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Total Synthesis of the Proposed Structures of the Novel Antimalarial Pyranone Cryptorigidifoliol E

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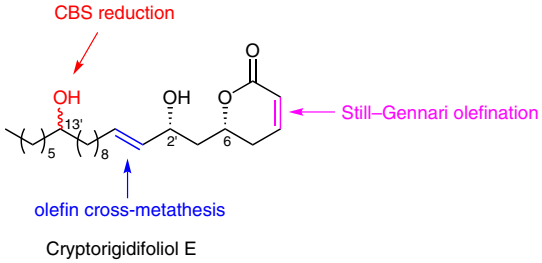

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Abstract The total syntheses of the proposed structures of the antimalarial lactone cryptorigidifoliol E are described. The synthetic sequence notably features a Bartlett–Smith halocyclization to give a chiral epoxide, followed by its regioselective ring-opening reaction, Still–Gennari olefination, Corey–Bakshi–Shibata (CBS) ynone reduction, and olefin cross-metathesis.

Key words total synthesis, cryptorigidifoliol E, lactones, Bartlett–Smith halocyclization, Corey–Bakshi–Shibata reduction, cross-metathesis

The δ-lactone moiety is a privileged scaffold, widely distributed among natural products. In particular, pyranones are extremely important because of their bioactivities, which include antifungal, antibacterial, antitumor, and antimalarial activities.[1] Five new antimalarial α,β-unsaturated δ-lactones were recently isolated from the root wood of *Cryptocarya rigidifolia* and were named cryptorigidifoliols A–E (Figure 1).[2] Inspired by the biological activity of these compounds and by the synthetic challenges offered by their structures, and because of our interest in this class of natural products,[3] we set out to synthesize cryptorigidifoliol E. As the absolute stereochemistry at C13′ had not been determined, we attempted to synthesize both epimers of the target molecule.

Our retrosynthetic analysis of compound **5** is shown in Scheme 1. Compounds **5a** and **5b** might be obtained from the two pairs of intermediates **6** and **7a** (for **5a**) and **6** and **7b** (for **5b**) by Grubbs catalyst assisted olefin cross-metathesis. The key lactone fragment **6** might in turn be obtained from enoate **8** by an acid-catalyzed one-pot acetonide deprotection, followed by lactonization. Enoate **8** might be prepared by Still–Gennari olefination and regioselective epoxide ring cleavage of epoxide **9**, which might in turn be prepared from the known homoallylic alcohol **10**.[4] Because the configuration of the C13′ stereogenic carbon had not been assigned, we proposed to synthesize both epimers of the target molecule. Accordingly, the pivotal enantiomeric olefins **7a** and **7b**, the other olefinic partners, might be synthesized from ynone **11**, and the lone stereogenic center might be generated by Corey–Bakshi–Shibata (CBS) reduction. Advantageously, both enantiomers might be obtainable merely by changing the catalyst. The silyl-protected ynone **11** might be prepared from commercially available octane-1,8-diol.

To begin our synthesis, we prepared the known optically active homoallylic alcohol **10**[4] from commercially available propane-1,3-diol (Scheme 2). Next, alcohol **10** was

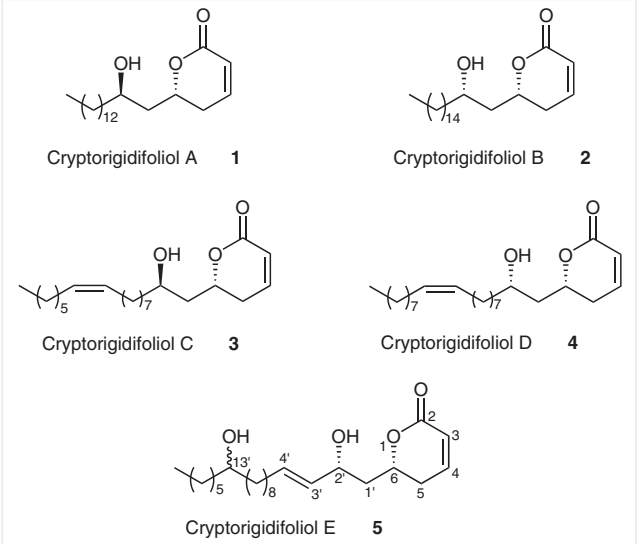
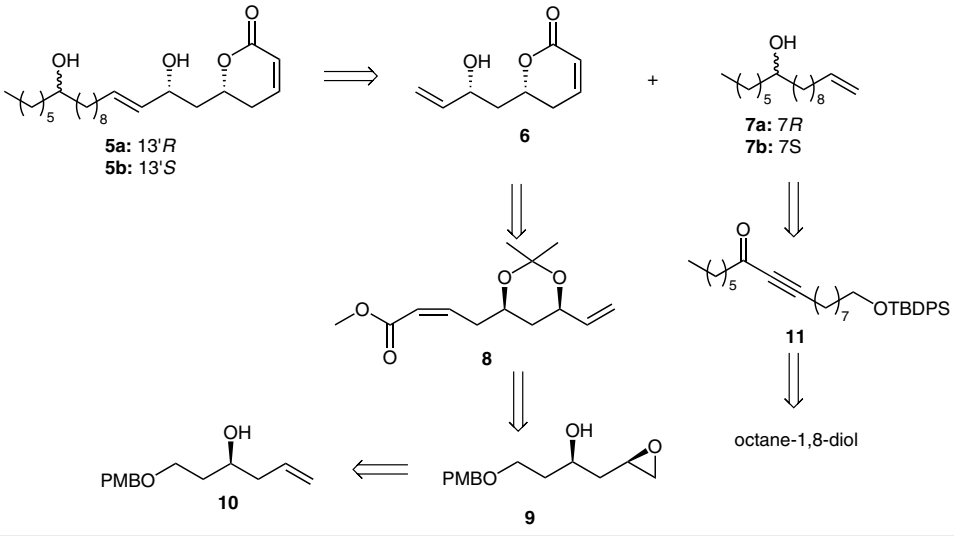


