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Total Synthesis and Structure Confirmation of Cryptocaryol A

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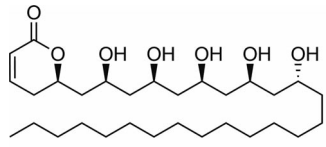
Dedicated to Dr. Mukund K. Gurjar on the occasion of his 60th birthday

Keywords: Natural products / Asymmetric synthesis / Synthetic methods / Protecting groups

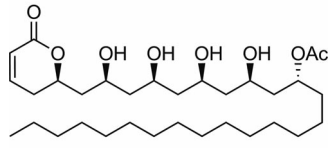
The first enantioselective total synthesis of Pdcd4-stabilizing cryptocaryol A, a secondary metabolite obtained from a tropical tree, has been achieved through an iterative approach to the 1,3-polyol motif. The key steps are a Maruoka allylation, a Reetz chelation-controlled allylation with 1,3-induction, iterative diastereoselective iodocyclization, and ring-closing metathesis reactions.

Introduction

The recent isolation of cryptocaryol A (**1**) and B (**2**), a new structural class of programmed cell death 4 (Pdcd4) stabilizing compounds from the Papua New Guinea collection of the plant *Cryptocarya* sp. have been reported by Gustafson et al. (Figure 1).[1] The genus *Cryptocarya* is disseminated throughout the tropic, subtropic, and temperate regions of the world, and its members produce an array of secondary metabolites including flavonoids such as cryptochinones A–F,[2] pavine and proaporphine alkaloids,[3] and a variety of 5,6-dihydro-α-pyrones exemplified by passiflor-icin,[4] (–)-pironetin,[5] fostriecin,[6] strictofolione,[7] callystatin A,[8] leptomycin,[9] kurzilactone,[10] rugulactone,[11] and cryptocaryone[12]. The degradation and EC_{50} values range from 1.3 to 4.9 μM. Pdcd4, also called apoptosis, plays a pivotal role in life and is an indispensable event in many biological processes such as embryogenic development, normal tissue turnover and metamorphosis.[13] The molecular mechanisms of programmed cell death reveal the existence of several distinct pathways. Recent observations suggest that Pdcd4 acts as a tumor suppressor gene and might represent a promising target for future antineoplastic therapy. In this aspect, natural products that bring out a specific and unique biological activity in mammalian cells represent valuable tools to target possible gene products. With activity in the low micromolar range, the crytocaryols represent a new structural class of natural products that can enhance the stability of Pdcd4 in response to tumor-promoting conditions. The relative and absolute stereochemistry of cryptocaryol A (**1**) was established by a series of elegant spectroscopic and degradative studies. 5,6-Dihydro-2*H*-ones modules having polyhydroxy or polyacetoxy groups have been widely explored by synthetic organic and medicinal chemists because of their broad range of biological activities. As part of our research interest in biologically potent active natural products[14] and because of its specific activity, we consider cryptocaryol A as an attractive synthetic target.



Cryptocaryol A (**1**)



Cryptocaryol B (**2**)

Figure 1. Structures of cryptocaryol A, and B.

The strategy is presented in Scheme 1. The key steps are a Maruoka allylation reaction followed by a chelation-controlled allylation with 1,3-induction to install two stereogenic centers. The remaining chiral centers could then be introduced by iterative iodocyclization reactions. The lactone moiety could be achieved through a ring-closing metathesis reaction. Herein, we describe our successful realization of this strategy for the first total synthesis of cryptocaryol A and its structure confirmation.

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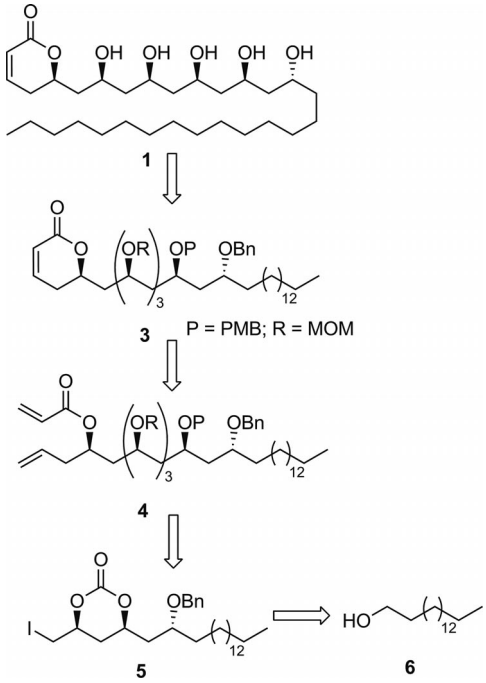
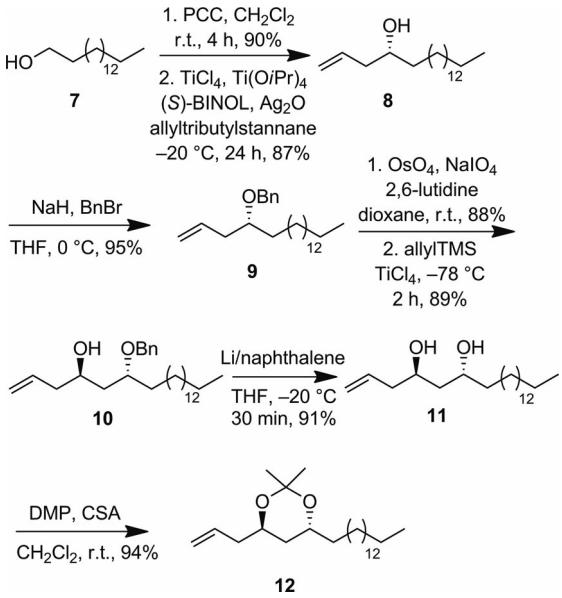


Scheme 1. Retrosynthetic analysis of cryptocaryol A.

