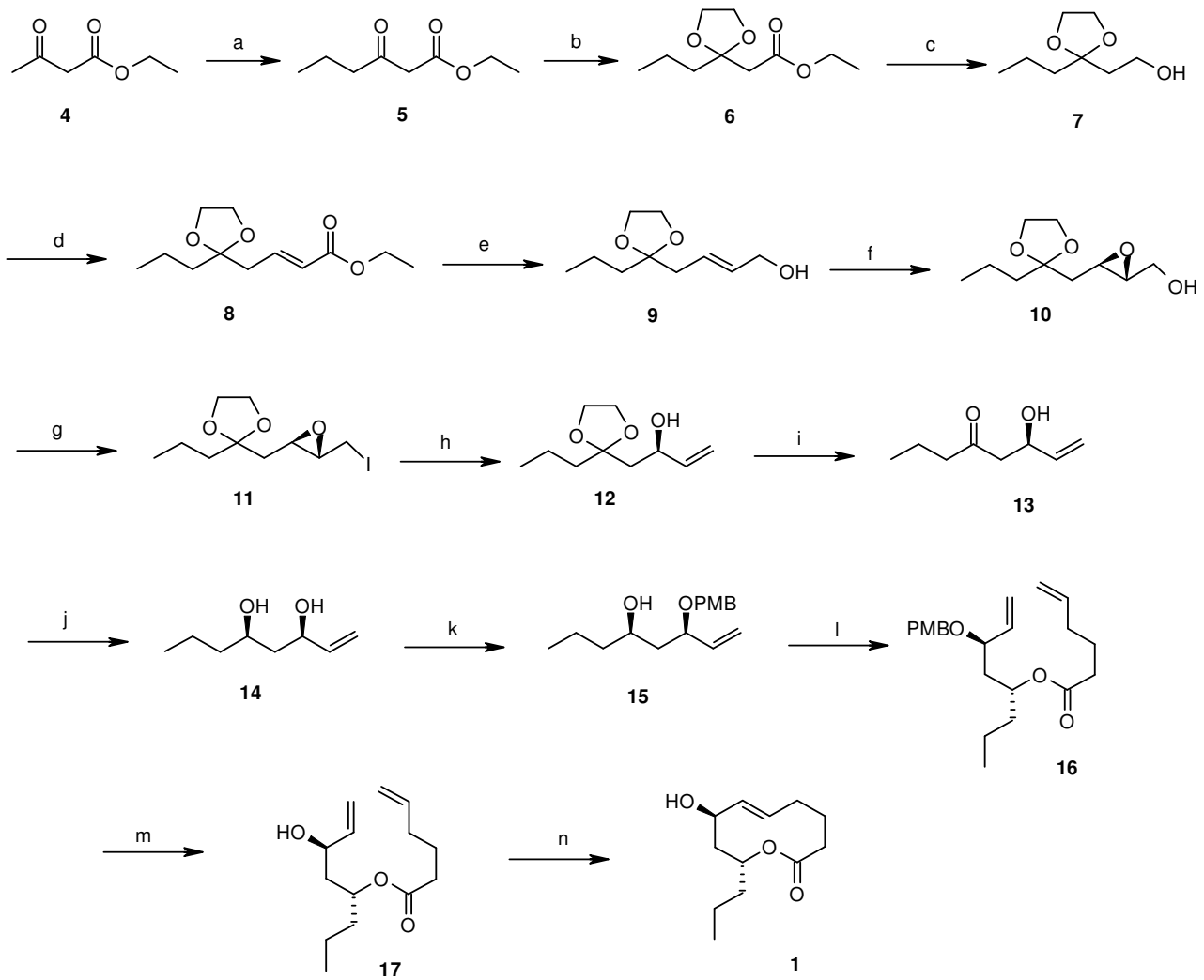


Scheme I — Retrosynthetic analysis of herbarumin-III

into the corresponding epoxy iodide[8] **11** by treatment with Ph_3P, imidazole and iodine for 1 hr in ether/acetonitrile (3:1) with 90% yield, which on reductive elimination with activated zinc dust[9] in refluxing ethanol for 2 hr afforded the chiral allylic alcohol **12** in 80% yield. Deprotection of the ketal **12** was achieved using acetone and water in the presence of PTSA to furnish hydroxyl ketone **13** in 98% yield[5b]. Then hydroxy ketone **13** was subjected to the hydroxyl directed *syn* stereoselective 1,3-asymmetric reduction using $NaBH_4/Et_2BOMe$ in THF/MeOH (4:1) at □78°C to provide the desired *syn*-1,3-diol **14** in 92% yield (syn:anti = 95:5)[10]. Chemoselective protection of secondary allylic alcohol with *p*-methoxy benzyl chloride gave the PMB ether **15** in 89% yield. The esterification compound **15** with 5-hexenoicacid in the presence of *N*,*N*-dicyclohexyl carbodiimide and a catalytic amount of DMAP provided the diene **16** in 86% yield. Deprotection of PMB group with 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone afforded the compound **17** in 97% yield, which was a precursor for RCM reaction. Compound **17** upon exposure to the Grubb's second generation catalyst under high dilution conditions gave the target natural product herbarumin III **1** in 83% yield[11]. The data for the synthetic molecule were in good agreement with the natural product[3].

Experimental Section

