Studies on the Total Synthesis of Amphidinolide O. A Stereoselective Synthesis of C12-C17 Fragment

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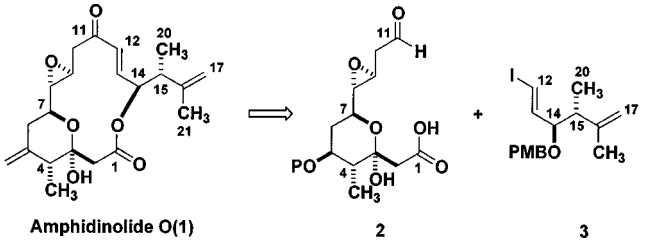
The amphidinolides are a series of cytotoxic macrolides isolated from the marine dinoflagellate *Amphidinium* sp., which is a symbiotic with Okinawan marine flatworm *Amphiscolops* sp. Amphidinolide O (**1**) exhibited *in vitro* cytotoxicity against L1210 and human epidermoid carcinoma KB cells (IC_{50}: 1.7 and 3.6 μg/mL, respectively).[1] Several synthetic strategies for amphidinolide A,[2] B,[3] C,[4] G,[5] H,[5] and L[5,6] have been reported to date and the total synthesis of three amphidinolides, J,[7] K,[8] and P[9] was recently completed by Williams group. Herein, we describe the stereoselective synthesis of the C12-C17 fragment **3** of amphidinolide O (**1**) using a titanium-mediated diastereoselective *anti*-aldol reaction as a key step.

Retrosynthetically, the amphidinolide O (**1**) can be bisected into two fragments: the C1-C11 fragment **2** bearing the epoxide and the hemiketal moieties and C12-C17 vinyl iodide fragment **3** (Scheme 1).

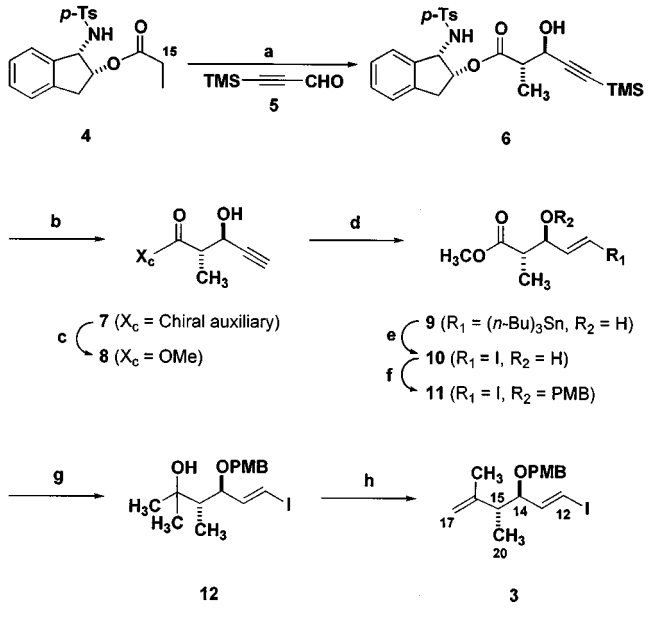
The synthesis of vinyl iodide fragment **3** started from chiral propionate ester **4** (Scheme 2). The (1*S*,2*R*)-*cis*-1-(*p*-methyl)benzenesulfonamido-2-indanyl ester **4** was prepared in 2 steps from commercially available optically active (1*S*,2*R*)-*cis*-aminoindan-2-ol.[10] The titanium enolate of **4** was generated by the following sequence of reactions, *i.e.*, treatment of **4** with $TiCl_4$ (1.2 equiv.) in CH_2Cl_2 at 0 °C-25 °C for 15 min, addition of *N*-ethyldiisopropylamine (4.0 equiv.) at 25 °C, and finally stirring of the resulting dark brown solution for 2 hr.

