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Stereoselective Synthesis of the Hydrophobic Side Chain of Scyphostatin

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The hydrophobic side chain of scyphostatin was synthesized by a convergent synthetic pathway. The key reactions were the enzymatic asymmetric acetylation of a *meso*-diol, construction of the C12'-C13' trisubstituted *E*-olefin moiety by Negishi coupling, and construction of the (2'E, 4'E, 6'E)-triene moiety by Horner–Wadsworth–Emmons olefination.

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Introduction

Scyphostatin 1 was isolated as a potent inhibitor of neutral sphingomyerinase (N-SMase) from the mycelial extract of *Dasyscyphus mollissima* by Ogita et al. (Sankyo Co.) in 1997 (Scheme 1).^[1] Scyphostatin 1 consists of a hydrophobic side chain 2 and a hydrophilic 4,5-epoxy-cyclohex-2-en-1-one moiety 3. Our interest in such biphilic natural products^[2,3] has inspired us to carry out synthetic studies on scyphostatin 1. Other groups have also reported their synthetic efforts.^[4] Recently, Katoh et al. reported the total synthesis of scyphostatin 1 from D-arabinose.^[5]

We planned a convergent strategy for the synthesis of Scyphostatin 1, namely, to synthesize the hydrophobic carboxylic acid 2 and the hydrophilic cyclohexenone 3 moieties separately and combine them at the final stage of the total synthesis. The structural features of the hydrophobic moiety 2 are three stereogenic centres (C8', C10', C14'), a trisubstituted





E-olefin moiety (C12'–C13'), and a (2'*E*,4'*E*,6'*E*)-triene moiety. When we commenced this project, the relative and absolute stereochemistry of the three stereocentres had yet not been established, and were later determined to be (8'*R*,10'*S*,14'*R*) in the form of either an ester or an amide by Kogen et al.^[6] and Hoye et al.,^[4h] independently. The report by Hoye et al. also describes the first stereoselective synthesis of the side chain.

In this paper, the stereoselective synthesis of the hydrophobic side chain up to the previously unreported free acid **2** is described. The difference in optical rotation values of the geometric isomers (2'E,4'E,6'E)-, (2'Z,4'E,6'E)-, (2'E,4'Z,6'E)-, and (2'E,4'E,6'Z)-**30** is also described.

Results and Discussion

Our initial synthetic strategy was based on the use of two Horner–Wadsworth–Emmons (HWE) olefinations to attach the three fragments as depicted in Scheme 2.^[7] For the middle part **4**, we envisioned that it could be stereoselectivity constructed from diol **6**. Incidentally, the use of diol **6** and the HWE reagent **5** were found to be the same reagents as those used in the method of Hoye et al.^[4h]

The absolute stereochemistry of (8'R,10'S) was introduced by asymmetric acetylation of *meso*-diol **6** using porcine pancreatic lipase (PPL; Scheme 3).^[8] Thus, the chiral alcohol 7 was obtained by the PPL-catalyzed asymmetric acetylation of the *meso*-diol **6** (62%, 99% *e.e.*).^[9] Protection of the chiral alcohol **7** with *tert*-butyldimethylsilyl chloride (TBSCl) followed by reduction with LiAlH₄ gave alcohol **9** (80%, two steps). Halogenation of the alcohol **9** with PPh₃–I₂ afforded iodide **10**, which was subsequently converted into phosphonate **4** (70%, two steps).

We shifted our focus to the formation of the C12'-C13' double bond by HWE olefination (Scheme 4). To



Scheme 2. Synthetic strategy via two WHE olefinations.



Scheme 3. Reagents and conditions: (*a*) PPL on Celite, vinyl acetate, Et₂O, 25°C (62%, 99% *e.e.*); (*b*) TBSCl, Et₃N, DMAP, THF, 25°C (99%); (*c*) LiAlH₄, THF, 0°C (81%); (*d*) PPh₃, I₂, imidazole, benzene, 25°C (99%); (*e*) (EtO)₂P(O)CH₂CO₂Et, NaH, DMSO, 25°C, then **10**, 25°C (71%).



Scheme 4.

establish a synthetic route, (2*S*)-2-methylbutanal (easily prepared from the commercially available alcohol) was used for the HWE olefination. Treatment of phosphonate **4** with (2*S*)-2-methylbutanal using NaH as a base gave a mixture of *E*- and *Z*-**11** (*E*-to-*Z* ratio 27 : 73, 66%).^[10] Unfortunately, epimerization at C14' was observed (diastereomeric ratio of *Z*-**11** 4 : 1), and improvements could not be achieved under milder conditions [LiCl, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and LiCl, diisopropylethylamine (DIPEA)].^[11,12] Therefore, we decided to make a few adjustments to our



Scheme 5. Synthetic strategy via Negishi coupling reaction and HWE olefination.



Scheme 6. Reagents and conditions: (*a*) DIBAL, CH_2Cl_2 , $-78^{\circ}C$, then H^+ , -78 to $25^{\circ}C$; (*b*) NaBH₄, MeOH, $0-25^{\circ}C$ (89%, two steps); (*c*) PMBOC(NH)CCl₃, PPTS, CH_2Cl_2 , $25^{\circ}C$ (99%); (*d*) TBAF, THF, $25^{\circ}C$ (99%); (*e*) (COCl)₂, DMSO, Et₃N, CH_2Cl_2 , $25^{\circ}C$; (*f*) PPh₃, CBr₄, THF, $0-25^{\circ}C$ (100%, two steps); (*g*) BuⁿLi, THF, $0^{\circ}C$, then MeI, $0-25^{\circ}C$ (89%); (*h*) (PhMe₂Si)₂CuLi · LiCN, THF, $-40^{\circ}C$ (99%); (*i*) DDQ, H₂O, CH₂Cl₂, $0^{\circ}C$ (81%); (*j*) PivCl, pyridine, $25^{\circ}C$ (82%); (*k*) NIS, CH₃CN, THF, $25^{\circ}C$ (96%).

original strategy. The site of one of the bond formations was changed from C12'-C13' to C11'-C12'. We anticipated that the use of the Negishi coupling reaction^[13] between organozinc compound **10'**, which could be generated from **10**, and vinyl iodide **12** would serve this purpose (Scheme 5).

The absolute configuration at C14' in the hydrophobic side chain **2** was introduced from commercially available methyl (2*S*)-3-hydroxy-2-methylpropionate (Scheme 6). The nitrile **13** was obtained from methyl (2*S*)-3-hydroxy-2-methylpropionate in four steps (91%).^[14] Treatment of nitrile 13 with diisobutylaluminum hydride (DIBAL) gave aldehyde 14. Alcohol 17 was obtained by a sequence of reduction with NaBH₄, protection with a *p*-methoxybenzyl (PMB) group, and deprotection of the TBS group (87%, four steps). Aldehyde 18, which was generated by Swern oxidation of 17, was elaborated to acetylene 20 by Corev and Fuchs' procedure (89%, three steps).^[15] Hydrosilylation of acetylene 20 with (PhMe2Si)2CuLi · LiCN afforded vinyl silane 21 in 99% yield.^[16] Although hydrostannylations of 20 with PdCl₂(PPh₃)₂/Bu₃SnH or (Bu₃Sn)CuCNLi were also examined, the reactions were unsatisfactory in terms of both yield and regioselectivity (67% yield, 11:1; 10% yield, 30:1, respectively). The PMB group of 21 had to be replaced by a pivalovl (Piv) group (66%, two steps), because the PMB group could not withstand the iododesilylation conditions. Treatment of vinyl silane 23 with N-iodosuccinimide (NIS)^[17] afforded vinyl iodide **12** in 96% yield. The geometry of vinyl iodide 12 was confirmed by differential NOE (dif-NOE) experiments: When the H14' methine proton was irradiated, the intensity of the H19' methyl proton signal was enhanced by 1.6%. HPLC analysis using a chiral column indicated that the optical purity of vinyl iodide 12 was 95% e.e. (the racemate of 12 was used as a control).

Subsequently, we focussed our attention on the construction of the C12'-C13' trisubstituted E-olefin moiety using the Negishi coupling reaction (Scheme 7). Treatment of iodide 10 in ether with Bu^tLi in the presence of ZnCl₂ at -78° C afforded organozinc compound 10' in situ. Complete consumption of iodide **10** required 3 equivalents of Bu^tLi.^[18] The reaction mixture was then warmed to 25°C. To the reaction mixture was added Pd(PPh₃)₄ (0.05 equiv) and vinyl iodide 12. Efficient conversion of vinvl iodide 12 required 2 equivalents of the organozinc compound. The reaction mixture was stirred at 25°C. After workup, 24 and a homo-coupling product 12' were obtained in 67 and 32% yields, respectively. When the coupling reaction was carried out at 0°C, the homo-coupling reaction of 12' was slightly suppressed (24, 85%; homo-coupling product 12', 7%). The geometry of 24 was confirmed by dif-NOE: When the H14' methine proton was irradiated, the intensity of the H19' methyl proton signal was enhanced by 2.7%. Moreover, NOE enhancement at H11' (1.1%) was observed when vinyl proton H13' was irradiated.

Synthesis of the hydrophobic side chain 2 was completed as follows (Scheme 8). Reduction of 24 with LiAlH₄ afforded alcohol 25 (97%). Dehydroxylation of the hydroxy group at C16' was achieved by mesylation of alcohol 25, followed by reduction of mesylate 26 with LiAlH₄, and 27 was obtained in 97% yield over two steps. Treatment of 27 with tetrabutyl ammonium fluoride (TBAF) gave alcohol 28 (99%). Alcohol 28 was oxidized to aldehyde 29 under Swern oxidation conditions, and HWE olefination of aldehyde 29 with phosphonate $5^{[19]}$ gave a mixture of four geometric isomers: (2'*E*,4'*E*,6'*E*)-, (2'*Z*,4'*E*,6'*E*)-, (2'*E*,4'*Z*,6'*E*) to (2'*Z*,4'*E*,6'*E*) to (2'*E*,4'*Z*,6'*E*) to (2'*Z*,4'*E*,6'*Z*) is approximately 10:1:1:1]. The four isomers were separated by high-performance liquid chromatography (HPLC). The





Scheme 8. Reagents and conditions: (*a*) LiAlH₄, THF, 0°C (97%); (*b*) MsCl, Et₃N, THF, 0°C (98%); (*c*) LiAlH₄, THF, 0–25°C (99%); (*d*) TBAF, THF, 25°C (99%); (*e*) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78° C; (*f*) **5**, LDA, THF, -78° C, then **16**, 0°C (85%); (*g*) 5 M LiOH, THF, 25°C (100%).

