An Efficient and Concise Synthesis of Biologically Interesting Pyranochromenes by Ethylenediamine Diacetate-Catalyzed Double Condensation of Substituted Trihydroxybenzenes to α,β-Unsaturated Aldehydes and Application to Natural Product Analoges

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Received July 28, 2007

A new methodology for the preparation of pyranochromenes was developed starting from substituted trihydroxybenzenes. This methodology was applied successfully to the total synthesis of biologically interesting compounds, clusiaphenone A, octandrenolone, O-methyloctandrenolone, *trans*-3''',4'''-dihydro-3''',4'''-dihydroxy-O-methyloctandrenolone, *trans*-3'',4''-dihydro-3'',4''-dihydroxy-O-methyloctandrenolone, flemiculosin, laxichalcone, and racemic 3-deoxy-Ms-II.

Key Words : Pyranochromene, Double condensation, Trihydroxybenzenes, Electrocyclization

Introduction

Pyranochromenes (Pyranobenzopyrans) are one of the important classes of heterocycles, and have attracted considerable interest in organic and natural product syntheses.[1] Molecules with the pyranochromene moiety are found widely in nature (Figure 1).[2] These compounds exhibit a range of biological and pharmacological properties including antioxidant, anticancer, anti-inflammatory, antiviral, antibacterial, and anti-HIV activities.[3] This wide range of biological activities has prompted studies into the development of a convenient and efficient methodology for synthesizing molecules with the pyranochromene moiety.

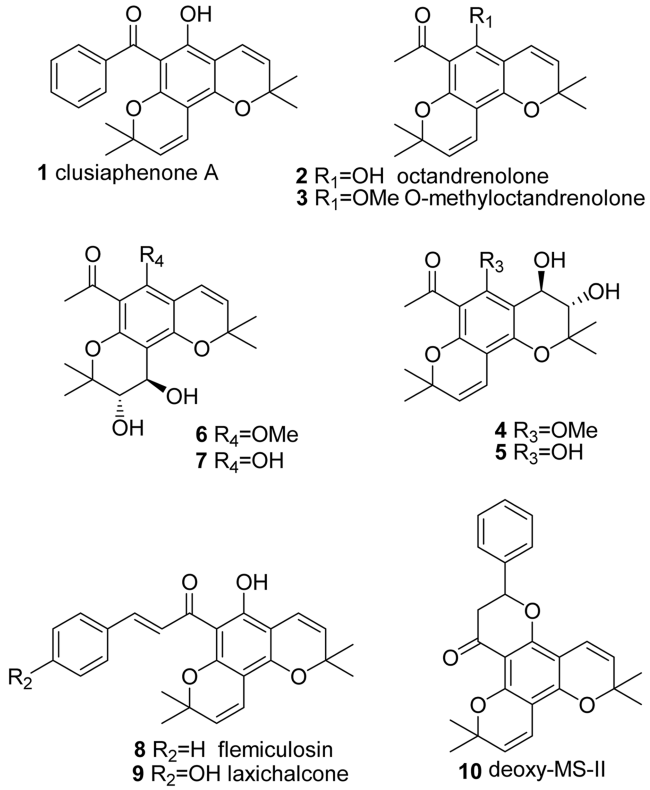
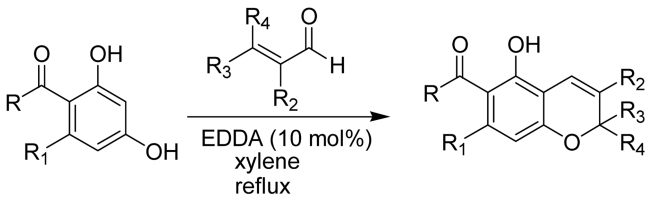


Figure 1. Selected natually occurring molecules with pyranochromenes.



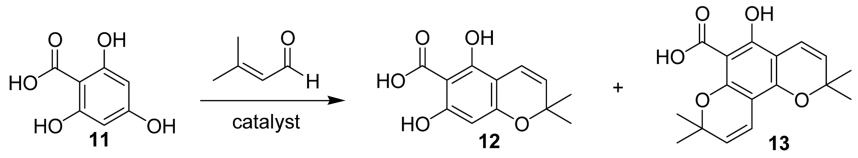
Scheme 1

Recently, we developed a new and efficient methodology for preparing a variety of benzopyrans using ethylenediamine diacetate-catalyzed reactions of substituted resorcinols to α,β-unsaturated aldehydes (Scheme 1).[4] We also reported the synthesis of biologically interesting natural products with benzopyran skeletons using this methodology.[5] As part of an ongoing examination of the efficacy of this methodology, this study investigated ethylenediamine diacetate-catalyzed double condensation of 1,3,5-trihydroxybenzenes with α,β-unsaturated aldehydes to yield pyranochromenes. We report herein a mild and facile methodology for preparing pyranochromenes starting from substituted trihydroxybenzenes. This methodology was applied as a key step to the synthesis of biologically interesting natural products containing pyranochromenes such as clusiaphenone A (**1**), octandrenolone (**2**), O-methyloctandrenolone (**3**), *trans*-3''',4'''-dihydro-3''',4'''-dihydroxy-O-methyloctandrenolone (**4**), *trans*-3'',4''-dihydro-3'',4''-dihydroxy-O-methyloctandrenolone (**6**), flemiculosin (**8**), laxichalcone (**9**), racemic 3-deoxy-Ms-II (**10**).

