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SYNTHESIS OF NEW (±) PTEROCARPANS BY HECK OXYARYLATION

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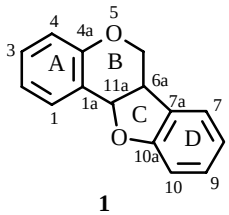
Among a wide variety of synthetic routes to pterocarpan prototypes, a mild approach uses a reaction known as Heck oxyarylation. This method involves a reaction between 2H-chromenes and 2-chloromercuriophenols in the presence of Li_2PdCl_4.

Key words: pterocarpans, 2*H*-chromenes, Heck oxyarylation.

Pterocarpans, the second largest group of natural isoflavonoids possessing a 6a,11a-dihydro-6*H*-benzofuro[3,2-c]chromene skeleton **1**, have received considerable attention due to their wide range of biological activities [1]. Many of them are phytoalexins and some exhibit activities such as antifungal, antimicrobial, antitumoral [2, 3], and anti-HIV [4]. Nakanishi and co-workers demonstrated that the pterocarpans cabenegrin A-I and A-II are the active components of a Brazilian folk medicine used against snake venoms [5], and recently Maurich and co-workers described the anti-clastogenic activity of pterocarpans [6]. The specific activities of these compounds are strongly related to the different substitution patterns at rings A and D.



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New types of pterocarpan representatives have been continuously isolated from plants. Additionally, synthesis chemists have an interest in obtaining new pterocarpan prototypes due to their important activities. Thus, our strategy was to synthesize new pterocarpans involved coupling 2*H*-chromenes and *ortho*-chloromercuriophenols by a Heck oxyarylation reaction. To the best of our knowledge, we have synthesized four new pterocarpans, **6** and **7a–c**, according to the route shown below.

Phenol **2a** was prepared by Baeyer-Villiger oxidation of commercial pyperonal with *meta*-chloroperbenzoic acid and subsequent hydrolysis of the formate obtained with NaOH 6 mol.L^{-1} [7]. Phenols **2b** and **2c**, which are commercially available, were used to prepare their respective 2*H*-chromenes **3b** and **3c** by condensation reaction with 3,3-dimethylacrolein in the presence of phenylboronic acid, and acetic acid in dry toluene under an N_2 atmosphere at 150°C for 5–24 hours [8]. As expected, the Heck oxyarylation reaction between 2*H*-chromene **3a** and 2-chloromercurio-4,5-methylenedioxyphenol (**4**) in the presence of Li_2PdCl_4 in dry acetone [9] for 24 hours afforded pterocarpan **6** (43% yield). The reaction of 2*H*-chromenes **3a–c** with 2-chloromercurio-4-formyl-6-methoxyphenol (**5**) in the same conditions of pterocarpan **6** afforded pterocarpans **7a–c** in lower yield (11%, 21%, and 20%, respectively). Thus, the synthesis of new (±) pterocarpans was achieved in two single steps. All reactions were monitored by TLC and all pterocarpans provided satisfactory PMR, ^{13}C NMR, IR, and mass spectra.

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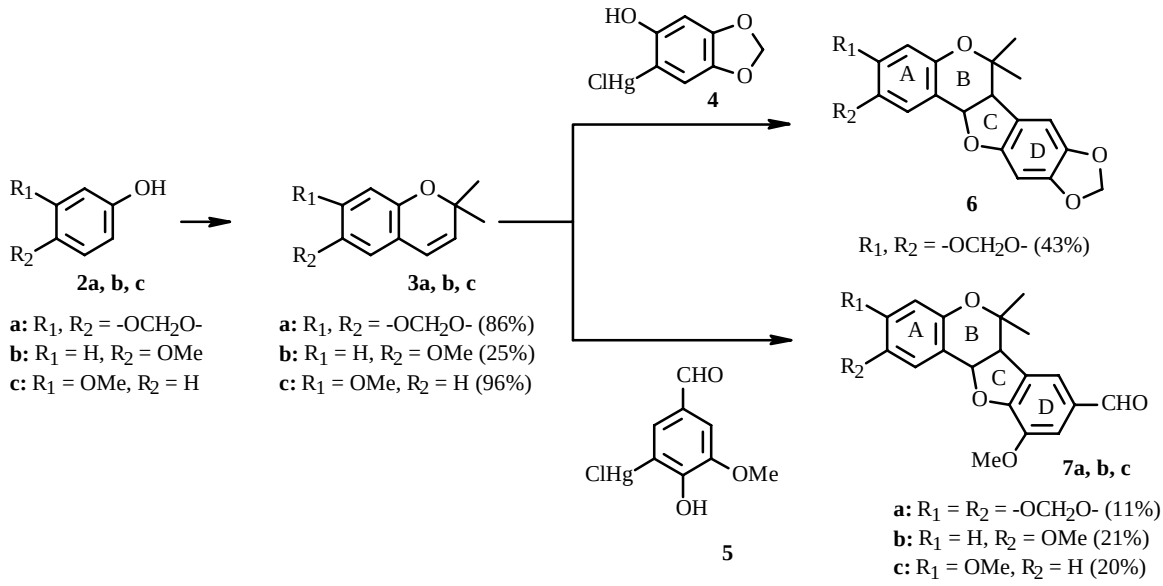