geometry of the (2',4',6')-triene moiety was confirmed by coupling constants in the ¹H NMR spectrum: for (2'*E*, '*E*, 6'*E*)-**30**, *J*_{H2',H3'} 15.3, *J*_{H4',H5'} 14.7, *J*_{H6'H7'} 15.1 Hz; for (2'Z,4'E,6'E)-30, $J_{\text{H2',H3'}}$ 11.4, $J_{\text{H4',H5'}}$ 15.1, $J_{\text{H6'H7'}}$ 14.9 Hz; for (2'E, 4'Z, 6'E)-**30**, $J_{H2', H3'}$ 15.0, $J_{H4', H5'}$ 11.4, $J_{\text{H6'H7'}}$ 14.9 Hz; for (2'E,4'E,6'Z)-**30**, $J_{\text{H2',H3'}}$ 15.5, $J_{\text{H4',H5'}}$ 14.5, $J_{\text{H6'H7'}}$ 11.0 Hz. We noticed that the optical rotation value of (2'E, 4'E, 6'E)-30 is negative and small, while those of (2'E,4'Z,6'E)- and (2'E,4'E,6'Z)-30 are large and positive (Scheme 9). We consider that the difference of the optical rotation values results from a distorted confomer of the triene moiety caused by allylic strain. Spectroscopic data (¹H and ¹³C NMR) and the optical rotation value of our synthetic ethyl tetraenate (2'E, 4'E, 6'E)-30 were compared with those of Hoye's four synthetic diastereomers.^[4h] Although the C10' signals in the ¹³C NMR spectrum appeared at δ 29.9, which was slightly shifted toward the reported value (δ 31.3), the other data were identical to those of the (8'R, 10'S, 14'R)diastereomer. Hydrolysis of ethyl ester of (2'E, 4'E, 6'E)-30 was performed by using 5 M LiOH, and hydrophobic carboxylic acid 2 was obtained without isomerization of the triene moiety (100%). The geometry of the carboxylic acid 2 was confirmed by the coupling constants in the ¹H NMR spectrum: J_{H2',H3'} 14.5, J_{H4',H5'} 14.3, J_{H6',H7'} 14.9 Hz.



[α]²²_D +59.8 (c 0.24, CHCl₃)

Scheme 9. Optical rotation values of (2'E,4'E,6'E)-, (2'Z,4'E,6'E)-, (2'E,4'Z,6'E)-, and (2'E,4'E,6'Z)-**30**.

Conclusion

The stereoselective synthesis of the hydrophobic carboxylic acid **2** of scyphostatin **1** was accomplished by a convergent synthetic pathway. The key reactions were enzymatic asymmetric acetylation of a *meso*-diol, construction of the C12'-C13' trisubstituted *E*-olefin moiety by Negishi coupling, and construction of the (2'E,4'E,6'E)-triene moiety by Horner–Wadsworth–Emmons olefination.

Experimental

All reactions were carried out under N₂. Tetrahydrofuran (THF) was distilled after refluxing over Na–benzophenone before use. CH_2Cl_2 was distilled over CaH₂ before use. Silica gel 60F₂₅₄ (Merck) was used for preparative thin-layer chromatography. NMR spectra were recorded on JEOL JNM-GSX270 or JNM-LA500 instruments. Internal references for ¹H NMR spectra were Me₄Si (TMS; 0.0 ppm) for CDCl₃ and CD₃OD (3.31 ppm). Chemical shifts for ¹³C NMR spectra were referenced to CDCl₃ (77.0 ppm) and CD₃OD (49.49 ppm). MS were recorded on a JEOL JMS-SX102A instrument under electron ionization (EI) conditions (70 eV). Optical rotations were recorded on a JASCO DIP-370 polarimeter. IR spectra were recorded on a Horiba FT-IR720. Elemental analyses were carried out on a Perkin–Elmer 2400II analyzer.

(2S,4R)-2,4-Dimethyl-5-hydroxypentyl Acetate 7^[8]

To a suspension of diol **6**^[20] (266 mg, 2.01 mmol) and PPL on Celite (1.02 g, 506 g mol⁻¹) in Et₂O (25 mL) was added vinyl acetate (0.8 mL, 8.68 mmol) at 25°C. After stirring the mixture for 18 h, the Celite was filtered off, and the filtrate was evaporated. The resulting residue was purified by column chromatography (SiO₂; EtOAc/hexane, 1 : 2) to give 7 (218 mg, 62%, 99% *e.e.*) as a colourless oil, R_F (EtOAc/hexane, 1 : 2) 0.20, $[\alpha]_{D}^{22}$ +10.3 (*c* 2.18, CHCl₃) [lit.^[8b] +10.4 (*c* 1.2, CHCl₃)]. δ_H (500 MHz, CDCl₃) 0.95 (3 H, d, *J* 4.0, 4-CH₃), 0.97 (3 H, d, *J* 4.0, 2-CH₃), 0.99–1.03 (1 H, m, H3), 1.41–1.48 (1 H, m, H3), 1.69–1.79 (1 H, m, H3), 1.86–1.95 (1 H, m, H2), 2.06 (3 H, s, OAc), 3.42 (1 H, dd, *J* 6.4, 10.7, H5), 3.51 (1 H, dd, *J* 5.5, 10.7, H5), 3.86 (1 H, dd, *J* 6.7, 10.7, H1), 3.96 (1 H, dd, *J* 5.5, 10.7, H1).

(2R,4S)-5-Acetoxy-2,4-dimethylpentyl Benzoate

To a mixture of 7 (16.9 mg, 0.10 mmol) in THF (1.0 mL) were added Et₃N (0.02 mL, 0.14 mmol) and BzCl (0.02 mL, 0.17 mmol) at 0°C. The mixture was stirred at 25°C for 3 h. The mixture was quenched with saturated NH₄Cl and the aqueous layer was extracted with Et₂O. The organic layer was washed with H₂O and brine, dried over anhydrous MgSO₄, filtered, and evaporated. The resulting residue was purified by PTLC (EtOAc/hexane, 1 : 5) to give the benzoate of 7 (24.9 mg, 92%) as a colourless oil, R_F (EtOAc/hexane, 1 : 5) 0.48, $[\alpha]_D^{22}$ – 1.57 (*c* 1.51, CHCl₃). δ_H (500 MHz, CDCl₃) 0.94 (3 H, d, J 6.7, 4-CH₃), 1.06 (3 H, d, J 6.7, 2-CH₃), 1.52–1.59 (2 H, m, H3), 1.92–2.11 (2 H, m, H2, H4), 2.02 (3 H, s, COCH₃), 3.88 (1 H, dd, J 6.4, 10.7, H5), 3.96 (1 H, dd, J 5.5, 10.7, H5), 4.12 (1 H, dd, J 6.4, 10.7, H1), 4.21 (1 H, dd, J 5.5, 10.7, H1), 7.43–7.58 (3 H, m, Ph), 8.03–8.06 (2 H, m, Ph). Found: *m*/z 278.1513. M⁺ requires 278.1518.

(2S,4R)-5-(tert-Butyldimethylsilyloxy)-2,4-dimethylpentyl Acetate $\boldsymbol{8}^{[21]}$

To a mixture of monoacetate 7 (419 mg, 2.40 mmol) in THF (5.0 mL) were added Et₃N (0.45 mL, 3.2 mmol), 4-dimethylaminopyridine (DMAP, 30.0 mg, 0.31 mmol), and TBSCl (424 mg, 2.81 mmol) at 0°C. The mixture was stirred at 25°C for 3 h. The mixture was quenched with saturated NH₄Cl and the aqueous layer was extracted with Et₂O. The organic layer was washed with H₂O and brine, dried over MgSO₄, filtered, and evaporated. The resulting residue was purified by bulb-tobulb distillation (120-130°C/1 mmHg) to give 8 (683 mg, 99%) as a colourless oil, R_F (EtOAc/hexane, 1:2) 0.72. v_{max} (film)/cm⁻¹ 2954, 2931, 2888, 1743, 1469, 1388, 1365, 1238, 1095. $\delta_{\rm H}$ (500 MHz, CDCl₃) -0.03 (6 H, s, SiCH₃), 0.89 (9 H, s, SiC(CH₃)₃), 0.88-0.91 (3 H, m, 4-CH₃), 0.94 (3 H, d, J 6.7, 2-CH₃), 1.24–1.33 (1 H, m, H3), 1.42–1.50 (1 H, m, H3), 1.65–1.73 (1 H, m, H4), 1.84–1.94 (1 H, m, H2), 2.04 (3 H, s, OCH₃), 3.36 (1 H, dd, J 6.1, 9.7, H5), 3.42 (1 H, dd, J 6.1, 9.7, H5), 3.82 (1 H, dd, J 6.7, 10.7, H1), 3.95 (1 H, dd, J 5.2, 10.7, H1). δ_C (125 MHz, CDCl₃) – 5.5 (2 C, SiCH₃), 17.4 (4-CH₃), 17.7 (2-CH₃), 18.2 (SiC(CH₃)₃), 20.8 (C3), 25.8 (3 C, SiC(CH₃)₃), 30.0 (COCH₃), 33.0 (C4), 37.4 (C2), 67.9 (C5), 69.3 (C1), 171.0 (COCH₃). Found: *m*/*z* 231.1417. $M^+ - Bu^t$ requires 231.1416.

(2S,4R)-5-(tert-Butyldimethylsilyloxy)-2,4-dimethylpentan-1-ol 9^[21]

To a mixture of LiAlH₄ (210 mg, 5.53 mmol) in THF (5.0 mL) was added acetate 8 (692 mg, 2.40 mmol) in THF (5.0 mL) at 0°C. The mixture was stirred for 4 h at 0-25°C. The mixture was quenched with H₂O, dilute HCl was added, and the aqueous layer was extracted with Et₂O. The organic layer was washed with H₂O and brine, dried over MgSO₄, filtered, and evaporated. The resulting residue was purified by column chromatography (SiO₂; EtOAc/hexane, 1:5) to give 9 (464 mg, 79%) as a colourless oil, $R_{\rm F}$ (EtOAc/hexane, 1:2) 0.61, $[\alpha]_{\rm D}^{22} - 1.12$ (c 2.03, CHCl₃) [lit.^[22] -1.2 (c 1.4, CHCl₃]. v_{max} (film)/cm⁻¹ 3351, 2954, 2927, 2857, 1469, 1388, 1361, 1253. δ_H (500 MHz, CDCl₃) 0.04 (6 H, s, SiCH₃), 0.90 (9 H, s, SiC(CH₃)₃), 0.91 (3 H, d, J 4.0, 4-CH₃), 0.94 (3 H, d, J 6.7, 2-CH₃), 1.40-1.56 (2 H, m, H3), 1.67-1.78 (2 H, m, H2, H4), 3.35–3.54 (4 H, m, H1, H5). δ_C (125 MHz, CDCl₃) –5.5 (2 C, SiCH₃), 17.6 (4-CH₃), 17.7 (2-CH₃), 18.3 (SiC(CH₃)₃), 25.6 (C3), 25.9 (3 C, SiC(CH₃)), 33.2 (C4), 37.2 (C2), 67.9 (C5), 68.3 (C1). Found: m/z 246.2025. M⁺ requires 246.2015.

