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Synthesis of C_2 symmetric hydroxylated biphenyls by microwave-assisted oxidative coupling of natural phenols

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ABSTRACT

Phenolic compounds, abundant in various plants, exhibit a range of biological properties such as anti-inflammatory, antiseptic, and antioxidant activities. C_2-symmetric biphenyl structures, present in many pharmacologically active substances, serve as fundamental backbones in many natural products, highlighting the significance of these compounds. This study introduces innovative microwave-assisted oxidative coupling methods for the synthesis of C_2 hydroxylated biphenyls starting from thirteen natural phenols, focusing on eco-friendliness and efficiency. This approach aims to minimize environmental impact while emphasizing safety and sustainability by employing microwaves in environmentally sustainable solvents like water. The proposed mechanisms for the oxidative coupling of phenols include various possible reaction pathways, encompassing both homo and hetero radical-radical couplings.

1. Introduction

Phenolic compounds, a group of phytochemical molecules with at least one phenol unit in their structure, can be classified as simple phenols and polyphenols depending on the number of phenol units in the molecule. These compounds, vital components of dietary antioxidants globally, are bioactive secondary metabolites. They encompass various compound families found abundantly in nature, including flavonoids, lignins, lignans, phenolic acids, tannins, phenylpropanoids, and stilbenes [1,2]. Naturally occurring phenols are present, as main components, in various medicinal herbs [3] exhibiting a wide range of biological properties including anti-inflammatory, antiseptic, antioxidant, and fungicidal activities [4,5]. It is proven that simple phenols provide innate defensive protection in many plant species, mainly due to their ability to prevent viruses, bacteria and fungi, and to protect plants from excessive ultraviolet radiation or other environmental factors [6].

C_2-symmetric hydroxylated biphenyls are found in diverse natural molecules, playing a significant role in various biological structures. Notably, these compounds are integral components of biologically relevant substances like lignins and ellagitannins [7]. The distinct pharmacophore structure of hydroxylated biphenyls, characterized by two aromatic rings connected by a single C–C bond, makes them particularly effective as specific ligands for receptor molecules that could be utilized for the discovery and design of therapeutics [8]. Generally, the dimeric structures endowed with C_2 symmetry exhibit higher biological activities than those of the corresponding monomers [9]. Our laboratory has a long-standing interest and experience in the synthesis and biological evaluation of natural-like hydroxylated biphenyls [10,11].

The reactions documented in the literature for the symmetric dimerization of phenols typically involve couplings mediated by oxidants such as $FeCl_3$ [12], $K_3Fe(CN)_6$ [13], $K_2S_2O_8$ [14] and $Mn(acac)_3$ [15] or by enzymatic catalyzed oxidative process [16]. The vast majority of these reactions involve the use of dangerous and carcinogenic organic solvents like dichloromethane and chlorobenzene. Unexpectedly, based on our current understanding, there is a scarcity of documented oxidative coupling reactions conducted utilizing microwaves [17], with existing studies not exploring the use of environmentally friendly solvents such as water or MeOH [18].

Our research group has recently dedicated efforts to enhancing reaction efficiency by utilizing microwave (MW) irradiation [19,20]. This technology offers a multitude of advantages, such as heightened yields and shortened reaction times. We recently documented a direct microwave-assisted oxidative coupling of vanillin, producing the corresponding dimer in remarkable yields [21]. The present study aims to explore a wider applicability of microwave-assisted oxidative coupling

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of various natural phenols. Our goal was to enhance sustainability and efficiency in synthesizing natural phenol dimers by investigating alternative eco-friendly methods. Specifically, we sought to employ safe solvent and sustainable microwave-assisted procedures to achieve this objective. We considered 13 commercial phenols **1a**-**13a** as starting material (Fig. 1). All these phenols are naturally occurring compounds with significant biological activities. They are sourced from various plants, including *zingiber officinalis* (**1a**) [22]; *red raspberry* (**2a**) [23]; *thymus vulgaris* (**3a**) [24]; *origanum vulgare* (**4a**) [25]; *vanilla planifolia* (**5a**) [26]; *Litsea costalis* (**6a**) [27]; *Strychnos cathayensis* (**7a**) [28]; *Solanum melongen* (**8a**) [29]; *Syzygium aromaticum* (**9a**) [30]; *Syzygium austroyunnanense* (**10a**) [31]; *Entandrophragma angolense* (**11a**) [32]; *Paeonia suffruticosa* (**12a**) [33]; *vanilla fragrans* (**13a**) [34].

The present study employed several typical oxidants commonly reported in the literature for coupling reactions of natural phenols. These reagents include methyltributyl ammonium permanganate (MTBAP), a quaternary ammonium permanganate salt; potassium persulfate ($K_2S_2O_8$), a potent oxidizing agent often used with iron sulfate ($FeSO_4$) as a catalyst; potassium ferricyanide ($K_3Fe(CN)_6$); di-*tert*-butyl peroxide (DTBP), an organic peroxide capable of generating free radicals to initiate the coupling reaction of phenolic compounds. In the literature these oxidants are pivotal in facilitating oxidative coupling reactions, resulting in the selective formation of C_2 symmetric dimers of commercial natural phenols (Scheme 1).

The synthesis of compounds **1b** [35], **2b** [36] and **13b** [37] were reported by our group through the oxidative coupling of the corresponding monomers using MTBAP in dichloromethane with yields ranging between 46 % and 65 %. Compounds **9b** and **10b** were prepared by Marques et al. [38] using the same oxidizing reagent in 52 % and 54 % yield respectively (Scheme 1 PANEL (A)). Dimer **13b** was synthesized in good yield but in a quite long reaction time, by Uyanik et al. employing aqueous hydrogen peroxide as the oxidizing agent, and calcium hypoiodite as catalyst [39]. In the literature, it is documented that thymol **3a** (Scheme 1 PANEL (B)). undergoes coupling reactions mediated by DTBP, primarily yielding the corresponding symmetric dimer **3b**, however, the yield of this reaction has not been specified [40]. Conversely, when carvacrol **4a** is subjected to the same reaction conditions, derivative, **4b** is obtained as a minor product, indicating a significantly lower reactivity or preference for alternative reaction pathways. Additionally, compounds **3b** and **4b** have undergone limited characterization. Compound **3b** was also previously obtained in good yield (68 %) through a microwave-assisted reaction with DTBP in chlorobenzene, a carcinogenic organic solvent [17]. The preparations of compounds **5b** [41] and **11b** [42] were described by efficient oxidative couplings of vanillin **5a** and apocynin **11a** respectively, in the presence of potassium persulfate and iron sulfate in water (Scheme 1 PANEL (C)). The synthesis of dimer **8b** does not appear to be reported in the literature. Conventional oxidative coupling of monomer **6a** has been described by Wang et al. [43] by carbonyl protection followed by oxidation with potassium ferricyanide within an alkaline environment. This strategy involves in situ protection of the carbonyl group as dimethyl ketal using trimethyl orthoformate (TMOF) and tetrabutylammonium tribromide ($TBABr_3$) as a catalyst, oxidative dimerization, and removal of the protective group (Scheme 1 PANEL (D)). Compounds **7b** and **12b** were mentioned as by-products in the synthesis of 2,3-dihydroxy-5-methoxyacetophenone and 2,5-dihydroxy-3-methoybenzaldeide respectively using potassium persulfate in alkaline medium [44], but their characterization was not provided, and yields were reported to be low without specific values given (Scheme 1 PANEL (E)).

