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Progress toward the Synthesis of Pochonin J

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Abstract

The construction of the C(1) - C(5) fragment of the resorcylic acid lactone pochonin J is described. The synthesis is marked by the installation of the cis-1,3-diol moiety in a highly stereoselective manner using Evans' intramolecular base-catalyzed oxyconjugate addition of a hemiacetal-derived nucleophile. The synthetic route presented affords an efficient pathway to the preparation of this critical architectural feature that should facilitate the development of this secondary metabolite as a potential drug candidate.

Keywords

Natural Products, Pochonin J, Resorcylic Acid Lactones

1. Introduction

The resorcylic acid lactones (RALs) constitute a structurally diverse family of secondary metabolites possessing a wide-array of biological properties [1] [2]. Representative members of this family of natural products are illustrated in (Figure 1). Pochonin J (**4**) was isolated from the culture broth of the fungus *Pochonia chlamydosporia* TF-0480 collected in the Tochigi Prefecture, Japan by Shinonaga in 2009 as part of a screening program to identify inhibitors of the secretory glycoprotein WNT-5A involved in mammalian hair growth [3]. While **4** displayed virtually no activity versus WNT-5A, no additional biological assays were reported. The absence of a detailed biological evaluation of pochonin J (**4**) was surprising given the fact that many RALs have been shown to be potent inhibitors of heat shock protein 90 (Hsp90) or mitogen-activated protein (MAP) kinases, which are attractive targets for cancer chemotherapy [4] [5].

Architecturally, pochonin J (**4**) is comprised of a 14-membered macrolactone possessing four chiral centers along the carbon framework [3]. At first glance, the most striking feature of **4** is the presence of a *trans*-fused tetrahydropyran ring, an unusual structural motif among biologically-active secondary metabolites. However, synthetic studies conducted by Jennings have recently called into

question the validity of the initial structural assignment for pochonin J (**4**) [6]. Upon completing the synthesis of *ent*-pochonin J, Jennings and coworkers discovered that several ^{1}H NMR chemical shifts did not align with the reported values for natural pochonin J. Given their findings, Jennings has proposed a structural revision, shown in (**Figure 2**), based on their consideration of the biosynthetic pathway leading to pochonin J [7]. Their proposal consists of an *intermolecular* Michael addition at C(8) leading to epoxy alcohol **6** followed by epoxide opening to furnish *cis*-tetrahydropyran **7**. However, we believe that an alternative biosynthetic pathway may be operative which is also illustrated in (**Figure 2**). We propose that epoxide opening at the C(5)-position occurs first, presumably involving an active site water molecule to afford *anti*-1,2-diol **9**. Next, an *intramolecular* Michael addition of the C(4)-OH group onto the enone will yield the *cis*-tetrahydropyran ring in **10** with the opposite stereochemistry as that proposed by Jennings. Our biosynthetic proposal has merit considering that Piel has recently discovered the existence of an enzymatic domain for the construction of 5- and 6-membered cyclic ethers within polyketides gene clusters [8]. Considering the ambiguity surrounding its proposed structure coupled with the possibility of elucidating its biosynthetic pathway, the lack of a thorough biological evaluation, and our interest in the development of natural products as potential medicinal agents, we elected to embark on a program directed towards the total synthesis of pochonin J.

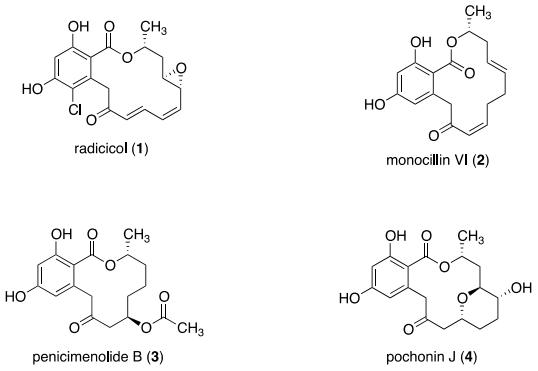


Figure 1. Representative members of the resorcylic acid lactone (RAL) family of natural products.

