Synthetic Study for Two 2*H*-Chromenic Acids, 8-Chlorocannabiorcichromenic Acid and Mycochromenic Acid

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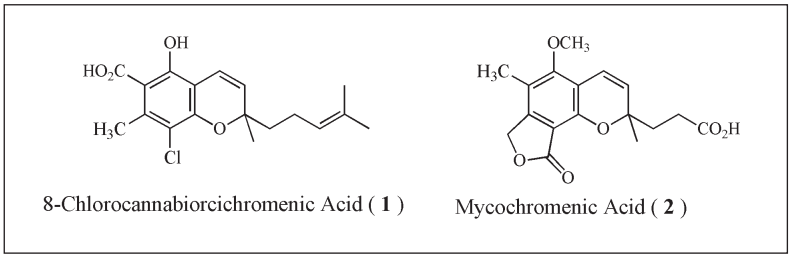

Two 2*H*-chromenes having a fully substituted benzene ring, 8-chlorocannabiorcichromene (**1**) and mycochromenic acid (**2**), were synthesized by a condensation of salicylaldehydes with isopropylidenemalonate or the thermal cyclization of corresponding propargyl ethers.

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There have been some reports on naturally occurring 2*H*-chromenes possessing a long side chain at position 2 [2]. They might be derived from an enzymic oxidative cyclization of corresponding *o*-geranylphenols. Some of them are isolated in racemic form, and others are isolated optically active. Two 2*H*-chromenes, 8-chlorocannabiorcichromenic acid (**1**) [3] and mycochromenic acid (**2**) [4], shown in Figure 1, both having a fully substituted benzene ring, were reported to be isolated in racemic form. In this paper, we report synthetic approaches to these chromenic acids **1** and **2**.

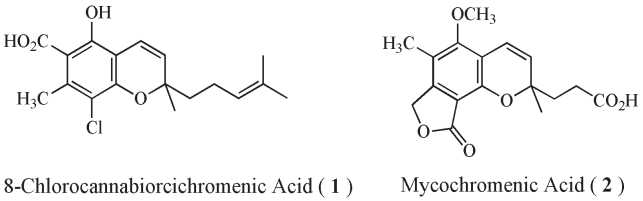
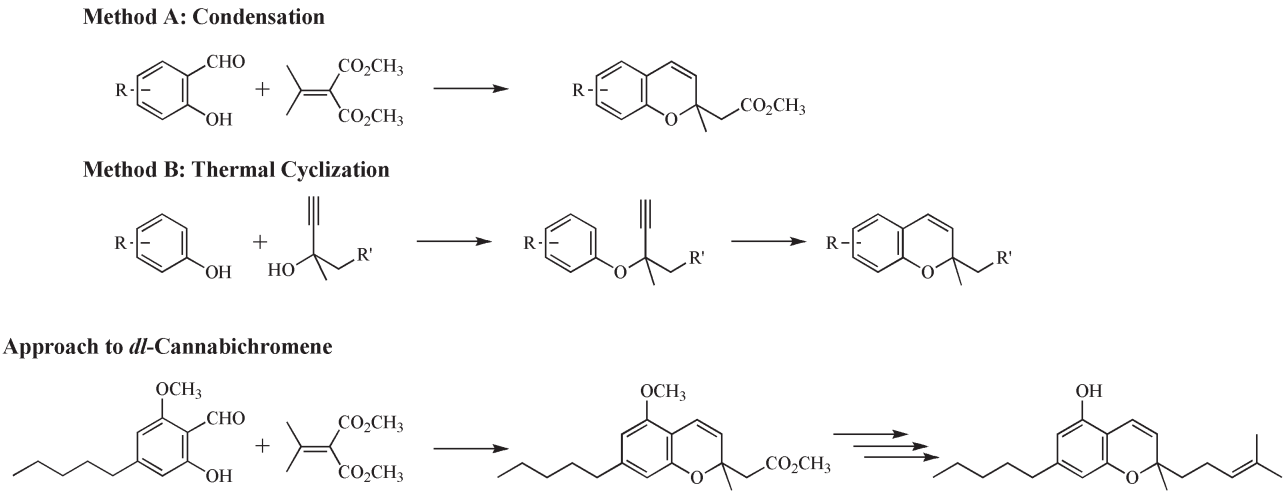


Figure 1. Two naturally occurring 2*H*-chromenes having a fully substituted benzene ring.

We have studied synthetic methods for naturally occurring 2*H*-chromenes. As shown in Scheme 1, in previous papers, we reported two preparative methods for 2*H*-chromenes having a long side-chain at position 2. One (Method A) is the condensation of salicylaldehydes with isopropylidenemalonate giving the corresponding 2-methyl-2*H*-chromene-2-acetates [5], and the other (Method B) is the thermal cyclization of phenyl propargyl ethers affording the corresponding 2*H*-chromenes [6]. We also reported a new approach to *dl*-cannabichromene *via*

Scheme 1



Previous Approaches to 2*H*-Chromenes Having a Long Side-chain at Position 2

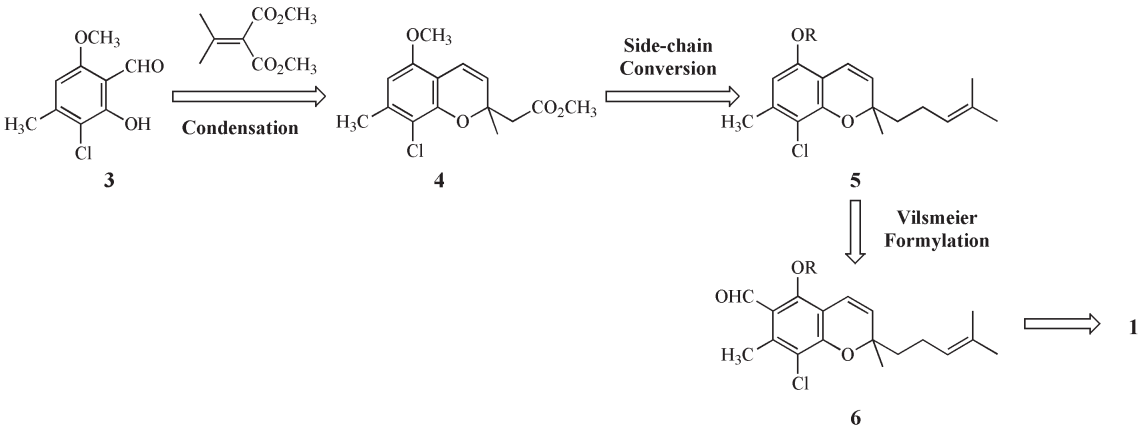
Method A; the condensation of 2-hydroxy-6-methoxy-4-pentenylbenzaldehyde with isopropylidenemalonate [7].

A synthetic strategy for 8-chlorcannabiorcichromenic acid **1** *via* Method A is shown in Scheme 2, 1) preparation of 3-chloro-2-hydroxy-6-methoxy-4-methylbenzaldehyde (**3**), 2) condensation of **3** with methyl isopropylidenemalonate providing methyl 8-chloro-5-methoxy-2,7-dimethyl-2*H*-chromene-2-acetate (**4**), 3) side-chain conversion to 8-chloro-2-methyl-2-(4-methyl-3-pentenyl)-5-(protected)oxy-2*H*-chromene (**5**), 4) Vilsmeier formylation affording the corresponding 6-carbaldehyde (**6**), 5) demethylation and oxidation leading to **1**.

As shown in Scheme 3, chlorosalicylaldehyde **3** was prepared from 2,6-dimethoxy-4-methylbenzaldehyde by chlorination with sulfuryl chloride followed by regioselective demethylation [8] with magnesium iodide etherate. Condensation of **3** with methyl isopropylidenemalonate gave the corresponding 2*H*-chromene **4**, which was then converted to the corresponding 2-methyl-2-(4-methyl-3-pentenyl)-2*H*-chromene **5a** *via* a five step side-chain conversion [7], 1) reduction with diisobutylaluminium hydride giving **7a**, 2) chlorination with thionyl chloride giving **7b**, 3) cyanation with sodium cyanide giving **7c**, 4) reduction with diisobutylaluminium hydride giving **7d**, 5) Wittig reaction with $(C_6H_5)_3P{=}C(CH_3)_2$ giving **5a**.

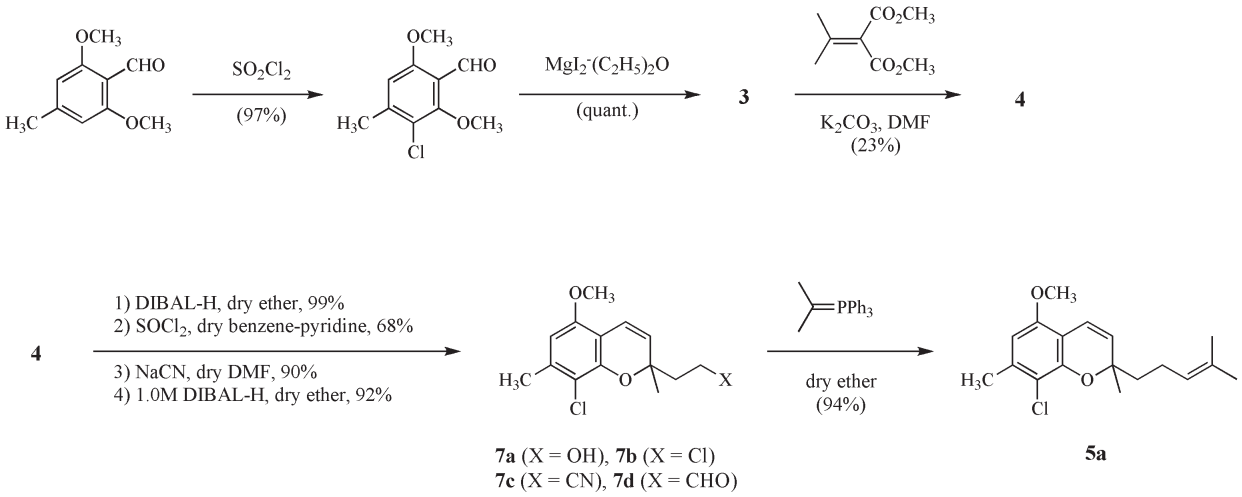
Vilsmeier formylation was found as an effective method to introduce a formyl group on the benzene ring of the 2*H*-chromenes, labile for the strong acidic conditions [9].