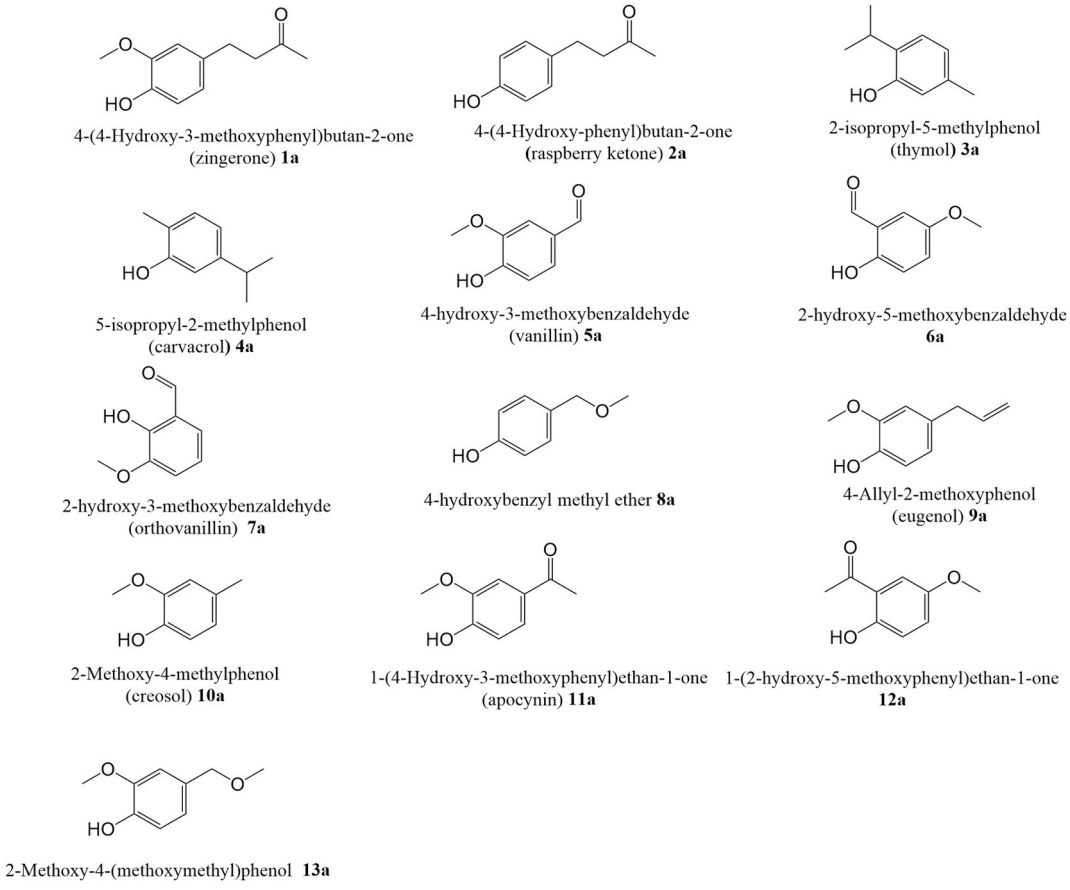
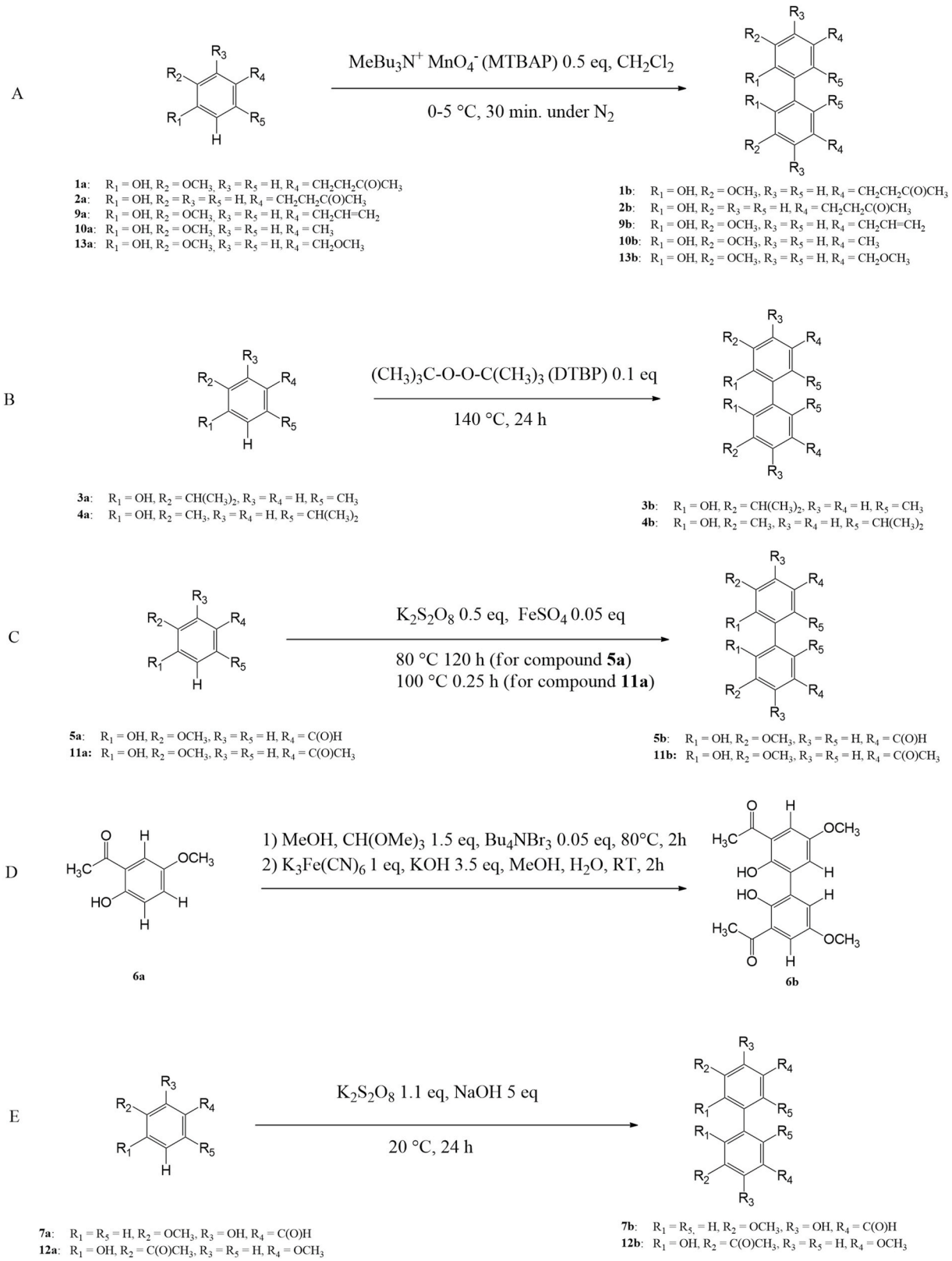


