Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of 1,2,4-Trimethoxybenzene and Its Selective Functionalization at C-3 by Directed Metalation

Ana P. L. Alves [a], Jose Augusto B. C. Júnior [a], Glaucia B. A. Slana [a], Jari N. Cardoso [a], Qiang Wang [a], Rosangela S. C. Lopes [a] & Claudio C. Lopes [a]

[a] Federal University of Rio de Janeiro, Institute of Chemistry, Department of Analytical Chemistry, Rio de Janeiro, Brazil

Published online: 08 Sep 2009.

To cite this article: Ana P. L. Alves , Jose Augusto B. C. Júnior , Glaucia B. A. Slana , Jari N. Cardoso , Qiang Wang , Rosangela S. C. Lopes & Claudio C. Lopes (2009) Synthesis of 1,2,4-Trimethoxybenzene and Its Selective Functionalization at C-3 by Directed Metalation, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:20, 3693-3709, DOI: 10.1080/00397910902805598

To link to this article: http://dx.doi.org/10.1080/00397910902805598

Synthetic Communications®, 39: 3693–3709, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910902805598

Taylor & Francis
Taylor & Francis Group

Synthesis of 1,2,4-Trimethoxybenzene and Its Selective Functionalization at C-3 by Directed Metalation

Ana P. L. Alves, Jose Augusto B. C. Júnior, Glaucia B. A. Slana, Jari N. Cardoso, Qiang Wang, Rosangela S. C. Lopes, and Claudio C. Lopes

Federal University of Rio de Janeiro, Institute of Chemistry, Department of Analytical Chemistry, Rio de Janeiro, Brazil

Abstract: A new and efficient strategy was developed for the preparation of 1,2,4-trimethoxybenzene (**3**, a powerful attractant of Euglossini bees) and its C-3 derivatives (**7a**–**j**), from vanillin (**2**) in 56% overall yield.

Keywords: Aromatic lithiation, directed metalation, Euglossini bees, regioselectivity, 1,2,4-trimethoxybenzene

INTRODUCTION

Indol (**1**) is one of the N-heterocyclic compounds most widespread among floral scents in nature, and 1,2,4-trimethoxybenzene can be found in the volatiles of *Cucurbita*, *Cymbidium*, *Hyacinthus*, *Pyrola*, and *Syringa* species.[1] The latter also can be obtained from the methylation of 1,4-dihydroxy-2-methoxybenzene by CH_3I, in the presence of potassium hydroxide (KOH).[2]

Vanillin (**2**) is the major component of natural vanilla, one of the most widely used and important flavoring materials worldwide, especially

Received October 8, 2008.

Address correspondence to Claudio C. Lopes, Federal University of Rio de Janeiro, Institute of Chemistry, Department of Analytical Chemistry, CT, Bloco A, s. 508, Rio de Janeiro, RJ, Brazil. E-mail: claudiosabbatini@uol.com.br

in the food and pharmaceutical industries. The natural source of vanilla is the *Vanilla* orchids.[3]

The aim of this work is to evaluate the ability of a mixture of semiochemicals, called TIV (1,2,4-trimethoxybenzene, indol, and vanillin), in attracting insects of a citrus orchard, in the county of Silva Jardim, Rio de Janeiro, Brazil. For the preparation of the TIV mixture, we have proposed a new low-cost synthetic route to 1,2,4-trimethoxybenzene (**3**).

RESULTS AND DISCUSSION

The mixture called TIV (Fig. 1) is formed by the semiochemicals indol (**1**), vanillin (**2**), both of which were purchased from Aldrich Co., and 1,2,4-trimethoxybenzene (**3**), which was synthesized in our laboratory from (**2**) through a low-cost and fast route (Fig. 2).

Our synthetic approach for the preparation of **3** started with the methylation of vanillin (**2**) by treatment with methyl iodide (CH_3I), in the presence of K_2CO_3, in CH_3COCH_3 under reflux, to obtain 3,4-dimethoxybenzaldehyde (**4**) in 95% yield.