Results and Discussion

To obtain the pyranochromene derivatives, the reaction of 2,4,6-trihydroxybenzoic acid (**11**) with 2.5 equiv of 3-

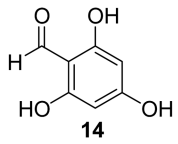
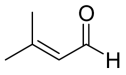
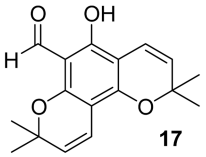
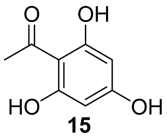
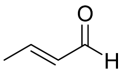
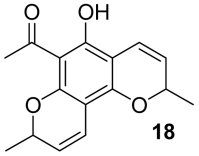
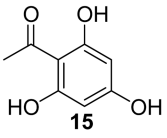
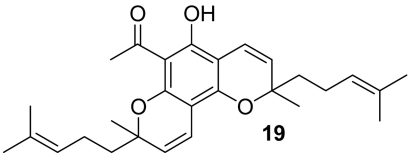
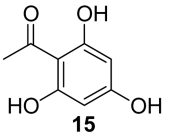
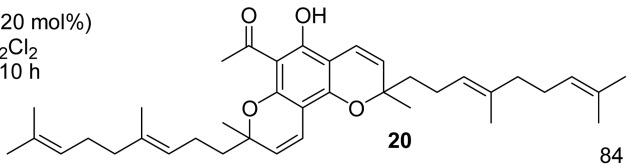
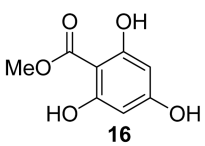
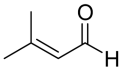
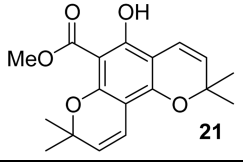
Table 1. Reaction of 1 with 3-methyl-2-butenal under several catalysts

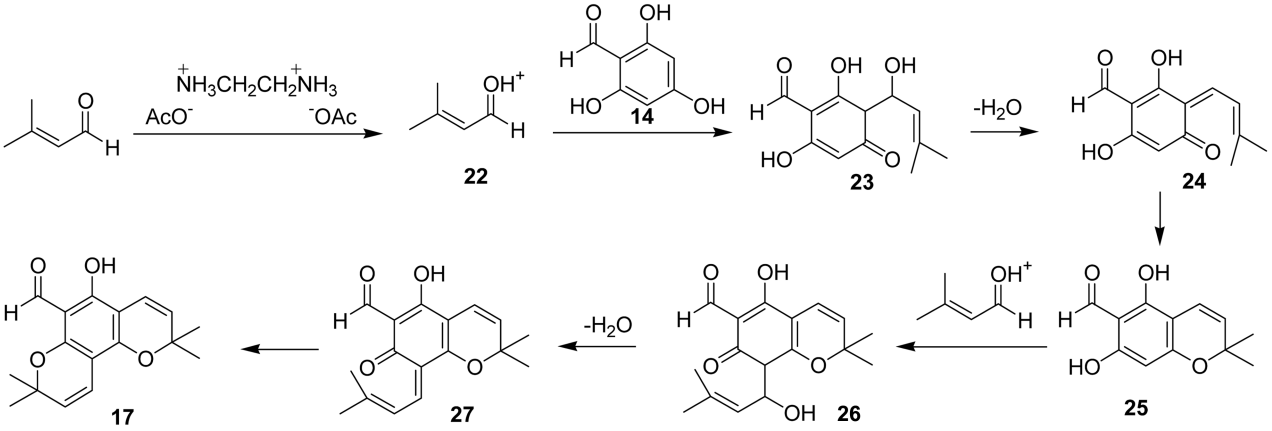


catalyst	condition	yield (%)	
		12	**13**
$InCl_3$ (20 mol %)	acetonitrile, reflux, 10 h	0	0
$Yb(OTf)_3$ (20 mol %)	acetonitrile, reflux, 10 h	0	0
pyridine (excess)	reflux, 10 h	0	0
$Ca(OH)_2$ (20 mol %)	methanol rt, 10 h	0	0
PPTS (20 mol %)	CH_2Cl_2, rt, 10 h	0	0
ethylenediamine diacetate (20 mol%)	benzene, reflux, 10 h	35	10
ethylenediamine diacetate (20 mol%)	toluene, reflux, 10 h	0	40
ethylenediamine diacetate (20 mol%)	$CHCl_3$, rt, 10 h	0	56
ethylenediamine diacetate (20 mol%)	CH_2Cl_2, rt, 10 h	0	91

methyl-2-butenal was first examined using several catalysts (Table 1). No adducts were produced using either indium (III) chloride (20 mol%) and ytterbium (III) triflate (20 mol%) as Lewis acid catalysts in refluxing acetonitrile. With pyridine and $Ca(OH)_2$ as base catalysts, no products were obtained. The use of PPTS as a mild acid gave no products. However, with ethylenediamine diacetate (20 mol%) as a catalyst, products were obtained. Reaction in refluxing

Table 2. Additional reactions of substituted trihydroxybenzenes and α,β-unsaturated aldehyde

entry	starting material	α,β-unsaturated aldehyde	condition	product	yield (%)
1	 **14**		EDDA (20 mol%) CH_2Cl_2 rt, 12 h	 **17**	69
2	 **15**		EDDA (20 mol%) CH_2Cl_2 rt, 12 h	 **18**	60
3	 **15**	citral	EDDA (20 mol%) CH_2Cl_2 rt, 10 h	 **19**	93
4	 **15**	*trans,trans*-farnesal	EDDA (20 mol%) CH_2Cl_2 rt, 10 h	 **20**	84
5	 **16**		EDDA (20 mol%) CH_2Cl_2 rt, 10 h	 **21**	80