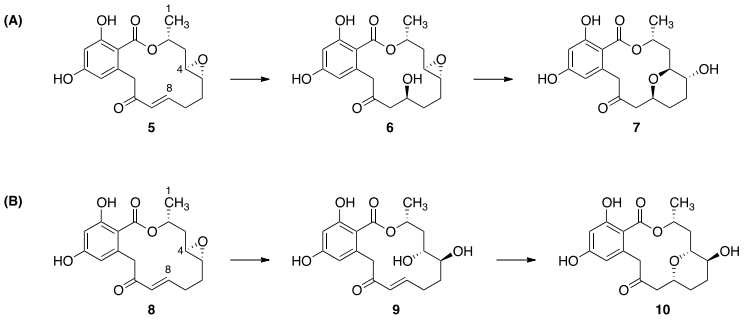


Figure 2. (A) Jennings' biosynthetic proposal for tetrahydropyran ring closure; (B) Pongdee's Biosynthetic Proposal for tetrahydropyran ring closure.

2. Results and Discussion

Our retrosynthetic analysis for pochonin J is illustrated in (Figure 3). From the outset, we envisioned a modular synthetic approach that would allow us to efficiently set either configuration of each chiral center. This flexibility would enable us to rapidly construct all of the possible diastereomers for pochonin J in our initial efforts focused on establishing its correct three-dimensional structure. For our synthetic approach, we viewed the construction of the C(1)-C(5) fragment **10** as a key objective since the stereochemistry present in this five carbon unit would assist in controlling the introduction of future chiral centers in pochonin J. Our work towards the synthesis of **10** is described below.

Our synthetic approach towards **13** originated from commercially-available ethyl 3(*R*)-hydroxybutyrate (**14**) as depicted in (Scheme 1). First, treatment of **14** with trimethylaluminum (Me_3Al) and *N*,*O*-dimethylhydroxylamine hydrochloride furnished Weinreb amide **15** in excellent yield [9] [10] [11]. At this juncture, we envisioned addition of a suitable organometallic reagent that would provide direct access to the C(1)-C(5) fragment of pochonin J following oxidative cleavage of the resulting π-bond. However, after exhaustive experimentation we were surprisingly unable to isolate any products from the reaction of **15** employing a variety of alkenyl or alkynyl nucleophiles.

With our initial efforts stalled, we redirected our efforts to elaborating Weinreb amide **15** to a suitably protected form of the C(1)-C(5) fragment of pochonin J as shown in (Scheme 2). Protection of the free alcohol in **15** as its *tert*-butyldiphenylsilyl (TBDPS) ether using the corresponding silyl chloride and Hünig's base (i-Pr_2NEt) provided silyl ether **19** in excellent yield. Next, reduction of the Weinreb amide functional group employing diisobutylaluminum hydride (DIBALH) followed by Masamune-Roush olefination of the resultant aldehyde afforded ethyl enoate **20** in good overall yield for the two-step process [12] [13]. At this stage, we were primed to install the requisite stereochemistry at C(4). To this end, deprotection of enoate **20** under standard conditions using tetrabutylammonium fluoride (TBAF) liberated the free hydroxyl group which underwent an Evans' oxyconjugate addition with benzaldehyde (PhCHO) to form benzylidene **21** [14] [15] [16]. Then, reduction of the ester moiety by treatment of **21** with lithium aluminum hydride afforded alcohol **22** in excellent yield followed by smooth conversion of the resultant primary alcohol to terminal olefin **23** employing the Grieco procedure [17] [18]. Lastly, oxidative cleavage of the **23** utilizing a two-step process involving osmium tetroxide and sodium periodate furnished the desired C(1)-C(5) fragment **24**.

3. Conclusions

In summary, we have developed a synthesis of the C(1) - C(5) fragment of pochonin J in only eleven linear steps beginning with ethyl 3(*R*)-hydroxybutyrate (**14**). A key step involved in our approach is the use of an Evans' oxyconjugate addition reaction to install the *cis*-1,3-diol motif with high stereoselectivity. The

