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Microwave-Assisted Solvent and Catalyst Free Synthesis of 2*H*-Pyrans

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This paper describes a simple and efficient method involving domino Knovenegal/6π electrocyclization for the preparation of a variety of 2*H*-pyrans using microwave irradiation under solvent- and catalyst-free conditions. This method offers the advantages of a green approach, high yields, and short reaction times. Sixteen compounds (**9a-p**) were obtained in good to excellent yields using the procedure.

Key Words : Catalyst free, Domino Knoevenagel/6π-electrocylization, Microwave, 2*H*-pyrans, Solvent-free.

Introduction

2*H*-Pyrans are important core units in a number of natural products.[1] The molecules bearing 2*H*-pyrans have a variety of interesting biological activities and medicinal applications.[2] Among these, seselin (**1**), an angular pyranocoumarin isolated from some Rutaceae species, has antinociceptive and anti-inflammatory activities.[3] α-Caryopterone (**2**), a pyranonaphthoquinone, isolated from *Zeyhera tuberculosa*, is used in Chinese traditional medicine, and has been shown to have antibacterial, antifungal, antitrypanosomal, antimalarial, and antitumor activities.[4] Zanthosimuline (**3**), a monoterpenoid pyranoquinoline alkaloid, was isolated from the root bark of Taiwanese *Zanthoxylum simulans*, and reduces multidrug resistance in KB-VI cancer cells. Huajiaosimuline (**4**) was found to exhibit a selective cytotoxicity profile and to have greatest activity on estrogen receptor-positive ZR-75-1 breast cancer cells.[5] On the other hand, calanolide A (**5**) has been reported to be a potent anti-HIV agent,[6] and recently, two prenylated indole alkaloids, 17-*epi*-notoamides Q (**6**) and M (**7**), have been isolated from an extract of the marine-derived *Aspergillus* sp. fungus, and have shown to have potent antibacterial activities (Figure 1).[7]

Due to their wide-ranging pharmacological applications, the synthesis of 2*H*-pyrans has received much attention. In a previous study, we described new methodologies for the synthesis of 2*H*-pyrans based on indium(III) chloride or ethylenediamine diacetate-catalyzed cycloaddition.[8] Subsequently, other approaches were described based on the uses of BF_3-Et_2O, $TiCl_4$, or $In(OTf)_3$ as Lewis catalysts,[9] phosphoric acids as Brønsted acid catalysts,[10] or EDDA/$ZnCl_2$ as co-catalysts.[11] However, environmentally benign and cost-effective approaches are still required for the production of 2*H*-pyrans. In particular, no microwave-assisted synthesis of 2*H*-pyrans has been previously reported.

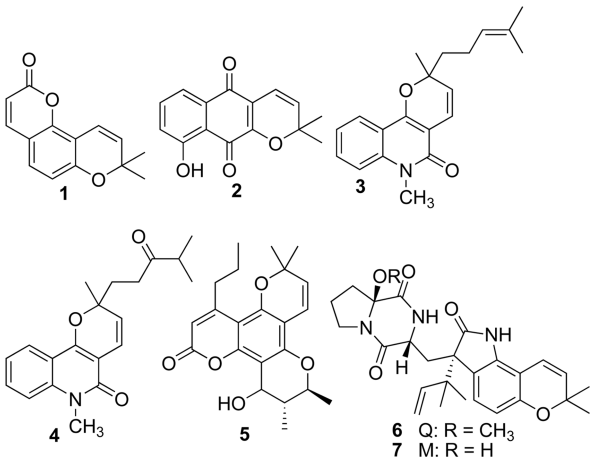
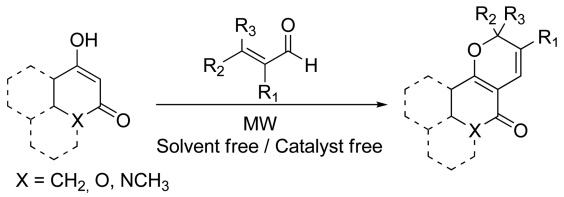


Figure 1. Selected biologically active and naturally occuring molecules bearing 2*H*-pyrans.