Solvents were dried over standard drying agents and freshly distilled prior to use. The reagents were purchased from Aldrich and Acros and were used without further purification unless otherwise stated. All moisture-sensitive reactions were carried out



Reagents and conditions: (a) i. NaH, *n*-BuLi ii. EtBr, THF at 0°C to RT, 30 min, 85%; (b) ethylene glycol, C_6H_6, 10 mol % PTSA, 4 hr, 98%; (c) LAH, THF, 0°C to RT, 4 hr, 88%; (d) i.$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, □78°C, 2 hr; ii.$Ph_3P{=}CHCO_2Et$, C_6H_6, reflux, 3 hr, 90% (over two steps);(e) DIBAL-H, CH_2Cl_2, 0°C to RT, 2 hr, 87%; (f) (-)-DET, $Ti(O^iPr)_4$, TBHP, 4Å MS, CH_2Cl_2, □20°C, 5 hr, 89%; (g) Ph_3P, imidazole, I_2, ether/acetonitrile (3:1), 0°C to RT, 1 hr, 90%; (h) activated Zn, EtOH, reflux, 1-2 hr, 80%; (i) acetone : water (3:1) cat PTSA, 1 hr, 98%; (j) $NaBH_4/Et_2BOMe$, THF/MeOH (4:1) at □78°C, 3 hr, 92%; (k) PMBCl, NaH, DMF, 0°C, 1 hr, 92%; (l) 5-hexenoic acid, DCC, cat. DMAP, CH_2Cl_2, 15 hr, 86%; (m) DDQ, CH_2Cl_2/H_2O (9:1), 0°C to RT, 30 min, 97%; (n) Grubb's II catalyst, CH_2Cl_2, reflux,15 hr, 83%.

Scheme II

under N_2 atmosphere. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* below 40°C. All column chromatographic (CC) separations were performed over silica gel (Acme's 60-120 mesh). ^1H NMR (300 MHz, 400 MHz, 500 MHz) and ^{13}C NMR (75 MHz) spectra were measured with Bruker Avance 300 instrument with tetramethylsilane as internal standard in $CDCl_3$; *J* values are given in Hz. IR spectra were recorded on a Perkin-Elmer IR-683 spectrophotometer with KBr optics. Optical rotations were measured with a Horiba high sensitive polarimeter SEPA-300. Mass spectra were recorded on Agilent Technologies 1100 Series (Agilent Chemistation Software).

