

Ring-closing metathesis mediated total synthesis of microcarpalide and herbarumin III

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Dedicated to Dr. A. V. Rama Rao on the occasion of his 70th birthday

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Abstract

Total synthesis of naturally occurring microcarpalide and herbarumin III are described. The ring-closing metathesis (RCM) approach to coin the medium sized rings present in their molecular structures form the basic premise of this investigation.

Keywords: Microcarpalide, herbarumin III, ring-closing metathesis (RCM), microfilament, phosphodiesterase

Introduction

Medium ring compounds having a ring size between 8 to 11¹ are increasingly being isolated from natural resources. By the virtue of their biological significance, the synthesis of these natural products has attracted attention of many groups. This article describes the RCM based approaches to the total synthesis of two medium ring sized natural products microcarpalide (**1**) and herbarumin III (**4**). Bio-assay guided purification of fermentation broth of *Ficus microcarpa* L led to the isolation of microcarpalide^{2a} (**1**), structurally related to a family of phytotoxins³ but differs in the hydroxylation pattern, the double bond position within the 10-membered lactone and the length of the side chain at C-10. Microcarpalide⁴ possesses microfilament disrupting activity. On similar lines, fermentation broth and mycelium of the fungus *Phoma herbarum* produced three new phytotoxic nonenolides named as herbarumin (I-III) (**2-4**). Herbarumin I-III interacts with bovine-brain calmodulin and inhibits the activation of the calmodulin-dependent enzyme camp phosphodiesterase.

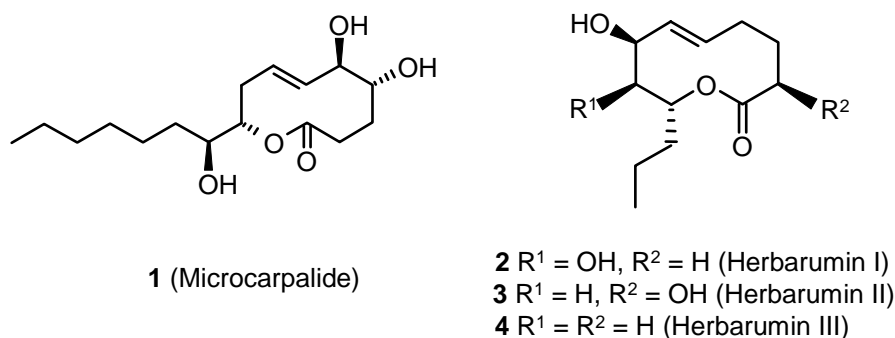
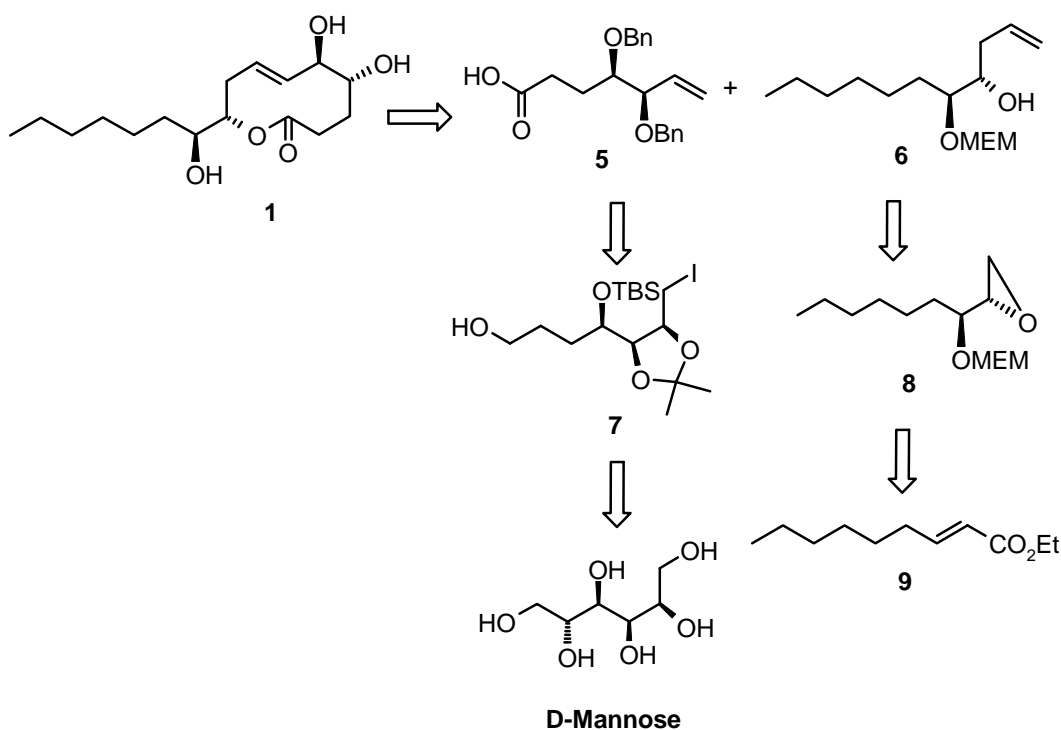


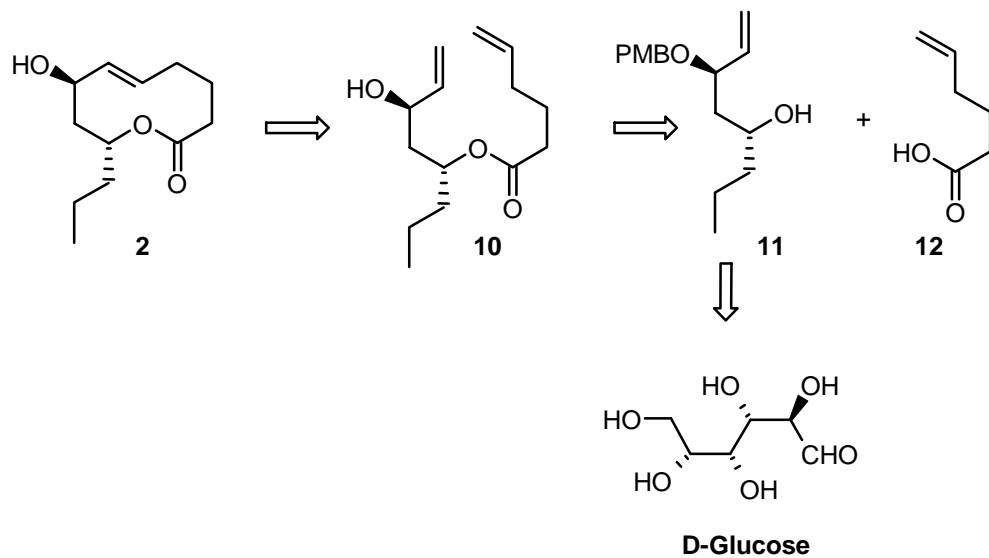
Figure 1. Structures of microcarpalide and herbarumins.

With RCM⁵ reaction destined to provide the oxecin ring framework, it was apparent that microcarpalide (**1**) was disassembled into fragments **5** and **6** having terminal olefins group whilst the hydroxyl and acid groups at the other ends of **5** and **6** ensured their union through esterification.⁶ Both the fragments (**5** & **6**) containing two chiral centers were realized by facile zinc mediated elimination⁷ and Sharpless asymmetric dihydroxylation⁸ as delineated in Scheme 1.



Scheme 1

On a similar premise, the synthetic strategy for herbarumin III (**4**)^{9,10} relied on the union of two fragments **11** and **12**. The synthesis of **11** was planned from D-glucose whose stereogenic centers at C-2 and C-4 were correlated with C-8 and C-10 of herbarumin III (**4**).

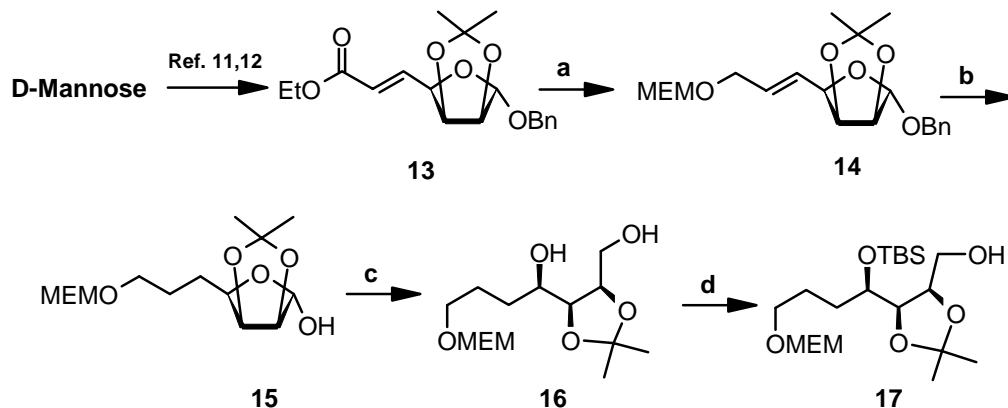


Scheme 2

Results and Discussions

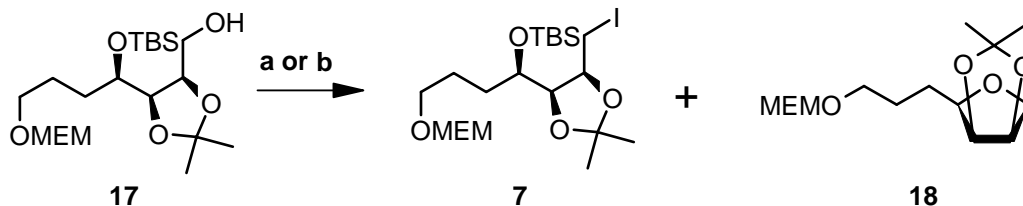
Total synthesis of microcarpalide (**1**)

D-mannose was converted into the conjugated ester derivative (**13**) by a reported sequence.^{11,12} Subsequent treatment of **13** with DIBAL-H in CH₂Cl₂ at -78 °C for 1h afforded the allyl alcohol whose primary hydroxyl was protected as the MEM-ether (**14**).¹³ The structural identity was secured by the interpretation of the ¹H NMR spectrum. For example, two singlets resonated at δ 4.67 and δ 3.4 were attributed to methylene and methoxyl groups of MEM. **14** was hydrogenolysed in the presence of Pd/C and consequently exposed to LAH in THF to produce the diol derivative (**16**).

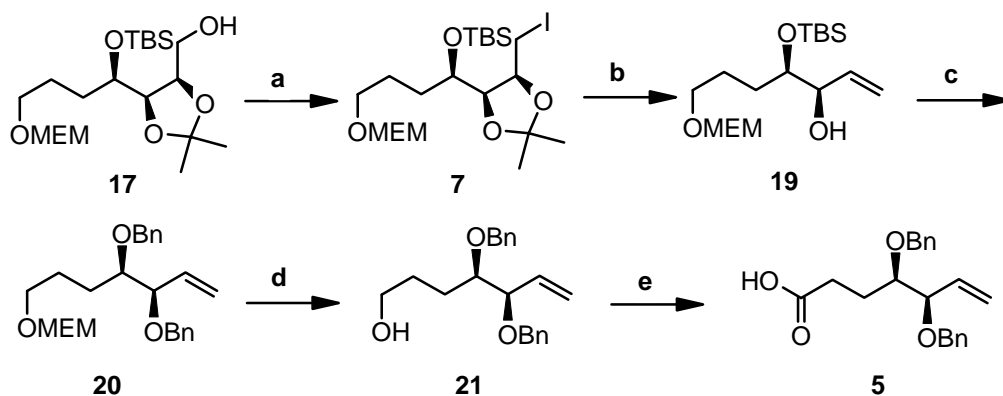


Scheme 3. *Reagents and conditions:* (a) (i) DIBAL-H, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$, 2 h, 92%; (ii) MEM-Cl, $i\text{Pr}_2\text{NEt}$, CH_2Cl_2 , rt, 10 h, 78%; (b) H_2 , 10% Pd-C, MeOH, 6 bar, $60\text{ }^\circ\text{C}$, 4 h, 96%; (c) LiAlH_4 , THF, rt, 1 h, 92%; (d) (i) $(\text{CH}_3)_3\text{CCOCl}$, pyridine, $0\text{ }^\circ\text{C}$ -rt, 1 h, 91%; (ii) TBSCl, DMF, imidazole, rt, 4 h, 90%; (iii) DIBAL-H, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, 1 h, 89%.