Fig. 1. Chemical structures of natural phenols **1a-13a**.



Scheme 1. Conventional oxidative dimerization of phenols: PANEL (A) **1a**, **2a**, **9a**, **10a**, and **13a;** PANEL (B) **3a** and **4a**; PANEL (C) **5a** and **11a**: PANEL (D) **6a**; PANEL (E) **7a** and **12a**.

2. Results and discussion

In this study, we replaced the use of hazardous organic solvents such as dichloromethane with water under microwave-mediated reaction conditions for the dimerization of phenols **1a**, **2a**, **8a**, **9a**, **10a**, and **13a** using MTBAP as oxidant. This modification enabled us to achieve yields of the corresponding dimers comparable to those obtained using dichloromethane but with markedly shorter reaction times. Monomer

2a demonstrates poor water solubility, hindering the formation of the corresponding dimer **2b**, which occurs in a relatively low yield (Table 1, entry 2). To address this issue, we carried out the corresponding microwave-assisted reaction also in methanol, an environmentally friendly compound listed as a safe solvent [18,45]. By employing MeOH as the solvent, not only the solubility of monomer **2a** was enhanced, but also the reaction efficiency was significantly improved. This enhancement led to a notable increase in yield from 30 % to 50 % with a reduction of reaction time.

We synthesized products **3b** and **4b** by using neat DTBP under microwave irradiation. Our process demonstrated notable efficiency, yielding 58 % for product **3b** and a remarkable 85 % for product **4b** (Table 1, entries 4 and 5). Furthermore, these reactions proceeded with reduced reaction times compared to conventional methods.

The presence of an electron-withdrawing group substituent like a carbonyl directly attached to the aromatic ring significantly hinders the coupling reactions when MTBAP was employed as oxidant. These findings were corroborated in our investigation involving phenolic substrates **5a**, **6a**, **7a**, **11a**, and **12a**, where the presence of MTBAP failed to produce the corresponding dimers in acceptable yields. Using microwaves, we achieved **5b** and **11b** in yields comparable to reported conventional methods but with significantly shorter reaction times (Table 1, entries 6 and 12).

For the synthesis of dimer **7b** and **12b** we chose to employ potassium persulfate and iron sulfate in water as oxidizing agents using both conventional and microwave-assisted methods. These reagents were selected due to their established capability to efficiently catalyze the coupling reaction of vanillin **5a** and apocynin **11a** which exhibit isomeric characteristics akin to phenols **7a** and **12a**. The conventional method resulted in a 23 % yield for compound **7b** and a 8 % yield for compound **12b**, while, microwave-assisted reactions produced **7b** and **12b** in 35 % and 10 % yields, respectively (Table 1, entries 8 and 13). These low yields obtained in the preparation of **6b** with MTBAP and of **7b** and **12b** with potassium persulfate and iron sulfate can be attributed to three factors: 1) the electron-withdrawing nature of the carbonyl group; 2) the plausible formation, during the oxidation, step of a stable quinone species **14**, which is analogous to quinone **15** documented in the literature and arising from the oxidative C–C homocoupling of 2,6-dimethoxy phenol [39]; 3) the probable formation of intramolecular six-membered cyclic structures emerging from the interaction between the phenolic hydroxyl group and the *ortho* carbonyl oxygen in phenols **6a**, **7a** and **12a** [46] (Fig. 2).

Considering the potential impact of a specific intramolecular hydrogen bond on the generation of the hydroxyl radical, crucial for the initial step of the oxidative radical coupling reaction of compounds **6a**, **7a**, and **12a** we aimed to enhance yields, particularly in the dimerization reaction of **6a** and **12a**. We employed a carbonyl protection approach followed by oxidation with $K_3Fe(CN)_6$ within an alkaline environment to achieve this. This one-pot, three-step method was previously validated by Wang et al. [43] inducing the dimerization of compound **6a** with a 56 % yield. This strategy involves in situ protection of the carbonyl group as dimethyl ketal using trimethyl orthoformate (TMOF) and tetrabutylammonium tribromide ($TBABr_3$) as a catalyst, oxidative dimerization, and removal of the protective group. Employing this synthetic approach, we obtained compound **12b** with a 57 % yield under conventional heating conditions. Notably, using the microwave-assisted method yielded a similar yield (60 %) with significantly reduced reaction times. Furthermore, the microwave-assisted dimerization of compound **6a** proceeded with an impressive 90 % yield (Table 1, entries 7 and 14). Compound **8b** has not been previously synthesized according to existing literature. Consequently, we successfully prepared dimer **8b** using conventional and microwave-assisted methods, using MTBAP as an oxidant. Due to the substantial insolubility of monomer **8a**, it was essential to employ as solvent a dichloromethane:acetone 5:2 mixture for conventional dimerization reaction and a water:acetone 5:2 mixture for microwave-mediated procedure (Table 1, entry 9). Both reactions proceeded with low yields, likely attributable to the electron-deficient nature of the aromatic ring, which lacks an electro-donating methoxy group.

