Synthetic Approach to Analogues of the Original Structure of Sclerophytin A

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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-pyrene 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 cladinoid ethers is the subclass cladiellins, which contain man-thene-type cyclohexene rings cis-fused to 11-oxacyclob[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 molecule3 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 opti
dene 5 that would be produced from the furyl 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 7, which was reduced with borane followed by protection of the alcohol 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 cyanoenobenzoate.6 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, SnCl4) 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 addition10 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 acetoacetate, which resulted in epoxidation and rearrangement10 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 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 20 and epoxide opening to give the enol 21 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 alkene or alcohol moieties of 22a to assemble the desired pyranone system. Our success was limited to the methylation 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-ido-3-butanone or 2-ido-3-methyl-3-buten) was unsuccessful, presumably due to the sterically encumbered nature of the propargylic alcohol. Chemoselective reduction of the alkyn 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 alkynec 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 aldo 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...
alkaline 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. 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 snyderphin A and a novel synthesis of 3-pyranones.

**Experimental Section**

(2R,5S)-2-Acetoxy-5-[[1,1-dimethyl]ethylidiphenylsilyloxy]methyl)tetrahydrofuran (9). To lactone 28 (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 NaHCO3 (250 mL), separated, and extracted with dichloromethane (4 × 150 mL). The combined extracts were washed with brine (2 × 200 mL), dried over MgSO4, 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 (10 mL) and trimethylsilylacetylene (0.5 mL) was added. In a separate flask, to cyanide 10a (1.68 g, 6.57 mmol) in diethyl ether (12 mL) at 0 °C was added dropwise over 30 min methylmagnesium iodide (3.0 M in Et2O, 4.5 mL, 13.7 mmol), and DMAP (268 mg, 2.2 mmol) in dichloromethane (2 mL) and Et3N (0.5 mL) was added. The mixture was stirred for 3 h, then warmed to 0 °C. The lithium trimethylsilylacetylide was acidic (pH 2). The layers were separated, and the aqueous layer was extracted with diethyl ether (5 mL) and brine (5 mL). The combined extracts were washed with saturated aq NaHCO3 (100 mL), dried over MgSO4, and evaporated to give a pale yellow oil. Column chromatography on silica gel (15% EtOAc/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: [α]25° +25° (c 3.3, CHCl3); IR (neat) 3072, 3049, 2957, 2957, 2932, 2891, 2859, 1472, 1428, 1391, 1190, 1113, 1074, 997, 823, 743, 704, 621 cm−1; 1H NMR (CDCl3, 400 MHz) δ 7.80–7.68 (m, 4H), 7.53–7.39 (m, 6H), 4.79 (dd, J = 7.3, 3.4, 1H), 4.40–4.32 (m, 1H), 3.79 (dd, J = 11.0, 4.0, 1H), 1.70 (dd, J = 11.0, 4.0, 1H), 2.14–2.01 (m, 4H), 1.13 (s, 9H); 13C NMR (CDCl3, 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; [α]25° +25° (c 8.2, CH2Cl2); IR (neat) 3073, 2975, 2930, 2859, 1473, 1429, 1390, 1361, 1190, 1113, 1072, 997, 885, 601 cm−1; 1H NMR (CDCl3, 400 MHz) δ 7.46–7.38 (m, 6H), 7.74–7.67 (m, 4H), 7.48–7.38 (m, 6H), 7.34–7.24 (m, 4H), 2.15–2.01 (m, 2H), 1.10 (s, 9H); 13C NMR (CDCl3, 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 + Na)2+ calcd for C25H33O2SiNa 417.2155, found 417.2145.

(2R,5S)-2-(1-Oxoyethyl)-5-[[1,1-dimethyl]ethylidiphenylsilyloxy]methyl)tetrahydrofuran (11). To cyanide 10b (0.681 g, 3.07 mmol) in diethyl ether (2 mL) at 0 °C was added dropwise over 30 min methylmagnesium iodide (3.0 M in Et2O, 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 MgSO4, and evaporated, and subjected to chromatography on silica gel (dichloromethane) to provide ketone 11 (0.589 g, 83%) as a pale yellow oil. [α]25° 37° (c 6.5, CHCl3); IR (neat) 3072, 2975, 2859, 1717, 1473, 1428, 1391, 1357, 1113, 1068, 1060, 824, 743, 704, 609 cm−1; 1H NMR (CDCl3, 400 MHz) δ 7.72–7.66 (m, 4H), 7.47–7.36 (m, 6H), 4.79 (dd, J = 9.9, 7.2, 1H), 4.19–4.12 (m, 1H), 3.79–3.70 (m, 2H), 2.21 (s, 3H), 2.20–2.08 (m, 2H), 1.90 (s, 9H); 13C NMR (CDCl3, 101 MHz) δ 201.8, 136.5, 133.4, 129.8, 127.8, 119.5, 82.7, 81.2, 65.8, 28.9, 27.4, 26.9, 26.1, 19.3; HRMS (CI) m/e [(M + H)2+] calcd for C30H35O2Si 383.2155, found 383.2145.

(5S,2R,5S)-α'-E thynyl-α-methyl-5-[[1,1-dimethyl]ethylidiphenylsilyloxy]methyl)tetrahydrofuran-2-carboxaldehyde (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-cool, 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, 0.225 mmol) was added to trimethylsilylecyclopropene (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 trimethylsilylecyclopropene 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-cool 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 spartula tip of NH4Cl 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.
The aqueous layer was extracted with diethyl ether (2 × 2 mL), and the combined extracts were washed with brine (2 × 2 mL) and dried (MgSO₄). Following evaporation, the mixture of crude propargylic alcohols was dissolved in 1 mL of methanol. Potassium carbonate (30% Et₃O/hexane) was added, and the mixture was stirred for 2 h. The mixture was quenched with aqueous sat. NH₄Cl (1 mL), diluted with diethyl ether (5 mL), and the combined extracts were washed with brine (3 mL), dried (MgSO₄), and evaporated. The residue was subjected to chromatography on silica gel (gradient elution, 15% EtOAc/hexane to 30% EtOAc/hexane) to give the methallyl ether (710 mg, 73%) as a colorless oil, followed by the starting material (465.2455) as a pale yellow oil. \([\alpha]_D^{20} -2(2-\text{Methyl-3-propenyloxy}-3-\text{butyn}-2-\text{yl})]-5-(\text{[1,1-dimethyl)ethyldiphenylsilyl]oxymethyl})\text{tetrahydrofuran} (27).\)

To methallyl ether (160 mg, 0.11 mmol) and potassium carbonate (820 mg, 5.93 mmol). The mixture was warmed to 21 °C, stirred for 15 min under hydrogen, the mixture was filtered through Celite, evaporated, and subjected to chromatography on silica gel (5% EtOAc/benzene) to give the ketone alkyne \(54\) (565 mg, 89%) as a pale yellow oil. \([\alpha]_D^{20} -2(2\text{-c,2,4,3,6,7,8-Hexahydronaphthalen-1-yl})\text{methanol} (52)\). Ketone alkyne \(52\) (548 mg, 1.17 mmol) was dissolved in 1 mL 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 a yellow, amorphous solid. The latter 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 saturatedaq NH₄Cl (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 (MgSO₄), 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 methanesulfonil 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 aqueaq NH₄Cl (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 (MgSO₄), and evaporated. Chromatography of the residue on silica gel (20% EtOAc/hexane) provided pyrane \(27\) (435 mg, 82%) as a pale yellow oil. \([\alpha]_D^{20} +2(2\text{-c,2,4,3,6,7,8-Hexahydronaphthalen-1-yl})\text{methanol} (48)\).