

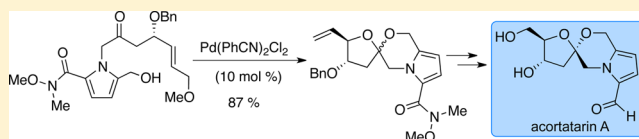
# Total Synthesis of Acortatarin A Using a Pd(II)-Catalyzed Spiroketalization Strategy

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**S** Supporting Information

**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**.<sup>1,2</sup> Zhang and co-workers named this compound pollenopyrroside B and also isolated the related spiroketal **2**, named pollenopyrroside A.<sup>1</sup> Hou, Cheng, and co-workers named compound **1** acortatarin A and also isolated the more highly oxidized analogue **3**, which was named acortatarin B.<sup>2</sup> Together with funebral **4**<sup>3</sup> and two additional acyclic compounds, magnolamide<sup>4</sup> and pyrraline,<sup>5</sup> these compounds comprise a small family of 2-formyl-5-hydroxymethylpyrrole-containing natural products.

Interestingly, pollenopyrroside B/acortatarin A<sup>6</sup> 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.<sup>2</sup> 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.<sup>1</sup> Three total syntheses have now been completed,<sup>7,8</sup> 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.<sup>9</sup> Furthermore, their NMR data was reported using acetone-*d*<sub>6</sub> as the solvent<sup>1</sup> while all other data has been reported in methanol-*d*<sub>4</sub>.<sup>2,7,8</sup>

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.<sup>2</sup> The

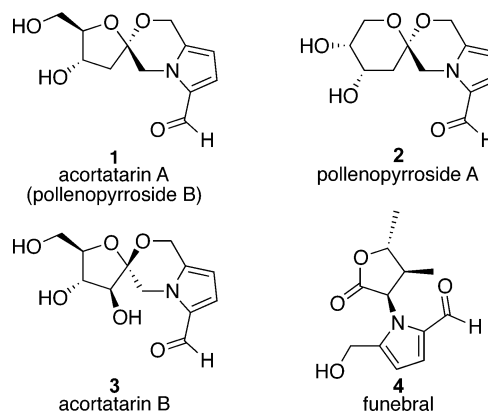


Figure 1. Acortatarin A and related natural products.

biological activities of these natural sources of acortatarin A also include antitumor and antioxidant properties.<sup>1</sup> Hou and Cheng demonstrated that acortatarin A was able to inhibit high-glucose-induced reactive oxygen species (ROS) in mesangial cells.<sup>2</sup> Evidence suggests that ROS in renal cells play an integral role in the development of diabetic nephropathy,<sup>10</sup> 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

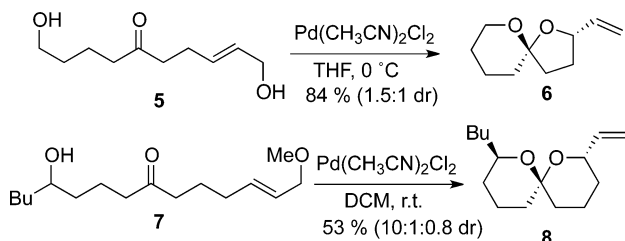
Previous work from our laboratory has focused on developing metal-catalyzed dehydrative cyclization reactions of unsaturated alcohols,<sup>11</sup> and we have recently been exploring a Pd(II)-catalyzed method for spiroketalization.<sup>12</sup> Given the interesting

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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

### Scheme 1. Pd(II)-Catalyzed Spiroketalization



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.<sup>13</sup>

From a retrosynthetic perspective, acortatarin A (Figure 2) would rely on conversion of the penultimate intermediate **9**,

