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Facile Synthesis of Pyranoxanthones, Dihydropyranoxanthones, and Their Analogues†

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This paper describes a concise and efficient synthetic route for the biologically interesting pyranoxanthones, dihydropyranoxanthones, and their derivatives. The key strategies involve pyranyl ring formation, methylation, catalytic hydrogenation, and catalytic dihydroxylation starting from 1,3-dihydroxyxanthen-9-one.

Key Words : 1,3-Dihydroxyxanthen-9-one, Pyranoxanthone, Dihydropyranoxanthone

Introduction

Xanthones have been shown to possess a variety of biologically interesting properties and activities such as inhibition of a PAF-induced platelet aggregation,[1] human lymphocyte proliferation,[2] PKC modulation,[3] antitumor,[4] and anti-inflammatory capabilities.[5] They have also been shown to be effective as allergy inhibitors[6] in preventing cardiac anaphylaxis,[7] as antifungals[8] and antimicrobials[9] in treating thrombosis,[10] and as bronchodilators in the treatment of asthma.[11] Among these, a number of pyranoxanthone derivatives **1-7** with a linear or angular pyranyl ring have been widely isolated from natural sources and they also possess various biological activities (Figure 1).[12] This wide range of biological activities has stimulated interest in the synthesis of pyranoxanthone skeletons.

Results and Discussion

Several synthetic approaches to pyranoxanthones have been reported. These methods include the reaction of 1,3-dihydroxyxanthone with 2-methyl-1,3-diene[13] or 3-chloro-3-methyl-1-butyne.[14] Recently, a novel microwave-assisted reaction was developed to synthesize angular and linear pyranoxanthoes as a mixture.[15] The application of these reactions is limited due to their harsh reaction conditions, unsatisfactory overall yields, and because they produce a mixture of isomers due to a low selectivity. There is still a demand for more convenient selective synthetic methods that can efficiently provide pyranxanthone derivatives.

Recently we reported on the synthesis of biologically interesting natural products containing the pyranyl moiety.[16] In our continuous effort to synthesize biologically active molecules, we investigated a facile synthetic route for pyranoxanthone and dihydropyranoxanthone derivatives. We report herein a simple and efficient synthesis of pyranoxanthones, dihydropyranoxanthones, and their derivatives.

In order to synthesize pyranoxanthones, dihydropyranoxanthones, and their derivatives, 1,3-dihydroxyxanthen-9-one (**10**) was first prepared in 80% yield from phloroglucinol (**8**) and salicylic acid (**9**) according to a known procedure (Scheme 1).[17]

The reaction of **10** with 3-methyl-2-butenal was next investigated using several catalysts. Refluxing with both $InCl_3$ and $Yb(OTf)_3$ as Lewis acid catalysts in acetonitrile for 12 h did not provide any adducts. With pyridine as a reactant and solvent, no products were obtained. The use of EDDA (20 mol %) as a mild Brønsted acid catalyst gave product **11** in low yield (10%). With 3 equiv. of $Ca(OH)_2$ in

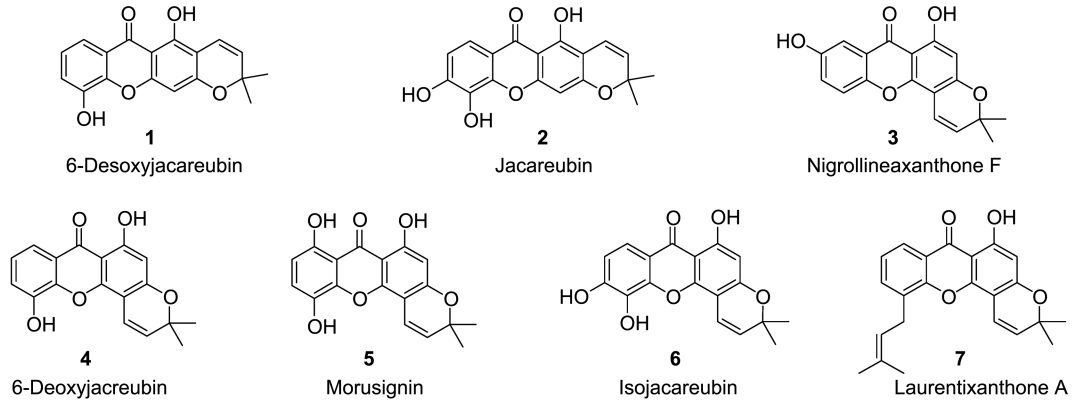
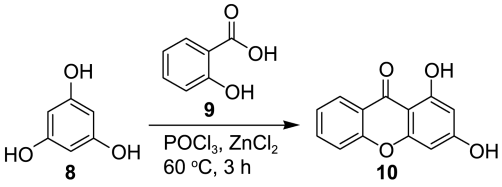


