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Short Report

The First Synthesis of (±)-3,4-Dihydroxy-8,9-methylenedioxypterocarpan, an Antitumoral Agent and its Coumestan Derivative

Alcides J. M. da Silva, Chaquip D. Netto and Paulo R. R. Costa*

Núcleo de Pesquisas de Produtos Naturais, Centro de Ciências da Saúde, Bloco H, Universidade Federal do Rio de Janeiro, 21.941-590 Rio de Janeiro - RJ, Brazil

Apresentamos a primeira síntese do (±)-3,4-diidroxi-8,9-metilenodioxipterocarpano, um isoflavonóide natural que apresenta atividade antitumoral. A etapa chave envolveu uma arilação de Heck entre o 7,8-dibenziloxicromeno e o organomercurial derivado do sesamol, seguido de reação de desbenzilação. O aduto de Heck foi também empregado na síntese do correspondente derivado cumestano, utilizando DDQ como agente oxidante.

We report the first synthesis of (±)-3,4-dihydroxy-8,9-methylenedioxypterocarpan, a natural isoflavonoid that shows antitumoral activity. The key step involved the Heck reaction between the 7,8-dibenzyloxychromen and the organomercurial derived from sesamol, followed by debenzylation. The Heck adduct was also employed in the synthesis of the corresponding coumestan derivative, using DDQ as oxidant agent.

Keywords: isoflavonoids, pterocarpan, DDQ, antitumoral agents, coumestan

Introduction

A great number of naturally occurring biologically active flavonoids is described in the literature. In the area of antitumor drug discovery, some flavonoids derivatives (chalcones, flavones, isoflavones, rotenoids *etc*.) were shown to be active *in vitro* and *in vivo*.[1] At the present time, cancer claims the lives of more than seven million people worldwide on an annual basis. Thus, the development of new cancer treating drugs is a must.[2] In 1995, Wall *et al*. isolated three pterocarpans from *Petalostemon purpureus* (Figure 1).[3] Compound (+)6a*S*, 11a*S* -3,4-Dihydroxy-8,9-methylenedioxypterocarpan (**1**) was active in a standard *in vitro* DNA strand-scission assay, and presented cytotoxity toward KB tumor cell line (ED_{50} = 0.9 μg mL^{-1}). Pterocarpans (**2**) and maackiain (**3**) [(+)-6a*S*,11a*S*-4-hydroxy-3-methoxy-8,9-methylene-dioxypterocarpan] were found to be moderately active for KB cells (ED_{50} values of 4.0 μg mL^{-1} and 5.6 μg mL^{-1}, respectively), but inactive in the DNA strand-scission assay. Since these compounds have the same pterocarpan skeleton and differ only in the pattern of substitution in ring A, we believe that the cathecol moiety in compound **1** is important for antitumoral activity. The enantiomers of **1** e **2** were also previously isolated from plants,[4] while **3** has been isolated only as a racemate. [5]

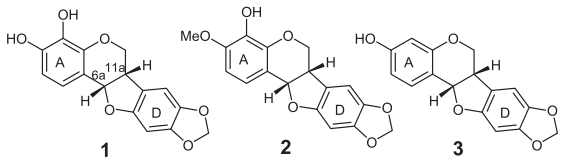


Figure 1. Natural pterocarpans.

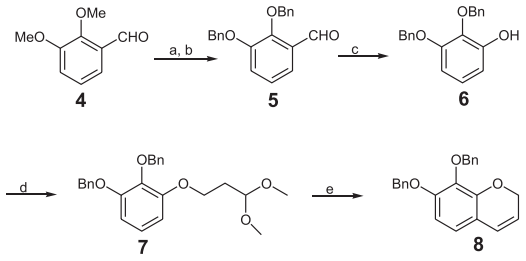
As part of a program aimed at synthesizing biologically active anticancer products,[6,7] we describe the first racemic synthesis of the natural product 3,4-dihydroxy-8,9-methylenedioxypterocarpan (**1**) and its derivative, 3,4-dihydroxy-8,9-methylenedioxycoumestan (**13**).

