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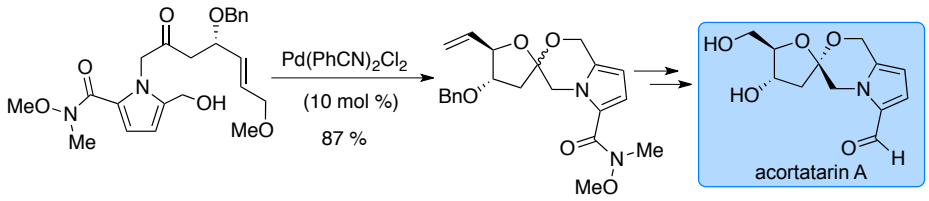


ABSTRACT

The total synthesis of acortatarin A relying on a Pd(II)-catalyzed spiroketalization is reported. This strategy allows a single stereocenter in the spiroketalization substrate to produce the target efficiently under mild conditions, installing the necessary oxygenation in the backbone through an allylic transposition. The synthesis also verifies that pollenopyrroside B and acortatarin A are the same compound, and electrochemical studies suggest that the reported bioactivity is not due to simple antioxidant properties.

INTRODUCTION

In 2010, two groups independently isolated and simultaneously reported the unique pyrrole-fused morpholine spiroketal natural product **1**.[1,2] Zhang and co-workers named this compound pollenopyrroside B and also isolated the related spiroketal **2**, named pollenopyrroside A.[1] Hou, Cheng, and co-workers named compound **1** acortatarin A and also isolated the more highly oxidized analogue **3**, which was named acortatarin B.[2] Together with funebral **4**[3] and two

additional acyclic compounds, magnolamide[4] and pyrraline,[5] these compounds comprise a small family of 2-formyl-5-hydroxymethylpyrrole-containing natural products.

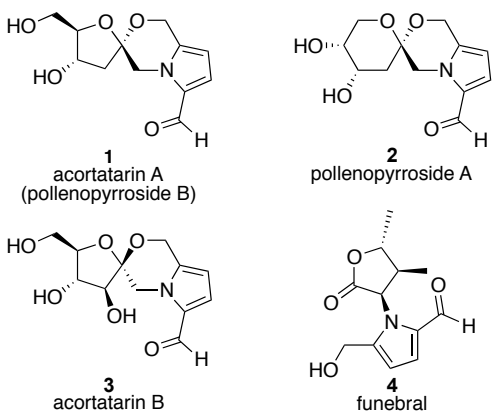


Figure 1. Acortatarin A and related natural products.

Interestingly, pollenopyrroside B/acortatarin A[6] is isolated in very small quantities from two unrelated sources, both of which are used in traditional Chinese medicine. Zhang and co-workers isolated 5 mg of acortatarin A from 15 kg of bee-collected *Brassica campestris* (rapeseed) pollen, while Cheng et al. obtained 7.3 mg from 50 kg of dry rhizome (rootstock) of *Acorus tatarinowii* Schott. In the latter report, a crystal structure was obtained for **1** and Mosher's ester analysis was used to assign the absolute configuration as the enantiomer of that shown in Figure 1.[2] The correct absolute configuration was proposed by Zhang and co-workers who made their assignment by analogy to **2**, for which they had obtained an X-ray crystal structure.[1] Three total syntheses have now been completed,[7,8] and since each utilizes starting materials from the chiral pool, the absolute configuration has been confirmed to be that illustrated in Figure 1 for the material isolated by Hou and Cheng. Although Zhang and co-workers' assignment was confirmed, to the best of our knowledge this has not been referenced

until this point.[9] Furthermore, their NMR data was reported using acetone-d_6 as the solvent[1] while all other data has been reported in methanol-d_4.[2,7,8]

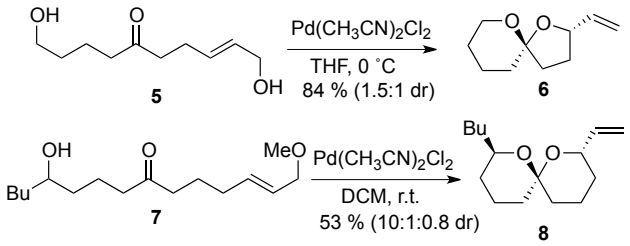
We initially became interested in acortatarin A because of its unique structure and the fact that both natural sources are used in traditional medicine to treat a variety of ailments, including central nervous system (CNS) disorders and prostatitis.[2] The biological activities of these natural sources of acortatarin A also include antitumor and antioxidant properties.[1] Hou and Cheng demonstrated that acortatarin A was able to inhibit high-glucose-induced reactive oxygen species (ROS) in mesangial cells.[2] Evidence suggests that ROS in renal cells play an integral role in the development of diabetic nephropathy,[10] and we sought to test whether **1** may act as an antioxidant or if perhaps a different manifold is responsible for its bioactivity. Herein, we report the total synthesis of acortatarin A using a Pd(II)-catalyzed spiroketalization strategy as the key step and a preliminary study of its electrochemical properties and the implications they may have on its mode of action.

RESULTS AND DISCUSSION

Previous work from our laboratory has focused on developing metal-catalyzed dehydrative cyclization reactions of unsaturated alcohols[11] and we have recently been exploring a Pd(II)-catalyzed method for spiroketalization.[12] Given the interesting and uncommon pyrrole-fused spiroketal architecture of acortatarin A, this target provided an attractive platform to test this method. The core structure of the natural product is comprised of a [6,5]-spiroketal. In studies on reaction scope, the parent spiroketal **6** was prepared from the acyclic substrate **5** in high yield, but with poor diastereoselectivity (Scheme 1). It was also observed that interchanging alcohols and ethers as leaving groups had no significant impact on the yield or

reaction time, although the few preliminary test reactions conducted produced [6,6]-spiroketals such as **8**. The acyclic substrates **5** and **7** are likely in equilibrium with their cyclic hemiketal counterparts under the reaction conditions. Alkoxypalladation followed by elimination then provides the spiroketal products.[13]

Scheme 1. Pd(II)-catalyzed spiroketalization.



From a retrosynthetic perspective, acortatarin A (Figure 2) would rely on conversion of the penultimate intermediate **9**, resulting from the key spiroketalization, to the natural product. This would require oxidative cleavage of the vinyl group, reduction of both the resulting aldehyde and Weinreb amide, and benzyl group removal. Spiroketal **9** should be available by Pd(II)-catalyzed cyclization of the acyclic precursor **10**, containing a single stereocenter. Using our method, the newly formed stereocenter at the allylic carbon should be set during the spiroketalization step, placing the vinyl group *trans* to the benzyl ether. Use of the methyl ether leaving group also seemed advantageous as it would eliminate the need for protecting group manipulation if an alcohol was required. Spiroketalization precursor **10** was envisioned to be available from 2,5-functionalized pyrrole **11** by *N*-alkylation with bromoketone **12**, which in turn should be prepared from allylic alcohol **13**.

