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Synthetic Approach to Analogues of the Original Structure of Sclerophytin A

Michael E. Jung* and Joseph Pontillo
Department of Chemistry and Biochemistry, University of California, Los Angeles, 405 Hilgard Avenue, Los Angeles, California 90095-1569

jung@chem.ucla.edu

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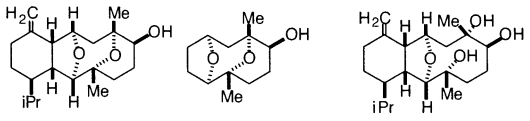
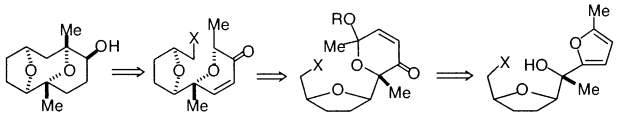
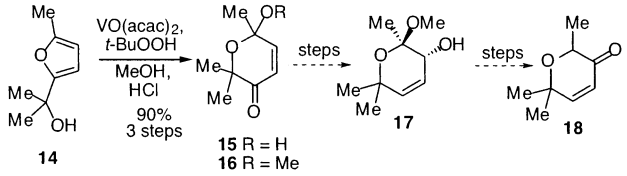
Abstract: A route to analogues of the original structure of sclerophytin A is described. The β-anomer of dideoxyribosyl nitriles **10a**,**b** (prepared from glutamic acid) was converted into the methyl ketone **11**. Addition of a silylated acetylide to **11** in diethyl ether/trimethylamine gave mainly **22a**. Alkylation with methallyl halide and ozonolysis gave the ketone **24,** which was then converted by hydrogenation and a second ozonolysis into the keto aldehyde **26**. A two-step aldol process afforded the desired 3-pyrone **27** in good overall yield. However, several methods for the conversion of this enone **27** into the desired sclerophytin analogue **2** failed.

Octocorals have produced an array of structurally intriguing and biologically active oxacyclic diterpenes.[1] Among the large family of 2,11-cyclized cembranoid ethers is the subclass cladiellins, which contain menthane-type cyclohexene rings cis-fused to 11-oxabicyclo-[6.2.1]undecane systems. Sharma and co-workers isolated a unique member of the cladiellin family, sclerophytin A, from the marine soft coral *Sclerophytum capitalis*, which exhibited strong cytotoxicity against the L1210 cell line (1.0 ng/mL) and which was assigned the novel tetracyclic diterpene structure **1**.[2] Because of its intriguing structure and potent cytotoxicity, we became interested in developing an efficient synthesis of this molecule and simpler derivatives, e.g., the tricyclic core **2** containing most of the functionality of the parent molecule. Although two groups have since successfully synthesized this important molecule[3] and have revised the structure of sclerophytin A to that shown in structure **3**,[4] nevertheless we think that our route offers an interesting approach to this unique compound. We hypothesized that the desired tricyclic analogue **2** could be obtained by an internal alkylation of the enone anion with a properly positioned leaving group X, as in **4**. The enone would then be available by functional group transposition of the opposite enone **5** that would be produced from the furfuryl alcohol **6**. We describe herein the utilization of this route to give the desired tricyclic core **2** and related derivatives.





The synthesis of the alcohol **6** began with the known lactone acid[5] **7**, which was reduced with borane followed by protection of the alcohol[6] as a *tert*-butyldiphenylsilyl ether to give the known lactone[7] **8** in 90% yield over 2 steps. This was reduced to the lactol and subsequent acetylation gave a 1:1 mixture of the crude anomeric acetates **9** in 92% yield over 2 steps. The acetate mixture was treated with trimethylsilyl cyanide in the presence of catalytic tin(IV) chloride to produce, in 94% yield, a 1:1 mixture of the cyanotetrahydrofurans **10a** and **10b** which was separable by column chromatography. The structure of the cyanide **10a** was confirmed by desilylation and benzoylation to give the known cyanobenzoate.[8] A number of conditions, e.g., several Lewis acids and Brønsted acids and bases that could potentially isomerize the undesired isomer **10a** to a mixture of isomers, failed. Reexposure to the original reaction conditions (TMSCN, $SnCl_4$) led only to decomposition of the substrate. Fortunately, since column chromatography was necessary only once in the high-yielding, six-step sequence, the desired cyanide **10b** could be prepared in multigram quantities. The cyanide was treated with methylmagnesium iodide, and subsequent hydrolysis of the resulting imine provided the desired ketone **11** in 83% yield. Initial experiments showed that the addition of 5-lithio-2-methylfuran **12** to the ketone **11** at low temperature resulted in the Cram chelation-controlled addition[9] to give a 3:1 mixture of the unstable furyl alcohols **13a**,**b**.



