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A Simple and Efficient Approach to 1,3-Polyols: Application to the Synthesis of Cryptocarya Diacetate

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Abstract: A highly enantio- and stereoselective synthetic strategy for both *syn*- and *anti*-1,3-polyols has been developed. The sequence involves iterative Jacobsen's hydrolytic kinetic resolution (HKR), diastereoselective iodine-induced electrophilic cyclization, and ring-closing metathesis (RCM). This protocol has subsequently been utilized for the synthesis of cryptocarya diacetate, a natural product with broad range of biological activity.

Keywords: asymmetric synthesis • hydrolytic kinetic resolution • lactones • polyols • ring-closing metathesis

Introduction

Optically active *syn*-and *anti*-1,3-polyols/5,6-dihydropyran-2-ones are ubiquitous structural motifs in various biologically active compounds.[1] Fascinated by their broad range of biological activity and structural diversity in compounds ranging from simple carbohydrates to complex alkaloids and polyketides, synthetic chemists continue to pursue their synthesis[2] by the development of new methodologies. The lactone ring constitutes a structural feature of many natural products, particularly those that are Michael acceptors (α,β-unsaturated). They possess interesting pharmacological properties, such as plant-growth inhibition, as well as antifeedant, antifungal, antibacterial, and antitumor properties.[3,4] The simplest structure with a *syn*-1,3-diol/5,6-dihydropyran-2-one motif is tarchonanthuslactone (**1**), isolated from *Tarchonanthustrilobus compositae*.[5] The related 6-substituted 5,6-dihydropyran-2-ones, such as cryptocarya diacetate (**2**) and cryptocarya triacetate (**3**), and more complex 1,3-polyols, such as passifloricin A (**4**) (Figure 1), were isolated from the leaves and bark of the South African plant *Cryptocarya latifolia*. Medicinal properties of these compounds range from the treatment of headaches and morning sickness to that of cancer, pulmonary diseases, and various bacterial and fungal infections.[6] Absolute and relative stereochemistry of cryptocarya acetate were determined by a combination of Mosher's ester and Rychnovsky ^{13}C NMR/acetonide analysis.[7] Further, it was confirmed by the enantioselective total synthesis of **2** from (*S*)-*tert*-butyl 3-hydroxybutyrate.[8] Recently O'Doherty et al. synthesized **2**

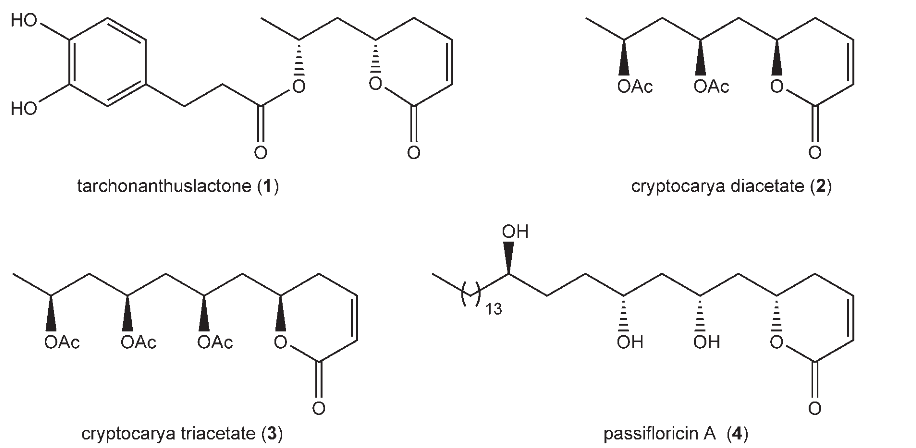

Figure 1. Examples of *syn*-1,3-polyols/5,6-dihydropyran-2-ones.

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from δ-hydroxy-1-enoate by using enantio- and regioselective Sharpless asymmetric dihydroxylation and a palladium-catalyzed reduction.[9] As a part of our research program, aimed at developing enantioselective syntheses of naturally occurring lactones,[10] we became interested in devising a practical and concise route to *syn*-1,3-polyols/5,6-dihydropyran-2-ones. Herein we report our successful endeavors towards the development of a general and practical route for 1,3-polyols and its subsequent application to the stereoselective total synthesis of cryptocarya diacetate (**2**), employing hydrolytic kinetic resolution (HKR),[11] diastereoselective iodine-induced electrophilic cyclization,[12] and ring-closing metathesis (RCM)[13] as the key steps. The HKR method utilizes the readily accessible cobalt-based chiral salen complex **5** as a catalyst (Figure 2) and water to resolve a racemic epoxide into an enantiomerically enriched epoxide and diol in high enantiomeric excess. Similarly the iodolactonization of an enantiomerically pure homoallylic alcohol directs the epoxidation of a double bond in a diastereoselective manner to afford the *syn*-epoxy alcohol.

