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Syntheses of (−)-Cryptocaryolone and (−)-Cryptocaryolone Diacetate via a Diastereoselective Oxy-Michael Addition and Oxocarbenium Allylation

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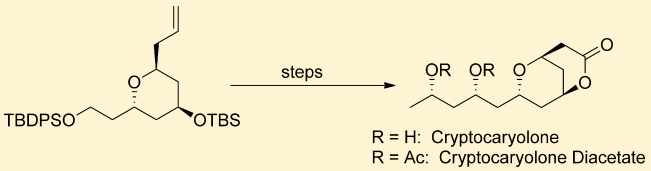
Supporting Information

ABSTRACT: The total syntheses of both (−)-cryptocaryolone and (−)-cryptocaryolone diacetate is presented herein. The usage of a diastereoselective oxy-Michael addition/benzylidene acetal formation coupled with a selective axial oxocarbenium allylation allowed for the preparation of the α-*C*-glycoside moiety present in the bicyclic bridged structure. In addition, the *syn*-1,3-diol of the linear portion was installed via a Wacker oxidation followed by a subsequent directed reduction of the appropriate homoallylic alcohol precursor.



INTRODUCTION

Natural product extracts borne from terrestrial plant sources have been the source of discovery for numerous biologically active compounds for many years within a diverse array of therapeutic areas.[1] Along this line, cryptocaryolone (**1**) and cryptocaryolone diacetate (**2**) are two dioxabicyclo[3.3.1]-nonan-3-one derivatives[2] that were obtained from the bark extract of *Cryptocarya latifolia*, as shown in Figure 1.[3] Isolation

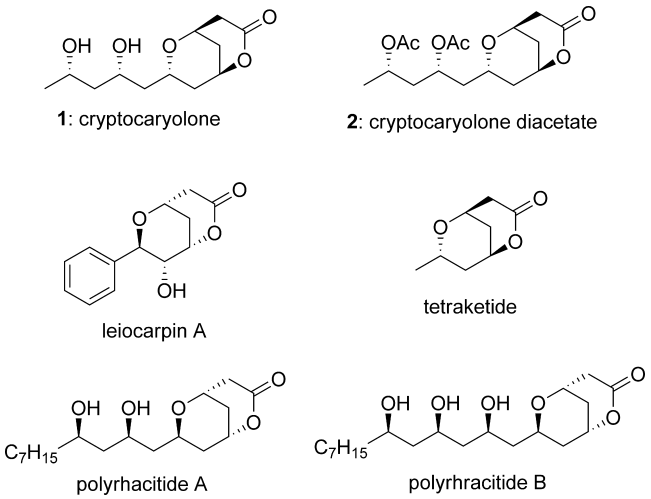


Figure 1. Structures of selected natural products containing a bridged bicyclic lactone core.

and structural determination of these molecules was disclosed by Horn in 1995 in which the relative and absolute stereochemistry was not determined after an inquisition to determine the molecular source of the bark extract's biological activity.[3] Their studies revealed that the extract, which has been used for the treatment of headaches, morning sickness, cancer, pulmonary diseases, and a variety of other bacterial and fungal infections, comprised both **1** and **2**, in addition to a few other structurally related compounds.

Not surprisingly, there has been modest interest with respect to the synthesis of both **1** and **2** (and other related bicyclic lactones) due to their somewhat unusual core.[4−7] Within this paper, we will describe a distinct synthetic approach to the preparation of both of these molecules via a highly diastereoselective oxy-Michael addition/benzylic acetal formation followed by an oxocarbenium allylation in order to generate the bicyclic core.

RESULTS AND DISCUSSION

Retrosynthetic Analysis of Cryptocaryolone (1) and Cryptocaryolone Diacetate (2). Most synthetic approaches to cryptocaryolone and related natural products (i.e., leiocarpin A and polyrhacitide A and B) have relied on an intramolecular oxy-Michael addition of an alcohol onto an α,β-unsaturated ester under either basic or acidic conditions for the creation of the polycyclic ester nucleus.[4−7] However, our retrosynthesis plan centered on forming the bicyclic ester core early in the synthetic sequence via an oxocarbenium allylation followed by intramolecular esterification. Thus, the late-stage installation of the *syn*-1,3-diol resident in both **1** and **2** would be accomplished via a directed reduction of the β-hydroxy ketone **3** as shown in Scheme 1. It was envisioned that the β-hydroxy ketone **3** would be obtained via a Wacker oxidation of the TES protected homoallylic alcohol precursor **4**. The usage of the Brown allylation protocol would allow for the conversion of the aldehyde generated from the oxidation of primary alcohol **5**, to furnish the homoallylic alcohol **4** with good/excellent levels of diastereoselectivity. Working further back, Yamaguchi lactoni-

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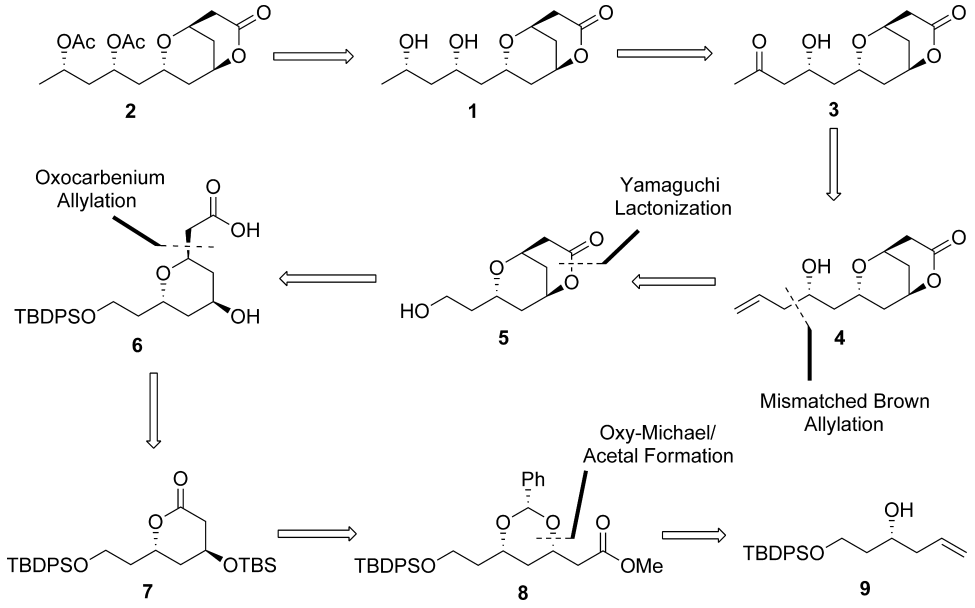
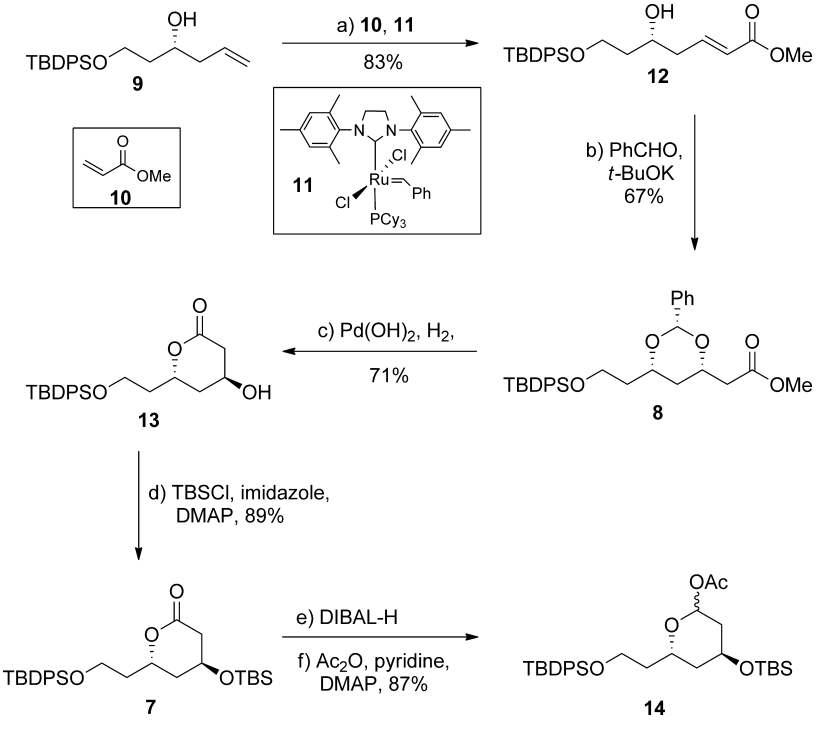
Scheme 1. Retrosynthetic Analysis of (−)-Cryptocaryolone (1) and (−)-Cryptocaryolone Diacetate (2)



