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First stereoselective total synthesis of an anti-fouling agent, C_2-symmetric natural macrolide trichobotryside A

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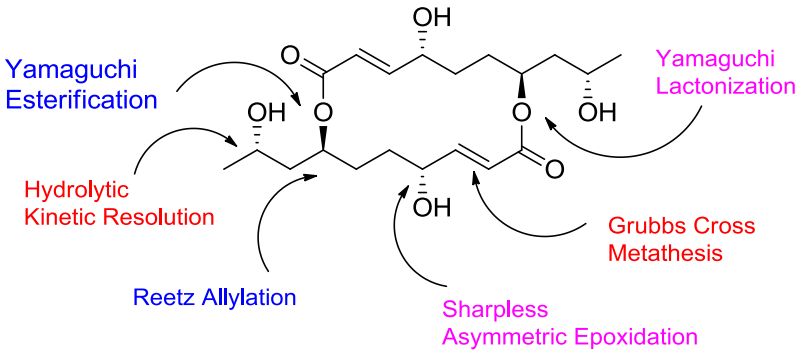
Abstract

A stereoselective total synthesis of 16-membered macrodiolide trichobotryside A has been accomplished. The key features are: regioselective epoxide opening, Reetz *anti*-allylation, Sharpless asymmetric epoxidation, cross metathesis and Yamaguchi protocols for esterification followed by macrolactonization.



Keywords: Macrodiolide, anti-fouling agent, Reetz allylation, Sharpless asymmetric epoxidation, Grubbs cross metathesis, Yamaguchi lactonization

Introduction

Marine organisms have been widely explored for potential bioactive lead compounds, within many different chemical classes of compounds such as peptides, terpenoids, steroids, alkaloids, macrolides and other polyketide lactones.[1-3] The macropolylides, essentially 16-membered macrodiolides such as pyrenophorol, pyrenophorin, and vermiculin (Figure 1) have strong antifungal and anthelmintic activity. Trichobotryside A is C_2-Symmetric 16-membered macrodiolide isolated by the Shu-Hua Qi group from deep sea sediment of the South China Sea fungal strain *Trychobotrys effuse* DFFSCS021. These compounds were screened against cancer cell lines as well as the HSV-1 virus. Trichobotryside A exhibits strong antifouling activity against *larva* settlement of *Bugula neritina* and *Balamus amphitrite* with EC_{50} values of 7.3, 2.5 μg/mL and LC_{50}/EC_{50} > 40.5, 37.4 respectively.[4-6] The structure of trichobotryside A was determined by ^1H and ^{13}C NMR data along with 2D-NMR experiments such as ^1H-^1H COSY, HSQC and HMBC spectra. The absolute configuration was established by methanolysis and the modified Mosher's method and its molecular formula determined on the basis of HRMS (ESI^+) 423.1987 ($M+Na^+$).[7-9]

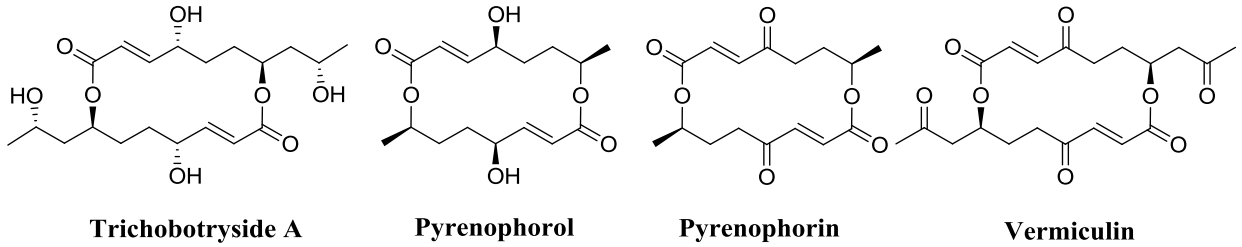
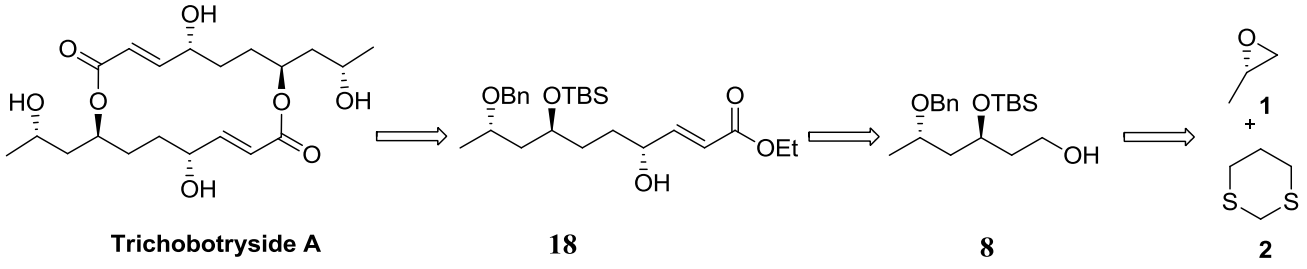


Figure 1

The biological activity and the structural fascination of trichobotryside A attracted us to carry out its total synthesis. As part of our regular research program in synthesis of biologically active natural and synthetic compounds, herein we demonstrate the first stereoselective total synthesis of the 16-membered macrodiolide trichobotryside A.

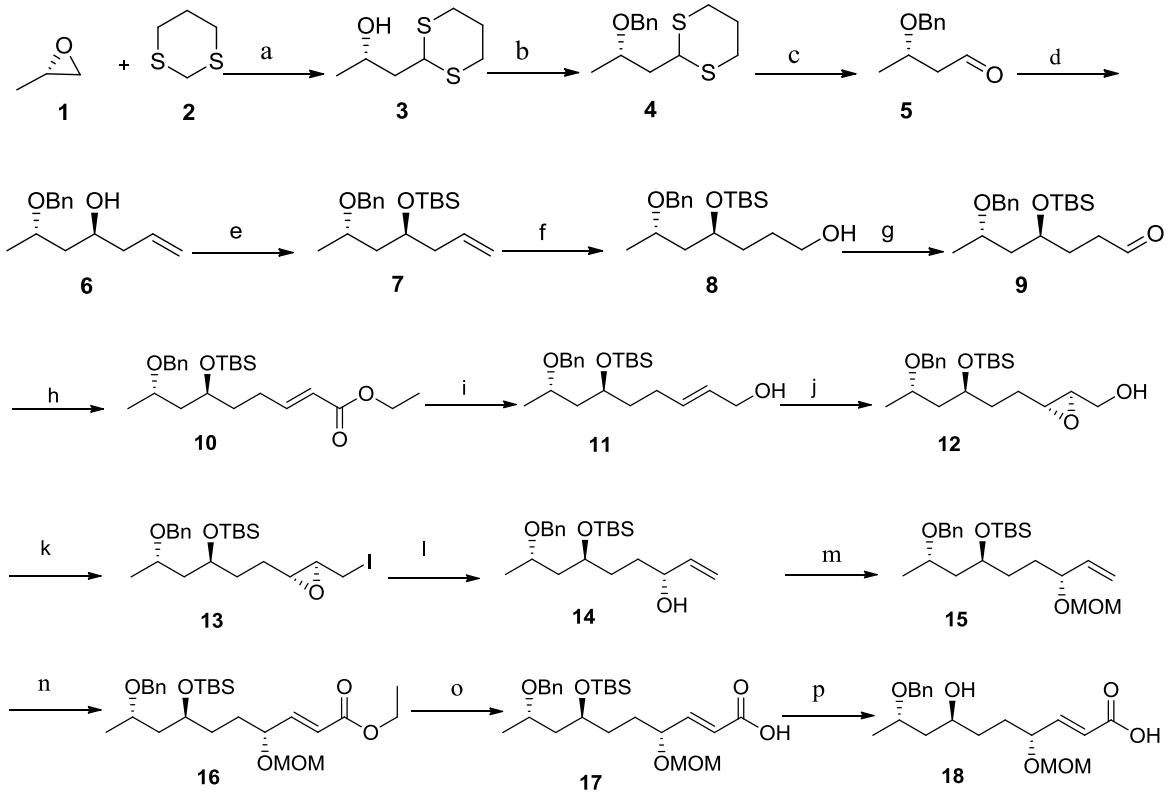
Results and Discussion

As envisaged in the retrosynthetic analysis (Scheme 1) trichobotryside A could be reached from the monomer **18** after Wittig, Sharpless epoxidation and cross metathesis. The intermediate **8** could be obtained after the Reetz allylation and hydroboration of commercially available propylene oxide (**1)** and dithiane **2**.



