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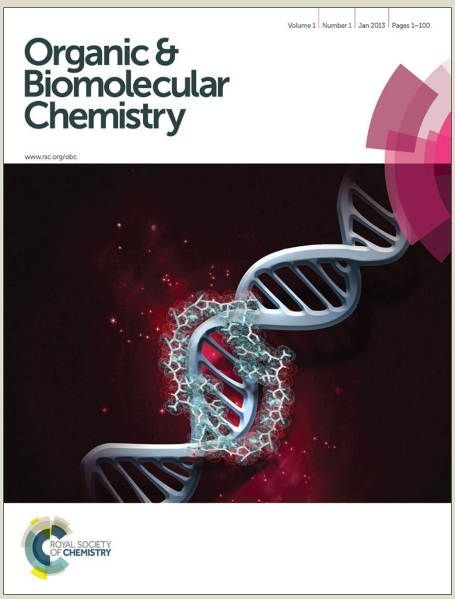

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ARTICLE

Total Synthesis of (−)-Cryptocaryol A

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A stereoselective total synthesis of (−)-cryptocaryol A (**1**) is described. Key features of the 17-step route include the use of three boron-mediated aldol reaction-reduction sequences to control all stereocenters and an Ando modification of the Horner-Wadsworth-Emmons olefination that permitted the installation of the *Z* double bond of the α-pyrone ring.

Introduction

(+)-Cryptocaryol A (**1**) was isolated in 2011 by Gustafson and co-workers from a collection of the plant *Cryptocarya* sp. in Papua New Guinea (Figure 1).[1] This natural product exhibits stabilizing activity (EC_{50} = 4.9 μM) toward Pdcd4 (programmed cell death 4),[1] a tumor suppressor protein that can inhibit neoplastic transformation[2] and is downregulated in several cancers.[3] Thus, the stabilization of this protein is a potential tumor prevention strategy.

The ability of (+)-cryptocaryol A (**1**) to stabilize Pdcd4 and the potential of this protein for cancer prevention and treatment motivated some research groups to synthesize this natural product. In 2013, the synthesis of a purported cryptocaryol A was published by Reddy and Mohapatra.[4] Wang and O'Doherty subsequently reported the first total synthesis of the natural product, confirming its relative and absolute stereochemistry.[5] The authors also synthesized several analogs of this compound to evaluate structure-activity relationships in cancer cell cytotoxicity.[6]

Herein, we report our total synthesis of (−)-cryptocaryol A (**1**).

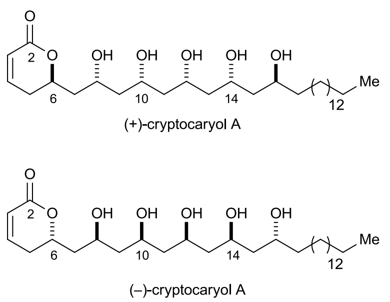
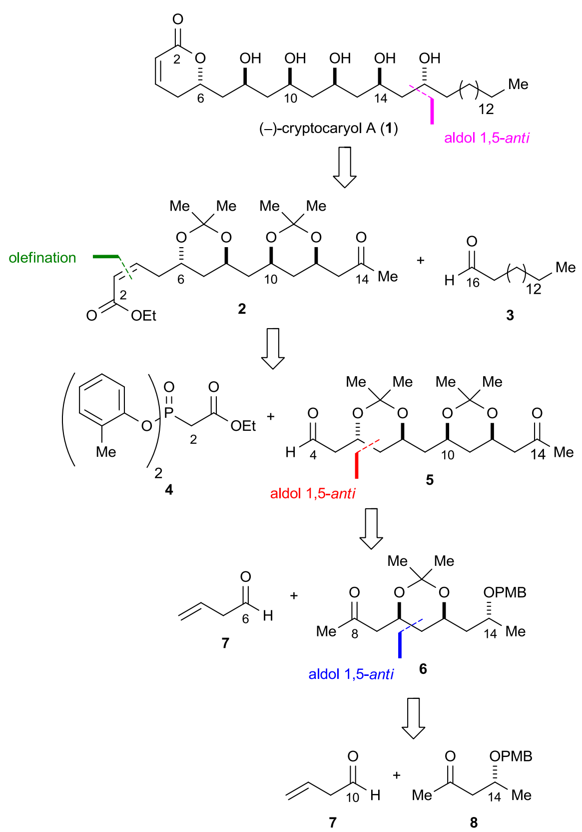


Figure 1. (+)- and (−)-cryptocaryol A (**1**).

Retrosynthetic Analysis of (−)-Cryptocaryol A (1)

Our disconnection approach[7] began with the formation of the C15-C16 bond via an aldol coupling between the boron enolate of methyl ketone **2** and aldehyde **3** (Scheme 1). The Z-olefin **2** could be prepared by a Horner-Wadsworth-Emmons coupling of the Ando phosphonate **4** and aldehyde **5**. An aldol reaction between methyl ketone **6** and aldehyde **7** could provide compound **5**, and finally, fragment **6** could be obtained from a boron-mediated aldol addition of methyl ketone **8** and aldehyde **7**.

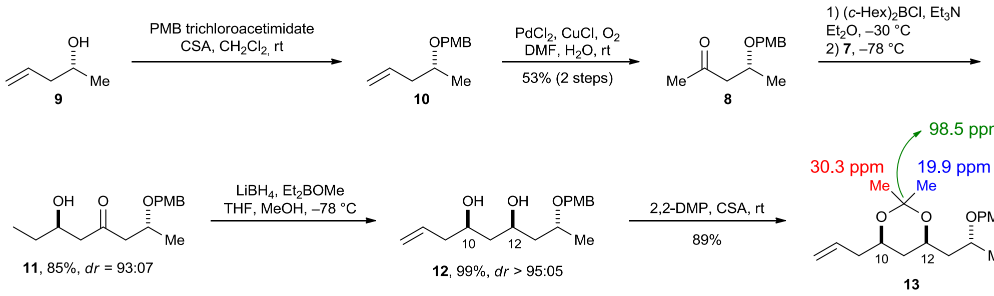


Scheme 1. Retrosynthetic analysis of (−)-**1**.

Results and Discussion

Our synthesis began with protection of the commercially available (*R*)-4-penten-2-ol (**9**) using *p*-methoxybenzyl-2,2,2-trichloroacetimidate and a catalytic amount of camphorsulfonic acid (CSA) to provide olefin **10**, which was converted to methyl ketone **8** via Wacker oxidation in 53% yield for the 2-

step sequence (Scheme 2).[8] The aldol reaction between the boron enolate of methyl ketone **8** and freshly prepared aldehyde

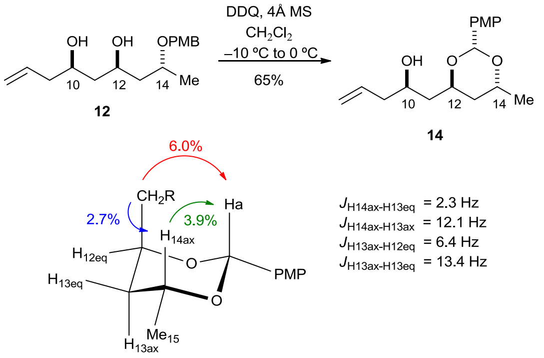


Scheme 2. Synthesis of acetonide **13**

7[9] provided the aldol adduct **11** in 85% yield with a diastereoselectivity of 93:07 favoring the 1,5-*anti* isomer.[10] Compound **11** was reduced with $LiBH_4$ and Et_2BOMe to furnish the 1,3-*syn* diol **12** in 99% yield and high diastereoselectivity (*dr* > 95:05).[11] Protection of **12** with 2,2-dimethoxypropane (2,2-DMP) provided acetonide **13** in 89% yield.[12]

^{13}C NMR analysis of compound **13** revealed chemical shifts of 19.9 and 30.3 ppm for the methyl groups and 98.5 ppm for the quaternary carbon, which correspond to a *cis* acetonide according to the Rychnovsky method.[13] Therefore, the relative configuration of the substituents at C10 and C12 of diol **12** is 1,3-*syn*.