Scheme 2. Synthesis of Oxocarbenium Precursor 14



zation and TBDPS deprotection would allow for the preparation of the primary alcohol **5** from the hydroxycarboxylic acid compound **6**. The acid **6** can be derived from the functionalization of the allylated α-*C*-glycoside segment by way of a bis-oxidation of the olefin moiety, which can be generated from the lactone **7** through a highly diastereoselective oxocarbenium allylation process. It was envisioned that lactone **7** would be generated from a sequential acetal deprotection/acid-catalyzed cyclization of the benzylidene acetal **8**. The lactone precursor **8** would be diastereoselectively prepared from the intramolecular oxy-Michael addition of benzaldehyde to the δ-hydroxy-(*E*)-α,β-unsaturated methyl ester, which would be generated by means of a Ru-catalyzed cross-metathesis of homoallylic alcohol **9** with methyl acrylate as reported previously by O'Doherty.[4a]

With this retrosynthetic plan in mind, our initial focus was to prepare acetate **14**, the precursor for the oxocarbenium allylation. As shown in Scheme 2, treatment of the previously reported TBDPS monoprotected homoallylic alcohol **9**[8] (prepared by an asymmetric allylboration of 3-((*tert*-butyldiphenylsilyl)oxy)propanal) with methyl acrylate (**10**) in the presence of Grubbs' second-generation catalyst (**11**) under standard olefin cross-metathesis conditions provided the δ-hydroxy-(*E*)-α,β-unsaturated methyl ester **12** in 83% yield as a single diastereomer.[4a,9,10] Following the Evans-acetal formation protocol, the δ-hydroxy enoate **12** was converted to the *syn*-

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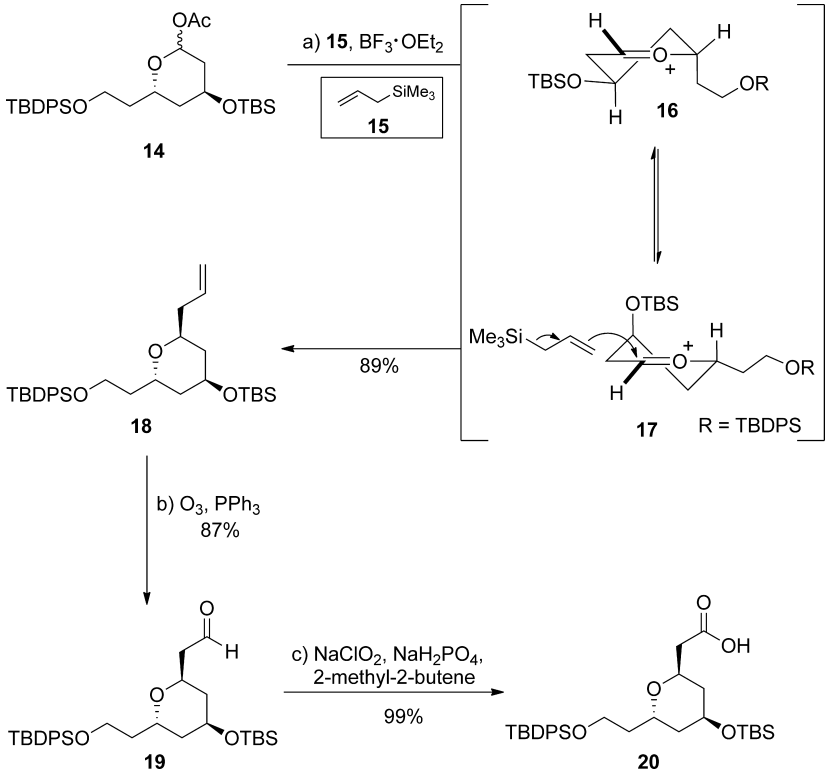
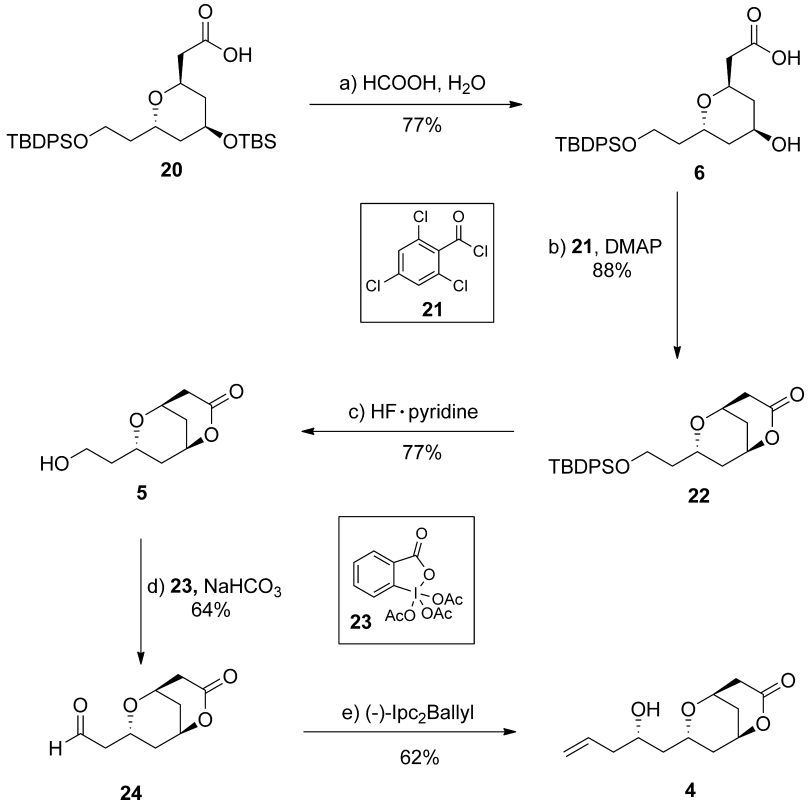
Scheme 3. Synthesis of Carboxylic Acid Intermediate 20 via an Oxocarbenium Allylation Process



