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TOTAL SYNTHESIS OF (±)-11-Q-METHYL-CAESALPIN J AND ITS C-13 EPIMER

Gábor Blaskó[1] and Geoffrey A. Cordell*

Program for Collaborative Research in the Pharmaceutical Sciences,
College of Pharmacy, University of Illinois at Chicago,
Chicago, Illinois 60612, U.S.A.

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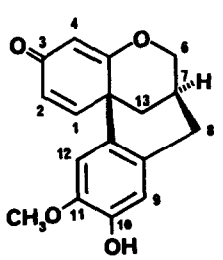
Summary: The biomimetic total syntheses of racemic 11-Q-methyl-caesalpin J (9) and 13-epi-11-Q-methyl-caesalpin J (10), via phenolic oxidative coupling of the accordingly substituted homoisoflavans 6 and 7, are described.

In a previous paper[2] we described the isolation and structure elucidation of two representatives of a new class of cyclized homoisoflavan derivatives, 10-hydroxy-11-methoxy-dracaenone (1) and 7,10-dihydroxy-11-methoxy-dracaenone (2), obtained from Dracaena loureiri Gagnep (Agavaceae). Together with caesalpin J (3), isolated from Caesalpinia sappan L. (Agavaceae)[3,4], these compounds constitute the first examples of the apparent phenolic oxidative coupling of a 7,3'-dihydroxy-homoisoflavan system to a tetracyclic skeleton to which we have given the name dracaenone[5].

Biomimetic phenolic oxidative coupling of appropriately substituted homoisoflavans led us to the first successful syntheses[6] of racemic 10-hydroxy-11-methoxy-dracaenone (1) and 7,10-dihydroxy-11-methoxy-dracaenone (2), respectively. As a continuation of our studies on the synthesis of cyclized homoisoflavans, we report here the total synthesis of 11-Q-methyl-caesalpin J (9) and its C-13 epimer (10) both of which possess an additional methoxy group at C-13 of the dracaenone skeleton.



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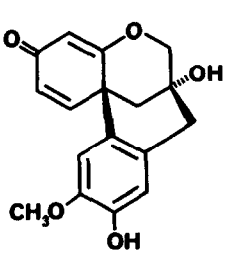

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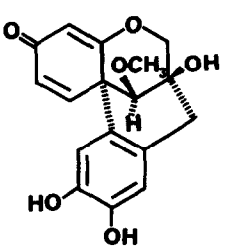

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In order to synthesize 11-Q-methyl-caesalpin J (9) we utilized the intermediate, 7,3'-dihydroxy-4'-methoxy-benzalchromanone, from which the syntheses of 1 and 2 had formerly been achieved[6]. Protection

