Ligand Free Palladium-Catalyzed Oxyarylation of Dihydronaphthalens and Chromenequinone with *o*-Iodophenols and 3-Iodolawsone in PEG-400: An Efficient Synthesis of 5-Carba-Pterocarpans and Pterocarpanquinones

Paula de Freitas de Moraes[a], Francisco V. Gaspar[a], Chaquip D. Netto[b], Raquel A. C. Leão[a], Carmen Nájera[c], Paulo R. R. Costa[a]*

[a] Laboratório de Química Bioorgânica, Instituto de Pesquisas de Produtos Naturais, Universidade Federal do Rio de Janeiro, Centro de Ciências da Saúde, Bloco H, Ilha da Cidade Universitária, 21941-590, Rio de Janeiro, RJ, Brazil

[b] Universidade Federal do Rio de Janeiro, *Campus* Macaé, Rio de Janeiro, RJ, Brazil

[c] Departamento de Química Orgánica, Facultad de Ciencias and Centro de Innovación en Química Avanzada (ORFEO-CINQA), Universidad de Alicante, apdo. 99, 03080-Alicante, Spain
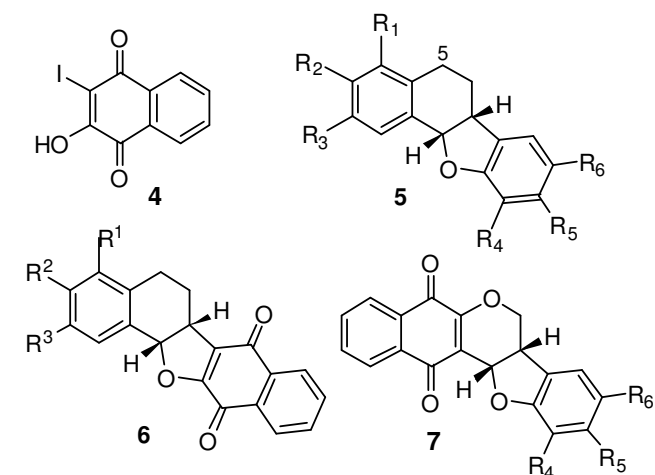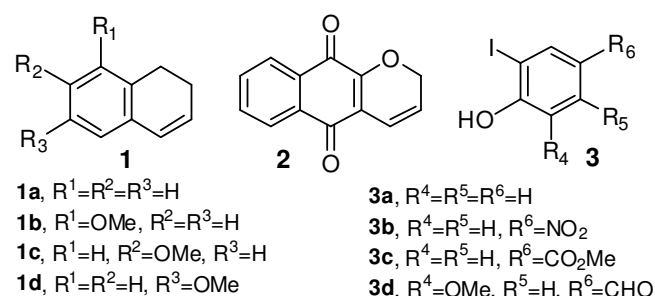
Fax: +55-21-25626512
E-mail: prrcosta2011@gmail.com

Abstract: Dihydronaphthalenes (**1a-d**) were oxyarylated with *o*-iodophenols (**3a-d**), in PEG-400 at 140 ºC or 170 ºC, leading regio- and stereoselectively to 5-carbapterocarpans (**5**). Using Pd(OAc)$_2$ (5-10 mol%) as pre-catalyst and Ag$_2$CO$_3$ (1.1 equiv) as base (Conditions A), products were obtained in good to excellent chemical yields, in only 5-30 min of reaction, despite of the pattern of substitution in **1** and **3**. Alternatively, when *p*-hydroxyacetophenone oxime-derived palladacycle (1 mol%) was used as pre-catalyst and dicyclohexylamine (2 equiv) as base (silver-free, Conditions B), adducts **5** were obtained from moderate to good yields, in 30 min to 4 h of reaction. Finally, the oxyarylation of dihydronaphthalens (**1**) and chromenquinone (**2**) with **3a-d** and **4** in PEG-400 under conditions A led regio- and stereoselectively to pterocarpanquinones **6** and **7** in moderate yield

Key words: oxyarylation reaction, PEG-400, 5-carba-pterocarpans, pterocarpanquinones, PEG.

In 1976 Horino and Inoue reported the synthesis of pterocarpin through a new regio and *cis*-stereoselective oxyarylation of 3-methoxy-2*H*-1-chromene with *o*-chloromercurysesamol.[1] In spite of the use of toxic *o*-mercuryphenols as intermediates and stoichiometric amounts of PdCl$_2$, the Inoue's oxyarylation was further used in the synthesis of several naturally occurring pterocarpans, coumestans and derivatives.[2] The first palladium catalyzed oxyarylation of 2*H*-1-chromens and dihydronaphthalenes with *o*-iodophenols was reported by Larock *et al*, under neutral conditions.[3] The group of Antus[4] also described the palladium catalyzed oxyarylation of 3-methoxy-2*H*-1-chromene with *o*-iodophenol in the presence of Ag$_2$CO$_3$ (cationic conditions). This oxyarylation was also investigated in our group and cationic intermediates were detected in EIS-MS.[5] Optimize conditions were developed under MW heating, using both Pd(OAc)$_2$ in acetone or *p*-hydroxyacetophenone oxime-derived palladacycle in DMA-H$_2$O as pre-catalyst.[6] New compounds with antineoplastic and antiparasitic properties were synthesized in our group by azaarylation and oxyarylation reaction but a restricted number of olefins were used in these studies.[7]

In this paper we report the oxyarylation of olefins **1** and **2** with *o*-iodophenols **3** and 3-iodolawsone (**4**) in PEG-400 as solvent (Figure 1) leading regio and stereoselectively to adducts **5**, **6** and **7**.

1a, R^1=R^2=R^3=H
1b, R^1=OMe, R^2=R^3=H
1c, R^1=H, R^2=OMe, R^3=H
1d, R^1=R^2=H, R^3=OMe

3a, R^4=R^5=R^6=H
3b, R^4=R^5=H, R^6=NO$_2$
3c, R^4=R^5=H, R^6=CO$_2$Me
3d, R^4=OMe, R^5=H, R^6=CHO

Figure 1. Olefins, *o*-iodophenols and adducts of oxyarylation studied in this work.