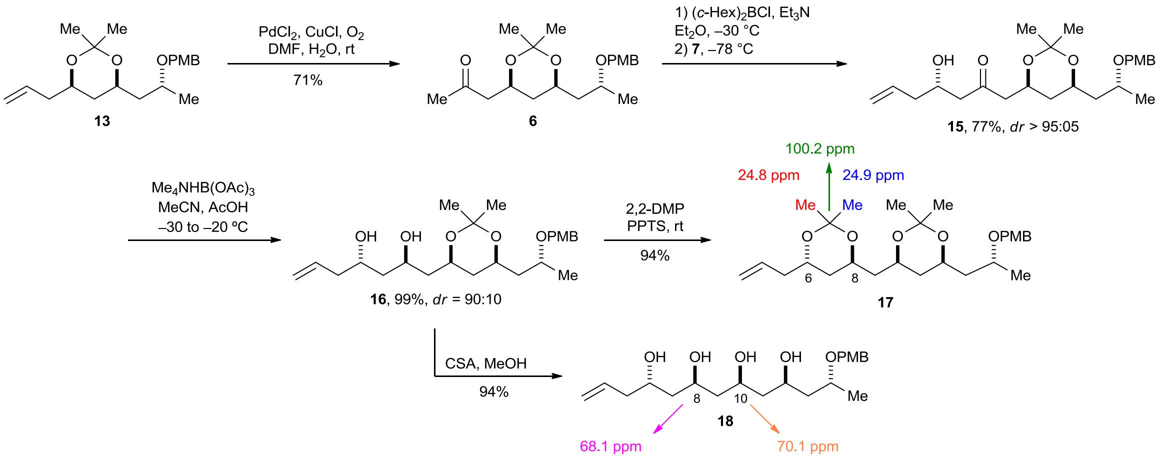
To establish the relative stereochemistry of aldol adduct **11**, the diol **12** was derivatized to its PMP acetal **14** (65%) by treatment with DDQ in the presence of molecular sieves (Scheme 3). NMR coupling constants, along with selective NOE experiments, indicated a *trans* relationship between the substituents at C12 and C14, demonstrating that the relative stereochemistry of aldol adduct **11** is 1,5-*anti*.



Scheme 3. Determination of the stereochemistry of aldol adduct **11**.

The next step was a Wacker oxidation of olefin **13** that afforded methyl ketone **6** in 71% yield. The subsequent aldol coupling of the boron enolate of methyl ketone **6** with aldehyde **7** provided aldol adduct **15** in 77% yield with a diastereoselectivity greater than 95:05 favoring the 1,5-*anti* isomer (Scheme 4). The β-hydroxy ketone **15** was stereoselectively reduced with $Me_4NHB(OAc)_3$ to afford diol **16** in 99% yield (*dr* = 90:10, 1,3-*anti*:1,3-*syn*).[14] Compound **16** was protected with 2,2-DMP and PPTS to provide acetonide **17** (94%).

The ^{13}C NMR spectrum of **17** presented chemical shifts of 24.8 and 24.9 ppm for the methyl groups and 100.2 ppm for the quaternary carbon, consistent with a *trans* acetonide according to the Rychnovsky method. Thus, the relative stereochemistry of diol **16** is 1,3-*anti*. To determine the relative stereochemistry



Scheme 4. Synthesis of acetonide **17**

of aldol adduct **15**, we applied a methodology described by Kishi and co-workers.[15] Removal of the acetonide of compound **16** with CSA gave tetraol **18** in 94% yield. ^{13}C NMR analysis of compound **18** revealed chemical shifts of 68.1 ppm for C8 and 70.1 ppm for C10, which correspond to an *anti*/*syn* and *syn*/*syn* relationship, respectively, according to Kishi's database.

Removal of the PMB ether of compound **17** with DDQ provided alcohol **19** in 91% yield (Scheme 5). Swern oxidation yielded methyl ketone **20** (94%), and aldehyde **5** was subsequently obtained via dihydroxylation followed by oxidative cleavage.[16] Then, a Horner-Wadsworth-Emmons reaction using the Ando phosphonate **4** furnished ester **2** in 87% yield (three steps) with a diastereoselectivity of 88:12 favoring the *Z* isomer.[17]

The next step involved an aldol reaction between the boron enolate generated from methyl ketone **2** and aldehyde **3** (Scheme 6) followed by an Evans reduction to afford diol **21**. Finally, removal of the acetonide groups and concomitant lactonization provided synthetic (−)-cryptocaryol A in less than 10% yield for 3 steps.[18]

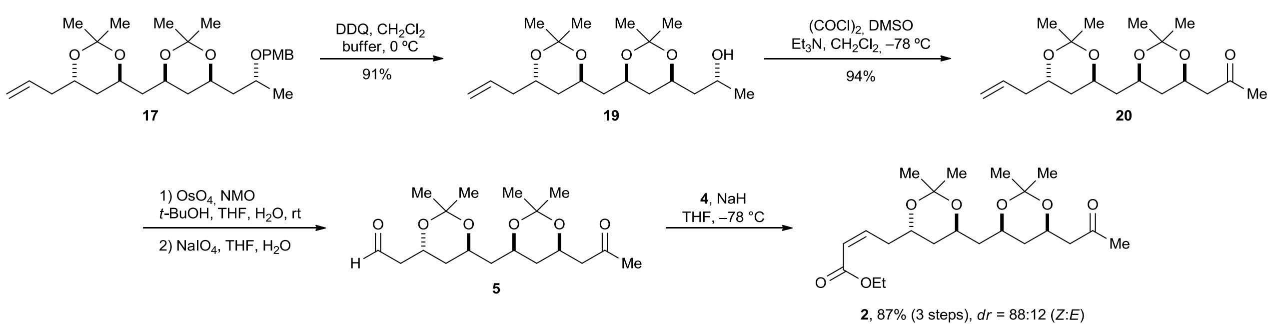
Spectral data (^{1}H and ^{13}C NMR, and HRMS) for the synthetic sample were in complete agreement with those reported in the literature for the natural product (Table 1).

Conclusions

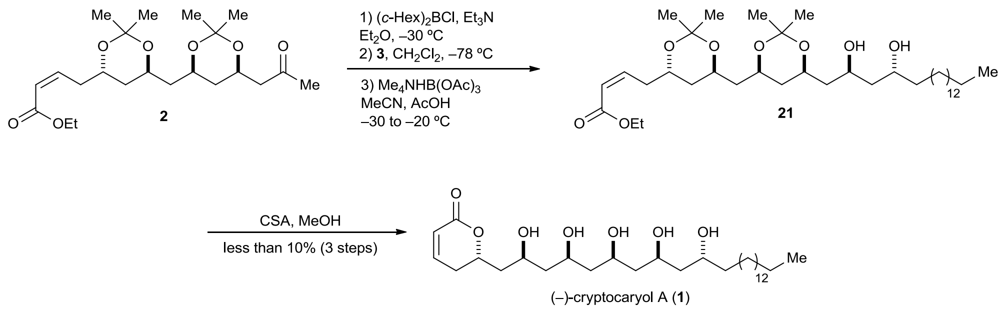
The asymmetric total synthesis of (−)-cryptocaryol A (**1**) was accomplished in 17 steps (longest linear sequence) from commercially available (*R*)-4-penten-2-ol (**9**). This approach is shorter than those previously described by Reddy and Mohapatra[4] (28 steps) and Wang and O'Doherty[5] (23 steps), although it is not the most efficient. The difficulties with the last three steps minimizes the efficiency of the approach. All six stereogenic centers were controlled by three boron-mediated aldol reaction-reduction sequences.