In order to introduce iodide at C-1, the protection-deprotection¹⁴⁻¹⁶ sequence on **16** was performed to obtain the primary hydroxyl derivative (**17**). Treatment of **17** with I_2 , TPP and imidazole in toluene at room temperature led to the formation of **7** in 40% yield. Addition of Et_3N marginally improved the yield of **7** (45%), however, the formation of the cyclized product **18** (15%) was also noticed (Scheme 4).^{17a} The iodination reaction carried out in the presence of I_2 , TPP and imidazole but in benzene-ether (2:1) medium^{17b} provided **7** in 86% yield. In the ^1H NMR spectrum of **7**, the resonances due to CH_2I were located at 3.12 as a triplet ($J = 10.4\text{ Hz}$), and at 3.27 as a doublet of doublet ($J = 10.4, 3.3\text{ Hz}$) (Scheme 5).



Scheme 4. *Reagents and conditions:* (a) I_2 , PPh_3 , imidazole, toluene, rt, 4 h, 40%; (b) I_2 , PPh_3 , imidazole, Et_3N , CH_2Cl_2 , rt, 2.5 h, 45% (**7**) and 15% (**18**).

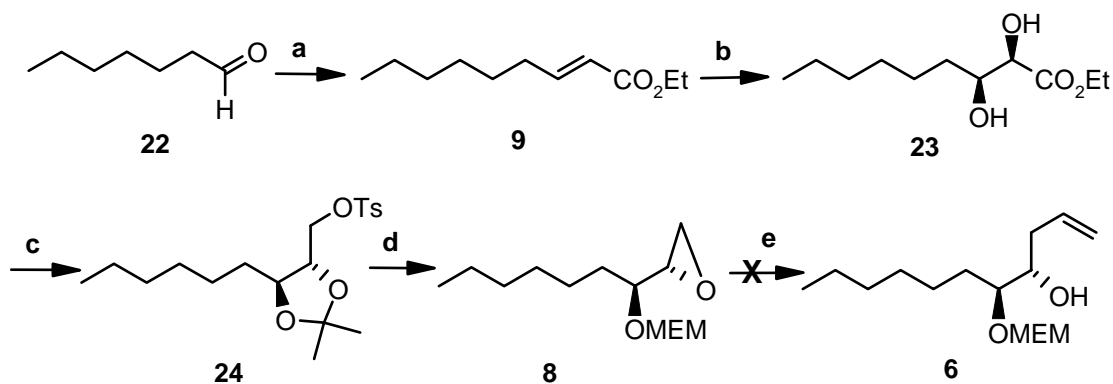


Scheme 5. Reagents and conditions: (a) I_2 , PPh_3 , imidazole, ether-benzene (2:1), rt, 1.5 h, 86%. (b) Zn, ethanol, reflux, 1.5 h, 96%. (c) (i) $n-Bu_4NF$, THF, 0 °C to rt, 4 h, 85%. (ii) NaH, BnBr, DMF, 0 °C- rt, 2.5 h, 86%. (d) PPTS, *t*-BuOH, 80 °C, 1.5 h, 85%. (e) (i) $(COCl)_2$, DMSO, Et_3N , CH_2Cl_2 , -78 °C, 1 h, 90%. (ii) $NaClO_2$, DMSO, NaH_2PO_4 , rt, 1.5 h, 92%.

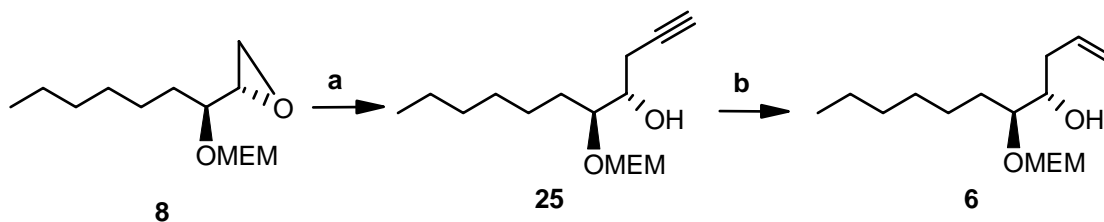
Conversion of **7** into **19** was accomplished by Zinc mediated elimination⁷ reaction in refluxing ethanol. In the 1H NMR spectrum of **19**, typical pattern for terminal olefinic protons were observed. The dibenzyl derivative **20** was produced by desilylation¹² followed by benzylation and deprotection of MEM group.¹⁸ Compound **21** was transformed into the acid derivative in two steps which first involved Swern oxidation and reaction with aqueous $NaClO_2$ in DMSO and phosphate buffer.¹⁹ 1H NMR and ^{13}C spectra of **5** were compatible with the assigned structure (Scheme 5).

The journey toward the synthesis of **6** began with commercially available 1-heptanal (**22**), which upon two-carbon Wittig homologation with $Ph_3P=CHCO_2Et$ in benzene at 80 °C gave **9** as a mixture of *trans* and *cis* isomers in the ratio of 85:15.²⁰ They were separated by silica gel chromatography and the major *trans* isomer was subjected to Sharpless asymmetric dihydroxylation procedure⁸ in the presence of $(DHQD)_2PHAL$, $K_2Fe(CN)_6$, K_2CO_3 , $MeSONH_2$ and $K_2OsO_4 \cdot 2H_2O$ in *t*-BuOH- H_2O (1:1) at 0 °C for 10 h to afford the diol **23**. The compound was thoroughly investigated by the 1H and ^{13}C NMR spectra and elemental analysis (Scheme 6). Enantiomeric purity of **23** was estimated to be 97.5% ee, by chiral HPLC analysis of the corresponding dibenzoate using a chiralcel OD column (1% *i*-propanol/*n*-hexane, flow rate 2.0 mL/min, $\lambda = 225$ nm). The diol **23** was treated with 2,2-dimethoxypropane-cat. *p*-TSA, reduction with DIBAL-H in CH_2Cl_2 at -78 °C followed by tosylation gave **24**.²¹ Acid hydrolysis,²² cyclisation with K_2CO_3 in MeOH followed by protection of hydroxyl group as the MEM group to afford **8**. The 1H NMR, ^{13}C NMR spectra and elemental analysis were in accordance with the structure of **8**. The ring opening reaction of the oxirane **8** with vinyl magnesium bromide in THF at 0 °C led to a mixture of products in which the require product **6** was formed as a minor product. This was partly attributed to side reactions particularly iodide mediated ring opening reaction (Scheme 6). However, the two step sequence involving opening of epoxide ring with lithium acetylide-EDA complex²³ in DMSO followed by partial reduction of the triple bond in

the presence of Lindlar's catalyst²⁴ afforded compound **6** (Scheme 7). The ¹H NMR spectrum of **6** showed resonances for terminal olefinic protons at δ 5.06-5.17 (multiplet), and at δ 5.88 (dt, J = 17.6, 10.6, 7.0 Hz). The ¹³C NMR spectrum indicated peaks at 117.1, 134.9 for olefinic carbons.

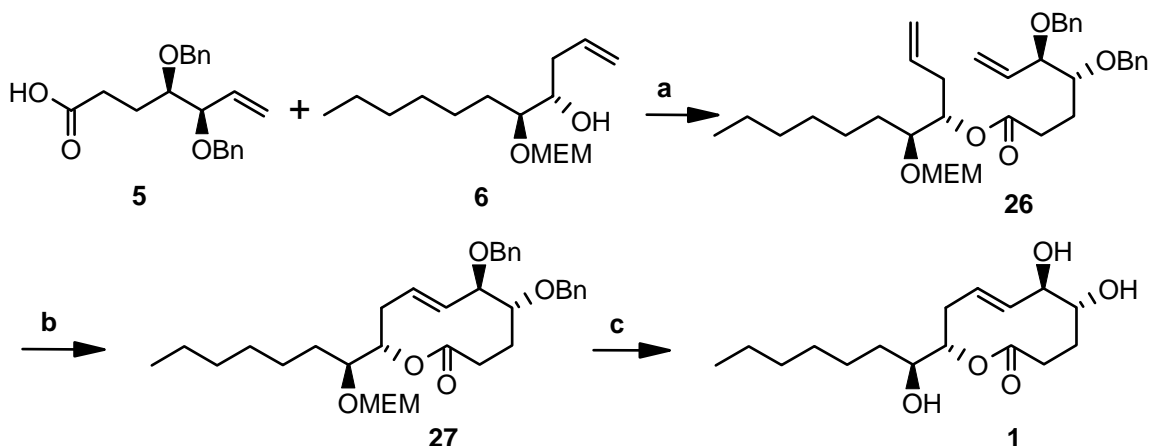


Scheme 6. Reagents and conditions: (a) $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$, benzene, 80 °C, 4 h, *trans*:*cis* (85:15), 89%. (b) AD-mix- α , *t*-BuOH, H_2O , 0 °C, 10 h, 94%. (c) (i) 2,2-dimethoxypropane, *p*-TsOH, CH_2Cl_2 , rt, 4 h, 96%. (ii) DIBAL-H, CH_2Cl_2 , -78 °C, 1 h, 97%. (iii) *p*-TsCl, pyridine, 0 °C-rt, 7 h, 96%. (d) (i) conc. HCl (cat.), MeOH, rt, 3 h, 87%. (ii) K_2CO_3 , MeOH, rt, 1.5 h, 85%. (iii) MEM-Cl, $^i\text{Pr}_2\text{NEt}$, CH_2Cl_2 , rt, 4 h, 91%. (e) vinylmagnesium bromide, CuCN, THF, -40 °C-0 °C, 12 h.



Scheme 7. Reagents and conditions: (a) $\text{LiC}\equiv\text{CH}$:ethylenediamine, DMSO, rt, 12 h, 86%. (b) H_2 , Pd/BaSO₄, quinoline, benzene, 1 bar, 0.5 h, 91%.

The coupling reaction of fragments **5** and **6** was performed in the presence of DCC⁶ and DMAP in CH_2Cl_2 . The structure of the derived ester **26** was confirmed by the ¹H and ¹³C NMR spectra (Scheme 8). In the ¹H NMR spectrum, a clear-cut down field shift of H-10 signal was observed, which indicated that the ester formation had indeed occurred.

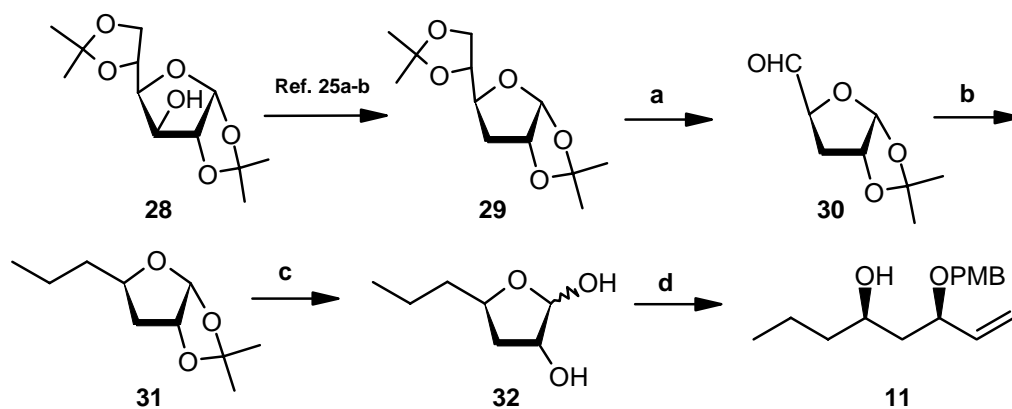


Scheme 8. Reagents and conditions: (a) DCC, DMAP, CH₂Cl₂, rt, 18 h, 76%. (b) (PCy₃)₂Ru(Cl)₂=CHPh (20 mol%), CH₂Cl₂, reflux, 28 h, 67%. (c) TiCl₄, CH₂Cl₂, 0 °C, 0.5 h, 76%.

