Stereoselective Formal Synthesis of Herbarumin III via Prins Cyclization

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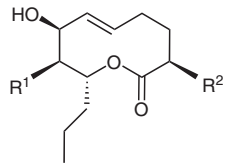
Abstract: The total synthesis of herbarumin III is described, proving the versatility of the Prins cyclization in the synthesis of natural products. The approach is convergent and highly stereoselective. Ring-closing metathesis and alkene-rearrangement reactions are utilized as key steps in the synthesis of the macrolactone.

Key words: herbarumins, Prins cyclization, alkene rearrangement, ring-closing metathesis



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

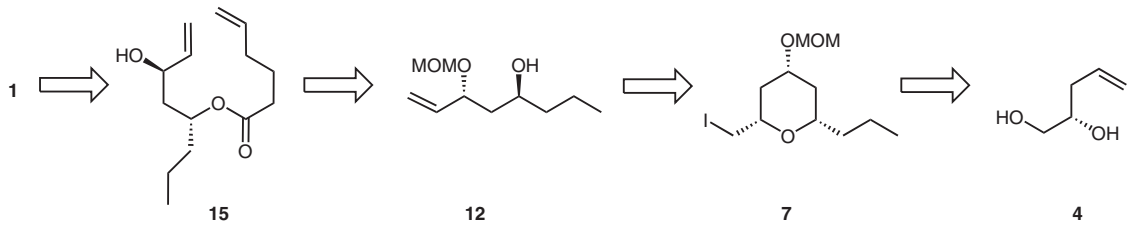
Figure 1

Herbarumin III (**1**) isolated[1a] from the fermentation broth and mycelium of the fungus *Phoma herbarum* displays significant phytotoxic effects against seedlings of *Amaranthus hypochondriacus*.[1b] The herbarumin macrolides **1**–**3** (Figure 1) interact with bovin brain calmodulin and inhibit the activation of the calmodulin-dependent enzyme cAMP phosphodiesterase. Construction of the ten-membered lactone ring and the stereocontrolled formation of the *syn*-1,3-diol unit are two major issues in the total synthesis of herbarumin III (**1**). In previous total syntheses of **1**,[2] the ten-membered lactone ring was synthesized by ring-closing metathesis (RCM) reaction[2a,b,d,e] and Yamaguchi's lactonization method.[2c] Asymmetric synthesis of the *syn*-1,3-diol moiety has been achieved using chiral pool methods,[2c] a chemoenzymatic method,[2c] an asymmetric allylation/Sharpless epoxidation method,[2e] and Jacobsen's hydrolytic kinetic resolution (HKR) method.[2f,g] Recently our group has developed a concise stereoselective total synthesis of herbarumin III utilizing Crimmins's aldol approach.[2i] Herein, we describe the stereoselective synthesis of herbarumin III (**1**) via Prins cyclization.

The Prins cyclization has emerged as a powerful synthetic tool for the construction of multi-substituted tetrahydropyran systems and has been utilized in the course of the synthesis of several natural products.[3] Our group has made a significant effort to explore the synthetic utility of Prins cyclization in the synthesis of various polyketide intermediates and has utilized the Prins cyclization in the synthesis of various natural products.[4] As a part of this ongoing programme, we have investigated the synthesis of herbarumin III (**1**).

In our retrosynthetic analysis (Scheme 1), we envisaged that the target molecule could be prepared from **15** through ring-closing metathesis. Compound **15** is viewed as being obtained from **12** via Mitsunobu inversion. It is proposed to obtain the 1,3-diol **12** from the iodide **8** via silica gel rearrangement and in turn pyran derivative **8** would be obtained via Prins cyclization of the homoallylic alcohol **4** and butyraldehyde.