Experimental

Materials and methods. Unless noted, all reactions were performed under an atmosphere of argon with dry solvents and magnetic stirring. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N) and acetonitrile (MeCN) were distilled from CaH_2. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone. Acetic acid (AcOH) was fractionally distilled from acetic anhydride and chromium (VI) oxide. Methanol (MeOH) was distilled from $Mg(OMe)_2$ and stored over molecular sieves. Dimethyl sulfoxide (DMSO) was distilled under reduced pressure from CaH_2 and stored over molecular sieves. Camphorsulfonic acid (CSA) was recrystallized from ethyl acetate. Yields refer to homogeneous materials obtained after purification of reaction products by flash column chromatography using silica gel (200-400 mesh). Analytical thin-layer chromatography was performed on silica-gel 60 and GF (5-40 μm thickness) plates, and visualization was accomplished using UV light and phosphomolybdic acid staining followed by heating. Optical rotations were measured with a sodium lamp and are reported as follows: $[\alpha]_D^{T\ (°C)}$ (*c* (g/100 mL), solvent). Melting points are uncorrected. For infrared spectra (IR), wavelengths of maximum absorbance (ν_{max}) are quoted in wavenumbers (cm^{-1}). ^{1}H and proton-decoupled ^{13}C NMR spectra were acquired in C_6D_6, $CDCl_3$, or CD_3OD at 250 MHz (^{1}H) and 62.5 MHz (^{13}C), at 400 MHz (^{1}H) and 100 MHz (^{13}C), at 500 MHz (^{1}H) and 125 MHz (^{13}C), or at 600 MHz (^{1}H) and 150 MHz (^{13}C). Chemical shifts (δ) are reported in ppm using residual undeuterated solvent as an internal standard (C_6D_6 at 7.16 ppm, $CDCl_3$ at 7.25 ppm, CD_3OD at 3.30 ppm, and TMS at 0.00 ppm for ^{1}H NMR spectra and C_6D_6 at 128.0 ppm, $CDCl_3$ at 77.0 ppm, CD_3OD at 49.0 ppm for ^{13}C NMR spectra). Multiplicity data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, br s = broad singlet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, dtd = doublet of triplet of doublets, dqd = doublet of quartet of doublets, m = multiplet, and br m = broad multiplet. The multiplicity is followed by the coupling constant(s) in Hz and integration. High-resolution mass spectra (HRMS) were measured using electrospray ionization (ESI). Samples were analyzed using a hybrid 7T Fourier transform ion cyclotron



Scheme 5. Synthesis of ester **2**.



Scheme 6. Completion of the synthesis of (−)-cryptocaryol A (**1**).

Table 1. ^{1}H and ^{13}C NMR Chemical Shifts of Natural[1] and Synthetic Cryptocaryol A (**1**)

Position	Natural Product[1]			Synthetic Product		
	δ ^{13}C	δ ^{1}H	multiplicity (*J* in Hz)	δ ^{13}C^{a}	δ ^{1}H^{a}	multiplicity (*J* in Hz)
2	167.0			167.0		
3	121.4	5.97	dd (9.8, 1.9)	121.4	5.97	dd (9.8, 1.9)
4	148.6	7.04	ddd (9.8, 6.0, 2.3)	148.5	7.05	ddd (9.4, 5.9, 2.4)
5a	31.0	2.45	m	30.9	2.45	m
5b		2.36	ddt (18.5, 11.8, 2.6)		2.36	ddt (18.5, 11.7, 2.5)
6	76.6	4.71	m	76.6	4.71	m
7a	43.9	1.94	ddd (14.5, 9.7, 2.3)	43.9	1.94	ddd (14.4, 9.9, 2.5)
7b		1.67	m		1.67	m
8	66.6	4.08	m	66.6	4.09	m
9	46.0	1.68	m	46.0	1.67	m
10	69.9	3.97	m	69.9	4.00	m
11	45.3	1.64	m	45.2	1.64	m
12	70.2	4.00	m	70.1	4.00	m
13	45.9	1.59	m	45.9	1.60	m
14	68.3	4.02	m	68.2	4.03	m
15	45.8	1.50	m	45.7	1.52	m
16	69.1	3.79	m	69.1	3.80	m
17	39.3	1.43	m	39.2	1.44	m
18	26.8	1.32	m	26.8	1.34	m
19-28	30.5-31.0	1.27-1.29	br s	30.5-30.9	1.27-1.29	br s
29	33.2	1.29	m	33.1	1.29	m
30	23.8	1.27	m	23.7	1.29	m
31	14.5	0.89	t (6.9)	14.4	0.89	t (7.0)

^{a} Assignment based on COSY, HSQC, and HMBC experiments.

nanoelectrospray ionization source. The nanoelectrospray conditions were a flow rate of 200 nL min^{-1}, back pressure of approximately 0.4 psi, and electrospray voltages of 1.5-2.0 kV over 60 s and were controlled by ChipSoft software. Mass resolution was fixed at 100,000 at *m/z* 400. Data were obtained as transient files (scans recorded in the time domain). All samples were evaluated in positive ESI(+) ion mode, and spectra were acquired in the *m/z* 150–1500 range. Samples were analyzed directly in a 10 µg mL^{-1} methanol solution without any sample treatment or dilution.

Synthesis

(*R*)-4-((4-Methoxybenzyl)oxy)pentan-2-one (8). To a solution of alcohol **9** (1.2 mL, 11.6 mmol) in CH_2Cl_2 (35 mL) at room temperature was added *p*-methoxybenzyl-2,2,2-trichloroacetimidate (4.8 mL, 23.3 mmol) and CSA (269 mg, 1.16 mmol). The reaction mixture was stirred under the same conditions for 15 h before being quenched by the addition of saturated aqueous solution of $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Compound **10** was partially purified by flash column chromatography using a solution of hexane/ethyl acetate (20:80) as the eluent.

A mixture of $PdCl_2$ (206 mg, 1.16 mmol) and CuCl (1.15 g, 11.6 mmol) in DMF (75 mL) and H_2O (12 mL) was purged with O_2 with vigorous stirring to activate the reaction medium. The reaction mixture was stirred for 30 min, yielding a deep-green mixture. After this period, a solution of olefin **10** (11.6 mmol) in DMF (6 mL) was added, and the reaction medium was stirred vigorously for 12 h under an O_2 atmosphere. The reaction was quenched by the addition of H_2O (50 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (4 ×). The combined organic layers were washed with H_2O (2 ×), brine (2 ×), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (80:20) as the eluent to provide methyl ketone 8 (1.36 g, 6.12 mmol, 53%) (2 steps) as a yellow oil. R_f 0.31 (80:20 hexane/ethyl acetate). $[\alpha]_D^{20}$ –28 (*c* 1.3 in $CHCl_3$). ^{1}H NMR (250 MHz, C_6D_6) δ 1.04 (d, *J* = 6.0 Hz, 3H), 1.71 (s, 3H), 2.01 (dd, *J* = 5.2 and 15.8 Hz, 1H), 2.44 (dd, *J* = 7.3 and 15.8 Hz, 1H), 3.30 (s, 3H), 3.83-3.97 (m, 1H), 4.25 (d, J = 11.2 Hz, 1H), 4.36 (d, J = 11.2 Hz, 1H), 6.77-6.82 (m, 2H), 7.18-7.24 (m, 2H). ^{13}C NMR (62.5 MHz, C_6D_6) δ 19.9 (CH_3), 30.5 (CH_3), 50.6 (CH_2), 54.7 (CH_3), 70.5 (CH_2), 71.4 (CH), 114.0 (CH), 129.3 (CH), 131.4 (C_0), 159.6 (C_0), 205.2 (C_0). IR (film) ν_{max}/cm^{-1} 2970, 2934, 2905, 2871, 2838, 1712, 1613, 1513, 1464, 1372, 1245, 1173, 1087, 1032, 820.

