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Stereoselective Total Synthesis of an Anti-Fouling Agent, C_2-Symmetricnatural Macrolide Trichobotryside A

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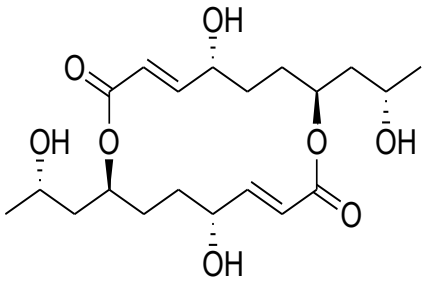
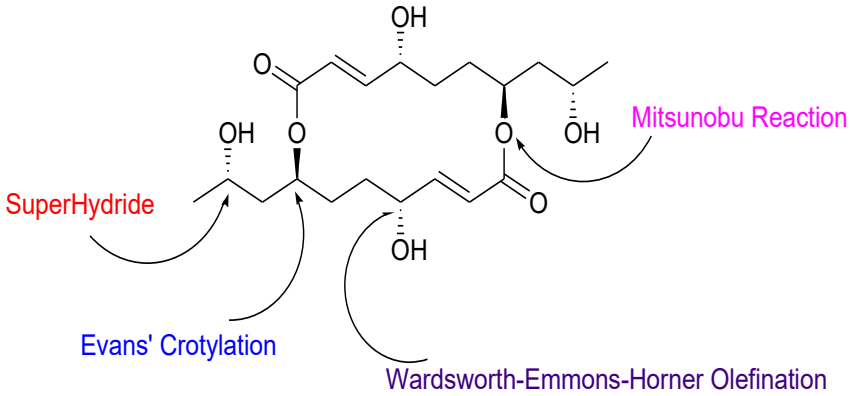
ABSTRACT

A stereoselective total synthesis of 16-membered macrodiolide trichobotryside A has been successfully completed. The key features are: Evans' Crotylation, regioselective epoxide opening, Wardsworth-Emmons-Horner Olefination and Mitsunobu Reaction.





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Keywords: *Macrodiolide; anti-fouling agent; Evans' Crotylation; Super Hydride; regioselective epoxide opening; Wardsworth-Emmons-Horner Olefination; Mitsunobu Reaction.*

Introduction

Marine organisms are a prolific source of structurally diverse and biologically active secondary metabolites, yielding lead compounds across classes such as peptides, terpenoids, steroids, alkaloids, macrolides, and polyketide-derived lactones [1]. Among these, the macropolylides—particularly 16-membered macrodiolides like pyrenophorol, pyrenophorin, and vermiculin—have received attention for their antifungal and anthelmintic properties [2]. A notable addition to this family is trichobotryside A, a C2-symmetric 16-membered macrodiolide isolated from the deep-sea sediment fungus Trichobotrys effusa (strain DFFSCS021) by Qi and co-workers [3]. Trichobotryside A and related analogues were evaluated against several cancer cell lines and herpes simplex virus type 1 (HSV-1), and showed potent antifouling activity by inhibiting the larval settlement of Bugula neritina and Balanus amphitrite (EC50 = 7.3 and 2.5 μg·mL−1, respectively) [3]. The structure was assigned by extensive 1H/13C and 2D NMR (1H–1H COSY, HSQC, HMBC); the absolute configuration was determined by methanolysis followed by the modified Mosher method, and HRMS confirmed the molecular formula ([M+Na]+ m/z 423.1987) [2], [3].

A recent addition to this class is **trichobotryside A**, a C_2-symmetric 16-membered macrodiolide isolated by the Shu-Hua Qi group from the deep-sea sediment-derived fungal strain *Trichobotrys effusa* DFFSCS021, collected from the South China Sea.[4] Trichobotryside A and its analogues were evaluated for their activity against several cancer cell lines and the herpes simplex virus type 1 (HSV-1). Remarkably, trichobotryside A demonstrated potent antifouling activity by inhibiting the larval settlement of *Bugula neritina* and *Balanus amphitrite*, with EC_{50} values of 7.3 μg/mL and 2.5 μg/mL, and LC_{50}/EC_{50} values exceeding 40.5 and 37.4, respectively.[5,6]