In view of the importance of the macrolide **1**, we have attempted its enantiomeric synthesis (Scheme 2). The asymmetric total synthesis of herbarumin III (**1**) started with chiral homoallyl alcohol **4**. Copper-mediated regioselective opening[5] of benzyl (*S*)-glycidyl ether with vinylmagnesium bromide followed by debenzylation through treatment with lithium or sodium in liquid ammonia produced homoallylic alcohol **4**. Prins cyclization of **4** with butyraldehyde in the presence of trifluoroacetic acid followed by hydrolysis of the resulting trifluoroacetate gave trisubstituted pyran **5**.[4c] The stereochemistry was assumed to be in accordance as it was well examined and has been



Scheme 1

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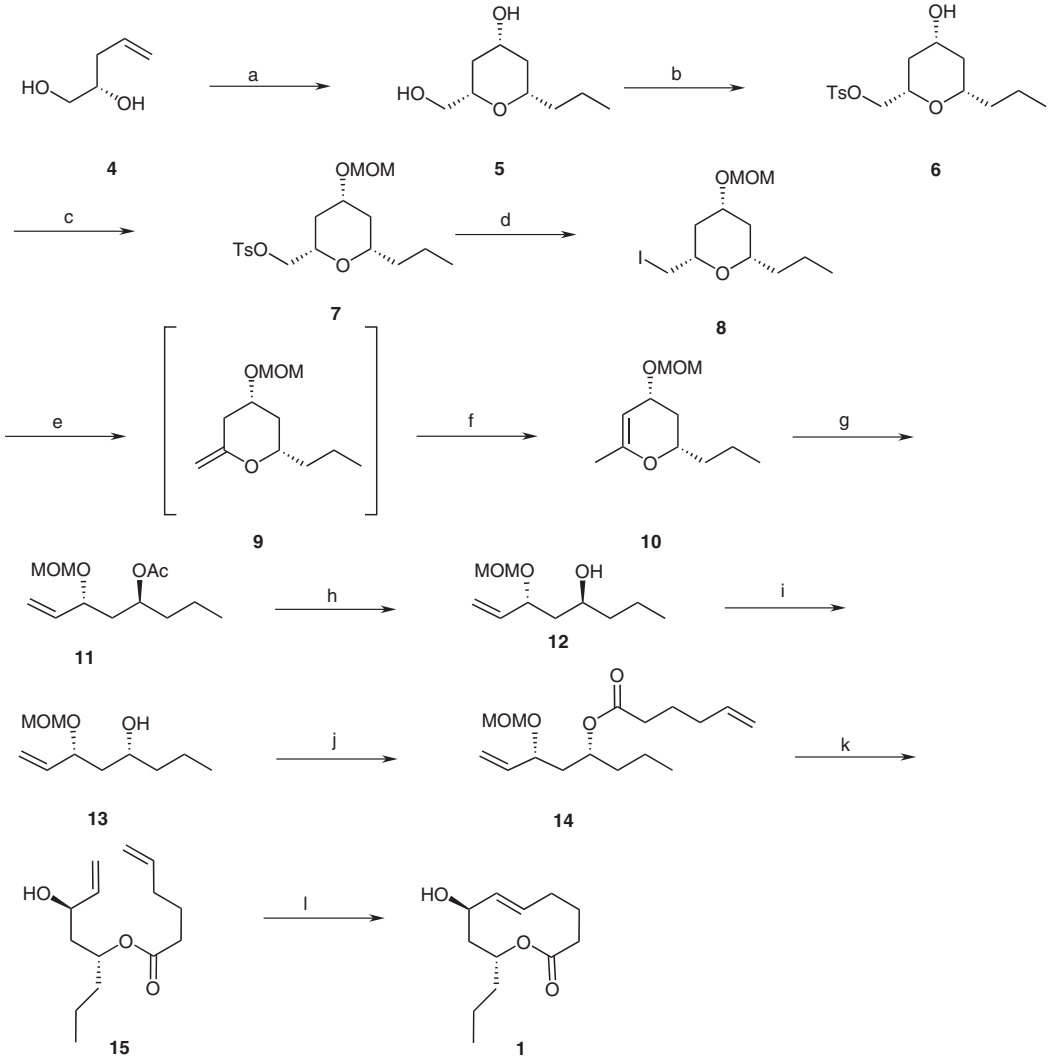
previously established.[4,5] However, it was proved after elaborating the compound **5** to the target molecule **1**, which in all respects was identical with that reported. Tosylation with 1.1 equivalents of tosyl chloride in the presence of triethylamine in dichloromethane produced the corresponding primary tosylate **6**.[4a] Protection of the secondary alcohol as the methoxymethyl ether **7** was performed with methoxymethyl chloride in dichloromethane in the presence of *N*,*N*-diisopropylethylamine.[6] Treatment of tosylate **7** with sodium iodide in refluxing acetone gave the corresponding iodo compound **8**. Elimination of HI[7] from **8** using sodium hydride in *N*,*N*-dimethylformamide produced enolic exocyclic alkene **9,** which on column chromatography revealed rearranged product **10**.

