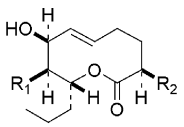
A short enantioselective total synthesis of the phytotoxic lactone herbarumin III

Joshodeep Boruwa, Naminita Gogoi and Nabin C. Barua*

Received 26th April 2006, Accepted 27th July 2006
First published as an Advance Article on the web 14th August 2006
DOI: 10.1039/b605982a

The phytotoxic lactone herbarumin III has been synthesized in 11% overall yield. The approach applied uses Keck's asymmetric allylation and Sharpless epoxidation to build the key fragment. Esterification with 5-hexenoic acid and a ring closing metathesis was used to arrive at the target.

The phytotoxic lactone Herbarumin III (Fig. 1) was isolated from the fermentation broth and mycelium of the fungus *Phoma herbarum* by Mata *et al.* in extremely low yield[1] along with known compounds Herbarumin I (**2**) and II (**3**).[2] Herbarumin III showed significant phytotoxic effects when tested against seedlings of *A. hypochondriacus.* This macrolide ($IC_{50} = 2 \times 10^{-4}$ M) inhibited radical growth with higher potency than dichlorophenoxy acetic acid [2.4 D ($IC_{50} = 2 \times 10^{-4}$ M)] used as a positive control. Notably, the phytotoxic effect of **1** was comparable to that of **2** and higher than that of **3**. Detailed biological investigations revealed that compounds **1–3** interacted with bovine-brain calmodulin and inhibited the activation of the calmodulin dependent enzyme cAMP phosphodiesterase.[1] These findings makes it clear that compounds **1–3** are promising lead structures in the search for novel herbicidal agents and should have medicinal interest as well.

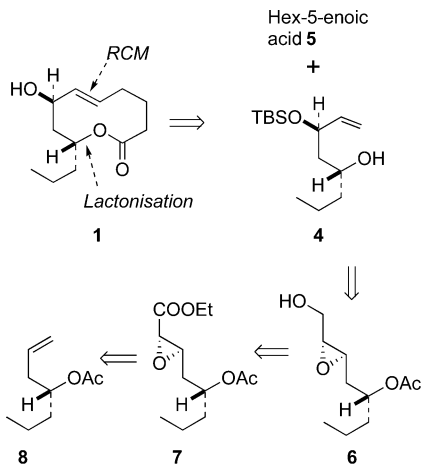


$R^1 = R^2 = H$: Herbarumin III (**1**)
$R^1 = OH$, $R^2 = H$: Herbarumin I (**2**)
$R^1 = R^2 = OH$: Herbarumin II (**3**)

Fig. 1

To our knowledge, only three syntheses of **1** have been reported to date. The first one was by Gurjar *et al.*, starting from D-glucose,[3a,b] then a chemoenzymatic synthesis was carried out by Nanda[3c] and more recently, while this manuscript was under preparation, Chattopadhyay *et al.* described another synthesis beginning from (*R*)-cyclohexylidene glyceraldehydes.[3d] Recently, we have been engaged in synthetic studies of naturally occurring lactones, resulting in the total synthesis of patulolides A and B, verbalactone and boronolide.[4] In context with this study, since a limited quantity of **1** is available, we undertook the synthesis of this demanding target.

Our planned approach to herbarumin III (**1**) involved the coupling of fragments **4** and **5** *via* esterification followed by ring closing metathesis. Encouraged by a previous successful implementation of RCM into the total synthesis of natural products containing a medium sized ring,[5] we chose this methodology for the formation of the 10-membered ring. For installation of stereochemistry at C-7 and C-9, we relied on Sharpless epoxidation and asymmetric allylation respectively (Scheme 1).



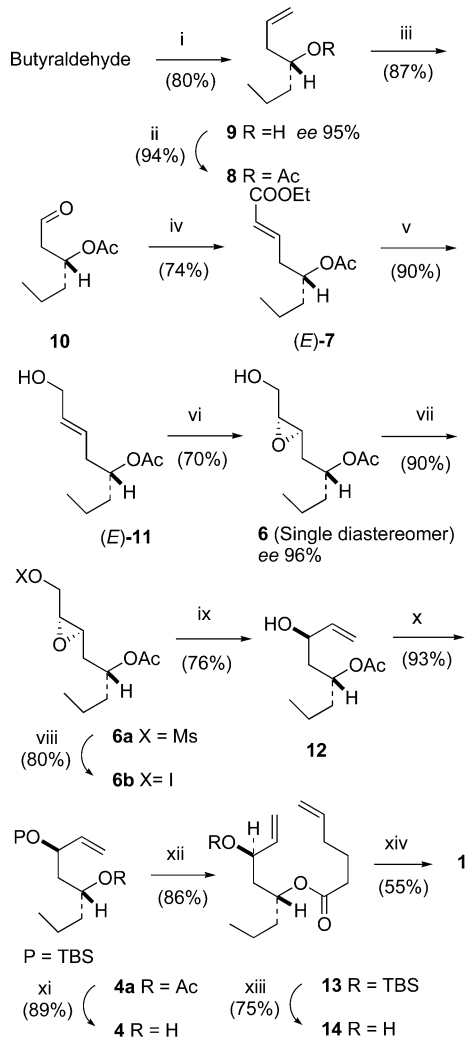
Scheme 1 Retrosynthetic approach to herbarumin III.