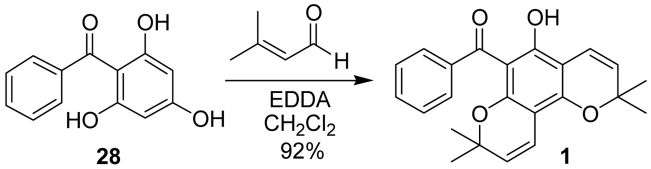


Scheme 2

benzene for 10 h gave two products, compounds **12** (35%) and **13** (10%), whereas the reaction in refluxing toluene for 10 h provided compound **13** in 40% yield as the sole product. Other solvents were surveyed to obtain the optimal reaction conditions. With chloroform at room temperature for 10 h, the cycloadduct **13** was obtained in 56% yield. Interestingly, the best yield (91%) was obtained in methylene chloride at room temperature for 10 h.

Additional reactions between several types of substituted trihydroxybenzenes with α,β-unsaturated aldehydes were also successful. The results are shown in Table 2. A reaction of 2,4,6-trihydroxybenzaldehyde (**14**) with 3-methyl-2-butenal using 20 mol% of ethylenediamine diacetate in methylene chloride at room temperature for 12 h afforded the adduct **17** in 69% yield (entry 1). Treating 2,4,6-trihydroxyacetophenone (**15**) with crotonaldehyde in methylene chloride for 12 h afforded the product **18** in 60% yield (entry 2). A higher yield of products was produced in the case of compounds with more highly substituted groups on the α,β-unsaturated aldehydes. For example, treatment of compound **15** with citral under 20 mol% of ethylenediamine diacetate gave compound **19** in 93% yield (entry 3), whereas reaction with *trans*, *trans*-farnesal provided compound **20** in 84% yield (entry 4). The dicycloadditon reaction of methyl 2,4,6-trihydroxy benzoate was also successful. Reaction of **16** with 3-methyl 2-butenal in methylene chloride at room temperature for 10 h gave compound **21** in 80% yield (entry 5). These reactions provide a rapid route for the synthesis of pyranochromene derivatives with a variety of substituents on the pyranyl rings.

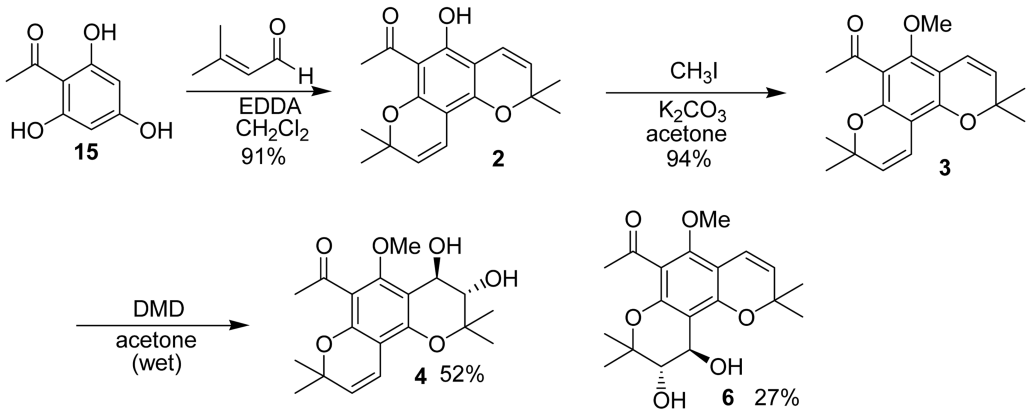
Although the precise mechanism of this reaction is unclear, it is best described in Scheme 2. The 3-methyl-2-butenal was first protonated by EDDA to give **22**, which was then attacked by 2,4,6-trihydroxybenzaldehyde (**14**) to yield intermediate **23**. Such a process was already suggested by Shigemasa to give aldol-type products through a $CaCl_2$-mediated reaction of resorcinol to enals.[6] The dehydration of compound **23** followed by electrocyclization of quinone methide **24** gave compound **25**, which underwent an attack to protonated enal to furnish **26**. Elimination of water to give another quinone methide **27** followed by the electocyclization finally afforded product **17**.[7]



