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A FACILE SYNTHESIS OF (5-HYDROXY-4-OXO-4*H*-PYRAN-2-YL)METHYL CARBOXYLATES AND THEIR ANTIVIRAL ACTIVITY AGAINST HEPATITIS C VIRUS

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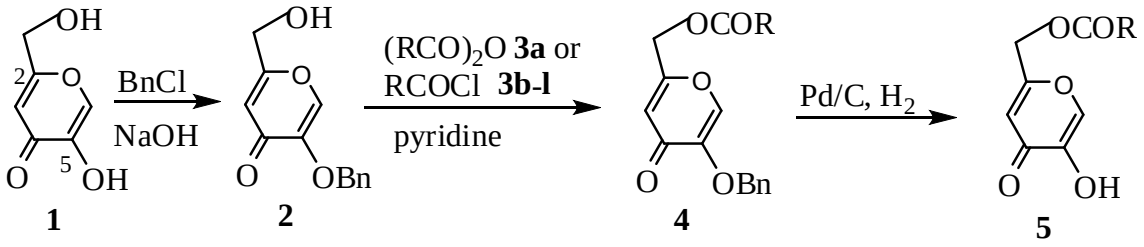
Abstract – 5-Benzyloxy-2-hydroxymethyl-4*H*-pyran-4-one (**2**) was synthesized from kojic acid (**1**) and subsequently reacted with carboxylic anhydride (**3a**) and a series of carboxylic acid chlorides (**3b**–**l**) to give the corresponding (5-benzyloxy-4-oxo-4*H*-pyran-2-yl)methyl carboxylates (**4a**–**l**). These compounds were then reductively debenzylated to afford the (5-hydroxy-4-oxo-4*H*-pyran-2-yl)methyl carboxylates (**5a-l**), which were tested for their inhibitory activities against the hepatitis C virus.

Hepatitis C virus (HCV) infection is a worldwide problem. In general, HCV infection proceeds to chronic infection,[1] which often induces cirrhosis of the liver and hepatocellular carcinoma.[2] Liver transplantation is currently the only treatment available to patients with the severe end-stage liver disorders caused by HCV infection.[3] To date, no protective vaccines have been developed for HCV,

and pegylated interferon (PEG-IFN) and the nucleoside analogue ribavirin are the standard treatments for HCV infection.[4-6] Unfortunately, however, many patients cannot tolerate the serious side effects associated with the use of PEG-IFN and ribavirin. It is well known that kojic acid, which is otherwise known as 5-hyroxy-2-hydroxymethyl-4*H*-pyran-4-one and isolated as a fermentation product of the *Aspergillus* species, inhibits tyrosinase activity through the chelation of copper,[7] which is essential for tyrosinase activity.[8] Kojic acid and its derivatives have also been reported to prevent photodamage[9] by inhibiting nitric oxide (NO) production,[10] express depigment activity,[11] and act as Histamine H_3 receptor ligands.[12] To the best of our knowledge, however, kojic acid and its derivatives have not been examined for their anti-HCV activity. Since kojic acid possesses a chelating moiety that enables it to form bidentate complexes with a variety of different metals, we describe herein a facile synthesis of (5-hydroxy-4-oxo-4*H*-pyran-2-yl)methyl carboxylates (**5**) possessing two such functional groups for chelating, and provide an evaluation of their anti-HCV activity.

