Article

Journal of the Brazilian Chemical Society

https://dx.doi.org/10.21577/0103-5053.20240005

J. Braz. Chem. Soc. **2024**, *35*, 7, e-20240005, 1-9

A Scalable Total Synthesis of Deoxyrhapontigenin from Low-Cost α-Resorcylic Acid

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A scalable total synthesis for deoxyrhapontigenin (DRG) was successfully accomplished using low-cost α-resorcylic acid as a starting material. Our approach initiates with the protection of phenolic groups using methoxymethyl, resulting in the synthesis of a derivative of the expensive 3,5-hydroxybenzaldehyde, a critical component for Wittig and Perkin approaches in stilbenoid synthesis. Additionally, the corresponding olefin for Heck reaction and formal synthesis of resveratrol were produced in over 85% yield. The synthesis of deoxyrhapontigenin was accomplished in seven steps from the initial carboxylic acid, yielding a product with an average purity higher than 98%, as confirmed by quantitative nuclear magnetic resonance (NMR) analysis.

Keywords: resveratrol, heck reaction, aerobic oxidation, multigram, Perkins reaction, Wittig reaction

Introduction

Deoxyrhapontigenin (DRG) is a polyoxygenated *E*-stilbenoid primarily found in *Rheum rhabarbarum*,[1] and in trace amounts in some red wines.[2] It is structurally analogous to resveratrol, differing by the presence of a methoxy group at position 4' (Figure 1). However, DRG remains relatively underexplored, and it has been reported to exhibit potent anti-inflammatory properties,[3] act as an antioxidant,[4] demonstrate antimicrobial activity,[5] serve as an antiviral agent against Zika virus (ZIKV),[6] act as an antifungal agent against *Candida albicans*,[7] function as an antidiabetic agent by inhibiting glucose transporters,[8] and function as an antiproliferative agent against doxorubicin-resistant breast cancer.[9] DRG also displays cytoprotectant activity by preventing bone loss through the inhibition of the RANKL/RANK signaling pathway,[10] preventing neuronal damage by modulating the TLR4/Cyclin B1/Sirt-1 pathway,[11] and is a probable active metabolite of resveratrol against Alzheimer's disease.[12]

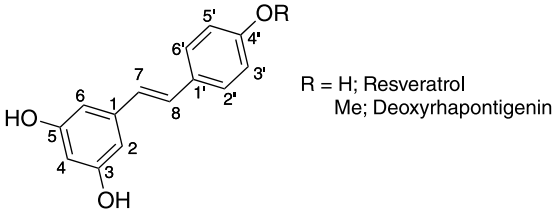

Figure 1. Resveratrol and deoxyrhapontigenin (DRG) structures and the carbon numbering used throughout this paper.

Among the reported methods for obtaining DRG, there are three primary approaches: direct isolation from its natural sources,[4,10,13] alkylation of resveratrol,[7] and direct purchase from chemical vendors.[3,11,14] These methods are suitable for obtaining milligram quantities of DRG; however, they are hampered by poor yields and high costs, rendering them impractical to produce the larger quantities required for *in vivo* studies. This limitation impedes the further clinical development of DRG and its derivatives. Chemical total synthesis, utilizing cost-effective reagents, emerges as a viable alternative for the scalable production of this desired compound. Given the structural similarity between DRG and resveratrol, the same synthetic methods are applicable to both. These methods have been extensively covered in literature reviews,[7,15-17] including Wittig olefinations, the Perkin reaction, and palladium-catalyzed C–C cross-couplings. Among these, Heck reactions offer several advantages compared to other methods, such as high *E*-stereoselectivity and the availability of simpler and more diverse starting materials.[18-20]

With the aim of achieving a multigram synthesis of DRG to facilitate further exploration of its biological or chemical potential, we designed a cost-effective and streamlined synthetic route. We began by using α-resorcylic acid, a more economical starting material compared to its aldehyde counterpart. We successfully reduced it directly with a borane-tetrahydrofuran (THF) solution,[21] yielding the corresponding alcohol in 74% yield, albeit with the

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Editor handled this article: Brenno A. D. Neto

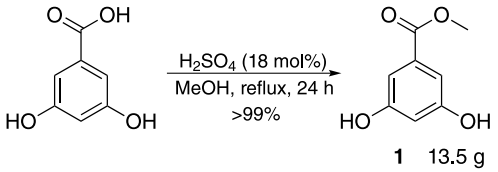
inconvenience of a recrystallization step in acetone. The subsequent requirement was to re-oxidize this alcohol to the corresponding aldehyde. This could only be achieved using stoichiometric quantities of pyridinium chlorochromate (PCC), pyridinium dichromate (PDC) for chromium-based methods, or manganese dioxide, all resulting in good yields. However, these stoichiometric heavy-metal oxidants involved a labor-intensive workup and purification process, which complicated scaling up the synthesis. To address these issues, we pursued a catalytic process to obtain the desired 3,5-hydroxybenzaldehyde.

Results and Discussion

Initially, we attempted a metal-free aerobic oxidation in a dimethyl sulfoxide (DMSO)/HBr system,[22] but, unfortunately, this approach proved unsuccessful. Subsequently, we explored transition-metal-free nitroxyl-based systems, specifically using (2,2,6,6-tetramethylpiperidin-1-yl) oxyl (TEMPO). We tested various conditions, including aerobic oxidation with NH_4NO_3 and HCl,[23] or $NaNO_2$/HCl[24] as cocatalysts, as well as *N*-haloimides as stoichiometric oxidants,[25,26] and even the TEMPO/Cu^I Stahl oxidation.[27] Regrettably, none of these attempts successfully generated the desired carbonyl compound. These findings appear to align with the property of the resorcylic core, which exhibits radical scavenging through a single-electron transfer mechanism[28] and can form inactive complexes with copper phenolates.[27] As a result, it became clear that protecting the phenolic hydroxyl groups was essential to achieve catalytic oxidation.