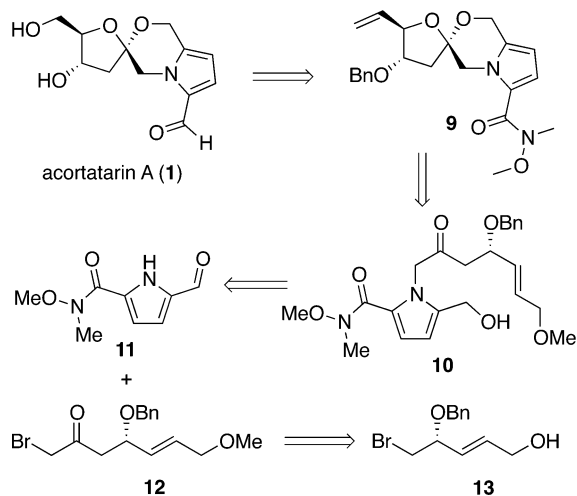
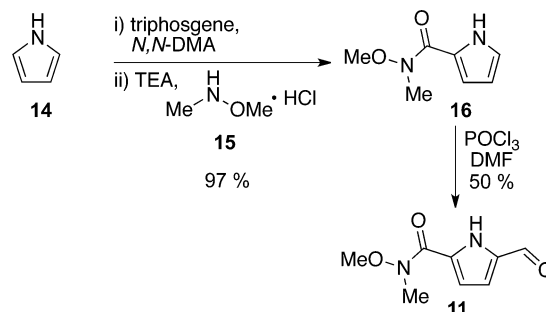


Figure 2. Retrosynthetic analysis of acortatarin A.

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**.

Initial experiments were focused on the preparation of the required pyrrole **11** (Scheme 2). This was accomplished from

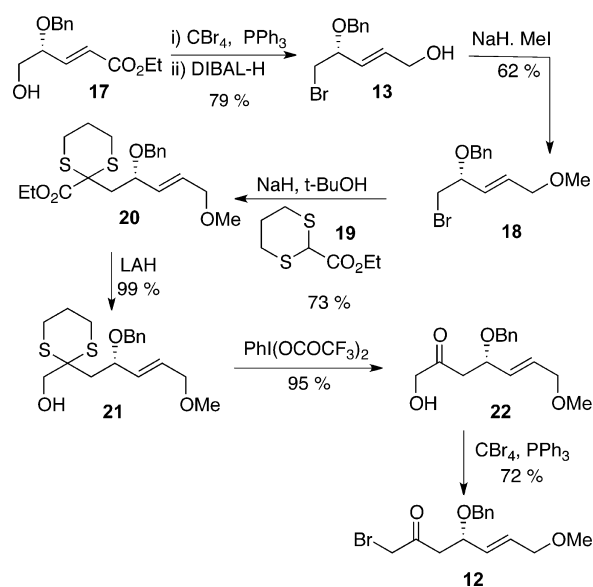
### Scheme 2. 2,5-Disubstituted Pyrrole Fragment



pyrrole by first using a one-pot acylation/amidation sequence<sup>14</sup> to provide the Weinreb amide **16** in 97% yield. A Vilsmeier-Haack formylation was then used for introduction of the aldehyde moiety.<sup>15</sup> 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.

The preparation of the alkylating agent, bromoketone fragment **12**, was explored and commenced with a one-pot bromination and reduction<sup>18</sup> of the known  $\delta$ -hydroxy ester **17**<sup>16</sup> to provide allylic alcohol **13** in 79% yield (Scheme 3).

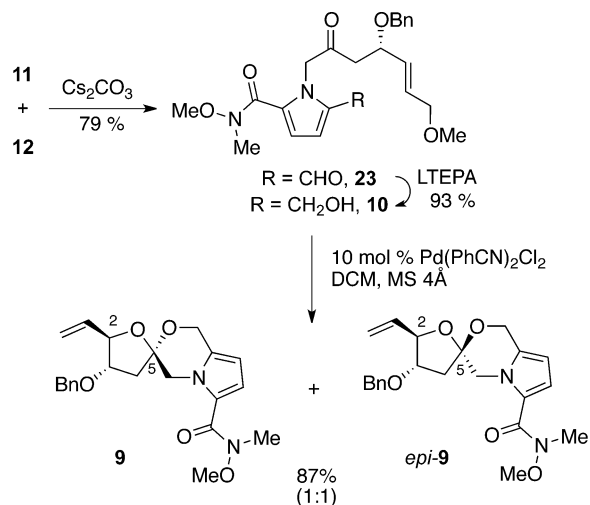
### Scheme 3. Synthesis of the Methyl Ether **12**