The titanium enolate of **4** was then treated with 3-trimethylsilyl-2-propyn-1-al (**5**) (2.0 equiv.),[11] which was already precomplexed with $TiCl_4$ (2.4 equiv.) at -78 °C, to provide the *anti*-aldol product **6** as a major product in 55% isolated yield.[10] TMS group of *anti*-aldol ester **6** was removed with tetra-*n*-butylammonium fluoride (1.5 equiv., 1.0 M in THF) in THF.[12] The chiral auxiliary ester **7** was directly esterified with a solution of methyl magnesium chloride (6.0 equiv., 3.0 M in THF) in methanol.[13] Hydrostannylation of acetylene **8** with tributyltin hydride (1.5 equiv.) and AIBN (cat.) followed by metal-halogen exchange with iodine (1.2 equiv.) in diethyl ether yielded the desired (*E*)-vinyl iodide **10** in 54% yield over 2 steps.[14]

The tertiary alcohol **12** was prepared from the iodide to **10** *via* a two-step sequence: PMB-protection[15] of secondary alcohol **10** with 4-methoxybenzyl trichloroacetimidate (1.0 equiv.) and *p*-toluenesulfonic acid (cat.) in CH_2Cl_2/*c*-hexane and then the addition of methyl magnesium chloride (3.0 equiv., 3.0 M in THF) in THF. Finally, dehydration with methanesulfonyl chloride (5.0 equiv.) and triethylamine (10.0 equiv.) in CH_2Cl_2 produced the target fragment **3** in 80% yield.[17]



Scheme 1. Retrosynthetic Analysis of Amphidinolide O (**1**).



Scheme 2. Reagents and reaction conditions: (a) $TiCl_4$, CH_2Cl_2, 0-25 °C, 15 min; *i*-Pr_2NEt, rt, 1 hr; **5**, $TiCl_4$, CH_2Cl_2, -78 °C, 2 hr, 55%; (b) TBAF, THF, rt, 2 hr, 80%; (c) CH_3MgCl, MeOH, rt, 12 hr, 78%; (d) *n*-Bu_3SnH, AIBN, 85 °C, 2 hr, 68%; (e) I_2, Et_2O, rt, 10 min, 80%; (f) PMB-TCA, TsOH, CH_2Cl_2/*c*-Hexane, rt, 12 hr, 60%; (g) CH_3MgCl, THF, rt, 1 hr, 70%; (h) MsCl, Et_3N, CH_2Cl_2, -10 °C, 30 min, 80%.

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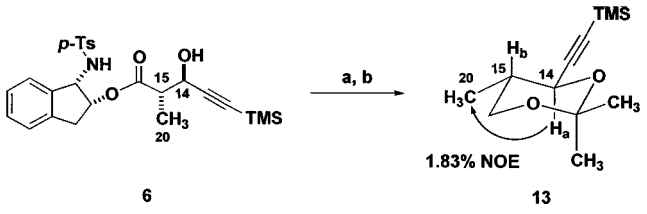

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Scheme 3. Determination of relative stereochemistry of aldol product **6**. (a) $LiAlH_4$, THF, 0 °C, 1 hr, 60%; (b) $(CH_3)_2C(OCH_3)_2$, PPTS, CH_2Cl_2, rt, 12 hr, 65%.

In order to establish the relative stereochemistry, the *anti*-aldol product **6** was converted to the acetonide **13** by reduction with lithium aluminum hydride (2.5 equiv.) in THF at 0 °C followed by exposure of resulting diol to 2,2-dimethoxypropane (10.0 equiv.) in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate in CH_2Cl_2 (Scheme 3).[10a] The relative stereochemistry at C14-C15 was confirmed unambiguously by ^1H NOE difference spectroscopy (1.83% enhancement of the 20-Me signal upon irradiation of H_a) and a coupling constant J_{ab} of 10.5 Hz , which suggests the *anti* configurational relationship in **6**.[10a,16]

In summary, we have achieved the stereoselective synthesis of C12-C17 fragment **3** from the chiral propionate ester **4** *via* 8 step sequences in 6.3% overall yield.