The 5-carbapterocarpans (**5**) are isosters[8] of naturally occurring pterocarpans[9] and can be used as a new scaffold to prepare bioactive compounds. The replacement of the oxygen atom in the B ring by a methylene in other groups of bioactive isoflavonoids (5-carbapterocarpens and 1-carbaisoflavanones) has led to products with the same pharmacological profile.[10] Carba-pterocarpanquinones **6** and pterocarpanquinones **7**, previously synthesized in our group, presented anti-neoplasic activity in hu-

man cancer cell lines and antileishmanial activity in culture and in mice.[7,17]

Looking for options to carry out oxyarylation reactions fast but under conventional heating, we envisaged that PEG could be used as solvent. PEG-400 has been used as a green solvent to accomplish palladium catalyzed Mizoroki-Heck and Stille reactions, Sonogashira and Suzuki-Miyaura cross-couplings.[11] Moreover, Razler *et al.* showed that PEG-2000 promotes the formation of palladium nanoparticles, increasing the catalyst efficiency in the Suzuki-Miyaura reaction.[12] The group of Corma reported a phosphine free highly active catalytic system for Suzuki and Sonogashira reactions[13] in which an oxime palladacycle is anchored in chlorinated PEG (PEG-PdL). More recently, palladacycles anchored to PEG has been used as a highly active catalytic system in Heck reactions.[14]

Our first goal was optimize the oxyarylation of **1a** with **3a** leading to **5aa** (Scheme 1, Table 1) in PEG. Razler *et al.* also demonstrated the formation of palladium nanoparticles on gelatin by the reduction of Pd^{2+} to Pd^0, following by the disappearance of the absorption at 420 nm, associated with cationic palladium species.[12] We also followed this reductive step by UV, heating the palladium source in PEG-400 at 140 °C. Using $Pd(OAc)_2$, we observed a total reduction of Pd^{II} to Pd^0 in only 5 min, while 30 min are required for palladacycle. Based on these results and after some experimentation we chosed $Pd(OAc)_2$ as pre-catalyst and Ag_2CO_3 as base, at 140 °C or 170 °C (Conditions A). Alternatively, this oxyarylation was also evaluated using *p*-hydroxyacetophenone oxime-derived palladacycle as pre-catalyst, DIPEA as base in the absence of Ag_2CO_3 (Conditions B). The results obtained are shown in Scheme 1, Table 1. The oxyarylation of **1a** with **3a** in the presence of 10 mol% of $Pd(OAc)_2$ and 1.5 equiv of Ag_2CO_3, in acetone under MW heating (60ºC, 40W), was used as reference and afforded the 5-carbapterocarpan **5aa** in 58% yield after 40 min of reaction (Table 1, entry 1).[6] When this reaction was performed in PEG-2000 and PEG-400 at 140 °C (Conditions A), **1a** was totally consumed in 40 min and 2 h, respectively, giving **5aa** in 87% and 45% yield, respectively (Table 1, entries 2 and 3). The efficiency in PEG-400 could be improved performing the reaction at 170 °C, giving **5aa** in 87% yield in only 10 min (Table 1, entry 4). However, in PEG-200 the oxyarylation reaction failed (Table 1, entry 5). Adduct **5aa** was obtained in a similar yield using 5 mol% of $Pd(OAc)_2$ in PEG-400 at 170 °C (Table 1, compare entries 4 and 6). In addition, in PEG-400 it was possible to reduce the amount of Ag_2CO_3 from 1.5 equiv to 1.1 equiv, without affecting the chemical yield.

The oxyarylation of **1a** with **3a** using 1 mol% of *p*-hydroxyacetophenone oxime-derived palladacycle and 2.0 equiv of Cy_2NH, in *N*,*N*-dimethylacetamide/water under MW heating (120ºC, 40W, 40 min) led to adduct **5aa** in 41% yield (Table 1, entry 7). In PEG-2000 at 140 °C the reaction was slower (3 h), product **5aa** being obtained in 80% yield (Table 1, entry 8). However, in PEG-400 at 140 °C no conversion was observed (data not shown), being necessary to increase the temperature to 170 °C to get **5aa** in 78% yield (Table 1, entry 10).

While faster reactions and slightly better yields of **5aa** were obtained under Conditions A, under Conditions B the use of Ag_2CO_3 is not required and in addition, a lower palladium loading was used. So, we decided to use both reaction conditions in the study of the scope of this reaction.

Dihydronaphthalen (**1a**),[6] methoxylated derivatives (**1b-d**) were selected as olefins for our study and can be easily obtained from the corresponding commercially available α-tetralones.[15] Commercially available *o*-iodophenol (**3a**) and its easily prepared *p*-substituted derivatives **3b** and **3c**, bearing electron withdrawing NO_2 and CO_2Me, respectively, were obtained by iodination of the correspondig phenols.[16] *O*-Iodophenol **3d**, substituted by CHO and MeO groups, prepared by iodination of vanillin[16] was considered as an option to install oxygenated groups at the D-ring, one of the limitations of this oxyarylation reaction.[6]

Pre-catalysts: $Pd(OAc)_2$ or

p-hydroxyacetophenone oxime-derived palladacycle
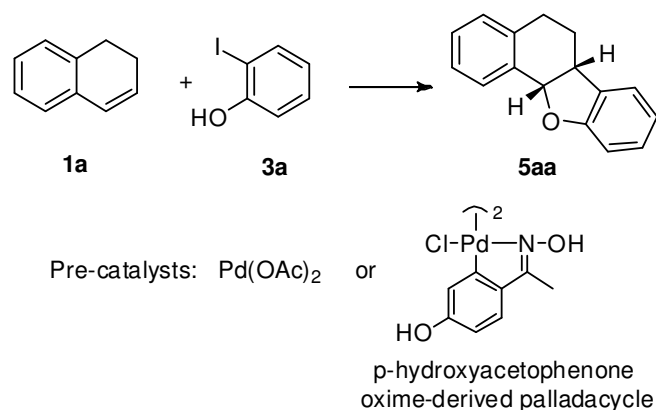
Scheme 1. Oxyarylation of **1a** with **3a**.

Table1. Optimizing the reaction conditions for the oxyarylation of **1a** with **3a**.