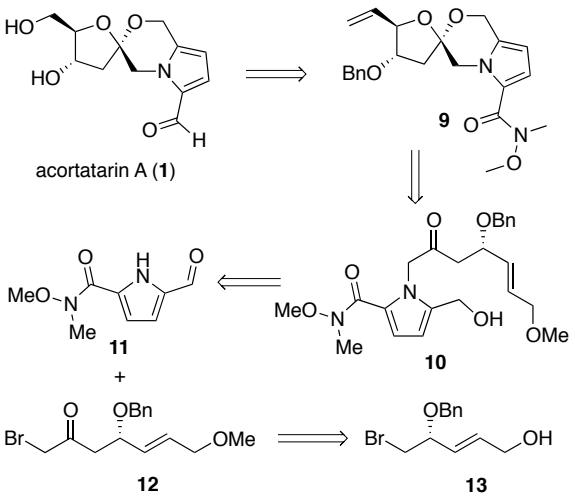
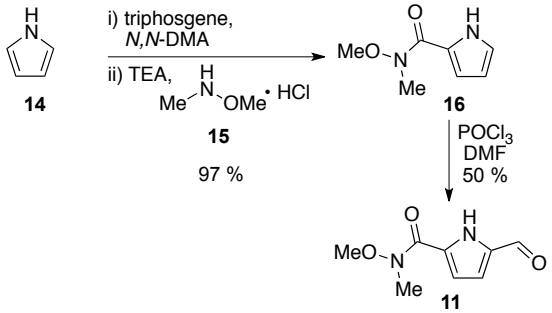


Figure 2. Retrosynthetic analysis of acortatarin A.

Initial experiments were focused on the preparation of the required pyrrole **11** (Scheme 2). This was accomplished from pyrrole by first using a one-pot acylation / amidation sequence[14] to provide the Weinreb amide **16** in 97% yield. A Vilsmeier-Haack formylation was then used for introduction of the aldehyde moiety.[15] Inclusion of the formyl group in pyrrole **11** proved to be crucial as compounds bearing other protected hydroxymethyl synthons were difficult to *N*-alkylate and/or unstable and difficult to work with.

Scheme 2. 2,5-Disubstituted pyrrole fragment.

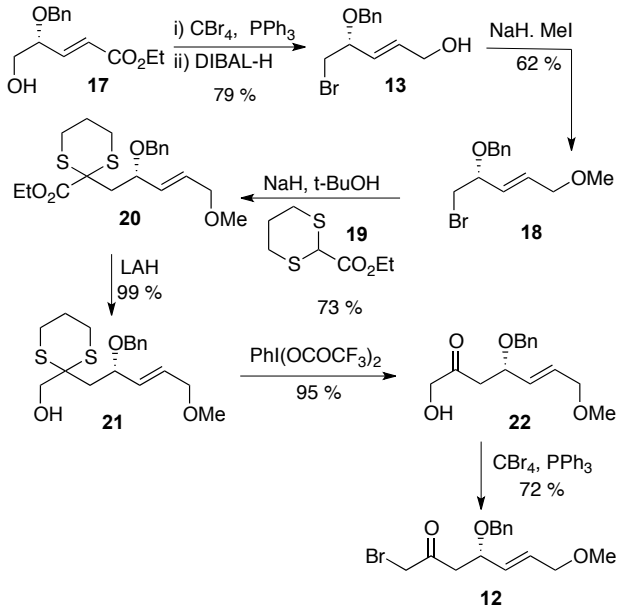


The preparation of the alkylating agent, bromoketone fragment **12**, was explored and commenced with a one-pot bromination and reduction[19] of the known δ-hydroxy ester **17**[16] to provide allyl alcohol **13** in 79% yield (Scheme 3). Methylation of the hydroxyl group with

methyl iodide and alkylation of dithiane **19**[17] with the resulting alkyl bromide **18** produced dithiane **20**. Conversion of the ester to a bromide and unmasking of the latent ketone were then required. Reduction of the ester was readily accomplished with LAH and the ketone revealed using oxidative conditions[18] to afford acyloin **22**. The Appel halogenation conditions used previously[19] were then employed to conclude the synthesis of bromoketone **12**.

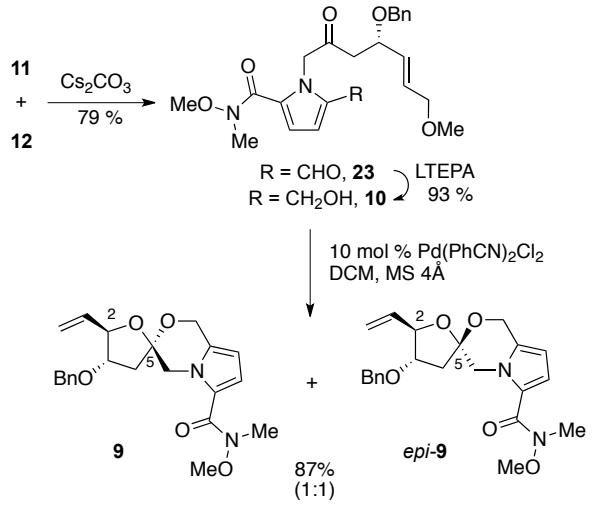
With both the pyrrole and bromoketone fragments in hand, a variety of alkylation protocols were tested for the union of these moieties and it was found that using 1 equivalent of Cs_2CO_3 in acetonitrile at 0 ˚C gave the best result (Scheme 4). Under these conditions, the competing elimination of the benzyloxy group, which was problematic with other conditions, was suppressed. To complete the synthesis of the cyclization precursor, a chemoselective reduction of an aldehyde in the presence of both a ketone and amide was needed. Initial synthetic plans avoided this issue by introducing the hydroxymethyl group in the correct oxidation state but proved untenable due to the problems of stability and nucleophilicity mentioned above. Reducing agents such as sodium borohydride and others failed to give a clean reaction, with varying amounts of reduced ketone observed even at low conversion. Fortunately, reduction of **23** with lithium tris(3-ethyl-3-pentyloxy)aluminohydride (LTEPA)[20] cleanly gave desired hydroxymethyl pyrrole **10** in 93% yield. Keto-alcohol **10** was found to exist in equilibrium with the corresponding hemiketal, on the NMR time scale, which seemed advantageous for the key spiroketalization.

Scheme 3. Synthesis of the methyl ether **12**.



In the event, hydroxyketone **10** was treated with $Pd(PhCN)_2Cl_2$ in CH_2Cl_2 with MS 4Å to produce **9** and *epi*-**9** as a separable 1:1 mixture of diastereomers in a combined yield of 87%. It was later found that these compounds were epimeric at the anomeric carbon C5 (see scheme 4 for numbering) and not at the allylic position C2, but at this stage, it was difficult to make the stereochemical assignment. Since the two products were separable and only oxidative cleavage of the olefin, reduction of the carbonyl groups, and benzyl deprotection remained, the synthesis was carried out independently on both diastereomers.

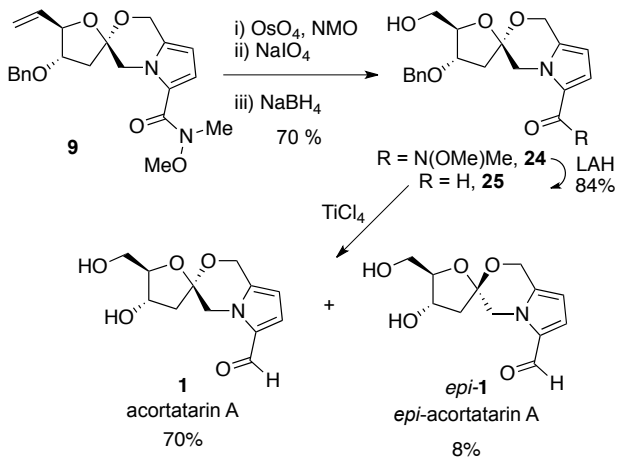
Scheme 4. Fragment coupling and spiroketalization.