In fact, we anticipated that rearranging the exocyclic alkene **9** proceeds to the more stable endocyclic alkene **10** in acidic medium after column chromatography. Incidentally, we ended up with the compound with rearrangement on silica gel during flash chromatography. To confirm that the elimination reaction itself did not result in the rearranged product, we have analyzed the ^{1}H NMR of the crude product of the elimination reaction, which clearly revealed the presence of two doublets at δ = 4.33 and 4.09 (J = 2.2 Hz, geminal coupling) and the absence of any characteristic signal for the rearranged product.

Then, the substrate **10** was subjected to ozonolysis to obtain the corresponding acetoxy aldehyde, which without purification was treated with a one-carbon ylide to furnish the open-chain alkene **11**.[4e] Hydrolysis of the acetate group in **11** using potassium carbonate in methanol resulted in the alcohol **12**. Alcohol **12**, when subjected to standard Mitsunobu inversion conditions (DEAD, Ph_3P, 4-nitrobenzoic acid, THF then K_2CO_3, MeOH),[8] yielded **13** with the required *syn*-1,3-diol system. Esterification of the free hydroxy group of **13** with hex-5-enoic acid in the presence of *N*,*N*′-dicyclohexylcarbodiimide and a catalytic amount of 4-(dimethylamino)pyridine readily provided the diene **14**[2e] and set the stage for macrocyclization by



Scheme 2 *Reagents and conditions*: (a) 1. PrCHO, TFA, CH_2Cl_2; 2. K_2CO_3, MeOH, r.t., 3 h, 52%; (b) Et_3N, TsCl, CH_2Cl_2, 0 °C to r.t., 3 h, 95%; (c) MOMCl, DIPEA, DMAP, CH_2Cl_2, 0 °C to r.t., 3 h, 98%; (d) NaI, acetone, reflux, 24 h, 95%; (e) NaH, DMF, r.t., 6 h; (f) silica gel rearrangement, 83%; (g) 1. O_3, Ph_3P, CH_2Cl_2, 2. $Ph_3P{=}CH_2$, THF, –78 to 0 °C, 74%; (h) K_2CO_3, MeOH, r.t., 2 h, 96%; (i) 4-$O_2NC_6H_4CO_2H$, DEAD, Ph_3P, THF, 0 °C to r.t., 30 min, then K_2CO_3, MeOH, r.t., 4 h, 75%; (j) hex-5-enoic acid, DCC, DMAP, CH_2Cl_2, 86%; (k) TFA–CH_2Cl_2 (1:4), 25 °C, 2 h, 85%; (l) Grubbs II catalyst, CH_2Cl_2, 25 °C, 12 h, 62%.

ring-closing metathesis. At the outset, the macrocyclization, deprotection of the methoxymethyl ether **14** using trifluoroacetic acid in dichloromethane (1:4) provided the corresponding alcohol **15**.[4g]

Compound **15** possessed all the structural requirements, as well as the sense of chirality to be converted into the target macrolide **1** via a ring-closing metathesis reaction. The ring-closing metathesis reaction provides a remarkable scope for the synthesis of medium-sized rings and macrocyclic products and has been used extensively.[9] Although due to the inherent ring strain, the construction of medium-sized (8–11-membered) cycloalkenes via the ring-closing metathesis reaction is very challenging, some precedents exist.[9] The presence of a suitable functionality and its distance from the C=C bonds play a key role in the success of the metathesis reaction. It has been reported[2] that the ring-closing metathesis proceeds satisfactorily with substrates possessing a hex-5-enoate ester moiety, which is present in the dienic derivative **15**. All these considerations gave us confidence in this endeavor. The diene **15** upon treatment with 5 mol% Grubbs II catalyst (II) under high dilution conditions (0.001 M in CH_2Cl_2) produces only herbarumin III (**1**) in 62% yield,[2f,9] which in all respects was identical to the reported natural product.[2]

