Total Synthesis of (+)-Cryptocaryol A Using a Prins Cyclization/Reductive Cleavage Sequence

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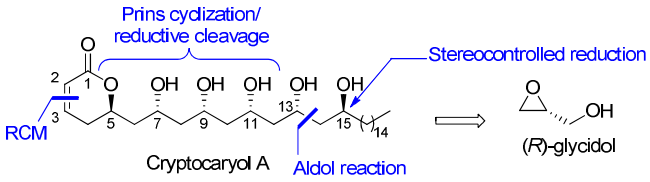


Abstract: The total synthesis of (+)-cryptocaryol A was achieved in 20 steps from (*R*)-glycidol. The key steps were a Prins cyclization/reductive cleavage sequence to construct the C5-C11 polyol fragment, a diastereoselective aldol reaction to control the stereogenic center at C13 and a stereocontrolled reduction to introduce the stereogenic center at C15.

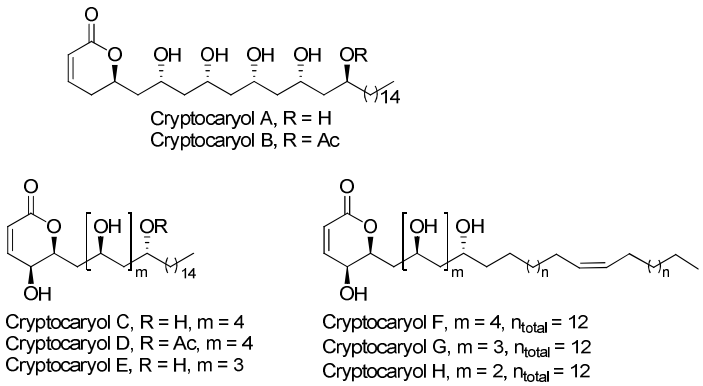
INTRODUCTION

Plants of the genus *Cryptocarya* have been identified as a rich source of secondary metabolites bearing a 5,6-dihydro-α-pyrone moiety.[1] Due to their important biological activities, these latter compounds have attracted considerable synthetic interest.[2] Our group has previously reported the synthesis of some members of this family, including passifloricin,[3] (–)-pironetin,[4] strictifolione,[5] and fostriecin,[6] and more recently, we became interested in the synthesis of (+)-cryptocaryol A.

Cryptocaryol A, in concomitance with cryptocaryols B-H (Figure 1), were isolated by Gustafson *et al.* in 2011 from the Papua New Guinea collection of the plant C*ryptocarya* sp.[7] These compounds have been reported to act as Pdcd4 (programmed cell death 4) stabilizers with EC_{50} values between 1.3 and 4.9 μM, Pdcd4 being a tumorgenesis and invasion suppressor protein,[8,9,10,11] whose expression is down-regulated in several cancers.[12] Thus, the stabilization of the expression of Pdcd4 might help to improve the efficiency of chemotherapies.[13]

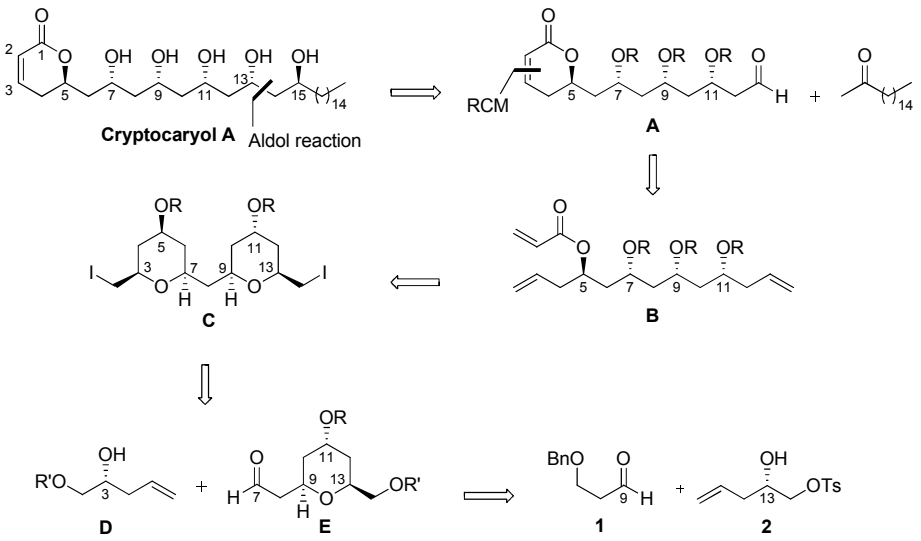
For our part, we were particularly interested in the synthesis of (+)-cryptocaryol A. The structure of (+)-cryptocaryol A was established by spectroscopic studies by Gustafson *et al.*[7] and then revised in 2013 by O'Doherty and Wang.[14] Cryptocaryol A is constituted by a 5,6-dihydro-α-pyrone and a 1,3-polyol segment. Three total syntheses of this molecule have been reported up to date: one total synthesis related to the first reported structure of cryptocaryol A,[15] and two total syntheses of the revised structure of (+)-cryptocaryol A[14] and its enantiomer.[16] Herein, we would like to report the total synthesis of (+)-cryptocaryol A by using our recently developed Prins cyclization/reductive cleavage sequence[17] to control four of the six stereogenic centers present in this molecule.

Figure 1. Cryptocaryols A-H



The synthesis of (+)-cryptocaryol A was envisaged from aldehyde **A** and heptadecan-2-one by using a diastereoselective reagent controlled boron-mediated aldol reaction to control the stereogenic center at C13 (Scheme 1). The lactone in compound **A** would be formed by utilizing a ring-closing metathesis applied to the unsaturated ester **B**, which would be synthesized from **C** by reductive cleavage. The *bis*-tetrahydropyran **C** would be the result of a Prins cyclization between the homoallylic alcohol **D** and the tetrahydropyranyl aldehyde **E**, which would be obtained by a Prins cyclization in between aldehyde **1** and (*S*)-homoallylic alcohol **2**.

Scheme 1. Retrosynthesis

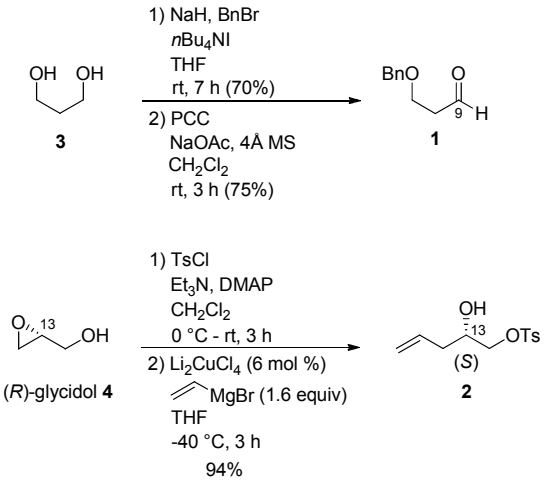


RESULTS AND DISCUSSION

The synthesis of (+)-cryptocaryol A started with the preparation of **1** and **2** (Scheme 2). Aldehyde **1**[18] was prepared in 52.5% overall yield from the commercially available 1,3-propanediol **3** after monoprotection (NaH, BnBr, *n*-Bu_4NI, THF, rt, 7 h, 70%) and oxidation

(PCC, NaOAc, 4Å MS, CH_2Cl_2, rt, 3 h, 75%). In parallel, the optically active (*S*)-homoallylic alcohol **2** was synthesized from (*R*)-glycidol **4** in 2 steps. After tosylation (TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 3 h, 98%), the epoxide was opened by treatment with vinylmagnesium bromide (1.6 equiv) in the presence of a catalytic amount of Li_2CuCl_4 (0.06 equiv, THF, - 40 °C, 3 h, 96%) to produce the desired (*S*)-homoallylic alcohol **2**.

