Synthesis of 4-Acetylisocoumarin: First Total Syntheses of AGI-7 and Sescandelin

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Abstract: A practical synthetic route to 4-acetylisocoumarins and the first total synthesis of AGI-7 (**5**) and sescandelin (**4**) are described. The readily available homophthalate **8** was transformed to the vinylogous amide ester **13** in high overall yield. Upon treatment of **13** with refluxing aqueous formic acid, the desired 4-acetylisocoumarin (**5**) and its regioisomer 3-methyl-4-formylisocoumarin (**17**) were produced in a 3:1 ratio. After separation of the desired product (**5**) from the unwanted minor isomer, the enantioselective reduction of AGI-7 by borane in the presence of Corey's (*S*)-oxazaborolidine reagent afforded (+)-sescandelin (**4**) with a 93% ee.

Among the naturally occurring isocoumarin derivatives, 4-substituted isocoumarins with no substituent at the 3-position are very rare,[1] and only a few synthetic methods for construction of the skeleton have been developed.[2−5] Ray[3] synthesized 4-methylisocoumarin by cyclization of acetonyl benzoate in sulfuric acid, and Usgaonkar[4] reported the synthesis of 4-carboxyisocoumarin from homophthalic acid with DMF−$POCl_3$. 4-Acetylisocoumarins have been prepared from 4-carboxyisocoumarins by addition of magnesium malonate to the corresponding acid chloride followed by hydrolysis in poor to modest overall yields.[5]

Some representative 4-substituted 3-nonsubstituted natural isocoumarins are oospoglycol (**1**),[6] oosponol (**2**),[7] 4-acetyl-6,8-dihydroxy-5-methylisocoumarin (**3**),[8] and (−)-sescandelin (**4**)[1,9] as shown in Figure 1. It has been

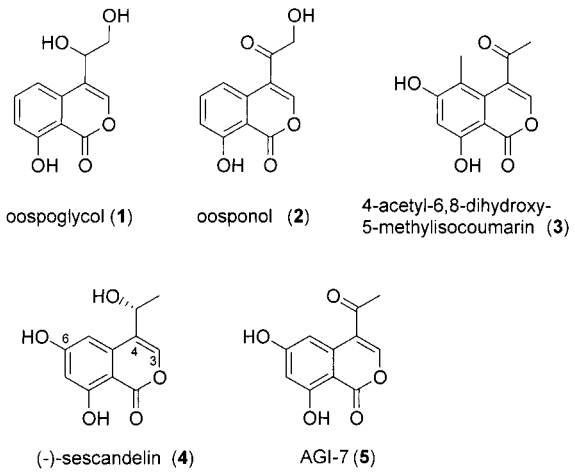

Figure 1. 4-Substituted 3-nonsubstituted natural isocoumarins.

reported that these isocoumarin compounds possess various interesting bioactivities including root-promoting activity and antibiotic activities against plant cells, bacteria, and plant-pathogenic fungi.[7,9,10]

In the screening of anti-angiogenic substances inhibiting differentiation of endothelial cells to a capillary-like structure on Matrigel, one of us isolated a new compound, 6,8-dihydroxy-4-acetylisocoumarin, which was named AGI-7 (**5**), along with sescandelin (**4**) from an unidentified fungal strain by bioassay-guided fractionation and isolation.[11] To further investigate the biochemical and pharmaceutical effects of sescandelin and AGI-7, especially in growth and proliferation of new blood vessels, we needed to synthesize these isocoumarins in large quantities. Herein, we report a practical and high-yielding synthetic route to 4-acetylisocoumarins and the first total syntheses of AGI-7 (**5**) and sescandelin (**4**).

