First stereoselective total synthesis of an anti-fouling agent, C\textsubscript{2}-symmetric natural macrolide trichobotryside A

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Abstract

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

Keywords: Macrolide, 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.\textsuperscript{1-3} The macropolylides, essentially 16-membered macrolides such as pyrenophorol, pyrenophorin, and vermiculin (Figure 1) have strong antifungal and anthelmintic activity. Trichobotryside A is C\textsubscript{2}-Symmetric 16-membered macrolide isolated by the Shu-Hua Qi group from deep sea sediment of the South China Sea fungal strain \textit{Trichobotrys 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 \textit{Bugula neritina} and \textit{Balamus amphitrite} with EC\textsubscript{50} values of 7.3, 2.5 µg/mL and LC\textsubscript{50}/EC\textsubscript{50} > 40.5, 37.4 respectively.\textsuperscript{4-6} The structure of trichobotryside A was determined by \textsuperscript{1}H and \textsuperscript{13}C NMR data along with 2D-NMR experiments such as \textsuperscript{1}H-\textsuperscript{1}H COSY, HSQC and HMBC spectra. The absolute configuration was established by methanalysis and the modified Mosher's method and its molecular formula determined on the basis of HRMS (ESI\textsuperscript{+}) 423.1987 (M+Na\textsuperscript{+}).\textsuperscript{7-9}

![Figure 1](image1.png)

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 macrolide 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](image2.png)
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.\(^1\) 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-\textit{anti}-allylation under Reetz conditions (TiCl\(_4\), CH\(_2\)Cl\(_2\), -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-\textit{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-\textit{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 aldehyde 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](attachment:scheme.png)
The allylic alcohol 11 was subjected to Sharpless asymmetric epoxidation with (-)-DET, Ti(OiPr)$_4$ and cumene hydroperoxide at -20 °C to give epoxy alcohol 12 in 80% yield with excellent diastereoselectivity (dr 19:1), established by $^1$H NMR spectroscopy. The free alcohol 12 was converted into iodide 13 in 77% yield by using molecular iodine, triphenylphosphine and imidazole in Et$_2$O/CH$_3$CN (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. 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 2$^\text{nd}$ generation catalyst in dry CH$_2$Cl$_2$ led to the formation of trans-olefinic ester 16 in 84% yield as confirmed by $^1$H 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, 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.

After the above experiments, the acid group in seco-acid 18 was converted into its methyl ester using N-nitroso-N-methyleurea 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 °C, 15 min, 96%; (b) 2,4,6-trichlorobenzoyl chloride, Et$_3$N, DMAP, dry CH$_2$Cl$_2$, rt, 90 min, 85%; (c) Me$_3$SnOH, EDC, 80 °C, 10 h; (d) HF.p.yridine, THF, rt, 6 h, 45%; (e) 2,4,6-trichlorobenzoyl chloride, Et$_3$N, DMAP, CH$_2$Cl$_2$, 40 °C, 29 h, 42%; (f) TiCl$_4$, CH$_2$Cl$_2$, rt, 2 h, 50%.

The methyl ester 20 was hydrolyzed in presence of trimethyltin hydroxide followed by deprotection of tert-butyltrimethylsilyl ether with HF.p.yridine 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$_2$Cl$_2$ to obtain trichobotryside A in 50% yield, as shown in Scheme 4.$^{38}$ The optical rotation of the synthesized trichobotryside A was [α]$_D^{25}$ +65.7 (c = 0.12, CH$_3$OH) and that of the natural product is [α]$_D^{20}$ +50.09 (c = 1.58, CH$_3$OH).$^7$

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 PerkinElmer 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 Finnegan 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-ButLi (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-methoxylxirane 1 (4.4 mL, 68.4 mmol) added and stirred for a further 1 h, then the reaction mixture was quenched with saturated NH₄Cl 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 Na₂SO₄ 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. [α]D²⁵ +23 (c = 1, CHCl₃); IR (neat): 3396, 2899, 1453, 1420, 1276, 1182, 1029, 869, 771 cm⁻¹;¹H NMR (400 MHz, CDCl₃): δ 4.20 (dd, 1H, J 6.3 Hz), 3.85 (dt, 1H, J 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);¹³C NMR (100 MHz, CDCl₃): 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 °C 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 (2 mL,20), at room temperature. The reaction was maintained under nitrogen for 12 h. After completion of the reaction as indicated by TLC, solvent was removed under reduced pressure and quenched with saturated NH₄Cl and extracted with EtOAc (2x50 mL), the combined organic layers were washed with brine, dried over Na₂SO₄ 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. [α]D²⁵ -3.24 (c = 1, CHCl₃); IR (neat): 3030, 2922, 2853, 1727, 1643, 1455, 1364, 772 cm⁻¹;¹H NMR (400 MHz, CDCl₃): 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);¹³C NMR (100 MHz, CDCl₃): 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 C₁₉H₂₂OS₂ (M+H)+ 269.1028; Found 269.1028.