(2*R*,6*R*)-6-Hydroxy-2-((4-methoxybenzyl)oxy)non-8-en-4-one (11). To a solution of methyl ketone **8** (1.06 g, 4.77 mmol) in Et_2O (50 mL) at −30 ºC was added (c-Hex)$_2$BCl (2.1 mL, 9.54 mmol) dropwise, followed by the addition of Et_3N (1.4 mL, 10.0 mmol) dropwise, which resulted in the formation of a white cloud. The mixture was stirred under the same conditions for 30 min. The reaction medium was then cooled to −78 ºC, and a solution of aldehyde **7Erro! Indicador não definido.** (~14.3 mmol) in CH_2Cl_2 (~5 mL) was added over 15 min using a syringe pump. The resulting mixture was stirred for 1 h at −78 ºC, followed by quenching via the addition of pH 7 phosphate buffer (10 mL). The mixture was warmed to 0 ºC, and MeOH (29 mL) and a solution of 30% H_2O_2 (10 mL) in MeOH (19 mL) were added dropwise. The reaction medium was stirred for 1 h under the same conditions. The volatiles were removed under reduced pressure, and the aqueous layer was extracted with Et_2O (4 ×). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (1 ×), brine (1 ×), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (70:30) as the eluent to provide the aldol adduct **11** (1.18 g, 4.04 mmol, dr = 93:07, 85%) as a colorless oil. The diastereoisomers were not separated at this stage. R_f 0.30 (70:30 hexane/ethyl acetate). $[\alpha]_D^{20}$ −43 (c 2.7 in $CHCl_3$). ^{1}H NMR (600 MHz, C_6D_6) δ 1.02 (d, J = 6.0 Hz, 3H), 2.01 (dd, J = 4.9 and 15.6, 1H), 2.03-2.08 (m, 1H), 2.12-2.17 (m, 1H), 2.18-2.25 (m, 2H), 2.45 (dd, J = 7.9 and 15.6 Hz, 1H), 3.00 (br s, 1H), 3.30 (s, 3H), 3.89-3.94 (m, 1H), 4.04 (br s, 1H), 4.21 (d, J = 11.2 Hz, 1H), 4.35 (d, J = 11.2 Hz, 1H), 4.98-5.02 (m, 2H), 5.77 (ddt, J = 7.0, 9.5 and 16.8 Hz, 1H), 6.79- 6.81 (m, 2H), 7.19-7.21 (m, 2H). ^{13}C NMR (125 MHz, C_6D_6) δ 19.7 (CH_3), 41.4 (CH_2), 50.0 (CH_2), 50.6 (CH_2), 54.7 (CH_3), 70.6 (CH_2), 71.4 (CH), 114.0 (CH), 117.3 (CH_2), 129.5 (CH), 131.1 (C_0), 135.1 (CH), 159.7 (C_0), 209.4 (C_0). IR (film) ν_{max}/cm^{-1} 3436, 3076, 2972, 2932, 2839, 1710, 1642, 1613, 1514, 1376, 1302, 1248, 1174, 1034, 918, 823. HRMS (ESI FT-ICR-MS) m/z: [M + Na]$^+$ Calcd for $C_{17}H_{24}O_4Na$ 315.15723, Found 315.15638.

(4*R*,6*R*,8*R*)-8-(4-Methoxybenzyloxy)non-1-ene-4,6-diol (12). To a solution of aldol adduct **11** (1.18 g, 4.04 mmol) in THF:MeOH (4:1) (20 mL) at −78 ºC was added Et_2BOMe (0.64 mL, 4.85 mmol). The solution was stirred for 15 min under these conditions, and $LiBH_4$ (2.4 mL, 4.85 mmol, 2.0 M in THF) was added. The reaction was stirred for 1.5 h and then warmed to −40 ºC. The reaction was quenched by the addition of pH 7 phosphate buffer (55 mL) and MeOH (100 mL). The reaction was warmed to 0 ºC, and 30% H_2O_2 (40 mL) was added dropwise. The mixture was stirred for 1 h, and the volatiles were removed under reduced pressure. The aqueous layer was extracted with EtOAc (4 ×). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (1 ×), brine (1 ×), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in MeOH, and the solvent was removed under reduced pressure in a 60 ºC bath to remove chelated boron species. This procedure was repeated 4 times to provide the diol **12** (1.18 g, 4.01 mmol, dr > 95:05, 99%) as a yellow oil. R_f 0.52 (50:50 hexane/ethyl acetate). $[\alpha]_D^{20}$ −35 (c 2.3 in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ 1.25 (d, J = 6.1 Hz, 3H), 1.50-1.53 (m, 2H), 1.63 (ddd, J = 2.9, 7.6 and 14.6 Hz, 1H), 1.70 (ddd, J = 3.5, 8.4 and 14.6 Hz, 1H), 2.17-2.28 (m, 2H), 3.72 (br s, 1H), 3.76 (br s, 1H), 3.80 (s, 3H), 3.84-3.94 (m, 2H), 4.12-4.17 (m, 1H), 4.38 (d, J = 11.2 Hz, 1H), 4.56 (d, J = 11.2 Hz, 1H), 5.08-5.12 (m, 2H), 5.74-5.90 (ddt, J = 7.1, 10.2 and 17.2 Hz, 1H), 6.87-6.90 (m, 2H), 7.24-7.27 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2 (CH_3), 42.2 (CH_2), 42.3 (CH_2), 43.1 (CH_2), 55.3 (CH_3), 70.0 (CH), 70.2 (CH_2), 71.7 (CH), 72.2 (CH), 113.9 (CH), 117.5 (CH_2), 129.5 (CH), 130.2 (C_0), 134.7 (CH), 159.3 (C_0). IR (film) ν_{max}/cm^{-1} 3401, 3075, 2967, 2936, 2911, 2870, 2839, 1641, 1613, 1587, 1514, 1441, 1302, 1249, 1175, 1110, 1077, 1035, 917, 821. HRMS (ESI FT-ICR-MS) m/z: [M + Na]$^+$ Calcd for $C_{17}H_{26}O_4Na$ 317.17288, Found 317.17204.

(4*R*,6*S*)-4-Allyl-6-((*R*)-2-((4-methoxybenzyl)oxy)propyl)-2,2-dimethyl-1,3-dioxane (13). To a solution of diol **12** (2.56 g, 8.69 mmol) in 2,2-DMP (122 mL) was added CSA (202 mg, 0.869 mmol). The reaction medium was stirred for 13 h. The solution was then diluted with Et_2O and saturated aqueous solution of $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with Et_2O (3 ×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (90:10) as the eluent to provide acetonide **13** (2.59 g, 7.76 mmol, 89%) as a colorless oil. R_f 0.51 (90:10 hexane/ethyl acetate). $[\alpha]_D^{20}$ −41 (c 2.7 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 1.08-1.15 (m, 1H), 1.18 (d, J = 6.0 Hz, 3H), 1.38 (s, 3H), 1.41 (s, 3H), 1.46 (dt, J = 2.5 and 13.0 Hz, 1H), 1.49-1.62 (m, 2H), 2.10-2.17 (m, 1H), 2.26-2.32 (m, 1H), 3.72-3.78 (m, 1H), 3.80 (s, 3H), 3.87 (dtd, J = 2.3, 6.3 and 12.3 Hz, 1H), 4.09 (ddt, J = 2.8, 8.8 and 11.5 Hz, 1H), 4.34 (d, J = 11.0 Hz, 1H), 4.52 (d, J = 11.0 Hz, 1H), 5.03-5.10 (m, 2H), 5.79 (ddt, J = 7.0, 10.0 and 17.1 Hz, 1H), 6.85-6.88 (m, 2H), 7.24-7.26 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9 (CH_3), 20.1 (CH_3), 30.3 (CH_3), 36.9 (CH_2), 40.8 (CH_2), 44.5 (CH_2), 55.3 (CH), 65.5 (CH), 68.7 (CH), 70.5 (CH_2), 70.7 (CH), 98.5 (C_0), 113.7 (CH), 117.0 (CH_2), 129.4 (CH), 131.0 (C_0), 134.2 (CH_2), 159.1 (C_0). IR (film) ν_{max}/cm^{-1} 3075, 2993, 2966, 2941, 2912, 2867, 2837, 1642, 1614, 1587, 1514, 1465, 1435, 1379, 1302, 1248, 1200, 1172, 1154, 1111, 1038, 948, 821, 753. HRMS (ESI FT-ICR-MS) m/z: [M + Na]$^+$ Calcd for $C_{20}H_{30}O_4Na$ 357.20418, Found 357.20343.