Ring closing metathesis reaction⁵ of **26** with Grubbs' catalyst (Cl₂PCy₃Ru=CHPh) in degassed CH₂Cl₂ afforded the ten-membered lactone derivative as a mixture of two geometrical isomers in 10:1 ratio whose silica gel purification gave the pure *E*-isomer (**27**). The ¹H NMR spectrum of **27** showed two olefinic protons at δ 5.64 and 5.73 (*J* = 15.8) (Scheme 8). For the deprotection of MEM-group, **27** was exposed to titanium tetrachloride^{10,21} in CH₂Cl₂ at 0 °C. However, this treatment resulted in the simultaneous removal of MEM as well benzyl ethers and led to the formation of microcarpalide (**1**) whose NMR spectrum in CD₃CN revealed two slowly inter-converting conformers in a ration of 76:24. The resonances due to H-10 were seen at 4.81 ppm for the major conformer and at 4.63 ppm for the minor. This conformer ratio is identical to the 3.5:1 value reported for natural product in the in the same solvent.

Total synthesis of herbarumin III (4)

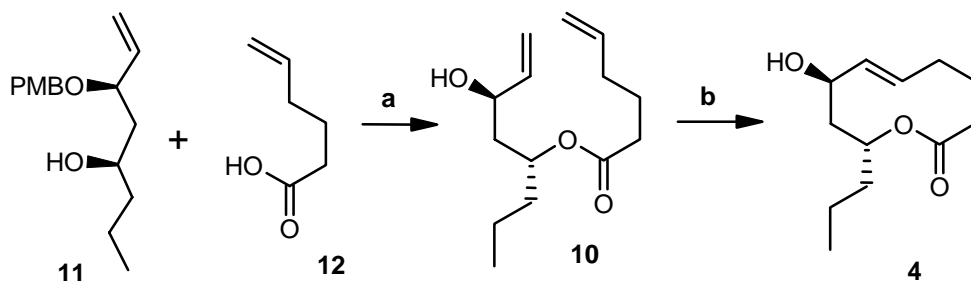
The synthesis of herbarumin III began with the preparation of fragment **11** from D-glucose. The 3-deoxy-derivative^{25a-b} of diacetonide-D-glucose selectively deprotected and then cleaved²⁶ to give the aldehyde **30** which was treated with EtPPh₃Br and *n*-BuLi at -78 °C and then hydrogenated by using 10% Pd/C to afford the *n*-propyl sugar derivative **31** (Scheme 9).



Scheme 9. *Reagents and conditions:* (a) (i) 0.8% H₂SO₄, MeOH, rt, 12 h, 84%. (ii) Silica gel supported NaIO₄, CH₂Cl₂, rt, 30 min, 95%. (b) (i) Br⁻P⁺Ph₃CH₂CH₃, *n*-BuLi, THF, -78 °C-0 °C, 3 h, 82%. (ii) H₂, Pd/C, 1 bar, rt, 3 h, 92%. (c) 20% AcOH in H₂O, conc. H₂SO₄ (catalytic), reflux, 6 h, 93%. (d) (i) IP⁺Ph₃CH₃, *n*-BuLi, THF, 0 °C-rt, 12 h, 76%. (ii) PMBCl, NaH, DMF, 0 °C, 1 h, 94%.

The 1,2-*O*-isopropylidene group of **31** was cleaved with 20% acetic acid and catalytic H₂SO₄ to afford the lactol derivative (**32**). Subsequent Wittig reaction²⁷ with Ph₃P=CH₂ to obtain the olefin which was converted in its PMB-ether derivative (**11**). The structure of (**11**) was confirmed by its ¹H and ¹³C NMR and mass spectral analysis.

The esterification reaction between **11** and 5-hexenoic acid²⁸ (**12**) was performed under Yamaguchi condition²⁹ and deprotection of PMB group gave **10** which was a precursor for RCM reaction (Scheme 10).



Scheme 10. *Reagents and conditions:* (a) (i) 2,4,6-trichlorobenzoyl chloride, DMAP, THF, **11** in THF, 0 °C-rt, 4 h, 82%; (ii) DDQ, CH₂Cl₂/H₂O (18:1), rt, 30 min, 94%. (b) (i) RuCl₂(=CHPh)-(PCy₃)₂, CH₂Cl₂, reflux, 4 days, 36% (52% starting material recovered), (ii) RuCl₂(=CHPh)-(PCy₃)(IEMS), CH₂Cl₂, reflux, 16 h, 78%.

The RCM of **10** in the presence of Grubbs' 2nd generation catalyst was efficient and high yielding, thus giving rise to dimmer as a minor product. The structure of **4** was confirmed by comparison of spectroscopic and optical rotation with reported values.⁹

Conclusions

In summary, RCM reaction has been judiciously used to complete the total synthesis of medium ring size natural products microcarpalide **1** and herbarumin III (**4**).

Experimental Section

General Procedures. Solvents were purified and dried by standard procedures before use. Column chromatography was carried out with silica gel (60-120 mesh). Infrared spectra were recorded with Shimadzu IR 420 and Perkin-Elmer 683 spectrometers. NMR spectra were recorded on Bruker AC-200 and Bruker DRX-500 machine in CDCl₃ with TMS as internal standard. Mass spectra were obtained with Finningen MAT 1210 mass spectrometer. Optical rotations were measured with digital polarimeter. Elemental analysis was done on elemental analyzer model 1108 EA. All reactions were monitored on 0.25 mm E-Merck pre-coated silica gel (TLC) plates (60F-254) with UV or I₂, anisaldehyde reagent in ethanol. Petroleum ether refers to mixture of hexanes with bp 60-80 °C.

2,3-O-Isopropylidene-5,6-dideoxy-7-O-[(2-methoxyethoxy)methyl]- α -D-lyxo-heptofuranose (15). To a solution of compound **13** (5.0 g, 14.36 mmol) in CH₂Cl₂ at -78 °C was added DIBAL-H (2.5 M toluene solution) (17.8 mL, 35.7 mmol). After stirring for 2 h at -78 °C, excess DIBAL-H was quenched with saturated sodium potassium tartrate solution. The solid was filtered, the filtrate concentrated and the residue purified on silica gel by eluting with light petroleum: EtOAc (1:1) to give **14** (4.03 g, 92%), as a colorless liquid. ¹H NMR (200 MHz): δ 1.30 (s, 3 H), 1.45 (s, 3 H), 1.91 (br s, OH), 4.09-4.23 (m, 3 H), 4.45-4.53 (m, 1 H), 4.58-4.80 (m, 3 H), 5.07 (m, 1 H), 5.71-6.00 (m, 2 H), 7.26-7.37 (m, 5 H); ¹³C NMR (50 MHz): δ 24.5, 25.8, 58.2, 62.0, 68.5, 68.6, 75.3, 80.1, 81.0, 85.0, 104.8, 111.8, 124.4, 125.2, 127.5, 128.1, 133.3, 134.4; Anal. Calcd for C₁₇H₂₂O₅: C, 66.65; H, 7.24. Found: C, 66.17; H, 7.09.

The above product (3.5 g, 11.43 mmol), DIPEA (3 mL), MEM-Cl (1.6 mL, 13.68 mmol) in CH₂Cl₂ (20 mL) were stirred at rt for 10 h and concentrated. The residue was dissolved in ethyl acetate, washed with water, brine and dried (Na₂SO₄). Solvent was evaporated and the residue purified on silica gel by eluting with light petroleum: EtOAc (3:2) to afford **14** (3.51 g, 78%) as a colorless liquid. ¹H NMR (200 MHz): δ 1.30 (s, 3 H), 1.46 (s, 3 H), 3.36-3.40 (m, 4 H), 3.50-3.62 (m, 3 H), 3.68-3.75 (m, 2 H), 4.15-4.23 (m, 1 H), 4.46-4.53 (m, 1 H), 4.67 (s, 2 H), 4.74-4.76 (m, 2 H), 5.10 (s, 2 H), 5.82-5.95 (m, 2 H), 7.26-7.32 (m, 5 H); ¹³C NMR (50 MHz): δ 24.9, 26.0, 58.7, 63.2, 66.8, 67.7, 68.7, 71.7, 75.6, 80.3, 81.4, 85.4, 94.5, 94.7, 105.2, 112.4, 126.8, 127.1, 127.6, 127.9, 128.3, 130.1, 131.0, 137.4; Anal. Calcd for C₂₁H₃₀O₇: C, 63.94; H, 7.67. Found: C, 64.10; H, 7.19.

The above product **14** (3.5 g, 8.88 mmol) and 10% Pd/C (100 mg) in MeOH (40 mL) were stirred under hydrogen at 55 psi at 60 °C for 4 h and filtered. The filtrate was concentrated to

give **15** (2.6 g, 96%) as a colorless liquid. ^1H NMR (200 MHz): δ 1.30 (s, 3 H), 1.43 (s, 3 H), 1.69-1.75 (m, 4 H), 2.87 (br s, OH), 3.38 (s, 3 H), 3.52-3.61 (m, 4 H), 3.65-3.68 (m, 2 H), 4.01-4.17 (m, 2 H), 4.54-4.65 (m, 2 H), 4.69 (s, 2H); Anal. Calcd for $\text{C}_{14}\text{H}_{26}\text{O}_7$: C, 54.89; H, 8.55. Found: C, 54.43; H, 8.71.

(2R,3S,4R)-1-(Trimethylacetyl)-2,3-isopropylidenedioxy-4-hydroxy-7-[(2-methoxyethoxy)methoxy]heptanol (16). To a solution of **15** (2.5g, 8.16 mmol) in THF (20 mL) at 0 °C was added LiAlH_4 (0.31 g, 8.07 mmol) and stirred at 0 °C for 1 h. Excess of LiAlH_4 was quenched by the addition of ethyl acetate. The solid formed was filtered, the filtrate concentrated and purified on silica gel by eluting with light petroleum: EtOAc (1:4) to afford **16** (2.3 g, 92%) as a colorless liquid. $[\alpha]_{\text{D}} + 18.2$ (c 2.8, CHCl_3); ^1H NMR (200 MHz): δ 1.35-1.48 (2 s, 6 H), 1.57-1.84 (m, 4 H), 2.25 (br s, OH), 3.37 (s, 3 H), 3.51-3.57 (m, 4 H), 3.63-3.77 (m, 5 H), 4.01 (dd, 1 H, $J = 6.8$, 3.4 Hz), 4.17 (dt, 1 H, $J = 6.8$, 5.1 Hz), 4.68 (s, 2 H); ^{13}C NMR (50 MHz): δ 24.6, 25.6, 26.8, 31.0, 58.4, 60.3, 66.2, 68.25, 71.3, 77.0, 94.9, 107.7.