Scheme 2. Synthesis of the required starting substrates

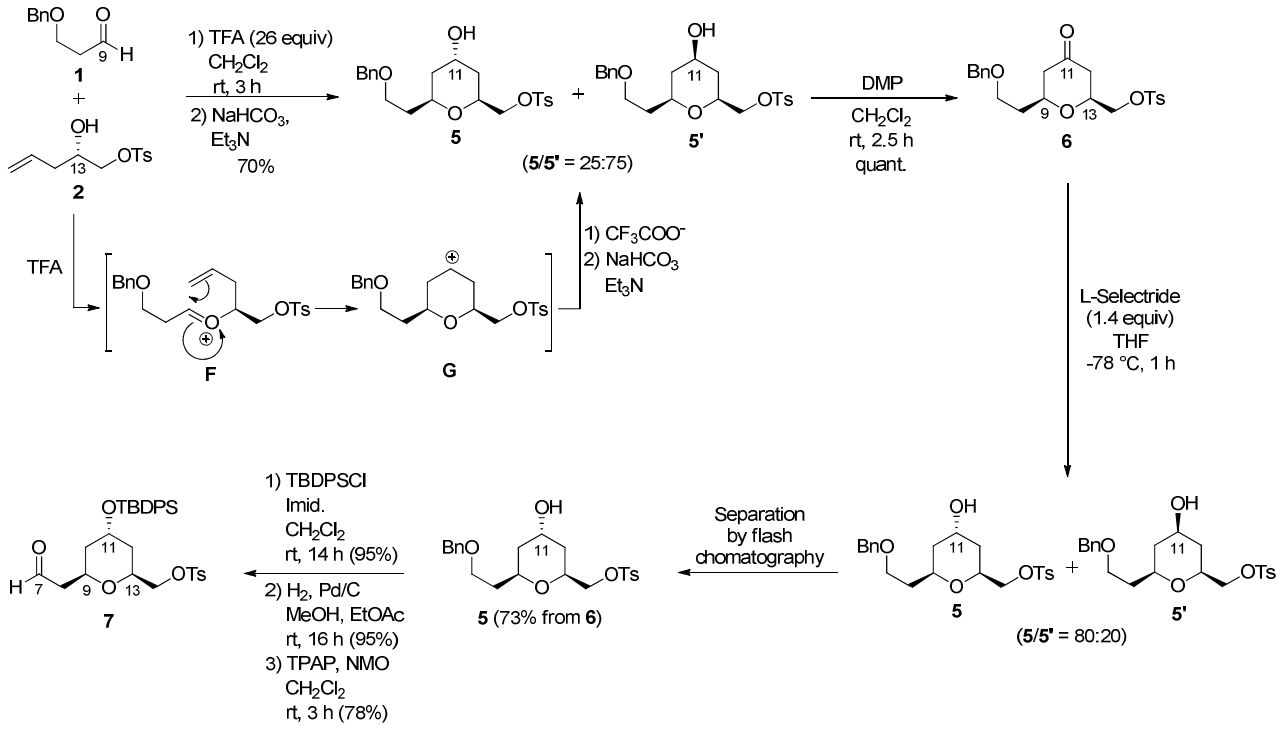


Having aldehyde **1** and the optically active homoallylic alcohol **2** in hand, a first Prins cyclization[19] was performed between these two compounds using TFA (26 equiv, CH_2Cl_2, rt, 3 h)[20] to produce, *via* the formation of intermediates **F** and **G** and after neutralization, a diastereomeric mixture of tetrahydropyranyl alcohols **5** and **5'** (**5**/**5'** = 25:75) in favor of the undesired 2,4,6-*cis*,*cis*-isomer **5'**[20] (Scheme 3). To convert **5'** into **5**, the mixture of **5** and **5'** was oxidized (DMP, CH_2Cl_2, rt, 2.5 h) to the corresponding tetrahydropyranone **6** (70% overall yield from **1** and **2**) and then diastereoselectively reduced. To control the stereogenic center at C11, an

equatorial attack of a hydride was required. Thus, the sterically hindered reducing agent L-selectride (1.4 equiv, THF, -78 °C, 1 h) was used and alcohols **5** and **5'** were obtained as a 80:20 mixture. After separation of the diastereomers by flash column chromatography on silica gel, alcohol **5** was isolated in 73% yield (Scheme 3).

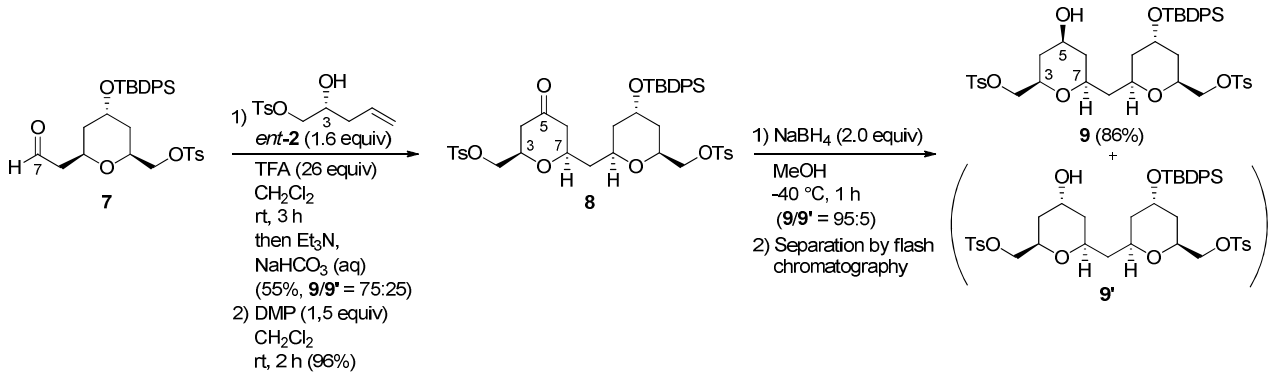
To synthesize the *bis*-tetrahydropyran of type **C**, a second Prins cyclization was envisaged and **5** had to be transformed into an aldehyde of type **E**. The trisubstituted tetrahydropyran **5** was transformed into aldehyde **7** in three steps. After protection of **5** as a *tert*-butyldiphenylsilyl ether (TBDPSCl, Imidazole, CH_2Cl_2, rt, 14 h), followed by a hydrogenolysis (Pd/C 5 mol %, H_2, MeOH/EtOAc = 3:1, rt, 16 h) and an oxidation of the resulting primary alcohol, the desired aldehyde **7** was isolated in 70% overall yield (Scheme 3).

Scheme 3. Synthesis of the tetrahydropyran of type E



Compound **7** was then involved in a second Prins cyclization using the (*R*)-homoallylic alcohol *ent*-**2**[21] [TFA (26 equiv), CH_2Cl_2, rt, 3 h, 55%], affording the *bis*-tetrahydropyran as a mixture of diastereomers, which was oxidized to ketone **8** [DMP (1.5 equiv), CH_2Cl_2, rt, 2 h, 96%] (Scheme 4) and then reduced. To control the stereogenic center at C5, the ketone in **8** was reduced by $NaBH_4$, affording a mixture of diastereomeric alcohols **9** and **9'** in a 95:5 ratio. After separation by flash column chromatography on silica gel, **9** was isolated in 86% yield (Scheme 4). This obtained functionalized *bis*-tetrahydropyran **9** is the key element in the synthesis of cryptocaryol A and it has to be transformed into a polyketide of type **B** to obtain the C1-C13 fragment.

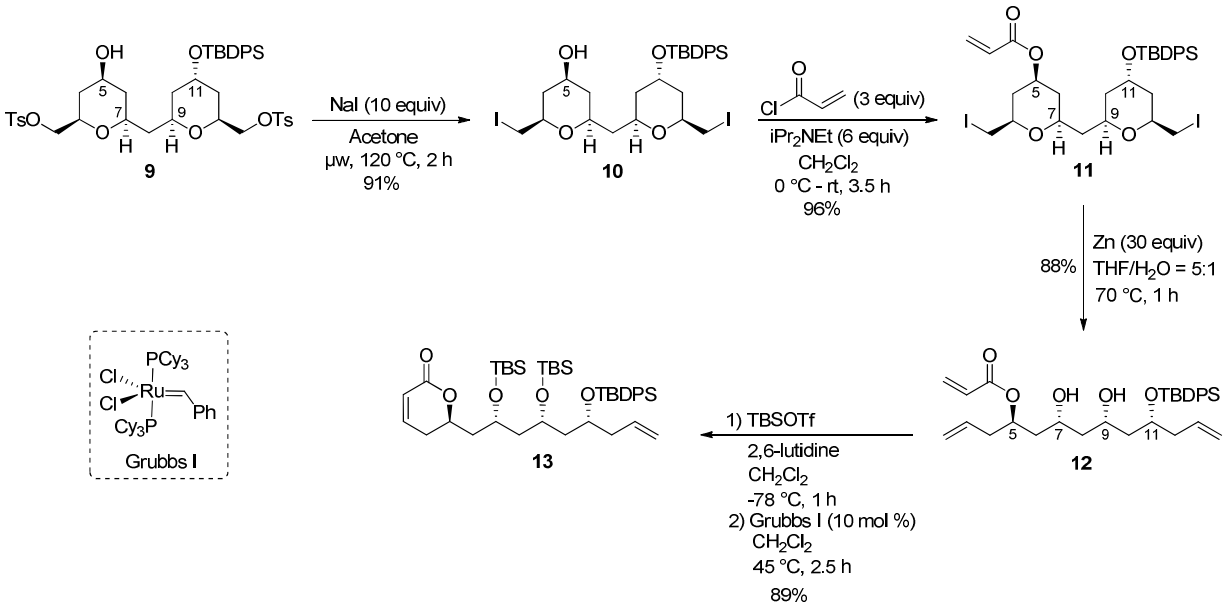
Scheme 4. Synthesis of *bis*-tetrahydropyran 9



To perform the ring-opening of the *bis*-tetrahydropyran **9** with zinc, the tosylate **9** was treated with NaI [10 equiv, acetone, μw, 120 °C, 2 h, 91%][20] to form the corresponding *bis*-iodide **10** (Scheme 5). As the reductive ring-opening of **10** would liberate three free hydroxyl groups, and as the hydroxyl at C5 has to be transformed to an ester to construct the lactone core

by ring-closing metathesis, we took advantage of the presence of the free hydroxyl group at C5 in the *bis*-tetrahydropyran **10** to introduce the unsaturated ester. Thus, **10** was transformed to ester **11** (acryloyl chloride, *i*Pr_2NEt, CH_2Cl_2, 0 °C to rt, 3.5 h, 96%) and the latter was reductively cleaved by treatment with zinc to produce polyol **12** in 88% yield. After protection (TBSOTf, 2,6-lutidine, CH_2Cl_2) and ring-closing metathesis using the first generation Grubbs catalyst (*c* = 0.01 M, CH_2Cl_2, 45 °C, 2.5 h), lactone **13** was isolated in 89% overall yield (Scheme 5).