The structure of trichobotryside A was elucidated using extensive NMR spectroscopy, including ^1H and ^{13}C NMR, as well as 2D NMR techniques such as ^1H–^1H COSY, HSQC, and HMBC. The absolute configuration was established by methanolysis followed by the modified Mosher's method. High-resolution mass spectrometry (HRMS, ESI^+) confirmed the molecular formula with a $[M+Na]^+$ peak at *m/z* 423.1987.[7–9]

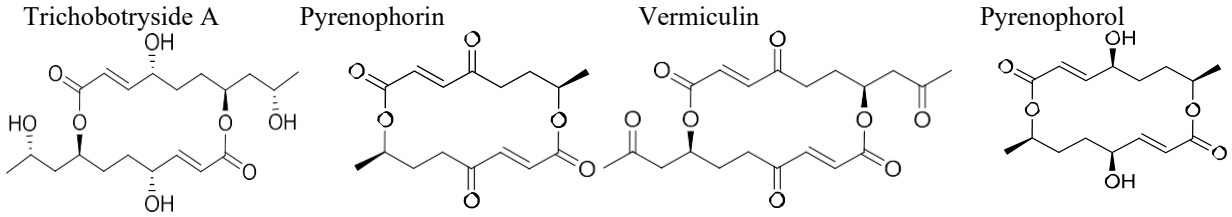
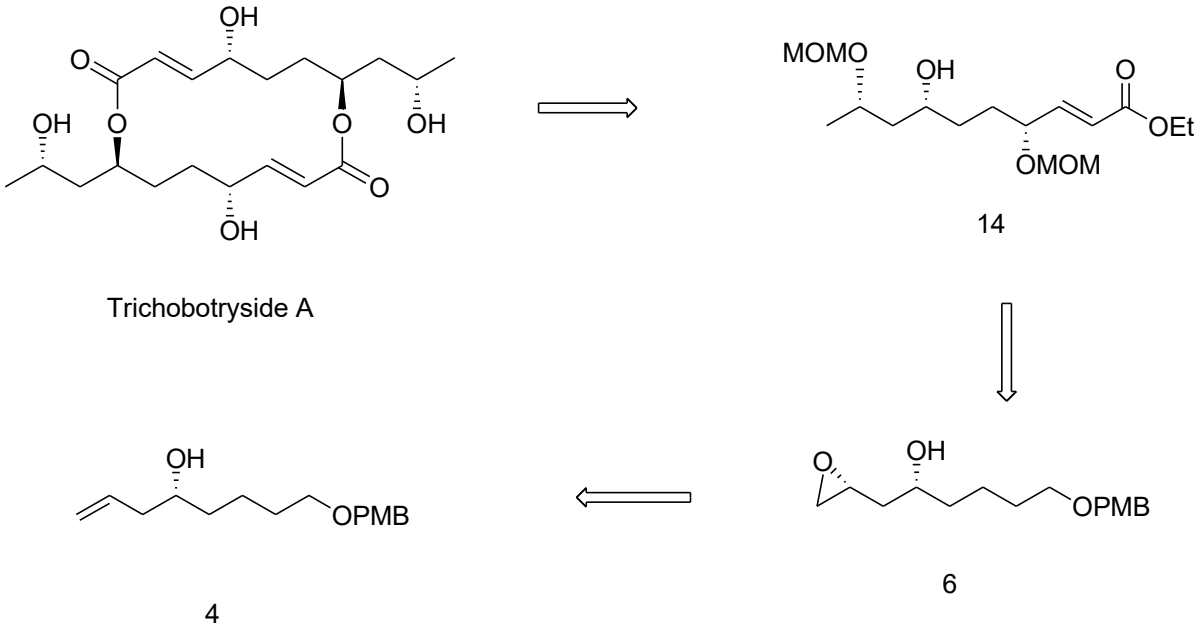


Figure 1. *Representative 16-membered macrodiolides with significant biological activity: trichobotryside A, pyrenophorin, vermiculin, and Pyrenophorol.*

The compelling biological activity and structural features of Trichobotryside A prompted us to undertake its total synthesis**.** We wanted to provide an alternate path which has a smaller number of steps and cost effective materials compare to its previous syntheses. As part of our on-going research program focused on the synthesis of biologically relevant natural products and analogues, we herein report the **stereoselective total synthesis** of trichobotryside A.