The introduction of a protecting group onto the phenolic hydroxyls in the presence of alcoholic hydroxyl would present highly inconvenient chemoselectivity problems. Therefore, the protection step should be conducted prior to the reduction and the chosen groups must be resistant to the following reaction conditions. The strategy of using borane also had to be rethought, as the yields are not suitable for a first step, and the purification is a hassle. Therefore, converting the α-resorcylic acid to its corresponding methyl ester opens more possibilities and could be advantageous if the combined yields surpass an 80% mark.

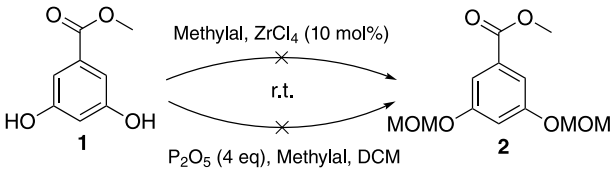
Using an alkylating agent, such as methyl iodide or dimethyl sulfate, could pose some challenges in terms of chemoselectivity, given the presence of acidic phenol groups. Therefore, Fischer esterification is a simpler method to obtain the desired ester without selectivity issues. Refluxing the α-resorcylic acid in methanol, under sulfuric acid catalysis, yielded the desired methyl 3,5-dihydroxybenzoate, **1**, in quantitative yield at a twelve-gram scale (see Scheme 1). This was achieved when using a brand-new bottle of solvent or high-performance liquid chromatography (HPLC)-grade methanol. Previously opened bottles led to diminished yields ranging from 8 to 20%, possibly due to moisture content.



Scheme 1. Fischer esterification of 3,5-dihydroxybenzoic acid.

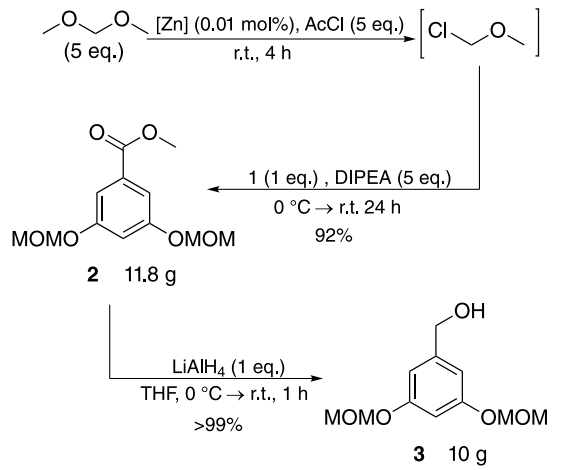
The protecting group to be installed at the phenolic positions must withstand the basic conditions of both the Heck reaction and carbonyl reduction. It should also be selectively cleaved in the presence of an aryl-alkyl ether. These criteria automatically rule out aryl esters, such as the commonly used acetate,[5,29,30] carbonates, carbamates, phosphinates, and sulfonates.[31] Both silyl ethers and acetal groups meet these criteria, but robust silyl ethers are bulky, significantly increasing the overall compound mass and thus reducing atom economy in the overall reaction. Additionally, they tend to be more expensive to purchase. As a result, the phenolic hydroxyls were protected in the form of acetal. Among the available options, tetrahydropyran-2-yl (THP) and methoxymethyl (MOM), the latter was preferred due to its smaller size, higher atom economy and eliminates the possibility of diastereomeric mixtures forming.

We then proceeded with the introduction of the MOM protecting group. Since MOM halides, such as chloromethyl and bromomethyl methyl ethers (MOMCl and MOMBr, respectively), are known to be carcinogenic, we sought an alternative method for introducing the group without the use of these reagents. The use of methylal (dimethoxymethane) catalyzed by zirconium tetrachloride has been reported to be highly effective,[32] making it a more cost-effective alternative to the considerably more expensive MOM halides. However, when we attempted the reaction of compound **1** with methylal in dichloromethane (DCM) using 10 mol% $ZrCl_4$ at room temperature, it did not yield the desired acetal; instead, it produced an orange polymeric substance. The same outcome was observed when we replaced zirconium(IV) tetrachloride with phosphorus(V) oxide[33] (see Scheme 2). These acid-catalyzed reactions typically proceed by forming a methoxycarbenium ion, which can be attacked by nucleophilic phenols or alcohols. However, given that the resorcylic core is electron-rich, an alternative pathway is possible: electrophilic aromatic substitution within the ring, leading to polymerization.



Scheme 2. Phenolic hydroxyls protection attempt, without use of carcinogens.

