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, NaBH₄/Et₂BOMe mediated stereoselective syn-1,3-asymmetric reduction, esterification and olefin metathesis.

Keywords: Macrolactone, alkylation, Sharpless epoxidation, NaBH₄, Et₂BOMe, stereoselective syn-1,3-reduction, ring-closing metathesis (RCM)

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. The selective protection of keto group of 5 with ethylene glycol using 10 mol% PTSA afforded the ester 6 in 98% yield. 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 and then homologated by a two-carbon Wittig ylide, (ethoxycarbonyl-methylene)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 CH₂Cl₂ at 0°C to 0°C gave the allyl alcohol 9 in 87% yield. The Sharpless epoxidation of allylic alcohol 9 with (-)-DET, Ti(OPr)₄ and tert-butyl hydroperoxide in CH₂Cl₂ gave the epoxide 10 in 89% yield. The epoxy alcohol 10 was then converted
into the corresponding epoxy iodide by treatment with Ph₃P, imidazole and iodine for 1 hr in ether/acetonitrile (3:1) with 90% yield, which on reductive elimination with activated zinc dust in refluxing ethanol for 2 hr afforded the chiral allylic alcohol in 80% yield. Deprotection of the ketal was achieved using acetone and water in the presence of PTSA to furnish hydroxyl ketone in 98% yield. Then hydroxy ketone was subjected to the hydroxyl directed syn stereoselective 1,3-asymmetric reduction using NaBH₄/Et₂BOMe in THF/MeOH (4:1) at 78°C to provide the desired syn-1,3-diol in 92% yield (syn:anti = 95:5). Chemoselective protection of secondary allylic alcohol with p-methoxy benzyl chloride gave the PMB ether in 89% yield. The esterification compound with 5-hexenoic acid in the presence of N,N-dicyclohexyl carbodiimide and a catalytic amount of DMAP provided the diene in 86% yield. Deprotection of PMB group with 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone afforded the compound in 97% yield, which was a precursor for RCM reaction. Compound upon exposure to the Grubb's second generation catalyst under high dilution conditions gave the target natural product herbarumin III in 83% yield. The data for the synthetic molecule were in good agreement with the natural product.

**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
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under N\(_2\) atmosphere. Organic solutions were dried over anhydrous Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo} below 40°C. All column chromatographic (CC) separations were performed over silica gel (Acme's 60-120 mesh). \(^1\)H 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 Chemstation 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. Na₂SO₄ 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. Rᵣ = 0.40 (SiO₂, 10% EtOAc in hexane). ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): δ 13.0, 13.6, 16.5, 44.3, 48.8, 60.7, 166.8, 202.4; IR (KBr): 2967, 2878, 1644, 1462, 1461, 1377, 1310, 1215, 1150, 947, 831, 771 cm⁻¹; ESI-MS: m/z 161 [M+H⁺]; HRMS: Calcd for C₈H₁₀O₃: 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 C₅H₁₀ (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 NaHCO₃ solution and then extracted with EtOAc (3×50 mL). The combined organic phase was washed with brine and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Flash chromatography of the crude product afforded ethylene ketal 6 (1.503 g, 98% yield). Rᵣ = 0.35 (SiO₂, 10% EtOAc in hexane). ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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 C₁₀H₁₄O₄: 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 Na₂SO₄ 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. Rᵣ = 0.25 (SiO₂, 30% EtOAc in hexane). ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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 C₈H₁₀O₂Na: 183.0997. Found: 183.0995.

(⁵-Ethyl-4-(2-propyl-1,3-dioxolan-2-yl)but-2-en-1-ol, 8: To a stirred solution of oxalyl chloride (0.74 mL, 8.43 mmol) in dry CH₂Cl₂ (13 mL) at □78°C, dry DMSO (1.2 mL, 16.87 mmol) in 8 mL dry CH₂Cl₂ was added dropwise. After 30 min, alcohol 7 (0.9 g, 5.63 mmol) in 15 mL dry CH₂Cl₂ was added over 10 min giving a copious white precipitate. After stirring for 2 hr at □78°C, Et₃N (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 CH₂Cl₂ (3×25 mL). The combined organic layers were washed with water (15 mL), dried over anhydrous Na₂SO₄ 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 (ethoxy carbonyl)-methylene)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. Rᵣ = 0.55 (SiO₂, 10% EtOAc in hexane). ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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 C₁₃H₁₆O₄Na: 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 CH₂Cl₂ (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 CHCl₃ (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. Rₜ = 0.43 (SiO₂, 30% EtOAc in hexane), ¹H NMR (300 MHz, CDCl₃): 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 = 0.91 Hz). ¹³C NMR (75 MHz, CDCl₃): 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 C₁₀H₁₅O₃Na: 211.0784. Found: 211.0780.

2((2R,3S)-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 I₂ (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 Na₂SO₄. The solvent was evaporated and the residue was purified by column chromatography to afford 11 (0.843 g, 90%) as a yellow liquid. Rₜ = 0.5 (SiO₂, 20% EtOAc in hexane), [α]D²⁷ = +8.4° (c 1.05, CHCl₃), ¹H NMR (300 MHz, CDCl₃): 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), 5.25 (dt, 1H, J = 7.5 Hz), 1.33-1.45 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 10.7, 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, 915, 894, 837, 756, 608 cm⁻¹; ESI-MS: m/z 335 [M+Na⁺]; HRMS: Calcd for C₁₆H₂₁O₃Na: 335.0120. Found: 335.0117.