Ethyl-3-oxo-hexanoate, **5**: To a suspension of NaH (60% in mineral oil, 0.6 g, 15 mmol) in THF (50 mL) was added a solution of ethyl acetoacetate dropwise **4** (1.3 mL, 10 mmol) at 0°C. The resulting mixture was stirred for 15 min, and then 1.6 N *n*-BuLi in hexane (9.4 mL, 15 mmol) was added at 0°C. The resulting orange solution was stirred at 0°C for an additional 10 min and then ethyl bromide (1.2 mL, 16

mmol) was added at 0°C. The resulting mixture was stirred at RT for 30 min and quenched with water and extracted with EtOAc (3×50 mL). The combined organic layers were washed with water (3×25 mL) and brine (2×5 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure and the crude product was subjected to flash chromatography to afford **5** (1.343 g, 85% yield) as a colorless oil. R_f = 0.40 (SiO_2, 10% EtOAc in hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (t, 3H, *J* = 7.5 Hz), 1.29 (t, 3H, *J* = 6.8 Hz), 1.62 (q, 2H, *J* = 6.8, 7.5 Hz), 2.50 (t, 2H, *J* = 6.8 Hz), 3.36 (s, 2H), 4.17 (q, 2H, *J* = 6.8, 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.0, 13.6, 16.5, 44.3, 48.8, 60.7, 166.8, 202.4; IR (KBr): 2967, 2878, 1743, 1716, 1644, 1462, 1411, 1369, 1314, 1232, 1157, 1066, 1028, 942, 852 cm^{-1}; ESI-MS: *m/z* 159 $[M+H]^+$; HRMS: Calcd for $C_8H_{15}O_3$: 159.1021. Found: 159.1025.

Ethyl-2-(2-propyl-1,3-dioxolan-2-yl)acetate, **6**: To a solution of β-ketoester **5** (1.2 g, 7.6 mmol) in C_6H_6 (25 mL), ethylene glycol (1.27 mL, 22.8 mmol) and *p*-TSA (0.127 g, 0.76 mmol) were added. The resulting mixture was allowed to reflux for 6 hr with concomitant removal of the water azeotropically by using the Dean-Stark apparatus. The resulting mixture was poured into a solution of ice and saturated $NaHCO_3$ solution and then extracted with EtOAc (3×50 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash chromatography of the crude product afforded ethylene ketal **6** (1.503 g, 98% yield). R_f = 0.35 (SiO_2, 10% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, 3H, *J* = 7.3 Hz), 1.27 (t, 3H, *J* = 7.3 Hz), 1.41 (q, 2H, *J* = 7.3, 8.0 Hz), 1.75 (t, 2H, *J* = 8.0 Hz), 2.57 (s, 2H), 3.89-4.0 (m, 4H), 4.12 (q, 2H, *J* = 6.6, 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 16.5, 39.6, 42.3, 60.1, 64.7, 109.1, 169.2; IR (KBr): 2963, 2878, 1736, 1644, 1462, 1371, 1271, 1217, 1179, 1071, 1037, 975, 948, 836 cm^{-1}; ESI-MS: *m/z* 225 $[M+Na]^+$; HRMS: Calcd for $C_{10}H_{18}O_4$: 225.1102. Found: 225.1111.

2-(2-Propyl-1,3-dioxolan-2-yl)ethanol, **7**: To a suspension of LAH (0.132 g, 3.5 mmol) in THF (30 mL) under nitrogen atmosphere at 0°C, ester **6** (1.4 g, 6.93 mmol) in THF was added slowly. The reaction mixture was stirred for 4 hr at RT. After completion, excess of LAH was quenched by addition of 15% NaOH solution (3 mL) and water (3 mL). The mixture was filtered through celite and washed with EtOAc. The crude filtrate was extracted with EtOAc (3×50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The resulting crude residue was purified by column chromatography over silica gel to afford the pure compound **7** (0.976 g, 88% yield) as a colorless liquid. R_f = 0.25 (SiO_2, 30% EtOAc in hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, 3H, *J* = 7.4 Hz), 1.30-1.44 (m, 2H), 1.55-1.63 (m, 2H), 1.87 (t, 2H, *J* = 5.5 Hz), 2.60-2.70 (brs, 1H), 3.65-3.73 (m, 2H), 3.93-4.0 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 16.9, 38.0, 39.2, 58.6, 64.6, 111.9; IR (KBr): 3423, 2960, 2879, 1654, 1461, 1377, 1310, 1215, 1150, 947, 831, 771 cm^{-1}; ESI-MS: *m/z* 161 $[M+H]^+$; HRMS: Calcd for $C_8H_{16}O_3Na$: 183.0997. Found: 183.0995.

