Supporting Information

IodoCyclization and Prins-Type Macrocyclization: An Efficient Formal Synthesis of Leucascandrolide A

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General methods: Air and/or moisture sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in an oven or flame-dried glassware. All anhydrous solvents were distilled prior to use: THF, toluene and t-butyl methyl ether from Na and benzophenone; CH₂Cl₂, DMSO from CaH₂; MeOH from Mg cake. Commercial reagents were used without purification. Column chromatography was carried out by using Spectrochem silica gel (60–120 mesh). Specific optical rotations [α]₀ are given in 10⁻¹ degcm²g⁻¹. Infrared spectra were recorded in CHCl₃/neat (as mentioned) and reported in wave number (cm⁻¹). ¹H and ¹³C NMR chemical shifts are reported in ppm downfield from tetramethylsilane and coupling constants (J) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

(R)-1-(4-Methoxybenzyloxy)hex-5-en-3-ol (10):

\[
\begin{align*}
&\begin{array}{c}
\text{OPMB} \\
\text{OH}
\end{array} \\
&\begin{array}{c}
\text{C=C=CHC=CH}
\end{array}
\end{align*}
\]

A freshly prepared vinyl magnesium bromide (76.9 mL, 76.92 mmol) (1 M solution in THF) was added drop wise to a solution of CuI (0.73 g, 3.85 mmol) in THF (50 mL) at –20 °C. The mixture was stirred from 30 minutes and chiral epoxide 9 (8.0 g, 38.46 mmol) was added in THF (50 mL) dropwise to the above mixture. After 2 h, the reaction (monitored by TLC) was quenched with saturated solution of NH₄Cl (75 mL) and diluted with diethyl ether (50 mL). The two layers were separated and the aqueous layer extracted with diethyl ether (3 x 75 mL). The combined organic layer was washed with brine (2 x 100 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced
pressure to get the crude mass. Purification by flash column chromatography over silica gel (ethyl acetate: hexane = 1:9) afforded the desired homoallyl alcohol 10 (7.7 g, 85%) as a colorless oil.

\[ \alpha \]_D\textsuperscript{25} +4.2 (c 0.95, CHCl₃); \textsuperscript{1}H NMR (300 MHz, CDCl₃) \( \delta \) 7.25 (d, \( J = 8.5 \) Hz, 2H), 6.87 (d, \( J = 8.5 \) Hz, 2H), 5.83 (m, 1H), 5.14-5.06 (m, 2H), 4.45 (s, 2H), 3.85 (m, 1H), 3.80 (s, 3H), 3.76-3.57 (m, 2H), 2.94 (br s, 1H), 2.23 (t, \( J = 6.8 \) Hz, 2H), 1.81-1.71 (m, 2H) ppm;

\textsuperscript{13}C NMR (75 MHz, CDCl₃) \( \delta \) 159.2, 134.8, 130.0, 129.3, 117.4, 113.8, 72.9, 70.4, 68.6, 55.2, 41.9, 35.8 ppm; IR (neat, KBr) 3434, 3074, 2933, 2862, 1613, 1513, 1464, 1302, 1249, 1174, 1019 cm\(^{-1}\); ESI HRMS \textit{m/z} calcd. [M + Na]^+: 259.1305, found 259.1306.

\textbf{\( R \)-1-Methoxy-4-((3-methoxyhex-5-enyloxy)methyl)benzene (11):}

![Structure](image)

To a suspension of NaH (1.38 g, 34.74 mmol, 60% in mineral oil) in dry THF (50 mL), homoallyl alcohol 10 (4.1 g, 17.37 mmol) dissolved in dry THF (100 ml), was slowly added at 0 °C under \textit{N}_2 atmosphere. The suspension was stirred for 1 h at room temperature. Then, methyl iodide (2.35 mL, 34.74 mmol) was added slowly at 0 °C to the above reaction mixture and then it was allowed to stir at room temperature for 4 h. After completion of the reaction (monitored by TLC), it was quenched with saturated solution of NH\textsubscript{4}Cl (50 mL) at 0 °C and diluted with ethyl acetate (100 mL). The two layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (2 x 75 mL), dried over anhydrous Na\textsubscript{2}SO\textsubscript{4} and solvent was removed under reduced pressure to obtain the crude mass which
on purification over silica gel column chromatography (ethyl acetate: hexane = 1:19) afforded methyl ether 11 (4.08 g, 94%) as a light yellow liquid.

$[\alpha]_D^{25} -15.5$ (c 0.95, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.21 (d, $J = 8.3$ Hz, 2H), 6.83 (d, $J = 9.1$ Hz, 2H), 5.77 (m, 1H), 5.09-5.00 (m, 2H), 4.40 (s, 2H), 3.78 (s, 3H), 3.56-3.44 (m, 2H), 3.38 (m, 1H), 3.32 (s, 3H), 2.25 (t, $J = 6.3$ Hz, 2H), 1.8-1.63 (m, 2H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 159.0, 134.4, 130.5, 129.1, 116.9, 113.6, 77.3, 72.5, 66.4, 56.6, 55.1, 37.8, 33.8 ppm; IR (neat, KBr) 3074, 2932, 2854, 2837, 1613, 1513, 1464, 1248, 1094, 1036, 915, 821 cm$^{-1}$; ESI HRMS $m/z$ calcd. for C$_{15}$H$_{22}$NaO$_3$ [M + Na]$^+$: 273.1461, found 273.1455.

(R,E)-5-Methoxy-7-(4-methoxybenzylidencyclohept-2-enal (12):  

\[
\text{OHC} \quad \text{OPMB}
\]

To a solution of methyl ether compound 11 (4.0 g, 16.0 mmol) in CH$_2$Cl$_2$ (10 mL) was added Hoveyda-Grubbs catalyst (0.98 mg, 1.6 mmol) followed by acrolein (9.0 g, 160.0 mmol) at room temperature under nitrogen atmosphere and the resulting mixture was stirred at the same temperature for 3 h. After completion of the reaction (monitored by TLC), it was concentrated to dryness under reduced pressure and the crude oil was directly purified by short flash column chromatography over silica gel (ethyl acetate: hexane = 1:7) furnished the desired $\alpha,\beta$ unsaturated aldehyde 12 (4.1 g, 92%) as a colorless liquid.