Scheme 1

The synthesis commenced with regioselective ring opening of enantiomerically enriched (*S*)-2-methyloxirane (**1**) with anion of 1,3-dithiane (**2**) using *n*-BuLi, HMPA, followed by protection of the secondary hydroxyl group with benzyl bromide to obtain (*S*)-2-[2-(benzyloxy)propyl]-1,3-dithiane (**4**) in quantitative yield.[10] Oxidative cleavage of dithiane **4** was performed smoothly with [bis(trifluoroacetoxy)iodo]benzene and $SrCO_3$ to afford aldehyde **5** in 65% yield.[11,12] The aldehyde was immediately subjected to chelation controlled 1,3-*anti*-allylation under Reetz conditions ($TiCl_4$, CH_2Cl_2, -78 °C, 1 h) using allyltrimethylsilane to furnish homoallylic alcohol **6** in 76% yield, with an excellent diastereomeric ratio (*dr* 95:5), confirmed by ^{1}H NMR spectroscopy.[13-15] The relative stereochemistry of 1,3-*anti*-diols (major isomer) was confirmed by chemical shift correlations of the acetonide carbons in ^{13}C NMR, as described by the Rychnovsky and Skalitzky protocol [deprotection of the benzyl group with Li-metal in liquid ammonia, followed by protection of the 1,3-diol as its acetonide with 2,2-DMP]. Examination of the ^{13}C spectrum of the acetonide showed chemical shift values of the acetonide methyl groups at δ 24.75 and 24.83 ppm and the ketal carbon at 100.1 ppm. These chemical shift values correlate with a twist boat conformation of a 1,3-*anti*-diol.[16,17] The secondary alcohol **6** was protected as its *tert*-butyldimethylsilyl ether and the terminal olefin was converted to primary alcohol **8** by hydroboration.[18] Oxidation of **8** under Swern conditions afforded aldehyde **9** in very good yield[19,20] and subsequent olefination of the aldehyde with a two carbon Wittig ylide in benzene under reflux afforded olefin **10** in 86% yield (95:5, *E*/*Z*).[21-23] The *E*/*Z* ratio was determined by ^{1}H NMR analysis of the crude product. Chemoselective reduction of ester **10** with DIBAL-H at -40 °C gave the allylic alcohol **11** in excellent yield.[24,25]

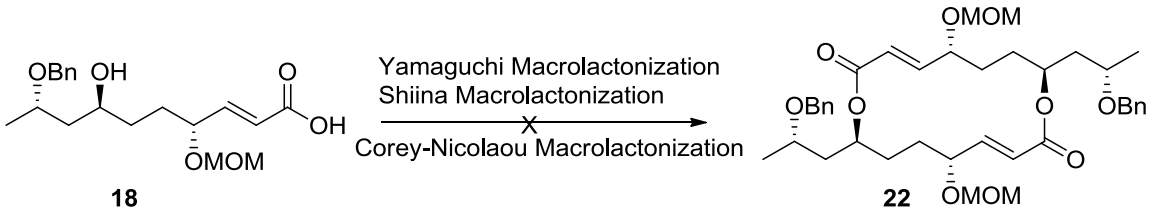


Scheme 2. *Reagents and Conditions*: (a) *n*-BuLi, HMPA, dry THF, -78 °C, 1 h, 92%; (b) NaH, BnBr, dry THF, 0 °C to rt, 4 h, 87%; (c) PIFA, $SrCO_3$, CH_3CN/H_2O, 9:1, 30 min, 65%; (d) $TiCl_4$, allyltrimethylsilane, dry CH_2Cl_2, -78 °C, 1 h, 76%; (e) *tert*-butyldimethylsilyl chloride, imidazole, CH_2Cl_2, rt, 4 h, 94%; (f) BH_3.DMS, NaOH, H_2O_2, dry THF, 12 h, 79%; (g) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, -78 °C, 3 h; (h) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 8 h, 86% (two steps); (i) DIBAL-H, dry CH_2Cl_2, -40 °C, 3 h, 94%; (j) (-)-DET, 4 Å, $Ti(O^iPr)_4$, cumene hydroperoxide, dry CH_2Cl_2, -20 °C, 12

h, 80%; (k) I_2, PPh_3, imidazole, Et_2O:CH_3CN (3:1), rt, 2 h, 77%; (l) Zn, NaI, EtOH, reflux, 5 h, 83%; (m) $MeOCH_2Cl$, DIPEA, dry CH_2Cl_2, DMAP, 6 h, 92%; (n) CH_2=$CHCO_2Et$, Grubbs 2nd generation catalyst, dry CH_2Cl_2, reflux, 12 h, 84%; (o) NaOH, CH_3OH, rt, 3 h, 92%; (p) TBAF, dry THF, reflux, 5 h, 95%.

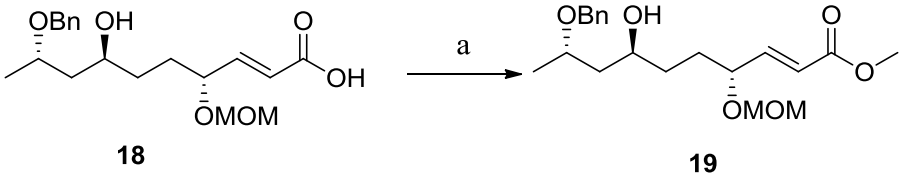
The allylic alcohol **11** was subjected to Sharpless asymmetric epoxidation with (-)-DET, Ti(O^iPr)$_4$ and cumene hydroperoxide at -20 ^oC to give epoxy alcohol **12** in 80% yield with excellent diastereoselectivity (*dr* 19:1), established by ^1H NMR spectroscopy.[26-28] The free alcohol **12** was converted into iodide **13** in 77% yield by using molecular iodine, triphenylphosphine and imidazole in Et_2O/CH_3CN (3:1) mixture. The iodo compound **13** was subjected to immediate reductive elimination using zinc in ethanol under reflux to achieve the rearranged allylic alcohol **14** in 83% yield.[29] The resulting secondary hydroxyl group in **14** was protected as its MOM ether by treating with methoxymethylchloride and diisopropylethylamine to furnish **15** in 92% yield. Cross metathesis of **15** with ethyl acrylate in the presence of Grubbs 2nd generation catalyst in dry CH_2Cl_2 led to the formation of *trans*-olefinic ester **16** in 84% yield[30-32] as confirmed by ^1H NMR spectroscopic data. The ester **16** on hydrolysis with 2 N NaOH in MeOH gave acid **17** in 92% yield and subsequent deprotection of the silyl group with TBAF in THF under reflux conditions furnished monomer *seco*-acid **18**) in 95% yield as shown in Scheme 2.