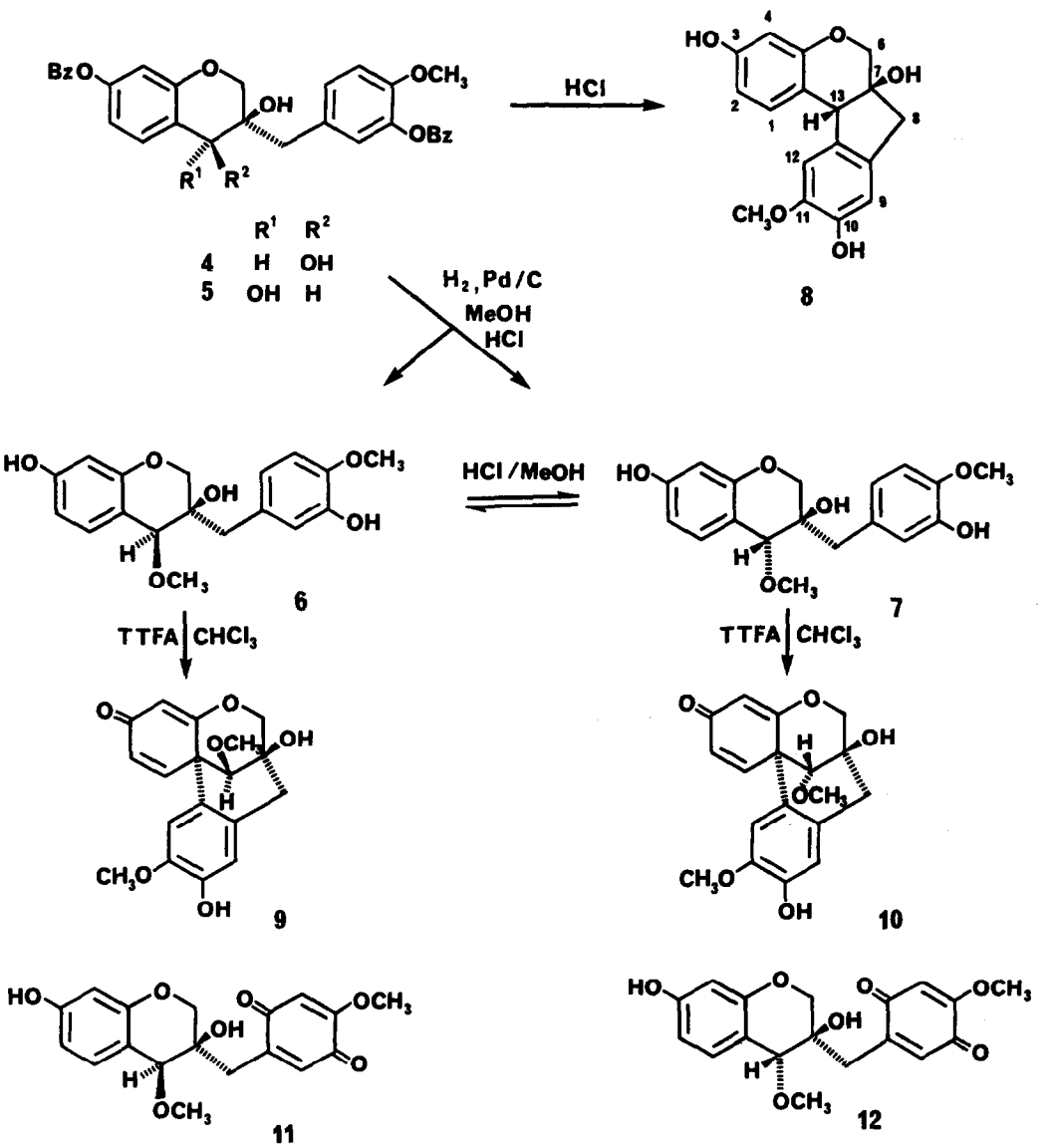
of the two phenolic hydroxy groups benzyl ethers and subsequent epoxidation of the C=C double bond with H_2O_2 and reduction of the epoxide with $LiAlH_4$ in dry THF gave, in 90% yield, a mixture of cis and trans dihydroxychromans **4** and **5** in the ratio of 2:3. Catalytic hydrogenation of **10** and **11** over Pd/C in MeOH containing 2% HCl gas afforded a complex reaction mixture, which, after separation, resulted in 3,7,3'-trihydroxy-4'-methoxy-homoisoflavan in 10% yield, two isomeric 3,7,3'-trihydroxy-4,4'-dimethoxy-homoisoflavans **6** and **7** in 26% and 39% yield, respectively, and 11-O-methyl-brazillin (**8**)[7] in 12% yield. Treatment of either **6** or **7** with methanol containing 2% HCl gas (or 5% tartaric acid in methanol) afforded the same 2:3 mixture of **6** and **7** suggesting an S_{N1} type solvolytic nucleophilic substitution of the 4-hydroxy group on the chromane nucleus to a methoxy substituent. Higher HCl gas concentrations in methanol (above 15%) or heating the reaction mixture uniformly afforded the cyclized product **8** probably due to a facile intramolecular electrophilic substitution reaction of the benzyl cation intermediate derived from either **6** or **7**. Determination of the relative stereochemistry of the 4-methoxy group on the trisubstituted chromane ring, however, proved to be rather difficult. In fact, it was not possible on compounds **6** and **7** due to their almost identical spectroscopic properties (Table 1). Stereochemical differentiation could, however, be achieved on the corresponding cyclized products **9** and **10** obtained by separate phenolic oxidative coupling of homoisoflavans **6** and **7**, respectively.

