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Environmentally friendly one-pot two-step sequential synthesis of biological active curcumin analogues

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ABSTRACT

In this study an efficient method to facilitate the sustainable synthesis of *O*-methyl dehydrozingerone dimer, and its monomer was developed. This one-pot two-step process involves *O*-methylation of phenolic compounds, using dimethyl carbonate as an alkylating green agent, followed by a Claisen Schmidt condensation in the presence of acetone under microwave irradiation without changing the nature of the base used for the entire synthetic process. The starting material vanillin dimer [6,6′-dihydroxy-5,5′-dimethoxy-[1,1′-biphenyl]-3,3′-dicarbaldehyde], was prepared by an innovative high-speed oxidative coupling reaction.

1. Introduction

Curcumin (diferuloylmethane) (Fig. 1a), the main product extracted from the rhizome of *Curcuma Longa*, has been largely used in traditional chinese medicine. Thanks to its capacity to modulate the action of many biological targets involved in human physiology, curcumin shows important anti-inflammatory [1], anti-cancer [2] and anti-oxidant [3] activities. Curcumin belongs to the class of natural polyphenols often used to prevent cardiovascular and neurodegenerative diseases and to treat bacterial and viral infections [4]. Unfortunately, curcumin undergoes autooxidative rapid degradation at physiological pH into several compounds including ferulic acid, vanillin and dehydrozingerone (DHZ) (Fig. 1b) making it an unlikely drug and an improbable nutraceutical candidate in food and supplement products [5].

Among polyphenols, hydroxylated biphenyls are widely distributed in nature, in fact they can be found in important biological compounds such as lignins [6] and ellagitannines [7]. Biphenyls have garnered considerable interest as potent ligands for receptor molecules implicated in the progression of diverse human diseases [8], thanks to the presence of its characteristic pharmacophore structure characterized by the presence of two aromatic rings linked by a single C–C bond. On this basis and in the context of the design and synthesis of new natural-inspired phenols and biphenols with potential biological activities, in our previous studies we synthetized *O*-methyl dehydrozingerone dimer **1** and *O*-methyl dehydrozingerone **2** starting from vanillin [9,10] (Fig. 2). These phenols, structurally related to curcumin, due to the presence of an α-β unsaturated ketone chain, exhibited higher bioavailability and stability than curcumin itself. Compounds **1**–**2** showed relevant activity as inhibitors of α-synuclein aggregation [10], antioxidants [11] and antitumorals [9]. Compound **1** demonstrated rapid cellular uptake on melanoma cell lines and effectively arrested the cell cycle at the G2/M phase transition in cells [12]. Significantly compound **1** exhibited greater efficacy in inhibiting cell proliferation and inducing apoptosis in various melanoma cell lines compared to monomer **2**, and even curcumin itself.

Our previous methods for the synthesis of compound 1 involved two steps starting from vanillin dimer **3** [13]: a) *O*-methylation of **3** in the presence of methyl iodide (MeI) and potassium carbonate in acetone to give *O*,*O*′-dimethyl vanillin dimer **4** and b) Claisen-Schmidt condensation reaction of **4** in acetone in the presence of aqueous sodium hydroxide to give compound **1** in a 42 % total yield [9] (Scheme 1a). Compound **2** was prepared starting from vanillin through Claisen-Schimdt condensation in the presence of NaOH and acetone to give DHZ and subsequent *O*-methylation reaction using MeI in 83 % total yield [10] (Scheme 1b).

MeI was employed in *O*-methylation reactions of vanillin dimer **3** and DHZ. It is known in the literature that methyl halides [14] and dimethyl sulfate (DMS) [15,16] are the most utilized agents in *O*-methylation of phenols, nevertheless, they are extremely toxic and pose serious risks to human health, presenting serious toxicological and carcinogenic risks related to their ability to methylate nucleic acids in living organisms [17].

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Given the substantial safety and environmental concerns associated with such methylating agents, it is highly recommended to explore alternative approaches. Ongoing research has been focused on the development of methods and reagents that are more environmentally friendly and less hazardous. One promising option is the use of dimethyl carbonate (DMC) which is a notably safer alternative compared to methyl halides and DMS. DMC offers several advantages: it is non-toxic reducing the health risks associated with exposure during experiments and is a cost-effective reagent, which can make it an economically viable choice for methylation reactions. An important benefit of DMC is its minimal environmental impact, producing carbon dioxide (CO_2) and methanol as by-products when it undergoes decomposition [18]. However, the use of DMC as methylating reagent necessitates lengthy reaction times [19] and high temperatures (>200 °C) in an autoclave, in the presence of solid catalysts such as lanthanum-magnesium mixed oxide (La_2O_3–MgO) [20].