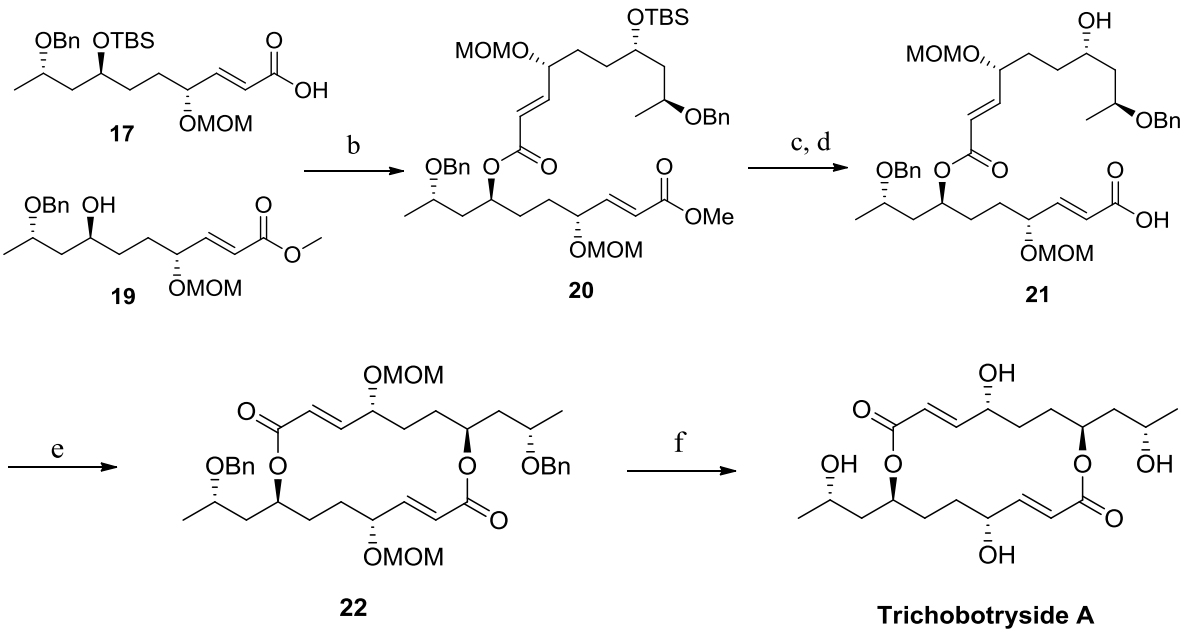
Macrodilactonization of *seco*-acid **18** was attempted as displayed in Scheme 3, by using Yamaguchi, Shiina and DMC conditions,[33,34] but the required dimer product **22** was not obtained and the starting material also could not be recovered. Whereas, Yamaguchi conditions at high dilution, yielded the dimer product **22**, but only in 5% yield and the starting material was decomposed.



Scheme 3

After the above experiments, the acid group in *seco*-acid **18** was converted into its methyl ester using *N*-nitroso-*N*-methylurea salt in presence of KOH and the afforded compound **19** was allied with compound **17** under Yamaguchi conditions to furnish **20** in 85% yield.





Scheme 4. *Reagents and Conditions*: (a) *N*-nitroso-*N*-methylurea, KOH, ether, 0 ^{o}C, 15 min, 96%; (b) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, dry CH_2Cl_2, rt, 90 min, 85%; (c) Me_3SnOH, EDC, 80 ^{o}C, 10 h; (d) HF.pyridine, THF, rt, 6 h, 45%; (e) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, CH_2Cl_2, 40 ^{o}C, 29 h, 42%; (f) $TiCl_4$, CH_2Cl_2, rt, 2 h, 50%.

The methyl ester **20** was hydrolyzed in presence of trimethyltin hydroxide followed by deprotection of *tert*-butyldimethylsilyl ether with HF.pyridine in THF to obtain *seco*-acid **21** in good yield over two steps.[35-37] Thus obtained *seco*-acid **21** was subjected to Yamaguchi macrolactonization to afford *bis*-MOM, *bis*-benzyl protected trichobotryside A **22** in 42% yield. Global deprotection of MOM and benzyl groups in **22** was achieved in a single step by using excess $TiCl_4$ in dry CH_2Cl_2 to obtain trichobotryside A in 50% yield, as shown in Scheme 4.[38] The optical rotation of the synthesized trichobotryside A was $[\alpha]_D^{25}$ +65.7 (*c* = 0.12, CH_3OH) and that of the natural product is $^{lit}[\alpha]_D^{20}$ +50.09 (*c* = 1.58, CH_3OH).[7]

Conclusions

The first stereoselective total synthesis of the naturally occurring, 16-membered macrodiolide, trichobotryside A has been accomplished in 16 steps with 0.54% overall yield. The key reactions involved are regioselective epoxide opening, Reetz *anti*-allylation, Sharpless asymmetric epoxidation, cross metathesis and Yamaguchi protocols for esterification followed by macrolactonization.

Experimental Section

General. All the air and moisture sensitive reactions were carried out under an inert atmosphere (nitrogen or argon). Oven-dried glass apparatus was used to perform all the reactions. Freshly distilled anhydrous solvents were used for air and moisture sensitive reactions. Commercially available reagents were used as such. Purification of compounds was carried out *via* column chromatography by using silica gel (60-120 mesh) packed in glass columns. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ and DMSO-d_6 solvents on 400 MHz and

500 MHz spectrometer respectively, using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c Spectrophotometer using KBr / Thin Film optics. Optical rotation values were recorded on a Horiba sepa 300 polarimeter using a 2 mL cell with a 10 mm path length. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. High resolution mass spectra (HRMS) (ESI^+) were obtained using either a TOF or a double focusing spectrometer.

(*S*)-1-(1,3-Dithian-2-yl)propan-2-ol (**3**). To a stirred solution of 1,3-dithiane (5 g, 41.6 mmol) in dry THF (50 mL) was added HMPA (25 mL, 145.6 mmol) and *n*-BuLi (26 mL, 1.6 M, hexanes, 41.6 mmol) at -78 °C under nitrogen. The mixture was warmed to 0 °C and stirred for 2 h. Then, the reaction mixture was cooled to -78 °C, and (*S*)-2-methyloxirane 1 (4.4 mL, 68.4 mmol) added and stirred for a further 1 h, then the reaction mixture was quenched with saturated NH_4Cl and warmed to rt. The solvent was removed under *vacuum*. The residue was dissolved in EtOAc (150 mL), washed with water, followed by brine and dried over Na_2SO_4 and concentrated under *vacuum*. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with hexane/EtOAc (4:1) mixture to give pure compound **3** (6.85 g, 92%) as a colorless oil. $[\alpha]_D^{25}$ +23 (*c* = 1, $CHCl_3$); IR (neat): 3396, 2899, 1453, 1420, 1276, 1182, 1029, 869, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.20 (dd, 1H, *J* 8.2, 6.1 Hz), 4.19 - 4.07 (m, 1H), 2.97 - 2.80 (m, 4H), 2.18 - 2.07 (m, 1H), 1.99 - 1.79 (m, 4H), 1.23 (d, 3H, *J* 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 64.9, 44.2, 30.2, 30.0, 25.8, 23.5; MS (ESIMS): *m/z* 201 $[M+Na]^+$.

(*S*)-2-[2-(Benzyloxy)propyl]-1,3-dithiane (**4**). To a stirred solution of NaH (2.2 g, 55 mmol, 60% mineral oil) in dry THF (30 mL) was added compound **3** [6.5 g, 36.5 mmol, dissolved in dry THF (20 mL) at 0 ^oC under nitrogen. After 45 minutes stirring was added benzyl bromide (5.2 mL, 43.8 mmol) and the reaction mixture slowly warmed to rt. Then a catalytic amount of tetrabutyl ammonium iodide was added and the stirring maintained for 12 hr. After completion of the reaction as indicated by TLC, solvent was removed under reduced pressure and quenched with saturated NH_4Cl and extracted with EtOAc (2x50 mL), the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under *vacuum.* The residue was purified by silica gel (60-120 mesh) column chromatography by eluting with Hexane/EtOAc (9:1) mixture to give compound **4** (8.5 g, 87%) as a colorless oil. $[\alpha]_D^{25}$ -3.24 (c = 1, $CHCl_3$). IR (neat): 3030, 2922, 2853, 1727, 1643, 1455, 1364, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 - 7.27 (m, 5H), 4.60 (d, 1H, *J* 11.6 Hz), 4.47 (d, 1H, *J* 11.3 Hz), 4.21 (dd, 1H, *J* 9.4 Hz), 3.85 (dt, 1H, *J* 8.6 Hz), 3.71 - 3.67 (m, 2H), 2.90 - 2.77 (m, 3H), 1.95 - 1.88 (m, 3H), 1.23 (d, 3H, *J* 6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 128.7, 128.4, 127.6, 126.8, 70.7, 43.9, 42.6, 36.8, 30.2, 29.5, 25.9, 21.8, 19.7; MS (ESIMS): *m/z* 269 $(M+H)^+$, 291 $(M+Na)^+$; HRMS (ESI) calcd for $C_{14}H_{21}OS_2$ $(M+H^+)$ 269.1028; Found 269.1028.