(*R*)-1-((2*R*,4*R*,6*R*)-2-(4-Methoxyphenyl)-6-methyl-1,3-dioxan-4-yl)pent-4-en-2-ol (14). To a solution of diol **12** (20 mg, 68 μmol) in CH_2Cl_2 (1.5 mL) was added activated 4 Å molecular sieves (21 mg). After 15 min, the mixture was cooled to −10 ºC, and DDQ (19 mg, 85 μmol) was added. The reaction medium was stirred for 5 min at −10 ºC and 2 h at 0 ºC. The crude product was then purified by flash column chromatography using a solution of hexane/ethyl acetate (60:40) as the eluent to provide the acetal **14** (13 mg, 44 µmol, 65%) as a yellow oil. R_f 0.59 (60:40 hexane/ethyl acetate). $[\alpha]_D^{20}$ +4 (*c* 1.1 in $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, Me_4Si) δ 1.28 (d, *J* = 6.1 Hz, 3H), 1.46-1.50 (m, 1H), 1.55 (dt, *J* = 3.5 and 14.5 Hz, 1H), 2.01 (ddd, *J* = 6.4, 11.6 and 13.4 Hz, 1H), 2.31 (m, 2H), 2.41 (ddd, *J* = 9.0, 11.0 and 14.6 Hz, 1H), 2.88 (br s, 1H), 3.78 (s, 3H), 3.92-3.96 (m, 1H), 4.12 (dqd, *J* = 2.4, 6.1 and 12.1 Hz, 1H), 4.43-4.48 (m, 1H), 5.11-5.16 (m, 2H), 5.85 (ddt, *J* = 7.2, 10.2 and 17.2 Hz, 1H), 5.85 (s, 1H), 6.85-6.88 (m, 2H), 7.40-7.41 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9 (CH_3), 36.1 (CH_2), 36.6 (CH_2), 41.7 (CH_2), 55.3 (CH_3), 68.8 (CH), 70.8 (CH), 73.0 (CH), 94.6 (CH), 113.8 (CH), 117.8 (CH_2), 127.5 (CH), 131.0 (C_0), 134.6 (CH), 160.0 (C_0). IR (film) ν_{max}/cm^{-1} 3460, 3075, 2973, 2936, 2919, 2868, 1641, 1615, 1590, 1518, 1442, 1398, 1377, 1304, 1249, 1172, 1118, 1034, 995, 920, 826, 777. HRMS (ESI FT-ICR-MS) m/z: [M + Na]$^+$ Calcd for $C_{17}H_{24}O_4Na$ 315.15723, Found 315.15641.

1-((4*S*,6*S*)-6-((*R*)-2-(4-Methoxybenzyloxy)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)propan-2-one (6). A mixture of $PdCl_2$ (157 mg, 0.886 mmol) and CuCl (877 mg, 8.86 mmol) in DMF (55 mL) and H_2O (9 mL) was purged with O_2 under vigorous stirring to activate the reaction medium. The reaction mixture was stirred for 30 min to obtain a deep-green mixture. A solution of olefin **13** (2.96 g, 8.86 mmol) in DMF (7 mL) was then added, and the reaction medium was stirred vigorously for 12 h under an O_2 atmosphere. The reaction was quenched by the addition of H_2O (45 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (4 ×). The combined organic layers were washed with H_2O (2 ×), brine (2 ×), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (70:30) as the eluent to provide methyl ketone **6** (2.20 g, 6.28 mmol, 71%) as a colorless oil. R_f 0.45 (70:30 hexane/ethyl acetate). $[\alpha]_D^{20}$ −47 (*c* 1.4 in $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$, Me_4Si) δ 1.06-1.20 (m, 1H), 1.17 (d, *J* = 6.2 Hz, 3H), 1.34 (s, 3H), 1.41 (s, 3H), 1.44-1.64 (m, 3H), 2.15 (s, 3H), 2.40 (dd, *J* = 5.1 and 16.0 HZ, 1H), 2.65 (dd, *J* = 7.3 and 16.0 Hz, 1H), 3.68-3.77 (m, 1H), 3.79 (s, 3H), 4.07-4.17 (m, 1H), 4.26-4.33 (m, 1H), 4.33 (d, *J* = 11.1 Hz, 1H), 4.52 (d, *J* = 11.1 Hz, 1H), 6.85-6.90 (m, 2H), 7.23-7.27 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 19.8 (CH_3), 20.0 (CH_3), 30.1 (CH_3), 31.0 (CH_3), 37.1 (CH_2), 44.3 (CH_2), 50.1 (CH_2), 55.2 (CH), 65.4 (CH), 65.7 (CH), 70.5 (CH_2), 70.6 (CH), 98.6 (C_0), 113.7 (CH), 129.3 (CH), 131.0 (C_0), 159.1 (C_0), 206.9 (C_0). IR (film) ν_{max}/cm^{-1} 2993, 2965, 2940, 2912, 2838, 1716, 1613, 1595, 1587, 1514, 1465, 1423, 1380, 1356, 1302, 1249, 1200, 1172, 1036, 842, 823, 753. HRMS (ESI FT-ICR-MS) m/z: [M + Na]$^+$ Calcd for $C_{20}H_{30}O_5Na$ 373.19909, Found 373.19834.

(*S*)-4-Hydroxy-1-((4*S*,6*S*)-6-((*R*)-2-((4-methoxybenzyl)oxy)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)hept-6-en-2-one (15). To a solution of methyl ketone **6** (600 mg, 1.71 mmol) in Et_2O (18 mL) at −30 ºC was added (*c*-Hex)$_2$BCl (0.75 mL, 3.42 mmol) dropwise, followed by the addition of Et_3N (0.50 mL, 3.59 mmol) dropwise, which resulted in the formation of a white cloud. The mixture was stirred under the same conditions for 30 min. After this period, the reaction medium was cooled to −78 ºC, and a solution of freshly prepared aldehyde **7Erro! Indicador não definido.** (~5.1 mmol) in CH_2Cl_2 (~2 mL) was added over 15 min using a syringe pump. The resulting mixture was stirred for 1 h at −78 ºC and then quenched by the addition of pH 7 phosphate buffer (3.3 mL). The mixture was warmed to 0 ºC, and MeOH (10 mL) and a solution of 30% H_2O_2 (3.3 mL) in MeOH (7 mL) were added dropwise. The reaction medium was stirred for 1 h under the same conditions. The volatiles were removed under reduced pressure, and the aqueous layer was extracted with Et_2O (4 ×). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (1 ×), brine (1 ×), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (70:30) as the eluent to provide aldol adduct **15** (551 mg, 1.31 mmol, *dr* > 95:05, 77%) as a colorless oil. R_f 0.24 (70:30 hexane/ethyl acetate). $[\alpha]_D^{20}$ −24 (*c* 2.3 in $CHCl_3$). ^1H NMR (500 MHz, C_6D_6) δ 0.99-1.08 (m, 2H), 1.10 (d, *J* = 6.1, 3H), 1.34 (s, 3H), 1.45 (s, 3H), 1.48-1.57 (m, 2H), 1.94 (dd, *J* = 4.2 and 15.6 Hz, 1H), 2.04-2.10 (m, 1H), 2.13-2.29 (m, 3H), 2.39 (dd, *J* = 8.1 and 15.7 Hz, 1H), 2.94 (br s, 1H), 3.34 (s, 3H), 3.75-3.82 (m, 1H), 4.04-4.10 (m, 1H), 4.18-4.23 (m, 1H), 4.27 (d, *J* = 11.3 Hz, 1H), 4.50 (d, *J* = 11.3 Hz, 1H), 4.99-5.02 (m, 2H), 5.74-5.82 (m, 1H), 6.84-6.87 (m, 2H), 7.28-7.29 (m, 2H). ^{13}C NMR (125 MHz, C_6D_6) δ 19.9 (CH_3), 20.3 (CH_3), 30.4 (CH_3), 37.4 (CH_2), 41.4 (CH_2), 45.0 (CH_2), 49.7 (CH_2), 50.1 (CH_2), 54.8 (CH_3), 65.7 (CH), 66.1 (CH), 67.2 (CH), 70.6 (CH_2), 70.8 (CH), 98.8 (C_0), 114.0 (CH), 117.3 (CH_2), 129.5 (CH), 131.8 (C_0), 135.1 (CH), 159.7 (C_0), 208.6 (C_0). IR (film) ν_{max}/cm^{-1} 3349, 3076, 2993, 2966, 2939, 2913, 2838, 1711, 1641, 1613, 1587, 1514, 1465, 1380, 1302, 1249, 1201, 1171, 1112, 1058, 1036, 944, 875, 822, 753. HRMS (ESI FT-ICR-MS) m/z: [M + Na]$^+$ Calcd for $C_{24}H_{36}O_6Na$ 443.24096, Found 443.24006.