Scheme 4. Synthesis of Homoallylic Alcohol 4 via Asymmetric Allylboration



benzylidene acetal **8** by addition of PhCHO and KO^{t}Bu over 2 h in 67% yield as a single diastereomer, as determined by ^{1}H NMR analysis.[11] Subsequent hydrogenolysis of **10** in the presence of H_2 and Pearlman's catalyst [$Pd(OH)_2$] at rt in HOAc followed by cyclization/transesterfication led to the formation of the hydroxy lactone **13** in 71% yield. Protection of the free hydroxyl group resident in **13** was achieved using standard silylating conditions (TBSCl and imidazole) and

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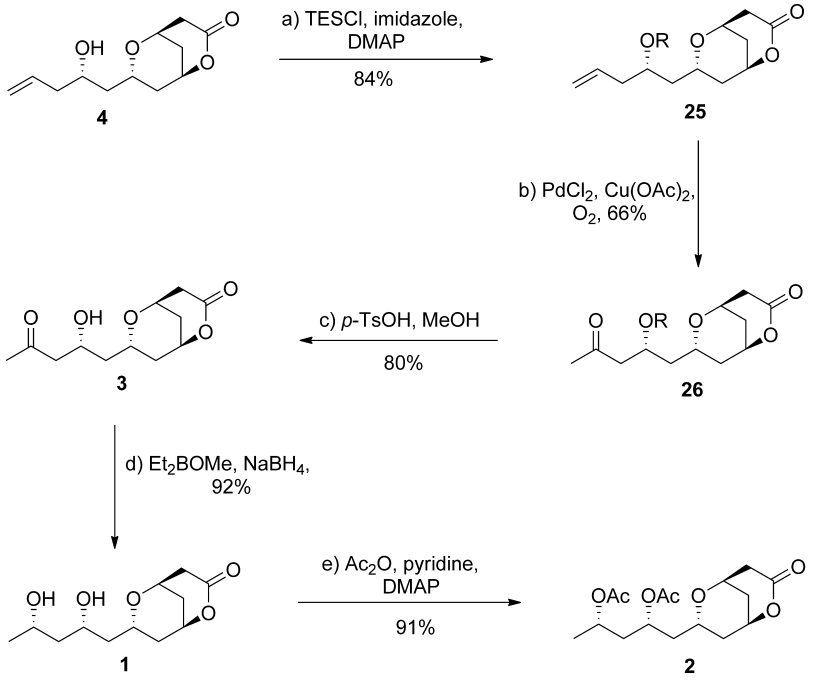
Scheme 5. Synthesis of (−)-Cryptocaryolone (1) and (−)-Cryptocaryolone Diacetate (2)



provided the TBS protected β-hydroxy lactone **7**. Partial reduction of the carbonyl moiety of **7** with DIBAL-H at −78 °C resulted in the formation of a diastereomeric mixture of lactols. Ensuing treatment of the lactol mixture (as a 4:1 ratio of epimers) in the presence of acetic anhydride and pyridine afforded intermediate **14** in 87% yield over two steps from **7**.[12]

With intermediate **14** in hand, we shifted our focus to the preparation of the α-*C*-glycoside subunit, by means of a stereoselective oxocarbenium allylation. As the result of previous synthetic endeavors, we were confident that our approach would allow for the preparation of the intended target with high levels of stereoselectivity in good to excellent yields.[13] With this in mind, the treatment of acetate **14** with $BF_3{\cdot}OEt_2$ at −78 °C presumably generated the oxocarbenium cation, which existed as two possible reactive conformers, **16** and **17**, as shown in Scheme 3. Conformer **16** maintains the C5 alkyl substituent in the pseudo axial position and the C3 silyloxy substituent in the equatorial position. Conversely, conformer **17** places the C5 substituent in the pseudo equatorial position and the C3 silyloxy substituent in the axial position.

On the basis of our previous observations and in accordance with Woerpel's reports, we predicted that **17** would be the "matched" conformer, and axial nucleophilic addition of allyltrimethylsilane (**15**) would stereoselectively furnish **18** via a chairlike transition state.[14] As expected, the α-*C*-glycoside **18** was isolated with a very high dr (>20:1) as a single stereoisomer in 89% yield. Ensuing ozonolysis of the olefin moiety resident in **18** followed by a reductive quench with PPh_3 provided aldehyde **19** in 87% yield. Subsequently, further oxidation of aldehyde **19** was accomplished by utilizing the Lindgren−Kraus−Pinnick protocol to afford the carboxylic acid **20** in virtually quantitative yield (99%).[15]

With carboxylic acid **20** in hand, our next challenge was to complete the bicyclic bridged structure and prepare the homoallylic alcohol precursor required for the preparation of the 1,3-*syn* diol moiety as delineated in Scheme 4. Selective removal of the TBS protecting group resident in carboxylic acid **20** was accomplished using a THF/HCOOH/H_2O (6:3:1) mixture at 0 °C to provide the hydroxy acid **6** in 77% yield. Ensuing exposure of **6** to standard Yamaguchi lactonization conditions afforded the TBDPS protected 2,6-dioxabicyclo[3.3.1]nonan-3-one compound **22** in 88% yield.[16] Cleavage of the TBDPS ether presented a bit of a challenge, due to the delicate nature of the bicyclic bridged moiety.

However, the use of a HF·pyridine buffered with additional pyridine at 0 °C readily allowed for desilylation and provided the primary alcohol **5** in 77% yield. Subsequent oxidation of the primary alcohol moiety of **5** was achieved by using $NaHCO_3$ buffered Dess−Martin periodinane (**23**) and afforded aldehyde **24** in 64% yield.[17] A mismatched asymmetric allylboration of aldehyde **24** with Brown's (−)-Ipc_2Ballyl reagent followed by basic oxidation (NaOH and H_2O_2) furnished homoallylic alcohol **4** in a modest 62% yield with a 6:1 dr (as determined by ^1H NMR of the crude reaction mixture) for the desired stereoisomer.[18]

In order to accomplish the syntheses of both **1** and **2**, homoallylic alcohol **4** must be converted to TES protected counterpart **25** followed by Wacker oxidation of the terminal alkene and final directed *syn*-reduction to provide the diol stereochemistry as shown in Scheme 5.

Thus, the treatment of **4** with TESCl, DMAP, and imidazole provided the silyl ether in 84% yield and set the stage for the oxidation of the terminal alkene resident in **25**. Ensuing exposure of **25** to the standard Wacker oxidation procedure as described by Smith and co-workers [$PdCl_2$ and $Cu(OAc)_2$ under an atmosphere of O_2] converted the olefin moiety into methyl ketone **26** in 66% yield.[19] Subsequent desilylation of **26** using *p*-TsOH in a 1:1 MeOH/CH_2Cl_2 solution at 0 °C afforded the β-hydroxy methyl ketone **3** in 80% yield. The utilization of a chelation-controlled reduction by means of Et_2BOMe and $NaBH_4$ allowed for the conversion of the β-hydroxy ketone moiety of **3** to the 1,3-*syn* diol and thus the completion of **1** in 92% yield and a dr of >20:1 as determined by ^1H NMR.[20] Finally, treatment of **1** with Ac_2O and pyridine

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afforded **2** in 91% yield. The spectral data (^{1}H NMR, 500 MHz; ^{13}C NMR, 125 MHz), optical rotations ($[\alpha]^{23}_D$ −21.1, *c* 0.52, CH_2Cl_2 for **1** and $[\alpha]^{23}_D$ −32.7, *c* 0.31, CH_2Cl_2 for **2**) and HRMS data of synthetic **1** and **2** were in agreement with the natural samples.[3,4] It is worth mentioning that our rotational data is very similar to She's values (in CH_2Cl_2);[4c] however, they are lower than that of the disclosure paper (−128 and −145 for **1** and **2**, in $CHCl_3$).[3]

CONCLUSION

In summary, both (−)-cryptocaryolone and (−)-cryptocaryolone diacetate were prepared in an efficient diastereoselective manner using an oxy-Michael addition followed by a stereoselective oxocarbenium allylation process. The late stage installation of the *syn*-1,3-polyol moieties resident in **1** and **2** also allow for the synthesis of additional natural products that possess the dioxabicyclo[3.3.1]nonan-3-one structure, such as *ent*- polyrhacitide A and B from a common intermediate.