(5-Hydroxy-4-oxo-4*H*-pyran-2-yl)methyl carboxylates (**5a-l**) were synthesized in three steps from kojic acid (**1**), as shown in Scheme 1. Thus, kojic acid (**1**) was reacted with benzyl chloride under basic conditions to give 5-benzyloxy-2-hydroxymethyl-4*H*-pyran-4-one (**2**). The 2-hydroxymethyl group of **2** was then esterified with carboxylic anhydride (**3a**) and a series of carboxylic acid chlorides (**3b**–**l**) to give the corresponding (5-benzyloxy-4-oxo-4*H*-pyran-2-yl)methyl carboxylates (**4a**–**l**), which were reductively debenzylated to afford the (5-hydroxy-4-oxo-4*H*-pyran-2-yl)methyl carboxylates (**5a-l**). Compound **2** was prepared from **1** in 88% yield according to the method previously described in the literature.[13a] The reaction of the compound **2** with propionic anhydride (**3a**) in pyridine gave (5-benzyloxy-4-oxo-4*H*-pyran-2-yl)methyl propionate **4a** in 75% yield, and the material was subsequently reductively debenzylated with hydrogen in the presence of Pd/C to give (5-hydroxy-4-oxo-4*H*-pyran-2-yl)methyl propionate **5a** in 72% yield. Similarly, the reactions of **2** with a variety of acyl chlorides (**3b**-**c**) and aroyl chlorides (**3d-l**) afforded the corresponding products (**4b-l**), which were also reductively debenzylated to give the corresponding products (**5b-l**). The results of these reactions are summarized in Table 1.



3a: R = Et, **3b**:R = $Me(CH_2)_{16}$,
3c: R = C_6H_5, **3d**:R=$C_6H_4CH_3$(*p*),
3e: R = C_6H_4OMe(*p*),
3f: R = C_6H_4OEt(*p*),
3g: R = C_6H_4F(*p*), **3h**:R=C_6H_4Cl(*p*),
3i: R = $C_6H_4CF_3$(*p*),
3j: R = $C_6H_3Me_2$(3,5-),
3k: R = 1-naphthyl, **3l**:R=2-naphthyl

4a, **5a**: R = Et
4b, **5b**: R = $Me(CH_2)_{16}$
4c, **5c**: R = C_6H_5
4d, **5d**: R = C_6H_4Me(*p*)
4e, **5e**: R = C_6H_4OMe(*p*)
4f, **5f**: R = C_6H_4OEt(*p*)
4g, **5g**: R = C_6H_4F(*p*)
4h, **5h**: R = C_6H_4Cl(*p*)
4i, **5i**: R = $C_6H_4CF_3$(*p*)
4j, **5j**: R = $C_6H_3Me_2$(3,5-)
4k, **5k**: R = 1-naphthyl
4l, **5l**: R = 2-naphthyl

Scheme 1

Table 1. Reaction of compound **2** with propionic anhydride (**3a**) and the acid chlorides (**3b**−**l**)

Entry	**3**	Product (yield, %)	
		4	**5**
1	**3a**	**4a** (75)	**5a** (72)
2	**3b**	**4b** (69)	**5b** (72)
3	**3c**	**4c** (88)	**5c** (88)
4	**3d**	**4d** (86)	**5d** (80)
5	**3e**	**4e** (63)	**5e** (79)
6	**3f**	**4f** (33)	**5f** (45)
7	**3g**	**4g** (80)	**5g** (81)
8	**3h**	**4h** (85)	**5h** (79)
9	**3i**	**4i** (63)	**5i** (48)
10	**3j**	**4j** (80)	**5j** (80)
11	**3k**	**4k** (84)	**5k** (81)
12	**3l**	**4l** (37)	**5l** (88)

With our compounds in hand, we proceeded to investigate the cytotoxicity and anti-HCV activity of kojic acid (**1**) and its derivatives (**5a-l**) in subgenomic HCV replicon cells (LucNeo#2). The results of these experiments are shown in Table 2. Compounds **5e** and **5l**, which contained a *p*-methoxy phenyl or 2-naphthyl group as their carboxylates, respectively, showed higher anti-HCV activity than the other compounds, but were less active than the HCV NS3 protease inhibitor telaprevir. Since products **5e** and **5l**, which have hydrophobic or bulky substituent, showed higher anti-HCV activity, the structure of the acceptor may have hydrophilic substituent and relatively wide cavity.

In summary, a series of (5-hydroxy-4-oxo-4*H*-pyran-2-yl)methyl carboxylates (**5a-l**) were easily synthesized from kojic acid in relatively good yields over three steps. Given that compounds **5e** and **5l** showed the highest levels of anti-HCV activity of this particular compound series, our laboratory is currently involved in the synthesis of further kojic acid derivatives.