(4S,6S)-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, CH₃CN:H₂O, 9:1) SrCO₃ (22 g, 149 mmol) was added at 0 °C, 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 Na₂CO₃ saturated solution (30 mL) and Na₂S₂O₃ (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 Na₂SO₄, and concentrated under vacuum. The product was purified by flash column chromatography to furnish (S)-3-(benzylox)butanal 5.

To a stirred solution of the above aldehyde 5 (3.5 g, 19.6 mmol) in CH₂Cl₂ (30 mL) TiCl₄ (1 M, 21.44 mL, CH₂Cl₂, 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 another 1 h, at -78 °C. After completion of the reaction (confirmed by TLC), the reaction mixture was quenched by adding saturated NaHCO₃ solution (50 mL) and stirred vigorously for 3 h at rt. The reaction mixture was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layer was washed with brine, dried with Na₂SO₄ 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. [α]D 20 +44 (c = 1, CHCl3); 1H NMR (400 MHz, CDCl3): 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 (bres, 1H, OH), 2.24 - 2.20 (m, 2H), 1.68 - 1.64 (m, 2H), 1.26 (d, 3H, J 6.2 Hz); 13C NMR (100 MHz, CDCl3): 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 C12H22O2 (M+H)+ 221.1534, found 221.1536.

[(4S,6S)-6-(Benzylxylo)hept-1-en-4-yl]oxy][(tert-butyl)dimethylsilane (7). To a stirred solution of compound 6 (2 g, 9.08 mmol) in dry CH2Cl2 (20 mL) at 0 °C, imidazole (1.23 g, 18.1 mmol) was added and stirred for 15 min, then TBDMSOTf (1.5 g, 10 mmol), dissolved in dry CH2Cl2 (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 CH2Cl2 (2 x 20 mL), the combined organic layers were washed with brine, dried over anhydrous Na2SO4 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. [α]D 20 +68.8 (c = 2, CHCl3); IR (neat): 3070, 2929, 2857, 1710, 1427, 1336, 1219, 1108, 702 cm−1; 1H NMR (400 MHz, CDCl3): 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, 3H), 0.07 (s, 3H), 0.05 (s, 3H); 13C NMR (100 MHz, CDCl3): 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 C20H33O2Si (M+H)+ 335.2402; Found 335.2400.

(4S,6S)-6-(Benzylxylo)-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 H2O2 (50 mL, 33% w/w H2O) 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 Na2SO4 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. [α]D 20 +32.1 (c = 2, CHCl3); IR (neat): 3395, 3069, 2929, 2857, 1710, 1427, 1336, 1219, 1108, 702 cm−1; 1H NMR (400 MHz, CDCl3): 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 (bres, 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); 13C NMR (100 MHz, CDCl3): 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 C20H33O2Si (M+H)+ 335.2513; Found 353.2506.

(6S,8S,E)-ethyl-8-(benzylxylo)-6-[(tert-butyldimethylsilyl)oxy]non-2-enoate (10). A solution of oxalyl chloride (1.2 mL, 15.3 mmol) in dry CH2Cl2 (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 CH2Cl2 (2 mL)] at the same temperature and stirred for further 3 h. Then, added Et3N (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 CH2Cl2 (3x10 mL). The combined organic layers were washed with brine, dried over Na2SO4 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 Na₂SO₄ 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). [α]₀^25 +43.7 (c = 1, CHCl₃); IR (neat): 3028, 2930, 2856, 1718, 1655, 1318, 1255, 1094, 984 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₂₄H₄₁O₄Si (M+H)^⁺ 421.2759; Found 421.2768.