Microwave-assisted organic synthesis (MAOS) has been known since 1986. The use of microwave irradiation as an energy source for the activation of chemical reactions often leads to remarkably reduced reaction times, simplified work-up procedures, higher yields and selectivity, lower quantities of side products, and purer reaction products. Furthermore, MAOS is considered a "green" technology, because it allows many organic reactions to be conducted under solvent-free conditions. This has generated considerable interest in the use of MAOS in academic, research, and industrial laboratories as evidenced by an exponential increase in the number of scientific papers, books,[12] and reviews[13] published on the topic. Microwave assisted organic reactions often proceed rapidly in the absence of catalyst,[14] and has been used to effect organic reactions, such as, pericyclic,[15] cyclization,[16] aromatic substitution,[17] oxidation,[18] alkylation,[19] decarboxylation,[20] radical,[21] and condensation[22] reactions and to synthesize peptides.[23]

Recently, we developed an environmentally benign method for the one-pot synthesis of pyrans based on domino Knoevenagel/6π-electrocyclization in water.[24] During our on-going research to devise green protocols that eliminate the need for



Scheme 1

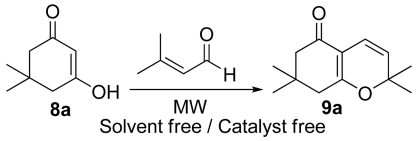
solvents, catalysts, and excess reagents, we devised a straightforward, inexpensive, and green protocol for the one-pot synthesis of 2*H*-pyrans using a microwave-assisted domino Knoevenagel/6π-electrocyclic reaction as shown in Scheme 1.

Results and Discussion

Initially, we carried out reactions with cyclic 1,3-dicarbonyls and α,β-unsaturated aldehydes using microwave irradiation under solvent- and catalyst-free conditions. The reaction was conducted using a 1:1.2 molar ratio of 5,5-dimethyl-1,3-cyclohexanedione (**8a**) and 3-methyl-2-butenal in a 300W microwave reactor. Homogenous mixtures of reactants at 80 °C, 100 °C, and 120 °C were irradiated for 36, 20, and 8 min, respectively, to afford the corresponding 2,2,7,7-tetramethyl-2,6,7,8-tetrahydro-chromen-5-one (**9a**) in good yields (Table 1). After optimizing the reaction conditions at 120 °C for 8 min, **9a** was obtained in 93% yield.

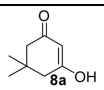
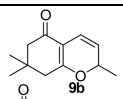
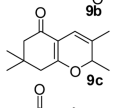
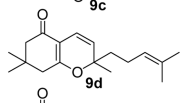
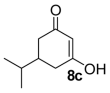
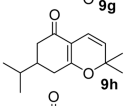
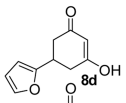
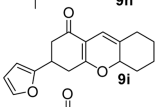
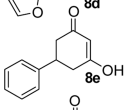
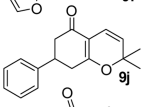
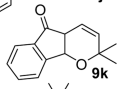
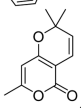
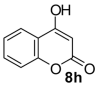
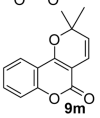
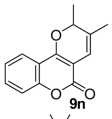
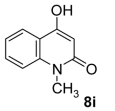
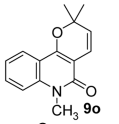
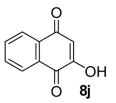
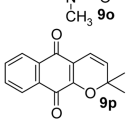
In order to examine applications of this protocol, various 1,3-dicarbonyls with different moieties were reacted with several α,β-unsaturated aldehydes under the above-mentioned optimized reaction conditions (Table 2). Reactions between 5,5-dimethyl-1,3-cyclohexanedione (**8a**) and crotonaldehyde, *trans*-2-methyl-2-butenal, or citral afforded cycloadducts **9b-9d** in 91, 72, and 94% yield, respectively (entries 1-3). Reactions between 1,3-cyclohexanedione (**8b**) and 3-methyl-2-butenal, crotonaldehyde, or *trans*-2-methyl-2-butenal afforded the desired products **9e-9g** in 89, 92, and 74% yield, respectively (entries 4-6). Similarly, reactions between 5-isopropyl-1,3-cyclohexanedione (**8c**), 5-phenyl-1,3-cyclohexanedione (**8e**), 1,3-indanedione (**8f**), 4-hydroxy-6-methyl-2-pyrone (**8g**), or 4-hydroxycoumarin (**8h**) and 3-methyl-2-butenal provided cycloadducts **9h** and **9j-9m** in 86-94% yield (entries 7, 9-12). In addition, the reaction between 4-hydroxycoumarin (**8h**) and *trans*-2-methyl-2-butenal afforded adduct **9n** in 78% yield (entry 13). Interestingly, the reaction between 5-(2-furyl)-1,3-cyclohexanedione (**8d**) and 1-cyclohexene-1-carboxaldehyde provided the expected product **9i** in 95% yield (entry 8). Finally, we attempted the syntheses of naturally occurring pyranoquinolinones and pyranonaphthoquinones. Microwave irradiation-induced reactions between 4-hydroxy-1-methyl-2(1*H*)-quinolone (**8i**) or 2-hydroxy-1,4-naphthoquinone (**8j**) and 3-methyl-2-butenal at 120 °C for 12 min provided *N*-methylflindersine (**9o**) or dehydro-α-lapachone (**9p**) in 74% and 91% yield, respectively (entries 14-15). All reactions proceeded smoothly to afford the corresponding products. The products **9a-p** were identified by spectral data.