(*E*)-Ethyl-4-(2-propyl-1,3-dioxolan-2-yl)but-2-enoate, **8**: To a stirred solution of oxalyl chloride (0.74 mL, 8.43 mmol) in dry CH_2Cl_2 (13 mL) at □78°C, dry DMSO (1.2 mL, 16.87 mmol) in 8 mL dry CH_2Cl_2 was added dropwise. After 30 min, alcohol **7** (0.9 g, 5.63 mmol) in 15 mL dry CH_2Cl_2 was added over 10 min giving a copious white precipitate. After stirring for 2 hr at □78°C, Et_3N (3.9 mL, 28.12 mmol) was added slowly and the reaction mass allowed to reach to RT over 30 min. Then the reaction mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were washed with water (15 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the aldehyde, which was directly used for further reaction.

To a stirred solution of the above crude aldehyde in benzene (20 mL) was added (ethoxycarbonylmethylene)triphenylphosphorane (3.1 g, 8.44 mmol) at RT. After refluxing for 3 hr in benzene, the solvent was evaporated and the residue was purified by column chromatography to afford **8** (0.89 g, 90% yield) as a colorless liquid. R_f = 0.55 (SiO_2, 10% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, 3H, *J* = 7.5 Hz), 1.30 (t, 3H, *J* = 6.8 Hz), 1.33-1.43 (m, 2H), 31.54-1.60 (m, 2H), 2.46 (dd, 2H, *J* = 1.5 Hz), 3.92 (m, 4H), 4.17 (q, 2H, *J* = 7.5, 6.8 Hz), 5.83 (m, 1H), 6.83-6.92 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 16.6, 39.8, 40.3, 59.9, 64.9, 110.3, 121.3, 124.1, 143.4, 166.0; IR (KBr): 2961, 2879, 1719, 1655, 1463, 1369, 1308, 1269, 1181, 1076, 982, 951, 833, 721 cm^{-1}; ESI-MS: *m/z* 251 $[M+Na]^+$; HRMS: Calcd for $C_{12}H_{16}O_4Na$: 251.1259. Found: 251.1267.

(*E*)-4-(2-Propyl-1,3-dioxolan-2-yl)but-2-en-1-ol, **9**: To an ice-cooled solution of **8** (0.1 g, 4.38 mmol) in dry CH_2Cl_2 (15 mL), DIBAL-H (9.65 mL, 9.65

mmol, 1M solution in toluene) was added slowly for 15 min. The reaction mixture was stirred at RT for 2 hr, and then cooled to 0°C, and quenched with methanol (1 mL) and sodium potassium tartarate solution (5 mL). The resulting mixture was passed through a short pad of celite. The filtrate was extracted with CH_2Cl_2 (3×25 mL), concentrated *in vacuo* and the residue was purified by column chromatography to afford compound **9** (0.71 g, 87% yield) as a colorless liquid. R_f = 0.43 (SiO_2, 30% EtOAc in hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (m, 3H, *J* = 7.5 Hz), 1.30-1.44 (m, 2H), 1.52-1.59 (m, 2H), 1.68-1.78 (brs, 1H), 2.31 (d, 2H, *J* = 6.0 Hz), 3.89-3.92 (m, 4H), 4.06 (d, 2H, *J* = 3.7 Hz), 5.62-5.68 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 16.4, 39.0, 39.9, 62.7, 64.6, 110.7, 126.1, 132.5; IR (KBr): 3414, 2956, 2878, 1657, 1432, 1370, 1307, 1203, 1145, 1078, 1006, 970, 835, 770 cm^{-1}; ESI-MS: *m/z* 209 $[M+Na]^+$; HRMS: Calcd for $C_{10}H_{18}O_3Na$: 209.1153. Found: 209.1145.