A model system was then employed in which the anion of 2-methylfuran **12** was added to acetone. The crude furyl alcohol **14** thus obtained was treated with *tert*-butyl hydroperoxide in the presence of catalytic vanadyl acetoacetonate, which resulted in epoxidation and rearrangement[10] to give, after hemiketal formation, the pyranone **15**. On treatment with methanol and catalytic acid, the

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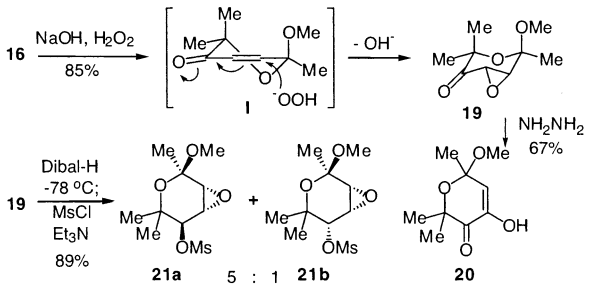
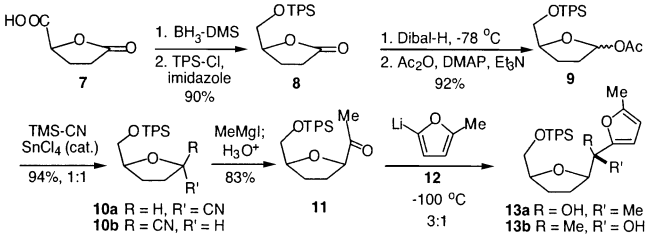
pyranone **16** was formed in 90% yield over 3 steps. It was then transposed to pyranone **18**, e.g., by enone epoxidation and Wharton fragmentation,[11] to give the allylic alcohol **17**, followed by oxidation and ketal reduction to yield the pyranone **18**. Thus the pyranone **16** was treated



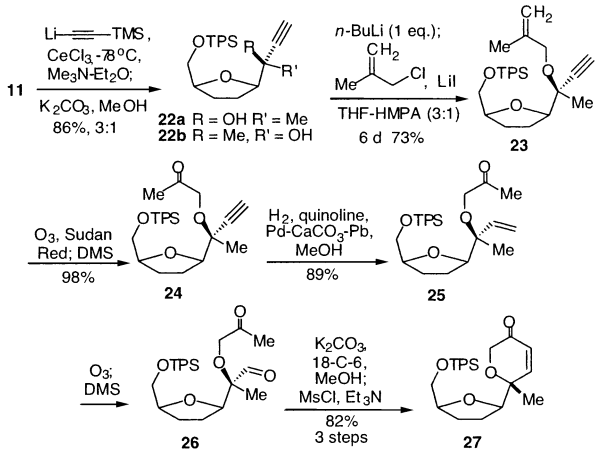
with hydrogen peroxide and base to provide the epoxide **19** as a single diastereomer in 85% yield. The stereochemical assignment is based on a presumed antiparallel nucleophilic attack on the anomerically locked conformer **I** via a chairlike transition state via the Valls and Toromanoff model.[12] This assignment was later confirmed by NMR analysis of the reduced alcohols and mesylates. Surprisingly, reaction with hydrazine gave none of the expected Wharton fragmentation product **17**. Steric hindrance about the ketone led to an alternate pathway in which hydrazine acted as a base, causing β-elimination and epoxide opening to give the enol **20** in 67% yield. The epoxy ketone **19** was thus reduced with DIBAL to provide an inseparable 5:1 mixture of the epoxy alcohols, which were transformed to the mesylates **21a** and **21b** in good yield. The mesylates were next treated with a variety of



reagents in the hope of inducing a mesylate reduction−fragmentation sequence[13] to afford **17**. However, all our attempts were unsuccessful, resulting in no reaction or decomposition of the substrate.