The synthesis began from known homophthalate **8**[12] (Scheme 1), which was synthesized as described previously.[12b] Diels−Alder reaction of diene **6** and allenedicarboxylate **7**, followed by aromatization with $Et_3NH^+F^-$, provided **8** in 69% yield. Protection of the phenol **8** as its dibenzyl ether **9** and basic hydrolysis of diester provided homophthalic acid **10** in 81% yield. A facile two-step transformation of homophthalic acid **10** to ketone **11** was conducted by employing literature procedure.[13] Reaction of **10** with acetic anhydride/pyridine followed by hydrolysis with aqueous sodium hydroxide gave ketone **11** in 76% yield. The ^{1}H NMR spectrum of **11** at room temperature showed two extremely broad singlets (δ 4.1−3.9 for the ArCH_2COCH_3 protons and δ 2.4−2.2 for the ArCH_2-COCH_3 protons). In contrast, that of methyl ester of **11** showed sharp singlets at δ 3.64 and 2.08. Two broad signals of **11** appeared at further downfield compare to the corresponding signals of methyl ester of **11**. This

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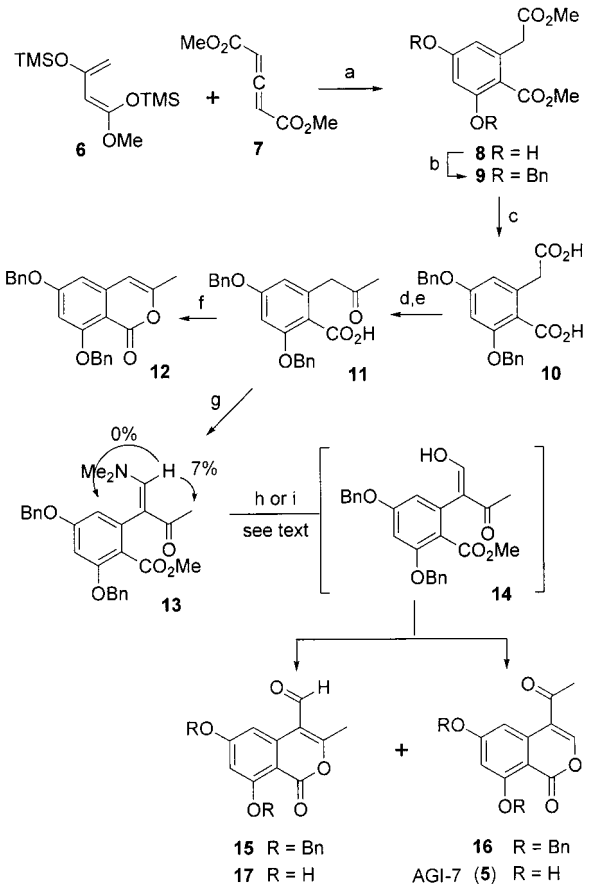
Scheme 1[a]



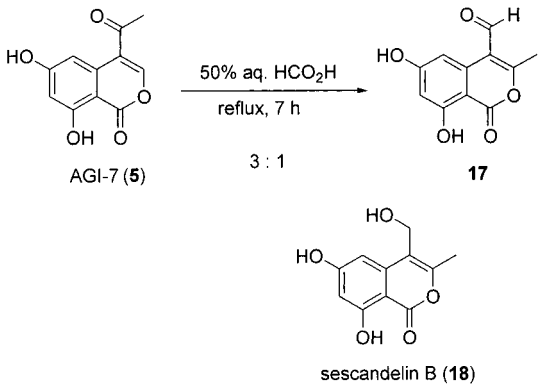
[a] Reagents and conditions: (a) neat, 0−25 °C, 70 min, then Et_3NHF, EtOH, rt, 40 min, 69%; (b) BnBr, K_2CO_3, acetone, KI, reflux, 2 days, 87%; (c) KOH, EtOH, H_2O, reflux, 24 h, 93%; (d) Ac_2O, pyr, Et_2O, rt, overnight; (e) 10% aq NaOH, H_2O, 60 °C, 1 h, 76% from **10**; (f) dimethylchloromethyleneammonium chloride, DMF, rt; or $POCl_3$, DMF, rt; (g) *N*,*N*-dimethylformamide dimethyl acetal, toluene, reflux, 5 h, 87%; (h) 70% aq AcOH, reflux, 5 h, 95% as a mixture of **16** and **15** (2:1); (i) 70% aq HCO_2H, reflux, 1 day, see text.

phenomenon suggests that the carboxylic acid group forms an intramolecular hydrogen bond with the neighboring ketone oxygen atom in compound **11**.