Table 2. Anti-HCV activity of compounds **1** and **5a-l** in LucNeo#2 cells

Compound	R	Inhibitory activity (μM)	
		EC_{50}	CC_{50}
1(Kojic acid)		>100	>100
5a	Et	>100	>100
5b	$Me(CH_2)_{16}$	63	>100
5c	C_6H_5	23.49	>100
5d	$C_6H_4Me(p)$	5.6	>100
5e	$C_6H_4OMe(p)$	2.55±0.61	>100
5f	$C_6H_4OEt(p)$	5.13±3.44	>100
5g	$C_6H_4F(p)$	7.3	>100
5h	$C_6H_4Cl(p)$	4.15	>100
5i	$C_6H_4CF_3(p)$	7.91±2.24	>100
5j	$C_6H_3Me_2(3,5\text{-})$	31	>100
5k	1-naphthyl	10.54	>100
5l	2-naphthyl	2.74±0.22	>100

EXPERIMENTAL

All melting points were measured on Yanagimoto Melt-temp apparatus and uncorrected. NMR spectra were measured at 400 MHz on the JNM GSX-400 (TMS as an internal standard). IR spectra were recorded with a JASCO IR Report-100 spectrometer. Mass spectra were recorded with a JEOL JMS-HX110A (FABMS) using *m*-nitrobenzyl alcohol as matrix. Elemental analysis was made using a Yanaco MT-5. PLC Silicagel 60 F_{254} (2 mm) was used for preparative TLC and Wakogel 200 was used for preparative column chromatography.

5-Benzyloxy-2-hydroxymethyl-4*H*-pyran-4-one (**2**) ….. A solution of kojic acid (**1**) (3.00 g, 21.1 mmol) benzyl chloride (3.85 g, 22.5 mmol) and sodium hydroxide (0.870 g, 21.8 mmol) in MeOH (40 mL) was refluxed for 5 h. After removing the solvent *in vacuo*, to the reaction mixture was added cold water (40 mL). The resulting solid was filtered and recrystallized from EtOH to give **2** (4.30 g, 88% yield).

2: mp 131 – 133 °C (lit., mp 132 °C,[13a] 134 –136 °C[13b]). ^{1}H NMR ($CDCl_3$) δ 2.12 (1H, s), 4.45 (2H, s), 5.08 (2H, s), 6.51 (1H, s), 7.36 (5H, m), 7.52 (1H, s). LR MS *m/z* 233(MH^+). HR MS (MH^+) calcd for $C_{13}H_{13}O_3$ 233.0814. Found: 233.0808.

(5-Hydroxy-4-oxo-4*H*-pyran-2-yl)methyl propionate (**5a**)….. Propionic anhydride (**3a**) (252 mg, 1.94 mmol) was added to a solution of **2** (300 mg, 1.29 mmol) in pyridine (12 mL) and the solution was heated at 60 °C for 20 h. After the solution was evaporated *in vacuo*, a mixture of 1M $NaHCO_3$ aqueous solution (50 mL) and $CHCl_3$ (50 mL) was added to the residue. The separated organic layer was dried by $MgSO_4$ and the filtrate was evaporated *in vacuo* to give **4a** (300 mg, 75% yield) which was used to the next reaction without further purification.

4a: ^{1}H NMR ($CDCl_3$) δ 1.20 (3H, t, *J* = 7.6 Hz), 2.45 (q, *J* = 7.6 Hz), 4.83 (2H, s), 5.05 (2H, s), 6.42 (1H, s), 7.33 (5H, m), 7.54 (1H, s).

A solution of **4a** (100 mg, 0.35 mmol) in MeOH (5 mL) containing 5% Pd-C (50 mg) was vigorously stirred for 1 h at room temperature under a hydrogen atmosphere. After the catalyst was removed by filtration, the filtrate was evaporated to dryness *in vacuo*. The residue was purified by the use of preparative TLC (eluent: EtOAc:hexane = 1:1) to give **5a** (50 mg, 72% yield).

5a: mp 77 – 79 °C (from EtOAc:hexane = 1:1, v/v). ^{1}H NMR ($CDCl_3$) δ 1.19 (3H, q, *J* = 7.6 Hz),

2.43 (2H, t, *J* = 7.6 Hz), 4.93 (2H, s), 6.48 (1H, s), 7.84 (1H, s). IR (KBr) 1730, 1679 cm^{-1}. LR MS *m/z* 199 (MH^+). HR MS calcd for $C_9H_{11}O_5$ 199.0603. Found: 199.0621.