The synthesis (Scheme 2) was initiated by employing the catalytic asymmetric allyl stannation protocol developed by Keck *et al.*[6] In the presence of a catalytic system comprising 1 equivalent of (*R*)-BINOL, 1 equivalent of $Ti(O–iPr)_4$ and 4 Å molecular sieves which had been pre-formed in refluxing CH_2Cl_2, the reaction of *n*-butanal and allyl tributylstannane provided the homoallylic alcohol **9** in 80% yield and 95% ee[7] $\{[\alpha]_D^{20} = +14.9\ (c\ 0.9, CH_2Cl_2)\}$.

Acetylation of the hydroxyl function with acetic anhydride catalyzed by iodine,[8] followed by oxidative cleavage of the olefinic bond using OsO_4 and $NaIO_4$ in the presence of 2,6-lutidine in dioxane–water[9] furnished the corresponding aldehyde **10**.

Chain elongation of **10** *via* Wittig olefination with triphenyl carbethoxymethyl phosphonium chloride supported on alumina under microwave irradiation[10] provided the α,β-unsaturated ester (*E*)-**7** as the major product (*E*–*Z* 14 : 1).[11] Since Sharpless epoxidation of *Z*-allylic alcohols is known to proceed with poor optical purity,[12] (*E*)-**7** was used for the rest of the synthesis. Thus, exposure of (*E*)-**7** to DIBAL in THF at −78 °C delivered the required allylic alcohol (*E*)-**11**. Katsuki–Sharpless epoxidation[13a,b] of this under the influence (−)-DET proceeded well to furnish the

Natural Products Chemistry Division, Regional Research Laboratory (CSIR), Jorhat, 785 006, Assam, India. E-mail: ncbarua2000@yahoo.co.in; Fax: +91-376-2370011



Scheme 2 *Reagents and conditions*: (i) (*R*)–BINOL, 4 Å ms, Ti(i–OPr)$_4$, allyltributyl tin, CH_2Cl_2, −78 to −20 °C; (ii) acetic anhydride, I_2; (iii) OsO_4, $NaIO_4$, 2,6-lutidine, dioxane–water; (iv) triphenyl carbethoxymethyl phosphonium chloride (1.2 eqv.), basic alumina, microwaves; (v) DIBAL, THF, −78 °C; (vi) Ti(i–OPr)$_4$, (−)-DET (diethyl tartrate), TBHP (*tert*-butylhydroperoxide), CH_2Cl_2, −20 °C; (vii) MsCl, Et_3N, CH_2Cl_2; (viii) NaI, acetone; (ix) Zn, I_2 (cat.), MeOH, reflux; (x) TBSCl, imidazole, DMF; (xi) K_2CO_3, MeOH; (xii) 5-hexenoic acid, DCC, DMAP (cat.), CH_2Cl_2; (xiii) TBAF, THF, 0 °C; (xiv) Grubbs catalyst, CH_2Cl_2, reflux.

epoxide **6** as a single diastereomer[14] with 96% ee, which set the C-7 stereocentre.

Installation of the allylic system needed for the final ring closing metathesis started with activation of the primary alcohol group in **6** as the corresponding mesylate. Exposure of the mesylate to NaI and reductive fragmentation of the derived iodoepoxide using Zn powder in refluxing MeOH[14] provided the allylic alcohol **12**. Protection of the free OH group of **12** as a TBS ether and subsequent removal of the acetate under basic conditions furnished **4**. Esterification of the free OH group of **4** with 5-hexenoic acid in the presence of DCC and catalytic DMAP readily provided the diene **13** and set the stage for macrocyclization by ring closing metathesis. At the outset of macrocyclization, deprotection of the TBS ether was effected with TBAF under standard conditions. Finally, ring closing metathesis with Grubbs second-generation catalyst following reported conditions[15] proceeded uneventfully to give Herbarumin III as a clear oil. The sign of optical rotation {$[a]_D^{20}$ = +17.6 (*c* 0.7, EtOH); lit.[1] $[a]_D^{20}$ = +22.0 (*c* I mg mL^{-1}, EtOH)} and spectral data closely matched with those reported for the natural product.[1]

Thus, we have synthesized this molecule starting from *n*-butanal in 11% overall yield. It is noteworthy that this inherently flexible approach opens a general way for the assembly of herbarumin III libraries differing in C-9 carbon chain and stereochemistry.