The next step was oxidation of the carbonyl carbon of the aldehyde (**4**). For this purpose, **4** was subjected to different reactional oxidation conditions (Table 1), employing H_2O_2 or *m*-CPBA as the oxidant agents.[4]

The first oxidation condition (sodium hydroxide, NaOH, in H_2O_2), aimed at the preparation of the phenol (**6**), used less severe and more ordinary reaction conditions (Table 1, Entry 1). However, this attempt was not adequate to yield **6**. Thus, another oxidant agent was employed, affording stronger oxidant conditions [3-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 reflux)], followed by basic hydrolysis (KOH/methanol [MeOH]) (Table 1, entry 2). It was possible now to obtain **6** in a poor yield (only 15%, from **4**). Moreover, the overall yield was 14%, which was not adequate for our purposes. Therefore, other reactions and experimental conditions were tried to improve the final yield.

The best result was obtained (Table 1, entry 3) when 3,4-dimethoxybenzaldehyde (**4**) was treated with *m*-CPBA in CH_2Cl_2 in a buffered

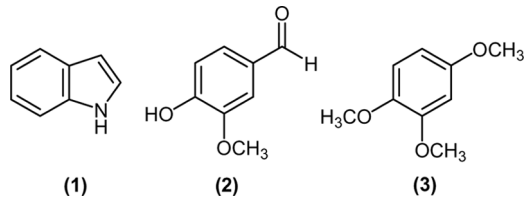


Figure 1. Semiochemicals in the TIV mixture.

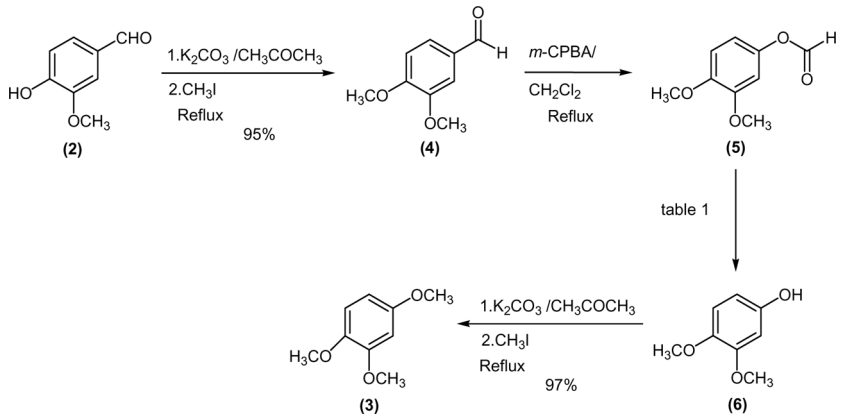


Figure 2. Synthetic approach for the preparation of 1,2,4-trimethoxybenzene (**3**) from vanillin (**2**).

reaction mixture with $NaHCO_3$ to form 3,4-dimethoxyphenyl formate **(5),** which was subjected to basic hydrolysis in KOH/MeOH to obtain 3,4-dimethoxyphenol (**6**) from **4** in 61% yield.

Finally, **6** was methylated by CH_3I in K_2CO_3/CH_3COCH_3 to afford **3** in 97% yield. The overall synthetic yield of **3** was 56%, which satisfied our aim of gettting this compound by a practical and cheap synthetic route.[5–8]

All compounds were characterized through infrared (IR), ^1H NMR, and ^{13}C NMR analysis.

Insects Attracted by TIV Mixture in Citrous Orchard: Preliminary Field Experiments

McPhail traps containing the TIV mixture were installed in a domestic citrus orchard in Bom Jesus Farm, at Silva Jardim, in the state of Rio de Janeiro, Brazil. In this type of trap, the insects are attracted not only

Table 1. Baeyer–Villiger's reaction yields from 3,4-dimethoxybenzaldehyde (**4**) and global route yields

Enters	Reagent	Yields (%) in **6**	Global yields (%) in **3**
1	3,4-Dimethoxybenzaldehyde[12] (4)	—	—
2	3,4-Dimethoxybenzaldehyde (4)	15	14
3	3,4-Dimethoxybenzaldehyde (4)	61	56

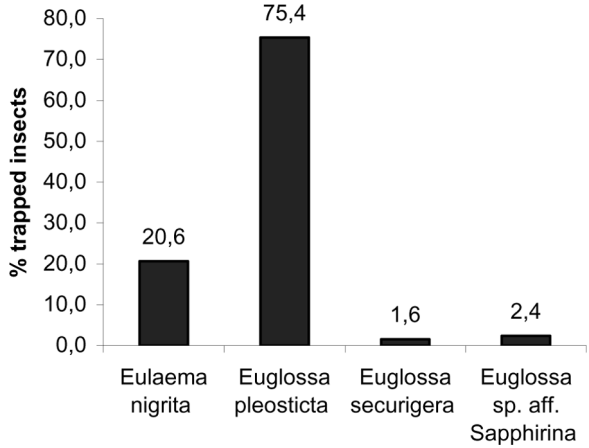


Figure 3. Euglossine bees attracted in field experiments.