(2*R*,4*S*)-1-((4*R*,6*S*)-6-((*R*)-2-(4-Methoxybenzyloxy)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)hept-6-ene-2,4-diol (16). To a slurry of $Me_4NHB(OAc)_3$ (1.65 g, 6.28 mmol) in MeCN (4.5 mL) was added AcOH (4.5 mL). The mixture was stirred at room temperature for 30 min and then cooled to −30 ºC. Then, a solution of aldol adduct **15** (662 mg, 1.57 mmol) in MeCN (4.5 mL) was added dropwise, followed by the addition of a solution of CSA (184 mg, 0.79 mmol) in MeCN (4.5 mL) and AcOH (4.5 mL). The reaction medium was warmed to −20 ºC and stirred for 18 h. The mixture was poured into an Erlenmeyer flask containing saturated aqueous solution of $NaHCO_3$ (134 mL). After gas liberation ceased, saturated aqueous solution of sodium potassium tartrate (134 mL) and Et_2O (190 mL) were added. The mixture was stirred vigorously for 3 h. Then, the layers were separated, and the aqueous layer was extracted with Et_2O (4 ×). The combined organic layers were washed with brine (1 ×), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide diol **16** (660 mg, 1.56 mmol, *dr* = 90:10, 99%) as a colorless oil. The diastereoisomers were not separated at this stage. R_f 0.24 (60:40 hexane/ethyl acetate). $[\alpha]_D^{20}$ −24 (*c* 1.9 in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (d, *J* = 6.1 Hz, 3H), 1.20-1.25 (m, 1H), 1.35 (s, 3H), 1.39-1.42 (m, 1H), 1.42 (s, 3H), 1.47-1.59 (m, 5H), 1.72 (dt, *J* = 9.9 and 14.3 Hz, 1H), 2.23-2.26 (m, 2H), 3.71-3.77 (m, 1H), 3.78 (s, 3H), 3.93-3.99 (m, 1H), 4.08-4.18 (m, 3H), 4.31 (d, *J* = 11.1 Hz, 1H), 4.51 (d, *J* = 11.1 Hz, 1H), 5.07-5.12 (m, 2H), 5.82 (ddt, *J* = 7.0, 10.2 and 17.2 Hz, 1H), 6.84-6.87 (m, 2H), 7.22-7.24 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.0 (CH_3), 20.1 (CH_3), 30.2 (CH_3), 37.6 (CH_2), 42.1 (CH_2), 42.3 (CH_2), 42.7 (CH_2), 44.3 (CH_2), 55.3 (CH_3), 65.4 (CH), 67.9 (CH), 69.6 (CH), 70.5 (CH and CH_2), 70.7 (CH), 98.7 (C_0), 113.8 (CH), 117.6 (CH_2), 129.4 (CH), 130.9 (C_0), 134.9 (CH), 159.1 (C_0). IR (film) ν_{max}/cm^{-1} 3436, 3075, 2993, 2941, 2915, 1641, 1614, 1587, 1514, 1464, 1434, 1380, 1302, 1249, 1201, 1168, 1110, 1060, 1036, 941, 872, 824, 753, 737. HRMS (ESI FT-ICR-MS) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{38}O_6Na$ 445.25661, Found 445.25562.

(4*S*,6*R*)-4-Allyl-6-(((4*S*,6*S*)-6-((*R*)-2-((4-methoxybenzyl)oxy)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxane (17). To a solution of diol **16** (794 mg, 1.88 mmol) in 2,2-DMP (30 mL) was added PPTS (236 mg, 0.940 mmol). The reaction medium was stirred for 13 h. The mixture was filtered through silica and Celite, and the residue was washed with EtOAc (5 ×) and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (80:20) as the eluent to provide acetonide **17** (818 mg, 1.77 mmol, 94%) as a colorless oil. R_f 0.69 (80:20 hexane/ethyl acetate). $[\alpha]_D^{20}$ −15 (*c* 1.9 in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ 1.12-1.14 (m, 1H), 1.18 (d, *J* = 6.1 Hz, 3H), 1.33 (s, 3H), 1.34 (s, 1H), 1.36 (s, 3H), 1.40 (s, 3H), 1.39-1.62 (m, 6H), 1.78-1.84 (m, 1H), 2.16-2.22 (m, 1H), 2.27-2.33 (m,1H), 3.74-3.78 (m, 1H), 3.80 (s, 3H), 3.83-3.88 (m, 1H), 3.92-4.01 (m, 1H), 4.08-4.12 (m,1H), 4.34 (d, *J* = 11.1 Hz, 1H), 4.52 (d, *J* = 11.1 Hz, 1H), 5.04-5.11 (m, 2H), 5.80 (ddt, *J* = 6.9, 10.2 and 17.1 Hz, 1H), 6.86-6.88 (m, 2H), 7.25-7.26 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.9 (CH_3), 20.0 (CH_3), 24.8 (CH_3), 24.9 (CH_3), 30.3 (CH_3), 37.1 (CH_2), 37.9 (CH_2), 40.1 (CH_2), 42.3 (CH_2), 44.5 (CH_2), 55.3 (CH_3), 62.8 (CH), 65.3 (CH), 65.7 (CH), 66.1 (CH), 70.6 (CH_2 and CH), 98.4 (C_0), 100.2 (C_0), 113.8 (CH), 116.8 (CH_2), 129.4 (CH), 131.0 (C_0), 134.4 (CH), 159.1 (C_0). IR (film) ν_{max}/cm^{-1} 3075, 2990, 2941, 2917, 1643, 1614, 1587, 1515, 1464, 1379, 1302, 1248, 1225, 1201, 1172, 1111, 1058, 1038, 996, 968, 960, 946, 915, 975, 822, 738. HRMS (ESI FT-ICR-MS) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{42}O_6Na$ 485.28791, Found 485.28718.