In conclusion, we have proved the versatility of the Prins cyclization in natural product synthesis by achieving the stereoselective formal synthesis of herbarumin III (**1**) employing an eleven-step sequence. Further applications of the Prins cyclization in the synthesis of natural products are in progress and will be disclosed in due course.

All reactions were carried out under an inert atmosphere unless mentioned following standard syringe/septum techniques. Solvents were dried and purified by conventional methods prior to use. The progress of reactions was monitored by TLC using glass plates precoated with silica gel 60 F254 to a thickness of 0.5 mm (Merck). Column chromatography was performed on silica gel (60–120 mesh) and neutral alumina using Et_2O, EtOAc, and hexane as eluents. Optical rotation values were measured with a Perkin-Elmer P241 polarimeter and Jasco DIP-360 digital polarimeter at 25 °C. IR spectra were recorded with a Perkin-Elmer FT-IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded with Varian Gemini 200 MHz, Bruker Avance 300 MHz, Varian Unity 400 MHz, or Varian Inova 500 MHz spectrometer using TMS as an internal standard in $CDCl_3$. MS were recorded on Micro mass VG-7070H for EI and VG Autospec M for FAB-MS**.**

(2*S*,4*S*,6*S*)-2-(Hydroxymethyl)-6-propyltetrahydro-2*H*-pyran-4-ol (5)

TFA (43.78 mL) was added slowly to a soln of **4** (3 g, 29.37 mmol) and butyraldehyde (6.35 g, 88.12 mmol) in CH_2Cl_2 (90 mL) at 25 °C under N_2. The mixture was stirred for 3.0 h and then sat. $NaHCO_3$ soln (200 mL) was added and pH was adjusted to >7 by addition of Et_3N. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 70 mL), the organic layers were combined, and the solvent was removed under reduced pressure. The trifluoroacetate obtained in this reaction was directly used in the next reaction without purification. The residue was dissolved in MeOH (40 mL) and stirred with K_2CO_3 (8.11 g) for 0.5 h. The MeOH was then removed under reduced pressure and H_2O (30 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. Purification of the crude product by column chromatography (silica gel) yielded **5** (2.65 g, 52%) as a colorless liquid; R_f = 0.3 (silica gel, 60% EtOAc–hexane).

$[\alpha]_D^{20}$ –0.2 (*c* 1.88, $CHCl_3$).

IR (neat): 3386, 2932, 2871, 1705, 1460, 1380, 1333, 1259, 1218, 1185, 1111, 1052, 980, 920, 847, 627 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.61 Hz, 3 H), 1.09–1.60 (m, 6 H), 1.78–1.95 (m, 2 H), 2.27 (s, 2 H), 3.27–3.62 (m, 4 H), 3.69–3.85 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.98, 18.63, 36.77, 37.47, 40.90, 65.55, 67.71, 75.45, 75.93.

HRMS (ESI): *m*/*z* [M^+ + Na] calcd for $C_9H_{18}NaO_3$: 197.2374; found: 197.1153.

(2*S*,4*S*,6*S*)-2-Propyl-6-(tosyloxymethyl)tetrahydro-2*H*-pyran-4-ol (6)

To soln of **5** (2.5 g, 14.3 mmol) in anhyd CH_2Cl_2 (25 mL) at 0 °C was added Et_3N (3.99 mL, 28.7 mmol). Then TsCl (2.87 g, 15.1 mmol) was added over 2 h, the mixture was allowed to warm to r.t. and stirred for 3 h. The mixture was treated with aq 1 M HCl (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was washed with sat. $NaHCO_3$ (15 mL) and H_2O (15 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography of the crude afforded **6** (4.47 g, 95%) as a gummy liquid; R_f = 0.6 (silica gel, 40% EtOAc–hexane).