With **11** in hand, we set out to explore formation of the 4-acetyl-3-nonsubstituted isocoumarin ring system. The initial attempts to obtain compound **16** using Vilsmeier reagents gave only 3-methylisocoumarin **12** without formation of the desired product. However, treatment of **11** with commercially available *N*,*N*-dimethylformamide dimethyl acetal in refluxing toluene effected the introduction of the vinylogous amide functionality[14] and concomitant esterification of carboxylic acid residue to afford **13** in 87% yield as a single compound. NOE difference experiments indicated that the stereochemistry of vinylogous amide was *E* as shown in Scheme 1.

Our attempts to prepare target the 4-acetylisocoumarin ring system from **13** began with acetic acid as an acid reaction solvent. Upon treatment of **13** with refluxing glacial acetic acid for 5 h, the desired 6,8-dibenzyloxy-4-acetylisocoumarin (**16**) and its regioisomer 6,8-dibenzyloxy-3-methyl-4-formylisocoumarin (**15**) were produced in a 1.5:1 ratio with a combined yield of 95%. Prolonged reaction times did not change the product ratio. In refluxing 70% aqueous acetic acid, compound **13** gave a 2:1 mixture of **16** and **15** in 95% crude yield. These intramolecular cycloadducts were perhaps formed via the intermediate **14**, which could be observed in the crude ^1H NMR spectrum obtained from the reaction mixture in 10 min at refluxing temperature or 20 min at 60 °C. When the acetic acid was replaced by formic acid, the selectivity in favor of 4-acetylisocoumarin was increased. The condition of refluxing 70% aqueous formic acid effected the intramolecular cyclization and concomitant deprotection of the benzyl protecting groups to afford a 3:1 mixture of **5** and **17**. Change of formic acid concentration from 70% to 50% or 90% did not alter the product ratio significantly.

Unfortunately, the separation of the desired product (**5** and **16**) from the unwanted minor isomer (**17** and **15**) was not an easy task. To circumvent this problem, the crude mixture of **5** and **17** was treated with Jones reagent to oxidize the aldehyde functional group of minor **15** to the carboxylic acid.[15] This treatment enabled the efficient



(1)

purification of AGI-7 (**5**) and did not affect the final isolated yield (56%) considerably. It is noteworthy that exposure of the purified **5** to 50% aqueous formic acid (7 h at refluxing temperature) led to a 3:1 regioisomeric mixture of **5** and **17** in almost quantitative yield (eq 1). This result suggested that the observed product distribution ratio during the intramolecular cyclization of **13** would be reflective of the thermodynamic equilibrium of the products under acidic conditions. Furthermore, the coexistence of sescandelin B (**18**) (eq 1), which has the same carbon numbers and an isocoumarin skeleton with sescandelin, implied that formation of both regioisomer **5** and **17** could also occur in the biosynthesis.[1,16]

Finally, AGI-7 (**5**) was reduced under Luche conditions[17] to provide (±)-sescandelin (**4**) as a racemate in 96% yield, of which ^1H and ^{13}C NMR spectral data were in good agreement with those reported[1,9,11] The enantioselective reduction of the carbonyl of AGI-7 (**5**) to the corresponding alcohol was achieved by using Corey's oxazaborolidine-catalyzed reduction.[18] Reduction of the ketone **5** by borane in the presence of 20 mol % of the (*S*)-oxazaborolidine reagent afforded (+)-sescandelin (**4**)

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in 88% yield with a 93% ee.[19] The observed optical rotation for (+)-**4** [$[\alpha]^{21}_D = +31.6$ (*c* 0.02, MeOH)] was comparable in magnitude and opposite in sign to the literature value[9] for naturally occurring (−)-**4** [$[\alpha]_D = -33$ (*c* 1.0, MeOH)].

In conclusion, the chemistry described herein provides a practical synthetic method of 4-acetylisocoumarin synthesis, and we were able to accomplish a total synthesis of the nonnatural (+)-sescandelin (**4**) and AGI-7 (**5**) in high overall yield. Further application of this methodology to various types of 4-substituted isocoumarin synthesis is now under investigation in this laboratory.

Experimental Section

General Methods. All chemicals were reagent grade and used as purchased. All reactions were performed under an inert atmosphere of dry argon or nitrogen using distilled dry solvents. Reactions were monitored by TLC analysis using silica gel thin layer plates. Flash column chromatography was carried out on silica gel (230−400 mesh). Melting points are uncorrected. Optical rotations were measured using sodium light (D line 589.3 nm).