To mitigate this side reactivity, protection in a basic medium is now required. Since dimethoxymethane is not an effective alkylating reagent under these conditions, its conversion to the more reactive halide is now also necessary. An efficient conversion of methylal to MOMCl is documented by Berliner and Belecki,[34] using Zn^{II} catalysis with acyl chloride. The choice of Zn^{II} salt, whether $Zn(OTf)_2$, $ZnCl_2$, or $Zn(OAc)_2$, yielded identical results, but we selected triflate due to its non-hygroscopic nature. When acetyl chloride is employed, the resulting *ex situ* MOMCl/methyl acetate solution can be directly introduced into the reaction mixture containing methyl α-resorcilate, *N*,*N*-diisopropylethylamine (DIPEA), and THF, yielding the protected compound **2** in a 92% yield. This process avoids any detectable polymerization and minimizes operator's exposure to hazardous species (see Scheme 3). Since both components are in solution, we did not encounter any mass transfer issues. However, the exothermic addition of MOMCl became more pronounced as the scale increased, necessitating the use of a large ice bath for control. When the MOMCl solution is diluted in toluene, as described in the original paper,[34] protection proceeds sluggishly due to the ester's insolubility in the medium. The use of non-anhydrous THF and DIPEA resulted in reduced yields, ranging from 80 to 85%. We experimented using the unpurified product directly in the subsequent steps, but this significantly lowered the yields,



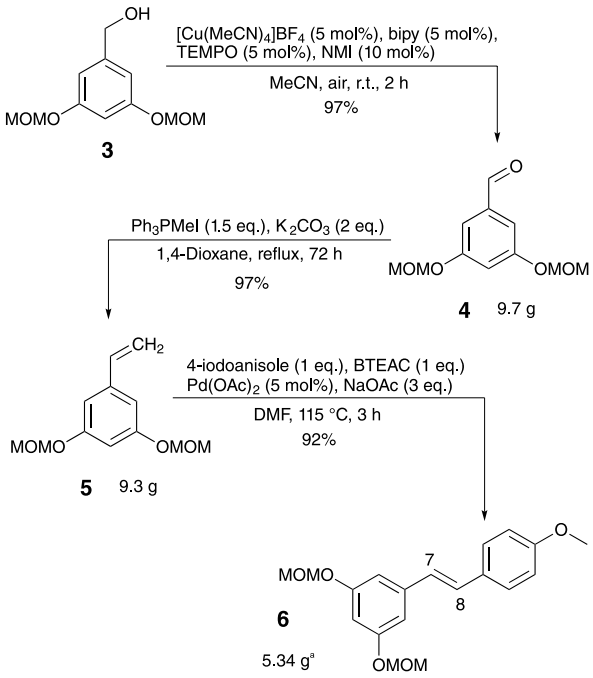
Scheme 3. Protection of phenolic positions with *ex situ* prepared MOMCl and subsequent reduction to the alcohol **3**.

justifying the need for a chromatographic purification step.

The Stahl oxidation[27] was chosen to oxidize compound **3** to the desired aldehyde **4**, which employs a Cu^{I} complex with 2,2'-bipyridine (bipy), TEMPO, and *N*-methylimidazole (NMI) as a base. While the commercially available tetrakis(acetonitrile)copper(I) tetrafluoroborate complex is an option, it can also be readily prepared by the disproportionation of copper(II) sulfate in aqueous acetonitrile with sodium tetrafluoroborate[35] (as illustrated in Scheme 4). Reducing the catalyst quantity from 5 to 2.5 mol% resulted in a halt of the oxidation reaction. Therefore, the standard conditions were employed, leading to the successful synthesis of compound **4** in a yield of approximately 97%. The product achieved high purity (> 96%) (Supplementary Information (SI) section, Figure S41) and did not require chromatographic purification, all within just two hours. This approach allows both reduction and oxidation to be completed in a single morning's workday. The obtained aldehyde **4** (with an overall yield of 88% over four steps) can then be utilized in the Perkin reaction and Wittig olefinations, connecting this work to the main methodologies for synthesizing polyoxygenated stilbenoids.

For the Wittig olefination using methyltriphenylphosphonium iodide, we initially attempted to use potassium *tert*-butoxide as the base in THF. However, the olefin **5** was only obtained in a 7% yield after 24 h. Substituting sodium hydride as the base increased the yield to 35% within the same 24 h timeframe. Extending the reaction time did not yield further benefits. When the reaction was conducted by refluxing anhydrous 1,4-dioxane with anhydrous potassium carbonate[36] for 72 h, the olefin **5** was isolated in an 81% yield, as shown in Scheme 4. This resulted in an overall yield of 84.8% over five steps starting from the α-resorcylic acid. Grinding K_2CO_3 into a fine powder further improved the yield to 97%. The olefin **5** serves as an intermediate in other palladium-catalyzed C–C coupling reactions, and it also contributes to the formal synthesis of resveratrol.[37]

After acquiring the necessary materials for the Heck-Mizoroki reaction, we initially attempted a previously published methodology,[12] which involved using *p*-iodoanisole as the arylating agent. We employed 5 mol% of palladium(II) acetate ($Pd(OAc)_2$) as the pre-catalyst, tributylamine (TBA) as the base, and benzyltriethylammonium chloride (BTEAC) as a phase transfer catalyst in *N*,*N*-dimethylformamide (DMF).[12] This procedure was swift, completed in approximately 40 min, and resulted in the formation of stilbene **6** with a yield

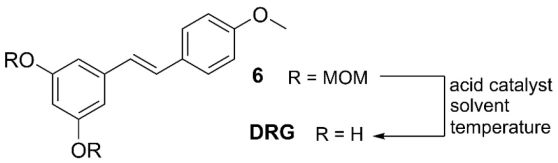


Scheme 4. Stahl oxidation of benezenemethanol **3**, Wittig olefination to **4**, and Heck-Mizoroki reaction for obtaining **6**. [a]Not all the olefin was used in a single coupling; 5.34 g and 92% yield are referring to 4.07 g starting material.