Scheme 2



Strategy for 8-Chlorocannabiorcichromenic Acid **1** *via* a Condensation Method

Scheme 3



Preparation of Chlorosalicylaldehyde **3** and Its Conversion to 2*H*-Chromene **5a**

Having a Long Side-chain

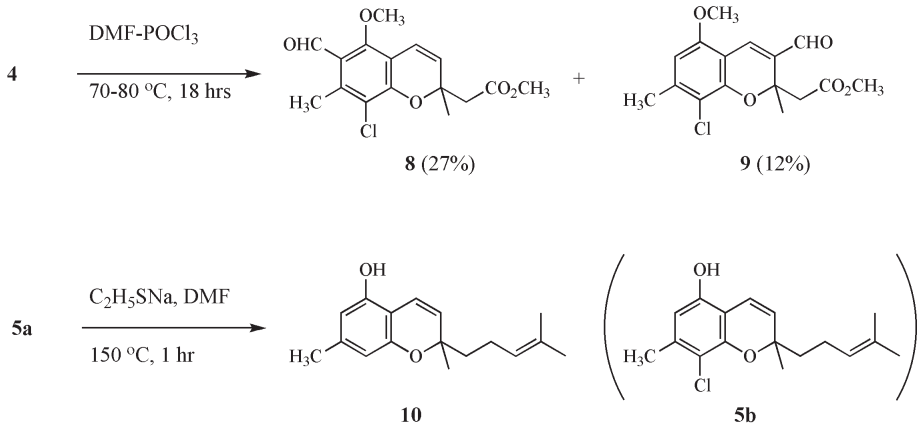
Prior to formylation of **5a**, a similar Vilsmeier formylation of 2*H*-chromene-2-acetate **4** was studied, and gave a mixture of 6-carbaldehyde **8** (27% yield) and 3-carbaldehyde **9** (12% yield) after treatment with *N,N*-dimethylformamide-phosphoryl chloride. Because of both the low yield and the difficult separation, Vilsmeier formylation of **5a** was discarded. The Kolbe reaction is a standard method for introducing a carboxyl group at the *o*-position of a phenolic hydroxyl group. So, demethylation of **5a** was attempted with sodium ethylthiolate, but it also caused dechlorination and gave phenol **10** instead of chlorophenol **5b**. The approaches to 8-chlorocannabiorcichromenic acid **1** using Method A (a condensation method) were thus unsuccessful.

A new strategy for 8-chlorocannabiorcichromenic acid **1** *via* Method B (a thermal cyclization) is shown in Scheme 5: 1) coupling of 3-chloro-4-hydroxy-3-methyl-6-(protected)oxybenzaldehyde (**11**) with 3,7-dimethyloct-6-en-1-yn-3-ol **12** providing **13**, 2) thermal cyclization affording the corresponding 2*H*-chromene **6**, 3) deprotection and oxidation leading 8-chlorocannabiorcichromenic acid **1**.

The chlorohydroxybenzaldehyde **11** was prepared from 3,5-dimethoxytoluene, as shown in Scheme 6. 3-Chloro-4,6-dimethoxy-2-methylbenzaldehyde **14** was prepared by Vilsmeier formylation of 3,5-dimethoxytoluene followed by chlorination with *N*-chlorosuccinimide. Demethylation of **14** with boron tribromide gave 3-chloro-4,6-dihydroxy-2-methylbenzaldehyde **11b**, which gave 3-chloro-4-hydroxy-6-methoxy-2-methylbenzaldehyde **11a** by a three step conversion: 1) methoxymethyl protection with chloromethyl methyl ether, 2) methylation with dimethyl sulfate, 3) deprotection with conc. hydrochloric acid-methanol.

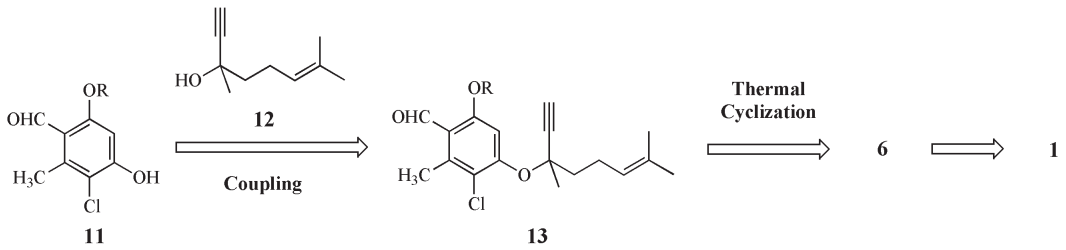
2*H*-Chromene **6a** having a long side-chain was prepared, as shown in Scheme 7, by coupling of **11a** with 3,7-dimethyloct-6-en-1-yn-3-yl methyl carbonate (**12'**) followed by thermal cyclization. Oxidation of **6a** with sodium chlorite gave the corresponding acid **15a**, but all attempts of demethylation were unsuccessful. Also, demethylation of **6a** with magnesium iodide etherate gave the corresponding chlorohydroxy-2*H*-chromene-6-carbaldehyde **6b**, but the subsequent oxidation to **1** was unsuccessful in any procedure. So, instead of methyl protection of the phenolic hydroxyl, methoxymethyl protection was then used in a similar conversion.

Scheme 4



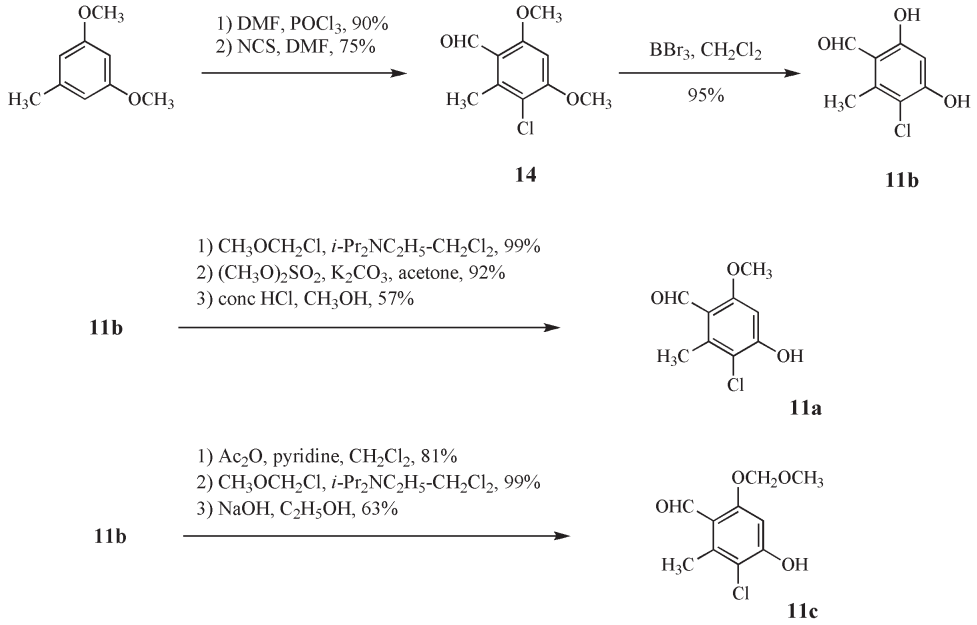
Formylation of Chloro-2*H*-chromene-2-acetate **4** and Demethylation of **5a**

Scheme 5



Strategy for 8-Chlorocannabiorcichromenic Acid **1** *via* Thermal Cyclization

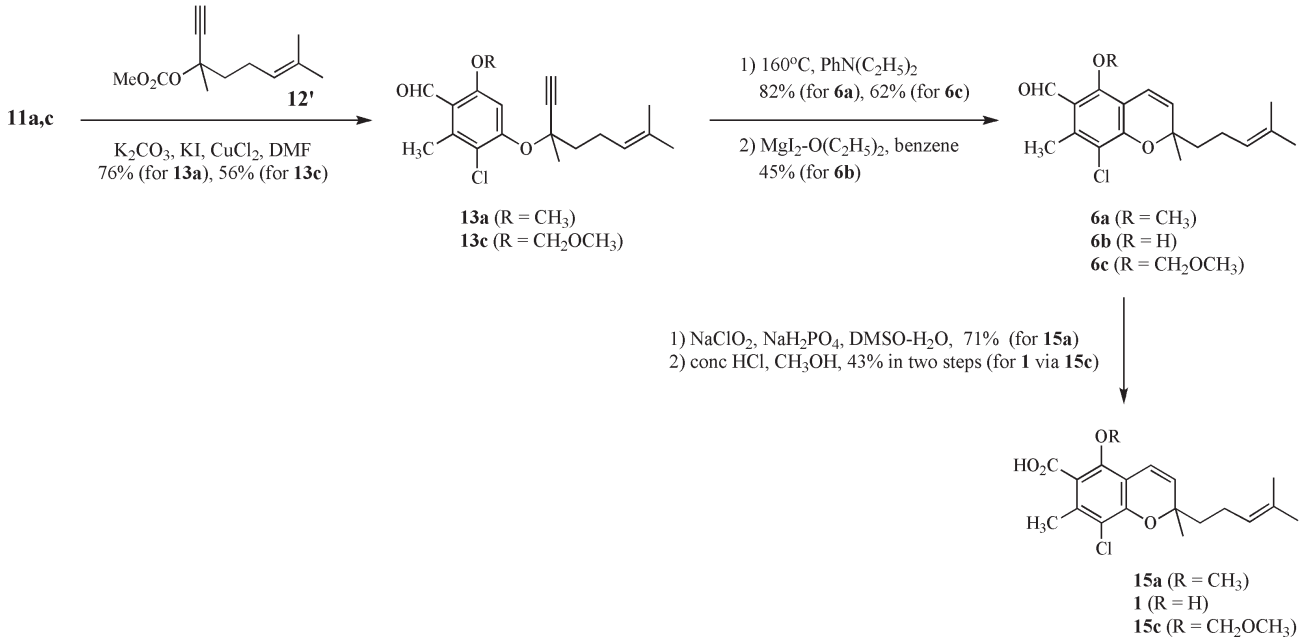
Scheme 6



Preparation of 3-Chloro-4-hydroxy-2-methylbenzaldehydes **11a,b,c**

As shown in Scheme 6, the methoxymethyl protected starting material **11c** was prepared from 3-chloro-4,6-dihydroxy-2-methylbenzaldehyde **11b** in three steps: 1) acetylation with acetic anhydride, 2) methoxymethyl protection with chloromethyl methyl etherate, 3) alkaline hydrolysis. As shown in Scheme 7, coupling of **11c** with 3,7-dimethyloct-6-en-1-yn-3-yl methyl carbonate (**12'**) gave the corresponding propargyl ether **13c** and the subsequent thermal cyclization gave methoxymethyl protected 2*H*-chromene **6c**. Then, 2*H*-chromene-6-carbaldehyde **6c** was subjected