Table 1. Reaction of 5,5-dimethyl-1,3-cyclohexanedione (**8a**) with 3-methyl-2-butenal under MW conditions



Power (W)	Temperature (°C)	Time (min)	Yield (%)
300	80	36	58
300	100	20	64
300	120	8	93

Table 2. Additional reactions of cyclic 1,3-dicarbonyls with α,β-unsaturated aldehydes for the synthesis of a variety of 2*H*-pyrans

Entry	1,3-dicarbonyls	α,β-unsaturated	Time (min)	Product	Yield
1			8		91
2			8		72
3		citral	12		94
4			12		89
5			8		92
6			8		74
7			10		88
8			8		95
9			10		86
10			12		94
11			10		94
12			12		86
13			12		78
14			12		74
15			12		91

Conclusion

A simple, inexpensive, and green protocol involving domino Knovenegal/6π electrocyclization is described for the preparation of 2*H*-pyrans using microwave irradiation. The

devised method avoids the use of high temperatures, extended reaction times, and need for solvents and catalysts. The method was successfully applied to the synthesis of biologically interesting and naturally occurring pyranocoumarins, pyranoquinolinone alkaloids, and pyranonaphthoquinones in good yields.

Experimental

Melting points were determined a Fisher-Johns apparatus using microcover glasses and are uncorrected. 1,3-Dicarbonyl compounds and α,β-unsaturated aldehydes were obtained from Aldrich Chemicals. Merck precoated silica gel plates (Art. 5554) with fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian VNS spectrometer (at 300 and 75 MHz, respectively) in $CDCl_3$. IR spectra were recorded on a FTIR (BIO-RAD) spectrophotometer. Microwave reactions were conducted using a CEM Focused MARS 5 (Microwave Accelerated Reaction System) reactor. The unit consists of a continuous, focused, variable microwave power delivery system (0 to 1200 W), a pressure control system (programmable from 0-300 psi (0-21 bar)), and a temperature control system (programmable from 25-250 °C).

General Procedure for the Synthesis of 2*H* Pyrans. The 1,3-dicarbonyl compound (1.0 mmol) and the α,β-unsaturated aldehyde (1.2 mmol) were measured into a reaction vessel, which was then sealed and placed in the Microwave reactor. Microwave irradiation was then generated at 300 W and the temperature increased from room temperature to 120 °C. The reaction mixture was then held at this temperature for 8-20 min. After cooling to room temperature, the reaction vessel was opened. Reaction completion was monitored by TLC, and the crude product was dissolved in ethyl acetate and purified by silica gel column chromatography using hexane-ethyl acetate (9:1) as eluent to afford the desired compounds.