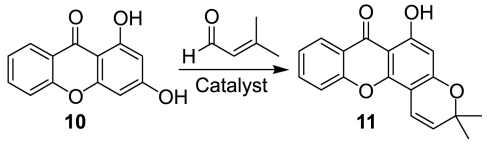
Figure 1. Selected natural pyranoxanthones

†This paper is dedicated to Professor Eun Lee on the occasion of his honourable retirement.



Scheme 1

Table 1. Reaction of 1,3-dihydroxyxanthen-9-one (**10**) with 3-methyl-2-butenal under several catalysts



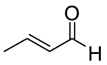
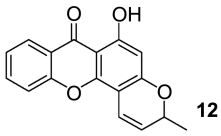
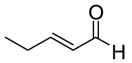
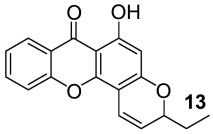
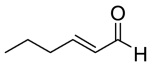
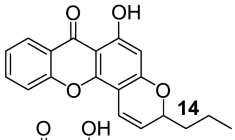
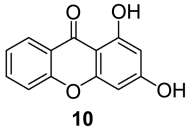
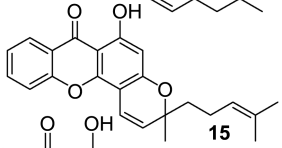
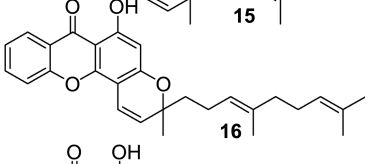
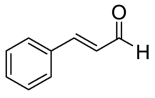
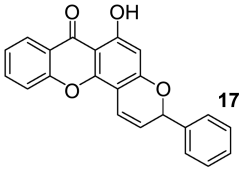
Catalyst	Conditions	Yield (%)
$InCl_3$ (20 mol %)	MeCN, reflux, 12 h	0
$Yb(OTf)_3$ (20 mol %)	MeCN, reflux, 12 h	0
Pyridine (excess)	reflux, 12 h	0
Ethylenediamine diacetate (20 mol %)	THF, reflux, 18 h	10
$Ca(OH)_2$ (3 eq)	MeOH, rt 20 h	70

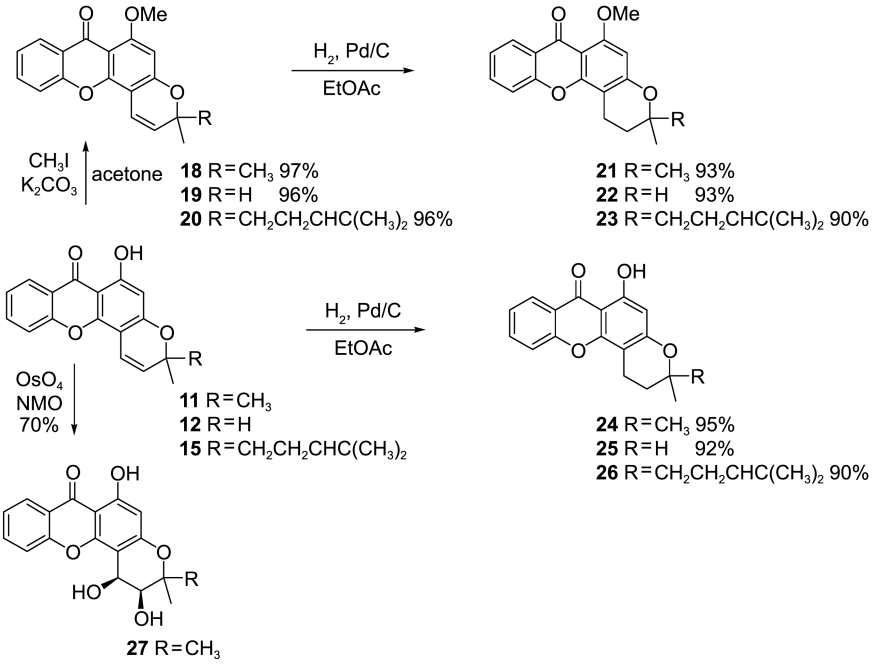
methanol at room temperature for 20 h, the desired product **11** was produced in 70% yield. Interestingly, in this reaction, any possible linear regioisomers was not detected. Such a process for producing benzopyrans by $Ca(OH)_2$-mediated reaction of resorcinol to enals was suggested by Shigemasa.[18] The exact assignment of **11** was confirmed through comparison with ^{1}H NMR data of the reported known compound.[19]

