A New Route to the Synthesis of Pyranoflavone and Pyranochalcone Natural Products and their Derivatives

Yong Rok Lee,* Do Hoon Kim

School of Chemical Engineering and Technology, Yeungnam University, Gyeongsan 712-749, Korea
Fax +82(53)8104631; E-mail: yrlee@yu.ac.kr

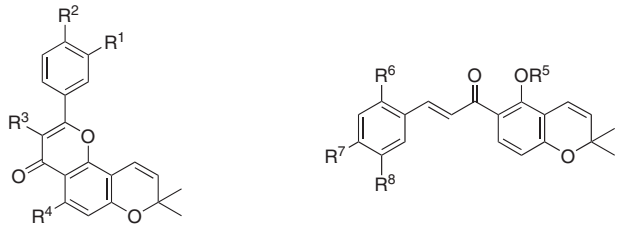
Received 23 May 2005; revised 5 September 2005

Abstract: The total synthesis of biologically active pyranoflavone natural products **1** and **2** was carried out starting from 2*H*-pyran. The synthesis of pyranochalcone natural products, lonchocarpin (**9**) and 4-hydroxylonchocarpin (**10**), and their derivatives **30**–**32** is described. This synthetic route also provides biologically interesting materials such as β-tubaic acid (**24**), desmethyl isoencecalin (**25**), and isoencecalin (**27**).

Key words: 2*H*-pyran, pyranoflavones, pyranochalcones, β-tubaic acid, desmethyl isoencecalin, isoencecalin

Pyranoflavones and pyranochalcones are an abundant subclass of the flavonoids and are widely distributed in nature.[1] Among these, pyranoflavones **1**–**4** were isolated from *Lonchocarpus subglaucescens* or *latifolius*, a tropical plant genus of more than 100 species found in America, Africa, and the Caribbean Islands (Figure 1).[2] Pyranoflavones **5**–**6** were isolated from *Atalantia racemosa*.[3] Pyranoflavones **7**–**8** were isolated from *Artocarpus chama* or *communis*, evergreen trees distributed over tropical regions of Asia.[4] Pyranochalcones **9**–**13** have been isolated from *Lonchocarpus utilus* or *subglaucescens* distributed in tropical America, Africa, and the Caribbean islands.[2a,5] Pyranochalcones **14**–**16** were primarily isolated from *Pongamia glabra*.[6] Members of the pyranoflavones and pyranochalcones have been associated with a wide variety of biological activities such as antimutagenic, antimicrobial, anti-ulcer, and antitumor activities and some plants are used in traditional medicines in China and Europe.[7] This wide range of biological properties has stimulated interest in the synthesis of naturally occurring pyranoflavones and pyranochalcones. Although there are currently several methods available to synthesize pyranoflavonoids, there are only a few synthetic routes to pyranoflavones and pyranochalcones.[8]

We recently reported a one-pot synthesis of 2*H*-pyrans using a tandem Knoevenagel–electrocyclic reaction in the presence of ytterbium (III) triflate or indium (III) chloride.[9] We used a 2*H*-pyran derivative as the key starting material in the construction of natural pyranoflavones and pyranochalcones. We describe herein the total synthesis of the two natural pyranoflavones **1** and **2** and the two natural pyranochalcones **9** and **10**.



1 $R^1 = R^2 = R^3 = R^4 = H$
2 $R^1 + R^2 = OCH_2O$, $R^3 = R^4 = H$
3 $R^1 = R^2 = R^4 = H$, $R^3 = OCH_3$ Karanjachromene
4 $R^1 + R^2 = OCH_2O$, $R^3 = OCH_3$, $R^4 = H$ Pongachromene
5 $R^1 = R^3 = H$, $R^2 = R^4 = OH$ Atalantoflavone
6 $R^1 = OCH_3$, $R^2 = R^4 = OH$, $R^3 = H$ Racemoflavone
7 $R^1 = R^2 = R^4 = OH$, $R^3 = H$ Artochamins C
8 $R^1 = H$, $R^2 = OCH_3$, $R^3 = CHOHCHC(CH_3)_2$, $R^4 = OH$ Artocommunol CE
9 $R^5 = R^6 = R^7 = R_8 = H$ Lonchocarpin
10 $R^5 = R^6 = R^8 = H$, $R^7 = OH$ 4-Hydroxylonchocarpin
11 $R^5 = R^6 = R^8 = H$, $R^7 = OCH_3$ 4-Methoxylonchocarpin
12 $R^5 = R^6 = H$, $R^7 = R^8 = OH$ 3,4-Dihydroxylonchocarpin
13 $R^5 = R^6 = H$, $R^7 = R^8 = OCH_3$ 3,4-Dimethoxylonchocarpin
14 $R^5 = R^6 = H$, $R^7 = OH$, $R^8 = OCH_3$ Pongachalcone II
15 $R^5 = R^6 = H$, $R^7 = R^8 = OCH_2O$ Glabrachromene II
16 $R^5 = H$, $R^6 = R^7 = R^8 = OCH_3$ Glabrachalcone

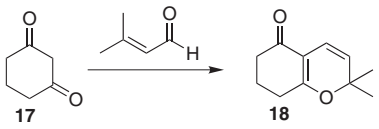
Figure 1

First, further investigation for the synthesis of 2*H*-pyrans was done concerning the reactions between 1,3-cyclohexanedione (**17**) and 3-methyl-2-butenal in the presence of several catalysts (Table 1). Both indium (III) chloride (50 mol%) and ytterbium (III) triflate (10 mol%) in refluxing acetonitrile gave **18** in 59 and 72% yields, respectively. With pyridine as reactant and solvent, **18** was obtained in 56% yield. Interestingly, with ethylenediamine diacetate (10 mol%) as catalyst, the cycloadduct was also produced in increased yield. The best yield was obtained in benzene (92%), and other solvents resulted in 61% (methanol) and 88% (dichloromethane).