EXPERIMENTAL

Laboratory solvents were purified and pre-dried before use. THF was first distilled from CaH_2 and afterwards with Na using benzophenone as an indicator. Toluene was also distilled from CaH_2. Acetone was distilled from K_2CO_3. Written procedures were used to prepare 2-chloromercurio-4,5-methylenedioxyphenol and 2-chloromercurio-4-formyl-6-methoxyphenol [10, 11]. TLC analyses were carried out on glass plates coated with TLC-grade silica gel. Melting points were determined with a Mettler FP80HT Central Processor. IR spectra were recorded on a Galaxy 3000, Mattson Instruments. PMR spectra were recorded on a BRUKER AVANCE DRX/400MHz and DPX/200MHz instrument using tetramethylsilane (TMS) as a standard and $CDCl_3$ as a solvent. ^{13}C NMR spectra were obtained at 50 and 100 MHz. Mass spectra were recorded on a gas chromatographer coupled to a mass spectrometer HP5989A.

General Synthesis Procedure of Pterocarpans 6 and 7a-c. To a mixture of PdCl2 (42.5 mg; 0.24 mmol) and LiCl (20.4 mg; 0.48 mmol) in dry acetone (7.0 mL), 2*H*-chromene (0.24 mmoL) in acetone (5.0 mL) was added. This mixture was stirred for 15 minutes and added to 2-chloromercuriophenol (0.24 mmol) in acetone (12 mL), and then the suspension obtained was stirred for 24 hours at room temperature. After this, brine was added and the mixture was extracted with dichloromethane. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The product was purified by column chromatography and crystallized from ethyl ether.

(±)-6a,11a-Dihydro-6,6-dimethyl-2,3,8,9-bis-methylenedioxy-6*H*-benzofuro[3,2c-][1]benzopyran (6). White solid, mp 172–176 ºC. IR spectrum (KBr, ν, cm^{-1}): 2999, 2990, 1690, 1500, 1470,1450 1150, 1050. PMR spectrum (400MHz, $CDCl_3$, δ, ppm, J/Hz): 0.90 (3H, s, CH_3), 1.49 (3H, s, CH_3), 3.25 (1H, d, $J_{H6a-H11a}$ = 8.0, H-6a), 5.41 (1H, d, $J_{H11a-H6a}$ = 8.0, H-11a), 5.91 (2H, s, CH_2), 5.93 (2H, s, CH_2), 6.43 (1H, s, H-10), 6.44 (1H, s, H-4), 6.73 (1H, s, H-7), 6.92 (1H, s, H-1). ^{13}C NMR spectrum (100MHz, $CDCl_3$, δ, ppm): 19.76 (CH_3), 27.46 (CH_3), 49.34 (C-6a), 79.52 (C-11a), 76.59 (C-6), 93.37 (C-10), 99.54 (C-4), 101.14 (CH_2), 101.27 (CH_2), 105.24 (C-7), 107.90 (C-1), 111.91 (C), 118.94 (C), 141.60 (C), 142.26 (C), 148.00 (C), 148.25 (C), 148.69 (C), 154.92 (C). Mass spectrum (EI, 70eV), *m/z* (I_{rel}, %): 340 [M^+] (12), 339 (44), 324 (100), 323 (23).

