

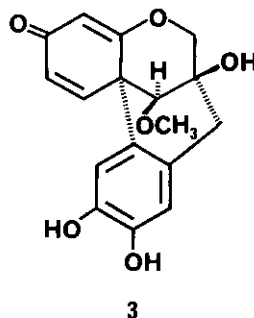
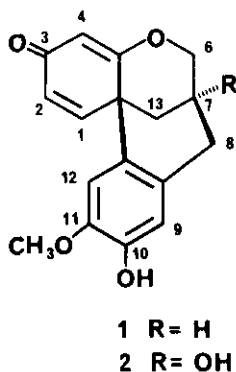
BIOMIMETIC TOTAL SYNTHESIS OF DRACAENONE DERIVATIVES¹Gábor Blaskó² and Geoffrey A. Cordell*

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Abstract — (±)-10-Hydroxy-11-methoxy-dracaenone (1) and (±)-7,10-dihydroxy-11-methoxy-dracaenone (2) were synthesized by phenolic oxidative coupling from the homoisoflavan derivatives 6 and 13, respectively.

INTRODUCTION

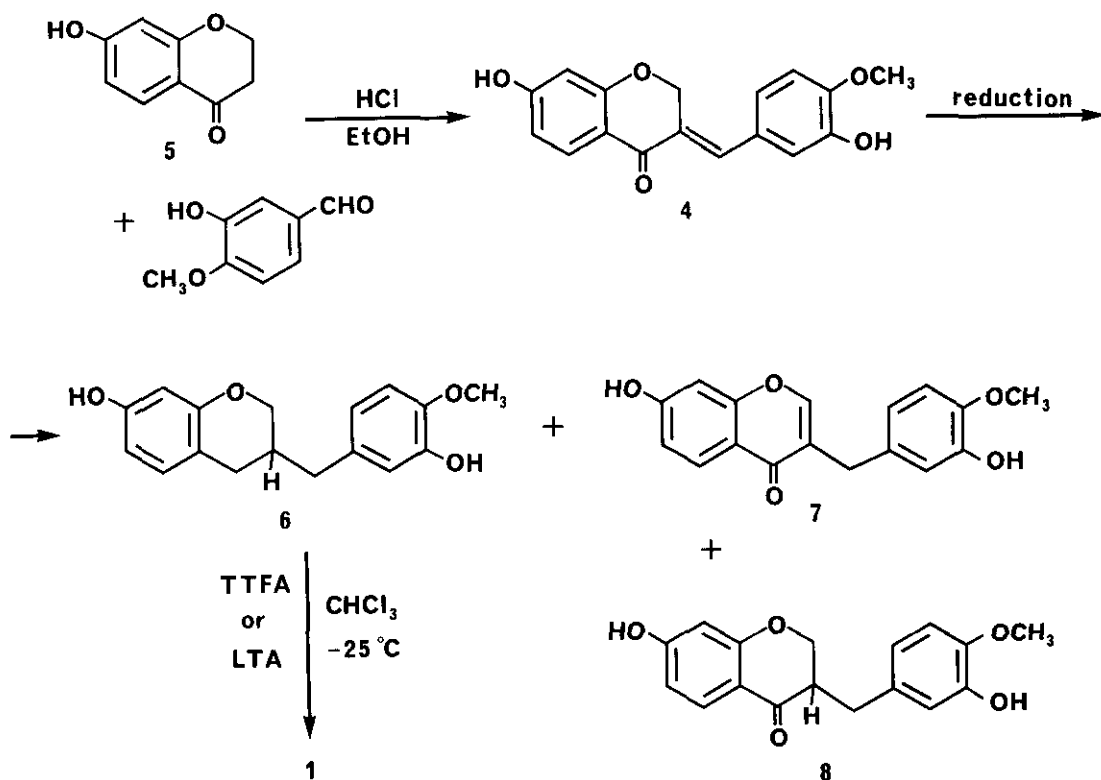
In a previous paper³ we described the isolation and structure determination of two representatives, 1 and 2, of a new class of cyclized homoisoflavan derivatives. Together with caesalpin J (3) from *Caesalpinia sappan*⁴ these compounds constitute the first examples of the apparent phenolic coupling of a 7,3'-dihydroxy-homoisoflavan system to a tetracyclic skeleton, to which we have given the name dracaenone⁵. It was reasoned that these isolates could be produced biomimetically via phenolic oxidative coupling of an appropriately substituted homoisoflavan. We report here on the successful realization of this goal, i.e. the synthesis, in racemic form, of the two isolates from *Dracaena loureiri* (Agavaceae); 10-hydroxy-11-methoxy-dracaenone (1) and 7,10-dihydroxy-11-methoxy-dracaenone (2).