(5-Hydroxy-4-oxo-4*H*-pyran-2-yl)methyl stearate (**5b**)….. Stearoyl chloride (**3b**) (312 mg. 1.03 mmol) was added to a solution of **2** (200 mg, 0.86 mmol) in pyridine (12 mL) and the solution was heated at 60 °C for 24 h. After the solution was evaporated *in vacuo*, a mixture of 1M $NaHCO_3$ aqueous solution (50 mL) and $CHCl_3$ (50 mL) was added to the residue. The separated organic layer was dried by $MgSO_4$ and the filtrate was evaporated *in vacuo* and the resulting oily residue was chromatographed by silica gel (eluent: EtOAc/hexane = 1:1, v/v) to afford **4b** (189 mg, 69% yield).

4b: δ 0.85 (3H, t, *J* = 7.6 Hz), 1.55 (28H, m), 1.66 (2H, m), 2.40 (t, *J* = 7.6 Hz), 4.84 (2H, s), 5.03 (2H, s), 6.42 (1H, s), 7.35 (5H, m), 7.54 (1H, s).

A solution of **4b** (100 mg, 0.20 mmol) in a 1:1 mixture of MeOH and $CHCl_3$ (6 mL) containing 5% Pd-C (50 mg) was vigorously stirred for 24 h at room temperature under a hydrogen atmosphere. After the catalyst was removed by filtration, the filtrate was evaporated to dryness *in vacuo*. The residue was purified by the use of preparative TLC (eluent: EtOAc:hexane = 1:1, v/v) to give **5b** (50 mg, 72% yield).

5b: mp 90 – 93 °C (from EtOAc:hexane = 1:1, v/v). ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, t, *J* = 7.6 Hz), 1.52 (28H, m), 1.64 (2H, m), 2.38 (2H, t, *J* = 7.6 Hz), 4.92 (2H, s), 6.48 (1H, s), 7.84 (1H, s). IR (KBr) 1732, 1655 cm^{-1}. LR MS *m/z* 409 (MH^+). *Anal*. Calcd for $C_{24}H_{41}O_5$: C, 70.55, H, 9.87. Found: C, 70.11, H, 9.90.

(5-Hydroxy-4-oxo-4*H*-pyran-2-yl)methyl benzoate (**5c**)….. The reaction of **2** (300 mg, 1.29 mmol) with benzoyl chloride (**3c**) (270 mg, 2.0 mmol) in pyridine (10 mL) was carried out, according to the similar reaction of **2** with **3b**, to give **4c** (380 mg, 88% yield) which was used to the next reaction without further purification.

4c: ^{1}H NMR ($CDCl_3$) δ 5.02 (2H, s), 5.18 (2H, s), 6.54 (1H, s), 7.40 (5H, m), 7.50 (2H, t, *J* = 8.5 Hz), 7.54 (1H, s), 7.62 (1H, t, *J* = 8.5 Hz), 8.05 (2H, d, *J* = 8.5 Hz).

The reduction of **4c** (100 mg, 0.30 mmol) in MeOH (5 mL) with Pd-C (50 mg) under a hydrogen atmosphere was carried out, according to the same treatment of **4b**, to afford **5c** (65 mg, 88%).

5c: mp 180 – 182 °C (from EtOAc: hexane = 1:1, v/v) (180-181 °C).[14] ^{1}H NMR ($CDCl_3$) δ 5.18 (2H, s), 6.60 (1H, s), 7.48 (2H, t, *J* = 8.5 Hz), 7.62 (1H, t, *J* = 8.5 Hz), 7.84 (1H, s), 8.07 (2H, d, *J* = 8.5 Hz).

IR (KBr) 1742, 1685 cm^{-1}. LR MS *m/z* 247 (MH^+). HR MS (MH^+) calcd for $C_{13}H_{11}O_5$.247.0603. Found: 247,0615.