$[\alpha]_D^{25} -10.4$ (c 0.55, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.48 (d, $J = 7.9$ Hz, 1H), 7.20 (d, $J = 8.5$ Hz, 2H), 6.84 (d, $J = 8.5$ Hz, 2H), 6.78 (m, 1H), 6.12 (dd, $J = 7.9$, 15.9 Hz, 1H), 4.40 (s, 2H), 3.79 (s, 3H), 3.57-3.42 (m, 3H), 3.33 (s, 3H), 2.63-2.40 (m, 2H),
1.85-1.63 (m, 2H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 193.7, 159.1, 154.4, 134.8, 129.2, 113.7, 76.6, 72.6, 66.0, 56.9, 55.1, 36.7, 34.0 ppm; IR (neat, KBr) 2935, 2861, 2837, 2740, 1690, 1513, 1248, 1093, 1034, 821 cm$^{-1}$; ESI HRMS m/z calcd. for C$_{16}$H$_{22}$NaO$_4$ [M+Na]$^+$: 301.1410, found 301.1407.

(E)-Ethy 3-((2$R$,3$R$)-3-((S)-2-methoxy-4-(4-methoxybenzyloxy)butyl)oxiran-2-yl)acrylate (13):

$$
\text{EtO}_2\text{C} \begin{array}{c}
\text{OMe}
\end{array}
\text{OPMB}
$$

To a stirred solution of $\alpha,\beta$ unsaturated aldehyde 12 (3.9 g, 14.03 mmol) in CH$_2$Cl$_2$ (40 mL) at 0 °C was added TMS-protected diphenyl prolinol catalyst (0.46 g, 1.40 mmol) followed by H$_2$O$_2$ (35 % aq., 1.23 mL, 18.23 mmol). The reaction mixture was stirred vigorously at room temperature until total consumption of the starting material (monitored by TLC). Then Ph$_3$P=CHCO$_2$Et (5.8 g, 16.83 mmol) was added in one portion at 0 °C and stirred for another 1 h at room temperature. After removal of the solvents under reduced pressure, the residue was purified by column chromatography over silica gel (ethyl acetate: hexane = 1:8) to give the desired epoxy compound 13 (3.69 g, 80%) as a colorless oil.

$\left[\alpha\right]_{D}^{25} +5.4$ (c 1.25, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.19 (d, $J = 8.5$ Hz, 2H), 6.82 (d, $J = 8.5$ Hz, 2H), 6.64 (dd, $J = 6.8$, 15.3 Hz, 1H), 6.07 (d, $J = 15.9$ Hz, 1H), 4.39 (s, 2H), 4.18 (q, $J = 6.7$ Hz, 2H), 3.79 (s, 3H), 3.55-3.41 (m, 3H), 3.34 (s, 3H), 3.17 (d, $J = 7.6$ Hz, 1H), 2.97 (dd, $J = 6.8$, 15.4 Hz, 1H), 1.86-1.64 (m, 4H), 1.29 (t, $J = 7.6$ Hz, 3H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 165.6, 159.2, 144.5, 130.4, 129.3, 123.8, 113.8, 75.9, 72.7, 66.1, 60.6, 58.6, 57.4, 56.7, 55.2, 37.0, 34.4, 14.2 ppm; IR (neat, KBr) 2979, 2935,
2861, 1720, 1657, 1613, 1513, 1303, 1249, 1182, 1092, 1035, 853, 821 cm⁻¹; ESI HRMS m/z calcd. C₂₀H₂₈NaO₆ for [M + Na]⁺: 387.1778, found 387.1791.

(4S,5R,7S,E)-Ethyl 5-hydroxy-7-methoxy-9-(4-methoxybenzyloxy)-4-methylnon-2-enoate (14):

The epoxy compound 13 (3.5 g, 9.3 mmol) was taken in a 250 mL RB and to it, CH₂Cl₂ (70 mL) was added under nitrogen atmosphere. The reaction mixture was cooled to −40 °C. Trimethyl aluminium (46.6 mL, 93.1 mmol, 2M in toluene) was slowly added under nitrogen atmosphere at the same temperature. After 10 min, H₂O (1.0 mL, 55.9 mmol) was added very carefully and slowly so that the internal temperature did not change. After effervescence ceased, it was allowed to stir for further 3 h at −40 °C and TLC showed the complete consumption of the starting material. It was quenched very slowly with saturated NH₄Cl (50 mL) and diluted with CH₂Cl₂ (100 mL). HCl (1.0 N, 50 mL) was added and vigorously stirred until a clear separation of the two layers took place. The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (2 x 100 mL). The combined organic layer was washed with brine (2 x 100 mL), dried over anhydrous Na₂SO₄, evaporated to dryness and then purified by silica gel column chromatography (ethyl acetate: hexane = 1:5) to get the desired product 14 (3.35 g, 92%) as a colorless oil.

\([\alpha]_{D}^{25} -4.5 (c 1.45, \text{CHCl}_3); \quad ^1\text{H} \text{NMR (300 MHz, CDCl}_3) \delta 7.18 (d, J = 8.3 \text{ Hz, 2H}), 6.93 (dd, J = 7.5, 15.9 \text{ Hz, 1H}), 6.82 (d, J = 8.3 \text{ Hz, 2H}), 5.78 (d, J = 15.9 \text{ Hz, 1H}), 4.38 (s, 2H), 4.17 (q, J = 6.8 \text{ Hz, 2H}), 3.85 (m, 1H), 3.79 (s, 3H), 3.61 (m, 1H), 3.51-3.42 (m, 2H), 3.33 (s, 3H), 2.95 (br. s, 1H), 2.31 (m, 1H), 1.92 (m, 1H), 1.77-1.63 (m, 2H), 1.45
(m, 1H), 1.29 (t, J = 6.8 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) δ 166.5, 159.1, 150.6, 130.3, 129.3, 121.8, 113.7, 76.8, 72.7, 71.4, 66.3, 60.2, 57.1, 55.2, 42.8, 36.6, 33.1, 15.5, 14.2 ppm; IR (neat, KBr) 3472, 2936, 2874, 2836, 1713, 1651, 1613, 1513, 1301, 1250, 1180, 1092, 1036, 847, 821 cm$^{-1}$; ESI HRMS m/z calcd. for C$_{21}$H$_{32}$NaO$_6$ [M + Na]$^+$: 403.2096, found 403.2083.