$[\alpha]_D^{20}$ +2.5 (*c* 0.96, $CHCl_3$).

IR (neat): 3425, 2957, 2869, 1781, 1739, 1598, 1454, 1360, 1243, 1176.6, 1189, 1096, 976, 815, 668 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.03 Hz, 3 H), 1.00–1.84, (m, 8 H), 2.42 (s, 3 H), 3.14–3.23 (m, 1 H), 3.42–3.54 (m, 1 H), 3.61–3.77 (m, 1 H), 3.89–3.94 (m, 2 H), 7.30–7.40 (d, *J* = 7.18 Hz, 2 H), 7.60–7.85 (d, *J* = 8.59 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.88, 18.40, 21.43, 36.68, 37.73, 40.48, 67.30, 72.08, 72.63, 75.42, 127.75, 129.64, 132.78, 144.65.

HRMS (ESI): *m*/*z* [M^+ + Na] calcd for $C_{16}H_{24}NaO_5S$: 351.4248; found: 351.1238.

(2*S*,4*S*,6*S*)-4-(Methoxymethoxy)-2-propyl-6-(tosyloxymethyl)tetrahydro-2*H*-pyran (7)

To **6** (3.0 g, 9.13 mmol) in anhyd CH_2Cl_2 (30 mL) at 0 °C were added successively DIPEA (4.69 mL, 27.40 mmol), DMAP (cat.), and MOMCl (1.47 g, 18.26 mmol). The mixture was stirred at r.t. for 3 h, quenched by addition of H_2O (10 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried (anhyd Na_2SO_4), and concentrated under vacuum to remove the solvent and the crude was purified by column chromatography to afford pure **7** (3.33 g, 98%) as a viscous liquid; R_f = 0.7 (silica gel, 10% EtOAc–hexane).

$[\alpha]_D^{20}$ +6.3 (*c* 0.85, $CHCl_3$).

IR (neat): 2955, 2876, 1630, 1598, 1451, 1362, 1210, 1179, 1143, 1098, 1039, 976, 939, 815, 668, 555 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 6.79 Hz, 3 H), 1.05–1.41 (m, 2 H), 1.24–1.55 (m, 4 H), 1.86–1.96 (m, 2 H), 2.47 (s, 3 H), 3.24 (m, 1 H), 3.32 (s, 3 H), 3.48–3.70 (m, 2 H), 3.91–4.02 (m, 2 H), 4.62 (s, 2 H), 7.31 (d, *J* = 8.30 Hz, 2 H), 7.74 (d, *J* = 8.30 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.91, 18.43, 21.46, 34.36, 37.86, 38.07, 55.12, 72.03, 72.4, 72.72, 75.47, 75.5, 94.31, 127.81, 129.63, 132.97, 144.57.

HRMS (ESI): *m*/*z* [M^+ + Na] calcd for $C_{18}H_{28}NaO_6S$: 395.4773; found: 395.1515.

(2*S*,4*S*,6*S*)-2-(Iodomethyl)-4-(methoxymethoxy)-6-propyltetrahydro-2*H*-pyran (8)

NaI (6.03 g, 40.27 mmol) was added to a soln of **7** (3.5 g, 9.4 mmol) in acetone (60 mL) and the mixture was heated to reflux for 24 h. Acetone was removed under reduced pressure. To the residue was added H_2O and CH_2Cl_2 and the organic layer was separated, dried (Na_2SO_4), concentrated, and chromatographed to afford **8** (2.51 g, 95%) as a colorless liquid; R_f = 0.7 (silica gel, 10% EtOAc–hexane).

$[\alpha]_D^{20}$ –22.0 (*c* 1.91, $CHCl_3$).