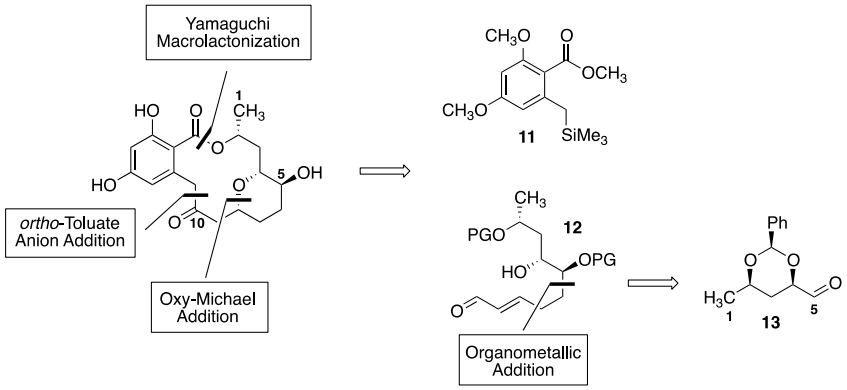
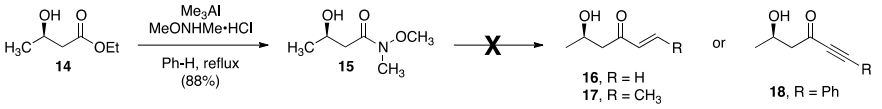
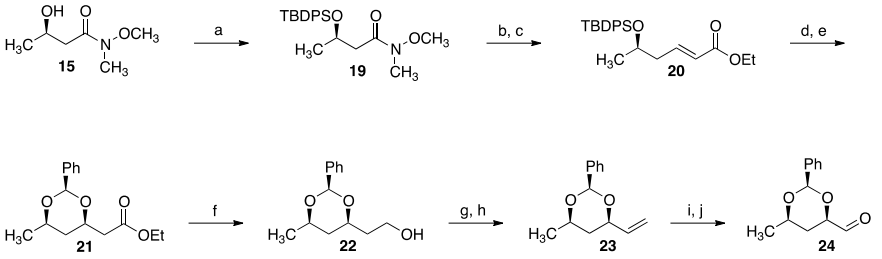


Figure 3. Retrosynthetic Analysis for Pochonin J.



Scheme 1. Initial approach to C(1)-C(5) fragment of pochonin J.



Scheme 2. Reagents and conditions: (a) TBDPS-CI, *i*-Pr_2NEt, CH_2Cl_2, 0˚C to RT, 95%; (b) DIBALH, Et_2O, −78˚C; (c) $(EtO)_2P(O)CH_2CO_2Et$, *i*-Pr_2NEt, LiCl, CH_3CH, 90% over two steps; (d) TBAF, THF, 80%; (e) *t*-BuOK, PhCHO, THF, 0˚C, 61%; (f) $LiAlH_4$, THF, 0˚C, 92%; (g) *o*-NO_2-PhSeCN, Bu_3P, THF; (h) 30% H_2O_2, THF, 74% over two steps; (i) OsO_4, THF/Me_2CO/pH 7 Buffer; (j) $NalO_4$, THF/pH 7 Buffer, 60% over two steps.

route that we have developed provides a new approach to access a critical structural feature that is present in many resorcylic acid lactone natural products and should find wide application for researchers engaged in this area of study. Furthermore, the efficiency of our synthetic scheme will allow us to explore our proposed biosynthetic proposal for pochonin J as well as perform additional biological testing. Our efforts along those lines will be presented in due course.

Experimental

General Procedures. All non-aqueous reactions were carried out in flame-dried round-bottomed flasks under an atmosphere of argon. Air- and moisture-sensitive liquids were transferred by oven-dried stainless-steel needles. Reactions were conducted at room temperature (approximately 22˚C) unless otherwise noted. Flash chromatography was performed with the indicated solvents using standard grade silica gel SiliaFlash® P60 (particle size 230 - 400 mesh) from Silicycle Incorporated. Reactions were monitored by thin-layer chromatography (TLC) us-

ing 0.25 mm thickness precoated glass-backed silica gel plates containing F254 indicator manufactured by Sorbent Technologies. Visualization was accomplished with UV light and ethanolic *p*-anisaldehyde, phosphomolybdic acid, or potassium permanganate stain solution followed by charring on a hot plate. Yields refer to chromatographically and spectroscopically pure compounds (>95%) unless otherwise stated.

Materials. Anhydrous reaction solvents were purchased from Sigma-Aldrich or Acros. All other commercial reagents were purchased from either Sigma-Aldrich or Acros and used as received without additional purification.