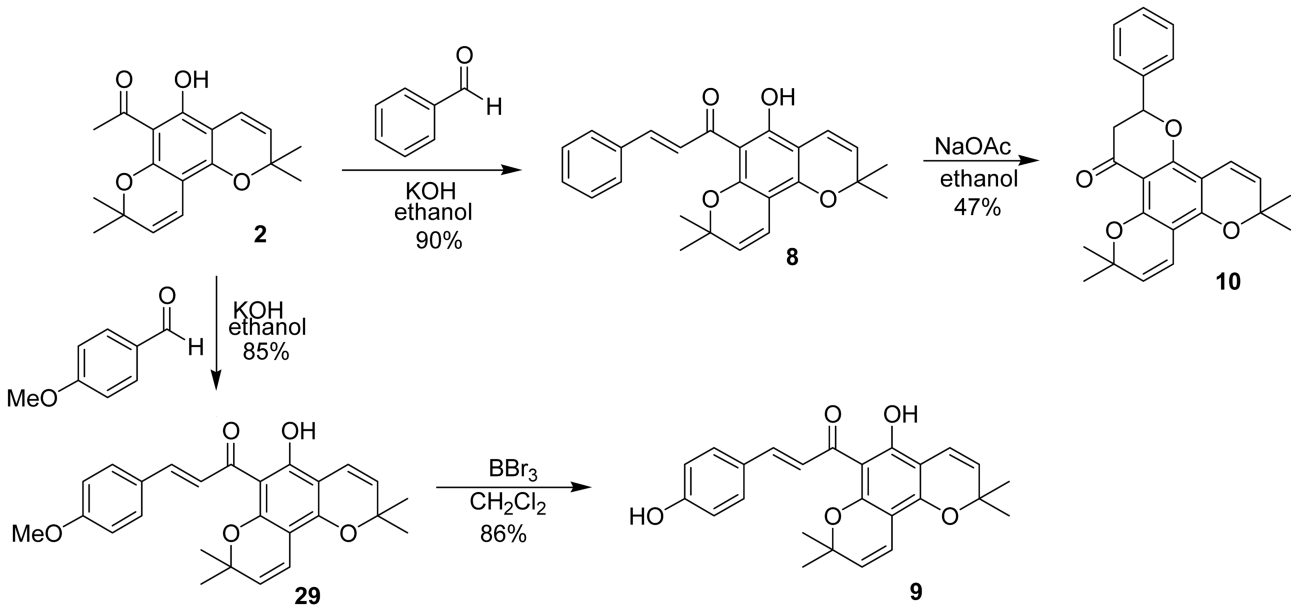
Scheme 3

As an application of this methodology, one-step synthesis of naturally occurring clusiaphenone A (**1**), isolated from *Clusia elipticifolia*,[8] was examined (Scheme 3). Reaction of 2,4,6-trihydroxybenzophenone (**28**) with 3-methyl-2-butenal in the presence of 20 mol% of ethylenediamine diacetate at room temperature for 10 h in methylene chloride affored product **1** in 92% yield.

The synthesis of other natural products octandrenolone (**2**), O-methyloctandrenolone (**3**), *trans*-3‴,4‴-dihydro-3‴,4‴-dihydroxy-O-methyloctandrenolone (**4**), and *trans*-3″,4″-dihydro-3″,4″-dihydroxy-O-methyloctandrenolone (**6**) was next attempted, as shown in Scheme 4. Octandrenolone (**2**), O-methyloctandrenolone (**3**), *trans*-3‴,4‴-dihydro-3‴,4‴-dihydroxy-O-methyloctandrenolone (**4**), and *trans*-3″,4″-dihydro-3″,4″-dihydroxy-O-methyloctandrenolone (**6**) with pyranochromene skeleton were isolated from the leaves of *Melicope ternate* and *M. erromangensis*.[2d,e] A reaction of compound **15** with 3-methyl-2-butenal using 20 mol% of ethylenediamine diacetate in methylene chloride at room temperature for 10 h afforded octandrenolone (**2**) in 91% yield. The spectral data of the synthetic material **2** were in agreement with the reported data.[2d] Previous known synthetic approaches suffered from low yields due to the many reaction steps and side reaction products.[6] The methylation of compound **1** with methyl iodide under K_2CO_3 in acetone afforded O-methyloctandrenolone (**3**) in a 94% yield. The spectral data of the synthetic material **3** agreed well with those reported in the literature.[2f] Treatment of compound **3** with dimethyldioxrane (1.1 equiv) in wet acetone at room temperature for 5 h gave *trans*-3‴,4‴-dihydro-3‴,4‴-dihydroxy-O-methyloctandrenolone (**4**) and *trans*-3″,4″-dihydro-3″,4″-dihydroxy-O-methyloctandrenolone (**6**) in 52 and 27%



Scheme 4



Scheme 5

yields, respectively, without any isolation of the expected epoxide product. The structure of compounds **4** and **6** was clearly assigned by comparing the chemical shift of methoxy group and the two methine protons on the pyranyl ring with the values reported in the literature.[2f] The formation of the *trans*-product may proceed via the epoxidation of olefin in the pyranyl ring followed by direct ring opening by the attack of water in acetone.

The synthesis of flemiculosin (**8**), laxichalcone (**9**), and racemic deoxy-MS-II (**10**) was carried out, as shown in Scheme 5. Flemiculosin (**8**) with a chalcone structure was isolated from *Flemengia fruticulosa*,[9] and its analogue laxichalcone (**9**) was isolated from the roots of *Derris laxiflora*.[10] (−)-3-Deoxy-MS-II (**10**) was isolated from the bark and leaf extracts of *Mundulea chapelieri*, and was reported to have potent cytotoxicity against a human ovarian cancer cell line.[11] Although one synthetic approach to flemiculosin (**8**), laxichalcone (**9**), and racemic 3-deoxy-MS-II (**10**) was recently reported,[12] this method has limitations due to the low yields from the 2-step reaction and the difficulty in isolating the products in *N*,*N*-dimethylaniline and DMF.[13] This serious problem was solved using our developed methodology. The condensation of compound **2** with benzaldehyde in the presence of KOH in ethanol at room temperature for 48 h gave flemiculosin (**8**) in 90% yield. The reaction of compound **8** with sodium acetate in refluxing ethanol afforded 3-deoxy-MS-II (**10**) as a racemate in 47% yield. The spectroscopic data of componds **8** and **10** were same as that reported in the literature.[9,11] On the other hand, the condensation of compound **2** with 4-methoxybenzaldehyde using KOH in ethanol at room temperature for 48 h gave compound **29** in 85% yield.[13] The removal of the methyl ether of compound **29** with c-HCl in methanol according to known procedure[14] was unsuccessful due to ring opening of the 2*H*-pyranyl rings. Fortunately, treating compound **29** with BBr_3 in methylene chloride at room temperature for 10 h afforded laxichalcone (**9**) in 86% yield. The spectroscopic data of compound **9** was same as that reported in the literature.[10]