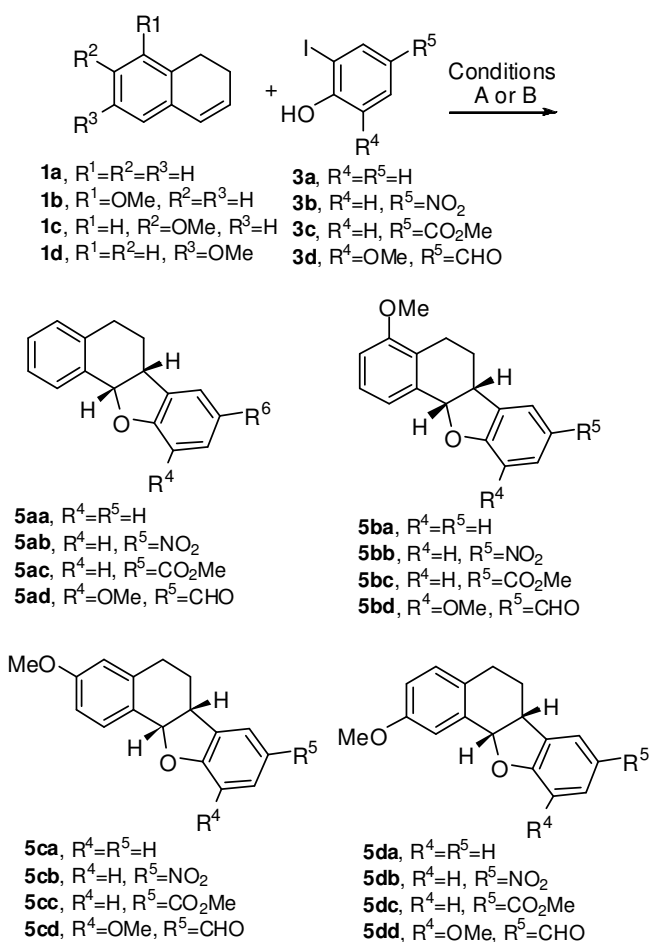| En-try	Cond [a]	Pd(mol%)	solvent	T (ºC)	Time [b]	Yield(%) [c]
1[c]	A	$Pd(OAc)_2$ (10)	acetone	60[d]	40 min	58
2	A	$Pd(OAc)_2$ (10)	PEG-2000	140	40 min	87
3	A	$Pd(OAc)_2$ (10)	PEG-400	140	2 h	45
4	A	$Pd(OAc)_2$ (10)	PEG-400	170	10 min	85
5	A	$Pd(OAc)_2$ (10)	PEG-200	140	2 h	-
6	A	$Pd(OAc)_2$ (5)	PEG-400	170	10 min	82
7[c]	B	palladacycle(1)	DMA/$H_2$0	120[d]	40 min	41
8	B	palladacycle (1)	PEG-2000	140	3 h	80
9	B	palladacycle (1)	PEG-400	140	3 h	-
10	B	palladacycle (1)	PEG-400	170	2 h	78

[a] Reaction followed by GC. [b] Isolated yield. [c] See ref. 6. [d] Under microwave irradiation (40 W, 60ºC). Condition A: base is Ag_2CO_3 (1.1 equiv). Condition B: base is Cy_2NH (2 equiv).

Once the product isolation was easier in PEG-400 than in PEG-2000, we decided to continue our study using this solvent. The

scope of the reaction was studied through the oxyarylation of dihydronaphthalene and methoxylated derivatives (**1a-d**) with substituted *o*-iodophenols **3a-d**, under the mentioned reaction conditions, A: Pd(OAc)$_2$ (10 or 5 mol%), Ag$_2$CO$_3$ (1.1 equiv.), PEG-400, 140 or 170^{0}C and B: *p*-hydroxyacetophenone oxime-derived palladacycle (1 mol%), Cy$_2$NH (2 equiv.), PEG-400, 140 or 170^{0}C (Scheme 2, Table 2).

In Scheme 2, Table 2, are shown the results obtained for the oxyarylation of **1a** with **3b-d**. Using conditions A, the oxyarylation of **1a** with **3b** and **3c** led to **5ab** and **5ac**, respectively, in excellent yields (Table 2, entries 1 and 2) while good yield of **5ad** were obtained in the reactions with **3d** (entry 3). Under conditions B, moderate to good yields were obtained (entries 4-6), in particular for electron poor *o*-iodophenols **3b** and **3c** (entries 4 and 5).

1a, R^1=R^2=R^3=H
1b, R^1=OMe, R^2=R^3=H
1c, R^1=H, R^2=OMe, R^3=H
1d, R^1=R^2=H, R^3=OMe

3a, R^4=R^5=H
3b, R^4=H, R^5=NO$_2$
3c, R^4=H, R^5=CO$_2$Me
3d, R^4=OMe, R^5=CHO

5aa, R^4=R^5=H
5ab, R^4=H, R^5=NO$_2$
5ac, R^4=H, R^5=CO$_2$Me
5ad, R^4=OMe, R^5=CHO

5ba, R^4=R^5=H
5bb, R^4=H, R^5=NO$_2$
5bc, R^4=H, R^5=CO$_2$Me
5bd, R^4=OMe, R^5=CHO

5ca, R^4=R^5=H
5cb, R^4=H, R^5=NO$_2$
5cc, R^4=H, R^5=CO$_2$Me
5cd, R^4=OMe, R^5=CHO

5da, R^4=R^5=H
5db, R^4=H, R^5=NO$_2$
5dc, R^4=H, R^5=CO$_2$Me
5dd, R^4=OMe, R^5=CHO

Scheme 2. Oxyarylation of **1a-e** with **3a-d**.

Table 2. Major conditions and yields for reaction shown in Scheme 2.

Entry	Cond[a]	T(°C)	1	3	5	Time (min)[b]	Yield (%)[c]
1	A	170	a	b	ab	30	91
2	A	170	a	c	ac	5	91
3[d]	A	170	a	d	ad	60	77
4	B	170	a	b	ab	120	66
5	B	170	a	c	ac	40	84
6	B	170	a	d	ad	240	47c
7	A	140	b	a	ba	10 (60)b	81 (85)b
8	A	140	b	b	bb	10 (60)b	93 (89)b
9	A	140	b	c	bc	15 (60)b	90 (88)b
10	A	140	b	d	bd	30 (60)b	10 (60)b
11	B	140	b	a	ba	120	70 (68)b
12	B	140	b	b	bb	180	43
13	B	140	b	c	bc	40	68
14	B	140	b	d	bd	180	64
15	A	140	c	a	ca	10 (40)b	80 (78)b
16	A	140	c	b	cb	20	89
17	A	140	c	c	cc	10	78
18	A	140	c	d	cd	30 (60)b	70 (75)b
19	B	140	c	a	ca	30	36
20	B	140	c	b	cb	120	68
21	B	140	c	c	cc	60	81
22	B	140	c	d	cd	240	30
23	A	140	d	a	da	5	80
24	A	140	d	b	db	40	80
25	A	140	d	c	dc	10	87
26	A	140	d	d	dd	60	68
27	B	140	d	a	da	40	30
28	B	140	d	b	db	180	70
29	B	140	d	c	dc	120	71
30	B	140	d	d	dd	240	38

[a]Reaction followed by CG and yields of purified products. [b]5 mol% of Pd(OAc)$_2$ was used in these cases. [c] PEG-2000 was used in this case.

Conditions A: Pd(OAc)$_2$ (10 mol%), Ag$_2$CO$_3$ (1.1 equiv.), PEG-400; Conditions B: Palladacycle (1 mol%), Cy$_2$NH (2 equiv.), PEG-400.