Results and Discussion

The key step[6,7] in our strategy to prepare compound **1** was the coupling of chromen **8** and the organomercurial **9** derived from sesamol.[8] The chromen was synthesized using 2,3-dimethoxybenzaldeyde (**4**) as starting material. Treatment of **4** with BBr_3 at –78 °C gave the cathecol derivative in an excellent yield.[9] This compound was bis-protected with the benzyl group leading to aldeyde **5**. The corresponding phenol **6** was prepared by Baeyer-Villiger

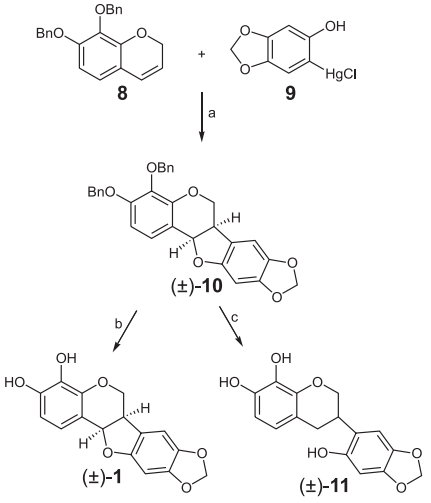
* e-mail: lqb@nppn.ufrj.br

oxidation using MCPBA. O-alkylation of the resulting phenol was acomplished by using 3-iodopropanal dimethylacetal, furnishing compound **7**. Cyclization of **7** in acid medium led to chromen **8** in good yield (Scheme 1).



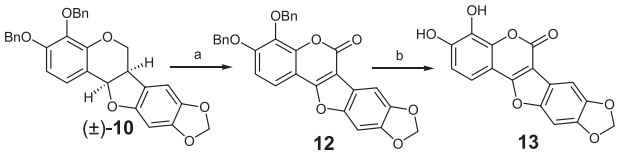
Scheme 1. Reagents and conditions: a) BBr_3, CH_2Cl_2, -78 °C, 95%; b) BnCl, K_2CO_3 , EtOH, Reflux, 60%; c) *m*CPBA, CH_2Cl_2, 90%; d) 3-iodo propanal dimethylacetal, KOH, THF, reflux; e) 20% aq. HCl, THF, rt, 70% (2 steps).

Compound **8** was allowed to react with **9** in the presence of lithium tetrachloropalladate II and acetone leading to *cis*-(±)-O–di-benzyl-pterocarpan **10**.[10] Finally, natural product **1** was obtained by hydrogenolysis of the benzyl groups using the catalytic amount of Pd-C (10% m/m) and all the spectroscopic data were similar to those observed in the natural product.[3] We also observed the clevage of the furan ring when an excess of Pd-C was used, to yield product **11**. (Scheme 2).



Scheme 2. Reagents and conditions: a) $PdCl_2$ / LiCl, acetone, 55%; b) H_2, Pd-C (10% m/m), 3 atm, acetone, 100%; c) H_2, Pd-C (excess), 3 atm, acetone, 60%.

Oxidation of the 3,4-di-O-benzyl-pterocarpan **10** with DDQ in THF at room temperature for 4 h led to the intermediate 3,4-di-O-benzylated coumestan **12**, which precipitated out of the solution, and was collected by filtration. The presence of the conjugated system in **12** was clearly showed by the batochromic shift observed in the UV spectrum.[11] The synthesis of coumestan **13** was acomplished by hydrogenolysis of the protecting benzyl groups in **12** (Scheme 3).



Scheme 3. Reagents and conditions: a) DDQ 2 mmol in THF; rt; b) H_2, Pd-C (10% m/m), 3 atm, acetone, 70%.

In summary, we have, for the first time, prepared natural pterocarpan **1** and its derivatives **11** and **13** in good overall yields. These compounds will be evaluated as antitumoral agents.

Experimental

General

Melting points were measured with a Fisher-Johns (Fisher Scientific Co) apparatus. Flash chromatography was performed using Merck silica gel 60, 230-400 mesh and Merck silica 60F 254 sheets. ^{1}H NMR and ^{13}C NMR were recorded on a Varian Gemini-200 instrument.