(2R, 4S) - 1 - (tert-Butyl dimethyl silyloxyl) - 5 - iodo-

2,4-dimethylpentane 10

To a mixture of alcohol **9** (241 mg, 0.98 mmol) in benzene (9.0 mL) were added imidazole (165 mg, 2.42 mmol), PPh₃ (644 mg, 2.46 mmol), and I₂ (505 mg, 1.99 mmol) at 25°C. The mixture was stirred at 25°C for 30 min. The mixture was quenched with saturated Na₂S₂O₃ and the aqueous layer was extracted with Et₂O. The organic layer was washed with H₂O and brine, dried over MgSO₄, filtered, and evaporated. The resulting residue was purified by column chromatography (SiO₂; EtOAc/hexane, 1:95) to give **10** (312 mg, 90%) as a colourless oil, R_F (EtOAc/hexane, 1:5) 0.87, $[\alpha]_D^{22}$ +3.50 (*c* 2.09, CHCl₃). v_{max} (film)/cm⁻¹ 2954, 2927, 2888, 2857, 1461, 1388, 1361, 1253, 1191,

1095, 1072. $\delta_{\rm H}$ (500 MHz, CDCl₃) 0.04 (6 H, s, SiCH₃), 0.89 (3 H, d, *J* 6.7, 4-CH₃), 0.90 (9 H, s, SiC(CH₃)₃), 0.99 (3 H, d, *J* 6.7, 2-CH₃), 1.38–1.45 (2 H, m, H3), 1.51–1.59 (1 H, m, H4), 1.60–1.68 (1 H, m, H2), 3.12 (1 H, dd, *J* 6.4, 9.8, H5), 3.26 (1 H, dd, *J* 4.0, 9.8, H5), 3.36 (1 H, dd, *J* 6.1, 9.8, H1), 3.44 (1 H, dd, *J* 5.5, 9.8, H1). $\delta_{\rm C}$ (125 MHz, CDCl₃) -5.4 (2 C, SiCH₃), 17.2 (2-CH₃), 18.0 (4-CH₃), 18.3 (SiC(CH₃)₃), 21.5 (C3), 26.0 (3 C, SiC(CH₃)₃), 31.9 (C4), 33.2 (C2), 40.2 (C5), 68.2 (C1). Found: C 43.7, H 8.3, *m/z* 299.0331. C₁₃H₂₉IOSi requires C 43.8, H 8.2%, M⁺ – Bu^t 299.0328.

*Ethyl 7-(tert-Butyldimethylsilyloxy)-2-(diethoxyphosphoryl)-*4,6-dimethylheptanoate **4**

To a mixture of NaH (65% in mineral oil, 49.6 mg, 1.24 mmol, washed with hexane) in dimethyl sulfoxide (DMSO; 1.0 mL) was added (EtO)₂P(O)CH₂CO₂Et (259 mg, 1.16 mmol) in DMSO (0.5 mL) at 25°C. The mixture was stirred at 25°C for 30 min, and to the solution was added the iodide 10 (413 mg, 1.16 mmol) in DMSO (1.0 mL) at 25°C. After stirring for 29 h, the mixture was quenched with saturated NH₄Cl, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layer was washed with H2O and brine, dried over MgSO4, filtered, and evaporated. The resulting residue was purified by column chromatography (SiO₂; EtOAc/hexane, 1:1) to give 4 as a mixture of diastereomers (ratio of major to minor approximately 6:4, colourless oil, 371 mg, 71%, 86% based on consumed 10), $R_{\rm F}$ (EtOAc) 0.65. $\delta_{\rm H}$ (500 MHz, CDCl₃) 0.03 (6 H, s, SiCH₃), 0.85 (3 H, d, J 6.7, 4-CH₃), 0.88 (3 H, d, J 6.1, 6-CH₃), 0.89 (9 H, s, SiC(CH₃)₃), 0.87-1.02 (3 H, m), 1.28 (3 H, t, J 7.2, CO₂CH₂CH₃), 1.32 (3 H, t, J 7.2, POCH₂CH₃), 1.33 (3 H, t, J 7.2, POCH2CH3), 1.39-1.52 (minor, 1 H, m), [1.53-1.61 (minor, m, 1 H), 2.10-2.19 (major, m, 1 H)], [1.63-1.71 (major, 1 H, m), 1.77-1.91 (minor, 1 H, m)], [3.01 (minor, ddd, J 5.1, 8.8, 24.1, H2), 3.08 (major, ddd, J 2.4, 12.2, 22.8, H2)], [3.27 (minor, dd, J 6.7, 9.4, H7), 3.33 (major, dd, J 6.7, 9.4, H7)], [3.41 (major, dd, J 5.4, 9.4, H7), 3.49 (minor, dd, J 4.7, 9.4, H7)], 4.09-4.25 (6 H, m, OCH₂CH₃). δ_C (125 MHz, CDCl₃) -5.4 (2 C, SiCH₃), [14.0 (minor, OCH₂CH₃), 14.1 (major, OCH2CH3)], [16.2 (minor, d, J 3.1, 2 POCH2CH3), 16.3 (major, d, J 3.1, 2 POCH₂CH₃)], 16.9 (6-CH₃), 17.8 (4-CH₃), 18.3 (SiC(CH₃)₃), [19.5 (major, C5), 20.4 (minor, C5)], 25.9 (3 C, SiC(CH₃)₃), [28.7 (major, d, J 14.5, C3), 29.8 (minor, d, J 13.5, C3)], [33.1 (major, d, J 4.1, C4), 34.2 (minor, d, J 5.2, C4)], [40.3 (minor, C6), 41.3 (major, C6)], [43.6 (major, d, J 130.4, C2), 43.9 (minor, d, J 130.4, C2)], [61.2 (major, CO2CH2CH3), 61.3 (minor, CO2CH2CH3)], [62.4 (minor, d, J 5.2, POCH₂CH₃), 62.5 (major, d, J 6.2, POCH₂CH₃)], [62.6 (minor, d, J 6.2, POCH₂CH₃), 62.7 (major, d, J 6.2, POCH₂CH₃)], [68.0 (minor, C7), 68.4 (major, C7)], [169.1 (major, d, J 5.2, CO₂CH₂CH₃), 169.7 (minor, d, J 5.2, CO₂CH₂CH₃)]. δ_P (202 MHz, CDCl₃) 24.0. Found: C 55.7, H 10.2, m/z 395.2019. C₂₁H₄₅O₆PSi requires C 55.7, H 10.0%, $M^+ - Bu^t$ 395.2019.

(2R,4S)-1-(tert-Butyldimethylsilyloxy)-6-ethoxycarbonyl-2,4,8-trimethyldec-6-ene 11

To a mixture of NaH (60% in mineral oil, 78.0 mg, 1.85 mmol, washed with hexane) in THF (10.0 mL) was added phosphonate 4 (800 mg, 1.77 mmol) in THF (2.0 mL) at 0°C. The mixture was stirred at 0°C for 30 min, and to the solution was added 2-methylbutanal (19.8 mg, 2.13 mmol) in THF (0.5 mL) at 0°C. After stirring at 0-25°C for 12 h, the mixture was quenched with saturated NH4Cl, and the aqueous layer was extracted with Et2O. The combined organic layer was washed with H2O and brine, dried over MgSO4, filtered, and evaporated. The resulting residue was purified by preparative TLC (silica gel; EtOAc/hexane, 1:1) to give E-11 and Z-11 as a mixture of diastereomers (colourless oil, 442 mg, 66%; ratio of E to Z, 27:73), R_F (EtOAc/hexane, 1:5) 0.71. δ_H for Z-11 (500 MHz, CDCl₃) 0.03 (6 H, s, SiCH₃), 0.83 (3 H, t, J 7.2, H10), [0.83 (d, J 6.7, 8R-4-CH₃), 0.84 (d, J 7.6, 8S-4-CH₃)], 0.88 (3 H, d, J 6.7, 2-CH₃), 0.89 (9 H, s, SiC(CH₃)₃), [0.96 (d, J 6.7, 8S-8-CH₃), 0.99 (d, J 6.4, 8R-8-CH₃)], 1.29 (3 H, t, J 7.0, CO₂CH₂CH₃), 1.23-1.40 (4 H, m, H3, H9), 1.58-1.67 (1 H, m, H4), 1.67-1.81 (2 H, m, H2,H5), 2.43 (1 H, dd, J 4.3, 13.4, H5), 2.85-2.95 (1 H, m, H8), 3.30 (1 H, dd, J 4.3, 13.4, H1), 3.44 (1 H, dd, J 5.5, 9.8, H1), 4.18 (2 H, q, J 7.0, CO₂CH₂CH₃), 5.51 (1 H, d, J 10.0, H7). δ_C (125 MHz, CDCl₃)

-5.4 (2 C, SiCH₃), 11.9, 14.3 [17.4 (8*R*), 17.5 (8*S*)], 18.3, 20.1, 20.4, 26.0 (3 C, SiC(CH₃)₃), 29.6 [30.1 (8*S*), 30.2 (8*R*)], [33.1 (8*S*), 33.2 (8*R*)], [35.1 (8*R*), 35.2 (8*S*)], [41.1 (8*S*), 41.2 (8*R*)], [42.0 (8*S*), 42.2 (8*R*)], 59.9, 68.5, [130.0 (8*S*), 130.1 (8*R*)], [147.9 (8*S*), 148.0 (8*R*)], [168.4 (8*S*), 168.5 (8*R*)]. Found: C 68.7, H 11.5, *m*/*z* 384.3074. C₂₂H₄₄O₃Si requires C 68.7, H 11.5%, M⁺ 384.3060.