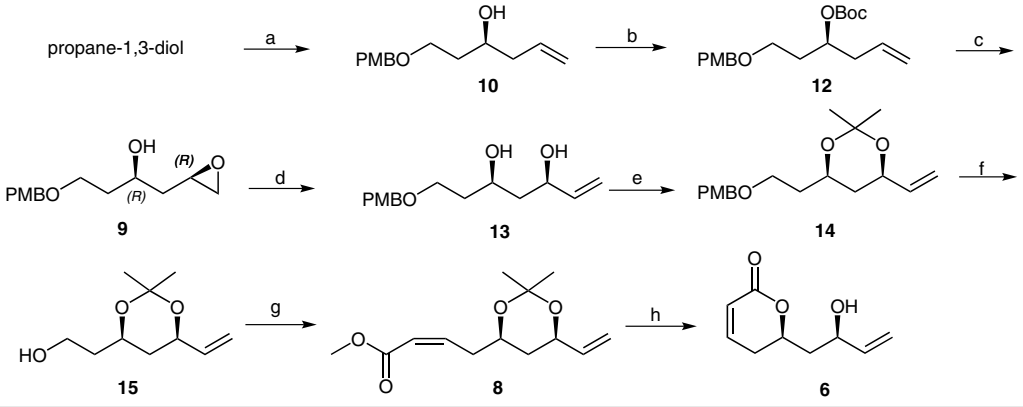
Figure 1 Structures of cryptorigidifoliols A–E



Scheme 1 Retrosynthetic analysis of cryptorigidifoliol E

treated with di-*tert*-butyl dicarbonate in the presence of DMAP to give the homoallylic *tert*-butyl carbonate **12** in 90% yield. Bartlett–Smith halocyclization[5] of carbonate **12** with *N*-iodosuccinimide (NIS) or iodine in MeCN at 0 °C, followed by treatment of the crude mixture with K_2CO_3 in methanol, delivered the epoxy alcohol **9**[6] in 66% yield. All the spectral data for this compound agreed with reference data, but the optical rotation had the opposite sign. Consequently, the stereochemistry of the epoxide-bearing carbon was initially assigned as *R*, on the basis of chemical correlation. Next, regioselective ring-opening of **9** with trimethylsulfonium iodide and BuLi in THF at –10 °C to 0 °C gave the corresponding diol **13** in 75% yield. The stereochemistry of the newly created stereogenic center in **13** was assigned by examination of the ^{13}C NMR spectra of the acetonide **14**, obtained from **13** by treatment with 2,2-dimethoxypropane in the presence of PPTS in CH_2Cl_2 at room temperature (90% yield). The ^{13}C NMR of **14** showed signals assigned to the acetonide methyl group at δ = 19.8 and 30.1 ppm, in accordance with Rychnovsky's model for a 1,3-*syn* relationship between the acetonide-attached carbons.[7] Thus the relative stereochemistry of the newly created stereogenic center was unequivocally assigned as *syn* to the existing one, and its absolute stereochemistry was confirmed as *R*.

In the next stage, deprotection of the PMB group in **14** with DDQ in CH_2Cl_2/H_2O (9:1) gave enol **15** in 87% yield. Further oxidation of the resulting alcohol **15** with Dess–Martin periodinane in CH_2Cl_2 at 0 °C gave the corresponding aldehyde, which was directly subjected to a Still–Gennari reaction[8] with methyl [bis(2,2,2-trifluoroeth-



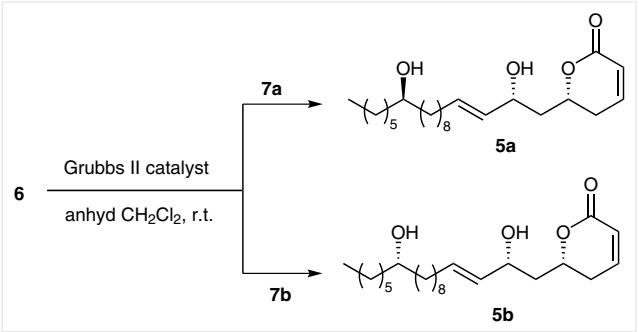
Scheme 2 *Reagents and conditions*: (a) Ref. 3; (b) $(Boc)_2O$, DMAP, CH_2Cl_2, r.t., 5 h, 90%; (c) NIS, MeCN, –40 to 0 °C, 20 h, then K_2CO_3, MeOH, 0 °C to r.t., 2 h, 66 % (two steps); (d) TMSI, BuLi, THF, –20 °C, 75%; (e) $Me_2C(OMe)_2$, PPTS, 0 °C to r.t., 6 h, 90%; (f) DDQ, CH_2Cl_2/H_2O (19:1), 0 °C to r.t., 1 h, 87%; (g) Dess–Martin periodinane, anhyd CH_2Cl_2, 0 °C, then $MeO_2CCH_2P(O)(OCH_2CF_3)_2$, NaH, THF, –78 °C, 1 h, 75% (two steps); (h) 3 N HCl, THF, r.t., 12 h, 79%.

oxy)phosphoryl]acetate in THF at –78 °C for one hour to afford the chromatographically separable α,β-unsaturated ester **8** as the major *Z*-isomer (*Z*/*E* = 92:8) in 75% yield. Subsequent acetonide deprotection and cyclization of ester **8** with 3 N HCl gave the required fragment **6** in 79% yield.

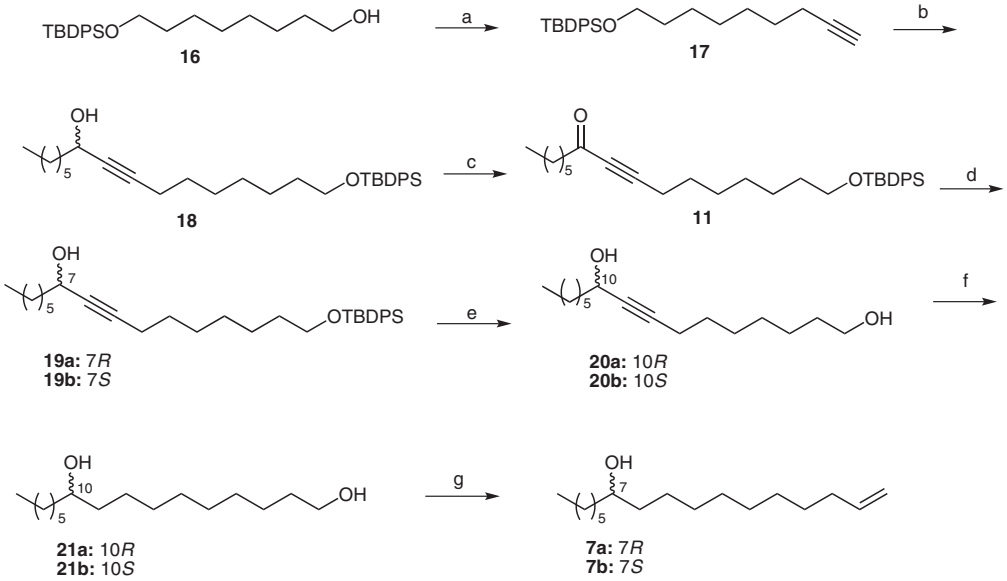
Next, we shifted our focus to the synthesis of the olefin fragments **7a** and **7b**. Selective protection of octane-1,8-diol by treatment with TBDPSCl and imidazole in CH_2Cl_2 gave the monoprotected derivative **16** in 80% yield. The primary alcohol group in compound **16** was oxidized under Swern conditions to afford the corresponding aldehyde, which upon Corey–Fuchs reaction[9] with CBr_4 and PPh_3 in CH_2Cl_2 at 0 °C gave a dibromo alkene; this was dehydrobrominated with BuLi at –78 °C to 0 °C to give the alkyne **17** in 68% yield over the three steps. Deprotonation of terminal alkyne **17** with BuLi, followed by addition of heptanal, gave the racemic propargylic alcohol **18** in 78% yield.