In conclusion, a new methodology for synthesizing

pyranochromenes was developed starting from substituted trihydroxybenzenes. The synthetic routes provided biologically interesting clusiaphenone A (**1**), octandrenolone (**2**), O-methyloctandrenolone (**3**), *trans*-3‴,4‴-dihydro-3‴,4‴-dihydroxy-O-methyloctandrenolone (**4**), *trans*-3‴,4‴-dihydro-3‴,4‴-dihydroxy-O-methyloctandrenolone (**6**), flemiculosin (**8**), laxichalcone (**9**), racemic 3-deoxy-Ms-II (**10**).

Experimental

All the experiments were carried out under a nitrogen atmosphere. 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). The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Model ARX (300 and 75 MHz, respectively) spectrometer in $CDCl_3$ using δ = 77.0 ppm as the solvent chemical shift. The IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. The HRMS and MS spectra were carried out at the Korea Basic Science Institute.

General Procedure for Synthesis of the Pyranochromenes (13, and 17-21). Ethylenediamine diacetate (36 mg, 0.2 mmol) was then added to a solution of substituted trihydroxybenzene (1.0 mmol) and α,β-unsaturated aldehyde (3.0 mmol) in methylene chloride (10 mL), and stirred at room temperature for 10-12 h. The removal of the solvent left an oily residue, which was then purified by column chromatography on silica gel to give the products.

5-Hydroxy-2,2,8,8-tetramethyl-2*H*,8*H*-pyrano[2,3-*f*]chromen-6-carboxylic Acid (13). A reaction of compound **11** (170 mg, 1.0 mmol) with 3-methyl-2-butenal (252 mg, 3.0 mmol) in methylene chloride (10 mL) afforded compound **13** (275 mg, 91%) as a solid: mp 98-99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.37 (1H, s), 11.50 (1H, s), 6.63 (1H, d, J = 10.0 Hz), 6.58 (1H, d, J = 10.0 Hz), 5.49 (1H, d, J = 10.0 Hz), 5.47 (1H, d, J = 10.0 Hz), 1.53 (6H, s), 1.43 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 160.0, 154.4, 152.8, 126.3, 124.9, 116.3, 115.9, 103.8, 102.3, 94.9, 81.2, 78.4, 28.3, 27.7; IR (KBr) 3229, 2976, 2928, 1691, 1647, 1591, 1439, 1368, 1292, 1248, 1171, 1128, 997, 818, 714 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{17}H_{18}O_5$: 302.1154. Found: 302.1152.

5-Hydroxy-2,2,8,8-tetramethyl-2*H*,8*H*-pyrano[2,3-*f*]chromen-6-carbaldehyde (17). A reaction of compound **14** (154 mg, 1.0 mmol) with 3-methyl-2-butenal (252 mg, 3.0 mmol) in methylene chloride (10 mL) afforded compound **17** (198 mg, 69%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.34 (1H, s), 10.05 (1H, s), 6. 57 (1H, d, J = 10.0 Hz), 6.51 (1H, d, J = 10.0 Hz), 5.45 (1H, d, J = 10.0 Hz), 5.43 (1H, d, J = 10.0 Hz), 1.42 (12H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.1, 159.4, 157.9, 156.9, 126.1, 125.9, 116.2, 115.8, 105.9, 102.4, 102.0, 78.9, 78.6, 28.3, 28.3; IR (neat) 2976, 1647, 1439, 1368, 1302, 1142, 1113, 999, 872, 796, 721 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{17}H_{18}O_4$: 286.1205. Found: 286.1207.

1-(5-Hydroxy-2,8-dimethyl-2*H*,8*H*-pyrano[2,3-*f*]chromen-6-yl)ethanone (18). A reaction of compound **15** (154 mg, 1.0 mmol) with crotonaldehyde (210 mg, 3.0 mmol) in methylene chloride (10 mL) afforded compound **18** (163 mg, 60%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.95 (1H, s), 6.67 (1H, dd, J = 10.0, 1.7 Hz), 6.59 (1H, dd, J = 10.0, 1.7 Hz), 5.49 (1H, d, J = 10.0 Hz), 5.47 (1H, d, J = 10.0 Hz), 5.06-4.99 (2H, m), 2.61 (3H, s), 1.47 (3H, d, J = 6.6 Hz), 1.42 (3H, d, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8, 160.8, 157.7, 155.8, 121.8, 121.3, 118.5, 118.0, 105.8, 103.4, 103.1, 73.2, 72.9, 33.5, 22.1, 21.5; IR (neat) 2978, 2932, 1601, 1433, 1366, 1319, 1292, 1262, 1200, 1148, 1117, 1028, 880, 733 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{16}H_{16}O_4$: 272.1049. Found: 272.1052.