Experimental Section

3-Trimethylsilyl-2-propyn-1-al (5). Solid pyridinium chlorochromate (1.85 g, 8.56 mmol, 1.1 equiv.) was added to a stirring solution of 3-trimethylsilyl-2-propyn-1-ol (1.0 g, 7.79 mmol, 1.0 equiv.) in dichloromethane (15 mL). Stirring continued in a sealed flask for 6 hr at room temperature. The solution was filtered through a pad of Celite, and the remaining black precipitant in the flask was rinsed with diethyl ether (50 mL) followed by filtration. The filtrates were combined and dried over anhydrous $MgSO_4$, filtered and concentrated to give aldehyde **5** as a brown oil in 50% yield (0.49 g). The crude aldehyde **5** was used without further purification. TLC R_f 0.60 (10% EtOAc in hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.22 (s, 9H), 9.20(s, 1H).

(1*S*,2*R*)-*N*-[2,3-Dihydro-2-((2*S*,3*S*)-3-hydroxy-2-methyl-5-trimethylsilyl-1-oxo-pent-4-ynoxy)-1*H*-inden-1-yl]-4-methylbenzenesulfonamide (6). To a solution of propionate ester **4** (1.0 g, 2.78 mmol, 1.0 equiv.) in dry CH_2Cl_2 (14 mL) was added 1 M solution of $TiCl_4$ (3.33 mL, 3.33 mmol, 1.2 equiv.) in CH_2Cl_2 dropwise *via* syringe under N_2 at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for an additional 15 min. *N*-ethyldiisopropyl- amine (1.94 mL, 11.22 mmol, 4.0 equiv.) was added to this solution dropwise at 25 °C by syringe. The color of the solution became brown after stirring for an additional 1 hr at 25 °C. In a separate flask, to a stirred solution of aldehyde **5** (706 mg, 5.56 mmol, 2.0 equiv.) in CH_2Cl_2 (28 mL) at -78 °C, was added a 1 M solution of $TiCl_4$ (6.67 mL, 6.67 mmol, 2.4 equiv.) in CH_2Cl_2. The resulting reaction mixture was stirred at -78 °C for 5 min, the above enolate solution was added to the aldehyde **5** solution dropwise *via* cannula over a period of 5 min. The reaction mixture was stirred at -78 °C for 2 hr and then it was quenched by addition of aqueous NH_4Cl solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford a residue which was purified by silica gel chromatography (20% EtOAc in hexane) to yield the title aldol product **6** (743 mg, 55%) as a white solid. TLC R_f 0.50 (33% EtOAc in hexane); m.p. 53-55 °C; $[\alpha]_D^{25}$ = -22.3 (*c* 2.77, $CHCl_3$); IR (KBr pellet) 3479, 3283, 3049, 2958, 2921, 2224, 1725, 1336, 1124 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.81 (d, 2H, J = 8 Hz), 7.32-7.15 (m, 6H), 6.02 (d, 1H, J = 10 Hz), 5.34 (t, 1H, J = 5 Hz), 4.92-4.89 (m, 1H), 4.35-4.32 (m, 1H), 3.10 (dd, 1H, J = 5 & 14 Hz), 2.93 (d, 1H, J = 6 Hz), 2.89 (d, 1H, J = 17 Hz), 2.69-2.63 (m, 1H), 2.44 (s, 3H), 1.19 (d, 3H, J = 7 Hz), 0.14 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.3, 143.6, 139.8, 138.4, 137.8, 129.8, 128.5, 127.4, 127.1, 124.4, 103.3, 91.8, 74.9, 64.6, 59.7, 47.0, 37.2, 21.5, 13.9, -0.3; GC/MS (m/z) calcd. for $C_{25}H_{31}NO_5SSi$ (M^-) 485.17, found 484.30; Anal. Calcd. for $C_{25}H_{31}NO_5SSi$: C, 61.83; H, 6.43; N, 2.88. Found: C, 61.88; H, 6.47; N, 2.77.