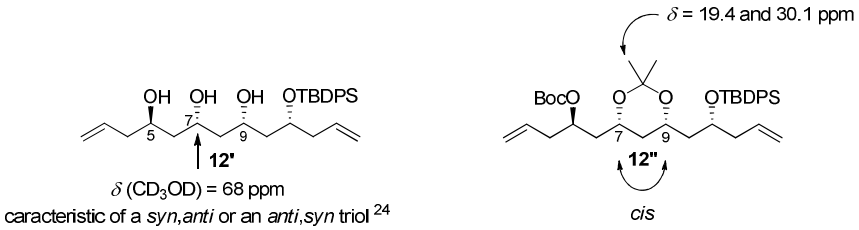
Scheme 5. Synthesis of the C1-C13 fragment



The proof of the relative stereochemistry between the substituents at C5, C7 and C9 in **12** is based on the structure elucidation of two previously synthesized compounds **12'**[17] and **12''**,[17] (Figure 2). Analysis of the ^{13}C NMR spectra of **12'** using Kishi's ^{13}C NMR database in CD_3OD[22] revealed the presence of a *syn*,*anti* or an *anti*,*syn* motif between the hydroxyls at C5, C7 and C9. Moreover, acetonide **12''**[17] allowed to confirm the *syn* relationship between the hydroxyl groups

at C7 and C9.[23] Thus, the stereochemistry of the substituents at C5, C7 and C9 in compound **12** was assumed to be *anti*,*syn* and was confirmed latter on by completion of the synthesis of (+)-cryptocaryol A.

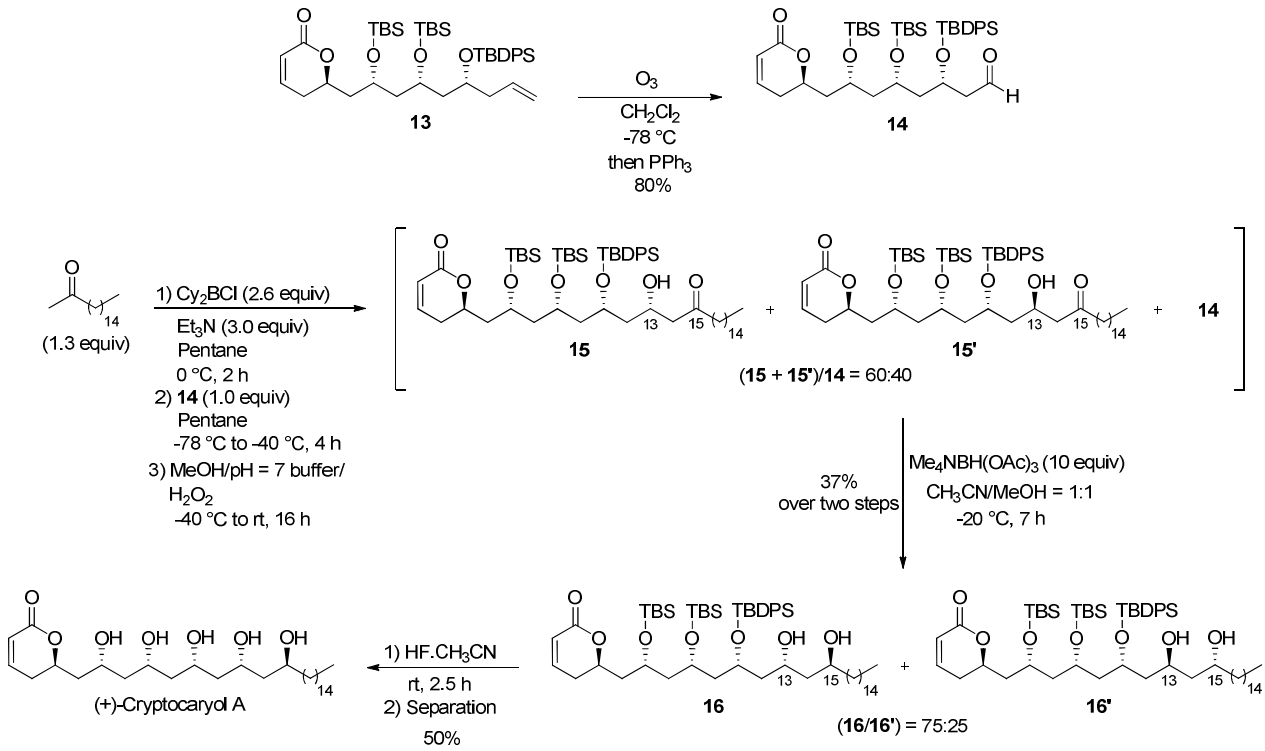
Figure 2.



To introduce the stereogenic center at C13, a chemoselective ozonolysis of the terminal double bond in **13** was performed by carefully monitoring the reaction by TLC and, after a few minutes, aldehyde **14** was isolated in 80% yield (Scheme 6). This aldehyde was then involved in a boron-mediated aldol reaction with heptadecan-2-one to afford the diastereomeric aldols **15** and **15'** as an inseparable mixture which contains also aldehyde **14** as a retroaldol reaction could not be avoided during the work-up (MeOH/buffer pH =7/H_2O_2 = 1:1:1).[24] A stereoselective reduction of the ketone at C15 using $Me_4NBH(OAc)_3$ (10 equiv) was performed to obtain an *anti*-relative stereochemistry between the hydroxyl groups at C13 and C15.[25] Diols **16** and **16'** were isolated in 37% yield over the two steps, again as a mixture of two inseparable diastereomers in a 75:25 ratio.[26] Fortunately, after treatment of these two diastereomers with HF.CH_3CN (rt, 2.5 h), (+)-cryptocaryol A was separated and isolated in 50% yield proving, *a posteriori*, that the major isomers **15** and **16** possess the required absolute configuration for the synthesis of this natural product. The ^{1}H NMR and ^{13}C NMR spectral data and optical rotation [synthetic: $[\alpha]_D^{20}$ + 15 (*c*

0.2, MeOH), reported:[14] $[\alpha]_D^{23}$ + 14 (*c* 0.2, MeOH)] for the synthetic cryptocaryol A matched with the reported data for (+)-cryptocaryol A.

Scheme 6. Completion of the synthesis



The total synthesis of (+)-cryptocaryol A was accomplished in 20 steps from the commercially available (*R*)-glycidol with an overall yield of 1.6%. The first stereogenic center of (+)-cryptocaryol A was induced by (*R*)-glycidol and the five other stereogenic centers were controlled by diastereoselective reactions. Three of them were controlled by two Prins cyclization/oxidation/reduction sequences, one by a boron-mediated aldol reaction and the sixth one by a directed 1,3-reduction of a β-hydroxyketone. This synthesis of cryptocaryol A is shorter than the previous syntheses reported by Reddy and Mohapatra (28 steps)[15] and O'Doherty and

Wang (23 steps),[14] and slightly longer than the synthesis recently reported by Dias *et al*. (17 steps)[16] but as efficient in terms of overall yield (1.6% *versus* 1.4%).

EXPERIMENTAL SECTION

General experimental methods: All reactions were carried out under anhydrous conditions, using flame-dried glassware and under an argon atmosphere. CH_2Cl_2, Et_3N and *i*Pr_2NEt were distilled from CaH_2; Et_2O and THF were distilled from Na/benzophenone. Other reagents were obtained from commercial suppliers and used as received. TLC was performed on silica gel plates with UV and *p*-anisaldehyde or $KMnO_4$ stain visualization. Flash chromatography was performed on silica gel (230-400 mesh). Optical rotations were measured using a polarimeter with a 1 dm path length. Infrared (IR) spectra were recorded on an ATR plate, wave numbers are indicated in cm^{-1}. ^1H NMR spectra were recorded at 400 MHz in $CDCl_3$ or CD_3OD and data are reported as follows: chemical shift in ppm from tetramethylsilane as an internal standard, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, m = multiplet or overlap of non-equivalent resonances, br = broad), integration. ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ or CD_3OD and data are reported as follows: chemical shift in ppm from tetramethylsilane with the solvent as an internal standard ($CDCl_3$, 77.16 ppm or CD_3OD, 49.00 ppm). Mass spectra were realized with a gas chromatograph-mass spectrometer by electronic impact. High resolution mass spectra (HRMS) were performed with an orbitrap mass analyzer by electrospray ionization.