(6S,8S,E)-8-(Benzyloxy)-6-[(tert-butyldimethylsilyloxy)non-2-en-1-ol (11). To a stirred solution of compound 10 (1.9 g, 4.5 mmol) in dry CH₂Cl₂ (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 CH₂Cl₂ (2x20 mL), the combined organic layers washed with H₂O, brine, dried over Na₂SO₄ 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. [α]₀^25 +43.9 (c = 1.5, CHCl₃); IR (neat): 3434, 3085, 2929, 2856, 1458, 1362, 1077, 920, 696 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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 (bs, 1H), 1.22 (d, 3H, J 6.2 Hz), 0.89 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): 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 C₂₂H₃₉O₃Si (M+H)^⁺ 379.2667; Found 379.2663.

{(2R,3R)-3-[(3S,5S)-5-(Benzyloxy)-3-[(tert-butyldimethylsilyloxy)hexyl]oxiran-2-yl]methanol (12). To a stirred suspension of activated molecular sieves powder in dry CH₂Cl₂ (15 mL) was added (-)-DET (0.75 mL, 4.4 mmol) and Ti(OPr)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 CH₂Cl₂ (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 CH₂Cl₂ (2x15 mL). The combined organic layers were washed with brine and dried over Na₂SO₄. 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. [α]₀^25 +39.5 (c = 1, CHCl₃); IR (neat): 3436, 2926, 2855, 1610, 1459, 1376, 1219, 1060, 835 cm⁻¹.; ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₂₂H₃₉O₄Si (M+H)^⁺ 395.2618; Found 395.2612.
{{[3S,5S]-5-(Benzyloxy)-1-[[2R,3S]-3-(iodomethyl)oxiran-2-yl]hexan-3-yl}oxy}{[tert-butyldimethylsilane (13). To a stirred solution of epoxy alcohol 12 (1.2 g, 3 mmol) in Et$_2$O/MeCN (3:1, 20 mL) solvent mixture was added triphenyl phosphine (0.8 g, 3.1 mmol) followed by imidazole (270 mg, 3.97 mmol) at 0 °C 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$_2$S$_2$O$_3$ (5 mL) and extracted with EtOAc (3x20 mL). The organic layers were washed with brine and dried over Na$_2$SO$_4$. 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, \text{CHCl}_3); IR (neat): 3029, 2928, 2855, 1495, 1433, 1252, 1097, 1005, 833, 692 \text{ cm}^{-1}; ^1H \text{ NMR} (400 MHz, CDCl$_3$): \delta 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$_3$): \delta 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 (EI): calcd for C$_{23}$H$_{36}$O$_3$Si (M+H)$^+$ 505.1631; Found 505.1629.}

{(3R,6S,8S)-8-(Benzyloxy)-6-[[tert-butyldimethylsilyl]oxy]non-1-ene-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, \text{CHCl}_3); IR (neat): 3364, 3031, 2952, 2856, 1714, 1456, 1376, 1219, 1060 \text{ cm}^{-1}; ^1H \text{NMR} (400 MHz, CDCl$_3$): \delta 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$_3$): \delta 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 (EI): calcd for C$_{22}$H$_{33}$O$_3$Si (M+H)$^+$ 379.2667; Found 379.2663.}

{(5R,8S)-[7S-2-(Benzyloxy)propyl]-10,11,11-tetramethyl-5-vinyl-2,4,9-trioxaoctadecane (15). To a stirred solution of compound 14 (0.7 g, 1.9 mmol) in dry CH$_2$Cl$_2$ (5 mL) was added DIPEA (0.93 mL, 5.5 mmol) at 0 °C, stirred for 10 minutes, then methoxymethyl chloride (0.61 mL, 6 M in methanol, 3.7 mmol). The reaction temperature slowly rised to 25 °C, 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$_2$Cl$_2$ (2x10 mL). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, 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, \text{CHCl}_3); IR (neat): 3012, 2943, 1442, 1347, 1182, 1182, 1119, 1023, 900 \text{ cm}^{-1}; ^1H \text{NMR} (400 MHz, CDCl$_3$): \delta 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$_3$): \delta 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$_{39}$O$_4$Si (M+H)$^+$ 423.2936; Found 423.29153.}

{(4R,7S,9S,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$_2$Cl$_2$ (10 mL) was added ethyl acrylate (0.53 mmol, 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. \([\alpha]_D^{25} +77.5 (c = 2, \text{CHCl}_3); \) IR (neat): 3068, 2930, 1702, 1658, 1452, 1389, 1372, 1200, 1155, 835 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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\(_3\)): \(\delta\) 166.7, 147.7, 133.0, 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\(_{37}\)O\(_6\)Si (M+H\(^+\)) 495.3124; Found 495.3136.

