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A new synthesis of the phytotoxic 10-membered lactone herbarumin I

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ABSTRACT

Herbarumin I a phytotoxic 10-membered lactone has been synthesized from D-(−)-isoascorbic acid in 12 steps with an overall yield of 16.8%. The methodology involved in generating the stereogenic center at C-8 is a Sharpless asymmetric epoxidation, as well 1,2-asymmetric induction followed by macrolactonization via RCM.

1. Introduction

Herbarumin I, a 10-membered macrolide was isolated from the culture of *Phoma herbarum* fungus by Mata and co-workers in 2000.[1] Since then, a series of other related 10-membered lactones have been isolated with phytotoxic activity. Herbarumin I remains to be the most phytotoxicity of the series on the seeding of *Amaranthus hypochondriacus*[1], holding promises as a lead compound for the discovery of new herbicides. The initial structural and stereochemical assignment of herbarumin I was established by Fürstner et al. through total synthesis.[2] Since then different total syntheses[3] have been reported. Herein we report an enantioselective total synthesis of herbarumin I from commercially available D-(−)-isoascorbic acid as a chiral source.

2. Results and discussion

Our retro synthetic approach is outlined in Scheme 1. The stereochemistry of the two contiguous stereogenic centers can be matched by the pattern displayed by D-(−)-isoascorbic acid. Therefore, this was chosen as a readily accessible starting material, which was converted on a gram scale into esters **3** and **14** using a known protocol.[4] This follows an effective route in the preparation of hex-5-enoic ester **12** and RCM resulted in herbarumin I (Scheme 1).

Using ester **2** as the starting material the chiral center at C-8 was generated by two different routes. Strategy one involves conversion of ester **2** into vinyl ketone **5** using Weinreb amide **4** followed by treatment with vinyl magnesium bromide.[5] Ketone **5** was reduced selectively by zincborohydride[6] with good diastereoselectivity (94:6) to afford alcohol **6** (Scheme 3). The intermediate **6** was also prepared starting from compound **2** involving the sequential functional group manipulations as shown in Scheme 2. This includes the reduction of TBS protected ester **14** using DIBAL-H in DCM at −78 °C followed by the two carbon Wittig olefination to afford the unsaturated ester **15** (*E*/*Z* ratio 85:15). This unsaturated ester was further reduced to allylic alcohol **16** using DIBAL-H and was subjected to a Sharpless asymmetric epoxidation to afford epoxide **17**. Opening of epoxide[7] was carried out when **17** was refluxed with TPP in CCl_4 followed by treatment with sodium metal in ether to produce allylic alcohol **18**. Deprotection of the TBDMS group followed by a benzyl protection of diol **19** afforded **7**.

Compound **7** prepared by both methods was matched in rotation and spectral values. Deprotection of primary acetonide in compound **7** with *p*TSA in MeOH furnished diol **8** in quantitative yield, which was further subjected to mono-tosylation in the presence of a catalytic amount of dibutyltin oxide to give **9** followed by subsequent exposure to K_2CO_3 to afford epoxide **10**. Treatment of **10** with EtMgBr in the presence of CuBr afforded alcohol **11**, which was esterified with hex-5-enoic acid using a Yamaguchi protocol[8] to furnish compound **12** in good yield. The RCM of **12** in the presence of Grubbs II generation catalyst[3a,9] led to the required protected lactone **13** in 84% yield. The ring closure metathesis was very smooth and benzyl protection did not hinder the formation of the required compound **13**. In previous reports the required *E*-isomer was achieved through Grubbs I catalyst whereas, Grubbs II led to the *Z*-isomer. In the present study the *E*-isomer was achieved in good yield when we used Grubbs II catalyst.

In fact, compared to the previous approaches[3] this reaction has given a higher yield and selectivity of the required *E*-isomer in 90:10 (*E*/*Z* ratio). Deprotection of the benzyl groups was achieved using $TiCl_4$ in DCM at 0 °C to provide the natural product herbarumin I **1** in 74% yield.[10] The physical and spectral data of synthetic herbarumin I are identical with those of the natural product.

3. Conclusion

In conclusion, we have reported an asymmetric total synthesis of herbarumin I, from D-(−)-isoascorbic acid involving two different strategies with an overall yield of 16.8%. The alcohol fragment **6** was synthesized in enantiomerically pure form by different