(4S,5R,7S,E)-7-Methoxy-9-(4-methoxybenzyloxy)-4-methylnon-2-ene-1,5-diol:

To a stirred solution of $\alpha,\beta$-unsaturated ester 14 (3.2 g, 8.2 mmol) was dissolved in CH$_2$Cl$_2$ (60 mL) and cooled to −78 °C under nitrogen atmosphere. DIBAL-H (14.5 mL, 20.4 mmol) was slowly added to it over a period of 5 min. After 30 min of stirring at the same temperature, TLC was checked which showed complete consumption of starting material. It was quenched by slow addition of saturated solution of sodium potassium tartrate (50 mL), diluted with CH$_2$Cl$_2$ (40 mL) and allowed to stir at room temperature for another 2 h to get a clear two separated layers. The organic layer was separated and the aqueous layer extracted with CH$_2$Cl$_2$ (3 x 50 mL). The combined organic layer was washed with brine (2 x 75 mL), dried over anhydrous Na$_2$SO$_4$, evaporated to dryness under vacuum which on silica gel column chromatography (ethyl acetate: hexane = 2:3) produced the desired $\alpha,\beta$-unsaturated alcohol (2.43 g, 88%).

$\left[\alpha\right]_D^{25} +3.9$ (c 0.73, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.19 (d, J = 8.9 Hz, 2H), 6.82 (d, J = 8.3 Hz, 2H), 5.60 (d, J = 5.3 Hz, 2H), 4.39 (s, 2H), 4.02 (d, J = 3.8 Hz, 2H), 3.78 (s, 3H), 3.67-3.55 (m, 2H), 3.52-3.41(m, 2H), 3.34 (s, 3H), 2.13 (m, 1H), 1.94-1.63 (m,
2H), 1.61-1.46 (m, 2H), 0.98 (d, J = 6.8 Hz, 3H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$
159.1, 134.3, 130.0, 129.3, 113.7, 76.6, 72.3, 71.9, 66.4, 63.4, 57.1, 55.2, 42.7, 37.1, 33.4,
16.3 ppm; IR (neat, KBr) 3408, 2933, 2871, 1612, 1513, 1302, 1248, 1087, 1035, 847,
821 cm$^{-1}$; ESI HRMS $m/z$ calcd. for C$_{19}$H$_{30}$NaO$_5$ [M + Na]$^+$: 361.1985, found 361.1982.

(4S,5R,7S,E)-5-Hydroxy-7-methoxy-9-(4-methoxybenzyl oxy)-4-methylnon-2-enal
(2):

To a stirred solution of diol (2.35 g, 6.95 mmol) in CH$_2$Cl$_2$ (40 mL) at 0 °C, iodobenzenediacetate (2.46 g, 7.65 mmol) followed by TEMPO (0.217 g, 1.39 mmol) was added and allowed to stir at ambient temperature for 3 h. After conversion of the primary alcohol completely to aldehyde (monitored by TLC), the reaction mixture was quenched with saturated solution of Na$_2$S$_2$O$_3$ (20 mL) and extracted with CH$_2$Cl$_2$ (3 x 40 mL). The combined organic layer was dried over anhydrous Na$_2$SO$_4$ and evaporation of solvent led to crude aldehyde which on purification by short flash chromatography over silica gel (ethyl acetate: hexane = 3:7) afforded aldehyde 2 (2.1 g, 90%) as a thick viscous liquid and used immediately for the next reaction.

$\left[\alpha\right]_D^{25}$ +2.1 (c 1.0, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.49 (d, J = 8.3 Hz, 1H), 7.20
(d, J = 9.1 Hz, 2H), 7.09 (m, 1H), 6.84 (d, J = 9.1 Hz, 2H), 6.08 (m, 1H), 4.40 (s, 2H),
3.84 (m, 1H), 3.80 (s, 3H), 3.64 (m, 1H), 3.52-3.43 (m, 2H), 3.34 (s, 3H), 2.43 (m, 1H),
1.95 (m, 1H), 1.80-1.67 (m, 2H), 1.55-1.44 (m, 2H), 1.10 (d, J = 6.8 Hz, 2H) ppm; $^{13}$C
NMR (75 MHz, CDCl$_3$) $\delta$ 194.1, 160.4, 159.2, 132.9, 130.2, 129.3, 113.7, 80.1, 72.7,
71.6, 66.2, 57.1, 55.2, 43.3, 36.7, 32.9, 15.6 ppm; IR (neat, KBr) 3459, 2936, 2874, 2837,
1689, 1613, 1513, 1302, 1248, 1089, 1034, 821 cm⁻¹; ESI HRMS m/z calcd. for C₁₉H₂₈NaO₅ [M + Na]: 359.1829, found 359.1830.

(2R,3S,6R)-6-Allyl-2-((S)-2-methoxy-4-(4-methoxybenzyloxy)butyl)-3-methyl-3,6-dihydro-2H-pyran (3):

To a stirred solution of δ-hydroxy α,β-unsaturated aldehyde 2 (2.0 g, 5.95 mmol), and allyltrimethyl silane (1.45 mL, 8.93 mmol) in THF (30 mL) was added iodine (0.15 g, 0.59 mmol) at 0 °C and allowed to come to room temperature. After completion of the reaction (as indicated by TLC), it was quenched with saturated solution of Na₂S₂O₃ (10 mL) and diluted with tert-butyl methyl ether (20 mL). The organic layer was separated and the aqueous layer extracted with tert-butyl methyl ether (TBME) (2 x 40 mL). The combined organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give pale yellow oil. This was finally purified by column chromatography over silica gel (ethyl acetate: hexane = 1:19) to obtain the cyclized product 3 (2.1 g, 96%).

[α]D²⁵ +14.2 (c 0.8 , CHCl₃); ¹H NMR (300 MHz, CDCl₃); δ 7.27 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 5.86 (m, 1H), 5.70-5.59 (m, 2H), 5.16-5.00 (m, 2H), 4.45-4.38 (m, 2H), 4.16 (m, 1H), 3.81-3.74 (m, 3H), 3.62 (m, 1H), 3.57-3.46 (m, 3H), 3.36-3.26 (m, 3H), 2.41 (m, 1H), 2.26 (m, 1H), 2.00-1.66 (m, 4H), 1.53 (m, 1H), 0.97 (d, J = 7.2 Hz, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃); δ 159.0, 135.2, 131, 130.6, 129.2, 127.9, 116.7, 113.7, 74.8, 72.6, 71.5, 71.0, 66.5, 57.0, 55.2, 38.8, 38.8, 34.2, 34.0, 18.0 ppm; IR (neat,
KBr) 3482, 2925, 2857, 1729, 1612, 1513, 1459, 1367, 1300, 1247, 1178, 1091, 1037, 914, 820, 723 cm
−1; ESI-HRMS m/z calcd. for C22H32NaO4 [M + Na]⁺: 383.2198, found 383.2195.