Experimental

General remarks

^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker DPX-300 NMR machine. IR spectra were recorded on a Perkin-Elmer 1640 FT-IR spectrometer. Optical rotations were measured on a Perkin-Elmer 343 polarimeter. Elemental analyses were done using a Perkin-Elmer series II CSNS/O Model 2400 analyzer. Mass spectra were recorded on a Bruker Daltonic Data Analysis 2.0 spectrometer. Column chromatography was performed with Merck silica gel (60–120 mesh) and preparative TLC was carried out on plates prepared with Merck Silica gel G. Moisture sensitive reactions were conducted under a dry nitrogen atmosphere. Diethyl ether and THF were distilled from benzophenone ketyl prior to use. Dichloromethane was distilled from P_2O_5 and stored over molecular sieves. All solvents were distilled at their boiling point, and other commercially available reagents were used as received, unless otherwise stated.

(4*R*)-Hept-1-en-4-ol (9). A mixture of (*R*)-BINOL (0.84 g, 2.92 mmol) and Ti(O–iPr)$_4$ (0.83 g, 2.92 mmol) in CH_2Cl_2 (30 mL) in the presence of 4 Å molecular sieves (2.4 g) was stirred under reflux. After 1 h, the reaction mixture was cooled to room temperature, and *n*-butyraldehyde (2.1 g, 29.2 mmol) was added and the resulting mixture was stirred for 10 min. The reaction mixture was then cooled to −78 °C and allyl tributylstannane (10.6 g, 32.0 mmol) was added to it and the stirring continued at −20 °C for 36 h. Saturated $NaHCO_3$ solution (5 mL) was added to quench the reaction, this was stirred for an additional 30 min and was then extracted with CH_2Cl_2 (40 mL). The organic phase was washed with water (15 mL), dried (Na_2SO_4), the solvent was evaporated and the residue was purified by chromatography on SiO_2 (EtOAc–hexane 1 : 9) to give 2.6 g (23.4 mmol, 80%) of **9** as a clear liquid. Ee 95%; $[a]_D^{20}$ = −13.1 (*c* 1.0, CH_2Cl_2). IR (neat): 3410 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, J = 6.5 Hz, 3 H), 1.30–1.52 (m, 4 H), 2.04–2.12 (m, 2 H), 2.33–2.39 (br s, 1 H), 3.55–3.60 (m, 1 H), 5.04 (dd, J = 16.0 & 11.2 Hz, 1 H), 5.14 (dd, J = 16.1 & 1.4 Hz, 1 H), 5.72–5.75 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.10, 19.00, 39.20, 42.20, 70.80, 117.30, 135.30; MS (ESI) *m*/*z* 137.2 (M^+ + Na); Anal. Cal. for $C_7H_{14}O$ (114.104): C, 73.63; H, 12.36. Found: C, 73.60; H, 12.26%.

(1*R*)-1-Allylbutyl acetate (8). To a stirred solution of **9** (2.5 g, 21.9 mmol) and acetic anhydride (4.5 g, 44.1 mmol), iodine (250 mg, 1.96 mmol) was added and the reaction mixture was stirred at room temperature for 10 min. 10% $Na_2S_2O_3$ solution (30 mL) was added and extracted with ether (80 mL). The reaction mixture was washed successively with 10% $NaHCO_3$ solution (3 × 20 mL) and H_2O (30 mL). The organic phase was dried

(Na_2SO_4), the solvent was evaporated and the residue was purified by chromatography on SiO_2 (EtOAc–hexane 1 : 10) to give 3.2 g (20.6 mmol, 94%) of **8** as a clear liquid. Ee 95%; $[\alpha]_D^{20} = -11.2$ (*c* 1.0, CH_2Cl_2). IR (neat): 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta =$ 0.95 (t, $J = 6.6$ Hz, 3 H), 1.31–1.60 (m, 4 H), 2.03–2.13 (m, 2 H), 2.17 (s, 3 H), 4.87–4.93 (m, 1 H), 5.02 (dd, $J = 16.0$ & 11.2 Hz, 1 H), 5.12 (dd, $J = 16.0$ & 1.6 Hz, 1 H), 5.74–5.79 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 13.99, 18.80, 20.85, 36.70, 37.10, 74.03, 116.75, 135.01, 170.11; MS (ESI) *m/z* 156.22 (M^+); Anal. Cal. for $C_9H_{16}O_2$ (156.115): C, 69.19; H, 10.32. Found: C, 69.10; H, 10.49%.