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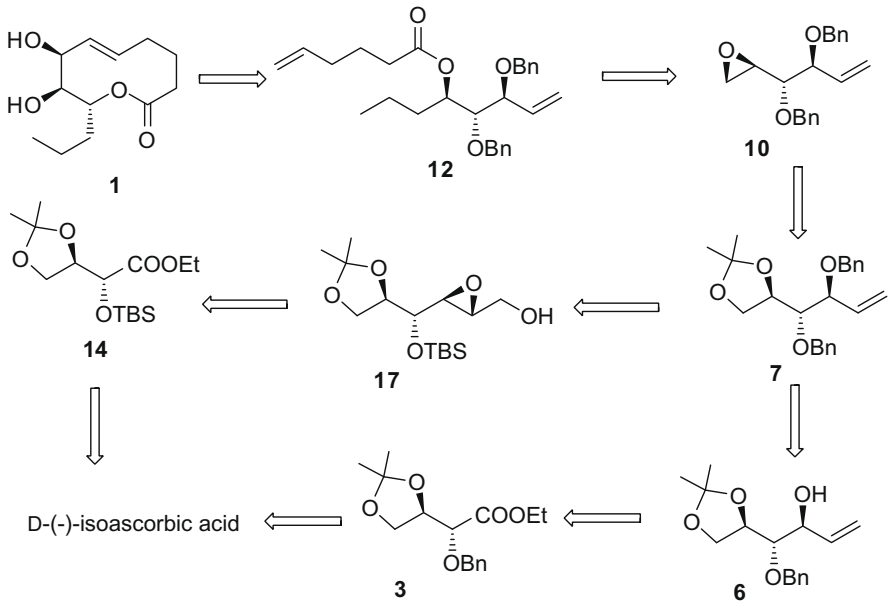
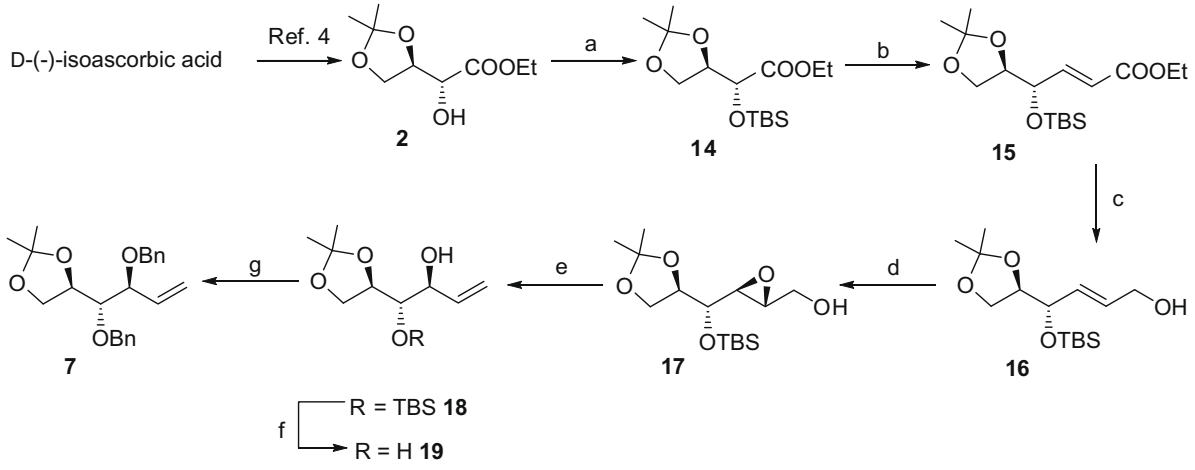


Scheme 1. Retro synthesis of herbarumin I.



Scheme 2. Reagents and conditions: (a) TBDMS-Cl, imidazole, DCM, rt, 3 h 96%; (b) (i) DIBAL-H, DCM, −78 °C, 30 min; (ii) two carbon ylide, DCM, 2 h, 82% (for two steps); (c) DIBAL-H, DCM, −78 °C, 30 min, 89%; (d) (−)-DET, $Ti(OPr_i)_4$, TBHP, molecular sieves 4 Å, DCM, −20 °C, 15 h, 76%; (e) (i) PPh_3, CCl_4, 80 °C, 6 h; (ii) sodium metal, ether, 8 h, 68% (for two steps); (f) TBAF, THF, 1.5 h, 97%; (g) NaH, BnBr, THF, rt, 2 h, 95%.

routes from the same chiron. The synthesis also featured epoxide opening with sodium metal in preparation of compound **18** and stereoselective induction of a 1,2-*anti* chiral alcohol using zinc-borohydride in the preparation of compound **6**. Opening of epoxide **10** with EtMgBr followed by a lactonization of **12** by RCM led to herbarumin I in enantiomerically pure form. The present synthesis will provide an access to a synthesis of variety of structural analogues of herbarumin I for biological studies.