EXPERIMENTAL SECTION

General Procedure. All of the reactions were performed under an inert atmosphere of Ar in flame-dried glassware. All starting materials and solvents were commercially available and were used without further purification. Deuterated chloroform ($CDCl_3$) was stored over molecular sieves (4 Å). The NMR spectra were recorded on a 500 MHz spectrometer. ^{1}H and ^{13}C NMR spectra were obtained using either $CDCl_3$ or C_6D_6 as the solvent with chloroform ($CHCl_3$, 7.26 ppm) or benzene (C_6H_6, 7.15 ppm) as the internal standard. High-resolution mass spectra were recorded on an EBE sector instrument using electron ionization (EI) at 70 eV. Column chromatography was performed using 60−200 μm silica gel. Analytical thin layer chromatography was performed on silica-coated glass plates with F-254 indicator. Visualization was accomplished by UV light (254 nm), $KMnO_4$, or ceric sulfate-PMA stain. Compound **9** has been previously reported.[8]

(*R*,*E*)-Methyl 7-((*tert*-butyldiphenylsilyl)oxy)-5-hydroxyhept-2-enoate (12). To a flame-dried round-bottom flask with a solution of **9** (2.80 g, 7.91 mmol, 1.00 equiv) in anhydrous CH_2Cl_2 (160 mL) under an atmosphere of Ar at rt was added methyl acrylate (9.27 mL, 103 mmol, 13.0 equiv) dropwise. To the resulting solution was added Grubbs' second-generation catalyst (0.335 g, 0.395 mmol, 0.05 equiv). The solution was allowed to stir for 16 h at rt. The reaction was then concentrated under reduced pressure and purified by flash chromatography (15% EtOAc/hexanes) to afford **12** as a brown viscous oil (2.70 g, 83%): TLC R_f = 0.240 in 20% EtOAc/hexanes; $[\alpha]^{23}_D$ = +6.0 (*c* 1.17, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.43 (m, 6H), 7.01 (ddd, *J* = 15.8, 7.6, 7.3 Hz, 1H), 5.91 (ddd, *J* = 15.8, 1.6, 1.3 Hz, 1H), 4.07 (m, 1H), 3.86 (m, 2H), 3.73 (s, 3H), 3.41 (d, *J* = 2.8 Hz, 1H), 2.41 (m, 2H), 1.75 (m, 1H), 1.67 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 145.5, 135.5, 132.8, 129.9, 127.8, 123.2, 70.5, 63.2, 51.4, 40.2, 37.9, 26.8, 18.9; IR (neat) cm^{-1} 3501, 2945, 1722, 1654, 823; HRMS (EI) calcd for $C_{24}H_{32}O_4Si$ [M − C_4H_9] 355.1366, found 355.1355.

Methyl-2-((2*S*,4*S*,6*S*)-6-(2-((*tert*-butyldiphenylsilyl)oxy)-ethyl)-2-phenyl-1,3-dioxan-4-yl)acetate (8). Ester **12** (4.39 g, 10.7 mmol, 1.00 equiv) was dissolved in anhydrous THF (110 mL) under Ar and cooled to 0 °C. To this stirred solution were added benzaldehyde (1.20 mL, 11.7 mmol, 1.10 equiv) and KO-*t*-Bu (0.119 g, 1.06 mmol, 0.10 equiv) sequentially. This addition was repeated four times for benzaldehyde and eight times for KO-*t*-Bu in 15 min intervals. The reaction was allowed to warm to rt and then quenched with pH 7 buffer solution (60 mL). The layers were separated, and extraction of the aqueous layer was done with Et_2O (3 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (8% EtOAc/hexanes) to afford **8** as a yellow viscous oil (3.70 g, 67%): TLC R_f = 0.38 in 10% EtOAc/hexanes; $[\alpha]^{23}_D$ = −82.0 (*c* 0.92, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.36 (m, 11H), 5.54 (s, 1H), 4.32 (m, 1H), 4.14 (m, 1H), 3.92 (m, 1H), 3.77 (m, 1H), 3.71 (s, 3H), 2.73 (dd, *J* = 15.5, 7.3 Hz, 1H), 2.51 (dd, *J* = 15.5, 6.0 Hz, 1H), 1.84 (m, 2H), 1.71 (dt, *J* = 12.9, 2.5 Hz, 1H), 1.46 (dt, *J* = 12.9, 11.4 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 138.5, 135.5, 133.8, 133.7, 129.6, 129.6, 128.5, 128.1, 127.6, 127.6, 126.1, 100.5, 73.3, 73.2, 59.5, 51.7, 40.8, 38.7, 36.7, 31.6, 26.9, 23.1; IR (neat) cm^{-1} 2958, 2859, 1741, 1475, 741, 703; HRMS (EI) calcd for $C_{31}H_{38}O_5Si$ [M − C_4H_9] 461.1784, found 461.1784.

(4*S*,6*S*)-6-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-4-hydroxytetrahydro-2*H*-pyran-2-one (13). To a solution of **8** (3.50 g, 6.75 mmol, 1.00 equiv) in acetic acid (100 mL) at rt was added $Pd(OH)_2$ (3.5 g). The mixture was then subjected to an atmosphere of H_2 and allowed to stir for 16 h. The catalyst was filtered off through Celite, and the filtrate was concentrated to leave a crude residue. The residue was purified by flash chromatography (38% EtOAc/hexanes) to afford **13** as a white solid (1.91 g, 71%): TLC R_f = 0.43 in 50% EtOAc/hexanes; $[\alpha]^{23}_D$ = −84.2 (*c* 0.57, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.40 (m, 6H), 4.93 (m, 1H), 4.32 (m, 1H), 3.88 (m, 1H), 3.81 (m, 1H), 2.69 (dd, *J* = 17.7, 5.0 Hz, 1H), 2.59 (ddd, *J* = 17.7, 3.8, 1.6 Hz, 1H), 2.31 (br s, 1H), 1.96 (m, 2H), 1.84 (m, 1H), 1.75 (ddd, J = 14.5, 11.4, 3.5 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 135.4, 135.4, 133.5, 133.4, 129.6, 127.6, 73.2, 62.3, 59.5, 38.5, 38.2, 35.9, 26.8, 19.1; IR (neat) cm^{-1} 3398, 2859, 1706, 1252, 950, 826; HRMS (EI) calcd for $C_{23}H_{30}O_4Si$ [M − C_4H_9] 341.1209, found 341.1208.