((2*R*,3*R*)-3-(2-Propyl-1,3-dioxolan-2-yl)methyl)-oxiran-2-yl)methanol, **10**: In a 50 mL two-necked round-bottomed flask, 8 mL of dry CH_2Cl_2 was added to 4 Å powered activated molecular sieves and the suspension was cooled to −20°C. Ti ($O^iPr)_4$ (0.2 mL, 0.7 mmol) and (-)-DET (0.12 mL, 0.7 mmol) in dry CH_2Cl_2 (5 mL) were added subsequently under vigorous stirring and the resulting mixture was allowed to stir for 30 min at −20°C. Then compound **9** (0.65 g, 3.5 mmol) in dry CH_2Cl_2 (6 mL) was added and the resulting mixture was stirred for another 30 min at −20°C and then *tert*-butylhydroperoxide (1.1 mL, 5.25 mmol) was added at −20°C and the resulting mixture was stirred at the same temperature for 5 hr. It was then warmed to 0°C and quenched with 2 mL of water and then allowed to stir for 1 hr at RT. After that 30% aqueous NaOH solution saturated with NaCl (1 mL) was added and the reaction mass stirred vigorously for another 30 min at RT. The resulting mixture was then filtered through celite rinsing with CH_2Cl_2. The organic phase was extracted with CH_2Cl_2 (3×25 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and purified by silica gel column chromatography to afford **10** (0.628 g, 89%) as a viscous liquid. R_f = 0.35 (SiO_2, 30% EtOAc in hexane). $[\alpha]^{28}_D$ = + 4.9° (*c* 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, 3H, *J* = 7.5 Hz), 1.33-1.45 (m, 2H), 1.59-1.67 (m, 2H), 1.72-1.93 (m, 2H), 2.85-2.90 (m, 1H), 3.01-3.06 (m, 1H), 3.60 (dd, 1H, *J* = 3.7, 8.3 Hz), 3.86 (dd, 1H, *J* = 3.0, 9.8 Hz), 3.94 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 16.7, 39.3, 39.9, 52.1, 58.0, 61.6, 64.8, 64.9, 110.3; IR (KBr): 3444, 2960, 2878, 1640, 1464, 1373, 1315, 1261, 1161, 1073, 949, 893, 834, 792, 760 cm^{-1}; ESI-MS: *m/z* 225 $[M+Na]^+$; HRMS: Calcd for $C_{10}H_{18}O_4Na$: 225.1102. Found: 225.1110.

2(((2*R*,3*S*)-3-(Iodomethyl)oxiran-2-yl)methyl)-2-propyl-1,3-dioxolane, **11**: To a stirred solution of **10** (0.6 g, 2.97 mmol) in ether/acetonitrile (3:1) (30 mL), TPP (1.17 g, 4.45 mmol) and imidazole (0.404 g, 5.94 mmol) were added at 0°C and stirred for 5 min. Then I_2 (1.13 g, 4.45 mmol) was added at 0°C and stirred for another 1 hr. Then the mixture was quenched with saturated sodium thiosulfate (25 mL) and extracted with EtOAc (3×30 mL). The organic layer was washed with water (20 mL), brine (15 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography to afford **11** (0.834 g, 90%) as a yellow liquid. R_f = 0.5 (SiO_2, 20% EtOAc in hexane). $[\alpha]^{27}_D$ = −8.4° (*c* 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (t, 3H, *J* = 7.4 Hz), 1.30-1.47 (m, 2H), 1.60-1.69 (m, 2H), 1.72-1.91 (m, 2H), 2.88 (t, 1H, *J* = 5.8 Hz), 2.92-3.02 (m, 2H), 3.25 (q, 1H, *J* = 4.7, 8.8 Hz), 3.89-4.02 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 4.5, 14.2, 16.8, 39.4, 39.9, 57.7, 58.6, 64.8, 64.9, 109.9; IR (KBr): 2959, 2877, 1461, 1364, 1315, 1158, 1076, 951, 894, 837, 756, 608 cm^{-1}; ESI-MS: *m/z* 335 $[M+Na]^+$; HRMS: Calcd for $C_{10}H_{17}O_3NaI$: 335.0120. Found: 335.0117.