The ynol **18** was oxidized with Dess–Martin periodinane to afford the ynone **11** in 90% yield. Asymmetric reduction of the ynone by using the CBS reagent (*R*)-(–)-2-Me-CBS-oxazaborolidine and $BH_3{\cdot}Me_2S$ gave the chiral propargylic alcohol **19a** in 90% yield and 96% ee [by chiral HPLC: ChiralPak IA 250 × 4.6 mm, 2% *i*-PrOH–hexane (flow rate: 1 mL/min), 205 nm; t_R = 10.129 min (2.05%), 10.558 min (97.94%)].[10] Similarly, reduction of ynone **11** with the CBS reagent (*S*)-(+)-2-Me-CBS-oxazaborolidine and $BH_3{\cdot}SMe_2$ gave the other isomer **19b** in 87% yield and 98% ee [by chiral HPLC: ChiralPak IA 250 × 4.6 mm, 2% *i*-PrOH–hexane (flow rate: 1 mL/min), 205 nm, t_R = 10.154 min (99.32%), 10.583 min (0.68%)].[10] Next, deprotection of the TBDPS ether group of **19a** and **19b** with TBAF gave the required diols **20a** and **20b**, respectively, in 80% yield. These were subjected to hydrogenation independently in the presence of palladium on charcoal to give the saturated diols **21a** and **21b** (92% yield), respectively. Selective oxidation of the primary alcohol of the chiral diols **21a** and **21b** with TEMPO and [bis(acetoxy)iodo]benzene in CH_2Cl_2 gave the intermediate aldehydes, which on further one-carbon Wittig olefination with methylene(triphenyl)phosphorane [prepared in situ by treating methyl(triphenyl)phosphonium iodide with BuLi at –78 °C] gave the desired products **7a** and **7b**, respectively, in 66% yield over two steps. The spectral data of both the compounds were similar, except for the sign of rotation. Whereas $[\alpha]_D^{20}$ for **7a** was –7.8 (*c* 0.23, $CHCl_3$), that of **7b** was +9.0 (*c* 0.58, $CHCl_3$).

Finally, having successfully prepared the required lactone **6** and the olefin fragments **7a** and **7b**, we coupled lac-



Scheme 4



Scheme 3 *Reagents and conditions*: (a) $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 1 h, then CBr_4, PPh_3, CH_2Cl_2, 0 °C, then BuLi, THF, –78 °C to –20 °C, 68% (three steps); (b) heptanal, BuLi, THF, –78 °C to 0 °C, 78%; (c) Dess–Martin periodinane, anhyd CH_2Cl_2, 0 °C, 90%; (d) [(*R*)-methyloxazaborolidine CBS catalyst for **19a**]/[(*S*)-methyloxazaborolidine CBS catalyst for **19b**], $BH_3{\cdot}SMe_2$, THF, –30 °C, 2–3 h, 90% (87% for **19b**); (e) TBAF, anhyd THF, 0 °C to r.t., 3 h, 80%; (f) H_2, Pd/C, EtOAc, r.t., 92%; (g) TEMPO, $PhI(OAc)_2$, anhyd CH_2Cl_2, r.t., 1 h; then $MePPh_3^+Br^-$, BuLi, anhyd THF, –78 °C to r.t., 2 h, 66% (two steps).

Table 1 ^{1}H and ^{13}C NMR Data[a] for the Natural Product and for the Synthetic Compounds **5a** and **5b**

Position	Natural Product		Synthetic product **5a**		Synthetic product **5b**	
	δ (^{13}C)	^{1}H (*J* Hz)	δ (^{13}C)	^{1}H (*J* Hz)	δ (^{13}C)	^{1}H (*J* Hz)
2	163.5		164.1		164.1	
3	121.3	6.03 br d (9.8)	121.3	6.02 dt (1.6, 9.7)	121.3	6.03 dt (1.6, 9.7)
4	145.0	6.90 m	145.1	6.89 m	145.1	6.89 m
5	29.2	2.44 m	29.2	2.44–2.40 m	29.3	2.46–2.40 m
6	72.5	4.69 m	75.9	4.56 m	75.9	4.57 m
1′, 5′	43.8, 32.9	1.79 m, 1.73 m 2.03 m	41.9, 32.0	1.79 m, 2.07–1.99 m 2.12 m	41.9, 32.1	1.79 m, 2.08–1.99 m 2.12 m
2′	63.3	4.63 m	69.7	4.37 q (6.8)	69.8	4.37 q (6.7)
3′	131.4	5.49 dd (7.0, 15.3)	131.6	5.46 tdd (1.3, 7.3, 15.2)	131.6	5.46 tdd (1.3, 7.3, 15.4)
4′	132.6	5.68 m	133.6	5.72 m	133.7	5.73 m
6′–11′ 15–16′	28.0, 29.6 29.6, 29.6 29.6, 29.6 29.6, 29.6	1.61–1.22 m	25.6, 25.6 28.9, 29.0 29.3, 29.4 29.4, 29.6	1.48–1.24 m	25.6, 25.6 29.0, 29.1 29.4, 29.5 29.5, 29.6	1.49–1.22 m
12′	42.1	1.61–1.49 m	37.5	1.48–1.24 m	37.5	1.49–1.22 m
13′	64.4	4.15 m	71.9	3.59 m	72.0	3.58 m
14′	42.1	1.61–1.49 m	37.4	1.8–1.24 m	37.4	1.49–1.22 m
17′	32.0	1.33–1.22 m	31.8	1.8–1.24 m	31.8	1.49–1.22 m
18′	22.8	1.33–1.22 m	22.6	1.8–1.24 m	22.6	1.49–1.22 m
19′	14.2	0.88 t (7.0)	14.0	0.88 t (6.8)	14.1	0.89 t (6.7)

[a] ^{1}H NMR in $CDCl_3$, 500 MHz; ^{13}C NMR in $CDCl_3$, 125 MHz.

tone **6** with the appropriate olefin fragment **7a** or **7b** by using Grubbs II catalyst[11] to afford the target C-13′ epimers **5a** and **5b**, respectively (Scheme4).