When 5-methoxydihydronaphthalene (**1b**) was allowed to react with *o*-iodophenol (**3a**) at 170ºC under Conditions A an extensive degradation was observed and only traces of adduct **5ba** could be detected by GC. However, this compound was obtained in 81% and 80% yields using 10 and 5 mol % of Pd(OAc)$_2$, respectively, in only 10 min of reaction time by lowering the temperature to 140ºC (Table 2, entry 7). Compounds **5bb**, **5bc** and **5bd** were also obtained by oxyarylation of **1b** with **3b-d**, in excellent yields, in 10 to 30 min under Conditions A at 140 ºC (Table 2, entries 8-10). Essentially the same yields were observed in the presence of 5 mol% of Pd(OAc)$_2$, although the reaction time increase to 1h (entries 8-10). Using Conditions B (entries 11-14), adducts **5** were obtained from moderate to good yield.

The same trend was also observed when **1c** and **1d** were oxyarylated with iodophenols **3a-d** (Table 2, entries 15-30). Under Conditions A (5 mol% Pd(OAc)$_2$), **5ca** to **5cd** and **5da** to **5dd** were obtained in excellent yields (entries 15-18 and 23-36) in few minutes, at 140ºC. On the other hand, compounds **5ca** and **5cd** (entries 19 and 22) as well as **5da** and **5dd** (entries 27 and 30) were obtained in moderate yields under Conditions B. However, products **5cb** and **5cc** (entries 20 and 21) as well as **5db** and **5dc** (entries 28 and 29) were isolated good yields.

Representative oxyarylation of **1a** with **3a** was scaled up to ~1g using conditions A, affording adduct **5aa** with similar yield (82 *versus* 72%). In addition, in this experiment Ag$_2$CO$_3$ was partially recuperated (70%) from the reaction medium, making the conditions A more environmentally appropriate. The recovered Ag$_2$CO$_3$ was used as base in other oxyarylations, leading to the adducts in essentially the same yield.

Next we evaluated the synthesis of **6** by oxyarylation of **1a** and **1c,d** with 3-iodolawsone (**4**) under conditions A. This reaction was discovered by da Silva and cols[17,18] and due to promising antineoplastic and anti-leishmanial activities, these compounds were

patented.[17] In previously results obtained for the preparation of **6a** from **1a**, the best yield was obtained by the use of Ag_2CO_3 (1.5 eq) as base, 3-iodolawsone (**4**) (2 eq) and pinacolone as solvent under reflux for 18 hours (57% yield).[17] In PEG-400 at 90 °C, the reaction between **1a** and **4** was faster (10 minutes), leading to adduct **6a** in 53% chemical yield (Scheme 3, Table 3, entry 1). The carbapterocarpanquinones **6b-d** were obtained with similar yields (entries 2-4).


a, $R^1=R^2=R^3=H$; **b**, $R^1=OMe$, $R^2=R^3=H$; **c**, $R^1=H$, $R^2=OMe$, $R^3=H$; **d**, $R^1=R^2=H$, $R^3=OMe$
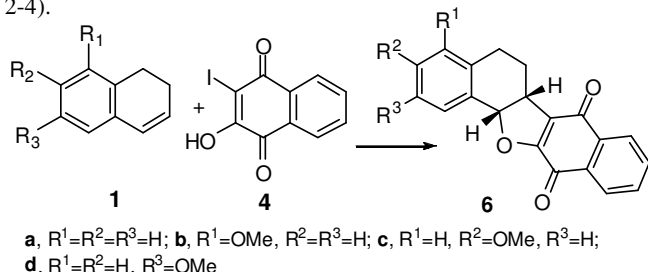
Scheme 3. Oxyarylation of **1** with **4**.

TABLE 3. Oxyarylation of **1a-d** with **4** under conditions A.

Entry	Cond[a]	T(°C)	1	6	Time (min)[b]	Yield (%)[c]
1	A	90	a	a	10	53
2	A	90	b	b	10	43
3	A	90	c	c	10	47
4	A	90	d	d	10	46

[a] Conditions A: Pd(OAc)$_2$ (10 mol%), Ag_2CO_3 (1.1 equiv.), PEG-400.

Finally, we studied the effect of PEG-400 on the oxyarylation of chromenquinone **2** with **3a-d** (Table 4). The pterocarpanquinone **7a** (know as LQB-118) has *in vitro* and *in vivo* activities as anti-cancer and antiparasitic.[7] Using conditions A, **7a** was obtained in 58% yield by the oxyarylation of **2** with **3a** (Scheme 4, Table 4, entry 1). We get a improvment on yield of this oxyarylation compared to the first synthesis of **7a** in acetone as solvent under reflux (40 % yield).[7d] When **2** was oxyarilated with **3b-c**, the yields of **7b,c** were lower, as in acetone (Scheme 4, Table 4, entries 2-4, 6), but the yield of **7d** increase from 14 to 30%.
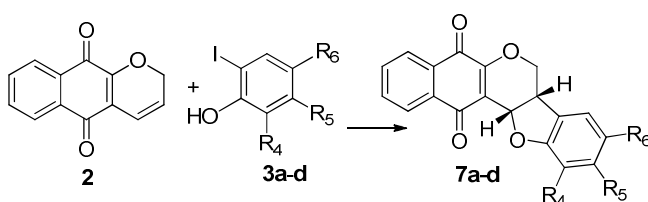
a, $R^4=R^5=R^6=H$; **b**, $R^4=R^5=H$, $R^6=NO_2$; **c**, $R^4=R^5=H$, $R^6=CO_2Me$; **d**, $R^4=OMe$, $R^5=H$, $R^6=CHO$

Scheme 4. Oxyarylation of **2** with **3a-d**.

Table 4. Major conditions and yield for reactions of Scheme 3.

Entry	Cond[a]	T(°C)	3	7	Time (min)[b]	Yield (%)[c]
1	A	90	3a	7a	10	58
2	A	90	3b	7b	10	11
3	A	90	3c	7c	10	23
4	A	90	3d	7d	10	30

[a] Conditions A: Pd(OAc)$_2$ (10 mol%), Ag_2CO_3 (1.1 equiv.), PEG-400.

Due the biological relevance of **7a**,[7] we scale up the synthesize of this compound. The oxyarilation of 14 mmol of **2** with **3a** (1.5 eq) furnished 2.5 g (58% yield) of **7a** after 30 min. of reaction under Conditions A at 90°C.