of 74%. Substituting the pre-catalyst from $Pd(OAc)_2$ to palladium(II) chloride ($PdCl_2$) or bis(triphenylphosphine) palladium(II) chloride [$Pd(PPh_3)_2Cl_2$] did not significantly affect the reaction time or yield. When we replaced TBA with anhydrous sodium acetate (NaOAc) as the base, the reaction time extended from 40 min to three hours. However, this change led to a concurrent increase in the yield of compound **6**, reaching 92% (as shown in Scheme 4). We also noted that the catalyst particles remained stable, and there was no palladium black precipitation. This suggested the possibility of further reducing the pre-catalyst loading, but it would come at the cost of even longer reaction times, a compromise we decided against at this point. In the ^{1}H nuclear magnetic resonance (NMR) analysis (SI section, Figures S11 to S13), the olefinic hydrogens displayed a doublet with a coupling constant of $^3J_{H7H8}$ 16.2 Hz, indicative of the *E* configuration of the double bond.

The final step for obtaining DRG is the cleavage of the MOM groups in acidic media (summarized in Table 1). First attempt was 4.8 mol L^{-1} HCl in refluxing methanol,[37] in an overall closed system, and DRG was obtained in 61% yield. Exchanging hydrochloric acid for *p*-toluenosulfonic acid (PTSA) decreased yield to only 44%. Other methodologies were also evaluated; CBr_4 in refluxing isopropanol[38] gave DRG in lower yield, 51%, and more complex chromatographic profile. $ZrCl_4$ in isopropanol,[32] $Zn(OTf)_2$,[39] $ZnCl_2$, and the use of propanethiol as carbenium scavenger all were unsuccessful. Attempts to improve the deprotection with diluted HCl were made; noting the initial difficulty of solubilizing the protected stilbene in methanol, a small quantity of acetone, 10% v/v, was added prior to acidification, and led to a modest 6% increase in yield, totalizing 67%. Performing this same procedure in an open vessel, with a short path distillation apparatus to condense any vapors into another flask, the deprotection yield was further increased to 91%. This represents a global yield of 71% in seven steps from the 3,5-dihydroxybenzoic acid.

Table 1. Deprotection of stilbene **6** for obtention of DRG



Acid catalyst	Solvent	Temperature / °C	Yield[c] / %
HCl 4.8 mol L^{-1}	MeOH	70 (reflux)	61
CBr_4	^{i}PrOH	83 (reflux)	51
PTSA	MeOH	70 (reflux)	44
$ZrCl_4$	^{i}PrOH	83 (reflux)	n.d.
$Zn(OTf)_2$	*i*PrOH	83 (reflux)	n.d.
$ZnCl_2$	DCM/PrSH	0	n.d.
HCl 4.8 M[a]	MeOH	70 (reflux)	67
HCl 4.8 M[b]	MeOH	70 (reflux)	91

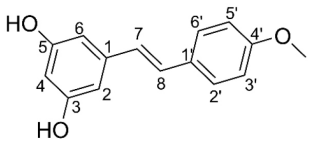
[a]Addition of 10% v/v of acetone to the methanol; [b]10% v/v acetone and performing in open vessel, with distillation of vapors; [c]isolated yield. n.d.: not determined; DCM: dichloromethane.

Our synthesis represents, within a comparable synthetic route, an increase of over 150% in the olefin **5** yield, within the same number of steps from α-resorcylic acid (87.5% *versus* 33.7%), and also an over three-fold increase in the obtainment of **6**, from 26 to 80% (six steps).[37] Compared to a Wittig strategy route, our yield on DRG is higher, 71% *vs*. 64%, and without introducing the 2:3 *E/Z* diastereomeric ratio.[40] Comparing the present route to one with Perkins reaction, the yields for DRG are comparable, 71% *versus* 77%.[41] This highlights the application of the present method and its synthetic efficiency.

With the aim of further development of biological testing of deoxyrhapontigenin, and chemical modification of the scaffold, the purity of the product obtained in the hydrolysis step is a critical factor. The use of absolute quantitative NMR (qNMR) was preferred to assess purity as it needs no chromatographic separation, since it relays in a mass relationship between the sample and a internal

standard.[42] For an appropriate qNMR experiment, the spin-lattice relaxation time, T_1, of the protons to be analyzed need to be known, to avoid incomplete relaxation and signal area distortions. We performed an inversion-recovery experiment of DRG in the quantification media, DMSO-d_6, with maleic acid as internal standard at 300 K, with exponential fitting of signal intensity (Table 2), to determine the ideal interscan time. Overall, the aromatic, olefinic and methyl hydrogens relax within two seconds, being H-4 in the resorcylic ring the slowest, in approximately 1.9 s. Hydrogens 5', 3' and 7 could not have their T_1 determined, as the corresponding signals overlapped, thus being unable to determine the relaxation time of each. Also, phenolic hydrogen times were not determined due to chemical exchange with residual water, hydroniums, and maleic acid's unionized labile protons.

Table 2. Spin-lattice relaxation (T_1) times for DRG



Hydrogen	T_1 / s	Standard deviation ($\times 10^{-3}$)
2'/6'	1.350	9.109
8	1.134	4.481
3'/5'	n.d.	n.d.
7	n.d.	n.d.
2/6	1.361	25.59
4	1.897	4.562
Me	1.064	9.586

Experimental conditions: 600 MHz, 300 K, DMSO-d_6 with maleic acid as internal standard. n.d.: not determined.