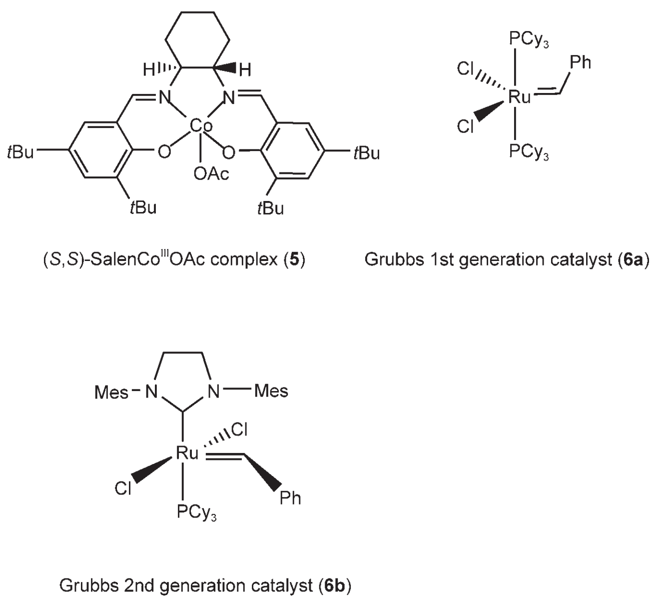
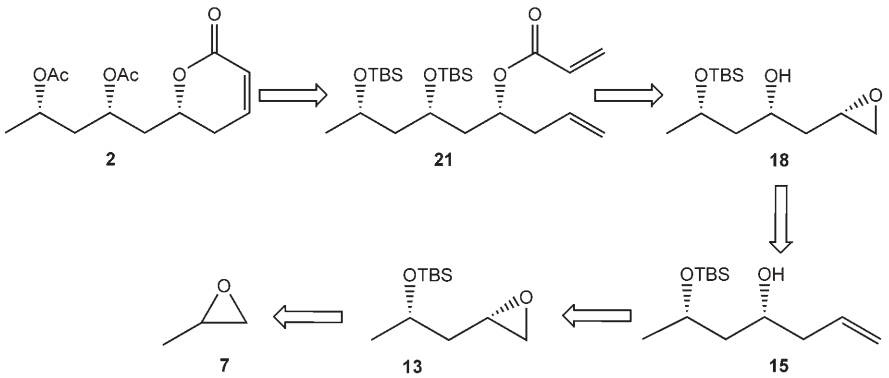


Figure 2. Catalysts used in the synthesis.

Results and Discussion

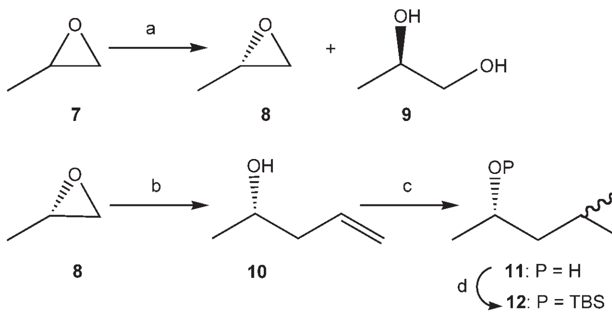
Our retrosynthetic strategy for the synthesis of **2** is outlined in Scheme 1. We envisioned that the lactone moiety could be constructed by the ring-closing metathesis of an acrylate ester **21**, which in turn could be obtained from epoxide **18**. The epoxide **18** could be prepared from homoallylic alcohol **15** by means of diastereoselective iodine-induced electrophilic cyclization, which in turn could be prepared from **13**. The epoxide **13** could be prepared by means of iterative HKR from racemic propylene oxide **7**.



Scheme 1. Retrosynthetic analysis of cryptocarya diacetate.

Synthesis of epoxide 12: Our synthesis of **2** requires three major reactions: Jacobsen's hydrolytic kinetic resolution, diastereoselective iodine-induced electrophilic cyclization to install the stereogenic centers, and ring-closing metathesis to construct the δ-lactone moiety. In designing a route to **2**, we chose propylene oxide as an appropriate starting material (Scheme 2). Thus, commercially available propylene oxide **7** was subjected to Jacobsen's HKR by using (*S*,*S*)-Salen-Co-OAc catalyst **5** (Figure 2) to give (*S*)-propylene oxide[11d] **8** as a single isomer; this compound was easily isolated from the more polar diol **9** by distillation.

With enantiomerically pure epoxide **8** in hand, our next task was to construct the *syn*-1,3-diol.[14] To establish the second stereogenic center with required stereochemistry, we examined the stereoselective epoxidation of a homoallylic alcohol. Thus (*S*)-propylene oxide **8** was treated with vinylmagnesium bromide in the presence of CuI to give the homoallylic alcohol **10** in excellent yield. We then proceeded to explore the stereoselective outcome of the epoxidation reaction with and without hydroxyl-group protection. To this end, the hydroxyl group of homoallylic alcohol **10** was first protected as the TBS ether, followed by epoxidation

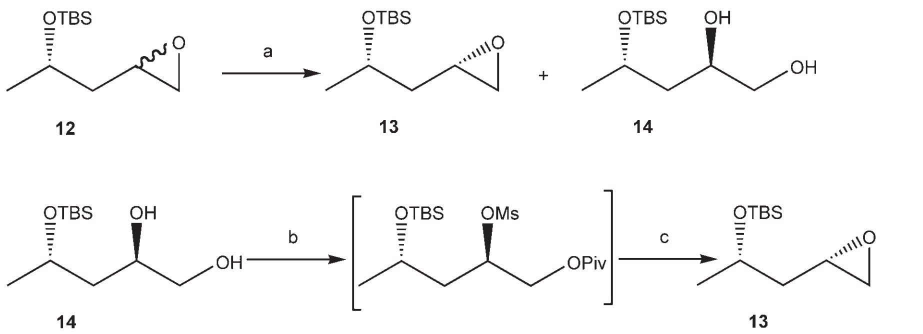


Scheme 2. Synthesis of epoxide **12**: a) *S*,*S*-Salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.55 equiv), 0°C, 14 h, (45% for **8**, 43% for **9**); b) Vinylmagnesium bromide, CuI, THF, −20°C, 12 h, 87%; c) *m*CPBA, CH_2Cl_2, 0°C to RT, 10 h, 96%; d) TBS-Cl (TBS = *tert*-butyldimethylsilyl), imidazole, CH_2Cl_2, 0°C to RT, 4 h, 95%.