(4*S*,6*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-6-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)tetrahydro-2*H*-pyran-2-one (7). To a stirred solution of **13** (3.83 g, 9.62 mmol, 1.00 equiv) in anhydrous DMF (24.0 mL) under Ar at 0 °C were added imidazole (1.96 g, 28.9 mmol, 3.00 equiv), DMAP (0.118 g, 0.962 mmol, 0.10 equiv), and *tert*-butyldimethylsilyl chloride (1.74 g, 11.5 mmol, 1.2 equiv) sequentially. The mixture was allowed to warm to rt and stir overnight. The mixture was then diluted with water and extracted by EtOAc. The aqueous layer was washed with EtOAc (3 × 25 mL). The combined organic layers were washed with water (3 × 20 mL), then dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (10% EtOAc/hexanes) to afford **7** as a yellow, viscous oil (4.45 g, 89%): TLC R_f = 0.37 in 20% EtOAc/hexanes; $[\alpha]^{23}_D$ = +13.3 (*c* 0.60, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.41 (m, 6H), 5.05 (m, 1H), 4.33 (m, 1H), 3.94 (m, 1H), 3.81 (m, 1H), 2.60 (m, 2H), 1.93 (m, 2H), 1.85 (m, 1H), 1.73 (ddd, *J* = 13.9, 11.7, 2.5 Hz, 1H), 1.08 (s, 9H), 0.91 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 135.4, 135.3, 133.5, 133.3, 129.5, 129.5, 127.6, 127.5, 72.9, 63.5, 59.4, 39.2, 38.4, 36.7, 26.7, 25.6, 19.0, 17.8, −5.0, −4.9; IR (neat) cm^{-1} 2932, 2857, 1738, 1472, 1253, 1087, 835; HRMS (EI) calcd for $C_{29}H_{44}O_4Si_2$ [M − C_4H_9] 455.2074, found 455.2091.

(4*S*,6*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-6-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)tetrahydro-2*H*-pyran-2-yl Acetate (14). To a solution of **7** (4.45 g, 8.69 mmol, 1.00 equiv) in anhydrous CH_2Cl_2 (54.0 mL), under an atmosphere of Ar, was added DIBAL-H (1.0 M in toluene, 10.9 mL, 1.25 equiv) at −78 °C. The reaction was stirred until there was no sign of starting material on TLC (4 h). The reaction was then quenched with an aqueous solution of saturated $NaHCO_3$, diluted with CH_2Cl_2, and warmed to rt with magnetic stirring. After the solution was washed with aqueous NH_4Cl, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was evaporated to yield the crude lactol. The product was dissolved in anhydrous CH_2Cl_2 (54.0 mL). To this solution were added pyridine (1.05 mL, 13.0 mmol, 1.50 equiv), Ac_2O (1.44 mL, 15.2 mmol, 1.75 equiv), and DMAP (0.106 g, 0.869 mmol, 0.100 equiv). The mixture was stirred at rt for 16 h, at which time the reaction was quenched with aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash chromatography (5% EtOAc/hexanes) to afford **14** as a colorless oil (4.21 g, 87%): TLC R_f = 0.57 in

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10% EtOAc/hexanes; $[\alpha]^{23}_{D}$ = +1.7 (*c* 0.58, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.39 (m, 6H), 6.07 (dd, *J* = 9.8, 2.2 Hz, 1H), 4.30 (m, 2H), 3.82 (m, 1H), 3.72 (m, 1H), 2.09 (s, 3H), 1.85 (m, 1H), 1.80 (m, 1H), 1.70 (m, 1H), 1.61 (m, 2H), 1.46 (m, 1H), 1.04 (s, 9H), 0.91 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 135.6, 135.5, 134.0, 133.8, 129.5, 127.6, 92.1, 68.6, 65.6, 60.0, 38.7, 38.6, 38.0, 26.8, 25.7, 21.2, 19.2, 17.9, −5.0, −4.9; IR (neat) cm^{-1} 2954, 2857, 1745, 1428, 1231, 1039, 773; HRMS (EI) calcd for $C_{31}H_{48}O_5Si_2$ [M − C_4H_9] 499.2336, found 499.2346.

(2-((2*S*,4*R*,6*S*)-6-Allyl-4-((*tert*-butyldimethylsilyl)oxy)-tetrahydro-2*H*-pyran-2-yl)ethoxy)(*tert*-butyl)diphenylsilane (18). Acetate **14** (4.21 g, 7.57 mmol, 1.00 equiv) and allyltrimethylsilane (3.02 mL, 18.9 mmol, 2.50 equiv) were dissolved in anhydrous CH_2Cl_2 (76 mL) under an atmosphere of Ar. Upon cooling to −78 °C, $BF_3{\cdot}OEt_2$ (1.89 mL, 15.1 mmol, 2.00 equiv) was added dropwise via syringe. Upon completion of the reaction, as monitored by TLC (0.5 h), the light yellow solution was quenched with a saturated solution of $NaHCO_3$ at −78 °C, and the reaction was allowed to warm to rt. The mixture was then extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were washed with brine. After drying with anhydrous Na_2SO_4 and evaporation of solvent, the crude product was purified by flash chromatography (5% EtOAc/hexanes) to afford **18** as a colorless oil (3.64 g, 89%): TLC R_f = 0.68 in 10% EtOAc/hexanes; $[\alpha]^{23}_{D}$ = −14.0 (*c* 0.57, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (m, 4H), 7.42 (m, 6H), 5.78 (m, 1H), 5.06 (d, *J* = 17.3 Hz, 1H), 4.99 (d, *J* = 10.1 Hz, 1H), 4.30 (m, 1H), 3.98 (m, 1H), 3.81 (m, 1H), 3.73 (m, 1H), 3.54 (m, 1H), 2.42 (m, 1H), 2.23 (m, 1H), 1.96 (m, 1H), 1.81 (ddd, *J* = 12.9, 3.8, 3.5 Hz, 1H), 1.67 (dd, *J* = 6.6, 4.7 Hz, 2H), 1.32 (m, 2H), 1.09 (s, 9H), 0.93 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6, 135.5, 135.3, 133.9, 133.7, 129.5, 127.6, 116.5, 69.1, 67.7, 65.3, 60.8, 39.9, 39.8, 38.9, 35.2, 26.8, 25.8, 19.1, 18.1, −4.6, −4.7; IR (neat) cm^{-1} 2954, 2854, 1645, 1428, 1109, 700; HRMS (EI) calcd for $C_{32}H_{50}O_3Si_2$ [M − C_4H_9] 481.2594, found 481.2601.

2-((2*R*,4*S*,6*S*)-4-((*tert*-Butyldimethylsilyl)oxy-6-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)tetrahydro-2*H*-pyran-2-yl)-acetaldehyde (19). A solution of **18** (3.64 g, 6.76 mmol, 1.00 equiv) dissolved in CH_2Cl_2 (68.0 mL) was cooled to −78 °C, and O_3 was bubbled through the solution until the starting material was consumed as indicated by TLC analysis (0.5 h). The solution was then purged with O_2, and the reaction was quenched via portionwise addition of PPh_3 (5.32 g, 20.3 mmol, 3.0 equiv) and stirred for 4 h. The resulting mixture was concentrated *in vacuo* to yield the crude aldehyde as a yellow solid. Purification by flash chromatography (5% EtOAc/hexanes) afforded **19** as a white solid (3.19 g, 87%): TLC R_f = 0.57 in 15% EtOAc/hexanes; $[\alpha]^{23}_{D}$ = −4.8 (*c* 0.62, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.70 (m, 4H), 7.41 (m, 6H), 4.31 (m, 1H), 4.16 (m, 1H), 4.05 (m, 1H), 3.80 (m, 1H), 3.72 (m, 1H), 2.84 (ddd, *J* = 16.7, 8.2, 2.2 Hz, 1H), 2.60 (ddd, J = 16.7, 5.0, 1.6 Hz, 1H), 1.89 (m, 2H), 1.67 (m, 3H), 1.43 (m, 1H), 1.09 (s, 9H), 0.93 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.2, 135.5, 133.8, 133.6, 129.5, 127.6, 127.5, 66.4, 65.3, 64.8, 60.4, 48.7, 38.9, 38.6, 35.8, 26.8, 25.8, 19.1, 17.9, −4.8; IR (neat) cm^{-1} 2950, 2857, 1726, 1105, 1035, 869; HRMS (EI) calcd for $C_{31}H_{48}O_4Si_2$ [M − C_4H_9] 483.2387, found 483.2403.

