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 11\(^1\) 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\(^2^a\) (1), structurally related to a family of phytotoxins\(^3\) 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. Microcarpalide\(^4\) 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 RCM\textsuperscript{5} 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\textsuperscript{6}. Both the fragments (5 & 6) containing two chiral centers were realized by facile zinc mediated elimination\textsuperscript{7} and Sharpless asymmetric dihydroxylation\textsuperscript{8} as delineated in 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).

\[
\begin{align*}
\text{HO} & \quad \text{HO} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{PMBO} & \quad \text{OH} \\
\text{OH} & \quad \text{OH} \\
\text{OH} & \quad \text{OH} \\
\text{OH} & \quad \text{CHO} \\
\text{D-Glucose}
\end{align*}
\]

\[
\begin{align*}
\text{HO} & \quad \text{HO} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{PMBO} & \quad \text{OH} \\
\text{OH} & \quad \text{OH} \\
\text{OH} & \quad \text{OH} \\
\text{OH} & \quad \text{CHO} \\
\text{D-Glucose}
\end{align*}
\]

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 CH$_2$Cl$_2$ at $-78 \, ^\circ\text{C}$ 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 $^1$H NMR spectrum. For example, two singlets resonated at $\delta$ 4.67 and $\delta$ 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, CH₂Cl₂, -78 °C to 0 °C, 2 h, 92%; (ii) MEM-Cl, iPr₂NEt, CH₂Cl₂, rt, 10 h, 78%; (b) H₂, 10% Pd-C, MeOH, 6 bar, 60 °C, 4 h, 96%; (c) LiAlH₄, THF, rt, 1 h, 92%; (d) (i) (CH₃)₃CCOC1, pyridine, 0 °C-rt, 1 h, 91%; (ii) TBSCl, DMF, imidazole, rt, 4 h, 90%; (iii) DIBAL-H, CH₂Cl₂, -78 °C, 1 h, 89%.

In order to introduce iodide at C-1, the protection-deprotection sequence on 16 was performed to obtain the primary hydroxyl derivative (17). Treatment of 17 with I₂, TPP and imidazole in toluene at room temperature led to the formation of 7 in 40% yield. Addition of Et₃N marginally improved the yield of 7 (45%), however, the formation of the cyclized product 18 (15%) was also noticed (Scheme 4). The iodination reaction carried out in the presence of I₂, TPP and imidazole but in benzene-ether (2:1) medium provided 7 in 86% yield. In the ¹H NMR spectrum of 7, the resonances due to CH₂I were located at 3.12 as a triplet (J = 10.4 Hz), and at 3.27 as a doublet of doublet (J = 10.4, 3.3 Hz) (Scheme 5).

Scheme 4. Reagents and conditions: (a) I₂, PPh₃, imidazole, toluene, rt, 4 h, 40%; (b) I₂, PPh₃, imidazole, Et₃N, CH₂Cl₂, 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$_4$NF, 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$_3$N, CH$_2$Cl$_2$, -78 °C, 1 h, 90%. (ii) NaClO$_2$, DMSO, NaH$_2$PO$_4$, rt, 1.5 h, 92%.

Conversion of 7 into 19 was accomplished by Zinc mediated elimination reaction in refluxing ethanol. In the $^1$H NMR spectrum of 19, typical pattern for terminal olefinic protons were observed. The dibenzyl derivative 20 was produced by desilylation followed by benzylation and deprotection of MEM group. 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. $^1$H 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$_3$P=CHCO$_2$Et in benzene at 80 °C gave 9 as a mixture of trans and cis isomers in the ratio of 85:15. They were separated by silica gel chromatography and the major trans isomer was subjected to Sharpless asymmetric dihydroxylation procedure in the presence of (DHQ)$_2$PHAL, K$_2$Fe(CN)$_6$, K$_2$CO$_3$, MeSONH$_2$ and K$_2$OsO$_4$·2H$_2$O in t-BuOH- H$_2$O (1:1) at 0 °C for 10 h to afford the diol 23. The compound was thoroughly investigated by the $^1$H 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 chiracel 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$_2$Cl$_2$ at –78 °C followed by tosylation gave 24. Acid hydrolysis, cyclisation with K$_2$CO$_3$ in MeOH followed by protection of hydroxyl group as the MEM group to afford 8. The $^1$H 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 complex in DMSO followed by partial reduction of the triple bond in
the presence of Lindlar’s catalyst\textsuperscript{24} afforded compound 6 (Scheme 7). The \textsuperscript{1}H NMR spectrum of 6 showed resonances for terminal olefinic protons at $\delta$ 5.06-5.17 (multiplet), and at $\delta$ 5.88 (dt, $J$ = 17.6, 10.6, 7.0 Hz). The \textsuperscript{13}C NMR spectrum indicated peaks at 117.1, 134.9 for olefinic carbons.