2. Results and discussion

Our research group has been recently interested in enhancing reaction efficiency using microwave (MW)-irradiation [21,22]. MW technology offers several advantages, such as high yields, reduced reactions time, the ability to perform reactions safely in sealed vessels and precise control of power pressure, temperature parameters, and stirring speed. The use of MW irradiation technology can be applied to a wide range of syntheses, including methylation [23], oxidative coupling of phenols [24] and condensation reactions [25]. The primary drawback of employing microwave-assisted methodologies is their impracticality for scale-up, as they impose limitations on the quantity of reagents and solvents that can be introduced into the reaction tube. It is important to specify that microwave-mediated reactions must always be performed with instruments with safety relief devices such as pressure relief valves to release excess pressure in case of emergencies. The pressure management technology used by CEM-Discover SP MW makes use of automated pressure control and is a safe way to perform pressurized reactions.

With the aim to improve synthesis sustainability of curcumin analogues **1** and **2** starting from vanillin dimer **3** and vanillin respectively, the objective of the present study was to investigate an alternative eco-friendly synthesis of these compounds by using a safe and sustainable methylating reagent, followed by a Claisen Schmidt condensation, by microwave-assisted one pot, two-step procedure.

Vanillin dimer **3** is a naturally occurring biphenyl derivative, it has been granted the "Generally Recognized as Safe" (GRAS) status and it is primarily utilized as a food additive for flavour enhancement [26]. Additionally, this compound exhibits promising anti-cancer properties by reducing the metastatic potential of human cancer cells. Its mechanism of action involves inhibition of the FAK/PI3K/AKT signalling pathway, which is associated with cancer cell proliferation and spread [27].

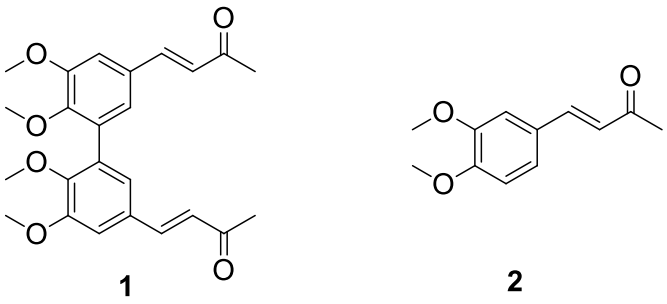


Fig. 2. *O*-methyl dehydrozingerone dimer **1** and *O*-methyl dehydrozingerone **2**.

Over the years, **3** has been synthesized starting from vanillin by different methods. It was commonly prepared by oxidative phenol-coupling using iron(III) chloride ($FeCl_3$) [28] or potassium persulfate ($K_2S_2O_8$)/iron(II) sulfate heptahydrate ($FeSO_4$) [10] as oxidants. Vanillin dimerization can be carried out also via enzyme-catalyzed reactions but these methodologies often have disadvantages due to the use of quite expensive reagents and long reaction times [29].

Few examples of microwave-assisted oxidative coupling reactions of phenols are known in the literature [30] and this dimerization generally involves phenols with electron-donating substituents or functional groups. Herein, we report for the first time the microwave-assisted oxidative coupling reaction of vanillin to give its dimer **3**, precursor of compound **1** in excellent yield (95 %) comparable to that achieved in the corresponding conventional synthesis but with significantly shorter times (5 min) in presence of $K_2S_2O_8$ and $FeSO_4$ in water (Scheme 2).

We are not aware of any other report on microwave-driven, rapid, and direct oxidative coupling reactions of vanillin.

Compounds **1** and **2** were synthetized starting from vanillin dimer **3** and vanillin respectively by microwave-assisted procedure. Utilizing one-pot protocol [31,32] within a single microwave vessel for the two-step synthesis enables to obtain the desired products more efficiently without the need to isolate the intermediate methylated compounds **4** and **5** (Scheme 3). This approach results in significant time and resource savings, simultaneously enhancing the overall chemical yield.

It is well known that the nature of the base has an important impact on the reaction yield both in phenols *O*-methylation reactions with DMC [33] and in Claisen Schmidt condensation between aromatic aldehydes and acetone [34].