(*R*)-1-(2-Propyl-1,3-dioxolan-2-yl)but-3-en-2-ol, **12**: To a stirred solution of **11** (0.8 g, 2.56 mmol) in EtOH (25 mL), activated zinc dust (1.66 g, 25.6 mmol) was added and stirring was continued at reflux temperature for 2 hr. The reaction mixture was passed through a short pad of celite. The filtrate was concentrated and the residue was purified by column chromatography to afford **12** (0.38 g, 80% yield) as a colorless liquid. R_f = 0.45 (SiO_2, 20% EtOAc in hexane). $[\alpha]^{27}_D$ = −7.3° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, 3H, *J* = 7.5 Hz), 1.33-1.45 (m, 2H), 1.59-1.66 (m, 2H), 1.70-1.87 (m, 2H), 3.48-3.55 (brs, 1H), 3.94-4.03 (m, 4H), 4.29-4.38 (m, 1H), 5.04 (dt, 1H, *J* = 10.6 Hz), 5.25 (dt, 1H, *J* = 17.4 Hz), 5.71-5.84 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 16.9, 39.4, 42.5, 64.4, 64.7, 68.7, 111.7, 113.8, 140.2; IR (KBr): 3503, 3082, 2960, 2879, 1710, 1644, 1428, 1380, 1304, 1264, 1195, 1151, 1073, 995, 921,

825 cm^{-1}; ESI-MS: *m/z* 209 $[M+Na]^+$; HRMS: Calcd for $C_{10}H_{18}O_3Na$: 209.1153. Found: 209.1155.

(*R*)-6-Hydroxyoct-7-en-4-one, **13**: To a solution of **12** (0.36 g, 1.93 mmol), catalytic *p*-TSA and acetone/water (3:2, 10 mL) were added and the stirring was continued at 23°C for 2 hr. After completion, the mixture was poured into a ice-cooled solution of saturated $NaHCO_3$ and extracted with Et_2O (3×15 mL). The combined organic layers were washed with brine (1×5 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting crude product was purified by column chromatography to afford the ketone **13** (0.269 g, 98%) as a colorless liquid. R_f = 0.40 (SiO_2, 20% EtOAc in hexane). $[\alpha]^{27}_D$ = + 21.5° (*c* 1.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (t, 3H, *J* = 7.8 Hz), 1.62 (q, 2H, *J* = 6.8, 7.8 Hz), 2.40 (t, 3H, *J* = 7.8 Hz), 2.56-2.60 (m, 2H), 2.85-3.0 (brs, 1H), 4.49-4.55 (m, 1H), 5.09 (d, 1H, *J* = 9.7 Hz), 5.26 (d, 1H, *J* = 17.5 Hz), 5.77-5.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.4, 16.7, 45.4, 48.6, 68.3, 114.5, 139.1, 210.9; IR (KBr): 3422, 2958, 2927, 2858, 1686, 1514, 1459, 1378, 1258, 1204, 1081, 1014, 904, 801 cm^{-1}; ESI-MS: *m/z* 165 $[M+Na]^+$; HRMS: Calcd for $C_8H_{14}O_2Na$: 165.0891. Found: 165.0898.

(3*R*,5*R*)-Oct-1-ene-3,5-diol, **14**: To a stirred solution of hydroxyl ketone **13** (0.25 g, 1.76 mmol) in dry tetrahydrofuran (14 mL) and anhydrous methanol (3.5 mL) at −78°C under argon was added a solution of methoxydiethylborane (1.94 mL, 1M solution in THF, 1.94 mmol) dropwise and the resulting mixture was stirred for 15 min. Then sodium borohydride (0.066 g, 1.94 mmol) was added and the resulting mixture was allowed to stir for 3 hr and then quenched with 1.9 mL of acetic acid. The mixture was diluted with ethyl acetate, washed with aqueous sodium bicarbonate solution (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography to afford compound **14** (0.233 g, 92%) as a colorless liquid. R_f = 0.15 (SiO_2, 20% EtOAc in hexane). $[\alpha]^{27}_D$ = + 2.4° (*c* 1.32, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (t, 3H, *J* = 6.7 Hz), 1.27-1.66 (m, 7H), 3.27-3.62 (brs, 1H), 3.84 (m,1H), 4.32 (m, 1H), 5.06 (d, 1H, *J* = 10.6 Hz), 5.22 (d, 1H, *J* = 17.3 Hz), 5.79-5.88 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 18.4, 40.1, 42.7, 72.1, 73.6, 114.3, 140.6; IR (KBr): 3354, 2958, 2930, 2871, 1718, 1645, 1458, 1314, 1132, 1074, 1021, 993, 923, 844 cm^{-1}; ESI-MS: *m/z* 167 $[M+Na]^+$; HRMS: Calcd for $C_8H_{16}O_2Na$: 167.1047. Found: 167.1040.