Results and Discussion

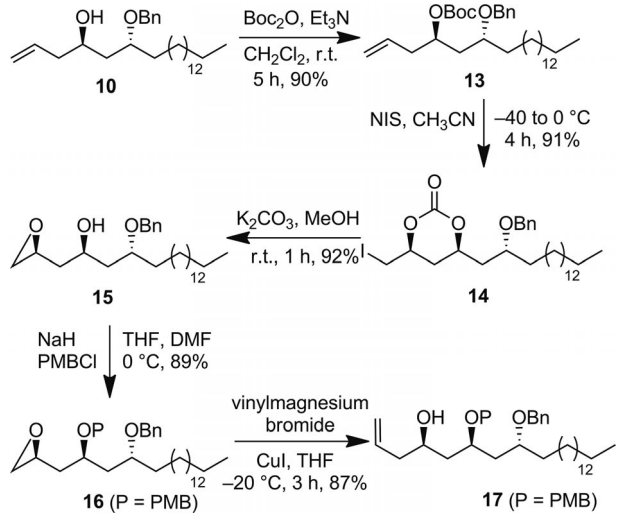
The oxidation of palmityl alcohol (**7**) with pyridinium chlorochromate (PCC) in CH_2Cl_2 at room temperature afforded hexadecanal, which – on treatment with allyltributyltin in the presence of Ti(*i*PrO)$_4$ and (*S*)-BINOL in CH_2Cl_2 at –20 °C – furnished homoallyl alcohol **8** in 87% yield with an enantiomeric excess >97% (Scheme 2).[15] Compound **8** was protected as its benzyl ether with benzyl bromide in the presence of NaH in *N*,*N*-dimethylformamide (DMF) to give **9** in 95% yield. To establish the second stereogenic center with the required stereochemistry, it was



Scheme 2. Synthesis of intermediate **12**.

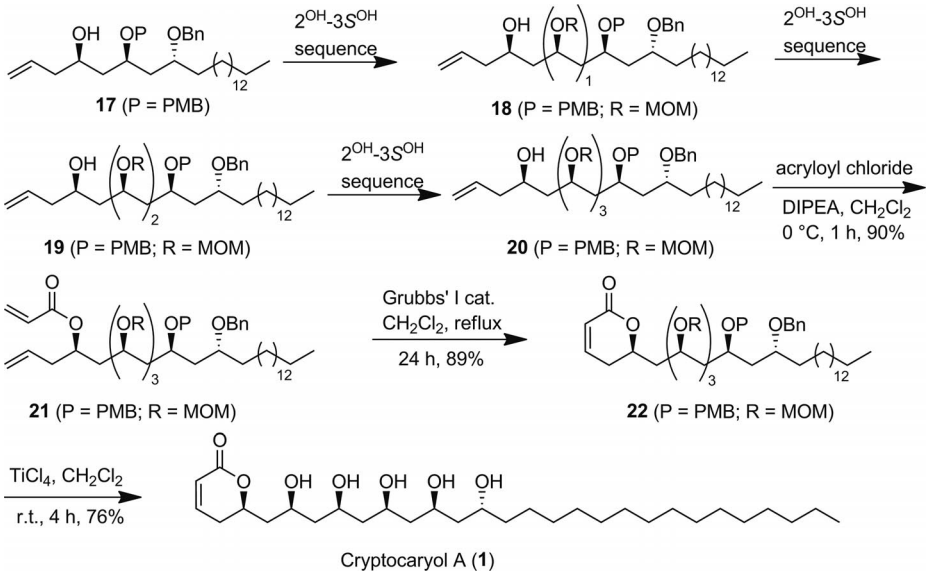
thought worthwhile to adopt a chelation-controlled stereoselective allylation reaction occurring through 1,3-induction.[16] Accordingly, oxidative cleavage of the olefin with OsO_4, $NaIO_4$, and 2,6-lutidine in 1,4-dioxane at room temperature afforded the corresponding aldehyde that was immediately treated with allyltrimethylsilane in the presence of $TiCl_4$ as Lewis acid at –78 °C to obtain homoallyl alcohol **10** in 89% yield with a diastereomeric excess >98% (Scheme 1). To assign the *anti* geometry according to the method reported by Rychnovsky and co-workers,[17] the benzyl group was deprotected with Li/naphthalene to give diol **11** in 91% yield. Diol **11** was subsequently transformed into isopropylidene derivative **12** with dimethoxypropane and a catalytic amount of camphorsulfonic acid in 94% yield. In the ^{13}C NMR spectrum of **12**, the resonance arising from the acetonide methyl groups appeared at δ = 24.75 and 24.83 ppm and that of the quaternary carbon atom at δ = 100.17 ppm, indicating a 1,3-*trans* relationship.

After confirming the stereocenters, compound **10** was treated with di-*tert*-butyl dicarbonate in the presence of 4-(dimethylamino)pyridine (DMAP) to form homoallylic *tert*-butyl carbonate **13** in 90% yield.[18] The next stereogenic center of the hexanol system was achieved through a Bartlett–Smith iodocarbonate cyclization reaction.[19] Accordingly, treatment of compound **13** with *N*-iodosuccinimide (NIS) in CH_3CN at 0 °C produced the desired iodocarbonate derivative **14** in 91% yield as the only product. Iodocarbonate **14** was treated with K_2CO_3 in MeOH that rapidly underwent hydrolysis to give in situ epoxy alcohol **15** in 92% yield. The secondary hydroxy group was protected as its *p*-methoxybenzyl (PMB) ether with PMBCl in the presence of NaH in DMF at 0 °C to afford epoxide **16** in 89% yield. Treatment of **16** with vinylmagnesium bromide in the presence of a catalytic amount of CuI[20] at 0 °C furnished homoallyl alcohol **17** in 87% yield (Scheme 3).