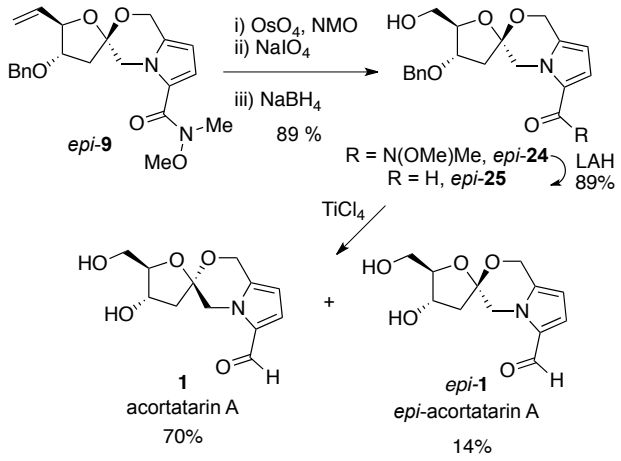
The end game sequence commenced with oxidative cleavage, and it was found that OsO_4 catalyzed dihydroxylation, followed by glycol cleavage was superior to ozonolysis (Schemes 5 and 6). Spiroketals **9** and *epi*-**9** were subjected to this reaction sequence, and subsequent reduction of the aldehyde furnished alcohols **24** and *epi*-**24** in 70% and 89% respectively, over the 3 steps. Reduction of the Weinreb amides to aldehydes **25** and *epi*-**25** was accomplished in good yield using an excess of LAH in THF. At this point, epimerization of the spiro compound *epi*-**25** with Brønsted acids (PPTS, *p*-TsOH, 1N HCl) was attempted, however conversion to the desired diastereomer **25** was unsuccessful leading only to recovered starting material.[21] Instead, compounds **25** and *epi*-**25** were each treated with $TiCl_4$ to yield acortatarin A and *epi*-acortatarin A in 78% and 84% combined yields respectively. Gratifyingly, this verified that the newly formed, non-epimerizable allylic ether stereocenter C2 was formed in the spiroketalization reaction with complete selectivity for the desired 1,2-*trans* relationship with respect to the benzyloxy group C3 (see scheme 4). Moreover, acortatarin A was the major product of both reactions with *epi*-**1** as the byproduct. It is interesting to note that the ring-expanded natural

product **2** was not formed. All spectral data and the optical rotation of synthetic acortatarin A satisfactorily matched previously reported values.[2,7] Additionally, ^{1}H and ^{13}C NMR spectra of acortatarin A were obtained in acetone-d_6 and confirmed that acortatarin A and pollenopyrroside B are indeed the same compound.

Scheme 5. Elaboration of **9** to acortatarin A.



Scheme 6. Elaboration of *epi*-**9** to acortatarin A.



It has been suggested that the bioactivity of **1** against ROS was due to antioxidant properties.[2] However, antioxidants typically contain more electron-rich aromatic groups such as phenols. While pyrrole is an electron-rich heterocycle, **1** contains an electron withdrawing group and no resonance donating substituents. To test the antioxidant activity of **1**, the oxidation

potential was measured by cyclic voltammetry.[22, 23] While the oxidation potential of most compounds considered antioxidants is below +0.70 V,[24] the first and second oxidation potentials of **1** were measured to be +1.74 V and +1.90 V, respectively. Interestingly, the cyclic voltammogram shows that the oxidation is not reversible. The high oxidation potentials measured contrast the values typically obtained for antioxidants and these data suggest that **1** is likely functioning by an alternative mechanism. This corroborates the original ROS experiments[2] that suggest that **1** actually inhibits ROS production instead of reacting with reactive oxygen species. Further studies on the mode of action of **1** are underway and will be reported in due course.

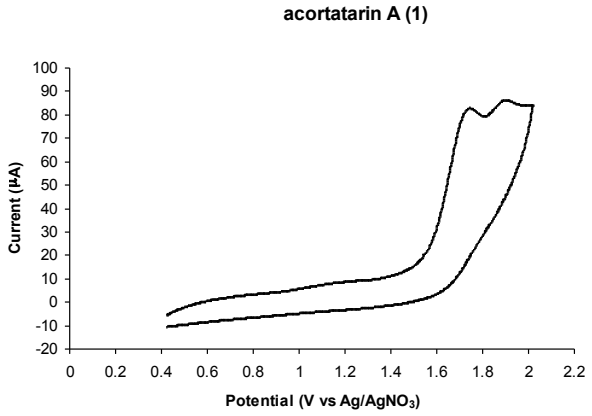


Figure 3. Voltammogram of **1** in CH_3CN.

CONCLUSION

In conclusion, the total synthesis of acortatarin A using a Pd(II)-catalyzed spiroketalization for the key step has been reported. The characterization data of synthetic **1** are identical to those reported for both acortatarin A and pollenopyrroside B, verifying that they are actually the same natural product. Furthermore, electrochemical studies suggest that the bioactivity of this compound may not be due to simple antioxidant properties.

EXPERIMENTAL SECTION

General

All reactions were carried out under an atmosphere of nitrogen unless otherwise specified. Anhydrous solvents were transferred via syringe to flame-dried glassware, which had been cooled under a stream of dry nitrogen. Anhydrous tetrahydrofuran (THF), acetonitrile, ether, dichloromethane (DCM), pentane, toluene were dried using a solvent purification system.

Analytical thin layer chromatography (TLC) was performed using 250 μm silica gel. Flash column chromatography was performed using 230-400 mesh 60 Å silica gel. The eluents employed are reported as volume:volume percentages. Melting points were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, CD_3OD or acetone-d_6 using tetramethylsilane as an internal standard. Chemical shift (δ) is reported in parts per million (ppm) downfield relative to tetramethylsilane, $CDCl_3$, CD_3OD, or acetone-d_6. Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Specific optical rotations were obtained using wavelength = 589 nm. Infrared spectra were obtained using film NaCl plate techniques. High resolution mass spectra (HRMS) were obtained with electrospray ionization using a TOF mass analyzer (ESI-MS), and are reported as m/e (relative ratio).

***N*-methoxy-*N*-methyl-1*H*-pyrrole-2-carboxamide (16).** According to a known procedure,[14] a solution of triphosgene (7.52 g, 25.3 mmol) in 35 mL toluene was added via dropping funnel to a stirred solution of *N,N*-dimethylaniline (9.63 mL, 76 mmol) and pyrrole (5.27 mL, 76 mmol) in toluene (75 mL) at 0 ˚C over 20 minutes. The resulting mixture was allowed to stir at room temperature for 2 hours. In a separate flask, triethylamine (25.4 mL, 182 mmol) was added to a suspension of *N,O*-dimethylhydroxylamine hydrochloride (**15**) (8.9 g, 91.2 mmol) in DCM (70 mL), and the mixture stirred at room temperature for 30 minutes. The free amine was filtered

into a clean dropping funnel, the filter cake washed with DCM, and the resulting solution added to the pyrrole mixture over 20 minutes at 0 ˚C. The reaction was allowed to reach room temperature overnight before it was concentrated, taken up in 150 mL EtOAc, and washed with a saturated aqueous solution of $NaHCO_3$, followed by H_2O, and then dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (50% EtOAc/hexanes) to furnish the product as a gray crystalline solid (11.39 g, 97%). R_f = 0.47 (50% EtOAc/hexanes); MP 112-114 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.72 (br s, 1H), 7.02 - 6.94 (m, 1H), 6.92 (ddd, *J* = 3.8, 2.4, 1.4 Hz, 1H), 6.45 - 6.13 (m, 1H), 3.78 (s, 3H), 3.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.6, 123.8, 122.0, 114.9, 110.7, 61.3, 33.2; IR (film): ν_{max} 3269, 2974, 2937, 1755, 1690, 1597, 1547, 1438, 1296, 1178, 1104, 1045, 749; HRMS (ESI) calcd for $C_7H_{10}N_2O_2Na$ $[M+Na]^+$ 177.0642, found 177.0632.