Synthesis of **1**

3-(Benzyloxy)propan-1-ol: To a suspension of sodium hydride (60 % in oil, 1.6 g, 40 mmol, 1 equiv) in dry THF (80 mL) was added dropwise 1,3-propanediol (2.9 mL, 40 mmol, 1 equiv). The mixture was stirred at rt for 45 min. *n*-Bu_4NI was then added (7.4 g, 20 mmol, 0.5 equiv), and benzylbromide (4.8 mL, 40 mmol, 1 equiv) was added dropwise. The reaction mixture was stirred for 7 h and quenched by addition of H_2O (80 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 × 80 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under *vacuum*. The crude material was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 8:2) to afford 3-(benzyloxy)propan-1-ol (4.67 g, 28.1 mmol, 70%) as a yellow oil. The spectral data match those reported in the literature.[18] **IR**: *v* 3375, 3030, 2943, 2863, 1496, 1454, 1365, 1205, 1073, 1026, 972, 910 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.38 - 7.26 (m, 5H), 4.53 (s, 2H), 3.79 (t, J = 5.7 Hz, 2H), 3.67 (t, J = 5.7 Hz, 2H), 2.27 (br s, 1H, OH), 1.87 (quint, J = 5.7 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 138.1, 128.5 (2C), 127.73, 127.69 (2C), 73.2, 69.1, 61.5, 32.2; **MS** (EI) *m/z*: 166 ($M^{+\cdot}$, 2), 147 (3), 130 (1), 120 (3), 107 (BnO^+, 97), 91 (Bn^+, 100), 79 (29), 77 (Ph^+, 13), 65 (19), 51 (7).

3-(Benzyloxy)propan-1-al (1): To a solution of 3-(benzyloxy)propan-1-ol (990 mg, 5.96 mmol, 1 equiv) in dry CH_2Cl_2 (45 mL) were added molecular sieves 4Å (2.2 g), NaOAc (150 mg, 1.83 mmol, 0.3 equiv) and PCC (1.93 g, 8.95 mmol, 1.5 equiv). The reaction mixture was stirred for 3 h, and Et_2O (400 mL) was added. After stirring for an additional 2 h, the mixture was filtered on florisil® and concentrated under *vacuum*. The crude material was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 8:2) to afford 3-(benzyloxy)propan-1-al **1** (733 mg, 4.47 mmol, 75%) as a yellow oil. The spectral data match those reported in the literature.[18] **IR**: *v* 3031, 2862, 2732, 1722, 1496, 1454, 1395, 1363, 1205,

1092, 1028, 909 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 9.80 (t, J = 1.8 Hz, 1H), 7.38-7.27 (m, 5H), 4.54 (s, 2H), 3.82 (t, J = 6.1 Hz, 2H), 2.70 (td, J = 6.1 and J = 1.8 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 201.2, 137.9, 128.5 (2C), 127.8, 127.7 (2C), 73.3, 63.9, 43.9; **MS** (EI) *m/z*: 164 ($M^{+\cdot}$, 1), 146 (1), 120 (8), 107 (BnO^+, 100), 91 (Bn^+, 97), 79 (44), 77 (Ph^+, 22), 65 (21), 57 (10), 51 (12).

{(2*S*,6*S*)-6-[2-(Benzyloxy)ethyl]-4-oxotetrahydro-2*H*-pyran-2-yl} methyl 4-methylbenzene sulfonate (6): To a solution of homoallylic alcohol **2**[17] (934 mg, 3.65 mmol, 1.5 equiv) and aldehyde **1** (400 mg, 2.44 mmol, 1.0 equiv) in dry CH_2Cl_2 (11.5 mL) was added dropwise TFA (4.7 mL, 63 mmol, 26 equiv). The mixture was stirred for 3 h at rt, and treated with a saturated aqueous $NaHCO_3$ solution (15 mL). The pH was adjusted to pH > 7 by addition of Et_3N and the resulting mixture was stirred at rt for 3 h and then diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under *vacuum*. Purification of the crude material by flash column chromatography on silica gel (petroleum ether/EtOAc = 66:34 to 5:5) afforded a mixture of the two diastereomeric alcohols **5'** and **5** in a 3:1 ratio (718 mg, 1.71 mmol, 70%) as a gummy liquid.

To a solution of the tetrahydropyranyl alcohols (mixture of diastereomers **5** and **5'**, 512 mg, 1.22 mmol, 1.0 equiv) in dry CH_2Cl_2 (12 mL) was added Dess-Martin periodinane (775 mg, 1.83 mg, 1.5 equiv). The mixture was stirred at rt for 2.5 h. Hexane (24 mL) was then added, the resulting precipitate was filtered through a pad of Celite®. The filtrate was concentrated under *vacuum* and purification of the resulting crude material by flash column chromatography on silica gel (petroleum ether/EtOAc = 7/3) afforded ketone **6** (510 mg, 1.22 mmol, quant.) as a colorless

gummy liquid. **[α]** $_D^{20}$ + 12.2 (*c* 0.55, $CHCl_3$), **IR**: *v* 3060, 2922, 2865, 1721, 1598, 1454, 1360, 1266, 1189, 1176, 1096, 983, 814 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): *δ* 7.78 (br d, *J* = 8.3 Hz, 2H), 7.36-7.25 (m, 7H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.09-4.01 (m, 2H), 3.81-3.71 (m, 2H), 3.58-3.47 (m, 2H), 2.43 (s, 3H), 2.37 (dd, *J* = 14.7 and *J* = 2.3 Hz, 1H), 2.28 (br d, *J* = 7.8 Hz, 2H), 2.22 (dd, *J* = 14.6 and *J* = 11.6 Hz, 1H), 1.88-1.73 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): *δ* 205.3, 145.1, 138.3, 132.8, 129.9 (2C), 128.4 (2C), 128.0 (2C), 127.7 (3C), 74.1, 73.8, 73.1, 71.0, 65.7, 47.4, 43.2, 36.2, 21.7; **HRMS** (ESI): Calculated for $C_{22}H_{26}O_6SNa$ [M + Na]$^+$: 441.1342, found: 441.1346.

{(2*S*,4*S*,6*S*)-6-[2-(Benzyloxy)ethyl]-4-hydroxytetrahydro-2*H*-pyran-2-yl}methyl 4-methyl benzenesulfonate (5): To a solution of ketone **6** (454 mg, 1.08 mmol, 1.0 equiv) in dry THF (15 mL), cooled to −78 °C, was added L-Selectride (1 M in THF, 1.5 mL, 1.5 mmol, 1.4 equiv). The mixture was stirred at −78 °C for 1 h and then quenched by addition of a saturated aqueous Rochelle salts solution (15 mL) and H_2O (15 mL). The mixture was warmed to rt and diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with H_2O, then brine, dried over $MgSO_4$, filtered and concentrated under *vacuum*. The crude material was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 6:4) and the alcohol **5** was isolated (332 mg, 0.790 mmol, 73%) as a single diastereomer and as a colorless gummy liquid. **[α]** $_D^{20}$ − 22.2 (*c* 0.58, $CHCl_3$), **IR**: *v* 3428, 3032, 2920, 2869, 1598, 1496, 1454, 1357, 1267, 1189, 1175, 1096, 1075, 975, 915, 813 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): *δ* 7.77 (br d, *J* = 8.4 Hz, 2H), 7.36-7.25 (m, 7H), 4.49 (d, *J* = 12.1 Hz, 1H), 4.46 (d, *J* = 12.1 Hz, 1H), 4.25 (m, 1H), 4.03-3.86 (m, 4H), 3.56-3.46 (m, 2H), 2.43 (s, 3H), 1.70-1.56 (m, 4H), 1.52-1.39 (m, 2H), 1.41 (br s, 1H, OH); **^{13}C**

NMR ($CDCl_3$, 100 MHz): δ 144.7, 138.6, 133.0, 129.8 (2C), 128.4 (2C), 128.0 (2C), 127.7 (2C), 127.6, 73.0, 72.5, 69.1, 68.8, 66.5, 64.0, 38.4, 36.1, 34.2, 21.7; **MS** (EI) *m/z*: 283 (1), 267 (3), 241 (3), 223 (2), 197 (5), 195 (2), 146 (8), 125 (9), 107 (BnO^+,19), 91 (100), 79 (13), 73 (16), 67 (13), 65 (13), 55 (10); **HRMS** (ESI): Calculated for $C_{22}H_{28}O_6SNa\,[M + Na]^+$: 443.1499, found: 443.1499.