*cis-(±)-3,4-di-O-benzyl-Pterocarpan (**10**)*

To a mixture of $PdCl_2$ (87 mg, 0.49 mmol) and LiCl (42 mg, 1.0 mmol) in acetone (5 mL) was added chromen **8** (158 mg, 0.46 mmols) in acetone (10 mL). This mixture was stirred for 15 min at 0 °C and then 2-chloromercurio-4,5-methylenedioxyphenol (172 mg, 0.42 mmol) in acetone (10 mL) was added. The suspension thus obtained was stirred for 12 h at 25 °C. After this time, brine (150 mL) was added to it and the mixture was extracted with acetyl acetate (3 x 50 mL), the organic extract dried (Na_2SO_4), and submitted to column chromatography to give the compound as a solid (128.6 mg, 56 %), mp. 170 °C.

^{1}H NMR ($CDCl_3$) (200 MHz) δ 7.38(10H, m,); 7.18(1H, d, *J* 8.6 Hz); 6.7(1H, d , *J* 8.6 Hz); 6.7 (1H,s); 6.42(1H, s); 5.9(2H, 2s); 5.48(1H, d, *J* 6.3 Hz); 5.1(4H, 2s); 4.3(1H, dd, *J* 6.0, 3.6 Hz); 3.6(2H, m). ^{13}C NMR $CDCl_3$ (200 MHz) δ 39.92 (CH); 66.39 (CH_2); 70.87 (CH_2); 75.00 (CH_2); 78.33 (CH); 93.55 (CH); 101.07 (CH_2); 104.59 (CH); 107.81 (CH); 114.26 (C); 117.65 (C); 125.36 (CH); 126-130 (10 CH); 136.73 (C); 137.43 (2 C); 141.52 (C);147.88 (C); 149.74 (C); 152.72 (C); 153.94 (C). LRMS (EI) *m/z* 480 (M^+), 389, 91(base). IR (KBr) ν_{max}/cm^{-1}: 3065 – 3031 (aromatic H), 1613 (aromatic ring).

*cis-(±)-3,4-Dihydroxy-8,9-methylenedioxypterocarpan (**1**)*

3,4-di-O-benzyl-pterocarpan **10** (31.8 mg, 0.07 mmol) in acetone was hydrogenated (3 atm) in the presence of Pd-C (10% by weight). After 30 min. the catalyst was filtered to give (21.0 mg) in 100% yield. ^{1}H NMR ($CDCl_3$) (200 MHz) δ 7.0(1H, d, *J* 8.5Hz); 6.73(1H, s); 6.68(1H, d, *J* 8.5 Hz); 6.44(1H, s); 5.92(2H, 2d, *J* 5.12 and 5.5 Hz); 5.5(1H, d, *J* 6.8 Hz); 4.32 (1H, dd, *J* 10.7 and 4.8 Hz); 3.7(1H, t , *J* 10.6 Hz); 3.57(1H, m). ^{13}C NMR $(CD_3)_2CO$ (200 MHz) δ 41.14 (CH), 67.83 (CH_2), 79.53 (CH), 93.90 (CH), 102.05 (CH_2), 105.87 (CH), 110.09 (CH), 113.52 (C), 119.31 (C), 121.87 (CH), 133.72 (C), 142.38 (C), 145.22 (C), 146.71 (C), 148,85 (C), 155,27 (C). LRMS (EI) *m/z* 300 (M^+), 175, 162(base), 150. IR (KBr) ν_{max}/cm^{-1}: 3513 and 3442 (OH), 3234-3031 (aromatic H), 1667 (aromatic ring). UV λ_{max}/nm (MeOH): 310.

*3,4-Dihydroxy-8,9-Methylenedioxycoumestan (**13**)*

To a solution of **10** (44.1mg, 0.09 mmol) in THF (3.5 mL) was added DDQ (41.3 mg, 0.18 mmol). The resulting mixture was stirred at room temperature for 12 h. The intermediate 3,4-di-O-benzylated coumestan **12** precipitated out of solution and it was collected by filtration and washed with cold hexane. The crude product was allowed to react with hydrogen (2 atm) in acetone for 6 h. After this time the catalyst was filtred (CELITE) and concentrated in vacuo to furnish a amorphous solid **13** (13.6 mg, 54.5%). ^{1}H NMR δ 7.42(1H, d, *J* 8.42 Hz); 7.36(1H, s); 7.34(1H, s); 7.02(1H, d, *J* 8.42); 6.16(2H, s). LRMS (EI, after derivatization with BSTFA + 1% trimethylchlorosilane)[12] *m/z* 456 (M^+), 441. IR (KBr) ν_{max}/cm^{-1}: 3435 (OH), 2921 (aromatic H), 1718 (C=O), 1632-1457 (aromatic ring). UV λ_{max}/nm (MeOH): 348.