(2R,3R,4R)-2,3-(Isopropylidenedioxy)-4-(tert-butyl dimethylsilyloxy)-7-[(2-methoxyethoxy)methoxy]hept-1-ol (17). The above product **16** (2.0 g, 6.5 mmol) in pyridine (10 mL) under nitrogen at 0 °C was added trimethylacetyl chloride (1.2 mL, 9.74 mmol) drop wise. After stirring for 1 h at rt, solvent was evaporated, the residue extracted with ethyl acetate and washed with 1N HCl, brine, dried (Na_2SO_4) and evaporated. The residue was purified on silica gel by eluting with petroleum ether: EtOAc (7:3) to give trimethylacetyl protected compound (2.31 g, 91%) as a colorless liquid. $[\alpha]_{\text{D}} + 24.2$ (c 2.5, CHCl_3); ^1H NMR (200 MHz): δ 1.21 (s, 9 H), 1.36-1.48 (2s, 6 H), 1.56-1.83 (m, 4 H), 3.39 (s, 3 H), 3.52-3.61 (m, 5 H), 3.64-3.70 (m, 2 H), 4.03 (t, 1 H, $J = 4.8$ Hz), 4.22-4.30 (m, 3 H), 4.7 (s, 2 H); ^{13}C NMR (50 MHz): δ 23.5, 24.6, 26.6, 26.9, 30.1, 58.2, 62.9, 66.2, 66.9, 68.0, 71.2, 74.5, 79.1, 94.8, 107.8; Anal. Calcd for $\text{C}_{19}\text{H}_{36}\text{O}_8$: C, 58.14; H, 9.25. Found: C, 57.91; H, 9.18.

A solution of above product (2.3 g, 58.9 mmol), imidazole (0.8 g, 11.7 mmol) and TBS-Cl (1.33 g, 8.82 mmol) in DMF (10 mL) under nitrogen was stirred at rt for 4 h. The reaction mixture was diluted with ether, washed with water, dried (Na_2SO_4) and purified on silica gel by eluting with light petroleum:EtOAc (4:1) to afford TBS-ether (2.6 g, 90%) as a colorless liquid. $[\alpha]_{\text{D}} + 41.1$ (c 3.6, CHCl_3); ^1H NMR (200 MHz): δ -0.05 (s, 6 H), 0.87 (s, 9 H), 1.31-1.43 (2s, 6 H), 1.51-1.85 (m, 4 H), 3.37 (s, 3 H), 3.49-3.55 (m, 4 H), 3.62-3.76 (m, 3 H), 3.99 (dd, 4 H, $J = 8.1$, 5.4 Hz), 4.67 (s, 2 H); ^{13}C NMR (50 MHz): δ -4.8, -4.3, 18.0, 25.2, 25.7, 26.8, 27.58, 30.46, 38.29, 58.4, 62.9, 66.3, 67.0, 70.0, 71.4, 74.6, 80.2, 95.0, 107.9, 177.4.

To the above product (2.5 g, 6.39 mmol) in CH_2Cl_2 (20 mL) under nitrogen and at -78 °C was added DIBAL-H (2.6 M in toluene, 6.2 mL, 62.6 mmol) drop wise. After 1 h, excess of DIBAL-H was quenched by using saturated aqueous sodium potassium tartrate solution. The organic layer was separated out and the aqueous layer extracted with CH_2Cl_2 . The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford the crude product which was purified on silica gel by using light petroleum:EtOAc (1:1) to give **17** (1.9 g, 89%) as a colorless liquid. $[\alpha]_{\text{D}} + 56.3$ (c 3.1, CHCl_3); ^1H NMR (200 MHz): δ -0.05 (s, 6 H), 0.87 (s, 9 H), 1.31-1.43 (2 s, 6 H), 1.51-1.72 (m, 4 H), 2.25 (br s, OH), 3.37 (s, 3 H), 3.48-3.76 (m, 9

H), 3.98-4.18 (m, 2 H), 4.67 (s, 2 H); ^{13}C NMR (50 MHz): δ -4.8, -4.3, 18.0, 25.0, 25.7, 27.8, 30.5, 58.4, 60.9, 66.3, 67.1, 70.0, 71.4, 77.4, 80.2, 95.0, 107.8; Anal. Calcd for $\text{C}_{20}\text{H}_{42}\text{O}_7\text{Si}$: C, 56.84; H, 10.02. Found: C, 56.79; H, 9.98.

(2S,3R,4R)-1-Iodo-2,3-isopropylidenedioxy-4-tert-butyldimethylsilyloxy-7-[(2-methoxyethoxy)methoxy]heptane (7) and (2S, 3R)-1,4-anhydro-2,3-isopropylidenedioxy-7-[(2-methoxyethoxy)methoxy]heptitol (18). A mixture of **17** (0.5 g, 2.82 mol), PPh_3 (0.46 g, 1.76 mmol), imidazole (0.12 g, 1.76 mmol) and Et_3N (0.25 mL) in CH_2Cl_2 was stirred at rt under nitrogen for 2.5 h. The reaction mixture was diluted with CH_2Cl_2 , washed with 20% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution, brine, dried (Na_2SO_4), evaporated. The residue was purified on silica gel by eluting with light petroleum: EtOAc (4:1) to obtain **7** (0.28 g, 45%). $[\alpha]_{\text{D}} + 84.8$ (*c* 2.2, CHCl_3); ^1H NMR (200 MHz): δ -0.07 (s, 6 H), 0.88 (s, 9 H), 1.34-1.49 (2s, 6 H), 1.53-1.83 (m, 4 H), 3.12 (t, 1 H, *J* = 10.4 Hz), 3.27 (dd, 1 H, *J* = 10.4, 3.3 Hz), 3.4 (s, 3 H), 3.52-3.58 (m, 4 H), 3.65-3.70 (m, 2 H), 3.78-3.81 (m, 1 H), 3.93 (dd, 1 H, *J* = 8.2, 5.3 Hz), 4.22 (m, 1 H), 4.7 (s, 2 H); ^{13}C NMR (50 MHz): δ -4.9, -4.4, 5.6, 18.0, 25.2, 25.6, 27.8, 30.2, 58.4, 66.3, 66.8, 70.0, 71.3, 77.0, 80.2, 94.9; Anal. Calcd for $\text{C}_{20}\text{H}_{41}\text{IO}_6\text{Si}$: C, 45.11; H, 7.76. Found: C, 44.98; H, 7.58.

Further elution gave **18** (0.015 g, 15%). $[\alpha]_{\text{D}} + 32.2$ (*c* 1, CHCl_3); ^1H NMR (200 MHz): δ 1.30 (s, 3 H), 1.46 (s, 3 H), 1.65-1.81 (m, 4 H), 3.38 (s, 3 H), 3.43-3.47 (m, 2 H), 3.52-3.60 (m, 4 H), 3.64-3.70 (m, 2 H), 3.96 (d, 1 H, *J* = 10.6 Hz), 4.5 (dd, 1 H, *J* = 6.3, 3.7 Hz), 4.7 (s, 2 H), 4.73 (dd, 1 H, *J* = 6.3, 3.7 Hz); Anal. Calcd for $\text{C}_{14}\text{H}_{26}\text{O}_6$: C, 57.91; H, 9.03. Found: C, 57.79; H, 9.12.

(3R,4R)-4-(tert-Butyldimethylsilyloxy)-7-[(2-methoxyethoxy)methoxy]hept-1-en-3-ol (19). A mixture of **7** (1.5 g, 2.82 mmol), Zinc (0.36 g, 5.64 mmol) in refluxing ethanol (15 mL) was stirred for 1.5 h and filtered. The filtrate was concentrated, and then purified on silica gel by using light petroleum: EtOAc (7:3) to obtain **19** (0.96 g, 96%) as an oil. $[\alpha]_{\text{D}} + 72.7$ (*c* 0.75, CHCl_3); ^1H NMR (200 MHz): δ -0.65 (s, 6 H), 0.89 (s, 9 H), 1.56-1.69 (m, 4 H), 2.38 (d, OH, *J* = 6.3 Hz), 3.40 (s, 3 H), 3.51-3.61 (m, 5 H), 3.70 (ddd, 2 H, *J* = 5.4, 3.5, 1.1 Hz), 3.95-4.04 (m, 1 H), 4.71 (s, 2 H), 5.19 (dt, 1 H, *J* = 10.2, 1.5 Hz), 5.31 (dt, 1 H, *J* = 17.3, 1.5 Hz), 5.84 (ddd, 1 H, *J* = 17.3, 10.2, 5.3 Hz); ^{13}C NMR (50 MHz): δ -4.9, 17.5, 25.0, 25.4, 58.2, 66.0, 67.2, 71.2, 73.8, 74.5, 94.7, 114.7, 137.8; Anal. Calcd for $\text{C}_{17}\text{H}_{36}\text{O}_5\text{Si}$: C, 58.58; H, 10.41. Found: C, 58.23; H, 10.15.

(4R,5R)-4,5-Bis-benzyloxy-7-[(2-methoxyethoxy)methoxy]hept-1-ene (20). A solution of **19** (2.0 g, 5.7 mmol) and 1 M solution of Bu_4NF (5.7 mL, 5.7 mmol) in THF (10 mL) was stirred at rt for 1 h and evaporated. The residue was purified on silica gel by eluting with light petroleum: EtOAc (3:7) to give diol (1.31 g, 85%), as a colorless liquid. $[\alpha]_{\text{D}} + 24.5$ (*c* 0.9, CHCl_3); ^1H NMR (200 MHz): δ 1.52-1.81 (m, 4 H), 3.39 (s, 3 H), 3.44-3.62 (m, 5 H), 3.65-3.71 (m, 2 H), 3.89 (t, 1 H, *J* = 1.3 Hz), 4.71 (s, 2 H), 5.22 (dt, 1 H, *J* = 10.2, 1.4 Hz), 5.34 (dt, 1 H, *J* = 17.2, 1.4 Hz), 5.84 (ddd, 1 H, *J* = 17.2, 10.5, 6.5 Hz); ^{13}C NMR (50 MHz): δ 25.5, 29.9, 58.5, 66.4, 67.5, 71.4, 73.8, 75.9, 95.0, 116.5, 137.6.

To the above product (1.5 g, 6.41 mmol) in DMF (10 mL) at 0 °C was added NaH (60 % dispersion in mineral oil (0.56 g, 14 mmol). After 15 min, benzyl bromide (1.7 mL, 14 mmol)

was introduced and the reaction stirred for 2 h at rt. Water was carefully added to the reaction mixture, extracted with ether, washed with water and dried (Na_2SO_4). On evaporation of solvent, the residue was purified by silica gel column chromatography by eluting with light petroleum:EtOAc (1:9) to afford **19** (2.34 g, 88%) as a colorless liquid. $[\alpha]_{\text{D}} + 8.9$ (*c* 1.4, CHCl_3); ^1H NMR (200 MHz): δ 1.44–1.76 (m, 4 H), 3.39 (s, 3 H), 3.47–3.55 (m, 5 H), 3.63–3.68 (m, 2 H), 3.9 (t, 1 H, $J = 6.4$ Hz), 4.25 (d, 1 H, $J = 12.1$ Hz), 4.55 (d, 1 H, $J = 11.4$ Hz), 4.65 (d, 1 H, $J = 12.1$ Hz), 4.68 (s, 2 H), 4.76 (d, 1 H, $J = 11.4$ Hz), 5.25–5.35 (m, 2 H), 5.82 (ddd, 1 H, $J = 18.5, 10.9, 7.6$ Hz), 7.23–7.32 (m, 10 H); ^{13}C NMR (50 MHz): δ 25.5, 27.2, 58.4, 66.3, 70.2, 71.5, 72.7, 80.6, 82.2, 95.0, 118.0, 127.0, 127.3, 127.5, 127.9, 135.1, 138.3, 138.6; Anal. Calcd for $\text{C}_{25}\text{H}_{34}\text{O}_5$: C, 72.43; H, 8.27. Found: C, 72.18; H, 8.13.