Scheme 3. Synthesis of intermediate **17**.

With **17** in hand, the stage was set for the introduction of the remaining stereogenic centers of cryptocaryol A through iterative use of the 2^{OH}-$3S^{OH}$ sequence as shown



Scheme 4. Synthesis of cryptocaryol A.

in Scheme 3. Three further cycles led to diastereomerically pure hexanol precursor **20**.[21] To complete the synthesis of cryptocaryol A, we now needed to construct the α-pyrone ring. To this end, esterification of alcohol **20** with acryloyl chloride afforded **21** in 90% yield, which set the stage for a ruthenium-catalyzed ring-closing metathesis reaction.[22] Treatment of diene **21** with second-generation Grubbs' catalyst (10 mol-%) in CH_2Cl_2 at reflux temperatures afforded lactone **22** in 89% yield (Scheme 4). Global deprotection was achieved with excess $TiCl_4$[23] in CH_2Cl_2 to complete the first total synthesis of cryptocaryol A (**1**) in 76% yield. The integrity of the synthetic cryptocaryol A (**1**) was assigned by analysis of the spectroscopic data (^1H and ^{13}C NMR) and analytical data {$[\alpha]_D^{25}$ = +11.4 (*c* = 1.5, MeOH); ref.[1] $[\alpha]_D$ = +12 (*c* = 0.1, MeOH)} that are in good agreement with the reported values for the natural product confirming the assigned structure of **1**.

Conclusions

We have demonstrated an efficient, highly stereoselective approach to accomplish the first total synthesis of cryptocaryol A from commercially available palmityl alcohol. An important element of our synthetic strategy is the use of asymmetric catalysis to establish the initial asymmetry followed by chelation-controlled 1,3-induction for the second stereocenter in addition to the use of an efficient iterative highly diastereo selective iodocyclization reaction to install the remaining four chiral centers with high overall yield. Application of the same protocol towards the synthesis of other cryptocaryols is in progress and will be reported in due course.

Experimental Section

General Methods: Experiments that required an inert gas were carried out under dry N_2 in flame-dried glassware. Et_2O and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone ketyl and transferred by syringe. Dichloromethane was freshly distilled from CaH_2. Tertiary amines were freshly distilled from KOH. Commercially available reagents were used as received. Unless detailed otherwise, "workup" refers to pouring the reaction mixture into brine, followed by extraction with the solvent indicated in parentheses. If the reaction medium was acidic (basic), an additional washing with 5% aq. $NaHCO_3$ (aq. NH_4Cl) was performed. Washing with brine, drying with anhydrous Na_2SO_4 and elimination of the solvent under reduced pressure was followed by chromatography on a silica gel column (60–120 μm) with the indicated eluent. When solutions were filtered through a Celite pad, the pad was washed with the same solvent used, and the washings combined with the main organic layer. NMR spectra were measured at 25 °C. The signals of the deuterated solvent ($CDCl_3$) were taken as the reference. Multiplicity assignments of ^{13}C signals were made by means of the DEPT pulse sequence. The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad. High-resolution mass spectra were recorded in the electron impact mode (EIMS, 70 eV) or in the fast atom bombardment (FAB) mode (*m*-nitrobenzyl alcohol matrix). IR spectroscopic data were measured with films on NaCl plates (oils) or KBr pellets (solids) and are given only for molecules with relevant functional groups (OH, C=O). Optical rotations were measured at 25 °C.

(*R*)-Octadec-1-en-4-ol (8): To a stirred solution of $TiCl_4$ (5.0 mL, 0.50 mmol), in CH_2Cl_2 (25 mL), was added (*i*PrO)$_4$Ti (4.25 mL, 1.5 mmol) at 0 °C under argon. The solution was allowed to warm to room temperature. After 1 h, silver oxide (2.3 g, 1.0 mmol) was added, and the reaction mixture was stirred in the dark for 5 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and treated with (*S*)-binaphthol (5.73 g, 2.0 mmol) at room temperature for 2 h to furnish chiral bis(*S*)-Ti^{IV} oxide. The in situ generated bis(*S*)-Ti^{IV} oxide in CH_2Cl_2 (75 mL) was cooled to –15 °C and treated sequentially with hexadecanal (25.0 g, 10.0 mmol) and allyltributyltin (35.0 mL, 11.0 mmol). The reaction mixture was cooled to 0 °C and stirred for 48 h. The reaction mixture was quenched with saturated $NaHCO_3$ (150 mL) solution and extracted with ethyl acetate (3 × 150 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Flash

chromatography of the residue on silica gel (ethyl acetate/hexane = 1:20) afforded homoallylic alcohol **8** (25.5 g, 87% yield) as a white solid. M.p. 44–45 °C. $[\alpha]_D^{25}$ = –2.5 (*c* = 2.2, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3326, 2954, 2850, 1720, 1248, 1219 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 5.80 (m, 1 H), 5.10 (m, 2 H), 3.60 (m, 1 H), 2.28 (m, 1 H), 2.13 (m, 1 H), 2.10 (br. s, 1 H), 1.50–1.40 (m, 3 H), 1.40–1.20 (br. m, 25 H), 0.87 (t, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 134.9, 118.04, 70.7, 41.9, 36.8, 31.9, 29.7, 29.3, 25.6, 22.6, 14.0 ppm. MS (ESI): *m*/*z* = 305 $[M + Na]^+$.