Synthesis of **7**

{(2*S*,4*S*,6*S*)-6-[2-(Benzyloxy)ethyl]-4-[(*tert*-butyldiphenylsilyl)oxy]tetrahydro-2*H*-pyran-2-yl}methyl 4-methylbenzenesulfonate (5a): To a solution of alcohol **5** (328 mg, 0.780 mmol, 1.0 equiv) and imidazole (106 mg, 1.56 mmol, 2.0 equiv) in dry CH_2Cl_2 (4.4 mL) was added TBDPSCl (0.30 mL, 1.16 mmol, 1.5 equiv) dropwise. After 16 h at rt, H_2O (6 mL) was added to the reaction mixture. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were then dried over $MgSO_4$, filtered and concentrated under *vacuum*. The crude material was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 95:5 to 9:1) to afford the silylated compound **5a** (488 mg, 0.741 mmol, 95%) as a colorless gummy liquid. $[\alpha]_D^{20}$ − 6.7 (*c* 0.95, $CHCl_3$); **IR**: *v* 3070, 2929, 2857, 1599, 1472, 1454, 1428, 1361, 1189, 1176, 1105, 1078, 1037, 981, 909, 821 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.78 (br d, *J* = 8.3 Hz, 2H), 7.63-7.60 (m, 4H), 7.47-7.27 (m, 13H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.21 (m, 1H), 4.13 (m, 1H), 4.06 (m, 1H), 3.98-3.88 (m, 2H), 3.54-3.48 (m, 2H), 2.42 (s, 3H), 1.72-1.62 (m, 2H), 1.53 (m, 1H), 1.44 (m, 1H), 1.28-1.17 (m, 2H), 1.07 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 144.6, 138.7, 135.7 (4C), 133.9 (2C), 133.2, 129.82, 129.79, 129.7 (2C), 128.4 (2C), 128.0 (2C), 127.73 (2C), 127.69 (2C), 127.6 (2C), 127.5, 73.0, 72.8, 69.4, 69.2, 66.8, 65.5, 38.6, 36.1, 34.6,

27.0 (3C), 21.7, 19.3; **MS** (EI) *m/z*: 279 (6), 278 (38), 277 (100), 201 (12), 183 (14), 152 (12), 77 (Ph^+, 26), 51 (15); **HRMS** (ESI): Calculated for $C_{38}H_{46}O_6SSiNa$ [M + Na]$^+$: 681.2677, found: 681.2681.

{(2*S*,4*S*,6*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-6-(2-hydroxyethyl)tetrahydro-2*H*-pyran-2-yl}methyl 4-methylbenzenesulfonate (5b): To a solution of benzyl alcohol **5a** (454 mg, 0.688 mmol, 1.0 equiv) in a mixture of EtOAc (1.6 mL) and MeOH (4.9 mL) was added palladium on activated charcoal (10% in weight, 36 mg, 0.034 mmol, 0.05 equiv). The medium was placed under a hydrogen atmosphere (1 atm) and stirred for 16 h. The mixture was then replaced under an argon atmosphere, filtered through a pad of Celite® and concentrated under *vacuum*. The crude material was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 7:3) to afford the alcohol **5b** (372 mg, 0.655 mmol, 95%) as a colorless gummy liquid. **[α]** $_D^{20}$ − 3.0 (*c* 1.05, $CHCl_3$); **IR**: *v* 3529, 3071, 2930, 2858, 1598, 1472, 1427, 1360, 1189, 1176, 1104, 1068, 1039, 977, 946, 909, 887, 820 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.79 (br d, J = 8.3 Hz, 2H), 7.63-7.60 (m, 4H), 7.46-7.41 (m, 2H), 7.40-7.35 (m, 4H), 7.33 (d, J = 8.3 Hz, 2H), 4.26-4.19 (m, 2H), 4.13 (m, 1H), 3.98 (dd, J = 10.5 and J = 3.5 Hz, 1H), 3.91 (dd, J = 10.5 and J = 6.7 Hz, 1H), 3.80-3.70 (m, 2H), 2.57 (br s, 1H, OH), 2.44 (s, 3H), 1.68-1.55 (m, 2H), 1.50-1.41 (br t_{app}, J = 1.6 Hz, 2H), 1.34-1.23 (br q_{app}, J = 1.2 Hz, 2H), 1.07 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 144.9, 135.7 (4C), 133.7 (2C), 133.0, 129.90 (2C), 129.88 (2C), 127.9 (2C), 127.78 (2C), 127.74 (2C), 72.8, 72.4, 69.7, 65.2, 61.4, 38.4, 37.7, 34.3, 27.0 (3C), 21.7, 19.3; **MS** (EI) *m/z*: 339 (17), 225 (10), 221 (21), 200 (20), 199 (100), 197 (13), 183 (20), 181 (15), 139 (16), 121 (10), 105 (10), 97 (38), 95 (20), 81 (14), 79 (16), 78 (13), 77 (28), 57 (12), 55 (10); **HRMS** (ESI): Calculated for $C_{31}H_{40}O_6SSiNa$ [M + Na]$^+$: 591.2207, found: 591.2204.

{(2*S*,4*S*,6*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-6-(2-oxoethyl)tetrahydro-2*H*-pyran-2-yl}methyl 4-methylbenzenesulfonate (7): To a solution of alcohol **5b** (372 mg, 0.655 mmol, 1.0 equiv) in dry CH_2Cl_2 (3 mL) were added NMO (114 mg, 0.98 mmol, 1.5 equiv), molecular sieves 4Å (315 mg) and tetrapropylammonium perruthenate (11.4 mg, 0.033 mmol, 0.05 equiv). The mixture was stirred at rt for 2 h, then filtered through a pad of silica, washed with EtOAc and concentrated under *vacuum*. The crude material was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 8:2) to afford the aldehyde **7** (290 mg, 0.512 mmol, 78%) as a colorless gummy liquid. $[\alpha]_D^{20}$ + 2.7 (*c* 0.52, $CHCl_3$); **IR**: *v* 3071, 2970, 2930, 2858, 1725, 1598, 1472, 1427, 1360, 1189, 1176, 1105, 1075, 1037, 981, 909, 820 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 9.68 (t, *J* = 2.3 Hz, 1H), 7.76 (br d, *J* = 8.4 Hz, 2H), 7.61 (m, 4H), 7.47-7.35 (m, 6H), 7.32 (br d, *J* = 8.4 Hz, 2H), 4.42 (m, 1H), 4.25-4.17 (m, 2H), 3.98-3.89 (m, 2H), 2.44 (s, 3H), 2.41 (ddd, *J* = 16.4, *J* = 8.1 and *J* = 2.7 Hz, 1H), 2.32 (ddd, *J* = 16.4, *J* = 4.9 and *J* = 2.0 Hz, 1H), 1.56-1.43 (m, 2H), 1.31-1.21 (br q_{app}, *J* = 1.3 Hz, 2H), 1.07 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 201.2, 144.8, 135.7 (4C), 133.6 (2C), 133.0, 129.9 (2C), 129.8 (2C), 128.0 (2C), 127.8 (4C), 72.4, 69.7, 67.6, 65.1, 49.3, 38.1, 34.2, 27.0 (3C), 21.7, 19.3; **HRMS** (ESI): Calculated for $C_{31}H_{38}O_6SSiNa$ $[M + Na]^+$: 589.2051, found: 589.2049.

{(2*S*,4*S*,6*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-6-[((2*R*,6*R*)-4-oxo-6-(tosyloxymethyl)tetrahydro-2*H*-pyran-2-yl)methyl]tetrahydro-2*H*-pyran-2-yl}methyl 4-methylbenzenesulfonate (8): To a solution of homoallylic alcohol *ent*-**2** (387 mg, 1.51 mmol, 1.5 equiv) and aldehyde **7** (570 mg, 1.01 mmol, 1.0 equiv) in dry CH_2Cl_2 (8.5 mL) was added dropwise TFA (1.96 mL, 26.2 mmol, 26 equiv). The mixture was stirred for 3 h at rt, and treated with a saturated aqueous solution of $NaHCO_3$ (15 mL). The pH was adjusted to a value pH > 7 by

addition of Et_3N and the resulting mixture was stirred at rt for an additional 2 h and then diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under *vacuum*. The crude material was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 6:4 to 5:5) to afford the tetrahydropyranyl alcohol as a mixture of diastereomers (*cis*/*trans* = 75:25, 456 mg, 0.556 mmol, 55%) and as a gummy liquid. To a solution of alcohols (mixture of diastereomers, 456 mg, 0.556 mmol, 1.0 equiv) in dry CH_2Cl_2 (6 mL) was added Dess-Martin periodinane (470 mg, 1.11 mmol, 2.0 equiv). The mixture was stirred at rt for 2 h. Hexane was then added, the resulting precipitate was filtered through a pad of Celite®. The filtrate was concentrated under *vacuum* and purification of the crude material by flash column chromatography on silica gel (petroleum ether/EtOAc = 7:3) afforded the corresponding ketone **8** (439 mg, 0.534 mmol, 96%) as a gummy liquid. $\mathbf{[\alpha]_D^{20}}$ + 3.3 (*c* 0.9, $CHCl_3$); **IR**: *v* 3028, 2930, 2858, 1722, 1599, 1495, 1454, 1428, 1361, 1347, 1189, 1177, 1160, 1096, 1029, 981, 815 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.80-7.75 (m, 4H), 7.62-7.56 (m, 4H), 7.46-7.30 (m, 10H), 4.21 (m, 1H), 4.11 (m, 1H), 4.06 (d, *J* = 4.6 Hz, 2H), 3.98 (m, 1H), 3.94 (d, *J* = 4.8 Hz, 2H), 3.78 (m, 1H), 3.66 (m, 1H), 2.43 (s, 3H), 2.42 (s, 3H), 2.40-2.30 (m, 3H), 2.22 (dd, *J* = 14.3 and *J* = 11.3 Hz, 1H), 1.77 (m, 1H), 1.48-1.39 (m, 3H), 1.30-1.17 (m, 2H), 1.04 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 205.4, 145.1, 144.8, 135.64 (2C), 135.61 (2C), 133.75, 133.72, 133.1, 132.7, 129.96 (2C), 129.92, 129.90, 129.86 (2C), 127.98 (2C), 127.93 (2C), 127.8 (4C), 73.84, 73.75, 72.5, 71.0, 69.6, 68.0, 65.3, 47.0, 43.3, 41.6, 38.3, 34.4, 27.0 (3C), 21.7 (2C), 19.2; **HRMS** (ESI): Calculated for $C_{43}H_{52}O_{10}S_2SiNa$ [M + Na]$^+$: 843.2663, found: 843.2672.