2-((2*R*,4*S*,6*S*)-4-((*tert*-Butyldimethylsilyl)oxy-6-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)tetrahydro-2*H*-pyran-2-yl)acetic Acid (20). To a solution of aldehyde **19** (3.19 g, 5.89 mmol, 1.00 equiv) in THF (59.0 mL) and *t*-BuOH (59.0 mL) was added 2-methyl-2-butene (6.23 mL, 58.9 mmol, 10.0 equiv) under vigorous stirring. $NaClO_2$ (2.66 g, 29.5 mmol, 5.00 equiv) and NaH_2PO_4 (3.53 g, 29.5 mmol, 5.00 equiv) were dissolved in water (19.6 mL), and the aqueous solution was added to the mixture, which was stirred at rt for 3.5 h. Once complete by TLC analysis, the mixture was diluted with water and extracted with CH_2Cl_2, followed by evaporation of the organic layer *in vacuo* to afford the acid **20** without further purification. (3.25 g, 99%): TLC R_f = 0.31 in 15% EtOAc/hexanes; $[\alpha]^{23}_{D}$ = −5.2 (*c* 0.95, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.39 (m, 6H), 4.34 (m, 1H), 4.02 (m, 2H), 3.77 (m, 1H), 3.69 (m, 1H), 2.79 (dd, *J* = 15.8, 8.5 Hz, 1H), 2.56 (dd, *J* = 15.8, 4.8 Hz, 1H), 1.87 (m, 2H), 1.65 (m, 2H), 1.46 (m, 2H), 1.04 (s, 9H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 135.6, 135.5, 133.9, 133.7, 129.6, 127.6, 67.2, 66.6, 64.6, 60.4, 39.7, 38.8, 38.5, 35.7, 26.9, 25.8, 19.2, 18.0, −4.7; IR (neat) cm^{-1} 3250, 2957, 2890, 1712, 1468, 1257, 910; HRMS (EI) calcd for $C_{31}H_{48}O_5Si_2$ [M − C_4H_9] 499.2336, found 499.2328.

2-((2*R*,4*S*,6*S*)-6-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-4-hydroxytetrahydro-2*H*-pyran-2-yl)acetic Acid (6). A solution of acid **20** (3.25 g, 5.83 mmol, 1.00 equiv) in 512 mL of a mixture of THF/HCOOH/H_2O (6:3:1) was stirred at 0 °C for 3 h. The mixture was neutralized with a saturated solution of $NaHCO_3$ (400 mL) and partitioned between 200 mL of EtOAc and 200 mL of brine. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (48% EtOAc/2% AcOH/50% hexanes) afforded **6** as a colorless viscous oil (2.01 g, 77%): TLC R_f = 0.39 in 48% EtOAc/2% AcOH/50% hexanes; $[\alpha]^{23}_{D}$ = −23.1 (*c* 0.74, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (m, 4H), 7.42 (m, 6H), 4.38 (br s, 1H), 3.99 (m, 2H), 3.83 (m, 1H), 3.76 (m, 1H), 2.63 (dd, *J* = 15.8, 7.6 Hz, 1H), 2.51 (dd, *J* = 15.8, 5.7 Hz, 1H), 2.00 (m, 2H), 1.84 (br d, *J* = 12.6 Hz, 1H), 1.69 (m, 2H), 1.33 (m, 1H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 135.4, 135.3, 133.7, 133.6, 129.5, 129.4, 127.5, 127.4, 68.9, 65.4, 64.0, 60.3, 40.4, 39.5, 37.4, 34.2, 26.7, 19.0; IR (neat) cm^{-1} 3432, 2854, 1723, 1429, 933, 822, 747; HRMS (EI) calcd for $C_{25}H_{34}O_5Si$ [M − C_4H_9 − H_2O] 367.1366, found 367.1371.

(1*S*,5*R*,7*S*)-7-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-2,6-dioxabicyclo[3.3.1]nonan-3-one (22). To a solution of hydroxyacid **6** (0.500 g, 1.13 mmol, 1.00 equiv) in THF (23 mL), under an atmosphere of Ar, cooled to 0 °C were added Et_3N (0.954 mL, 6.85 mmol, 6.06 equiv) and 2,4,6-trichlorobenzoyl chloride (0.689 mL, 4.41 mmol, 3.90 equiv). After being stirred at rt for 4 h, the reaction mixture was diluted with toluene (28.0 mL). This mixture was then added dropwise, over 6.5 h, into a solution of DMAP (4.14 g, 33.9 mmol, 30.0 equiv) in toluene (226 mL) at 100 °C and allowed to stir overnight. The reaction was then cooled to rt and washed successively with 0.5 M HCl solution (100 mL), saturated aqueous $NaHCO_3$ solution (100 mL), and then brine (100 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated under vacuum, and then purified by flash chromatography (30% EtOAc/hexanes) to afford **22** as a colorless viscous oil (0.420 g, 88%): TLC R_f = 0.37 in 30% EtOAc/hexanes; $[\alpha]^{23}_{D}$ = −13.5 (*c* 0.41, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.38 (m, 6H), 4.80 (bs, 1H), 4.26 (bs, 1H), 4.05 (m, 1H), 3.82 (m, 1H), 3.74 (m, 1H), 2.79 (bd, *J* = 19.2 Hz, 1H), 2.71 (dd, *J* = 19.2, 5.0 Hz, 1H), 1.99 (bd, *J* = 11.0 Hz, 1H), 1.91 (bd, *J* = 13.9 Hz, 1H), 1.84 (bd, *J* = 13.6 Hz, 1H), 1.74 (m, 2H), 1.54 (ddd, J = 13.6, 11.7, 2.2 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 135.2, 133.5, 129.3, 127.4, 72.7, 65.6, 62.2, 59.5, 38.4, 36.8, 36.2, 29.5, 26.6, 18.9; IR (neat) cm^{-1} 3070, 2926, 2858, 1734, 1472, 1242, 1088, 703; HRMS (EI) calcd for $C_{25}H_{32}O_4Si$ [M − C_4H_9] 367.1362, found 367.1364.

(1*S*,5*R*,7*S*)-7-(2-Hydroxyethyl)-2,6-dioxabicyclo[3.3.1]nonan-3-one (5). To a stirred solution of **22** (0.533 g, 1.26 mmol, 1.00 equiv) in THF (13.0 mL) at 0 °C in a polyethylene bottle was added HF·pyridine stock solution (HF·Py/Py/THF (1:2:5)) (4.76 mL). The resulting mixture was stirred at 0 °C for 40 min and then allowed to warm to rt and stirred for an additional 4 h. The reaction was then quenched by slow addition of a saturated solution of $NaHCO_3$, and the resulting mixture was stirred for 10 min at rt. The mixture was then diluted with $CHCl_3$, and the layers were separated. The aqueous layer was extracted by $CHCl_3$ (3 × 15), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (5% MeOH/CH_2Cl_2) to afford **5** as a colorless oil (0.180 g, 77%); TLC R_f = 0.25 in 6% MeOH/CH_2Cl_2; $[\alpha]^{23}_{D}$ = −37.5 (*c* 1.65, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.88 (br s, 1H), 4.37 (br s, 1H), 3.99 (m, 1H), 3.74 (t, *J* = 5.4 Hz, 2H), 2.89 (bd, *J* = 19.2 Hz, 1H), 2.78 (dd, *J* = 19.2, 5.4 Hz, 1H), 2.43 (bs, 1H), 2.02 (m, 2H), 1.93 (m, 1H), 1.75 (m, 2H), 1.65 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 72.7, 65.9, 65.5, 60.3, 37.7, 36.9, 36.4, 29.6; IR (neat) cm^{-1} 3410, 2954, 1719, 1084, 780; HRMS (EI) calcd for $C_9H_{14}O_4$ [M] 186.0892, found 186.0894, calcd for $C_9H_{14}O_4$ [M − H_2O] 168.0786, found 168.0785.