2-((2R,5S,6R)-6-((S)-2-methoxy-4-(4-methoxybenzyloxy)butyl)-5-methyl-5,6-dihydro-2H-pyran-2-yl)acetaldehyde (15):

![Chemical Structure]

To a stirred solution of the compound 3 (1.8 g, 5.0 mmol) in 1,4-dioxane (25 mL) was added 2,6-lutidine (2.33 mL, 20.0 mmol) at room temperature. NaIO₄ (4.28 g, 20.0 mmol) was dissolved in distilled water (10 mL) and then added to the above reaction mixture. Finally, OsO₄ (0.5 mL, 0.5 mmol, 1 M solution in toluene) was added and stirring was continued for 3 h under dark at room temperature. After completion of the reaction (as indicated by TLC), the reaction mixture was quenched with saturated aq. NaHSO₃ (30 mL) solution. Organic solvent was removed under reduced pressure and the residual aqueous layer was extracted with t-butyl methyl ether (3 x 50 mL). The combined organic layer was washed with 1 N HCl (3 x 50 mL) to remove excess 2,6-lutidine. The organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain the crude mass which was passed through a small pad of silica gel (ethyl acetate: hexane = 1:3) to afford aldehyde 15 as a colorless liquid which was immediately used for the next step.
2-((2R,5S,6R)-6-((S)-2-Methoxy-4-(4-methoxybenzyl)oxy)butyl)-5-methyl-5,6-dihydro
-2H-pyran-2-yl)acetic acid:

To a solution of aldehyde 15 (1.78 g, 4.92 mmol) in tert-butyl alcohol (25 mL), 2-methyl-2-butene (5.8 mL, 5.8 mmol, 1 M solution in THF) was added at room temperature. NaH₂PO₄ (1.8 g, 11.6 mmol) and sodium chlorite (0.59 g, 7.38 mmol) were dissolved in water (10 mL) to make a clear solution which subsequently added to the reaction mixture at 0 °C. It was then allowed to stir for further 3 h at room temperature. The reaction mixture was diluted with water (15 mL). The organic solvent was removed under reduced pressure and the aqueous layer extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate: hexane = 2:5) to afford the acid (1.53 g, 81% over two steps) as a colorless oil.

\[ \alpha \text{D}^{25} +28.9 \ (c \ 1.16, \ CHCl₃) \]; \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 7.24 (d, \( J = 8.3 \) Hz, 2H), 6.84 (d, \( J = 8.3 \) Hz, 2H), 5.66 (s, 2H), 4.60 (m, 1H), 4.42 (s, 2H), 3.79 (s, 3H), 3.36-3.41 (m, 4H), 3.31 (s, 3H), 2.64 (dd, \( J = 9.1, 15.1 \) Hz, 1H), 2.45 (dd, \( J = 4.5, 15.1 \) Hz, 1H), 1.98 (t, \( J = 6.8 \) Hz, 1H), 1.81 (q, \( J = 6.0 \) Hz, 1H), 1.72 (m, 1H), 1.52 (dt, \( J = 1.5, 9.0 \) Hz, 1H), 0.96 (d, \( J = 6.8 \) Hz, 1H) ppm; \(^{13}\)C NMR (75 MHz, CDCl₃) \( \delta \) 174.8, 159.1, 132.1, 130.3, 129.3, 126.6, 113.7, 75.1, 72.7, 71.5, 68.7, 66.6, 56.6, 55.2, 39.0, 38.0, 34.1, 34.0, 17.7 ppm; IR (neat, KBr) 3029, 2931, 2876, 1732, 1713, 1612, 1513, 1301, 1248, 1094,
1035, 847, 821 cm\(^{-1}\); ESI HRMS \emph{m/z} calcd. for C\(_{21}H_{30}NaO_6\) [M + Na]: 401.1935, found 401.1949.

**Methyl 2-((2\textit{R},5\textit{S},6\textit{R})-6-((\textit{S})-2-methoxy-4-(4-methoxybenzyloxy)butyl)-5-methyl-5,6-dihydro-2\textit{H}-pyran-2-yl)acetate (16):**

![Chemical Structure](image)

To a stirred solution of acid (1.3 g, 3.44 mmol) in ether at 0 °C, was added freshly prepared diazomethane solution in ether (25 mL). It was stirred for 10 min at the same temperature and then quenched with saturated solution of Na\(_2\)S\(_2\)O\(_3\) (10 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h to evaporate excess diazomethane. The organic layer was separated and the aqueous layer extracted with diethyl ether (2 x 40 mL). The combined organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na\(_2\)SO\(_4\) and evaporated under reduced pressure to get the crude mass. The crude mass was purified by silica gel column chromatography (ethyl acetate: hexane = 1:8) to afford methyl ester 16 (1.29 g, 96%) as a light yellow liquid.

\([\alpha]_D^{25} +25.1 \,(c\;2.0,\;CHCl_3)\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.20 (d, \(J = 9.0\) Hz, 2H), 6.81 (d, \(J = 8.3\) Hz, 2H), 2.64 (s, 2H), 4.58 (m, 1H), 4.39 (s, 2H), 3.78 (s, 3H), 3.64 (s, 3H), 3.55-3.36 (m, 4H), 3.32 (s, 3H), 2.61 (dd, \(J = 9.1, 15.1\) Hz, 1H), 2.41 (dd, \(J = 4.5, 15.1\) Hz, 1H), 1.98-1.42 (m, 5H), 0.97 (d, \(J = 6.8\) Hz, 3H) ppm; \(^1^3\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 171.5, 159.1, 132.1, 131.9, 129.2, 127.0, 113.7, 74.8, 72.6, 71.3, 68.7, 66.6, 57.0, 55.2, 51.6, 39.1, 38.8, 36.7, 34.1, 17.8 ppm; IR (neat, KBr) 3027, 2951, 2875, 1737, 1612,
Pd/C (10%) (50 mg) was added to a stirred solution of the compound 16 (1.2 g, 3.06 mmol) in toluene (20 mL) followed by catalytic amount of triethylamine at room temperature under hydrogen atmosphere. The mixture was stirred for 1 h at room temperature. After complete consumption of the starting material (monitored by TLC), the black reaction mass was filtered through a pad of Celite and then thoroughly washed with ethyl acetate (3 x 15 mL). The filtrate was concentrated under reduced pressure and purification of the crude product by silica gel column chromatography (ethyl acetate: hexane = 1:7) furnished the desired product 17 (1.12 g, 93%) as a colorless liquid. 