Scheme 7

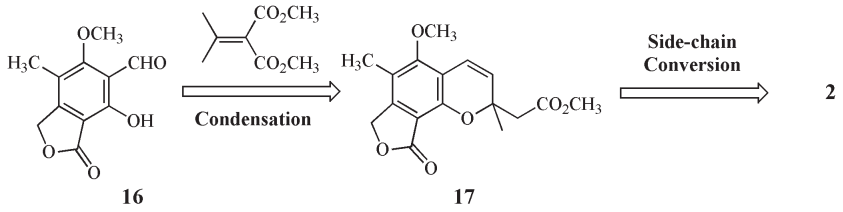


Preparation of 2*H*-Chromene **6a,c** Having a Long Side-chain *via* Thermal Cyclization and Further Conversion to 8-Chlorocannabiorcichromenic Acid **1**

to oxidation with sodium chlorite to give the corresponding acid **15c**, which was readily deprotected to give 8-chlorocannabiorcichromenic acid **1**. Thus, 3-chloro-4-hydroxy-6-(methoxymethyloxy)-2-methylbenzaldehyde **11c**, the starting material for 8-chlorocannabiorci-chromenic acid **1**, was prepared from 3,5-dimethoxy-toluene in 6 steps (32% overall yield), and was converted to 8-chlorocannabiorcichromenic acid **1** in 4 steps (15% overall yield).

A strategy for mycochromenic acid **2** using a condensation method is shown in Scheme 8, 1) condensation of 6-formyl-7-hydroxy-5-methoxy-4-methylphthalide (**16**) with isopropylidenemalonate affording the corresponding 2-methyl-2*H*-chromene-2-acetate (**17**), 2) side-chain conversion leading mycochromenic acid **2**.

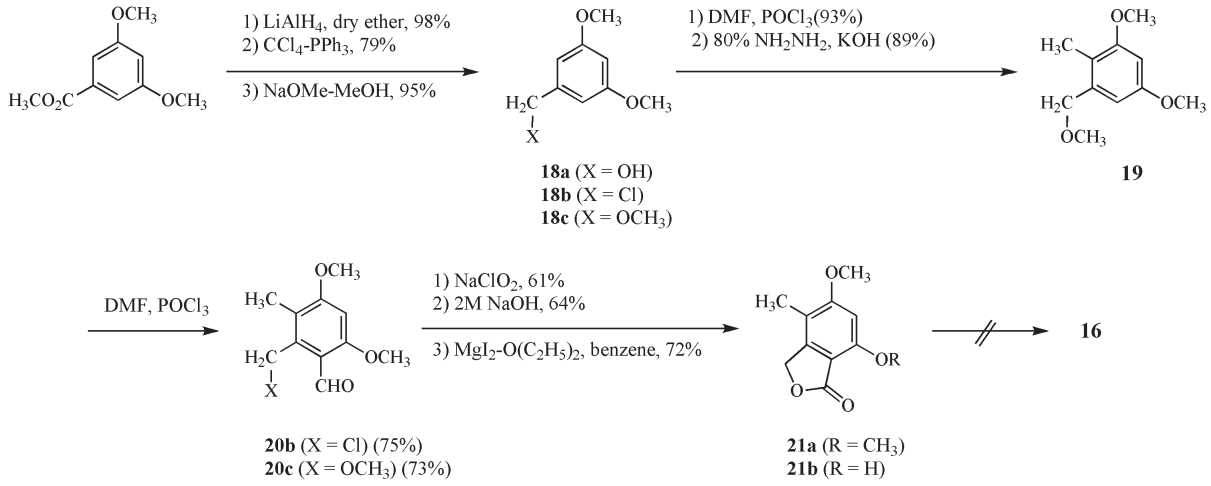
Scheme 8



Strategy for Mycochromenic Acid **2** *via* Condensation Method

Preparation of 6-formyl-7-hydroxy-5-methoxy-4-methylphthalide (**16**) is shown in Scheme 9. 3,5-Dimethoxy-2-methylbenzyl methyl ether **19** was prepared from methyl 3,5-dimethoxybenzoate in five steps: 1) lithium aluminium hydride reduction of 3,5-dimethoxybenzoate giving 3,5-dimethoxybenzylalcohol **18a** [10], 2) Chlorination with carbontetrachloride-triphenyl phosphine giving **18b**, 3) Methoxylation with sodium methylate giving **18c**, 4) Vilsmeier formylation giving 2,4-dimethoxy-6-(methoxymethyl)benzaldehyde, 5) Wolf-Kishner reduction giving **19**. Vilsmeier formylation of **19** under mild conditions (at room temperature for one night) gave the corresponding *o*-(methoxymethyl)benzaldehyde **20c**. A similar formylation under more severe conditions (at 80-90 °C for 8 hrs) caused further chlorination and gave *o*-(chloromethyl)benzaldehyde **20b**, which was converted to 5,7-dimethoxy-4-methylphthalide (**21a**) [11] by oxidation with sodium chlorite followed by lactonization with alkali. Demethylation of **21a** with magnesium iodide etherate gave 7-hydroxy-5-methoxy-4-methylphthalide (**21b**) [12].

Scheme 9



Preparation of Phthalides **21a,b** and Following Formylation to **16**

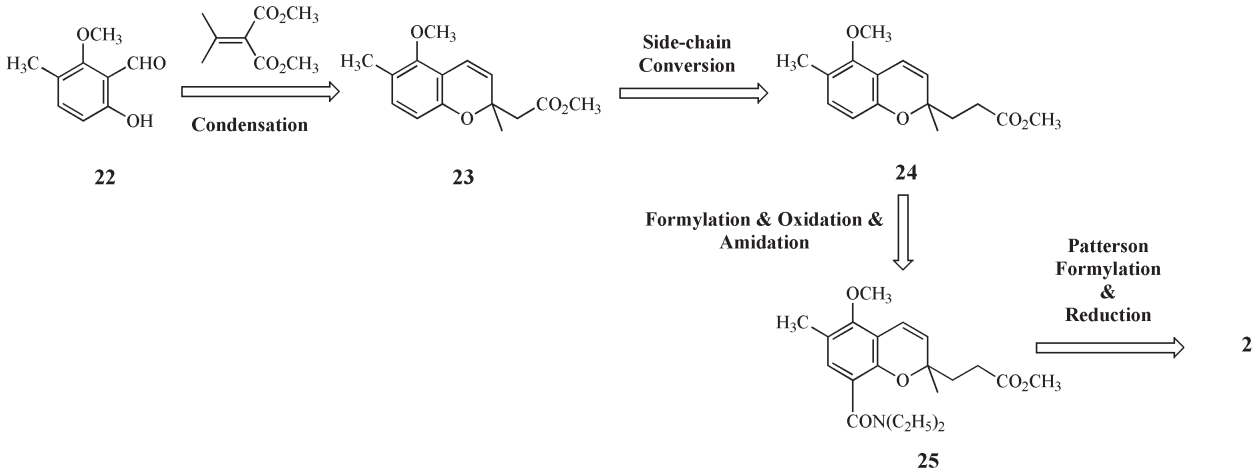
However, all attempts to convert **21a,b** to 6-formylphthalide **16** were unsuccessful.

A different approach to mycochromenic acid **2** *via* Method A (a condensation method) is shown in Scheme 10: 1) condensation of 2-hydroxy-6-methoxy-5-methyl-

benzaldehyde (**22**) with isopropylidenemalonate providing the corresponding 2-methyl-2*H*-chromene-2-acetate (**23**), 2) side-chain conversion to 2*H*-chromene-2-propionate **24**, 3) 8-formylation followed by oxidation and carbamidation affording **25**, 4) Patterson-formylation-reduction [13] leading mycochromenic acid **2**.

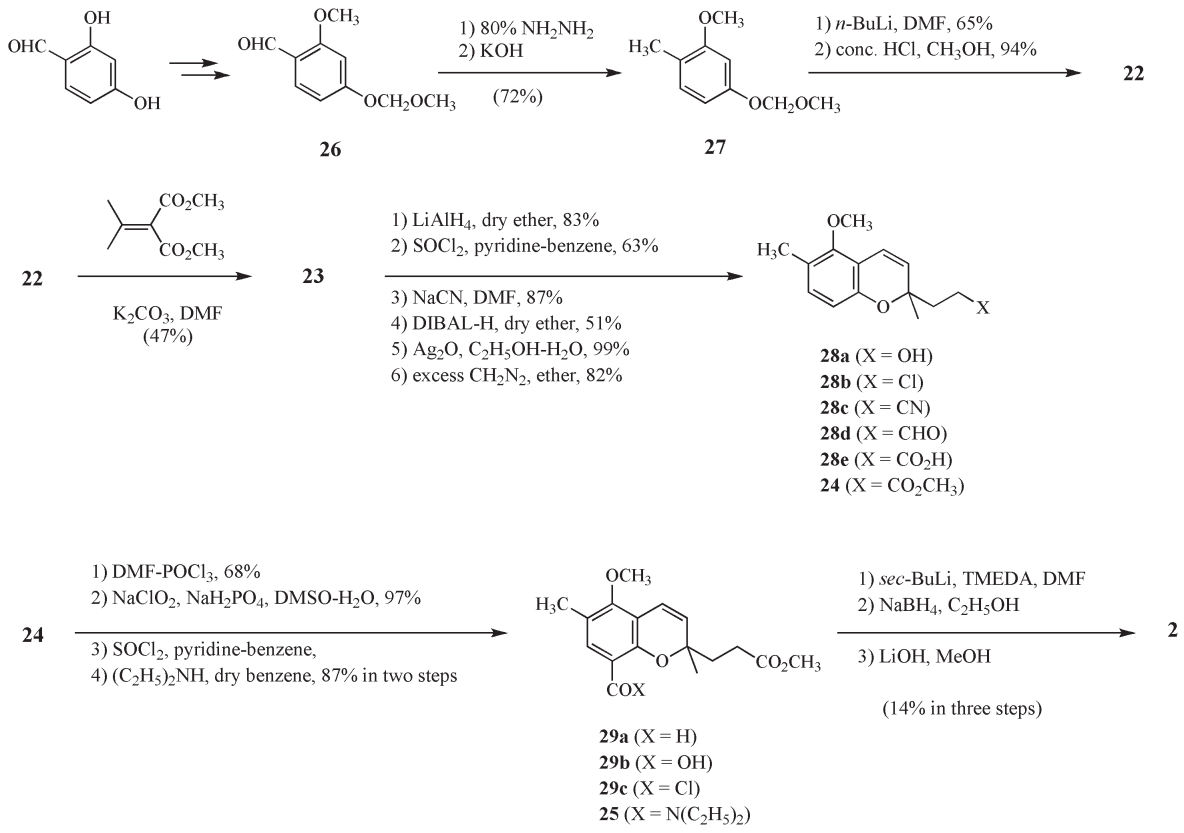
As shown in Scheme 11, 6-hydroxy-2-methoxy-3-methylbenzaldehyde **22** was prepared from 2,4-dihydroxybenzaldehyde in five steps: 1) selective protections of 2,4-dihydroxybenzaldehyde giving **26**, 2) Wolf-Kishner reduction giving **27**, 3) formylation with *n*-butyllithium- *N,N*-dimethylformamide followed by deprotection giving **22**.