 $\delta_{\rm H}$ for E-11 (500 MHz, CDCl₃) [0.02 (s, 8S-SiCH₃), 0.03 (s, 8R-SiCH₃)], 0.82 (3 H, dd, J 7.0, 11.0, H10), [0.85 (d, J 4.3, 8S-4-CH₃), 0.86 (d, J 4.6, 8R-4-CH₃)], 0.89 (9 H, s, SiC(CH₃)₃), [0.90 (d, J 6.7, 8S-2-CH₃), 0.91 (d, J 6.4, 8R-2-CH₃)], [0.98 (d, J 6.7, 8S-8-CH₃), 0.99 (d, J 6.7, 8R-8-CH₃)], 1.29 (3 H, t, J 7.1, CO₂CH₂CH₃), 1.30-1.44 (4 H, m, H3,H9), 1.65-1.79 (2 H, m, H2,H4), [1.97 (dd, J 9.4, 13.8, 8R-H5), 2.03 (dd, J 8.8, 12.5, 8S-H5)], [2.32 (dd, J 5.5, 12.5, 8S-H5), 2.37 (dd, J 5.8, 13.8, 8R-H5)], 2.37-2.43 (1 H, m, H8), 3.31 (1 H, dd, J 7.0, 9.3, H1), 3.45 (1 H, dd, J 5.3, 9.4, H1), [4.17 (q, J 7.1, 8S-CO₂CH₂CH₃), 4.18 (q, J 7.1, 8R-CO₂CH₂CH₃)], [6.53 (d, J 11.0, 8*R*-H7), 6.55 (d, J 10.7, 8S-H7)]. δ_C (125 MHz, CDCl₃) -5.4 (2 C, SiCH₃), [11.8 (8S), 11.9 (8R)], 14.3, 17.3, 17.5 [18.3 (8R), 19.8 (8S)], [20.2 (8S), 20.3 (8R)], 25.9 (3 C, SiC(CH₃)₃), [29.6 (8R), 29.7 (8S)], [30.1 (8S), 30.4 (8R)], [33.2 (8R), 33.3 (8S)], [33.7 (8S), 33.8 (8*R*)], [34.7 (8*R*), 34.8 (8*S*)], [41.4 (8*R*), 41.6 (8*S*)], 60.3 [68.3 (8*S*), 68.4 (8*R*)], [130.1 (8*R*), 130.2 (8*S*)], [148.7 (8*R*), 148.8 (8*S*)], 168.5 $(CO_2CH_2CH_3)$. Found: m/z 327.2342. M⁺ – Bu^t requires 327.2324.

(3R)-4-(tert-Butyldimethylsilyloxy)-3-methylbutan-1-ol 15

DIBAL (1.0 M solution in toluene, 75 mL, 75 mmol) was added to a solution of **13** (10.6 g, 49.8 mmol) in CH₂Cl₂ (125 mL) at -78° C. After stirring the mixture at -78° C for 1 h, saturated NH₄Cl was added to the reaction mixture at -78° C. The reaction mixture was warmed to 25°C and stirred for 30 min. The mixture was extracted with Et₂O. The organic layer was washed with H₂O and brine, dried over Na₂SO₄, and filtered. Evaporation of the solution afforded the crude aldehyde **14** as colourless oil. The crude product was used for the next reaction without further purification, R_F (EtOAc/hexane, 1 : 10) 0.37. δ_H (500 MHz, CDCl₃) 0.03 (6 H, s, SiCH₃), 0.88 (9 H, s, SiC(CH₃)₃), 0.94 (3 H, d, *J* 6.7, 3-CH₃), 2.16–2.31 (2 H, m, H2), 2.46–2.54 (1 H, m, H3), 3.36 (1 H, dd, *J* 7.2, 9.3, H4), 3.56 (1 H, dd, *J* 4.9, 9.3, H4), 9.77 (1 H, t, *J* 2.1, CHO). δ_C (125 MHz, CDCl₃) -5.5 (2 SiCH₃), 16.7 (3-CH₃), 18.2 (SiC(CH₃)₃), 25.9 (3 C, SiC(CH₃)₃), 31.4 (C2), 48.2 (C3), 67.7 (C4), 202.6 (CHO).

To a solution of the crude aldehyde 14 in MeOH (125 mL) was added NaBH₄ (1.90 g, 50.1 mmol) at 0°C. The reaction mixture was stirred at 25°C for 24 h and quenched with satuarted NH₄Cl. The aqueous layer was extracted with Et2O and the combined organic layer was washed with H₂O and brine, dried over Na₂SO₄, filtered, and evaporated. The crude product was purified by column chromatography (SiO₂; EtOAc/hexane, 1:10) and alcohol 15 was obtained as a colourless oil (9.8 g, 89%), $R_{\rm F}$ (EtOAc/hexane, 1 : 10) 0.27, $[\alpha]_{\rm D}^{22}$ +6.9 (c 9.84, CHCl₃) {(3*S*)-15, lit.^[14b] $[\alpha]_{\rm D}^{27}$ -6.96 (c 4.80, CHCl₃)}. $v_{\rm max}$ (film)/cm⁻¹ 3347, 2956, 2857, 1463, 1388, 1361, 1255, 1093, 1052, 1006. δ_H (500 MHz, CDCl₃) 0.07 (6 H, s, SiCH₃), 0.90 (3 H, d, J 5.2, 3-CH₃), 0.91 (9 H, s, SiC(CH₃)₃), 1.51–1.64 (2 H, m, H2), 1.72–1.83 (1 H, m, H3), 3.43 (1 H, dd, J 7.3, 10.2, H4), 3.53 (1 H, dd, J 4.6, 10.2, H4), 3.59–3.66 (1 H, m, H1), 3.67–3.75 (1 H, m, H1). $\delta_{\rm C}$ (125 MHz, CDCl₃) -5.5 (2 C, SiCH₃), 17.3 (3-CH₃), 18.3 (SiC(CH₃)₃), 25.8 (3 C, SiC(CH₃)₃), 33.9 (C2), 38.0 (C3), 61.1 (C1), 68.7 (C4). Found: m/z 161.0998. M⁺ – Bu^t 161.0997.

(2R)-1-(tert-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-2-methylbutane 16

A mixture of **15** (671.8 mg, 3.08 mmol) in CH₂Cl₂ (30 mL) was added to a solution of PMBC(NH)CCl₃ (2.17 g, 7.69 mmol) and PPTS (387.0 mg, 1.54 mmol) in CH₂Cl₂ (10 mL) at 0°C. The reaction mixture was stirred at 25°C for 1 day and quenched with saturated NH₄Cl. The aqueous layer was extracted with CH₂Cl₂ and the combined organic layer was washed with H₂O and brine, dried over Na₂SO₄, filtered, and evaporated. The resulting residue was purified by column chromatography (SiO₂; EtOAc/hexane, 1 : 20) to give **16** as a colourless oil (1.04 g, 99%), $R_{\rm F}$ (CH₂Cl₂) 0.77, $[\alpha]_{\rm D}^{22}$ + 0.39 (c 10.4, CHCl₃). $v_{\rm max}$ (film)/cm⁻¹ 2954, 2929, 2856, 1513, 1245, 1100, 1020. $\delta_{\rm H}$ (500 MHz, CDCl₃) 0.03 (6 H, s, SiCH₃), 0.89 (9 H, s, SiC(CH₃)₃), 0.90 (3 H, d, *J* 6.1, 2-CH₃), 1.34–1.44 (1 H, m, H2), 1.70–1.80 (2 H, m, H4), 3.39 (1 H, dd, *J* 5.6, 10.1, H1), 3.46 (1 H, dd, *J* 5.5, 10.1, H1), 3.49 (1 H, dd, *J* 2.2, 7.0, H4), 3.50 (1 H, dd, *J* 2.1, 7.0, H4), 3.81 (3 H, s, OCH₃), 4.44 (2 H, s, CH₂Ar), 6.88 (2 H, d, *J* 8.4, C₆*H*₄OCH₃), 7.26 (2 H, d, *J* 8.4, C₆*H*₄OCH₃). $\delta_{\rm C}$ (125 MHz, CDCl₃) –5.4 (2 C, SiCH₃), 16.8 (2-CH₃), 18.3 (SiC(CH₃)₃), 25.9 (3 C, SiC(CH₃)₃), 33.0 (C2), 33.2 (C3), 55.2 (OCH₃), 68.2 (CH₂Ar), 68.4 (C1), 72.5 (C4), 113.7 (2 C, Ar), 129.2 (2 C, Ar), 130.8 (*ipso*-Ar), 159.1 (*ipso*-Ar). Found: *m*/*z* 338.2277. M⁺ requires 338.2279.

(2R)-4-(4-Methoxylbenzyloxy)-2-methylbutan-1-ol 17

TBAF (1.0 M solution in THF, 3.6 mL, 3.6 mmol) was added to a solution of 16 (801.0 mg, 2.37 mmol) in THF (4.0 mL) at 0°C. After being stirred for 6 h, the reaction mixture was quenched with saturated NH₄Cl and the aqueous layer was extracted with Et2O. The combined organic layer was washed with H2O and brine, dried over Na2SO4, filtered, and evaporated. The resulting residue was purified by column chromatography (SiO₂; EtOAc/hexane, 1:10) to give 17 as a colourless oil (526.8 mg, 99%), $R_{\rm F}$ (EtOAc/hexane, 1:10) 0.12, $[\alpha]_{\rm D}^{22}$ + 9.66 (c 5.70, CHCl₃) {(2S)-17: lit.^[23] $[\alpha]_{D}^{25}$ -7.9 (c 2.34, CHCl₃)}. v_{max} (film)/cm⁻¹ 3421, 2954, 2911, 2869, 2838, 1610, 1511, 1247, 1089, 1033. δ_H (500 MHz, CDCl₃) 0.90 (3 H, d, J 6.7, 2-CH₃), 1.52-1.61 (1 H, m, H3), 1.62-1.71 (1 H, m, H3), 1.75-1.85 (1 H, m, H2), 2.62-2.68 (1 H, m, OH), 3.38-3.35 (1H, m, H1), 3.46-3.52 (2H, m, H1, H4), 3.54-3.59 (1H, m, H4), 3.80 (3 H, s, OCH₃), 4.45 (2 H, s, CH₂Ar), 6.88 (2 H, d, J 8.5, CH₂C₆H₄OCH₃), 7.25 (2 H, d, J 8.5, CH₂C₆H₄OCH₃). δ_C (125 MHz, CDCl₃) 17.2 (2-CH₃), 34.1 (C2), 34.2 (C3), 55.2 (OCH₃), 68.1 (CH₂Ar), 68.4 (C1), 72.8 (C4), 113.8 (2 C, Ar), 129.4 (2 C, Ar), 130.1 (ipso-Ar), 159.3 (*ipso*-Ar). Found: m/z 224.1412. M⁺ requires 224.1408.

(3R)-1,3-Dibromo-4-(4-methoxybenzyloxy)-3-methylpent-1-ene 19

To a solution of (COCl)₂ (1.0 mL, 11.6 mmol) in CH₂Cl₂ (30 mL) was slowly added DMSO (0.83 mL, 11.6 mmol) at -78° C. After stirring the mixture for 30 min, 17 (1.31 g, 5.82 mmol) in CH₂Cl₂ (28 mL) was added to the reaction mixture. The reaction mixture was stirred at -78° C for 45 min and Et₃N (4.9 mL, 34.9 mmol) was added. The resulting mixture was stirred at -78°C for 1 h, warmed to 25°C, and quenched with saturated NH₄Cl. The aqueous layer was extracted with CH₂Cl₂ and the combined organic layer was washed with H2O and brine, dried over Na₂SO₄, and filtered. After evaporation, crude product 18 was obtained as a colourless oil. The crude product 18 was used for the next reaction without further purification, $R_{\rm F}$ (EtOAc/hexane, 1:4) 0.35. $\delta_{\rm H}$ (500 MHz, CDCl₃) 1.10 (3 H, d, J 7.0, 2-CH₃), 1.64–1.72 (1 H, m, H3), 1.99-2.07 (1 H, m, H3), 2.49-2.56 (1 H, m, H2), 3.45-3.55 (2 H, m, H4), 3.80 (3 H, s, OCH₃), 4.41 (2 H, s, CH₂Ar), 6.87 (2 H, d, J 8.7, Ar), 7.23 (2 H, d, J 8.7, Ar), 9.63 (1 H, d, J 1.8, CHO). Found: m/z (FAB) 223.1333. M⁺ requires 223.1334.