(1*S*,2*R*)-*N*-[2,3-Dihydro-2-((2*S*,3*S*)-3-hydroxy-2-methyl-1-oxo-pent-4-ynoxy)-1*H*-inden-1-yl]-4-methylbenzenesulfonamide (7). To a 0 °C solution of aldol product **6** (1.0 g, 2.05 mmol, 1.0 equiv.) in 10 mL THF was added a 1 M solution of tetra-*n*-butylammonium fluoride (3.07 mL, 3.07 mmol, 1.5 equiv.) in THF. The cooling bath was removed and the solution was stirred at room temp for 2 hr and then it was quenched by addition of H_2O. The aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. Column chromatography (25% EtOAc in hexane) gave 681 mg (80%) of the title compound 7 as a white solid. TLC R_f 0.50 (50% EtOAc in hexane); m.p. 140-142 °C; $[\alpha]_D^{25}$ = -13.9 (*c* 0.42, $CHCl_3$); IR (KBr pellet) 3511, 3045, 2974, 2361, 1718, 1373, 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.82 (d, 2H, J = 8 Hz), 7.32-7.16 (m, 6H), 5.91 (d, 1H, J = 9.5 Hz), 5.34 (ddd, 1H, J = 1.5, 5 & 5 Hz), 4.93-4.90 (m, 1H), 4.38-4.35 (m, 1H), 3.12 (dd, 1H, J = 5 & 17 Hz), 3.01 (d, 1H, J = 6 Hz), 2.92 (d, 1H, J = 17 Hz), 2.73-2.67 (m, 1H), 2.48 (d, 1H, J = 2.5 Hz), 2.45 (s, 3H), 1.76 (br s, 1H), 1.21 (d, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.2, 143.7, 139.7, 138.4, 137.7, 129.8, 128.5, 127.4, 127.1, 124.9, 124.4, 82.0, 75.2, 74.7, 63.9, 59.7, 46.8, 37.3, 21.5, 13.8; GC/MS (m/z) calcd. for $C_{22}H_{23}NO_5S$ (M^+) 413.13, found 411.10; Anal. Calcd. for $C_{22}H_{23}NO_5S$: C, 63.90; H, 5.61; N, 3.39. Found: C, 63.95; H, 5.53; N, 3.35.

Methyl (2*S*,3*S*)-3-hydroxy-2-methyl-4-pentynoate (8). To a 0 °C solution of 400 mg (0.96 mmol, 1.0 equiv.) of aldol product 7 in 4 mL of anhydrous methanol was added *via* cannula a suspension formed by the addition of 1.93 mL (5.76 mmol, 6.0 equiv., 3.0 M in THF) of methyl

magnesium chloride to 4 mL of anhydrous methanol. After the reaction mixture was stirred at room temperature for 12 hr, it was quenched by the addition of 4 mL of pH 7 phosphate buffer. Volatiles were removed *in vacuo*. The residue was dissolved in 1.0 M aqueous hydrochloric acid, extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (25% EtOAc in hexane) afforded 107 mg (78%) of the title compound **8** as a colorless oil. TLC R_f 0.35 (33% EtOAc in hexane); $[\alpha]_D^{27}$ = +21.0 (*c* 0.65, $CHCl_3$); IR (neat) 3456, 2985, 2117, 1727, 1459, 1268 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.53 (ddd, 1H, *J* = 2, 7 & 7Hz), 3.74 (s, 3H), 2.94 (d, 1H, *J* = 6.5 Hz), 2.79-2.73 (m, 1H), 2.49 (d, 1H, *J* = 2 Hz), 1.31 (d, 3H, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.93, 82.41, 74.1, 64.1, 52.0, 45.9, 13.8; GC/MS (m/z) calcd. for $C_7H_{10}O_3$ (M^-) 142.06, found 142.97.