(4*R*,6*R*)-6-(4-Methoxybenzyloxy)oct-7-en-4-ol, **15**: A solution of **14** (0.22 g, 1.53 mmol) in dry DMF (3 mL) was added dropwise to a well-stirred solution of NaH (0.061 g, 1.53 mmol) in dry DMF (2 mL) at 0°C under N_2. After 30 min, a solution of PMBCl (0.238 g, 1.53 mmol) in dry DMF (2 mL) was added dropwise to the above mixture at 0°C. The resulting mixture was stirred for 1 hr and then quenched with ice cooled water and extracted with Et_2O (3×20 mL). The combined organic extracts were washed with brine (1×10 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent followed by purification by silica gel column chromatography afforded **15** in 92% yield as a colorless oil. R_f = 0.50 (SiO_2, 20% EtOAc in hexane). $[\alpha]^{28}_D$ = −28.3° (*c* 1.32, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, 3H, *J* = 7.5 Hz), 1.23-1.46 (m, 4H), 1.48-1.59 (m, 1H), 1.59-1.75 (m, 1H), 3.34-3.46 (brs, 1H), 3.67-3.77 (m, 1H), 3.79 (s, 3H), 3.92-4.01 (m, 1H), 4.26 (d, 1H, *J* = 11.3 Hz), 4.54 (d, 1H, *J* = 11.3 Hz), 5.17-5.26 (m, 2H), 5.65-5.81 (m, 1H), 6.82 (d, 2H, *J* = 8.3 Hz), 7.19 (d, 2H, *J* = 9.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 18.4, 39.6, 42.6, 55.1, 69.7, 70.8, 77.5, 81, 113.7, 117.4, 138.1, 159.1; IR (KBr): 3456, 3074, 2955, 2868, 1718, 1612, 1513, 1461, 1420, 1302, 1248, 1175, 1070, 1034, 928, 821, 756 cm^{-1}; ESI-MS: *m/z* 287 $[M+Na]^+$; HRMS: Calcd for $C_{16}H_{24}O_3Na$: 287.1623. Found: 287.1636.

(4*R*,6*R*)-6-(4-Methoxybenzyloxy)oct-7-en-4-yl-hex-5-enoate, **16**: To a stirred solution of **15** (0.3 g, 1.14 mmol) in dry CH_2Cl_2 (10 mL), DCC (0.35 g, 1.7 mmol) and cat. DMAP were added at 0°C. After 10 min, 5-hexenoic acid (0.194 g, 1.7 mmol) in dry CH_2Cl_2 (10 mL) was added and the stirring was continued at RT for 15 hr. The solvent was evaporated and the residue was purified by column chromatography to afford **16** (0.351 g, 86% yield) as a colorless liquid. R_f = 0.45 (SiO_2, 10% EtOAc in hexane). $[\alpha]^{30}_D$ = + 20.7° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87 (t, 3H, *J* = 6.8 Hz), 1.20-1.35 (m, 2H), 1.37-1.55 (m, 2H), 1.57-1.70 (m, 3H), 1.87-1.96 (m, 1H), 2.00-2.09 (m, 2H), 2.12-2.23 (m, 2H), 3.64-3.74 (m, 1H), 3.78 (s, 3H), 4.19 (d, 1H, *J* = 11.7 Hz), 4.48 (d, 1H, *J* = 11.7 Hz), 4.91-5.03 (m, 3H), 5.15-5.27 (m, 2H), 5.63-5.79 (m, 2H), 6.80 (d, 2H, *J* = 7.8 Hz), 7.18 (d, 2H, *J* = 7.8); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 24.0, 33.0, 33.7, 36.5, 39.9, 55.1, 69.5, 71, 77.3, 113.6, 115.2, 118, 129.3, 129.6, 137.6, 138.2, 159, 173; IR (KBr): 3075, 2925, 2854,

1731, 1640, 1611, 1513, 1461, 1377, 1302, 1248, 1174, 1103, 1036, 994, 922, 821, 756 cm^{-1}; ESI-MS: *m/z* 383 $[M+Na]^+$; HRMS: Calcd for $C_{22}H_{32}O_4Na$: 383.2198. Found: 383.2188.