1-(5-Hydroxy-2,8-dimethyl-2,8-bis-(4-methyl-3-pentenyl)-2*H*,8*H*-pyrano[2,3-*f*]chromen-6-yl)ethanone (19). A reaction of compound **15** (154 mg, 1.0 mmol) with citral (456 mg, 3.0 mmol) in methylene chloride (10 mL) afforded compound **19** (406 mg, 93%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.00 (1H, s), 6.66 (1H, d, J = 10.0 Hz), 6.60 (1H, d, J = 10.0 Hz), 5.38 (1H, d, J = 10.0 Hz), 5.35 (1H, d, J = 10.0 Hz), 5.10-5.03 (2H, m); 2.62 (3H, s), 2.14-2.01 (4H, m), 1.87-1.67 (4H, m), 1.63 (6H, s), 1.54 (6H, s), 1.40 (3H, s), 1.39 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.5, 160.9, 157.4, 155.6, 132.4, 132.1, 124.5, 124.3, 124.1, 123.7, 117.3, 117.0, 105.6, 102.3, 102,0, 81.3, 80.9, 42.0, 41.9, 33.7, 27.4, 27.3, 26.1, 23.5, 23.0, 18.0; IR (neat) 2971, 2926, 1599, 1429, 1364, 1298, 1192, 1105, 1074, 1001, 897, 837, 729 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{28}H_{36}O_4$: 436.2614. Found: 436.2612.

1-[2,8-Bis-(4,8-dimethylnona-3,7-dieny)-5-hydroxy-2,8-dimethyl-2*H*,8*H*-pyrano[2,3-*f*]chromen-6-yl)ethanone (20). A reaction of compound **15** (154 mg, 1.0 mmol) with *trans, trans*-farnesal (661 mg, 3.0 mmol) in methylene chloride (10 mL) afforded compound **20** (481 mg, 84%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.03 (1H, s), 6.67 (1H, d, J = 10.0 Hz), 6.62 (1H, d, J = 10.0 Hz), 5.38 (1H, d, J = 10.0 Hz), 5.37(1H, d, J = 10.0 Hz), 5.10-5.05 (2H, m), 2.64 (3H, s), 2.10-1.85 (14H, m), 1.81-1.70 (2H, m), 1.65 (9H, s), 1.57 (9H, s), 1.40 (3H, s), 1.40 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9, 161.6, 157.9, 156.2, 136.6, 136.3, 132.1, 125.4, 125.3, 125.1, 124.8, 124.7, 124.6, 118.0, 117.7, 106.2, 103.0, 102.7, 102.6, 81.9, 81.5, 42.7, 42.6, 40.7, 34.2, 32.6, 28.0, 27.9, 27.7, 27.6, 26.7, 24.0, 23.7, 23.5, 18.7, 16.9; IR (neat) 2926, 1601, 1429, 1366, 1296, 1153, 1105, 1001, 895, 729 cm^{-1}; MS (EI) 572 (M^+), 423, 422, 421, 285, 231, 69; HRMS *m/z* (M^+) calcd for $C_{38}H_{52}O_4$: 572.3866. Found: 572.3863.

5-Hydroxy-2,2,8,8-tetramethyl-2*H*,8*H*-pyrano[2,3-*f*]chromen-6-carboxylic acid methyl ester (21). A reaction of compound **16** (184 mg, 1.0 mmol) with 3-methyl-2-butenal (252 mg, 3.0 mmol) in methylene chloride (10 mL) afforded compound **21** (253 mg, 80%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.96 (1H, s), 6.60 (1H, d, J = 10.0 Hz), 6.52 (1H, d, J = 10.0 Hz), 5.40 (1H, d, J = 10.0 Hz), 5.39 (1H, d, J = 10.0 Hz), 3.84 (3H, s), 1.38 (12H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 159.2, 156.3, 154.3, 125.9, 125.8, 116.8, 116.7, 78.2, 77.9, 52.4, 28.7, 28.1; IR (KBr) 2924, 1732, 1651, 1443, 1366, 1290, 1246, 1211, 1142, 999, 883, 740 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{18}H_{20}O_5$: 316.1311. Found: 316.1310.

Clusiaphenone A(1)[8]. Ethylenediamine diacetate (36 mg, 0.2 mmol) was then added to a solution of 2,4,6-trihydr-

oxybenzophenone (230 mg, 1.0 mmol) and 3-methyl-2-butenal (252 mg, 3.0 mmol) in methylene chloride (10 mL), and stirred at room temperature for 10 h. The removal of the solvent left an oily residue, which was then purified by column chromatography on silica gel to give compound **1** (333 mg, 92%) as a solid: mp 146-147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.72 (1H, s), 7.47-7.35 (5H, m), 6.68 (1H, d, J = 10.0 Hz), 6.49 (1H, d, J = 10.0 Hz), 5.47 (1H, d, J = 10.0 Hz), 5.26 (1H, d, J = 10.0 Hz), 1.45 (6H, s), 0.96 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 159.7, 156.1, 155.4, 142.7, 129.8, 127.4, 127.1, 125.3, 125.0, 116.0, 115.8, 105.0, 102.2, 102.0, 78.2, 77.7, 28.4, 27.4; IR (KBr) 2980, 1645, 1589, 1447, 1429, 1312, 1286, 1138, 1113, 875, 713 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{23}H_{22}O_4$: 362.1518. Found: 362.1520.