IR (neat): 3447, 2957, 2928, 1735, 1670, 1595, 1458, 1517, 1458, 1375, 1273, 1152, 1036, 918, 754 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 6.79 Hz, 3 H), 1.09–1.22 (m, 2 H), 1.31–1.62 (m, 4 H), 1.84–1.90 (dddd, *J* = 12.84, 2.26, 2.26 Hz, 1 H), 2.15–2.20 (dddd, *J* = 12.08, 2.26, 2.26 Hz, 1 H), 3.14–3.17 (m, 2 H), 3.29–3.39 (m, 5 H), 3.61–3.73 (m, 1 H), 4.63–4.68 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.75, 13.93, 18.65, 37.97, 38.13, 38.19, 55.17, 72.60, 74.99, 75.59, 94.35.

HRMS (ESI): *m*/*z* [M^+ + Na] calcd for $C_{11}H_{21}INaO_3$: 351.1871; found: 351.0418.

(2*S*,4*R*)-4-(Methoxymethoxy)-6-methyl-2-propyl-3,4-dihydro-2*H*-pyran (10)

To a soln of **11** (2.5 g, 7.6 mmol) in DMF (100 mL) at 0 °C was added NaH (60% in oil, 0.91 g, 38.0 mmol). The mixture was stirred at r.t. 6 h and then the reaction was quenched with H_2O at 0 °C. The resultant mixture was diluted with EtOAc, washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 10% EtOAc–hexane) gave **9**, which on column chromatography revealed rearranged product **10** (1.26 g, 83%) as a colorless clear oil; R_f = 0.6 (silica gel, 10% EtOAc–hexane).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 6.79 Hz, 3 H), 1.25–1.71 (m, 7 H), 1.91–2.14 (m, 2 H), 3.53 (s, 3 H), 3.85 (m, 1 H), 4.24 (m, 1 H), 4.49 (s, 1 H), 4.63 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.06, 98.02, 94.74, 70.63, 70.46, 55.24, 42.53, 41.49, 22.08, 18.77, 14.13.

LC-MS: *m*/*z* = 199 (M – 1), 169, 140, 139, 110, 102, 101, 81.

(3*R*,5*S*)-5-Acetoxy-3-(methoxymethoxy)octadec-1-ene (11)

Ozone was bubbled through a soln of **10** (1.0 g, 4.99 mmol) in CH_2Cl_2 (12 mL) at –78 °C until no unreacted starting material was observed (TLC). The mixture was purged with N_2 to remove the excess ozone and cooled to 0 °C, Ph_3P (2.61 g, 9.98 mmol) was added, and the mixture was stirred for 2 h. The mixture was concentrated in vacuo. After addition of hexane, the mixture was filtered through a Celite pad; the residue was washed with hexane. The filtrate was dried (Na_2SO_4), concentrated under reduced pressure, and the crude aldehyde was subjected to the next reaction without further purification.

To the ylide generated from methylenetriphenylphosphorane (6.05 g, 14.97 mmol) and *t*-BuOK (2.80 g, 25.0 mmol) in anhyd THF was added at 0 °C a soln of the aldehyde in anhyd THF (12 mL) and the mixture was stirred for 2 h at this temperature. THF was removed under reduced pressure and to the residue was added EtOAc (15 mL) and the soln was washed with brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography afforded **11** (0.85g, 74%, 2 steps) as a colorless oil; R_f = 0.7 (silica gel, 10% EtOAc–hexane).

$[\alpha]_D^{20}$ –122.6 (*c* 1, $CHCl_3$).

IR (neat): 2959, 2932, 1738, 1463, 1372, 1241, 1155, 1098, 1031, 924 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 6.61 Hz, 3 H), 1.25–1.74 (m, 6 H), 2.02 (s, 3 H), 3.30 (s, 3 H), 3.93–4.04 (m, 1 H), 4.39–4.64 (dd, *J* = 7.34, 6.79 Hz, 2 H), 4.97–5.09 (m, 1 H), 5.14–5.24 (m, 2 H), 5.56–5.73 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.91, 18.21, 21.13, 36.88, 40.11, 55.66, 70.77, 73.98, 93.87, 117.14, 138.67, 170.54.

HRMS (ESI): *m*/*z* [M^+ + Na] calcd for $C_{12}H_{22}NaO_4$: 253.3007; found: 253.1424.