Since the addition of **12** to **11** had proceeded with reasonable diastereoselectivity, other nucleophilic organometallic reagents were considered. Addition of lithium (trimethylsilyl)acetylide to **11** in THF proceeded in low yield (<50%) and with no diastereoselectivity to furnish a 1:1 mixture of the propargylic alcohols. The results did not improve by using the Grignard reagent, changing the solvent, or adding various Lewis acids. However, the reaction of lithium (trimethylsilyl)acetylide in (1:1 diethyl ether/trimethylamine), as described by Carreira and Dubois,[14] dramatically improved the diastereoselectivity to 3:1 in favor of the chelation-controlled product **22a**. In addition, use of the corresponding organocerium reagent[15] in the mixed solvent system greatly improved the nucleophilicity without compromising the diastereoselectivity of the reaction. Thus a separable 3:1 mixture of the propargylic alcohols **22a** and **22b** was obtained in 86% yield after desilylation.

We next explored methods to functionalize the alkyne or alcohol moieties of **22a** to assemble the desired pyranone system. Our success was limited to the methallylation of the lithium alkoxide of **22a** with methallyl iodide (generated in situ) to give the ether **23** in 73% yield. Attempted *O*-alkylation with other reagents (e.g., 2-iodo-3-butanone or 2-iodo-3-methyl-3-butene) was unsuccessful, presumably due to the sterically encumbered nature of the propargylic alcohol. Chemoselective reduction of the alkyne in **23** was thwarted by competing reduction of the terminal olefin. Thus a slightly longer route was undertaken in which **23** was first subjected to ozonolysis to give the keto alkyne **24** in 98% yield. Catalytic hydrogenation afforded the keto alkene **25** in 89% yield. A second ozonolysis provided the unstable keto aldehyde **26**, which was immediately subjected to mild aldol conditions[16] and elimination to give the enone **27** in excellent yield (82%, 3 steps).



At this point it was necessary to install the methyl group at the α-position of the pyranone system of **27** to give **28**. Surprisingly, treatment of **27** with a variety of bases (e.g. LDA, LiHMDS, NaH) and methyl iodide only

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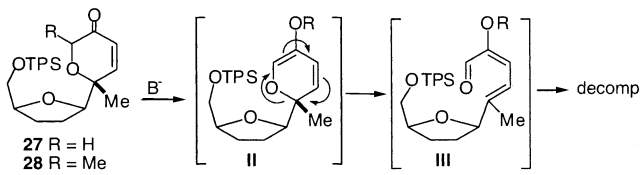
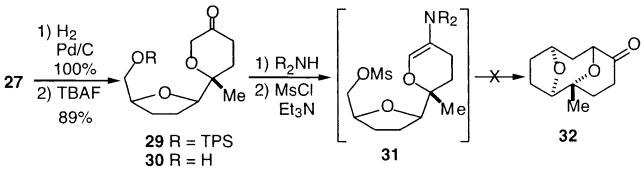
led to decomposition. We then attempted to form the corresponding silyl enol ether with TMSOTf in the presence of triethylamine.[17] Most of the substrate decomposed but crude NMR and IR analysis clearly revealed that an aldehyde moiety was present. It is possible that an electrocyclic rearrangement of the intermediate enol ether (or enolate) **II** gave the unstable aldehyde **III**, which rapidly decomposed. This implied that the key



alkylative cyclization step of the synthesis would be compromised due to a competing electrocyclic rearrangement. Hydrogenation and desilylation of **27** gave the hydroxy dihydropyranone **30** (via **29**) in 89% yield. But all attempts at forming the enolate or enamine, e.g., the morpholine enamine of the mesylate **31**, gave no tricyclic material, e.g., **32**, but only decomposition. Thus we were forced to abandon this route to the tricyclic core, namely the alcohol **2**.