TABLE 1. ^1H- and ^{13}C-NMR Spectral Assignments of Homoisoflavan Derivatives **6**, **7**, **11** and **12**

	6		**7**		**11**		**12**	
C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C
2	3.52 (d, 10)	70.40	3.73 (d, 11)	69.28	3.83 (d, 11)	67.01	3.71 (d, 11)	68.09
	3.80 (d, 10)	-	3.94 (d, 11)		4.01 (d, 11)	-	3.90 (d, 11)	
3	-	67.56	-	68.76	-	69.57	-	69.61
4	3.63 (s)	79.24	3.45 (s)	76.03	3.33 (s)	78.19	3.31 (s)	77.21
4a	-	112.99	-	111.53	-	111.73	-	111.27
5	6.77 (d, 8)	133.12	6.82 (d, 8)	132.01	7.02 (d, 8)	131.99	6.99 (d, 8)	131.84
6	6.36 (dd, 8,2)	108.97	6.25 (dd, 8,2)	106.77	6.44 (dd, 8,2)	107.90	6.28 (dd, 8 2)	107.02
7	-	159.82	-	158.20		158.78	-	158.25
8	6.25 (d, 2)	103.39	6.17 (d, 2)	102.18	6.35 (d, 2.5)	102.21	6.15 (d, 2.5)	102.10
8a	-	154.93	-	154.53	-	157.24	-	157.98
9	2.43 (s)	n.a.	2.52 (d, 13)	n.a.	2.63 (d, 14)	32.46	2.62 (d, 14)	32.11
			2.74 (d, 13)		2.72 (d, 14)		2.77 (d, 14)	
1'	-	129.82	-	128.84	-	144.36	-	144.20
2'	6.61 (d, 2)	112.59	6.74 (d, 2)	111.62	6.66 (s)	133.02	6.68 (s)	133.13
3'	-	147.07	-	145.98	-	181.47	-	181.60
4'	-	146.63	-	145.65	-	153.20	-	153.12
5'	7.01 (d, 8)	118.87	6.91 (d, 8)	118.27	5.93 (s)	107.46	6.14 (s)	107.45
6'	6.42 (dd, 8,2)	122.11	6.63 (dd, 8,2)	121.33	-	186.73	-	186.95
OMe	3.29 (s)	57.64	3.22 (s)	55.58	3.41 (s)	56.84	3.33 (s)	56.27
OMe	3.73 (s)	56.58	3.74 (s)	55.19	3.82 (s)	56.22	3.79 (s)	55.58

Spectra were recorded in DMSO-d_6. Chemical shift values are given in ppm (δ) using TMS as internal standard. Coupling constants are given in Hz in parentheses. n.a.: hidden by solvent.

The oxidative cyclization was performed with thallium tristrifluoroacetate (TTFA)[6,8,9] in dry chloroform at -25°C. Oxidation of homoisoflavan 6 gave 11-O-methyl-caesalpin J (9) in 34% yield. From the reaction mixture, 12% unreacted starting material (6) and 15% non-cyclized p-quinone type side product 11 could also be isolated. On the other hand, oxidation of the isomeric homoisoflavan 7 afforded 13-epi-11-O-methyl-caesalpin J (10) and p-quinone 12 in 28% and 17% yields, respectively, in addition to 22% of the starting material 7 recovered from the reaction mixture. The ^1H-^1H COSY spectrum of 9 measured in CD_3OD exhibited a strong W coupling between 6-H_α and 13-H_α, supporting the β- (axial) orientation of the 13-methoxy group in 9. This coupling, however, was absent in the ^1H-^1H COSY spectrum of compound 10 measured in CD_3OD but was replaced by a W coupling between 8-H_α and 13-H_β establishing the α steric position of the 13-methoxy group in compound 10.



Determination of the relative steric position of the 13-methoxy group in the cyclized homoisoflavans 9 and 10 permitted retrospective determination of the relative stereochemistry in the parent homoisoflavans 6 and 7, respectively, assuming complete retention of the relative configuration of the C-4 stereo center during the cyclization reaction. It should be noted that no epimerization was observed when either 9 or 10 was treated with methanol containing 2% HCl gas. Complete ^{1}H- and ^{13}C-NMR assignments of 11-O-methyl-caesalpin J (9) and its C-13 epimer (10) are shown in Table 2.

TABLE 2. ^{1}H- and ^{13}C-NMR Spectral Assignments of 11-O-Methyl-caesalpin J (9) and its epimer 10