To a solution of CBr₄ (3.86 g, 11.6 mmol) in CH₂Cl₂ (18 mL) was added PPh3 (6.11 g, 23.3 mmol) in CH2Cl2 (28 mL) at 0°C, and the solution was stirred at 25°C. After 20 min, a solution of the crude product 18 in CH₂Cl₂ (28 mL) was added to the reaction mixture at 0°C. The reaction mixture was stirred at 25°C for 12 h and quenched with saturtaed NH₄Cl. The aqueous layer was extracted with CH₂Cl₂ and the organic layer was washed with H2O and brine, dried over Na2SO4, filtered, and evaporated. Purification by column chromatography (SiO₂; EtOAc/hexane, 1:20) gave 19 as a colourless oil (2.2 g, 100%), $R_{\rm F}$ (EtOAc/hexane, 1:10) 0.23, $[\alpha]_{D}^{22}$ -24.4 (c 8.03, CHCl₃) {lit.^[24] $[\alpha]_{D}^{26}$ -18.8 (c 1.17, CHCl₃)}. v_{max} (film)/cm⁻¹ 2958, 2929, 2857, 2834, 1612, 1511, 1245, 1110, 1050. δ_H (500 MHz, CDCl₃) 1.02 (3 H, d, J 6.7, 3-CH₃), 1.54-1.64 (1 H, m, H4), 1.65-1.73 (1 H, m, H4), 2.61-2.72 (1 H, m, H3), 3.38-3.48 (2 H, m, H5), 3.81 (3 H, s, OCH₃), 4.41 (1 H, d, J 11.5, CH₂Ar), 4.44 (1 H, d, J 11.5, CH₂Ar), 6.19 (1 H, d, J 9.4, H2), 6.88 (2 H, d, J 8.7, Ar), 7.27 (2 H, d, J 8.7, Ar). δ_C (125 MHz, CDCl₃) 19.3 (3-CH₃), 35.6 (C4), 36.0 (C3), 55.3 (OCH₃), 67.8 (CH₂Ar), 72.8 (C5), 87.7 (C1), 113.8 (2 C, Ar), 129.3 (2 C, Ar), 130.5 (ipso-Ar), 143.8 (C2), 159.2 (*ipso*-Ar). Found: *m*/*z* 375.9677. M⁺ requires 375.9674.

(4R)-6-(4-Methoxybenzyloxy)-4-methylhex-2-yne 20

To a solution of 19 (1.50 g, 3.95 mmol) in THF (7.9 mL) was added n-butyllithium (1.57 M solution in THF, 6.2 mL, 9.9 mmol) at 0°C. The reaction mixture was stirred at 25°C for 30 min and MeI (1.3 mL, 20 mmol) was added to the solution at 0°C. After stirring the mixture at 25°C for 12 h, saturated NH₄Cl was added and the aqueous layer was washed with H₂O and brine, dried over Na₂SO₄, filtered, and evaporated. The crude product was purified by column chromatography (SiO₂; EtOAc/hexane, 1:30) to give **20** as a colourless oil (819.9 mg, 89%), $R_{\rm F}$ (EtOAc/hexane, 1:10) 0.33, $[\alpha]_{\rm D}^{22}$ -65.4 (*c* 42.0, CHCl₃). $v_{\rm max}$ $(\text{film})/\text{cm}^{-1}$ 2964, 2933, 2917, 2857, 2836, 1612, 1513, 1105, 1025. δ_{H} (500 MHz, CDCl₃) 1.14 (3 H, d, J 7.0, 4-CH₃), 1.59-1.75 (2 H, m, H5), 1.77 (3 H, s, H1), 2.52-2.63 (1 H, m, H4), 3.55-3.60 (2 H, m, H6), 3.80 (3 H, s, OCH₃), 4.44 (2 H, s, CH₂Ar), 6.87 (2 H, d, J 8.5, Ar), 7.27 (2 H, d, J 8.5, Ar). δ_C (125 MHz, CDCl₃) 3.47 (C1), 21.5 (4-CH₃), 22.9 (C5), 37.2 (C4), 55.3 (OCH₃), 68.1 (CH₂Ar), 72.6 (C6), 75.8 (C3), 83.2 (C2), 113.7 (2 C, Ar), 129.2 (2 C, Ar), 130.8 (ipso-Ar), 159.1 (ipso-Ar). Found: C 77.4, H 8.8, m/z 232.1463. C15H20O2 requires C 77.6, H 8.7%, M⁺ 232.1473.

(2E,4R)-2-Dimethylphenylsilyl-6-(4-methoxybenzyloxy)-4-methylhex-2-ene 21

To a suspension of Li (580.6 mg, 83.7 mmol) in THF (60 mL) was added PhMe₂SiCl (5.0 mL, 30 mmol) at -10° C. The reaction mixture was stirred at -10°C for 2 days. The generated red solution of PhMe₂SiLi (33.2 mL, 6.59 mmol) was added to CuCN (743.4 mg, 8.30 mmol) at 0°C and the mixture was stirred at 25°C for 30 min. To the reaction mixture was added a solution of 20 (963.3 mg, 4.15 mmol) in THF (3.0 mL) at -40°C. After stirring the mixture at -40°C for 2 days, saturated NH4Cl was added to the reaction mixture, and the reaction mixture was then warmed to 25°C, and filtered through Celite. The aqueous layer was extracted with Et2O and the combined organic layer was washed with H2O and brine, dried over Na2SO4, filtered, and evaporated. Purification by column chromatography (SiO2; EtOAc/hexane, 1:40) gave 21 as a colourless oil (1.53 g, 99%), $R_{\rm F}$ (EtOAc/hexane, 1:10) 0.33, $[\alpha]_{\rm D}^{22}$ $-33.9 (c 23.3, CHCl_3). v_{max} (film)/cm^{-1} 2956, 2925, 2854, 1614, 1513,$ 1247, 1108. δ_H (500 MHz, CDCl₃) 0.31 (6 H, s, SiCH₃), 0.95 (3 H, d, J 6.7, 4-CH₃), 1.44-1.54 (1 H, m, H5), 1.63-1.73 (1 H, m, H5), 1.64 (3 H, d, J 1.6, H1), 2.72–2.81 (1 H, m, H4), 3.36 (1 H, dt, J 7.3, 9.2, H6), 3.42 (1 H, ddd, J 5.2, 7.2, 9.2, H6), 3.79 (3 H, s, OCH₃), 4.38 (2 H, s, CH₂Ar), 5.54 (1 H, dq, J 1.6, 9.1, H3), 6.86 (2 H, d, J 8.5, Ar), 7.23 (2 H, d, J 8.5, Ar), 7.30–7.35 (3 H, m, Ph), 7.45–7.49 (2 H, m, Ph). δ_C (125 MHz, CDCl₃) -3.4 (2 C, SiCH₃), 14.8 (C1), 20.7 (4-CH₃), 29.3 (C5), 37.0 (C4), 55.1 (OCH₃), 68.4 (CH₂Ar), 72.6 (C6), 113.7 (2 C, Ar), 127.6 (2 C, Ph), 128.7 (C3), 129.2 (2 C, Ar), 130.6 (ipso-Ar), 132.7 (C2), 133.9 (2 C, Ph), 138.8 (ipso-Ph), 147.1 (ipso-Ph), 159.1 (ipso-Ar). Found: C 74.7, H 8.9, m/z 368.2172. C23H32O2Si requires C 75.0, H 8.8%, M⁺ 368.2187.

(3R,4E)-5-Dimethylphenylsilyl-3-methylhex-4-en-1-ol 22

To a mixture of 21 (687.7 mg, 1.87 mmol) in CH₂Cl₂ (19 mL) and H₂O (1.9 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (900 mg, 3.96 mmol) at 0°C. The mixture was stirred at 25°C for 2 h and quenched with saturated Na2CO3. The aqueous layer was extracted with CH2Cl2. The combined organic layer was washed with H2O and brine, dried over Na2SO4, filtered, and evaporated. The resulting residue was purified by column chromatography (SiO₂; EtOAc/hexane, 1:10) to give 22 as a colourless oil (366.4 mg, 80%), R_F (CH₂Cl₂) 0.42, $[\alpha]_D^{22}$ -34.8 (c 5.37, CHCl₃). v_{max} (film)/cm⁻¹ 3390, 2956, 2925, 2869, 1427, 1247, 1108, 1051. δ_H (500 MHz, CDCl₃) 0.32 (6 H, s, SiCH₃), 0.98 (3 H, d, J 6.7, 3-CH₃), 1.46-1.55 (1 H, m, H2), 1.58-1.66 (1 H, m, H2), 1.68 (3 H, d, J 1.8, H6), 2.70-2.82 (1 H, m, H3), 3.54-3.67 (2 H, m, H1), 5.60 (1 H, dq, J 1.8, 9.4, H4), 7.32-7.35 (3 H, m, Ph), 7.45-7.50 $(2~\text{H}, m, \text{Ph}).~\delta_C~(125~\text{MHz}, \text{CDCl}_3) - 3.4~(2~\text{C}, \text{SiCH}_3), 14.9~(\text{C6}), 20.8$ (3-CH₃), 29.4 (C2), 40.1 (C3), 61.6 (C1), 127.7 (2 C, Ph), 128.8 (C4), 133.1 (C5), 133.9 (2 C, Ph), 138.6 (ipso-Ph), 147.1 (ipso-Ph). Found: *m*/*z* 248.1596. M⁺ requires 248.1601.