Methylation of the hydroxyl group with methyl iodide and alkylation of dithiane **19**<sup>17</sup> 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<sup>18</sup> to afford acyloin **22**. The Appel halogenation conditions used previously<sup>19</sup> 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 equiv of Cs<sub>2</sub>CO<sub>3</sub> in acetonitrile at 0 °C gave the best result (Scheme 4). Under

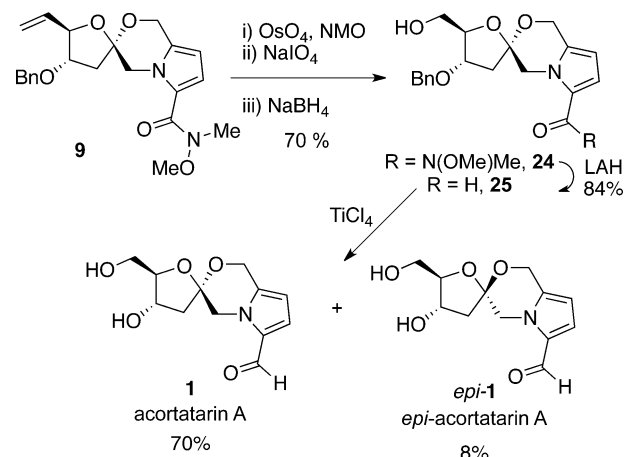
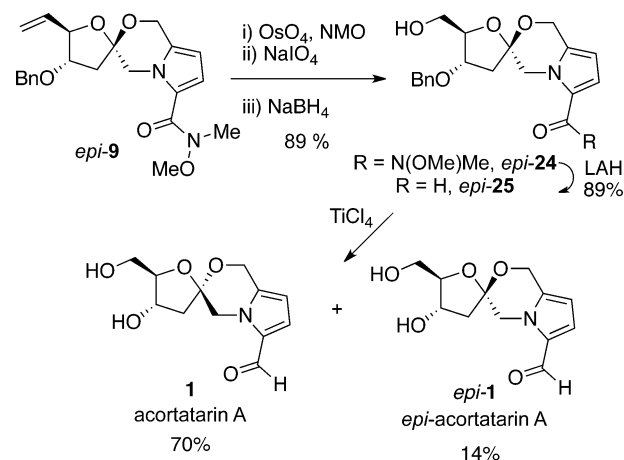
Scheme 4. Fragment Coupling and Spiroketalization



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)aluminumhydride (LTEPA)<sup>20</sup> 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.

In the event, hydroxyketone **10** was treated with Pd-(PhCN)<sub>2</sub>Cl<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> with MS 4 Å 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.

The end game sequence commenced with oxidative cleavage, and it was found that OsO<sub>4</sub>-catalyzed dihydroxylation, followed by glycol cleavage, was superior to ozonolysis (Schemes 5 and 6). Spiroketal **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 three 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, 1 N HCl) was attempted; however, conversion to the desired diastereomer **25** was unsuccessful leading only to recovered starting material.<sup>21</sup> Instead, compounds **25** and *epi-25* were each treated with TiCl<sub>4</sub> to yield acortatarin A and *epi-acortatarin A* in 78% and 84% combined yields respectively.

Scheme 5. Elaboration of **9** to Acortatarin AScheme 6. Elaboration of *epi-9* to Acortatarin A

Gratifyingly, this verified that the newly formed, nonepimerizable 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.<sup>2,7</sup> Additionally, <sup>1</sup>H and <sup>13</sup>C NMR spectra of acortatarin A were obtained in acetone-*d*<sub>6</sub> and confirmed that acortatarin A and pollenopyrroside B are indeed the same compound.