The relatively low yields observed in many oxidative couplings of phenols can be attributed to the complexity of the reaction mechanisms that produces numerous parallel reactions besides the expected C_2 symmetric dimers. The initial step in these reactions involves the formation of phenoxyl radical, which undergoes delocalization across the aromatic ring, resulting in various resonance structures. For instance, in neutral solution compound **1a**, in the presence of MTBAP, undergoes radical oxidation, resulting in the formation of phenoxyl radical **A** delocalized at the *ortho* and *para* positions, giving rise to radical species **B**, **C**, and **D** (Scheme 2). In addition to the **D-D** homo-coupling, which produces the expected C_2 symmetric dimer **1b**, many other homo- and hetero-coupling reactions such as **C-A** and **B-A** can occur, leading to the formation of asymmetric dimers with quinone structures. Finally, reactions between phenoxyl radicals **A** can result in the formation of symmetric peroxide dimer **A-A**.

Table 1
Conventional methods and microwave-assisted synthesis of dimers **1b-13b**.

			Conventional methods				Microwave-assisted synthesis			
Entry	**Dimer**	**Oxidant**	**Solvent**	**Temp. (°C)**	**Time (h)**	**Yield (%)**[a]	**Solvent**	**Temp (°C)**	**Time (h)**	**Yield (%)**[a]
1	**1b**	MTBAP	CH_2Cl_2	RT	1	65	H_2O	100	0.13	59
2	**2b**	MTBAP	CH_2Cl_2	RT	1	46	H_2O	100	0.13	30
3	**2b**	MTBAP	CH_2Cl_2	RT	1	46	MeOH	84	0.08	50
4	**3b**	DTBP	neat	140	24	NR	neat	150	0.13	58
5	**4b**	DTBP	neat	140	24	NR	neat	150	0.13	85
6	**5b**	$Na_2S_2O_8/FeSO_4$	H_2O	80	120	95	H_2O	100	0.13	92
7	**6b**	$K_3Fe(CN)_6$/KOH	H_2O/MeOH	80	2+3[b]	56	H_2O/MeOH	80	0.13 + 0.5[c]	90
8	**7b**	$Na_2S_2O_8/FeSO_4$	H_2O	100	3	23	H_2O	100	0.13	35
9	**8b**	MTBAP	CH_2Cl_2/acetone	RT	5	20	H_2O/acetone	95	0.5	29
10	**9b**	MTBAP	CH_2Cl_2	RT	0.25	52	H_2O	100	0.13	57
11	**10b**	MTBAP	CH_2Cl_2	RT	0.25	54	H_2O	100	0.13	63
12	**11b**	$Na_2S_2O_8/FeSO_4$	H_2O	100	0.25	95	H_2O	100	0.13	92
13	**12b**	$Na_2S_2O_8/FeSO_4$	H_2O	100	1	8	H_2O	100	0.13	10
14	**12b**	$K_3Fe(CN)_6$/KOH	H_2O/MeOH	80/RT	2+3[b]	57	H_2O/MeOH	80	0.5 + 0.25[d]	60
15	**13b**	MTBAP	CH_2Cl_2	RT	0.5	60	H_2O	100	0.16	84

NR = not reported; RT = room temperature.
[a] Overall isolated yield, after purification by flash chromatography.
[b] 2 h at 80 °C for carbonyl protection then 3 h at RT for coupling reaction (according to Ref 44).
[c] 0.13 h at 80 °C for carbonyl protection then 0.5 h at 80 °C for coupling reaction (under MW irradiation).
[d] 0.5 h at 80 °C for carbonyl protection then 0.25 h at 80 °C for coupling reaction (under MW irradiation).

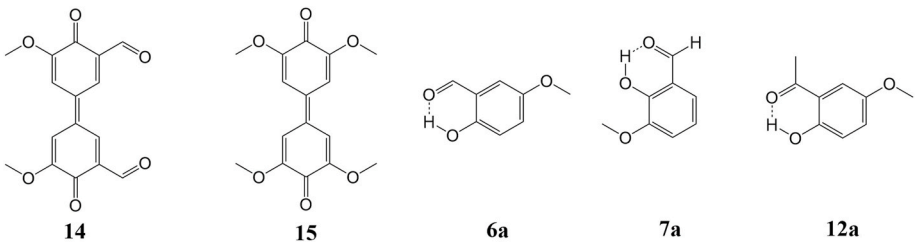
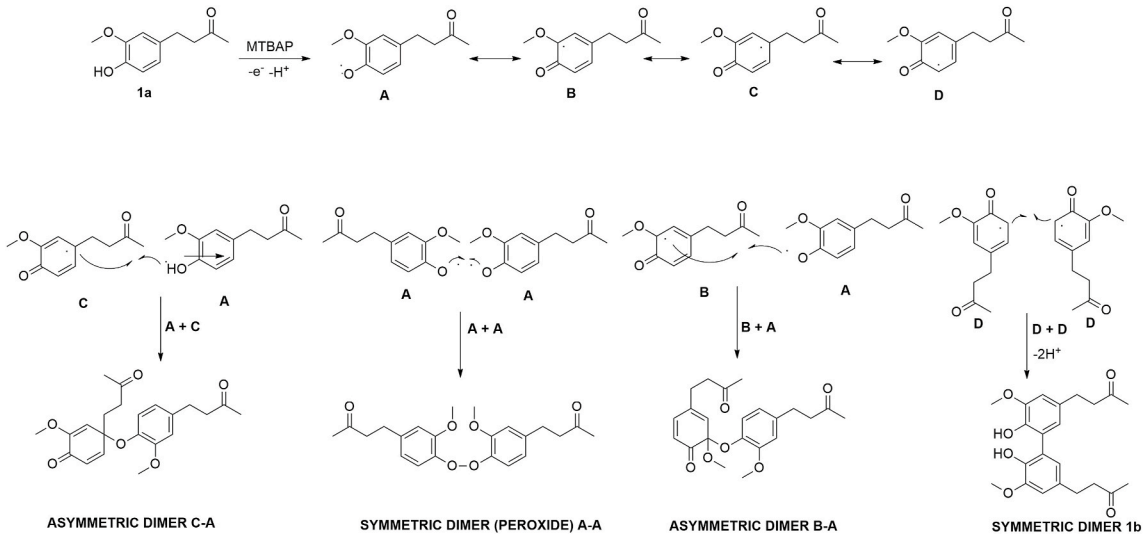


Fig. 2. Structures of quinones **14** and **15** and intramolecular hydrogen bonding in **6a**, **7a** and **12a**.