{(2*S*,4*S*,6*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-6-[((2*S*,4*S*,6*R*)-4-hydroxy-6-(tosyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)methyl]tetrahydro-2*H*-pyran-2-yl}methyl 4-methylbenzene sulfonate (9):[17] To a solution of ketone **8** (424 mg, 0.516 mmol, 1.0 equiv) in anhydrous MeOH (26.8 mL), cooled to −40 °C was added $NaBH_4$ (40 mg, 1.04 mmol, 2.0 equiv). The mixture was stirred at −40 °C for 1 h and then quenched by addition of H_2O (20 mL). The mixture was warmed to rt, MeOH was evaporated under *vacuum* and the residue diluted with EtOAc (60 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine (80 mL), dried over $MgSO_4$, filtered and concentrated under *vacuum*. The crude material was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 6:4) and the alcohol **9** (364 mg, 0.440 mmol, 86%) was isolated as a single diastereomer and as a colorless gummy liquid. **$[\alpha]_D^{20}$** + 1.2 (*c* 2.3, $CHCl_3$); **IR**: *v* 3537, 3020, 2928, 2857, 1599, 1428, 1360, 1215, 1189, 1176, 1098, 1038, 1020, 981, 815 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.62-7.56 (m, 4H), 7.46-7.28 (m, 10H), 4.19 (m, 1H), 4.13 (m, 1H), 4.03-3.89 (m, 5H), 3.77 (m, 1H), 3.53 (m, 1H), 3.38 (m, 1H), 2.43 (s, 3H), 2.41 (s, 3H), 1.99-1.91 (m, 3H), 1.67 (m, 1H), 1.48-1.40 (m, 2H), 1.38-1.11 (m, 5H), 1.03 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 144.85, 144.81, 135.68 (2C), 135.63 (2C), 133.84, 133.78, 133.1, 132.9, 129.85 (6C), 128.0 (2C), 127.9 (2C), 127.76 (2C), 127.74 (2C), 72.83, 72.81, 72.5, 71.9, 69.7, 68.4, 67.5, 65.4, 41.4, 40.3, 38.3, 37.0, 34.5, 27.0 (3C), 21.7 (2C), 19.2; **HRMS** (ESI): Calculated for $C_{43}H_{54}O_{10}S_2SiNa$ $[M + Na]^+$: 845.2820, found: 845.2825.

(2*S*,4*S*,6*R*)-2-{[(2*S*,4*S*,6*S*)-4-(*tert*-Butyldiphenylsilyl)oxy-6-(iodomethyl)tetrahydro-2*H*-pyran-2-yl]methyl}-6-(iodomethyl)tetrahydro-2*H*-pyran-4-ol (10):[17] To a solution of

tosylated *bis*-tetrahydropyran **9** (351 mg, 0.426 mmol, 1.0 equiv) in pure acetone (7.5 mL) was added NaI (639 mg, 4.26 mmol, 10 equiv). The mixture was heated at 120 °C under microwave irradiation, in a sealed vial, for 2 h. H_2O (4.5 mL) and EtOAc (4.5 mL) were then added. The layers were separated, the aqueous layer was extracted with EtOAc (10 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under *vacuum*. The crude material was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 75:25) to afford the the *bis*-iodinated compound **10** (285 mg, 0.39 mmol, 91%) as a gummy liquid. $[\alpha]_D^{20}$ − 9.7 (*c* 1.65, $CHCl_3$); **IR**: *v* 3385, 3070, 2927, 2856, 1589, 1471, 1427, 1362, 1185, 1106, 1080, 1036, 919 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.66-7.61 (m, 4H), 7.46-7.35 (m, 6H), 4.22 (m, 1H), 4.14 (m, 1H), 3.96-3.84 (m, 2H), 3.62 (m, 1H), 3.36 (m, 1H), 3.21-3.09 (m, 4H), 2.22 (m, 1H), 2.06 (m, 1H), 1.91 (m, 1H), 1.76 (m, 1H), 1.66 (br s, 1H, OH), 1.55-1.47 (m, 2H), 1.34-1.15 (m, 4H), 1.09 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 135.7 (4C), 133.9 (2C), 129.8 (2C), 127.7 (4C), 75.0, 72.7, 71.8, 69.1, 67.9, 66.0, 41.5, 40.8, 40.1, 38.7, 38.5, 27.1 (3C), 19.3, 10.4, 8.8; **HRMS** (ESI): Calculated for $C_{29}H_{40}I_2O_4SiNa$ $[M + Na]^+$: 757.0677, found: 757.0679.

(2*R*,4*S*,6*R*)-2-{[(2*S*,4*S*,6*S*)-4-(*tert*-Butyldiphenylsilyl)oxy-6-(iodomethyl)tetrahydro-2H-pyran-2-yl]methyl}-6-(iodomethyl)tetrahydro-*2H*-pyran-4-yl acrylate (11): To a solution of alcohol **10** (285 mg, 0.388 mmol, 1.0 equiv) in dry CH_2Cl_2 (5.4 mL) cooled to 0 °C were added diisopropylethylamine (0.38 mL, 2.30 mmol, 5.9 equiv) and acryloyl chloride (0.090 mL, 1.11 mmol, 2.9 equiv) dropwise. The mixture was warmed to rt and stirred for 3.5 h. The reaction was quenched by addition of H_2O (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$,

filtered and concentrated under *vacuum*. The crude material was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 90:10) to afford the protected *bis*-tetrahydropyran **11** (295 mg, 0.374 mmol, 96%) as a colorless very viscous liquid. $[\alpha]_D^{20}$ − 5.6 (*c* 0.33, $CHCl_3$); **IR**: *v* 2954, 2928, 2856, 1725, 1619, 1471, 1428, 1406, 1361, 1297, 1255, 1189, 1158, 1107, 1083, 1050, 1003, 836 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.68-7.62 (m, 4H), 7.47-7.36 (m, 6H), 6.43 (dd, *J* = 17.3 and *J* = 1.4 Hz, 1H), 6.12 (dd, *J* = 17.3 and *J* = 10.4 Hz, 1H), 5.85 (dd, *J* = 10.4 and *J* = 1.4 Hz, 1H), 5.05 (m, 1H), 4.23 (m, 1H), 4.16 (m, 1H), 3.94 (m, 1H), 3.66 (m, 1H), 3.41 (dtd, *J* = 11.1, *J* = 5.7 and *J* = 1.9 Hz, 1H), 3.17 (d, *J* = 5.7 Hz, 2H), 3.14 (d, *J* = 5.9 Hz, 2H), 2.29 (br d, *J* = 12.2 Hz, 1H), 2.05 (br d, *J* = 12.3 Hz, 1H), 1.91 ($quint_{app}$, *J* = 7.1 Hz, 1H), 1.78 (m, 1H), 1.58-1.48 (m, 2H), 1.46-1.21 (m, 4H), 1.09 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 165.5, 135.76 (2C), 135.72 (2C), 133.94, 133.93, 131.0, 129.8 (2C), 128.6, 127.75 (2C), 127.74 (2C), 74.6, 72.5, 71.7, 70.1, 69.0, 66.0, 41.6, 38.7, 38.4, 37.1, 36.5, 27.1 (3C), 19.4, 10.3, 8.5; **HRMS** (ESI): Calculated for $C_{32}H_{42}I_2O_5SiNa$ $[M + Na]^+$: 811.0783, found: 811.0782.

(4*R*,6*R*,8*S*,10*R*)-10-(*tert*-Butyldiphenylsilyl)oxy-6,8-dihydroxytrideca-1,12-dien-4-yl acrylate (12): To a solution of iodinated *bis*-tetrahydropyran **11** (290 mg, 0.368 mmol, 1.0 equiv) in a mixture of THF (10 mL) and H_2O (2.5 mL) was added activated zinc (722 mg, 11.04 mmol, 30 equiv). The mixture was heated at 70 °C in a sealed vial for 1 h, and was then filtered through a pad of Celite®. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under *vacuum*. The crude material was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 80:20) to afford the protected tetraol **12** (174 mg, 0.324 mmol, 88%)

as a colorless oil. $[\alpha]_D^{20}$ − 27.6 (*c* 1.1, $CHCl_3$); **IR**: *v* 3429, 3073, 2932, 2857, 1721, 1639, 1472, 1428, 1407, 1362, 1296, 1199, 1110, 1079, 997, 917 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.70-7.64 (m, 4H), 7.45-7.33 (m, 6H), 6.47 (br d, *J* = 17.3 Hz, 1H), 6.16 (dd, *J* = 17.3 Hz, *J* = 10.4 Hz, 1H), 5.90 (br d, *J* = 10.4 Hz, 1H), 5.76 (m, 1H), 5.64 (m, 1H), 5.17 (m, 1H), 5.10 (br d, *J* = 18.0 Hz, 1H), 5.09 (br d, *J* = 9.7 Hz, 1H), 4.93 (br d, *J* = 10.2 Hz, 1H), 4.85 (br d, *J* = 17.2 Hz, 1H), 3.98-3.89 (m, 3H), 3.76 (br s, 1H), 3.62 (br t_{app}, *J* = 9.5 Hz, 1H), 2.37 (br t_{app}, *J* = 6.2 Hz, 2H), 2.25-2.12 (m, 2H), 1.67 (m, 1H), 1.60-1.48 (m, 3H), 1.39 (m, 1H), 1.28 (m, 1H), 1.04 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 167.1, 135.92 (2C), 135.90 (2C), 134.3, 134.2, 133.8, 133.3, 131.7, 129.8, 129.7, 128.2, 127.7 (2C), 127.5 (2C), 118.1, 117.4, 71.8, 70.7, 70.2, 68.2, 43.6, 42.9, 42.6, 41.7, 39.2, 27.0 (3C), 19.3; **HRMS** (ESI): Calculated for $C_{32}H_{44}O_5SiNa$ $[M + Na]^+$: 559.2850, found: 559.2847.