It has been suggested that the bioactivity of **1** against ROS was due to antioxidant properties.<sup>2</sup> 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.<sup>22,23</sup> While the oxidation potential of most compounds considered antioxidants is below +0.70 V,<sup>24</sup> the first and second oxidation potentials of **1** were measured to be +1.74 and +1.90 V, respectively. Interestingly, the cyclic voltammogram shows that the oxidation is not reversible (Figure 3). The high oxidation potentials measured contrast the values typically obtained for antioxidants and these data suggest that **1** is likely functioning

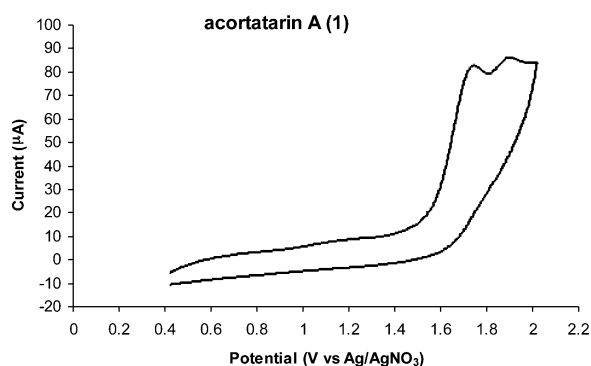


Figure 3. Voltammogram of **1** in CH<sub>3</sub>CN.

by an alternative mechanism. This corroborates the original ROS experiments<sup>2</sup> 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.

## 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 Methods.** 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, and 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. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded in CDCl<sub>3</sub>, CD<sub>3</sub>OD or acetone-*d*<sub>6</sub> using tetramethylsilane as an internal standard. Chemical shift (δ) is reported in parts per million (ppm) downfield relative to tetramethylsilane, CDCl<sub>3</sub>, CD<sub>3</sub>OD, or acetone-*d*<sub>6</sub>. 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,<sup>13</sup> a solution of triphosgene (7.52 g, 25.3 mmol) in 35 mL of 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 min. The resulting mixture was allowed to stir at room temperature for 2 h. 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 was stirred at room temperature for 30 min. 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 min at 0 °C. The reaction was allowed to reach room temperature overnight before it was concentrated, taken up in 150 mL of EtOAc, and washed with a

saturated aqueous solution of NaHCO<sub>3</sub>, followed by H<sub>2</sub>O, and then dried (Na<sub>2</sub>SO<sub>4</sub>) 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*<sub>f</sub> = 0.47 (50% EtOAc/hexanes). Mp: 112–114 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 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). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 161.6, 123.8, 122.0, 114.9, 110.7, 61.3, 33.2. IR (film): ν<sub>max</sub> 3269, 2974, 2937, 1755, 1690, 1597, 1547, 1438, 1296, 1178, 1104, 1045, 749. HRMS (ESI): calcd for C<sub>7</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>Na [M + Na]<sup>+</sup> 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 equiv of the Vilsmeier reagent (prepared by dropwise addition of 0.65 mL of POCl<sub>3</sub> to 0.65 mL of 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<sub>2</sub>CO<sub>3</sub> (15 mL) with stirring (15 min). The mixture was extracted with EtOAc, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. Column chromatography (30% EtOAc/hexanes) afforded the title compound as a crystalline white solid (591 mg, 50%). *R*<sub>f</sub> = 0.34 (50% EtOAc/hexanes). Mp: 118–120 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 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). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 180.3, 160.1, 133.6, 129.4, 120.2, 115.6, 61.7, 33.3. IR (film): ν<sub>max</sub> 3240, 1677, 1612, 1391, 1216, 1193, 811, 751. HRMS (ESI): calcd for C<sub>8</sub>H<sub>10</sub>N<sub>2</sub>O<sub>3</sub>Na [M + Na]<sup>+</sup> 205.0584, found 205.0582.