(4*S*,6*S*)-6-(Benzyloxy)hept-1-en-4-ol (**6**). To a stirred suspension of dithiane compound **4** (8 g, 29.8 mmol) in solvent mixture (80 mL, CH_3CN:H_2O, 9:1) $SrCO_3$ (22 g, 149 mmol) was added at 0 ^oC, followed by PIFA (12.8 g, 29.8 mmol). The stirring was continued for 30 min at rt and the completion of reaction confirmed by TLC, then the reaction mixture was quenched by adding Na_2CO_3 saturated solution (30 mL) and $Na_2S_2O_3$ (5 g) stirred at rt for 30 min and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under *vacuum*. The product was purified by flash column chromatography to furnish (*S*)-3-(benzyloxy)butanal **5**.

To a stirred solution of the above aldehyde **5** (3.5 g, 19.6 mmol) in CH_2Cl_2 (30 mL) $TiCl_4$ (1 M, 21.44 mL, CH_2Cl_2, 21.44 mmol) was added slowly at -78 °C. After 20 min, allyltrimethylsilane (4.7 mL, 29.3 mmol) was added and stirring continued for further 1 h, at -78 °C. After completion of the reaction (confirmed by TLC), the reaction mixture was quenched by adding saturated $NaHCO_3$ solution (50 mL) and stirred vigorously for 3 h at rt. The reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layer was washed with brine, dried with Na_2SO_4 and concentrated under *vacuum.* The residue was purified by column chromatography over

silica gel (60-120 mesh) by eluting with hexanes:EtOAc (85:15) mixture to afford allylic alcohol **6** (3.28 g, 14.9 mmol, 76%) (*dr* 95:5) as a colorless liquid. $[\alpha]_D^{25}$ +44 (*c* = 1, $CHCl_3$). $^{Lit}[\alpha]_D^{25}$ +45.2 (*c* = 3.12, $CHCl_3$);[15] IR (neat): 3439, 3030, 2931, 1641, 1432, 1343, 1343, 1145, 1027, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 - 7.27 (m, 5H), 5.88 - 5.78 (m, 1H), 5.13 - 5.06 (m, 2H), 4.63 (d, 1H, *J* 11.6 Hz), 4.46 (d, 1H, *J* 11.6 Hz), 3.98 - 3.92 (m, 1H), 3.87 - 3.83 (m, 1H), 2.7 (brs, 1H, OH), 2.24 - 2.20 (m, 2H), 1.68 - 1.64 (m, 2H), 1.26 (d, 3H, *J* 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 138.3, 134.9, 128.3, 127.6, 127.5, 117.3, 72.5, 70.5, 67.5, 42.3, 42.2, 19.2; MS (ESIMS): *m/z* 243 $(M+Na)^+$; HRMS (ESI): calcd for $C_{14}H_{21}O_2$ $(M+H)^+$ 221.1534, found 221.1536.

{[(4*S*,6*S*)-6-(Benzyloxy)hept-1-en-4-yl]oxy}(*tert*-butyl)dimethylsilane (7). To a stirred solution of compound 6 (2 g, 9.08 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C, imidazole (1.23 g, 18.1 mmol) was added and stirred for 15 min, then TBDMSCl (1.5 g, 10 mmol), dissolved in dry CH_2Cl_2 (5 mL), was added followed by catalytic amount of DMAP and stirred at rt for 4 h. Completion of reaction was confirmed by TLC and water was added and extracted with CH_2Cl_2 (2 x 20 mL), the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under *vacuum*. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with hexane/EtOAc 9:1 mixture to furnish corresponding TBDMS protected olefin **7** (2.85 g, 94%) as colorless liquid. $[\alpha]_D^{25}$ +68.8 (*c* = 2, $CHCl_3$); IR (neat): 3070, 2929, 2857, 1710, 1427, 1336, 1219, 1108, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 - 7.27 (m, 5H), 5.88 - 5.79 (m, 1H), 5.06 - 5.01 (m, 2H), 4.59 (d, 1H, *J* 11.4 Hz), 4.41 (d, 1H, *J* 11.4 Hz), 4.04 - 3.98 (m, 1H), 3.70 - 3.78 (m, 1H), 2.30 - 2.18 (m, 2H), 1.74 (dt, 1H, *J* 14.2, 8.8 Hz), 1.50 (dt, 1H, *J* 12.6, 8.7 Hz), 1.22 (d, 3H, *J* 6.1 Hz), 0.90 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1, 134.7, 128.4, 127.3, 127.2, 116.9, 72.1, 70, 68.6, 44.7, 42.6, 25.9, 20.1, 18.1, -4.1, -4.5; MS (ESIMS): *m/z* 335 $(M+H)^+$; HRMS (ESI^+): calcd for $C_{20}H_{35}O_2Si$ $(M+H)^+$ 335.2402; Found 335.2400.

(4*S*,6*S*)-6-(Benzyloxy)-4-[(*tert*-butyldimethylsilyl)oxy]heptan-1-ol (8). To a stirred solution of compound **7** (2.8 g, 8.4 mmol) in dry THF (25 mL) borane-dimethylsulfide (1.6 mL, 16.7 mmol) was added at 0 °C. The reaction mixture was allowed to rt and stirred for 2 h. After consumption of starting material as indicated by TLC, the reaction mixture was cooled to 0 °C, NaOH solution (100 mL, 3 M) was added followed by H_2O_2 (50 mL, 33% w/w H_2O) and the reaction mixture was stirred for 12 h at rt. Then, solvent was removed under *vacuum* and extraction was performed with EtOAc (3 x 30 mL). The organic layers were washed with brine, dried over Na_2SO_4 and concentrated under *vacuum.* The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with hexane:EtOAc (8:2) mixture to afford **8** (2.32 g, 79%) as colorless liquid. $[\alpha]_D^{25}$ +32.1 (*c* = 2, $CHCl_3$); IR (neat): 3395, 3069, 2929, 2857, 1710, 1427, 1336, 1219, 1108, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 - 7.27 (m, 5H), 4.59 (d, 1H, *J* 11.4 Hz), 4.41 (d, 1H, *J* 11.4 Hz), 3.95 - 4.05 (m, 1H), 3.67 - 3.72 (m, 1H), 3.64 - 3.57 (m, 2H), 1.98 (brs, 1H), 1.77 - 1.63 (m, 2H), 1.61 - 1.54 (m, 4H), 1.22 (d, 3H, *J* 6.1 Hz), 0.89 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 128.2, 127.4, 127.3, 72.1, 70.1, 68.9, 63.1, 44.4, 34.2, 27.6, 25.9, 2.1, 18.1, -4.2, -4.6; MS (ESIMS): *m/z* 375 $(M+Na)^+$; HRMS (ESI^+): calcd for $C_{20}H_{37}O_3Si$ $(M+H)^+$ 353.2513; Found 353.2506.

(6*S*,8*S*,*E*)-ethyl-8-(benzyloxy)-6-[(*tert*-butyldimethylsilyl)oxy]non-2-enoate (10). A solution of oxalyl chloride (1.2 mL, 15.3 mmol) in dry CH_2Cl_2 (5 mL) and DMSO (1.9 mL, 26.8 mmol) was stirred at -78 °C for 30 minutes and then added a solution of alcohol **8** [(2.3 g, 6.5 mmol, dissolved in CH_2Cl_2 (2 mL)] at the same temperature and stirred for further 3 h. Then, added Et_3N (1.95 mL, 13.9 mmol) at 0 °C and stirred for further 45 minutes. The reaction mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give aldehyde compound **9** in quantitative yield as a pale yellow syrup, which was used for next reaction without purification.