(3*R*)-3-Acetoxy-hexanal (10). To a solution of the acetate **8** (3.0 g, 19.2 mmol) in dioxane–H_2O (160 mL 3 : 1) was added 2,6-lutidine (4.1 g, 38.3 mmol), OsO_4 (4% solution in i-PrOH, 0.037 mL) and $NaIO_4$ (16.4 g, 76.9 mmol). The mixture was stirred at room temperature; upon completion, water (50 mL) was added and extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was dried (Na_2SO_4) and the solvent was evaporated to give 2.64 g (16.7 mmol, 87%) of **10** as a pale yellow liquid, which, without further purification was applied in the next step.

(5*R*)-5-Acetoxy-oct-2-enoic acid ethyl ester ((*E*)-7). To a mixture of aldehyde **10** (2.5 g, 15.8 mmol) and triphenyl carbethoxymethyl phosphonium chloride (7.3 g, 18.9 mmol) in CH_2Cl_2 (50 mL), basic alumina (13.3 g) was added and the mixture was stirred thoroughly. The solvent was completely removed under vacuum and the solid mass was put under microwave irradiation (60%, 360 Watt) for 5 min. To this, $CHCl_3$ (60 mL) was added, stirred vigorously and then filtered. The filter pad was washed thoroughly with $CHCl_3$ and the combined washings were evaporated to afford a solid mass, which was purified by chromatography on SiO_2 (EtOAc–hexane 1 : 12) to give 2.66 g (11.7 mmol, 74%) of (*E*)-**7** as a gum. Ee 95%; $[\alpha]_D^{20} = +12.4$ (*c* 0.9, CH_2Cl_2). IR (neat): 1740, 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.85$ (t, $J = 7.2$ Hz, 3 H), 1.25 (t, $J = 6.8$ Hz, 3 H), 1.30–1.34 (m, 4 H), 2.11 (s, 3 H), 2.40–2.52 (m, 2 H), 4.19 (q, $J =$ 7.2 & 12.5 Hz, 2 H), 4.90–4.96 (m, 1 H), 5.82 (d, $J = 15.6$ Hz, 1 H), 6.78–6.91 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 13.90, 14.16, 18.89, 20.80, 33.70, 37.19, 60.03, 74.00, 121.46, 150.08, 166.50, 170.11; MS (ESI) *m/z* 228.3 (M^+); Anal. Cal. for $C_{12}H_{20}O_4$ (228.14): C, 63.14; H, 8.83. Found: C, 63.10; H, 8.95%.

(1*R*)-Acetoxy-5-hydroxy-1-propyl-pent-3-ene ((*E*)-11). To a stirred solution of the ester (*E*)-**7** (2.5 g, 10.9 mmol) in dry CH_2Cl_2 (10 mL) cooled to −78 °C, DIBAL (1 M solution in hexane) (13 mL, 1.2 equiv.) was added slowly under N_2 and the mixture was stirred at the same temperature for 2 h. Water was added drop-wise to quench the reaction, which was warmed to room temperature and then extracted with ether (3 × 30 mL). The organic phase was dried (Na_2SO_4) and the solvent was evaporated to afford a slight brown residue, which was chromatographed on SiO_2 (EtOAc–hexane 1 : 8) to give 1.82 g (9.8 mmol, 90%) of (*E*)-**11** as a clear liquid. Ee 95%; $[\alpha]_D^{20} = +13.7$ (*c* 0.8, CH_2Cl_2). IR (neat): 3374 (br), 1741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 7.6$ Hz, 3 H), 1.28–1.36 (m, 4 H), 2.13 (s, 3 H), 2.21–2.26 (br s, 1 H), 2.40–2.50 (m, 2 H), 3.98–4.04 (m, 2 H), 4.90–4.95 (m, 1 H), 5.59–5.67 (m, 1 H), 5.72–5.81 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 13.99, 18.80, 20.85, 33.80, 37.10, 60.82, 74.09, 129.74, 132.40, 170.10; MS (ESI) *m/z* 186.3 (M^+); Anal. Cal. for $C_{10}H_{18}O_3$ (186.13): C, 64.49; H, 9.74. Found: C, 64.60; H, 9.58%.

