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Synthesis of New Pterocarpans and Rapid O-Alkylation under Microwave Irradiation

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ABSTRACT: *Herein, it is described five new pterocarpans. Pterocarpans* **8** *and* **9** *were synthesized by classical [3 + 2] cycloaddition reaction of 2H-chromene* **7a** *and* **7b** *with 2-methoxy-1,4-benzoquinone. Pterocarpan* **8** *was O-alkylated in the absence of solvents using a domestic microwave oven as a heat source and a classical O-alkylation method with traditional heating. In this way three more new pterocarpans were obtained.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:239–244, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20175

INTRODUCTION

Pterocarpans with a *cis*-6a,11a-dihydro-6*H*-benzofuro[3,2-*c*] chromene skeleton **1** (Fig. 1) constitute the second largest natural isoflavonoid group and have received considerable attention on the account of their medicinal properties [1,2].

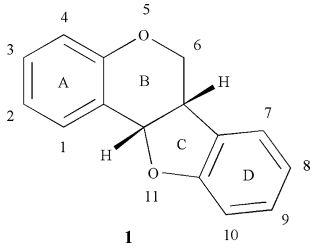

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FIGURE 1 Basic structure of pterocarpans.

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Recently, Maurich et al. described anticlastogenic activity of two pterocarpans, erybraedin C (**2**) and bitucarpin A (**3**) [3]. Already, Joseph et al. reported larvicidal and mosquitocidal activity of pterocarpans neoduline (**4**), nepseudin (**5**), and 4-methoxyneoduline (**6**) [4] (Fig. 2).

Other substituted pterocarpans exhibit activities such as anti-HIV, antitumoral, against snake venoms [5,6]. Many pterocarpans are phytoalexins and possess antifungal and antibacterial activity [7]. It has been reported that the pterocarpan ring system with oxygenated substituents at C-8 and C-9 appears to be necessary for their potent activity. In some cases, the presence of prenyl substituents in rings A and D may also be important for some of the biological activities of pterocarpans [7]. The benzyl group is described as a bioisoster of prenyl [6]. New types of pterocarpans are being continuously synthesized and isolated from plant sources.

Thus, in the synthesis of pterocarpans, it is essential to use methodologies that allow varying the substituents at rings A and D. Recent attempts have comprised mainly Heck arylation [6] and conventional [3 + 2] cycloaddition reaction of 2*H*-chromenes with 2-alkoxy-1,4-benzoquinones [8,9].

Recently, there has been a growing interest in the application of microwave irradiation to improve reaction rates and to the formation of clean products [10]. Microwave irradiation has been extensively used in solvent-free conditions. It provides an opportunity to work with open vessels, and thus avoid the risk of explosion when reactions are carried out in a domestic microwave oven [10,11]. In addition, avoiding organic solvents during reactions leads to a clean, efficient, and economical technology: work-up is considerably simplified