The results of similar reactions of **2** with **3d-l** and the reduction of **4d-l** to afford **(5-hydroxy-4-oxo-4*H*-pyran-2-yl)methyl *p*-methylbenzoate** (**5d**), **(5-Hydroxy-4-oxo-4*H*–pyran-2-yl)methyl *p*-methoxybenzoate** (**5e**), **(5-Hydroxy-4-oxo-4H-pyran-2-yl)methyl *p*- ethoxybenzoate** (**5f**), **(5-Hydroxy-4-oxo-4*H*-pyran-2-yl)methyl *p*-fluorobenzoate** (**5g**), **(5-Hydroxy-4-oxo-4*H*-pyran-2-yl)methyl *p*-chlorobenzoate** (**5h**), **(5-Hydroxy-4-oxo-4*H*-pyran-2-yl)methyl *p*-trifluoromethylbenzoate** (**5i**), **(5-Hydroxy-4-oxo-4*H*-pyran-2-yl)methyl 3,5-methylbenzoate** (**5j**), **(5-Hydroxy-4-oxo-4*H*-pyran-2-yl)methyl 1-naphthylbenzoate** (**5k**), **(5-Hydroxy-4-oxo-4*H*-pyran-2-yl)methyl 2-naphthylbenzoate** (**5l**) are summarized in Table 3.

The anti-HCV activity of the test compounds was determined in LucNeo#2 cells by the previously described method with some modifications.[15] Briefly, the cells (5×10^3 cells/well) were cultured in a 96-well plate in the absence of G418 and in the presence of various concentrations of the compounds. After incubation at 37 °C for 3 days, the culture medium was removed, and the cells were washed twice with phosphate-buffered saline (PBS). Lysis buffer was added to each well, and the lysate was transferred to the corresponding well of a non-transparent 96-well plate. The luciferase activity was measured by addition of the luciferase reagent in a luciferase assay system kit (Promega) using a luminometer with automatic injectors (Berthold Technologies).

Table 3. Reaction condition and result between **2** and **3**, and reduction of **4** to give **5**