![Scheme 6](image)

**Scheme 6. Reagents and conditions:** (a) Ph$_3$P=CHCO$_2$Et, benzene, 80 °C, 4 h, \textit{trans}:\textit{cis} (85:15), 89%. (b) AD-mix-$\alpha$, t-BuOH, H$_2$O, 0 °C, 10 h, 94%. (c) (i) 2,2-dimethoxypropane, $p$-TsOH, CH$_2$Cl$_2$, rt, 4 h, 96%. (ii) DIBAL-H, CH$_2$Cl$_2$, -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$_2$CO$_3$, MeOH, rt, 1.5 h, 85%. (iii) MEM-Cl, iPr$_2$NEt, CH$_2$Cl$_2$, rt, 4 h, 91%. (e) vinylmagnesium bromide, CuCN, THF, -40 °C-0 °C, 12 h.

![Scheme 7](image)

**Scheme 7. Reagents and conditions:** (a) LiC≡CH:ethylenediamine, DMSO, rt, 12 h, 86%. (b) H$_2$, Pd/BaSO$_4$, quinoline, benzene, 1 bar, 0.5 h, 91%.

The coupling reaction of fragments 5 and 6 was performed in the presence of DCC\textsuperscript{6} and DMAP in CH$_2$Cl$_2$. The structure of the derived ester 26 was confirmed by the \textsuperscript{1}H and \textsuperscript{13}C NMR spectra (Scheme 8). In the \textsuperscript{1}H 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)2 Ru(Cl)2=CHPh (20 mol%), CH2Cl2, reflux, 28 h, 67%. (c) TiCl4, CH2Cl2, 0 °C, 0.5 h, 76%.

Ring closing metathesis reaction 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 tetrachloride10,21 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 ratio 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-derivative25a-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) I⁺P⁺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 comrisision 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-7-0-[(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. $^1$H NMR (200 MHz): $\delta$ 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 C$_{14}$H$_{26}$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 oC was added LiAlH$_4$ (0.31 g, 8.07 mmol) and stirred at 0 oC 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. $[\alpha]_D + 18.2$ (c 2.8, CHCl$_3$); $^1$H NMR (200 MHz): $\delta$ 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): $\delta$ 24.6, 25.6, 26.8, 31.0, 58.4, 60.3, 66.2, 71.3, 77.0, 94.9, 107.7.

$(2R,3R,4R)-2,3$-(Isopropylidenedioxy)-4-((tert-butyldimethylsilyloxy)-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 oC 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$_2$SO$_4$) 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. $[\alpha]_D + 24.2$ (c 2.5, CHCl$_3$); $^1$H NMR (200 MHz): $\delta$ 1.21 (s, 9 H), 1.36-1.48 (2 s, 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): $\delta$ 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 C$_{19}$H$_{36}$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$_2$SO$_4$) 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. $[\alpha]_D + 41.1$ (c 3.6, CHCl$_3$); $^1$H NMR (200 MHz): $\delta$ -0.05 (s, 6 H), 0.87 (s, 9 H), 1.31-1.43 (2 s, 6 H), 1.51-1.85 (m, 4 H), 3.37 (s, 3 H), 3.49-3.76 (m, 9
H), 3.98-4.18 (m, 2 H), 4.67 (s, 2 H); 13C 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 C20H42O7Si: C, 56.84; H, 10.02. Found: C, 56.79; H, 9.98.