Synthesis of **13**

(4*R*,6*S*,8*S*,10*R*)-6,8-bis[(*tert*-Butyldimethylsilyl)oxy]-10-(*tert*-butyldiphenylsilyl)oxy trideca-1,12-dien-4-yl acrylate (12a): To a solution of diol **12** (98 mg, 0.18 mmol, 1.0 equiv) in CH_2Cl_2 (4.4 mL) cooled to -78 °C were added 2,6-lutidine (0.13 mL, 1.1 mmol, 6.1 equiv) and then TBSOTf (0.17 mL, 0.74 mmol, 4.0 equiv). The mixture was stirred at -78 °C and after 1 h, the reaction was quenched by addition of H_2O (4 mL) and the mixture was warmed to rt. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under *vacuum*. The crude material was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 98:2) to afford the protected tetraol **12a** (130 mg, 0.170 mmol, 93%) as a colorless oil. $[\alpha]_D^{20}$ − 35.2 (*c* 1.2, $CHCl_3$); **IR**: *v* 3073, 2954, 2929, 2894, 2857, 1724, 1639, 1472, 1463,

1428, 1406, 1383, 1361, 1296, 1256, 1193, 1111, 1064, 1004, 984, 917, 836 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.72-7.66 (m, 4H), 7.46-7.34 (m, 6H), 6.39 (dd, J = 17.3 and J = 1.5 Hz, 1H), 6.09 (dd, J = 17.3 and J = 10.4 Hz, 1H), 5.78 (dd, J = 10.4 and J = 1.5 Hz, 1H), 5.75 (m, 1H), 5.62 (m, 1H), 5.11-5.03 (m, 3H), 4.93 (dd, J = 10.2 and J = 2.0 Hz, 1H), 4.84 (dd, J = 17.1 and J = 2.0 Hz, 1H), 3.93-3.75 (m, 3H), 2.42-2.28 (m, 2H), 2.20-2.08 (m, 2H), 1.83 (ddd, J = 14.2, J = 10.1 and J = 2.3 Hz, 1H), 1.74 (m, 1H), 1.66-1.52 (m, 2H), 1.47-1.37 (m, 2H), 1.07 (s, 9H), 0.87 (s, 9H), 0.86 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H), -0.01 (s, 3H), -0.04 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 165.8, 135.91 (2C), 135.85 (2C), 134.4, 134.0 (2C), 133.5, 130.3, 129.7, 129.6, 128.9, 127.7 (2C), 127.5 (2C), 117.8, 117.2, 70.9, 70.6, 66.8, 65.8, 46.2, 45.1, 41.8, 40.8, 39.1, 27.1 (3C), 25.9 (6C), 19.4, 17.93, 17.90, -3.96, -4.01, -4.2, -4.9; **HRMS** (ESI): Calculated for $C_{44}H_{72}O_5Si_3Na$ $[M + Na]^+$: 787.4580, found: 787.4586.

(*R*)-6-[(2*S*,4*S*,6*R*)-2,4-*bis*(*tert*-Butyldimethylsilyloxy)-6-(*tert*-butyldiphenylsilyloxy)non-8-en-1-yl)-5,6-dihydro-*2H*-pyran-2-one (13): To a solution of diene **12a** (127 mg, 0.166 mmol, 1.0 equiv) in CH_2Cl_2 (17 mL) was added the 1st generation Grubbs catalyst (14 mg, 0.017 mmol, 0.1 equiv). The mixture was heated at reflux for 3 h. The reaction mixture was then cooled to rt and concentrated under *vacuum*. The crude material was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 93:7) to afford the unsaturated lactone **13** (117 mg, 0.159 mmol, 96%) as a brown oil. **$[\alpha]_D^{20}$** − 19.8 (*c* 1.3, $CHCl_3$); **IR**: *v* 3073, 3017, 2953, 2930, 2893, 2857, 1722, 1472, 1463, 1428, 1387, 1252, 1217, 1110, 1059, 1004, 917, 836, 823 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.70-7.65 (m, 4H), 7.45-7.32 (m, 6H), 6.85 (ddd, J = 9.6, J = 5.5 and J = 2.5 Hz, 1H), 6.01 (br dd, J = 9.7 and J = 1.6 Hz, 1H), 5.65 (ddt, J = 17.3, J = 10.2 and J = 7.0 Hz, 1H), 4.96 (dd, J = 10.2 and J = 1.9 Hz, 1H), 4.85 (dd, J = 17.1 and J = 1.7 Hz, 1H), 4.53 (m, 1H), 4.10 (m, 1H), 3.88 (m, 1H), 3.82 (m, 1H),

2.27-2.04 (m, 4H), 1.91 (ddd, J = 14.0, J = 9.8 and J = 2.3 Hz, 1H), 1.80-1.53 (m, 3H), 1.45-1.37 (m, 2H), 1.05 (s, 9H), 0.85 (s, 18H), 0.08 (s, 3H), 0.04 (s, 6H), 0.03 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 164.0, 144.9, 135.91 (2C), 135.88 (2C), 134.4, 134.34, 134.25, 129.6 (2C), 127.6 (2C), 127.5 (2C), 121.7, 117.3, 74.2, 70.6, 66.6, 65.0, 46.0, 44.8, 42.4, 41.7, 30.1, 27.1 (3C), 25.9 (6C), 19.4, 18.0, 17.9, -4.2 (2C), -4.7 (2C); **HRMS** (ESI): Calculated for $C_{42}H_{68}O_5Si_3Na$ [M + Na]$^+$: 759.4267, found: 759.4272.

(4*R*,6*S*,8*S*,10*R*)-10-[(*tert*-Butyldiphenylsilyl)oxy]trideca-1,12-diene-4,6,8-triol (12'):[17] To a solution iodinated *bis*-tetrahydropyran **10** (32 mg, 0.044 mmol, 1.0 equiv) in pure ethanol (1 mL) were added activated zinc (86 mg, 1.31 mmol, 30 equiv) and NH_4Cl (23.5 mg, 0.44 mmol, 10 equiv). The mixture was heated at 90 °C in a sealed vial for 4 h, then diluted with EtOAc, filtered through a pad of Celite® and concentrated under *vacuum*. The crude material was then purified by column chromatography on silica gel (petroleum ether/EtOAc = 7:3 to 65:35) to afford the tetraol **12'** (16 mg, 0.033 mmol, 76%) as a colorless oil. **$[\alpha]_D^{20}$** − 25.2 (*c* 0.75, $CHCl_3$); **IR**: ν 3358, 3072, 2932, 2857, 1641, 1428, 1362, 1110, 1090, 998, 915, 822 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.73-7.68 (m, 4H), 7.48-7.36 (m, 6H), 5.83 (m, 1H), 5.54 (m, 1H), 5.16-5.08 (m, 2H), 4.92 (d_{app}, 1H, J = 10.2 Hz), 4.80 (d_{app}, 1H, J = 17.3 Hz), 4.15 (m, 1H), 4.06 (m, 1H), 4.00-3.93 (m, 2H), 2.32-2.21 (m, 2H), 2.13 (t_{app}, 2H, J = 6.6 Hz), 1.73-1.53 (m, 5H), 1.35 (m, 1H), 1.05 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 135.88 (2C), 135.86 (2C), 134.9, 133.9, 133.3 (2C), 130.0, 129.8, 127.8 (2C), 127.6 (2C), 117.74, 117.67, 73.1, 71.8, 70.4, 68.1, 43.5, 42.9, 42.12, 42.08, 42.06, 27.0 (3C), 19.3; **^{13}C NMR** (CD_3OD, 100 MHz): δ 137.12 (2C), 137.09 (2C), 136.3, 135.8, 135.5, 135.3, 130.9 (2C), 128.8 (2C), 128.7 (2C), 117.7, 117.4, 72.0, 68.61,

68.55, 68.3, 45.6, 45.4, 44.8, 43.8, 42.3, 27.7 (3C), 20.2; **HRMS** (ESI): Calculated for $C_{29}H_{42}O_4SiNa$ $[M + Na]^+$: 505.2745, found: 505.2742.