Results and Discussion

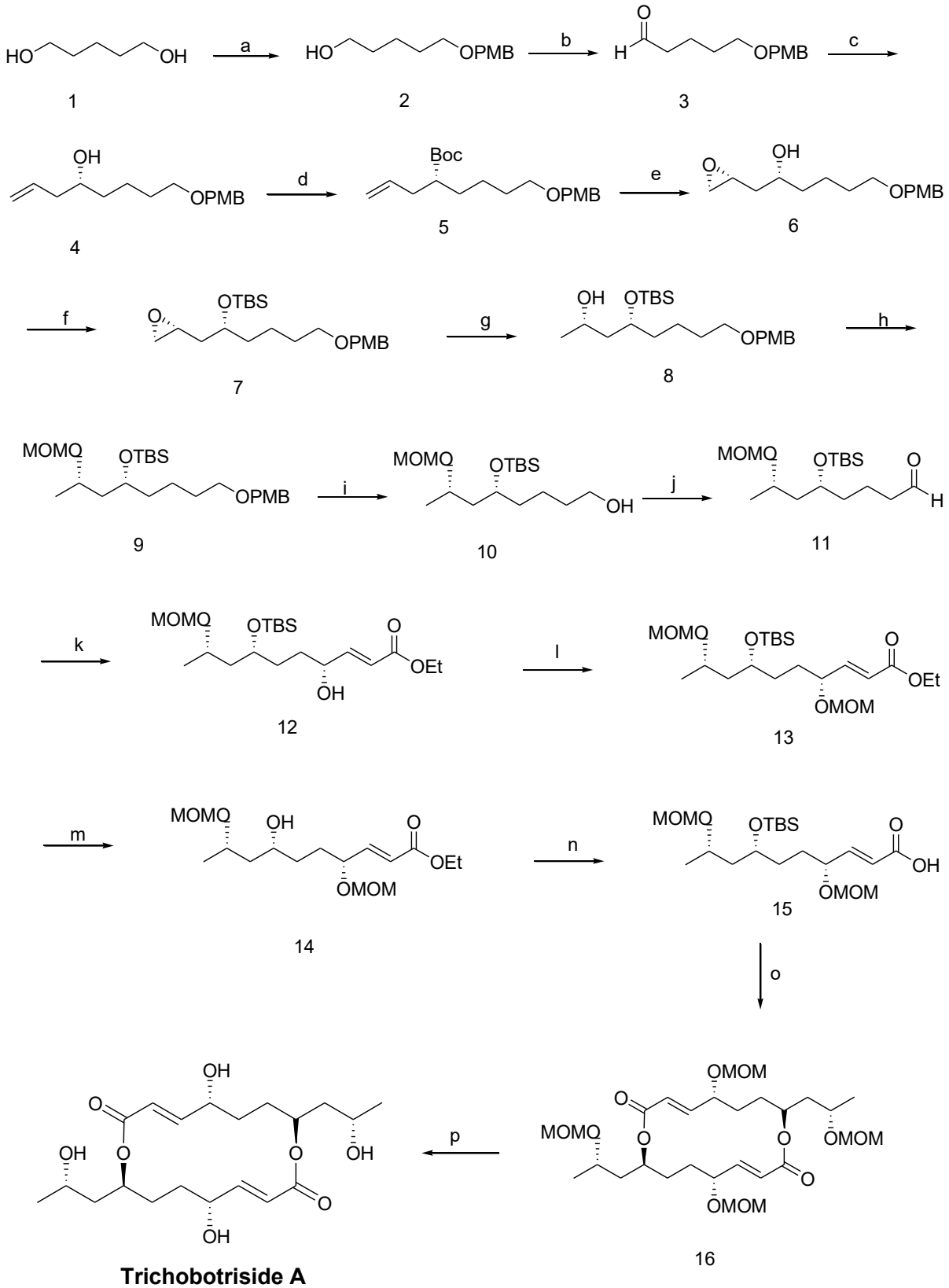
As shown in the retrosynthetic analysis (Scheme 1) trichobotryside A is obtained from monomer **(15)** by subjecting it to Mitsunobu reaction. The intermediate **(10)** has been reached after the Evans' Crotylation and regioselective epoxide opening of cheaply sourced 1,5 - Pentanediol (**1)**