DISCUSSION

In order to synthesize the range of functionality displayed by the isolates 1 and 2, benzalchromanone 4 appeared to be an appropriate intermediate from which both of the target natural products could be achieved. The starting material for the synthesis of 4, 7-hydroxychromanone (5), was prepared according to a literature procedure⁶ through the condensation of resorcinol and 3-chloropropionyl chloride in nitrobenzene in the presence of AlCl_3 . Condensation of 5 with isovanillin in ethanol saturated with HCl gas afforded benzalchromanone 4 in 65 % yield, which on the basis of nmr evidence was indicated to be a mixture of the *E*- and *Z*-isomers in the ratio of 95:5, respectively, which subsequently were separated by column chromatography.

Transfer hydrogenation of 4 in 98 % formic acid at 80 °C on the presence of $\text{Pd}(\text{C})$ resulted in three products. Chromatographic separation on silica gel led to the target homoisoflavan 6 in 42 % yield, together with lesser amounts (20 % yield of each) of the homoisoflavone 7 and the homois-



Scheme 1. Synthesis of (±)-10-Hydroxy-11-methoxy-dracaenone (1)

flavanone 8. An improved yield of 6 (64 %) was obtained through catalytic hydrogenation over Pd(C) in 20 % HCl gas/EtOH at atmospheric pressure. In this case, compound 8 was obtained in only 10 % yield together with traces of 7. Characteristic ^1H -nmr data of compounds 4, 6-8 are presented in Table 1.