2,2,7,7-Tetramethyl-2,6,7,8-tetrahydro-chromen-5-one (9a)[24]**:** Yield 93%; mp 38-40 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.21 (1H, d, *J* = 9.9 Hz), 5.05 (1H, d, *J* = 9.9 Hz), 2.09 (2H, s), 2.06 (2H, s), 1.21 (6H, s), 0.88 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 170.1, 122.7, 115.8, 109.6, 79.8, 50.4, 42.5, 32.2, 28.4, 28.3; IR (KBr) 2959, 2870, 1645, 1633, 1586, 1454, 1416, 1351, 1324, 1299, 1251, 1206, 1131, 1090, 1047, 976, 928 cm^{-1}.

2,7,7-Trimethyl-2,6,7,8-tetrahydro-chromen-5-one (9b)[24]**:** Yield 91%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (1H, d, *J* = 9.9 Hz), 5.24 (1H, dd, *J* = 9.9, 3.1 Hz), 4.96-4.94 (1H, m), 2.33-2.19 (4H, m), 1.34 (3H, d, *J* = 6.3 Hz), 1.01 (3H, s), 1.00 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 170.7, 118.5, 117.0, 110.1, 73.9, 50.2, 41.9, 32.1, 28.3, 28.2, 21.5; IR (neat) 2926, 1645, 1611, 1455, 1399, 1375, 1266, 1188, 1130, 1010, 905 cm^{-1}.

2,3,7,7-Tetramethyl-2,6,7,8-tetrahydro-chromen-5-one (9c)[8a]**:** Yield 72%; mp 80-82 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (1H, s), 4.80 (1H, q, *J* = 6.4 Hz), 2.28-2.20 (4H, m), 1.70 (3H, s), 1.31 (3H, d, *J* = 6.4 Hz), 1.05 (3H, s), 1.02 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.2, 167.5, 126.8, 111.5, 110.1, 76.9, 50.2, 41.7, 32.0, 28.7, 27.6, 19.0, 18.5; IR (KBr) 2963, 1645, 1634, 1622, 1558, 1471, 1455, 1418, 1404, 1387, 1373, 1260, 1238, 1067, 1030, 877 cm^{-1}.

2,7,7-Trimethyl-2-(4-methyl-pent-3-enyl)-2,6,7,8-tetrahydrochromen-5-one (9d)[24]**:** Yield 94%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.41 (1H, d, *J* = 9.9 Hz), 5.14 (1H, d, *J* = 9.9 Hz), 5.08-5.02 (1H, m), 2.24-2.16 (4H, m), 2.05-1.97 (2H, m), 1.79-1.66 (1H, m), 1.59 (3H, s), 1.55 (3H, s), 1.53-1.48 (1H, s), 1.33 (3H, s), 1.04 (3H, s), 1.03 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.1, 170.2, 131.7, 123.5, 121.2, 116.1, 108.9, 82.2, 50.2, 42.2, 41.5, 32.0, 28.4, 28.0, 27.3, 25.5, 22.3, 17.4; IR (neat) 3386, 2961, 2930, 1719, 1646, 1596, 1415, 1356, 1234, 1194, 1142, 1067, 931, 889, 748 cm^{-1}.

2,2-Dimethyl-2,6,7,8-tetrahydro-chromen-5-one (9e)[24]**:** Yield 89%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.34 (1H, d, *J* = 10.0 Hz), 5.19 (1H, d, *J* = 10.0 Hz), 2.36-2.31 (4H, m), 1.95-1.85 (2H, m), 1.35 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.8,171.5, 122.9, 115.8, 110.6, 79.7, 36.4, 28.6, 28.4, 20.6; IR (neat) 2926, 1645, 1611, 1455, 1399, 1375, 1266, 1188, 1130, 1010, 905 cm^{-1}.