5-formyl-*N*-methoxy-*N*-methyl-1*H*-pyrrole-2-carboxamide (11). To pyrrole **16** (1.0 g, 6.49 mmol) in DMF (4.3 mL) at 0 ˚C was added 1.1 eq. of the Vilsmeier reagent (prepared by dropwise addition of 0.65 mL $POCl_3$ to 0.65 mL DMF at 5 ˚C) and the solution stirred for 1 h at 50 ˚C. The contents of the flask were cooled to room temperature, poured into 10 g crushed ice, and quenched by the slow addition of saturated aqueous K_2CO_3 (15 mL) with stirring (15 min). The mixture was extracted with EtOAc, dried over Na_2SO_4, and concentrated. Column chromatography (30% EtOAc/hexanes) afforded the title compound as a crystalline white solid (591 mg, 50 %). R_f = 0.34 (50% EtOAc/hexanes); MP 118-120 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.18 (br s, 1H), 9.66 (s, 1H), 6.98 - 6.95 (m, 1H), 6.94 - 6.92 (m, 1H), 3.79 (s, 3H), 3.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.3, 160.1, 133.6, 129.4, 120.2, 115.6, 61.7, 33.3; IR (film): ν_{max} 3240, 1677, 1612, 1391, 1216, 1193, 811, 751; HRMS (ESI) calcd for $C_8H_{10}N_2O_3Na$ $[M+Na]^+$ 205.0584, found 205.0582.

(*R*,*E*)-4-(benzyloxy)-5-bromopent-2-en-1-ol (13). Based on a similar literature procedure,[19] a solution of (*R*,*E*)-ethyl 4-(benzyloxy)-5-hydroxypent-2-enoate[16] (**17**) (250 mg, 1.0 mmol) and CBr_4 (663 mg, 2.0 mmol) in 6 mL of dichloromethane was treated with PPh_3 (525 mg, 2.0 mmol), and the mixture stirred at 45 ˚C for 30 min before cooling to -78 ˚C. DIBAL-H (5.0 mL of a 1.0 M solution in toluene, 5 mmol) was then added in a dropwise fashion, and the resulting mixture allowed to stir for 30 min. The reaction was then quenched with 10 mL of a saturated aqueous solution of Rochelle's salt, and allowed to warm to ambient temperature over 2 h. The biphasic system was separated, and the aqueous phase extracted with DCM (3 x 20 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the crude material by flash chromatography (40 % EtOAc/hexanes) provided the allylic alcohol as a colorless oil (214 mg, 79 %). R_f = 0.59 (60% EtOAc/hexanes); $[\alpha]^{25}_D$ = -31.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 - 7.33 (m, 5H), 5.95 (dtd, *J* = 15.6, 5.1, 0.9 Hz, 1H), 5.68 (ddt, *J* = 15.6, 7.4, 1.7 Hz, 1H), 4.56 (dd, *J* = 73.5, 11.9 Hz, 2H), 4.21 (d, *J* = 3.5 Hz, 2H), 4.06 (dddd, *J* = 7.4, 6.4, 5.2, 0.8 Hz, 1H), 3.53 - 3.34 (m, 2H), 1.44 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.1, 134.6, 128.7, 128.6, 128.1, 128.0, 78.7, 71.1, 62.9, 35.1; IR (film): ν_{max} 3379, 3030, 2866, 1454, 1217, 1090, 739, 698; HRMS (ESI) calcd for $C_{12}H_{15}BrO_2Na_2$ $[M+2Na]^+$ 317.0155, found 317.0699.

(*R*,*E*)-(((1-bromo-5-methoxypent-3-en-2-yl)oxy)methyl)benzene (18). To a suspension of NaH (660 mg, 27.51 mmol) in THF (69 mL) at 0 ˚C was added allylic alcohol **13** (7.46 g, 27.51 mmol) in 69 mL THF over 10 min. After the mixture was stirred for an additional 5 min., iodomethane (4.28 mL, 68.8 mmol) was added dropwise in a dropwise fashion, followed by stirring for 45 min. at the same temperature. The reaction was then quenched with a saturated aqueous solution of NH_4Cl, and extracted with DCM (3 x 150 mL). The combined organic

extracts were concentrated under reduced pressure and purified by column chromatography on silica gel (7% EtOAc/hexanes) to afford the title compound as a colorless oil (4.82 g, 62 %). R_f = 0.58 (25% EtOAc/hexanes); $[\alpha]^{25}_D$ = -28.6 (*c* 1.91, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 - 7.29 (m, 5H), 6.04 - 5.84 (m, 1H), 5.69 (ddtd, *J* = 15.6, 7.4, 1.5, 0.5 Hz, 1H), 4.58 (dd, *J* = 91.0, 11.9 Hz, 2H), 4.07 (dddt, *J* = 7.2, 6.5, 5.1, 0.7 Hz, 1H), 4.00 (ddd, *J* = 5.5, 1.5, 0.6 Hz, 2H), 3.50 - 3.39 (m, 2H), 3.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.1, 132.2, 130.2, 128.7, 128.1, 128.1, 129.0, 78.8, 72.3, 71.1, 58.4, 35.2; IR (film): ν_{max} 3030, 2927, 2870, 1452, 1383, 1102, 1066, 974, 738, 698; HRMS (ESI) calcd for $C_{12}H_{13}BrNaO$ $[M\text{-}MeOH\text{-}Na]^+$ 275.0047, found 275.0901.

(*S*,*E*)-ethyl 2-(2-(benzyloxy)-5-methoxypent-3-en-1-yl)-1,3-dithiane-2-carboxylate (20). Ethyl 1,3-dithiane-2-carboxylate[17] (**19**) (4.88 g, 25.24 mmol) in DMF (35 mL) was added slowly to a stirred suspension of NaH (606 mg, 25.24 mmol) and catalytic *t*-BuOH in DMF (35 mL) at 0 ˚C over 10 min and allowed to continue stirring for an additional 45 min. Bromide **18** (3.60 g, 12.62 mmol) in DMF (35 mL) was then added dropwise to the reaction mixture, and the temperature was maintained for 5 h. After the reaction was complete by TLC analysis, the solution was diluted with Et_2O and poured into a cold saturated aqueous solution of NH_4Cl. The organic phase was separated, and the aqueous layer extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (5-10% EtOAc/hexanes) of the crude material afforded the title compound as a colorless oil (3.68 g, 73 %). R_f = 0.41 (25% EtOAc/hexanes); $[\alpha]^{25}_D$ = -9.91 (*c* 0.76, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 - 7.14 (m, 5H), 5.96 - 5.76 (m, 1H), 5.72 - 5.59 (m, 1H), 4.42 (dd, *J* = 67.2, 11.0 Hz, 2H), 4.25 (td, *J* = 8.3, 3.5 Hz, 1H), 4.13 - 3.84 (m, 4H), 3.36 (s, 3H), 3.31 (ddd, *J* = 14.2, 11.6, 2.6 Hz,, 1H), 3.12 (ddd, *J* = 14.2, 11.6, 2.6 Hz, 1H), 2.71 (ddd, *J* = 14.3, 5.2,