(4R,5R)-4,5-Bis-benzyloxy-hept-6-enoic acid (5). A solution of **20** (0.9 g, 2.11 mmol) and PPTS (5.27 g, 21 mmol) in *t*-BuOH (20 mL) was heated at 80 °C for 1.5 h. Solvent was removed, residue extracted with ethyl acetate, washed with water, brine, dried (Na_2SO_4), evaporated. The residue was purified on silica gel by eluting with EtOAc:light petroleum (2:3) to give **21** (0.59 g, 85%) as a colorless liquid. $[\alpha]_{\text{D}} + 10.4$ (*c* 1.3, CHCl_3); ^1H NMR (200 MHz): δ 1.43–1.70 (m, 4 H), 1.83 (s, OH), 3.46–3.57 (m, 3 H), 3.93 (t, 1 H, $J = 6.4$ Hz), 4.38 (d, 1 H, $J = 11.9$ Hz), 4.54 (d, 1 H, $J = 11.4$ Hz), 4.63 (d, 1 H, $J = 11.9$ Hz), 4.75 (d, 1 H, $J = 11.4$ Hz), 5.25–5.35 (m, 2 H), 5.8 (ddd, 1 H, $J = 16.6, 10.8, 7.5$ Hz), 7.22–7.31 (m, 10 H); ^{13}C NMR (50 MHz): δ 27.1, 28.7, 62.3, 70.4, 73.0, 80.9, 82.2, 118.6, 121.7–128.1 (m), 135.1, 138.3, 138.4.

The above product (0.52 g, 1.59 mmol) in CH_2Cl_2 (3 mL) was added to a stirred solution of DMSO (0.34 mL, 4.76 mmol) and $(\text{COCl})_2$ (0.17 mL, 1.98 mmol) in CH_2Cl_2 (5 mL) at –78 °C under nitrogen. The reaction was stirred for 30 min, quenched and worked up in the usual fashion to give a residue which was stirred with aq. NaClO_2 (0.19 g in 2 mL water, 2.08 mmol) DMSO (2 mL), NaH_2PO_4 (0.16 g, 1.05 mmol). After 2 h, the reaction mixture was diluted with water, extracted with EtOAc, dried (Na_2SO_4), concentrated. The residue was passed through a column of silica gel by eluting with light petroleum:EtOAc (9:1) to give **5** (0.43 g, 90%) as a colorless liquid. $[\alpha]_{\text{D}} + 16.8$ (*c* 0.7, CHCl_3); ^1H NMR (200 MHz): δ 1.61–1.80 (m, 1 H), 1.83–1.99 (m, 1 H), 2.33–2.44 (m, 2 H), 3.52 (ddd, 1 H, $J = 9.3, 6.0, 3.7$ Hz), 3.90 (t, 1 H, $J = 6.5$ Hz), 4.38 (d, 1 H, $J = 12.2$ Hz), 4.52 (d, 1 H, $J = 11.3$ Hz), 4.64 (d, 1 H, $J = 12.1$ Hz), 4.76 (d, 1 H, $J = 11.3$ Hz), 5.32 (br dd, 1 H, $J = 18.4, 1.7$ Hz), 5.36 (br dd, 1 H, $J = 9.1, 1.8$ Hz), 5.81 (br ddd, 1 H, $J = 18.3, 10.9, 7.5$ Hz), 7.25–7.33 (m, 10 H); ^{13}C NMR (50 MHz): δ 26.3, 30.9, 70.5, 73.3, 80.2, 82.7, 96.1, 118.8, 127.4, 127.6, 127.9, 135.1, 138.6, 178.7; Anal. Calcd for $\text{C}_{15}\text{H}_{30}\text{O}_4$: C, 65.66; H, 11.02. Found: C, 65.07; H, 10.83.

Ethyl (2R,3S)-2,3-Dihydroxy nonoate (23). To a mixture of $\text{K}_3[\text{Fe}(\text{CN})_6]$ (26.67 g, 81.2 mmol), K_2CO_3 (11.2 g, 81.2 mmol), $(\text{DHQ})_2$ PHAL (0.211 g, 0.27 mmol), MeSO_2NH_2 (2.57 g, 27.1 mmol) and $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$ (0.211 g, 0.1 mmol) in *t*-BuOH: H_2O (200 mL total volume, 1:1 mixture) at 0 °C was added olefin **9** (5 g, 27.1 mmol) and stirred at 0 °C. After 10 h, sodium sulphite (10.2 g) was added, solvent removed under vacuum. The residue was extracted with ethyl acetate, washed with 2 N KOH, water, brine, dried (Na_2SO_4) and evaporated. The residue on purification by silica gel chromatography by eluting with light petroleum: EtOAc (4:1) to

afford the diol **23** (5.56 g, 94%) as a colorless liquid. $[\alpha]_D - 10.7$ (*c* 1.0, CHCl₃); ¹H NMR (200 MHz): δ 0.87 (t, 3 H, *J* = 6.6 Hz), 1.21-1.38 (m, 8 H), 1.44-1.51 (m, 2 H), 1.56 (t, 3 H, *J* = 7.4 Hz), 2.50 (br.s, OH), 3.88 (dt, 1 H, *J* = 6.4, 2.1 Hz), 4.08 (d, 1 H, *J* = 2.1 Hz), 4.28 (q, 2 H, *J* = 7.4 Hz); ¹³C NMR (50 MHz): δ 13.8, 22.3, 25.5, 29.0, 31.5, 33.2, 61.5, 72.4, 73.3, 173.5; Anal. Calcd for C₁₁H₂₂O₄: C, 60.52; H, 10.16. Found: C, 60.27; H, 10.43.

(2R,3S)-2,3-(Isopropilidenedioxy)-1-(*p*-toluene sulphonyl) nonane (24). A solution of **23** (5.5 g, 25.2 mmol), 2,2-dimethoxypropane (3.7 mL, 30.27 mmol) and catalytic *p*-TSA in CH₂Cl₂ (50 mL) was stirred at room temperature for 4 h. It was diluted with CH₂Cl₂, washed with NaHCO₃, water, brine, concentrated and purified by silica gel chromatography by using light petroleum: EtOAc (9:1) to afford protected product (6.26 g, 96%) as a colorless liquid. $[\alpha]_D - 17.6$ (*c* 1.4, CHCl₃); ¹H NMR (200 MHz): δ 0.89 (t, 3 H, *J* = 6.4 Hz), 1.21-1.42 (m, 10 H), 1.40-1.43 (2s, 6 H), 1.57 (t, 3 H, *J* = 7.4 Hz), 4.05-4.12 (m, 2 H), 4.25 (q, 2 H, *J* = 7.4 Hz); ¹³C NMR (50 MHz): δ 13.6, 22.2, 25.2, 28.8, 31.3, 33.2, 61.0, 78.9, 110.3, 170.5; Anal. Calcd for C₁₄H₂₆O₄: C, 65.09; H, 10.14. Found: C, 64.87; H, 10.37.

To a solution of above product (5.2 g, 20.1 mmol) in CH₂Cl₂ (50 mL) at -78 °C was added DIBAL-H (2.5 M solution in toluene, 20 mL, 50 mmol). After stirring at -78 °C for 1h, excess of DIBAL-H was quenched by the addition of saturated aqueous sodium potassium tartarate. The solid was filtered, filtrate concentrated and the residue purified on silica gel eluting with light petroleum: EtOAc (3:2) to give alcohol (4.2 g, 97%) as a colorless liquid. $[\alpha]_D - 24.5$ (*c* 1.1, CHCl₃); ¹H NMR (200 MHz): δ 0.86 (t, 3 H, *J* = 6.2 Hz), 1.26-1.37 (m, 8 H), 1.39-1.40 (2 s, 6 H), 1.46-1.59 (m, 2 H), 1.8 (br s, OH), 3.53 (dd, 1 H, *J* = 11.3, 3.8 Hz), 3.67 (m, 2 H), 3.81-3.91 (m, 1 H); ¹³C NMR (50 MHz): δ 13.8, 22.4, 25.8, 26.9, 27.2, 29.2, 31.6, 33.0, 62.2, 77.2, 81.9, 108.4, 27.1, 28.7, 62.3, 70.4, 73.0, 80.9; Anal. Calcd for C₁₂H₂₄O₃: C, 66.63; H, 11.18. Found: C, 66.81; H, 10.98.

Above product (4.1 g, 19.0 mmol), TsCl (4.43 g, 22.76 mmol) and pyridine (20 mL) were stirred at rt for 7 h. Pyridine was removed under vacuum and the residue extracted with EtOAc, washed with 1 N HCl, water, brine, dried (Na₂SO₄) and evaporated. The residue was purified by silica gel column chromatography by eluting with light petroleum: EtOAc (4:1) to give **24** (6.74 g, 96%) as a colorless liquid. $[\alpha]_D - 16.4$ (*c* 3.6, CHCl₃); ¹H NMR (200 MHz): δ 0.89 (t, 3 H, *J* = 6.9 Hz), 1.27-1.31 (m, 11 H), 1.37 (s, 3 H), 1.46-1.58 (m, 2 H), 2.46 (s, 3 H), 3.77-3.81 (m, 2 H), 4.07-4.11 (m, 2 H), 7.35 (d, 2 H, *J* = 8.2 Hz), 7.81 (d, 2 H, *J* = 8.2 Hz); ¹³C NMR (50 MHz): δ 13.3, 20.7, 21.7, 25.0, 25.6, 26.5, 28.4, 30.9, 32.3, 68.6, 76.0, 77.5, 108.3, 127.2, 129.1, 132.4, 144.2; Anal. Calcd for C₂₁H₃₀O₅S: C, 63.93; H, 7.66, S, 8.13. Found: C, 63.79; H, 7.83, S, 8.32.

(2S)-2-[1-{{(1S)-(2-Methoxyethoxy)methoxy}heptyl}oxirane (8). To a solution of **24** (6.5 g, 17.56 mmol) in MeOH (30 mL) was added HCl (cat.) and the mixture was stirred at room temperature for 3 h. Solvent was removed in vacuum and the residue extracted with EtOAc, washed with water, brine, dried (Na₂SO₄) and evaporated. The residue was purified by silica gel chromatography eluting with light petroleum: EtOAc (3:2) to afford diol (5.1 g, 87%) as a colorless liquid. $[\alpha]_D - 23.41$ (*c* 1.6, CHCl₃); ¹H NMR (200 MHz): δ 0.88 (t, 3 H, *J* = 6.5 Hz),

1.27 (m, 8 H), 1.41-1.53 (m, 2 H), 2.05 (br s, OH), 2.46 (s, 3 H), 3.55-3.63 (m, 1 H), 3.70-3.76 (m, 1 H), 4.09 (dd, 2 H, $J = 4.9, 3.3$ Hz), 7.36 (d, 2 H, $J = 8.4$ Hz), 7.81 (d, 2 H, $J = 8.4$ Hz); ^{13}C NMR (50 MHz): δ 13.8, 21.4, 22.3, 25.3, 29.0, 29.2, 31.5, 33.1, 70.6, 71.3, 128.0, 129.8, 132.4, 144.9; Anal. Calcd for $\text{C}_{16}\text{H}_{26}\text{O}_5\text{S}$: C, 58.16; H, 7.93, S, 9.70. Found: C, 58.33; H, 8.08; S, 9.86.

Above product (5.0 g, 15.13 mmol) was dissolved in MeOH (30 mL) and K_2CO_3 (3.13 g, 22.68 mmol) was added. The mixture was stirred at room temperature for 1.5 h and concentrated. The residue was dissolved in water and extracted with ethyl acetate, washed with water, dried (Na_2SO_4) and evaporated. Purification on silica gel using light petroleum: EtOAc (4:1) as an eluent afforded pure epoxide (2.03 g, 85%) as a colorless liquid. $[\alpha]_{\text{D}} - 5.0$ (c 1.2, CHCl_3); ^1H NMR (200 MHz, CDCl_3): δ 0.96 (t, 3 H, $J = 6.4$ Hz), 1.24-1.41 (m, 8 H), 1.56-1.64 (m, 2 H), 2.72 (dd, 1 H, $J = 4.9, 2.5$ Hz), 2.82 (t, 1 H, $J = 4.9$ Hz), 2.97 (dt, 1 H, $J = 6.8, 2.5$ Hz), 3.43 (br m, 1 H); ^{13}C NMR (50 MHz): δ 13.8, 22.4, 25.1, 29.1, 29.2, 31.6, 34.1, 45.0, 55.5, 71.7; Anal. Calcd for $\text{C}_9\text{H}_{18}\text{O}_2$: C, 68.31; H, 11.47. Found: C, 68.08; H, 11.73.