The core synthesis has begun with the formation of enantioselective alcohol(4) from its aldehyde precursor **3** using $TiCl_4$, Allyltrimethylsilane, (Evans' Crotylation) followed by protection of the secondary hydroxyl group with tert-butyloxy carbonyl protecting group leading to the formation of compound **5**. Further, this N-Boc-protected alkene 5 is converted into stereoselective epoxide **6** in quantitative yield, using NIS (N-Iodo Succinamide), Silver Trifolate (AgOTf) and Base (Et3N). Then, the chiral epoxide is opened regioselectively with hydroxylation (super hydride) to yield secondary alcohol **8**, with 93% yield, which is confirmed by H1 NMR. Later, the hydroxyl group is protected by MOM **9** and the PMB group is deprotected to release free the terminal hydroxide **10**, which was further oxidized into aldehyde **11** by the Swern oxidation.

Further, the Aldehyde is subjected to sequential reactions, initially with nitrosobenzene, DMSO and D-proline, thereafter with Triethylphosphonoacetate, DBU and LiCl,CH_3CN resulted in alpha,beta unsaturated ester **12** in 74% yield (97:3, *E*/*Z*). The resulting secondary hydroxyl group in **12** was protected as its MOM ether by treating with methoxymethylchloride and diisopropylethylamine to furnish **13** in 72% yield. After deprotection of the silyl group with TBAF in THF under reflux conditions yielded the ester **14,** which on hydrolysis with 2 N NaOH in MeOH gave acid **15** in 92% yield. Compound **15** in THF was treated with PPh_3 at 0°C, followed by DEAD. The mixture was warmed to rt and stirred for 2.15 h, quenched, and extracted to afford intermediate **16**, which upon MOM deprotection with $TiCl_4$ at 0 °C to rt (2 h) afforded **Trichobotryside A** in 40% yield.

Scheme 2. *Reagents and Conditions*: (a) *PMBCl, NaH, dry THF, rt*, 1 h, 94%; (b) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, -78°C, 3 h; (c) $TiCl_4$, allyltrimethylsilane, dry CH_2Cl_2, -78°C, 1 h, 76%; (d) BOCCl, NaH, dry THF, rt, 3h, 78% ; (e) N-Iodo Succinamide, DCM, $NaHCO_3$, rt, 1h, 74% ; (f) *tert*-butyldimethylsilyl chloride, imidazole, CH_2Cl_2, rt, 4 h, 94%; (g) $LiEt_3BH$(super-Hydride), dry THF, -78 °C, 2h, 93% ; (h) $MeOCH_2Cl$, DIPEA, dry CH_2Cl_2, DMAP, 6 h, 90% ; (i) DDQ, DCM, rt, 2h; (j) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, -78°C, 3h, 67% (k) Nitrosobenzene, DMSO, L-proline Triethylphosphonoacetate, DBU, LiCl, CH3CN, 74% ; (l) $MeOCH_2Cl$, DIPEA, dry CH_2Cl_2, DMAP, 6 h, 72% ; (m) TBAF, dry THF, reflux, 5 h, 95%. (n) NaOH, CH3OH, rt, 3 h, 75%; (o) Mitsunobu Reaction(PPh_3 + DEAD or DIAD), dry THF, Rt, 3h; (p) TiCl4, DCM (CH2Cl2), rt, 3.5 h, 40%.



Conclusion

The stereoselective total synthesis of trichobotryside A, a 16-membered macrodiolide of natural origin, has been achieved in 16 linear steps, affording the target molecule in 0.61% overall yield. The synthesis was enabled by

a sequence of key transformations, including Evans' Crotylation, Super Hydride, regioselective epoxide opening, Wardsworth-Emmons-Horner Olefination, and Mitsunobu Reaction.

Experimental Section

All reactions sensitive to air or moisture were conducted under an inert nitrogen or argon atmosphere using oven-dried glassware. For such reactions, freshly distilled anhydrous solvents were employed, while other reagents were used as received from commercial suppliers. Products were purified by silica gel column chromatography (60–120 mesh) using glass columns.