$\left[\alpha\right]_D^{25} +30.4 \ (c \ 1.9, \text{CHCl}_3); \ ^1H \text{ NMR} \ (300 \ MHz, \text{CDCl}_3) \ \delta \ 7.29 \ (d, \ J = 8.5 \ Hz, 2H), \ 6.88 \ (d, \ J = 8.7 \ Hz, 2H), \ 4.47 \ (s, \ 2H), \ 4.26 \ (m, \ 1H), \ 3.86 \ (m, \ 3H), \ 3.60-3.42 \ (m, \ 4H), \ 3.37 \ (s, \ 3H), \ 2.70 \ (dd, \ J = 8.1, \ 14.9 \ Hz, \ 1H), \ 2.50 \ (dd, \ J = 5.8, \ 14.9 \ Hz, \ 1H), \ 1.89-1.32 \ (m, \ 7H), \ 1.03 \ (d, \ J = 6.2 \ Hz, \ 3H) \ ppm; \ ^{13}C \text{ NMR} \ (75 \ MHz, \text{CDCl}_3) \ \delta \ 171.9, \ 159.1, \ 130.7, \ 129.2, \ 113.7, \ 74.9, \ 73.3, \ 72.6, \ 68.0 \ 66.7, \ 57.2, \ 55.2, \ 51.5, \ 38.3, \ 38.2, \ 34.3, \ 33.6, \ 27.5, \ 26.3, \ 18.3 \ ppm; \ IR \ (\text{neat, KBr}) \ 2933, \ 2873, \ 1740, \ 1612, \ 1513, \ 1460, \ 1301, \ 1248, \ 1171, \ 1092, \ 1036, \ 846, \ 821 \ cm^{-1}; \ ESI \text{ HRMS} \ m/z \ \text{calcd. for C}_{22}\text{H}_{34}\text{NaO}_6 \ [\text{M + Na}^+]^+: \ 417.2248, \ \text{found} \ 417.2240.$
Dimethyl 3-((2S,5S,6R)-6-((S)-2-methoxy-4-(4-methoxybenzyl)oxy)butyl)-5-methyl-tetrahydro-2H-pyran-2-yl)-2-oxopropylphosphonate (18):

To a stirred solution of the dimethyl methyl phosphonate (1.26 g, 10.15 mmol) in THF (30 mL), n-BuLi (4.1 mL, 10.15 mmol, 2.5 M in hexane) was slowly added at −78 °C under nitrogen atmosphere and allowed to slowly warm to 0 °C. After 1 h, the reaction mixture was again cooled to −78 °C and to it, ester 17 (1.0 g, 2.54 mmol) dissolved in THF (15 mL) was slowly added and stirred at the same temperature for 1 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was quenched with saturated NH₄Cl (30 mL), diluted with ethyl acetate (50 mL) and allowed to come to room temperature. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine (100 mL) and dried over Na₂SO₄. The organic layer was concentrated under reduced pressure to obtain the crude mass which on purification by silica gel column chromatography (ethyl acetate: hexane = 5:1) afforded the desired keto phosphonate 18 (1.12 g, 92%) as a colorless liquid which was immediately used for next step without further characterization.

To a stirred solution of the keto phosphonate 18 (1.0 g, 2.06 mmol) in THF (20 mL) was added NaHMDS (2.67 mL, 2.67 mmol, 1M in THF) at −78 °C under nitrogen atmosphere and allowed to come to 0 °C. After 1 h, the reaction mixture was again cooled to −78 °C and isovaleraldehyde (0.354 g, 4.12 mmol) was slowly added to it and stirred at the same temperature for 1 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was quenched with saturated NH₄Cl (20 mL), diluted with ethyl acetate (50 mL) and allowed to come to room temperature. The two layers were separated and the aqueous layer extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine (2 x 50 mL) and dried over anhydrous Na₂SO₄. The organic layer was concentrated to dryness under reduced pressure to get the crude product which on purification by silica gel column chromatography (ethyl acetate: hexane = 1:6) furnished the desired keto 19 (0.74 g, 81%) as a colorless liquid.

\[ \alpha \] \text{D}^{25} +19.1 (c 1.4, CHCl₃); \text{¹H NMR (300 MHz, CDCl₃) } \delta 7.27 (d, J = 8.3 Hz, 2H), 6.87 (d, J = 8.3 Hz, 2H), 6.81 (dd, J = 8.3, 15.9 Hz, 1H), 6.11 (d, J = 15.9 Hz, 1H), 4.43 (s, 2H), 4.30 (m, 1H), 3.80 (s, 3H), 3.56-3.46 (m, 4H), 3.30 (s, 3H), 2.90 (dd, J = 6.8, 15.9 Hz, 1H), 2.70 (dd, J = 6.8, 15.9 Hz, 1H), 2.09 (t, J = 6.8 Hz, 2H), 1.85-1.24 (m, 10H), 0.96 (d, J = 6.0 Hz, 3H), 0.92 (dd, J = 6.8, 15.9 Hz, 6H) ppm; \text{¹³C NMR (75 MHz, CDCl₃) } \delta
To a 50 mL round bottom flask charged with a magnetic stir bar was added S-CBS catalyst (0.087 g, 0.314 mmol) in THF (15 mL) under argon. The reaction was cooled to –20 °C and BH$_3$•Me$_2$S (1.57 mL, 3.14 mmol, 2M in THF) was added. To this reaction mixture, a solution of ketone 19 (0.71 g, 1.57 mmol) dissolved in THF (8 mL) was added dropwise. The reaction was stirred for 8 h at –20 °C and TLC checked which showed complete consumption of the starting material. MeOH (5 mL) was carefully added to quench excess BH$_3$. The reaction was diluted with saturated aqueous NH$_4$Cl (20 mL) and extracted with ethyl acetate (3 x 40 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried with anhydrous Na$_2$SO$_4$, and concentrated under reduced pressure. The crude oil was purified by silica gel column chromatography (ethyl acetate: hexane = 1:5) giving the desired alcohol 7 (0.576 g, 82%) as a colorless liquid.
$\alpha_D^{25} +17.9 \ (c \ 0.9, \text{CHCl}_3)$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.26 (d, $J = 8.3$ Hz, 2H), 6.87 (d, $J = 8.3$ Hz, 2H), 5.62 (m, 1H), 5.46 (dd, $J = 6.0, 15.3$ Hz, 1H), 4.44 (s, 2H), 4.33 (m, 1H), 3.95 (m, 1H), 3.80 (s, 3H), 3.67-3.57 (m, 2H), 3.57-3.50 (t, $J = 6.0$ Hz, 2H), 3.35 (s, 3H), 1.94-1.32 (m, 14H), 1.01 (d, $J = 6.2$ Hz, 3H), 0.87 (d, $J = 6.6$ Hz, 6H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 159.1, 134.2, 133.8, 130.3, 129.4, 113.7, 74.9, 73.6, 72.6, 68.7, 66.9, 66.5, 57.2, 55.2, 41.6, 40.8, 37.3, 34.0, 32.9, 28.2, 27.5, 26.0, 22.3, 22.2, 18.5 ppm; IR (neat, KBr) 3454, 2951, 2929, 2869, 1613, 1513, 1302, 1248, 1090, 1038, 820 cm$^{-1}$; ESI HRMS $m/z$ calcd. for C$_{27}$H$_{44}$NaO$_5$ [M + Na]$^+$: 471.3081, found 471.3069.