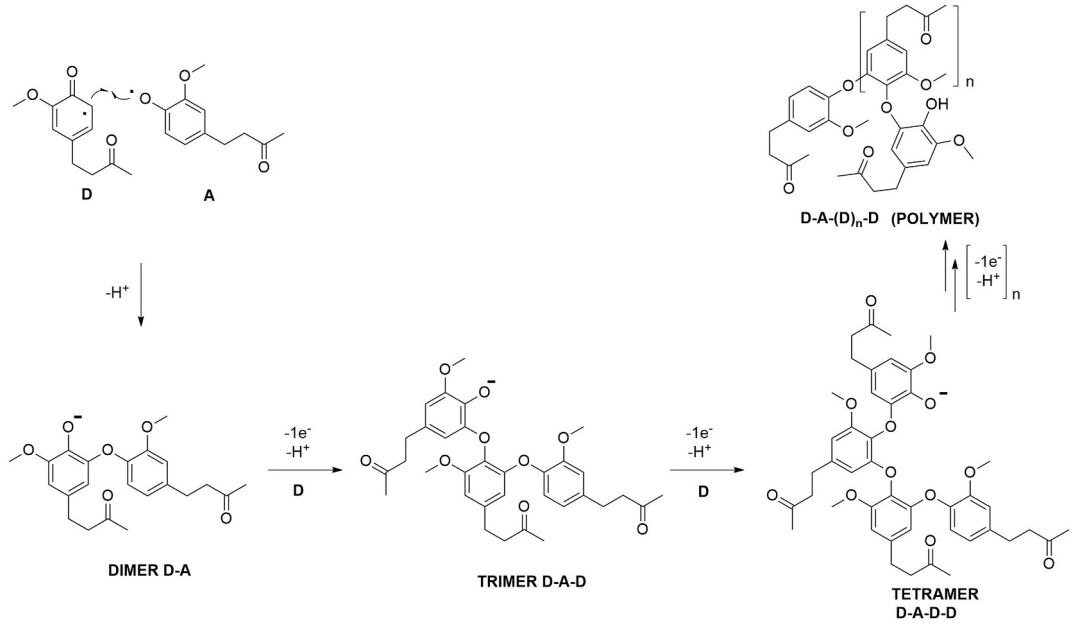


Scheme 2. Hypothetical homo- and hetero-oxidative coupling of radical resonance structures **A**, **B**, **C** and **D**.

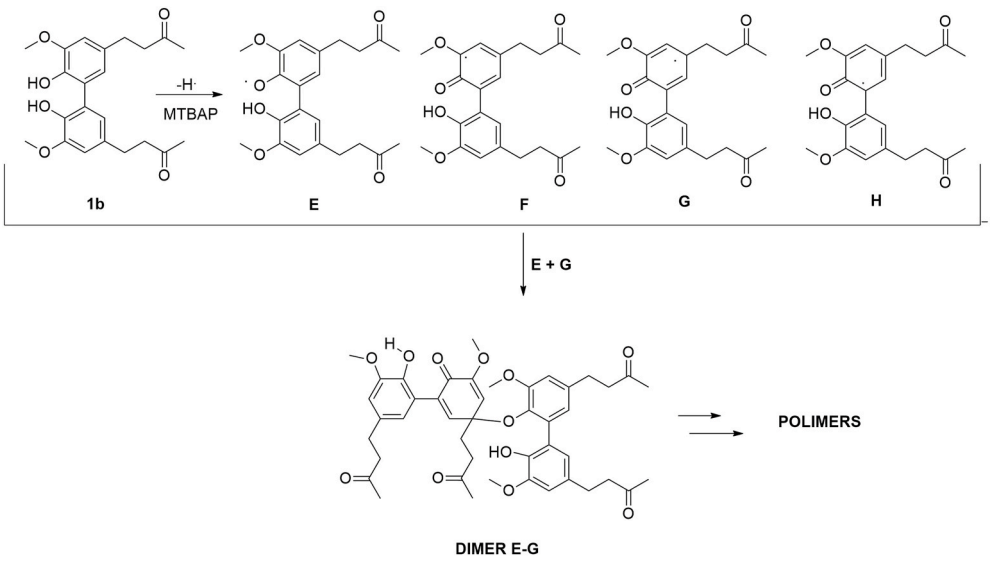
The reaction mechanism becomes increasingly complex due to the potential involvement of polymerization reactions. For example, dimer **D-A** could generate a polymeric structure through various intermediate steps like trimer **D-A-D** and tetramer **D-A-D-D** (Scheme 3).

Furthermore, another possible mechanistic pathway involves the over-oxidation of the expected dimer **1b**. The oxidation of this symmetric dimer could generate phenoxyl radical **E** and dimeric quinonic structures **F**, **G** and **H**. These quinonic structures can further evolve into complex polymeric forms structurally distinct from those anticipated for **1a** polymerization (Scheme 4).

In this study, a comparative analysis was undertaken to assess the percentage yields and overall reaction times for the synthesis of natural



Scheme 3. Polymerization of **1a** by MTBAP *via* over-oxidation of dimer **D-A**.