The above aldehyde **9** (1.89 g, 5.4 mmol) was dissolved in dry benzene (20 mL) and added Wittig ylide (2.4 g, 6.9 mmol). The reaction mixture was refluxed for 8 h. After completion of the reaction (monitored by TLC)

solvent was removed under reduced pressure and residue was extracted with EtOAc (2x20 mL). The organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with hexane/EtOAc (9:1) mixture to give ester compound **10** (1.95 g, 86%) as pale yellow liquid (95:5, *E*/*Z*). $[\alpha]_D^{25}$ +43.7 (*c* = 1, $CHCl_3$); IR (neat): 3028, 2930, 2856, 1718, 1655, 1318, 1255, 1094, 984 cm^{-1}.; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 - 7.25 (m, 5H), 6.96 (q, 1H, *J* 15.5, 13.8 Hz), 5.80 (dt, 1H, *J* 15.6, 3.7 Hz), 4.59 (d, 1H, *J* 11.4 Hz), 4.40 (d, 1H, *J* 11.4 Hz), 4.18 (q, 2H, *J* 7.0 Hz), 3.93 - 3.99 (m, 1H), 3.63 - 3.71 (m, 1H), 2.28 - 2.20 (m, 2H), 1.64 - 1.74 (m, 1H), 1.51 - 1.61 (m, 3H), 1.28 (t, 3H, *J* 7.0 Hz), 1.22 (d, 3H, *J* 6.1 Hz), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 149.2, 138.9, 128.2, 127.4, 127.3, 121.1, 72.1, 70.1, 68.5, 60.1, 44.7, 36, 27.2, 25.8, 20.1, 14.2, -4.2, -4.4; MS (ESIMS): *m/z* 443 $(M+Na)^+$; HRMS (ESI): calcd for $C_{24}H_{41}O_4Si$ $(M+H)^+$ 421.2759; Found 421.2768.

(6*S*,8*S*,*E*)-8-(Benzyloxy)-6-[(*tert*-butyldimethylsilyl)oxy]non-2-en-1-ol (11). To a stirred solution of compound **10** (1.9 g, 4.5 mmol) in dry CH_2Cl_2 (15 mL) was added DIBAL-H (13.6 mL, 1 M, toluene, 13.6 mmol) at -40 °C, and stirred for 3 h. After completion of reaction (monitored by TLC) the reaction mixture was quenched with saturated Rochelle salt solution (10 mL) stirred at rt for 3 h and extracted with CH_2Cl_2 (2x20 mL), the combined organic layers washed with H_2O, brine, dried over Na_2SO_4 and concentrated under *vacuum.* The crude product was purified by flash column chromatography using silica gel (60-120 mesh) by eluting with hexane/EtOAc (8:2) mixture to afford allylic alcohol **11** (1.6 g, 94%) as colorless oil. $[\alpha]_D^{25}$ +43.9 (*c* = 1.5, $CHCl_3$); IR (neat): 3434, 3085, 2929, 2856, 1458, 1362, 1077, 920, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 - 7.27 (m, 5H), 5.70 - 5.59 (m, 2H), 4.59 (d, 1H, *J* 11.4 Hz), 4.41 (d, 1H, *J* 11.4 Hz), 4.05 (d, 2H, *J* 5.3 Hz), 3.90 - 3.97 (m, 1H), 3.70 - 3.77 (m, 1H), 2.10 - 2.05 (m, 2H), 1.69 - 1.76 (m, 2H), 1.57 - 1.50 (m, 2H), 1.45 (brs, 1H), 1.22 (d, 3H, *J* 6.2 Hz), 0.89 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139, 133.1, 128.9, 128.5, 127.4, 127.3, 72.2, 70.1, 68.1, 63.6, 44.8, 37.2, 27.3, 25.9, 20.1, 18.1, -4.1, -4.4; MS (ESIMS): *m/z* 401 $(M+Na)^+$; HRMS (ESI^+): calcd for $C_{22}H_{39}O_3Si$ $(M+H)^+$ 379.2667; Found 379.2663.

{(2*R*,3*R*)-3-[(3*S*,5*S*)-5-(Benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]hexyl]oxiran-2-yl}methanol (12). To a stirred suspension of activated molecular (300 mg, 4 Å) sieves powder in dry CH_2Cl_2 (15 mL) was added (-)-DET (0.75 mL, 4.4 mmol) and $Ti(O^iPr)_4$ (1.2 mL, 4.1 mmol) at rt and the resulting mixture was stirred for 30 minutes. Then, the reaction mixture was cooled to -20 °C and added a solution of the allylic alcohol **11** (1.5 g, 4 mmol) in dry CH_2Cl_2 (4 mL) dropwise. The resulting mixture was stirred for further 30 minutes at -20 °C. Then added Cumene hydroperoxide (1.65 mL, 3.6 M in toluene, 6 mmol) dropwise and the resulting mixture stirred at the same temperature for 12 h. The reaction mixture was allowed to warm to 0 °C, quenched with water and stirred for 2 h at rt. Then added NaOH (20 mL, 30%) solution mixed with brine and continued stirring vigorously further 30 minutes at rt. The mixture was filtered through Celite bed and the filter cake was washed with CH_2Cl_2 (2x15 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc/hexane (3:7) mixture to afford epoxyalcohol **12** (1.25 g, 80%) as pale yellow liquid. $[\alpha]_D^{25}$ +39.5 (*c* = 1, $CHCl_3$); IR (neat): 3436, 2926, 2855, 1610, 1459, 1376, 1219, 1060, 835 cm.$^{-1}$.; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 - 7.27 (m, 5H), 4.59 (d, 1H, *J* 11.3 Hz), 4.38 (d, 1H, *J* 11.3 Hz), 3.92 - 4.01 (m, 1H), 3.83 (dq, 1H, *J* 12.4, 8.1 Hz), 3.63 - 3.72 (m, 1H), 3.53 - 3.59 (m, 1H), 2.93 - 2.86 (m, 2H) 1.74 - 1.65 (m, 3H), 1.64 - 1.48 (m, 3H), 1.22 (d, 3H, *J* 6.1 Hz), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 128.3, 127.5, 127.4, 72.1, 70.1, 68.5, 61.6, 58.5, 55.9, 44.8, 33.7, 26.8, 25.8, 20.1, 18.1, -4.1, -4.5; MS (ESIMS): *m/z* 417 $(M+Na)^+$; HRMS (ESI): calcd for $C_{22}H_{39}O_4Si$ $(M+H)^+$ 395.2618; Found 395.2612.

{[(3*S*,5*S*)-5-(Benzyloxy)-1-[(2*R*,3*S*)-3-(iodomethyl)oxiran-2-yl]hexan-3-yl]oxy}(*tert*-butyl)dimethylsilane (13). To a stirred solution of epoxy alcohol **12** (1.2 g, 3 mmol) in Et_2O/MeCN (3:1, 20 mL) solvent mixture was added triphenyl phosphene (0.8 g, 3.1 mmol) followed by imidazole (270 mg, 3.97 mmol) at 0 ^oC and the mixture was stirred for 10 minutes. Then added I_2 (0.85 g, 3.4 mmol) at 0 °C and the mixture was stirred for 2 h at rt. Then the reaction mixture was quenched with saturated $Na_2S_2O_3$ (5 mL) and extracted with EtOAc (3x20 mL). The organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated and residue was purified by column chromatography on silica gel (60-120 mesh) by eluting with EtOAc/hexane (1:9) mixture to afford iodo compound **13** (1.18 g, 77%) as a colorless liquid. $[\alpha]_D^{25}$ +31.7 (*c* = 0.7, $CHCl_3$); IR (neat): 3029, 2928, 2855, 1495, 1433, 1252, 1097, 1005, 833, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 - 7.27 (m, 5H), 4.59 (d, 1H, *J* 11.4 Hz), 4.39 (d, 1H, *J* 11.4 Hz), 3.91 - 3.99 (m, 1H), 3.64 - 3.73 (m, 1H), 3.21 (dd, 1H, *J* 14.4, 9.5 Hz), 3.02 - 2.93 (m, 2H), 2.77 (dt, 1H, *J* 5.2 Hz), 1.72 - 1.48 (m, 6H), 1.22 (d, 3H, *J* 6.1 Hz), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 128.3, 127.5, 127.3, 72.1, 70.1, 68.5, 62.5, 58.3, 44.8, 33.6, 26.8, 20.1, 18.5, -4.1, -4.4; MS (ESIMS): *m/z* 527 $(M+Na)^+$; HRMS (ESI): calcd for $C_{22}H_{38}O_3ISi$ $(M+H)^+$ 505.1631; Found 505.1629.