(3R,4E)-3-Methyl-5-dimethylphenylsilylhex-4-en-1-yl 2',2'-Dimethylpropionate 23

To a mixture of 22 (766.3 mg, 3.09 mmol) and pyridine (1.25 mL, 15.4 mmol) in CH₂Cl₂ (15 mL) was added pivaloyl chloride (0.57 mL, 4.63 mmol) at 0°C. The mixture was stirred at 25°C for 12 h, quenched with saturated NH4Cl, and evaporated. The aqueous layer was extracted with CH2Cl2. The combined organic layer was washed with H2O and brine, dried over Na2SO4, filtered, and evaporated. The resulting residue was purified by column chromatography (SiO2; EtOAc/hexane, 1:40) to give 23 as a colourless oil (926.5 mg, 90%), $R_{\rm F}$ (CH₂Cl₂) 0.71, $[\alpha]_{\rm D}^{22}$ -33.9 (c 23.2, CHCl₃). v_{max} (film)/cm⁻¹ 2958, 2925, 1727, 1155. δ_{H} (500 MHz, CDCl₃) 0.33 (6 H, s, SiCH₃), 1.00 (3 H, d, J 6.7, 3-CH₃), 1.20 (9 H, s, COC(CH₃)₃), 1.51-1.59 (1 H, m, H2), 1.64-1.72 (1 H, m, H2), 1.66 (3 H, d, J 1.8, H6), 2.70-2.82 (1 H, m, H3), 3.97 (1 H, ddd, J 6.4, 6.9, 11.0, H1), 4.08 (1 H, dt, J 5.5, 11.0, H1), 5.56 (1 H, dq, J 1.8, 9.4, H4), 7.31–7.40 (3 H, m, Ph), 7.46–7.53 (2 H, m, Ph). δ_C (125 MHz, CDCl₃) -3.4 (SiCH₃), 1.0 (SiCH₃), 14.8 (C6), 20.6 (3-CH₃), 27.2 (3 C, COC(CH₃)₃), 29.2 (COC(CH₃)₃), 35.8 (C2), 38.7 (C3), 62.8 (C1), 127.7 (2 C, Ph), 128.8 (C5), 133.4 (C4), 133.9 (2 C, Ph), 138.6 (ipso-Ph), 146.4 (ipso-Ph), 178.6 (CO₂). Found: C 72.2, H 9.7, m/z 332.2183. C₂₀H₃₂O₂Si requires C 72.2, H 9.9%, M⁺ 332.2172.

(3R,4E)-5-Iodo-3-methylhex-4-en-1-yl 2',2'-Dimethylpropionate 12

To a mixture of 23 (403.2 mg, 1.21 mmol) in THF (0.6 mL) and MeCN (2.4 mL) was added NIS (686.0 mg, 3.05 mmol) at 25°C. The mixture was stirred at 25°C for 2 days and quenched with saturated Na₂S₂O_{3.} The aqueous layer was extracted with Et2O. The combined organic layer was washed with H2O and brine, dried over Na2SO4, filtered, and evaporated. The resulting residue was purified by column chromatography (SiO₂; EtOAc/hexane, 1:40) to give **12** as a colourless oil (378.1 mg, 96%), $R_{\rm F}$ (EtOAc/hexane, 1:10 (twice)) 0.71, $[\alpha]_{\rm D}^{22}$ -69.4 (c 18.7, CHCl₃). v_{max} (film)/cm⁻¹ 2360, 2331, 1635, 1165. δ_{H} (500 MHz, CDCl₃) 1.00 (3 H, d, J 6.7, 3-CH₃), 1.20 (9 H, s, C(CH₃)₃), 1.50-1.58 (1 H, m, H2), 1.61-1.70 (1 H, m, H2), 2.37 (3 H, d, J 1.2, H6), 2.51-2.60 (1 H, m, H3), 3.97 (1 H, ddd, J 5.8, 6.2, 11.1, H1), 4.09 (1 H, dt, J 5.7, 11.1, H1), 5.94 (1 H, dq, J 1.2, 10.1, H4). δ_C (125 MHz, CDCl₃) 20.4 (3-CH₃), 27.2 (3 C, C(CH₃)₃), 27.6 (C(CH₃)₃), 32.5 (C6), 35.5 (C2), 38.7 (C3), 62.4 (C1), 93.4 (C5), 145.9 (C4), 178.4 (CO2). Found: C 44.5, H 6.5, m/z 324.0586. C12H21IO2 requires C 44.5, H 6.5%, M⁺ 324.0573.

(3R,4E,7S,9R)-10-(tert-Butyldimethylsilyloxy)-3,7,9-trimethyldec-4-en-1-yl 2',2'-Dimethylpropionate 24

To ZnCl₂ (339.1 mg, 2.49 mmol), which was flame-dried under vacuum, was added **10** (886.6 mg, 2.49 mmol) in Et₂O (5.5 mL). The solution was cooled to -78° C and Bu^{*I*}Li (1.47 M solution in pentane, 4.98 mL, 7.46 mmol) was added. After being stirred at -78° C for 5 min, the reaction mixture was warmed to 0°C. After 1.5 h, Pd(PPh₃)₄ (8.81 mg, 5.67 × 10⁻² mmol) was added to the reaction mixture at 0°C. To the reaction mixture was slowly added **12** (366.7 mg, 1.13 mmol) in THF (5.5 mL) at 0°C. The mixture was stirred at 0°C for 2.5 h and quenched with saturated NH₄Cl. The aqueous layer was extracted with Et₂O and the combined organic layer was washed with H₂O and brine, dried over Na₂SO₄, filtered, and evaporated. The crude product was purified by column chromatography (SiO₂; EtOAc/hexane, 1:30) to give a mixture of **24** and **12'** (**24**: colourless oil, 411.9 mg, 85%; **12'**: colourless oil, 32.7 mg, 7%).

For **24**, R_F (EtOAc/hexane, 1 : 10) 0.54, $[\alpha]_D^{22} - 22.9$ (*c* 7.20, CHCl₃). v_{max} (film)/cm⁻¹ 2956, 2927, 2857, 1731, 1481, 1471, 1165, 1100. δ_H (500 MHz, CDCl₃) 0.04 (6 H, s, SiCH₃), 0.79 (3 H, d, *J* 6.4, 7-CH₃), 0.82–0.92 (1 H, m, H8), 0.88 (3 H, d, *J* 6.4, 9-CH₃), 0.89 (9 H, s, SiC(CH₃)₃), 0.96 (3 H, d, *J* 7.0, 3-CH₃), 1.19 (9 H, s, C(CH₃)₃), 1.22– 1.34 (1 H, m, H8), 1.43–1.52 (1 H, m, H2), 1.55 (3 H, s, 5-CH₃), 1.57–1.74 (4 H, m, H2, H6, H7, H9), 2.01 (1 H, dd, *J* 4.0, 12.8, H6), 2.45–2.56 (1 H, m, H3), 3.32 (1 H, dd, *J* 6.7, 9.8, H10), 3.45 (1 H, dd, *J* 5.5, 9.8, H10), 3.96 (1 H, dt, *J* 9.4, 10.8, H3), 4.07 (1 H, dt, *J* 7.6, 10.8, H1), 4.86 (1 H, d, *J* 9.4, H4). δ_C (125 MHz, CDCl₃) – 5.4 (2 C, SiCH₃), 16.1 (5-CH₃), 17.7 (9-CH₃), 18.3 (SiC(CH₃)₃), 19.9 $(7-CH_3)$, 21.3 $(3-CH_3)$, 26.0 $(3 \text{ C}, \text{SiC}(CH_3)_3)$, 27.2 $(3 \text{ C}, \text{COC}(CH_3)_3)$, 28.1 (C7), 29.2 (C3), 33.1 (C9), 36.3 (C2), 38.7 (COC(CH_3)_3), 41.4 (C8), 47.6 (C6), 63.0 (C1), 68.4 (C10), 131.6 (C4), 133.5 (C5), 178.6 (CO_2). Found: C 70.2, H 11.9, m/z 426.3529. C₂₅H₅₀O₃Si requires C 70.4, H 11.8%, M⁺ 426.3536.

For **12'**, $\delta_{\rm H}$ (500 MHz, CDCl₃) 1.00 (6 H, d, *J* 6.7, 3-CH₃, 8-CH₃), 1.19 (18 H, s, COC(*CH*₃)₃), 1.50–1.59 (2 H, m, H2, H9), 1.64–1.72 (2 H, m, H2, H9), 1.76 (6 H, s, 5-CH₃, 6-CH₃), 2.57–2.68 (2 H, m, H3, H8), 3.92–3.99 (2 H, m, H1, H10), 4.03–4.10 (2 H, m, H1, H10), 5.23 (2 H, d, *J* 9.4, H4, H7). Found: *m*/*z* 394.3083. M⁺ requires 394.3083.

(3R,4E,7S,9R)-10-(tert-Butyldimethylsilyloxy)-3,7,9-trimethyldec-4-en-1-ol 25

To a suspension of LiAlH₄ (35.1 mg, 0.91 mmol) in THF (4.5 mL) was added 24 (191.7 mg, 0.45 mmol) in THF (1.0 mL) at 0°C. The reaction mixture was stirred at 25°C for 6 h and quenched with H₂O. The formed precipitate was filtered off. The filtrate was washed with H2O and brine, dried over Na₂SO₄, filtered, and evaporated. The resulting residue was purified by column chromatography (SiO2; EtOAc/hexane, 1:10) to give 25 as a colourless oil (149.7 mg, 97%), R_F (CH₂Cl₂) 0.23, $[\alpha]_D^{22}$ –19.3 (*c* 7.24, CHCl₃). v_{max} (film)/cm⁻¹ 3365, 2954, 2927, 2857, 1471, 1461, 1251, 1093. δ_H (500 MHz, CDCl₃) 0.04 (6 H, s, SiCH₃), 0.79 (3 H, d, J 6.4, 7-CH₃), 0.82-0.87 (1 H, m, H8), 0.88 (3 H, d, J 6.7, 9-CH₃), 0.89 (9 H, s, SiC(CH₃)₃), 0.95 (3 H, d, J 6.7, 3-CH₃), 1.23-1.31 (1 H, m, H8), 1.40-1.50 (2 H, m, H2, OH), 1.56-1.74 (4 H, m, H2, H6, H7, H9), 1.58 (3 H, d, J 1.2, 5-CH₃), 2.00 (1 H, dd, J 3.8, 11.6, H6), 2.47-2.57 (1 H, m, H3), 3.31 (1 H, dd, J 6.7, 9.6, H10), 3.45 (1 H, dd, J 5.2, 9.6, H10), 3.55–3.67 (2 H, m, H1), 4.90 (1 H, dd, J 1.2, 9.1, H4). δ_C (125 MHz, CDCl₃) – 5.4 (2 C, SiCH₃), 16.1 (5-CH₃), 17.7 (9-CH₃), 18.3 (SiC(CH₃)₃), 20.0 (7-CH₃), 21.5 (3-CH₃), 26.0 (3 C, SiC(CH₃)₃), 28.1 (C7), 29.4 (C3), 33.1 (C9), 40.5 (C2), 41.3 (C8), 47.7 (C6), 61.7 (C1), 68.3 (C10), 132.1 (C4), 133.3 (C5). Found: m/z 342.2958. M⁺ requires 342.2954.