Scheme 10



Another Strategy for Mycochromenic Acid **2** *via* Condensation Method

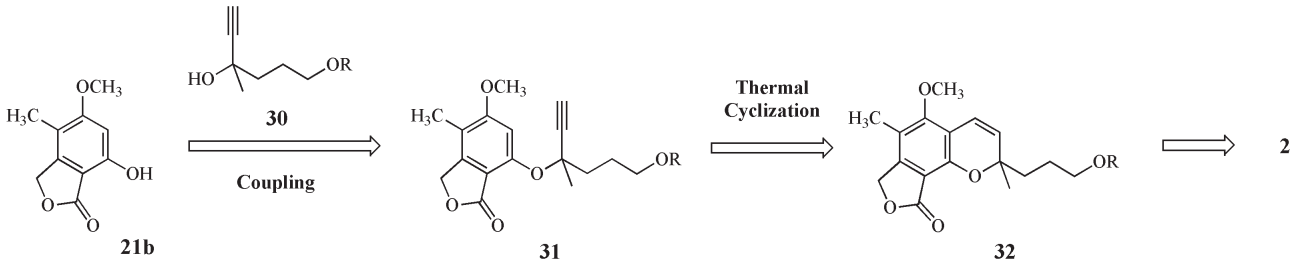
Scheme 11



Preparation of 2-(2-Methoxycarbonyl)ethyl-2*H*-Chromene-8-carbamide **25**, and Further Conversion to Mycochromenic Acid **2**

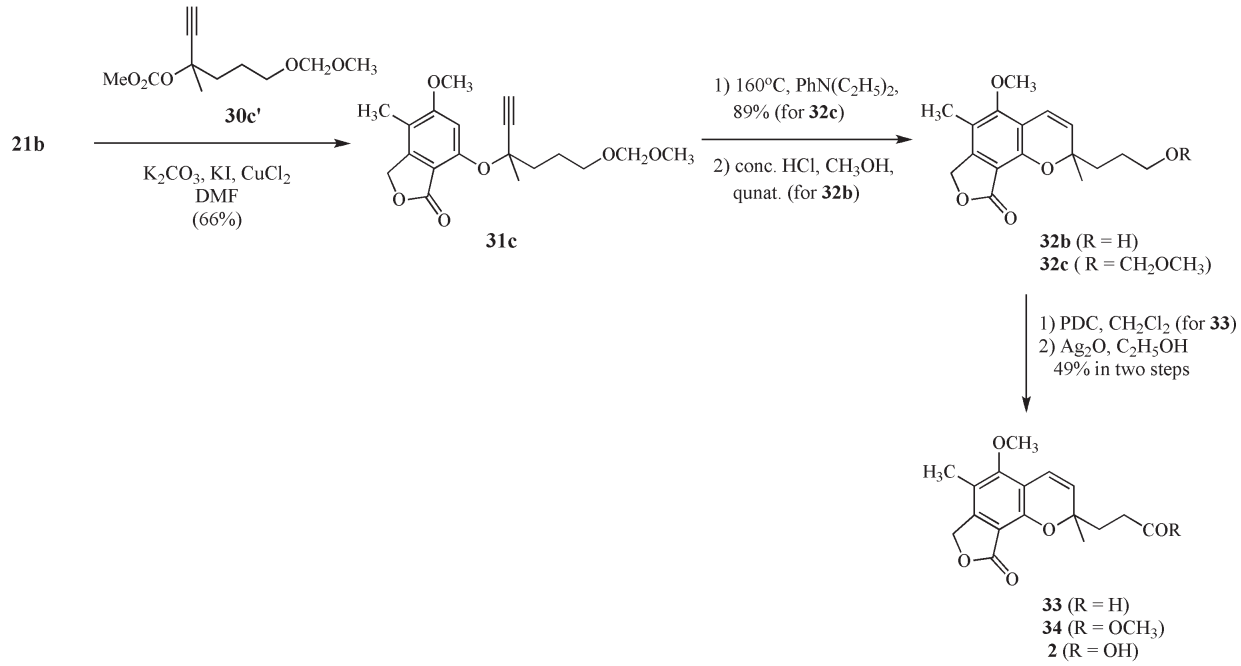
Condensation of **22** with isopropylidenemalonate gave the corresponding 2*H*-chromene-2-acetate **23**. 2*H*-Chromene-2-acetate **23** was then converted to the corresponding 2*H*-chromene-2-propionate **25** in six steps: 1) lithium aluminium hydride reduction of **23** giving the corresponding alcohol **28a**, 2) chlorination with thionyl chloride giving chloride **28b**, 3) cyanation with sodium cyanide giving nitrile **28c**, 4) diisobutylaluminium hydride reduction giving aldehyde **28d**, 5) oxidation with silver oxide giving the corresponding acid **28e**, 6) esterification with diazomethane giving the methyl ester **24**. 2*H*-Chromene-2-propionate **24**, thus obtained, was then converted *N,N*-diethyl-8-carbamide **25** in four steps: 1) Vilsmeier formylation of **24** giving the corresponding 8-carbaldehyde **29a**, 2) oxidation with sodium chlorite giving the 8-carboxylic acid **29b**, 3) chlorination with thionyl chloride giving the acid chloride **29c**, 4) amidation with diethylamine giving carbamide **25**. 2*H*-Chromene-8-carbamide **25**, thus obtained, was then converted to mycochromenic acid **2** in two steps: 1) Selective formylation (in Patterson Method) *ortho* to the 8-carboxamide by metallation with *sec*-butyllithium-tetramethylethylenediamine (TMEDA) followed by treating with *N,N*-dimethylformamide giving the corresponding 7-carbaldehyde, 2) Reduction with sodium borohydride giving mycochromenic acid **2**. Thus, methyl 5-methoxy-2,6-dimethyl-2*H*-chromene-2-acetate (**23**), a key intermediate for mycochromenic acid **2**, was prepared from 2,4-dihydroxybenzaldehyde in 5 steps (18% overall yield), then converted to corresponding 2*H*-chromene-2-propionate **24** by a 6-step side chain conversion (19% overall yield). This gave the corresponding *N,N*-diethyl-2*H*-chromene-8-carboxamide **25**, in 4 steps (57% yield), which are then converted to mycochromeic acid **2** in 3 steps (14% yield). However, this procedure was not very

Scheme 12



Strategy for Mycochromenic Acid **2** *via* Thermal Cyclization

Scheme 13



Preparation of Mycophenolic Acid **2** *via* Thermal Cyclization

effective because of the multi-steps and a low overall yield. So, another strategy for mycochromenic acid **2** was planned as shown below.

This new strategy for mycochromenic acid **2** *via* thermal cyclization is shown in Scheme 12: 1) coupling of 7-hydroxy-5-methoxy-4-methylphthalide **21b** with 3-methyl-6-(protected)oxy-hex-1-yn-3-ol **30** providing the corresponding propargyl ether **31**, 2) thermal cyclization affording the corresponding 2*H*-chromene **32**, 3) deprotection and oxidation leading mycochromenic acid **2**.

7-Hydroxyphthalide **21b** was converted to the corresponding 2*H*-chromene **32b** in three steps, 1) coupling of **21b** with 6-(methoxymethyoxy)-3-methyl-hex-1-yn-3-yl methyl carbonate **30c'** giving the corresponding propargyl ether **31c**, 2) thermal cyclization of **31c** giving the corresponding 2*H*-chromene **32c**, 3) deprotection giving 2*H*-chromene-2-propanol **32b**. Oxidation of **32b** with pyridinium dichromate (PDC) gave a mixture of the corresponding 2*H*-chromene-2-propal **33** and mycochromenic acid **2**, and the mixture was oxidized with silver oxide effectively to give mycochromenic acid **2** (49%, two step yield) as the sole product.

EXPERIMENTAL

Melting points were taken on a micro melting point apparatus and are uncorrected. Ir spectra were obtained in liquid films or potassium bromide (KBr) disks on a FT/IR spectrophotometer, and ^{1}H nmr spectra were obtained in deuteriochloroform ($CDCl_3$) solution on a 90 or 400 MHz spectrometer. Elemental analyses were performed on a micro CHN analyzer. Mass spectra were recorded under electron ionization (EI) conditions on a mass spectrometer.

General Procedure for Condensation Method.

To a solution of salicylaldehyde (3.00 mmol) and dimethyl isopropylidenemalonate (517 mg, 3.00 mmol) in dry *N,N*-dimethylformamide (20 mL) was added anhydrous potassium carbonate (1.25 g, 9.00 mmol), and the mixture was stirred at 130 °C for 7 hrs. After removal of the solvent *in vacuo* the residue was treated with water and the mixture was extracted with ethyl ether. The organic layer was washed with 5% aqueous sodium hydroxide solution, and brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residual oil was chromatographed on a silica gel column to afford the corresponding 2*H*-chromene-2-acetate.

Methyl 8-Chloro-5-methoxy-2,7-dimethyl-2*H*-chromene-2-acetate (**4**).

This compound was obtained in 23% yield; colorless crystals eluted with hexane-benzene (7:3); ir (KBr disk): ν 1739 cm^{-1}; ^{1}H nmr ($CDCl_3$, 90 MHz): δ 1.54 (s, 3H), 2.34 (s, 3H), 2.68 (s, 2H), 3.59 (s, 3H), 3.72 (s, 3H), 5.62 (d, *J* = 10 Hz, 1H), 6.25 (s, 2H), 6.60 ppm (d, *J* = 10 Hz, 1H); ms (EI): m/z 296 and 298 (M^+), 223 (M^+-$CH_2CO_2CH_3$).