3.1 Hz, 2H), 2.58 (dd, *J* = 14.4, 9.0 Hz, 1H), 2.23 (dd, *J* = 14.4, 3.7 Hz, 1H), 2.13 (ddt, *J* = 13.7, 5.3, 2.6 Hz, 1H), 2.01 - 1.82 (m, 1H), 1.18 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 138.5, 132.6, 130.0, 128.3, 127.6, 76.3, 72.5, 71.0, 62.0, 58.3, 52.7, 44.9, 28.1, 28.0, 25.1, 14.2; IR (film): ν_{max} 2979, 2927, 1723, 1204, 1094, 1027, 737, 698; HRMS (ESI) calcd for $C_{20}H_{28}O_4S_2Na$ $[M+Na]^+$ 419.1329, found 419.1326.

(*S*,*E*)-(2-(2-(benzyloxy)-5-methoxypent-3-en-1-yl)-1,3-dithian-2-yl)methanol (21). To ester **20** (3.62 g, 9.11 mmol) in THF (60 mL) at 0 ˚C was added LAH (864 mg, 22.8 mmol) in 3 portions over 5 min. After 2.5 h, the reaction was quenched at the same temperature via slow addition of 60 mL of a saturated aqueous solution of Rochelle's salt. The mixture was stirred for 2 h, then extracted with EtOAc (3 x 175 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated to yield the title compound as a colorless oil, which was used without further purification (3.23 g, 99 %). R_f = 0.20 (25% EtOAc/hexanes); $[\alpha]^{25}_D$ = -32.9 (*c* 0.26, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 - 7.14 (m, 5H), 5.83 (dtd, *J* = 15.6, 5.5, 0.7 Hz, 1H), 5.68 (ddt, *J* = 15.6, 7.8, 1.4 Hz, 1H), 4.46 (dd, *J* = 92.7, 11.1 Hz, 2H), 4.30 - 4.19 (m, 2H), 3.96 (d, *J* = 6.2 Hz, 2H), 3.90 - 3.69 (m, 2H), 3.36 (s, 1H), 3.20 (t, *J* = 7.3 Hz, 1H), 2.87 (dddd, *J* = 29.0, 14.4, 10.2, 3.0 Hz, 2H), 2.75 - 2.57 (m, 2H), 2.25 (dd, *J* = 15.4, 9.1 Hz, 1H), 2.14 - 1.96 (m, 2H), 1.91 (dtt, *J* = 13.4, 10.1, 3.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.6, 132.7, 130.0, 128.7, 128.4, 128.1, 76.5, 72.4, 71.0, 65.6, 58.4, 53.5, 44.2, 26.4, 25.9, 25.4; IR (film): ν_{max} 3454, 2930, 2360, 2341, 1063, 981, 909, 738, 699; HRMS (ESI) calcd for $C_{18}H_{26}O_3S_2Na$ $[M+Na]^+$ 377.1223, found 377.1221.

(*S*,*E*)-4-(benzyloxy)-1-hydroxy-7-methoxyhept-5-en-2-one (22). To dithiane **21** (78 mg, 0.22 mmol) in THF-MeOH-H_2O 5:9:1 (1.5 mL) was added [bis(trifluoroacetoxy)iodo]benzene[18] (146 mg, 0.33 mmol) in 1 portion at 0 ˚C. The reaction mixture was quenched after 45 min. with

$NaHCO_3$ (1.0 mL, saturated aqueous solution), and then extracted with Et_2O. The crude product was purified by flash chromatography (40 % EtOAc/hexanes) to furnish the ketone (55 mg, 95 %) as a colorless oil. R_f = 0.35 (50% EtOAc/hexanes); $[\alpha]^{25}_D$ = -35.9 (*c* 2.40, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 - 7.14 (m, 5H), 5.85 (dtd, *J* = 15.8, 5.3, 0.7 Hz, 1H), 5.65 (ddt, *J* = 15.6, 7.7, 1.4 Hz, 1H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.41 - 4.28 (m, 2H), 4.25 (t, *J* = 5.1 Hz, 2H), 3.96 (dd, *J* = 5.3, 1.5 Hz, 2H), 3.36 (s, 3H), 3.10 (t, *J* = 5.0 Hz, 1H), 2.79 (dd, *J* = 14.8, 8.8 Hz, 1H), 2.52 (dd, *J* = 14.9, 4.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.0, 137.9, 131.2, 130.9, 128.6, 128.0, 100.1, 75.9, 72.2, 70.9, 69.7, 58.4, 40.0; IR (film): ν_{max} 3393, 2783, 1723, 1090, 1070, 740, 699; HRMS (ESI) calcd for $C_{15}H_{20}O_4Na$ $[M+Na]^+$ 287.1254, found 287.1248.

(*S*,*E*)-4-(benzyloxy)-1-bromo-7-methoxyhept-5-en-2-one (12). To alcohol **22** (1.26 g, 4.77 mmol) and CBr_4 (1.90 g, 5.72 mmol) in 48 mL DCM was added PPh_3 (1.50 g, 5.72 mmol). The solution changed color from yellow to dark brown, then orange after stirring for 1 h. The reaction mixture was diluted with Et_2O, then filtered over a pad of silica, and the filter cake washed with additional Et_2O. The filtrate and washings were concentrated, then chromatographed (20 % EtOAc/hexanes) to yield the title compound as a colorless oil (1.13 g, 72 %). R_f = 0.32 (20% EtOAc/hexanes); $[\alpha]^{23}_D$ = -6.06 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 - 7.20 (m, 5H), 5.88 (dtd, *J* = 15.6, 5.4, 0.9 Hz, 1H), 5.68 (ddt, *J* = 15.6, 7.7, 1.5 Hz, 1H), 4.59 (d, *J* = 11.3 Hz, 1H), 4.43 - 4.31 (m, 2H), 3.98 (dd, *J* = 5.5, 1.4 Hz, 2H), 3.95 (d, *J* = 0.4 Hz, 2H), 3.38 (s, 3H), 3.02 (dd, *J* = 15.4, 8.7 Hz, 1H), 2.75 (dd, *J* = 15.4, 4.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.8, 138.1, 131.3, 130.8, 128.7, 128.1, 128.0, 76.3, 72.3, 71.0, 58.5, 46.2, 35.9; IR (film): ν_{max} 2873, 2825, 1725, 1587, 1452, 1383, 1093, 1069, 739, 699; HRMS (ESI) calcd for $C_{15}H_{19}BrO_3Na$ $[M+Na]^+$ 349.0418, found 349.0400.