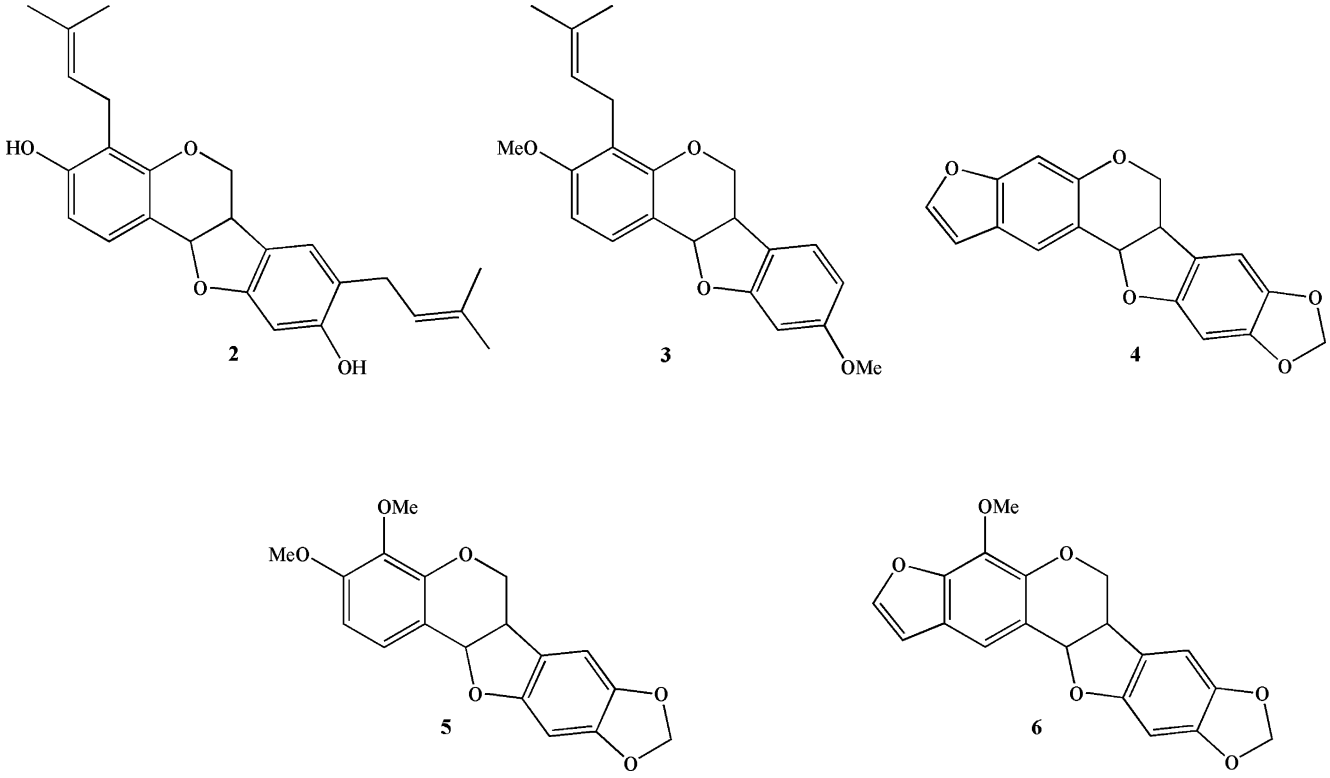


FIGURE 2 Chemical structure of pterocarpans erybraedin C (**2**), bitucarpin A (**3**), neoduline (**4**), nepseudin (**5**), and 4-methoxyneoduline (**6**).

(some reactions use high boiling solvents that are difficult to remove), cost is reduced, reactivity and sometimes selectivity are enhanced without dilution [12]. Reactions under "dry conditions," i.e., in the absence of solvent on solid support with or without catalysts, were developed in the late 1980s [13].

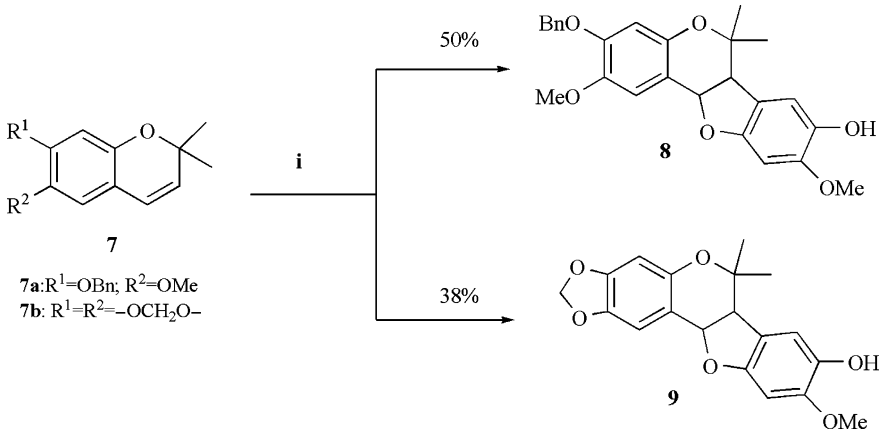
The target of present study was to synthesize new pterocarpans and to evaluate the efficiency of microwave irradiation to O-alkylation of pterocarpans skeleton.