**\(4R, 7S, 9S, E\)-9-(Benzyloxy)-7-[\(\text{tert}-\text{butyldimethyilsilyloxy}\)]-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 with EtOAc (2x20 mL). The combined organic layers were separated, washed with brine, dried over Na\(_2\)SO\(_4\), and 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. \([\alpha]_D^{25} +111.2 (c = 0.4, \text{CHCl}_3); \) IR (neat): 3293, 3165, 2926, 2857, 1702, 1658, 1452, 1389, 1372, 1200, 1155, 835 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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\(_3\)): \(\delta\) 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\(_{15}\)H\(_{29}\)O\(_6\)Si (M+H\(^+\)) 467.2823; Found 467.2823.

**\(4R, 7S, 9S, E\)-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), the reaction mixture was quenched with saturated NH\(_4\)Cl 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\(_2\)SO\(_4\), and 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. \([\alpha]_D^{25} +72.6 (c = 1, \text{CHCl}_3); \) IR (neat): 3435, 3365, 2926, 1702, 1658, 1452, 1376, 1271, 1149, 1030, 772 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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\(_3\)): \(\delta\) 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\(_{11}\)H\(_{19}\)O\(_3\) (M+Na\(^+\)) 353.1963; Found 353.1958.

**\(4R, 7S, 9S, E\)-Methyl 9-(benzyloxy)-7-hydroxy-4-(methoxymethoxy)dec-2-enoate (19).** To a stirred solution of N-Nitroso-N-Methyleurea 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\(_2\)SO\(_4\), 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\(_2\)SO\(_4\) 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 \textbf{19} (20 mg, 96%) as colorless liquid. [α]₀²⁵ +77.4 (c = 0.5, CHCl₃); IR (neat): 3340, 2956, 2858, 1723, 1460, 1256,1170, 1043, 833.9 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₂₀H₃₁O₆ (M+H)⁺ 367.2120; Found 367.2115.

\textbf{(4R,7S,9S,E)-(2S,4S,7R,E)-2-(Benzylxylo)-10-methoxy-7-(methoxymethoxy)-10-oxodec-8-en-4-y1-9-(benzyloxy)-7-[(tert-butyldimethylsilyl)oxy]-4-(methoxymethoxy)dec-2-enolate} \textbf{(20)}. To a stirred solution of compound \textbf{17} (50 mg, 142 µmol) in dry CH₂Cl₂ (5 mL) was added compound \textbf{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 Et₃N (43 µL, 426 µmol) at rt. The resulting mixture was stirred for 5 minutes and added DMAP (68 mg, 568 µmol) followed by TCBC (44.4 µL 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 \textbf{20} (57.5 mg, 85%) as sticky material. [α]₀²⁵ +180.3 (c = 0.3, CHCl₃); IR (neat): 2927, 2855, 1723, 1605, 1453, 1376, 1219, 1029, 772 cm⁻¹.; ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₄₅H₇₀O₁₃SiNa (M+Na)⁺ 837.4594; Found 837.4579.

\textbf{(4R,7S,9S,E)-9-(Benzylxylo)-7-{[(4R,7S,9S,E)-9-(benzyloxy)-7-hydroxy-4-(methoxymethoxy)dec-2-enoyl]oxy}-4-(methoxymethoxy)dec-2-enolic acid} \textbf{(21)}. To a stirred solution of compound \textbf{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 were washed with solution of KHSO₄ (0.01 N, 3x5 mL), brine, dried over Na₂SO₄ 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.pyr dine (0.01 mL, 337.4 µmol, 70% HF.30% pyridine) at 0 °C. Then slowly warmed to rt and stirred for 6 h. After completion of the reaction (monitored by TLC), the mixture was cooled to 0 °C and quenched with saturated NaHCO₃ (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 Na₂SO₄ and 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. [α]₀²⁵ +226.1 (c = 0.2, CHCl₃); IR (neat): 3424, 3031, 2981, 2926, 2854, 1716, 1639, 1494, 1452, 1028, 1148, 1070, 741 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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, 3.25).
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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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