(2S,3R,4R)-1-Iodo-2,3-isopropylidenedioxy-4-terminatedimethylsilyloxy-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), PPh3 (0.46 g, 1.76 mmol), imidazole (0.12 g, 1.76 mmol) and Et3N (0.25 mL) in CH2Cl2 was stirred at rt under nitrogen for 2.5 h. The reaction mixture was diluted with CH2Cl2, washed with 20% aqueous Na2S2O3 solution, brine, dried (Na2SO4), evaporated. The residue was purified on silica gel by eluting with light petroleum: EtOAc (4:1) to obtain 7 (0.28 g, 45%). [α]D + 84.8 (c 2.2, CHCl3); 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); 13C 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 C20H41IO6Si: C, 45.11; H, 7.76. Found: C, 44.98; H, 7.58.

Further elution gave 18 (0.015 g, 15%). [α]D + 32.2 (c 1, CHCl3); 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 C14H26O6: 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 (4:1) to obtain 19 (0.96 g, 96%) as an oil. [α]D + 72.7 (c 0.75, CHCl3); 1H NMR (200 MHz): δ -0.65 (s, 6 H), 0.89 (s, 9 H), 1.56-1.69 (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 C17H36O5Si: 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 Bu4NF (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 (7:3) to obtain 20 (0.96 g, 96%) as an oil. [α]D + 24.5 (c 0.9, CHCl3); 1H NMR (200 MHz): δ 1.52–1.81 (m, 4 H), 3.39 (s, 3 H), 3.44–3.62 (m, 5 H), 3.70 (ddd, 2 H, J = 5.4, 3.5, 1.1 Hz), 3.95-4.04 (m, 1 H), 4.71 (s, 2 H), 5.22 (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, 10.5, 6.5 Hz); 13C 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 (Na₂SO₄). 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. [α]D + 8.9 (c 1.4, CHCl₃); 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 (dd, 1 H, J = 18.5, 10.9, 7.6 Hz), 7.23-7.32 (m, 10 H); 13C 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 C₂₅H₃₄O₅: 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 (Na₂SO₄), 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. [α]D +10.4 (c 1.3, CHCl₃); 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); 13C 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 CH₂Cl₂ (3 mL) was added to a stirred solution of DMSO (0.34 mL, 4.76 mmol) and (COCl)₂ (0.17 mL, 1.98 mmol) in CH₂Cl₂ (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. NaClO₂ (0.19g in 2 mL water, 2.08 mmol) DMSO (2 mL), NaH₂PO₄ (0.16g, 1.05 mmol). After 2 h, the reaction mixture was diluted with water, extracted with EtOAc, dried (Na₂SO₄), 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. [α]D + 16.8 (c 0.7, CHCl₃); 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 dd, 1 H, J = 18.3, 10.9, 7.5 Hz), 7.25-7.33 (m, 10 H); 13C 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 C₁₅H₃₀O₄: 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 K₃[Fe(CN)₆] (26.67g, 81.2 mmol), K₂CO₃ (11.2 g, 81.2 mmol), (DHQ)₂ PHAL (0.211g, 0.27 mmol), MeSO₂NH₂ (2.57g, 27.1 mmol) and K₂OsO₄.2H₂O (0.211 g, 0.1 mmol) in t-BuOH:H₂O (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 (Na₂SO₄) 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, CHCl$_3$); $^1$H NMR (200 MHz): $\delta$ 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); $^{13}$C NMR (50 MHz): $\delta$ 13.8, 22.3, 25.5, 29.0, 31.5, 33.2, 61.5, 72.4, 73.3, 173.5; Anal. Calcd for C$_{11}$H$_{22}$O$_4$: 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 CH$_2$Cl$_2$ (50 mL) was stirred at room temperature for 4 h. It was diluted with CH$_2$Cl$_2$, washed with NaHCO$_3$, 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, CHCl$_3$); $^1$H NMR (200 MHz): $\delta$ 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); $^{13}$C NMR (50 MHz): $\delta$ 13.6, 22.2, 25.2, 28.8, 31.3, 33.2, 61.0, 78.9, 110.3,170.5; Anal. Calcd for C$_{14}$H$_{26}$O$_4$: 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 CH$_2$Cl$_2$ (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 1 h, 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, CHCl$_3$); $^1$H NMR (200 MHz): $\delta$ 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); $^{13}$C NMR (50 MHz): $\delta$ 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 C$_{12}$H$_{24}$O$_3$: 