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2-((1*R*,3*R*,5*S*)-7-Oxo-2,6-dioxabicyclo[3.3.1]nonan-3-yl)-acetaldehyde (24). To a solution of alcohol **5** (0.213 g, 1.14 mmol, 1.00 equiv) in CH_2Cl_2 (143 mL) at rt was added $NaHCO_3$ (0.480 g, 5.72 mmol, 5.00 equiv) followed by DMP (0.581 g, 1.37 mmol, 1.20 equiv). The resulting mixture was stirred for 2 h before being quenched with $NaHCO_3$ (70 mL, satd aq) and $Na_2S_2O_3$ (70 mL, satd aq). The layers were separated, the aqueous layer was extracted with $CHCl_3$ (3 × 100 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (65% EtOAc/hexanes) was used to purify aldehyde **24** as a colorless oil (0.134 g, 64%); TLC R_f = 0.30 in 80% EtOAc/hexanes; $[\alpha]^{23}_D$ = −1.6 (*c* 6.70, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.69 (dd, *J* = 2.8, 1.6 Hz, 1H), 4.87 (m, 1H), 4.31 (m, 2H), 2.85 (d, *J* = 19.2 Hz, 1H), 2.76 (dd, *J* = 19.2, 5.4 Hz, 1H), 2.56 (ddd, *J* = 16.4, 7.9, 2.8 Hz, 1H), 2.49 (ddd, *J* = 16.4, 4.1, 1.3 Hz, 1H), 2.05 (m, 1H), 1.97 (m, 1H), 1.90 (m, 1H), 1.62 (ddd, *J* = 13.9, 11.7, 2.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.7, 169.1, 72.4, 65.9, 65.7, 61.4, 48.7, 36.2, 29.2; IR (neat) cm^{-1} 2958, 1723, 1384, 1198, 1065, 734; HRMS (EI) calcd for $C_9H_{12}O_4$ [M + H] 185.0814, found 185.0817.

(1*S*,5*R*,7*S*)-7-((*S*)-2-Hydroxypent-4-en-1-yl)-2,6-dioxabicyclo-[3.3.1]nonan-3-one (4). To a flame-dried round-bottom flask under Ar, allylMgBr (1.0 M in Et_2O, 1.22 mL) was added dropwise into a solution of (−)-Ipc$_2$BOMe (0.411 g, 1.30 mmol, 1.80 equiv) in anhydrous Et_2O (3.26 mL) at 0 °C. The reaction was allowed to stir at rt for 1 h before being cooled to −78 °C. The aldehyde **24** (0.134 g, 0.730 mmol, 1.00 equiv) was dissolved in THF (1.00 mL), added dropwise into the borane solution and allowed to stir for 1 h, then allowed to warm to rt slowly over the course of 1 h. A solution of pH 7 buffer (0.575 mL) was added followed by slow addition of 30% H_2O_2 solution (1.07 mL). The mixture was refluxed at 35 °C for 3 h. After cooling to rt, the biphasic solution was separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under pressure. The crude product was purified by flash chromatography (65% EtOAc/hexanes) to afford **4** as a colorless viscous oil (0.102 g, 62%); TLC R_f = 0.16 in 70% EtOAc/hexanes; $[\alpha]^{23}_D$ = −28.1 (*c* 3.20, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (m, 1H), 5.06 (m, 2H), 4.85 (m, 1H), 4.37 (br s, 1H), 3.98 (m, 1H), 3.83 (m, 1H), 3.17 (br s, 1H), 2.86 (br d, *J* = 19.2 Hz, 1H), 2.78 (dd, *J* = 19.2, 5.4 Hz 1H), 2.19 (m, 2H), 2.00 (m, 2H), 1.92 (m, 1H), 1.61 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 134.4, 117.5, 72.5, 70.3, 66.6, 65.9, 41.9, 41.7, 37.1, 36.3, 29.4; IR (neat) cm^{-1} 3456, 2946, 1730, 1639, 1339, 1198, 1077, 913; HRMS (EI) calcd for $C_{12}H_{18}O_4$ [M + H] 227.1283 found 227.1275, calcd for $C_{12}H_{18}O_4$ [M − OH] 209.1178, found 209.1178.

(1*S*,5*R*,7*S*)-7-((*S*)-2-((Triethylsilyl)oxy)pent-4-en-1yl)-2,6-dioxabicyclo[3.3.1]nonan-3-one (25). To a solution of alcohol **4** (0.0740 g, 0.327 mmol, 1.00 equiv), imidazole (0.084 g, 1.24 mmol, 3.77 equiv, and DMAP (0.011 g, 0.093 mmol, 0.280 equiv) in DMF (1.50 mL) at 0 °C was added chlorotriethylsilane (0.103 g, 0.681 mmol, 2.10 equiv) dropwise. The reaction mixture was allowed to stir at rt for 16 h. It was then poured into a saturated $NaHCO_3$ solution (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with water (3 × 10 mL) and brine, dried over $MgSO_4$, and filtered, and the solvent was removed under pressure. The crude oil was purified by flash chromatography (25% EtOAc/hexanes) to afford **25** as a colorless oil (0.0930 g, 84%); TLC R_f = 0.21 in 20% EtOAc/hexanes; $[\alpha]^{23}_D$ = −7.7 (*c* 4.66, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (m, 1H), 5.04 (m, 2H), 4.86 (m, 1H), 4.32 (br s, 1H), 3.89 (m, 2H), 2.83 (br d, *J* = 19.2 Hz, 1H), 2.75 (dd, *J* = 19.2, 5.0 Hz, 1H), 2.23 (m, 2H), 2.00 (m, 2H), 1.89 (m, 1H), 1.73 (m, 1H), 1.55 (m, 2H), 0.94 (t, *J* = 8.2 Hz, 9H), 0.57 (q, *J* = 8.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 134.6, 117.2, 72.9, 68.2, 65.7, 62.8, 42.9, 41.7, 37.2, 36.4, 29.8, 6.8, 5.0; IR (neat) cm^{-1} 2956, 2876, 1735, 1640, 1237, 1078, 1003, 727; HRMS (EI) calcd for $C_{18}H_{32}O_4Si$ [M + H] 341.2148 found 341.2136, calcd for $C_{18}H_{32}O_4Si$ [M − C_2H_5] 311.1679, found 311.678.