Methyl (2*S*,3*S*)-3-hydroxy-2-methyl-5-tributylstannanyl-(4*E*)-pentenoate (9). Acetylene **8** (200 mg, 1.41 mmol, 1.0 equiv.), *n*-Bu_3SnH (0.57 mL, 2.11 mmol, 1.5 equiv.), and AIBN (12 mg, 0.07 mmol, 0.05 equiv.) were stirred under nitrogen at 85 °C for 2 hr. The reaction mixture was cooled to room temperature. Purification by column chromatography (10% EtOAc in hexane) afforded 414 mg (68%) of the title compound **9** as a colorless oil. TLC R_f 0.23 (10% EtOAc in hexane); $[\alpha]_D^{27}$ = +6.5 (*c* 0.67, $CHCl_3$); IR (neat) 3494, 2956, 2852, 1726, 1459, 1375 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.26 (d, 1H, *J* = 19 Hz), 5.98 (dd, 1H, *J* = 6 & 19 Hz), 4.17-4.13 (m, 1H), 3.70 (s, 1H), 1.52-1.46 (m, 6H), 1.33-1.26 (m, 6H), 1.18 (d, 3H, *J* = 6 Hz), 0.91-0.87 (m, 15H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.9, 147.5, 131.1, 77.2, 51.7, 45.1, 29.1, 29.0, 28.9, 27.4, 27.2, 27.0, 14.1, 13.7, 10.9, 10.8, 9.5, 8.2, 8.1; GC/MS (m/z) calcd. for $C_{19}H_{38}O_3Sn$ (M^+) 432.18, found 435.25; Anal. Calcd. for $C_{19}H_{38}O_3Sn$: C, 52.68; H, 8.84. Found: C, 52.56; H, 8.85.

Methyl (2*S*,3*S*)-5-iodo-3-hydroxy-2-methyl-(4*E*)-pentenoate (10). A solution of iodine (70 mg, 0.28 mmol, 1.2 equiv.) in dry ether (2 mL) was added dropwise *via* cannula over a period of 1 min to a cold (0 °C), stirred solution of vinyl stannane **9** (100 mg, 0.23 mmol, 1.0 equiv.) in the same solvent (2 mL). The reaction mixture was stirred an additional 10 min at room temperature and quenched with saturated $Na_2S_2O_3$ solution. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (20% EtOAc in hexane) afforded 414 mg (68%) of the title compound **10** as a white solid. TLC R_f 0.27 (20% EtOAc in hexane); m.p. 36-38 °C; $[\alpha]_D^{27}$ = +7.7 (*c* 0.47, $CHCl_3$); IR (KBr pellet) 3274, 2361, 1722, 1458, 1334, 1190, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.58 (dd, 1H, *J* = 6.5 & 14.5 Hz), 6.47 (d, 1H, *J* = 14.5 Hz), 4.20-4.16 (m, 1H), 3.72 (s, 3H), 2.85 (d, 1H, *J* = 6 Hz), 2.61-2.56 (m, 1H), 1.20 (d, 1H, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.4, 145.4, 79.3, 76.1, 52.0, 44.6, 13.9; GC/MS (m/z) calcd. for C-$H_{11}IO_3$ (M^-) 269.98, found 237.71 (-CH_3OH).

Methyl (2*S*,3*S*)-5-iodo-3-*p*-methoxybenzyloxy-2-methyl-(4*E*)-pentenoate (11). To a stirred solution of the alcohol **10** (100 mg, 0.37 mmol, 1.0 equiv.) and *p*-toluenesulfonic acid (4 mg, 0.019 mmol, 0.05 equiv.) in CH_2Cl_2/*c*-hexane (2 mL) at 0 °C was added 4-methoxybenzyl trichloroacetimidate (104 mg, 0.37 mmol, 1.0 equiv.) in CH_2Cl_2 (2 mL) and then stirring was continued at room temperature for 12 hr. The reaction mixture was quenched with H_2O at room temperature. The reaction mixture were filtered through a pad of Celite, evaporated *in vacuo*. Column chromatography (10% EtOAc in hexane) gave 86 mg (60%) of the title compound **11** as a colorless oil. TLC R_f 0.29 (10% EtOAc in hexane); $[\alpha]_D^{27}$ = +69.1 (*c* 0.81, $CHCl_3$); IR (neat) 2949, 2838, 1737, 1610, 1513, 1458, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.19-7.17 (m, 2H), 6.88-6.86 (m, 2H), 6.42-6.40 (m, 2H), 4.52 (d, 1H, *J* = 11.5 Hz), 4.31 (d, 1H, *J* = 11.5 Hz), 3.95-3.91 (m, 2H), 3.81 (s, 3H), 3.68 (s, 3H), 2.68-2.62 (m, 1H), 1.09 (d, 3H, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.6, 159.2, 158.1, 143.9, 129.7, 129.3, 113.8, 83.0, 80.4, 70.7, 55.3, 51.8, 44.3, 13.3; GC/MS (m/z) calcd. for $C_{15}H_{19}IO_4$ (M^-) 390.03, found 262.95 (-I).