In the next step, the synthesis of pyranoflavone natural products was attempted as shown in Scheme 1. Transformation of **18** with LDA at –78 °C, followed by treatment with ethyl cyanoformate, gave **19** in 83% yield. Oxidation of **19** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing dioxane afforded **20** in 90% yield. Currently, there are a number of methods available for the preparation of the 4-pyrone ring of flavones, including the Allan–Robinson method,[10] the Baker–Venkataraman rearrangement,[11] synthesis from chalcones,[12] and an intramolecular Wittig reaction.[13] Among these, we

SYNTHESIS 2006, No. 4, pp 0603–0608
Advanced online publication: 11.01.2006
DOI: 10.1055/s-2006-926294; Art ID: F09205SS

Table 1 Effect of Catalysts and Solvents in the Reaction of **17** and 3-Methyl-2-butenal

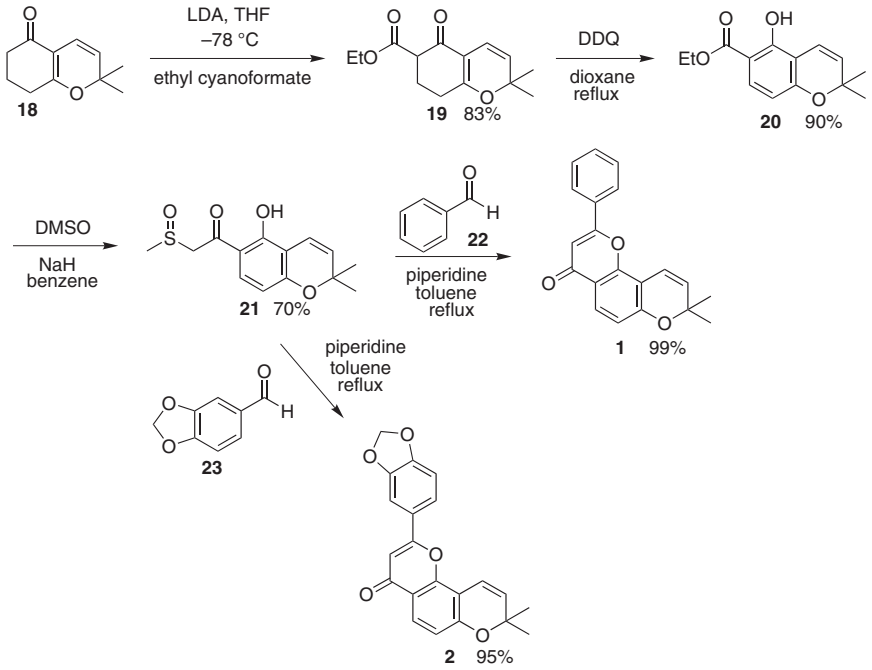


17 **18**

Catalyst	Conditions	Yield (%)
$InCl_3$ (50 mol%)	MeCN, reflux, 5 h	59
$Yb(OTf)_3$ (10 mol%)	MeCN, reflux, 5 h	72
Pyridine (excess)	$MgSO_4$, reflux, 5 h	56
Ethylenediamine diacetate (10 mol%)	MeOH, r.t., 5 h	61
Ethylenediamine diacetate (10 mol%)	CH_2Cl_2, r.t., 7 h	88
Ethylenediamine diacetate (10 mol%)	Benzene, reflux, 3 h	92

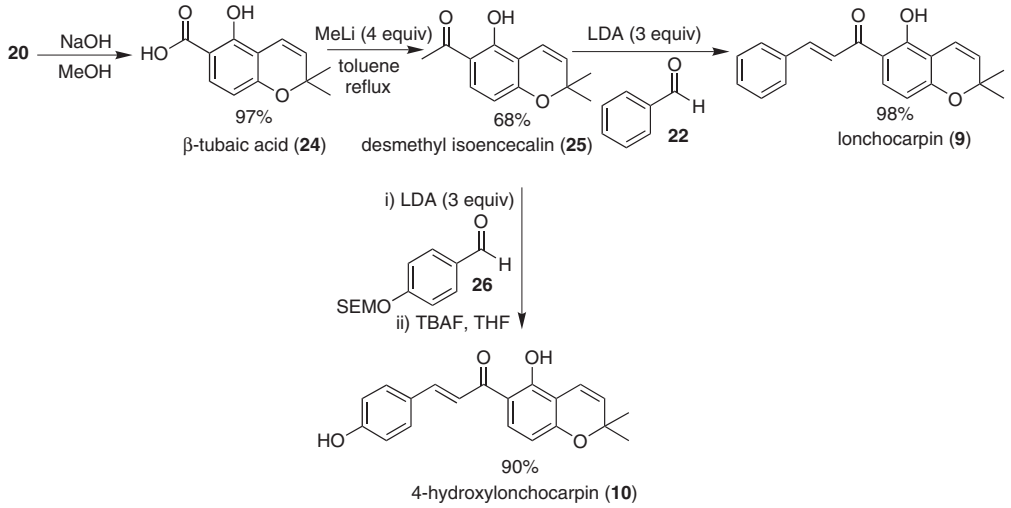
attempted construction of the 4-pyrone ring by using the von Strandtmann approach.[14] Treatment of **20** with dimsyl anion in benzene afforded β-keto sulfoxide **21** (70%), which was easily converted by treatment with **22** and **23** in the presence of piperidine, first at 40 °C and then at 110 °C, to the corresponding pyranoflavones **1** and **2** in 99 and 95% yields, respectively. The spectroscopic properties of our synthetic materials are in agreement with those reported in the literature.[2a] The synthesis of pyranoflavones **1** and **2** has been reported before. In connection with an on-going program for the development of new drug candidates as potent anti-HIV agents, the total synthesis of **1** was carried out by Lee and co-workers.[8a] Another group has also achieved the synthesis of **2** starting from 2,4-dihydroxyacetophenone in low yield.[8b]