$(R)$-tert-Butyl(1-(4-methoxybenzyloxy)hex-5-en-3-yloxy)dimethylsilane (20):

To a stirred solution of alcohol 10 (0.5 g, 2.12 mmol) in CH$_2$Cl$_2$ (30 mL) under nitrogen atmosphere, was added 2,6-lutidine (0.6 mL, 5.29 mmol) followed by TBSOTf (0.97 mL, 4.24 mmol) at 0 $^\circ$C and allowed to stir for 30 min. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with water (20 mL) and diluted with CH$_2$Cl$_2$ (50 mL). The organic layer was separated and quickly washed with 1 N HCl (2 x 50 mL) to remove excess 2,6-lutidine. The organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na$_2$SO$_4$, evaporated to dryness under vacuum to obtain the crude product which on purification by silica gel column chromatography purification (ethyl acetate: hexane produced = 1:19) furnished the desired TBS ether 20 (0.69 g, 93%).

$\alpha_D^{25} -8.1 \ (c \ 0.33, \text{CHCl}_3)$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.19 (d, $J = 9.1$ Hz, 2H), 6.81 (d, $J = 8.3$ Hz, 2H), 5.77 (m, 1H), 5.04-4.96 (m, 2H), 4.36 (q, $J = 7.5$, 18.8 Hz, 2H), 3.87
(m, 1H), 3.78 (s, 3H), 3.45 (m, 2H), 2.19 (m, 2H), 1.68 (m, 2H), 0.87 (s, 9H), 0.03 (d, J = 3.7 Hz, 6H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) δ 159.0, 134.9, 130.6, 129.2, 116.9, 113.6, 72.5, 68.9, 66.6, 55.1, 42.2, 36.6, 25.8, 18.0, −4.4, −4.8; IR (neat, KBr) 3075, 2999, 2953, 2930, 2857, 1613, 1513, 1463, 1249, 1093, 1040, 912, 836 cm$^{-1}$; ESI HRMS m/z calcd. for C$_{20}$H$_{34}$NaO$_3$Si [M + Na]$^+$: 373.2169, found 373.2181.

**(R)-3-(tert-Butyldimethylsilyloxy)hex-5-en-1-ol (21):**

To a solution of PMB protected compound 20 (0.55 g, 1.57 mmol) in CH$_2$Cl$_2$ (20 mL) and water (2 mL) was added DDQ (0.535 g, 2.36 mmol) at room temperature and allowed to stir for 2 h at the same temperature. After completion of the reaction, it was quenched with saturated NaHCO$_3$ (20 mL) solution. The two layers were separated and the aqueous layer extracted with CH$_2$Cl$_2$ (2 x 30 mL). The combined organic layer was washed with brine (2 x 40 mL), dried over anhydrous Na$_2$SO$_4$ and evaporated to dryness to give red colored crude product which on purification by silica gel column chromatography (ethyl acetate: hexane = 1:7) to afford the desired primary alcohol 21 (0.34 g, 94%) as a colorless liquid.

$[^{[a]}]D_{25}^{25} = -26.0$ (c 0.46, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) δ 5.74 (m, 1H), 5.09-4.99 (m, 2H), 3.95 (m, 1H), 3.83-3.62 (m, 2H), 2.28 (t, J = 6.6 Hz, 2H), 2.16 (br s, 1H), 1.76 (m, 1H), 1.63 (m, 1H), 0.89 (s, 9H), 0.09 (d, J = 2.4 Hz, 6H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) δ 134.5, 117.2, 71.0, 59.9, 41.6, 25.7, 35.7, 17.9, −4.5, −4.9 ppm; IR (neat, KBr) 3350, 3078, 2953, 2930, 2858, 1641, 1463, 1255, 1071 cm$^{-1}$; ESI HRMS m/z calcd. for C$_{12}$H$_{26}$NaO$_2$Si [M + H]$^+$: 231.1780, found 231.1775.
(R)-3-(tert-Butyldimethylsilyloxy)hex-5-enal (22):

\[
\begin{align*}
\text{CHO} \\
\text{OTBS}
\end{align*}
\]

To a stirred solution of primary alcohol 21 (0.25 g, 1.09 mmol) and solid anhydrous NaHCO₃ (1.0 g) in CH₂Cl₂ (25 mL) at 0 °C, was added Dess-Martin periodinane (0.69 g, 1.63 mmol). The reaction mixture was stirred at 0 °C for 3 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through a Celite bed and washed with CH₂Cl₂ (50 mL). The filtrate was washed with saturated NaHCO₃ (2 x 30 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 40 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and solvent removed under reduced pressure to get crude aldehyde 22 (0.24 g) as a pale yellow liquid which was directly used in the next step.