1H and 13C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 on 400 and 500 MHz spectrometers, respectively, with TMS as an internal standard. Infrared spectra were obtained on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr pellets or thin films. Mass spectra were acquired on a Finnigan MAT 1020 spectrometer operating at 70 eV, while high-resolution mass spectra (HRMS, ESI+) were collected using either a TOF or a double-focusing instrument.

(S)-6-(4-Methoxybenzyloxy)hept-1-en-2-ol (4):

A solution of 1,5-pentanediol (10.4 g, 100 mmol) in dry THF (50 mL) was treated with NaH (1.15 g, 50 mmol) and PMBCl (4.6 mL, 50 mmol, in hexanes) at –78 °C under N_2. The mixture was warmed to 0°C, stirred for 2 h, quenched with sat. NH_4Cl, and extracted. Purification by silica gel chromatography (hexane/EtOAc 5:2) afforded ether 2, which was oxidized with $(COCl)_2$ (3.18 g, 92%) to give aldehyde 3. To a solution of aldehyde 3 (5.6 g, 25.22 mmol) in DMSO (50 mL) at –78°C was added $TiCl_4$ (1.2 M in CH_2Cl_2, 21.44 mL, 31.36 mmol), followed after 20 min by allyltrimethylsilane (3.96 mL, 26.3 mmol). Stirring was continued 1 h at –78 °C. The reaction was quenched with sat. $NaHCO_3$ (50 mL), stirred 3 h at rt, and extracted with CH_2Cl_2 (20 mL). The combined extracts were washed with brine, dried, and concentrated. Chromatography (hexane/EtOAc 85:15) afforded 4 (3.28 g, 12.41 mmol, 76%, dr 95:5) as a colorless liquid. 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 (ESI) m/z 286.33 $[M+Na]^+$. HRMS (ESI) calcd for $C_{16}H_{23}O_3$ $[M+H]^+$ 264.35, found 264.25.

(S)-tert-Butyl (6-(4-methoxybenzyloxy)hept-1-en-2-yl) carbonate (5):

To a solution of 4 (3.28 g, 12.41 mmol) in dry THF was added NaH (0.45 g, 18.61 mmol) at 0°C, and the mixture was stirred 30 min before addition of BocCl (2.1 g, 14.89 mmol). After 1 h, the reaction was quenched with sat. NH_4Cl, extracted, and purified by silica gel chromatography (hexane/EtOAc 5:2) to give 5 (3.53 g, 78%). IR (neat) 3300–3100, 2980–2850, 1720–1680, 1640–1620, 1510–1450, 1250–1000, 750–700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.5–7.3 (m, 4H), 5.80 (m, 3H), 5.2 (dd, 2H), 4.4 (m, 2H), 3.8 (m, 2H), 3.4 (s, 3H), 1.5 (s, 9H), 2.5–1.0 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 132.1, 114.5, 79.3, 72.5, 55.3, 29.2. MS (ESI) m/z 387.46 $[M+Na]^+$. HRMS (ESI) calcd for $C_{21}H_{32}O_5$ $[M+H]^+$ 365.47, found 365.465.

(2S,6S)-2-(4-Methoxybenzyloxy)-6-(oxiran-2-yl)heptan-1-ol (6):

Compound 5 (3.53 g, 9.67 mmol) in dry CH_3CN under N_2 was treated with NIS (2.6 g, 11.6 mmol, 1.2 equiv) at 0 °C for 42 min, then warmed to rt. $NaHCO_3$ (1.2 equiv) was added and stirring continued 1–2 h. The mixture was quenched with $Na_2S_2O_3$, extracted with EtOAc, washed, dried, and concentrated. Chromatography (hexane/EtOAc 7:3) gave 6 (2.15 g, 74%) as a light yellow liquid. IR (neat) 3436, 2926, 2855, 1610, 1459, 1376, 1219, 1060, 835 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–6.98 (m, 4H), 4.45 (s, 2H), 3.70 (s, 3H), 3.45 (m, 1H), 3.14 (m, 2H), 2.74–1.25 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.7, 78.3, 72.1, 70.1, 56.8, 58.5, 51.2, 40.1, 38.7, 29.8, 22.1. MS (ESI) m/z 302.34 $[M+Na]^+$. HRMS (ESI) calcd for $C_{16}H_{23}O_4$ $[M+H]^+$ 280.36, found 280.352.