Anal. Calcd for $C_{15}H_{17}ClO_4$: C, 60.71; H, 5.77. Found: C, 60.68; H, 5.75.

Methyl 5-Methoxy-2,6-methyl-2*H*-chromene-2-acetate (**23**).

This compound was obtained in 47% yield as a colorless oil eluted with 100% hexane; ir (liquid film): ν 1728 cm^{-1}; ^{1}H nmr ($CDCl_3$, 90 MHz): δ 1.55 (s, 3H), 2.18 (s, 3H), 2.71 (d, *J* = 14 Hz, 1H), 2.73 (d, *J* = 14 Hz, 1H), 3.64 (s, 3H), 3.72 (s, 3H), 5.77 (d, *J* = 10 Hz, 1H), 6.56 (d, *J* = 8 Hz, 1H), 6.65 (d, *J* = 10 Hz, 1H), 6.90 ppm (d, *J* = 8 Hz, 1H); ms (EI): m/z 262 (M^+), 189 (M^+-$CH_2CO_2CH_3$).

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.66; H, 6.97.

General Procedure for Thermal Cyclization Methods.

Coupling.

Under an argon atmosphere, to a suspension of phenol (1.00 mmol), potassium carbonate (261 mg, 2.0 mmol), potassium iodide (279 mg, 1.7 mmol), and copper (II) chloride (1.00 μmol), in *N,N*-dimethylformamide (10 mL) was added the methyl propargyl carbonate (2.0 mmol), and the mixture was stirred at 60 °C for 5 hrs. The resulting mixture was treated with water and extracted with ethyl acetate. The organic layer was washed with 10% hydrochloric acid, 5% sodium hydroxide solution, and brine, and dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo* the residue was purified by chromatography on a silica gel column to afford the corresponding propargyl ether.

3-Chloro-6-methoxy-2-methyl-4-(3,7-dimethyloct-6-en-1-yn-3-yl)oxybenzaldehyde (**13a**).

This compound was obtained in 76% yield as a colorless oil eluted with hexane-ethyl acetate (98:2); ir (liquid film): ν 3292, 2112, 1681 cm^{-1}; ^{1}H nmr ($CDCl_3$, 400 MHz): δ 1.64 (br s, 3H), 1.70 (br s, 6H), 1.92-2.00 (ddd, *J* = 14, 12, 5 Hz, 1H), 2.01-2.09 (ddd, *J* = 14, 11, 5 Hz, 1H), 2.22-2.43 (m, 2H), 2.67 (s, 3H), 2.75 (s, 1H), 3.88 (s, 6H), 5.14-5.19 (m, 1H), 7.29 (s, 1H), 10.49 ppm (s, 1H).

3-Chloro-6-(methoxymethyl)oxy-2-methyl-4-(3,7-dimethyloct-6-en-1-yn-3-yl)oxybenzaldehyde (**13c**).

This compound was obtained in 56% yield as a colorless oil eluted with hexane-ethyl acetate (95:5); ir (liquid film): ν 3290, 2117, 1683 cm^{-1}; ^{1}H nmr ($CDCl_3$, 400 MHz): δ 1.64 (br s, 3H), 1.70 (br s, 6H), 1.91-1.982 (ddd, *J* = 14, 12, 5 Hz, 1H), 2.25-2.41 (ddd, *J* = 14, 11, 5 Hz, 1H), 2.25-2.41 (m, 2H), 2.67 (s, 3H), 2.72 (s, 1H), 3.51 (s, 3H), 5.14-5.18 (m, 1H), 5.22-5.26 (dd,), 7.52 (s, 1H), 10.52 ppm (s, 1H).

5-Methoxy-7-(6-methoxymethyloxy-3-methyl-hex-1-yn-3-yl)oxy-4-methyl-1(3*H*)-isobenzofuranone (**31c**).

This compound was obtained in 66% yield as colorless crystals eluted with hexane-ethyl acetate (60:40); mp 84-86 °C; ir (KBr disk): ν 3235, 2112, 1749 cm^{-1}; ^{1}H nmr ($CDCl_3$, 400 MHz): δ 1.68 (br s, 3H), 2.06 (s, 3H), 1.92-2.19 (m, 4H), 2.68 (s, 3H), 3.37 (s, 3H), 3.61-3.64 (t, *J* = 6 Hz, 2H), 3.89 (s, 3H), 4.64 (s, 2H), 5.09 (s, 2H), 7.19 ppm (s, 1H)); ms (EI): m/z 348 (M^+), 245 (M^+-$CH_2CH_2CH_2OCH_2OCH_3$).

Anal. Calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.73; H, 7.23.

Thermal Cyclization.

Under an argon atmosphere, the propargyl ether (1.00 mmol) was dissolved in *N,N*-dimethylaniline (5 mL), and the solution was heated at 160 °C for 1.5-3 hrs. After cooling, the mixture

was diluted with ethyl acetate. The solution was washed with 10% hydrochloric acid, saturated sodium hydrogen carbonate solution, and brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The oily residue was purified by chromatography on a silica gel column to afford the corresponding 2*H*-chromene.

8-Chloro-5-methoxy-2,7-dimethyl-2-(4-methylpent-3-enyl)-2*H*-chromene-6-carbaldehyde (**6a**).

This compound was obtained in 82% yield (1.5 h) as a colorless oil eluted with hexane-ethyl acetate (95:5); ir (liquid film): ν 1684 cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.49 (s, 3H), 1.56 (br s, 3H), 1.65 (d, *J* = 1 Hz, 3H), 1.67-1.85 (m, 2H), 2.01-2.16 (m, 2H), 2.67 (s, 3H), 3.84 (s, 3H), 5.08-5.12 (m, 1H), 5.65-5.68 (d, *J* = 10 Hz, 1H), 5.59-6.61 (d, *J* = 10 Hz, 1H), 10.35 ppm (s, 1H); ms (EI): m/z 334 and 336 (M^+), 251 and 253 (M^+-CH_2-prenyl).

8-Chloro-5-(methoxymethyloxy)-2,7-dimethyl-2-(4-methylpent-3-enyl)-2*H*-chromene-6-carbaldehyde (**6c**).

This compound was obtained in 62% yield (2 hrs) as a colorless oil eluted with hexane-ethyl acetate (95:5); ir (liquid film): ν 1684 cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.48 (s, 3H), 1.56 (br s, 3H), 1.65 (d, *J* = 1 Hz, 3H), 1.67-1.69-1.84 (m, 2H), 2.10-2.16 (m, 2H), 2.66 (s, 3H), 3.58 (s, 3H), 5.03 (s, 2H), 5.07-5.11 (m, 1H), 5.65-5.67 (d, *J* = 10 Hz, 1H), 6.58-6.61 (d, *J* = 10 Hz, 1H), 10.35 ppm (s, 1H); ms (EI): m/z 364 and 366 (M^+), 281 and 283 (M^+-CH_2-prenyl), 235 and 237 (M^+-CH_2-prenyl-MOM-H), 221 and 223 (M^+-CH_2-prenyl-OMe-CHO).

3,8-Dihydro-5-methoxy-8-(3-methoxymethyloxy)propyl-4,8-dimethyl-1-furo[3,4-*h*]chromen-1-one (**32c**);.

This compound was obtained in 89% yield (2 hrs) as a colorless oil eluted with hexane-ethyl acetate (70:30); ir (liquid film): ν 1766 cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.50 (s, 3H), 1.74-1.82 (m, 2H), 1.84-1.94 (m, 2H), 2.11 (s, 3H), 3.33 (s, 3H), 3.52-3.54 (t, *J* = 6 Hz, 2H), 3.79 (s, 3H), 4.59 (s, 2H), 5.09 (s, 3H), 5.64-5.66 (d, *J* = 10 Hz, 1H), 6.60-6.62 ppm (d, *J* = 10 Hz, 1H); ms (EI): m/z 348 (M^+), 333 (M^+-CH_3), 245 (M^+-$CH_2CH_2CH_2O$ CH_2OCH_3).

Anal. Calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.53; H, 6.88.

Side-chain Conversion of 2*H*-Chromene-2-acetate **4** to **5a** or **23** to **24**.

Diisobutylaluminium Hydride Reduction of **4**.

A solution of methyl 8-chloro-2,7-dimethyl-2*H*-chromene-2-acetate **4** (875 mg, 3.00 mmol) in dry diethyl ether (12 mL) was reduced by treatment with 1.0 *M* diisobutylaluminium hydride hexane solution (6.9 mL, 6.9 mmol) at –78 °C for 4 hrs. The mixture was treated with saturated sodium hydrogen carbonate solution and then with 10% hydrochloric acid, and extracted with diethyl ether. The organic layer was washed with saturated sodium hydrogen carbonate solution, and brine, and dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo*, the residue was purified by chromatography on a silica gel column to afford the corresponding 2*H*-chromene-2-ethanol **7a**.

8-Chloro-5-methoxy-2,7-dimethyl-2*H*-chromene-2-ethanol (**7a**).

This compound was obtained as a colorless oil eluted with 100% benzene; 99% yield; ir (liquid film): ν 3385 cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.46 (s, 3H), 1.91-2.12 (m, 2H), 2.33 (s, 3H), 3.79 (s, 3H), 3.70-3.90 (m, 2H), 5.51 (d, *J* = 10 Hz, 1H), 6.31 (s, 1H), 6.66 ppm (d, *J* = 10 Hz, 1H); ms (EI): m/z 268 and 270 (M^+), 253 and 255 (M^+-CH_3), 223 and 225 (M^+-CH_2CH_2OH).

Anal. Calcd. for $C_{14}H_{17}ClO_3$: C, 62.57; H, 6.38. Found: C, 62.60; H, 6.42.

Lithium Aluminium Hydride Reduction of **23**.

A solution of methyl 5-methoxy-2,6-dimethyl-2*H*-chromene-2-acetate **23** (392 mg, 1.65 mmol) in dry ethyl ether (10 mL) was reduced by refluxing with a solution of lithium aluminium hydride (75.1 mg, 1.98 mmol) in dry ethyl ether (15 mL) for 30 min. The mixture was treated with a saturated sodium hydrogen carbonate solution and then 10% hydrochloric acid, and extracted with ethyl ether. The organic layer was washed with saturated sodium hydrogen carbonate solution, and brine, and dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo*, the residue was purified by chromatography on a silica gel column to afford corresponding 2*H*-chromene-2-ethanol **28a**.