Scheme 4. Polymerization of **1*b*** under oxidative conditions.

phenol dimers by both conventional methods and microwave-assisted techniques to determine whether oxidative coupling of phenols under MW irradiation confers any advantages over traditional methods. The proposed new microwave-mediated reactions substituted the use of hazardous organic solvents such as dichloromethane with water, offering a safer, non-toxic, economically feasible, and environmentally friendly solvent alternative option. In the majority of our microwave-mediated dimerizations, dimers are obtained with comparable (Table 1, entries 1–3, 6, 8–14) or higher yields (Table 1, entries 4, 5, 7, 15) than those obtained using traditional methods. Moreover, all microwave-assisted reactions documented in this study demonstrated notably reduced reaction times in comparison to conventional methods, albeit with the need, in some cases, to use higher temperatures. It's crucial to emphasize that microwave-mediated reactions necessitate instruments equipped with safety features like pressure relief valves to handle emergencies by releasing excess pressure. Microwave management technology utilizes specialized ovens to ensure safety through automated pressure control, providing a secure means for conducting pressurized reactions. We maintain that eco-friendly alternative methods reported in this paper for the synthesis of C_2-symmetric natural-inspired biphenols **1b**–**13b**, present notable advantages in terms of safety and sustainability. These methods prioritize the utilization of environmentally benign solvents, thereby decreasing the production of hazardous waste and mitigating the environmental footprint typically associated with conventional synthetic routes. Additionally, by employing microwave-assisted reactions, we not only enhance the efficiency of the synthesis but also mitigate potential safety risks associated with prolonged reaction stirring. One major limitation of this methodology is its challenge in scaling up, as it restricts the amount of reagents and solvents that can be accommodated within the reaction tube. All newly synthesized compounds underwent thorough characterization employing ^{1}H and ^{13}C nuclear magnetic resonance (NMR) techniques.

3. Conclusion

In summary, we have successfully developed alternative methods for synthesizing natural-inspired C_2-symmetric biphenols by microwave-assisted oxidative coupling in water or MeOH as sustainable solvents. Our alternative, eco-friendly procedures for synthesizing C_2 phenol dimers provide substantial benefits in terms of safety and sustainability thereby mitigating the environmental impact linked with conventional synthetic pathways. Furthermore, through the adoption of microwaves, we could not only improve the synthesis efficiency but also alleviate potential safety hazards associated with prolonged stirring during reactions. Overall, our approach promotes safer working conditions, minimizes environmental harm, and contributes to sustainable chemistry practices.

4. Experimental section

4.1. General information

Reagents were obtained from Sigma Aldrich, Munich, Germany, and were used without further purification. Microwave reactions were carried out on a MW instrument (CEM-Discover SP MW, Matthews, NC, USA). ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or acetone d6 or DMSO-d_6 solution at 600 and 150 MHz, respectively, with a 600 MHz NMR spectrometer Bruker Advance III HD, (Palo Alto, CA, USA). Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and dd (doublet of doublets). Elemental analysis was performed using an elemental analyzer model 240 C (PerkinElmer, Waltham, MA, USA). Flash chromatography was carried out with silica gel 60 (230–400 mesh) (VWR, Radnor, AF, USA) eluting with an appropriate solution in the stated v:v proportions. The reactions were monitored by analytical thin-layer chromatography (TLC) with 0.25 mm thick silica gel plates (60 F 254) (Sigma Aldrich, Munich, Germany). The melting points were determined on a 530 apparatus (Büchi, Flawil, Switzerland) and are uncorrected. The purity of new compounds was judged to be >98 % by ^{1}H NMR spectral determination.

4.2. General procedure for oxidative microwave-induced coupling reactions of *1a, 2a, 8a, 9a, 10a* and *13a* with tetrabutylammonium permanganate (MTBAP) in water. Synthesis of *1b, 2b, 8b, 9b, 10b* and *13b*

To a solution of natural phenol **1a** or **2a** or **9a** or **10a** or **13a** (3 mmol) in H_2O (15 mL) or **8a** (3 mmol) in H_2O:acetone 5:2 (15 mL) at rt, was added MTBAP (1.5 mmol). The mixture was subsequently subjected to stirring under microwave (MW) irradiation at 300 W and held at 100 °C for the times indicated in Table 1. The solution was cooled at rt, dichloromethane was added, and the organic layer was separated, washed with a 10 % aqueous solution of HCI (3 x 5 mL), and with saturated aqueous sodium bisulfite solution, dried over anhydrous Na_2SO_4, filtered and roto evaporated under reduced pressure. The product obtained was purified by flash chromatography on silica gel

using a mixture 1:1 of ethyl aceate: petroleum ether as eluent to obtain dimers **1b** or **2b** or **8b** or **9b** or **10b** or **13b** in 59 %, 30 %, 29 %, 57 %, 63 % and 84 % yield respectively.

1b: mp = 86–87 °C [lit [35] 85–86 °C]; ^{1}H NMR ($CDCl_3$) δ ppm 2.15 (s, 6H), 2.76–2.88 (series of m, 8H), 3.92 (s, 6H), 6.02 (bs, 2H), 6.71 (d, J = 2.0 Hz, Ar, 2H), 6.73 (d, J = 2.0 Hz, Ar, 2H); ^{13}C NMR ($CDCl_3$) δ ppm 29.53 30.16, 45.49, 56.13, 110.66, 122.71, 124.39, 132.92, 140.92, 147.20, 208.11; Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78; Found: C, 68.45; H, 6.72.

2b: mp 82–83 °C [lit [36] 83–84 °C]; ^{1}H NMR ($CDCl_3$) δ ppm 2.15 (s, 6H), 2.76–2.88 (series of m, 8H), 6.92 (d, J = 7.6 Hz, Ar, 2H), 7.06, (d, J = 2.4 Hz, Ar, 2H), 7.09 (dd, J = 2.4, 7.6 Hz, Ar, 2H); ^{13}C NMR ($CDCl_3$) δ ppm 28.87, 30.13, 45.31, 116.86, 124.23, 129.57, 131.03, 133.91, 151.25, 208.51; Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79; Found: C, 73.62; H, 6.70.

8b: colorless oil; ^{1}H NMR (acetone d6) δ ppm 3.31 (s, 6H), 4.39 (s, 4H), 6.97 (d, J = 8 Hz, Ar, 2H), 7.22 (dd, J = 2.0 and 8.4 Hz, Ar, 2H), 7.25 (d, J = 2.0 Hz, Ar, 2H); ^{13}C NMR (acetone d6) δ 35.87, 73.81, 116.29, 125.89, 128.42, 130.51, 131.32, 153.48; Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61; Found: C, 70.07; H, 6.66.

9b: mp 105–106 °C [lit [47] 103–105 °C]; ^{1}H NMR ($CDCl_3$) δ ppm 3.39 (d, J = 6.7 Hz, 4H), 3.94 (s, 6H), 5.10 (m, 4H), 6.01 (m, 2H), 6.75 (d, J = 1.9 Hz, Ar, 2H), 6.78 (d, J = 1.9 Hz, Ar, 2H); ^{13}C NMR ($CDCl_3$) δ ppm 39.99, 56.11, 110.70, 115.74, 123.12, 124.40, 131.94, 137.66, 140.92, 147.22; Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79; Found: C, 73.67; H, 6.71.