Conclusion

PEG-400 was employed for the first time as solvent in oxyarylation reactions. Once this solvent is neither volatile nor toxic, having several applications in medicine,[19] it is possible to work safely at higher temperatures. PEG-400 quickly reduce Pd^{II} from Pd(OAc)$_2$ or *p*-hydroxyacetophenone oxime-derived palladacycle to Pd^0 and the oxyarylations do not require the use of ligands. The oxyarylations of electron rich olefins (dihydronaphthalens **1a-d**) with *o*-iodophenols (**2a-d**), using Pd(OAc)$_2$ (5-10 mol %) as pre-catalyst and Ag_2CO_3 (1.1 equiv.) as base at 140 or 170 °C, are very fast (5-30 min), leading to adducts in good to excellent chemical yields and complete regio- and stereoselectivity, in spite of the pattern of substitution in the synthetic precursors. Alternatively, for the oxyarylations involving *o*-iodophenol and more activated *p*-nitro and *p*-carbomethoxy-*o*-iodophenols, the use of 4-hydroxyacetophenone oxime-derived palladacycle (1 mol %) as pre-catalyst and dicyclohexylamine (2 equiv.) as base in PEG-400 at 140 °C led to products in good yields, using a low catalytic load (1 mol%) in the absence of Ag_2CO_3.

Dihydronaphthalens (**1a-d**) also reacts fast with 3-iodolawsone **4**, leading to carbapterocarpanquinones **6a-d** in moderated yield.

In contrast with **1a-d**, electron poor olefin **2** reacts with *o*-iodophenols substituted by electron withdrawing groups leading to adducts in poor yields. However, reasonable yields are obtained with *o*-iodophenol (**3a**). In addition, products obtained in the reactions performed in acetone under MW heating need to be carefully purified by chromathography in silica gel while those obtained in PEG-400 required just a filtration in a pad of silica gel.

Experimental

General Experimental Section. ^{1}H and ^{13}C NMR spectra were recorded in CDCl$_3$ on 400 MHz NMR spectrometer using TMS as internal standard. Low-resolution electron impact (GC-EI) mass spectra were obtained at 70 eV using a Shimadzu QP-5000, and HRMS (GC-EI) were recorded using a Finnigan MAT 95S instrument. Analytical TLC was performed using Schleicher & Schuell F1400/LS silica gel plates, and the spots were visualized under UV light (λ=254 nm). Melting points were determined with a Fisatom 430 apparatus and are uncorrected. For flash chromatography, we employed Merck silica gel 60 (0.040–0.063 mm).

General Procedure for Oxyarylation Reactions

Conditions A: A mixture of the selected dihydronaphthalenes **1a-d** (0.5 mmol), *o*-iodophenols **3a-d** (1.0 mmol), Pd(OAc)$_2$ (5-10 mol%), Ag_2CO_3 (1.1 equiv.) and PEG-400 (2.0 mL) was heated in a flask under magnetic stirring at the temperature indicated in Tables 1 and 2. After the reaction time indicated, the mixture was cooled to rt and it was filtered through a pad of celite, using ethyl acetate (15 mL) as solvent. The organic layer was washed with distilled water (1 x 5 mL) and brine (3 x 5 mL), dried over anhydrous sodium sulfate and filtered. The solvent was evaporated in vacuo and the resulting oils were purified by flash chromatography on silica gel (3% AcOEt/hexane as eluent), leading to pure products **5**.

In one experiment **1a** (0.988 g, 7.26 mmol) was oxyarylated with **3a** (3.194 g, 14.52 mmol, 0.5 mol%) in Conditions A, using Pd(OAc)$_2$ (81.46 mg, 0.36 mmol). Compound **5aa** was obtained as a viscous oil in 72% yield (1.203 g). In this experiment the reaction was passed through a filter paper and the filtrate was washed with ethyl acetate (50 mL). The solution was treated as described above. The solid was washed with HNO$_3$ 10M (20mL), NaHCO$_3$ (2 x 20mL), H$_2$O (2 x 20mL) and dried under vacuum, leading to re-covered Ag$_2$CO$_3$ (1.541 g, 70%). This recovered Ag$_2$CO$_3$ was used in other oxyarylations, leading to products in similar chemical yields.

Conditions B: A mixture of the selected dihydronaphthalenes **1a-d** (0.5 mmol), *o*-iodophenols **3a-d** (1.0 mmol), palladacycle (1 mol%), Cy$_2$NH (2.0 equiv.) and PEG-400 (2 mL) was heated in a flask under magnetic stirring at the temperature indicated in Tables 1 and 2. The reaction was worked-up as above.

6a*R**,11a*S**)-4-Methoxy-5,6,6a,11a-tetrahydronaphtho[1,2-b]benzofuran (5ba): ^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.78 – 1.68 (m, 1H), 2.13 – 1.98 (m, 1H), 2.61 – 2.49 (m, 1H), 2.84 – 2.71 (m, 1H), 3.66 – 3.55 (m, 1H), 3.82 (s, 3H), 5.63 (d, *J* = 8.2 Hz, 1H), 6.91 – 6.77 (m, 3H), 7.12 (t, *J* = 8.1 Hz, 1H), 7.20 (d, *J* = 7.4 Hz, 1H), 7.26 (dd, *J* = 13.6, 5.7 Hz, 2H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: , 20.33, 26.97, 40.81, 55.61, 81.66, 109.57, 109.69, 120.59, 122.29, 124.34, 127.02, 127.65, 128.32, 131.90, 134.38, 156.51, 159.19.

(6a*R**,11a*S**)-4-Methoxy-8-nitro-5,6,6a,11a-tetrahydronaphtho[1,2-b]benzofuran (5bb): ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.14 (s, 1H), 8.09 (dd, *J* = 8.8, 1.8 Hz, 1H), 7.28 (dd, *J* = 14.7, 6.7 Hz, 1H), 7.16 (d, *J* = 7.7 Hz, 1H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.79 (d, *J* = 8.8 Hz, 1H), 5.83 (d, *J* = 8.5 Hz, 1H), 3.82 (s, 3H), 3.74 (m, 1H), 2.79 – 2.56 (m, 2H), 2.10 (m, 1H), 1.78 (m, 1H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 164.77, 156.46, 142.01, 133.05, 127.40, 127.34, 127.15, 125.97, 122.03, 120.79, 110.02, 109.46, 84.14, 55.47, 40.07, 26.78, 19.78.