In conclusion, we have developed an interesting method for the production of bicyclic analogues of the original structure of sclerophytin A and a novel synthesis of 3-pyranones.

Experimental Section

(2*R*S,5*S*)-2-Acetyloxy-5-([(1,1-dimethyl)ethyldiphenylsilyl]oxymethyl)tetrahydrofuran (9). To lactone **8**[7] (10.1 g, 28.5 mmol) in dichloromethane (120 mL) cooled to −78 °C was added dropwise over 1.5 h diisobutylaluminum hydride (1.0 M in dichloromethane, 34 mL, 34 mmol). The solution was stirred for an additional 0.5 h at −78 °C, then quenched with methanol (30 mL) and warmed to room temperature. The mixture was diluted with saturated aq $NaHCO_3$ (250 mL), separated, and extracted with dichloromethane (4 × 150 mL). The combined extracts were washed with brine (2 × 200 mL), dried over $MgSO_4$, and concentrated to give the lactols as viscous, colorless oil (10.1 g, 100%), which was used without further purification. To a mixture of the lactols (5.15 g, 14.4 mmol), triethylamine (4.5 mL, 32 mmol), and DMAP (268 mg, 2.2 mmol) in dichloromethane (25 mL) was added dropwise over 5 min acetic anhydride (1.65 mL, 17 mmol). The solution was stirred for 3 h, then evaporated. The residue was dissolved in ethyl acetate (100 mL), washed with saturated aq NH_4Cl (75 mL), and separated. The aqueous layer was extracted with ethyl acetate (2 × 50 mL), and the combined extracts were washed with brine (2 × 100 mL), dried over $MgSO_4$, and evaporated. The acetates **9** (5.7 g, 98%) were isolated as a pale yellow oil, and used without further purification.

(2*R*,5*S*)-5-([(1,1-Dimethyl)ethyldiphenylsilyl]oxymethyl)-tetrahydrofuran-2-carbonitrile (10a) and (2*S*,5*S*)-5-([(1,1-Dimethyl)ethyldiphenylsilyl]oxymethyl)tetrahydrofuran-2-carbonitrile (10b). To an ice-cold solution of acetates **9** (3.98 g, 9.59 mmol) in 75 mL of dichloromethane was added trimethylsilyl cyanide (TMSCN, 1.40 mL, 10.6 mmol), followed by tin(IV) chloride (0.28 mL, 2.4 mmol). The solution was stirred at 0 °C for 30 min, then quenched with ice-cold water (35 mL) and diluted with dichloromethane (150 mL). The aqueous layer was extracted with dichloromethane (2 × 150 mL), and the combined extracts were washed with saturated aq $NaHCO_3$ (150 mL) and brine (150 mL), dried over $MgSO_4$, and evaporated to give a yellow oil. Column chromatography on silica gel (15% Et_2O/hexane) gave cyanide **10a** (1.74 g) as a colorless oil, followed by cyanide **10b** (1.70 g) as a white solid (combined yield 94%). Cyanide **10a**: $[\alpha]_D^{20}$ 6° (*c* 3.3, CH_2Cl_2); IR (neat) 3071, 3049, 2957, 2932, 2891, 2859, 1472, 1428, 1391, 1190, 1113, 1074, 997, 823, 743, 704, 621 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.80−7.68 (m, 4H), 7.53−7.39 (m, 6H), 4.79 (dd, J = 7.3, 3.4 Hz, 1H), 4.40−4.32 (m, 1H), 3.79 (dd, J = 11.0, 4.0 Hz, 1H), 3.70 (dd, J = 11.0, 4.0 Hz, 1H), 2.46−2.01 (m, 4H), 1.13 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 135.7, 133.3, 129.8, 127.9, 119.5, 80.8, 67.0, 65.5, 31.7, 26.9, 26.6, 19.3. Cyanide **10b**: mp 63−64 °C; $[\alpha]_D^{20}$ −25° (*c* 8.2, CH_2Cl_2); IR (neat) 3073, 2959, 2930, 2859, 1473, 1429, 1390, 1361, 1190, 1113, 1072, 997, 885, 601 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.73−7.67 (m, 4H), 7.46−7.38 (m, 6H), 4.69 (dd, J = 7.4, 4.2 Hz, 1H), 4.21−4.13 (m, 1H), 3.76 (d, J = 4.8 Hz, 2H), 2.39−2.21 (m, 2H), 2.15−2.01 (m, 2H), 1.10 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 135.7, 133.3, 129.8, 127.8, 119.5, 82.0, 66.5, 65.6, 32.0, 27.4, 26.8, 19.3; HRMS (CI) *m/e* ((M + NH_4)$^+$) calcd for $C_{22}H_{31}O_2SiN_2$ 383.2155, found 383.2145.