Additional reactions of **10** with a variety of α,β-unsaturated aldehydes were carried out in the presence of 3 equiv. of $Ca(OH)_2$ in methanol at room temperature. The results are collected in Table 2. Reaction of **10** with crotonaldehyde at room temperature for 18 h afforded product **12** in 75% yield (entry 1, Table 2). Similarly, treatment with *trans*-2-pentenal at room temperature for 20 h gave **13** in 36% yield, whereas reaction with *trans*-2-hexen-1-al at room temperature for 20 h provided product **14** in 45% yield (entries 2 and 3). In order to synthesize the various analogues, **10** was further reacted with citral and *trans*,*trans*-farnesal with a long chain. Reaction of **10** with citral and *trans*,*trans*-farnesal at room temperature for 17 h produced **15** and **16** in 72 and 48% yield, respectively (entries 4 and 5). With *trans*-cinnamaldehyde, the desired product **17** was obtained in 45% yield (entry 6). These reactions provided a rapid synthetic route to a variety of pyranoxanthone derivatives with substituents on the pyranyl rings.

Next, conversion of the synthesized pyranoxanthones **11**, **12**, and **15** to their derivatives and dihydropyranoxanthones was attempted (Scheme 2). Compounds **11**, **12**, and **15** were methylated and hydrogenated to afford their derivatives. The reaction of **11**, **12**, and **15** with methyl iodide in the presence of potassium carbonate in refluxing acetone for 2 h produced compounds **18-20** in 97, 96, and 96% yields, respectively.

Table 2. Synthesis of pyranoxanthone derivativs **12-17**

Entry	Starting material	α,β-unsaturated aldehyde	Time (h)	Product	Yield (%)
1			18	 **12**	75
2			20	 **13**	36
3			20	 **14**	45
4	 **10**	citral	17	 **15**	72
5		*trans*, *trans*-farnesal	17	 **16**	48
6			18	 **17**	45



Scheme 2

The catalytic hydrogenation of **18-20** over Pd/C (30 psi) at room temperature for 2 h provided **21-23** in 93, 93, and 90% yields, respectively, whereas the reaction of **11**, **12**, and **15** at the same conditions afforded **24-26** in 95, 92, and 90% yield, respectively. The direct catalytic dihydroxylation of **11** with osmium tetroxide using 2 equiv. of NMO in *t*-BuOH/THF/H_2O (10 : 3 : 1) at room temperature for 4 h gave dihydropyranoxanthone **27** with the *cis*-diol in 70% yield.

In conclusion, a concise and efficient synthetic route for biologically interesting pyranoxanthone, dihydropyranoxanthone and their derivatives was developed. The syntheses of these compounds were accomplished by pyranyl ring formation, methylation, catalytic hydrogenation, and catalytic dihydroxylation starting from 1,3-dihydroxyxanthen-9-one, which was prepared from commercially available phloroglucinol and salicylic acid.