(3*S*,5*S*,7*S*)-5,7-*bis*(*tert*-Butyldimethylsilyloxy)-3-(*tert*-butyldiphenylsilyloxy)-8-((2*R*)-6-oxo-3,6-dihydro-*2H*-pyran-2-yl)octanal (14): A solution of alkene **13** (92.0 mg, 0.125 mmol, 1.0 equiv) in CH_2Cl_2 (6.1 mL) was cooled to -78 °C. Ozone was bubbled through the solution and the reaction was monitored by TLC to prevent the ozonolysis of the α,β-unsaturated ester double bond. After completion of the reaction, oxygen and then argon were bubbled through the solution. PPh_3 (50 mg, 0.19 mmol, 1.5 equiv) was then added and the solution was progressively warmed to rt overnight. The reaction mixture was dried over $MgSO_4$, filtered and concentrated under *vacuum*. The crude material was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 93:7 to 9:1) to afford the aldehyde **14** (74 mg, 0.10 mmol, 80%) as a colorless viscous liquid. $[\alpha]_D^{20}$ − 3.6 (*c* 1.0, $CHCl_3$); **IR**: *v* 3072, 2954, 2930, 2894, 2857, 2712, 1726, 1590, 1472, 1463, 1428, 1388, 1362, 1253, 1110, 1063, 1024, 1005, 937, 836, 824 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 9.67 (dd, J = 3.1 Hz, J = 1.7 Hz, 1H), 7.69-7.64 (m, 4H), 7.46-7.34 (m, 6H), 6.86 (m, 1H), 6.01 (m, 1H), 4.50 (m, 1H), 4.37 (quint, J = 6.0 Hz, 1H), 4.03 (m, 1H), 3.80 (quint, J = 6.0 Hz, 1H), 2.55 (ddd, J = 15.8 Hz, J = 5.2 Hz, J = 1.6 Hz, 1H), 2.43 (ddd, J = 15.8 Hz, J = 5.6 Hz, J = 3.2 Hz, 1H), 2.28-2.20 (m, 2H), 1.87-1.74 (m, 3H), 1.60 (ddd, J = 14.0, J = 6.9 and J = 4.4 Hz, 1H), 1.48-1.34 (m, 2H), 1.04 (s, 9H), 0.85 (s, 9H), 0.81 (s, 9H), 0.04 (s, 3H), 0.03 (s, 6H), -0.03 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 202.0, 164.0, 145.0, 135.9 (4C), 133.7, 133.5, 130.0, 129.9, 127.8 (2C), 127.7 (2C), 121.6, 74.3, 66.9, 66.3, 64.9, 50.3, 45.8, 45.3, 42.4, 30.1, 27.0 (3C), 25.89 (3C), 25.85 (3C), 19.3, 18.0, 17.9, -4.16 (2C), -4.24, -4.7; **HRMS** (ESI): Calculated for $C_{41}H_{66}O_6Si_3Na$ $[M + Na]^+$: 761.4059, found: 761.4065.

(*R*)-6-{(2*S*,4*S*,6*R*,8*R*,10*S*)-2,4-*bis*[(*tert*-Butyldimethylsilyl)oxy]-6-[(*tert*-butyldiphenylsilyl)oxy]-8,10-dihydroxypentacosyl}-5,6-dihydro-2*H*-pyran-2-one (16): To a solution of heptadecan-2-one (18.8 mg, 0.0739 mmol, 1.3 equiv) in freshly distilled pentane (0.5 mL), cooled to 0 °C, were added Et_3N (24 µL, 0.17 mmol, 3.0 equiv) and chlorodicyclohexylborane (0.15 mL, 1M in hexanes, 0.15 mmol, 2.6 equiv). The mixture was stirred at 0 °C for 2 h and then cooled to -78 °C. A solution of aldehyde **14** (41 mg, 0.055 mmol, 1.0 equiv) in pentane (1 mL) was then added and the mixture was stirred at -78 °C and progressively warmed to -40 °C. After 4 h at -40 °C, the reaction was quenched by the addition of a mixture of MeOH/pH = 7 buffer/35% aqueous H_2O_2 = 1:1:1 (1.5 mL) and the solution was progressively warmed to rt overnight. A saturated aqueous $Na_2S_2O_3$ solution (1.5 mL) was then added dropwise and the mixture was stirred for 30 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under *vacuum*. The crude material was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 95:5 to 9:1) to afford a fraction containing the hydroxyketone as a mixture of diastereomers **15** and **15'**, accompanied with the inseparable residual aldehyde **14** and as a colorless liquid. This mixture was then dissolved in CH_3CN (1.6 mL) and glacial acetic acid (1.6 mL) was added. The solution was cooled to -20 °C and $Me_4NBH(OAc)_3$ (80 mg, 0.305 mmol, 10 equiv) was added. The reaction mixture was stirred at -20 °C for 7 h and then quenched by the addition of a saturated aqueous $NaHCO_3$ solution (5 mL) dropwise. After stirring for 1 h, the mixture was diluted with EtOAc, the layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution (2 × 10 mL), then with brine (10

mL), dried over $MgSO_4$, filtered and concentrated under *vacuum*. The crude material was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 9:1 to 8:2) to afford the diol (20 mg, 0.020 mmol, 37%) as a mixture of diastereomers **16** and **16'** in a 75:25 ratio in favor of the desired *syn*,*anti*-isomer and as a colorless oil. **IR** (mixture of diastereomers): *v* 3446, 2926, 2855, 1715, 1471, 1428, 1388, 1361, 1254, 1108, 1059, 1004, 908, 836, 824 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz, *syn* major diastereomer): δ 7.73-7.66 (m, 4H), 7.44-7.34 (m, 6H), 6.87 (ddd, J = 9.4, J = 5.4 and J = 2.9 Hz, 1H), 6.00 (br d, J = 9.9 Hz, 1H), 4.50 (m, 1H), 4.25 (m, 1H), 4.08-3.93 (m, 3H), 3.80 (m, 1H), 3.18 (br s, 1H, OH), 3.05 (br s, 1H, OH), 2.27-2.18 (m, 2H), 2.13 (m, 1H), 1.82-1.54 (m, 4H), 1.53-1.20 (m, 33H), 1.03 (s, 9H), 0.88 (t, J = 6.6 Hz, 3H), 0.84 (s, 18H), 0.02 (s, 3H), 0.00 (s, 3H), -0.02 (s, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz, *syn* major diastereomer): δ 164.8, 145.7, 135.8 (4C), 134.4, 134.3, 129.7 (2C), 127.7 (4C), 121.3, 74.7, 70.8, 68.2, 67.0, 66.7, 64.8, 44.0 (2C), 43.9, 43.8, 42.7, 37.6, 31.9, 29.9, 29.7 (9C), 29.4, 27.0 (3C), 25.9 (6C), 25.8, 22.7, 19.4, 17.91, 17.87, 14.2, -4.2, -4.5 (2C), -4.8; **HRMS** (ESI): Calculated for $C_{58}H_{102}O_7Si_3Na$ $[M + Na]^+$: 1017.6826, found: 1017.6811.

(+)-Cryptocaryol A: To a solution of diols **16** and **16'** (mixture of diastereomers, 19 mg, 0.019 mmol, 1 equiv) in dry MeCN (0.8 mL) stirred at rt was added HF (48% aqueous solution, 0.080 mL, 0.19 mmol, 100 equiv) dropwise. The mixture was stirred at rt for 2.5 h, a saturated aqueous $NaHCO_3$ solution (1 mL) was added dropwise and the solution was stirred for 30 min. The mixture was diluted with CH_2Cl_2 (5 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under *vacuum*. The crude material was purified by preparative TLC (CH_2Cl_2/MeOH = 9:1) to afford pure (+)-cryptocaryol A (5 mg, 9.5 μmol, 50%) as a white

amorphous solid. The spectral data are in agreement with those reported in the literature.[14,15,16] $[\alpha]_D^{20}$ + 15 (*c* 0.2, MeOH); $[\alpha]_{D\ litt}^{20}$ + 14 (*c* 0.2, MeOH);[14] **IR**: *v* 3401, 2917, 2850, 1721, 1596, 1456, 1410, 1265, 1136, 1097, 1018, 843 cm^{-1}; **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.05 (ddd, J = 9.8, J = 6.0 and J = 2.7 Hz, 1H), 5.98 (br d, J = 9.8 Hz, 1H), 4.72 (m, 1H), 4.09 (m, 1H), 4.05-3.95 (m, 3H), 3.81 (m, 1H), 2.50-2.32 (m, 2H), 1.95 (ddd, J = 14.4, J = 9.9 and J = 2.4 Hz, 1H), 1.73-1.54 (m, 7H), 1.52 (t_{app}, J = 6.0 Hz, 2H), 1.47-1.41 (m, 2H), 1.35-1.28 (m, 26H), 0.90 (t, J = 6.9 Hz, 3H), OH not visible; **^{13}C NMR** (CD_3OD, 100 MHz): δ 166.9, 148.5, 121.4, 76.6, 70.1, 69.9, 69.1, 68.2, 66.5, 46.0, 45.9, 45.7, 45.2, 43.8, 39.2, 33.1, 30.9, 30.8 (9C), 30.5, 26.8, 23.7, 14.4; **HRMS** (ESI): Calculated for $C_{30}H_{56}O_7Na$ $[M + Na]^+$: 551.3918, found: 551.3913.

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SUPPORTING INFORMATION

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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