Instrumentation. Infrared spectra were recorded using a Perkin-Elmer Spectrum One FT-IR spectrometer equipped with a Universal ATR Sampling Accessory and are reported in terms of frequency of absorption (cm^{-1}). ^1H NMR spectra were measured at 400 MHz on a JEOL ECS-400 spectrometer and are reported relative to deuterated solvent signals. Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, bt = broad triplet, q = quartet, dd = doublet of doublets, qt = quartet of triplets, sex = sextuplet, m = multiplet, app = apparent), coupling constants (Hz), and integration. ^{13}C NMR spectra were measured at 100 MHz on a JEOL ECS-400 spectrometer and are reported relative to deuterated solvent signals. Accurate mass measurements were performed by Dr. William Boggess of the Mass Spectrometry and Proteomics Facility at the University of Notre Dame. Optical rotations were measured using a Jasco P-2000 digital polarimeter and are reported as follows $[\alpha]_\lambda^T$, (c g/100 mL, solvent).

Weinreb amide (19): To a solution of alcohol **15** (3.50 g, 23.9 mmol) in anhydrous CH_2Cl_2 at 0˚C was added *i*-Pr_2NEt (7.80 mL, 47.8 mmol) and TBDPSCl (8.00 mL, 26.3 mmol) and the reaction was warmed to room temperature overnight. The reaction was poured into saturated aqueous $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with 1.0 M HCl (1 × 100 mL) and brine (1 × 100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (5:1 hexanes:EtOAc) to afford 9.38 g of **19** as a clear oil (95%): $[\alpha]_D^{22}$ = −6.47 (c = 0.121, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 - 7.67 (m, 4H), 7.42 - 7.33 (m, 6H), 4.41 (app sex, J = 6.4 Hz, 1H), 3.58 (s, 3H), 3.11 (s, 3H), 2.80 (dd, J = 14.2, 6.4 Hz, 1H), 2.41 (dd, J = 14.2, 6.4 Hz, 1H), 1.11 (d, J = 6.0 Hz, 3H), 1.03 (s, 9H); ^{13}C NMR (100 MHz) δ 172.0, 135.8, 135.7, 134.4, 133.9, 129.5, 129.4, 127.5, 127.4, 66.9, 61.1, 41.7, 31.8, 26.8, 23.7, 19.1; IR (neat): 2963, 2932, 2857, 1660; HRMS (ESI) calcd for $C_{22}H_{32}NO_3Si$ $(M + H)^+$ 386.2151, found 386.2146.

Ethyl enoate (20): To a solution of Weinreb amide **19** (1.00 g, 2.69 mmol) in anhydrous Et_2O (15.0 mL) at −78˚C was added DIBALH (2.95 mL of a 1.0 M solution in hexanes, 2.95 mmol) and the reaction continued stirring for 30 min. The reaction was quenched by the addition of 1.0 M HCl (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine

(1 × 35 mL), filtered through a pad of Celite using EtOAc (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide 0.850 g of crude aldehyde that was used without further purification.

To a mixture of LiCl (0.230 g, 5.36 mmol) in anhydrous CH_3CN (39.0 mL) at room temperature was added triethylphosphonoacetate (0.740 mL, 3.72 mmol), *i*-Pr_2NEt (0.560 mL, 3.50 mmol), crude aldehyde (0.760 g, 2.60 mmol), and the reaction continued stirring overnight. The reaction was quenched by the addition of 1.0 M HCl (30 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (1 × 35 mL), filtered through a pad of Celite, and concentrated *in vacuo*. The residue was purified by flash column chromatography (19:1 hexanes:EtOAc) to afford 0.960 g (90% from Weinreb amide **19**) of **20** as a clear oil (90%): $[\alpha]_D^{22}$ = +25.1 (c = 0.138, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 - 7.65 (m, 4H), 7.42 - 7.34 (m, 6H), 6.91 (dt, J = 15.6, 7.6 Hz, 1H), 5.75 (dt, J = 15.6, 1.2 Hz, 1H), 4.17 (q, J = 3.2 Hz, 2H), 3.95 (app sex, J = 6.0 Hz, 1H), 2.36 - 2.24 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H), 1.08 (d, J = 6.4 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz) δ 166.3, 145.5, 135.8, 134.2, 133.9, 129.6, 129.5, 127.5, 127.4, 123.3, 68.4, 60.1, 42.0, 26.9, 23.1, 19.1, 14.2; IR (neat): 2964, 2931, 2896, 1719; HRMS (ESI) calcd for $C_{24}H_{33}O_3Si$ $(M + H)^+$ 397.2199, found 397.2193.