RESULTS AND DISCUSSION

As shown in Scheme 1, the new pterocarpans **8** and **9** were obtained by the synthetic methodology described by Subburaj et al. [9], which involved classical [3 + 2] cycloaddition reaction between 2*H*-chromene **7a** and **7b** [14] with 2-methoxy-1,4-benzoquinone using dichloromethane as a solvent at room temperature for 18 h. It afforded pterocarpan **8** with a yield of 50% and **9** with 38%.

Trying to explore the application of microwave irradiation in the absence of solvents, and evaluate the technology to pterocarpan skeleton, we report here the O-alkylation of the new pterocarpan **8** using a domestic microwave oven as a heat source (Scheme 2) [15]. Thus, pterocarpan **8** was O-alkylated in solvent-free conditions using a domestic microwave oven as a heat source and a classical phenol O-alkylation method for comparison. Three other new O-substituted pterocarpans at ring D (Table 1) were obtained.

For the O-alkylation by using a domestic microwave oven as a heat source, pterocarpan **8** was dissolved in dichloromethane, adsorbed onto silica gel, and a few drops of aqueous sodium hydroxide were added. The mixture was irradiated in an open vessel with a domestic microwave oven for 50 s. Next, excess organic halide was added and the mixture was irradiated again for the appropriate times according to Table 1. Pterocarpan **10a** (entry 1) and **10b** (entry 2) were obtained with reasonable yields. The same condition was attempted for pterocarpan **10c** (entry 3); however, it did not afford the O-alkylated product. Thus, the reaction to obtain **10c** was carried out without silica gel and with a smaller halide excess (entry 3) with 40% yield. In this way, we repeated the reaction described in entry 1 without silica gel to try to improve its yield. Product **10a** was obtained in higher yield and using smaller excess halide under this condition. In all



SCHEME 1 (**i**) 2-Methoxy-1,4-benzoquinone, $ZnCl_2$, dichloromethane, at room temperature, 18 h [9].

cases, pterocarpan **8** was stable under microwave heating.

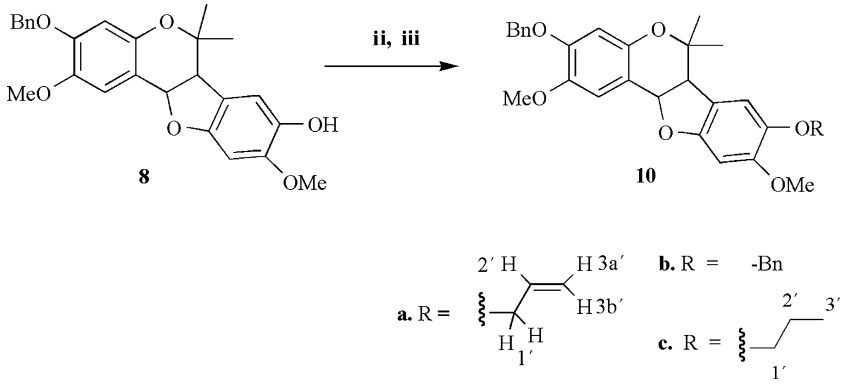
After reaction, the work-up procedure involved treatment with an appropriate solvent (e.g., dichloromethane), simple solvent filtration, and evaporation. The crude products were purified by silica gel column chromatography. All the products provided satisfactory ^{1}H NMR, ^{13}C NMR, mass, and IR spectra.