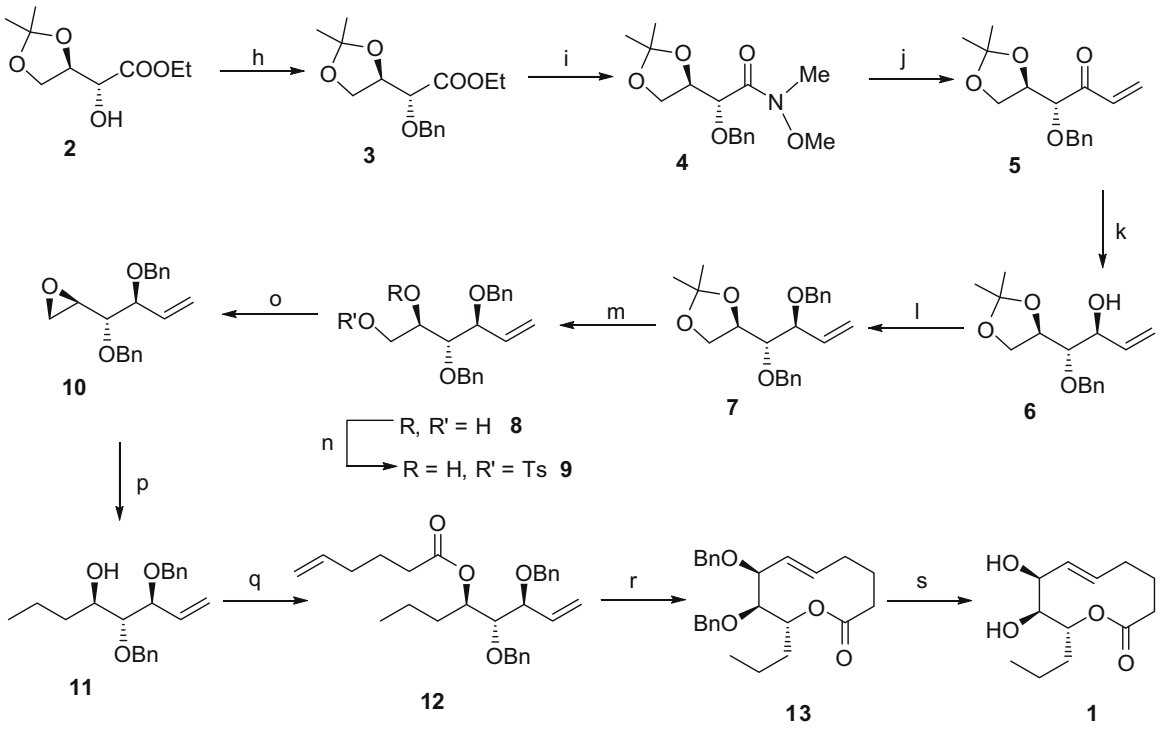
4. Experimental

4.1. General methods

All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on silica gel of 60-120 mesh. IR (FT-IR) spectra were measured as KBr pellets or as films between KBr plates. Optical rotations were recorded on HORIBA SEPA-300 polarimeter, 10 ml cell. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian Gemini 200 and Brucker Avance 300. Chemical shifts were reported in parts per million with respect to internal TMS. Coupling constants (J) are quoted in hertz. Mass spectra were obtained on MS-ESI, HRMS mass spectrometers.

4.1.1. (*R*)-Ethyl 2-(benzyloxy)-2-((*R*)-2,2-dimethyl-1,3-dioxalan-4-yl)acetate 3

To a solution of ascorbate **2** (5 g, 24.5 mmol) in dry DCM (50 mL) was added silver oxide (8.5 g, 36.7 mmol) followed by benzyl bromide (3.59 mL, 26.2 mmol). The reaction mixture was stirred for 12 h at room temperature and was filtered through a pad of Celite. The filtrate was evaporated to dry and was purified over silica gel column chromatography (92:8 hexane–EtOAc) to furnish a pure compound **3** (6.26 g, 87%) as a colorless liquid. $[\alpha]_D^{20} = +26.5$ (c 2.0, MeOH); IR: 2933, 1743, 1254, 1076, 840 cm^{-1}; ^1H NMR



Scheme 3. Reagents and conditions: (h) BnBr, Ag_2O, DCM, rt, 12 h, 87%; (i) NH(Me)(OMe), C_3H_7MgBr, THF, −10 °C, 1 h, 90%; (j) vinyl magnesium bromide, THF, −78 °C then rt, 2 h, 78%; (k) $ZnBH_4$, ether, −50 °C, 1 h, 86%; (l) NaH, BnBr, 0 °C to rt 2 h, 95%; (m) PTSA, MeOH, 2 h, 98%; (n) TsCl, Et_3N, Bu_2SnO, rt, 4 h; (o) K_2CO_3, MeOH, 1 h, 85% (for the two steps); (p) C_2H_5MgBr, Cu_2Br_2, THF, −30 °C, 75%; (q) Hex-5-enoic acid, Et_3N, 2,4,6-trichloro benzoyl chloride, DMAP, toluene, 3 h, 87%; (r) Grubb's II catalyst, DCM, reflux, 12 h, 84%; (s) $TiCl_4$, DCM, 0 °C, 1 h, 74%.

(300 MHz, $CDCl_3$): δ 7.26–7.39 (m, 5H); 4.62–4.65 (d, J = 11.70 Hz, 1H); 4.44–4.48 (d, J = 11.70 Hz, 1H); 4.14–4.30 (m, 3H); 3.92–4.01 (m, 2H); 3.86 (d, J = 6.61 Hz, 1H); 1.38 (s, 3H); 1.31 (s, 3H); 1.27–1.32 (t, J = 7.17 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): 170.1, 137.0, 128.3, 128.0, 128.0, 109.7, 96.2, 79.1, 75.9, 77.7, 66.2, 60.8, 26.7, 25.5, 14.3; ESI-MS: 317 [(M+Na)$^+$]; HRMS calcd for $C_{16}H_{22}O_5Na$ 317.1365, found 317.1354.