(*R*)-[(Nonadec-1-en-4-yloxy)methyl]benzene (9): Alcohol **8** (24.6 g, 87.3 mmol) in THF (150 mL) was added slowly to a suspension of NaH [5.2 g, (60%), 131.0 mmol] in anhydrous THF (100 mL) at 0 °C. After 20 min, benzyl bromide (6.8 mL, 88.1 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 12 h. After completion (monitored by TLC), the reaction mixture was quenched with ice-cooled water and extracted with ethyl acetate (3 × 150 mL). The combined organic layers were dried with Na_2SO_4, concentrated under reduced pressure, and purified by silica gel column chromatography (ethyl acetate/hexane = 1:22) to afford compound **9** (30.79 g, 95%) as a colorless liquid. $[\alpha]_D^{25}$ = +8.3 (*c* = 1.6, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3067, 2956, 1641, 1094 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.26–7.34 (m, 5 H), 5.80 (m, 1 H), 5.10–5.01 (m, 2 H), 4.57–4.43 (m, 2 H), 3.2–3.4 (m, 2 H), 2.34–2.26 (m 2 H), 1.55–1.44 (m, 3 H), 1.33–122 (m, 25 H), 0.89 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.9, 135.1, 128.3, 128.2, 127.7, 127.5, 127.3, 116.7, 78.5, 70.8, 38.3, 33.8, 31.9, 29.6, 29.3, 25.3, 22.6, 14.1 ppm. MS (ESI): *m*/*z* = 395 $[M + Na]^+$.

(4*R*,6*R*)-6-(Benzyloxy)henicos-1-en-4-ol (10): To a solution of **9** (26.2 g, 70.1 mmol) in 1,4-dioxane/water (3:1; 160 mL), 2,6-lutidine (140.2 mL, 140.2 mmol), OsO_4 (345 mg, 1.4 mmol) followed by $NaIO_4$ (59.6 g, 280.3 mmol) were sequentially added at room temperature, and the mixture was stirred for 1 h. After completion of the reaction (monitored by TLC), 1,4-dioxane was removed under reduced pressure, and the residue was diluted with CH_2Cl_2 (100 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were quickly washed with 1 N HCl (2 × 150 mL) to remove excess 2,6-lutidine followed by brine (2 × 150 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude aldehyde that – on purification by a short flash column chromatography on silica gel (ethyl acetate/hexane = 1:3) – afforded the corresponding aldehyde (23.0 g, 87%) as a colorless liquid, which was used immediately. To a solution of the above aldehyde (23.0 g, 61.4 mmol) in anhydrous CH_2Cl_2 (460 mL), $TiCl_4$ (61.4 mL, 61.4 mmol; 1 M in CH_2Cl_2) was added at –78 °C. After 10 min, allyltrimethylsilane (11.8 mL, 73.6 mmol) was added and the reaction mixture stirred under nitrogen at same temperature for 2 h. The reaction mixture was poured into water (200 mL), and the organic phase was separated. The aqueous phase was extracted with diethyl ether (2 × 150 mL). The combined organic layers were washed with 10% $NaHCO_3$ (2 × 100 mL) and brine (2 × 100 mL). The organic layers were dried with Na_2SO_4, concentrated under reduced pressure, and purified by silica gel column chromatography (ethyl acetate/hexane = 1:14) to afford **10** (22.8 g, 89%) as a colorless liquid. $[\alpha]_D^{25}$ = –13.2 (*c* = 1.1, $CHCl_3$). IR (neat) $\tilde{\nu}_{max}$ = 33450, 2926, 2853, 1612 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.34–7.26 (m, 5 H), 5.80 (m, 1 H), 5.11–5.02 (m, 2 H), 4.63–4.40 (m, 2 H), 3.92 (m, 1 H), 3.65 (m 1 H), 2.53 (br. s, 1 H), 2.19–2.17 (m, 2 H), 1.51–1.57 (m, 4 H), 1.34–1.22 (m, 24 H), 0.89 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.3, 134.9, 128.3, 127.8, 127.6, 117.4, 76.9, 71.1, 67.6, 42.1, 39.3, 33.3, 31.8, 29.6, 29.5, 29.3, 25.3, 22.6, 14.0 ppm. HRMS (ESI): calcd. for $C_{28}H_{48}O_2Na$ $[M + Na]^+$ 439.3551; found 439.3511.

(4*R*,6*R*)-6-(Benzyloxy)henicos-1-en-4-yl *tert*-Butyl Carbonate (13): To a solution of alcohol **10** (20 g, 48.1 mmol) in CH_2Cl_2 (150 mL), di-*tert*-butyl dicarbonate $[(Boc)_2O$; 22.1 mL, 96.1 mmol], followed by Et_3N (13.4 mL, 96.1 mmol) and DMAP (2.9 g, 27.7 mmol) were added at room temperature. After stirring for 5 h, the solvent was evaporated under reduced pressure to give the crude product, which – on purification by column chromatography on silica gel (ethyl acetate/hexane = 1:19) – gave *tert*-butyloxycarbonyl (Boc) protected **13** (22.2 g, 90%) as a colorless oil. $[\alpha]_D^{25}$ = –38.2 (*c* = 1.0, $CHCl_3$). IR (neat) $\tilde{\nu}_{max}$ = 2925, 2854, 1739, 1459, 1167 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.36–7.25 (m, 5 H), 5.76 (m, 1 H), 5.12–4.94 (m, 3 H), 4.63–4.40 (m, 2 H), 3.47 (m, 1 H), 2.37–2.30 (m, 2 H), 1.72–1.64 (m, 2 H), 1.46 (s, 9 H), 1.40–1.36 (m, 2 H), 1.29–1.20 (m, 24 H), 0.88 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 153.2, 138.6, 133.4, 128.3, 128.0, 127.5, 117.8, 81.6, 75.6, 73.5, 71.5, 39.5, 39.0, 34.1, 32.0, 29.5, 29.3, 27.7, 24.8, 22.6, 14.1 ppm. HRMS (ESI): calcd. for $C_{33}H_{56}O_4Na$ $[M + Na]^+$ 539.4071; found 539.4040.