	9			10		
C	^{1}H[a]	^{1}H[b]	^{13}C[b]	^{1}H[a]	^{1}H[b]	^{13}C[b]
1	7.06 (d, 10)	7.04 (d, 10)	147.78	7.20 (d, 10)	7.07 (d, 10)	146.10
2	6.51 (dd, 10, 2)	6.41 (dd, 10, 2)	129.97	6.55 (dd, 10, 2)	6.48 (dd, 10, 2)	129.50
3	-	-	187.69	-	-	186.87
4	5.58 (d, 2)	5.47 (d, 2)	109.09	5.60 (d, 2)	5.52 (d, 2)	109.04
4a	-	-	174.58	-	-	174.48
6α	4.16 (d, 11)	4.02 (bs)	74.87	3.79 (dd, 11, 2)	3.72 (dd, 11, 2)	77.80
6β	4.10 (d, 11)			4.19 (d, 11)	4.13 (d, 11)	
7	-	-	67.94	-	-	69.25
8α	3.18 (d, 16)	3.13 (bs)	42.37	2.93 (d, 16)	2.88 (d, 16)	37.62
8β	3.32 (d, 16)			3.31 (d, 16)	3.17 (d, 16)	
9	6.62 (s)	6.61 (s)	115.24	6.63 (s)	6.59 (s)	115.45
10	-	-	146.79	-	-	146.29
11	-	-	146.17	-	-	145.77
12	6.40 (s)	6.31 (s)	109.74	6.39 (s)	6.29 (s)	109.92
12a	-	-	127.87	-	-	128.73
12b	-	-	52.13	-	-	51.35
13	3.86 (bs)	3.84 (s)	83.58	3.50 (s)	3.46 (s)	82.90
11-OMe	3.68 (s)	3.58 (s)	55.67	3.63 (s)	3.53 (s)	55.73
13-OMe	3.56 (s)	3.47 (s)	61.17	3.67 (s)	3.58 (s)	61.56

[a] Recorded in CD_3OD; [b] Recorded in DMSO-d_6

All of the compounds synthesized were evaluated in the P-388 and KB lymphocytic leukemia test systems *in vitro* according to established protocols[10,11]. Only homoisoflavan-quinone derivatives 11 and 12 exhibited cytotoxic activity. Compound 11 displayed an ED_{50} = 6.88 μg/ml against the KB and ED_{50} = 0.93 μg/ml against the P-388 test systems. Compound 12 was found to be inactive against the KB test, but showed ED_{50} = 3.6 μg/ml against the P-388 leukemia test system. ^{1}H- and ^{13}C-NMR assignments of homoisoflavan-quinones 11 and 12 are summarized in Table 1.

In summary, the total syntheses of (±)-11-O-methyl-caesalpin J (9) and its C-13 epimer 10 has been achieved via biomimetic phenolic oxidative coupling of homoisoflavans 6 and 7; compounds which may subsequently also prove to be natural products.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot-stage apparatus and are uncorrected. Preparative column chromatography was performed on Silica gel 60 (70-230 mesh) (E. Merck). Thin-layer chromatography (tlc) was performed on Silica gel GHLF Uniplates (Analtech Inc.). IR spectra were recorded by a Nicolet MX-1 interferometer. ^{1}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. ^{13}C-NMR spectra were measured at 90.8 MHz using a Nicolet NMC-360 spectrometer. Chemical shifts (δ) are reported in ppm using TMS as internal standard. All compounds synthesized gave satisfactory mass spectra (data are not reported) determined with a Varian MAT 112S double focusing mass spectrometer operating at 80 eV.

7-Hydroxy-3-(3'-hydroxy-4'-methoxybenzylidene)-chroman-4-one, 7-Benzyloxy-3,9-epoxy-3-(3'-benzyloxy-4-methoxybenzyl)-chroman-4-one and 7-Benzyloxy-3,4-dihydroxy-3-(3'-benzyloxy-4-methoxy-benzyl)-chromans (4) and (5).

Details on the preparation of these starting materials, together with their physical and spectroscopic properties, are described in Ref. 6.

3,7,3'-Trihydroxy-4,4'-dimethoxy-homoisoflavans 6 and 7.

Atmospheric hydrogenation of a mixture of 4 and 5 (1.2 g, 2.4 mmol) in MeOH (50 ml) containing 2% HCl gas over Pd(C) catalyst (0.2 g) followed by neutralization with NH_3 in MeOH and by the usual work up procedure, including purification by column chromatography using $CHCl_3$-MeOH (100:2) as eluent, afforded the following materials in order of elution;

(±)-6 (207 mg, 26%), mp: 134-135°C; $C_{18}H_{20}O_6$ (Found: C, 64.79; H, 6.09. Calc.: C, 65.04; H, 6.07); ^{1}H- and ^{13}C-NMR spectral data are shown in Table 1.