(3*R*,6*S*,8*S*)-8-(Benzyloxy)-6-[(*tert*-butyldimethylsilyl)oxy]non-1-en-3-ol (14). To a stirred solution of iodo compound **13** (1.15 g, 2.28 mmol) in EtOH (15 mL) was added activated Zn dust (1.5 g, 23 mmol) and catalytic amount of sodium iodide, then the reaction mixture was stirred at reflux for 4 h. After complete conversion of starting material (monitored by TLC), the mixture was passed through celite bed. The filtrate was concentrated and the residue was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc/hexane (2:8) mixture to afford allylic alcohol **14** (0.72 g, 83%) as colorless liquid. $[\alpha]_D^{25}$ +46.9 (*c* = 1, $CHCl_3$); IR (neat): 3364, 3031, 2952, 2856, 1714, 1456, 1376, 1219, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 - 7.25 (m, 5H), 5.81 - 5.89 (m, 1H), 5.21 (dt, 1H, *J* 17.2 Hz), 5.09 (dt, 1H, *J* 10.3 Hz), 4.59 (d, 1H, *J* 11.4 Hz), 4.40 (d, 1H, *J* 11.4 Hz), 4.05 (q, 1H, *J* 11.5, 5.7 Hz), 3.95 - 4.02 (m, 1H), 3.64 - 3.71 (m, 1H), 2.26 (brs, 1H, OH), 1.71 - 1.77 (m, 1H), 1.66 - 1.51 (m, 5H), 1.21 (d, 3H, *J* 6.1 Hz), 0.89 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.1, 138.9, 127.4, 127.3, 114.4, 73.2, 72.1, 70.1, 69, 44.5, 33.8, 32.1, 25.9, 20, 18.1, -4.2, -4.6; MS (ESIMS): *m/z* 379 $(M+H)^+$, 401 $(M+Na)^+$; HRMS (ESI^+): calcd for $C_{22}H_{39}O_3Si$ $(M+H)^+$ 379.2667; Found 379.2663.

(5*R*,8*S*)-8-[(*S*)-2-(Benzyloxy)propyl]-10,10,11,11-tetramethyl-5-vinyl-2,4,9-trioxa-10-siladodecane (15). To a stirred solution of compound **14** (0.7 g, 1.9 mmol) in dry CH_2Cl_2 (5 mL) was added DIPEA (0.93 mL, 5.5 mmol) at 0 ^oC, stirred for 10 minutes, then methoxymethyl chloride (0.61 mL, 6 M in methanol, 3.7 mmol). The reaction temperature slowly rised to 25 ^oC, then added catalytic amount of DMAP and then stirred for 6 h. After completion of reaction (monitored by TLC), water was added and extracted with CH_2Cl_2 (2x10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under vacuum. The crude product was purified by flash column chromatography using silica gel (60-120 mesh) by eluting with hexane / EtOAc (9:1) mixture to afford compound **15** (0.72 g, 92%) as colorless liquid. $[\alpha]_D^{25}$ +105 (*c* = 1, $CHCl_3$); IR (neat): 3012, 2943, 1442, 1347, 1182, 1182, 1119, 1023, 900 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 - 7.24 (m, 5H), 5.59 - 5.69 (m, 1H), 5.20 - 5.15 (m, 2H), 4.69 (d, 1H, *J* 6.7 Hz), 4.58 (d, 1H, *J* 11.5 Hz), 4.52 (d, 1H, *J* 6.7 Hz), 4.40 (d, 1H, *J* 11.4 Hz), 3.93 (m, 1H), 3.63 - 3.71 (m, 1H), 3.35 (s, 3H), 1.75 - 1.63 (m, 2H), 1.59 - 1.40 (m, 4H), 1.21 (d, 3H, *J* 6.1 Hz), 0.88 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1, 138.3, 128.3, 127.4, 127.2, 117.2, 93.6, 77.6, 72.2, 70.1, 69.8, 55.3, 33.5, 30.3, 25.9, 18.1, -4.2, -4.5; MS (ESIMS): *m/z* 423 $(M+H)^+$, 445 $(M+Na)^+$; HRMS (ESI): calcd for $C_{25}H_{43}O_4Si$ $(M+H)^+$ 423.2936; Found 423.29153.

(4*R*,7*S*,9*S*,*E*)-Ethyl-9-(benzyloxy)-7-[(*tert*-butyldimethylsilyl)oxy]-4-(methoxymethoxy)dec-2-enoate (16). To a stirred solution of compound **15** (0.7 g, 1.7 mmol) in dry CH_2Cl_2 (10 mL) was added ethyl acrylate (0.53 mL, 5 mmol), then the mixture was degassed with N_2 for 20 minutes. Then added Grubbs II catalyst (42 mg, 0.05

mmol) under argon atmosphere. Then the mixture was refluxed for 12 h. After completion of reaction (monitored by TLC), the solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (60-120 mesh) by eluting with EtOAc/hexane (1:9) mixture to afford compound **16** (0.69 g, 84%) as colorless liquid. $[\alpha]_D^{25}$ +77.5 (*c* = 2, $CHCl_3$); IR (neat): 3068, 2930, 2857, 1695, 1454, 1357, 1107, 986 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 - 7.24 (m, 5H), 6.79 (dd, 1H, *J* 15.7, 6.3 Hz), 5.96 (dd, 1H, *J* 15.7, 1.2 Hz), 4.62 - 4.55 (m, 3H), 4.39 (d, 1H, *J* 11.4 Hz), 4.20 (q, 2H, *J* 14.3, 7.2 Hz), 4.17 - 4.13 (m, 1H), 3.90 - 3.99 (m, 1H), 3.63 - 3.70 (m, 1H), 3.35 (s, 3H), 1.72 - 1.58 (m, 4H), 1.55 -1.41 (m, 2H), 1.29 (t, 3H, *J* 7.2 Hz), 1.21 (d, 3H, *J* 6.1 Hz), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 147.7, 139.0, 128.3, 127.4, 127.3, 121.9, 94.5, 75.3, 72.1, 70.1, 68.8, 60.4, 55.5, 44.9, 33.1, 29.6, 25.9, 20.1, 18.1, 14.2, -4.2, -4.5; MS (ESIMS): *m/z* 495 $(M+H)^+$, 517 $(M+Na)^+$; HRMS (ESI): calcd for $C_{27}H_{47}O_6Si$ $(M+H)^+$ 495.3124; Found 495.3136.

(4*R*,7*S*,9*S*,*E*)-9-(Benzyloxy)-7-[(*tert*-butyldimethylsilyl)oxy]-4-(methoxymethoxy)dec-2-enoic acid (17). To a stirred solution of compound **16** (0.67 g, 1.4 mmol) in methanol (5 mL) was added NaOH solution (1.36 mL, 3 N, 4.1 mmol) at 0 °C. Then the reaction mixture slowly warmed to rt and stirred for 3 h. After completion of reaction (monitored by TLC), the solvent was removed under vacuum and extracted was with EtOAc (2x20 mL). The combined organic layers were separated, washed with brine, dried over Na_2SO_4, concentrated under *vacuum*. The crude product was purified by column chromatography on silica gel (60-120 mesh) by eluting with EtOAc/hexane (3:7) mixture to afford compound **17** (0.58 g, 92%) as colorless liquid. $[\alpha]_D^{25}$ +111.2 (*c* = 0.4, $CHCl_3$); IR (neat): 2923, 2853, 1739, 1461, 1252, 1061, 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 - 7.24 (m, 5H), 6.91 (dd, 1H, *J* 15.6, 5.9 Hz), 5.98 (dd, 1H, *J* 15.7, 1.3 Hz), 4.62 - 4.57 (m, 2H), 4.40 (d, 1H, *J* 11.4 Hz), 4.15 - 4.23 (m, 1H), 3.91 - 3.99 (m, 1H), 3.63 - 3.73 (m, 1H), 3.35 (s, 3H), 1.72 - 1.58 (m, 4H), 1.56 - 1.39 (m, 2H), 1.21 (d, 3H, *J* 6.1 Hz), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 150.6, 138.9, 129.2, 127.4, 127.3, 120.7, 94.6, 75.3, 72.1, 68.8, 55.6, 44.8, 33.1, 29.5, 25.8, 20.1, 18.1, -4.2, -4.5; MS (ESIMS): *m/z* 467 $(M+H)^+$; HRMS (ESI): calcd for $C_{25}H_{43}O_6Si$ $(M+H)^+$ 467.2823; Found 467.2823.