Experimental

All reactions were conducted under nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) with a fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck, City, State, Country). The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Model ARX (300 and 75 MHz, respectively) spectrometer in $CDCl_3$ as the solvent chemical shift. The IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. The HRMS spectra were carried out at the Korea Basic Science Institute.

General Procedure for the Synthesis of Pyranoxanthones 11-17. To a solution of **10** (228 mg, 1.0 mmol) in methanol (10 mL) was added α,β-unsaturated aldehyde (3.0 mmol) and calcium hydroxide (222 mg, 3.0 mmol). The reaction mixture was stirred at room temperature for 17-20 h under nitrogen atmosphere. The reaction mixture was filtered and removal of the solvent at reduced pressure left dark colored solid, which was then purified by column chromatography on silica gel with hexane/EtOAc (10:1) to give products.

Compound 11: 70%; mp 172-173 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.04 (1H, s), 8.10 (1H, m), 7.55 (1H, m), 7.29-7.21 (2H, m), 6.62 (1H, d, *J* = 10.2 Hz), 6.22 (1H, s), 5.50 (1H, d, *J* = 9.9 Hz), 1.39 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.9, 161.0, 157.8, 157.2, 156.0, 134.9, 127.6, 125.8, 124.0, 120.6, 117.7, 115.5, 104.7, 103.8, 95.2, 78.4, 28.5; IR(KBr) 3458, 2974, 1622, 1462, 1310, 1142 cm^{-1}; HRMS *m/z* $(M)^+$ calcd for $C_{18}H_{14}O_4$: 294.0892. Found: 294.0890.

Compound 12: 75%; mp 158-159 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.15 (1H, s), 8.23 (1H, m), 7.47 (1H, m), 7.43-7.36 (2H, m), 6.78 (1H, d, *J* = 10.2 Hz), 6.34 (1H, s), 5.63 (1H, dd, *J* = 9.9 Hz, 4.2 Hz), 5.11 (1H, m), 1.49 (3H, d, *J* = 5.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.7, 161.1, 157.6, 157.1, 155.8, 134.8, 125.7, 123.9, 123.4, 120.5, 117.5, 116.7, 104.9, 103.8, 94.8, 72.8, 21.7; IR (KBr) 3451, 2924, 1613, 1464, 1306, 1217, 1144 cm^{-1}; HRMS *m/z* $(M)^+$ calcd for $C_{17}H_{12}O_4$: 280.0736. Found: 280.0734.

Compound 13: 36%; mp 105-107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.09 (1H, s), 8.19-8.16 (1H, dd, *J* = 8.1 Hz, 1.5 Hz), 7.68-7.62 (1H, td, *J* = 7.2 Hz, 1.8 Hz), 7.37-7.29 (2H, m), 6.76 (1H, d, *J* = 10.2 Hz), 6.29 (1H, s), 5.62-5.58 (1H, dd, *J* = 10.2 Hz, 3.3 Hz), 4.90 (1H, m), 1.80-1.73 (2H, m), 1.0 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.9, 161.6, 157.7, 157.4, 156.0, 135.0, 125.9, 124.1, 122.3, 120.7, 117.7, 117.3, 105.1, 103.9, 94.9, 77.8, 29.1, 9.0; IR (KBr) 3463, 2956, 2931, 1620, 1466, 1393, 1200, 1147, 824, 758 cm^{-1}; HRMS *m/z* $(M)^+$ calcd for $C_{18}H_{14}O_4$: 294.0892. Found: 294.0890.

Compound 14: 45%; mp 131-133 °C; ^{1}H NMR (300

MHz, $CDCl_3$) δ 13.09 (1H, s), 8.17 (1H, d, *J* = 7.8 Hz), 7.64 (1H, t, *J* = 7.2 Hz), 7.37-7.28 (2H, m), 6.74 (1H, d, *J* = 10.2 Hz), 6.28 (1H, s), 5.62-5.58 (1H, dd, *J* = 10.2 Hz, 3.3 Hz), 4.95 (1H, m), 1.84-1.66 (2H, m), 1.53-1.41 (2H, m), 0.94 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.9, 161.5, 157.8, 157.3, 156.0, 135.0, 125.9, 124.1, 122.7, 120.7, 117.7, 117.1, 105.2, 104.0, 95.0, 76.6, 38.2, 18.0, 14.1; IR (KBr) 3463, 2949, 2869, 1737, 1645, 1618, 1465, 1222, 1146, 829, 753 cm^{-1}; HRMS *m/z* $(M)^+$ calcd for $C_{19}H_{16}O_4$: 308.1049. Found: 308.1050.