Benzylidene (21): To a solution of enoate **20** (1.50 g, 3.78 mmol) in anhydrous THF (15.0 mL) at room temperature was added TBAF (4.50 mL of a 1.0 M solution in THF, 4.50 mmol) and the reaction continued stirring overnight. The reaction was quenched by the addition of saturated aqueous NH_4Cl (45 mL), extracted with EtOAc (3 × 35 mL). The combined organic layers were washed with brine (1 × 35 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (3:1 hexanes:EtOAc) to afford 0.479 g of alcohol as a clear oil (80%): $[\alpha]_D^{22}$ = −9.71 (c = 0.116, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (dt, J = 16.0, 7.2 Hz, 1H), 5.87 (dt, J = 16.0, 1.2 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.94 (app sex, J = 6.4 Hz, 1H), 2.35 - 2.31 (m, 2H), 1.73 (bs, 1H), 1.25 (t, J = 6.8 Hz, 3H), 1.21 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz) δ 166.3, 144.9, 123.9, 66.7, 60.3, 41.7, 23.1, 14.2; IR (neat): 3454, 2974, 2931, 1716, 1699; HRMS (ESI) calcd for $C_8H_{14}NaO_3$ $(M + Na)^+$ 181.0841, found 181.0835.

To a solution of alcohol (0.997 g, 6.38 mmol) in anhydrous THF (64.0 mL) at 0˚C was added benzaldehyde (0.71 mL, 7.02 mmol) and potassium *tert*-butoxide (0.072 g, 0.638 mmol) and the reaction continued stirring for 15 mins. Over the course of 30 mins, additional potassium *tert*-butoxide (0.072 g, 0.638 mmol) was added at 15 min intervals at which time the reaction was allowed to warm to room temperature overnight. The reaction was quenched by the addition of pH 7 buffer (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (1 × 50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (19:1 hexanes:EtOAc) to afford 1.02 g of **21** as an off-white solid (61%):

$[\alpha]_D^{22}$ = –9.22 (c = 0.033, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 7.63 - 7.61 (m, 1H), 7.15 - 7.11 (m, 3H), 7.07 - 7.03 (m, 1H), 5.38 (s, 1H), 4.14 - 4.07 (m, 1H), 3.93 - 3.87 (m, 2H), 3.47 - 3.40 (m, 1H), 2.56 (dd, J = 15.6, 7.6 Hz, 1H), 2.20 (dd, J = 15.6, 7.6 Hz, 1H), 1.16 - 1.11 (m, 2H), 1.04 (d, J = 6.4 Hz, 3H), 0.89 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz) δ 171.5, 140.8, 129.8, 129.1, 128.0, 102.2, 74.6, 73.8, 61.5, 42.4, 39.3, 22.7, 15.3; IR (neat): 2980, 2911, 2876, 1724; HRMS (ESI) calcd for $C_{15}H_{21}O_4$ $(M + H)^+$ 265.1440, found 265.1434.

Alcohol (22): To a solution of benzylidene **21** (0.627 mg, 2.37 mmol) in anhydrous THF (38.0 mL) at 0˚C was added lithium aluminum hydride (2.84 mL of a 1.0 M solution in THF, 2.84 mmol) and the reaction continued stirring for 1 hr. The reaction was quenched by the addition of EtOAc (70.0 mL) and warmed to room temperature at which time water (20.0 mL) was added and the mixture was stirred vigorously for 5 min. The reaction was dried with Na_2SO_4, filtered using EtOAc (1.0 L), and concentrated *in vacuo*. The residue was purified by flash column chromatography (4:1 hexanes:EtOAc) to afford 0.527 g of **22** as a white solid (92%): $[\alpha]_D^{22}$ = –16.9 (c = 0.020, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 7.60 - 7.58 (m, 2H), 7.15, 7.03 (m, 3H), 5.33 (s, 1H), 3.66 - 3.59 (m, 2H), 3.56 - 3.50 (m, 1H), 3.49 - 3.41 (m, 1H), 1.84 (bs, 1H), 1.69 - 1.61 (m, 1H), 1.46 - 1.39 (m, 1H), 1.19 - 1.10 (m, 1H), 1.07 (d, J = 6.0 Hz, 3H), 0.93 (dt, J = 12.8, 2.0 Hz, 1H); ^{13}C NMR (100 MHz) δ 139.0, 128.0, 127.1, 125.9, 100.3, 74.5, 72.1, 58.8, 38.0, 37.9, 20.9; IR (neat): 3290, 2963, 2921, 1340; HRMS (ESI) calcd for $C_{13}H_{19}O_3$ $(M + H)^+$ 223.1334, found 223.1329.