**(*R,E*)-4-(Benzyloxy)-5-bromopent-2-en-1-ol (13).** Based on a similar literature procedure,<sup>18</sup> a solution of (*R,E*)-ethyl 4-(benzyloxy)-5-hydroxypent-2-enoate<sup>15</sup> (**17**) (250 mg, 1.0 mmol) and CBr<sub>4</sub> (663 mg, 2.0 mmol) in 6 mL of dichloromethane was treated with PPh<sub>3</sub> (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 × 20 mL). The combined organics were dried over Na<sub>2</sub>SO<sub>4</sub>, 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*<sub>f</sub> = 0.59 (60% EtOAc/hexanes). [α]<sub>D</sub><sup>25</sup> = –31.8 (c 1.00, CHCl<sub>3</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.38–7.33 (m, 5H), 5.95 (dtd, *J* = 15.6, 5.1, 0.9 Hz, 1H), 5.68 (dtd, *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 (ddd, *J* = 7.4, 6.4, 5.2, 0.8 Hz, 1H), 3.53–3.34 (m, 2H), 1.44 (br s, 1H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 138.1, 134.6, 128.7, 128.6, 128.1, 128.0, 78.7, 71.1, 62.9, 35.1. IR (film): ν<sub>max</sub> 3379, 3030, 2866, 1454, 1217, 1090, 739, 698. HRMS (ESI): calcd for C<sub>12</sub>H<sub>15</sub>BrO<sub>2</sub>Na<sub>2</sub> [M + 2Na]<sup>+</sup> 317.0155, found 317.0699.

**(*R,E*)-((1-Bromo-5-methoxypent-3-en-2-yl)oxy)methylbenzene (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 of 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<sub>4</sub>Cl and extracted with DCM (3 × 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*<sub>f</sub> = 0.58 (25% EtOAc/hexanes). [α]<sub>D</sub><sup>25</sup> = –28.6 (c 1.91, CHCl<sub>3</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 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 (ddd, *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). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): 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<sub>max</sub> 3030, 2927, 2870, 1452, 1383, 1102, 1066, 974, 738, 698. HRMS (ESI): calcd for C<sub>12</sub>H<sub>13</sub>BrNaO [M – MeOH – Na]<sup>+</sup> 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<sup>16</sup> (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<sub>2</sub>O and poured into a cold saturated aqueous solution of NH<sub>4</sub>Cl. The organic phase was separated and the aqueous layer extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, 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*<sub>f</sub> = 0.41 (25% EtOAc/hexanes). [ $\alpha$ ]<sub>D</sub><sup>25</sup> = -9.91 (c 0.76, CHCl<sub>3</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  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). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  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):  $\nu_{\max}$  2979, 2927, 1723, 1204, 1094, 1027, 737, 698. HRMS (ESI): calcd for C<sub>20</sub>H<sub>28</sub>O<sub>4</sub>S<sub>2</sub>Na [M + Na]<sup>+</sup> 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 three 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 and then extracted with EtOAc (3 × 175 mL). The organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to yield the title compound as a colorless oil, which was used without further purification (3.23 g, 99%). *R*<sub>f</sub> = 0.20 (25% EtOAc/hexanes). [ $\alpha$ ]<sub>D</sub><sup>25</sup> = -32.9 (c 0.26, CHCl<sub>3</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  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). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  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):  $\nu_{\max}$  3454, 2930, 2360, 2341, 1063, 981, 909, 738, 699. HRMS (ESI): calcd for C<sub>18</sub>H<sub>26</sub>O<sub>3</sub>S<sub>2</sub>Na [M + Na]<sup>+</sup> 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<sub>2</sub>O 5:9:1 (1.5 mL) was added [bis(trifluoroacetoxy)iodo]benzene<sup>17</sup> (146 mg, 0.33 mmol) in one portion at 0 °C. The reaction mixture was quenched after 45 min with NaHCO<sub>3</sub> (1.0 mL, saturated aqueous solution) and then extracted with Et<sub>2</sub>O. The crude product was purified by flash chromatography (40% EtOAc/hexanes) to furnish the ketone (55 mg, 95%) as a colorless oil. *R*<sub>f</sub> = 0.35 (50% EtOAc/hexanes). [ $\alpha$ ]<sub>D</sub><sup>25</sup> = -35.9 (c 2.40, CHCl<sub>3</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  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). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  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):  $\nu_{\max}$  3393, 2783, 1723, 1090, 1070, 740, 699. HRMS (ESI): calcd for C<sub>15</sub>H<sub>20</sub>O<sub>4</sub>Na [M + Na]<sup>+</sup> 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<sub>4</sub> (1.90 g, 5.72 mmol) in 48 mL of DCM was added PPh<sub>3</sub> (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<sub>2</sub>O and then