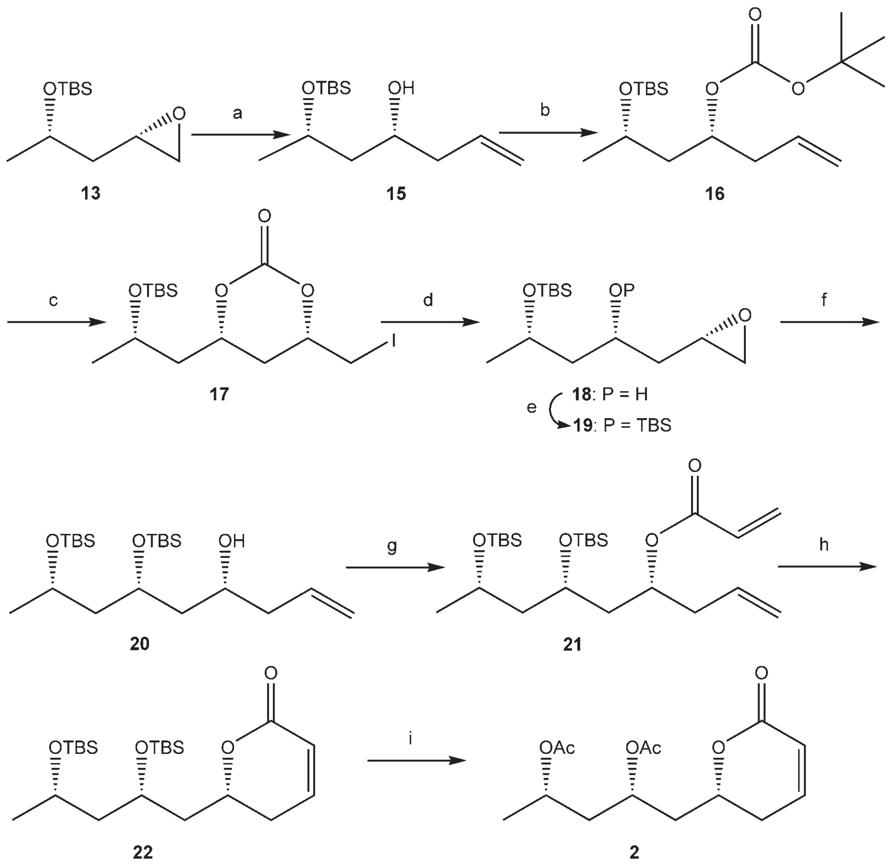
with *m*CPBA (*m*CPBA = *meta*-chloroperbenzoic acid). The epoxide produced was found to be a mixture of two diastereomers (*anti*/*syn* 3:1) with the desired *syn*-isomer of **12** obtained as the minor component. In contrast, the epoxidation of homoallylic alcohol **10**, followed by hydroxy-group protection as the TBS ether (TBS = *tert*-butyldimethylsilyl) produced the epoxide **12** in favor of the desired *syn*-isomer (*syn*/*anti* 1.2:1). The two diastereomers could not be differentiated by TLC.

Synthesis of the diastereomerically pure epoxide and conversion of diol 14 into epoxide 13: The next step in the synthesis was to construct the diastereomerically pure epoxides by means of Jacobsen's hydrolytic kinetic resolution (Scheme 3). To this end, the epoxide **12** was treated with (*S*,*S*)-Salen-Co-OAc complex (0.5 mol%) and water (0.55 equiv) in THF (0.55 equiv) to afford the epoxide **13** as a single stereoisomer (as determined by ^{1}H and ^{13}C NMR spectral analysis) in 46% yield and the diol **14** in 45% yield. Epoxide **13** could easily be separated from the more polar diol **14** by silica-gel column chromatography.

We required a substantial amount of epoxide **13** for the synthesis of target molecule **2**. As the HKR method provided the desired epoxide **13** along with unwanted diol **14** in almost equal amounts, we decided that it would be appropriate to convert the diol into the required epoxide by means of an internal nucleophilic substitution of a secondary mesylate (Ms = mesyl).[15] Accordingly, chemoselective pivalation of diol **14** with pivaloyl chloride, followed by mesylation of the secondary hydroxyl and treatment of the crude mesylate product with K_2CO_3 in methanol led to the deprotection of the pivaloyl ester. Concomitant ring closure by intramolecular S_N2 displacement of the mesylate furnished the epoxide **13** in 61% overall yield (Scheme 3).



Scheme 3. Synthesis of diastereomerically pure epoxide **13** and conversion of diol **14** into epoxide **13**: a) *S*,*S*-Salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.55 equiv), THF, 0°C, 24 h (46% for **13**, 45% for **14**); b) i) PivCl, Et_3N, cat. DMAP, RT, 2 h; ii) MsCl, Et_3N, DMAP, 0°C to RT, 1 h; c) K_2CO_3, MeOH, RT, overnight (61% for three steps).



Scheme 4. Synthesis of cryptocarya diacetate: a) Vinylmagnesium bromide, THF, CuI, −20°C, 1 h, 82%; b) Boc_2O, DMAP, CH_3CN, RT, 5 h, 90%; c) IBr, PhMe, −85°C, 1 h; d) K_2CO_3, MeOH, RT, 2 h, 81% from both the steps; e) TBS-Cl (TBS = *tert*-butyldimethylsilyl), imidazole, DMF, 0°C to RT, 22 h, 89%; f) Vinylmagnesium bromide, THF, CuI, −20°C, 1 h, 80%; g) Acryloyl chloride, Et_3N, CH_2Cl_2, 0°C to RT, 5 h, 82%; h) $(PCy_3)_2Ru(Cl)_2$=CH−Ph (20 mol%), CH_2Cl_2, $Ti(iPrO)_4$ (0.03 equiv), reflux, 6 h, 84%; i) i) TBAF, THF, RT, overnight; ii) Ac_2O, pyridine, 2 h, 75% from both the steps.