(3*S*,4*S*)-2,3-Dimethyl-2-hydroxy-6-iodo-4-*p*-methoxybenzyloxy-(5*E*)-heptenoate (12). To a solution of ester **11** (100 mg, 0.25 mmol, 1.0 equiv.) in THF (2mL) at 0 °C was added methylmagnesium chloride (0.25 mL, 3.0 equiv., 3.0 M in THF) and stirring was continued for 1 hr. The reaction mixture was quenched with saturated ammonium chloride. The mixture was extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (25% EtOAc in hexane) to provide the tertiary alcohol **12** (70 mg, 70%) as a colorless oil. TLC R_f 0.45 (33% EtOAc in hexane); $[\alpha]_D^{27}$ = +58.2 (*c* 0.1, $CHCl_3$); IR (neat) 3053, 2986, 1522, 1421, 1265, 909, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.24-7.21(m, 2H), 6.89-6.87 (m, 2H), 6.47-6.33 (m, 2H), 4.56 (d, 1H, *J* = 11 Hz), 4.27 (d, 1H, *J* = 11 Hz), 3.80 (s, 3H), 3.75-3.72 (m, 1H), 1.84-1.78 (m, 1H), 1.58 (br s, 1H), 1.15 (s, 3H), 1.07 (s, 3H), 0.78 (d, 3H, *J* = 8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.5, 145.6, 129.9, 129.7, 128.8, 113.9, 85.8, 80.1, 73.2, 70.4, 55.3, 46.5, 29.5, 23.5, 13.7; GC/MS (m/z) calcd. for $C_{16}H_{23}IO_3$ (M^+) 390.07, found 393.09; Anal. Calcd. for $C_{16}H_{23}IO_3$: C, 49.24; H, 5.94. Found: C, 49.20; H, 5.92.

(3*S*,4*S*)-2,3-Dimethyl-6-iodo-4-(*p*-methoxybenzyloxy) hexa-1,5-diene (3). To a stirred solution of tertiary alcohol **12** (100 mg, 0.25 mmol, 1.0equiv.) in 2 mL of CH_2Cl_2 was added methanesulfonyl chloride (0.1 mL, 1.28 mmol, 5.0 equiv.) and then triethylamine (0.36 mL, 2.56 mmol, 10.0 equiv.) at -10 °C by syringe. The mixture was stirred at -10 °C. The reaction progress was monitered by TLC. The reaction mixture was quenched with H_2O, extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and evaporated *in vacuo*. Purification by column chromatography (3.3% EtOAc in hexane) afforded 76 mg (80%) of the title compound **3** as a white solid. TLC R_f 0.31 (3.3% EtOAc in hexane); $[\alpha]_D^{27}$ = +47.1 (*c* 0.08, $CHCl_3$); IR (neat) 2963, 2862, 1611, 1513, 1458, 1248, 1037, 1172 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.15-7.14 (m, 2H), 6.80-6.78 (m, 2H), 6.38 (dd, 1H, *J* = 8 & 14.5 Hz), 6.21 (d, 1H, *J* = 14.5 Hz), 4.73-4.72 (m, 1H), 4.68-4.67 (m, 1H), 4.46 (d, 1H, *J* = 12 Hz), 4.21 (d, 1H, *J* = 11.5

Hz), 3.73 (s, 3H), 3.58-3.55 (m, 1H), 2.34-2.28 (m, 1H), 1.56 (s, 3H), 0.89 (d, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.1, 146.6, 145.5, 130.2, 129.3, 113.7, 111.8, 83.5, 78.5, 77.5, 70.2, 55.3, 45.0, 20.1, 15.4, 13.6; GC/MS (m/z) calcd. for $C_{16}H_{22}IO_2^-$ (M^-) 372.06, found 244.98 (-I).

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