A mixture of above product (2.0 g, 12.6 mmol), MEM-Cl (1.73 mL, 15.17 mmol) and DIPEA (3.28 mL, 18.97 mmol) in CH_2Cl_2 (15 mL) were stirred at room temperature for 4 h and concentrated. The residue was extracted with ethyl acetate, washed with water, dried (Na_2SO_4), evaporated and was purified by silica gel chromatography using light petroleum: EtOAc (4:1) to afford **8** (2.83 g, 91%) as a colorless liquid. $[\alpha]_{\text{D}} - 41.06$ (c 1.7, CHCl_3); ^1H NMR (200 MHz): δ 0.87 (t, 3 H, $J = 6.4$ Hz), 1.2-1.36 (m, 8 H), 1.55-1.62 (m, 2 H), 2.5 (dd, 1 H, $J = 4.9, 2.6$ Hz), 2.74 (dd, 1 H, $J = 4.9, 3.9$ Hz), 2.93 (ddd, 1 H, $J = 7.0, 4.2, 2.7$ Hz), 3.22-3.32 (m, 1 H), 3.37 (s, 3 H), 3.51-3.77 (m, 4 H), 4.73 (d, 1 H, $J = 6.9$ Hz), 4.92 (d, 1 H, $J = 6.9$ Hz); ^{13}C NMR (50 MHz): δ 13.3, 21.8, 24.6, 28.6, 31.0, 42.6, 53.7, 57.9, 66.2, 71.0, 77.0, 93.5; Anal. Calcd for $\text{C}_{13}\text{H}_{26}\text{O}_4$: C, 63.38; H, 10.64. Found: C, 63.28; H, 10.23.

(4S,5S)-5-[(2-Methoxyethoxy)methoxy]undec-1-en-4-ol (6). To a solution of **8** (1.5 g, 6.08 mmol) in DMSO (5 mL) at 0 °C was added lithium acetylide-EDA complex (0.82 g, 8.87 mmol) in one portion. The reaction mixture was stirred at 0 °C for 30 min and over night at rt. The excess of reagent was quenched with saturated ammonium chloride solution and extracted with EtOAc, washed with water, brine, dried (Na_2SO_4), concentrated. The residue was purified by silica gel chromatography by eluting with light petroleum: EtOAc (7:3) to afford the alkyne product (1.42 g, 86%) as a colorless liquid. $[\alpha]_{\text{D}} + 10.1$ (c 1.05, CHCl_3); ^1H NMR (200 MHz): δ 0.87 (t, 3 H, $J = 6.4$ Hz), 1.21-1.27 (m, 8 H), 1.47-1.65 (m, 2 H), 1.99 (t, 1 H, $J = 3.6$ Hz), 2.05 (s, OH), 2.43 (ddd, 2 H, $J = 11.9, 10.7, 2.4$ Hz), 3.42 (s, 3 H), 3.56 (t, 2 H, $J = 3.6$ Hz), 3.62-3.86 (m, 4 H), 4.82 (d, 2 H, $J = 3.6$ Hz), 4.92 (d, 1 H, $J = 6.9$ Hz); ^{13}C NMR (50 MHz): δ 13.8, 22.3, 23.3, 24.9, 29.1, 30.5, 31.5, 58.6, 67.3, 70.0, 70.7, 71.5, 80.4, 80.6, 95.4; Anal. Calcd for $\text{C}_{15}\text{H}_{28}\text{O}_4$: C, 66.14; H, 10.36. Found: C, 66.28; H, 10.21.

Above product (1.0 g, 3.67 mmol), Lindlar catalyst (20 mg) and quinoline (5 mg) in benzene (10 mL) were stirred under hydrogen atmosphere at 1 bar for 30 min. The catalyst was filtered, concentrated and the residue extracted with ethyl acetate, it was washed with 1 N HCl, water, dried (Na_2SO_4) and purified by silica gel column chromatography eluting with light petroleum: EtOAc (7:3) to give **6** (0.93g, 91%) as a colorless oil. $[\alpha]_{\text{D}} + 38$ (c 0.9, CHCl_3); ^1H NMR

(200MHz): δ 0.90 (t, 3 H, J = 6.6 Hz), 1.21-1.38 (m, 8 H), 1.44-1.61 (m, 2 H), 2.1-2.39 (m, 2 H), 2.81 (s, OH), 3.37-3.49 (m, 1 H), 3.39 (s, 3 H), 3.52-3.84 (m, 5 H), 4.7-4.87 (m, 2 H), 5.06-5.17 (m, 2 H), 5.88 (br ddt, 1 H, J = 17.4, 10.6, 7.0 Hz); ^{13}C NMR (50 MHz): δ 14.1, 22.6, 25.1, 29.4, 30.8, 31.7, 37.8, 58.9, 67.6, 71.7, 72.0, 82.4, 95.9, 117.1, 134.9; Anal. Calcd for $\text{C}_{15}\text{H}_{30}\text{O}_4$: C, 65.66; H, 11.02. Found: C, 65.07; H, 10.83.

(4R,5R)-4,5-Bis-benzyloxy-hept-6-enoic acid, (1'S,1''S)-1'-[(2-methoxyethoxy)methoxy]-3'-butenyl ester (26). To a solution of compounds **5** (0.07 g, 0.25 mmol), **6** (0.08 g, 0.25 mmol) and DMAP (5 mg) in CH_2Cl_2 (2 mL) was added DCC (0.057 g, 0.27 mmol). The reaction mixture was stirred at rt for 18 h, filtered and evaporated to afford a residue, which on purification by silica gel column chromatography eluting with light petroleum: EtOAc (7:3) afforded **26** (0.11 g, 76%) as a colorless liquid. $[\alpha]_{\text{D}} + 10.7$ (c 1.0, CHCl_3); ^1H NMR (500 MHz): δ 0.87 (t, 3 H, J = 6.9 Hz), 1.21-1.34 (m, 8 H), 1.46-1.54 (m, 2 H), 1.67-1.74 (m, 1 H), 1.88-1.95 (m, 1 H), 2.25-2.46 (m, 4 H), 3.37 (s, 3 H), 3.49-3.54 (m, 3 H), 3.58 (br ddd, 1 H, J = 6.2, 5.6, 4.3 Hz), 3.66-3.73 (m, 2 H), 3.87 (t, 1 H, J = 6.7 Hz), 4.38 (d, 1 H, J = 11.9 Hz), 4.52 (d, 1 H, J = 11.4 Hz), 4.62 (d, 1 H, J = 11.9 Hz), 4.71-4.77 (m, 3 H), 4.99-5.07 (m, 3 H), 5.27-5.33 (m, 2 H), 5.71 (dddd, 1 H, J = 17.1, 10.1, 7.6, 6.6 Hz), 5.80 (ddd, 1 H, J = 17.3, 10.6, 7.6 Hz), 7.25-7.30 (m, 10 H); ^{13}C NMR (125 MHz): δ 14.1, 22.6, 25.4, 26.3, 29.4, 30.5, 31.8, 34.7, 59.0, 67.5, 70.6, 71.8, 73.4, 78.1, 80.2, 82.60, 96.2, 117.6, 118.8, 127.5, 127.5, 127.7, 127.9, 128.33, 134.08, 135.2, 138.6, 138.7, 172.8; Anal. Calcd for $\text{C}_{36}\text{H}_{52}\text{O}_7$: C, 72.45; H, 8.78. Found: C, 72.08; H, 9.13.

(5R,6R,7E,10S)-10-[(1'S)-1'-[(2-Methoxyethoxy)methoxy]-5,6-bis-benzyloxy-3,4,5,6,9,10-hexa hydro-2H-oxecin-2-one (27). A mixture of compound **26** (0.1 g, 0.16 mmol) and Grubbs' catalyst (0.03 g, 0.0034 mmol) in degassed CH_2Cl_2 (100 mL) was stirred under reflux for 28 h. The reaction mixture evaporated and then purified on silica gel by eluting with light petroleum: EtOAc (7:3) to afford *E*-**27** (0.063 g, 67 %). $[\alpha]_{\text{D}} - 41.1$ (c 0.52, CHCl_3); ^1H NMR (500 MHz): δ 0.87 (t, 3 H, J = 6.9 Hz), 1.26-1.32 (m, 8 H), 1.54-1.59 (m, 3 H), 2.02 (ddd, 1 H, J = 15.2, 10.6, 6.2 Hz), 2.17 (ddd, 1 H, J = 14.7, 10.6, 1.4), 2.24-2.30 (m, 2 H), 2.61 (dd, 1 H, J = 14.7, 9.2 Hz), 3.38 (s, 3 H), 3.54-3.56 (m, 2 H), 3.67-3.78 (m, 4 H), 4.07 (br. d, 1 H, J = 4.5 Hz), 4.47 (d, 1 H, J = 11.9 Hz), 4.48 (d, 1 H, J = 12.5 Hz), 4.54 (d, 1 H, J = 11.9 Hz), 4.65 (d, 1 H, J = 12.5 Hz), 4.78-4.81 (m, 2 H), 5.15 (dt, 1 H, J = 9.2, 4.6 Hz), 5.64 (dd, 1 H, J = 15.8, 2.1 Hz), 5.64-5.73 (m, 1 H), 7.28-7.35 (m, 10 H); ^{13}C NMR (125 MHz): δ 14.0, 22.6, 25.0, 29.4, 31.2, 31.7, 36.1, 59.0, 67.4, 71.3, 71.5, 71.8, 78.2, 95.4, 126.5, 127.2, 127.5, 127.6, 128.3, 128.4, 131.7, 138.5, 138.8, 175.17; Anal. Calcd for $\text{C}_{34}\text{H}_{48}\text{O}^-_7$: C, 71.80; H, 8.51. Found: C, 71.97; H, 8.98.

Microcarpalide (1). To a solution of **27** (0.053 g, 0.1 mmol) in anhydrous CH_2Cl_2 (2 mL) under nitrogen at 0 °C was added TiCl_4 (0.1 mL, 1 mmol). After 30 min, excess of reagent was quenched with water, extracted with CH_2Cl_2 , washed with water, dried (Na_2SO_4), evaporated. The reaction mixture was purified on silica gel by eluting with light petroleum: EtOAc (2:3) to afford **1**, which existed as a two slowly inter-converting conformers in a 76: 24 ratio (0.022 g, 76 %). $[\alpha]_{\text{D}} - 23.2$ (c 0.7, MeOH); Lit.,^{2a} $[\alpha]_{\text{D}} - 22$ (c 0.67, MeOH); ^1H NMR (500 MHz, CD_3CN): (Major conformer) δ 0.92 (t, 3 H, J = 6.8 Hz), 1.28-1.38 (m, 8 H), 1.42-1.48 (m, 2 H), 1.72-1.83

(m, 1 H), 2.12-2.23 (m, 4 H), 2.28-2.37 (m, 2 H), 2.51 (br m, 1 H), 2.88 (br s, OH), 3.12 (br s, OH), 3.58 (br m, 1 H), 3.81 (br m, 1 H), 4.14 (br m, 1 H), 4.85 (ddd, 1 H, $J = 7.9, 4.7, 3.4$ Hz), 5.53 (dddd, 1 H, $J = 15.8, 7.2, 5.0, 2.1$ Hz), 5.73 (dd, 1 H, $J = 15.8, 2.2$ Hz); ^{13}C NMR (125 MHz, CD_3CN): δ 14.4, 23.3, 26.1, 26.4, 29.9, 32.5, 34.2, 36.7, 72.3, 72.8, 73.5, 79.7, 126.6, 134.5, 176.3; Anal. Calcd for $\text{C}_{16}\text{H}_{28}\text{O}_5$: C, 64.02; H, 9.40. Found: C, 64.17; H, 9.75.