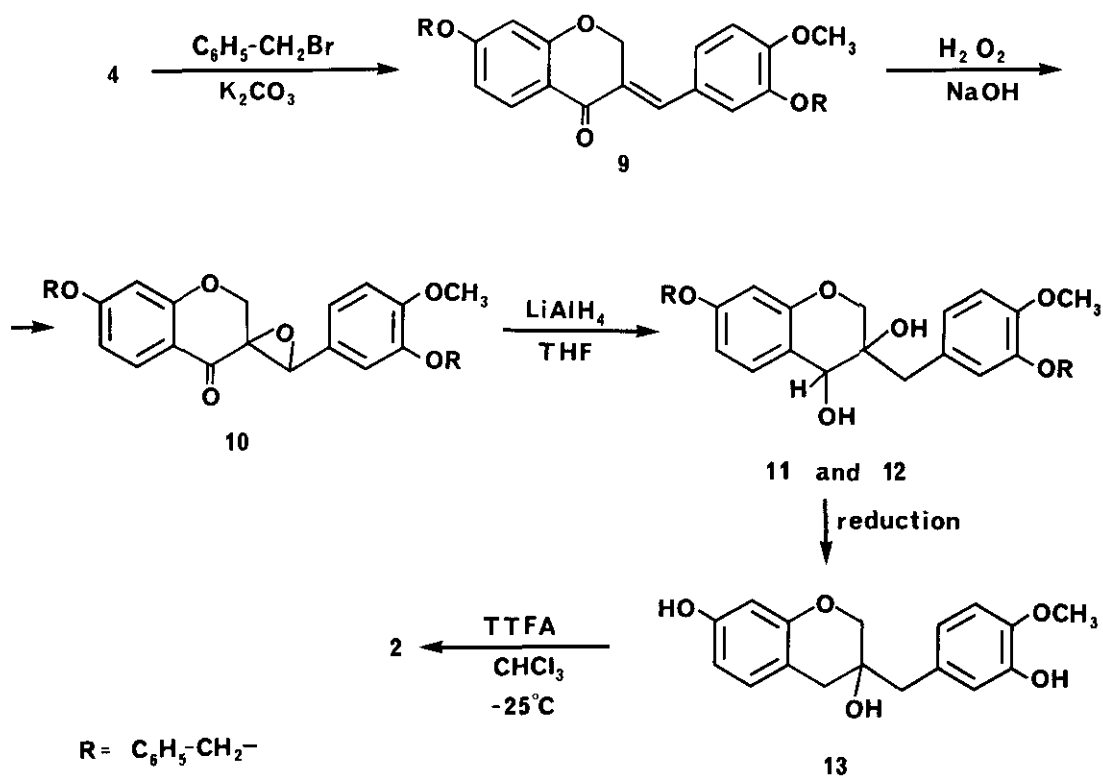
Compound 6 is appropriately substituted for para-para phenolic oxidative coupling in order to obtain 10-hydroxy-11-methoxy-dracaenone (1). Two reagents have thus far been utilized to perform this reaction. The appropriate para-para coupling was achieved in 24 % yield with lead tetraacetate (LTA) in dry chloroform in the presence of 3 mole equivalent of trichloroacetic acid⁷

TABLE 1. ^1H -NMR DATA OF COMPOUNDS 4, 6-8^a

PROTON	COMPOUND				
	<u>E-4</u>	<u>Z-4</u>	<u>6</u>	<u>7</u>	<u>8</u>
2	5.36 s	5.00s	3.69 dd (10.2) (2.0)	8.12 s	4.09 dd (11.2) (9.3)
	-	-	4.04 dd (10.2) (2.0)		4.29 dd (11.2) (4.8)
3	-	-	2.10 m		2.84 m
4	-	-	2.31 dd (15.5)	-	-
			2.57 dd (15.5) (4.5)		
5	7.75 d (9.0)	7.31 d (9.0)	6.77 d (8.4)	7.90 d (9.0)	7.66 d (9.0)
6	6.56 dd (9.0) (2.0)	6.54 dd (9.0) (2.0)	6.27 dd (8.4) (2.0)	6.92 dd (9.0) (2.5)	6.52 dd (9.0) (2.6)
8	6.34 d (2.0)	6.35 d (2.0)	6.16 d (2.0)	6.84 d (2.5)	6.32 d (2.6)
9	7.56 s	7.59 s	2.38 dd (14.0) (7.8)	3.55 s	2.51 dd (13.6) (9.8)
			2.47 dd (14.0) (6.5)		2.97 dd (13.6) (4.8)
2'	6.87 s	6.92 s	6.65 d (2.0)	6.74 d (2.0)	6.67 d (2.0)
5'	6.88 d (8.7)	6.94 d (8.5)	6.82 d (8.5)	6.80 d (7.5)	6.83 d (8.5)
6'	7.03 d (8.7)	7.02 d (8.6)	6.57 dd (8.5) (2.0)	6.67 dd (7.5) (2.0)	6.60 dd (8.5) (2.0)
OCH ₃	3.84 s	3.81 s	3.74 s	3.72 s	3.74 s
OH	9.31 s	9.11 s	8.87 s	8.84 s	8.90 s
OH	10.66 s	10.63 s	9.15 s	10.77 s	10.58 s

^a All spectra were recorded in DMSO-d₆. Chemical shifts (δ) are given in ppm using TMS as internal standard. Coupling constants are given in Hz in parentheses. The assignments of the signals were fully supported by COSY experiments.