Octandrenolone (2)[2d]**.** Ethylenediamine diacetate (36 mg, 0.2 mmol) was then added to a solution of 2,4,6-trihydroxyacetophenone (168 mg, 1.0 mmol) and 3-methyl-2-butenal (252 mg, 3.0 mmol) in methylene chloride (10 mL), and stirred at room temperature for 10 h. The removal of the solvent left an oily residue, which was then purified by column chromatography on silica gel to give compound **2** (273 mg, 91%) as a solid: mp 88-90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.98 (1H, s), 6.63 (1H, d, J = 10.0 Hz), 6.56 (1H, d, J = 10.0 Hz), 5.44 (1H, d, J = 10.0 Hz), 5.41 (1H, d, J = 10.0 Hz), 2.63 (3H, s), 1.58 (6H, s), 1.42 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.6, 160.9, 157.1, 155.4, 125.7, 125.1, 116.8, 116.6, 105.9, 102.7, 102.6, 78.6, 78.5, 33.6, 28.7, 28.4; IR (KBr) 3401, 1642, 1599, 1464, 1427, 1362, 1302, 1283, 1196, 1140, 1119, 882, 729 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{18}H_{20}O_4$: 300.1362. Found: 300.1363.

O-Methyloctandrenolone (3) [2d]**.** Methyl iodide (85 mg, 0.6 mmol) in acetone (1 mL) was added to a solution of compound **2** (150 mg, 0.5 mmol) and potassium carbonate (345 mg, 2.5 mmol) in acetone (5 mL). The reaction mixture was stirred at room temperature for 10 h. The solvent was evaporated under reduced pressure. The residue was treated with water, acidified with a 1 N-HCl solution, and extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel to give compound **3** (148 mg, 94%) as a liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 (1H, d, J = 10.0 Hz), 6.48 (1H, d, J = 10.0 Hz), 5.55 (1H, d, J = 10.0 Hz), 5.52 (1H, d, J = 10. 0 Hz), 3.77 (3H, s), 2.52 (3H, s), 1.56 (6H, s), 1.43 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.6, 153.4, 151.2, 150.3, 127.7, 127.6, 117.4, 116.5, 116.0, 108.1, 106.3, 77.1, 76.6, 63.4, 32.5, 27.8, 27.7; IR (neat) 2972, 1700, 1593, 1134, 999, 883, 741 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{19}H_{22}O_4$: 314.1518. Found: 314.1516.

***trans*-3''',4'''-Dihydro-3''',4'''-dihydroxy-O-methyloctandrenolone (4) and *trans*-3'',4''-Dihydro-3'',4''-dihydroxy-O-methyloctandrenolone (6)**[2e]**.** Dimethyldioxirane (15.4 mL, 0.052 M in acetone, 0.8 mmol) was added to a solution of compound **3** (126 mg, 0.4 mmol) in wet acetone (10 mL) at room temperature. The mixture was stirred at room temperature for 5 h and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel to give compound **4** (73 mg, 52%) and **6** (38 mg, 17%). Compound **4**: mp 138-139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (1H, d, J = 10.0 Hz), 5.49 (1H, d, J = 10.0 Hz), 4.70 (1H, d, J = 7.0 Hz), 3.83 (3H, s), 3.72 (1H, d, J = 7.0 Hz), 2.51 (3H, s), 1.47 (3H, s), 1.43 (3H, s), 1.39 (3H, s), 1.23 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.7, 156.5, 151.6, 149.6, 127.4, 117.3, 116.1, 109.6, 106.4, 78.5, 77.1, 75.1, 67.6, 62,4, 28.1, 27.3, 25.7, 19.2; IR (KBr) 3445, 2976, 1693, 1586, 1468, 1181, 1132, 802, 736 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{19}H_{24}O_6$: 348.1573. Found: 348.1575. Compound **6**: mp 129-130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.47 (1H, d, J = 10.0 Hz), 5.52 (1H, d, J = 10.0 Hz), 4.71 (1H, d, J = 7.0 Hz), 3.75 (3H, s), 3.75 (1H, d, J = 7.0 Hz), 2.45 (3H, s), 1.60 (3H, s), 1.44 (6H, s), 1.24 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.6, 153.7, 153.3, 150.2, 127.0, 118.1, 116.4, 108.1, 108.0, 79.1, 78.0, 75.0, 67.8, 63.1, 32.3, 28.1, 28.0, 25.6, 19.4; IR (KBr) 3454, 2976, 1695, 1635, 1591, 1466, 1181, 1130, 887, 742 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{19}H_{24}O_6$: 348.1573. Found: 348.1574.

Flemiculosin (8)[9]**.** To a solution of **2** (150 mg, 0.5 mmol) in ethanol (10 mL) and water (2 mL) was added potassium hydroxide (112 mg, 2.0 mmol) and benzaldehyde (64 mg, 0.6 mmol) at room temperature. The reaction mixture was stirred for 48 h at room temperature. After acidified with 2 N-HCl (20 mL), the mixture was extracted with ethyl acetate (3 × 30 mL), washed with water, and dried over anhydrous sodium sulfate. The removal of the solvent left an oily residue, which was then purified by column chromatography on silica gel to give compound **8** (175 mg, 90%) as a solid: mp 98-99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (1H, d, J = 15.6 Hz), 7.75 (1H, d, J = 15.6 Hz), 7.60-7.57 (2H, m), 7.43-7.34 (3H, m), 6.67 (1H, d, J = 10. 0 Hz), 6.56 (1H, d, J = 10.0 Hz), 4.88 (2H, d, J = 10.0 Hz), 1.53 (6H, s), 1.44 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.3, 161.9, 156.6, 155.7, 142.5, 136.0, 130.5, 129.4, 128.7, 128.0, 125.8, 125.2, 117.0, 116.7, 106.4, 103.0, 102.9, 78.7, 77.6, 28.8, 28.5; IR (KBr) 2975, 2928, 1640, 1588, 1551, 1450, 1424, 1343, 1186, 1157, 1115, 1001, 878, 768, 723 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{25}H_{24}O_4$: 388.1675. Found: 388.1673.