5-Methoxy-2,6-dimethyl-2*H*-chromene-2-ethanol (**28a**).

This compound was obtained as a colorless oil eluted with 100% benzene; 83%; ir (liquid film): ν 3386 cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.40 (s, 3H), 1.98 (t, *J* = 6 Hz, 2H), 2.19 (s, 3H), 3.72 (s, 3H), 3.85 (t, *J* = 6 Hz, 2H), 5.60 (d, *J* = 10 Hz, 1H), 6.47 (d, *J* = 8 Hz, 1H), 6.66 (d, *J* = 10 Hz, 1H), 6.90 ppm (d, *J* = 8 Hz, 1H); ms (EI): m/z 234 (M^+), 219 (M^+-CH_3), 189 (M^+-CH_2CH_2OH).

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.47; H, 7.66.

Chlorination.

To a solution of thionyl chloride (0.92 mL, 12.6 mmol) in dry benzene (35 mL) was added a solution of alcohol **7a** or **28a** (6.00 mmol) in dry benzene (23 mL) and dry pyridine (1.02 mL, 12.6 mmol), and the mixture was refluxed for 2 hrs. After cooling, the mixture was treated with 10% hydrochloric acid, and extracted with ethyl ether. The organic layer was washed with a saturated sodium hydrogen carbonate solution, and brine, and dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo*, the residue was purified by chromatography on a silica gel column to afford the corresponding chloride.

8-Chloro-2-(2-chloroethyl)-5-methoxy-2,7-dimethyl-2*H*-chromene (**7b**).

This compound was obtained as a colorless oil eluted with hexane-ethylacetate (9:1); 68% yield; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.46 (s, 3H), 1.46 (s, 3H), 2.19 (t, *J* = 6 Hz, 2H), 2.33 (s, 3H), 3.64 (t, *J* = 6 Hz, 2H), 3.79 (s, 3H), 3.70-3.90 (m, 2H), 5.49 (d, *J* = 10 Hz, 1H), 6.30 (s, 1H), 6.67 ppm (d, *J* = 10 Hz, 1H); ms (EI): m/z 286 and 288 (M^+), 271 and 273 (M^+-CH_3), 223 and 225 (M^+-CH_2CH_2Cl).

Anal. Calcd. for $C_{14}H_{16}Cl_2O_2$: C, 58.55; H, 5.62. Found: C, 58.66; H, 5.87.

2-(2-Chloroethyl)-5-methoxy-2,6-dimethyl-2*H*-chromene (**28b**).

This compound was obtained as a colorless oil eluted with 100% benzene; 63% yield; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.40 (s, 3H), 2.18 (m, 2H), 2.19 (s, 3H), 3.63 (dd, J = 7 and 9 Hz, 2H), 3.72 (s, 3H), 5.57 (d, *J* = 10 Hz, 1H), 6.49 (d, *J* = 8 Hz, 1H), 6.67 (d, *J* = 10 Hz, 1H), 6.91 ppm (d, *J* = 8 Hz, 1H); ms (EI): m/z 252 and 254 (M^+), 237 and 239 (M^+-CH_3), 189 (M^+-CH_2CH_2Cl).

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.47; H, 7.66.

Cyanation.

To a solution of sodium cyanide (676 mg, 12.5 mmol) in dry *N,N*-dimethylformamide (35 mL) was added chloride **7b** or **28b** (4.00 mmol) in dry DMF (20 mL), and the mixture was stirred at 115 °C for 3 hrs. After cooling, the mixture was diluted with water, saturated with sodium chloride, and extracted with ethyl ether. The organic layer was washed with a 5% sodium hydroxide solution, and brine, and dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo* the residue was purified by chromatography on a silica gel column to afford the corresponding cyanide.

8-Chloro-5-methoxy-2,7-dimethyl-2*H*-chromene-2-propanonitrile (**7c**).

This compound was obtained as a colorless oil eluted with hexane-ethylacetate (9:1); 90% yield; ir (liquid film): ν 2248 cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.45 (s, 3H), 2.05 (t, *J* = 9 Hz, 2H), 2.36 (s, 3H), 2.61 (t, *J* = 9 Hz, 2H), 3.79 (s, 6H), 5.46 (d, *J* = 10 Hz, 1H), 6.32 (s, 1H), 6.73 ppm (d, *J* = 10 Hz, 1H); ms (EI): m/z 277 and 279 (M^+), 262 and 264 (M^+-CH_3), 223 and 225 (M^+-CH_2CH_2CN).

Anal. Calcd. for $C_{15}H_{16}NO_2Cl$: C, 64.87; H, 5.81; N, 5.04. Found: C, 64.70; H, 5.82; N, 4.99.

5-Methoxy-2,6-dimethyl-2*H*-chromene-2-propanonitrile (**28c**).

This compound was obtained as a colorless oil eluted with 100% benzene; 87%; ir (liquid film): ν 2248 cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.39 (s, 3H), 1.85-2.10 (m, 2H), 2.18 (s, 3H), 2.30-2.60 (m, 2H), 3.72 (s, 3H), 5.52 (d, *J* = 10 Hz, 1H), 6.48 (d, *J* = 8 Hz, 1H), 6.72 (d, *J* = 10 Hz, 1H), 6.92 ppm (d, *J* = 8 Hz, 1H); ms (EI): m/z 243 (M^+), 228 (M^+-CH_3), 189 (M^+-CH_2CH_2CN).

Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.03; H, 7.21; N,5.80.

Diisobutylaluminium Hydride Reduction.

To a solution of cyanide **7c** or **28c** (1.00 mmol) in dry ethyl ether (4 mL) was added 1.0 *M* diisobutylaluminium hydride hexane solution (1.16 mL, 1.16 mmol) at –78 °C, and the mixture was stirred at room temeperature for 3 hrs. The resulting mixture was treated with a saturated ammonium chloride solution and then with 10% hydrochloric acid, and extracted with diethyl ether. The organic layer was washed with a saturated sodium hydrogen carbonate solution, and brine, and dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo* the residue was purified by chromatography on a silica gel column to afford the corresponding aldehyde.

8-Chloro-5-methoxy-2,7-dimethyl-2*H*-chromene-2-propanal (**7d**).

This compound was obtained as a colorless oil eluted with hexane-ethyl acetate (95:5); 92% yield; ir (liquid film): ν 1725 cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.43 (s, 3H), 2.03 (t, *J* = 7 Hz, 2H), 2.33 (s, 3H), 2.64 (t, *J* = 7 Hz, 2H), 3.79 (s, 3H), 5.45 (d, *J* = 10 Hz, 1H), 6.30 (s, 1H), 6.68 (d, *J* = 10 Hz, 1H), 9.79 ppm (br s, 1H); ms (EI): m/z 280 and 282 (M^+), 265 and 267 (M^+-CH_3), 262 and 264 (M^+-H_2O), 247 and 249 (M^+-CH_3-H_2O), 223 and 225 (M^+-CH_2CH_2CHO).

5-Methoxy-2,6-dimethyl-2*H*-chromene-2-propanal (**28d**).

This compound was obtained as a colorless oil eluted with 100% benzene; 51% yield; ir (liquid film): ν 1725 cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.39 (s, 3H), 2.01 (t, *J* = 8 Hz, 2H), 2.18 (s, 3H), 2.60 (dt, J = 8 and 2 Hz, 2H), 3.72 (s, 3H), 5.51 (d, *J* = 10 Hz, 1H), 6.46 (d, *J* = 8 Hz, 1H), 6.66 (d, *J* = 10 Hz, 1H), 6.90 (d, *J* = 8 Hz, 1H), 9.76 ppm (d, *J* = 2 Hz, 1H); ms (EI): m/z 246 (M^+), 231 (M^+- CH_3), 189 (M^+-CH_2CH_2CHO). HRMS. Calcd for $C_{15}H_{18}O_3$: M 246.125. Found: M^+: 246.125.

Wittig Reaction of **7d** to form **5a**.

Under an argon atmosphere, to a suspension of 2-propyltriphenylphosphonium bromide (779 mg, 2.02 mmol) in dry ethyl ether (10 mL) was added 1.6 *M n*-butyllithium hexane solution (1.01 mL, 1.68 mmol) with ice cooling. Aldehyde **7d** (189 mg, 0.67 mmol) in dry ethyl ether (3 mL) was added to the Wittig reagent, and the mixture was stirred with ice cooling for 1 hr. The mixture was acidified with saturated ammonium chloride solution and then treated with saturated sodium chloride, and extracted with ethyl ether. The organic layer was washed with brine, and dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo* the residue was purified by chromatography on a silica gel column to afford 2-methyl-2-(4-methyl-3-pentenyl)-2*H*-chromene (**5a**); a colorless oil eluted with hexane-benzene (9:1); 94%; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.34 (s, 3H), 1.49 (br s, 3H), 1.57 (br s, 3H), 1.42-1.71 (m, 2H), 1.91-2.19 (m, 2H), 2.25 (s, 3H), 5.00 (br t, *J* = 7 Hz, 1H), 5.41 (d, *J* = 10 Hz, 1H), 6.19 (s, 1H), 6.55 ppm (d, *J* = 10 Hz, 1H); ms (EI): m/z 306 and 308 (M^+), 223 and 225 (M^+-CH_2CH_2CHO).

Oxidation of **28d** to **28e**.

To a solution of sodium hydroxide (40 mg) in water (1.5 mL) was added a solution of silver nitrate (78.0 mg, 0.422 mmol) in water (1.5 mL). Then, a solution of aldehyde **28d** (52.0 mg, 0.211 mmol) in ethanol (0.6 mL) was added to the silver oxide suspension, and the mixture was refluxed for 1.5 hrs. The resulting silver was removed by filtration, and was washed with hot water and then with ethyl ether. The filtrates were combined and washed with diethyl ether. The aqueous solution were combined, acidified with 10% hydrochloric acid, and extracted with ethyl ether. The ether layer was washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo*, the residue was purified by chromatography on a silica gel column to afford 2-methyl-2*H*-chromene-2-propanoic acid (**28e**); a colorless oil; 99%; ir (liquid film): ν 1710 cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.39 (s, 3H), 1.80-2.10 (m, 2H), 2.18 (s, 3H), 2.30-2.60 (m, 2H), 3.72 (s, 3H), 5.51 (d, *J* = 10 Hz, 1H), 5.20-6.40 (m, 1H), 6.47 (d, *J* = 8 Hz, 1H), 6.67 (d, *J* = 10 Hz, 1H), 6.90 ppm (d, *J* = 8 Hz, 1H); ms (EI): m/z 262 (M^+), 247 (M^+-CH_3), 189 (M^+-$CH_2CH_2CO_2H$).