Synthesis of cryptocarya diacetate (2): The synthesis of cryptocarya diacetate (**2**) was accomplished by starting from epoxide **13** (Scheme 4). Thus, **13** was first treated with vinylmagnesium bromide in the presence of CuI in THF at −20°C to give the homoallylic alcohol **15** in 82% yield. With substantial amounts of homoallylic alcohol in hand, we then investigated the stereoselective epoxidation of the carbon–carbon double bond. As a direct approach, the diastereoselective epoxidation of the homoallylic alcohol **15** was examined without success by using Sharpless's protocol[16] with *tert*-butyl hydroperoxide in the presence of vanadium acetylacetonate. The desired *syn*-epoxy alcohol **18** was isolated in moderate yield with low selectivity. To improve the diastereoselectivity of this reaction, we applied a three-step sequence based on a modified Cardillo iodo cyclization procedure.[12] Following this methodology, the homoallylic *tert*-butyl carbonate **16** was prepared from the corresponding alcohol **15** in 90% yield by treatment with di-*tert*-butyl dicarbonate in the presence of DMAP (DMAP = 4-dimethylaminopyridine) in acetonitrile. The diastereoselective iodine-induced electrophilic cyclization of the homoallylic *tert*-butyl carbonate **16** with IBr at low temperature (−85 °C) furnished the iodo carbonate **17**, which was directly treated with K_2CO_3 in methanol to give the desired *syn*-epoxy alcohol **18** as a single diastereomer in 81% yield. The epoxy alcohol **18** was treated with TBS chloride to furnish the TBS-protected epoxide **19** in 89% yield. The opening of the epoxide **19** with vinylmagnesium bromide in the presence of CuI in THF at −20 °C furnished the homoallylic alcohol **20** in 80% yield. Alcohol **20** was esterified with acryloyl chloride in the presence of Et_3N and catalytic amount of DMAP to afford the acryloyl ester **21** in 82% yield.

Subsequent ring-closing metathesis of ester **21** with commercially available Grubbs 1st generation catalyst **6a** in the presence of $Ti(iPrO)_4$ (0.03 equiv) in refluxing CH_2Cl_2 for 6 h (Scheme 4) afforded the α,β-unsaturated δ-lactone **22** in 84% yield. In the absence of $Ti(iPrO)_4$, the reaction was found to be sluggish; however, the reaction proceeded well with a comparable yield, without the addition of any $Ti(iPrO)_4$, when 5 mol% of Grubbs 2nd generation catalyst **6b** was used. Now all that remained to complete the synthesis was to remove the TBS group and acetylate the resulting diol. Thus desilylation of **22** with TBAF (TBAF = *tetra*-butylammonium fluoride) produced a diol, which was directly acylated by the addition of acetic anhydride and pyridine to give cryptocarya diacetate (**2**) in 75% yield. The physical and spectroscopic data of **2** were in full agreement with the literature data.[8,9]

Conclusion

A practical and efficient strategy has been developed for the syntheses of 1,3-polyols/5,6-dihydropyran-2-ones. This synthetic protocol has been utilized for the synthesis of cryptocarya diacetate. The stereocenters in this compound were incorporated by hydrolytic kinetic resolution and diastereoselective iodine-induced electrophilic cyclization. Construction of the lactone moiety was achieved by ring-closing metathesis. This synthetic strategy, which is amenable to both *syn*- and *anti*-1,3-polyols, has significant potential for extension to the synthesis of a variety of other biologically important natural products containing 1,3-polyol-substituted 5,6-dihydropyran-2-one. Currently studies are in progress in this direction.

Experimental Section

(*S*)-Propylene oxide (8): The racemic propylene oxide **7** was resolved to chiral epoxide **7** in high enantiomeric excess by the HKR method, following a literature procedure.[11d] $[\alpha]_D^{25} = -11.3$ (neat) (lit. [11d] $[\alpha]_D^{25} = -11.6$ (neat)).

(*S*)-Pent-4-en-2-ol (10): A round-bottomed flask was charged with copper(I)iodide (1.64 g, 8.6 mmol), gently heated under vacuum, slowly cooled with a flow of argon, and then dry THF (20 mL) was added. The resulting suspension was cooled to −20 °C with vigorous stirring and then vinylmagnesium bromide (1 M in THF, 172 mL, 172.4 mmol) was injected into the mixture. A solution of propylene oxide **8** (5 g, 86.1 mmol) in THF (10 mL) was added slowly to the above reagent, and the mixture was stirred at −20 °C for 12 h. After this time, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and the organic layer produced was washed with brine, dried (Na_2SO_4), and then concentrated to afford the crude homoallylic alcohol **10**, which was purified by distillation to give the pure product (6.5 g, 87%) as a colorless liquid. B.p. 115 °C (lit. [17] 115 °C); $[\alpha]_D^{25} = +10.86$ ($c = 3.2$ in Et_2O) (lit. [17] $[\alpha]_D^{24} = -9.84$ ($c = 3.2$ in Et_2O) for (*R*)-pent-4-en-2-ol); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.77$–5.85 (m, 1 H), 5.12 (d, $J = 6.6$ Hz, 1 H), 5.09 (d, $J = 2.4$ Hz, 1 H), 3.80–3.86 (m, 1 H), 2.22–2.38 (m, 2 H), 1.82 (s, 1 H), 1.18 ppm (d, $J = 6.1$, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 134.6$, 116.6, 66.5, 43.2, 22.1 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3400$, 3078, 2931, 2975, 1562, 1457, 1432, 1243, 1071, 914 cm^{-1}.