(R)-3-(tert-Butyldimethylsilyloxy)hex-5-enoic acid (8):

\[
\begin{align*}
\text{CO₂H} \\
\text{OTBS}
\end{align*}
\]

To a solution of aldehyde 22 (0.24 g, 1.05 mmol) in tert-butyl alcohol (15 mL), 2-methyl-2-butene (1.59 mL, 1.56 mmol, 1M solution in THF) was added at room temperature. Sodium dihydrogen phosphate (0.49 g, 3.15 mmol) and sodium chlorite (0.14 g, 1.56 mmol) were dissolved in water (5 mL) to make a clear solution which subsequently added to the reaction mixture at 0 °C. It was allowed to stir for further 3 h at room temperature. After completion of the reaction (monitored by TLC), it was diluted with ethyl acetate (30 mL). The two layers were separated and the aqueous layer extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (2 x 19)}
(50 mL), dried over anhydrous Na$_2$SO$_4$ and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography over silica gel (ethyl acetate: hexane = 1:9) to afford the desired acid 8 (0.22 g, 86% over two steps) as a colorless oil. 

$[\alpha]_D^{25} -18.9$ (c 0.7, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.78 (m, 1H), 5.12-5.02 (m, 2H), 4.18 (m, 1H), 2.52-2.37 (m, 2H), 2.28 (t, $J = 6.8$ Hz, 2H), 0.86 (s, 9H), 0.06 (d, $J = 6.6$ Hz, 6H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 177.6, 133.7, 118.1, 68.8, 41.9, 41.7, 25.7, 17.9, −4.5, −5.0; IR (neat, KBr) 3079, 2956, 2930, 2858, 1713, 1642, 1463, 1256, 1089 ppm; ESI HRMS $m/z$ calcd. for C$_{12}$H$_{24}$NaO$_3$ [M + Na]$^+$: 267.1387, found 267.1385.


To a stirred solution of the acid 8 (0.49 g, 2.01 mmol) in dry toluene (10 mL) at 0 °C, Et$_3$N (0.31 mL, 4.02 mmol) followed by 2,4,6-trichlorobenzoyl chloride (0.63 mL, 4.02 mmol) was added and stirred for 30 min at room temperature. DMAP (1.22, 10.04 mmol) and alcohol 7 (0.45 g, 1.004 mmol) was dissolved in dry toluene (10 mL) and this was added to the above mentioned solution at 0 °C and allowed to stir at room temperature for 6 h. After completion of the reaction (monitored by TLC), it was diluted with ethyl acetate (50 mL) and water (25 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 x 40 mL). The combined organic layer was
washed with Na$_2$CO$_3$ (2 x 250 mL), brine (2 x 50 mL), dried over anhydrous Na$_2$SO$_4$ and solvent evaporated under reduced pressure to give a colorless oil which on purification by silica gel column chromatography (ethyl acetate: hexane = 1:12) furnished the desired coupled product 23 (0.63 g, 93%, based on the starting alcohol) as a colorless liquid.

$[\alpha]_D^{25} +14.3$ (c 0.7, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.21 (d, $J = 8.5$ Hz, 2H), 6.81 (d, $J = 8.9$ Hz, 2H), 5.83-5.62 (m, 2H), 5.40-5.19 (m, 2H), 5.07-4.99 (m, 2H), 4.39 (s, 2H), 4.16 (m, 1H), 3.81 (m, 1H), 3.78 (s, 3H), 3.60-3.42 (m, 3H), 3.36 (s, 3H), 2.41-2.35 (m, 2H), 2.31-2.18 (m, 2H), 2.01-1.23 (m, 14H), 0.92-0.83 (m, 18H), 0.03 (d, $J = 15.8$ Hz, 6H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.7, 159.0, 134.3, 132.9, 129.7, 129.2, 128.2, 117.6, 113.7, 74.3, 72.6, 71.8, 68.7, 67.7, 66.5, 56.8, 55.2, 42.3, 41.9, 41.5, 38.8, 36.5, 34.7, 33.5, 28.2, 28.0, 26.9, 25.8, 22.3, 22.2, 18.2, 18.0, −4.6, −4.8 ppm; IR (neat, KBr) 3076, 2953, 2928, 2856, 1734, 1613, 1513, 1463, 1302, 1249, 1171, 1091, 1037, 836 cm$^{-1}$; ESI HRMS $m/z$ calcd. for C$_{39}$H$_{70}$NO$_7$Si [M + NH$_4$]$^+$: 692.4916, found 692.4883.


To a solution of the compound 23 (0.31 g, 0.445 mmol) in CH$_2$Cl$_2$ (15 mL) and water (1 mL) at 0 °C, was added DDQ (0.152 g, 0.667 mmol) and allowed to stir for 2 h at room
temperature. The reaction mixture was quenched with saturated NaHCO₃ solution (10 mL) and diluted with CH₂Cl₂ (15 mL). The two layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 25 mL). The combined organic layer was washed with brine (2 x 40 mL), dried over anhydrous Na₂SO₄ and evaporated to give red colored crude product which on purification by silica gel column chromatography (ethyl acetate: hexane = 1:5) afforded the desired primary alcohol 24 (0.23 g, 95%) as a colorless liquid. [α]D²⁵ +23.0, (c = 0.52, CHCl₃); IR (neat, KBr) 3466, 3077, 2953, 2930, 1734, 1641, 1462, 1253, 1171, 1087, 836 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 5.87-5.62 (m, 2H), 5.43-5.26 (m, 2H), 5.08-4.99 (m, 2H), 4.17 (m, 1H), 3.87-3.72 (m, 2H), 3.72-3.60 (m, 2H), 3.42 (s, 3H), 3.6 (m, 2H), 2.41 (d, J = 5.5 Hz, 2H), 2.34-2.15 (m, 2H), 2.06-1.24 (m, 14H), 0.94 (d, J = 5.7 Hz, 3H), 0.9-0.8 (m, 15H), 0.04 (d, J = 11.9 Hz, 6H) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 171.1, 134.3, 133.0, 129.5, 117.6, 76.4, 72.9, 71.7, 68.7, 67.5, 59.8, 56.8, 42.2, 41.9, 41.5, 38.0, 36.6, 36.1, 35.1, 34.7, 28.4, 28.2, 28.0, 26.9, 25.8, 22.2, 18.3, −4.6, −4.8 ppm; ESI HRMS m/z calcd. for C₃₁H₅₈NaO₆Si [M + Na]⁺: 577.3895, found 577.3916.