10b: mp 131–134 °C [lit [47] 132–134 °C]; ^{1}H NMR ($CDCl_3$) δ ppm 3.3 (s, 6H), 3.94 (s, 6H), 6.74, (d, J = 2.0 Hz, Ar, 2H), 6.75 (d, J = 2.0 Hz, Ar, 2H); ^{13}C NMR ($CDCl_3$) δ ppm 21.18, 56.07, 111.32, 123.45, 124.36, 129.64, 140.36, 147.07; Anal. Calcd. for $C_{16}H_{18}O_4$: C, 73.60; H, 6.79; Found: C, 73.69; H, 6.69.

13b: mp 103–144 °C; ^{1}H NMR (acetone d6) ppm 3.31 (s, 6H), 3.87 (s, 6H), 4.37 (s, 4H), 6.85 (d, J = 2.0 Hz, Ar, 2H), 6.93 (d, J = 2.0 Hz, Ar, 2H); ^{13}C NMR (acetone d6) ppm δ 55.51, 56.86, 74.20, 110.06, 122.93, 125.02, 12.39, 143.22, 147.74; Anal. Calcd. for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63; Found: C, 64.70; H, 6.67.

*4.3. Procedure for oxidative microwave-induced coupling reaction of **2a** with tetrabutylammonium permanganate in methanol. Synthesis of **2b***

To a solution of natural phenol **2a** (0.49 g, 3 mmol) in methanol (15 mL), MTBAP (479 mg, 1.5 mmol) was added. The mixture was stirred under microwave (MW) irradiation at 300 W and held at 84 °C for 8 min. The solution was cooled at rt and the solvent evaporated. Dichloromethane (30 mL) and water (15 mL) were added, the organic layer separated, washed with a 10 % aqueous solution of HCl (3 x 5 mL), and then saturated aqueous sodium bisulfite solution (20 mL) and dried over anhydrous Na_2SO_4, filtered and roto evaporated under reduced pressure. The obtained brown solid was purified by flash chromatography on silica gel using a mixture 1:1 of ethyl acetate: petroleum ether as eluent to obtain **2b** (0.24 g, 50 %) whose physical characteristics matched those reported in section 4.2.

*4.4. General procedure for oxidative microwave-induced coupling reactions of **3a** and **4a** with di-tert-butyl peroxide (DTBP). Synthesis of **3b** and **4b***

A mixture of phenol **3a** or **4a** (12.0 mmol) and DTBP (36.0 mmol) was stirred under MW irradiation at 150 °C for 30 min. The obtained brown solid was purified by flash chromatography on silica gel using a mixture 2:1 of petroleum ether: ethyl acetate as eluent to obtain dimer **3b** (58 %) or **4b** (85 %).

3b: mp 83–85 °C; ^{1}H NMR ($CDCl_3$) δ ppm ($CDCl_3$) 1.26 (d, J = 6.8 Hz, 6H), 1.27 (d, J = 6.8 Hz, 6H), 1.96 (s, 6H), 3.29 (m, 2H), 4.79 (bs, 2H), 6.89 (d, J = 7.6 Hz, Ar, 2H), 7.20 (d, J = 7.6 Hz, Ar, 2H); ^{13}C NMR ($CDCl_3$) δ ppm 19.25, 22.49, 22.63, 27.14, 119.40, 122.18, 126.72, 132.58, 135.66, 151.00; Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78; Found: C, 80.57; H, 8.86.

4b: mp 150–152 °C; ^{1}H NMR ($CDCl_3$) δ ppm 1.10 (d, J = 6.8 Hz, 6H), 1.14 (d, J = 6.8 Hz, 6H), 2.28 (s, 6H), 2.49 (m, 2H), 4.68 (bs, 2H), 6.97 (d, J = 8.0 Hz, Ar, 2H), 7.24 (d, J = 8.0 Hz, Ar, 2H); ^{13}C NMR ($CDCl_3$) δ ppm 15.90, 23.53, 24.87, 30.27, 117.55, 117.62, 121.83, 131.77, 147.47, 151.68; Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78; Found: C, 80.47; H, 8.76.

*4.5. General procedure for oxidative microwave-induced coupling reactions of **5a, 7a, 11a** and **12a** with potassium persulfate and iron sulfate heptahydrate. Synthesis of **5b, 7b, 11b** and **12b***

To a solution of phenol **5a** or **7a** or **11a** or **12a** (3.3 mmol) in 15 mL of water, $FeSO_47H_2O$ (0.16 mmol) was portion-wise added at rt. The solution was stirred for 1 min and then $K_2S_2O_8$ (1.66 mmol) was added. The solution was then stirred under MW irradiation at 100 °C for 8 min. The formed brown precipitate was filtered. The solid was dissolved in an aqueous NaOH (10 %) solution. Aqueous HCl (10 %) solution was added, and the brown precipitate was purified by flash chromatography on silica gel using a mixture 1:1 of petroleum ether: ethyl acetate as eluent to obtain dimers **5b** or **7b** or **11b** or **12b** in 92 %, 35 %, 92 % and 10 % yield respectively.

5b: mp = >275 °C [lit [41] > 270 °C]; ^{1}H NMR (DMSO-d_6) δ ppm 3.94 (s, 6H), 7.43 (d, J = 1.9 Hz, Ar, 2H), 7.44 (d, J = 1.9 Hz, Ar, 2H), 9.82 (s, 2H); ^{13}C NMR (DMSO-d_6) δ ppm 56.50, 109.63, 125.04, 128.21, 128.63, 148.63, 150.91, 191.64; Anal. Calcd. for $C_{16}H_{14}O_6$: C, 63.58; H, 4.67; Found: C, 63.59; H, 4.60.

7b mp = 110–112 °C [lit [44] 80–100 °C]; ^{1}H NMR (acetone d6) δ ppm 4.01 (s, 6H), 7.62 (d, J = 2.4 Hz, Ar, 2H), 7.69 (dd, J = 1.20, 2.4 Hz, Ar, 2H), 10.20 (d, J = 1.20 Hz, 2H), 10.57 (s, 2H); ^{13}C NMR (acetone d6) δ ppm 55.91, 116.46, 120.91, 121.52, 131.61, 148.74, 150.65, 195.47; Anal. Calcd. for $C_{16}H_{14}O_6$: C, 63.58; H, 4.67; Found: C, 63.65; H, 4.64.