Trying to show that the microwave technology is advantageous for the O-alkylation of pterocarpans, compound **8** was also submitted to the classical phenol O-alkylation method with traditional heating. Pterocarpans **10a–10c** were obtained by heating pterocarpan **8** in the presence of halide, a weak base (K_2CO_3), and acetone [16]. Traditional heating results are summarized in Table 1 and compared with those of microwave irradiation.

As shown in Table 1, microwave heating was more efficient than traditional heating in the O-alkylation of pterocarpan **8**. Reaction time was reduced from hours to minutes by using microwave heating and, in general, yields were also better. Furthermore, the relatively low cost of domestic microwave ovens when compared with a specialized microwave system makes them affordable to academic chemists [17].

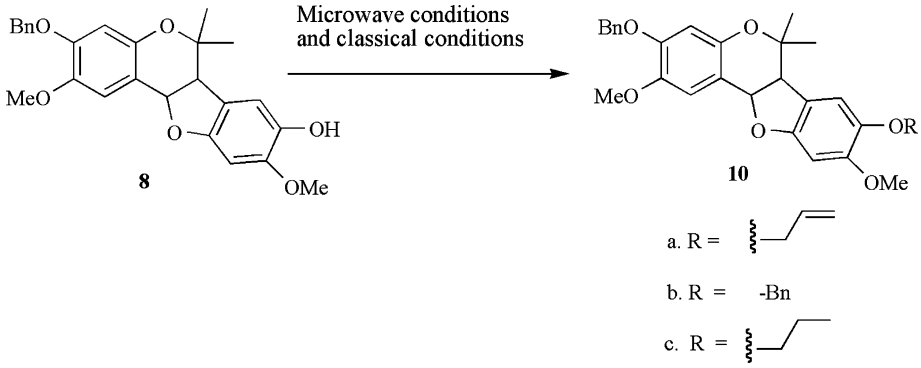
To the best of our knowledge, it is the first time that a pterocarpan is O-alkylated using a domestic microwave oven as a heat source. Domestic microwave heating showed to be an attractive and efficient technique to vary groups in the C-8 position of the pterocarpan **8** skeleton to obtain new compounds in reasonable yields rapidly.

Here, it is described five new pterocarpans. The new pterocarpans **8** and **9** were synthesized by conventional [3 + 2] cycloaddition reaction [9]. From pterocarpan **8** it was possible to easily synthesize three other new pterocarpans, **10a–10c**, which were obtained by O-alkylation in the absence of any organic solvent by domestic microwave irradiation and



SCHEME 2 (**ii**) NaOH aq, MW, 50 s; (**iii**) RX, MW, silica gel, 2.40–8.00 min [15] (see Table 1). *Compound **10c** was obtained without silica gel.

TABLE 1 O-Alkylation of Pterocarpan **8** under Domestic Microwave Irradiation and Traditional Heating



			Microwave Conditions			*Classical Conditions*		
Entry	*RX*	*Product*	*RX/Pterocarpan/Silica (mmol/mmol/g)*	*Time (min)*	*Yield[a] (%)*	*RX/Pterocarpan/K_2CO_3 (mmol)*	*Time (h)*	*Yield[a] (%)*
1	Allyl bromide	**10a**	First: 1.5/0.1/0.5	2.40	47	0.50/0.18/0.27	22	55
			Second: 1.0/0.1[b]	2.40	61			
2	Benzyl bromide	**10b**	1.3/0.13/0.5	2.40	79	0.65/0.18/0.27	2.30	89
3	Bromo propane	**10c**	First: 2.6/0.13/0.5	8.00	0	0.90/0.18/0.27	37	28
			Second: 1.3/0.13[b]	8.00	40			

[a]Isolated yield after column chromatography.
[b]Without silica gel.

a classical phenol O-alkylation method with traditional heating. Reactions using microwave heating showed to be more efficient to O-alkylation of pterocarpan skeleton.