Alkene (23): To a solution of alcohol **22** (0.150 g, 0.675 mmol) in anhydrous THF (7.0 mL) at room temperature was added *o*-nitrophenylselenocyanate (0.169 g, 0.743 mmol) and tributylphosphine (0.202 mL, 0.810 mmol) and the reaction continued stirring for 30 mins. The solvent was removed *in vacuo* to afford 0.235 g of selenide as an orange solid.

To a solution of selenide (0.235 g, 0.578 mmol) in anhydrous THF (8.0 mL) at room temperature was added hydrogen peroxide (0.589 mL of a 30% solution in water, 5.20 mmol) and the reaction continued stirring overnight. The reaction was poured into Et_2O (40 mL) and 10% NaOH (11 mL) and extracted with Et_2O (1 × 15 mL). The combined organic layers were washed with 10% NaOH (3 × 10 mL), brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (100:1 hexanes:EtOAc) to afford 0.102 g of **23** as a yellow oil (74%): $[\alpha]_D^{22}$ = –11.9 (c = 0.010, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 7.66 - 7.64 (m, 2H), 7.15 - 7.03 (m, 3H), 5.77 (ddd, J = 16.0, 10.6, 5.2 Hz, 1H), 5.38 (s, 1H), 5.22 (dt, J = 17.2 1.6 Hz, 1H), 4.96 (dt, J = 10.4, 1.6 Hz, 1H), 3.92 - 3.87 (m, 1H), 3.47 - 3.39 (m, 1H), 1.30 - 1.21 (m, 1H), 1.05 (d, J = 6.0 Hz, 3H), 1.03 (dt, J = 12.8, 2.4 Hz, 1H); ^{13}C NMR (100 MHz) δ 140.8, 139.7, 129.8, 129.0, 128.0, 115.7, 102.1, 78.2, 73.9, 39.7, 22.8; IR (neat): 2974, 2844, 1333; HRMS (ESI) calcd for $C_{13}H_{17}O_2$ $(M + H)^+$ 205.1229, found 205.1223.

Aldehyde 24: To a solution of olefin **23** (0.050 g, 0.245 mmol) in THF (0.75

mL), acetone (0.75 mL), and pH 7 Buffer (0.75 mL) at room temperature was added *N*-methylmorpholine-*N*-oxide (0.086 g, 0.735 mmol) and OsO_4 (0.024 mL of a 2.5% solution in *tert*-butanol, 0.0122 mmol) and the reaction continued stirring overnight. The reaction was cooled to 0˚C and saturated aqueous $NaHSO_3$ (10 mL) was added. The ice bath was removed and the mixture was stirred for an additional 30 min, then was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (1 × 10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide 0.058 g of crude diol that was used without further purification.

To a solution of the crude diol (0.058 g, 0.243 mmol) in anhydrous THF (1.5 mL) and pH 7 Buffer (0.50 mL) was added $NaIO_4$ (0.062 g, 0.292 mmol) and the reaction continued stirring for 3 hr. The reaction was diluted with EtOAc (10 mL) and washed with saturated aqueous $NaHCO_3$. The combined organic layers were dried over $NaSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:2 hexanes:EtOAc) to afford 0.030 g of **24** as a yellow oil (60%): $[\alpha]_D^{22}$ = +26.4 (*c* = 0.007, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 9.39 (s, 1H), 7.56 - 7.54 (m, 2H), 7.16 - 7.05 (m, 3H), 5.14 (s, 1H), 3.49 (dd, *J* = 12.0, 3.6 Hz, 1H), 3.26 - 3.18 (m, 1H), 1.19 - 1.04 (m, 2H), 0.92 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz) δ 199.5, 138.3, 128.7, 128.1, 126.4, 100.5, 79.9, 72.2, 32.5, 21.1; IR (neat): 2971, 2927, 1737, 1454; HRMS (ESI) calcd for $C_{12}H_{14}O_3$ $(M + H)^+$ 207.1021, found 207.1016.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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