2,4-Bis-benzyloxy-6-methoxycarbonylmethylbenzoic Acid Methyl Ester (9). A mixture of homophthalate **8**[12] (2.20 g, 9.16 mmol), K_2CO_3 (8.20 g, 59.33 mmol), KI (1.64 g, 9.88 mmol), and excess benzyl bromide (7.0 mL, 58.85 mmol) in acetone (60 mL) was refluxed for 2 days with stirring. After the mixture was cooled to room temperature, solid K_2CO_3 was filtered off. The filtrate was concentrated in vacuo. The subsequent residue was diluted with EtOAc (100 mL) and washed with 1 N aqueous HCl two times and water two times. The organic layer was dried ($MgSO_4$) and evaporated under vacuum. The residue was purified by column chromatography (hexanes/EtOAc = 4:1) to afford 3.35 g (87%) of **9** as a light yellow solid: $R_f = 0.32$ (hexanes/EtOAc = 3:1); mp 84−85 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.69 (s, 3H), 3.70 (s, 2H), 3.86 (s, 3H), 5.04 (s, 2H), 5.07 (s, 2H), 6.52 (d, $J = 2.4$ Hz, 1H), 6.54 (d, $J = 2.4$ Hz, 1H), 7.30−7.41 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.2, 167.6, 160.8, 158.1, 136.5, 136.3, 135.2, 128.6, 128.5, 128.2, 127.8, 127.5, 126.9, 116.7, 109.0, 100.1, 70.6, 70.2, 52.0, 51.9, 39.5; IR (KBr) ν_{max} 1736, 1705, 1606, 1167 cm^{-1}; HRMS calcd for $C_{25}H_{24}O_6$ (M^+) 420.1573, found 420.1584. Anal. Calcd for $C_{25}H_{24}O_6$: C, 71.41; H, 5.75. Found: C, 71.54; H, 5.82.

2,4-Bis-benzyloxy-6-carboxymethylbenzoic Acid (10). A mixture of ester **9** (3.0 g, 7.14 mmol), KOH (2.41 g, 43.0 mmol), EtOH (60 mL), and water (20 mL) was refluxed for 24 h. After being cooled to room temperature, the solution was acidified with 1 N aqueous HCl to pH 2 and then extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. After purification by short flash chromatography using EtOAc, 2.61 g (93%) of **10** was obtained as a light yellow solid: $R_f = 0.23$ (EtOAc/CH_3OH = 4:1); mp 157−158 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 3.71 (s, 2H), 5.05 (s, 2H), 5.09 (s, 2H), 6.58 (d, $J = 2.1$ Hz, 1H), 6.64 (d, $J = 2.4$ Hz, 1H), 7.28−7.44 (m, 10H); ^{13}C NMR (CD_3OD, 75 MHz) δ 174.6, 171.2, 162.2, 159.1, 138.2, 138.1, 137.0, 129.5, 129.4, 129.0, 128.8, 128.7, 128.3, 118.5, 110.7, 100.8, 71.7, 71.2, 40.3; IR (KBr) ν_{max} 3429, 1716, 1604, 1172 cm^{-1}; HRMS calcd for $C_{23}H_{20}O_6$ (M^+) 392.1260, found 392.1231. Anal. Calcd for $C_{23}H_{20}O_6$: C, 70.40; H, 5.14. Found: C, 70.67; H, 5.33.