4.1.2. (*R*)-2-(Benzyloxy)-2-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-*N*-methoxy-*N*-methylacetamide 4

A solution of dried THF (50 mL) containing a mixture of ester **3** (5 g, 17 mmol) and Weinreb's salt (2.5 g, 25.5 mmol) was cooled to −10 °C and was added a solution of isopropyl magnesium bromide (25.5 mL of a 1 M soln in THF, 25.5 mmol). The reaction mixture was stirred at the same temperature for 1 h and was quenched with saturated NH_4Cl. The organic layer was extracted with EtOAc. Combined extract was washed with brine, dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure afforded a crude reaction mixture, which was purified using silica gel chromatography (90:10 hexane–EtOAc) and furnished a pure compound **4** (4.7 g, 90%) as a colorless liquid. $[\alpha]_D^{20} = +14.7$ (c 1.8, MeOH); IR: 2933, 1667, 1073 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22–7.33 (m, 5H); 4.59–4.63 (d, J = 12.08 Hz, 1H); 4.47–4.52 (d, J = 12.08 Hz, 1H); 4.29–4.40 (m, 2H); 3.96–4.08 (m, 2H); 3.61 (s, 3H); 3.19 (s, 3H); 1.39 (s, 3H); 1.31 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): 170.6, 137.5, 128.2, 127.8, 127.7, 109.2, 96.2, 75.5, 72.1, 66.3, 61.3, 32.2, 26.4, 25.2; ESI-MS: 332 [(M+Na)$^+$]; HRMS calcd for $C_{16}H_{23}NO_5Na$ 332.1474, found 332.1462.

4.1.3. (*R*)-1-(Benzyloxy)-1-((*R*)-2,2-dimethyl-1,3-dioxalan-4-yl) but-3-en-2-one 5

To a solution of amide **4** (4 g, 12.9 mmol) in dry THF (60 mL) at −78 °C was added vinyl magnesium bromide (15.5 mL of a 1 M soln in THF, 15.5 mmol) slowly over 20 min. The reaction mixture was stirred at the same temperature for 1 h and then slowly warmed to room temperature over 2 h. The reaction was quenched by the addition of saturated NH_4Cl. The organic layer was extracted with EtOAc. Combined organic extract was successively washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. Purification upon silica gel chromatography (95:5 hexane–EtOAc) furnished a pure compound **5** (2.7 g, 78%) as a yellow oil. $[\alpha]_D^{20} = +22.1$ (c 1.2, MeOH); IR: 2917, 1757, 1713,1634,1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.38 (m, 5H); 6.74–6.85 (dd, J = 17.37, 10.57 Hz, 1H); 6.37–6.45 (dd, J = 17.37, 1.70 Hz, 1H); 5.76–6.45 (dd, J = 10.57, 1.70 Hz, 1H); 4.58–4.62 (d, J = 11.52 Hz, 1H); 4.46–4.51 (d, J = 11.52 Hz, 1H); 4.29–4.35 (q, J = 11.89, 6.23 Hz, 1H); 3.93–4.08 (m, 3H); 1.40 (s, 3H); 1.32 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): 198.7, 136.9, 132.1, 129.7, 128.5, 128.1, 110.0, 83.7, 75.8, 72.9, 66.4, 26.4, 25.1; ESI-MS: 299 [(M+Na)$^+$]; HRMS calcd for $C_{16}H_{20}O_4Na$ 299.1259, found 299.1247.

4.1.4. (1*S*,2*S*)-1-(Benzyloxy)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-2-ol 6

A solution of ketone **5** (2 g, 7.24 mmol) in 20 mL dry diethyl ether under N_2 atmosphere was cooled to −50 °C and $ZnBH_4$ (2.7 mL of a 2 M solution in THF, 5.43 mmol) was added slowly for the period of 10 min. After stirring for 1 h at the same temperature, the reaction mixture was quenched by addition of saturated NH_4Cl. The resulting mixture was extracted with diethyl ether. Combined organic layer was washed with brine, dried over Na_2SO_4, evaporated in vacuo. The residue was chromatographed on silica gel (90:10 hexane–EtOAc) to give **6** (1.7 g, 86%) as a colorless oil. $[\alpha]_D^{20} = +6.9$ (c 1.3, MeOH); IR: 3473, 2955, 2858, 1727; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18–7.32 (m, 5H); 5.32–5. 96 (m, 3H); 4.58–4.63 (d, J = 12.08 Hz, 1H); 4.31–4.40 (d, J = 12.08 Hz, 1H); 3.77–4.11 (m, 5H); 2.45 (s, 1H); 1.33 (s, 3H); 1.28 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): 141.0, 134.0, 128.4, 127.4, 126.9, 120.0, 108.8, 81.0, 75.1, 73.8, 70.3, 66.3, 26.8, 25.4; ESI-MS:

301[(M+Na)$^+$]; HRMS calcd for $C_{16}H_{22}O_4Na$ 301.1415, found 301.1405.

4.1.5. (*R*)-4-((1*S*,2*S*)-1,2-Bis(benzyloxy)but-3-enyl)-2,2-dimethyl-1,3-dioxolane 7

Alcohol **6** (1.2 g, 4.32 mmol) in dry THF (20 mL) was added to a solution containing NaH (207 mg, 8.63 mmol) dry THF (15 mL) at 0 °C followed by benzyl bromide (0.63 mL, 5.179 mmol). The reaction mixture was allowed to stir for 2 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl. The organic layer was extracted with EtOAc. The combined organic layer washed with brine, dried over Na_2SO_4, solvent was removed under reduced pressure. Purification of the crude mass using silica gel column chromatography (95:5 hexane–EtOAc) furnished pure benzylated ether **7** (1.5 g, 95%) as a colorless liquid. $[\alpha]_D^{20} = +31.8$ (*c* 2.7, MeOH); IR: 3063, 2928, 1735, 1604, 1454, 1213, 1066 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.21–7.33 (m, 10H); 5.79–6.0 (m, 1H); 5.28–5.37 (m, 2H); 4.76–4.87 (d, *J* = 11.75 Hz, 1H); 4.65–4.71 (d, *J* = 7.34 Hz, 1H); 4.62–4.65 (d, *J* = 7.34 Hz, 1H); 4.35–4.41 (d, *J* = 11.75 Hz, 1H); 3.99–4.17 (m, 2H); 3.91–3.95 (dd, *J* = 5.87, 2.93 Hz, 1H); 3.71–3.76 (dd, *J* = 6.61, 2.93 Hz, 1H); 1.37 (s, 3H); 1.31 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): 138.5, 134.7, 128.2, 127.9, 127.5, 127.4, 127.3, 119.3, 108.7, 81.5, 81.4, 75.1, 74.0, 70.4, 66.3, 26.6, 25.4; ESI-MS: 391 [(M+Na)$^+$]; HRMS calcd for $C_{23}H_{28}O_4Na$ 391.1885, found 391.1875.