Therefore, an interscan delay of 30 s exceeded the need of up to ten times the slowest T_1, therefore suitable for quantification of DRG and consequently purity assessment. The quantification of three separate prepared samples of DRG were assessed (Table S1, SI section), with up to 99.5% purity and a mean purity of 98.18 ± 0.06% was established for this streamlined synthetic route.

Conclusions

Although our work is not a complete overhaul of existing methodologies in literature, we established a practical, streamlined, highly efficient synthetic route with simple reactions that are easily scalable into multigram quantities and integrable into diverse synthetic strategies. Our prepared aldehyde **4**, also in multigram, scale and 90% yield in four steps, is a common starting material with the other two main strategies for stilbenoid preparations, Perkin, and Wittig reactions. We also presented an alternate path for the formal synthesis of resveratrol, by means of the common vinylbenzene intermediary **5**, in 87% over five steps. For conclusion, not only deoxyrhapontigenin was obtained in larger quantities, 3.6 g, and yields, 71% in seven steps, but also in high enough purity, 98.18 ± 0.06%, for biological evaluation.

Experimental

α-Resorcylic acid was bought from Acros Organics (Geel, Belgium), all other reagents, anhydrous THF and 1,4-dioxane were purchased from Sigma-Aldrich (St. Louis, USA). Hexane and ethyl acetate were bought from Scavicco (Belo Horizonte, Brazil). The $[Cu(MeCN)_4]BF_4$ (CAS: 15418-29-8) complex was synthesized according to the literature[35] and used without further purification. All reactions in dry media were also performed in inert atmosphere, argon. All reported yields are the maximum observed, they can be up to 6% lower given slight variation in weighing reagents, solvent quality, and manipulation losses. NMR experiments were done in either an Avance III Nanobay 400 MHz or an AVANCE NEO 600 MHz (Bruker, Billerica, USA) of LAREMAR (High Resolution Magnetic Resonance Laboratory, UFMG, Belo Horizonte, Brazil). High resolution mass spectrometry (HRMS) was performed in a LCMS-IT-TOF with electrospray ionization (ESI, Shimadzu, Kyoto, Japan) (Chemistry Department, UFMG, Belo Horizonte/Brazil) or in a Q-Exactive (quadrupole-orbitrap hybrid) with heated-ESI (Thermo Scientific, Waltham, USA) from CRTI (Regional Center for Technological Development and Innovation, UFG, Goiânia, Brazil). Fourier transform infrared (FTIR) spectra were acquired on a spectrometer Frontier with attenuated total reflectance (ATR) accessory (PerkinElmer, Waltham, USA). Melting temperatures were obtained with a GEHAKA PF-1500 (São Paulo, Brazil) melting point apparatus and are uncorrected. Gas-chromatography coupled to mass spectrometry (GC-MS) analysis were performed on a QP2010-Ultra (Shimadzu, Kyoto, Japan). Further details are available in the SI section.

Procedures

Methyl 3,5-dihydroxybenzoate (**1**) (CAS: 2150-44-9)

In a 500 mL round bottom flask, 12.5 g (81.10 mmol) of α-resorcylic acid, 200 mL of methanol and 0.75 mL of concentrated sulfuric acid (94-98%) were refluxed for at

least 20 h, until no more resorcylic acid could be detected by thin layer chromatography (TLC, 2:1 ethyl acetate/hexane). The crude solution was then evaporated under reduced pressure to dryness. The resulting solid was partitioned with 200 mL ethyl acetate and 100 mL saturated $NaHCO_3$ solution. The organic phase was washed with another 100 mL of $NaHCO_{3(sat)}$ until no more effervescence was observed. The combined aqueous phases were extracted once with 100 mL of ethyl acetate. Once the organic phases were combined, it was washed once with 75 mL of saturated NaCl solution, and then dried with anhydrous sodium sulfate. 13.5 g (99%) of off-white solid were obtained, used without further purification (> 96% purity, GC).

Melting temperature: 167-168 °C; (lit.[43] 168-169 °C); IR (ATR) ν / cm^{-1} 3376, 3323, 3090, 3074, 2998, 2951, 1689, 1306, 1162, 966, 766; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.64 (s, 2H, OH), 6.82 (d, $^4J_{H2/6\text{-}H4}$ 2.1 Hz, 2H, H2/H6), 6.45 (t, $^4J_{H2/6\text{-}H4}$ 2.1 Hz, 1H, H4), 3.79 (s, 3H, COOCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.3 (1, C7), 158.6 (2, C3/5), 131.3 (1, C1), 107.2 (2, C2/6), 107.1 (1, C4), 52.0 (1, COO*C*H3) (lit.[43]); MS (EI) *m*/*z*, (%) 137 (100), 168 (52.7) [M$^{\bullet+}$], 109 (49.4); HRMS (IT-TOF + ESI) *m*/*z*, calcd. for [M – H]$^-$: 167.0350; found: 167.0342.