(4*R*,7*S*,9*S*,*E*)-9-(Benzyloxy)-7-hydroxy-4-(methoxymethoxy)dec-2-enoic acid (18). To a stirred solution of compound **17** (0.57 g, 1.2 mmol) in dry THF (5 mL) was added TBAF (1.9 mL, 1 M in THF, 1.8 mmol) at 0 °C. Then the reaction mixture was refluxed for 5 h. After completion of the reaction (monitored by TLC), then the reaction mixture was quenched with saturated NH_4Cl and solvent was removed under reduced pressure. The residue was extracted with EtOAc (2x10 mL). The combined organic layers were washed with brine dried over Na_2SO_4, concentrated under vacuum. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc/hexane (8:2) mixture to afford **18** (0.41 g, 95%) as pale yellow liquid. $[\alpha]_D^{25}$ +72.6 (*c* = 1, $CHCl_3$).; IR (neat): 3435, 3365, 2926, 1702, 1658, 1452, 1376, 1271, 1149, 1030, 772 cm^{-1}.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 - 7.27 (m, 5H), 6.92 (dd, 1H, *J* 15.7 Hz), 5.99 (d, 1H, *J* 15.7 Hz), 4.64 - 4.59 (m, 2H), 4.44 (d, 1H, *J* 11.5 Hz), 4.22 - 4.27 (m, 1H), 3.94 - 3.84 (m, 2H), 3.37 (s, 3H), 1.84 - 1.77 (m, 1H), 1.73 - 1.60 (m, 2H), 1.58 - 1.48 (m, 2H), 1.26 (d, 3H, *J* 6.2 Hz).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 150.2, 138.3, 128.5, 127.7, 120.9, 94.9, 75.3, 72.6, 70.5, 68.3, 57.7, 42.7, 32.9, 31.1, 19.1; MS (ESIMS): *m/z* 375 $(M+Na)^+$; HRMS (ESI): calcd for $C_{19}H_{29}O_6$ $(M+H)^+$ 353.1963; Found 353.1958.

(**4*R*,7*S*,9*S*,*E*)-Methyl-9-(benzyloxy)-7-hydroxy-4-(methoxymethoxy)dec-2-enoate (19)**. To a stirred solution of *N*-Nitroso-*N*-Methylurea salt (53 mg, 0.06 mmol) in dry ether was added KOH solution (0.2 mL, 2 N, 0.05 mmol) at 0 °C and stirred for 10 minutes, the pale yellow color results the formation of diazomethane. The ether layer was separated, passed through Na_2SO_4, at cooling condition immediately poured into *seco*-acid **18** (20 mg, 56.8 μmol), which was dissolved in dry ether (2 mL) and stirred for 10 minutes. After completion of the reaction (monitored by TLC), organic layers were separated, washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography using silica gel (60-

120 mesh) by eluting with hexane/EtOAc (6:4) mixture to afford **19** (20 mg, 96%) as colorless liquid. $[\alpha]_D^{25}$ +77.4 (*c* = 0.5, $CHCl_3$).; IR (neat): 3340, 2956, 2858, 1723, 1460, 1256,1170, 1043, 833.9 $cm.^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 - 7.27 (m, 5H), 6.82 (dd, 1H, *J* 15.7, 6.3 Hz), 5.98 (dd, 1H, *J* 15.7, 1.35 Hz), 5.45 (q, 1H, *J* 11.1 Hz), 4.65 - 4.58 (m, 2H), 4.44 (d, 1H, *J* 11.6 Hz), 4.22 (q, 1H, *J* 11.8, 5.5 Hz), 3.94 - 3.85 (m, 2H), 3.74 (s, 3H), 3.37 (s, 3H), 1.86 - 1.75 (m, 1H), 1.68 - 1.47 (m, 5H), 1.42 (d, 3H, *J* 5.5 Hz).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 148, 138.2, 128.4, 127.7, 121.4, 102.9, 94.6, 75.2, 72.6, 70.5, 68.2, 55.7, 51.6, 42.6, 32.9, 31.1, 29.6, 19.; MS (ESIMS): *m/z* 367 $(M+H)^+$; HRMS (ESI^+): calcd for $C_{20}H_{31}O_6$ $(M+H)^+$ 367.2120; Found 367.2115.

(4*R*,7*S*,9*S*,*E*)-(2*S*,4*S*,7*R*,*E*)-2-(Benzyloxy)-10-methoxy-7-(methoxymethoxy)-10-oxodec-8-en-4-yl-9-(benzyloxy)-7-[(*tert*-butyldimethylsilyl)oxy]-4-(methoxymethoxy)dec-2-enoate (20). To a stirred solution of compound **17** (50 mg, 142 µmol) in dry CH_2Cl_2 (5 mL) was added compound **19** (19.6 mg, 54 µmol) and the mixture was concentrated under reduced pressure and dried at high vacuum. The resulting thick paste was dissolved in toluene (0.6 mL) and under stirring was added Et_3N (43 µmL, 426 µmol) at rt. The resulting mixture was stirred for 5 minutes and added DMAP (68 mg, 568 µmol) followed by TCBC (44.4 µmL 284 µmol) and continued stirring for 30 minutes then the solution becomes sticky. At this moment was added toluene (1 mL) and shaken manually then stirred for 1 h. After completion of reaction (monitored by TLC) the reaction mixture concentrated under *vacuum*. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with hexane/EtOAc (8:2) mixture to afford compound **20** (57.5 mg, 85%) as sticky material. $[\alpha]_D^{25}$ +180.3 (*c* = 0.3, $CHCl_3$).; IR (neat): 2927, 2855, 1723, 1605, 1453, 1376, 1219, 1029, 772 cm^{-1}.; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34 - 7.25 (m, 10H), 6.77 (ddd, 1H, *J* 15.7, 10.1, 6.1 Hz), 5.95 (ddd, 2H, *J* 15.7, 9.1, 7.8 Hz), 5.22 - 5.28 (m, 1H), 4.62 - 4.50 (m, 6H), 4.37 (dd, 2H, *J* 15.4, 11.4 Hz), 4.11 - 4.18 (m, 1H), 3.99 - 3.93 (m, 1H), 3.73 (s, 3H), 3.71 - 3.64 (m, 1H), 3.35 (s, 3H), 3.33 (s, 3H), 1.75 - 1.59 (m, 8H), 1.54 - 1.43 (m, 2H), 1.20 (t, 6H, *J* 5.8 Hz), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 165.7, 147.8, 147.6, 139, 138.5, 128.3, 128.2, 127.9, 127.5, 127.4, 121.9, 121.7, 94.6, 75.4, 74.9, 72.1, 71.5, 71.2, 70.1, 68.8, 55.6, 51.6, 44.8, 42.2, 33.2, 30.5, 29.6, 25.9, 20.1, 19.8, 18, -4.1, -4.5; MS (ESIMS): *m/z* 838 $(M+Na)^+$; HRMS (ESI^+): calcd for $C_{45}H_{70}O_{11}SiNa$ $(M+Na)^+$ 837.4594; Found 837.4579.