(2*R*,5*S*)-2-(1-Oxoethyl)-5-([(1,1-dimethyl)ethyldiphenylsilyl]oxymethyl)tetrahydrofuran (11). To cyanide **10b** (0.681 g, 1.86 mmol) in diethyl ether (12 mL) at 0 °C was added dropwise over 30 min methylmagnesium iodide (3.0 M in Et_2O, 1.9 mL, 5.7 mmol). The mixture was stirred for an additional 5.5 h, then treated with hydrochloric acid (1.2 M) until the mixture was acidic (pH 2). The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined extracts were washed with water (2 × 15 mL) and brine (2 × 15 mL), dried over $MgSO_4$, evaporated, and subjected to chromatography on silica gel (dichloromethane) to provide ketone **11** (0.589 g, 83%) as a pale yellow oil. $[\alpha]_D^{20}$ 37° (*c* 6.5, CH_2Cl_2); IR (neat) 3072, 2959, 2859, 1717, 1473, 1428, 1391, 1357, 1113, 1068, 1006, 824, 743, 704, 609 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72−7.66 (m, 4H), 7.47−7.36 (m, 6H), 4.79 (dd, J = 9.9, 7.2 Hz, 1H), 4.19−4.12 (m, 1H), 3.79−3.70 (m, 2H), 2.21 (s, 3H), 2.22−2.08 (m, 1H), 2.03−1.92 (m, 2H), 1.89−1.78 (m, 1H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 210.8, 135.6, 133.4, 129.8, 127.7, 84.4, 81.2, 65.8, 28.9, 27.4, 26.9, 26.1, 19.3; HRMS (CI) *m/e* ((M + H)$^+$) calcd for $C_{23}H_{31}O_3Si$ 383.2042, found 383.2039.

(α*S*,2*R*,5*S*)-α-Ethynyl-α-methyl-5-([(1,1-dimethyl)ethyldiphenylsilyl]oxymethyl)tetrahydrofuran-2-methanol (22b) and (α*R*,2*R*,5*S*)-α-Ethynyl-α-methyl-5-([(1,1-dimethyl)ethyldiphenylsilyl]oxymethyl)tetrahydrofuran-2-methanol (22a). Anhydrous cerium(III) chloride powder (58.0 mg, 0.235 mmol) was stirred in THF (0.5 mL) for 2 h. The THF was removed in vacuo, and the flask was back-filled with argon and cooled to −78 °C. An ice-cold, 1:1 mixture of diethyl ether/trimethylamine (0.5 mL) was added. In a separate flask, *n*-butyllithium (1.80 M in hexanes, 0.130 mL, 0.235 mmol) was added to trimethylsilylacetylene (33 μL, 0.235 mmol) in 1:1 diethyl ether/trimethylamine (0.5 mL) at −78 °C, stirred for 30 min, then warmed to 0 °C. The lithium trimethylsilylacetylide solution thus formed was transferred via cannula to the cerium(III) chloride suspension. The whole mixture was warmed to 0 °C, stirred for 20 min, then recooled to −78 °C. An ice-cold solution of ketone **11** (36 mg, 0.094 mmol) in 1:1 diethyl ether/trimethylamine (0.5 mL) was added, and the whole mixture was stirred at −78 °C for 2 h. A spatula tip of NH_4Cl was then added, and the mixture was warmed to 21 °C. Diethyl ether (5 mL) and water (2 mL) were added, and the mixture was separated.