(4*S*,6*R*,8*R*,10*R*,12*R*)-12-((4-Methoxybenzyl)oxy)tridec-1-ene-4,6,8,10-tetraol (18). To a solution of compound **16** (21 mg, 50 μmol) in MeOH (1.3 mL) was added a catalytic amount of CSA. The reaction medium was stirred for 1.5 h. The reaction medium was concentrated under reduced pressure, and the residue was purified by flash column chromatography using a gradient of ethyl acetate/hexane (80:20) in ethyl acetate as the eluent to provide tetraol **18** (18 mg, 47 μmol, 94%) as an amorphous white solid. R_f 0.36 (80:20 hexane/ethyl acetate). $[\alpha]_D^{20}$ −15 (*c* 0.9 in MeOH). ^{1}H NMR (500 MHz, MeOD) δ 1.21 (d, *J* = 6.26 Hz, 3H), 1.46-1.69 (m, 8H), 2.20-2.24 (m, 2H), 3.77 (s, 3H), 3.80-3.90 (m, 2H), 3.93-4.03 (m, 3H), 4.39 (d, *J* = 10.9 Hz, 1H), 4.54 (d, *J* = 10.9 Hz, 1H), 5.02-5.08 (m, 2H), 5.85 (ddt, *J* = 7.1, 10.2 and 17.2 Hz, 1H), 6.87-6.89 (m, 2H), 7.26-7.28 (m, 2H). ^{13}C NMR (125 MHz, MeOD) δ 20.5 (CH_3), 43.8 (CH_2), 45.0 (CH_2), 45.9 (CH_2 and CH_2), 46.0 (CH_2), 55.7 (CH_3), 68.1 (CH and CH), 68.7 (CH), 70.1 (CH), 71.6 (CH_2), 73.3 (CH), 114.7 (CH), 117.3 (CH_2), 130.6 (CH), 132.1 (C_0), 136.4 (CH), 160.8 (C_0). IR (film) ν_{max}/cm^{-1} 3374, 2938, 2911, 2838, 1641, 1613, 1587, 1514, 1441, 1375, 1338, 1302, 1265, 1247, 1174, 1147, 1108, 1068, 1034, 917, 846, 821, 734, 703. HRMS (ESI FT-ICR-MS) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{34}O_6Na$ 405.22531, Found 405.22465.

(*R*)-1-((4*S*,6*S*)-6-(((4*R*,6*S*)-6-Allyl-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)propan-2-ol (19). To a solution of PMB ether **17** (765 mg, 1.65 mmol) in CH_2Cl_2:phosphate buffer pH 7 (9:1) (33 mL) at 0 ºC was added DDQ (563 mg, 2.48 mmol). The mixture was stirred for 1 h under the same conditions, followed by quenching via the addition of a solution of H_2O:saturated aqueous solution of $NaHCO_3$ (1:1) (7 mL). The resulting mixture was filtered over Celite washed with CH_2Cl_2 (6 ×) and concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane/ethyl acetate (70:30) as the eluent to provide alcohol **19** (514 mg, 1.50 mmol, 91%) as a yellow oil. R_f 0.33 (70:30 hexane/ethyl acetate). $[\alpha]_D^{20}$ +4 (*c* 1.9 in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18 (d, *J* = 6.3 Hz, 3H), 1.32 (s, 6H), 1.36 (s, 3H), 1.42 (s, 3H), 1.38-1.49 (m, 5H), 1.59-1.60 (m, 2H), 1.77-1.83 (m, 1H), 2.14-2.20 (m, 1H), 2.25-2.31 (m,1H), 2.77 (br s, 1H), 3.81-3.86 (m, 1H), 3.91-4.06 (m, 3H), 4.16-4.17 (m, 1H), 5.01-5.08 (m, 2H), 5.77 (ddt, *J* = 6.9, 10.1 and 17.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.6 (CH_3), 23.4 (CH_3), 24.8 (CH_3), 24.9 (CH_3), 30.2 (CH_3), 36.0 (CH_2), 37.8 (CH_2), 40.1 (CH_2), 42.1 (CH_2), 43.7 (CH_2), 62.8 (CH), 64.6 (CH), 65.7 (CH), 66.1 (CH), 67.1 (CH), 98.6 (C_0), 100.2 (C_0), 116.9 (CH_2), 134.4 (CH). IR (film) ν_{max}/cm^{-1} 3470, 3077, 2990, 2941, 1820, 1743, 1693, 1603, 1461, 1444, 1380, 1266, 1225, 1201, 1170, 1113, 1018, 998, 970, 948, 916, 875, 814, 738, 703. HRMS (ESI FT-ICR-MS) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{34}O_5Na$ 365.23039, Found 365.22978.

1-((4*R*,6*R*)-6-(((4*R*,6*S*)-6-Allyl-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)propan-2-one (20). To a solution of oxalyl chloride (0.11 mL, 1.35 mmol) in CH_2Cl_2 (5.3 mL) at −78 ºC was added DMSO (0.19 mL, 2.71 mmol) dropwise. The reaction medium was stirred for 30 min, followed by the dropwise addition of a solution of alcohol **19** (309 mg, 0.902 mmol) in CH_2Cl_2 (2.6 mL). The solution was stirred for 30 min at −78 ºC. Et_3N (0.63 mL, 4.51 mmol) was added dropwise, and the resulting slurry was warmed to 0 ºC and stirred for 1 h. The reaction was then diluted with Et_2O and saturated aqueous solution of NH_4Cl. The layers were separated, and the aqueous layer was extracted with Et_2O (4 ×). The combined organic layers were washed with H_2O (2 ×), brine (2 ×), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane/ethyl acetate (70:30) as the eluent to provide methyl ketone **20** (291 mg, 0.85 mmol, 94%) as a colorless oil. R_f 0.43 (70:30 hexane/ethyl acetate). $[\alpha]_D^{20}$ +2.1 (*c* 2.4 in $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.14 (d, *J* = 11.7 Hz, 1H), 1.32 (s, 9H), 1.41 (s, 3H), 1.43-1.47 (m, 1H), 1.54-1.60 (m, 3H), 1.76-1.81 (m, 1H), 2.14 (s, 3H), 2.16-2.19 (m, 1H), 2.25-2.30 (m, 1H), 2.41 (dd, *J* = 5.5 and 16.0 Hz, 1H), 2.65 (dd, *J* = 7.0 and 16.0 Hz, 1H), 3.81-3.86 (m, 1H), 3.90-3.95 (m, 1H), 3.97-4.01 (m, 1H), 4.27-4.31 (m, 1H), 5.02-5.08 (m, 2H), 5.77 (ddt, *J* = 7.0, 10.4 and 17.2 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.7 (CH_3), 24.8 (CH_3), 24.9 (CH_3), 30.1 (CH_3), 31.1 (CH_3), 36.4 (CH_2), 37.8 (CH_2), 40.1 (CH_2), 42.0 (CH_2), 50.1 (CH_2), 62.8 (CH), 65.4 (CH), 65.7 (CH), 66.1 (CH), 98.6 (C_0), 100.2 (C_0), 116.9 (CH_2), 134.4 (CH), 207.0 (C_0). IR (film) ν_{max}/cm^{-1} 3077, 2990, 2941, 2920, 1716, 1643, 1430, 1379, 1223, 1199, 1169, 1125, 1101, 1047, 997, 935, 916, 878, 834, 700, 658, 628, 596. HRMS (ESI FT-ICR-MS) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{32}O_5Na$ 363.21474, Found 363.21400.

(*Z*)-Ethyl 4-((4*S*,6*R*)-6-(((4*R*,6*R*)-2,2-dimethyl-6-(2-oxopropyl)-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)but-2-enoate (2). To a solution of olefin **20** (0.16 g, 0.47 mmol) in a mixture of *t*-BuOH:THF:H_2O (10:2:1) (2.34 mL) was added NMO (0.11 g, 0.94 mmol) and OsO_4 (0.06 mL, 9.4 µmol, 4% wt. in H_2O). The reaction medium was stirred for 3 h. The reaction was quenched by the addition of Na_2SO_3 (250 mg) and then diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (6 ×). The combined organic layers were washed with brine (1 ×), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the corresponding diol, which was used in the next step without further purification.