by the odour stimulus (semiochemical mixture) but also by a visual sign, the yellow color of the trap interior. Once inside the trap, insects are not able to escape because they fly toward the superior colorless piece and ultimately die without food and energy.

After 7 days of exposure (Fig. 3), four species of insects were captured and sent for identification at the University of Sao Paulo (Departament of Biology of the Faculty of Philosophy, Sciences, and Literature of Ribeirão Preto). None of the insects captured was observed in blank traps (without TIV). In Table 2, we list the four species attracted by the TIV mixture in the preliminary test.

All insects attracted by the TIV mixture belong to the most important genus of the Euglossini tribe: *Eulaema* sp. and *Euglossa* sp.

Euglossine bees (Apidae: Euglossini) are an important exclusively neotropical pollinator group that are most closely related with certain Angiosperm families. Without specifically trying to collect pollen, they

Table 2. Field experiment results

	Traps		
Species	Average	Total	Blanks
Eulaema nigrita Lepeletier, 1841	4.33	26	—
Euglossa pleosticta Dressler, 1982	15.83	95	—
Euglossa securigera Dressler, 1982 (sensu Moure)	0.33	2	—
Euglossa sp. aff. Sapphirina Moure, 1968	0.5	3	—

are able to secure pollination of species of *Caesalpiniaceae*, *Maranthaceae*, *Euphorbiaceae*, *Araceae*, *Gesneriaceae*, *Bignoniaceae*, *Orchidaceae*, and others.[8] They are known as orchid bees.

Male euglossine bees are the only pollinators of some orchids (e.g., *Gongora*, *Castasctum*, and *Coryanthes*). They are attracted to the essences produced by these orchids' flowers. The mechanism of attraction of these essences is not well understood, but they may act as a sexual attractant.[9] Euglossine bees are described as a group of brightly colored tropical insects. Many species are green, blue, purple, gold, or red. However, in the Eulaema generus, the insects are bigger with less metallic-colored bright bodies. They have tongues that, in some species, may be twice as long as the body. The long tongue allows them to reach nectar in deep-throated tropical flowers. Many species of Eulema bees collect nectar, pollen, and other substances from orchids.

Our mixture of semiochemicals (TIV) captured four species of euglossine bees (Table 2): *Eulaema nigrita* Lepeletier (1841), *Euglossa pleosticta* Dressler (1982), and *Euglossa securigera* Dressler (1982), and *sensu* Moure and *Euglossa* sp. *aff. Sapphirina* Moure (1968).

Eulaema nigrita and *Euglossa pleosticta* were the most attracted species under the tested conditions, with 21% and 75% respectively (Fig. 3).

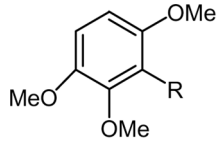
Eulaema nigrita is an important natural pollinator of *Passiflora* sp. The natural fertilization of its flowers is rare because of the autoincompatibility, yielding small fruits with few seeds. Pollinization in the commercial crops of *Passiflora* sp. is naturally done by insects of *Eulaema* and *Xylocopa* sp. or artificially by people.

Euglossa sp. are important in orchid pollinization. Those flowers are cultivated for their fragrances and exotic beauty. Thus, all insects captured may have commercial importance. TIV mixture application in orchid cultivation and *Passiflora* sp. crops is proposed with the aim of increasing the population of pollinators in these areas and therefore improving the production of flowers and fruits.

Synthesis of 1,2,4-Trimethoxybenzene C-3 Derivatives (7a–j)

The success of species attraction by the TIV mixture in a citrus orchard and the good yields obtained in the preparation of 1,2,4-trimethoxybenzene encouraged the synthesis of 1,2,4-trimethoxybenzene C-3 derivatives (Fig. 4) to evaluate their insect attractant potential for future studies.