EXPERIMENTAL

General

Microwave irradiation was carried out with a General Electric JEI 1145 AWA domestic microwave oven 2450 MHz. ^{1}H NMR and ^{13}C NMR spectra were recorded on either Bruker Avance DRX/400 or DPX/200 in $CDCl_3$ with TMS as an internal standard. IR spectra were recorded on a Mattson Instruments Galaxy 3000. Mass spectra were recorded on an electronic impact mass spectrometer VG-AutoSpec 70eV. Melting points were determined with a Mettler FP80HT central processor. All reaction mixtures were analyzed on silica gel by TLC. Column chromatography was performed on silica gel 60 Merck.

Synthesis of Pterocarpan **8** *and* **9** *[9]*

Dry $ZnCl_2$ (2.0 mmol) was added to a solution of 2-methoxy-1,4-benzoquinone (1.3 mmol) in 5.0 mL of dry dichloromethane. The mixture was well stirred for 15 min. Then, a solution of 2*H*-chromene (1.0 mmol) in 3.0 mL dry dichloromethane was added and the reaction was monitored by TLC. After 18 h, the mixture was quenched by adding water, extracted with dichloromethane, dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by column chromatography.

General Procedure for the O-Alkylation of Pterocarpan **8** *under Microwave Heating*

Pterocarpan **8** (0.1 mmol) was adsorbed onto silica gel, and a few drops of aqueous sodium hydroxide (0.6 mmol) were added. The mixture was heated in an open flask in a domestic microwave oven for 50 s. Subsequently, the reaction mixture was allowed to cool and excess halide was added. The mixture was heated again in a domestic microwave oven for specific reaction times (Table 1) and was monitored by TLC. After reaction, the mixture was first washed off under stirring with dichloromethane. Next, silica gel was removed by filtration, and the solvent was evaporated under reduced pressure. All products were purified by silica gel column chromatography.

Product Characterization

*(±) 6a,11a-Dihydro-3-benzyloxy-2,9-dimethoxy-8-hydroxy-6,6-dimethyl-6H-benzofuro[3,2-c][1]benzopyran (***8***).* Yellow solid, mp: 165–170°C. H^1 NMR

($CDCl_3$, 400 MHz) δ: 0.87 (s, 3H, Me), 1.50 (s, 3H, Me), 3.28 (d, 1H, H-6a, $J = 7.6$ Hz), 3.86 (s, 3H, MeO), 3.89 (s, 3H, MeO), 5.10 (d, 1H, PhCH_2, $J = 12.0$ Hz), 5.14 (d, 1H, PhCH_2, $J = 12.0$ Hz), 5.42 (d, 1H, H-11a, $J = 7.6$ Hz), 6.49 (s, 1H, H-10), 6.50 (s, 1H, H-4), 6.87 (s, 1H, H-7), 7.01 (s, 1H, H-1), 7.26-7.45 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 19.86 (Me), 27.48 (Me), 49.48 (C-6a), 56.12, 56.54 (MeO), 70.74 (PhO*C*H_2), 76.54 (C-6), 78.97 (C-11a), 94.25 (C-10), 103.58 (C-4), 110.98 (C-7), 111.40 (C-1a), 112.12 (C-1), 119.07 (C-7a), 127.30, 127.88, 128.54 (Ar), 136.97(C *ipso*), 139.75 (C-8), 144.48 (C-2), 146.83 (C-9), 147.23 (C-4a), 149.69 (C-3), 153.56 (C-10a). IR (KBr) 3400, 2800, 1615, 1490, 1450, 1340, 1210, 1125, 1180, 1120 cm^{-1}. MS (70 eV, EI) *m/z*: 434 [M$^{+\bullet}$] (17), 419 (13), 343 (29), 91 (100).