Methyl(6a*R**,11a*S**)-4-methoxy-5,6,6a,11a-tetrahydronaphtho[1,2-b]benzofuran-8-carboxylate (5bc): ^{1}H NMR (500 MHz, CDCl$_3$) δ: 1.81- 1.73 (m, 1H), 2.13 – 2.04 (m, 1H), 2.63 – 2.55 (m, 1H), 2.75 – 2.69 (m, 1H), 3.70 - 3.65 (m, 1H), 3.81 (s, 3H), 3.88 (s, 3H), 5.74 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.88 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.94 (s, 1H); ^{13}C NMR (101 MHz, CDCl$_3$) δ:167.06, 163.47, 156.53, 133.78, 131.99, 127.52, 127.10, 126.20, 122.81, 122.12, 109.76, 109.44, 83.04, 55.58, 51.86, 40.14, 26.87, 19.91.

(6a*R**,11a*S**)-4,10-Dimethoxy-5,6,6a,11a-tetrahydronaphtho[1,2-b]benzofuran-8-carbaldehyde (5bd): ^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.77 - 1.85 (m, 1H), 2.13 – 2.00 (m, 1H), 2.76 – 2.54 (m, 2H), 3.75 (m, 1H), 3.81 (s, 3H), 3.90 (s, 3H), 5.85 (d, *J* = 8.6 Hz, 1H), 6.83 (dd, *J* = 6.5, 2.6 Hz, 1H), 7.25 (dd, *J* = 6.8, 2.7 Hz, 2H), 7.31 (d, *J* = 0.9 Hz, 1H), 7.43 (s, 1H), 9.83 (s, 1H); ^{13}C NMR (101 MHz, CDCl) δ:190.62,156.30, 153.63, 19.80, 145.00, 133.46, 133.21, 133.11, 131.27, 127.03, 122.54, 120.78, 111.61, 109.94, 84.20, 55.99, 55.49, 40.44, 26.85.

(6a*R**,11a*S**)-3-Methoxy-5,6,6a,11a-tetrahydronaphtho[1,2-b]benzofuran (5ca): ^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.87 – 1.79 (m, 1H), 2.02 – 1.98 (m, 1H), 2.72 – 2.55 (m, 2H), 3.65 – 3.63 (m,1H), 3.79 (s, 3H), 5.64 (d, *J* = 8.4 Hz, 1H), 6.67 (d, *J* = 2.2 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.90 – 6.81 (m, 2H), 7.11 (td, *J* = 7.8, 1.0 Hz, 1H), 7.22 (d, *J* = 7.3 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 159.44, 159.42, 140.54, 131.50, 131.38, 128.27, 125.75, 124.35, 120.47, 113.30, 112.60, 109.53, 81.78, 55.27, 41.03, 28.08, 27.83.

(6a*R**,11a*S**)-3-Methoxy-8-nitro-5,6,6a,11a-tetrahydronaphtho[1,2-b]benzofuran (5cb): ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.14 (s, 1H), 8.10 (d, *J* = 2.1 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 2H), 6.86 (dd, *J* = 8.4, 2.6 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 2.3 Hz, 2H), 5.87 (d, *J* = 8.7 Hz, 2H), 3.81 (s, 3H), 3.79 – 3.76 (m, 1H), 2.67 – 2.64 (m, 2H), 2.15 – 2.05 (m, 1H), 1.90 – 1.86 (m, 1H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 165.04, 159.82, 141.91, 140.38, 132.83, 131.54, 126.04, 124.20, 120.92, 113.37, 112.91, 109.32, 84.41, 55.31, 40.20, 27.92, 27.33.

Methyl(6a*R**,11a*S**)-3-methoxy-5,6,6a,11a-tetrahydronaphtho[1,2-b]benzofuran-8-carboxylate (5cc): ^{1}H NMR (400 MHz, CDCl$_3$$_3$) δ 7.93 (s, 1H), 7.88 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 6.85 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.68 (d, *J* = 2.5 Hz, 1H), 5.77 (d, *J* = 8.6 Hz, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 3.79 – 3.70 (m, 1H), 2.70 – 2.57 (m, 2H), 2.13 – 2.00 (m, 1H), 2.1 - 1.90 (m,1H); [13]C NMR (101 MHz, CDCl$_3$) δ: 157.76, 157.39, 142.80, 138.87, 133.04, 131.26, 129.19, 127.87, 127.14, 126.84, 118.58, 113.15, 112.05, 105.70, 55.14, 53.66, 44.87, 30.16, 29.77.

(6a*R**,11a*S**)-3,10-Dimethoxy-5,6,6a,11a-tetrahydronaphtho[1,2-b]benzofuran-8-carbaldehyde (5cd):^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.99 – 1.86 (m, 1H), 2.12 - 2.06 (m, 1H), 2.76 – 2.52 (m, 2H), 3.56 – 3.44 (m, 1H), 3.80 (s, 3H), 3.90 (s, 3H), 5.90 (d, *J* = 8.8 Hz, 1H), 6.67 (d, *J* = 2.6 Hz, 1H), 6.84 (dd, *J* = 8.4, 2.7 Hz, 1H), 7.26 (s, 1H), 7.42 (s, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 9.83 (s, 1H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 190.91, 159.95, 154.38, 145.01, 141.12, 132.78, 132.08, 131.83, 131.42, 124.46, 120.62, 113.26, 112.55, 111.57, 84.41, 55.84, 55.15, 28.01, 27.34.

(6a*R**,11a*S**)-2-Methoxy-5,6,6a,11a-tetrahydronaphtho[1,2-b]benzofuran (5da):^{1}H NMR (400 MHz, CDCl$_3$) δ 7.25 – 7.22 (m, 1H), 7.15 – 7.02 (m, 3H), 6.92 – 6.77 (m, 3H), 5.62 (d, *J* = 8.5 Hz, 1H), 3.83 (s, 3H), 3.68 – 3.62 (m, 1H), 2.68 – 2.53 (m, 2H), 2.10 – 1.99 (m, 1H), 1.78 – 1,73 (m, 1H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 159.21, 158.34, 134.31, 131.39, 130.78, 129.50, 128.27, 124.31, 120.51, 114.88, 114.45, 109.66, 82.11, 55.36, 41.18, 28.43, 26.79.

(6a*R**,11a*S**)-2-Methoxy-8-nitro-5,6,6a,11a-tetrahydronaphtho[1,2-b]benzofuran (5db):^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.14 (s, 1H), 8.10 (d, *J* = 2.4 Hz, 1H), 7.10 (s, 1H), 7.08 – 7.04 (m, 1H), 6.86 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 1H), 5.83 (d, *J* = 8.7 Hz, 1H), 3.84 (s, 3H), 3.84 – 3.75 (m, 1H), 2.69 – 2.59 (m, 2H), 2.22 – 2.07 (m, 1H), 1.90 – 1.77 (m, 1H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 165.13, 158.85, 142.16, 133.15, 131.03, 130.01, 129.51, 126.17, 120.92, 115.34, 114.35, 109.48, 85.11, 55.16, 39.88, 28.04, 26.64.