To a stirred solution of primary alcohol 24 (0.15 g, 0.271 mmol) and solid anhydrous NaHCO₃ (0.2 g) in CH₂Cl₂ (10 mL), Dess-Martin periodinane (0.173 g, 4.062 mmol) was added at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 4 h. After completion of reaction (monitored by TLC), the reaction mixture was filtered through a Celite bed and thoroughly washed with CH₂Cl₂ (50 mL). The filtrate was washed with saturated NaHCO₃ (30 mL) solution. The aqueous layer was again extracted with CH₂Cl₂ (2 x 40 mL). The combined organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to get the crude aldehyde 6 (0.16 g) which was immediately used for next step without further purification and characterization.

**Macrolide (4):**

![Macrolide Structure]

TMSOAc (1.71 mL, 11.21 mmol) was added to a solution of aldehyde 6 (0.16 mg, 0.28 mmol) in AcOH (15.0 mL) at room temperature. TESOTf (1.23 mL, 7.02 mmol) was added dropwise to the resulting solution at the same temperature. After 30 min, the reaction mixture was poured into diethyl ether (100 mL) and washed with NaHCO₃ (4 x 100 mL). The aqueous layer was again extracted with diethyl ether (3 x 50 mL). The combined organic layer was washed with brine (2 x 100 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to obtain the crude product which was dissolved in MeOH (10 mL) and then treated with K₂CO₃ (0.37 g, 2.89 mmol) at room temperature.
temperature. The reaction mixture was stirred for 3 h at room temperature. After completion of the reaction (monitored by TLC), it was concentrated under reduced pressure. The residue was dissolved in water (10 mL) and diethyl ether (20 mL). The two layers were separated and the aqueous layer extracted with diethyl ether (3 x 20 mL). The combined organic layer was washed with brine (2 x 25 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was finally purified by flash column chromatography over silica gel (ethyl acetate: hexane = 1:2) to afford the macrolide 4 (0.104 g, 72% over three steps).

[α]D²⁵ +54.7 (c 1.18, EtOH); ¹H NMR (300 MHz, CDCl₃) δ 5.71 (m, 1H), 5.41-5.32 (m, 2H), 3.91 (m, 1H), 3.87 (m, 1H), 3.77-3.66 (m, 1H), 3.59-3.47 (m, 2H), 3.36 (s, 3H), 3.22 (m, 1H), 2.57 (dd, J = 4.5, 13.6 Hz, 1H), 2.44-2.30 (m, 3H), 2.09-1.96 (m, 3H), 1.95-1.83 (m, 4H), 1.36-1.23 (m, 8H), 1.17 (d, J = 6.8 Hz, 3H), 1.03 (m, 1H), 0.85 (d, J = 6.8 Hz, 6H) ppm; ¹³C NMR (150 MHz, CDCl₃) δ 169.3, 132.4, 130.0, 73.6, 73.5, 73.0, 72.2, 70.8, 68.0, 63.0, 57.3, 43.0, 42.8, 41.6, 41.0, 40.8, 39.1, 35.4, 30.9, 28.1, 27.1, 24.1, 22.2, 18.2 ppm; IR (neat, KBr) 3452, 2954, 2925, 2854, 1736, 1643, 1261, 1083, 1034 cm⁻¹; ESI HRMS m/z calcd. for C₉₂H₄₂NaO₆ [M + Na]⁺: 461.2874, found 461.2876.
$^1$H NMR of 9 (CDCl$_3$, 300 MHz)
$^{13}$C NMR of 9 (CDCl$_3$, 75 MHz)
$^1$H NMR of 10 (CDCl$_3$, 300 MHz)
$^{13}$C NMR of 10 (CDCl$_3$, 75 MHz)
$^1$H NMR of 11 (CDCl$_3$, 300 MHz)
$^{13}$C NMR of 11 (CDCl$_3$, 75 MHz)
$^1$H NMR of 12 (CDCl$_3$, 300 MHz)
$^{13}$C NMR of 12 (CDCl$_3$, 75 MHz)
$^1$H NMR of 13 (CDCl$_3$, 400 MHz)
$^{13}$C NMR of 13 (CDCl$_3$, 75 MHz)
$^1$H NMR of 14 (CDCl$_3$, 300 MHz)
$^{13}$C NMR of 14 (CDCl$_3$, 75 MHz)

S 36
$^1$H NMR of allyl alcohol (CDCl$_3$, 300 MHz)
$^{13}$C NMR of allyl alcohol (CDCl$_3$, 75 MHz)
$^1$H NMR of 2 (CDCl$_3$, 300 MHz)
$^{13}C$ NMR of 2 (CDCl$_3$, 75 MHz)
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Detector A Ch1 225nm

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HPLC Chromatogram of 3 (Filter Column)

D:\LabSolutions\Common\Data\Project\mhp\manas-360...
HPLC Chromatogram of 3 (Purification By Column Chromatography)
$^1$H NMR of the acid (CDCl$_3$, 300 MHz)
$^1$H NMR of the acid (CDCl$_3$, 75 MHz)
$^1$H NMR of 16 (CDCl$_3$, 300 MHz)
$^{13}$C NMR of 16 (CDCl$_3$, 75 MHz)
$^1$H NMR of 17 (CDCl$_3$, 300 MHz)
$^{13}\text{C NMR of 17 (CDCl}_3, \text{ 75 MHz)}$
$^1$H NMR of 19 (CDCl$_3$, 300 MHz)
$^{13}$C NMR of 19 (CDCl$_3$, 75 MHz)
$^1\text{H NMR of 7 (CDCl}_3, 300 \text{ MHz)}$
$^{13}$C NMR of 7 (CDCl$_3$, 75 MHz)
$^{1}$H NMR of 20 (CDCl$_3$, 300 MHz)
$^{13}$C NMR of 20 (CDCl$_3$, 75 MHz)
$^1$H NMR of 21 (CDCl$_3$, 300 MHz)
$^{13}$C NMR of 21 (CDCl$_3$, 75 MHz)
$^1$H NMR of 8 (CDCl$_3$, 300 MHz)
$^{13}$C NMR of 8 (CDCl$_3$, 75 MHz)
$^1\text{H NMR of } 23 (\text{CDCl}_3, 400 \text{ MHz})$
$^{13}$C NMR of 23 (CDCl$_3$, 100 MHz)
$^1$H NMR of 24 (CDCl$_3$, 300 MHz)
$^{13}$C NMR of 24 (CDCl$_3$, 75 MHz)
$^1$H NMR of 4 (CDCl$_3$, 300 MHz)
$^{13}$C NMR of 4 (CDCl$_3$, 75 MHz)