Field studies about the use of 1,2,4-trimethoxybenzene C-3 derivatives (**7a–j**) as semiochemicals could not be found. Therefore, an evaluation of these compounds as strong candidates as insect attractants for pest or pollinators studies seemed promising.



(7)

7a. R =CH_3 **7f**. R =D
7b. R =COH **7g**. R =$CON(Et)_2$
7c. R =Br **7h**. R =$COOCH_3$
7d. R =COOH **7i**. R =$CH_2CH{=}CH_2$
7e. R =$Si(CH_3)_3$ **7j**. R =$B(OH)_2$

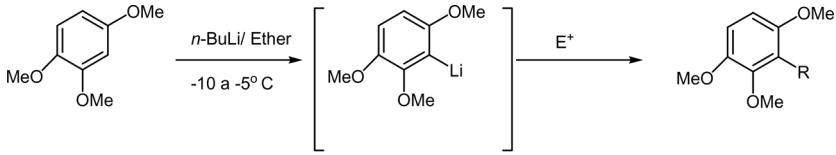
Figure 4. 1,2,4-Trimethoxybenzene C-3 derivatives.

Based on the experience of our research group in metalation reactions using *n*-butyl-lithium, the study of this reaction in the preparation of **7a**–**j** was decided. The synthesis of 10 derivates at carbon 3, to explore the fact that this carbon is activated by the presence of two ortho-directing metalation groups (D*o*M), the methoxy in C-2 and C-4, was proposed.

Organolithium reagents are characterized by the presence of a C–Li covalent bond. They can act as bases or nucleophiles, because of the difference in electronegativity between C and Li, creating a polarization in which C is partially negative.

The most-used solvents in metalation reaction with lithium are ethyl ether, tetrahydrofuran (THF), pentane, and hexane. In fact, the organolithium reagents are found in aggregated states that depend on the type of lithium reagent and the solvents. If the solvation of the organolithium is low, the lithium reagent interacts more, and thus the aggregation state is greater. However, if the solvent complexes the organolithium, the aggregation state is lower, and the ionic character of the C-Li covalent bond becomes greater. The more deoligomerized the lithium reagent, the more reactive it is.[10]

The D*o*M reaction (Fig. 5) comprises the deprotonation of a site *ortho* to a heteroatom-containing DMG (directed metalation group) by a strong base, normally an alkyllithium reagent, leading to an ortho-lithiated species (**8**).[11]



(3) (8) (7)

Figure 5. Directed metalation reaction for the preparation of 1,2,4-trimethoxybenzene C-3 derivatives.

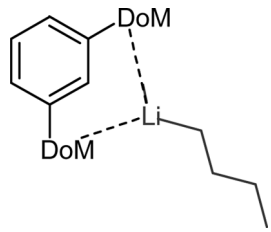


Figure 6. Prior-coordination complex formed between the alkyllithium reagent and the D*o*M of the aromatic substrate.

First, there is formation of a precoordination complex (Fig. 6) between the alkyllithium reagent and the D*o*M group of the aromatic substrate. This coordination complex is paramount to involvement of the complexed-induced proximity effect (CIPE). Facilitated by the proximity of the lithium atom to an ortho-hydrogen on the substrate, a lithium/ortho-H exchange occurs. The species formed, upon treatment with electrophilic reagents, yields 1,2-disubstituted products (**7**).[12]

The second synthetic step of this work was the selective metalation reaction of **3** to prepare its C-3 derivatives (**7a**–**j**). Selectivity was expected on account of the D*o*Ms (–OCH_3) in positions 2 and 4, which directed the metalation to position 3 preferentially relative to positions 5 and 6. According to Snieckus,[11] the cooperative effect of 1,3-interrelated DMGs promotes metalation at their common site, which means position 2.

Because of the complexity of the organolithium reactions, different experimental conditions were tried (Table 3) to establish optimum yields. Methyl iodide was chosen as an electrophile to test conditions that could be extrapolated to the synthesis of the other derivatives.

Table 3. Experimental conditions tested in the directed metalation reaction of 1,2,4-trimethoxybenzene using CH_3I as electrophile

Enters	Organolithium reagents*	Solvents	Reaction time**(h)	yields (7a) (%)
1	*s*-BuLi	Ether	1,5	—
2	*n*-BuLi	Ether	1,5	75
3	*n*-BuLi	Thf	1,5	30
4	*n*-BuLi	Hexane	2	—
5	*n*-BuLi	Thf	3	15
6	*n*-BuLi	Ether	3	67

*There were employed 1,1,eq of the organolithium reagent and CH_3I.
**Time of the reaction before the addition of the electrophile.