3-[(2*R*)-2-Acetoxy pentyl]-(2*R*,3*S*)-oxiranyl methanol (6). To a stirred mixture of activated 4 Å molecular sieves (0.43 g) in dry CH_2Cl_2 (40 mL) cooled to −20 °C, (−)-DET (0.112 g, 0.54 mmol) and $Ti(O\text{-}i\text{-}Pr)_4$ (0.13 mL, 0.05 equiv.) were added sequentially with stirring. To this, TBHP (3.1 mL, 2 equiv, 5.8 M in CH_2Cl_2) was added and the resulting mixture was stirred for 20 min, whereupon (*E*)-**11** (1.7 g, 9.1 mmol) was added and stirring was continued at −20 to −15 °C for 2.5 h. Then the reaction mixture was warmed to 0 °C, water (30 mL) was added and the mixture was stirred for another 30 min, while allowing it to warm to room temperature. Hydrolysis of the tartrate was then effected by adding 6.0 mL of a 30% aqueous solution of NaOH saturated with NaCl, followed by vigorous stirring. When a phase separation occurred, the lower organic phase was removed and the aqueous phase was further extracted with CH_2Cl_2 (2 × 30 mL). The combined extract was dried (Na_2SO_4), the solvent was evaporated and the residue was chromatographed on SiO_2 (EtOAc–hexane 1 : 7) to give 1.3 g (6.4 mmol, 70%) of **6** as a clear liquid. Ee 96%; $[\alpha]_D^{20} = +16.0$ (*c* 0.7, CH_2Cl_2). IR (neat): 3401 (br), 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.86$ (t, $J = 7.3$ Hz, 3 H), 1.27–1.35 (m, 4 H), 2.17 (s, 3 H), 2.22–2.29 (br s, 1 H), 2.42–2.51 (m, 2 H), 2.70–2.78 (m, 1 H), 2.91–3.00 (m, 1 H), 3.94–4.02 (m, 2 H), 4.90–4.96 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 13.89, 18.78, 20.98, 30.80, 37.25, 65.50, 74.27, 170.11; MS (ESI) *m/z* 202.3 (M^+); Anal. Cal. for $C_{10}H_{18}O_4$ (202.12): C, 59.39; H, 8.97. Found: C, 59.45; H, 8.90%.

(2*R*)-2-(Acetoxy pentyl)-1-[3-(methanesulfonyloxy methyl)-(2*R*,3*S*)-oxiranyl butane] (6a). A solution of the epoxy alcohol **6** (1.2 g, 5.94 mmol) and triethylamine (0.88 g, 8.88 mmol) in dry CH_2Cl_2 (25 mL) was treated with methanesulfonyl chloride (1.02 g, 8.94 mmol) at 0 °C under a N_2 atmosphere. The reaction mixture was stirred for 3 h (from 0 °C to rt). It was diluted with Et_2O and washed with water, dried (Na_2SO_4), the solvent was evaporated and the residue was chromatographed on silica gel (EtOAc–petroleum ether 1 : 8) to give 1.5 g (5.35 mmol, 90%) of **6a** as a viscous liquid. Ee 96%; $[\alpha]_D^{20} = +10.5$ (*c* 1.0, $CHCl_3$). IR (neat): 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.90$ (t, $J = 8.0$ Hz, 3 H), 1.25–1.37 (m, 4 H), 2.16 (s, 3 H), 2.40–2.49 (m, 2 H), 2.72–2.79 (m, 1 H), 2.90–2.97 (m, 1 H), 3.10 (s, 3 H), 3.99–4.18 (m, 2 H), 4.92–4.98 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 13.97, 18.70, 20.85, 21.93, 30.02, 32.00, 36.72, 37.90, 65.66, 74.07, 170.20; MS (ESI) *m/z* 280.3 (M^+); Anal. Cal. for $C_{11}H_{20}O_6S$ (280.098): C, 47.13; H, 7.19. Found: C, 47.00; H, 7.25%.

(2*R*)-2-(Acetoxy pentyl)-1-[3-(iodomethyl)-(2*R*,3*S*)-oxiranyl butane] (6b). To a solution of **6a** (1.3 g, 4.64 mmol) in acetone (20 mL), NaI (1.04 g, 6.94 mmol) was added with stirring. After stirring for 5 h at room temperature, water (5 mL) was added and extracted with Et_2O (50 mL). The organic phase was dried (Na_2SO_4), the solvent was evaporated and the residue was chromatographed on SiO_2 (EtOAc–hexane 1 : 10) to give 1.16 g (3.71 mmol, 80%) of **6b** as a colorless liquid. Ee 96%; $[\alpha]_D^{20} =$ +6.9 (*c* 1.0, $CHCl_3$). IR (neat): 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.89$ (t, $J = 7.6$ Hz, 3 H), 1.27–1.38 (m, 4 H), 2.13 (s, 3 H), 2.45–2.54 (m, 2 H), 2.74–2.80 (m, 1 H), 2.92–2.99 (m, 1 H), 3.44–3.52 (m, 2 H), 4.90–4.99 (m, 1 H); ^{13}C NMR (75 MHz,

$CDCl_3$): δ = 13.90, 18.79, 20.80, 30.08, 32.02, 36.70, 37.96, 65.66, 74.00, 170.12; MS (ESI) *m/z* 312.2 (M^+); Anal. Cal. for $C_{10}H_{17}IO_3$ (312.022): C, 38.48; H, 5.49. Found: C, 38.40; H, 5.59%.