4.1.6. (2*R*,3*S*,4*S*)-3,4-Bis(benzyloxy)hex-5-ene-1,2-diol 8

To a solution of compound **7** (1.2 g, 3.26 mmol) in MeOH (20 mL) was added PTSA (18 mg, 5 mol %) and was stirred at room temperature for 2 h. After completion of reaction, $NaHCO_3$ was added and stirred for additional 15 min. The compound was extracted into DCM and the organic layer was washed with water, brine, dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure followed by column chromatographic purification (80:20 hexane–EtOAc) afforded a pure compound **8** (1 g, 98%) as a colorless liquid. $[\alpha]_D^{20} = +47.8$ (*c* 0.7, $CHCl_3$); IR: 3420, 3064, 2925, 1722, 1453, 1274, 1093 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42–7. 20 (m, 10H); 5.93–5.82 (dd, *J* = 15.86, 9.06 Hz, 1H); 5.54–5.40 (m, 1H); 5.06–4.97 (d, *J* = 11.33 Hz, 1H); 4.93–4.86 (dd, *J* = 9.06, 4.53 Hz, 1H); 4.76–4.72 (d, *J* = 12.08 Hz, 1H); 4.61–4.57 (d, *J* = 11.34 Hz, 1H); 4.26–4.22 (d, *J* = 12.08 Hz, 1H); 3.78–3.71 (m, 2H); 2.43–1.56 (m, 6H); 1.35–0.96 (m, 4H); 0.84–0.80 (t, *J* = 7.55 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): 138.1, 137.9, 135.3, 128.4, 128.2, 128.0, 127.8, 127.7, 119.6, 96.2, 82.0, 81.1, 74.0, 72.1, 70.5, 63.2; ESI-MS: 351[(M+Na)$^+$]; HRMS calcd for $C_{20}H_{24}O_4Na$ 351.1572, found 351.1580.

4.1.7. (*R*)-2-((1*S*,2*S*)-1,2-Bis(benzyloxy)but-3-enyl)oxirane 10

To a solution of **8** (900 mg, 2.74 mmol), dibutyltin oxide (13 mg, 0.05 mmol), and Et_3N (0.39 mL, 2.74 mmol) in dry DCM was added *p*-toluenesulfonyl chloride (340 mg, 2.74 mmol) at 0 °C under N_2 atmosphere. After stirring for 4 h at room temperature, the reaction mixture was extracted with DCM. The organic extract was successively washed with water, brine, and dried over anhydrous Na_2SO_4. Removal of solvent under reduced under reduced pressure afforded a crude mass which was then carried out to next step without any purification.

To a stirred solution of monotosylate derivative **9** in dry MeOH (15 mL) was added K_2CO_3 (1.13 g, 8.22 mmol) under a N_2 atmosphere. After being stirred for 1 h, MeOH was evaporated under reduced pressure keeping the temperature below 30 °C. The residue was extracted with DCM. The organic extract was washed with water, brine, and dried over anhydrous Na_2SO_4. Removal of a solvent under reduced pressure afforded a crude mass. Purification of the crude mass by silica gel column chromatography (90:10 hexane–EtOAc) afforded epoxide **10** (730 mg, 85%) as a colorless liquid. $[\alpha]_D^{20} = +26.2$ (*c* 2.6, MeOH); IR: 3063, 2925, 1724, 1453, 1270, 1099 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.24–7. 38 (m,1H); 5.8–5.94 (m, 1H); 5.32–5.40 (dd, *J* = 13.59, 2.26 Hz, 2H); 4.81–4.86 (d, *J* = 12.08 Hz, 1H); 4.61–4.68 (dd, *J* = 11.39, 9.06 Hz, 2H); 4.22–4.46 (d, *J* = 1.08 Hz, 1H); 3.93–3.97 (t, *J* = 6.79, 12.84 Hz, 1H); 3.06–3.11 (m, 2H); 2.77–2.79 (m, 1H); 2.57–2.59 (dd, *J* = 2.26, 4.53 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): 134.50, 127.81, 127.78, 127.29, 127.12, 127.00, 119.03, 81.11, 79.30, 72.86, 69.90, 50.74, 44.50; ESI-MS: 333 [(M+Na)$^+$]; HRMS calcd for $C_{20}H_{22}O_3Na$ 333.1467, found 333.1456.