2,4-Bis-benzyloxy-6-(2-oxopropyl)benzoic Acid (11). Pyridine (447 μL) was added to a stirred mixture of **10** (900 mg, 2.29 mmol) in acetic anhydride (2.5 mL) under argon. The solid was dissolved instantly. After 2 min, it gave rise to a precipitate and solidified. Dry Et_2O (20 mL) was added to facilitate the stirring. The solid was filtered and washed with Et_2O after being stirred overnight. The obtained solid was suspended in water (20 mL) and was heated at 60 °C. To it was added dropwise 10% aqueous NaOH solution. The solid was quickly dissolved, and additional sodium hydroxide solution was added until pH 11. Heating and stirring were continued for an additional 0.5 h. Then, the solution was acidified to pH 2 with 10% aqueous HCl. After cooling, the cloudy reaction solution was extracted with EtOAc four times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The resulting solid was further purified by flash chromatography (hexanes/EtOAc = 1:1, then 100% EtOAc) to afford 681 mg of **11** (76%) as a gray solid: $R_f = 0.38$ (100% EtOAc); mp 134−136 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.2−2.4 (br s, 3H), 3.9−4.1 (br s, 2H), 5.07 (s, 2H), 5.17 (s, 2H), 6.50 (br s, 1H), 6.67 (br s, 1H), 7.32−7.45 (m, 10H); ^{13}C NMR ($CDCl_3$,75 MHz) δ 205.5, 165.8, 162.1, 159.6, 142.5, 135.7, 134.4, 129.0, 128.7, 128.4, 127.8, 127.5, 112.8, 111.9, 100.0, 72.4, 70.3, 50.6, 29.9; IR (KBr) ν_{max} 3414, 1718, 1604, 1167 cm^{-1}; HRMS calcd for $C_{24}H_{22}O_5$ (M^+) 390.1467, found 390.1419. Anal. Calcd for $C_{24}H_{22}O_5$: C, 73.83; H, 5.68. Found: C, 74.08; H, 5.85.

2-(1-Acetyl-2-(dimethylamino)vinyl)-4,6-bis-benzyloxybenzoic Acid Methyl Ester (13). To acid **11** (390 mg, 1.0 mmol) in toluene (50 mL) was added *N*,*N*-dimethylformamide dimethyl acetal (1.33 mL, 10.0 mmol) slowly under argon. The resulting mixture was heated to reflux for 5 h. After reaction, the toluene was evaporated under reduced pressure, and the subsequent residue was subjected to column chromatography (100% EtOAc) to give 400 mg (87%) of pure **13** as a yellow oil: $R_f = 0.27$ (100% EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.90 (s, 3H), 2.62−2.78 (br s, 6H), 3.75 (s, 3H), 5.05 (s, 2H), 5.09 (s, 2H), 6.40 (d, $J = 2.1$ Hz, 1H), 6.56 (d, $J = 2.4$ Hz, 1H), 7.26−7.41 (m, 10H), 7.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.5, 168.1, 159.5, 156.4, 149.0, 138.9, 136.4, 136.3, 128.6, 128.4, 128.1, 127.8, 127.4, 126.9, 120.5, 110.6, 107.0, 100.2, 70.4, 70.1, 52.0, 42.6, 27.3; IR (KBr) ν_{max} 1730, 1653, 1597, 1564, 1269, 1157 cm^{-1}; HRMS calcd for $C_{28}H_{29}NO_5$ (M^+) 459.2046, found 459.2043. Anal. Calcd for $C_{28}H_{29}NO_5$: C, 73.08; H, 6.31; N, 2.98. Found: C, 73.09; H, 6.31; N, 2.98.

4-Acetyl-6,8-bis-benzyloxyisochromen-1-one (16). The vinylogous amide ester **13** (2.1 g, 4.57 mmol) was refluxed in 70% aqueous acetic acid (70 mL) for 5 h. It was concentrated under reduced pressure. The residue was treated with EtOAc and then washed with brine, saturated aqueous $NaHCO_3$, and brine successfully. The organic layer was concentrated to give a white powder (1.73 g, 95%) as a mixture of **16** and **15** in a ratio of 2:1.