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The aqueous layer was extracted with diethyl ether (2 × 2 mL), and the combined extracts were washed with brine (2 × 2 mL) and dried ($MgSO_4$). Following evaporation, the mixture of crude propargylic alcohols was dissolved in 1 mL of methanol. Potassium carbonate (33 mg, 0.24 mmol) was added, and the mixture was stirred for 2 h. The mixture was quenched with aqueous sat. NH_4Cl (1 mL), diluted with diethyl ether (5 mL), and separated. The aqueous layer was extracted with diethyl ether (2 × 5 mL), and the combined extracts were washed with brine (3 × 5 mL), dried ($MgSO_4$), and evaporated. The residue was subjected to chromatography on silica gel (gradient elution, 15% Et_2O/ hexane to 30% Et_2O/hexane) to give alcohol **22b** (8 mg) as a viscous, colorless oil, followed by alcohol **22a** (25 mg) as a white solid (combined yield 86%).

Alcohol **22b**: $[\alpha]_D^{20}$ 16° (*c* 3.2, CH_2Cl_2); IR (neat) 3440, 3280, 3073, 2959, 2934, 2859, 1473, 1404, 1427, 1363, 1113, 1084, 1009, 988, 824, 799, 741, 704, 691, 612 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.83−7.66 (m, 4H), 7.53−7.35 (m, 6H), 4.20−4.09 (m, 1H), 3.94 (dd, J = 5.6, 5.6 Hz, 1H), 3.81 (dd, J = 10.8, 4.6 Hz, 1H), 3.67 (dd, J = 10.8, 4.1 Hz, 1H), 3.17 (bs, 1H), 2.30 (s, 1H), 2.26−1.84 (m, 4H), 1.50 (s, 3H), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 135.7, 133.3, 129.8, 127.8, 85.5, 85.3, 80.6, 72.3, 70.4, 65.6, 27.5, 27.4, 27.0, 26.9, 19.2. Alcohol **22a**: mp 71−72 °C; $[\alpha]_D^{20}$ −4° (*c* 1.5, CH_2Cl_2); IR (neat) 3433, 3306, 2959, 2934, 2861, 1473, 1404, 1429, 1113, 1080, 824, 743, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.76−7.66 (m, 4H), 7.48−7.35 (m, 6H), 4.19−4.12 (m, 1H), 4.04 (dd, J = 6.7, 6.7 Hz, 1H), 3.85 (dd, J = 10.9, 4.2 Hz, 1H), 3.60 (dd, J = 10.9, 3.5 Hz, 1H), 3.26 (bs, 1H), 2.45 (s, 1H), 2.12−1.85 (m, 4H), 1.44 (s, 3H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 135.7, 133.2, 129.8, 127.8, 87.4, 85.6, 80.0, 70.8, 68.8, 65.5, 27.3, 26.8, 25.6, 25.1, 19.2; HRMS (CI) *m/e* (M^+) calcd for $C_{25}H_{32}O_3Si$ 408.2121, found 408.2127.