(S)-2-(tert-Butyldimethylsilyloxy)-6-(4-methoxybenzyloxy) oxiraneheptane(7):

Compound 6 (2.15 g, 9.08 mmol) in dry CH_2Cl_2 (30 mL) was treated with imidazole (0.68 g, 10.01 mmol) at 0 °C for 15 min, followed by TBDMSCl (1.39 g, 9.25 mmol) and a catalytic amount of DMAP. The mixture was stirred 4 h at rt, quenched with water, extracted, and purified by silica gel chromatography (hexane/EtOAc 8:2) to yield 7 (2.70 g, 89%). IR (neat) 2950, 2850, 1250–1050, 1110–1150, 1710, 1427, 1336, 1219, 1108, 850–900 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.26 (m, 2H), 6.92–6.90 (m, 2H), 4.45 (s, 2H), 3.75–3.80 (s, 3H), 3.45–3.40 (m, 1H), 2.80–2.45 (m, 2H), 1.75–1.40 (m), 0.95 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 134.2, 132.1, 131.2, 128.4, 126.3, 125.2, 118.7, 78.5, 73.5, 68.6, 55.0, 39.3, 34.7, 29.9, 28.1, 22.3. MS (ESI) m/z 417.60 $[M+Na]^+$. HRMS (ESI) calcd for $C_{22}H_{38}SiO_4$ $[M+H]^+$ 395.62, found 395.5918.

(2S,5S)-2-Hydroxy-5-(tert-butyldimethylsilyloxy)octyl4-methoxybenzylether(8):

To a solution of epoxide 7 (2.70 g, 6.85 mmol) in dry THF (30 mL) at 0 °C under argon was added $LiEt_3BH$ (1.0 M in THF, 8.22 mmol, 8.2 mL) dropwise over 20 min. The mixture was stirred at 0 °C to rt for 3 h, quenched with saturated NH_4Cl at 0 °C, and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification by column chromatography (hexane/EtOAc, 8:2) furnished **8** (2.50 g, 93%) as a viscous oil. IR (neat) ν_max 3350, 2925, 1610, 1275, 1219, 1108, 875 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–6.80 (m, 4H, Ar-H), 4.45 (s, 2H, PMB-CH_2), 3.75 (s, 3H, OMe), 1.75–1.40 (m, aliphatic), 0.95 (s, 9H, tBu), 0.11 (s, 6H, $SiMe_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 134.2, 132.1, 131.2, 128.4, 126.3, 125.2, 118.7, 78.5, 73.5, 68.6, 55.0, 39.3, 34.7, 29.9, 28.1, 22.3; MS (ESI) m/z 419.62 $[M+Na]^+$; HRMS (ESI) calcd for $C_{22}H_{40}O_4Si$ $[M+H]^+$ 397.64, found 397.639.

(2S,4S)-1-(para-Methoxybenzyloxy)-4-(tert-butyldimethylsilyloxy)-2(methoxymethoxy)heptane(9):

To a solution of alcohol 8 (2.50 g, 6.31 mmol) in dry CH_2Cl_2 (11 mL) at 0 °C were added DIPEA (1.10 g, 7.79 mmol) and MOMCl (0.65 g, 8.11 mmol), followed by DMAP (cat.). The mixture was warmed to rt and stirred for 5 h. After quenching with water, the layers were separated and the organic phase was washed with brine, dried (Na_2SO_4), and concentrated. Column chromatography (hexane/EtOAc, 8:2) afforded 9 (2.50 g, 90%) as a pale yellow oil. IR (neat) ν_max 2800, 1600, 1150, 900 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–6.85 (m, 5H, Ar-H), 4.70 (s, 1H), 4.40 (s, 2H, OCH_2O), 3.80 (m, 2H), 3.45 (s, 3H, PMB-OMe), 3.20 (s, 3H, MOM), 1.89–1.25 (m, 13H, aliphatic), 0.85 (s, 9H, tBu), –0.90 (s, 6H, $SiMe_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.1, 129.3, 114.3, 94.5, 77.4, 71.3, 70.0, 55.6, 45.1, 36.2, 30.1, 26.5, 23.6, 21.4, 18.8, –0.6; MS (ESI) m/z 463.67 $[M+Na]^+$; HRMS (ESI) calcd for $C_{24}H_{44}O_5Si$ $[M+H]^+$ 441.69, found 441.593.