(4*S*,6*S*)-4-[(*R*)-2-(Benzyloxy)heptadecyl]-6-(iodomethyl)-1,3-dioxan-2-one (14): To a stirred solution of Boc-protected **13** (18.0 g, 34.8 mmol) in acetonitrile (270 mL), *N*-iodosuccinimide (11.7 g, 52.2 mmol) was added at –40 °C. The resulting mixture was then warmed up and stirred at 0 °C for 4 h. After completion of the reaction (monitored by TLC), it was quenched with aqueous $Na_2S_2O_3$ solution (100 mL). Acetonitrile was removed under reduced pressure. The reaction mixture was then diluted with CH_2Cl_2 (100 mL), and the two layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were washed with brine (2 × 100 mL) dried with Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (ethyl acetate/hexane = 1:9) to obtain iodocarbonate **14** (19.0 g) as a colorless liquid, which was not very stable and used immediately.

(2*S*,4*R*)-4-(Benzyloxy)-1-[(*S*)-oxiran-2-yl]nonadecan-2-ol (15): To a solution of iodocarbonate **14** (19.0 g, 32.3 mmol) in MeOH (200 mL), K_2CO_3 (11.1 g, 80.7 mmol) was added, and the resulting mixture was stirred at 25 °C for 1 h. After completion of the reaction (monitored by TLC), methanol was evaporated under reduced pressure. The residue was diluted with H_2O (100 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to afford the crude product, which – on purification by column chromatography on silica gel (ethyl acetate/hexane = 1:5) – furnished desired epoxy alcohol **15** (12.9 g, 84% over two steps) as a colorless liquid. $[\alpha]_D^{25}$ = –11.0 (*c* = 1.5, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3461, 2924, 1717, 1456, 1220, 1080 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.26–7.38 (m, 5 H), 4.58–4.48 (m, 2 H), 3.67 (m, 1 H), 3.03 (m, 1 H), 2.87 (br. s, 1 H), 2.71 (m, 1 H), 2.45 (m, 1 H), 1.83–1.63 (m, 3 H), 1.62–1.82 (m, 3 H), 1.32–1.22 (m, 26 H), 0.89 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 129.7, 128.4, 128.0, 127.7, 77.0, 71.2, 66.7, 50.0, 46.6, 40.0, 39.7, 33.3, 31.9, 29.3, 25.4, 22.6, 14.1 ppm. HRMS (ESI): calcd. for $C_{28}H_{49}O_3$ $[M + H]^+$ 433.3676; found 433.3650.

(*S*)-2-{(2*S*,4*R*)-4-(Benzyloxy)-2-[(4-methoxybenzyl)oxy]nonadecyl}-oxirane (16): To a suspension of NaH (2.1 g, 55.4 mmol) in anhydrous DMF (75 mL), compound **15** (12.0 g, 27.7 mmol) in THF (50 mL) was added slowly at 0 °C. After 20 min, *p*-methoxybenzyl chloride (4.1 mL, 30.5 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction (monitored by TLC), it was quenched with ice-cooled

water and extracted with diethyl ether (3 × 100 mL). The combined organic extracts were dried with Na_2SO_4, concentrated under reduced pressure, and purified by silica gel column chromatography (ethyl acetate/hexane = 1:6) to afford **16** (13.65 g, 89%) as a colorless liquid. $[\alpha]_D^{25}$ = –17.2 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3444, 2925, 2854, 1612, 1513 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.28–7.32 (m, 5 H), 7.21 (d, *J* = 8.3 Hz, 2 H), 6.84 (d, *J* = 8.3 Hz, 2 H), 4.50–4.43 (m, 2 H), 4.32–4.26 (m, 2 H), 3.77 (m, 1 H), 3.64 (m, 1 H), 3.04 (m, 1 H), 2.76 (m, 1 H), 2.47 (m, 1 H), 1.80–1.71 (m, 2 H), 1.82–1.59 (m, 4 H), 1.32–1.22 (m 26 H), 0.88 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.8, 138.9, 129.4, 128.3, 127.7, 127.4, 113.7, 75.6, 73.5, 70.8, 70.7, 55.2, 49.2, 46.8, 40.4, 37.1, 34.0, 32.0, 30.0, 29.7, 29.3, 24.8, 22.6, 14.1 ppm. HRMS (ESI): calcd. for $C_{36}H_{56}O_4Na$ [M + Na]$^+$ 575.4072; found 575.4096.