(4*R*,7*S*,9*S*,*E*)-9-(Benzyloxy)-7-{[(4*R*,7*S*,9*S*,*E*)-9-(benzyloxy)-7-hydroxy-4-(methoxymethoxy)dec-2-enoyl]oxy}-4-(methoxymethoxy)dec-2-enoic acid (21). To a stirred solution of compound **20** (55 mg, 67.48 µmol) in ethylene dichloride (2.5 mL) was added trimethyltin hydroxide (122 mg, 674.70 µmol) at rt and the reaction mixture was refluxed for 10 h. After completion of reaction (monitored by TLC), solvent was removed under reduced pressure and the resulting residue was dissolved in water and extracted with EtOAc (3x5 mL) and the combined organic layers washed with solution of $KHSO_4$ (0.01 N, 3x5 mL), brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was used for further reaction without purification.

The above acid compound was dissolved in dry THF (2 mL) and added HF.pyridine (0.01 mL, 337.4 µmol, 70% HF.30% pyridine) at 0 ^oC. Then slowly warmed to rt and stirred for 6 h. After completion of the reaction (monitored by TLC), the mixture was cooled to 0 ^oC and quenched with saturated $NaHCO_3$ (5 mL), followed by 0.05 N HCl (5 mL). The reaction mixture was extracted with EtOAc (2x10 mL), the combined organic layers were washed with brine and dried over Na_2SO_4 concentrated under *vacuum*. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc/ MeOH (9:1) mixture to afford, compound 21 in 23 mg (45% over two steps) as sticky material. $[\alpha]_D^{25}$ +226.1 (*c* = 0.2, $CHCl_3$).; IR (neat): 3424, 3031, 2981, 2926, 2854, 1716, 1639, 1494, 1452, 1028, 1148, 1070, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 - 7.24 (m, 10H), 6.89 (ddd, 1H, *J* 15.7, 6.1 Hz), 6.80 (ddd, 1H, *J* 18.5, 9.1 Hz), 5.91 - 6.02 (m, 2H), 5.22 - 5.28 (m, 1H), 4.67 - 4.56 (m, 4H), 4.52 (d, 1H, *J* 11.1 Hz), 4.44 (d, 1H, *J* 11.6 Hz), 4.36 (d, 2H, *J* 11.1 Hz), 4.27 - 4.16 (m, 2H), 3.96 - 3.84 (m, 2H), 3.58 - 3.51 (m, 1H), 3.37 (s, 3H), 3.34 (s, 3H), 2.85 (brs, 1H,

OH), 2.42 - 2.30 (m, 1H), 2.06 - 1.98 (m, 1H), 1.85 - 1.58 (m, 8H), 1.56 - 1.45 (m, 2H), 1.26 (d, 3H, *J* 6.1 Hz), 1.20 (d, 3H *J* 6.1 Hz).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 165.7, 150, 149.4, 147.8, 138.5, 138.2, 128.4, 128.3, 127.9, 127.7, 127.4, 121.9, 121.3, 121, 94.7, 75.3, 74.8, 72.6, 71.5, 71.2, 70.8, 70.5, 68.3, 68.2, 55.6, 49.4, 42.6, 42, 32.9, 32.8, 31.1, 31, 30.6, 30.2, 29.6, 19.8, 19, 17.6; MS (ESIMS): *m/z* 686 $(M-H)^+$; HRMS (ESI^+): calcd for $C_{38}H_{56}O_{11}$ $(M+H)^+$ 688.3797; Found 688.3817.

(3*E*,5*R*,8*S*,11*E*,13*R*,16*S*)-8,16-Bis[(*S*)-2-(benzyloxy)propyl]-5,13-bis(methoxymethoxy)-1,9-dioxacyclohexadeca-3,11-diene-2,10-dione (22). To a stirred solution of the *seco*-acid **21** (15 mg, 21.86 µ mol) in toluene (8.1 mL) was added TCBC (53.33 µ mL, 218.6 µ mol) and Et_3N (33.45 µL, 240.46 µ mol) at rt. The resulting reaction mixture was stirred for 1 hr and diluted by the addition of toluene (8.1 mL). Then, the reaction mixture was added to a solution of DMAP (11 mg, 87.4 µ mol, in toluene 20.2 mL) at 40 °C, over 5 h, *via* syringe pump. After the addition was completed, stirring was continued for 24 h. Then the solvent was removed under reduced pressure and the residue was loaded on silica gel (60-120 mesh) by eluted with hexane/EtOAc (7:3) mixture to give compound **22** (6.15 mg, 42%) as a white sticky material. $[\alpha]_D^{25}$ +108.2 (*c* = 0.5, $CHCl_3$).; IR (neat): 2924, 2853, 1725, 1550, 1516, 1463, 1415, 1378, 1261, 1219, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 - 7.29 (m, 10H), 6.76 (dd, 2H, *J* 15.8, 5.6 Hz), 5.89 (dd, 2H, *J* 15.8, 1.2 Hz), 5.39 (sextet, 2H, *J* 11.9, 7.6 Hz), 4.63 - 4.56 (m, 4H), 4.53 (d, 2H, *J* 11.1 Hz), 4.44 - 4.40 (m, 2H), 4.39 (d, 1H, *J* 11.1 Hz), 3.55 - 3.48 (m, 2H), 3.35 (s, 6H), 2.05 - 1.87 (m, 2H), 1.79 - 1.59 (m, 10H), 1.20 (d, 6H, *J* 6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 147.6, 138.4, 128.3, 128, 127.5, 122.7 94.3, 73.7, 71.5, 70.9, 70.2, 39.7, 29.6, 27.9, 26.8, 19.8; MS (ESIMS): *m/z* 692 $(M+Na^+)$; HRMS (ESI^+): calcd for $C_{38}H_{52}O_{10}Na$ $(M+Na)^+$ 691.3460; Found 691.3465.

(3*E*,5*R*,8*S*,11*E*,13*R*,16*S*)-5,13-Dihydroxy-8,16-bis[(*S*)-2-hydroxypropyl]-1,9-dioxacyclohexadeca-3,11-diene-2,10-dione (trichobotryside A). To a stirred solution of compound **22** (4 mg, 6 µmol) in dry CH_2Cl_2 (1 mL) was added $TiCl_4$ (0.1 mL, dissolved in dry CH_2Cl_2 10 mL) dropwise at 0 ^oC. The reaction mixture was slowly warmed to rt and stirred for 2 h. After completion of the reaction (monitored by TLC), the mixture was quenched by adding saturated $NaHCO_3$ (5 mL) and extracted with chloroform (2x5 mL), the combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The sticky foam material was purified by column chromatography on silica gel (100-200 mesh) by eluting with $CHCl_3/CH_3OH$ (8:2) mixture to give target molecule trichobotryside A (1.2 mg, 50%). $[\alpha]_D^{25}$ +65.7 (*c* = 0.12, CH_3OH), $^{lit}[\alpha]_D^{20}$ +50.1 (*c* = 1.58, CH_3OH); IR (neat): 3436, 3395, 3081, 2930, 1644, 1467, 1253, 1082, 773 cm^{-1}; 1H NMR (500 MHz, DMSO-d_6): δ 6.76 (dd, 2H, *J* 15.7 Hz), 5.81 (dd, 2H, *J* 15.7 Hz), 5.41 (brs, OH), 5.34 - 5.30 (m, 1H), 5.05 (d, 2H, *J* 4.2 Hz), 4.47 - 4.42 (m, 2H), 3.54 - 3.49 (m, 2H), 1.99 - 1.94 (m, 8H), 1.52 - 1.42 (m, 4H), 1.05 (d, 6H, *J* 6.1 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ 164.9, 150.9, 120.2, 70.7, 69.8, 62, 40.6, 29.1, 25.9, 22.2; MS (ESIMS): *m/z* 423 $(M+Na^+)$; HRMS (ESI): calcd for $C_{20}H_{32}O_8Na$ $(M+Na)^+$ 423.1986; Found 423.2009.

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Supplementary Material

Copies of ^{1}H NMR, ^{13}C NMR spectra associated with this paper can be found in the online version.

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