(3R,4E,7S,9R)-10-(tert-Butyldimethylsilyloxy)-3,5,7,9-tetramethyldec-4-en-1-yl Methanesulfonate **26**

To a solution of 25 (300.4 mg, 0.88 mmol) in THF (5.0 mL) were added Et₃N (0.37 mL, 2.63 mmol) and MsCl (0.1 mL, 1.32 mmol) in THF (0.4 mL) at 0°C. The reaction mixture was stirred at 25°C for 3 h and quenched with saturated NH₄Cl. The aqueous layer was extracted with Et₂O and the combine organic layer was washed with H₂O and brine, dried over Na₂SO₄, and filtered. After concentration, purification by column chromatography (SiO₂; EtOAc/hexane, 1:30) gave 26 as a colourless oil (360.4 mg, 98%), $R_{\rm F}$ (CH₂Cl₂) 0.65. $v_{\rm max}$ (film)/cm⁻¹ 2956, 2927, 2856, 1643, 1471, 1461, 1359, 1294, 1176, 1091. $\delta_{\rm H}$ (500 MHz, CDCl₃) 0.03 (6 H, s, SiCH₃), 0.79 (3 H, d, J 6.4, 7-CH₃), 0.82-0.93 (1 H, m, H8), 0.88 (3 H, d, J 6.7, 9-CH₃), 0.89 (9 H, s, SiC(CH₃)₃), 0.97 (3 H, d, J 6.7, 3-CH₃), 1.23-1.31 (1 H, m, H8), 1.55-1.74 (4 H, m, H2, H6, H7, H9), 1.57 (3 H, s, 5-CH₃), 1.75-1.84 (1 H, m, H2), 2.03 (1 H, dd, J 4.3, 12.2, H6), 2.49-2.60 (1 H, m, H3), 2.97 (3 H, s, CH₃SO₂), 3.33 (1 H, dd, J 6.7, 9.3, H10), 3.45 (1 H, dd, J 5.2, 9.3, H10), 4.10-4.17 (1 H, m, H1), 4.19-4.25 (1 H, m, H1), 4.83 (1 H, d, J 9.4, H4). δ_C (125 MHz, CDCl₃) -5.4 (2 C, SiCH₃), 16.1 (5-CH₃), 17.6 (9-CH₃), 18.3 (SiC(CH₃)₃), 19.8 (7-CH₃), 21.3 (3-CH₃), 25.9 (3 C, SiC(CH₃)₃), 28.1 (C7), 28.8 (C3), 33.1 (C9), 36.6 (C2), 37.3 (CH₃SO₂), 41.4 (C8), 47.6 (C6), 68.3 (C1), 68.9 (C10), 130.5 (C4), 134.6 (C5). Found: m/z 363.2038. M⁺ – Bu^t requires 363.2025.

(3R,4E,7S,9R)-10-(tert-Butyldimethylsilyloxy)-3,5,7,9-tetramethyldec-4-ene **2**7

To a suspension of LiAlH₄ (45.5 mg, 1.21 mmol) in THF (3.0 mL) was added **26** (249.7 mg, 0.59 mmol) in THF (2.0 mL) at 0°C. The mixture was stirred at 25°C for 6 h and quenched. The formed precipitate was filtered off and the filtrate was washed with H₂O and brine, dried over Na₂SO₄, filtered, and evaporated. The resulting residue was purified by column chromatography (SiO₂; EtOAc/hexane, 1:30) to give **27** as a colourless oil (191.4 mg, 99%), R_F (EtOAc/hexane, 1:10) 0.77, $[\alpha]_D^{22} - 7.14 (c 3.78, CHCl_3). v_{max}$ (film)/cm⁻¹ 2958, 2927, 2856, 2360,

2331, 1635, 1463, 1259, 1049. $\delta_{\rm H}$ (500 MHz, CDCl₃) 0.03 (6 H, s, SiCH₃), 0.80 (3 H, d, *J* 6.1, 7-CH₃), 0.83 (3 H, t, *J* 7.3, H1), 0.88 (3 H, d, *J* 7.0, 9-CH₃), 0.91 (9 H, s, SiC(CH₃)₃), 0.94 (3 H, d, *J* 7.0, 3-CH₃), 0.86–0.92 (1 H, m, H2), 1.15–1.24 (1 H, m, H8), 1.25–1.36 (2 H, m, H2), 1.56 (3 H, d, *J* 1.2, 5-CH₃), 1.61–1.75 (3 H, m, H6, H7, H9), 1.94–2.05 (1 H, m, H6), 2.19–2.29 (1 H, m, H3), 3.31 (1 H, dd, *J* 7.0, 9.6, H10), 3.46 (1 H, dd, *J* 4.9, 9.6, H10), 4.85 (1 H, d, *J* 9.4, H4). $\delta_{\rm C}$ (125 MHz, CDCl₃) –5.4 (2 C, SiCH₃), 12.0 (C1), 16.2 (5-CH₃), 17.8 (9-CH₃), 18.4 (SiC(CH₃)₃), 20.1 (7-CH₃), 21.1 (3-CH₃), 26.0 (3 C, SiC(CH₃)₃), 28.2 (C7), 30.5 (C3), 33.2 (C9), 34.1 (C2), 41.2 (C8), 47.9 (C6), 68.3 (C10), 132.4 (C5), 132.9 (C4). Found: C 73.6, H 12.9, *m*/z 326.3004. C₂₀H₄₂O₂Si requires C 73.5, H 12.4%, M⁺ 326.3005.

(2R,4S,6E,8R)-2,4,6,8-Tetramethyldec-6-en-1-ol 28

To a solution of 27 (123.3 mg, 0.38 mmol) in THF (3.8 mL) was added TBAF (1.0 M solution in THF. 0.76 mL, 0.76 mmol) at 25°C. The reaction mixture was stirred at 25°C for 6 h and quenched with saturated NH₄Cl. The aqueous layer was extracted with Et₂O and the combined organic layer was washed with H2O and brine, dried over Na2SO4, filtered, and evaporated. The resulting residue was purified by column chromatography (SiO2; EtOAc/hexane, 1:20) to give 28 as a colourless oil (79.4 mg, 99%), $R_{\rm F}$ (CH₂Cl₂) 0.32, $[\alpha]_{\rm D}^{22}$ -17.0 (c 1.20, CHCl₃) {lit.^[4h] $[\alpha]_D^{25}$ -14.4 (c 1.10, CHCl₃)}. v_{max} (film)/cm⁻¹ 3629, 2958, 2915, 2871, 2360, 2331, 1457, 1376, 1039. δ_H (500 MHz, CDCl₃) 0.82 (3 H, d, J 6.1, 4-CH₃), 0.83 (3 H, t, J 7.3, H10), 0.89 (3 H, d, J 10.4, 2-CH₃), 0.92–0.97 (1 H, m, H3), 0.93 (3 H, d, J 6.7, 8-CH₃), 1.14–1.24 (1 H, m, H3), 1.27-1.36 (2 H, m, H9), 1.37-1.50 (1 H, m, OH), 1.56 (3 H, d, J 1.2, H5), 1.62–1.70 (2 H, m, H2, H5), 1.71–1.79 (1 H, m, H4), 1.99 (1 H, dd, J 9.1, 16.5 Hz, H5), 2.19-2.22 (1 H, m, H8), 3.36 (1 H, dd, J 6.9, 10.8 Hz, H1), 3.53 (1 H, dd, J 5.0, 10.8, H1), 4.86 (1 H, dd, J 9.1, H7). δ_C (125 MHz, CDCl₃) 11.6 (C10), 15.8 (6-CH₃), 17.1 (2-CH₃), 19.8 (4-CH₃), 20.6 (8-CH₃), 27.8 (C4), 30.1 (C8), 32.8 (C2), 33.7 (C9), 40.5 (C3), 47.3 (C5), 67.9 (C1), 131.8 (C6), 132.7 (C7). Found: m/z 212.2141. M⁺ requires 212.2140.

Ethyl (2E, 4E, 6E, 8R, 10S, 12E, 14R)-8, 10, 12, 14-Tetramethylhexadeca-2,4,6, 12-tetraenoate **30**

DMSO (0.21 mL, 3.0 mmol) in CH₂Cl₂ (4.0 mL) was slowly added to a solution of (COCl)₂ (0.20 mL, 2.25 mmol) in CH₂Cl₂ (0.5 mL) at -78°C. After stirring the mixture for 30 min, 28 (158.9 mg, 0.75 mmol) in CH₂Cl₂ (4.0 mL) was added at -78°C. To the solution was added Et₃N (1.56 mL, 11.2 mmol) at -78°C. After being stirred at -78°C for 1 h, the reaction mixture was warmed to 25°C and stirred for 30 min. The reaction mixture was guenched with saturated NH₄Cl and the agueous layer was extracted with CH2Cl2. The combined organic layer was washed with H2O and brine, dried over Na2SO4, and filtered. After evaporation, crude product 29 was obtained. The crude product was used for the next reaction without further purification, R_F (EtOAc/hexane, 1:10) 0.50. δ_H (500 MHz, CDCl₃) 0.76 (3 H, t, J 7.5, H10), 0.77 (3 H, d, J 6.7, 4-CH₃), 0.83 (3 H, d, J 6.7, 8-CH₃), 0.98-1.06 (1 H, m, H3), 1.01 (3 H, d, J 7.0, 2-CH₃), 1.08–1.17 (1 H, m, H3), 1.48 (3 H, d, J 0.9, 6-CH₃), 1.54-1.62 (1 H, m, H4), 1.21-1.30 (2 H, m, H9), 1.63-1.72 (1 H, m, H5), 1.89 (1 H, dd, J 6.4, 13.1, H5), 2.11-2.22 (1 H, m, H2), 2.34-2.44 (1 H, m, H8), 4.80 (1 H, d, J 9.1, H7), 9.48 (1 H, d, J 2.7, CHO).