2-Methyl-2,6,7,8-tetrahydro-chromen-5-one (9f)[24]**:** Yield 92%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.41 (1H, d, *J* = 10.0 Hz), 5.25 (1H, dd, *J* = 10.0, 3.0 Hz), 4.98 (1H, m), 2.40-2.32 (4H, m), 2.02-1.88 (2H, m), 1.38 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.9, 172.3, 118.8, 117.1, 111.1, 73.8, 36.3, 28.2, 21.5, 20.5; IR (neat) 2960, 1651, 1633, 1422, 1408, 1370, 1224, 1140, 1054, 947 cm^{-1}.

2,3-Dimethyl-2,6,7,8-tetrahydro-chromen-5-one (9g)[8a]**:** Yield 74%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09 (1H, s), 4.74 (1H, q, *J* = 6.4 Hz), 2.33-2.24 (4H, m), 1.90- 1.63 (2H, m), 1.64 (3H, s), 1.25 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.6, 164.5, 145.2, 120.2, 114.2, 79.7, 41.7, 32.0, 26.9, 20.6, 18.5; IR (neat) 2940, 1645, 1615, 1452, 1403, 1383, 1234, 1193, 1169, 1070, 1010, 931 cm^{-1}.

7-Isoprpyl-2,2-dimethyl-2,6,7,8-tetrahydro-chromen-5-one (9h)[24]**:** Yield 88%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.34 (1H, d, *J* = 9.9 Hz), 5.18 (1H, d, *J* = 9.9 Hz), 2.47-2.39 (1H, m), 2.38-2.31 (1H, m), 2.20-2.01 (2H, m), 1.87-1.75 (1H, m), 1.59-1.47 (1H, m), 1.40 (3H, s), 1.34 (3H, s), 0.90 (6H, d, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.1, 171.6, 122.7, 115.7, 110.0, 79.8, 53.4, 40.5, 39.4, 32.4, 31.9, 28.6, 28.1, 19.5; IR (neat) 2964, 2878, 1651, 1594, 1462, 1416, 1331, 1252, 1203, 1144, 1093, 1048, 1002, 910, 872, 820 cm^{-1}.

3-(Furan-2-yl)-2,3,4,5,6,7,8,10a-octahydro-1*H*-xanthen-1-one (9i): Yield 95%; 162-164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (1H, s), 6.25-6.23 (1H, m), 6.04-6.00 (2H, m), 3.40-3.31 (1H, m), 2.70-2.44 (3H, m), 2.35-2.31 (1H, m), 2.12-2.01 (1H, m), 1.94-1.81 (2H, m), 1.73-1.58 (3H, s), 1.42-1.37 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.0, 169.1, 155.9, 141.4, 110.0, 108.2, 104.5, 80.0, 60.2, 40.5, 34.8, 32.7, 26.9, 24.3, 20.9; IR (KBr) 3487, 3056, 2968, 2885, 1651, 1594, 1462, 1416, 1331, 1252, 1203, 1144, 1093, 1048, 1002, 910, 872, 820 cm^{-1}.

2,2-Dimethyl-7-phenyl-2,6,7,8-tetrahydro-chromen-5-

one (9j)[24]**:** Yield 86%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.25 (2H, m), 7.21-7.16 (3H, m,), 6.37 (1H, d, J = 9.9 Hz), 5.20 (1H, d, J = 9.9 Hz), 3.34-3.23 (1H, m), 2.65-2.48 (4H, m), 1.38 (3H, s), 1.31 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.8, 170.7, 142.6, 128.7, 126.9, 126.6, 123.0, 115.0, 110.2, 80.2, 43.5, 38.7, 36.1, 28.6, 28.2; IR (neat) 3487, 3056, 2971, 2925, 1723, 1644, 1590, 1454, 1415, 1330, 1252, 1203, 1142, 1090, 1048, 919, 887, 819 cm^{-1}.