filtered over a pad of silica, and the filter cake was washed with additional Et<sub>2</sub>O. 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*<sub>f</sub> = 0.32 (20% EtOAc/hexanes). [ $\alpha$ ]<sub>D</sub><sup>23</sup> = -6.06 (c 1.00, CHCl<sub>3</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  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). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  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):  $\nu_{\max}$  2873, 2825, 1725, 1587, 1452, 1383, 1093, 1069, 739, 699. HRMS (ESI): calcd for C<sub>15</sub>H<sub>19</sub>BrO<sub>3</sub>Na [M + Na]<sup>+</sup> 349.0418, found 349.0400.

**(S,E)-1-(4-(Benzyloxy)-7-methoxy-2-oxohept-5-en-1-yl)-5-formyl-N-methoxy-N-methyl-1H-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<sub>2</sub>CO<sub>3</sub> (228 mg, 0.70 mmol) in two portions over 0.5 h at 0 °C. The mixture was stirred for 8 h, diluted with EtOAc (50 mL), and washed with H<sub>2</sub>O and brine. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated, and purified by column chromatography (33–50% EtOAc/hexanes) to yield 236 mg, 79% of the aldehyde as a yellow oil. *R*<sub>f</sub> = 0.51 (50% EtOAc/hexanes). [ $\alpha$ ]<sub>D</sub><sup>23</sup> = +11.5 (c 0.10, CHCl<sub>3</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  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). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  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):  $\nu_{\max}$  2926, 1732, 1668, 1634, 1522, 1447, 1374, 1261, 1211, 1098. HRMS (ESI): calcd for C<sub>23</sub>H<sub>28</sub>N<sub>2</sub>O<sub>6</sub>Na [M + Na]<sup>+</sup> 451.1847, found 451.1825.

**(2R,4S,5R)-4-(Benzyloxy)-N-methoxy-N-methyl-5-vinyl-1',4',4',5'-tetrahydro-3H-spiro[furan-2,3'-pyrrolo[2,1-c][1,4]oxazine]-6'-carboxamide (9) and (2S,4S,5R)-4-(Benzyloxy)-N-methoxy-N-methyl-5-vinyl-1',4',4',5'-tetrahydro-3H-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<sup>19</sup> (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<sub>2</sub> gas ceased. The resulting mixture was extracted with EtOAc, washed with a saturated aqueous solution of NaHCO<sub>3</sub> followed by brine, and then dried over Na<sub>2</sub>SO<sub>4</sub>. 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)<sub>2</sub>Cl<sub>2</sub> (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*<sub>f</sub> = 0.55 (50% EtOAc/hexanes). [ $\alpha$ ]<sub>D</sub><sup>23</sup> = +66.5 (c 0.15, CHCl<sub>3</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  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). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  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):  $\nu_{\max}$  3445, 2925, 2361, 2343, 1622, 1496, 1456, 1351, 1098, 1053, 1026. HRMS (ESI): calcd for C<sub>22</sub>H<sub>26</sub>N<sub>2</sub>O<sub>5</sub>Na [M + Na]<sup>+</sup> 421.1742, found 421.1740.