(1*R*)-Acetoxy-(3*R*)-hydroxy-1 propyl-pent-4-ene (12). A mixture of **6b** (1.0 g, 3.2 mmol), iodine (36 mg, 0.28 mmol) and freshly activated zinc (0.52 g, 8.0 mmol) in anhydrous MeOH (10 mL) was refluxed for 8 h under a N_2 atmosphere. The solution was filtered and the residue was washed with MeOH (2 × 20 mL). The filtrates were combined and concentrated. The residue was taken up in ethyl acetate (30 mL) and washed with water (2 × 20 mL) and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on SiO_2 (6% EtOAc in hexane) to give 0.452 g (2.43 mmol, 76%) of **12** as a colorless liquid. Ee 96%; $[a]_D^{20} = -5.9$ (*c* 1.0, $CHCl_3$). IR (neat): 3410, 1725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.2 Hz, 3 H), 1.28–1.36 (m, 4 H), 1.86–2.00 (m, 2 H), 2.11 (s, 3 H), 2.21–2.29 (br s, 1 H), 4.18–4.26 (m, 1 H), 4.89–4.96 (m, 1 H), 5.02 (d, *J* = 8.6 Hz, 1 H), 5.18 (d, *J* = 15.2 Hz, 1 H), 5.58–5.71 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.99, 18.88, 20.85, 37.10, 41.00, 71.92, 74.27, 114.82, 141.48, 170.11; MS (ESI) *m/z* 186.3 (M^+); Anal. Cal. for $C_{10}H_{18}O_3$ (186.125): C, 64.49; H, 9.74. Found: C, 64.30; H, 9.90%.

(1*R*)-Acetoxy-(3*R*)-[(*tert*-butyldimethylsilyl)oxy]-1-propyl-pent-4-ene (4a). To a solution of **12** (0.350 g, 1.88 mmol) and imidazole (0.253 g, 3.72 mmol) in dry DMF (4 mL) was added TBSCl (0.283 g, 1.88 mmol) at room temperature and the mixture was stirred for 16 h. The reaction mixture was diluted with water (3 mL) and extracted with diethyl ether (2 × 10 mL). The organic phase was washed with brine (1 × 5 mL), dried (Na_2SO_4) and concentrated to afford the crude product. Column chromatography (9% EtOAc in hexane) of the crude product afforded **4a** (0.53 g, 1.76 mmol, 93%) as a colorless liquid. Ee 96%; $[a]_D^{20} = -8.9$ (*c* 1.0, $CHCl_3$). IR (neat): 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.06 (s, 6 H), 0.88 (s, 9 H), 0.91 (t, *J* = 6.7 Hz, 3 H), 1.22–1.34 (m, 4 H), 1.85–2.02 (m, 2 H), 2.16 (s, 3 H), 4.03–4.12 (m, 1 H), 4.88–4.96 (m, 1 H), 5.04 (d, *J* = 8.5 Hz, 1 H), 5.20 (d, *J* = 15.4 Hz, 1 H), 5.56–5.75 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.74, −4.74, 13.90, 17.92, 18.80, 20.80, 25.81, 26.90, 29.90, 37.19, 41.30, 70.92, 74.67, 115.82, 139.48, 170.31; MS (ESI) *m/z* 300.5 (M^+); Anal. Cal. for $C_{16}H_{32}O_3Si$ (300.212): C, 62.18; H, 9.69. Found: C, 62.00; H, 9.85%.

(3*R*)-[(*tert*-Butyldimethylsilyl)oxy]-oct-1-en-(5*R*)-ol (4). Compound **4a** (0.45 g, 1.5 mmol) was dissolved in a 0.3 M K_2CO_3 solution in MeOH (10 mL) and the reaction mixture was stirred at room temperature for 6 h. After being neutralized with 0.2 M HCl, the mixture was extracted five times with chloroform. The organic phase was dried (Na_2SO_4), the solvent was evaporated and the residue was chromatographed on SiO_2 (EtOAc–hexane 1 : 5) to give 0.345 g (1.34 mmol, 89%) of **4** as a colorless oil. Ee 96%; $[a]_D^{20} = -17.9$ (*c* 1.0, $CHCl_3$). IR (neat): 3410 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.06 (s, 6 H), 0.78 (s, 9 H), 0.93 (t, *J* = 6.5 Hz, 3 H), 1.20–1.30 (m, 4 H), 1.86–2.00 (m, 2 H), 2.21–2.29 (br s, 1 H), 4.04–4.13 (m, 1 H), 4.19–4.26 (m, 1 H), 5.03 (d, *J* = 8.5 Hz, 1 H), 5.24 (d, *J* = 15.6 Hz, 1 H), 5.60–5.75 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.74, −4.74, 13.98, 17.90, 19.80, 25.80, 26.95, 29.95, 40.25, 41.00, 70.09, 70.99, 115.45, 139.22; MS (ESI) *m/z* 258.5 (M^+); Anal. Cal. for $C_{14}H_{30}O_2Si$ (258.202): C, 65.06; H, 11.70. Found: C, 65.00; H, 11.66%.