(±)-7 (310 mg, 39%), mp: 181-182°C; $C_{18}H_{20}O_6$ (Found: C, 65.01; H, 6.15. Calc.: C, 65.04; H, 6.07); ^{1}H- and ^{13}C-NMR spectral data are shown in Table 1.

(±)-3,7,3'-trihydroxy-4'-methoxy-homoisoflavan (72 mg, 10%), mp: 146-148°C; for spectral data see Ref. 6.

(±)-8 (86 mg, 12%), mp: 205-206°C.

Treatment of homoisoflavan 6 (20 mg, 0.06 mmol) with MeOH (2 ml) containing 2% HCl gas at room temperature for 6 h followed by preparative tlc afforded homoisoflavan 6 (7 mg, 35%) and its epimer 7 (11 mg, 55%). A similar ratio of products 6 and 7 was observed when homoisoflavan 7 was similarly treated with methanol containing either 2% HCl gas or 5% tartaric acid.

(±)-11-O-Methyl-brazilin (8).

A mixture of 6 and 7 (0.4 g, 1.2 mmol) was dissolved in MeOH (10 ml) containing 15% HCl gas and kept overnight at room temperature. Evaporation of the solvent in vacuo followed by crystallization from MeOH gave (±)-8 (314 mg, 87%), mp: 215-216°C; $C_{17}H_{16}O_5$ (Found: C, 67.97; H, 5.40. Calc.: C, 67.98; H, 5.37); ^{1}H-NMR (DMSO-d_6) δ 2.76 (1H, d, 16.5, 8-H_a), 2.87 (1H, d, 16.5, 8-H_b), 3.62 (1H, d, 11.3, 6-H_a), 3.84 (1H, d, 11.3, 6-H_b), 3.71 (3H, s, 11-OCH_3), 3.88 (1H, s, 13-H), 6.20 (1H, d, 2.5, 4-H), 6.41 (1H, dd, 8.5, 2.5, 2-H), 6.58 (1H, s, 12-H), 6.83 (1H, s, 9-H), and 7.25 (1H, d, 8.5, 1-H); ^{13}C-NMR (DMSO-d_6) δ 131.70 (C-1), 108.90 (C-2), 156.46 (C-3), 102.74 (C-4), 153.99 (C-4a), 76.45 (C-6), 69.55 (C-7), 41.84 (C-8), 131.91 (C-8a), 112.08 (C-9), 146.52 (C-10), 145.76 (C-11), 114.30 (C-12), 135.31 (C-12a), 49.94 (C-13), 114.34 (C-13a), and 55.90 (11-OCH_3).

(±)-11-O-Methyl-caesalpin J (9).

To a solution of the homoisoflavan **6** (200 mg, 0.6 mmol) in dry $CHCl_3$ (70 ml), thallium tristrifluoracetate (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 (20 ml), the organic phase was dried and evaporated. Separation of the crude reaction mixture by column chromatography using $CHCl_3$-MeOH (100:1) as eluent afforded:

(±)-**11** (31 mg, 15%), mp: 165-166°C; $C_{18}H_{18}O_7$ (Found: C, 62.77; H, 5.16. Calc.: C, 62.41; H, 5.24); ^{1}H- and ^{13}C-NMR spectral data are shown in **Table 1**.

(±)-**9** (67 mg, 34%), mp: 228-229°C; $C_{18}H_{18}O_6$ (Found: C, 65.62; H, 5.63. Calc.: C, 65.43; H, 5.50); ^{1}H- and ^{13}C-NMR spectral data are summarized in Table 2.

(±)-**6** (24 mg, 12%).

(±)-13-Epi-11-O-methyl-caesalpin J (10).

To a solution of the homoisoflavan **7** (100 mg, 0.3 mmol) in dry $CHCl_3$, thallium tristrifluoracetate (200 mg, 0.37 mmol) was added at -25°C, and the reaction mixture maintained at this temperature for 6 h. After extraction with water (10 ml), the organic phase was dried and evaporated. Separation of the crude reaction mixture by column chromatography using $CHCl_3$-MeOH (100:1) as eluent gave:

(±)-**12** (18 mg, 17%), amorphous; ^{1}H- and ^{13}C-NMR spectral data are shown in **Table 1**.

(±)-**10** (28 mg, 28%), mp: 214-216°C; $C_{18}H_{18}O_6$ (Found: C, 65.74; H, 5.68. Calc.: C, 65.43; H, 5.50); ^{1}H- and ^{13}C-NMR spectral data are summarized in Table 2.

(±)-**7** (22 mg, 22%).

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References and Notes

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