3-Deoxy-5,6-dideoxy-1,2-O-isopropylidene- α -D-ribohept-5-enofuranoside (30). Compound **29** (12.0 g, 48.75 mmol) was stirred with 0.8% H_2SO_4 (10 mL) in methanol (300 mL) at ambient temperature for 12 h. After completion of the reaction (checked by TLC), the reaction mixture was neutralized with solid NaHCO_3 , filtered, concentrated and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography using acetone: ethyl acetate (1:4) to afford diol (8.42 g, 84%) as white solid. MP.: 81-82 °C; $[\alpha]_{\text{D}} -14.0$ (c 1.2, EtOH); ^1H NMR (200 MHz): δ 1.16 (s, 3 H), 1.34 (s, 3 H), 1.68 (t, 1 H, $J = 12.01$ Hz), 1.92 (d, 1 H, $J = 12.02$ Hz), 3.37 (m, 1 H), 3.51 (d, 1 H, $J = 11.25$ Hz), 3.68 (br s, 1 H), 3.83 (br s, 2 H, 2-OH), 4.01 (m, 1 H), 4.58 (s, 1 H), 5.84 (s, 1 H); ^{13}C NMR (50 MHz): δ 26.1, 26.7, 33.8, 63.5, 72.4, 78.4, 80.5, 105.2, 116.2; Anal: Calc for $\text{C}_9\text{H}_{16}\text{O}_5$: C, 53.43; H, 7.84; found: C, 53.13; H, 7.13.

To a stirred solution of above diol (7.10 g, 34.88 mmol) in CH_2Cl_2 (150 mL), was added sodium meta periodate (72.0 g) adsorbed over silica gel (200-400 mesh) at 0 °C, and left at ambient temperature for 30 min. After complete consumption of starting material (checked by TLC), the reaction mixture was filtered through sintered funnel, residue thoroughly washed with CH_2Cl_2 (2x50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford the crude aldehyde **30** (5.68 g, 95%) as viscous liquid which was used as such for the next reaction.

3-Deoxy-5,6-dideoxy-1,2-O-isopropylidene- α -D-ribohept furanoside (31). *n*-Butyl lithium (49 mL, 1.6 M in hexane) was slowly added to a stirred solution of ethylene triphenylphosphonium bromide (29.0 g, 78.2 mmol) in anhydrous THF (200 mL) at -78 °C under nitrogen atmosphere. The stirring was continued at the same temperature for 1 h. To the red wine colored solution, was added crude aldehyde **30** (5.38 g, 31.27 mmol) in THF (50 mL) drop wise at -78 °C. The stirring was continued for additional 3 h at 0 °C. After complete consumption of starting material (checked by TLC), the reaction was quenched by slow addition of saturated ammonium chloride solution, extracted with ethyl acetate (2x100 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4 , concentrated. The residue was purified by silica gel chromatography using ethyl acetate: light petroleum (1:9) to afford the Wittig product as a colorless liquid (4.71 g, 82%). $[\alpha]_{\text{D}} -23.4$ (c 1.45, CHCl_3); ^1H NMR (500 MHz): δ 1.31 (s, 3 H), 1.53 (s, 3 H), 1.55 (dd, 1 H, $J = 13.2, 4.2$ Hz), 1.70 (d, 3 H, $J = 6.9$ Hz), 2.11 (dd, 1 H, $J = 13.2, 4.2$ Hz), 4.60 (t, 1 H, $J = 4.3$ Hz), 4.95 (m, 1 H), 5.36 (t, 1 H, $J = 8.7$ Hz), 5.63 (m, 1 H), 5.69 (d, 1 H, $J = 3.9$ Hz); ^{13}C NMR (125 MHz): δ 13.5, 26.1, 26.7, 39.5, 73.0, 80.6, 105.2, 110.7, 128.2, 129.0.; Anal. Calcd for $\text{C}_{10}\text{H}_{16}\text{O}_3$: C, 65.19; H, 8.75 Found: C, 64.76; H, 8.92.

Palladium charcoal (100 mg) was added to the above product (4.60 g, 27.17 mmol) in ethyl acetate (40 mL). It was stirred under H_2 atmosphere (1 atmosphere) at rt for 3 h. The reaction

mixture was filtered, thoroughly washed the solid residue with ethyl acetate, concentrated to afford crude product which was purified by silica gel column chromatography using ethyl acetate: light petroleum (1:9) to give **31** as a colorless liquid (4.27 g, 92%). $[\alpha]_D - 12.5$ (*c* 0.80, CHCl_3); $^1\text{H NMR}$ (500 MHz): δ 0.94 (t, 3 H, $J = 7.58$ Hz), 1.26 (m, 2 H), 1.29 (s, 3 H), 1.41 (m, 2 H), 1.49 (s, 3 H), 1.61 (m, 1 H), 2.05 (m, 1 H), 4.15 (m, 1 H), 4.68 (s, 1 H), 5.76 (s, 1 H); $^{13}\text{C NMR}$ (125 MHz): δ 14.1, 19.2, 26.0, 26.5, 36.3, 39.0, 77.5, 80.4, 105.1, 110.5; MS (EI): m/z 187 $[\text{M}+\text{H}]^+$; Anal. Calcd for $\text{C}_{10}\text{H}_{18}\text{O}_3$: C, 64.48; H, 9.74. Found: C, 63.98; H, 9.16.

Oct-1-ene-(3R, 5R)-diol (32). Compound **31** (4.30 g, 23.11 mmol) in 20% aqueous acetic acid (40 mL) and few drops of concentrated H_2SO_4 was refluxed for about 6 h. Then reaction mixture was brought to rt, neutralized by addition of solid sodium carbonate. It was partitioned between ethyl acetate and water, the organic layer was washed with brine, dried over Na_2SO_4 , concentrated to obtain the crude product which was passed through a short bed of silica gel using ethyl acetate: light petroleum (1:1) to afford the pure lactol **32** (3.14 g, 93%). This unstable product was used immediately in next step without characterization.

(3R)-(4-Methoxybenzyloxy)-oct-1-ene-(5R)-ol (11). To the solution of methylene triphenyl phosphonium iodide (26.0 g, 64.5 mmol) in anhydrous THF (175 mL), was added *n*-butyl lithium (40 mL, 1.6 M in hexane) drop wise at 0 °C under N_2 atmosphere. After 1 h, lactol **32** (3.14 g, 21.50 mmol) in THF (30 mL) was slowly added while maintaining the reaction temperature 0 °C. The reaction mixture was brought to rt slowly and allowed to stir for additional 11 h. The reaction mixture was quenched with saturated ammonium chloride solution, extracted with ethyl acetate (3x100 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), concentrated to get the crude product which was purified by silica gel column chromatography using ethyl acetate: light petroleum (1:3) to afford diol as a colorless liquid (2.35 g, 76 %). $[\alpha]_D + 32$ (*c* 0.8, CHCl_3); $^1\text{H NMR}$ (500 MHz): δ 0.91 (t, 3 H, $J = 0.91$ Hz), 1.32-1.47 (m, 4 H), 1.52-1.59 (m, 2 H), 3.85 (br s, 1 H), 4.32 (br s, 1 H), 5.05 (d, 1 H, $J = 10.81$, Hz) 5.21 (d, 1 H, $J = 10.81$ Hz), 5.83 (ddd, 1 H, $J = 16.29, 10.39, 5.90$ Hz); $^{13}\text{C NMR}$ (125 MHz): δ 13.8, 18.3, 39.8, 42.5, 73.0, 114.0, 140.5; Anal. Calcd. for $\text{C}_8\text{H}_{16}\text{O}_2$: C, 66.63 H, 11.18 Found: C, 66.21 H, 10.45.

To a solution of diol (1.0 g, 6.94 mmol) in dry dimethyl formamide (DMF) (8 mL), was added sodium hydride (199 mg, 8.33 mmol) at 0 °C under N_2 atmosphere and allowed to stir at rt for 45 min. *p*-Methoxy benzyl chloride (PMB-Cl) (1.30 g, 8.32 mmol) in DMF (2 mL) was added drop wise. After stirring 1 h under this condition, the reaction mixture was quenched with cold water, extracted with ether (2x50 mL), dried (Na_2SO_4), and concentrated to afford the crude product. Purification by silica gel column chromatography using ethyl acetate: petroleum ether (3:7) gave pure product **11** as colorless liquid (1.72 g, 94%). $[\alpha]_D - 5.8$ (*c* 0.55, CHCl_3); $^1\text{H NMR}$ (200 MHz): δ 0.94 (t, 3 H, $J = 6.9$ Hz), 1.40-1.25 (m, 4 H), 1.75-1.62 (m, 2 H) 3.56 (br s, 1 H), 3.79 (s, 4 H), 4.01 (m, 1 H), 4.28 (d, 1 H, $J = 11.1$ Hz), 4.56 (d, 1 H, $J = 11.1$ Hz), 5.32-5.16 (m, 2 H), 5.74 (m, 1 H), 6.85 (d, 2 H, $J = 8.3$ Hz), 7.22 (d, 2 H, $J = 8.3$ Hz); $^{13}\text{C NMR}$ (50 MHz): δ 14.1, 18.6, 39.8, 42.5, 55.2, 69.8, 71.1, 81.2, 113.9, 117.5, 124.5, 129.9, 138.3, 159.3; Anal. Calcd for $\text{C}_{16}\text{H}_{24}\text{O}_3$: C, 72.69; H, 9.15. Found: C, 73.24; H, 9.08

(3R)-Hydroxy-1-propyl-pent-4-enyl hex-(5R)-enoate (10). To a solution of 5-hexenoic acid **12** (500 mg, 4.38 mmol) in THF, was added triethyl amine (1.0 mL, 6.57 mmol) and 2, 4, 6-trichloro benzoyl chloride (1.0 mL, 6.57 mmol) under nitrogen atmosphere at 0 °C and the reaction mixture was allowed to stir under this condition for 1 h. To this, alcohol **11** (925 mg, 3.50 mmol) in THF (5 mL) and catalytic amount of 4-dimethyl aminopyridine (DMAP) were added successively at 0 °C. Stirring was continued for additional 3 h at rt. The reaction mixture was quenched with water and extracted with ethyl acetate (3x50 mL). The combined organic layers were thoroughly washed with saturated sodium bicarbonate solution, brine, dried (Na₂SO₄), and concentrated to afford the crude product which was purified by silica gel column chromatography using ethyl acetate: light petroleum (1:19) to afford the ester as a colorless liquid (1.03 g, 82 %). [α]_D + 31.1 (*c* 0.60, CHCl₃); ¹H NMR (200 MHz): δ 0.86 (t, 3 H, *J* = 6.6 Hz), 1.26 (m, 2 H), 1.43 (m, 2 H), 1.65 (m, 3 H), 2.03 (m, 3 H), 2.20 (t, 2 H, *J* = 7.1 Hz), 3.73 (m, 1 H), 3.78 (s, 3 H), 4.23 (d, 1 H, *J* = 11.4 Hz), 4.50 (d, 1 H, *J* = 11.4 Hz), 5.28-4.95 (m, 5 H), 5.85-5.61 (m, 2 H), 6.84 (d, 2 H, *J* = 8.3 Hz), 7.21 (d, 2 H, *J* = 8.3 Hz); NMR (50 MHz, CDCl₃): δ 13.9, 18.4, 24.1, 33.1, 33.7, 36.6, 40.0, 55.1, 69.5, 71.0, 77.3, 113.6, 115.3, 118.0, 129.3, 130.5, 137.7, 138.3, 159.0, 172.8; Anal. Calcd for C₂₂H₃₂O₄: C, 73.30; H, 8.95 Found: C, 73.68; H, 9.24.