(3*R*)-[(*tert*-Butyldimethylsilyl)oxy]-1-propyl-pent-4-enyl hex-(5*R*)-enoate (13). To a stirred solution of **4** (0.26 g, 1.0 mmol) in CH_2Cl_2 (10 mL) was added DCC (0.31 g, 1.5 mmol) followed by a catalytic amount of DMAP at 0 °C. After 5 min, 5-hexenoic acid (0.172 g, 1.5 mmol) was added and the mixture was stirred for 17 h at room temperature. Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (20 mL). The layers were separated, the organic layer was washed successively with 10% aqueous HCl, saturated $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4), the solvent was evaporated and the residue was purified by chromatography on SiO_2 (EtOAc–hexane 1 : 8) to give 0.308 g (0.87 mmol, 86%) of ester **13** as a yellow oil. Ee 96%; $[a]_D^{20} = +13.6$ (*c* 1.0, $CHCl_3$). IR (neat): 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.09 (s, 6 H), 0.86 (s, 9 H), 0.92 (t, *J* = 6.6 Hz, 3 H), 1.22–1.34 (m, 4 H), 1.37–1.40 (m, 2 H), 1.45–1.56 (m, 2 H), 1.85–2.01 (m, 2 H), 2.20 (t, *J* = 7.1 Hz, 2 H), 3.78–3.86 (m, 1 H), 4.23–4.35 (m, 1 H), 5.05 (d, *J* = 8.6 Hz, 2 H), 5.20 (d, *J* = 16.0 Hz, 2 H), 5.58–5.71 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.74, −4.74, 13.90, 17.92, 18.80, 25.80, 26.95, 28.80, 33.74, 34.23, 37.10, 41.25, 70.99, 114.48, 115.45, 129.30, 138.60, 139.22, 159.00, 172.70; MS (ESI) *m/z* 354.61 (M^+); Anal. Cal. for $C_{20}H_{38}O_3Si$ (354.259): C, 67.74; H, 10.80. Found: C, 67.70; H, 11.00%.

(3*R*)-Hydroxy-1-propyl-pent-4-enyl hex-(5*R*)-enoate (14). To a solution of **13** (0.25 g, 0.71 mmol) in THF (8 mL), TBAF (1.3 mL, 1.26 mmol, 1 M in THF) was added at 0 °C. After stirring for 3 h at ambient temperature, the mixture was quenched with water (2 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic phase was dried (Na_2SO_4), the solvent was evaporated and the residue was chromatographed on SiO_2 (EtOAc–hexane 1 : 6) to give 0.119 g (0.53 mmol, 75%) of **14** as a viscous liquid. Ee 96%; $[a]_D^{20} = +6.6$ (*c* 1.0, $CHCl_3$). IR (neat): 3410, 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.4 Hz, 3 H), 1.23–1.37 (m, 2 H), 1.50–1.92 (m, 6 H), 2.06 (q, *J* = 6.8 & 12.4 Hz, 2 H), 2.28 (t, *J* = 7.2, 2 H), 2.48 (br s, 1 H), 4.13 (q, *J* = 6.5 & 12.4 Hz, 1 H), 4.88–5.24 (m, 5 H), 5.64–5.90 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.99, 18.80, 28.80, 33.70, 34.20, 37.30, 41.00, 71.99, 74.27, 114.82, 115.48, 136.60, 141.48, 170.70; MS (ESI) *m/z* 226.3 (M^+); Anal. Cal. for $C_{14}H_{24}O_3$ (226.157): C, 69.96; H, 10.06. Found: C, 69.52; H, 9.67%.