11b: mp = 263 °C [lit [48] 260 °C]; ^{1}H NMR (DMSO-d_6) δ ppm 2.42 (s, 6H), 3.83 (s, 6H), 7.38 (d, J = 2.0 Hz, Ar, 2H), 7.40 (d, J = 2.0 Hz, Ar, 2H), 9.38 (s, 2H); ^{13}C NMR (DMSO-d_6) δ ppm 26.76, 55.46, 110.14, 124.94, 125.75, 128.35, 147.92, 149.56, 196.67; Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49; Found: C, 65.54; H, 5.54.

12b mp = 200–202 °C [lit [44] 202 °C]; ^{1}H NMR (DMSO-d_6) δ ppm 2.571 (s, 6H), 3.81 (s, 6H), 7.17 (d, J = 6.0 Hz, Ar, 2H), 7.44 (d, J = 6.0 Hz, Ar, 2H); ^{13}C NMR (DMSO-d_6) δ ppm 27.78, 56.30, 114.53, 119.62, 126.09, 127.19, 151.11, 153.93, 205.95; Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49; Found: C, 65.65; H, 5.54.

*4.6. General procedure for oxidative microwave-induced coupling reactions of **6a** and **12a** with potassium hexacyanoferrate and potassium hydroxide. Synthesis of **6b** and **12b***

A solution of phenol **6a** or **12a** (1.31 mmol), $(CH_3O)_3CH$ (1.98 mmol) and $TBABr_3$ (0.066 mmol) in MeOH (2 mL), was stirred under MW irradiation at 80 °C for 8 min for **6a** or 30 min for **12a**. When the reaction was completed, it was allowed to cool down to room temperature and diluted with 25 mL of MeOH. A solution of $K_3Fe(CN)_6$ (1.31 mmol) and KOH (4.6 mmol) in 25 mL of water was added dropwise at room temperature. The mixture was stirred under MW irradiation at 80 °C for 30 min (**6a**) or 15 min (**12a**). The mixture was acidified to pH = 1 by 1 M HCl and stirred for 30 min at rt. The crude product was filtered and further purified by flash chromatography on silica gel to obtain dimer **6b** as yellow solid (90 % yield) or dimer **12b** as yellow solid (60 % yield). Compound **12b** physical characteristics matched those reported in section 4.5.

6b: mp = 152–153 °C [lit [49] 152–156 °C]; ^{1}H NMR (acetone d6) δ ppm 3.74, (s, 6H), 7.16 (d, J = 6.0 Hz, Ar, 2H), 7.27 (d, J = 6.0 Hz, Ar, 2H), 9.92 (s, 2H); ^{13}C NMR (acetone d6) δ ppm 55.41, 115.88, 120.74, 126.45, 152.34, 153.33, 164.89, 197.32; Anal. Calcd. for $C_{16}H_{14}O_6$: C, 63.58; H, 4.67; Found: C, 63.60; H, 4.70.

4.7. General procedure for oxidative conventional coupling reactions of 7a and 12a with potassium persulfate and iron sulfate heptahydrate. Synthesis of 7b and 12b

To a solution of phenol **7a** or **12a** (3.3 mmol) in 15 mL of water, $FeSO_47H_2O$ (0.16 mmol) was portion-wise added at rt. The solution was stirred for 1 min and added $K_2S_2O_8$ (1.66 mmol). The solution was then stirred at 100 °C for 3 h or 1 h respectively. The solution was cooled at rt, and the formed brown precipitate was filtered. The solid was dissolved in an aqueous NaOH (10 %) solution. Aqueous HCl (10 %) solution was added, and the brown residue was purified by flash chromatography on silica gel using a mixture 1:1 of petroleum ether: ethyl acetate as eluent to obtain dimers **7b**, or **12b** in 23 % and 8 % yield respectively. Physical characteristics of **7b** and **12b** matched those reported in section 4.5.

4.8. General procedure for oxidative conventional coupling reactions of 8a and 13a with tetrabutylammonium permanganate (MTBAP). Synthesis of 8b and 13b

To a solution of phenol **8a** (1.3 mmol) in CH_2Cl_2 (5 mL) and acetone (2 mL) or **13a** (1.3 mmol) in CH_2Cl_2 (7 mL) at rt, was added a solution of MTBAP (0.66 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was then stirred at rt °C for 30 min (for **13a**) or 5 h (for **8a**). The solution was evaporated and the solid residue was solubilized in dichloromethane, washed with a 0.1 M solution of HCl (3 x 5 mL), and a saturated aqueous solution of sodium bisulfite, dried over anhydrous Na_2SO_4, filtered and roto evaporated under reduced pressure. The product obtained was purified by flash chromatography on silica gel using a mixture of 1:2 of ethyl acetate: petroleum ether as eluent to obtain dimer **8b** (20 %) or **13b** (60 %). The physical characteristics of **8b** and **13b** matched those reported in section 4.2.

4.9. Procedure for oxidative conventional coupling reactions of 12a with potassium hexacyanoferrate and potassium hydroxide. Synthesis of 12b

A solution of phenol **12a** (0.2 g, 1.31 mmol), trimethoxymethane (0.21 g, 1.98 mmol) and tetrabutylammonium tribromide (0.032 g, 0.066 mmol) in MeOH (2 mL), was stirred at 80 °C for 2 h. When the reaction was completed, it was allowed to cool down to room temperature and diluted with 25 mL of MeOH. A solution of $K_3Fe(CN)_6$ (0.44 g, 1.31 mmol) and KOH (0.26 g, 4.6 mmol) in 25 mL of water was added dropwise at room temperature. The mixture was stirred at rt for 3 h. The mixture was acidified to pH = 1 by 1 M HCl and stirred for 30 min at rt. The crude product was filtered and purified by flash chromatography on silica gel to obtain dimer **12b** as yellow solid (0.12 g, 57 % yield). Compound **12b** physical characteristics matched those reported in section 4.5.

CRediT authorship contribution statement

Davide Fabbri: Writing – original draft, Project administration, Methodology, Investigation, Conceptualization. **Paola Carta:** Validation, Methodology, Investigation, Data curation. **Maria Antonietta Dettori:** Validation, Methodology, Investigation, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2024.134142.

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