Methyl(6a*R**,11a*S**)-2-methoxy-5,6,6a,11a-tetrahydronaphtho[1,2-b]benzofuran-8-carboxylate (5dc): ^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.82 – 1.77 (m, 1H), 2.15 – 2.00 (m, 1H), 2.68 – 2.51 (m, 2H), 3.75 – 3.69 (m,1H), 3.84 (s, 3H), 3.88 (s, 3H), 5.73 (d, *J* = 8.7 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.84 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 2H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.94 (s, 1H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 166.98, 163.40,

158.27, 133.55, 131.74, 131.30, 130.84, 129.48, 126.29, 122.92, 115.11, 109.23, 83.21, 55.38, 51.87, 40.38, 28.08, 26.48.

(6aR^*,11aS^*)-2,10-Dimethoxy-5,6,6a,11a-tetrahydronaphtho[1,2-b]benzofuran-8-carbaldehyde (5dd): ^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.83 (s, 1H), 7.42 (t, J = 3.6 Hz, 1H), 7.13 (d, J = 2.5 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.84 (dd, J = 8.4, 2.6 Hz, 1H), 5.84 (d, J = 11.0 Hz, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 3.81 - 3.78 (m, 1H), 2.66 – 2.56 (m, 2H), 2.15 – 2.05 (m, 1H), 1.95 – 1.44 (m, 1H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 190.85, 158.36, 153.82, 144.87, 133.00, 132.83, 131.42, 131.17, 130.79, 129.38, 120.89, 115.39, 114.59, 111.54, 84.54, 55.91, 55.53, 28.07, 26.34.

Oxy-arylation of dihydronaphthalens with 3-iodolawsone under Conditions A.

A mixture of the selected dihydronaphthalenes **1a-d** (0.5 mmol), o-3-iodolawsone **4** (1.0 mmol), Pd(OAc)$_2$ (10 mol%), Ag$_2$CO$_3$ (1.1 equiv.) and PEG-400 (4.0 mL) was heated (in a flask under magnetic stirring at 90^{0}C for 10 min.. After the mixture was cooled to rt and it was filtered through a pad of celite, using ethyl acetate (35 mL) as solvent. The organic layer was washed with brine (3 x 50 mL), dried over anhydrous sodium sulfate and filtered. The solvent was evaporated in vacuo and the resulting oils were purified by flash chromatography on silica gel (5% AcOEt/hexane as eluent), leading to pure products **6a-d**.

(6aR^*,13aS^*)-6,6a-dihydrodinaphtho[1,2-b:2',3'-d]furan-7,12(5H,13aH)-dione (6a): ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.09 (td, J = 7.5, 1.1 Hz, 2H), 7.74 (td, J = 7.5, 1.4 Hz, 1H), 7.68 (td, J = 7.5, 1.4 Hz, 1H), 7.59 (dd, J = 5.2, 3.8 Hz, 1H), 7.31 (dd, J = 5.6, 3.4 Hz, 2H), 7.22 – 7.16 (m, 1H), 5.92 (d, J = 9.8 Hz, 1H), 3.94 (dt, J = 9.7, 7.0 Hz, 1H), 2.77 (ddd, J = 15.4, 8.4, 3.9 Hz, 1H), 2.67 (ddd, J = 15.7, 8.0, 3.8 Hz, 1H), 2.24 – 2.13 (m, 1H), 2.02 (tdd, J = 11.7, 7.7, 3.9 Hz, 1H).

(6aS^*,13aS^*)-4-methoxy-6,6a-dihydrodinaphtho[1,2-b:2',3'-d]furan-7,12(5H,13aH)-dione (6b): ^{1}H NMR (400 MHz, cdcl$_3$) δ 8.00 (ddd, J = 8.9, 7.7, 1.2 Hz, 1H), 7.65 (td, J = 7.5, 1.5 Hz, 1H), 7.59 (td, J = 7.5, 1.5 Hz, 1H), 7.24 – 7.07 (m, 1H), 6.78 (dd, J = 7.9, 1.2 Hz, 1H), 5.79 (d, J = 9.5 Hz, 1H), 3.83 – 3.77 (m, 1H), 3.74 (s, 1H), 2.71 (ddd, J = 16.5, 7.4, 4.0 Hz, 1H), 2.53 (ddd, J = 16.6, 8.8, 4.0 Hz, 1H), 2.14 – 2.07 (m, 1H), 1.88 – 1.78 (m, 1H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 182.39, 177.99, 160.01, 156.30, 134.12, 133.15, 132.92, 131.90, 127.99, 127.09, 126.28, 125.95, 122.47, 120.50, 110.30, 108.62, 84.73, 55.53, 39.56, 24.75, 19.76.

(6aR^*,13aS^*)-3-methoxy-6,6a-dihydrodinaphtho[1,2-b:2',3'-d]furan-7,12(5H,13aH)-dione (6c): ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.08 (t, J = 7.7 Hz, 2H), 7.76 – 7.71 (m, 1H), 7.70 – 7.64 (m, 1H), 7.48 (d, J = 8.5 Hz, 1H), 6.84 (dd, J = 8.4, 2.5 Hz, 1H), 6.70 (d, J = 2.2 Hz, 1H), 5.91 (d, J = 9.7 Hz, 1H), 3.91 (dt, J = 9.7, 6.3 Hz, 1H), 3.81 (s, 3H), 2.80 – 2.68 (m, 1H), 2.63 (ddd, J = 11.9, 7.0, 4.3 Hz, 1H), 2.19 – 2.02 (m, 2H); ^{13}C NMR (101 MHz, cdcl$_3$) δ 182.42, 178.03, 160.30, 159.98, 141.20, 134.14, 133.18, 132.92, 132.05, 131.45, 130.23, 126.29, 125.93, 123.21, 113.39, 112.64, 85.27, 55.29, 39.72, 27.46, 25.49.

(6aR^*,13aS^*)-2-methoxy-6,6a-dihydrodinaphtho[1,2-b:2',3'-d]furan-7,12(5H,13aH)-dione (6d): ^{1}H NMR (400 MHz, cdcl$_3$) δ 8.09 (ddd, J = 7.2, 5.7, 1.3 Hz, 2H), 7.74 (td, J = 7.5, 1.4 Hz, 1H), 7.68 (td, J = 7.5, 1.4 Hz, 1H), 7.12 (d, J = 2.7 Hz, 1H), 7.09 (d, J = 8.4 Hz, 1H), 6.87 (dd, J = 8.4, 2.7 Hz, 1H), 5.87 (d, J = 9.7 Hz,

1H), 3.90 (ddd, J = 9.7, 7.7, 5.7 Hz, 1H), 3.84 (s, 3H), 2.71 (ddd, J = 15.5, 8.0, 3.8 Hz, 1H), 2.65 – 2.56 (m, 1H), 2.25 – 2.14 (m, 1H), 2.02 – 1.91 (m, 1H); ^{13}C NMR (101 MHz, cdcl$_3$) δ 182.37, 177.99, 160.00, 158.34, 134.17, 133.14, 132.96, 131.73, 131.45, 131.16, 129.48, 126.85, 126.31, 125.97, 115.78, 114.51, 84.96, 55.46, 39.83, 26.49, 25.71.