at -25°C , but an improved yield (37 %) of 1 was obtained with thallium tristrifluoroacetate (TTFA)⁸ in dry chloroform at -25°C . Synthetic 1 was identical in every physical and spectroscopic detail (co-tlc, uv, ir, ^1H -nmr, ^{13}C -nmr, ms) with natural 1³, except for optical rotation. With the synthesis of $(\pm)$ -1 in hand, attention focused on the synthesis of the corresponding 7-hydroxy derivative, 2. Benzalchromanone 4 was protected with benzyl bromide in refluxing methyl ethyl ketone in the presence of K_2CO_3 to give 9 in 92% yield. Epoxidation of 9 with 30% H_2O_2 in acetone-methanol (4:1) in the presence of 2N NaOH afforded 10 in 86% yield, and reduction of the epoxide with LiAlH_4 in dry THF gave, in 90% yield, a mixture of the *cis* and *trans* dihydroxychromans 11 and 12 in the ratio of 3:2. Either prior to, or following, separation, the isomeric dihydroxychromans 11 and 12 were subjected to catalytic hydrogenation over $\text{Pd}(\text{C})$ in ethanol in the presence of a catalytic amount of HCl at atmospheric pressure to afford the 3-hydroxy-homoisoflavan derivative 13 in 72% yield. As anticipated, debenzylation also occurred



Scheme 2. Synthesis of $(\pm)$ -7,10-Dihydroxy-11-methoxy-draceanone (2)

under these conditions. $^1\text{H-Nmr}$ data of compounds 9-13 are shown in Table 2. Phenolic oxidative coupling of 13 with thallium tristrifluoroacetate in dry chloroform at -25°C gave (+)-7,10-dihydroxy-11-methoxy-dracaenone (2) in 12% yield, identical in every respect with natural 2, except for optical rotation.

Thus, the total synthesis of the new cyclized homoisoflavan derivatives 1 and 2 isolated from *Dracaena loureiri* has been achieved. Contained within the biomimetic route, and utilized as intermediates, are compounds such as homoisoflavans 6 and 13, homoisoflavone 7 and homoisoflavanone 8 which may subsequently also prove to be natural products.

TABLE 2. $^1\text{H-NMR}$ DATA OF COMPOUNDS 9-13

PROTON	COMPOUND				
	<u>9</u>	<u>10</u>	<u>11</u>	<u>12</u>	<u>13</u>
2	5.37 d (2.2)	4.08 d (12.1) 4.58 d (12.1)	3.79 d (12.2) 4.00 d (12.2)	3.62 d (12.8) 3.81 d (12.8)	3.90 d (10.5) 4.12 d (10.5)
4	-	-	4.02 s	4.24 d (5.0)	2.41 d (16.0) 2.62 (16.0)
5	7.82 d (8.8)	7.77 d (8.7)	7.24 d (8.2)	7.16 d (9.0)	6.70 d (8.5)
6	6.78 dd (8.8) (1.7)	6.81 dd (8.7) (1.6)	6.58 dd (8.2) (2.4)	6.61 dd (9.0) (2.4)	6.41 dd (8.5) (2.0)
8	6.65 d (1.7)	6.65 d (1.6)	6.49 d (2.4)	6.47 d (2.4)	6.30 d (2.0)
9	7.65 s	4.48 s	2.66 d (13.5) 2.93 d (13.5)	2.66 d (14.0) 2.71 d (14.0)	2.48 d (14.0) 2.59 d (14.0)
2'	7.12 d (2.0)	7.05 d (1.4)	6.94 s	6.77 d (2.0)	6.58 d (1.8)
5'	7.10 d (8.7)	7.04 d (8.7)	7.05 d (8.5)	6.81 d (8.5)	6.85 d (8.5)
6'	7.03 dd (8.7) (2.0)	6.93 dd (8.7) (1.4)	6.87 d (8.5)	6.74 dd (8.5) (2.0)	6.48 dd (8.5) (1.8)
OCH ₃	3.84 s	3.79 s	3.89 s	3.85 s	3.87 s
OCH ₂	5.16 s	5.09 s	5.02 s	5.01 s	-
OCH ₂	5.20 s	5.20 s	5.21 d (9.1)	5.13 s	-
2xC ₆ H ₅	7.3 - 7.50 m	7.33 - 7.45 m	7.30 - 7.45 m	7.30 - 7.45 m	-