1-Oxiranyl-propan-2-ol (11): To a stirred solution of olefin **10** (6 g, 69.7 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added *m*CPBA (50%, 28.85 g, 83.6 mmol). The reaction mixture was stirred at room temperature for 10 h and then quenched with saturated $NaHCO_3$ solution. The resulting mixture was extracted with CH_2Cl_2, washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), concentrated, and then purified by silica-gel column chromatography (petroleum ether/EtOAc 9:1) to yield the epoxide **11** (6.83 g, 96%) as a colorless liquid and as a diastereomeric mixture (1.1:1). $[\alpha]_D^{25} = +12.2$ ($c = 0.79$ in $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 4.06$–4.10 (m, 1 H), 3.02–3.05 (m, 1 H), 2.81–2.84 (m, 1 H), 2.52–2.54 (m, 1 H), 1.82–1.86 (m, 1 H), 1.71–1.74 (m, 1 H), 1.18 ppm (d, $J = 6.3$ Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) both diastereomers: $\delta = 66.5$, 66.3, 49.6, 49.3, 47.2, 46.3, 42.9, 42.3, 25.7, 24.2 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3436$, 3192, 2968, 2932, 2852, 1471, 1379, 1265, 1206, 1101, 944, 878 cm^{-1}; elemental analysis (%) calcd for $C_5H_{10}O_2$ (102.13): C 58.80, H 9.87; found: C 58.69, H 9.82.

***tert*-Butyldimethyl(1-methyl-but-3-enyloxy)silane (12)**: Imidazole (8.0 g, 117.5 mmol) was added to a stirred solution of alcohol **11** (6 g, 58.8 mmol) in CH_2Cl_2 (25 mL). *tert*-Butyl dimethylchlorosilane (10.63 g, 70.5 mmol) was then added to this solution at 0 °C, and reaction was stirred at room temperature for 4 h. After this time, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were washed with brine, dried (Na_2SO_4), and then concentrated. Silica-gel column chromatography of the crude product (petroleum ether/EtOAc 19:1) provided **12** (12.08 g, 95%) as a colorless liquid.

Compounds 13 and 14: A solution of epoxide **12** (5 g, 23.1 mmol) and (*S,S*)-Salen-Co^{III}-OAc (0.076 g, 0.12 mmol) in THF (0.3 mL) was stirred at 0 °C for 5 min and then distilled water (229 μL, 12.7 mmol) was added. After stirring for 24 h, this mixture was concentrated and purified by silica-gel column chromatography (petroleum ether/EtOAc 19:1) to afford **13** (2.3 g, 46%) as a yellow liquid. Continued chromatography with petroleum ether/EtOAc 3:2) provided the diol **14** (2.25 g, 45%) as a brown liquid and as a single diastereomer.

Epoxide 13: $[\alpha]_D^{25} = +9.6$ ($c = 0.53$ in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.01$–4.08 (m, 1 H), 3.02–3.04 (m, 1 H), 2.76–2.80 (m, 1 H), 2.46–2.50 (m, 1 H), 1.67–1.71 (m, 1 H), 1.50–1.52 (m, 1 H), 1.19 (d, $J = 6.3$ Hz, 3 H), 0.87 (s, 9 H), 0.03 (s, 3 H), 0.02 ppm (s, 3 H); ^{13}C NMR

(50 MHz, $CDCl_3$): $\delta = 66.3$, 48.8, 45.8, 42.1, 25.4, 23.3, 17.6, −5.0, −5.3 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3018$, 2958, 2930, 1858, 1472, 1463, 1377, 1256, 1216, 1101, 1005, 938, 878, 760 cm^{-1}; elemental analysis (%) calcd for $C_{11}H_{24}O_2Si$ (216.39): C 61.05, H 11.18, Si 12.98; found: C 61.12, H 11.08, Si 12.96.

Diol 14: $[\alpha]_D^{25} = -33.8$ ($c = 0.92$ in $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 4.22$–4.31 (m, 1H), 4.04–4.14 (m, 1H), 3.46–3.70 (m, 2H), 1.67–1.81 (m, 2H), 1.32–1.50 (m, 2H), 1.27 (d, $J = 6.1$ Hz, 3H), 0.90 (s, 9H), 0.10 ppm (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 68.9$, 66.7, 66.3, 41.1, 25.6, 23.4, 17.7, −4.7, −5.1 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3430$, 3018, 2957, 2931, 2859, 1652, 1471, 1379, 1256, 1212, 1101, 1036, 971, 869, 758 cm^{-1}; elemental analysis (%) calcd for $C_{11}H_{26}O_3Si$ (234.41): C 56.36, H 11.18, Si 11.98; found: C 56.72, H 11.07, Si 11.28.

Conversion of 14 into 13: Diol **14** (2 g, 8.5 mmol) was dissolved in dry CH_2Cl_2 (25 mL) under argon and treated with pivaloyl chloride (1.13 g, 9.4 mmol), Et_3N (1.03 g, 10.2 mmol), and catalytic amount of DMAP. The resulting mixture was stirred at room temperature for 2 h and then worked up (extraction with CH_2Cl_2). Removal of volatiles under reduced pressure gave an oily crude monopivalate. This compound was then dissolved in dry CH_2Cl_2 (30 mL) under argon and treated with MsCl (0.978 g, 8.5 mmol), Et_3N (1.033 g, 10.2 mmol), and catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 1 h and then quenched with water. The water layer was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a crude product, which was dissolved in MeOH (20 mL) and treated with K_2CO_3 (1.17 g, 8.5 mmol). This mixture was stirred overnight at room temperature and then filtered through Celite. Removal of the volatiles under reduced pressure, followed by column chromatography on silica gel (petroleum ether/EtOAc 19:1) produced the epoxide **13** (1.13 g, overall yield 61%) as a yellow liquid. $[\alpha]_D^{25} = +9.8$ ($c = 0.50$ in $CHCl_3$).