(7*R*,9*R*)-7-Hydroxy-9-propyl-5-nonen-9-olide (1). A mixture of **14** (91 mg, 0.40 mmol) in anhydrous CH_2Cl_2 (10 mL) and Grubbs second generation catalyst (15 mg, 0.003 mmol) was degassed with N_2 for 15 min, and refluxed for 16 h. The solvent was evaporated to leave a dark brown residue. The crude product was purified by preparative TLC (EtOAc–hexane 1 : 7) to give analytically pure Herbarumin III (**1**) as a gum (46 mg, 0.22 mmol, 55%). Ee 96%; $[a]_D^{20} = +17.6$ (*c* 0.7, EtOH). IR (neat): 3430 (br), 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.6 Hz, 3 H), 1.23–1.33 (m, 2 H), 1.42–1.53 (m, 2 H), 1.54 (dd, *J* = 13.8 & 8.6 Hz, 1 H), 1.67–1.77 (m, 1 H), 1.79–1.82 (m, 1 H), 1.84–1.93 (m, 1 H), 1.96–1.98 (m, 1 H), 2.00–2.04 (m, 1 H), 2.06–2.12 (m, 1 H), 2.28 (dd, *J* = 6.1 & 13.0 Hz, 1 H), 2.37–2.42 (m, 1 H), 4.43 (t, *J* = 2.5 Hz, 1 H), 5.26–5.38 (m, 1 H), 5.42–5.49 (m, 1 H), 5.68 (d, *J* = 16.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.80, 18.70, 26.30, 33.90, 34.80, 37.60, 40.30, 67.55, 68.48, 124.70, 134.60, 176.70; MS (ESI) *m/z* 212.2 (M^+); Anal. Cal. for $C_{12}H_{20}O_3$ (212.112): C, 67.89; H, 9.50. Found: C, 67.62; H, 9.78%.

Acknowledgements

We would like to thank Director RRL Jorhat for providing facilities and Dr A. K. Saikia (IITG) for recording NMR spectra. JB is grateful to CSIR, New Delhi for the Research Fellowship.

References

1 J. F. Rivero-Cruz, M. Macias, C. M. Cerda-Garcia-Rojas and R. Mata, *J. Nat. Prod.*, 2003, **66**, 511.
2 J. F. Rivero-Cruz, G. G. Aguirre, C. M. Cerda-Garcia-Rojas and R. Mata, *Tetrahedron*, 2000, **56**, 5337.
3 (*a*) M. K. Gurjar, S. Karmakar and D. K. Mohapatra, *Tetrahedron Lett.*, 2004, **45**, 4525; (*b*) M. K. Gurjar, R. Nagaprasad, C. V. Ramanna, S. Karmakar and D. K. Mohapatra, *ARKIVOC*, 2005, 237; (*c*) S. Nanda, *Tetrahedron Lett.*, 2005, **46**, 3661; (*d*) A. Salaskar, A. Sharma and S. Chattopadhyay, *Tetrahedron: Asymmetry*, 2006, **17**, 325.
4 (*a*) D. Kalita, A. T. Khan, N. C. Barua and G. Bez, *Tetrahedron*, 1999, **55**, 5177; (*b*) S. Gogoi, N. C. Barua and B. Kalita, *Tetrahedron Lett.*, 2004, **45**, 5577; (*c*) J. Boruwa and N. C. Barua, *Tetrahedron*, 2006, **62**, 1193.
5 (*a*) A. Fürstner and C. Müller, *Chem. Commun.*, 2005, 5583; for a review on the synthesis of medium sized rings by RCM, see: (*b*) M. E. Maier, *Angew. Chem., Int. Ed.*, 2000, **39**, 2073; for a review on RCM, see: (*c*) K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem., Int. Ed.*, 2006, **44**, 4490; (*d*) J. Prunet, *Angew. Chem., Int. Ed.*, 2003, **42**, 2826.
6 (*a*) G. E. Keck, K. H. Tarbet and L. S. Geraci, *J. Am. Chem. Soc.*, 1993, **115**, 8467; (*b*) G. E. Keck, D. Krishnamurthy and M. C. Grier, *J. Org. Chem.*, 1993, **58**, 6543; (*c*) N. Gogoi, J. Boruwa and N. C. Barua, *Eur. J. Org. Chem.*, 2006, 1722.
7 The enantiomeric excess of compounds was determined by HPLC analysis carried out in a Waters 510 HPLC system. Chiracel OD packed in an SS column of 4.6 mm id × 250 m was used; see ref. 6*c*.
8 P. Phukan, *Tetrahedron Lett.*, 2004, **45**, 4785.
9 W. Yu, Y. Mei, Y. Kang, Z. Hua and Z. Jin, *Org. Lett.*, 2004, **6**, 3217.
10 Unpublished result from our group.
11 The *E*–*Z* ratio was determined from the ^{1}H NMR spectrum of the mixture. The isomers were separated by chromatography (ethyl acetate–petroleum ether 1 : 15).
12 C. Bonini and C. Righi, *J. Chem. Soc., Chem. Commun.*, 1994, 2767.
13 (*a*) T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 5974; (*b*) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune and K. B. Sharpless, *J. Am. Chem. Soc.*, 1987, **109**, 5765.
14 J. S. Yadav and P. Srihari, *Tetrahedron: Asymmetry*, 2004, **15**, 81.
15 A. Furstner and K. Radkowaski, *Chem. Commun.*, 2001, 671.