(3*R*,5*S*)-3-(Methoxymethoxy)octadec-1-en-5-ol (12)

Compound **11** (0.5 g, 2.17 mmol) was dissolved in MeOH (10 mL) and K_2CO_3 (0.6 g, 4.34 mmol) was added. The mixture was stirred at r.t. for 4 h and then it was diluted with H_2O (15 mL) and extracted with CH_2Cl_2 (3 × 10 mL). Removal of solvent under reduced pressure followed by flash chromatography afforded **12** (0.39 g, 96%) as a colorless liquid; R_f = 0.4 (30% EtOAc–hexane).

$[\alpha]_D^{20}$ –113.5 (*c* 1, $CHCl_3$).

IR (neat): 3443, 2955, 2930, 1637, 1461, 1419, 1381, 1216, 1152, 1097, 1034, 922 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.03 Hz, 3 H), 1.35–1.69 (m, 6 H), 3.39 (s, 3 H), 3.79–3.91 (m, 1 H), 4.25–4.34 (m, 1 H), 4.51–4.67 (dd, *J* = 7.03, 6.25 Hz, 2 H), 5.15–5.26 (m, 2 H), 5.66–5.83 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.02, 18.78, 39.59, 42.34, 55.68, 67.74, 75.40, 94.40, 116.59, 137.91.

(3*R*,5*R*)-3-(Methoxymethoxy)octadec-1-en-5-ol (13)

To a stirred mixture of **12** (0.3 g, 1.53 mmol), Ph_3P (1.33 g, 5.0 mmol), and 4-nitrobenzoic acid (0.34 g, 2.0 mmol) in anhyd THF (10 mL) at 0 °C was added DEAD (0.88 g, 5.0 mmol) via a syringe. The mixture was then stirred at r.t. for 0.5 h, diluted with H_2O (10 mL), and extracted with EtOAc (2 × 15 mL). The solvent was removed and the crude product was dissolved in MeOH (10 mL) and K_2CO_3 (0.44 g, 3.18 mmol) was added. The mixture was stirred at r.t. for 4 h and then it was diluted with H_2O (15 mL) and extracted with CH_2Cl_2 (3 × 10 mL). Removal of solvent under reduced pressure followed by flash chromatography afforded **13** (0.22 g, 75%) as a colorless liquid; R_f = 0.4 (30% EtOAc–hexane).

$[\alpha]_D^{20}$ –100.5 (*c* 1, $CHCl_3$).

IR (neat): 3443, 2956, 2930, 1637, 1461, 1419, 1381, 1216, 1152, 1097.83, 1034, 922 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.03 Hz, 3 H), 1.26–1.79 (m, 6 H), 3.39 (s, 3 H), 3.74–3.85 (m, 1 H), 4.19–4.30 (m, 1 H), 4.48–4.73 (dd, *J* = 7.03, 6.25 Hz, 2 H), 5.18–5.27 (m, 2 H), 5.56–5.74 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.05, 18.58, 39.74, 42.43, 55.72, 70.48, 77.58, 93.46, 117.82, 137.57.

HRMS (ESI): *m*/*z* [M^+ + Na] calcd for $C_{10}H_{20}NaO_3$: 211.2640; found: 211.1306.

(4*R*,6*R*)-6-(Methoxymethoxy)oct-7-en-4-yl Hex-5-enoate (14)

To a soln of **12** (0.2 g, 1.06 mmol) in CH_2Cl_2 (10 mL) was added hex-5-enoic acid (0.13 g, 1.16 mmol) and DCC (0.24 g, 1.16 mmol) at r.t. DMAP (0.06 g, 0.53 mmol) was added and the mixture was stirred at r.t. for 15 h. Filtration of the mixture, evaporation of the solvent, and column chromatography of the resulting crude afforded **14** (0.26 g, 86%) as a colorless oil; R_f = 0.2 (silica gel, 20% EtOAc–hexane).

$[\alpha]_D^{20}$ –89.0 (*c* 1, $CHCl_3$).