Electronic Supplementary Information

^{1}H NMR, ^{13}C NMR and mass spectra for compounds **1** and **13** are available as PDF file at http://jbcs.sbq.org.br.

Acknowledgements

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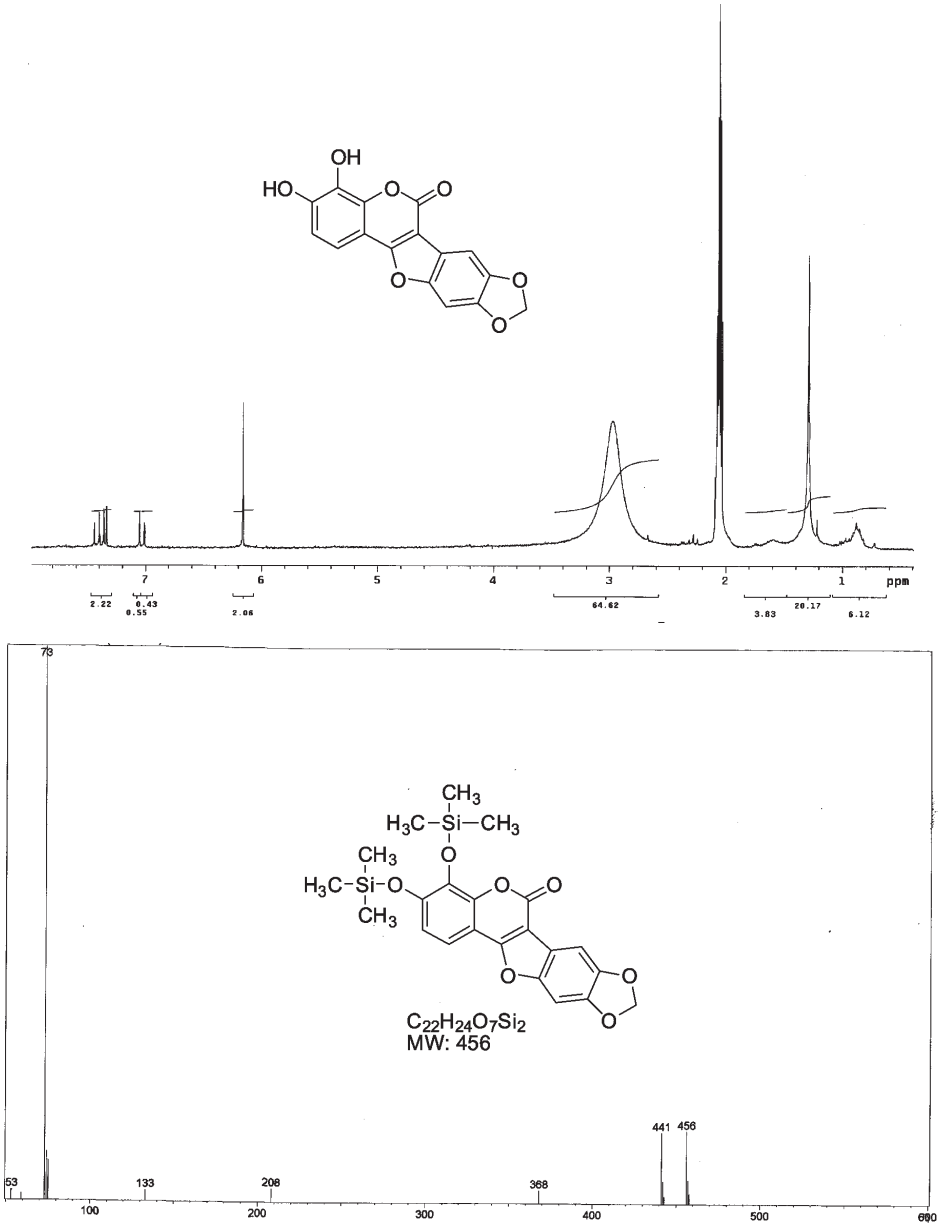

Figure 1. ^{1}H NMR and mass spectra for compound **13**.