NMR analysis of the synthetic products **5a** and **5b** showed some differences from the reported NMR data. In particular, differences in the ^{1}H NMR spectra were observed with respect to the chemical shifts of the H-2′ and H-13′ protons (Table 1). The ^{1}H NMR chemical shifts of H-2′ and H-13′ of the natural product were reported to occur at δ = 4.43 and 4.15 ppm as multiplets, whereas those of H-2′ and H-13′ of the synthetic **5a** appeared as multiplets at δ = 4.37 and 3.59 ppm, respectively, and those of **5b** appeared as multiplets at δ = 4.37 and 3.58 ppm, respectively. Likewise, significant differences were noted in the ^{13}C chemical shifts of the chiral carbon atoms C6, C2′, and C13′. The ^{13}C chemical shifts of C6, C2′, and C13′ in the natural product occurred at δ = 72.5, 63.3, and 64.4 ppm, respectively, whereas the resonances of the same carbon atoms appeared at δ = 75.9, 69.7, and 71.9 ppm, respectively, for synthetic **5a** and at δ = 75.9, 69.8, and 72.0 ppm, respectively, for **5b**. Additionally, the ^{13}C chemical shifts for C12′ and C14′ also showed different chemical shifts for the natural and synthetic compounds.

The specific rotation for synthetic **5a** was $[\alpha]_D^{20}$ –4.8 (*c* 0.28, MeOH) and that of **5b** was $[\alpha]_D^{20}$ –10.0 (*c* 0.13, MeOH), compared with the reported value of $[\alpha]_D^{20}$ –25.0 (*c* 0.4, MeOH) for the natural product. It is pertinent to mention that the absolute stereochemistry of the two stereogenic carbons C6-OH and C2′-OH, were unequivocally assigned by Kingston et al.[2] and confirmed by us in the current study. However, because the configuration of the C13′ stereogenic center was not assigned, we synthesized both intermediates (**7a** and **7b**) by an unambiguous method and we obtained the epimeric targets **5a** and **5b**; nevertheless, the spectral data for the two synthetic compounds **5a** and **5b** did not match the reported data for the natural compound.

In conclusion, we have completed a synthesis of the two proposed structures of cryptorigidifoliol E: **5a** and **5b**. Noteworthy steps included an NIS- or I_2-assisted Bartlett–Smith halocyclization, a stereoselective ring-opening reaction, a Still–Gennari olefination, an acid-catalyzed one-pot deprotection–lactonization procedure, a CBS reduction, and, finally, an olefin cross-metathesis. The stereocontrolled synthesis of **5a** and **5b** suggests that a revision of the structure of natural cryptorigidifoliol E might be necessary.

NMR spectra were recorded on Bruker Avance spectrometers with $CDCl_3$ as solvent. ^1H NMR spectra were recorded at 300, 400, or 500 MHz, and ^{13}C NMR spectra were recorded at 100 or 125 MHz, as specified. Reactions were carried out under N_2 in anhydrous solvents. All reactions were monitored by TLC on silica-coated plates that were visualized by exposure to UV radiation and/or by α-naphthol charring. Organic solutions were dried (Na_2SO_4) and concentrated below 40 °C under reduced pressure. All column chromatographic separations were performed on silica gel (60–120 mesh) with EtOAc and hexane as eluents. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials. Air-sensitive reagents were transferred by syringe and double-ended needle. Optical rotations were measured on an Anton Paar MCP-200 polarimeter. High-resolution mass spectra were recorded by using a Thermo Scientific Orbitrap.

tert-Butyl (1*S*)-1-{2-[(4-Methoxybenzyl)oxy]ethyl}but-3-en-1-yl Carbonate (12)

Di-*tert*-butyl dicarbonate (5.83 g, 25.42 mmol), DMAP (0.77 g, 6.35 mmol), and Et_3N (3.53 mL, 25.42 mmol) were added to a stirred solution of alcohol **10** (3.0 g, 12.71 mmol) in CH_2Cl_2 (30 mL) at 0 °C, and the mixture was stirred at 0 °C to r.t. for 20 h. The mixture was then diluted with 3% aq HCl (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic fractions were dried (Na_2SO_4), filtered, and concentrated, and the crude product was purified by column chromatography [silica gel, hexane–EtOAc (9:1)] to give a colorless oil; yield: 3.84 g (90%); $[\alpha]_D^{20}$ +27.2 (*c* 1.5, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.8 Hz, 2 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 5.78 (m, 1 H), 5.14–5.04 (m, 2 H) 4.88 (quint, *J* = 6.2 Hz, 1 H), 4.41 (s, 2 H), 3.79 (s, 3 H), 3.53–3.46 (m, 2 H), 2.40–2.33 (m, 2 H), 1.88 (q, *J* = 6.4 Hz, 2 H), 1.47 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 153.1, 133.3, 130.3, 129.2, 117.8, 113.6, 82.8, 73.8, 72.6, 66.1, 55.1, 38.8, 33.8, 27.7.

HRMS: *m/z* [M + NH_4]$^+$ calcd for $C_{19}H_{32}NO_5$: 354.2279; found: 354.2275.

(2*R*)-4-[(4-Methoxybenzyl)oxy]-1-[(2*R*)-oxiran-2-yl]butan-2-ol (9)

NIS (4.66 g, 20.8 mmol) was slowly added to a solution of carbonate **12** (3.5 g, 10.41 mmol) in anhyd MeCN (30 mL) at –40 °C. The mixture was then warmed to 0 °C and stirred for about 12h. When the reaction was complete (TLC), it was quenched with sat. aq $Na_2S_2O_3$ (20 mL). Sat. aq $NaHCO_3$ (20 mL) was added, and the mixture was extracted with Et_2O (3 × 30 mL), dried (Na_2SO_4), and concentrated by evaporation.