Esterification of **28e** with Diazomethane.

To a solution of acid **28e** (156 mg, 0.595 mmol) in methanol (2 ml) was added a cold diazomethane in ethyl ether solution (containing of *ca*. 1 mmol of diazomethane), and the resulting solution was placed in a refrigerator for 24 hrs. The solution was treated with acetic acid to quench the excess diazomethane, and diluted with ethyl ether. The ethereal solution was washed with a saturated sodium hydrogen carbonate solution and brine, and dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo* the residue was purified by chromatography on a

silica gel column to afford methyl 2-methyl-2*H*-chromene-2-propanoate (**24**); a colorless oil; 82%; ir (liquid film): ν 1740 cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.38 (s, 3H), 1.98-2.10 (m, 2H), 2.18 (s, 3H), 2.30-2.50 (m, 2H), 3.64 (s, 3H), 3.72 (s, 3H), 5.52 (d, *J* = 10 Hz, 1H), 6.46 (d, *J* = 9 Hz, 1H), 6.66 (d, *J* = 10 Hz, 1H), 6.89 ppm (d, *J* = 9 Hz, 1H); ms (EI): m/z 276 (M^+), 261 (M^+-CH_3), 189 (M^+-$CH_2CH_2CO_2CH_3$).

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.43; H, 7.49.

Demethylation of **6a** with Magnesium iodide.

Under an argon atmosphere, iodine (31 mg, 0.12 mmol) was added to a suspension of magnesium metal (3.4 mg, 0.14 mmol) in dry benzene (1.5 mL) and dry ethyl ether (0.42 mL), and the mixture was stirred at room temperature for 15 hrs. A solution of aldehyde **6a** (0.100 mmol) in dry benzene (1.5 mL) was added to the magnesium iodide etherate solution, and the mixture was refluxed for 2 hrs. After cooling, the mixture was treated with 10% hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with a saturated sodium hydrogen carbonate solution and brine, and dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo* the residue was purified by chromatography on a silica-gel column to afford 8-chloro-5-hydroxy-2,7-dimethyl-2-(4-methylpent-3-enyl)-2*H*-chromene-6-carbaldehyde (**6b**); 45%; colorless oil eluted with hexane-ethyl acetate (98:2); ir (liquid film): ν 1663 cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.48 (s, 3H), 1.57 (br s, 3H), 1.65 (d, *J* = 1 Hz, 3H), 1.67-1.86 (m, 2H), 2.09-2.15 (m, 2H), 2.59 (s, 3H), 3.84 (s, 3H), 5.08-5.12 (m, 1H), 5.53-5.56 (d, *J* = 10 Hz, 1H), 6.69-6.72 (d, *J* = 10 Hz, 1H), 10.12 (s, 1H), 12.68 ppm (s, 1H); ms (EI): m/z 320 and 322 (M^+), 235 and 237 (M^+-C_6H_{11}).

Demethylation of **5a** with Sodium Ethanethiolate.

Under an argon atmosphere, to a suspension of 60% oily sodium hydride (75.9 mg, 1.90 mmol) in dry *N,N*-dimethylformamide (5 mL) was added first ethanethiol (0.14 mL, 1.90 mmol) by a syringe, and then a solution of 8-chloro-5-methoxy-2*H*-chromene **5a** (194 mg, 0.63 mmol) in dry *N,N*-dimethylformamide (2 mL). After the mixture had been stirred at 150 °C for 1 hr, it was cooled, diluted with water, acidified with 10% hydrochloric acid, and extracted with ethyl ether. The organic layer was washed with brine, and dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo* the residue was purified by chromatography on a silica gel column to afford 2,7-dimethyl-2-(4-methylpent-3-enyl)-2*H*-chromen-5-ol (**10**); a colorless oil eluted with hexane-benzene (1:1); 50%; ir (liquid film): ν 3393 cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.37 (s, 3H), 1.57 (br s, 3H), 1.65 (br s, 3H), 1.42-1.71 (m, 2H), 1.91-2.19 (m, 2H), 2.19 (s, 3H), 5.10 (br t, J = 7 Hz, 1H), 5.47 (d, *J* = 10 Hz, 1H), 6.11 (s, 1H), 6.22 (s, 1H), 6.61 ppm (d, *J* = 10 Hz, 1H); ms (EI): m/z 258 (M^+), 243 (M^+-CH_3).

Oxidation of Aldehydes **6a,b** to the Correspondng Carboxylic Acids **15a** and **1**.

To a solution of the aldehyde (136 mg, 0.500 mmol) in dimethylsulfoxide (7 mL) was added a solution of sodium dihydrogen phosphate (30 mg, 0.19 mmol) in water (1,5 mL). Under ice cooling, sodium chlorite (127 mg, 1.41 mmol) in water (1.5 mL) was added, and the solution was stirred at room temperature for 17 hrs. The mixture was diluted with a sodium hydrogen carbonate solution and washed with dichloromethane. The alkaline aqueous layer was collected, acidified with 10% hydrochloric acid, and extracted with dichloromethane. The organic layer was washed with brine, and dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo* the residue was purified by chromatography on a silica gel column to afford the corresponding acids **15a** and **1**.

8-Chloro-5-methoxy-2,7-dimethyl-2-(4-methylpent-3-enyl)-2*H*-chromene-6-carboxylic Acid (**15a**).

This compound was obtained in 71% yield as a colorless oil eluted with hexane-ethyl acetate (9:1); ir (liquid film): ν 1699 cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.47 (s, 3H), 1.57 (br s, 3H), 1.66 (br s, 3H), 1.68-1.95 (m, 2H), 2.10-2.16 (m, 2H), 2.46 (s, 3H), 3.84 (s, 3H), 5.08-5.12 (m, 1H), 5.65-5.68 (d, *J* = 10 Hz, 1H), 6.55-6.58 ppm (d, *J* = 10 Hz, 1H); ms (EI): m/z 350 and 352 (M^+), 267 and 269 (M^+-C_6H_{11}).

8-Chloro-5-hydroxy-2,7-dimethyl-2-(4-methylpent-3-enyl)-2*H*-chromene-6-carboxylic Acid (**1**).

This compound was obtained in 43% yield as colorless crystals eluted with hexane-ethyl acetate (85:15); ir (liquid film): ν 1684 cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.47 (s, 3H), 1.57 (br s, 3H), 1.65 (d, *J* = 1 Hz, 3H), 1.68-1.84 (m, 2H), 2.10-2.16 (m, 2H), 2.68 (s, 3H), 5.08-5.12 (m, 1H), 5.53-5.55 (d, *J* = 10 Hz, 1H), 6.73-6.75 (d, *J* = 10 Hz, 1H), 11.56 ppm (s, 1H); ms (EI): m/z 336 (M^+), 292 (M^+-CO_2), 253 (M^+-C_6H_{11}), 235 (M^+-C_6H_{11}-H_2O), 209 (M^+-C_6H_{11}-CO_2). Hrms. Calcd for $C_{18}H_{21}ClO_4$: M 336.0889. Found: M^+: 336.1128.

Formylation of 2*H*-Chromene-2-acetate **4** and 2*H*-Chromene-2-pronionate **24**.

Under ice cooling, to dry *N,N*-dimethylformamide (0.40 mL, 5.0 mmol) was added phosphoryl chloride (0.48 mL, 5.0 mmol), and the mixture was stirred at room temperature for 20 min, and then heated to 60 °C. To the heated Vilsmeier mixture was added 2*H*-chromene-2-acetate **4** or 2*H*-chromene-2-propionate **24** (0.50 mmol), and the mixture was stirred at 70-80 °C for 18 hrs. After cooling, the mixture was treated with sodium carbonate solution (1.30 g in 12 mL H_2O), stirred at 50 °C for 1 hr, and extracted with dichloromethane. The organic layer was washed with a saturated sodium hydrogen carbonate solution and brine, and dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo* the residue was purified by chromatography on a silica gel column to afford the corresponding aldehyde. Starting material **4** (36 mg, 22%) was recovered, and a mixture of 6-carbaldehyde **8** and 3-carbaldehyde **9** was obtained. After preparative TLC with hexane-ethyl acetate (8:2), the mixture of carbaldehydes gave pure **8** and **9**. Formylation of **24** gave **29a**.

Methyl 8-Chloro-6-formyl-5-methoxy-2,7-dimethyl-2*H*-chromene-2-acetate (**8**).

This compound was obtained as colorless crystals; 27% yield (calcd. yield 35% based on the reacted **4**); mp 119-121 °C; ir (KBr disk): ν 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.66 (s, 3H), 2.66 (s, 3H), 2.79 (s, 2H), 3.66 (s, 3H), 3.85 (s, 3H), 5.87 (d, *J* = 10 Hz, 1H), 6.64 (d, *J* = 10 Hz, 1H), 10.36 ppm (s, 1H); ms (EI): m/z 324 and 326 (M^+), 309 and 311 (M^+-CH_3), 251 and 253 (M^+-$CH_2CO_2CH_3$).

Methyl 8-Chloro-3-formyl-5-methoxy-2,7-dimethyl-2*H*-chromene-2-acetate (**9**).

This compound was obtained as a colorless oil in 12% yield (calcd. yield 15% based on the reacted **4**); ^1H nmr ($CDCl_3$, 400

MHz): δ 1.62 (s, 3H), 2.67 (s, 3H), 2.75 (s, 2H), 3.66 (s, 3H), 3.85 (s, 3H), 6.32 (s, 1H), 7.52 (s, 1H), 9.46 ppm (s, 1H).

Methyl 8-Formyl-5-methoxy-2,6-dimethyl-2*H*-chromene-2-propanoate (**29a**).

This compound was obtained as a pale yellow oil eluted with hexane-ethyl acetate (8:2); 68% yield; ir (liquid film): ν 1738, 1681 cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.46 (s, 3H), 1.90-2.20 (m, 2H), 2.21 (s, 3H), 2.30-2.50 (m, 2H), 3.65 (s, 3H), 3.78 (s, 3H), 5.63 (d, *J* = 10 Hz, 1H), 6.67 (d, *J* = 10 Hz, 1H), 7.50 (s, 1H), 10.35 ppm (s, 1H); ms (EI): m/z 304 (M^+), 289 (M^+-CH_3), 217 (M^+-CH_2CH_2CN). Hrms. Calcd for $C_{17}H_{20}O_5$: M 304.131. Found: M^+ 304.126.