Methyl 3,5-bis(methoxymethoxy)benzoate (**2**) (CAS: 76280-59-6)

In a 125 mL round-bottom flask methylal (21.3 mL, 240 mmol) and $Zn(OTf)_2$ (0.005 g, 0.014 mmol) were added. The flask was maintained in a room temperature water bath, then, acetyl chloride (17.2 mL, 241 mmol) was added dropwise under vigorous stirring. Finalizing the addition, the reaction mixture was stirred at room temperature (r.t.) for 4 h, obtaining a colorless solution. The solution contains chloromethyl methyl ether, a toxic and carcinogenic liquid. Use necessary safety gear and avoid contact. All glassware should be decontaminated in a diluted aqueous ammonia or ammonium chloride bath inside the fumehood prior to cleaning. To a 500 mL double-necked round-bottom flask equipped with a 100 mL addition funnel and inert atmosphere, **1** (8.4 g, 50 mmol), anhydrous THF (110 mL) and anhydrous DIPEA (42 mL, 241 mmol), were added then cooled to 0 °C. The previously prepared alkylating solution was cannulated to the addition funnel and added dropwise over 30 min under vigorous stirring. After the addition, the reaction mixture was stirred at r.t. for 24 h, obtaining an orange suspension. Then, the reaction was quenched with saturated NH_4Cl solution (60 mL) and stirred for another 40 min, resulting in a yellow biphasic system. After partitioning, the aqueous layer was extracted with 4 × 75 mL of AcOEt. The combined organic phases were washed, sequentially, with 2 × 50 mL 1 M HCl, 2 × 50 mL saturated $NaHCO_3$ solution and 2 × 50 mL saturated NaCl solution. The organic phase was dried with anhydrous Na_2SO_4 and all solvent removed under reduced pressure. The resulting yellow oil was purified by silica column chromatography (25% EtOAc/hexane; Rf = 0.61). After vacuum drying, 11.787 g (92%) of colorless oil were obtained. Trace impurities can give a yellowish hue to the oil.

IR (ATR) ν / cm^{-1} 3005, 2956, 2901, 2835, 1724, 1593, 1297, 1142, 1015, 769; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, $^4J_{H2/6\text{-}H4}$ 2.3 Hz, 2H, H2/6), 6.92 (t, $^4J_{H2/6\text{-}H4}$ 2.3 Hz, 1H, H4), 5.19 (s, 4H, OCH_2O), 3.90 (s, 3H, COOCH_3), 3.48 (s, 6H, CH_2OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.8 (1, C7), 158.3 (2, C3/5), 132.4 (1, C1), 110.9 (2, C2/6), 109.9 (1, C4), 94.7 (2, O*C*H$_2$O), 56.4 (2, O*C*H$_3$), 52.5 (1, COO*C*H$_3$) (Lit.[37]); MS (EI) *m*/*z*, (%) 45 (100), 256 (11.10) [M$^{\bullet+}$], 225 (3.83); HRMS (Q-Orbitrap + H-ESI) *m*/*z*, calcd. for [M + H]$^+$: 257.1020; found: 257.1020.

3,5-bis(Methoxymethoxy)benzenemethanol (**3**) (CAS: 76280-60-9)

To a 250 mL round-bottom flask, **2** (11.3 g, 44.1 mmol) was added and the atmosphere inertized with argon. Then, anhydrous THF (130 mL) was added, and the obtained solution cooled to 0 °C. To the mixture, under vigorous stirring, $LiAlH_4$ (2.0 g, 52.7 mmol) was added in small portions and then stirred at r.t. for 1.5 h. The mixture was again cooled to 0 °C and quenched, sequentially, with 2 mL water, 2 mL $NaOH_{(aq)}$ 10%$_{m/v}$ and 3 × 2 mL water. After the suspension color changed to white, anhydrous $MgSO_4$ was added as needed for drying and stirred for at least 20 min. The suspension was vacuum filtered, washing the solid cake with 200 mL AcOEt, portioned. All the volatiles were removed under reduced pressure and further dried in vacuum, furnishing 10.07 g (quantitative) of colorless oil, used without further purification. Rf = 0.26 (25% AcOEt/hexane).

IR (ATR) ν / cm^{-1} 3350, 3011, 2954, 2945, 2902, 2826, 1595, 1457, 1312, 1298, 1143, 1002, 992, 926, 847; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (d, $^4J_{H2/6\text{-}H4}$ 2.2 Hz, 2H, H2/6), 6.64 (t, $^4J_{H2/6\text{-}H4}$ 2.2 Hz, 1H, H4), 5.15 (s, 4H, OCH_2O), 4.62 (d, $^3J_{H7\text{-}OH}$ 5.5 Hz, 2H, H7), 3.47 (s, 6H, OCH_3), 1.93 (t, $^3J_{H7\text{-}OH}$ 5.5 Hz, 1H, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$,) δ 158.6 (2, C3/5), 143.7 (1, C7), 108.1 (2, C2/6), 104.3 (1, C4), 94.6 (2, O*C*H$_2$O), 65.3 (1, C7), 56.3 (2, O*C*H$_3$) (lit.[37]); MS (EI) *m*/*z*, (%) 45 (100), 228 (8.8) [M$^{\bullet+}$], 168 (2.1); HRMS (Q-Orbitrap + H-ESI) *m*/*z*, calcd. for [M + Na]$^+$: 251.0890; found: 251.0890.