The synthesis of pyranochalcone natural products lonchocarpin (**9**) and 4-hydroxylonchocarpin (**10**), was achieved starting from compound **20** (Scheme 2). Lonchocarpin (**9**) and 4-hydroxylonchocarpin (**10**), isolated from Cubé resin, were shown to interrupt mitochondrial electron transport by inhibition of NADH.[5] The synthetic route to pyranochalcones **9** and **10** has already been reported by Nicolaou.[8c] Hydrolysis of **20** by treatment with NaOH in methanol gave β-tubaic acid (**24**, 97%), which was isolated from the roots of *Derris elliptica* and was shown to exhibit strong antimicrobial activity.[15] The methods available for the preparation of β-tubaic acid suffer from the disadvantage of many reaction steps or low yields.[16] Thus simpler and more convenient methods for its synthesis are needed. The spectral data of our synthetic material **24** are consistent with those reported in the literature.[16] Treatment of **24** with an excess of MeLi afforded desmethyl isoencecalin (**25**, 68%), which was isolated from *Blepharispermum subseeile*.[17] It was also shown to have strong antifungal, antibacterial, and antiimplantation activities.[18] Before its isolation from a natural source, **25** had already been synthesized by other groups.[19] In order to build the chalcone skeletons, an aldol reaction was next attempted by treatment with several bases. Reaction of **25** with benzaldehyde in methanolic KOH and NaOH gave no products, possibly because of the presence of the acidic phenol group. However, we were able to introduce the chalcone skeleton by treatment with LDA. When **25** was treated with **22** in the presence of an excess of LDA, lonchocarpin (**9**) was obtained in 98% yield. Reaction of **25** with aldehyde **26**, followed by cleavage of the [2-(trimethylsilyl)ethoxy]methyl ether (SEM ether) with tetrabutylammonium fluoride (TBAF), gave 4-hydroxylonchocarpin (**10**) in 90% yield. The spectral data of our synthetic materials **9** and **10** agreed with those reported in the literature.[8a,20]



18 **19** 83% **20** 90% **21** 70% **1** 99% **23** **2** 95%

Scheme 1



Scheme 2

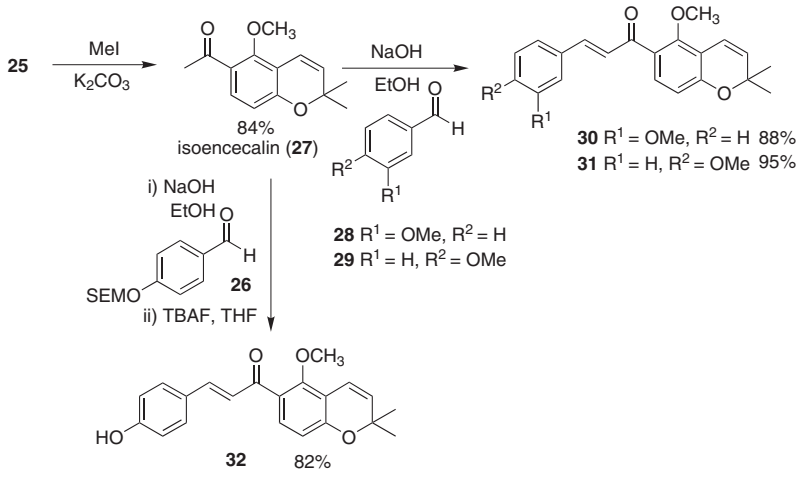
Finally, the synthesis of pyranochalcone derivatives was attempted from desmethyl isoencecalin (**25**) as depicted in Scheme 3. Methylation of **25** with methyl iodide in the presence of potassium carbonate in acetone gave isoencecalin (**27**) in 84% yield.[19a,21] Treatment of **27** with aldehydes **28** and **29** in ethanolic NaOH solution gave pyranochalcones **30** and **31** as unnatural products in 88 and 95% yields, respectively. On the other hand, reaction of **27** with aldehyde **26** in ethanolic NaOH solution, followed by cleavage of the silyl ether group with TBAF, gave **32** in 82% yield.

In conclusion, a new synthetic route to biologically active pyranoflavones and pyranochalcones was developed starting from 2*H*-pyran. The synthetic routes yield pyranoflavone natural products **1** and **2**, and pyranochalcone natural products and their derivatives, lonchocarpin (**9**), 4-hydroxylonchocarpin (**10**) and **30**–**32**. This synthetic route also provides biologically interesting β-tubaic acid (**24**), desmethyl isoencecalin (**25**), and isoencecalin (**27**).