*(±) 6a,11a-Dihydro-3-benzyloxy-9-dimethoxy-8-hydroxy-2,3-methylenedioxy-6,6-dimethyl-6H-benzofuro[3,2-c][1]benzopyran (***9***).* Yellow solid, mp: 156–160°C. H^1 NMR ($CDCl_3$, 400 MHz) δ: 0.87 (s, 3H, Me), 1.50 (s, 3H, Me), 3.29 (d, 1H, H-6a, $J = 7.6$ Hz), 3.86 (s, 3H, MeO), 5.38 (d, 1H, H-11a, $J = 7.6$ Hz), 5.91 (d, 1H, OCH_2O, $J = 1.36$ Hz), 5.93 (d, 1H, OCH_2O, $J = 1.36$ Hz), 6.44 (s, 1H, H-4), 6.47 (s, 1H, H-10), 6.86 (s, 1H, H-7), 6.92 (s, 1H, H-1). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 19.85 (Me), 27.82 (Me), 49.48 (C-6a), 56.16 (MeO), 76.70 (C-6), 79.18 (C-11a), 94.31 (C-10), 99.61 (C-4), 101.14 (O*C*H_2O), 107.95 (C-1), 110.96 (C-7), 112.21, 119.01, 139.80, 142.27, 146.89, 148.34, 148.67, 153.68 (C *ipso*). IR (KBr) 3000, 2800, 1615, 1490, 1450, 1340, 1210, 1125, 1180, 1120 cm^{-1}. MS (70 eV, EI) *m/z*: 342 [M$^{+\bullet}$] (43), 327 (100), 343 (29), 282 (6), 69 (9).

*(±) 6a,11a-Dihydro-8-alyloxy-3-benzyloxy-2,9-dimethoxy-8-hydroxy-6,6- dimethyl-6H-benzofuro[3,2-c]-[1]benzopyran (***10a***).* Yellow solid, mp: 47–50°C. H^1 NMR ($CDCl_3$, 400 MHz) δ: 0.85 (s, 3H, Me), 1.49 (s, 3H, Me), 3.29 (d, 1H, H-6a, $J = 7.6$ Hz), 3.84 (s, 3H, MeO), 3.90 (s, 3H, MeO), 4.52–4.50 (m, 2H, H-1′), 5.10 (d, 1H, PhCH_2, $J = 12.2$ Hz), 5.15 (d, 1H, PhCH_2, $J = 12.2$ Hz), 5.27 (ddd, 1H, $J_{3b'2'} = 17.0$ Hz, $J_{3b'3a'} = 1.6$ Hz, $J_{3b'1'} = 2.8$ Hz), 5.37 (ddd, 1H, $J_{3a'2'} = 10.0$ Hz, $J_{3a'3b'} = 1.3$ Hz, $J_{3a'1'} = 3.2$ Hz), 5.45 (d, H-11a, $J = 7.6$ Hz), 6.03–6.13 (m, 1H, H-2′), 6.50 (s, 1H, H-10), 6.51 (s, 1H, H-4), 6.86 (s, 1H, H-7), 7.01 (s, 1H, H-1), 7.34–7.45 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 19.90, 27.60 (Me), 49.60 (C-6a), 56.07, 56.63 (MeO), 70.84 (PhOCH_2), 71.79 (C-1′), 76.70 (C-6), 79.20 (C-11a), 95.31 (C-10), 103.73 (C-4), 111.46 (C-1a), 113.18 (C-7), 117.81 (C-3′), 112.30 (C-1), 118.21 (C-7a), 127.32, 127.89, 128.56 (Ar), 133.94 (C-2′), 136.77 (C *ipso*), 142.19 (C-8), 144.61 (C-2), 147.29 (C-9), 149.81 (C-4a), 151.19 (C-3), 155.21 (C-10a). IR (KBr): 2800, 1610, 1490, 1450, 1210, 1120, 1160, 1180 cm^{-1}. MS (70 eV, EI) *m/z*: 474 [M$^{+\bullet}$] (17), 456 (23), 433 (22), 383 (78), 91 (100).