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 (Na$_2$SO$_4$) and evaporated. The residue was purified by silica gel column chromatography by eluting with light petroleum: EtOAc (3:2) to give alcohol (4.2 g, 97%) as a colorless liquid. $[\alpha]_D - 16.4$ (c 3.6, CHCl$_3$); $^1$H NMR (200 MHz): $\delta$ 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); $^{13}$C NMR (50 MHz): $\delta$ 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 C$_{21}$H$_{30}$O$_5$S: C, 66.93; 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 (Na$_2$SO$_4$) 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, CHCl$_3$); $^1$H NMR (200 MHz): $\delta$ 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); ¹³C 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 C₁₆H₂₆O₅S: 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 K₂CO₃ (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 (Na₂SO₄) 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. [α]D - 5.0 (c 1.2, CHCl₃); ¹H NMR (200 MHz, CDCl₃): 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); ¹³C 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 C₉H₁₈O₂: 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 CH₂Cl₂ (15 mL) were stirred at room temperature for 4 h and concentrated. The residue was extracted with ethyl acetate, washed with water, dried (Na₂SO₄), and evaporated. Purification by silica gel chromatography using light petroleum: EtOAc (4:1) to afford 8 (2.83 g, 91%) as a colorless liquid. [α]D - 41.06 (c 1.7, CHCl₃); 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 (dd, 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); ¹³C 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 C₁₃H₂₆O₄: 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 overnight at rt. The excess of reagent was quenched with saturated ammonium chloride solution and extracted with EtOAc, washed with water, brine, dried (Na₂SO₄), and evaporated. 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. [α]D + 10.1 (c 1.05, CHCl₃); 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); ¹³C 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 C₁₅H₂₈O₄: C, 63.14; H, 10.36. Found: C, 63.28; 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 (Na₂SO₄) and purified by silica gel column chromatography eluting with light petroleum: EtOAc (7:3) to give 6 (0.93 g, 91%) as a colorless oil. [α]D + 38 (c 0.9, CHCl₃); 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 ddd, 1 H, J = 17.4, 10.6, 7.0 Hz); 13C 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 C15H30O4: 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′-(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 CH2Cl2 (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. [α]D + 10.7 (c 1.0, CHCl3); 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, 3 H), 5.71 (dddd, 1 H, J = 17.1, 10.1, 7.6, 6.6 Hz), 7.25-7.30 (m, 10 H); 13C 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, 128.3, 134.0, 135.2, 138.6, 138.7, 172.8; Anal. Calcd for C36H52O7: 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 CH2Cl2 (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 27 (0.063 g, 67 %). [α]D – 41.1 (c 0.52, CHCl3); 1H NMR (500 MHz, CD3CN): (Major conformer) 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); 13C 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, 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 C34H48O7: 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 CH2Cl2 (2 mL) under nitrogen at 0 °C was added TiCl4 (0.1 mL, 1 mmol). After 30 min, excess of reagent was quenched with water, extracted with CH2Cl2, washed with water, dried (Na2SO4), 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 %). [α]D – 23.2 (c 0.7, MeOH); Lit.,29 [α]D – 22 (c 0.67, MeOH); 1H NMR (500 MHz, CD2CN): (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), 4.14 (br m, 1 H), 4.85 (ddd, 1 H, J = 7.9, 4.7, 3.4 Hz), 5.53 (ddd, 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\(_3\)CN): \(\delta\) 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 C\(_{16}\)H\(_{28}\)O\(_5\): C, 64.02; H, 9.40. Found: C, 64.17; H, 9.75.