All experiments were carried out under 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). Melting points were determined in capillary tubes on a Fisher–Johns apparatus and are uncorrected. IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker Model ARX (300 MHz) spectrometer in $CDCl_3$ using 7.26 ppm as the solvent chemical shift. ^{13}C NMR spectra were recorded on a Bruker Model ARX (75 MHz) spectrometer in $CDCl_3$ using 77.0 ppm as the solvent chemical shift. HRMS mass spectra were carried out on Jeol JMS-700 spectrometer by the Korea Basic Science Institute (Daegu).

2,2-Dimethyl-2,6,7,8-tetrahydrochromen-5-one (18)

To a solution of 1,3-cyclohexanedione (1.12 g, 10.0 mmol) and 3-methyl-2-butenal (1.68 g, 20.0 mmol) in benzene (50 mL) was added ethylenediamine diacetate (180 mg, 1.00 mmol) at r.t. The reaction mixture was refluxed for 3 h and then cooled to r.t. H_2O was added and the solution was extracted with EtOAc. Evaporation of solvent and purification by column chromatography on silica gel gave **18** (1.639 g, 92%) as a liquid.



Scheme 3

IR (neat): 2926, 1645, 1611, 1455, 1399, 1375, 1266, 1188, 1130, 1010, 905 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.38 (d, *J* = 10.0 Hz, 1 H), 5.21 (d, *J* = 10.0 Hz, 1 H), 2.39–2.34 (m, 4 H), 1.99–1.90 (m, 2 H), 1.37 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.3, 172.1, 123.2, 116.1, 110.9, 80.1, 36.8, 29.0, 28.5, 28.5, 21.0.

HRMS: *m*/*z* [M^+] calcd for $C_{11}H_{14}O_2$: 178.0994; found: 178.0996.

2,2-Dimethyl-5-oxo-5,6,7,8-tetrahydro-2*H*-chromene-6-carboxylic Acid Ethyl Ester (19)

To a solution of LDA (10.0 mmol) in dry THF (50 mL) was added a solution of **18** (1.50 g, 8.4 mmol) in THF (2 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 1 h and ethyl cyanoformate (1.25 g, 12.6 mmol) in THF (2 mL) was added at –78 °C. The resulting mixture was stirred at –78 °C for 1 h, then allowed to warm to r.t. and stirring was continued overnight. Sat. NH_4Cl soln (30 mL) was added carefully dropwise and the aq layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting oil was purified by flash column chromatography on silica gel to give **19** (1.746 g, 83%) as a liquid.

IR (neat): 2980, 1738, 1659, 1591, 1416, 1366, 1323, 1267, 1206, 1142, 1096, 1011, 893 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.38 (d, *J* = 10.0 Hz, 1 H), 5.24 (d, *J* = 10.0 Hz, 1 H), 4.40–4.14 (m, 2 H), 3.34 (dd, *J* = 8.8, 4.9 Hz, 1 H), 2.58–2.10 (m, 4 H), 1.38 (s, 3 H), 1.37 (s, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H).

HRMS: *m*/*z* [M^+] calcd for $C_{14}H_{18}O_4$: 250.1205; found: 250.1202.

5-Hydroxy-2,2-dimethyl-2*H*-chromene-6-carboxylic Acid Ethyl Ester (20)

A mixture of **19** (1.60 g, 6.39 mmol) and DDQ (2.18 g, 9.6 0 mmol) in dry dioxane (40 mL) was heated under reflux for 3 h. The resulting mixture was cooled in an ice bath and the solids were removed by filtration through Celite. The filtrate was evaporated under reduced pressure and purified by flash column chromatography on silica gel to give **20** (1.429 g, 90%) as a liquid.

IR (neat): 2978, 2930, 1672, 1613, 1462, 1397, 1375, 1331, 1265, 1194, 1138, 1113, 1073, 1015, 899 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 11.24 (s, 1 H), 7.61 (d, *J* = 8.8 Hz, 1 H), 6.69 (d, *J* = 10.0 Hz, 1 H), 6.31 (d, *J* = 8.8 Hz, 1 H), 5.55 (d, *J* = 10.0 Hz, 1 H), 4.34 (q, *J* = 7.1 Hz, 2 H), 1.42 (s, 6 H), 1.37 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7, 159.3, 158.7, 130.8, 128.6, 116.5, 109.6, 108.8, 105.9, 77.9, 61.4, 30.1, 28.6, 14.7.

HRMS: *m*/*z* [M^+] calcd for $C_{14}H_{16}O_4$: 248.1049; found: 248.1050.

1-(5-Hydroxy-2,2-dimethyl-2*H*-chromen-6-yl)-2-methanesulfinylethanone (21)

A mixture of dry DMSO (2.6 mL) and NaH (0.263 g, 10.4 mmol, 95%) in dry benzene (30 mL) was heated under N_2 at 80 °C for 2 h. The solution was cooled to 35 °C and treated dropwise with **20** (1.30 g, 5.24 mmol) in dry benzene (4 mL). The reaction mixture was then stirred for 1 h and quenched with sat. NH_4Cl soln (30 mL). The mixture was extracted with EtOAc (3 × 30 mL). 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 **21** (1.028 g, 70%) as a liquid.

IR (neat): 2932, 2888, 1628, 1603, 1481, 1429, 1379, 1333, 1289, 1215, 1190, 1161, 1115, 1100, 1015, 899 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 12.50 (s, 1 H), 7.49 (d, *J* = 8.9 Hz, 1 H), 6.66 (d, *J* = 10.1 Hz, 1 H), 6.37 (d, *J* = 8.9 Hz, 1 H), 5.58 (d, *J* = 10.1 Hz, 1 H), 4.24 (q, 2 H), 2.73 (s, 3 H), 1.44 (s, 6 H).