Oxy-arylation of chromenquinone (2) with o-iodonaphenols (3a-d) under Condition A.

A mixture of chromenequinone (**2**) (0.5 mmol), o-iodophenol (**3a-d**) (0.75 mmol), Pd(OAc)$_2$ (10 mol%), Ag$_2$CO$_3$ (1.1 equiv.) and PEG-400 (4.0 mL) was heated (in a flask under magnetic stirring at 90^{0}C for 10 min.. After the mixture was cooled to rt and it was filtered through a pad of celite, using ethyl acetate (35 mL) as solvent. The organic layer was washed with brine (3 x 50 mL), dried over anhydrous sodium sulfate and filtered. The solvent was evaporated in vacuo and the resulting oils were purified by flash chromatography on silica gel (20% AcOEt/hexane as eluent), leading to pure products **7a-e** and **9**.

(7aS^*,12aS^*)-7,7a-dihydro-5H-benzo[g]benzofuro[3,2-c]chromene-5,13(12aH)-dione (7a): ^{1}H NMR (400 MHz, cdcl$_3$) δ 8.17 (dd, J = 7.6, 1.1 Hz, 1H), 8.11 (dd, J = 7.6, 1.3 Hz, 1H), 7.78 (td, J = 7.5, 1.5 Hz, 1H), 7.72 (td, J = 7.5, 1.4 Hz, 1H), 7.27 (dd, J = 7.1, 3.0 Hz, 1H), 7.21 (t, J = 7.8 Hz, 1H), 6.93 (td, J = 6.7, 3.0 Hz, 2H), 5.65 (d, J = 6.7 Hz, 1H), 4.58 (ddd, J = 11.3, 5.3, 0.8 Hz, 1H), 3.79 (t, J = 11.2 Hz, 1H), 3.61 – 3.54 (m, 1H); ^{13}C NMR (50 MHz, cdcl$_3$) δ 183.25, 179.28, 158.73, 157.01, 134.55, 133.38, 131.86, 130.57, 129.58, 126.49, 126.42, 125.11, 124.50, 121.23, 118.14, 110.79, 72.31, 67.09, 38.38.

(7aS^*,12aS^*)-9-nitro-7,7a-dihydro-5H-benzo[g]benzofuro[3,2-c]chromene-5,13(12aH)-dione (7b): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.29 – 8.10 (m, 4H), 7.80 (tt, J = 8.9, 6.6 Hz, 2H), 7.01 (d, J = 9.6 Hz, 1H), 5.89 (d, J = 7.0 Hz, 1H), 4.65 (dd, J = 11.3, 5.1 Hz, 1H), 3.97 – 3.83 (t, J= 11.0 Hz, 1H), 3.83 – 3.70 (m, 1H); ^{13}C NMR (101 MHz,) δ 179.02, 164.18, 157.43, 142.58, 134.96, 133.88, 131.84, 130.72, 127.21, 126.83, 126.78, 121.23, 117.26, 110.94, 74.75, 66.61, 38.08, 29.72.

(7aS^*,12aS^*)-methyl-5,13-dioxo-7,7a,12a,13-tetrahydro-5H-benzo[g]benzofuro[3,2-c]chromene-9-carboxylate (7c): ^{1}H NMR (400 MHz, CDCl3), δ (ppm): 8.21–8.13 (2H, m); 7.99 (1H, s); 7.97 (1H, d, J = 8.6 Hz); 7.82–7.73 (2H, m); 6.95 (1H, d, J = 8.3 Hz); 5.77 (1H, d, J = 6.8 Hz); 4.61 (1H, dd, J = 5.1, 11.3 Hz); 3.89 (3H, s); 3.82 (1H, t, J = 11.0 Hz); 3.68–3.63 (1H, m).

(7aS^*,12aS^*)-11-methoxy-5,13-dioxo-7,7a,12a,13-tetrahydro-5H-benzo[g]benzofuro[3,2-c]chromene-9-carbaldehyde (7d):

^{1}H NMR (400 MHz, cdcl$_3$) δ 9.86 (s, 1H), 8.20 (dd, J = 7.5, 1.1 Hz, 1H), 8.15 (dd, J = 7.6, 1.2 Hz, 1H), 7.81 (td, J = 7.5, 1.5 Hz, 1H), 7.75 (td, J = 7.5, 1.5 Hz, 1H), 7.47 (d, J = 0.8 Hz, 1H), 7.41 (d, J = 1.4 Hz, 1H), 5.86 (dd, J = 6.8, 0.7 Hz, 1H), 4.64 (ddd, J = 11.3, 5.2, 0.8 Hz, 1H), 3.94 (s, 3H), 3.84 (t, J = 11.2 Hz, 1H), 3.73 – 3.66 (m, 1H); ^{13}C NMR (101 MHz, acetone) δ 184.97, 177.57, 173.99, 151.95, 147.81, 140.55, 129.62, 128.40, 126.72, 126.71, 125.42, 122.01, 121.47, 121.43, 115.14, 112.25, 107.91, 69.24, 61.70, 50.84, 33.03.

Scale up of pterocarpanquinone 7a: (LQB-118)

A mixture of chromenequinone (**2**) (2.97 g, 14 mmol), o-iodophenol (**3a**) (3.7 g, 16.8 mmol), Pd(OAc)$_2$ (314.3 mg, 1.4

mmol, 10 mol%), Ag$_2$CO$_3$ (4.25 g, 15.4 mmols, 1.1 equiv.) and PEG-400 (100.0 mL) was heated in a flask under magnetic stirring at 90^{0}C for 30 min.. After the mixture was cooled to rt and it was filtered through a pad of celite, using ethyl acetate (250 mL) as solvent. The organic layer was washed with brine (3 x 150 mL), dried over anhydrous sodium sulfate and filtered. The solvent was evaporated in vacuo and the resulting oil was purified by flash chromatography on silica gel (125g) (30% AcOEt/hexane as eluent), leading to 2.5 g (8.1 mmol) of **7a** in 58% yield .

Acknowledgments

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