(2S,3S)-2-(Methoxymethoxy)-3-(tert-butyldimethylsilyloxy)octan-1-ol(10):

PMB ether 9 (2.50 g, 5.68 mmol) in CH_2Cl_2 (10 mL) was treated with DDQ (1.54 g, 6.81 mmol) at rt for 3 h. The mixture was quenched with 10% $NaHCO_3$, extracted with CH_2Cl_2 (3 × 10 mL), dried (Na_2SO_4), and concentrated. The crude residue was purified by column chromatography (hexane/EtOAc, 7:3) to afford 10 (1.20 g, 67%) as a colorless oil. IR (neat) ν_max 3390, 2845, 1610, 1443, 1221, 1060, 842 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.67–4.42 (d, 2H), 3.70–3.54 (m, 2H), 3.45 (m, 2H), 3.37 (s, 1H), 1.85–1.27 (m, 11H), 0.91 (s, 9H, tBu), 0.13 (s, 6H, $SiMe_2$), –0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 95.1, 78.3, 70.2, 69.4, 64.1, 56.1, 56.8, 44.9, 37.5, 33.2, 26.2, 22.8, 21.8; MS (ESI) m/z 347.56 $[M+Na]^+$; HRMS (ESI) calcd for $C_{16}H_{40}O_4Si$ $[M+H]^+$ 325.58, found 325.578.

Ethyl(2S,3S)-3-(tert-butyldimethylsilyloxy)-2-(methoxymethoxy)oct-6-enoate(12):

Oxalyl chloride (1.2 mL, 15.3 mmol) in CH_2Cl_2 (5 mL) and DMSO (1.9 mL, 26.8 mmol) was stirred at –78 °C for 45 min, followed by addition of alcohol **10** (1.2 g, 3.7 mmol in CH_2Cl_2, 5 mL). The mixture was stirred 2 h, Et_3N (0.45

g, 4.44 mmol) was added at 0 °C, and after 40 min, the mixture was quenched with water and extracted. The crude aldehyde **11** was obtained quantitatively and used directly. To a solution of **11** (1 g, 3.10 mmol) and nitrosobenzene (0.40 g, 3.72 mmol) in DMSO (8 mL) was added L-proline (0.45 g, 3.87 mmol). After 30 min stirring (color change green→orange), a precooled solution of triethylphosphonoacetate (0.87 g, 3.92 mmol), DBU (1.2 mL, 3.15 mmol), and LiCl (0.15 g, 3.53 mmol) in CH_3CN (5 mL) was added at 0 °C. After 1.5 h at 0–10 °C, the mixture was treated with NH_4Cl (0.50 g) and $CuCl_2·5H_2O$ (0.79 g, 3.52 mmol) in MeOH (15 mL), stirred 24 h, extracted, and purified to afford **12** (0.90 g, 74%) as a yellow syrup. IR (neat) ν 3390, 2845, 2701, 1735, 1660, 1304, 1221, 1060, 853 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.85 (m, 1H), 5.99 (m, 1H), 4.61–4.49 (q, J = 7.2 Hz, 2H), 4.17 (m, 1H), 3.40 (s, 3H), 1.80–1.42 (m, 4H), 1.25 (t, J = 7.2 Hz, 3H), 1.12 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 120.9, 95.1, 77.3, 71.2, 69.5, 60.1, 55.2, 44.5, 32.2, 26.2, 22.8, 21.8, 19.6, 14.6, –0.51; HRMS (ESI) calcd for $C_{20}H_{44}SiO_6$ $(M+H)^+$ 409.65, found 409.65.