**Spiro Compound epi-9.** *R*<sub>f</sub> = 0.68 (50% EtOAc/hexanes). [ $\alpha$ ]<sub>D</sub><sup>23</sup> = -85.9 (c 0.26, CHCl<sub>3</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  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).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  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):  $\nu_{\text{max}}$  3445, 2925, 2361, 2343, 1622, 1496, 1456, 1351, 1098, 1053, 1026. HRMS (ESI): calcd for  $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_5\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  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– $\text{H}_2\text{O}$  10:1 (5.5 mL) was added NMO (70 mg, 0.595 mmol) then  $\text{OsO}_4$  (4 wt % in  $\text{H}_2\text{O}$ ) (45  $\mu\text{L}$ ), and the mixture was allowed to stir for 24 h. The reaction was quenched with 100 mg of  $\text{Na}_2\text{SO}_3$  followed by stirring for 0.5 h. The resulting mixture was then diluted with EtOAc (85 mL), washed with  $\text{H}_2\text{O}$  and 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, and then treated with  $\text{NaIO}_4$  (102 mg, 0.476 mmol). Stirring was continued for 12 h, at which time the reaction was quenched with 2 mL of phosphate buffer and diluted with EtOAc, and the phases were 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  $\text{NaBH}_4$  (13 mg, 0.357 mmol). After 1 h, the reaction mixture was quenched with 2 mL of  $\text{H}_2\text{O}$  and diluted with EtOAc, and the layers were 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.  $[\alpha]_{\text{D}}^{23} = -19.1$  (c 0.65,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  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).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  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):  $\nu_{\text{max}}$  2926, 2855, 2363, 2346, 1719, 1686, 1654, 1560, 1508, 1458, 1350, 1260, 1106, 1042. HRMS (ESI): calcd for  $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_6\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  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).  $[\alpha]_{\text{D}}^{23} = +94.5$  (c 1.20,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  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).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  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):  $\nu_{\text{max}}$  2926, 2855, 2363, 2346, 1719, 1686, 1654, 1560, 1508, 1458, 1350, 1260, 1106, 1042. HRMS (ESI): calcd for  $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_6\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  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 of 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 for an additional 1 h, and then the reaction was quenched with  $\text{KHSO}_4$  (92 mg) followed by 5 mL of 1 N HCl. The reaction was diluted with 70 mL of EtOAc, separated, and then dried over  $\text{Na}_2\text{SO}_4$ . 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).  $[\alpha]_{\text{D}}^{23} = -31.6$  (c 0.20,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  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).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  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):  $\nu_{\text{max}}$  2920, 2852, 2360, 2342, 1716, 1652, 1558, 1507, 1465, 1260, 1185, 1042. HRMS (ESI): calcd for  $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  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).  $[\alpha]_{\text{D}}^{23} = +87.8$  (c 0.68,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  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).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  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):  $\nu_{\text{max}}$  2920, 2852, 2360, 2342, 1716, 1652, 1558, 1507, 1465, 1260, 1185, 1042. HRMS (ESI): calcd for  $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  366.1320, found 366.1299.

**Acortatarin A (1) and epi-Acortatarin A (epi-1).** According to a known procedure,<sup>7</sup> to spiro compound 25 (31 mg, 0.090 mmol) in DCM (3.0 mL) was added 0.9 mL of  $\text{TiCl}_4$  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  $\text{NaHCO}_3$  (3.0 mL) and extracted with EtOAc (3  $\times$  50 mL), and the combined extracts were dried over  $\text{Na}_2\text{SO}_4$ . 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).  $[\alpha]_{\text{D}}^{23} = +185.2$  (c 0.15, MeOH).  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  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).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  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  $\text{C}_{12}\text{H}_{15}\text{NO}_5\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  276.0850, found 276.0851.  $^1\text{H}$  NMR (500 MHz, acetone- $d_6$ ):  $\delta$  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).  $^{13}\text{C}$  NMR (125 MHz, acetone- $d_6$ ):  $\delta$  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  $\text{C}_{12}\text{H}_{15}\text{NO}_5\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  276.0850, found 276.0851.

**epi-Acortatarin A (epi-1).**  $R_f = 0.30$  (100% EtOAc).  $[\alpha]_{\text{D}}^{23} = -73.1$  (c 0.05, MeOH).  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  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  $\text{C}_{12}\text{H}_{15}\text{NO}_5\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  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.

## ■ ASSOCIATED CONTENT

## S Supporting Information

<sup>1</sup>H and <sup>13</sup>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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## Notes

The authors declare no competing financial interest.

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