Compound 15: 72%; mp 67-68 °C ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.14 (1H, s), 8.21 (1H, dd, *J* = 8.1 Hz, 1.8 Hz), 7.67 (1H, m), 7.41-7.31 (2H, m), 6.75 (1H, d, *J* = 10.2 Hz), 6.32 (1H, s), 5.52 (1H, d, *J* = 9.9 Hz), 5.07 (1H, t, *J* = 6.9 Hz), 2.15-2.05 (2H, m), 1.78-1.66 (2H, m), 1.64 (3H, s), 1.55 (3H, s), 1.43 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.6, 161.2, 157.6, 157.1, 134.7, 131.9, 126.3, 125.7, 123.8, 120.5, 117.5, 115.9, 104.3, 103.6, 94.8, 80.7, 41.7, 27.2, 25.6, 22.6, 17.6; IR (KBr) 3714, 2968, 2928, 1649, 1624, 1464, 1311, 1214, 1149 cm^{-1}; HRMS *m/z* $(M)^+$ calcd for $C_{23}H_{22}O_4$: 362.1518. Found: 362.1520.

Compound 16: 48%; oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.12 (1H, s), 8.20-8.17 (1H, dd, *J* = 8.1 Hz, 1.5 Hz), 7.68-7.62 (1H, td, *J* = 8.7 Hz, 1.8 Hz), 7.38-7.29 (2H, m), 6.74 (1H, d, *J* = 10.2 Hz), 6.30 (1H, s), 5.52 (1H, d, *J* = 10.2 Hz), 5.09-5.02 (2H, m), 2.14-1.90 (8H, m), 1.64 (3H, s), 1.55 (6H, s), 1.43 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.8, 161.4, 157.8, 157.3, 156.1, 135.8, 134.9, 131.5, 126.5, 125.9, 124.4, 124.1, 123.7, 120.7, 117.7, 116.0, 104.5, 103.8, 95.0, 81.0, 41.9, 39.8, 27.4, 26.8, 25.8, 22.7, 17.8, 16.1; IR (KBr) 3480, 2969, 2923, 1652, 1613, 1462, 1321, 1225, 1153, 827, 758 cm^{-1}; HRMS *m/z* $(M)^+$ calcd for $C_{28}H_{30}O_4$: 430.2144.. Found: 430.2142.

Compound 17: 45%; mp 177-179 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.87 (1H, s), 8.12 (1H, d, *J* = 7.8 Hz), 7.58 (1H, t, *J* = 7.2 Hz), 7.35-7.26 (6H, m), 6.94 (1H, d, *J* = 10.2 Hz), 6.16 (1H, s), 5.93-5.8 (1H, m), 5.72-5.68 (1H, dd, *J* = 10.2 Hz, 3.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.0, 160.8, 158.1, 157.5, 156.1, 140.2, 135.1, 129.0, 128.9, 127.3, 126.0, 124.2, 121.5, 120.8, 117.8, 117.3, 104.8, 104.2, 95.1, 78.5; IR (KBr) 3468, 3069, 1646, 1621, 1464, 1302, 1227, 1136, 821, 754 cm^{-1}; HRMS *m/z* $(M)^+$ calcd for $C_{22}H_{14}O_4$: 342.0892. Found: 342.0893.