3,5-bis(Methoxymethoxy)benzaldehyde (**4**) (CAS: 76280-61-0)

A 500 mL round-bottom flask was charged with **4** (10.154 g, 44.12 mmol) and 140 mL of MeCN. To

the solution, sequentially, $[Cu(MeCN)_4]BF_4$ (0.86 g, 2.31 mmol), 2,2'-bipyridine (0.37 g, 2.31 mmol), TEMPO (0.36 g, 2.31 mmol) and *N*-methyl-imidazol (390 µL, 4.62 mmol) were added. The dark mixture was stirred, open vessel, at r.t. for 2 h. After complete conversion of the starting material (TLC, 25% AcOEt/hexane; Rf = 0.55), the dark solution was concentrated to approximately $^2/_3$ of the initial volume under reduced pressure, and then diluted with 100 mL of diethyl ether. The mixture was then poured over a sintered glass funnel (internal diameter (ø) 92 mm, G2 porosity) with 5 cm of packed silica gel (40-63 µm) for vacuum filtration. The silica was washed with 20% EtOAc/hexane (total volume ca. 400 mL) until no more aldehyde could be detected by 2,4-dinitrophenylhydrazine stain on spot-test. All the volatiles were removed under reduced pressure, furnishing 9.72 g (97%) of orange-yellowish oil, used without further purification (> 96% purity, GC-MS). All characterization was performed with a purified aliquot.

IR (ATR) ν / cm^{-1} 2994, 2956, 2938, 2904, 2828, 2731, 1701, 1593, 1290, 1080, 1022, 922; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H, H7), 7.21 (d, $^4J_{H2/6\text{-}H4}$ 2.3 Hz, 2H, H2/6), 6.98 (t, $^4J_{H2/6\text{-}H4}$ 2.3 Hz, 1H, H4), 5.21 (s, 4H, OCH_2O), 3.49 (s, 6H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8 (1, C7), 159.0 (2, C3/5), 138.7 (1, C1), 111.4 (1, C4), 110.6 (2, C2/6), 94.7 (1, OCH$_2$O), 56.4 (2, OCH$_3$) (lit.[37]); MS (EI) *m*/*z*, (%) 45 (100), 226 (31.9) [M$^{\bullet+}$], 164(6.3); HRMS (Q-Orbitrap + H-ESI) *m*/*z*, calcd. for $[M + H]^+$: 227.0914; found: 227.0914.

1-Ethenyl-3,5-bis(methoxymethoxy)benzene (**5**) (CAS: 1438867-27-6)

To a 250 mL round-bottom flask containing **4** (9.72 g, 42.98 mmol), powdered methyltriphenylphosphonium iodide (26 g, 64.5 mmol) and finely powdered anhydrous K_2CO_3 (12 g, 86 mmol) were added, followed by atmosphere inertization with Ar. Then, anhydrous 1,4-dioxan (150 mL) was added, and the mixture heated to reflux under vigorous stirring for 72 h. The complete conversion of the starting alcohol was confirmed by TLC (aldehyde Rf = 0.62 in 12.5% AcOEt/hexane), the reaction was quenched by addition of acetone (5 mL) and refluxed by 30 min. After cooling to room temperature, the reaction mixture was concentrated to $^1/_3$ of initial volume and then diluted with cold Et_2O (50 mL). The slurry was filtered over a silica gel plug (ø 92 mm, ca. 4 cm high) and washed with 50% EtOAc/hexane (ca. 200 mL). The filtrated was concentrated and purified by silica-gel column chromatography with an eluent gradient 0→20% EtOAc/hexane. After vacuum removal of solvents, 9.316 g (97%) of colorless oil was obtained.

IR (ATR) ν / cm^{-1} 3009, 2996, 2956, 2902, 1589, 1287, 1140, 1014, 990, 850, 680, 664; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (d, $^4J_{H2/6H4}$ 2.2 Hz, 2H, H2/6), 6.65 (t, $^4J_{H2/6H4}$ 2.2 Hz, 1H, H4), 6.63 (dd, $^3J_{H7H8'}$ 10.8 and $^3J_{H7H8}$ 17.5 Hz, 1H, H7), 5.72 (d, $^3J_{H7H8}$ 17.5 Hz, 1H, H8), 5.25 (d, $^3J_{H7H8'}$ 10.8 Hz, 1H, H8'), 5.16 (*s*, 4H, OCH_2O), 3.48 (s, 6H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6 (2, C3/5), 140.0 (1, C1), 136.8 (1, C7), 114.8 (1, C8), 107.9 (2, C2/6), 104.6 (1, C4), 94.7 (2, OCH_2O), 56.3 (2, OCH_3) (lit.[37]); MS (EI) *m*/*z*, (%) 224 (100) [M$^{\bullet+}$], 164 (22.3), 89 (15); HRMS (Q-Orbitrap + H-ESI) *m*/*z*, calcd. for $[M + H]^+$: 225.1121; found: 225.1121.

1,3-*bis*(Methoxymethoxy)-5-[(1*E*)-2-(4-methoxyphenyl) ethenyl] benzene (**6**) (CAS: 1438867-47-0)

To a 200 mL round-bottom flask were added **5** (4.07 g, 17.6 mmol), 4-iodoanisole (4.23 g, 17.7 mmol), benzyltriethylammonium chloride (4.10 g, 18 mmol); NaOAc (4.43 g, 54 mmol) and DMF (50 mL). The solution was flushed with argon and heated to 115 °C, with vigorous stirring. Then, $Pd(OAc)_2$ (0.20 g, 0.89 mmol) was added to the hot solution and the flask sealed with a glass stopper. After 3 h at the said temperature, the reaction mixture was cooled to room temperature, and concentrated to $^1/_5$ of initial volume under reduced pressure. The residue was suspended with 150 mL of EtOAc and filtered over a celite plug (ø 35 mm, ca. 35 mm high), washing with ca. 300 mL 50% AcOEt/hexane (until no more product was detected in the drippings by TLC; 12.5% AcOEt/hexane, Rf = 0.39). The filtrated was incorporated into silica-gel and purified by column chromatography isocratically with 12.5% (1:7) AcOEt/hexane. After solvent removal and vacuum drying, an off-white solid (5.34 g, 92%) was obtained.