(4*R*,6*R*,8*R*)-8-(Benzyloxy)-6-[(4-methoxybenzyl)oxy]tricos-1-en-4-ol (17): To a solution of **16** (12.0 g, 21.7 mmol) in anhydrous THF (140 mL) under nitrogen, CuI (0.41 g, 2.17 mmol) was added, and the resulting mixture was stirred at 25 °C for 30 min. It was cooled to –20 °C, C_3H_5MgBr (65 mL, 1.0 M in THF) slowly added, and the mixture stirred at the same temperature for 30 min. It was then slowly warmed to room temperature. After 2 h (monitored by TLC), it was quenched with saturated NH_4Cl solution (75 mL) and diluted with ethyl acetate (100 mL). The organic phase was separated and the aqueous phase extracted with ethyl acetate (3 × 75 mL). The combined organic layers were washed with brine (2 × 150 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to afford the crude product that – after purification by column chromatography on silica gel (ethyl acetate/hexane = 1:4) – gave **17** (10.99 g, 87%) as a colorless liquid. $[\alpha]_D^{25}$ = –13.6 (*c* = 0.8, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3450, 2925, 1612, 1461, 1248, 1066 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.32–7.21 (m, 5 H), 7.15 (d, *J* = 8.5 Hz, 2 H), 6.78 (d, *J* = 8.5 Hz, 2 H), 5.75 (m, 1 H), 5.02–4.92 (m, 2 H), 4.55–4.49 (m, 4 H), 3.79 (m, 1 H), 3.70 (m, 1 H), 3.75 (s, 3 H), 3.50 (m,1 H), 2.96 (br. s, 1 H), 2.19–2.12 (m, 2 H), 1.74–1.65 (m, 2 H), 1.63–1.45 (m, 4 H), 1.33–1.22 (m, 26 H), 0.88 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.2, 138.6, 134.8, 130.2, 129.5, 128.3, 127.8, 127.5, 117.4, 76.3, 76.0, 70.6, 69.8, 55.2, 42.5, 41.3, 39.8, 33.9, 31.9, 29.8, 29.6, 29.3, 24.8, 22.6, 14.1 ppm. HRMS (ESI): calcd. for $C_{38}H_{60}O_4Na$ [M + Na]$^+$ 603.4388; found 603.4380.

(4*R*,6*R*,8*S*,10*R*)-10-(Benzyloxy)-8-[(4-methoxybenzyl)oxy]-6-(methoxymethoxy)pentacos-1-en-4-ol (18): To a solution of the terminal epoxide **17d**[21] (6.0 g, 9.4 mmol) in anhydrous THF (60 mL) under nitrogen was added CuI (0.178 g, 0.9 mmol) and the resulting mixture stirred at ambient temperature for 30 min. C_3H_5MgBr (28.1 mL, 1.0 M in THF) was slowly added at –20 °C and stirring continued at the same temperature for 30 min. It was slowly warmed to room temperature. After 2 h (monitored by TLC), the reaction was quenched with saturated NH_4Cl solution (60 mL) and diluted with ethyl acetate (60 mL). The organic phase was separated and the aqueous phase extracted with ethyl acetate (3 × 60 mL). The combined organic layers were washed with brine (2 × 75 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to afford the crude product, which – after purification by column chromatography on silica gel (ethyl acetate/hexane, 1:4) – furnished homoallyl alcohol **18** (5.71 g, 92%) as a colorless liquid. $[\alpha]_D^{25}$ = –9.3 (*c* = 1.1, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3469, 2925, 2854, 1719, 1248, 1036 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.33–7.26 (m, 5 H), 7.19 (d, *J* = 8.7 Hz, 2 H), 6.82 (d, *J* = 8.7 Hz, 2 H), 5.76 (m, 1 H), 5.13–5.04 (m, 2 H), 4.68–4.48 (m, 3 H), 4.42–4.22 (m, 3 H), 3.84 (m, 1 H), 3.77 (s, 3 H), 3.67 (m, 1 H), 3.56 (m, 1 H), 3.33 (s, 3 H), 3.31 (m, 1 H), 2.97 (br. s, 1 H), 2.21–2.14 (m, 2 H), 1.71–1.44 (m, 8 H), 1.32–1.22 (m, 26 H), 0.88 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.1, 138.9, 134.8, 130.6, 129.6, 128.2, 127.8, 127.4, 117.6, 113.7, 95.4, 75.8, 75.0, 72.5, 70.7, 70.3, 70.0, 55.8, 55.2, 42.1, 41.4, 40.3, 40.0, 33.9, 31.9, 30.0, 29.7, 29.3, 24.9, 22.7, 14.1 ppm. HRMS (ESI): calcd. for $C_{42}H_{68}O_6Na$ [M + Na]$^+$ 691.5016; found 691.4893.