*(±) 6a,11a-Dihydro-3,8-dibenzyloxy-2,9-dimethoxy-6,6-dimethyl-6H-benzofuro[3,2-c][1]benzopyran (***10b***).* Yellow solid, mp: 46–48°C. H^1 NMR ($CDCl_3$, 400 MHz) δ: 0.77 (s, 3H, Me), 1.33 (s, 3H, Me), 3.21 (d, 1H, H-6a, $J = 7.6$ Hz), 3.85 (s, 3H, MeO), 3.87 (s, 3H, MeO), 5.03–5.13 (m, 4H, $2 \times$ PhCH_2), 5.40 (d, 1H, H-11a, $J = 7.6$ Hz), 6.49 (s, 1H, H-10), 6.50 (s, 1H, H-4), 6.56 (s, 1H, H-7), 7.00 (s, 1H, H-1), 7.18–7.45 (m, 10H, Ar). ^{13}C NMR ($CDCl_3$ 100 MHz) δ: 19.76, 27.37 (Me), 49.39 (C-6a), 56.04, 56.55 (MeO), 70.75, 73.06 (PhOCH_2), 76.43 (C-6), 79.13 (C-11a), 95.27 (C-10), 103.65 (C-4), 111.36 (C-1a), 112.23 (C-7), 114.48 (C-1), 118.18 (C-7a), 127.26, 127.58, 127.75, 127.83, 128.41, 128.50 (Ar), 136.97 (C ipso), 137.44 (C ipso), 141.92 (C-8), 144.53 (C-2), 147.22 (C-9), 149.73 (C-4a), 151.53 (C-3), 155.41 (C-10a). IR (KBr): 3000, 2800, 1610, 1490, 1450, 1200, 1160, 1180, 1120 cm^{-1}. MS (70 eV, EI) *m/z* (rel. intensity): 524 [M$^{+\bullet}$] (20), 433 (39), 91(100).

*(±) 6a,11a-Dihydro-3-benzyloxy-2,9-dimethoxy-8-propyloxy -6, 6-dimethyl-6H-benzofuro[3, 2-c][1]-benzopyran (***10c***).* Yellow solid, mp: 42–43°C. H^1 NMR ($CDCl_3$, 200 MHz) δ: 0.86 (s, 3H, Me), 1.04 (t, 3H, H-3′, $J = 7.3$ Hz), 1.50 (s, 3H, Me), 3.29 (d, 1H, H-6a, $J = 7.6$ Hz), 3.82 (s, 3H, MeO), 3.89 (s, 3H, MeO), 3.92 (t, H-1′, $J = 6.8$ Hz), 5.12 (s, 2H, PhCH_2), 5.44 (d, 1H, H-11a, $J = 7.6$ Hz), 6.50 (s, 2H, H-4, H-10), 6.85 (s, 1H, H-7), 7.01 (s, 1H, H-1), 7.29–7.45 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 10.45 (C-3′), 19.84 (Me), 22.73 (C-2′), 27.62 (Me), 49.56 (C-6a), 56.04, 56.52 (MeO), 70.73 (PhOCH_2), 72.40 (C-1′), 76.74 (C-6), 79.11 (C-11a), 95.30 (C-10), 103.58 (C-4), 111.39 (C-1a), 112.12 (C-7), 112.39 (C-1), 118.18 (C-7a), 127.27, 127.85, 128.52 (Ar), 136.68 (C ipso), 142.75 (C-8), 144.50 (C-2), 147.10 (C-9), 149.68 (C-4a), 151.02 (C-3), 154.83 (C-10a). IR (KBr): 3000, 2800, 1610, 1490, 1450, 1210, 1120, 1160, 1180 cm^{-1}. MS (70 eV, EI) *m/z*: 476 [M$^{+\bullet}$] (5), 385 (11), 91 (100).

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