Compound 18: To a solution of **11** (294 mg, 1 mmol) in acetone (10 mL) was added iodomethane (426 mg, 3 mmol) and potassium carbonate (414 mg, 3 mmol). The reaction mixture was refluxed for 2 h under nitrogen atmosphere. The reaction mixture was filtered and removal of the solvent at reduced pressure left the residue, which was then purified by column chromatography on silica gel with hexane/EtOAc (7:1) to give **18** (299 mg, 97%) as a solid. mp 106-107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (1H, dd, *J* = 10.8 Hz, 1.5 Hz), 7.60 (1H, m), 7.37-7.29 (2H, m), 6.72 (1H, d, *J* = 9.9 Hz), 6.61 (1H, s), 5.68 (1H, d, *J* = 9.9 Hz), 3.93 (3H, s), 1.46 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 159.2, 158.6, 156.3, 155.0, 133.9, 130.2, 126.5, 123.7, 122.5, 117.1, 115.9, 112.2, 100.6, 77.9, 62.6, 28.3; IR (KBr) 2929, 1645, 1605, 1461, 1303, 1228, 1131 cm^{-1}; HRMS *m/z* $(M)^+$ calcd for $C_{19}H_{16}O_4$: 308.1049. Found: 308.1051.

Compound 19: To a solution of **12** (280 mg, 1 mmol) in acetone (10 mL) was added iodomethane (426 mg, 3 mmol) and potassium carbonate (414 mg, 3 mmol). The reaction mixture was refluxed for 2 h under nitrogen atmosphere. The reaction mixture was filtered and removal of the solvent at reduced pressure left the residue, which was then purified by column chromatography on silica gel with hexane/EtOAc (7:1) to give **19** (282 mg, 96%) as a solid. mp 111-112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (1H, m), 7.51 (1H, m), 7.28-7.19 (2H, m), 6.69 (1H, d, *J* = 10.2 Hz), 6.51 (1H, s), 5.62 (1H, dd, *J* = 10.2 Hz, 3.0 Hz), 5.00 (1H, m), 3.86 (3H, s), 1.39 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 159.7, 158.7, 156.4, 155.2, 134.0, 126.7, 126.2, 123.9, 122.7, 117.5, 117.3, 112.7, 110.8, 100.5, 72.7, 62.8, 21.9; IR (KBr) 2933, 1607, 1462, 1140, 1077 cm^{-1}; HRMS *m/z* $(M)^+$ calcd for $C_{18}H_{14}O_4$: 294.0892. Found: 294.0889.

Compound 20: To a solution of **15** (362 mg, 1 mmol) in acetone (10 mL) was added iodomethane (426 mg, 3 mmol) and potassium carbonate (414 mg, 3 mmol). The reaction mixture was refluxed for 2 h under nitrogen atmosphere. The reaction mixture was filtered and removal of the solvent at reduced pressure left the residue, which was then purified by column chromatography on silica gel with hexane/EtOAc (7:1) to give **20** (361 mg, 96%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (1H, m), 7.55 (1H, m), 7.31-7.19 (2H, m), 6.71 (1H, d, *J* = 10.5 Hz), 6.54 (1H, s), 5.57 (1H, d, *J* = 10.5 Hz), 3.88 (3H, s), 2.04-1.96 (2H, m), 1.77-1.70 (2H, m), 1.57 (3H, s), 1.49 (3H, s), 1.37 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 159.8, 158.8, 156.5, 155.3, 134.0, 132.2, 129.2, 126.7, 23.9, 122.8, 117.3, 116.7, 112.3, 110.6, 100.5, 80.6, 62.8, 41.9, 27.4, 25.8, 22.8, 17.8; IR (neat) 2923, 1650, 1605, 1459, 1373, 1305, 1143, 1083 cm^{-1}; HRMS *m/z* $(M)^+$ calcd for $C_{24}H_{24}O_4$: 376.1675. Found: 376.1673.