(R)-1-(2-Propyl-1,3-dioxolan-2-yl)butan-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. Rₜ = 0.45 (SiO₂, 20% EtOAc in hexane), [α]D²⁷ = +7.3° (c 1.0, CHCl₃), ¹H NMR (300 MHz, CDCl₃): 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), ¹³C NMR (75 MHz, CDCl₃): 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,
(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 NaHCO₃ and extracted with Et₂O (3×15 mL). The combined organic layers were washed with brine (1×5 mL), dried over anhydrous Na₂SO₄ 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. Rᵋ = 0.40 (SiO₂, 20% EtOAc in hexane). [α]ᵋ²/D = + 21.5° (c 1.15, CHCl₃); ¹H NMR (500 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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 C₅H₄O₂Na: 165.0891. Found: 165.0898.

(3R,5R)-Oct-1-ene-3,5-diol, 14: To a stirred solution of hydroxy 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 was 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 Na₂SO₄ and concentrated in vacuo. The crude residue was purified by column chromatography to afford compound 14 (0.233 g, 92%) as a colorless liquid. Rᵋ = 0.15 (SiO₂, 20% EtOAc in hexane). [α]ᵋ²/D = + 2.4° (c 1.32, CHCl₃); ¹H NMR (500 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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 C₁₀H₁₀O₂Na: 167.1047. Found: 167.1040.

(4R,6R)-6-(4-Methoxybenzylxoy)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 N₂. 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 was quenched with ice cooled water and extracted with Et₂O (3×20 mL). The combined organic extracts were washed with brine (1×10 mL) and dried over anhydrous Na₂SO₄. Removal of the solvent followed by purification by silica gel column chromatography afforded 15 in 92% yield as a colorless oil. Rᵋ = 0.50 (SiO₂, 20% EtOAc in hexane). [α]ᵋ²/D = +28.3° (c 1.32, CHCl₃); ¹H NMR (300 MHz, CDCl₃): 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), 5.15-5.26 (m, 2H), 5.65-5.81 (m, 1H), 6.82 (d, 2H, J = 8.3 Hz), 7.19 (d, 2H, J = 9.1 Hz); ¹³C NMR (75 MHz, CDCl₃): 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 C₁₆H₂₃O₃Na: 287.1623. Found: 287.1636.

(4R,6R)-6-(4-Methoxybenzylxoy)oct-7-en-4-yl-hex-5-enoate, 16: To a stirred solution of 15 (0.3 g, 1.14 mmol) in dry CH₂Cl₂ (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 CH₂Cl₂ (10 mL) was added and the stirring was continued at RT for 1 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. Rᵋ = 0.45 (SiO₂, 10% EtOAc in hexane). [α]ᵋ³₀/D = + 20.7° (c 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃): 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 Hz); ¹³C NMR (75 MHz, CDCl₃): 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, 1513, 1460, 1377, 1247, 1175, 1032, 993, 918, 820, 749 cm⁻¹; ESI-MS: [M+Na]⁺ 383; HRMS: Calcd for C₁₂H₂₃O₄Na: 383.2198. Found: 383.2188.

(4R,6R)-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 CH₂Cl₂ (11.2 mL) and H₂O (0.8 mL) at 0°C, and the resulting mixture was stirred at RT for 30 min. Then the mixture was quenched with saturated NaHCO₃ (2 mL) and extracted with CH₂Cl₂ (3×15 mL). The combined organic extracts were washed with brine (1×10 mL) and dried over anhydrous Na₂SO₄ and concentrated in vacuo. The crude residue was purified by column chromatography to afford 17 (0.187 g, 97%) as a colorless liquid. Rᵣ = 0.55 (SiO₂, 20% EtOAc in hexane). [α]ᵈ = + 1.0° (c 1.0, CHCl₃). ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): δ 13.9, 18.4, 24.0, 33.3, 36.8, 39.8, 70.6, 71.5, 114.9, 115.4, 136.3, 140.4, 173.5; IR (KBr): 3445, 2926, 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 C₁₃H₂₆O₃Na: 263.1623. Found: 263.1625.

Herbarumin-III, 1: Grubbs’s catalyst II (0.018 g, 0.052 mmol) was dissolved in CH₂Cl₂ (10 mL) and was added dropwise to a refluxing solution of a compound 17 (0.1 g, 0.42 mmol) in CH₂Cl₂ (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). Rᵣ = 0.55 (SiO₂, 20% EtOAc in hexane). [α]ᵈ = + 18.5° (c 1.0, EtOH). ¹H NMR (500 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): δ 13.8, 18.4, 24.0, 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 C₁₂H₂₀O₄Na: 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 NaBH₄·Et₂BOMe 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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References

7. (a) Hale K J, Lennon J A, Soraya Manaviazar S & Javaid M