Oxidation of **29a** with Sodium Chlorite.

To a solution of aldehyde **29a** (136 mg, 0.500 mmol) in dimethylsulfoxide (7 mL) was added a solution of sodium dihydrogen phosphate (30 mg, 0.19 mmol) in water (1,5 mL). Under ice cooling, sodium chlorite (127 mg, 1.41 mmol) in water (1.5 mL) was added, and the solution was stirred at room temperature for 17 hrs. The mixture was alkalified with a sodium hydrogen carbonate solution and washed with dichloromethane. The alkaline aqueous layer was collected, acidified with 10% hydrochloric acid, and extracted with dichloromethane. The organic layer was washed with brine, and dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo* the residue was purified by chromatography on a silica gel column to afford corresponding acid 5-methoxy-2-(2-methoxycarbonyl)ethyl-2,6-dimethyl-2*H*-chromene-8-carboxylic acid (**29b**); a pale yellow oil eluted with hexane-ethyl acetate (7:3); 97%; ir (liquid film): ν 2608-3296, 1737 cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.53 (s, 3H), 2.20-2.30 (m, 2H), 2.24 (s, 3H), 2.30-2.60 (m, 2H), 3.66 (s, 3H), 3.79 (s, 3H), 5.67 (d, *J* = 10 Hz, 1H), 6.72 (d, *J* = 10 Hz, 1H), 7.83 ppm (s, 1H); ms (EI): m/z 320 (M^+), 305 (M^+-CH_3), 233 (M^+-$CH_2CH_2CO_2CH_3$).

Anal. Calcd. for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.51; H, 6.33.

Carboxamidation of **29b** to **29d**.

To a solution of carboxylic acid **29b** (0.300 mmol) in dry benzene (5 mL) was added a solution of thionyl chloride (0.043 mL, 0.60 mmol) in dry benzene (5 mL), and the mixture was refluxed for 1 hr. After removal of the benzene and the excess thionyl chloride, the residual crude acid chloride **29c** was diluted with dry benzene (5 mL) and stirred with a solution of diethylamine (66 mg, 0.90 mmol) in dry benzene (10 mL) at room temperature for 1 hr. The mixture was treated with sodium hydrogen carbonate solution, and extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo*, the residue was purified by chromatography on a silica gel column to afford *N,N*-diethyl-5-methoxy-2-(2-methoxycarbonyl)ethyl-2,6-dimethyl-2*H*-chromene-8-carboxamide (**25**); a pale yellow oil eluted with hexane-ethyl acetate (7:3); 87%; ir (liquid film): ν 1739, 1633 cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.05 (t, *J* = 7 Hz, 3H), 1.23 (t, *J* = 7 Hz, 3H), 1.36 (s, 3H), 2.04 (m, 2H), 2.18 (s, 3H), 2.43 (m, 2H), 3.21 (m, 2H), 3.64 (s, 3H), 3.72 (s, 3H), 5.58 (d, *J* = 10 Hz, 1H), 6.65 (d, *J* = 10 Hz, 1H), 6.86 ppm (s, 1H); ms (EI): m/z 375 (M^+), 360 (M^+-CH_3), 287 (M^+-$CH_2CH_2CO_2CH_3$).

Anal. Calcd. for $C_{16}H_{29}NO_5$: C, 67.18; H, 7.79; N, 3.73. Found: C, 66.94; H, 7.55; N, 3.57.

Patterson Conversion of **25** to Mycochromenic Acid **2**.

Under an argon atmosphere, a solution of tetramethylethylenediamine (88.5 μL, 0.589 mmol) and 1.0 *M sec*-butyl lithium cyclohexane solution (78.9 μL, 0.586 mmol) in dry THF (1.67 mL) was cooled to –90 °C. A solution of **25** (100 mg, 0.266 mmol) in dry tetrahydrofuran (1.13 mL) was added cautiously to the cooled *sec*-butyl lithium solution, and the mixture was stirred for 1 hr at the same temperature. A solution of *N,N*-dimethylformamide (46.8 mg, 0.586 mmol) in dry tetrahydrofuran (0.6 mL) was added to the mixture, which was allowed to warm to –30 °C and stirred for 1 hr at that temperature. After quenching with ice-water, the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and then dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo*, the residue was purified by chromatography on a silica gel column to afford the crude 7-carbaldehyde (22 mg). To a solution of this aldehyde in ethanol (0.1 mL) was added sodium borohydride (2.00 mg, 5.03 μmol), and the mixture was stirred at room temperature for 24 hrs. After quenching the excess amount of sodium borohydride with acetic acid for 1 hr, the mixture was poured onto saturated aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo* the residue was purified on a silica gel column to afford the methyl ester **34** (14 mg); a colorless oil eluted with hexane-ethyl acetate (95:5); ir (liquid film): ν 1766, 1739 cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.50 (s, 3H), 1.90-2.20 (m, 2H), 2.11 (s, 3H), 2.30-2.70 (m, 2H), 3.65 (s, 3H), 3.78 (s, 3H), 5.09 (s, 2H), 5.62 (d, *J* = 10 Hz, 1H), 6.63 ppm (d, *J* = 10 Hz, 1H); ms (EI): m/z 332 (M^+), 245 (M^+-$CH_2CH_2CO_2CH_3$).

To a solution of methyl ester **34** (14 mg) in methanol (5 mL) and water (5 mL) was added lithium hydroxide monohydrate (3.90 mg, 92.7 μmol), and the mixture was stirred at room temperature for 2 hrs. The resulting mixture was diluted with a saturated sodium hydrogen carbonate solution and washed with ethyl ether. The alkaline aqueous layer was collected, acidified with 10% hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo* the residue afforded pure mycochromenic acid **2** (12 mg) without further purification.

Mycochromenic Acid **2** was obtained as colorless crystals; 14% (from **25**); mp 162-163 °C; ir (KBr disk): ν 1744, 1717 cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.52 (s, 3H), 2.05-2.17 (m, 2H), 2.11 (s, 3H), 2.50-2.70 (m, 2H), 3.78 (s, 3H), 5.10 (s, 2H), 5.62 (d, *J* = 10 Hz, 1H), 6.64 ppm (d, *J* = 10 Hz, 1H); ^{13}C nmr ($CDCl_3$, 400 MHz): δ 10.9, 26.3, 29.7, 35.9, 61.7, 68.4, 79.2, 108.4, 114.7, 116.3, 117.8, 128.9, 147.8 159.5, 168.9 ppm; ms (EI): m/z 318 (M^+), 245 (M^+-$CH_2CH_2CO_2H$).

Side-Chain Conversion of **32c** to Mycochromenic Acid **2**.

Deprotection.

To a solution of pyranophthalide **32c** (53 mg, 0.15 mmol) in methanol (3 mL), was added a catalytic amount of concentrated hydrochloric acid, and the mixture was refluxed for 3 hrs. After cooling, the mixture was concentrated *in vacuo*, and the residue was diluted with ethyl acetate. The ethyl acetate layer was washed with a saturated sodium hydrogen carbonate solution and brine, and dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo*, the residue was purified by chromatography

on a silica gel column to afford the corresponding alcohol, 8-(3-hydroxypropyl)-5-methoxy-4,8-dimethyl-3,8-dihydro-1-furo-[3,4-*h*]chromenone **32b** (46 mg); colorless crystals eluted with hexane-ethylacetate (7:3); mp 125-126°C; 99%; ir (KBr disk): ν 3534, 1750 cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.50 (s, 3H), 1.72-1.94 (m, 4H), 2.11 (s, 3H), 3.61-3.73 (m, 2H), 3.79 (s, 3H), 5.10 (s, 2H), 5.63-5.66 (d, *J* = 10 Hz, 1H), 6.60-6.62 ppm (d, *J* = 10 Hz, 1H); ms (EI): m/z 304 (M^+), 289 (M^+-CH_3)., 245 (M^+-$CH_2CH_2CH_2OH$), 230 (M^+-$CH_2CH_2CH_2OH$-CH_3).

Pyridinium Dichromate Oxidation.

A solution of alcohol **32b** (34 mg, 0.11 mmol) and pyridinium dichromate (61 mg, 0.22 mmol) in dichloromethane (1 mL) was stirred at room temperature for 24 hrs. The mixture was filtered and the residue was washed with ethyl acetate. The filtrate was concentrated *in vacuo*, and the new residue was passed through a short silica gel column to remove the inorganic precipitates and washed with ethyl acetate. The ethyl acetate solution was washed with 10% hydrochloric acid, a saturated sodium hydrogen carbonate solution, and brine, and dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo*, the residue was purified by chromatography on a silica gel column. Starting material **32b** (11mg) was recovred, and the corresponding aldehyde, 5-methoxy-4,8-dimethyl-1-oxo-3,8-dihydrofuro[3,4-*h*]chromene-8-propioaldehyde **33** (10 mg) was obtained.

3,8-Dihydro-5-methoxy-4,8-dimethyl-1-oxofuro[3,4-*h*]chromen-one-8-propioaldehyde **33**.

This compound was obtained as colorless crystals in 30% yield (calcd. yield 44% based on the reacted **32b**); ir (KBr disk): ν 1763 cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz): δ 1.43 (s, 3H), 2.04 (s, 3H), 2.00-2.08 (m, 2H), 2.61-2.66 (m, 2H), 3.72 (s, 3H), 5.03 (s, 2H), 5.54-5.57 (d, *J* = 10 Hz, 1H), 6.65-6.67 (d, *J* = 10 Hz, 1H), 9.73 ppm (s, 1H).

Silver Oxide Oxidation.

To a solution of sodium hydroxide (5.3 mg, 0.13 mmol) in water (0.2 mL) was added a solution of silver nitrate (11 mg, 66 μmol) in water (0.2 mL). A solution of aldehyde **33** (10 mg, 33 μmmol) in ethanol (0.3 mL) was added to the silver oxide suspension, and the mixture was refluxed for 2 hrs. The mixture was been filtered to remove the silver and washed with hot water and ethyl acetate. The filtrate was acidified with 10% hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer was washed with brine, and dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo*, the residue was purified by chromatography on a silica gel column to afford mycochromenic acid **2** (6 mg).

Mycochromenic acid, thus obtained, was identical with the natural mycochromenic acid and that synthesized by Patterson's method

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