2,2-Dimethyl-2*H*-indeno[1,2-*b*]pyran-5-one (9k)[8e]**:** Yield 94%; mp 158-159 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (1H, d, J = 7.8 Hz), 7.41 (1H, t, J = 7.8 Hz), 7.19-7.12 (2H, m), 6.34 (1H, d, J = 10.0 Hz), 5.17 (1H, d, J = 10.0 Hz), 1.35 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.0, 160.9, 158.8, 153.1, 132.0, 126.1, 123.9, 122.7, 116.7, 115.6, 100.2, 80.5, 28.5; IR (KBr) 3064, 2926, 1725, 1640, 1458, 1364, 1284, 1215, 1159, 1114, 1037, 908 cm^{-1}.

2,2,7-Trimethyl-2*H*-pyrano[4,3-*b*]pyran-5-one (9l)[10b]**:** Yield 94%; mp 64-66 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31 (1H, d, J = 9.9 Hz), 5.72 (1H, s), 5.30 (1H, d, J = 9.9 Hz), 2.15 (3H, s), 1.38 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 162.9, 161.4, 123.8, 115.2, 99.2, 96.8, 79.1, 28.3, 19.1; IR (KBr) 2926, 1645, 1611, 1455, 1399, 1375, 1266, 1188, 1130, 1010, 905 cm^{-1}.

2,2-Dimethyl-2*H*-pyrano[3,2-*c*]chromen-5-one (9m)[24]**:** Yield 86%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (1H, dd, J = 7.8, 1.6 Hz), 7.47 (1H, m), 7.24-7.17 (2H, m), 6.47 (1H, d, J = 9.9 Hz), 5.45 (1H, d, J = 9.9 Hz), 1.48 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 158.8, 153.1, 132.0, 126.1, 123.9, 122.7, 116.7, 115.5, 100.2, 80.5, 28.5; IR (neat) 3073, 2978, 2930, 1715, 1642, 1566, 1493, 1458, 1416, 1362, 1327, 1281, 1217, 1192, 1157, 1115, 1038, 992, 909 cm^{-1}.

2,3-Dimethyl-2*H*-pyrano[3,2-*c*]chromen-5-one (9n)[8a]**:** Yield 78%; mp 59-60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (1H, dd, J = 7.8, 1.6 Hz), 7.43 (1H, m), 7.27-7.19 (2H, m), 6.29 (1H, s), 5.07 (1H, q, J = 7.9 Hz), 1.72 (3H, s), 1.45 (3H, d, J = 7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 158.8, 153.1, 126.2, 123.6, 122.4, 118.3, 115.8, 115.4, 100.4, 80.3, 21.7, 17.1; IR (KBr) 3061, 2984, 2926, 2859, 1707, 1644, 1570, 1495, 1427, 1372, 1269, 1219, 1202, 1155, 1127, 1084, 1028, 924, 901 cm^{-1}.

***N*-Methylflindersine (9o)**[24]**:** Yield 74%; mp 80-81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (1H, d, J = 8.1 Hz), 7.51 (1H, dd, J = 8.3, 7.3 Hz), 7.23 (1H, d, J = 8.4 Hz), 7.19 (1H, dd, J = 8.3, 7.3 Hz), 6.68 (1H, d, J = 9.9 Hz), 5.46 (1H, d, J = 9.9 Hz), 3.62 (3H, s), 1.44 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 155.1, 139.3, 130.7, 126.2, 123.0, 121.6, 117.9, 116.0, 113.9, 105.8, 78.6, 29.2, 28.1; IR (KBr) 2976, 1645, 1505, 1464, 1418, 1360, 1325, 1211, 1154, 1123, 1092, 1044, 1005, 987, 895 cm^{-1}.

Dehydro-α-lapachone (9p)[24]**:** Yield 91%; mp 141-142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08- 8.06 (2H, m), 7.69-7.65 (2H, m), 6.63 (1H, d, J = 10.2 Hz), 5.70 (1H, d, J = 10.2 Hz), 1.53 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.6, 179.6, 152.2, 133.8, 133.0, 131.4, 131.3, 130.7, 126.0, 117.6, 115.3, 80.3, 28.2; IR (KBr) 2928, 1641, 1578, 1453, 1414, 1329, 1271, 1190, 1131, 953, 793, 708 cm^{-1}.

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