3-Deoxy-MS-II (10)[11]**.** To a solution of sodium acetate (246 mg, 3.0 mmol) in ethanol (10 mL) was added **8** (117 mg, 0.3 mmol). The reaction mixture was refluxed for 48 h. The solvent was distilled off under reduced pressure and the residue was dissolved in water (20 mL). After acidified with 2 N-HCl (20 mL), the mixture was extracted with ethyl acetate (3 × 30 mL), washed with water, and dried over anhydrous sodium sulfate. The removal of the solvent left an oily residue, which was then purified by column chromatography on silica gel to give compound **10** (55 mg, 47%) as a solid: mp 145-146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 - 7.34 (5H, m), 6.59 (1H, d, J = 10.0 Hz), 6.55 (1H, d, J = 10.0 Hz), 5.48 (1H, d, J = 10. 0 Hz), 5.43 (1H, d, J = 10.0 Hz), 5.38 (1H, dd, J = 13.1, 3.0 Hz), 2.95 (1H, dd, J = 16.5, 13.1 Hz), 2.76 (1H, d, J = 16.5, 3.0 Hz), 1.53 (3H, s), 1.47 (3H, s), 1.44 (3H, s), 1.42 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ

188.8, 157.6, 156.0, 154.3, 139.2, 128.9, 128.6, 126.5, 126.3, 126.0, 116.4, 115.9, 105.6, 104.7, 102.3, 79.0, 77.8, 77.7, 45.9, 28.6, 28.2, 28.0, 28.9; IR (KBr) 2976, 2926, 1682, 1642, 1574, 1453, 1366, 1196, 1140, 1119, 1011, 764, 731 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{25}H_{24}O_4$: 388.1675. Found: 388.1676.

1-(5-Hydroxy-2,2,8,8-tetramethyl-2*H*,8*H*-pyrano[2,3-*f*]chromene-6-yl)-3-(4-methoxyphenyl0propenone (29)[13]. To a solution of **2** (150 mg, 0.5 mmol) in ethanol (10 mL) and water (2 mL) was added potassium hydroxide (112 mg, 2.0 mmol) and 4-methoxybenzaldehyde (95 mg, 0.7 mmol) at room temperature. The reaction mixture was stirred for 48 h at room temperature. The solvent was distilled off under reduced pressure and the residue was dissolved in water (20 mL). After acidified with 2 N-HCl (20 mL), the mixture was extracted with ethyl acetate (3 × 30 mL), washed with water, and dried over anhydrous sodium sulfate. Removal of the solvent followed by flash column chromatography on silica gel gave **29** (178 mg, 85%) as a solid: mp 125-126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.49 (1H, s), 7.98 (1H, d, J = 15.6 Hz), 7.4 (1H, d, J = 15.6 Hz), 7.54 (2H, d, J = 8.8 Hz), 6.92 (2H, d, J = 8.8 Hz), 6.67 (1H, d, J = 10.0 Hz), 6.60 (1H, d, J = 10.0 Hz), 5.46 (2H, d, J= 10.0 Hz), 3.83 (3H, s), 1.53 (6H, s), 1.43 (6H, s); IR (KBr) 2975, 2932, 1634, 1607, 1543, 1510, 1460, 1422, 1344, 1292, 1155, 1115, 1032, 879, 827, 704 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{26}H_{26}O_5$: 418.1780. Found: 418.1778.

Laxichalcone (9)[10]**.** To a solution of boron tribromide (0.3 mL, 1.0 M in CH_2Cl_2, 0.3 mmol) in methylene chloride (10 mL) was added compound **31** (100 mg, 0.2 mmol) and the reaction mixture was stirred at room temperature for 10 h. Addition of ice water (20 mL), the mixture was extracted with methylene chloride (3 × 30 mL), washed with water, and dried over anhydrous sodium sulfate. Removal of the solvent followed by flash column chromatography on silica gel gave **9** (83 mg, 86%) as a solid: mp 174-175 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.45 (1H, s), 7.97 (1H, d, J = 15.6 Hz), 7.72 (1H, d, J = 15.6 Hz), 7.48 (2H, d, J = 8.6 Hz), 6.85 (2H, d, J = 8.6 Hz), 6.59 (1H, d, J = 10.0 Hz), 6.54 (1H, d, J = 10.0 Hz), 5.44 (2H, d, J = 10.0 Hz), 1.52 (6H, s), 1.43 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.9, 157.6, 156.0, 154.2, 39.3, 128.8, 128.5, 126.7, 126.3, 126.1, 116.4, 115.9, 105.5, 104.7, 102.4, 79.0, 78.0, 77.8, 46.0, 28.6, 28.3, 28.0, 27.9; IR (KBr) 3333, 2976, 1604, 1443, 1346, 1281, 1157, 1076, 880, 831, 739 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{25}H_{24}O_5$: 404.1624. Found: 404.1626.

Acknowledgment. This work was supported by grant No. RTI04-01-04 from the Regional Technology Innovation Program of the Ministry of Commerce, Industry, and Energy (MOCIE).

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