We started studying the yields of metalation with *n*-BuLi and *s*-BuLi in our work conditions (Table 3, entries 1 and 2). Entry 1 suggests that the presence of the methoxy groups at C-2 and C-4 of (**3**) may be a steric restriction to a more hindered base in relation to its linear analog.

The results obtained with *n*-BuLi (entry 2) encouraged testing other conditions to evaluate solvent effects. Therefore, ethyl ether, hexane, and THF were used as solvents. Although *n*-BuLi presents hexameric structure in nonpolar hydrocarbons, which permits little, if any, directed metalation of aromatic substrates, Slucom et al.[12] published a work in which the directed metalation of 1,2- and 1,3-dimethoxybenzenes and 1,2,4-trimethoxybenzenes were done in this solvent, in good yields. According to Slucom,[12] those compounds possess DMGs sufficiently able to complex and thereby deoligomerize *n*-BuLi. Thus, they could function simultaneously as both the substrate and as the catalyst. In this way, the reagent itself would first deoligomerize the alkyllithium reagent to a reactive dimer, and subsequently, once in this reactive form, the aromatic reagent could react to generate a lithiated aromatic intermediate.[12] However, the results reported in the literature could not be duplicated in our laboratory, when hexane was used as solvent (Table 3, entry 4).

n-BuLi exists in a tetrameric form in diethylether, whereas a mixture of the dimeric and tetrameric structures exist in THF. The dimer is considered as the most reactive of the *n*-BuLi oligomeric forms.[12]

The yields in the reactions using THF as solvent (Table 3, entries 3 and 4) were not better than the ones obtained in the reactions using ethyl ether. We believe that such results may be related to the fact that they are sufficiently polar to deoligomerize alkyllithium reagents and also readily dissolve arene substrates.[12] Thus, from those results, the conditions of entry 2 (Table 3) to synthesize the other derivatives of **3** were adopted. The reaction time was also analyzed but did not seem to affect the results.

All C-3 derivatives (**7a–j**) were prepared, and structures were characterized through IR, ^{1}H NMR, and ^{13}C NMR analysis.

CONCLUSIONS

By employing a low-cost approach, 1,2,4-trimethoxybenzene (**3**) was synthesized in 56% overall yield, after a study to determine optimum conditions to prepare **6** from **4**. Ten 1,2,4-trimethoxybenzene C-3 derivatives (**7a–j**) were also prepared in excellent yield, using the metalation reaction with *n*-BuLi.

The preliminary field study was conducted in a citrous orchard, located at Bom Jesus Farm in Silva Jardim, and showed promising results

in attracting insects with the TIV mixture. Pollinators (orchid bees) were captured, especially *Eulaema nigrita* Lepeletier (1841) and *Euglossa pleosticta* Dressler (1982), both of which are important in the *Passiflora* sp. crops and orchid cultivars, respectively. In this way, TIV mixtures may be used in those crops or cultivars to increase the population of pollinators.

A field study of the C-3 derivatives (**7a**–**j**) to evaluate their potential as insect attractants as well as the contribution of each individual TIV mixture constituent to attract insects are planned for future work. The determination of the optimum proportion of each component in the mixture is also intended.

EXPERIMENTAL

General Methods

Solvents and reagents were purchased from Vetec, Aldrich, Merck, Grupo Química, Isotec Inc., and Acros Organics. All solvents were dried and purified prior to use. All reactions were performed under anhydrous conditions and were conducted in oven-dried glassware under an argon atmosphere. Air-sensitive solutions were transferred via oven-dried syringe needles or an oven-dried cannula under positive pressure of argon. Ether was distilled from Na/benzophenone ketyl.

IR spectra were recorded on Magma IR-760-Nicolet spectrometer. Fourier transform (FT)-IR spectra were taken in over KBr windows and absorption maxima are reported in centimeters^{-1}.

Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were recorded on Varian Gemini 200-MHz or Brucker 300-MHz spectrometers. FT-NMR spectra were done in $CDCl_3$ or dimethylsulfoxide (DMSO)-d_6. Chemical shifts (δ) are reported relative to tetramethylsilane (TMS; $\delta_{TMS} = 0$) in parts per million, and the g constants (J) are reported in hertz. The following abbreviations were employed for multiplicities: s (singlet), d (dublet), dd (double dublet), dt (double triplet), q (quartet), and m (multiplet).

High-resolution mass spectra (HRMS) were taken on Atlas MS-12, Consolidated 12–110 B, or Finnegan 400 mass spectrometers at 70 eV at the University of California (Berkeley, USA). Where mass spectral (MS) data are given, the peak value is immediately followed by its relative abundance in parentheses.

Melting points were recorded on a Mel-TempII capillary melting-point apparatus (Aldrich), and temperatures (uncorrected) are reported in degrees C.

Chromatography

All reactions were followed by thin-layer chromatography (TLC), on 0.2 mm silica-gel 60 F_{254} plates (Merck). Plates were visualized by spraying with 2,4-dinitrophenylhydrazine, *p*-anisaldehyde, or iron chloride solutions or under ultraviolet (UV) light.

In cases where a product was purified by column chromatography, silica-gel 60 flash chromatography was used (230–400 mesh ASTM, Merck).

Field Experiments

Field experiments were carried out at Bom Jesus Farm (off interstate BR 101, Km 35, Silva Jardim county), Rio de Janeiro. The baited traps were placed February 1–7, 2004, and removed after 7 days.

Indol (**1**), vanillin (**2**), and 1,2,4-trimethoxybenzene (**3**) are all volatile substances, known as flower semiochemicals.[1] A mixture of these chemicals, named the TIV mixture, was tested in a citrus orchard (about 120 m × 5 m), in a preliminary study for evaluating the insect responses to baited traps (McPhail type one, Biocontrole, Brazil). 1,2,4-Trimethoxybenzene (**3**) was synthesized in our laboratory from vanillin (**2**), and indol (**1**) and vanillin (**2**) were purchased from Vetec (Brazil).

The traps with 300 mg of TIV were fixed at 1.5 m high in orange trees. The mixture was used at a dosage of 100 mg of each single chemical per trap. Control traps received no TIV. Distance between traps was at least 5 m. The average temperature was 35°C during 7 days of field experiments.

After the 7-day field test, traps were sent to the University of Sao Paulo, where insect species were identified.

Synthesis of 1,2,4-Trimethoxybenzene (3) from Vanilin (2)

Preparation of 3,4-Dimethoxybenzaldehyde (**4**)

In a three-neck, round-bottom flask with a reflux condenser, a suspension of vanilin (500 mg, 3.29 mmol, mol. wt. 152.00 g/mol) and K_2CO_3 (500 mg 3.62 mmol mol. wt. 138.21 g/mol) in anhydrous CH_3COCH_3 (40 mL) was stirred at 40–45°C, under an argonium atmosphere. After 1 h, CH_3I (716 mg, 0.32 mL, 4.94 mmol, mol wt. 144.92 g/mol, d = 2.26 g/mL) was added dropwise, and the resulting mixture was refluxed for 7 h. The solvent was then removed under reduced pressure, and the

resulting solid was poured into HCl 5% (10 mL) and extracted with EtOAc (3×20 mL). The organic layer was then washed with brine, dried over Na_2SO_4, evaporated to dryness, and purified by silica-gel chromatography (5–20% EtOAc/hexanes to yield 3,4-dimethoxybenzaldehyde (**4**) as a pale yellow solid (518.75 mg; 95%), mp 43–45°C; IR (KBr, cm^{-1}): 3077, 3019, 2999, 2920, 2849, 2765 (O=**C-H**), 1.686 (**C**=**O**), 1275 (**C-O-C**), 1018 (**C-O-C**), 802; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 9.84 (s, 1H, CO**H**), 7.48–7.39 (m, 2H, **H**-Ar), 6.97 (d, $J = 8$ Hz, 1H, **H**-Ar), 3.96 (s, 3H, O**C**$\mathbf{H_3}$), 3.93 (s, 3H, O**C**$\mathbf{H_3}$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 191.0 (**C**=O), 154.6 (**C**-OCH_3), 149.7 (**C**-OCH_3), 130.2 (**C**-CHO), 127.0 (H-$\mathbf{C}_{ar}$), 110.5 (H-$\mathbf{C}_{ar}$), 109.0 (H-$\mathbf{C}_{ar}$), 56.3 (O**C**H_3), 56.1 (O**C**H_3).