(±)-6a,11a-Dihydro-2,3-methylenedioxy-8-formyl-10-methoxy-6,6-dimethy-6*H*-benzofuro[3,2c-][1]benzopyran (7a). Brown solid, mp 201–203°C. IR (KBr, ν, cm^{-1}): 2977, 2935, 1251, 1045, 1692. PMR spectrum (400MHz, $CDCl_3$, δ, ppm, J/Hz): 0.91 (3H, s, CH_3), 1.57 (3H, s, CH_3), 3.50 (1H, d, $J_{H6a-H11a}$= 7.60, H-6a), 3.96 (3H, s, H-13), 5.63 (1H, d, $J_{H11a-H6a}$ = 7.60, H-11a), 5.93 (d, 1H, OCH_2O, J_{gem} = 1.36) and 5.95 (d, 1H, OCH_2O, J_{gem} = 1.36), 6.45 (1H, s, H-4), 7.05 (1H, s, H-1), 7.40 (1H, s, H-9), 7.46 (1H, s, H-7), 9.86 (1H, s, CHO). ^{13}C NMR spectrum (100MHz, $CDCl_3$, δ, ppm): 20.01 (CH_3) and 27.52 (CH_3), 49.11 (C-6a), 56.16 (C-13), 76.01 (C-6), 81.31 (C-11a), 99.58 (C-4), 101.29 (CH_2), 108.28 (C-1), 110.73 (C-1a), 112.63 (C-9), 121.28 (C-7), 130.01 (C-7a), 131.43 (C-8), 142.49 (C-2 or C-3), 145.20 (C-10), 148.36 (C-4a), 149.13 (C-3 or C-2), 154.36 (C-10a), 190.77 (CHO). *m/z* (I_{rel}, %): 353 [M-1] (22), 337 (100), 337 (27), 308 (9).

(±)-6a,11a-Dihydro-8-formyl-2,10-dimethoxy-6,6-dimethyl-6*H*-benzofuro[3,2c-][1]benzopyran (7b). White solid, mp 131–132°C; IR spectrum (KBr, ν, cm^{-1}): 3030, 2970, 2830, 1240, 1034, 1680. PMR spectrum (200MHz, $CDCl_3$, δ, ppm, J/Hz): 0.90 (3H, s, CH_3), 1.59 (3H, s, CH_3), 3.55 (1H, d, $J_{H6a-H11a}$ = 7.92, H-6a), 3.82 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 5.70 (1H, d, $J_{H11a-H6a}$ = 7.92, H-11a), 6.86-6.87 (2H, m, H-3 and H-4), 7.17 (1H, d, J_{H1-H3} = 2.36, H-1), 7.40 (1H, s, H-9), 7.48 (1H, s, H-7), 9.87 (1H, s, CHO) ^{13}C NMR spectrum (100MHz, $CDCl_3$, δ, ppm): 20.10 (CH_3), 27.61 (CH_3), 49.46 (C-6a), 75.71 (C-6), 113.40 (C-1), 117.74 (C-1a), 119.00 (C-3), 119.31 (C-4), 121.36 (C-7), 130.10 (C-7a), 146.88 (C-4a), 154.26 (C-10a), 154.34 (C-2). Mass spectrum (EI, 70eV), *m/z* (I_{rel}, %): 340 [M^+] (6), 339 (25), 324 (100), 323 (19).

(±)-6a,11a-Dihydro-8-formly-3,10-dimethoxy-6,6-dimethyl-6*H*-benzofuro[3,2c-][1]benzopyran (7c). White solid, mp 125–127°C. IR (KBr, ν, cm^{-1}): 3039, 2974, 2836, 1240, 1034, 1683. PMR spectrum (200MHz, $CDCl_3$, δ, ppm, J/Hz): 0.90 (3H, s, CH_3), 1.55 (3H, s, CH_3), 7.53 (1H, d, J_{H1-H2} = 8.50, H-1), 6.63 (1H, dd, J_{H2-H1} =8.50, J_{H2-H4}= 2.40 H-2), 6.47 (1H, d, J_{H4-H2} = 2.40, H-4), 3.52 (1H, d, $J_{H6a-H11a}$ = 7.60, H-6a), 7.48 (1H, s, H-7), 7.40 (1H, s, H-9), 5.69 (1H, d, $J_{H11a-H6a}$ = 7.60, H-11a), 3.80 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 9.86 (1H, s, CHO). ^{13}C NMR spectrum (100MHz, $CDCl_3$, δ, ppm): 20.28 (CH_3) and 27.52 (CH_3), 49.08 (C-6a), 55.32 (C-12), 56.12 (C-13), 76.12 (C-6), 80.94 (C-11a), 102.29 (C-4), 108.87 (C-2), 111.07 (C-1a), 121.33 (C-7), 131.17 (C-1), 130.09 (C-7a), 154.25 (C-4a), 154.53 (C-10a), 161.41 (C-3), 190.47 (CHO). Mass spectrum (EI, 70eV), *m/z* (I_{rel}, %): 340 [M^+] (6), 339 (19), 324 (100), 175 (3) 323 (18).

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