Compound 21: To a solution of **18** (308 mg, 1 mmol) in ethyl acetate (10 mL) was added Pd/C (10 wt %, 0.05 g) and the suspension was hydrogenated over 30 psi for 2 h at room temperature. The reaction mixture was filtered through celite and removal of the solvent at reduced pressure left the residue, which was then purified by column chromatography on silica gel with hexane/EtOAc (7:1) to give **21** (288 mg, 93%) as a solid. mp 139-140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (1H, m), 7.53 (1H, m), 7.30-7.19 (2H, m), 6.55 (1H, s), 3.88 (3H, s), 2.76 (2H, t, *J* = 6.9 Hz), 1.76 (2H, t, *J* = 6.9 Hz), 1.30 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 160.4, 159.3, 157.3, 155.4, 133.9, 126.7, 123.5, 122.8, 117.3, 112.8, 110.0, 100.9, 76.2, 61.4, 32.1, 26.9, 16.8; IR (KBr) 2951, 1645, 1608, 1457, 1308, 1123 cm^{-1}; HRMS *m/z* $(M)^+$ calcd for $C_{19}H_{18}O_4$: 310.1205. Found: 310.1202.

Compound 22: To a solution of **19** (294 mg, 1 mmol) in ethyl acetate (10 mL) was added Pd/C (10 wt %, 0.05 g) and the suspension was hydrogenated over 30 psi for 2 h at room temperature. The reaction mixture was filtered through celite and removal of the solvent at reduced pressure left the

residue, which was then purified by column chromatography on silica gel with hexane/EtOAc (7:1) to give **22** (275 mg, 93%) as a solid. mp 165-166 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (1H, m), 7.54 (1H, m), 7.28-7.18 (2H, m), 6.54 (1H, s), 4.15-4.09 (1H, m), 3.86 (3H, s), 2.91 (1H, m), 2.62 (1H, m), 1.97 (1H, m), 1.59 (1H, m), 1.34 (3H, d, J = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 161.1, 159.3, 157.2, 155.3, 133.9, 126.7, 123.5, 122.7, 117.2, 113.6, 110.1, 100.4, 73.4, 61.4, 28.4, 19.1; IR (KBr) 2931, 1645, 1609, 1458, 1295, 1137 cm^{-1}. HRMS *m/z* $(M)^+$ calcd for $C_{18}H_{16}O_4$: 296.1049. Found: 296.1052.

Compound 23: To a solution of **20** (376 mg, 1 mmol) in ethyl acetate (10 mL) was added Pd/C (10 wt %, 0.05 g) and the suspension was hydrogenated over 30 psi for 2 h at room temperature. The reaction mixture was filtered through celite and removal of the solvent at reduced pressure left the residue, which was then purified by column chromatography on silica gel with hexane/EtOAc (15:1) to give **23** (342 mg, 90%) as a solid. mp 106-107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (1H, m), 7.52 (1H, m), 7.29-7.18 (2H, m), 6.55 (1H, s), 3.88 (3H, s), 2.77-2.71 (2H, m), 1.82-1.72 (2H, m), 1.57-1.45 (3H, m), 1.35-1.27 (2H, m), 1.24 (3H, s), 1.14-1.06 (2H, m), 0.80 (3H, s), 0.78 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 160.5, 159.3, 157.3, 155.4, 133.9, 126.7, 123.5, 122.8, 117.2, 113.0, 109.9, 100.9, 78.4, 61.4, 40.0, 39.4, 30.2, 28.0, 24.3, 22.7, 21.4, 16.5; IR (KBr) 2942, 1652, 1606, 1456, 1305, 1132 cm^{-1}; HRMS *m/z* $(M)^+$ calcd for $C_{24}H_{28}O_4$: 380.1988. Found: 380.1990.

Compound 24: To a solution of **11** (294 mg, 1 mmol) in ethyl acetate (10 mL) was added Pd/C (10 wt %, 0.05 g) and the suspension was hydrogenated over 30 psi for 2 h at room temperature. The reaction mixture was filtered through celite and removal of the solvent at reduced pressure left the residue, which was then purified by column chromatography on silica gel with hexane/EtOAc (7:1) to give **24** (281 mg, 95%) as a solid. mp 135-136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.12 (1H, s), 8.14 (1H, m), 7.57 (1H, m), 7.33-7.22 (2H, m), 6.25 (1H, s), 2.65 (2H, t, J = 6.9 Hz), 1.77 (2H, t, J = 6.9 Hz), 1.31 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.9, 161.9, 160.7, 156.2, 155.7, 134.9, 125.9, 123.7, 120.7, 117.7, 104.2, 103.0, 95.2, 76.6, 31.9, 26.9, 16.1; IR (KBr) 3465, 2928, 1617, 1460, 1306, 1218, 1135 cm^{-1}; HRMS *m/z* $(M)^+$ calcd for $C_{18}H_{16}O_6$: 296.1049. Found: 296.1049.