6-(*tert*-Butyldimethylsilanyloxy)hept-1-en-4-ol (15): A round-bottomed flask was charged with copper(I)iodide (0.88 g, 4.6 mmol), gently heated under vacuum, and then slowly cooled under a flow of argon. THF (20 mL) was then added and the resulting suspension was cooled to −20°C, stirred, and vinylmagnesium bromide (1 M in THF, 18.5 mL, 18.5 mmol) added. A solution of epoxide **13** (1.0 g, 4.6 mmol) in THF (15 mL) was added to the above reagent and the mixture was stirred at −20°C for 1 h. After consumption of starting material, the reaction mixture was quenched with saturated aqueous NH_4Cl. The water layer was extracted with EtOAc (3×50 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Purification of crude product by silica-gel column chromatography (petroleum ether/EtOAc 9:1) afforded **15** (0.92 g, 82%) as a colorless liquid. $[\alpha]_D^{25} = +32.8$ ($c = 0.76$ in $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 5.74$–5.93 (m, 1H), 5.15 (d, $J = 6.9$ Hz, 1H), 5.06 (d, $J = 2.9$ Hz, 1H), 4.03–4.23 (m, 1H), 3.80–3.86 (m, 1H), 2.19–2.26 (m, 2H), 1.53–1.60 (m, 2H), 1.21 (d, $J = 7$ Hz, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.09 ppm (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 134.9$, 117.1, 70.3, 69.5, 45.3, 42.0, 25.8, 24.4, 17.8, −4.0, −4.9 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3460$, 2959, 2857, 1640, 1448, 1376, 1255, 1078 cm^{-1}; elemental analysis (%) calcd for $C_{13}H_{28}O_2Si$ (244.45): C 63.87, H 11.55, Si 11.49; found: C 63.82, H 11.38, Si 11.36.

Carbonic acid *tert*-butyl ester 1-[2-(*tert*-butyldimethylsilanyloxy)propyl]-but-3-enyl ester (16): $(Boc)_2O$ ($(Boc)_2O$ = di-*tert*-butyldicarbonate, 2.68 g, 12.3 mmol) and DMAP (0.400 g, 3.3 mmol) were added to a solution of alcohol **15** (2 g, 8.2 mmol) in CH_3CN (40 mL). After stirring for 5 h, the solvent was evaporated under reduced pressure and the resulting residue dissolved in EtOH (30 mL), and imidazole (2.79 g, 41.0 mmol) was added. This mixture was stirred at room temperature for 15 min and then CH_2Cl_2 was added. The organic layer was washed with water, dried (Na_2SO_4), and then concentrated. Purification of the crude product by silica-gel column chromatography (petroleum ether/EtOAc 19:1) produced **16** (1.94 g, 90%) as a colorless liquid. $[\alpha]_D^{25} = -20.84$ ($c = 1.2$ in $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 5.72$–5.87 (m, 1H), 5.15 (d, $J = 7.5$ Hz, 1H), 5.06 (d, $J = 2.9$ Hz, 1H), 4.79–4.90 (m, 1H), 3.85–4.0 (m, 1H), 2.32–2.45 (m, 2H), 1.79–1.90 (m, 1H), 1.58–1.69 (m, 1H), 1.48 (s, 9H), 1.19 (d, $J = 6.9$ Hz, 3H), 0.89 (s, 9H), 0.06 ppm (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 153.2$, 133.5, 117.9, 81.6, 73.9, 65.6, 43.5, 38.9, 27.8, 25.8, 23.5, 18.1, −4.4, −4.8 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3020$, 2958, 2931, 2858, 1737, 1643, 1521, 1473, 1463, 1394, 1370, 1280, 1216, 1115, 1092, 994 cm^{-1}; elemental analysis (%) calcd for $C_{18}H_{36}O_4Si$ (344.56): C 62.74, H 10.53, Si 8.15; found: C 62.72, H 10.37, Si 8.02.

4-[2-(*tert*-Butyldimethylsilanyloxy)propyl]-6-iodomethyl[1,3]dioxan-2-one (17): A solution of IBr (1 M in CH_2Cl_2, 0.80 g, 9.3 mmol) was slowly added to a solution of carbonate **16** (2 g, 5.8 mmol) in toluene at −85°C. After the mixture had been stirred at −85°C for 1 h, it was quenched with a mixture of aqueous $Na_2S_2O_3$ (20%)/aqueous $NaHCO_3$ (5%) 1:1 and then diluted with ether (20 mL). The aqueous phase was extracted with ether (2×50 mL) and the organic extracts were washed with brine, dried (Na_2SO_4), and then concentrated under reduced pressure. The residue produced was used directly for the next step in the synthesis due to extensive decomposition.