AGI-7 (5). The vinylogous amide ester **13** (165 mg, 0.36 mmol) was refluxed in 70% aqueous formic acid (15 mL) for 1 day. After reaction, mixture was concentrated under reduced pressure, and the resulting residue was treated with EtOAc and washed with saturated aqueous $NaHCO_3$ two times and brine once. The separated organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give a white powder. To the above crude product in acetone (15 mL) cooled in ice bath was added freshly prepared Jones reagent (2 mL; 0.56 g of chromium trioxide in 0.9 mL of sulfuric acid and 2.4 mL of water) dropwise. It was stirred at 0 °C for 30 min and then at room temperature for 30 min. Water (30 mL) was added, and the mixture was stirred for another 10 min. The reaction mixture was then neutralized with saturated aqueous $NaHCO_3$, saturated with NaCl, and extracted with EtOAc four times. The combined organic extracts were washed with brine once, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The resulting residue was further purified by column chromatography (hexanes/acetone = 2:1) to give 45 mg (56%) of pure AGI-7 as a white solid: $R_f = 0.25$ (hexanes/acetone = 2:1); mp 240 °C dec; ^{1}H NMR (acetone-d_6, 300 MHz) δ 2.53 (s, 3H), 6.49 (d, $J = 2.4$ Hz, 1H), 7.72 (d, $J = 2.4$ Hz, 1H), 8.47 (s, 1H), 9.81 (br s, 1H), 11.0 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 196.4, 166.4, 163.7, 163.3, 155.2, 135.1, 116.9, 104.1, 102.7, 98.5, 28.5; IR (KBr) ν_{max} 3422, 3188, 1685, 1651, 1165 cm^{-1}; HRMS calcd for $C_{11}H_8O_5$ (M^+) 220.0372, found 220.0379. Anal. Calcd for $C_{11}H_8O_5$: C, 60.00; H, 3.66. Found: C, 60.35; H, 3.76.

Sescandelin (4). Racemic Reduction. To a solution of AGI-7 (**5**) (33 mg, 0.15 mmol) and cerium chloride heptahydrate (170 mg, 0.45 mmol) in MeOH (10 mL) was added sodium borohydride (17 mg, 0.45 mmol). The mixture was stirred at room temperature for 10 minutes, and then the reaction was quenched with acetone. The solvent was evaporated, and the

(19) The enantiomeric excess of **4** was determined by chiral stationary phase HPLC analysis after transformation to the known triacetyl derivative[9] (CHIRALPAK AD-H, hexane/2-propanol (4: 1, v/v), flow rate 1.0 mL/min, retention time 8.12 min (+)-isomer and 8.85 min (−)-isomer, detected at 254 nm).

residue was diluted with CH_2Cl_2. The organic layer was washed with 0.5 N aqueous HCl and brine, dried ($MgSO_4$), and concentrated. After purification by short column chromatography (hexanes/acetone = 1:1), 31 mg of racemic sescandelin was obtained as a white solid in 96% yield.

Enantioselective Reduction: AGI-7 (**5**) (35 mg, 0.16 mmol) in THF (10 mL) was treated with (*S*)-oxazaborolidine reagent[18] (1-butyl-3,3-diphenyltetrahydropyrrolo[1,2-*c*][1,3,2]oxazaborole, 60 μL, 0.5 M solution in THF) and borane−methyl sulfide complex (80 μL, 0.16 mmol) at −78 °C, and stirring was continued for 19 h at this temperature. The reaction was quenched with water, diluted with EtOAc, and then washed with 1 N aqueous HCl to remove the pyrrolidine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The residue was applied to column chromatography (hexanes/acetone = 1:1) to furnish 32 mg of sescandelin as a white solid in 88% yield: $[\alpha]^{21}_D$ = +31.6 (*c* 0.02, MeOH); R_f = 0.39 (hexanes/acetone = 3:4); mp 187−188 °C; ^{1}H NMR (acetone-d_6, 300 MHz) δ 11.47 (s, 1H, *OH*), 9.64 (s, 1H, *OH*), 7.42 (s, 1H), 6.74 (d, J = 2.1 Hz, 1H), 6.45 (d, J = 2.1 Hz, 1H), 4.95 (m, 1H), 4.39 (d, J = 4.5 Hz, 1H, *OH*), 1.50 (d, J = 6.6 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.7, 165.5, 163.5, 141.7, 137.6, 122.2, 102.0, 101.8, 98.9, 63.3, 23.3; IR (KBr) ν_{max} 3451, 3135, 1688, 1650, 1622, 1520 cm^{-1}; HRMS calcd for $C_{11}H_{10}O_5$ (M^+) 222.0528, found 222.0525. Anal. Calcd for $C_{11}H_{10}O_5$: C, 59.46; H, 4.54. Found: C, 59.71; H, 4.74.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of compounds **9**, **10**, **11**, **13**, **5**, and **4**; ^{1}H NMR spectra of the methyl ester of **11** as well as crude **12**, **14**, and a mixture of **5** and **17** from eq 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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