Entry	**2**	**3**		**4**			**5**
4	200 mg (0.86 mmol)	**3d** 200 mg (1.7 mmol)	→	**4d** (260 mg, 86%)	**4d** (100 mg, 0.29 mmol)	→	**5d** (50 mg, 80%), mp 135-136 ºC (EtOAc/hexane = 1:1) ^{1}H NMR ($CDCl_3$) δ 2.43 (3H, s), 5.15 (2H, s), 6.59 (1H, s), 7.29 (2H, d, *J* = 8.0 Hz), 7.87 (1H, s), 8.03 (2H, d, *J* = 8.0 Hz), IR (KBr) 1740, 1695 cm^{-1}. LR MS *m/z* 261 (MH^+). *Anal.* Calcd for $C_{14}H_{12}O_5$: C, 64.61, H, 4.65. found: C, 64.49, H, 4.64.
				^{1}H NMR ($CDCl_3$) δ 2.40 (3H, s), 5.05 (2H, s), 5.09 (2H, s), 6.54 (1H, s), 7.29 (2H, t, *J* = 8.0 Hz), 7.38 (5H, m), 7.59 (1H, s), 8.05 (2H, d, *J* = 8.0 Hz).			
5	200 mg (0.86 mmol)	**3e** 220 mg (1.3 mmol)	→	**4e** (303 mg, 63%)	**4e** (100 mg, 0.27 mmol)	→	**5e** (59 mg, 79%), mp 152-154 ºC (EtOAc/hexane = 1:1) ^{1}H NMR ($CDCl_3$) δ 3.88 (3H, s), 5.16 (2H, s), 6.59 (1H, s), 6.95 (2H, d, *J* = 8.5 Hz), 7.87 (1H, s), 8.03 (2H, d, *J* = 8.5 Hz), IR (KBr) 1740, 1690 cm^{-1}. LR MS *m/z* 277 (MH^+). *Anal.* Calcd for $C_{14}H_{12}O_6$: C, 60.87, H, 4.38. Found: C, 60.57, H, 4.38.
				^{1}H NMR ($CDCl_3$) δ 3.86 (3H, s), 5.05 (2H, s), 5.10 (2H, s), 6.53 (1H, s), 6.95 (2H, d, *J* =8.5 Hz), 7.38(5H, m), 7.59 (1H, s), 8.03 (2H, d, *J* = 8.5 Hz).			
6	200 mg (0.86 mmol)	**3f** 277 mg (1.5 mmol)	→	**4f** (107 mg, 33%)	**4f** (90 mg, 0.24 mmol)	→	**5f** (31 mg, 45%), mp 146-149 ºC (EtOAc/hexane = 1:1) ^{1}H NMR ($CDCl_3$) δ 1.45 (3H, t, *J* = 7.0 Hz), 4.10 (2H, q, *J* = 7.0 Hz), 5.15 (2H, s), 6.59 (1H, s), 6.92 (1H, s), 6.94 (2H, d, *J* = 8.8 Hz), 7.87 (1H, s), 8.01 (2H, d, *J* = 8.8 Hz). IR (KBr) 1742, 1685 cm^{-1}. LR MS *m/z* 291 (MH^+). HR MS (MH^+) calcd for $C_{15}H_{15}O_6$. 291.0869. Found: 291.0871.
				^{1}H NMR ($CDCl_3$) δ 1.46 (3H, t, *J* = 7.0 Hz), 4.10 (2H, q, *J* = 7.0 Hz), 5.08 (2H, s), 5.10 (2H, s), 6.53 (1H, s), 6.93(2H, d, *J* = 8.8 Hz), 7.35(5H, m), 7.55 (1H, s), 8.01(2H, d, *J* = 8.8 Hz).			
7	200 mg (0.86 mmol)	**3g** 204 mg (1.3 mmol)	→	**4g** (240 mg, 80%)	**4g** (100 mg, 0.28 mmol)	→	**5g** (60 mg, 81%), mp 130-132 ºC (EtOAc/hexane = 1:1) ^{1}H NMR ($CDCl_3$) δ 5.18 (2H, s), 6.59 (1H, s), 7.15 (2H, m), 7.87 (1H,s), 8.09 (2H, m). IR (KBr) 1735, 1671 cm^{-1}. LR MS *m/z* 265 (MH^+). HR MS (MH^+). calcd for $C_{13}H_{10}FO_5$. 265.0512. Found: 265.0497.
				^{1}H NMR ($CDCl_3$) δ 5.07 (2H, s), 5.12 (2H, s), 6.54 (1H, s), 7.13 (2H, m), 7.38 (5H, m), 7.60 (1H, s), 8.11 (2H, m).			
8	200 mg (0.86 mmol)	**3h** 220 mg (1.3 mmol)	→	**4h** (270 mg, 85%)	**4h** (100 mg, 0.27 mmol)	→	**5h** (60 mg, 79%), mp 131-134 ºC (EtOAc/hexane = 1:1) ^{1}H NMR ($CDCl_3$) δ 5.18 (2H, s), 6.59 (1H, s), 7.46 (2H, d, *J* = 8.0 Hz), 7.88 (1H, s), 8.02 (2H, d, *J* = 8.0 Hz). IR (KBr) 1740, 690 cm^{-1}. LR MS
				^{1}H NMR ($CDCl_3$) δ 5.08 (2H, s), 5.14 (2H, s), 6.53 (1H, s),			