We conducted a study on the synthesis of compound **1** using dimethyl carbonate (DMC) as both reagent and solvent. To facilitate this reaction, we added tetrabutylammonium bromide (TBAB) as a phase transfer catalyst (PTC) to the heterogeneous mixture, in the presence of different bases at 140 °C or 160 °C for 30 min. After the reaction was cooled to ambient temperature, acetone was added to the mixture for a

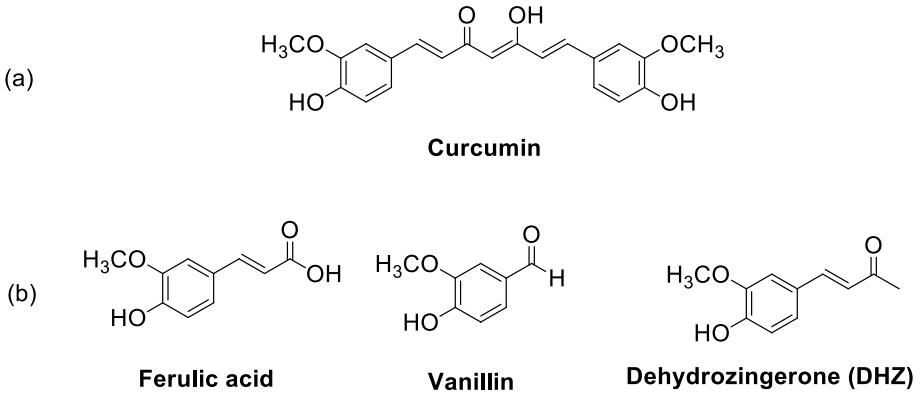
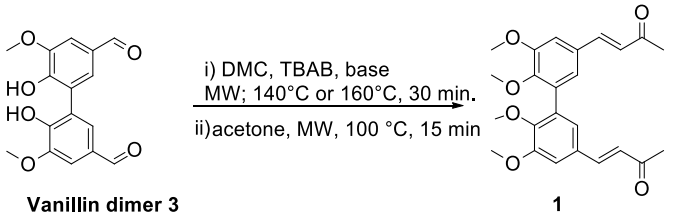


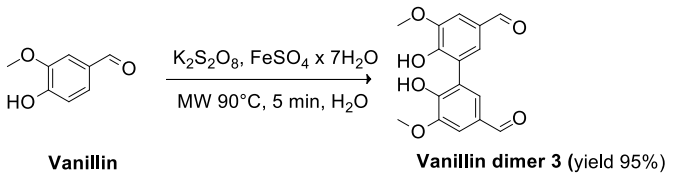
Fig. 1. Chemical structures of (a) Curcumin; (b) Ferulic acid, Vanillin and Dehydrozingerone (DHZ).

further MW heating cycle of 15 min at 100 °C to obtain *O*-methyl DHZ dimer **1**. We carried out a comparative study using various inorganic and organic bases such as sodium carbonate (Na_2CO_3), potassium carbonate (K_2CO_3), caesium carbonate (Cs_2CO_3) and 1,8-diazabiciclo[5.4.0] undec-7-ene (DBU) for both methylation and Claisen Schmidt condensation steps to increase yields and process sustainability (Table 1).



Comparisons of reaction yields in Table 1 identify K_2CO_3 as the best base (entries 3–4). Use of Cs_2CO_3 (entries 6–7), which is an excellent base in an aprotic solvent, unexpectedly led to lower yield compared to K_2CO_3 and Na_2CO_3 at both temperatures. The use of Na_2CO_3 (entries 1–2) induces slightly lower yields than the corresponding potassium salt. Very low yields of **1** were obtained when the reactions were carried out in the presence of the organic base DBU, both at 140 °C and 160 °C (entries 9–10). The highest yields were consistently achieved when the reactions were conducted at a temperature of 140 °C in all cases. Once the optimal conditions have been highlighted in terms of base (K_2CO_3) and temperature (140 °C) (Scheme 3a) the same parameters were used for the synthesis of monomer **2** (Scheme 3b). In the absence of TBAB, (entries 5 and 8), only the starting material was recovered. This result could be due to the role of the phase transfer catalyst tetrabutylammonium halide, essential for optimizing reaction conditions, enhancing solubility, promoting efficient reagent interaction, and ensuring a controlled and effective reaction [35].