4-(*tert*-Butyldimethylsilanyloxy)-1-oxiranyl-pentan-2-ol (18): K_2CO_3 (2.09 g, 15.1 mmol) was added to a solution of cyclic carbonate **17** (2.09 g, 5.0 mmol) in anhydrous MeOH (20 mL) at room temperature and the resulting reaction mixture was stirred for 2 h. After this time, the mixture was diluted with ether (20 mL) and quenched with a mixture of saturated aqueous $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ 1:1. The aqueous phase was extracted with ether (3×50 mL) and the organic extracts were washed with brine, dried (Na_2SO_4), and then concentrated. Purification of the crude product by silica-gel column chromatography (petroleum ether/EtOAc 7:3) afforded the epoxide **18** (1.22 g, 81% from both the steps) as a colorless oil. $[\alpha]_D^{25} = +21.58$ ($c = 0.88$ in $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 4.09$–4.16 (m, 1H), 3.96–4.03 (m, 1H), 3.08–3.14 (m, 1H), 2.79 (dd, $J = 4.8$, 4.0 Hz, 1H) 2.52 (dd, $J = 5.1$, 2.8 Hz, 1H), 1.69–1.74 (m, 2H), 1.63–1.67 (m, 2H), 1.22 (d, $J = 6.1$ Hz, 3H), 0.91 (s, 9H), 0.13 (s, 3H), 0.12 ppm (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ 69.6, 69.2, 49.5, 46.5, 45.6, 39.9, 25.7, 24.4, 17.8, −3.9, −4.9 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3471$, 3019, 2957, 2931, 2859, 2400, 1662, 1377, 1258, 1216, 1082, 836, 758 cm^{-1}; elemental analysis (%) calcd for $C_{13}H_{28}O_3Si$ (260.45): C 59.95, H 10.84, Si 10.78; found: C 59.82, H 10.79, Si 10.85.

2-[2,4-Bis-(*tert*-butyldimethylsilanyloxy)pentyl]oxirane (19): Imidazole (0.52 g, 7.6 mmol) was added to a stirred solution of alcohol **18** (1 g, 3.8 mmol) in DMF (5 mL); this was followed by the addition of *tert*-butyldimethylchlorosilane (0.69 g, 4.6 mmol) at 0°C. The resulting reaction mixture stirred at room temperature for 22 h and was then quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3×100 mL). The resulting organic extracts were washed with brine, dried (Na_2SO_4), and then concentrated. Purification of crude product by silica-gel column chromatography (petroleum ether/EtOAc 9:1) produced **19** (1.28 g, 89%) as a colorless oil. $[\alpha]_D^{25} = +10.62$ ($c = 0.84$ in $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 4.21$–4.28 (m, 1H), 3.99–4.04 (m, 1H), 3.11–3.21 (m, 1H), 2.80 (dd, $J = 4.9$, 4.0 Hz, 1H), 2.54 (dd, $J = 5$, 2.9 Hz, 1H), 1.72–1.76 (m, 2H), 1.65–1.71 (m, 2H), 1.21 (d, $J = 6.1$, 3H), 0.89 (s, 18H), 0.12 (s, 6H), 0.11 ppm (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 69.6$, 66.8, 65.7, 49.2, 47.8, 43.1, 25.8, 24.0, 18.1, −4.3, −4.4 ppm; IR ($CHCl_3$): $\tilde{\nu} =$ 2957, 2931, 2888, 2858, 1619, 1473, 1464,1384, 1362, 1257, 761 cm^{-1}; elemental analysis (%) calcd for $C_{19}H_{42}O_3Si_2$ (374.71): C 60.90, H 11.30, Si 14.99; found: C 60.81, H 11.49, Si 14.87.

6,8-Bis-(*tert*-butyldimethylsilanyloxy)non-1-en-4-ol (20): A round-bottomed flask was charged with copper(I)iodide (51 mg, 0.27 mmol), gently heated under vacuum, and then slowly cooled under a flow of argon. THF (10 mL) was then added and the resulting suspension was cooled to −20°C whilst stirring; this was followed by the addition of vinylmagnesium bromide (1 M in THF, 5.34 mL, 5.4 mmol). A solution of epoxide **19** (1 g, 2.7 mmol) in THF (10 mL) was then added to the above reagent and the mixture was stirred at −20°C for 1 h. After completion of the reaction, the mixture was quenched with saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and then concentrated. Purification of crude product by silica-gel column chromatography (petroleum ether/EtOAc 9:1) afforded **20** (0.86 g, 80%) as a colorless liquid. $[\alpha]_D^{25} = +11.34$ ($c = 0.46$ in $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 5.74$–5.96 (m, 1H), 5.15 (d, $J = 6.1$ Hz, 1H), 5.07 (d, $J = 2.9$ Hz, 1H), 4.13–4.22 (m, 1H), 3.94–4.07 (m, 1H), 3.77–3.84 (m, 1H), 2.26 (ddd, $J =$ 18.0, 12.3, 7.0 Hz, 2H), 1.70–1.74 (m, 2H), 1.62–1.68 (m, 2H), 1.16 (d, $J =$

6.1 Hz, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.12 (s, 6H), 0.07 ppm (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 134.9, 117.2, 69.1, 67.7, 65.7, 45.7, 42.4, 40.0, 25.8, 24.4, 17.9, −4.1, −4.9 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3469, 3079, 3006, 2956, 2931, 2887, 1642, 1472, 1463, 1376, 1257, 1216, 1064, 918, 837, 759, 667 cm^{-1}; elemental analysis (%) calcd for $C_{21}H_{46}O_3Si_2$ (402.76): C 62.62, H 11.51, Si 13.95; found: C 62.81, H 11.74, Si 13.85.