* e-mail: lqb@nppn.ufrj.br

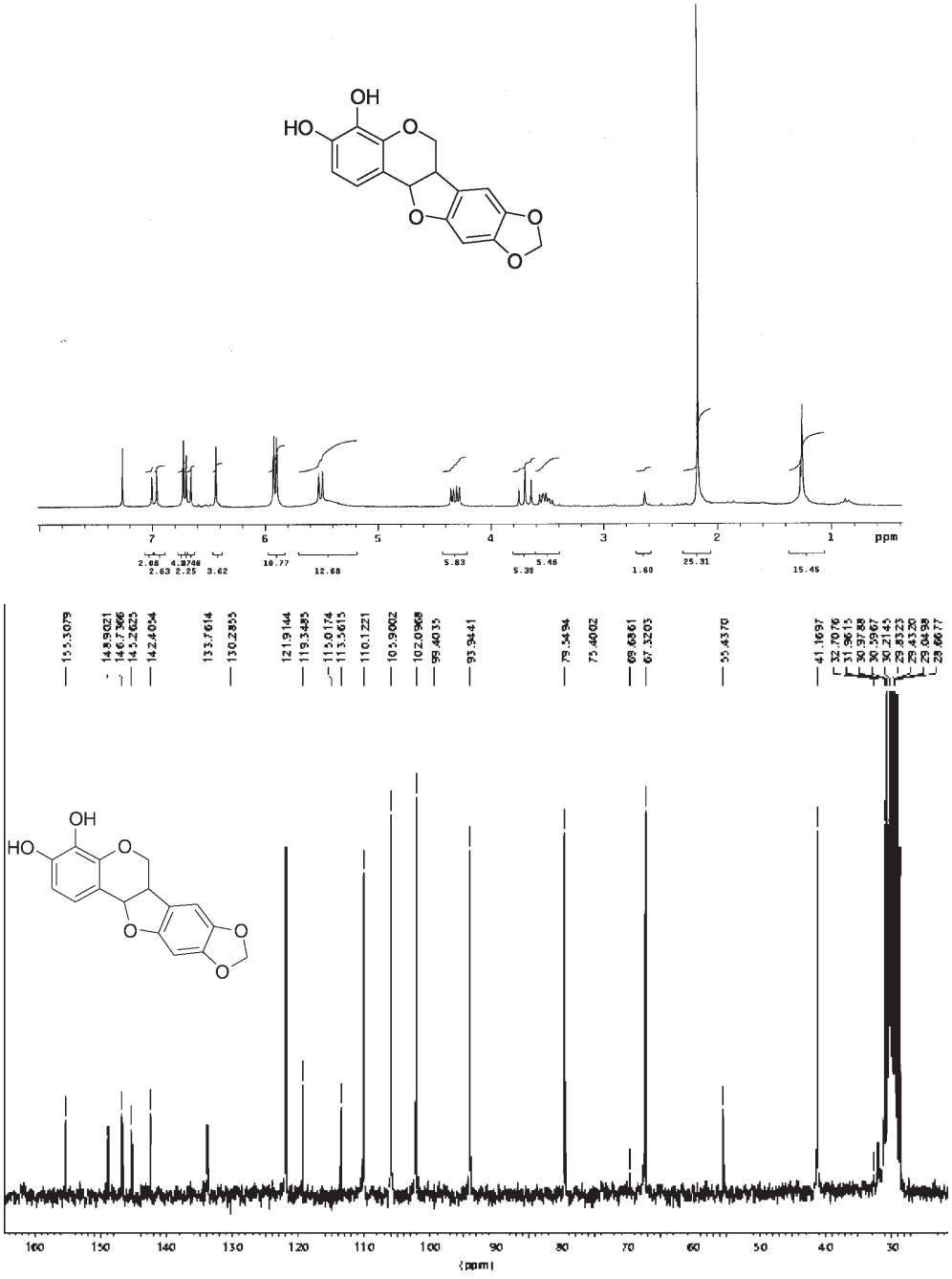

Figure 2. ^{1}H NMR and ^{13}C NMR for compound **1**.