(1*S*,5*R*,7*S*)-7-((*R*)-4-Oxo-2-((triethylsilyl)oxy)pentyl)-2,6-dioxabicyclo[3.3.1]nonan-3-one (26). A suspension of **25** (0.0930 g, 0.273 mmol, 1.00 equiv), $PdCl_2$ (0.00500 g,0.0273 mmol, 0.100 equiv), and $Cu(OAc)_2$ (0.0100 g, 0.0546 mmol, 0.200 equiv) in DMF/H_2O (7:1) (2.73 mL) was placed under an atmosphere of O_2 and stirred at rt for 24 h. The reaction was then diluted with Et_2O and water. The aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was then purified by flash chromatography (40% EtOAc/hexanes) to afford **26** as a colorless oil (0.064 g, 66%); TLC R_f = 0.21 in 35% EtOAc/hexanes; $[\alpha]^{23}_D$ = −18.3 (*c* 0.49, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.86 (br s, 1H), 4.31 (m, 2H), 3.88 (m, 1H), 2.83 (br d, *J* = 19.2 Hz, 1H), 2.75 (dd, *J* = 19.2, 5.0 Hz, 1H), 2.59 (d, *J* = 6.3 Hz, 2H), 2.13 (s, 3H), 1.98 (m, 2H), 1.88 (m, 1H), 1.75 (ddd, *J* = 14.2, 7.9, 4.7 Hz, 1H), 1.57 (m, 2H), 0.91 (t, *J* = 7.9 Hz, 9H), 0.55 (q, *J* = 7.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.5, 169.4, 72.9, 65.6, 65.4, 62.3, 50.6, 43.3, 37.2, 36.4, 31.5, 29.7, 6.8, 4.9; IR (neat) cm^{-1} 2952, 2878, 1731, 1074, 1007, 742; HRMS (EI) calcd for $C_{18}H_{32}O_5Si$ [M − C_2H_5] 327.1628 found 327.1633, calcd for $C_{18}H_{32}O_5Si$ [M + H] 357.2097, found 357.2104.

(1*S*,5*R*,7*S*)-7-((*R*)-2-Hydroxy-4-oxopentyl)-2,6-dioxabicyclo-[3.3.1]nonan-3-one (3). To a solution of **26** (0.0580 g, 0.163 mmol, 1.00 equiv) in a 1:1 MeOH/DCM (2.71 mL) at 0 °C was added *p*-TsOH (0.00300 g, 0.0163 mmol, 0.10 equiv). The resulting solution was stirred at 0 °C for 2 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (5 mL), and the solution was extracted with $CHCl_3$ (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*, and the residue was purified by column chromatography (2% MeOH/CH_2Cl_2) to afford **3** as a colorless oil (0.0310 g, 80%); TLC R_f = 0.11 in 80% EtOAc/hexanes; $[\alpha]^{23}_D$ = −22.2 (*c* 1.57, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.88 (m, 1H), 4.37 (m, 1H), 4.24 (m, 1H), 4.02 (m, 1H), 3.41 (d, *J* = 1.9 Hz, 1H), 2.88 (bd, *J* = 19.2 Hz, 1H), 2.79 (dd, *J* = 19.2, 5.4 Hz, 1H), 2.62 (dd, *J* = 16.7, 7.9 Hz, 1H), 2.55 (dd, *J* = 17.0, 4.4 Hz, 1H), 2.17 (s, 3H), 2.03 (m, 2H), 1.93 (m, 1H), 1.68 (m, 1H), 1.63 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.3, 169.2, 72.6, 66.4, 65.9, 65.5, 50.2, 41.8, 36.9, 36.4, 30.8, 29.5; IR (neat) cm^{-1} 3172, 2955, 2881, 1712, 1351, 1063, 785; HRMS (EI) calcd for $C_{12}H_{18}O_5$ [M − H_2O] 224.1049, found 224.1051, calcd for $C_{12}H_{18}O_5$ [M + H] 243.1232, found 243.1232.

(−)-Cryptocaryolone (1). To a solution of **3** (0.0150 g, 0.0640 mmol, 1.00 equiv) in THF (0.508 mL) cooled to −78 °C was added diethylmethoxyborane (1.0 M in THF, 0.0700 mL, 0.0700 mmol, 1.10 equiv) followed by MeOH (0.129 mL). The reaction mixture was then stirred for 30 min, after which solid $NaBH_4$ (0.00300 g, 0.0700 mmol, 1.10 equiv) was added in three portions. The mixture was allowed to stir for 2 h at −78 °C before being quenched with a mixture of pH 7 phosphate buffer (0.0920 mL), methanol (0.138 mL), and 30% H_2O_2 (0.0460 mL). This mixture was allowed to warm to rt and stirred at rt for 18 h. The organic solvent was evaporated *in vacuo*, and the aqueous layer was extracted with $CHCl_3$ (3 × 5 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* gave the crude product, which was purified by flash chromatography (2% MeOH/CH_2Cl_2) to give **1** as a colorless oil (0.014 g, 94%); TLC R_f = 0.21 in 6% MeOH/CH_2Cl_2; $[\alpha]^{23}_D$ = −21.1 (*c* 0.52, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 4.05 (m, 2H), 3.63 (m, 4H), 3.33 (br s, 1H), 2.40 (br d, *J* = 19.2 Hz, 1H), 2.01 (dd, *J* = 19.2, 5.4 Hz, 1H), 1.50 (m, 1H), 1.37 (m, 3H), 1.23 (d, *J* = 6.0 Hz, 3H), 1.13 (dt, *J* = 13.9, 2.2 Hz, 1H), 1.03 (m, 2H), 0.88 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 167.7, 72.5, 71.8, 68.2, 66.8, 66.0, 45.7, 43.1, 37.2, 36.4, 29.1, 24.2; IR (neat) cm^{-1} 3424, 2923, 2853, 1721, 1339, 1072; HRMS (EI) calcd for $C_{12}H_{20}O_5$ [M + H] 245.1389, found 245.1391.

(−)-Crytpocaryolone Diacetate (2). To a solution of **1** (5.00 mg, 0.0200 mmol, 1.00 equiv) in CH_2Cl_2 (1.30 mL) at 0 °C were added pyridine (0.00900 mL, 0.111 mmol, 5.40 equiv), Ac_2O (0.00800 mL, 0.0820 mmol, 4.00 equiv), and DMAP (1.00 mg, 0.010 mmol, 0.50 equiv). The reaction was allowed to stir overnight and then was quenched with solid $NaHCO_3$. The solvent was removed *in vacuo*, and the product was purified by column chromatography (50% EtOAc/hexanes) to afford **2** as a colorless oil (0.00600 g, 91%); TLC R_f = 0.25 in 70% EtOAc/hexanes; $[\alpha]^{23}_D$ = −32.7 (*c* 0.31, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.08 (m, 1H), 4.95 (m, 1H), 4.87 (m, 1H), 4.32

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(br s, 1H), 3.88 (m, 1H), 2.86 (br d, J = 19.2 Hz, 1H), 2.76 (dd, J = 19.2, 5.4 Hz, 1H), 2.03 (s, 3H), 2.02 (s, 3H), 1.90 (m, 3H), 1.69 (m, 2H), 1.57 (m, 3H), 1.22 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 170.4, 169.5, 72.8, 68.3, 67.9, 65.8, 63.1, 39.9, 39.7, 36.9, 36.2, 29.6, 21.3, 21.2, 20.1; IR (neat) cm^{-1} 3449, 2927, 2853, 1735, 1374, 1240, 1020, 785; HRMS (EI) calcd for $C_{16}H_{24}O_7$ [M + H] 329.1600, found 329.1606, calcd for $C_{16}H_{24}O_7$ [M − CH_3CO_2] 269.1389, found 269.1384.

■ ASSOCIATED CONTENT

Supporting Information

Full spectroscopic characterization (^{1}H and ^{13}C NMR) data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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