3-Deoxy-5,6-dideoxy-1,2-O-isopropylidene-\(\alpha\)-D-ribohept-5-enofuranoside (30). Compound 29 (12.0 g, 48.75 mmol) was stirred with 0.8% H\(_2\)SO\(_4\) (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\(_2\)SO\(_4\) 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; \([\alpha]_D\) -14.0 (c 1.2, EtOH); \(^1\)H NMR (200 MHz): \(\delta\) 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): \(\delta\) 26.1, 26.7, 33.8, 63.5, 72.4, 78.4, 80.5, 105.2, 116.2; Anal: Calc for C\(_9\)H\(_{16}\)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\(_2\)Cl\(_2\) (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\(_2\)Cl\(_2\) (2x50 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\) 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-\(\alpha\)-D-riboshept-5-enofuranoside (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\(_2\)SO\(_4\), 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%). \([\alpha]_D\) - 23.4 (c 1.45, CHCl\(_3\)); \(^1\)H NMR (500 MHz): \(\delta\) 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): \(\delta\) 13.5, 26.1, 26.7, 39.5, 73.0, 80.6, 105.2, 110.7, 128.2, 129.0.; Anal. Calcd for C\(_{10}\)H\(_{16}\)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, 31.27 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, CHCl₃); \(^1\)H NMR (500 MHz): \(\delta 0.94\) (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); \(^{13}\)C NMR (125 MHz): \(\delta 14.1, 19.2, 26.0, 26.5, 36.3, 39.0, 77.5, 80.4, 105.1, 110.5\); MS (EI): m/z 187 [M+H]+; Anal. Calcd for C₁₀H₁₈O₃: 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 H₂SO₄ 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 Na₂SO₄, 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 oC under N₂ 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 oC. 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 (Na₂SO₄), 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, CHCl₃); \(^1\)H NMR (500 MHz): \(\delta 0.91\) (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); \(^{13}\)C NMR (125 MHz): \(\delta 13.8, 18.3, 39.8, 42.5, 73.0, 114.0, 140.5\); Anal. Calcd for C₈H₁₆O₂: 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 N₂ 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 (Na₂SO₄), 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, CHCl₃); \(^1\)H NMR (200 MHz): \(\delta 0.94\) (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); \(^{13}\)C NMR (50 MHz): \(\delta 14.1, 18.6, 39.8, 42.5, 55.2, 69.8, 71.1, 81.2, 113.9, 117.5, 124.5, 129.9, 138.3, 159.3\); Anal. Calcd for C₁₆H₂₄O₃: 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 %). $\left[\alpha\right]_D^0 + 31.1$ (c 0.60, CHCl3); $^1$H NMR (200 MHz): $\delta$ 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); $^1$H NMR (50 MHz, CDCl3): $\delta$ 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 purified by column chromatography using ethyl acetate: light petroleum (1:19) afforded compound 10 as a oily liquid (313 mg, 94 %). $\left[\alpha\right]_D^0 + 3.6$ (c 1.1, CHCl3); $^1$H NMR (200 MHz): $\delta$ 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); $^{13}$C NMR (50 MHz): $\delta$ 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 CH$_2$Cl$_2$ (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%). $[\alpha]_D + 20.6$ (c 1.2, EtOH); IR (CHCl$_3$): 3443, 3019, 2962, 1723, 1640 cm$^{-1}$; $^1$H NMR (500 MHz): $\delta$ 0.91 (t, 3 H, $J = 7.4$ Hz), 1.33 (m, 2 H), 1.42 (m, 1 H), 1.54 (ddddd, 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), $\delta$ 5.62 (d, 1 H, $J = 16.1$ Hz); $^{13}$C NMR (125 MHz): $\delta$ 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 C$_{12}$H$_{20}$O$_3$: C, 67.89; H, 9.50. Found: C, 67.42; H, 9.84

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References