HRMS: *m*/*z* [M^+] calcd for $C_{14}H_{16}O_4S$: 280.0769; found: 280.0767.

6″,6″-Dimethylpyrano-[2″,3″:7,8]-flavone (1)

A solution of benzaldehyde (**22**) (0.178 g, 1.68 mmol) in dry toluene (3 mL) was slowly added to a warm solution (40 °C) of **21** (0.40 g, 1.4 mmol) in dry toluene (20 mL) containing a catalytic amount of piperidine (4 drops) and the resulting mixture was allowed to reflux for 3 h. After distillation of the solvent, the residue was purified by flash column chromatography on silica gel to give **1** (0.429 g, 99%) as a solid.

Mp 135–136 °C (lit[2a] 137 °C).

IR (KBr): 3055, 2984, 2920, 2851, 1647, 1591, 1576, 1441, 1397, 1381, 1366, 1215, 1190, 1130, 1113, 1080, 1030, 839 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.7 Hz, 1 H), 7.90–7.87 (m, 2 H), 7.53–7.51 (m, 3 H), 6.92 (d, *J* = 10.0 Hz, 1 H), 6.84 (d, *J* = 8.7 Hz, 1 H), 6.74 (s, 1 H), 5.74 (d, *J* = 10.0 Hz, 1 H), 1.53 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.4, 162.8, 157.7, 152.6, 132.4, 131.6, 130.7, 129.4, 129.3, 126.4, 126.3, 126.2, 115.4, 115.3, 115.2, 109.6, 107.5, 77.9, 28.0, 28.0.

3′,4′-Methylenedioxy-6″,6″-dimethylpyrano-[2″,3″:7,8]-flavone (2)

A solution of aldehyde **23** (0.32 g, 2.1 mmol) in dry toluene (3 mL) was slowly added to a warm solution (40 °C) of **21** (0.50 g, 1.8 mmol) in dry toluene (20 mL) containing a catalytic amount of piperidine (4 drops); the resulting mixture was allowed to reflux for 3 h. After distillation of the solvent, the residue was purified by flash column chromatography on silica gel to give **2** (0.590 g, 95%) as a solid.

Mp 230–232 °C (lit[2a] 231.9 °C).

IR (KBr): 2982, 2920, 1640, 1584, 1503, 1449, 1395, 1381, 1337, 1294, 1254, 1215, 1115, 1076, 1036, 930, 862 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.8 Hz, 1 H), 7.44 (d, *J* = 8.3 Hz, 1 H), 7.31 (s, 1 H), 6.96–6.82 (m, 3 H), 6.61 (s, 1 H), 6.07 (s, 2 H), 5.74 (d, *J* = 10.2 Hz, 1 H), 1.53 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.9, 162.4, 157.5, 152.2, 150.6, 148.5, 130.5, 126.0, 125.9, 121.1, 117.7, 115.2, 115.0, 115.0, 109.5, 108.7, 106.3, 106.1, 101.8, 77.7, 28.2, 28.2.

β-Tubaic Acid (24)

Compound **20** (1.10 g, 4.43 mmol) was refluxed with 20% NaOH soln (3 mL) in MeOH (20 mL) for 5 h. MeOH was evaporated under reduced pressure, the residue was treated with ice-water and acidified with 2 N HCl soln. 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 **24** (0.946 g, 97%) as a solid.

Mp 159–160 °C.

IR (KBr): 3000 (br, OH), 1657, 1462, 1426, 1383, 1335, 1263, 1211, 1165, 1111, 1071, 947, 895 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 10.88 (s, 1 H), 7.67 (d, *J* = 8.8 Hz, 1 H), 6.67 (d, *J* = 10.0 Hz, 1 H), 6.35 (d, *J* = 8.8 Hz, 1 H), 5.56 (d, *J* = 10.0 Hz, 1 H), 1.44 (s, 6 H).

Desmethyl isoencecalin (25)

Compound **24** (0.850 g, 3.87 mmol) was refluxed with MeLi (15.4 mmol) in toluene (30 mL) for 5 h. The resulting mixture was cooled in an ice bath and quenched with a sat. NH_4Cl soln (30 mL). The mixture was extracted with EtOAc (3 × 30 mL). The combined or-

ganic 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 **25** (0.572 g, 68%) as a solid.

Mp 101–103 °C.

IR (neat): 2976, 2930, 1630, 1618, 1487, 1426, 1366, 1329, 1273, 1211, 1165, 1125, 1071, 896 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 12.95 (s, 1 H), 7.49 (d, *J* = 8.8 Hz, 1 H), 6.69 (d, *J* = 10.0 Hz, 1 H), 6.31 (d, *J* = 8.8 Hz, 1 H), 5.56 (d, *J* = 10.0 Hz, 1 H), 2.51 (s, 3 H), 1.43 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.1, 160.1, 160.0, 132.0, 128.6, 116.2, 114.2, 109.6, 108.7, 78.1, 28.7, 26.6.

Lonchocarpin (9)

To a solution of **25** (0.250 g, 1.15 mmol) in dry THF (20 mL) and LDA (3.3 mmol) was added benzaldehyde (**22**) (0.146 g, 1.38 mmol) in THF (1 mL) at –78 °C. The resulting mixture was stirred at –78 °C for 1 h, then allowed to warm to r.t., and stirring was continued overnight. Sat. NH_4Cl soln (30 mL) was added dropwise carefully and the aq layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting oil was purified by flash column chromatography on silica gel to give **9** (0.344 g, 98%) as a solid.