^a Spectra of compounds 9, 10, 13 were recorded in DMSO- d_6 , while compounds 11 and 12 were measured in CDCl_3 solution. Chemical shifts (δ) are given in ppm using TMS as internal standard. Coupling constants are given in Hz in parentheses. The assignments of the signals were fully supported by COSY experiments.

EXPERIMENTAL

Melting points were determined on a Kofler-type hot-stage apparatus and are uncorrected. Preparative column chromatography was performed on Silica gel 60 (70-230 mesh) (E. Merck). Thin-layer chromatography was performed on Silica gel GHLF uniplates (Analtech Inc.). $^1\text{H-Nmr}$ spectra were obtained on a Varian XL-300 spectrometer operating at 300 MHz. For the homonuclear COSY spectra the standard Varian pulse program was used. All compounds gave satisfactory mass spectra (not reported), which were recorded on a Varian MAT 112S double focusing mass spectrometer operating at 80 eV.

7-Hydroxy-3-(3'-hydroxy-4'-methoxybenzylidene)-chroman-4-ones (E-4 and Z-4).

7-Hydroxychromanone (5)⁶ (3.28 g, 0.02 mol) and isovanillin (3.34 g, 0.022 mol) were dissolved in abs. EtOH (40 ml). The solution was saturated with HCl gas while its temperature was maintained at 30-40 °C with external cooling. The reaction mixture was kept at room temperature overnight, then poured into cold water (300 ml). The crude mixture was filtered and dried. Separation by column chromatography using CHCl_3 -MeOH (100:2) as eluent afforded Z-4 (0.19 g, 3%, mp. 193-194 °C) and E-4 (3.68 g, 62%, mp 221-222 °C).

(+)-7-Hydroxy-3-(3'-hydroxy-4'-methoxybenzyl)chroman (6),

7,3'-Dihydroxy-4'-methoxyhomo-isoflavone (7) and

(+)-7,3'-Dihydroxy-4'-methoxy-homoisoflavanone (8).

A, A solution of 4 (1.5 g, 5.0 mmol) in 98% formic acid (40 ml) was added under nitrogen atmosphere to a suspension of Pd(C) catalyst (0.5 g) in 98% formic acid (10 ml), and the reaction mixture kept at 80 °C for 4 h. After filtration, the reaction mixture was neutralized (pH 7) with saturated aqueous Na_2CO_3 solution and thoroughly extracted with CHCl_3 (3x70 ml). The organic layer was dried and evaporated. Separation of the reaction mixture by column chromatography using CHCl_3 -MeOH (100:2) as eluent gave (+)-6 (0.60 g, 42%, mp 133-135 °C), 7 (0.30 g, 20%, mp 196-197 °C) and (+)-8 (0.31 g, 20%, mp 157-158 °C).

B, Atmospheric hydrogenation of 4 (1.5 g, 5.0 mmol) in EtOH (50 ml) containing 20% HCl gas over Pd(C) catalyst (0.2 g) followed by the usual work up including separation by column chromatography, afforded (+)-6 (0.92 g, 64%) and (+)-8 (0.15 g, 10%).

(+)-10-Hydroxy-11-methoxy-dracaenone (1).