(4*R*,6*R*,8*R*,10*S*,12*R*)-12-(Benzyloxy)-6,8,10-tris(methoxymethoxy)-heptacos-1-en-4-ol (19): To a solution of terminal epoxide **18d**[21] (4.5 g, 6.1 mmol) in anhydrous THF (140 mL) under nitrogen, CuI (0.11 g, 0.61 mmol) was added and the resulting mixture stirred at 25 °C for 30 min. It was cooled to –20 °C and C_3H_5MgBr (18.5 mL, 1.0 M in THF) slowly added to it. The reaction mixture was stirred at the same temperature for 30 min. It was then slowly warmed to room temperature. After 1.5 h (monitored by TLC), it was quenched with saturated NH_4Cl solution (30 mL) and diluted with ethyl acetate (50 mL). The organic phase was separated and the aqueous phase extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude product that – on purification by column chromatography on silica gel (ethyl acetate/hexane = 1:3) – furnished **19** (4.05 g, 88%) as a colorless liquid. $[\alpha]_D^{25}$ = –10.6 (*c* = 2.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3472, 2926, 1613, 1247, 1095 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.36–7.27 (m, 5 H), 7.21 (d, *J* = 8.3 Hz, 2 H), 6.84 (d, *J* = 8.3 Hz, 2 H), 5.82 (m, 1 H), 5.15–5.05 (m, 1 H), 4.72–4.40 (m, 6 H), 4.34–4.23 (m, 2 H), 3.80 (m, 1 H), 3.77 (s, 3 H), 3.75–3.66 (m, 2 H), 3.60 (m, 1 H), 3.39 (s, 3 H), 3.35 (m, 1 H), 3.31 (s, 3 H), 3.05 (br. s, 1 H), 2.26–2.16 (m, 2 H), 2.03–1.81 (m, 2 H), 1.80–1.59 (m, 8 H), 1.30–1.22 (m, 26 H), 0.88 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.1, 139.0, 134.7, 130.8, 129.3, 128.2, 127.6, 127.3, 117.5, 113.7, 95.6, 95.1, 75.8, 74.7, 72.8, 72.3, 70.7, 70.3, 69.7, 55.8, 55.1, 42.1, 41.0, 40.4, 40.2, 40.1, 34.0, 31.8, 29.8, 29.6, 29.3, 24.9, 22.6, 14.1 ppm. HRMS (ESI): calcd. for $C_{46}H_{76}O_8Na$ [M + Na]$^+$ 779.5432; found 779.5428.

(4*R*,6*R*,8*R*,10*S*,12*S*,14*R*)-14-(Benzyloxy)-12-[(4-methoxybenzyl)-oxy]-6,8,10-tris(methoxymethoxy)nonacos-1-en-4-ol (20): To a solution of MOM ether **19d**[21] (0.5 g, 0.6 mmol) in anhydrous THF (10 mL) under nitrogen, CuI (0.01 g, 0.06 mmol) was added, and the resulting mixture was stirred at 25 °C for 30 min. It was cooled to –20 °C and C_3H_5MgBr (2.4 mL, 1.0 M in THF) slowly added to it; the reaction mixture was stirred at the same temperature for 20 min. It was then slowly warmed to room temperature. After 1 h (monitored by TLC), it was quenched with saturated NH_4Cl solution (10 mL) and diluted with ethyl acetate (20 mL). The organic layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (2 × 10 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to afford the crude product that – on purification by column chromatography on silica gel (ethyl acetate/hexane = 1:3) – furnished homoallyl alcohol **20** (0.42 g, 82%) as a colorless liquid. $[\alpha]_D^{25}$ = –8.3 (*c* = 1.25, $CHCl_3$): IR (neat): $\tilde{\nu}_{max}$ = 3470, 2926, 1718, 1248, 1035 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.37–7.27 (m, 5 H), 7.21 (d, *J* = 8.3 Hz, 2 H), 6.84 (d, *J* = 8.3 Hz, 2 H), 5.78 (m, 1 H), 5.15–5.05 (m, 2 H), 4.72–4.55 (m, 6 H), 4.55–4.41 (m, 2 H), 4.31–4.21 (m, 2 H), 3.83–3.78 (m, 3 H), 3.76 (m, 1 H), 3.75–3.69 (m, 2 H), 3.61 (m, 1 H), 3.37 (s, 3 H), 3.36 (m, 1 H), 3.34 (s, 2 H), 3.77 (s, 3 H), 3.74–3.66 (m, 2 H), 3.60 (m, 1 H), 3.38 (s, 3 H), 3.35 (s, 3 H), 3.30 (s, 3 H), 2.28–2.18 (m, 2 H), 2.02–1.43 (m, 12 H) 1.29–1.20 (m, 26 H), 0.88 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.0, 139.1, 135.0, 129.3, 128.1, 127.6, 127.3, 117.4, 113.7, 95.7, 95.2, 95.0, 75.7, 74.5 72.7, 72.4, 72.1, 70.8, 70.2, 69.6, 55.8, 55.7, 55.1, 42.1, 40.8, 40.4, 40.2, 39.8, 34.0, 31.8, 29.9, 29.6, 29.3, 24.9, 22.6,

14.1 ppm. HRMS (ESI): calcd. for $C_{50}H_{84}O_{10}Na$ [M + Na]$^+$ 867.5957; found 867.5958.

(4*R*,6*S*,8*S*,10*S*,12*S*,14*R*)-14-(Benzyloxy)-12-[(4-methoxybenzyl)-oxy]-6,8,10-tris(methoxymethoxy)heptacos-1-en-4-yl Acrylate (21): To a solution of **20** (0.3 g, 0.35 mmol) in CH_2Cl_2 (8 mL), DMAP (12.8 mg, 0.10 mmol) and *i*Pr_2NEt (0.18 mL, 1.0 mmol, 3 equiv.) were added. The reaction mixture was cooled to –78 °C, and acryloyl chloride (0.04 mL, 0.5 mmol, 1.5 equiv.) was added. After 1 h at –78 °C, the reaction mixture was poured into brine. The layers were separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:3) to obtain acrylate **21** (0.28 g, 90%) as a colorless liquid. $[\alpha]_D^{25}$ = –11.4 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2925, 2853, 1723, 1613, 1218, 1035 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.34–7.27 (m, 5 H), 7.22 (d, *J* = 8.4 Hz, 2 H), 6.84 (d, *J* = 8.4 Hz, 2 H), 6.38 (dd, *J* = 16.1, 1.3 Hz, 2 H), 6.09 (m, 1 H), 5.84–5.69 (m, 2 H), 5.13–5.04 (m, 2 H), 4.64–4.54 (m, 6 H), 4.53–4.43 (m, 2 H), 4.30–4.21 (m, 2 H), 3.79 (m, 1 H), 3.77 (s, 3 H), 3.74–3.66 (m, 3 H), 3.61 (m, 1 H), 3.37 (s, 3 H), 3.36 (m, 1 H), 3.35 (s, 3 H), 3.28 (s, 3 H), 2.50–2.28 (m, 2 H), 1.98–1.77 (m, 5 H), 1.75–1.61 (m, 5 H), 1.57–1.43 (m, 2 H), 1.33–1.20 (m, 26 H), 0.88 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 165.5, 159.0, 139.1, 133.3, 130.9, 130.5, 129.4, 128.7, 128.2, 127.6, 127.2, 118.0, 113.7, 95.6, 95.5, 95.4, 75.7, 72.7, 72.4, 72.3, 72.2, 70.8, 70.7, 70.2, 55.8, 55.7, 55.2, 40.6, 40.3, 40.0, 39.9, 38.6, 38.5, 34.5, 34.1, 31.9, 29.7, 29.6, 29.3, 24.9, 22.6, 14.1 ppm. HRMS (ESI): calcd. for $C_{53}H_{86}O_{11}Na$ [M + Na]$^+$ 921.6060; found 921.6062.