Mp 92–94 °C.

IR (KBr): 3055, 2972, 2932, 1638, 1588, 1483, 1352, 1279, 1235, 1211, 1114, 1046, 898 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 13.64 (s, 1 H), 7.86 (d, *J* = 15.5 Hz, 1 H), 7.70 (d, *J* = 8.9 Hz, 1 H), 7.64–7.60 (m, 2 H), 7.54 (d, *J* = 15.5 Hz, 1 H), 7.41–7.33 (m, 3 H), 6.74 (d, *J* = 10.0 Hz, 1 H), 6.52 (d, *J* = 8.9 Hz, 1 H,), 5.58 (d, *J* = 10.0 Hz, 1 H), 1.44 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.3, 161.4, 160.3, 144.7, 135.2, 131.1, 131.0, 129.4, 128.9, 128.6, 120.7, 116.2, 114.5, 109.8, 108.8, 78.3, 28.8.

4-Hydroxylonchocarpin (10)

To a solution of **25** (0.250 g, 1.15 mmol) in dry THF (20 mL) and LDA (3.3 mmol) was added aldehyde **26** (0.347 g, 1.37 mmol) in THF (1 mL) at –78 °C. The resulting mixture was stirred at –78 °C for 1 h, then allowed to warm to r.t., and stirring was continued overnight. Sat. NH_4Cl soln (30 mL) was added dropwise carefully and the aq layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting oil was purified by flash column chromatography on silica gel to give **10** (0.332 g, 90%) as a solid.

Mp 199–201 °C.

IR (KBr): 3379, 1634, 1606, 1580, 1512, 1289, 1248, 1235, 1167, 1116, 896 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 13.60 (s, 1 H), 7.82 (d, *J* = 15.5 Hz, 1 H), 7.72 (d, *J* = 8.8 Hz, 1 H), 7.55 (d, *J* = 8.6 Hz, 2 H), 7.43 (d, *J* = 15.5 Hz, 1 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 6.74 (d, *J* = 10.1 Hz, 1 H), 6.37 (d, *J* = 8.8 Hz, 1 H), 5.59 (d, *J* = 10.1 Hz, 1 H), 1.46 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.0, 163.0, 160.8, 158.4, 144.4, 130.6, 130.5, 128.1, 117.8, 116.0, 115.9, 115.8, 108.3, 108.2, 77.4, 28.4.

Isoencecalin (27)

To a solution of **25** (1.20 g, 5.50 mmol) and K_2CO_3 (1.147 g, 8.30 mmol) in acetone (30 mL) was added MeI (0.937g, 6.60 mmol) in acetone (2 mL). The reaction mixture was stirred at r.t. for 10 h. The solvent was evaporated under reduced pressure, the residue was treated with H_2O and acidified with 1 N HCl soln. 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 **27** (1.073 g, 84%) as a solid.

Mp 102–103 °C.

IR (KBr): 2978, 1673, 1592, 1463, 1371, 1271, 1115, 1070, 988, 891 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 8.5 Hz, 1 H), 6.56 (m, 2 H), 5.63 (d, *J* = 10.0 Hz, 1 H), 3.76 (s, 3 H), 2.55 (s, 3 H), 1.40 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.2, 158.4, 157.3, 131.5, 130.8, 124.7, 116.9, 115.1, 113.0, 77.2, 63.4, 30.6, 28.4.

(*E*)-1-(5-Methoxy-2,2-dimethyl-2*H*-chromen-6-yl)-3-(3-methoxyphenyl)propenone (30)

To a solution of **27** (0.20 g, 0.86 mmol) in EtOH (10 mL) and H_2O (2 mL) was added NaOH (0.07 g, 1.8 mmol) and *m*-anisaldehyde **28** (0.141 g, 1.03 mmol) at r.t. The reaction mixture was stirred for 6 h at r.t. Evaporation of EtOH and extraction with EtOAc (3 × 50 mL), washing with 2 N HCL soln and brine, drying over $MgSO_4$ and removal of the solvent, followed by flash column chromatography on silica gel gave **30** (0.266 g, 88%) as a liquid.

IR (neat): 2974, 2936, 1654, 1636, 1596, 1463, 1370, 1319, 1261, 1162, 1110, 1076, 1050, 984, 888 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.66 d, *J* = 15.3 Hz, (1 H), 7.53 (d, *J* = 8.5 Hz, 1 H), 7.48 (d, *J* = 15. 3 Hz, 1 H), 7.30 (dd, *J* = 8.1, 8.0 Hz, 1 H), 7.20 (d, *J* = 8.0 Hz, 1 H), 7.10 (s, 1 H), 6.90 (d, *J* = 8.1 Hz, 1 H), 6.62 (dd, *J* = 10.0, 8.5 Hz, 2 H), 5.66 (d, *J* = 10.0 Hz, 1 H), 3.80 (s, 3 H), 3.73 (s, 3 H), 1.43 (6 H, s).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.1, 160.3, 158.8, 156.9, 143.4, 136.9, 131.8, 131.0, 130.3, 126.9, 125.9, 121.4, 116.8, 116.4, 115.2, 113.8, 113.2, 77.3, 63.8, 55.7, 28.5.

HRMS: *m*/*z* [M^+] calcd for $C_{22}H_{22}O_4$: 350.1518; found: 350.1516.