(*S*,*E*)-1-(4-(benzyloxy)-7-methoxy-2-oxohept-5-en-1-yl)-5-formyl-*N*-methoxy-*N*-methyl-1*H*-pyrrole-2-carboxamide (23). To pyrrole **11** (128 mg, 0.70 mmol) and bromide **12** (229 mg, 0.70 mmol) in MeCN (5 mL) was added Cs_2CO_3 (228 mg, 0.70 mmol) in 2 portions over 0.5 h at 0 ˚C. The mixture was stirred for 8 h, then diluted with EtOAc (50 mL) and washed with H_2O and brine. The organic phase was dried over Na_2SO_4, concentrated, and purified by column chromatography (33-50% EtOAc/hexanes) to yield 236 mg, 79 % of the aldehyde as a yellow oil. R_f = 0.51 (50% EtOAc/hexanes); $[\alpha]^{23}_D$ = +11.5 (*c* 0.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.38 - 7.29 (m, 5H), 6.95 (d, *J* = 4.2 Hz, 1H), 6.86 (d, *J* = 4.2 Hz, 1H), 5.96 - 5.54 (m, 4H), 4.56 (d, *J* = 11.4 Hz, 1H), 4.42 (d, *J* = 11.4 Hz, 1H), 4.40 - 4.32 (m, 1H), 3.95 (dd, *J* = 5.6, 1.5 Hz, 2H), 3.63 (s, 3H), 3.34 (s, 3H), 3.26 (s, 3H), 2.92 (dd, *J* = 15.9, 8.0 Hz, 1H), 2.69 (dd, *J* = 15.9, 4.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.1, 181.1, 161.3, 138.4, 133.4, 131.9, 130.3, 128.5, 127.9, 127.7, 123.2, 115.2, 75.4, 72.4, 70.8, 61.7, 58.2, 56.4, 46.6, 33.4, 29.9; IR (film): ν_{max} 2926, 1732, 1668, 1634, 1522, 1447, 1374, 1261, 1211, 1098; HRMS (ESI) calcd for $C_{23}H_{28}N_2O_6Na$ $[M+Na]^+$ 451.1847, found 451.1825.

(2*R*,4*S*,5*R*)-4-(benzyloxy)-*N*-methoxy-*N*-methyl-5-vinyl-1',4,4',5-tetrahydro-3*H*-spiro[furan-2,3'-pyrrolo[2,1-*c*][1,4]oxazine]-6'-carboxamide (9) and (2*S*,4*S*,5*R*)-4-(benzyloxy)-*N*-methoxy-*N*-methyl-5-vinyl-1',4,4',5-tetrahydro-3*H*-spiro[furan-2,3'-pyrrolo[2,1-*c*][1,4]oxazine]-6'-carboxamide (*epi*-9). Aldehyde **23** (1.12 g, 2.62 mmol) in THF (17.0 mL) was cooled to 0 ˚C and treated with 13.0 mL of LTEPA[20] (0.2 M in THF). After 2.5 h, TLC analysis indicated the reaction was complete, and the mixture was quenched via slow addition of 5 % AcOH until evolution of H_2 gas ceased. The resulting mixture was extracted with EtOAc, washed with a saturated aqueous solution of $NaHCO_3$ followed by brine and then dried over Na_2SO_4. The extracts were concentrated under reduced pressure and subjected to

flash chromatography (60 % EtOAc/hexanes) to yield a mixture of ketoalcohol **10** and the corresponding hemiketal (1.05 g, 93 %) as a viscous yellow oil, which was used in the key Pd-catalyzed cyclization.

The ketoalcohol **10** (20 mg, 0.046 mmol) obtained above was dissolved in 5.0 mL DCM with 4 Å MS and cooled to 0 ˚C. To the solution was added $Pd(PhCN)_2Cl_2$ (1.8 mg) and stirring was continued for 12 h. The reaction was filtered over a silica plug with EtOAc, and the combined organics were concentrated in vacuo. The crude material was purified by chromatography to yield **9** (8 mg, 43 %) and ***epi*-9** (8 mg, 43 %) as viscous yellow oils.

Spiro compound 9: R_f = 0.55 (50% EtOAc/hexanes); $[\alpha]^{23}_D$ = +66.5 (*c* 0.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 - 7.27 (m, 5H), 6.98 (d, *J* = 4.1 Hz, 1H), 5.91 (d, *J* = 4.2 Hz, 1H), 5.82 (dddd, *J* = 17.2, 10.4, 6.7, 0.5 Hz, 1H), 5.34 (dt, *J* = 17.1, 1.1 Hz, 1H), 5.17 (dt, *J* = 10.4, 1.1 Hz, 1H), 5.01 (d, *J* = 14.5 Hz, 1H), 4.84 (d, *J* = 14.8 Hz, 1H), 4.63 - 4.49 (m, 4H), 4.33 (d, *J* = 14.2 Hz, 1H), 3.92 (ddd, *J* = 7.9, 5.0, 3.4 Hz, 1H), 3.69 (s, 3H), 3.29 (s, 3H), 2.30 (dd, *J* = 14.1, 3.2 Hz, 1H), 2.23 (dd, *J* = 14.1, 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 138.0, 136.1, 131.0, 128.7, 128.0, 117.5, 117.1, 103.3, 103.0, 85.6, 82.0, 77.5, 77.2, 77.0, 72.2, 61.1, 58.5, 51.8, 42.7, 33.7, 29.9; IR (film): ν_{max} 3445, 2925, 2361, 2343, 1622, 1496, 1456, 1351, 1098, 1053, 1026; HRMS (ESI) calcd for $C_{22}H_{26}N_2O_5Na$ $[M+Na]^+$ 421.1742, found 421.1740.

Spiro compound *epi*-9: R_f = 0.68 (50% EtOAc/hexanes); $[\alpha]^{23}_D$ = -85.9 (*c* 0.26, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 - 7.28 (m, 5H), 6.97 (d, *J* = 4.1 Hz, 1H), 5.93 (ddd, *J* = 17.4, 10.4, 7.9 Hz, 1H), 5.88 (d, *J* = 4.1 Hz, 1H), 5.32 (ddd, *J* = 17.1, 1.0 Hz, 1H), 5.20 (ddd, *J* = 10.3, 1.4, 1.0 Hz, 1H), 5.02 (d, *J* = 14.7 Hz, 1H), 4.77 (d, *J* = 14.7 Hz, 1H), 4.63 (d, *J* = 14.1 Hz, 1H), 4.59 - 4.51 (m, 3H), 4.32 (d, *J* = 13.9 Hz, 1H), 4.22 (ddd, *J* = 7.2, 6.8, 5.1 Hz, 1H), 3.68 (s, 3H),

3.29 (s, 3H), 2.51 (dd, *J* = 13.1, 6.7 Hz, 1H), 2.13 (dd, *J* = 13.1, 6.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4, 137.9, 137.8, 130.5, 128.7, 128.0, 127.9, 122.3, 118.0, 116.9, 103.6, 102.9, 86.8, 82.2, 72.3, 61.1, 58.9, 52.1, 43.1, 33.7, 29.9. IR (film): ν_{max} 3445, 2925, 2361, 2343, 1622, 1496, 1456, 1351, 1098, 1053, 1026; HRMS (ESI) calcd for $C_{22}H_{26}N_2O_5Na$ $[M+Na]^+$ 421.1742, found 421.1740.