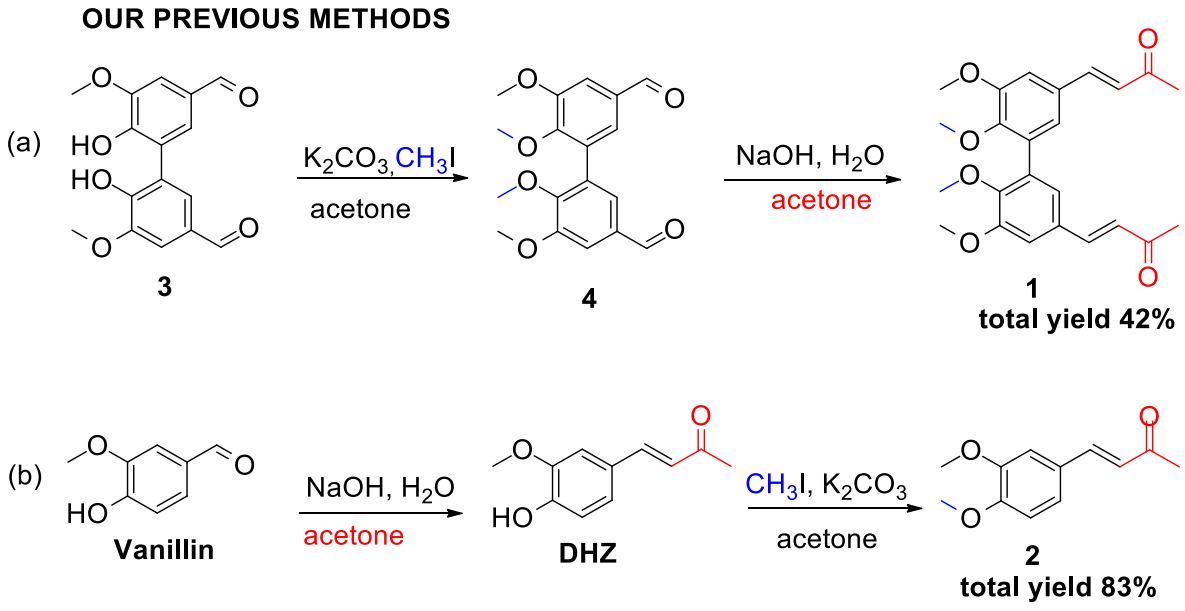
The main advantages of this environmentally friendly procedure for the synthesis of **1** and **2** can be summarized in the following points: absence of workup after the first step, use of a sustainable methylating agent like DMC, use of the same inorganic base for the two reactions, reduced reactions times compared to the classic synthetic procedures reported in the literature and finally higher overall yields (71 % and 86 % for **1** and **2** respectively) compared to our previous methods (42 % and 83 % for **1** and **2** respectively). ^{1}H NMR and ^{13}C NMR spectra of compounds **1**, **2** and **3**, consistent with the proposed structure and in good agreement with the literature data, are provided in the supplementary data.



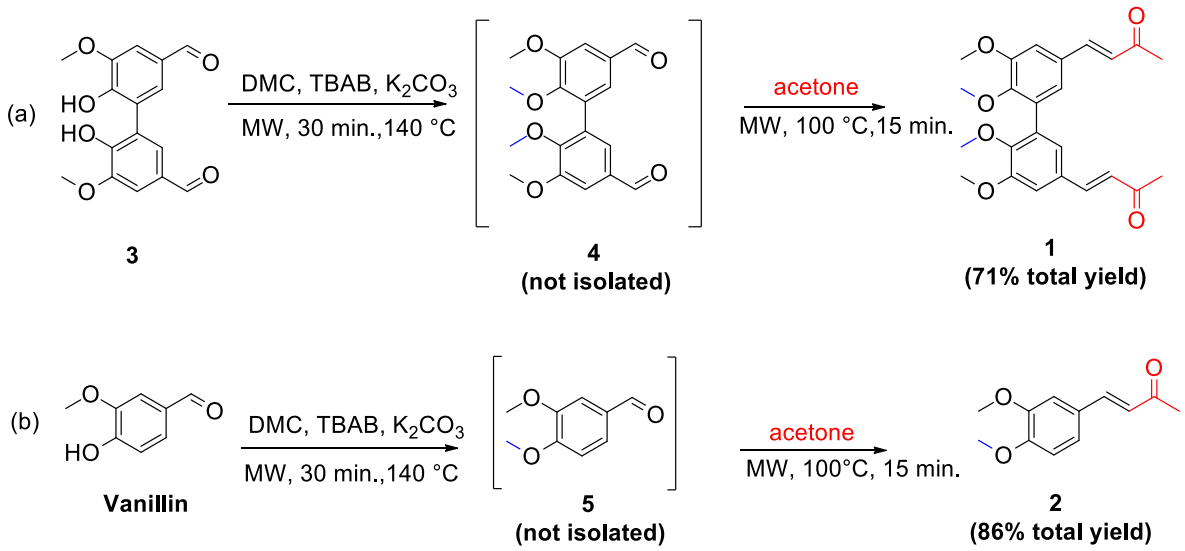
Scheme 2. Microwave assisted oxidative coupling of vanillin.