The residue was dissolved in MeOH (25 mL) and the solution was cooled to 0 °C. K_2CO_3 (3.36 g, 24.74 mmol) was added and the mixture was stirred at r.t. for 1 h. The solvent MeOH was removed under reduced pressure, and the crude residue was washed with H_2O (3 × 20 mL) and extracted with EtOAc (2 × 50 mL). The organic layer was dried (Na_2SO_4), concentrated, and purified by column chromatography [silica gel, hexane–EtOAc (1:1)] to give a colorless oil; yield: 1.74 g (66%, two steps); $[\alpha]_D^{20}$ –4.3 (*c* 1.0, $CHCl_3$).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 4.45 (s, 2 H), 4.05 (m, 1 H), 3.80 (s, 3 H), 3.70 (m, 1 H), 3.63 (m, 1 H), 3.24 (m, 1 H), 3.09 (m, 1 H), 2.77 (m, 1 H), 2.50 (dd, *J* = 2.7, 4.8 Hz, 1 H), 1.91–1.58 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 129.8, 129.2, 113.7, 72.9, 69.4, 68.5, 55.2, 49.9, 46.5, 39.7, 36.2.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{14}H_{20}NaO_4$: 275.1255; found: 275.1253.

(3*R*,5*R*)-7-[(4-Methoxybenzyl)oxy]hept-1-ene-3,5-diol (13)

A 2.5 M soln of BuLi in THF (7.56 mL, 19.01 mmol) was added to a stirred mixture of trimethylsulfonium iodide (3.88 g, 19.01 mmol) in THF (25 mL) at –10 °C. The solution was stirred for 30 min, then a solution of epoxide **9** (1.6 g, 6.34 mmol) in THF (10 mL) was added and the mixture was stirred for 2 h at r.t. until the reaction was complete. The reaction was cautiously quenched with sat. aq NH_4Cl (5 mL), and the mixture was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel, hexane–EtOAc (1:1)] to a colorless liquid; yield: 1.26 g (75%); $[\alpha]_D^{20}$ –12.7 (*c* 0.5, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 5.86 (ddd, *J* = 5.8, 10.5, 17.1 Hz, 1 H), 5.25 (dt, *J* = 1.3, 17.1 Hz, 1 H), 5.08 (dt, *J* = 1.3, 10.3 Hz, 1 H), 4.45 (s, 2 H), 4.37 (m, 1 H), 4.09 (s, 1 H), 3.80 (s, 3 H), 3.72–3.60 (m, 2 H), 1.85–1.56 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 140.6, 129.8, 129.3, 114.1, 113.8, 73.1, 73.0, 72.0, 68.4, 55.2, 43.1, 36.8.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{15}H_{22}NaO_4$: 289.1412; found: 289.1410.

(4*R*,6*R*)-4-{2-[(4-Methoxybenzyl)oxy]ethyl}-2,2-dimethyl-6-vinyl-1,3-dioxane (14)

2,2-Dimethoxypropane (1.05 mL, 8.64 mmol) and PPTS (0.217 g, 0.84 mmol) were added to a solution of diol **13** (1.15 g, 4.32 mmol) in anhyd CH_2Cl_2 (15 mL) at 0 °C, and the mixture was stirred at r.t. for 3 h. The crude product was then mixed with CH_2Cl_2 (5 mL) and sat. aq $NaHCO_3$ (5 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic phases were dried (Na_2SO_4) and concentrated, and the residue was purified by chromatography [silica gel, hexane–EtOAc (9:1)] to give a colorless oil; yield: 1.18 g (90%); $[\alpha]_D^{20}$ +12.6 (*c* 0.68, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.5 Hz, 2 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 5.81 (ddd, *J* = 5.8, 10.5, 16.5 Hz, 1 H), 5.24 (dt, *J* = 1.3, 17.2 Hz, 1 H), 5.11 (dt, *J* = 1.3, 10.5 Hz, 1 H), 4.42 (d, *J* = 1.7 Hz, 2 H), 4.34 (m, 1 H), 4.07 (m, 1 H), 3.80 (s, 3 H), 3.60–3.47 (m, 2 H), 1.84–1.65 (m, 2 H), 1.53 (dt, *J* = 2.5, 12.8 Hz, 1 H), 1.46 (s, 3 H), 1.41 (s, 3 H), 1.32 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1, 138.7, 130.5, 129.2, 115.2, 113.7, 98.6, 72.6, 70.2, 65.7, 55.2, 36.7, 36.4, 30.1, 19.8.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{18}H_{26}NaO_4$: 329.1724; found: 329.1723.

2-[(4*R*,6*R*)-2,2-Dimethyl-6-vinyl-1,3-dioxan-4-yl]ethanol (15)

DDQ (1.63 g, 7.18 mmol) was added to a solution of dioxane **14** (1.1 g, 3.59 mmol) in 19:1 H_2O/CH_2Cl_2 (10 mL) at 0 °C, and the mixture was stirred at r.t. for 1 h. When the reaction was complete, sat. aq $NaHCO_3$ (25 mL) was added and the mixture was filtered. The filter was washed with CH_2Cl_2 (3 × 30 mL), and the combined filtrates were washed sequentially with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography [silica gel, hexane–EtOAc (7:3)] to give a colorless oil; yield: 0.58 g (87%); $[\alpha]_D^{20}$ +15.5 (*c* 0.89, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 5.82 (m, 1 H), 5.27 (dq, *J* = 1.3, 17.2 Hz, 2 H), 5.14 (m, 1 H), 4.39 (m, 1 H), 4.17 (m, 1 H), 3.83–3.73 (m, 2 H), 1.81–1.70 (m, 2 H), 1.55 (dt, *J* = 2.6, 12.9 Hz, 1 H), 1.51 (s, 3 H), 1.48–1.38 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.4, 115.4, 98.7, 70.3, 68.7, 60.5, 38.0, 36.4, 30.1, 19.7.

MS: *m/z* = 209 [M + Na]$^+$.

Methyl (2*Z*)-4-[(4*R*,6*R*)-2,2-Dimethyl-6-vinyl-1,3-dioxan-4-yl]but-2-enoate (8)

A solution of alcohol **15** (0.5 g, 2.68 mmol) in anhyd CH_2Cl_2 (10 mL) was cooled to 0 °C, Dess–Martin periodinane (1.36 g, 3.2 mmol) was added, and the mixture was stirred at r.t. for 2 h. The reaction was then quenched with sat. aq $Na_2S_2O_3$ and $NaHCO_3$ (10 mL). The mixture was diluted with CH_2Cl_2 (20 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The extracts were washed sequentially with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo to give the corresponding aldehyde, which was used in the next step without further characterization.