Melting temperature: 87-88 °C (lit.[37] 84-86 °C); IR (ATR) ν / cm^{-1} 3080, 3032, 2989, 2957, 2902, 2831, 1589, 1516, 1140, 1076, 1040, 1028, 956, 916, 847, 831, 678; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45-7.43 (m, 2H, H3'/H5'), 7.03 (d, $^3J_{H7H8}$ 16.2 Hz, 1H, H8), 6.90-6.89 (m, 2H, H2'/6'), 6.89 (d, $^3J_{H7H8}$ 16.2 Hz, 1H, H7), 6.85 (d, $^4J_{H2/6H4}$ 2.0 Hz, 2H, H2/6), 6.63 (t, $^4J_{H2/6H4}$ 2.0 Hz, 1H, H4), 5.19 (s, 4H, OCH_2O), 3.83 (s, 3H, OCH$_3$), 3.50 (s, 6H, CH$_2$OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.4 (1, C4'), 158.5 (2, C3/C5), 139.9 (1, C1), 129.0 (1, C1'), 128.9 (1, C8), 127.8 (2, C3'/C5'), 126.3 (1, C7), 114.2 (2, C2'/C6'), 107.7 (2, C2/C6), 104.0 (1, C4), 94.5 (2, OCH$_2$O), 56.1 (2, CH$_2$OCH$_3$), 55.4 (1, CH$_3$) (lit.[37]); MS (EI) *m*/*z*, (%) 330 (100) [M$^{\bullet+}$], 121(53.2), 253 (24.4); HRMS (Q-Orbitrap + H-ESI) *m*/*z*, calcd. for $[M + H]^+$: 331.1540; found: 331.1540.

Desoxyrhapontigenin (DRG) (CAS: 33626-08-3)

To a 500 mL round-bottom flask with a short-path distillation apparatus, **6** (5.34 g, 16.19 mmol), acetone (20 mL) and methanol (200 mL) were added. The mixture was heated to 70 °C, under stirring, to completely dissolve all solids; then, 4.8 M HCl (7 mL, 33.6 mmol) were added to the hot solution. Any vapors formed were distilled off the system. After 2.5 h, the acidic solution was neutralized with solid $NaHCO_3$, and the solids filtered off. The filtrate was concentrated and purified by column chromatography isocratically with 40% AcOEt/hexane (Rf = 0.64). After drying in vacuum, an off-white to yellowish solid was obtained (3.56 g, 91%).

Melting temperature: 165-167 °C (lit.[44] 164-167 °C); IR (ATR) ν / cm^{-1} 3350, 3056, 3014, 2958, 2848, 1598, 1485, 1458, 1237, 1149, 1162, 996, 817, 674; ^{1}H NMR (600 MHz, acetone-d_6) δ 8.20 (s, 2H, O*H* ×2), 7.52-7.49 (m, 2H, H3'/H5'), 7.05 (d, $^3J_{H7H8}$ 16.5 Hz, 1H, H7), 6.94-6.91 (m, 2H, H2'/H6'), 6.94 (d, $^3J_{H7H8}$ 16.5 Hz, 1H, H8), 6.56 (d, $^4J_{H2/6H4}$ 2.2 Hz, 2H, H2/6), 6.29 (t, $^4J_{H2/6H4}$ 2.2 Hz, 1H, H4), 3.81 (s, 3H, O*C*H_3); ^{13}C NMR (150 MHz, acetone-d_6) δ 160.4 (1, C4'), 159.6 (2, C3/C5), 140.8 (1, C1), 131.0 (1, C1'), 128.8 (1, C7), 128.6 (2, C3'/C5'), 127.5 (1, C8), 114.9 (2, C2'/C6'), 105.7 (2, C2/C6), 102.8 (1, C4), 55.6 (1, *C*H_3) (lit.[12]); purity (qNMR, 600 MHz, 300 K, DMSO-d_6, triplicate) 98.18 ± 0.06%; HRMS (Q-Orbitrap + H-ESI): *m*/*z*, calcd. for $[M - H]^-$: 241.0870; found: 241.0870.

Supplementary Information

Supplementary information (detailed analytical conditions, NMR and FTIR spectra and chromatographic data) is available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgments

Authors are thankful to the financial support provided by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq; grants 140436/2019-7, 313114/2021-8 and 440733/2018-9), Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG; grant No. APQ-02187-17), and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)-Finance Code 001. This work was made possible by the INCT on Urease Inhibitors of Agricultural and Medicinal Interest which is financially supported by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). We would also like to thank the Laboratório de Ressonância Magnética de Alta Resolução (LAREMAR) from UFMG for the analysis' subsid, Dr Ivana Lula for her guidance in NMR acquisition and the BioAnalytical Facility NEPS-DQ at the Universidade Federal de Minas Gerais, Belo Horizonte, MG, for the support with (bio)chemical analyses during this work. Ângelo de Fátima is supported by CNPq Research Fellowship.

Author Contributions

Yuri de Freitas Rego was responsible for formal analysis, methodology, investigation, validation and writing (original draft, review and editing); Ângelo de Fátima for conceptualization, funding acquisition, project administration, resources, supervision and writing (review and editing).

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Submitted: November 16, 2023
Published online: January 12, 2024