(*E*)-1-(5-Methoxy-2,2-dimethyl-2*H*-chromen-6-yl)-3-(4-methoxyphenyl)propenone (31)

To a solution of **27** (0.290 g, 1.25 mmol) in EtOH (10 mL) and H_2O (2 mL) was added NaOH (0.10 g, 2.5 mmol) and *p*-anisaldehyde (**29**) (0.204 g, 1.49 mmol) at r.t. The reaction mixture was stirred for 6 h at r.t. Evaporation of EtOH and extraction with EtOAc (3 × 50 mL), washing with 2 N HCl soln and brine, drying over $MgSO_4$ and removal of the solvent, followed by flash column chromatography on silica gel gave **31** (0.416 g, 95%) as a liquid.

IR (neat): 2970, 2934, 2839, 1647, 1592, 1512, 1369, 1253, 1173, 1076, 1042, 985, 888 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 15.8 Hz, 1 H), 7.56–7.50 (m, 3 H), 7.38 (d, *J* = 15.8 Hz, 1 H), 6.89 (d, *J* = 8.7 Hz, 2 H), 6.63 (d, *J* = 10.0 Hz, 1 H), 6.61 (d, *J* = 8.6 Hz, 1 H), 5.67 (d, *J* = 10.0 Hz, 1 H), 3.82 (s, 3 H), 3.73 (s, 3 H), 1.44 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.1, 161.8, 157.7, 156.6, 143.5, 132.3, 131.6, 131.0, 130.5, 128.2, 126.1, 124.3, 116.9, 115.2, 114.8, 114.7, 113.0, 77.2, 63.7, 55.7, 28.4.

HRMS: *m*/*z* [M^+] calcd for $C_{22}H_{22}O_4$: 350.1518; found: 350.1518.

(*E*)-3-(4-Hydroxyphenyl)-1-(5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)propenone (32)

To a solution of **27** (0.320 g, 1.38 mmol) in EtOH (10 mL) and H_2O (2 mL) was added NaOH (0.110 g, 2.75 mmol) and aldehyde **26** (0.407 g, 1.61 mmol) at r.t. The reaction mixture was stirred for 6 h at r.t. Evaporation of EtOH and extraction with EtOAc (3 × 50 mL), washing with 2 N HCl soln and brine, drying over $MgSO_4$, and removal of the solvent gave the residue. To a solution of the residue

in THF (10 mL) was added a 1.0 M TBAF soln in THF (2.1 mL, 2.1 mmol) and the mixture was stirred at r.t. for 3 h. After distillation of the solvent, the residue was purified by flash column chromatography on silica gel to give **32** (0.380 g, 82%) as a solid.

Mp 147–148 °C.

IR (KBr): 2977, 2935, 1634, 1590, 1514, 1372, 1282, 1169, 1114, 1079, 985, 889 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 15.8 Hz, 1 H), 7.52–7.47 (m, 3 H), 7.37 (d, *J* = 15.8 Hz, 1 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 6.62 (d, *J* = 10.0 Hz, 1 H), 6.61 (d, *J* = 8.6 Hz, 1 H), 5.67 (d, *J* = 10.0 Hz, 1 H), 3.76 (s, 3 H), 1.42 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.4, 159.1, 158.0, 156.7, 144.7, 134.1, 131.7, 131.1, 130.9, 127.7, 125.9, 123.8, 116.8, 116.7, 116.5, 114.9, 113.1, 77.4, 63.8, 28.5.

Acknowledgment

This work was supported by the Korea Research Foundation Grant (KRF-2003-041-C00183).

References

(1) (a) Wagner, H.; Farkas, L. In *The Flavonoids*; Harorne, J. B.; Mabry, T. J.; Mabry, H., Eds.; Academic Press: New York, **1975**, 127. (b) Gripenberg, J. In *The Chemistry of Flavonoid Compounds*; Geissman, T. A., Ed.; MacMillan: New York, **1962**, 409. (c) Wollenweber, E. In *The Flavonoids*; Harborne, J. B., Ed.; Chapman & Hall: London, **1994**, 259. (d) In *The Handbook of Natural Products*, Vol. 2; Harborne, J. B.; Baxter, H., Eds.; John Wiley & Sons Ltd.: London, **1999**, 1.

(2) (a) Magalhães, A. F.; Azevedo Tozzi, A. M. G.; Noronha Sales, B. H. L.; Magalhães, E. G. *Phytochemistry* **1996**, *42*, 1459. (b) Magalhães, A. F.; Tozzi, A. M. A.; Magalhães, E. G.; Nogueira, M. A.; Queiroz, S. C. N. *Phytochemistry* **2000**, *55*, 787.

(3) Banerji, A.; Luthria, D. L.; Prabhu, B. R. *Phytochemistry* **1988**, *27*, 3637.

(4) (a) Chan, S.-C.; Ko, H.-H.; Lin, C.-N. *J. Nat. Prod.* **2003**, *66*, 427. (b) Wang, Y.-H.; Hou, A.-J.; Chen, L.; Chen, D.-F.; Sun, H.-D.; Zhao, Q.-S.; Bastow, K. F.; Nakanish, Y.; Wang, X.-H.; Lee, K.-H. *J. Nat. Prod.* **2004**, *67*, 757.

(5) Fang, N.; Casida, J. E. *J. Nat. Prod.* **1999**, *62*, 205.

(6) (a) Saini, T. R.; Pathak, V. P.; Khanna, R. N. *J. Nat. Prod.* **1983**, *46*, 936. (b) Pathak, V. P.; Saini, T. R.; Khanna, R. N. *Phytochemistry* **1983**, *22*, 1303. (c) Subrahmanyam, K.; Madhusudhana Rao, V.; Jagannadha Rao, K. V. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1997**, *15*, 12.