Compound 25: To a solution of **12** (280 mg, 1 mmol) in ethyl acetate (10 mL) was added Pd/C (10 wt %, 0.05 g) and the suspension was hydrogenated over 30 psi for 2 h at room temperature. The reaction mixture was filtered through celite and removal of the solvent at reduced pressure left the residue, which was then purified by column chromatography on silica gel with hexane/EtOAc (7:1) to give **25** (260 mg, 92%) as a solid. mp 169-170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (1H, m), 7.66 (1H, m), 7.40-7.27 (2H, m), 6.33 (1H, s), 4.22 (1H, m), 2.85 (1H, m), 2.60 (1H, m), 2.06 (1H, m), 1.69 (1H, m), 1.42 (3H, d, J = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.8, 162.5, 160.5, 156.0, 155.4, 134.7, 125.7, 123.6, 120.5, 117.5, 104.9, 103.0, 94.5, 73.5, 28.0, 21.0, 18.1; IR (KBr) 3447, 2934, 1619, 1456, 1292, 1136 cm^{-1}; HRMS *m/z* $(M)^+$ calcd for $C_{17}H_{14}O_4$: 282.0892. Found: 282.0890.

Compound 26: To a solution of **15** (362 mg, 1.0 mmol) in ethyl acetate (10 mL) was added Pd/C (10 wt %, 0.05 g) and the suspension was hydrogenated over 30 psi for 2 h at room temperature. The reaction mixture was filtered through celite and removal of the solvent at reduced pressure left the residue, which was then purified by column chromatography on silica gel with hexane/EtOAc (15:1) to give **26** (328 mg, 90%) as a solid. mp 104-105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (1H, m), 7.67 (1H, m), 7.41-7.31 (2H, m), 6.34 (1H, s), 2.73-2.69 (2H, m), 1.91-1.76 (2H, m), 1.70-1.53 (3H, m), 1.49-1.38 (2H, m), 1.33 (3H, s), 1.29-1.20 (2H, m),0.89 (3H, s), 0.87 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.6, 161.7, 160.4, 155.9, 134.6, 125.6, 123.4, 120.5, 117.4, 104.2, 102.7, 94.9, 78.5, 39.7, 39.2, 29.8, 27.8, 24.0, 22.5, 21.3, 15.6; IR (KBr) 3454, 2943, 1627, 1464, 1381, 1307, 1144 cm^{-1}; HRMS *m/z* $(M)^+$ calcd for $C_{23}H_{26}O_4$: 366.1831. Found: 366.1835.

Compound 27: To a solution of osmium tetroxide (20 mg, 0.08 mmol) and *N*-methylmorpholine-*N*-oxide (164 mg, 1.4 mmol) in *t*-BuOH/THF/H_2O (10:3:1, 5 mL) was added **11** (205 mg, 0.70 mmol) and the reaction mixture was stirred at room temperature for 4 h. Saturated $NaHSO_3$ solution (30 mL) was added, the mixture was stirred for 1 h, and extracted with CH_2Cl_2. Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel using hexane/ethyl acetate (4:1) to give **27** (160 mg, 70%) as a solid. mp 207-208 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (1H, m), 7.69 (1H, m), 7.43-7.33 (2H, m), 6.4 (1H, s), 5.14 (1H, d, J = 4.8 Hz), 3.85 (1H, d, J = 4.8 Hz), 1.52 (3H, s), 1.33 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.5, 162.5, 160.8, 156.8, 136.2, 125.7, 124.8, 120.1, 118.1, 107.7, 102.7, 94.7, 80.2, 71.5, 60.4, 27.4, 21.8; IR (KBr) 3482, 2976, 2923, 1622, 1466, 1323, 1140 cm^{-1}; HRMS *m/z* $(M)^+$ calcd for $C_{18}H_{16}O_6$: 328.0947. Found: 328.0945.

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