To a solution of the previously prepared diol in a mixture of THF:phosphate buffer pH 7 (2:1) (4.8 mL) was added $NaIO_4$ (0.20 g, 0.94 mmol). The reaction medium was stirred for 15 min. The layers were separated, and the aqueous layer was extracted with EtOAc (3 ×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, providing aldehyde **5**, which was used in the next step without further purification.

To a slurry of NaH (44 mg, 1.1 mmol, 60% w/w in mineral oil) in THF (6 mL) at 0 ºC was added a solution of phosphonate **4** (0,49 g, 1.4 mmol) in THF (4.3 mL). The mixture was stirred for 10 min under the same conditions, and the temperature was cooled to −78 ºC. Then, a solution of aldehyde **5** in THF (4.0 mL) was added dropwise, and the reaction medium was stirred for 30 min. The mixture was warmed to 0 ºC, and the reaction was quenched by the addition of saturated aqueous solution of NH_4Cl (21 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 ×). The combined organic layers were washed with brine (1 ×), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane/dichloromethane/ethyl acetate (6:2:2) as the eluent to provide olefin **2** (0.17 g, 0.41 mmol, *dr* = 88:12, 87%) in 3 steps as a colorless oil. The isomers were easily separated at this stage. R_f 0.44 (60:20:20 hexane/CH_2Cl_2/ethyl acetate). $[\alpha]_D^{20}$ +13 (*c* 2.0 in $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.14 (q, *J* = 11.8 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.31 (s, 9H), 1.40 (s, 3H), 1.45-1.84 (m, 5H), 2.14 (s, 3H), 2.41 (dd, *J* = 5.4 and 16.1 Hz, 1H), 2.61-2.77 (m, 2H), 2.88-3.00 (m, 1H), 3.82-4.04 (m, 3H), 4.13 (q, *J* = 7.1 Hz, 2H), 4.24-4.34 (m, 1H), 5.80-5.84 (dt, *J* = 1.6 and 11.7 Hz, 1H), 6.29 (dt, *J* = 7.0 and 11.7 Hz, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.2 (CH_3), 19.6 (CH_3), 24.7 (CH_3 and CH_3), 30.1 (CH_3), 31.1 (CH_3), 34.9 (CH_2), 36.4 (CH_2), 37.8 (CH_2), 42.0 (CH_2), 50.0 (CH_2), 59.8 (CH_2), 62.8 (CH), 65.4 (CH), 65.6 (CH), 66.1 (CH), 98.6 (C_0), 100.3 (C_0), 121.0 (CH), 146.1 (CH), 166.3 (C_0), 207.0 (C_0). IR (film) ν_{max}/cm^{-1} 2999, 2941, 2921, 1716, 1645, 1417, 1379, 1224, 1174, 1100, 1035, 1008, 937, 876, 823. HRMS (ESI FT-ICR-MS) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{36}O_7Na$ 435.23587, Found 435.23490.

(−)-Cryptocaryol A (1). To a solution of methyl ketone **2** (148 mg, 0.36 mmol) in Et_2O (17 mL) at −30 ºC was added (*c*-Hex)$_2$BCl (0.16 mL, 0.72 mmol) dropwise, followed by the dropwise addition of Et_3N (0.11 mL, 0.76 mmol), which resulted in the formation of a white cloud. The mixture was stirred under the same conditions for 30 min. After this period, the reaction medium was cooled to −78 ºC, and a solution of aldehyde **3** (168 mg, 0.70 mmol) in CH_2Cl_2 (1.1 mL) was added dropwise. The resulting mixture was stirred for 1 h at −78 ºC, and the reaction was then quenched by the addition of pH 7 phosphate buffer (1 mL). The mixture was warmed to 0 ºC, and MeOH (2 mL) and a solution of 30% H_2O_2 (1 mL) in MeOH (1.5 mL) were added dropwise. The reaction medium was stirred for 1 h under the same conditions. The volatiles were removed under reduced pressure, and the aqueous layer was extracted with Et_2O (4 ×). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (1 ×), brine (1 ×), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The corresponding aldol adduct was partially purified by flash column chromatography using a solution of hexane/dichloromethane/ethyl acetate (70:10:20) as the eluent.

To a slurry of $Me_4NHB(OAc)_3$ (758 mg, 2.88 mmol) in MeCN (1.0 mL) was added AcOH (1.0 mL). The mixture was stirred at room temperature for 30 min before being cooled to −30 ºC. Then, a solution of the previously prepared aldol adduct (0.36 mmol) in MeCN (1.0 mL) was added dropwise, followed by the addition of a solution of CSA (42 mg, 0.18 mmol) in MeCN (1.0 mL) and AcOH (1.0 mL). The reaction medium was warmed to −20 ºC and stirred for 18 h. The mixture was poured into an Erlenmeyer flask containing saturated aqueous solution of $NaHCO_3$ (30 mL). After gas liberation ceased, saturated aqueous solution of sodium potassium tartrate (30 mL) and Et_2O (45 mL) were added. The mixture was stirred vigorously for 3 h. Then, the layers were separated, and the aqueous layer was extracted with Et_2O (4 ×). The combined organic layers were washed with brine (1 ×), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The diol **21** was partially purified by flash column chromatography using hexane/ethyl acetate (60:40) as the eluent.

To a solution of compound **21** (0.36 mmol) in MeOH (0.5 mL) was added a catalytic amount of CSA. The reaction medium was stirred for 1 h. The reaction medium was concentrated under reduced pressure, and the residue was purified by flash column chromatography using a solution of chloroform/methanol (90:10) as the eluent to provide (−)-cryptocaryol A (**1**) (3 mg, 6 μmol, less than 10%) as an amorphous white solid. R_f 0.31 (90:10 $CHCl_3$/MeOH). $[\alpha]_D^{20}$ −8 (*c* 0.06 in MeOH). ^{1}H NMR (500 MHz, MeOD) δ 0.89 (t, *J* = 7.0 Hz, 3H), 1.27-1.29 (br m, 24H), 1.34 (m, 2H), 1.44 (m, 2H), 1.52 (m, 2H), 1.60 (m, 2H), 1.64 (m, 2H), 1.67 (m, 3H), 1.94 (ddd, *J* = 2.5, 9.9 and 14.4, 1H), 2.36 (ddt, *J* = 2.5, 11.7 and 18.5 Hz, 1H), 2.45 (m, 1H), 3.80 (m, 1H), 4.00 (m, 2H), 4.03 (m, 1H), 4.09 (m, 1H), 4.71 (m, 1H), 5.97 (dd, *J* = 1.9 and 9.8 Hz, 1H), 7.05 (ddd, *J* = 2.4, 5.9 and 9.4, 1H). ^{13}C NMR (125 MHz, MeOD) δ 14.4 (CH_3), 23.7 (CH_2), 26.8 (CH_2), 30.5-30.9 (10 CH_2), 33.1 (CH_2), 39.2 (CH_2), 43.9 (CH_2), 45.2 (CH_2), 45.7 (CH_2), 45.9 (CH_2), 46.0 (CH_2), 66.6 (CH), 68.2 (CH), 69.1 (CH), 69.9 (CH), 70.1 (CH), 76.6 (CH), 121.4 (CH), 148.5 (CH), 167.0 (C_0). IR (film) ν_{max}/cm^{-1} 3367, 2915, 2849, 1716, 1595, 1453, 1395, 1326, 1266, 1139, 1092, 1037, 844, 809, 722. HRMS (ESI FT-ICR-MS) m/z: $[M + Na]^+$ $C_{30}H_{56}O_7Na$ 551.39237, Found 551.39164.

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Notes and references

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† Electronic Supplementary Information (ESI) available: ^{1}H NMR, ^{13}C NMR, IR, and HRMS spectra of the prepared compounds. See DOI: 10.1039/b000000x/

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18 We tried several different experiments to optimize the last steps, but none of then led to better results. These experiments are described in the Electronic Supplementary Information file.