4.1.8. (4*R*,5*R*,6*S*)-5,6-Bis(benzyloxy)oct-7-en-4-ol 11

A solution of EtMgBr (5.79 mL of a 1 M soln in THF, 5.79 mmol) was added dropwise to a stirred and cooled (-30 °C) solution of Cu_2Br_2 (333 mg) in dry THF (20 mL). After stirring for 10 min, epoxide **10** (600 mg, 1.93 mmol) in THF (10 mL) was added. Stirring was continued for 10 h, slowly warming the mixture to 0 °C. The mixture was poured into saturated NH_4Cl. The organic layer was extracted with diethyl ether. The organic layer was successively washed with brine and dried over anhydrous Na_2SO_4. Removal of a solvent under reduced pressure afforded a crude reaction mixture. Purification of crude mass using silica gel column chromatography (85:15 hexane–EtOAc) afforded a pure compound **11** (480 mg, 75%) as a colorless liquid. $[\alpha]_D^{20} = +9.1$ (*c* 3.0, MeOH); IR: 3449, 2958, 2924, 1722, 1454, 1271, 1069, 749, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.20 (m, 10H); 5.96–5.82 (m, 1H); 5.35–5.20 (m, 2H); 4.74–4.70 (d, *J* = 11.33 Hz, 1H); 4.63–4.59 (d, *J* = 11.70 Hz, 1H); 4.51–4.48 (d, *J* = 11.33 Hz, 1H); 4.39–4.33 (d, *J* = 11.70 Hz, 1H); 4.03–3.96 (m, 1H); 3.69–3.65 (m, 1H); 3.34–3.31 (dd, *J* = 5.47, 3.77 Hz, 1H); 2.46 (br s, 1H); 1.56–1.20 (m, 4H); 0.94–0.83 (t, *J* = 6.98 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): 135.55, 128.34, 128.28, 128.03, 127.78, 127.73, 127.63, 119.29, 82.55, 80.73, 73.84, 70.52, 35.55, 18.93, 14.01; ESI-MS: 363 [(M+Na)$^+$]; HRMS calcd for $C_{22}H_{28}O_3Na$ 363.1936, found 363.1924.

4.1.9. (4*R*,5*R*,6*S*)-5,6-Bis(benzyloxy)oct-7-en-4-yl hex-5-enoate 12

Et_3N (0.13 mL, 0.94 mmol) and 2,4,6-trichlorobenzoyl chloride (0.13 mL, 0.88 mmol) were added to a stirred solution of hex-5-enoic acid (0.1 mL, 0.88 mmol) in anhydrous THF (10 mL) under N_2 at room temperature. The resulting mixture was allowed to stir for 2 h before it was filtered through a pad of silica gel. The filtrate was concentrated to dryness. The residue was dissolved in toluene (10 mL) and alcohol **11** (300 mg, 0.88 mmol) and DMAP (538 mg, 4.41 mmol) were added. The mixture was stirred at room temperature for 3 h and was diluted with EtOAc, and the organic layer was separated. The aqueous layer was extracted with EtOAc. The combined organic extracts were washed with saturated $NaHCO_3$, brine, and dried over anhydrous Na_2SO_4. The resulting mixture was filtered, and the solvent was evaporated in vacuo to afford a residue. The residue was purified by silica gel column chromatography (96:4 hexane–EtOAc) afforded pure product **12** (335 mg, 87%) as a colorless liquid. $[\alpha]_D^{20} = +6.4$ (*c* 2.6, MeOH); IR: 3068, 2930, 1733, 1641, 1455, 1093 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.25 (m, 10H); 6.05–5.84 (m, 1H); 5.82–5.63 (m, 1H); 5.41–5.37 (d, *J* = 2.93 Hz, 1H); 5.37–5.31 (dd, *J* = 1.46, 11.02 Hz, 1H); 5.25–5.17 (m, 1H); 5.05–4.94 (m, 2H); 4.81-4.75 (d, *J* = 11.75 Hz, 1H); 4.61–4.59 (d, *J* = 3.67 Hz, 1H); 4.55–4.54 (d, *J* = 2.93 Hz, 1H); 4.32–4.22 (d, *J* = 11.02 Hz, 1H); 3.92 -3.80 (dd, *J* = 5.87, 7.34 Hz, 1H); 3.59–3.55 (dd, *J* = 3.67, 5.87 Hz, 1H); 2.29–2.20 (m, 2H); 2.12–2.0 (m, 2H); 1.75–1.42 (m, 5H); 1.37–1.06 (m, 2H); 0.89–0.78 (t, *J* = 7.34 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): 173.11, 138.24, 138.14, 137.76, 128.99, 128.29, 128.20, 128.08, 127.96, 127.59, 127.53, 119.43, 115.20, 81.32, 80.58, 74.30, 72.80, 70.27, 33.63, 33.08, 24.03, 18.68, 13.90; ESI-MS: 460 [(M+Na)$^+$]; HRMS calcd for $C_{28}H_{36}O_4Na$ 459.2511, found 459.2522.