3. Conclusion

In summary, we have successfully developed a one-pot two-step sequential microwave-assisted reaction methodology for the synthesis of two bioactive curcumin analogues, denoted as compounds **1** and **2**. This method involves an exhaustive O-methylation followed by a Claisen-Schmidt condensation. Furthermore, we have detailed a rapid microwave-assisted oxidative coupling of vanillin, resulting in the formation of the corresponding dimer **3** with excellent yields. The efficiency of our approach is notably heightened by capitalizing on the synergies between microwave-assisted synthesis and a single-pot protocol, leading to significantly increased yields and reduced reaction times compared to conventional synthesis methods outlined in existing literature. One notable advantage of our procedure is the elimination of the need for intermediate product purification. This not only circumvents time-consuming working-up processes but also minimizes the generation of chemical wastes, contributing to a more environmentally friendly synthesis. Our investigations delved into the impact of various inorganic and organic bases, as well as different temperatures, on the overall yield of compounds, providing valuable insights into optimizing reaction conditions. These findings underscore the versatility of our synthetic approach, suggesting its applicability for the efficient preparation of other biologically active O-alkoxy curcumin-related derivatives. In essence, our straightforward synthetic method not only expands the scope of curcumin analogues synthesis but also holds promise for broader applications in the efficient production of diverse bioactive compounds.



Scheme 1. Synthesis of (a) compounds **1** and (b) **2**.



Scheme 3. Optimized one-pot two-step microwave-assisted synthesis of a) compound **1** and b) compound **2.**

Table 1
Influence of base and temperature on one-pot two step MW synthesis of compound **1**.

Entry	Base	Temp (°C)	Yield[b] (%)
1	Na_2CO_3	140	60
2	Na_2CO_3	160	54
3	K_2CO_3	140	71
4	K_2CO_3	160	68
5	[a]K_2CO_3	140	[c]nr
6	Cs_2CO_3	140	44
7	Cs_2CO_3	160	38
8	[a]Cs_2CO_3	140	[c]nr
9	DBU	140	8
10	DBU	160	5

Reactions were performed using 1 equiv. of compound **3**, 1.2 equiv. of TBAB, 48 equiv. of DMC, 6.6 equiv. of base and acetone as reagent/solvent (7 ml); [a]in absence of TBAB; [b]total yields of one-pot two step synthesis. [c]nr = no reaction.

4. Experimental section

4.1. General

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 DMSO-d6 solution at 600 and 150 MHz, respectively, with a 600 MHz NMR spectrometer Bruker Avance III HD, (Palo Alto, CA, USA). Full characterization data, including copies of ^{1}H NMR and ^{13}C NMR spectra (see Supplementary Material), have been reported for the known (**1**, **2** and **3**) compounds. Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or dd (doublet of doublets). Elemental analysis was performed using an elemental analyzer model 240C (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. Reaction was monitored by analytical thin-layer chromatography (TLC) with 0.25 mm thick silica gel plates (60 F 254) (Sigma Aldrich, Munich, Germany). Melting point was determined on a 530 apparatus (Büchi, Flawil, Switzerland) and is uncorrected. The purity of new compounds was judged to be >98 % by ^{1}H NMR spectral determination.

4.2. General procedure for compound *1*

To a solution of vanillin dimer **3** (0.66 mmol) in DMC (32 mmol), TBAB (0.8 mmol) and base (4.4 mmol) were added at room temperature. The solution was then stirred under MW irradiation at 140 or 160 °C for 30 min. To the reaction mixture, allowed to cool at RT, acetone (7 ml) was added. The solution was then stirred under MW irradiation at 100 °C for 15 min. The solution was cooled at rt and washed with water (10 mL). The solution was then roto-evaporated to remove acetone, extracted with dichloromethane (3x20 mL), washed with HCl 1 N, dried over Na_2SO_4 and evaporated to afford a brown solid. The crude material was purified by flash chromatography using a 1:1 mixture of ethyl ether: petroleum ether as eluent to obtain **1** as a white solid.