(7) (a) Welton, A. F.; Tobias, L. D.; Fiedler-Nagy, C.; Anderson, W.; Hope, W.; Meyers, K.; Coffey, J. W. In *Plant Flavonoids in Biology and Medicine*; Cody, V.; Middleton, E. Jr.; Harbone, J. B., Eds.; Alan R. Liss Inc.: New York, **1986**, 231. (b) Demizu, S.; Kajiyama, K.; Hiraga, Y.; Kinoshida, T.; Koyama, K.; Takahashi, K.; Tamura, Y.; Okada, K.; Kinoshida, T. *Chem. Pharm. Bull.* **1992**, *40*, 392. (c) Haraguchi, H.; Tanimoto, K.; Tamura, Y.; Mizutani, K.; Kinoshita, T. *Phytochemistry* **1998**, *48*, 125. (d) Mitscher, L. A.; Park, Y. H.; Clark, D.; Beal, J. L. *J. Nat. Prod.* **1980**, *43*, 259. (e) Nishino, H.; Yoshioko, K.; Iwashima, A.; Takizawa, H.; Konishi, S.; Okamoto, H.; Pkabe, H.; Shibata, S.; Fujiki, H.; Sugimura, T. *Jpn. J. Cancer Res.* **1986**, *77*, 33. (f) Okada, K.; Tamura, Y.; Yamamoto, M.; Inoue, Y.; Takagaki, R.; Takahashi, K.; Demizu, S.; Kajiyama, K.; Hiraga, Y.; Kinoshita, T. *Chem. Pharm. Bull.* **1989**, *37*, 2528. (g) van Marle, J.; Arasen, P. N.; Lind, A.; van Weeren-Kramer, J. *Eur. J. Pharmacol.* **1981**, *72*, 219. (h) Zani, F.; Cuzzoni, M. T.; Daglia, M.; Benvenuti, S.; Vampa, G.; Mazza, P. *Planta Med.*. **1993**, *59*, 502.

(8) (a) Yu, D.; Chen, C.-H.; Brossi, A.; Lee, K.-H. *J. Med. Chem.* **2004**, *47*, 4072. (b) Tan, W.; Li, W.-D. Z.; Huang, C.; Li, Y. *Synth. Commun.* **1999**, *29*, 3369. (c) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q. *Angew. Chem. Int. Ed.* **2000**, *39*, 734. (d) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barleenga, S.; Mitchell, H. J.. *J. Am. Chem. Soc.* **2000**, *122*, 9939. (e) Narender, T.; Gupta, S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3913.

(9) (a) Lee, Y. R.; Kweon, H. I.; Koh, W. S.; Min, K. R.; Kim, Y.; Lee, S. H. *Synthesis* **2001**, 1851. (b) Lee, Y. R.; Kim, D. H.; Shim, J.-J.; Kim, S. K.; Park, J. H.; Cha, J. S.; Lee, C.-S. *Bull. Korean Chem. Soc.* **2002**, *23*, 998.

(10) Allan, J.; Robinson, R. *J. Chem. Soc., Trans.* **1924**, *125*, 2192.

(11) (a) Baker, W. *J. Chem. Soc.* **1933**, 1381. (b) Madal, H. S.; Venkataraman, K. *J. Chem. Soc.* **1934**, 1767.

(12) (a) Iinuma, M.; Iwashima, K.; Matsuura, S. *Chem. Pharm. Bull.* **1984**, *32*, 4935. (b) Hoshino, Y.; Oohinata, T.; Takeno, N. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2351.

(13) (a) Hercouet, A.; LeCorre, M.; LeFloc'h, Y. *Synthesis* **1982**, 597. (b) LeFloc'h, Y.; LeFeuvre, M. *Tetrahedron Lett.* **1986**, *27*, 5503.

(14) von Strandtmann, M.; Klutchko, S.; Cohen, M. P.; Shavel, J. *J. Heterocycl. Chem.* **1972**, *9*, 171.

(15) Yoshihiko, O.; Hiromichi, M.; Katsura, M. *Agric. Biol. Chem.* **1976**, *40*, 1245.

(16) (a) Ahluwalia, V. K.; Jolly, R. S.; Tehim, A. K. *Tetrahedron* **1982**, *38*, 3673. (b) Nickl, J. *Chem. Ber.* **1958**, *91*, 1372.

(17) Kulkarni, M. M.; Nagasampagi, B. A.; Deshpande, S. G.; Sharma, R. N. *Phytochemistry* **1987**, *26*, 2969.

(18) Agarwal, S. K.; Verma, S.; Singh, S. S.; Tripathi, A. K.; Khan, Z. K.; Kumar, S. *J. Ethnopharm.* **2000**, *71*, 231.

(19) (a) Ahluwalia, V. K.; Arora, K. K. *Tetrahedron* **1981**, *37*, 1437. (b) Jain, A. C.; Lal, P.; Seshadri, T. R. *Indian J. Chem.* **1969**, *7*, 1072.

(20) Luyengi, L.; Lee, I.-S.; Mar, W.; Fong, H. H. S.; Pezzuto, J. M.; Kinghorn, A. G. *Phytochemistry* **1994**, *36*, 1523.

(21) Mukerjee, S. K.; Sarkar, S. C.; Seshadri, T. R. *Indian J. Chem.* **1970**, *8*, 861.