(2*R*,5*S*)-2-[*R*-2-(2-Methyl-3-propenyloxy)-3-butyn-2-yl]-5-[[(1,1-dimethyl)ethyldiphenylsilyl]oxymethyl)tetrahydrofuran (23). To alcohol **22a** (0.861 g, 2.11 mmol) and anhydrous lithium iodide (1.13 g, 8.84 mmol) in THF (7 mL) at −78 °C was added dropwise *n*-butyllithium (2.35 M in hexanes, 0.900 mL, 2.12 mmol). Stirring was continued for an additional 20 min, then HMPA (3.5 mL) was added, and the mixture was warmed to 0 °C. Methallyl chloride (0.83 mL, 8.40 mmol) was then added dropwise, and the mixture was warmed to 21 °C and stirred in the dark for 4 d. The mixture was quenched with aqueous sat. NH_4Cl (5 mL), diluted with diethyl ether (10 mL), and separated. The aqueous layer was extracted with diethyl ether (3 × 10 mL), and the combined extracts were washed with brine (3 × 10 mL), dried ($MgSO_4$), and evaporated. The residue was subjected to chromatography on silica gel (gradient elution, 10% Et_2O/hexane to 30% Et_2O/hexane) to give the methallyl ether **23** (710 mg, 73%) as a colorless oil, followed by the starting alcohol **22a** (215 mg, 75% conversion). $[\alpha]_D^{20}$ 4° (*c* 5.7, CH_2Cl_2); IR (neat) 3299, 2932, 2859, 1473, 1429, 1361, 1113, 1100, 897, 824, 741, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.74−7.67 (m, 4H), 7.52−7.46 (m, 6H), 4.96 (s, 1H), 4.83 (s, 1H), 4.16−4.05 (m, 2H), 3.98−3.88 (m, 2H), 3.77 (dd, J = 10.2, 5.2 Hz, 1H), 3.64 (dd, J = 10.2, 6.5 Hz, 1H), 2.24 (s, 1H), 2.11−1.85 (m, 4H), 1.72 (s, 3H), 1.47 (s, 3H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 142.7, 135.7, 133.7, 129.5, 127.6, 111.2, 84.6, 83.5, 80.3, 75.9, 74.2, 68.1, 66.1, 28.0, 27.0, 26.9, 23.3, 19.7, 19.3; HRMS (CI) *m/e* ($(M + NH_4)^+$) calcd for $C_{29}H_{42}NO_3Si$ 480.2934, found 480.2940.

(2*R*,5*S*)-2-[*R*-2-(2-Oxopropyl)-3-butyn-2-yl]-5-([(1,1-dimethyl)ethyldiphenylsilyl]oxymethyl)tetrahydrofuran (24). To methallyl ether **23** (163 mg, 352 mmol) in a 1:1 mixture of diethyl ether/methanol (10 mL) was added 3 drops of Sudan Red solution (0.1 wt % in methanol). The resulting pink solution was cooled to −78 °C, and ozone was bubbled through just until the solution became colorless. Dimethyl sulfide (0.15 mL) was added, and the mixture was slowly warmed 21 °C and stirred for an additional 6 h. Evaporation of the solvent, followed by chromatography on silica gel (20% EtOAc/hexane), provided keto alkyne **24** (160 mg, 98%) as a pale yellow oil. $[\alpha]_D^{20}$ −5° (*c* 1.5, CH_2Cl_2); IR (neat) 3300, 2957, 2932, 2859, 1718, 1478, 1428, 1360, 1113, 824, 741, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.85−7.63 (m, 4H), 7.50−7.33 (m, 6H), 4.30−4.05 (m, 3H), 3.96 (dd, J = 6.9, 6.9 Hz, 1H), 3.77 (dd, J = 10.3, 5.3 Hz, 1H), 3.63 (dd, J = 10.3, 6.2 Hz, 1H), 2.32 (s, 1H), 2.14 (s, 3H), 2.17−1.85 (m, 4H), 1.45 (s, 3H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 207.9, 135.7, 133.7, 129.6, 127.6, 84.2, 82.5, 80.4, 76.5, 75.4, 70.6, 66.0, 27.8, 26.9, 26.8, 23.0, 19.3 (one upfield carbon not resolved); HRMS (CI) *m/e* ($(M + H)^+$) calcd for $C_{28}H_{37}O_4Si$ 465.2461, found 465.2455.