(2*S*,4*S*,5*R*)-4-(benzyloxy)-5-(hydroxymethyl)-*N*-methoxy-*N*-methyl-1',4,4',5-tetrahydro-3*H*-spiro[furan-2,3'-pyrrolo[2,1-*c*][1,4]oxazine]-6'-carboxamide (*epi*-24). To spiro compound *epi*-***9*** (95 mg, 0.238 mmol) in THF-H_2O 10:1 (5.5 mL) was added NMO (70 mg, 0.595 mmol) then OsO_4 (4 wt. % in H_2O) (45 μL) and the mixture was allowed to stir for 24 h. The reaction was quenched with 100 mg of Na_2SO_3 followed by stirring for 0.5 h. The resulting mixture was then diluted with EtOAc (85 mL), washed with H_2O, then brine, and concentrated. The crude diol was then immediately subjected to periodate cleavage.

The oil obtained above was dissolved in THF-pH 7 buffer 5:1 (7.2 mL), cooled to 0 ˚C, then treated with $NaIO_4$ (102 mg, 0.476 mmol). Stirring was continued for 12 h, at which time the reaction was quenched with 2 mL of phosphate buffer, diluted with EtOAc, and phases separated. The organic layer was concentrated under reduced pressure to furnish the crude aldehyde, which was dissolved in EtOH (6 mL), cooled to 0 ˚C, and treated with $NaBH_4$ (13 mg, 0.357 mmol). After 1 h, the reaction mixture was quenched with 2 mL H_2O, diluted with EtOAc, and the layers separated. The organic phase was washed with brine and concentrated to give essentially pure title compound (92 mg, 89 %). R_f = 0.39 (50% EtOAc/hexanes) as a yellow oil; $[\alpha]^{23}_D$ = -19.1 (*c* 0.65, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 - 7.27 (m, 5H), 6.98 (d, *J* = 4.1 Hz, 1H), 5.91 (d, *J* = 4.1 Hz, 1H), 5.00 (d, *J* = 14.7 Hz, 1H), 4.82 (d, *J* = 14.7 Hz, 1H), 4.69 (d, *J* = 14.2 Hz, 1H), 4.59 - 4.44 (m, 2H), 4.36 (d, *J* = 14.2 Hz, 1H), 4.33 - 4.25 (m, 2H), 3.69 (s,

3H), 3.30 (s, 3H), 2.55 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.17 (dd, *J* = 13.5, 6.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 137.6, 129.8, 128.5, 127.9, 127.7, 116.8, 104.1, 102.8, 86.5, 78.4, 72.0, 64.2, 61.0, 59.0, 51.9, 43.5, 33.5, 29.7; IR (film): ν_{max} 2926, 2855, 2363, 2346, 1719, 1686, 1654, 1560, 1508, 1458, 1350, 1260, 1106, 1042; HRMS (ESI) calcd for $C_{21}H_{26}N_2O_6Na$ $[M+Na]^+$ 425.1691, found 425.1677.

(2*R*,4*S*,5*R*)-4-(benzyloxy)-5-(hydroxymethyl)-*N*-methoxy-*N*-methyl-1',4,4',5-tetrahydro-3*H*-spiro[furan-2,3'-pyrrolo[2,1-*c*][1,4]oxazine]-6'-carboxamide (24). Prepared from spiro compound **9** as described for spiro compound *epi*-**24**. Yield: 70 mg, 70 %, yellow oil; R_f = 0.42 (75% EtOAc/hexanes); $[\alpha]^{23}_D$ = +94.5 (*c* 1.20, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 - 7.28 (m, 5H), 6.99 (d, *J* = 4.0 Hz, 1H), 5.92 (d, *J* = 4.1 Hz, 1H), 4.99 (d, *J* = 14.8 Hz, 1H), 4.85 (d, *J* = 14.8 Hz, 1H), 4.68 - 4.55 (m, 2H), 4.52 (d, *J* = 12.2 Hz, 1H), 4.28 (d, *J* = 14.1 Hz, 1H), 4.26 - 4.20 (m, 2H), 4.19 - 4.04 (m, 1H), 3.76 (dd, *J* = 12.1, 3.1 Hz, 1H), 3.69 (s, 3H), 3.56 (dd, *J* = 12.2, 4.0 Hz, 1H), 3.28 (s, 3H), 2.31 (dd, *J* = 14.1, 2.4 Hz, 1H), 2.17 (dd, *J* = 14.1, 8.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.4, 138.0, 131.0, 128.7, 128.0, 122.0, 117.2, 103.9, 103.0, 85.6, 78.2, 72.2, 62.7, 61.1, 58.6, 51.5, 43.0, 33.6, 29.9; IR (film): ν_{max} 2926, 2855, 2363, 2346, 1719, 1686, 1654, 1560, 1508, 1458, 1350, 1260, 1106, 1042; HRMS (ESI) calcd for $C_{21}H_{26}N_2O_6Na$ $[M+Na]^+$ 425.1691, found 425.1677.

(2*S*,4*S*,5*R*)-4-(benzyloxy)-5-(hydroxymethyl)-1',4,4',5-tetrahydro-3*H*-spiro[furan-2,3'-pyrrolo[2,1-*c*][1,4]oxazine]-6'-carbaldehyde (*epi*-25). To spiro compound *epi*-**24** (92 mg, 0.212 mmol) in 5 mL THF at -78 ˚C was added LAH (16 mg, 0.423 mmol), and the temperature allowed to rise to 0 ˚C over 0.5 h. The temperature was maintained an additional 1 h, then the reaction was quenched with $KHSO_4$ (92 mg) then 5 mL 1 N HCl. The reaction was diluted with

70 mL EtOAc, separated, then dried over Na_2SO_4. The dry organics were concentrated to yield an essentially pure compound (61 mg, 84 %) as a viscous orange oil. R_f = 0.55 (66% EtOAc/hexanes); $[\alpha]^{23}_D$ = -31.6 (*c* 0.20, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.62 - 7.26 (m, 5H), 6.91 (d, *J* = 4.1 Hz, 1H), 6.00 (d, *J* = 4.1 Hz, 1H), 5.02 (d, *J* = 15.5 Hz, 1H), 4.82 (d, *J* = 15.5 Hz, 1H), 4.77 (d, *J* = 14.3 Hz, 1H), 4.53 (d, *J* = 2.5 Hz, 2H), 4.37 - 4.22 (m, 3H), 3.76 (dd, *J* = 11.9, 3.4 Hz, 1H), 3.66 (dd, *J* = 11.9, 5.1 Hz, 2H), 2.55 (dd, *J* = 13.5, 6.3 Hz, 1H), 2.18 (dd, *J* = 13.6, 6.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 137.7, 134.3, 131.3, 128.7, 128.1, 127.9, 124.3, 105.0, 103.7, 86.7, 78.5, 72.2, 64.3, 58.7, 51.7, 43.4; IR (film): ν_{max} 2920, 2852, 2360, 2342, 1716, 1652, 1558, 1507, 1465, 1260, 1185, 1042; HRMS (ESI) calcd for $C_{19}H_{21}NO_5Na$ $[M+Na]^+$ 366.1320, found 366.1299.