(*R*)-6-{(2*S*,4*S*,6*S*,8*S*,10*R*)-10-(Benzyloxy)-8-[(4-methoxybenzyl)-oxy]-2,4,6-tris(methoxymethoxy)pentacosyl}-5,6-dihydro-2*H*-pyran-2-one (22): To a stirred solution of acrylic ester **21** (0.2 g, 0.22 mmol) in freshly prepared anhydrous CH_2Cl_2 (100 mL), Grubbs 1st generation catalyst (18 mg, 0.02 mmol) in freshly prepared anhydrous CH_2Cl_2 (100 mL) was added dropwise at room temperature for 30 min. The reaction mixture was heated to reflux for 24 h. After completion of the reaction (monitored by TLC), the solvent was removed under vacuum to obtain the crude product that – on purification by silica gel column chromatography (ethyl acetate/hexane = 1:3) – afforded lactone **22** (0.17 g, 89%). $[\alpha]_D^{25}$ = –11.4 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3013, 2926, 2853, 1725, 1219 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.34–7.27 (m, 5 H), 7.22 (d, *J* = 8.3 Hz, 2 H), 6.87 (m, 1 H), 6.84 (d, *J* = 8.3 Hz, 2 H), 6.02 (d, *J* = 9.8 Hz, 1 H), 4.70–4.39 (m, 8 H), 4.31–4.20 (m, 2 H), 4.12 (dd, *J* = 7.6, 6.8 Hz, 2 H), 3.86 (m, 1 H), 3.81–3.66 (m, 5 H), 3.60 (m, 1 H), 3.40–3.25 (m, 10 H), 2.48–2.21 (m, 2 H), 2.04–1.43 (m, 10 H), 1.36–1.15 (m, 26 H), 0.88 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 164.2, 159.0, 144.8, 139.0, 130.8, 129.4, 129.4, 129.3, 128.2, 127.6, 127.3, 121.4, 113.7, 95.7, 95.6, 95.5, 77.2, 75.7, 75.2, 72.7, 72.3, 71.6, 70.8, 70.2, 55.7, 55.2, 40.6, 40.3, 40.0, 39.6, 39.5, 34.0, 31.9, 29.9, 29.7, 29.6, 29.3, 29.2, 22.6, 14.1 ppm. HRMS (ESI): calcd. for $C_{51}H_{82}O_{11}Na$ [M + Na]$^+$ 893.5749; found 893.5757.

Cryptocaryol A (1): To a stirred solution of **22** (80 mg, 0.09 mmol) in CH_2Cl_2 (5 mL), $TiCl_4$ (4.59 mL, 4.59 mmol, 1 M in CH_2Cl_2) was added at 0 °C and the reaction mixture stirred at room temperature for 4 h. After completion of the reaction (monitored by TLC), it was quenched with a saturated solution of $NaHCO_3$ (10 mL). The organic phase was separated and the aqueous phase extracted with ethyl acetate (5 × 15 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product that – on purification by column chromatography on silica gel (methanol/chloroform = 1:19) – furnished **1** (37 mg, 76%) as a colorless liquid. $[\alpha]_D^{25}$ = +11.4 (*c* = 1.5, MeOH). IR (neat): $\tilde{\nu}_{max}$ = 3367, 2920, 2851, 1715, 1425, 1335, 1094 cm^{-1}. ^{1}H NMR (CD_3OD, 500 MHz): δ = 7.04 (m, 1 H), 5.97 (dd, *J* = 9.8, 2.1 Hz, 1 H), 4.69 (m, 1 H), 4.07–3.97 (m, 4 H), 3.80 (m, 1 H), 2.52 (m, 1 H), 2.39 (m, 1 H), 1.98 (m, 1 H), 1.87 (m, 1 H), 1.72–1.57 (m, 7 H), 1.54–1.50 (m, 2 H), 1.46–1.42 (m, 2 H), 1.32–1.24 (br. m, 26 H), 0.89 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (CD_3OD, 75 MHz): δ = 167.0, 148.4, 121.3, 77.3, 69.9, 69.8, 69.0, 68.1, 67.3, 46.0, 45.7, 45.3, 45.0, 43.0, 39.2, 33.1, 30.8, 30.5, 30.2, 26.8, 23.8, 14.5 ppm. HRMS (ESI): calcd. for $C_{30}H_{56}O_7Na$ [M + Na]$^+$ 551.3918; found 551.3915.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra of all key intermediates and final products.

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