				6.53 (1H, s), 7.35 (5H, m), 7.43 (2H, d, *J* = 8.0 Hz), 7.60 (1H, s), 8.00 (2H, d, *J* = 8.0 Hz).			*m/z* 281 (MH+). HR MS (MH^+) calcd for $C_{13}H_{10}ClO_5$. 281.0217. Found: 281.0219. *Anal*. Calcd for $C_{13}H_{19}ClO_5$: C, 55.63, H, 3.23. Found: C, 56.17, H, 3.17
9	200 mg (0.86 mmol)	**3i** 270 mg (1.3 mmol)	→	**4i** (220 mg, 63%)	**4i** (100 mg, 0.25 mmol)	→	**5i** (37 mg, 48%), mp 124-127 ºC (EtOAc/hexane = 3:1) ^{1}H NMR ($CDCl_3$) δ 5.22 (2H, s), 6.61 (1H, s), 7.74 (2H, d, *J* = 8.4 Hz), 7.89 (1H, s), 8.18 (2H, d, *J* = 8.4 Hz). IR (KBr) 1740, 1690 cm^{-1}. LR *MS m/z* 315 (MH^+). HR MS (MH^+) calcd for $C_{14}H_{10}F_3O_5$. 315.0408. found: 315.0408.
				^{1}H NMR ($CDCl_3$) δ 5.05 (2H, s), 5.15 (2H, s), 6.56 (1H, s), 7.04 (5H, s), 7.60 (1H, s), 7.70 (2H, d, *J* = 8.4 Hz), 8.10 (2H, d, *J* = 8.4 Hz).			
10	200 mg (0.86 mmol)	**3j** 217 mg (1.3 mmol)	→	**4j** (250 mg, 80%)	**4j** (100 mg, 0.27 mmol)	→	**5j** (59 mg, 80%), mp 171-173 ºC (EtOAc/hexane = 1:1) ^{1}H NMR ($CDCl_3$) δ 2.38 (6H, s), 5.17 (2H, s), 6.63(1H, s), 7.25 (1H, s), 7.25 (1H, s), 7.68 (2H, s), 7.89 (1H, s). R (KBr) 1740, 1690 cm^{-1}. LR MS *m/z* 275 (MH^+). HR MS (MH^+) calcd for $C_{15}H_{15}O_5$. 275.0919. Found: 275.0907.
				^{1}H NMR ($CDCl_3$) δ 2.38 (6H, s), 5.02 (2H, s), 5.10 (2H, s), 6.56 (1H, s), 7.24 (1H, s), 7.35 (5H, s), 7.60 (1H, s), 7.70 (2H, s).			
11	200 mg (0.86 mmol)	**3k** 246 mg (1.3 mmol)	→	**4k** (280 mg, 84%)	**4k** (100 mg, 0.26 mmol)	→	**5k** (60 mg, 81%), mp 170-173 ºC (EtOAc/hexane = 1:1) ^{1}H NMR ($CDCl_3$) δ 5.27 (2H, s), 6.66 (1H, s), 7.54 (2H, m), 7.65 (1H, m), 7.90 (1H, s), 7.91 (1H, d, *J* = 8.0 Hz), 8.09, 8.29, 8.94 (each 1H, d, *J* = 8.0 Hz). IR (KBr) 1740, 1690 cm^{-1}. LR MS *m/z* 297 (MH^+). *Anal*. Calcd for $C_{17}H_{12}O_5$: C, 68.91, H, 4.08. Found: C, 68.45, H, 4.19.
				^{1}H NMR ($CDCl_3$) δ 5.10 (2H, s), 5.20 (2H, s), 6.60 (1H, s), 7.36 (5H, m), 7.54 (2H, m), 7.60 (1H, s), 7.90 , 8.09, 8.29, 8.95 (each 1H, d, *J* = 8.0 Hz).			
12	200 mg (0.86 mmol)	**3l** 246 mg (1.3 mmol)	→	**4l** (126 mg, 37%)	**4l** (100 mg, 0.26 mmol)	→	**5l** (65 mg, 88%), mp 188-191 ºC (EtOAc/hexane = 1:1) ^{1}H NMR ($CDCl_3$) δ 5.26 (2H, s), 6.67 (1H, s), 7.61 (3H, m), 7.90 (1H, s), 7.92, 7.99, 8.07, 8.66 (each 1H, d, *J* = 8.0 Hz). IR (KBr) 1740, 1690 cm^{-1}. LR MS. *m/z*297 (MH^+). HR MS (MH+) calcd for $C_{17}H_{17}O_5$. 297.0763. Found: 297.0765.
				^{1}H NMR ($CDCl_3$) δ 5.10 (2H, s), 5.18 (2H, s), 6.61 (1H, s), 7.38 (5H, m), 7.60 (3H, m), 7.63 (1H, s), 7.99, 8.07, 8.64 (each 1H, d, *J* = 8.0 Hz).			

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