Methyl [bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (1.11 g, 3.49 mmol) was added to a stirred suspension of NaH (0.11 g, 4.58 mmol) in anhyd THF (10 mL) at 0 °C, and the resulting solution was stirred for 45 min at 0 °C then cooled to –78 °C. A solution of the aldehyde (0.43 mg, 2.33 mmol) in anhyd THF (5 mL) was added dropwise over 5 min and the resulting mixture was stirred at –78 °C for 1 h. The reaction was then quenched by adding NH_4Cl (10 mL), and the mixture was extracted with EtOAc (3 × 30 mL). The organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was purified by column chromatography [silica gel, hexane–EtOAc (9:1)] to give a colorless liquid; yield: 0.42 g (75%); $[\alpha]_D^{20}$ +32.9 (*c* 0.8, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.38 (dt, *J* = 7.9, 11.4 Hz, 1 H), 5.90–5.77 (m, 2 H), 5.25 (dt, *J* = 1.3, 17.2 Hz, 1 H), 5.12 (dt, *J* = 1.3, 10.5 Hz, 1 H), 4.35 (m, 1 H), 4.01 (m, 1 H), 3.71 (s, 3 H), 2.94 (m, 1 H), 2.76 (m, 1 H), 1.57 (dt, *J* = 2.5 Hz, 1 H), 1.47 (s, 3 H), 1.43 (s, 3 H), 1.34 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.6, 145.9, 138.5, 120.6, 115.4, 98.7, 70.0, 68.1, 51.0, 36.2, 35.4, 30.1, 19.7.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{13}H_{20}NaO_4$: 263.1254; found: 263.1253.

(6*R*)-6-[(2*R*)-2-Hydroxybut-3-en-1-yl]-5,6-dihydro-2*H*-pyran-2-one (6)

A stirred solution of enoate **8** (0.3 g, 1.25 mmol) in THF (5 mL) was treated by dropwise addition of 3 M aq HCl (2 mL), and the solution was stirred for 12 h at r.t. When the reaction was complete, the mixture was carefully neutralized with sat. aq $NaHCO_3$ (20 mL) at 0 °C then extracted with EtOAc (3 × 30 mL). The organic extracts were dried (Na_2SO_4), concentrated, and purified by column chromatography [silica gel, hexane–EtOAc (1:1)] to give a colorless oil; yield: 0.165 g (79%); $[\alpha]_D^{20}$ +96.7 (*c* 0.6, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (m, 1 H), 6.02 (dt, *J* = 1.8, 9.9 Hz, 1 H), 5.89 (m, 1 H), 5.31 (dt, *J* = 1.3, 17.2 Hz, 1 H), 5.17 (dt, *J* = 1.2, 10.3 Hz, 1 H), 4.60 (m, 1 H), 4.42 (q, *J* = 6.3, 13.0 Hz, 1 H), 2.47–2.41 (m, 2 H), 2.12 (m, 1 H), 1.84 (dt, *J* = 5.3, 14.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.1, 145.2, 139.8, 121.1, 115.8, 75.8, 69.8, 41.1, 29.4.

HRMS: *m/z* [M + H]$^+$ calcd for $C_9H_{13}O_3$: 169.0861; found: 169.0859.

tert-Butyl(non-8-yn-1-yloxy)diphenylsilane (17)

DMSO (3.06 mL, 38.46 mmol) was added dropwise to a solution of oxalyl chloride (1.72 mL, 19.62 mmol) in CH_2Cl_2 (50 mL) at –78 °C under N_2. After 30 min, a solution of pyranone **16** (5.0 g, 13.08 mmol) in CH_2Cl_2 was added dropwise. After 1 h, Et_3N (10.92 mL, 78.51 mmol) was added, and the mixture was allowed to warm to r.t. over 1 h. The reaction was quenched with H_2O (20 mL) and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed sequentially with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash chromatography [silica gel, hexane–EtOAc (8:2)] to give a colorless liquid.

CBr_4 (7.74 g, 23.38 mmol) was added to a solution of PPh_3 (12.26 g, 46.79 mmol) in CH_2Cl_2 (60 mL) at 0 °C, and the mixture was stirred for 30 min. A solution of the aldehyde prepared above (4.47 g, 11.7 mmol) in CH_2Cl_2 (10 mL) was added, and the mixture was stirred for 1 h at 0 °C. Hexane (150 mL) was added to the mixture to precipitate a solid. The mixture was filtered through a pad of silica and the solvents were evaporated under reduced pressure to give the crude dibromoalkene, which was dissolved in THF. The solution was cooled to –78 °C and a 2.5 M solution of BuLi in hexane (8.37 mL, 0.93 mmol) was added dropwise. The mixture was allowed to warm to –20 °C and stirred at –20 °C for 1 h. The reaction was then quenched by addition of sat. aq NH_4Cl (15 mL), and the mixture was warmed to r.t. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography [silica gel, hexane–EtOAc (9:1)] to give a colorless oil; yield: 3.32 g (68%, three steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69–7.64 (m, 4 H), 7.44–7.34 (m, 6 H), 3.65 (t, *J* = 6.4 Hz, 2 H), 2.17 (td, *J* = 2.5, 7.0 Hz, 2 H), 1.93 (t, *J* = 2.7 Hz, 1 H), 1.60–1.47 (m, 4 H), 1.41–1.23 (m, 6 H), 1.05 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.5, 134.1, 129.4, 127.5, 84.7, 68.0, 63.9, 32.4, 28.8, 28.7, 28.4, 26.8, 25.6, 19.2, 18.3.

HRMS: *m/z* [M + H]$^+$ calcd for $C_{25}H_{35}OSi$: 379.2457; found: 379.2462.

16-{[*tert*-Butyl(diphenyl)silyl]oxy}hexadec-8-yn-7-ol (18)

Alkyne **17** (3.2 g, 8.46 mmol) was dissolved in THF (25 mL), and the solution was cooled to –78 °C. A 2.5 M solution of BuLi in hexane (4.06 mL, 10.15 mmol) was added slowly and the mixture was stirred for 30 min while the temperature was gradually increased to –10 °C. Heptanal (1.17 g, 10.08 mmol) was added dropwise, and the mixture was stirred for 1 h at r.t. The reaction was then quenched with sat. aq NH_4Cl (10 mL), and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated by rotary evaporation. The residue was purified by chromatography [silica gel, hexane–EtOAc (9:1)] to give a colorless liquid; yield: 3.24 g (78%).