(2*R*,4*S*,5*R*)-4-(benzyloxy)-5-(hydroxymethyl)-1',4,4',5-tetrahydro-3*H*-spiro[furan-2,3'-pyrrolo[2,1-*c*][1,4]oxazine]-6'-carbaldehyde (25). Prepared from **24** as described for spiro compound *epi*-**25**. Yield: 50 mg, 89 %, orange oil. R_f = 0.66 (75% EtOAc/hexanes); $[\alpha]^{23}_D$ = +87.8 (*c* 0.68, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.47 - 7.28 (m, 5H), 6.92 (d, *J* = 4.1 Hz, 1H), 6.02 (d, *J* = 4.1 Hz, 1H), 5.01 (dd, *J* = 15.5, 1.1 Hz, 1H), 4.87 (d, *J* = 15.5 Hz, 1H), 4.68 - 4.56 (m, 2H), 4.53 (d, *J* = 12.1 Hz, 1H), 4.32 - 4.20 (m, 2H), 4.16 (ddd, *J* = 8.3, 4.7, 2.4 Hz, 1H), 3.78 (dd, *J* = 12.2, 3.1 Hz, 1H), 3.73 - 3.65 (m, 1H), 3.59 (dd, *J* = 12.0, 3.9 Hz, 1H), 2.33 (dd, *J* = 14.2, 2.4 Hz, 1H), 2.20 (dd, *J* = 14.2, 8.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.0, 137.9, 135.3, 131.2, 128.1, 128.0, 124.5, 105.1, 103.4, 85.9, 78.1, 72.3, 62.6, 58.1, 51.0, 42.8, 30.0;IR (film): ν_{max} 2920, 2852, 2360, 2342, 1716, 1652, 1558, 1507, 1465, 1260, 1185, 1042; HRMS (ESI) calcd for $C_{19}H_{21}NO_5Na$ $[M+Na]^+$ 366.1320, found 366.1299.

Acortatarin A (1) and *epi*-Acortatarin A (*epi*-1). According to a known procedure[7], spiro compound **25** (31 mg, 0.090 mmol) in DCM (3.0 mL) was added 0.9 mL of $TiCl_4$ solution (1.0M

/ DCM) at 0 ˚C, and the reaction stirred for 3 h. At the same temperature, the reaction was then quenched with a saturated aqueous solution of $NaHCO_3$ (3.0 mL), extracted with EtOAc (3 x 50 mL), and the combined extracts dried over Na_2SO_4. Careful purification by column chromatography (100% EtOAc) separated the anomeric mixture yielding acortatarin A (**1**) (16 mg, 70 %) and (*epi*-**1**) (1.5 mg, 7 %) as off-white crystals.

Acortatarin A (1): R_f = 0.29 (100 % EtOAc); $[\alpha]^{23}_D$ = +185.2 (*c* 0.15, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 9.36 (s, 1H), 7.02 (d, *J* = 4.1 Hz, 1H), 6.08 (d, *J* = 4.1 Hz, 1H), 5.02 (d, *J* = 15.8 Hz, 1H), 4.85 (d, *J* = 15.8 Hz, 1H), 4.59 (d, *J* = 14.0 Hz, 1H), 4.29 (ddd, *J* = 8.3, 4.5, 2.7 Hz, 1H), 4.23 (d, *J* = 14.0 Hz, 1H), 4.07 (td, *J* = 4.8, 3.2 Hz, 1H), 3.71 (dd, *J* = 12.1, 3.3 Hz, 1H), 3.62 (dd, *J* = 12.1, 4.9 Hz, 1H), 2.35 (dd, *J* = 14.1, 8.3 Hz, 1H), 2.15 (dd, *J* = 14.0, 2.7 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 180.4, 137.8, 132.6, 126.2, 106.4, 104.7, 89.4, 72.4, 63.2, 58.9, 52.2, 46.1; HRMS (ESI) calcd for $C_{12}H_{15}NO_5Na$ $[M+Na]^+$ 276.0850, found 276.0851.

^{1}H NMR (500 MHz, Acetone-d_6) δ 9.48 (s, 1H), 6.99 (d, *J* = 4.1 Hz, 1H), 6.07 (d, *J* = 3.8 Hz, 1H), 5.01 (d, *J* = 15.1 Hz, 1H), 4.85 (d, *J* = 15.5 Hz, 1H), 4.55 (d, *J* = 14.1 Hz, 1H), 4.36 (dt, *J* = 7.6, 3.5 Hz, 1H), 4.21 (d, *J* = 14.0 Hz, 1H), 4.11 (q, *J* = 4.3 Hz, 1H), 3.70 (dd, *J* = 12.0, 3.5 Hz, 1H), 3.63 (dd, *J* = 12.0, 4.4 Hz, 1H), 2.41 (dd, *J* = 13.9, 8.1 Hz, 1H), 2.15 (dd, *J* = 13.9, 2.7 Hz, 1H); ^{13}C NMR (125 MHz, Acetone-d6) δ 179.0, 135.9, 132.2, 124.3, 105.4, 105.3, 104.0, 89.5, 62.7, 58.2, 51.7, 45.8; HRMS (ESI) calcd for $C_{12}H_{15}NO_5Na$ $[M+Na]^+$ 276.0850, found 276.0851.

***epi*-Acortatarin A (*epi*-1):** R_f = 0.30 (100 % EtOAc); $[\alpha]^{23}_D$ = -73.1 (*c* 0.05, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 9.38 (s, 1H), 7.03 (d, *J* = 4.1 Hz, 1H), 6.07 (d, *J* = 3.9 Hz, 1H), 5.10 (d, *J* = 15.9 Hz, 1H), 4.82 (d, *J* = 15.7 Hz, 1H), 4.68 (d, *J* = 13.9 Hz, 1H), 4.52 - 4.30 (m, 1H), 4.23 (d, *J* = 14.8 Hz, 1H), 4.09 - 3.87 (m, 1H), 3.71 (dd, *J* = 11.8, 4.5 Hz, 1H), 3.62 (dd, *J* = 11.6, 6.9 Hz,

1H), 2.51 (dd, J = 13.3, 6.9 Hz, 1H), 2.10 (dd, J = 13.3, 6.9 Hz, 1H). HRMS (ESI) calcd for $C_{12}H_{15}NO_5Na$ $[M+Na]^+$ 276.0850, found 276.0851.

Acortatarin A (1) and *epi*-Acortatarin A (*epi*-1). Compounds (**1**) and (*epi*-**1**) were prepared from spiro compound *epi*-**25** as described for the preparation of the same compounds from spiro compound **25**.

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Supporting Information Available: ^{1}H- and ^{13}C-NMR spectra for all new compounds. Additional details on the electrochemical experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Tan and co-workers correctly conclude that acortatarin A and pollenopyrroside B are the same natural product based on X-ray structures of a related natural product, pollenopyrroside A (ref 1). Although spectra of natural pollenopyrroside B were reported in acetone-d_6, to date, no spectra of synthetic acortatarin A/pollenopyrroside B in acetone-d_6 have appeared.

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(22) See Supporting Information for full details.

(23) Although the presence of water shifts oxidation potential towards more negative values, acetonitrile was used as solvent due to lack of solubility of the analytes and the internal standard in water. At the moment, it is unclear if acortatarin A exists in the bilayer, as many antioxidants do, or elsewhere. Additionally, acetonitrile was used to allow comparison to the oxidation potential of the well known antioxidant vitamin E. For leading references see: Tan, Y. S.; Chen, S.; Hong, W. M.; Kan, J. M.; Kewk, E. S. H.; Lim, S. Y.; Lim, Z. H.; Tessensohn, M. E.; Zhang, Y.; Webster, R. D. *Phys. Chem. Chem. Phys.,* **2011**, *13*, 12745.

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