(3E,3′E)-4,4′-(5,5′,6,6′-tetramethoxy-[1,1′-biphenyl]-3,3′-diyl)bis(but-3-en-2-one) (**1**) mp 165–168 °C [lit [9]. 165–167 °C)]; ^{1}H NMR δ 2.30 (s, 6H), 3.64 (s, 6H), 3.88 (s, 6H), 6.57 (d, J = 16 Hz, 2H), 6.99 (d, J = 2.0 Hz, Ar, 2H), 7.05 (d, J = 2.0 Hz, Ar, 2H), 7.40 (d, J = 16 Hz, 2H); ^{13}C NMR δ 27.48, 55.95, 60.87, 110.88, 124.14, 126.451, 129.85, 132.36, 143.04, 149.11, 153.06, 198.19; Anal. Calcd for $C_{24}H_{26}O_6$: C, 70.23; H, 6.38. Found: C, 70.30; H, 6.35.

4.3. Experimental procedure

4.3.1. Synthesis of (E)-4-(3,4-dimethoxyphenyl)but-3-en-2-one (*2*)

To a solution of vanillin (0.2 g, 1.32 mmol) in DMC (2.7 mL, 31 mmol), TBAB (0.25 g, 0.8 mmol) and K_2CO_3 (0.63 g, 4.3 mmol) were added at room temperature. The solution was then stirred under MW irradiation at 140 °C for 30 min. To the reaction mixture, allowed to cool to RT, acetone (7 ml) was added. The solution was then stirred under MW irradiation at 100 °C for 15 min. The solution was cooled at rt and washed with water (10 mL). The solution was then roto-evaporated to remove acetone, extracted with dichloromethane (3x20 mL), washed with HCl 1 N, dried over Na_2SO_4 and evaporated to afford a brown solid. The crude material was purified by flash chromatography using a 3:7 mixture of ethyl ether: petroleum ether as eluent to obtain **2** as a white solid; (0.23 g, 86 %): mp 84–88 °C [lit [10]. 86–87 °C)]; ^{1}H NMR δ 2.39 (s, 3H), 3.94 (s, 6H), 6.63 (d, J = 18 Hz, 1H), 6.90 (d, J = 8.3 Hz, Ar, 1H), 7.10 (d, J = 1.2 Hz, Ar, 1H), 7.15 (dd, J = 1.2, 8.3 Hz, Ar, 1H), 7.49 (d, J = 18 Hz, 1H); ^{13}C NMR δ 27.32, 55.90, 55.98, 109.72, 111.14, 122.99, 125.26, 127.36, 143.48, 149.32, 151.40, 198.26; Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 70.00; H, 6.85.

4.3.2. Synthesis of 6,6′-dihydroxy-5,5′-dimethoxy-[1,1′-biphenyl]-3,3′-dicarbaldehyde (3)

To a solution of vanillin (0.5 g, 3.3 mmol) in 15 mL of water, $FeSO_4$ $7H_2O$ (0.04 g, 0.16 mmol) was portion-wise added at RT. The solution was then stirred for 1 min at RT and $K_2S_2O_8$ (0.45 g, 1.66 mmol) was added. The solution was then stirred under MW irradiation at 100 °C for 5 min. The solution was cooled at rt, and the formed brown precipitate was filtered off. The solid was dissolved in an aqueous NaOH (10 %) solution. Aqueous HCl (10 %) solution was added, and the brown precipitate was filtered. (0.42 g, 85 %); mp 280–288 °C [lit[2]. 270 °C)]; ^{1}H NMR (DMSO-d6) δ ppm: 3.94 (s, 6H); 7.43 (s, 2H); 7.44 (s, 2H); 9.82 (s, 2H); ^{13}C NMR (DMSO-d6) δ ppm: 56.53, 109.69, 125.05, 128.24, 128.60, 148.64, 150.90, 191.62; Anal. Calcd for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67; Found: C, 63.61; H, 4.62.

CRediT authorship contribution statement

Maria Antonietta Dettori: Conceptualization, Data curation, Methodology, Validation, Writing – original draft. **Paola Carta:** Data curation, Formal analysis, Methodology. **Davide Fabbri:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

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

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2024.133867.

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