(2*R*,5*S*)-2-[(*R*)-2-(2-Oxopropyl)-3-buten-2-yl]-5-([(1,1-dimethyl)ethyldiphenylsilyl]oxymethyl)tetrahydrofuran (25). To keto alkyne **24** (633 mg, 1.36 mmol) in methanol (35 mL) was added quinoline (0.32 mL) and Lindlar catalyst (5% palladium on calcium carbonate poisoned with lead, 87 mg). The flask was flushed with hydrogen gas. After being stirred for 15 min under hydrogen, the mixture was filtered through Celite, evaporated, and subjected to chromatography on silica gel (5% Et_2O/benzene) to give the keto alkene **25** (565 mg, 89%) as a pale yellow oil. $[\alpha]_D^{20}$ −2° (*c* 2.4, CH_2Cl_2); IR (neat) 2959, 2932, 2859, 1719, 1473, 1428, 1356, 1113, 999, 824, 741, 704, 608 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.89−7.60 (m, 4H), 7.55−7.30 (m, 6H), 5.82−5.71 (m, 1H), 5.18−5.28 (m, 2H), 4.12−4.03 (m, 1H), 4.00−3.86 (m, 3H), 3.70 (dd, J = 10.4, 4.8 Hz, 1H), 3.63 (dd, J = 10.4, 5.8 Hz, 1H), 2.12 (s, 3H), 1.96−1.73 (m, 4H), 1.26 (s, 3H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 208.4, 138.8, 135.6, 133.6, 129.6, 127.7, 117.1, 85.0, 80.1, 80.0, 69.5, 65.9, 27.7, 26.9, 26.8, 26.3, 19.3, 18.1; HRMS (EI) *m/e* (M^+) calcd for $C_{28}H_{38}O_4Si$ 466.2539, found 466.2539.

(6*R*)-6-Methyl-6-[(2*R*,5*S*)-5-([(1,1-dimethyl)ethylphenylsilyloxy]methyl)tetrahydrofuran-2-yl]pyran-2[3*H*]-one (27). Keto alkene **25** (548 mg, 1.17 mmol) was dissolved in a 1:1 mixture of diethyl ether/methanol (35 mL) and cooled to −78 °C. Ozone was bubbled through for 1 min, and TLC analysis showed that all the starting material had been consumed. Dimethyl sulfide (0.77 mL) was added, and the mixture was slowly warmed to 21 °C, then stirred for an additional 12 h. Evaporation of the solvent provided the crude keto aldehyde **26** as an unstable, colorless oil, which was immediately dissolved in methanol (75 mL). To the solution was added 18-crown-6 (30 mg, 0.11 mmol) and potassium carbonate (820 mg, 5.93 mmol). The mixture was stirred for 2.5 h, then diluted with diethyl ether (100 mL) and washed with saturated aq NH_4Cl (2 × 50 mL). The aqueous layer was extracted with diethyl ether (2 × 50 mL), and the combined extracts were washed with brine (2 × 100 mL), dried ($MgSO_4$), and evaporated. The residue was dissolved in 25 mL of dichloromethane, and DMAP (21 mg, 0.176 mmol) and triethylamine (0.60 mL, 4.3 mmol) were added. The mixture was cooled to 0 °C, and methanesulfonyl chloride (0.11 mL, 1.5 mmol) was added dropwise. The mixture was warmed to 21 °C, stirred for 3 h, then diluted with diethyl ether (100 mL) and washed with saturated aq NH_4Cl (2 × 50 mL). The aqueous layer was extracted with diethyl ether (2 × 50 mL), and the combined extracts were washed with brine (2 × 100 mL), dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica gel (20% EtOAc/hexane) provided pyranone **27** (435 mg, 82%) as a pale yellow oil. $[\alpha]_D^{20}$ −20° (*c* 2.2, CH_2Cl_2); IR (neat) 3071, 2957, 2930, 2857, 1692, 1471, 1428, 1388, 1105, 997, 824, 741, 702, 608 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.80−7.61 (m, 4H), 7.60−7.32 (m, 6H), 7.08 (d, J = 10.6 Hz, 1H), 6.03 (d, J = 10.6 Hz, 1H), 4.26 (s, 2H), 4.12−4.00 (m, 1H), 4.00−3.90 (m, 1H), 3.78 (dd, J = 10.8, 4.2 Hz, 1H), 3.66 (dd, J = 10.8, 4.2 Hz, 1H), 2.03−1.77 (m, 4 H), 1.43 (s, 3H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 194.9, 153.2, 135.6, 138.4, 129.7, 127.7, 126.3, 84.0, 80.3, 76.1, 67.5, 65.4, 26.9, 26.8, 26.5, 20.4, 19.3; HRMS (CI) *m/e* ($(M - H)^+$) calcd for $C_{27}H_{33}O_4Si$ 449.2155, found 449.2148.

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Supporting Information Available: Experimental procedures for compounds **16**, **19**, **20**, **21ab**, **29**, and **30** and reactions of **11** and **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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