Acrylic acid 1-[2,4-bis-(*tert*-butyldimethylsilanyloxy)pentyl]but-3-enyl ester (21): Acryloyl chloride (0.27 g, 0.24 mL, 3.0 mmol) was added dropwise under argon to a solution of **20** (1.2 g, 3.0 mmol) and triethylamine (1.2 g, 1.7 mL, 11.9 mmol) in dry CH_2Cl_2 (15 mL) at 0°C, and the mixture was stirred for 5 h at room temperature. After this time, the mixture was filtered through a pad of Celite and then poured into water. The resulting organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3×40 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and then concentrated. Purification of the crude product by silica-gel column chromatography (petroleum ether/EtOAc 19:1) afforded the acrylate **21** (1.12 g, 82%) as a colorless oil. $[\alpha]_D^{25}$ = +25.84 (c = 0.98 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.43 (dd, J = 17.3, 1.8 Hz, 1H), 6.11 (dd, J = 17.1, 10.2 Hz, 1H), 5.82 (dd, J = 10.3, 2.1 Hz, 1H), 5.70–5.75 (m, 1H), 5.09–5.12 (m, 2H), 5.04–5.06 (m,1H), 3.79–3.96 (m, 2H), 2.29–2.43 (m, 2H), 1.69–1.83 (m, 2H), 1.41–1.58 (m, 2H), 1.15 (d, J = 6.1 Hz, 3H), 0.89 (s, 18H), 0.06 (s, 6H), 0.04 ppm (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.8, 133.4, 130.3, 128.9, 117.9, 70.9, 66.1, 65.5, 48.5, 40.8, 39.0, 25.9, 24.4, 17.9, −4.0, −4.1 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3081, 2952, 2932, 2896, 2850, 2710, 2401, 1719, 1639, 1619, 1472, 1463, 1438, 1407, 1377, 1362, 1297, 1275, 1215, 1199, 1067, 1048, 967, 919, 759 cm^{-1}; elemental analysis (%) calcd for $C_{24}H_{48}O_4Si_2$ (456.81): C 63.10, H 10.59, Si 12.30; found: C 63.18, H 10.64, Si 12.15.

6-[2,4-Bis-(*tert*-butyldimethylsilanyloxy)pentyl]-5,6-dihydropyran-2-one (22): 1st generation Grubbs catalyst **6a** (0.073 g, 0.09 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a refluxing solution of **21** (0.40 g, 0.9 mmol) and Ti(iPrO)$_4$ (7 mg, 0.03 mmol) in dry CH_2Cl_2 (100 mL). The mixture was refluxed for 6 h, after which time all the starting material had been consumed. Removal of the solvent under reduced pressure, followed by purification of the crude product by silica-gel column chromatography (petroleum ether/EtOAc 8:2) afforded **22** (0.315 g, 84%) as a colorless oil. $[\alpha]_D^{25}$ = +42.69 (c = 0.82 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.88 (ddd, J = 9.6, 5.8, 2.1 Hz, 1H), 6.05 (ddd, J = 9.6, 1.9, 1.6 Hz, 1H), 4.54–4.65 (m, 1H), 4.09–4.22 (m, 1H), 3.87–4.02 (m, 1H), 2.29–2.39 (m, 2H), 1.95–2.07 (m, 1H), 1.74–1.78 (m, 1H), 1.60–1.66 (m, 2H), 1.17 (d, J = 6.1 Hz, 3H), 0.88 (s, 18H), 0.09 (s, 6H), 0.07 ppm (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 163.9, 144.8, 121.5, 74.4, 66.2, 65.3, 48.2, 42.7, 30.1, 25.8, 24.3, 17.9, −4.2, −4.3 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3020, 2955, 2930, 2887, 2857, 1721, 1472, 1463, 1423, 1387, 1361, 1255, 1216, 1180, 1061, 975, 836 cm-^{1}; elemental analysis (%) calcd for $C_{22}H_{44}O_4Si_2$ (428.75): C 61.63, H 10.34, Si 13.10; found: C 61.58, H 10.46, Si 13.05.

Cryptocarya diacetate (2): TBAF (2.1 mL, 1 M solution in THF) was added dropwise to a solution of the lactone **22** (0.30 g, 0.7 mmol) and benzoic acid (0.26 g, 2.1 mmol) in THF (5 mL). The reaction mixture was stirred at room temperature overnight, and then concentrated and extracted with EtOAc (3×30 mL). Evaporation of the solvent produced the crude diol, which was directly used for the next step.

Ac_2O (1.15 g, 1.06 mL, 11.3 mmol), pyridine (5 mL), and a catalytic amount of DMAP were added to a solution of the crude diol in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 2 h, after which time saturated sodium bicarbonate (1 mL) was added. The resulting layers were separated and the aqueous layer was extracted with diethyl ether (3×25 mL). The organic layers were combined and dried over anhydrous Na_2SO_4. Evaporation of the solvent, followed by the purification of the crude product by silica-gel column chromatography (petroleum ether/EtOAc 4:1) afforded cryptocarya diacetate (**2**) (0.149 g, 75% from both the steps) as a colorless oil. $[\alpha]_D^{25}$ = +53.6 (c = 1 in $CHCl_3$) (lit. [4] $[\alpha]_D^{22}$ = +55.8 (c = 1.06 in $CHCl_3$)); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.89 (ddd, J = 9.7, 6.1, 2.3 Hz, 1H), 6.03 (ddd, J = 9.7, 2.1, 1.3 Hz, 1H), 5.08–5.24 (m, 1H), 4.90–5.04 (m, 1H), 4.43–4.55 (m, 1H), 2.49 (ddd, J = 18, 6.5, 5 Hz, 1H), 2.30–2.38 (m, 1H), 2.19 (ddd, J = 14.7, 8.6, 6.5 Hz, 1H), 2.05 (s, 3H), 2.02 (s, 3H), 2.0–1.95 (m, 1H), 1.93–1.83 (m, 2H), 1.27 ppm (d, J = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.5, 170.3, 163.6, 144.5, 121.3, 74.9, 67.8, 67.6, 40.4, 39.5, 29.2, 21.2, 21.1, 20.0 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3010, 2962, 1732, 1438, 1365, 1233, 1167, 1118, 1032, 984 cm^{-1}.

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