(4*R*,6*R*)-6-Hydroxyoct-7-en-4-yl hex-5-enolate, **17**: DDQ (0.274 g, 1.21 mmol) was added to a solution of **16** (0.29 g, 0.81 mmol) in CH_2Cl_2 (11.2 mL) and H_2O (0.8 mL) at 0°C, and the resulting mixture was stirred at RT for 30 min. Then the mixture was quenched with sat.$NaHCO_3$ (2 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were washed with brine (1×10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography to afford **17** (0.187 g, 97%) as a colorless liquid. R_f = 0.55 (SiO_2, 20% EtOAc in hexane). $[\alpha]^{30}_D$ = + 1.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 (t, 3H, *J* = 7.5 Hz), 1.15-1.42 (m, 5H), 1.44-1.58 (m, 1H), 1.61-1.85 (m, 3H), 1.97-2.08 (m, 2H), 2.18-2.32 (m, 2H), 3.58-3.71 (brs, 1H), 4.07-4.18 (q, 1H, *J* = 6.0, 6.8 Hz), 4.68-5.28 (m, 5H), 5.63-5.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 18.4, 24.0, 33, 33.7, 36.8, 39.8, 70.6, 71.5, 114.9, 115.4, 136.3, 140.4, 173.5; IR (KBr): 3455, 3078, 2958, 2928, 2869, 1732, 1642, 1611, 1513, 1460, 1377, 1035, 1247, 1175, 1032, 993, 918, 820, 749 cm^{-1}; ESI-MS: *m/z* 263 $[M+Na]^+$; HRMS: Calcd for $C_{14}H_{24}O_3Na$: 263.1623. Found: 263.1625.

Herbarumin-III, **1**: Grubbs's catalyst II (0.018 g, 0.052 mmol) was dissolved in CH_2Cl_2 (10 mL) and was added dropwise to a refluxing solution of a compound **17** (0.1 g, 0.42 mmol) in CH_2Cl_2 (200 mL). The resulting mixture was allowed to stir for 15 hr at the same temperature. After completion as indicated by TLC, the solvent was removed *in vacuo*, and the crude residue was purified by column chromatography to afford the target molecule **1** (0.073 g, 83% yield). R_f = 0.55 (SiO_2, 20% EtOAc in hexane). $[\alpha]^{28}_D$ = + 18.5° (*c* 1.0, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (t, 3H, *J* = 7.8 Hz), 1.27-1.37 (m, 1H), 1.37-1.46 (m, 1H), 1.50-1.59 (m, 1H), 1.69-1.90 (m, 3H), 1.94-2.06 (m, 3H), 2.28 (dd, 1H, *J* = 5.8, 11.7 Hz), 2.33-2.43 (m, 1H), 4.42 (t, 1H, *J* = 2.9 Hz), 5.23-5.31 (m, 1H), 5.42-5.51 (m, 1H), 5.60 (d, 1H, *J* = 15.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 18.4, 26.0, 34.6, 33.6, 37.3, 40.5, 68.0, 67.8, 124.8, 134.5, 176.8; IR (KBr): 3445, 2926, 2857, 1725, 1613, 1457, 1374, 1267, 1122, 771 cm^{-1}; ESI-MS: *m/z* 235 $[M+Na]^+$; HRMS: Calcd for $C_{12}H_{20}O_3Na$: 235.1310. Found: 235.1307.

Conclusion

In conclusion, a simple and concise total synthesis of herbarumin III **1** has been accomplished by terminal alkylation of β-ketoester, reductive epoxide ring opening, stereoselective *syn*-1,3-reduction by $NaBH_4$-Et_2BOMe and Grubbs olefin metathesis as the key steps. Application of this strategy to the total synthesis of other analogues is currently in progress.

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