To a solution of above ester (500 mg, 1.38 mmol) in acetonitrile (10 mL) and water (0.5 mL) was added 2,3-Dichloro-5,6-dicyano benzoquinone (DDQ) (407 mg, 1.79 mmol). Reaction mixture was stirred at rt for 30 min. After completion (monitored by TLC), the reaction mixture was extracted with ethyl acetate (3x40 mL). The combined organic fractions were washed with saturated sodium bicarbonate solution followed by brine, dried (Na₂SO₄), concentrated to afford the crude product which was on purification by silica gel column chromatography using acetate: light petroleum (1:19) afforded compound **10** as a oily liquid (313 mg, 94 %). [α]_D + 3.6 (*c* 1.1, CHCl₃); ¹H NMR (200 MHz): δ 0.87 (t, 3 H, *J* = 7.1 Hz), 1.39-1.22 (m, 2 H), 1.90-1.48 (m, 6 H), 2.05 (q, 2 H, *J* = 14.1, 6.9 Hz), 2.25 (t, 2 H, *J* = 7.2 Hz), 2.48 (br s, 1 H), 4.11 (q, 1 H, *J* = 12.5, 6.4 Hz), 5.22-4.87 (m, 5 H), 5.89-5.63 (m, 2 H); ¹³C NMR (50 MHz): δ 13.8, 18.3, 24.0, 33.0, 33.7, 36.6, 41.5, 70.3, 71.4, 114.7, 115.3, 137.5, 140.5, 173.3; Anal. Calcd for C₁₄H₂₄O₃: C, 69.96; H, 10.06. Found: C, 69.52; H, 9.67.

Herbarumin III (4)

Ring closing metathesis of diene 10 with first generation Grubbs' catalyst. A mixture of **10** (100 mg, 0.40 mmol) in anhydrous CH₂Cl₂ (100 mL) and Grubbs' first generation catalyst (45 mg, 0.05 mmol) was degassed with argon for 15 min and refluxed for 4 days by the time TLC showed the consumption of only half of the starting diene. At this stage, the reaction was stopped and allowed to bring to room temperature. Solvent was removed under reduced pressure to leave highly dark brown colored residue. The crude product was purified by column chromatography using ethyl acetate: light petroleum (1:9) to afford herbarumin III (**4**) as colorless liquid (31 mg, 36 %).

Ring closing metathesis of diene 10 with second generation Grubbs' catalyst. A mixture of **10** (100 mg, 0.40 mmol) in anhydrous CH₂Cl₂ (100 mL) and Grubbs' second generation catalyst (15 mg, 0.003 mmol) was degassed with argon for 15 min, and refluxed for 16 h. Solvent was removed under reduced pressure to leave highly dark brown colored residue. The crude product was purified by ethyl acetate: light petroleum (1:9) to afford analytically pure herbarumin III (**4**) as a colorless liquid (68 mg, 76 %). [α]_D + 20.6 (*c* 1.2, EtOH); IR (CHCl₃): 3443, 3019, 2962, 1723, 1640 cm⁻¹; ¹H NMR (500 MHz): δ 0.91 (t, 3 H, *J* = 7.4 Hz), 1.33 (m, 2 H), 1.42 (m, 1 H), 1.54 (dddd, 1 H, *J* = 13.8, 9.3, 8.6, 4.9 Hz), 1.77 (m, 1 H), 1.82 (m, 1 H), 1.84 (m, 1 H), 1.98 (m, 1 H), 1.99 (m, 1 H), 2.00 (m, 1 H), 2.28 (dd, 1 H, *J* = 6.1, 13.0 Hz), 2.37 (m, 1 H), 4.42 (t, 1 H, *J* = 2.4 Hz), 5.30 (m, 1 H) 5.46 (m, 1 H), δ 5.62 (d, 1 H, *J* = 16.1 Hz); ¹³C NMR (125 MHz): 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; Anal. Calcd for C₁₂H₂₀O₃: C, 67.89; H, 9.50. Found: C, 67.42; H, 9.84

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References

1. Brown, H. C.; Fletcher, R. S.; Johansen, R. B. *J. Am. Chem. Soc.* **1951**, *73*, 214. (b) Eliel, E. in *Stereochemistry of Carbon Compounds* McGraw-Hill: New York, 1962; p 189.
2. Ratnayake, A. S.; Yoshida, W. Y.; Moobery, S. L.; Hemscheidt, T. *Org. Lett.* **2001**, *3*, 3479. (b) Cooper, J. A. *J. Cell Biol.* **1987**, *105*, 1473.
3. Bodo, B.; Molho, L.; Davoust, D.; Molho, D. *Phytochemistry* **1983**, *22*, 447. (b) Evidente, A.; Lanzetta, R.; Capasso, R.; Vurro, M.; Bottalico, A. *Phytochemistry* **1993**, *34*, 999. (c) Evidente, A.; Capasso, R.; Abouzeid, M.A.; Lanzetta, R.; Vurro, M.; Bottalico, A. *J. Nat. Prod.* **1993**, *56*, 1937. (d) Rivero-Cruz, J. F.; Garcia-Aguirre, G.; Cerda-Gracias-Rojas.; Mata, R. *Tetrahedron* **2000**, *56*, 5337. (e) Rivero-Cruz, J. F.; Macias, M.; Garcia-Aguirre, G.; Cerda-Gracias-Rojas.; Mata, R. *J. Nat. Pro.* **2003**, *66*, 511.
4. Murga, J.; Falomir, E.; Garcia-Fortanet, J.; Carda, M.; Marco, J. A. *Org. Lett.* **2002**, *4*, 3447. (b) Gurjar, M. K.; Nagaprasad, R.; Ramana, C. V. *Tetrahedron Lett.* **2003**, *44*, 2873. (c) Davoli, P.; Spaggiari, A.; Castagnetti, L.; Prati, F. *Org. Biomol. Chem.* **2004**, *2*, 38. (d) Banwell, G. M.; Loong, J. T. D. *Heterocycles* **2004**, *62*, 713. (e) Ishigami, K.; Kitahara, T. *Heterocycles* **2003**, *63*, 765.
5. Reviews: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (b) Fürstner, A. *Angew. Chem.* **2000**, *112*, 3140; *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (d) Fürstner, A. *Top. Catal.* **1997**, *4*, 285. (e) Schuster, M.; Blechert, S. *Angew. Chem.* **1997**, *109*, 2124; *Angew. Chem., Int. Ed.* **1997**, *36*,

2037. (f) Schrock, R. R. *Top Organomet. Chem.* **1998**, *1*, 1. (g) Maier, M. E. *Angew. Chem.* **2000**, *112*, 2153; *Angew. Chem., Int. Ed.* **2000**, *39*, 2073. For syntheses of 10-membered rings by RCM, see: (h) Fürstner, A.; Müller, T. *Synlett* **1997**, 1010. (i) Chang, S.; Grubbs, R. H. *Tetrahedron Lett.* **1997**, *38*, 4757. (j) Gerlach, K.; Quitschalle, M.; Kalesse, M. *Synlett* **1998**, 1108. (k) Fink, B. E.; Kym, P. R.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 4334. (l) Oishi, T.; Nagumo, Y.; Hirama, M. *Chem. Commun.* **1998**, 1041. (m) Quitschalle, M.; Kalesse, M. *Tetrahedron Lett.* **1999**, *40*, 7765. (n) Delgado, M.; Martin, J. D. *J. Org. Chem.* **1999**, *64*, 4798. (o) Bamford, S. J.; Goubitz, K.; Van Lingen, H. L.; Luker, T.; Schenk, H.; Hiemstra, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 345. (p) Nakashima, K.; Ito, R.; Sono, M.; Tori, M. *Heterocycles* **2000**, *53*, 301. (q) Cho, S. C.; Dussault, P. H.; Lisec, A. D.; Jensen, E. C.; Nickerson, K. W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 193. (r) Nevalainen, M.; Koskinen, A. M. P. *Angew. Chem.* **2001**, *113*, 4184; *Angew. Chem., Int. Ed.* **2001**, *40*, 4060. (s) Heinrich, M. R.; Steglich, W. *Tetrahedron Lett.* **2001**, *42*, 3287. (t) Banwell, M. G.; Bray, A. M.; Edwards, A. J.; Wong, D. J. *New J. Chem.* **2001**, *25*, 1347. (u) Telsler, J.; Beumer, R.; Bell, A. A.; Ceccarelli, S. M.; Montio, D.; Gennari, C. *Tetrahedron Lett.* **2001**, *42*, 9187.
6. Keck, E. G.; Boden, P. E. *J. Org. Chem.* **1985**, *50*, 2394.
 7. Rama Rao, A. V.; Reddy, E. R.; Joshi, B. V.; Yadav, J. S. *Tetrahedron Lett.* **1987**, *28*, 6497.
 8. (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. (b) Kolb, H. C.; Van-Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
 9. Rivero-Cruz, J. S.; Macias, M.; Cerda-Garcia, C. M.; Mata, R. *J. Nat. Prod.* **2003**, *66*, 511.
 10. Gurjar, M. K.; Karmakar, S.; Mohapatra, D. K. *Tetrahedron Lett.* **2004**, *45*, 4525.
 11. (a) Moore, B. S.; Cho, H.; Casati, R.; Kennedy, E.; Reynolds, K. A.; Mocek, U.; Beale, J. M.; Floss, H. G. *J. Am. Chem. Soc.* **1993**, *115*, 5254. (b) Coutrot, P.; Grison, C.; Lecouvey, M. *Bull. Soc. Chim. Fr.* **1997**, *134*, 27.
 12. Criegee, R. *Ber.* **1931**, *64*, 260.
 13. Corey, E. J.; Gras, J. -L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.
 14. Robins, M. J.; Hawrelak, S. D.; Kanai, T.; Siefert, J. -M.; Mengel, R. *J. Org. Chem.* **1979**, *44*, 1317.
 15. Corey, E. J.; Venkateswarulu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
 16. Nicaolou, K. C.; Webber, S. E. *Synthesis* **1986**, 453.
 17. (a) Corey, E. J.; Pyne, S.G. *Tetrahedron Lett.* **1983**, *24*, 4833. (b) Smith, A. B., III; Qiu, Y.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12011.
 18. Monti, H.; Leandri, G.; Klos-Ringuet, M.; Corriol, C. *Synth. Commun.* **1983**, *13*, 1021.
 19. (a) Mancuo, A. J.; Swern, D. *Synthesis* **1981**, 165. (b) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567.
 20. Liav, A.; Goren, M. B. *Carbohydr. Res.* **1984**, *131*, C8.
 21. (a) Angyal, S. J.; Beveridge, R. J. *Carbohydr. Res.* **1978**, *65*, 279. (b) Liu, G.; Wang, Z. *Synthesis* **2001**, 119.

22. Hanack, M.; Kunzmann, E.; Schumacher, W. *Synthesis* **1978**, 26.
23. Lindlar, H.; Dubuis, R. *Organic Syntheses*, Wiley: New York 1973, *Collect. Vol. V*, p 880.
24. Bhatt, M. V.; Kulkarni, S. V. *Synthesis* **1983**, 249.
25. (a) Schmidt, O. T. In *Methods in Carbohydrate Chemistry*; Whistler, R. L.; Wolfrom, M. L., Ed.; Academic Press Inc.: New York, 1963; Vol. 2, p318. (b) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
26. Zhong, Y. L.; Shing, T. K. M. *J. Org. Chem.* **1997**, 62, 2622.
27. Freeman, F.; Robarge, K. D. *Carbohydr. Res.* **1986**, 154, 270.
28. Krapcho, A. P. *Synthesis* **1982**, 805 and 893.
29. Jnanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, 52, 1989.