4.1.10. (8*S*,9*R*,10*R*,*E*)-8,9-Bis(benzyloxy)-10-propyl-3,4,5,8,9, 10-hexahydro-2*H*-oxecin-2-one 13

A solution of **12** (100 mg, 0.23 mmol) and Grubb's II catalyst (19 mg, 0.02 mmol) in degassed anhydrous DCM (250 mL) was refluxed for 12 h. Then the mixture was quenched with ethyl vinyl ether (5 mL) and concentrated in vacuo. The residue was purified by silica gel column chromatography (95:5 hexane–EtOAc) afforded a pure product **13** (78 mg, 84%) as a colorless liquid. $[\alpha]_D^{20} = +13.5$ (*c* 1.1, MeOH); IR: 3030, 2927, 1726, 1452, 1200, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.42–7. 20 (m, 10H); 5.93–5.82 (dd, *J* = 9.06, 15.86 Hz, 1H); 5.54–5.40 (m, 1H); 5.06–4.97 (d, *J* = 11.33 Hz, 1H,); 4.93–4.86 (dd, *J* = 4.53, 9.06 Hz, 1H); 4.76–4.72 (d, *J* = 12.08 Hz, 1H); 4.61- 4.57 (d, *J* = 11.34 Hz, 1H); 4.26–4.22 (d, *J* = 12.08 Hz, 1H); 3.78–3.71 (m, 2H); 2.43–1.56 (m, 6H); 1.35–0.96 (m, 4H); 0.84–0.80 (t, *J* = 7.55 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): 175.38, 138.67, 138.56, 135.07, 129.65, 129.33, 128.87, 128.70, 128.22, 128.06, 127.51, 127.34, 127.27, 96.09, 84.08, 79.88, 74.85, 73.24, 69.06, 34.33, 33.90, 33.52, 29.64, 26.08, 18.33, 13.75; ESI-MS: 432 [(M+Na)$^+$]; HRMS calcd for $C_{26}H_{32}O_4Na$ 431.2198, found 431.2192.

4.1.10.1. (*R*)-Ethyl 2-(*tert*-butyldimethylsilyloxy)-2-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)acetate 14. Colorless liquid; $[\alpha]_D^{20} = +24$ (*c* 1.5, $CHCl_3$); IR: 2933, 2859, 1750, 1473, 1371, 1256, 1155, 1074, 840, 779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.96–4.26 (m, 6H); 1.41 (s, 3H); 1.33 (s, 3H); 1.25–1.32 (t, *J* = 7.17 Hz, 3H); 0.89 (s, 9H); 0.08 (s, 3H); 0.07 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): 171.4, 109.5, 72.6, 65.3, 60.9, 26.6, 25.6, 25.3, 18.1, 14.1; ESI-MS: 341 [(M+Na)$^+$]; HRMS calcd for $C_{15}H_{30}O_5NaSi$ 341.1760, found 341.1756.

4.1.10.2. (*S*,*E*)-Ethyl 4-(*tert*-butyldimethylsilyloxy)-4-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate 15. Colorless liquid; $[\alpha]_D^{20} = -3.1$ (*c* 5.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.83–6.95 (dd, *J* = 15.62, 4.68 Hz, 1H); 5.92–6.02 (dd, *J* = 15.62, 1.56 Hz, 1H); 3.82–4.30 (m, 6H); 1.39 (s, 3H); 1.31 (s, 3H); 1.25–1.34 (t, *J* = 7.03 Hz, 3H); 0.92 (s, 9H); 0.09 (s, 3H); 0.05 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): 200.3, 165.6, 147.3, 121.8, 109.5, 96.2, 78.3, 72.3, 65.8, 60.2, 26.8, 26.0, 25.4, 18.3, 14.4. IR: 2935, 1723, 1659, 1258, 1075, 839 cm^{-1}; ESI-MS: 341 [(M+Na)$^+$]. HRMS calcd for $C_{17}H_{32}O_5NaSi$ 318.1863, found 318.1858.

4.1.10.3. (*S*,*E*)-4-(*tert*-Butyldimethylsilyloxy)-4-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-en-1-ol 16. Yellow liquid; $[\alpha]_D^{20} = +6.9$ (*c* 4.0, MeOH); IR: 3449, 2924, 1628, 1219,772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.76–5.86 (td, *J* = 4.53, 9.82, 15.86 Hz, 1H). 5.60–5.69 (dd, *J* = 5.28, 15.86 Hz, 1H); 3.80–4.13 (m, 6H); 2.89 (br s, 1H); 1.38 (s, 3H); 1.30 (s, 3H); 0.89 (s, 9H); 0.08 (s, 3H); 0.04 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): 131.4, 109.3, 78.9, 73.1, 66.1, 62.7, 26.6, 25.7, 18.0; ESI-MS: 325 [(M+Na)$^+$]; HRMS calcd for $C_{15}H_{30}O_4NaSi$ 325.1811, found 325.1804.

4.1.10.4. ((2*R*,3*S*)-3-((*R*)-(*tert*-Butyldimethylsilyloxy)((*R*)-2, 2-dimethyl-1,3-dioxolan-4-yl)methyl)oxiran-2-yl)methanol 17. Colorless oil; $[\alpha]_D^{20} = +15.5$ (*c* 4.0, MeOH); IR: 3449, 2932, 2859, 1744, 1472, 1376, 1254, 1071, 837, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.00–4.08 (m, 2H); 3.82–3.94 (m, 3H); 3.60–3.66 (dd, *J* = 12.65, 3.96 Hz, 1H); 3.15–3.18 (m, 1H); 3.10–3.12 (m, 1H); 2.37 (br s, 1H); 1.42 (s, 3H); 1.35 (s, 3H); 0.87 (s, 9H); 0.08 (s, 6H); ^{13}C NMR (300 MHz, $CDCl_3$): 109.4, 77.1, 70.3, 66.1, 61.3, 55.8, 54.4, 26.5, 25.7, 25.2, 18.1; ESI-MS: 341 [(M+Na)$^+$]; HRMS calcd for $C_{15}H_{30}O_5NaSi$ 341.1760, found 341.1749.