Ethyl(2S,3S)-3-(tert-butyldimethylsilyloxy)-2-(methoxymethoxy)oct-6-enoate(13):

Compound **12** (0.90 g, 2.20 mmol) in CH_2Cl_2 (6 mL) was treated with DIPEA (0.35 mL, 2.64 mmol) at 0 °C, stirred 15 min, then MOMCl (0.21 mL, 2.52 mmol) and catalytic DMAP were added. After stirring 5 h at rt, the mixture was quenched, extracted, and purified by flash chromatography (hexane/EtOAc 9:1) to afford **13** (0.70 g, 72%) as a colorless liquid. IR (neat) ν 3012, 2943, 1442, 1347, 1182, 1119, 1023, 900 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.82 (m, 1H), 5.89 (d, 1H), 5.20–5.15 (m, 2H), 4.69 (d, J = 6.7 Hz, 1H), 4.58 (d, J = 11.5 Hz, 1H), 4.52 (d, J = 6.7 Hz, 1H), 4.40 (d, J = 11.4 Hz, 1H), 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, J = 6.1 Hz, 3H), 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; HRMS (ESI) calcd for $C_{22}H_{48}SiO_7$ $(M+H)^+$ 453.70, found 453.68.

Ethyl(2S,3S)-3-(methoxymethoxy)-2-hydroxyoct-6-enoate(14):

To a solution of **13** (0.70 g, 1.58 mmol) in THF (15 mL) was added TBAF (0.50 mL, 2 M in THF, 1.9 mmol) at 0 °C. The reaction was refluxed 5 h, quenched, extracted, and purified by chromatography (EtOAc/hexane 8:2) to give **14** (0.38 g, 73%) as a light yellow liquid. IR (neat) ν 3435, 3365, 2926, 1702, 1658, 1452, 1376, 1271, 1149, 1030, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.86 (m, 1H), 5.97 (m, 1H), 4.84–4.52 (m, 2H), 4.34 (m, 1H), 4.22–4.27 (m, 1H), 3.37 (s, 6H), 1.84–1.42 (m, 9H), 1.33–1.20 (m, 2H), 1.58–1.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 148.2, 136.3, 122.5, 94.9, 77.3, 76.1, 74.6, 71.5, 66.3, 45.7, 32.9, 31.1, 20.1, 14.2; HRMS (ESI) calcd for $C_{16}H_{34}O_7$ $(M+H)^+$ 339.44, found 339.43.

(2S,3S)-3-(Methoxymethoxy)-2-hydroxyoct-6-enoicacid(15):

Compound **14** (0.38 g, 1.12 mmol) in MeOH (5 mL) was treated with NaOH (0.50 mL, 3 N, 1.4 mmol) at 0 °C, warmed to rt, and stirred for 3 h. After workup and purification (EtOAc/hexane 3:7), **15** (0.26 g, 75%) was obtained as a colorless liquid. IR (neat) ν 2923, 2853, 1739, 1461, 1252, 1061, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.84 (m, 1H), 5.99 (d, J = 15.6, 5.9 Hz, 1H), 4.98 (s, 4H), 4.72–4.57 (m, 2H), 3.25 (m, 6H), 1.22–1.18 (d, J = 6.1 Hz, 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; HRMS (ESI) calcd for $C_{14}H_{30}O_7$ $(M+H)^+$ 311.39, found 311.39.

(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(trichobotrysideA):

Compound **15** (0.26 g, 0.83 mmol) in THF was treated with PPh_3 (0.27 g, 1.20 mmol) at 0 °C, followed by DEAD (0.21 mL, 1.20 mmol). The mixture was warmed to rt and stirred 2.15 h, quenched, and extracted to afford intermediate **16**, which upon MOM deprotection with $TiCl_4$ (0.1 mL in CH_2Cl_2) at 0 °C to rt (2 h) furnished **Trichobotryside A** (35 mg, 40%) as a sticky foam. $[\alpha]_D^{25}$ +65.7 (c 0.12, CH_3OH) [lit. $[\alpha]_D^{20}$ +50.1 (c 1.58, CH_3OH)]; IR (neat) ν 3436, 3395, 3081, 2930, 1644, 1467, 1253, 1082, 773 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 6.76 (dd, J = 15.7 Hz, 2H), 5.81 (dd, J = 15.7 Hz, 2H), 5.41 (br s, OH), 5.34–5.30 (m, 1H), 5.05 (d, J = 4.2 Hz, 2H), 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, J = 6.1 Hz, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.9, 150.9, 120.2, 70.7, 69.8, 62.0, 40.6, 29.1, 25.9, 22.2; HRMS (ESI) calcd for $C_{20}H_{32}O_8Na$ $(M+Na)^+$ 423.1986, found 423.2009.

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