IR (neat): 3168, 2928, 1732, 1631, 1384, 1244, 1154, 1100, 1033 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.03 Hz, 3 H), 1.25–1.40 (m, 4 H), 1.49–1.78 (m, 2 H), 1.84–1.98 (m, 2 H), 2.04–2.14 (m, 2 H), 2.23–2.30 (m, 2 H), 3.34 (s, 3 H), 3.93–4.04 (m, 1 H), 4.44–4.64 (dd, *J* = 7.03, 7.03 Hz, 2 H), 4.92–5.04 (m, 3 H), 5.13–5.20 (m, 2 H), 5.53–5.82 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.91, 18.36, 24.15, 33.08, 33.81, 36.48, 39.89, 55.45, 70.81, 74.53, 93.65, 115.29, 118.03, 137.69, 172.95.

HRMS (ESI): *m*/*z* [M^+ + Na] calcd for $C_{16}H_{28}NaO_4$: 307.3911; found: 307.1882.

(3*R*,5*R*)-5-(Hex-5-enoyloxy)oct-1-en-3-ol (15)

Compound **14** (0.1 g, 0.35 mmol) was dissolved in CH_2Cl_2 (1 mL) and TFA (0.10 mL, 1.40 mmol) was added dropwise at 25 °C. The mixture was stirred at this temperature for 2 h and then quenched with sat. $NaHCO_3$ soln (8 mL) and extracted with CH_2Cl_2 (2 × 8 mL). The combined organic extracts were washed with brine (8 mL) and concentrated in vacuo and the residue was subjected to column chromatography to afford the pure **15** (0.071 g, 85%) as a colorless oil; R_f = 0.5 (silica gel, 30% EtOAc–hexane).

$[\alpha]_D^{20}$ +1.0 (*c* 1, $CHCl_3$).

IR (neat): 3442, 2927, 2857, 1731, 1630, 1173 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, 3 H), 1.10–1.45 (m, 4 H), 1.5–1.90 (m, 4 H), 2.00 (s, 1 H), 2.00–2.18 (m, 2 H), 2.24–2.32 (m, 2 H), 4.20–4.30 (s, 1 H), 4.90–5.62 (m, 5 H), 5.68–5.90 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.98, 18.42, 24.06, 32.99, 33.88, 36.78, 41.61, 70.55, 71.59, 114.86, 115.34, 137.64, 140.50, 173.48.

HRMS (ESI): *m*/*z* [[M^+ + Na]] calcd for $C_{14}H_{24}NaO_3$: 263.3384; found: 263.1622.

(7*R*,9*R*,5*E*)-7-Hydroxy-9-propylnon-5-en-9-olide (Herbarumin III, 1)

Grubbs II catalyst (0.88 mg, 5 mol%) was dissolved in CH_2Cl_2 (10 mL) and was added dropwise to a soln of **15** (0.05 g, 0.20 mmol) in CH_2Cl_2 (40 mL). The mixture was stirred at 25 °C for 12 h, by which time all of the starting material had been consumed (TLC). The solvent was removed under vacuum and the crude product was purified by column chromatography (silica gel) to give **1** (0.027 g, 62%) as a colorless oil; R_f = 0.3 (silica gel, 30% EtOAc–hexane).

$[\alpha]_D^{20}$ +20.2 (*c* 1.24, EtOH).

IR (neat): 3442, 2959, 2927, 1725, 1630, 1383 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, 3 H), 1.32–1.42 (m, 2 H), 1.49–1.76 (m, 2 H), 1.77–1.85 (m, 2 H), 1.98–2.02 (m, 3 H), 2.02 (m, 1 H), 2.24–2.29 (m, 1 H), 2.37–2.42 (m, partially D_2O exchangeable, 2 H), 4.42–4.47 (m, 1 H), 5.10–5.21 (m, 1 H), 5.34–5.44 (m, 1 H), 5.59–5.64 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 18.4, 26.0, 33.7, 34.6, 37.4, 40.6, 67.8, 68.0, 124.9, 134.6, 176.7.

HRMS (ESI): *m*/*z* [M^+ + Na] calcd for $C_{12}H_{20}NaO_3$: 235.2854; found: 235.1303.

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