4.1.10.5. (1*S*,2*S*)-1-(*tert*-Butyldimethylsilyloxy)-1-((*R*)-2, 2-dimethyl-1,3-dioxolan-4-yl)but-3-en-2-ol 18. Colorless liquid; $[\alpha]_D^{20} = +27.7$ (*c* 1.5, MeOH); IR: 3473, 2955, 2858, 1727, 1254, 1073 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.80–5.92 (m, 1H); 5.28–5.35 (td, *J* = 15.67, 1.51 Hz, 1H); 5.18–5.22 (td, *J* = 10.57, 1.51 Hz, 1H); 4.20–4.24 (m, 1H); 4.00–4.06 (m, 1H); 3.92–3.97 (t, *J* = 7.93 Hz, 1H); 3.85–3.89 (dd, *J* = 4.72, 3.39 Hz, 1H); 3.79–3.84 (t, *J* = 7.74 Hz, 1H); 2.38 (br s, 1H); 1.37 (s, 3H); 1.30 (s, 3H); 0.88 (s, 9H); 0.10 (s, 6H); ^{13}C NMR (300 MHz, $CDCl_3$): 135.8, 116.8, 108.2, 75.8, 75.0, 72.3, 65.7, 26.5, 25.8, 19.6; ESI-MS: 325 [(M+Na)$^+$]; HRMS calcd for $C_{15}H_{30}O_4NaSi$ 325.1811, found 325.1800.

4.1.11. Herbarumin I 1

To a solution of **13** (50 mg, 0.12 mmol) in dry DCM (10 mL) was added a solution of $TiCl_4$ (0.039 mL, 0.36 mmol) in dry DCM (2 mL) under N_2 at 0 °C. The reaction was monitored by TLC until the starting material was consumed. Water was added and the compound was extracted into DCM. The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude mass purified by silica gel chromatography and (80:20 hexane–EtOAc) afforded pure compound **1** (20 mg, 74%) as a colorless solid. $[\alpha]_D^{20} = +11.5$ (*c* 0.5, EtOH); IR: 3030, 2927, 1726, 1452, 1200, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.57 (d, *J* = 15.8 Hz, 1H); 5.50 (m, 1H); 4.87 (td, *J* = 9.4, 2.2 Hz, 1H); 4.35 (br s, 1H), 3.41 (d, *J* = 9.4 Hz, 1H); 2.43 (br s, OH, 1H); 2.22–2.33 (m, 2H); 2.07–1.80 (m, 3H); 1.48–1.70 (m, 3H); 1.30–1.20 (m, 3H); 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): 176.3, 130.7, 124.5, 73.5, 73.2, 70.13, 34.4, 33.6, 33.08, 24.6, 17.9, 13.82; ESI-MS: 251 [(M+Na)$^+$]; HRMS calcd for $C_{12}H_{20}O_4Na$ 251.1259, found 251.1251.

References

1. Rivero-Cruz, J. F.; Garcia-Aguieee, G.; Cerda-Garcia-Rojas, C. M.; Mata, R. *Tetrahedron* **2000**, *56*, 5337–5344.
2. Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061–7069.
3. (a) Furstner, A.; Radkowski, K. *Chem. Commun.* **2001**, 671–672; (b) Aparecido Sabino, A.; Pilli, R. A. *Tetrahedron Lett.* **2002**, *43*, 2819–2821; (c) Diez, E.; Dixon, D. J.; Ley, S. V.; Polara, A.; Rodriguez, F. *Helv. Chim. Acta* **2003**, *86*, 3717–3729; (d) Gurjar, M. K.; Karmakar, S.; Mohapatra, D. K. *Tetrahedron Lett.* **2004**, *45*, 4525–4526; (e) Nanda, S. *Tetrahedron Lett.* **2005**, *46*, 3661–3663; (f) Salaskar, A.; Sharma, A.; Chattopadhyay, S. *Tetrahedron: Asymmetry* **2006**, *17*, 325–329; (g) Nagaiah, K.; Sreenu, D.; Srinivasa Rao, R.; Yadav, J. S. *Tetrahedron Lett.* **2007**, *48*, 7173–7176.
4. Abushanab, E.; Vemishetti, P.; Leiby, R. W.; Singh, H. K.; Mikkilineni, A. B.; Wu, D. C. J.; Saibaba, R.; Panzica, R. P. *J. Org. Chem.* **1988**, *53*, 2598–2602.
5. Paterson, I.; Anderson, E. A.; Dalby, S. M.; Lim, J. H.; Genovino, J.; Maltas, P.; Moessner, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3016–3020.
6. Narasimhan, S.; Balakumar, R. *Aldrichim. Acta* **1998**, *31*, 19–26.
7. Sharma, G. V. M.; Laxmi Reddy, K. *Tetrahedron: Asymmetry* **2006**, *17*, 3197–3202.
8. Jnanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
9. Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792–803.
10. Sharma, G. V. M.; Janardhan Reddy, J.; Laxmi Reddy, K. *Tetrahedron Lett.* **2006**, *47*, 6531–6535.