A, To a solution of the homoisoflavone 6 (200 mg, 0.7 mmol) in dry CHCl_3 (50 ml), trichloroacetic acid (410 mg, 2.53 mmol) and lead tetraacetate (370 mg, 0.84 mmol) were added at -25 °C, and the reaction mixture was maintained at this temperature for 8 h. After extraction with water (2x10 ml) the organic layer was dried and evaporated. Purification by column chromatography using CHCl_3 as eluent gave (+)-1 (48 mg, 24, mp 247-249 °C, lit. mp³ of (-)-1 263-265 °C).

B, Under similar reaction conditions as above, the oxidation of the homoisoflavan 6 (200 mg, 0.7 mmol) with thallium tris(trifluoroacetate) (460 mg, 0.85 mmol) gave ($\pm$)-1 (74 mg, 37%).

7-Benzylloxy-3-(3'-benzylloxy-4'-methoxybenzylidene)-chroman-4-one (9).

A mixture of compound 4 (4.0 g, 13.4 mmol), anhydrous K_2CO_3 (20 g, 0.14 mol) and benzyl bromide (4.2 ml, 36 mmol) was refluxed in methyl ethyl ketone (100 ml) for 24 h. After evaporation, $CHCl_3$ (200 ml) was added to the residue and the mixture extracted with water (2x30 ml). The organic layer was dried and evaporated to give 9 (5.88 g, 92%, mp 154-155 °C).

(\pm)-7-Benzylloxy-3,9-epoxy-3-(3'-benzylloxy-4-methoxybenzyl)-chroman-4-one (10).

To a stirred solution of 9 (1.5 g, 3.0 mmol) in acetone (100 ml) and MeOH (25 ml) 30% aqueous H_2O_2 solution (10 ml) and 2N NaOH (10 ml) were added and the reaction mixture kept at room temp. for 24 h. The precipitate was filtered, washed with water and dried to afford 10 (1.33 g, 86%, mp 112-113 °C), which did not require further purification.

(\pm)-7-Benzylloxy-3,4-dihydroxy-3-(3'-benzylloxy-4-methoxybenzyl)-chromans (11 and 12).

To a solution of 10 (1.0 g, 2.0 mmol) in freshly distilled THF (50 ml) $LiAlH_4$ (220 mg, 5.8 mmol) was added, and the reaction mixture refluxed for 4 h. After cooling, excess $LiAlH_4$ was decomposed with water (5 ml), the THF was removed by distillation and the residue was treated with $CHCl_3$ (100 ml). The resulting precipitate was removed by filtration and the washed with $CHCl_3$ (2x30 ml) and the combined organic layer was extracted with water (30 ml). The $CHCl_3$ layer was dried and evaporated to afford a mixture of 11 and 12 (0.91 g, 90%). For spectroscopic investigation the two isomers were separated by column chromatography using $CHCl_3$ -MeOH (100:1) as eluent.

(\pm)-3,7-Dihydroxy-3-(3'-hydroxy-4'-methoxybenzyl)-chroman (13).

Atmospheric hydrogenation of a mixture of 11 and 12 (0.8 g, 1.6 mmol) in EtOH (20 ml) over Pd(C) catalyst (0.1 g) in the presence of 3 drops of HCl/EtOH followed by the usual work up procedure including purification by column chromatography using $CHCl_3$ -MeOH (100:2) as eluent, resulted in ($\pm$)-13 (346 mg, 72%, mp 146-148 °C).

(\pm)-7,10-Dihydroxy-11-methoxy-dracaenone (2).

To a solution of the homoisoflavan 13 (180 mg, 0.6 mmol) in dry $CHCl_3$ (50 ml), thallium tris(trifluoroacetate) (400 mg, 0.74 mmol) was added at -25 °C, and the reaction mixture maintained at this temperature for 8 h. After extraction with water (15 ml), the organic phase was dried and evaporated. Purification by column chromatography using $CHCl_3$ -MeOH (100:1) as eluent afforded ($\pm$)-2 (21 mg, 12%).

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