The spectral data (^{1}H and ^{13}C NMR and HRMS) for **18** were identical to those of **19a**.

16-{[*tert*-Butyl(diphenyl)silyl]oxy}hexadec-8-yn-7-one (11)

A solution of alcohol **18** (3.1 g, 6.3 mmol) in anhyd CH_2Cl_2 (30 mL) was cooled to 0 °C, Dess–Martin periodinane was added (3.2 g, 7.54 mmol), and the mixture was stirred at r.t. for 2 h. The reaction was then quenched with sat. aq $Na_2S_2O_3$ and $NaHCO_3$ (20 mL), and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated. Purification of the crude product by column chromatography [silica gel, hexane–EtOAc (9:1)] gave a colorless liquid; yield: 2.77 g (90%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.64 (m, 4 H), 7.44–7.34 (m, 6 H), 3.69–3.64 (m, 2 H), 2.54–2.49 (m, 2 H), 2.34 (t, *J* = 7.1, Hz, 2 H), 1.70–1.62 (m, 2 H), 1.60–1.51 (m, 4 H), 1.44–1.24 (m, 12 H), 1.05 (s, 9 H), 0.88 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.4, 135.4, 134.0, 129.4, 127.5, 94.1, 80.8, 63.8, 45.5, 32.4, 31.4, 28.7, 28.7, 28.6, 27.6, 26.8, 25.5, 24.0, 22.4, 19.1, 18.8, 13.9.

HRMS: *m/z* [M + H]$^+$ calcd for $C_{32}H_{47}O_2Si$: 491.3345; found: 491.3350.

(7*R*)-16-{[*tert*-Butyl(diphenyl)silyl]oxy}hexadec-8-yn-7-ol (19a)

A 1 M solution of (*R*)-CBS reagent in toluene (5.34 mL, 5.34 mmol) was added to a stirred solution of ynone **11** (1.31 g, 2.65 mmol) in anhyd THF (15 mL) at –30 °C. BH_3·SMe_2 (1.25 mL, 13.33 mmol) was then added dropwise over 5 min, and the mixture was stirred for 1.5 h at –30 °C. The reaction was quenched by addition of MeOH (1 mL), and the mixture was stirred for another 10 min then concentrated under vacuum. The residue was purified by column chromatography [silica gel, hexane–EtOAc (6:4)] to give a colorless oil; yield: 1.18 g (90%, 96% ee); $[\alpha]_D^{20}$ +1.6 (*c* 0.9, $CHCl_3$).

HPLC: Chiral Pak IA (250 × 4.6 mm), 2% *i*-PrOH–hexane (flow rate: 1 mL/min), 205 nm; t_R = 10.129 min (2.05%), 10.558 min (97.94%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69–7.64 (m, 4 H), 7.44–7.35 (m, 6 H), 4.34 (t, *J* = 5.7 Hz, 1 H), 3.65 (t, *J* = 6.5 Hz, 2 H), 2.19 (td, *J* = 1.9 Hz, 2 H), 1.72–1.60 (m, 2 H), 1.59–1.24 (m, 18 H), 1.05 (s, 9 H), 0.88 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.4, 134.1, 129.4, 127.5, 85.4, 81.3, 63.9, 62.7, 38.2, 32.4, 31.7, 28.9, 28.8, 28.7, 28.6, 26.8, 25.6, 25.1, 22.5, 19.2, 18.6, 14.0.

MS: *m/z* = 515 [M + Na]$^+$.

(7*S*)-16-{[*tert*-Butyl(diphenyl)silyl]oxy}hexadec-8-yn-7-ol (19b)

A 1 M solution of (*R*)-CBS reagent in toluene (5.34 mL, 5.34 mmol) was added to a stirred solution of ynone **11** (1.31 g, 2.65 mmol) in anhyd THF (15 mL) at –30 °C. BH_3·SMe_2 (1.25 mL, 13.33 mmol) was then added dropwise over 5 min, and the mixture was stirred for 1.5 h at –30 °C. The reaction was quenched by addition of MeOH (1 mL) and the mixture was stirred for another 10 min, then concentrated under vacuum. The residue was purified by column chromatography [silica gel, hexane–EtOAc (6:4)] to give a colorless oil; yield: 1.14 g (87%, 98% ee); $[\alpha]_D^{20}$ –2.1 (*c* 0.17, $CHCl_3$).

HPLC: Chiral Pak IA (250 × 4.6 mm), 2% *i*-PrOH–hexane (flow rate: 1 mL/min), 205 nm; t_R = 10.154 min (99.32%), 10.583 min (0.68%).

Spectral data (^{1}H and ^{13}C NMR and MS) for **19b** were identical to those of **19a**.

(10*R*)-Hexadec-8-yne-1,10-diol (20a)

To a stirred solution of ynol **19a** (1.0 g, 2.03 mmol) in anhyd THF (10 mL) was treated with a 1.0 M solution of TBAF in THF (3.04 mL, 3.04 mmol) at 0 °C, and the mixture was stirred for 1 h at r.t. The solvent was then evaporated under reduced pressure and the residue was purified by column chromatography [silica gel, hexane–EtOAc (7:3)] to give a colorless liquid; yield: 0.412 g (80%); $[\alpha]_D^{20}$ +1.7 (*c* 0.5, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.34 (tt, *J* = 1.8, 6.5 Hz, 1 H), 3.64 (t, *J* = 6.7 Hz, 2 H), 2.20 (td, *J* = 1.9, 7.0 Hz, 2 H), 1.73–1.61 (m, 2 H), 1.61–1.47 (m, 4 H), 1.47–1.25 (m, 14 H), 0.89 (t, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 85.2, 81.4, 62.8, 62.6, 38.1, 32.5, 31.7, 28.9, 28.7, 28.6, 28.4, 25.5, 25.1, 22.5, 18.5, 14.0.

MS: *m/z* = 277 [M + Na]$^+$.

(10*R*)-Hexadec-8-yne-1,10-diol (20b)

This was prepared by the same procedure as for **20a**; yield: 0.43 g (82%); $[\alpha]_D^{20}$ –2.8 (*c* 0.2, $CHCl_3$). Spectral data (^{1}H and ^{13}C NMR and MS) for **20b** were identical to those of **20a**.