To an LDA solution [diisopropylamine (0.19 mL, 1.35 mmol), BuⁿLi (1.57 M in THF, 0.55 mL, 0.86 mmol), THF (2.0 mL), 0°C, 30 min] was added phosphonate **5** (413.3 mg, 1.50 mmol) in THF (3.0 mL) at -78° C. After the mixture was stirred for 30 min, the crude aldehyde **29** in THF (3.0 mL) was added at -78° C. The solution was stirred at -78° C for 2 h and quenched with H₂O. The aqueous layer was extracted with Et₂O and the combined organic layer was washed with H₂O and brine, dried over Na₂SO₄, filtered, and evaporated. The resulting residue was purified by column chromatography (SiO₂; EtOAc/hexane, 1:30) to give a mixture of (2*E*,4*E*,6*E*)-, (2*Z*,4*E*,6*E*)-, (2*E*,4*Z*,6*E*)-, and (2*E*,4*E*,6*Z*)-**30** (212.7 mg, 85%). The four geometric isomers were separated by HPLC (Wako Sil-II; hexane/PrⁱOH, 4000:1). For (2*E*,4*E*,6*E*)-**30**, *R*_F (EtOAc/hexane, 1:10) 0.42, [α]_{D2}²² -1.57 (*c* 0.19,

CHCl₃) {lit.^[4h] $[\alpha]_D^{25} - 2.35 (c \ 0.34, CHCl_3)$ }. $v_{max} (film)/cm^{-1} 2958$, 2923, 2871, 2358, 2343, 1714, 1617, 1455, 1369, 1270, 1250, 1120, 1005. δ_H (500 MHz, CD₃OD) 0.83 (3 H, d, J 6.4, 10-CH₃), 0.86 (3 H, t, J 7.5, H16), 0.91 (3 H, d, J 6.6, 14-CH₃), 0.97-1.07 (1 H, m, H9), 1.01 (3 H, d, J 6.6, 8-CH₃), 1.14-1.24 (1 H, m, H15), 1.28 (3 H, t, J 7.1, OCH2CH3), 1.30-1.35 (1 H, m, H15), 1.35-1.40 (1 H, m, H9), 1.54 (3 H, d, J 1.2, 12-CH₃), 1.56-1.63 (1 H, m, H10), 1.80 (1 H, dd, J 7.2, 13.0, H11), 1.90 (1 H, dd, J 7.2, 13.0, H11), 2.20-2.31 (1 H, m, H14), 2.32-2.42 (1 H, m, H8), 4.18 (2 H, q, J 7.1, OCH2CH3), 4.84 (1 H, dq, J 1.2, 9.6, H13), 5.76 (1 H, dd, J 8.7, 15.1, H7), 5.87 (1 H, d, J 15.3, H2), 6.17 (1 H, dd, J 10.7, 15.1, H6), 6.30 (1 H, dd, J 11.2, 14.7, H4), 6.60 (1 H, ddd, J 0.5, 10.7, 14.7, H5), 7.30 (1 H, ddd, J 0.5, 11.2, 15.3, H3). δ_C (125 MHz, CD₃OD) 13.0 (C16), 15.0 (OCH₂CH₃), 16.8 (C18), 20.3 (C19), 22.0 (C17), 22.3 (C20), 29.9 (C10), 32.1 (C15), 35.8 (C14), 36.7 (C8), 45.6 (C9), 50.0 (C11), 61.8 (OCH₂CH₃), 121.2 (C2), 129.6 (C4), 130.3 (C6), 133.9 (C12), 134.6 (C13), 143.3 (C5), 146.9 (C3), 147.7 (C7), 169.4 (CO₂). Found: C 79.2, H 11.2, m/z 332.2707. C₂₂H₃₆O₂ requires C 79.5, H 10.9%, M⁺ 332.2715.

For (2Z,4E,6E)-**30**, $R_{\rm F}$ (EtOAc/hexane, 1 : 10) 0.42, $[\alpha]_{\rm D}^{22}$ - 0.42 (*c* 0.21, CHCl₃). $\delta_{\rm H}$ (500 MHz, CDCl₃) 0.80 (3 H, d, J 6.4, 10-CH₃), 0.84 (3 H, t, J 7.6, H16), 0.90 (3 H, d, J 6.4, 14-CH₃), 0.99–1.05 (1 H, m, H9), 1.00 (3 H, d, J 6.7, 8-CH₃), 1.07–1.12 (1 H, m, H9), 1.16–1.23 (2 H, m, H9, H15), 1.30 (3 H, t, J 7.3, OCH₂CH₃), 1.52 (3 H, d, J 0.9, 12-CH₃), 1.57–1.59 (1 H, m, H10), 1.73–1.79 (1 H, m, H11), 1.86–1.91 (1 H, m, H11), 2.20–2.28 (1 H, m, H11), 2.31–2.38 (1 H, m, H8), 4.19 (2 H, q, J 7.3, OCH₂CH₃), 4.84 (1 H, d, J 9.1, H13), 5.60 (1 H, d, J 11.4, H2), 5.71 (1 H, dd, J 8.8, 14.9, H7), 6.19 (1 H, dd, J 10.7, 14.9, H6), 6.45 (1 H, dd, J 10.7, 15.1, H5), 6.58 (1 H, t, J 11.4, H3), 7.42 (1 H, dd, J 11.4, 15.1, H4). Found: *m*/*z* 332.2724. M⁺ requires 332.2715.

For (2E, 4Z, 6E)-**30**, $R_{\rm F}$ (EtOAc/hexane, 1 : 10) 0.42, $[\alpha]_{\rm D}^{22} + 21.5$ (*c* 0.15, CHCl₃). $\delta_{\rm H}$ (500 MHz, CDCl₃) 0.82 (3 H, d, *J* 6.4, 10-CH₃), 0.83 (3 H, t, *J* 6.4, H16), 0.90 (3 H, d, *J* 6.7, 14-CH₃), 0.95–1.00 (1 H, m, H9), 1.00–1.07 (1 H, m, H15), 1.01 (3 H, d, *J* 6.7, 8-CH₃), 1.15–1.37 (2 H, m, H9, H15), 1.30 (3 H, t, *J* 7.2, OCH₂CH₃), 1.52 (3 H, d, *J* 1.2, 12-CH₃), 1.56–1.58 (1 H, m, H10), 1.77 (1 H, dd, *J* 7.3, 13.4, H11), 1.89 (1 H, dd, *J* 7.0, 13.4, H11), 2.19–2.28 (1 H, m, H14), 2.34–2.42 (1 H, m, H8), 4.22 (2 H, q, *J* 7.2, OCH₂CH₃), 4.84 (1 H, d, *J* 9.1, H13), 5.70 (1 H, dd, *J* 8.3, 14.9, H7), 5.85 (1 H, d, *J* 15.0, H2), 5.99 (1 H, t, *J* 11.4, H4), 6.28 (1 H, t, *J* 14.4, H5), 6.56 (1 H, dd, *J* 11.4, 14.9, H6), 7.74 (1 H, dd, *J* 11.4, 15.0, H3). Found: m/z 332.2711. M⁺ requires 332.2715.

For (2E, 4E, 6Z)-**30**, $R_{\rm F}$ (EtOAc/hexane, 1 : 10) 0.42, $[\alpha]_{\rm D}^{22}$ +59.8 (*c* 0.24, CHCl₃). $\delta_{\rm H}$ (500 MHz, CDCl₃) 0.79 (3 H, d, *J* 6.7, 10-CH₃), 0.84 (3 H, t, *J* 7.4, H16), 0.89 (3 H, d, *J* 6.7, 14-CH₃), 0.97 (3 H, d, *J* 6.7, 8-CH₃), 0.99–1.03 (1 H, m, H9), 1.03–1.08 (1 H, m, H15), 1.14–1.36 (2 H, m, H9, H15), 1.30 (3 H, t, *J* 7.1, OCH₂CH₃), 1.46–1.51 (1 H, m, H10), 1.51 (3 H, d, *J* 1.2, 12-CH₃), 1.78 (1 H, dd, *J* 7.2, 13.0, H11), 1.87 (1 H, dd, *J* 7.2, 13.0, H11), 2.18–2.28 (1 H, m, H14), 2.73–2.83 (1 H, m, H8), 4.21 (2 H, q, *J* 7.1, OCH₂CH₃), 4.84 (1 H, d, *J* 8.8, H13), 5.37 (1 H, t, *J* 11.0, H7), 5.86 (1 H, d, *J* 15.5, H2), 6.05 (1 H, t, *J* 11.0, H6), 6.29 (1 H, dd, *J* 11.3, 14.5, H4), 6.84 (1 H, dd, *J* 11.0, 14.5, H5), 7.34 (1 H, dd, *J* 11.3, 15.5, H3). Found: m/z 332.2706. M⁺ requires 332.2715.

(2E, 4E, 6E, 8R, 10S, 12E, 14R)-8, 10, 12, 14-Tetramethylhexadeca-2, 4, 6, 12-tetraenoic acid **2**

To a solution of (2E, 4E, 6E)-**30** (25.8 mg, 8.0×10^{-2} mmol) in MeOH (8.0 mL) was added 5.0 M LiOH (0.54 mL, 3.20 mmol) at 25°C, and the reaction mixture was stirred at 25°C. After 2 days, MeOH was removed under vacuum. The residue was extracted with EtOAc and the combined organic layer was washed with brine, dried over Na₂SO₄, filtered, and evaporated. Purification by column chromatography (SiO₂; CHCl₃/MeOH, 15 : 1) gave (2*E*,4*E*,6*E*)-**2** as a colourless oil (23.4 mg, 100%), $R_{\rm F}$ (EtOAc/hexane, 2 : 1) 0.58, $[\alpha]_{\rm D}^{22}$ – 3.53 (*c* 0.41, CHCl₃). $v_{\rm max}$ (film)/cm⁻¹ 3446, 2958, 2915, 2869, 2360, 2329, 1683, 1614, 1265, 1100. $\delta_{\rm H}$ (500 MHz, CDCl₃) 0.80 (3 H, d, *J* 6.4, 10-CH₃), 0.84 (3 H, t, *J* 7.5, H16), 0.90 (3 H, d, *J* 6.7, 14-CH₃), 0.97–1.06 (1 H, m, H9), 1.00 (3 H, d, *J* 6.7, 8-CH₃), 1.13–1.24 (1 H, m, H15), 1.24–1.38 (2 H, m, H9, H15), 1.53 (3 H, s, 12-CH₃), 1.53–1.59 (1 H, m, H10), 1.76

(1 H, dd, J 7.5, 13.4, H11), 1.89 (1 H, dd, J 6.9, 13.4, H11), 2.18–2.29 (1 H, m, H14), 2.30–2.42 (1 H, m, H8), 4.84 (1 H, d, J 9.4, H13), 5.76 (1 H, dd, J 8.5, 14.9, H7), 5.84 (1 H, d, J 14.5, H2), 6.12 (1 H, dd, J 10.7, 14.9, H6), 6.24 (1 H, dd, J 11.4, 14.3, H4), 6.56 (1 H, dd, J 10.7, 14.3, H5), 7.39 (1 H, dd, J 11.4, 14.5, H3), 11.2–12.5 (1 H, br s, CO₂H). $\delta_{\rm C}$ (125 MHz, CDCl₃) 12.0 (C16), 16.2 (C18), 19.5 (C19), 21.0 (C17), 21.3 (C20), 28.3 (C10), 30.5 (C15), 34.1 (C14), 35.0 (C8), 43.9 (C9), 48.3 (C11), 119.1 (C2), 127.6 (C4), 128.2 (C6), 132.0 (C12), 133.1 (C13), 142.5 (C5), 147.1 (C3), 147.2 (C7), 172.9 (CO₂). Found: C 79.0, H 10.6, *m*/z 304.2397. C₂₀H₃₂O₂ requires C 78.9, H 10.6%, M⁺ 304.2402.

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