(10*R*)-Hexadecane-1,10-diol (21a)

A solution of diol **20a** (0.3 g, 1.18 mmol) in EtOAc (8 mL) was stirred with 10% Pd/C (40 mg) under H_2 (balloon) for 3 h at r.t. The mixture was then filtered through Celite, which was washed with EtOAc (30 mL). The filtrate was evaporated in vacuo, and the residue was purified by column chromatography [silica gel, hexane–EtOAc (7:3)] to give a white solid; yield: 0.28 g (92%); mp 64 °C; $[\alpha]_D^{20}$ +6.8 (*c* 0.17, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.64 (t, *J* = 6.7 Hz, 2 H), 3.58 (m, 1 H), 1.62–1.53 (m, 4 H), 1.49–1.22 (m, 22 H), 0.89 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 72.0, 63.0, 37.5, 37.4, 32.7, 31.8, 29.6, 29.5, 29.3, 25.7, 25.6, 22.6, 14.0.

MS: *m/z* = 281 [M + Na]$^+$.

(*S*)-Hexadecane-1,10-diol (21b)

This was prepared by the same procedure as for **20a**; yield: 0.27 g (90%); $[\alpha]_D^{20}$ –5.9 (*c* 0.3, $CHCl_3$). The spectral data (^{1}H and ^{13}C NMR and MS) and mp for **21b** were identical to those of **21a**.

(7*R*)-Heptadec-16-en-7-ol (7a)

TEMPO (0.048 g, 0.307 mmol) and $PhI(OAc)_2$ (0.74 g, 2.32 mmol) were added to a solution of diol **21a** (0.2 g, 0.775 mmol) in anhyd CH_2Cl_2 (3 mL), and the mixture was stirred for 1 h. The reaction was then quenched with sat. aq $Na_2S_2O_3$ (10 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (5 × 10 mL). The organic phases were combined, dried (Na_2SO_4), and concentrated to give a crude product that was used in the next step without purification.

Methyltriphenylphosphonium bromide (0.62 g, 1.73 mmol) was dissolved in THF (8 mL) and the solution was cooled to –78 °C. A 2.5 M solution of BuLi in hexane (0.68 mL, 1.71 mmol) was added dropwise with stirring, and the solution was stirred for a further 30 min. A solution of the crude aldehyde product (0.15 g, 0.58 mmol) in anhyd THF (5 mL) was added, and the mixture was stirred for an additional 1 h. The reaction was then quenched with sat. aq NH_4Cl (15 mL), and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed sequentially with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography [silica gel, hexane–EtOAc (9:1)] to give a colorless liquid; yield: 0.13 g (66%, two steps); $[\alpha]_D^{20}$ –7.8 (*c* 0.23, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81 (m, 1 H), 5.04–4.90 (m, 2 H), 3.58 (m, 1 H), 2.09–1.98 (m, 2 H), 1.53–1.24 (m, 24 H), 0.89 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.1, 114.0, 72.0, 37.4, 33.7, 31.8, 29.6, 29.5, 29.4, 29.3, 29.0, 28.9, 25.6, 25.6, 22.6, 14.0.

MS: *m/z* = 277 [M + Na]$^+$.

(*S*)-Heptadec-16-en-7-ol (7b)

This was prepared by the same procedure as for **7a**; yield: 0.13 g (67%); $[\alpha]_D^{20}$ +9.0 (*c* 0.58, $CHCl_3$).

The spectral data (^{1}H and ^{13}C NMR and MS) for **7b** were identical to those of **7a**.

(6*R*)-6-[(2*R*,3*E*,13*R*)-2,13-Dihydroxynonadec-3-en-1-yl]-5,6-dihydro-2*H*-pyran-2-one (5a)

Grubbs II catalyst (0.01 g, 0.011 mmol) was added to a stirred solution of enol **7a** (0.03 g, 0.118 mmol) and lactone **6** (0.04 g, 0.238 mmol) in anhyd CH_2Cl_2 (2 mL), and mixture was stirred at r.t. for 5 h. When the reaction was complete, the solvent was removed under reduced pressure and the residue was purified by column chromatography [silica gel, hexane–EtOAc (1:1)] to give a colorless liquid; yield: 0.027 g (60%); $[\alpha]_D^{20}$ –4.8 (*c* 0.28, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.89 (m, 1 H), 6.02 (dt, *J* = 1.6, 9.7 Hz, 1 H), 5.72 (m, 1 H), 5.46 (tdd, *J* = 1.3, 7.3, 15.2 Hz, 1 H), 4.56 (m, 1 H), 4.37 (q, *J* = 6.8 Hz, 1 H), 3.59 (m, 1 H), 2.44–2.40 (m, 2 H), 2.12 (m, 1 H), 2.07–1.99 (m, 2 H), 1.79 (m, 1 H), 1.48–1.24 (m, 24 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.1, 145.1, 133.6, 131.6, 121.3, 75.9, 71.9, 69.7, 41.9, 37.5, 37.4, 32.0, 31.8, 29.6, 29.4 (2 C), 29.3, 29.2, 29.0, 28.9, 25.6 (2 C), 22.6, 14.0.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{24}H_{42}NaO_4$: 417.2977; found: 417.2975.

(6*R*)-6-[(2*R*,3*E*,13*S*)-2,13-Dihydroxynonadec-3-en-1-yl]-5,6-dihydro-2*H*-pyran-2-one (5b)

Prepared from **7b** (0.028 g, 0.11 mmol) and lactone **6** (0.037 g, 0.22 mmol) by the same method as for **5a** as a colorless liquid; yield: 0.024 g (58%); $[\alpha]_D^{20}$ –10.0 (*c* 0.13, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.89 (m, 1 H), 6.03 (dt, *J* = 1.6, 9.7 Hz, 1 H), 5.73 (m, 1 H), 5.46 (tdd, *J* = 1.3, 7.3, 15.4 Hz, 1 H), 4.57 (m, 1 H), 4.37 (q, *J* = 6.7 Hz, 1 H), 3.58 (m, 1 H), 2.46–2.40 (m, 2 H), 2.12 (m, 1 H), 2.08–1.99 (m, 2 H), 1.79 (m, 1 H), 1.49–1.22 (m, 24 H), 0.89 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.1, 145.1, 133.7, 131.6, 121.3, 75.9, 72.0, 69.8, 41.9, 37.5, 37.4, 32.1, 31.8, 29.6, 29.5 (2 C), 29.4, 29.3, 29.1, 29.0, 25.6 (2 C), 22.6, 14.1.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{24}H_{42}NaO_4$: 417.2977; found: 417.2975.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562779.

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