Preparation of 3,4-Dimethoxyphenol (**6**)

In a three-neck, round-bottom flask with a reflux condenser, *m*-CBPA 70% (3.6 g, 20.00 mmol, mol. wt. 172.50 g/mol) and $NaHCO_3$ (0.58 g, 7.00 mmol, mol. wt. 84.00 g/mol) were added with stirring to a solution of 3,4-dimethoxybenzaldehyde (**4**) (1.66 g, 10.00 mmol, mol. wt. 166.00 g/mol) in anhydrous CH_2Cl_2 (50 mL). The mixture was allowed to reflux for about 10–15 h. Most CH_2Cl_2 was separated by distillation, and the resulting material was dissolved in EtOAc (50 mL). The organic layer was poured into $NaHSO_3$ 10% (3×15 mL), washed with brine, dried over Na_2SO_4, and evaporated to dryness to yield 3,4-dimethoxyphenyl formate (**5**) as a pale red oil (83.5%); IR (KBr, cm^{-1}): 3087, 3074, 3006, 2959, 2939, 2913, 2875, 2838 (O=**C-H**), 1738 (**C**=**O**), 1266 (**C-O-C**), 1026 (**C-O-C**), 867; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 8.29 (s, 1H, OO**C-H**), 6.86 (d, 1H, **H**-Ar), 6.67 (s, 2H, broad, **H**-Ar), 3.87 (s, 3H, O**C**$\mathbf{H_3}$), 3.83 (s, 3H, O**C**$\mathbf{H_3}$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 159.7 (O**C**OH), 149.6 (**C**-OCH_3), 147.3 (**C**-OCHO), 143.6 (**C**-OCH_3), 112.4 (H-$\mathbf{C}_{ar}$), 111.3 (H-$\mathbf{C}_{ar}$), 105.3 (H-$\mathbf{C}_{ar}$), 56.2 (O**C**H_3), 56.1 (O**C**H_3).

Afterwards, the crude product (**5**) was dissolved in MeOH (5 mL) under an N_2 atmosphere. Then, a solution of KOH 10% (10 mL) was added dropwise, allowing basic hydrolysis of **5**. The mixture was poured into HCl 5% (5–15 mL), extracted with EtOAc (3×15 mL), washed with brine (3×10 mL), dried over Na_2SO_4, and evaporated to dryness to yield 3,4-dimethoxyphenol (**6**) as a red oil (61%, from 15); IR (KBr, cm^{-1}): 3396 (**O-H**), 3087, 3044, 3003, 2959, 2938, 2835, 1224 (**C-O-C**), 1025 (**C-O-C**), 835; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.73 (d, $J = 8$ Hz, 1H, **H**-Ar), 6.47 (s, 1H, **H**-Ar), 6.36 (d, $J = 8$ Hz, 1H, **H**-Ar), 3.81 (s, 3 H, O**C**$\mathbf{H_3}$), 3.81 (s, 3 H, O**C**$\mathbf{H_3}$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 150.4 (**C**-OCH_3), 150.0 (**C**-OCH_3), 143.2 (**C**-OH), 112.7 (H-$\mathbf{C}_{ar}$), 106.0 (H-$\mathbf{C}_{ar}$), 100.8 (H-$\mathbf{C}_{ar}$), 56.7 (O**C**H_3), 55.9 (O**C**H_3).

Preparation of 1,2,4-Trimethoxybenzene (**3**)

In a three-neck, round-bottom flask with a reflux condenser, a suspension of crude 3,4-dimethoxyphenol (**6**) (500 mg, 3.29 mmol, mol. wt. 152.00 g/mol) and K_2CO_3 (986.7 mg, 7.14 mmol, mol wt. 138.21 g/mol) in anhydrous CH_3COCH_3 (30 mL) was stirred at 40–45°C, under an argonium atmosphere. After 1 h, CH_3I (1.41 g, 0.62 mL, 9.74 mmol, mol wt. 144.92 g/mol, d = 2.26 g/mL) was added dropwise, and the resulting mixture was refluxed for 7 h.

The solvent was then removed under reduced pressure, and the resulting oil was poured into HCl 5% (10 mL) and extracted with EtOAc (3×20 mL). The organic layer was then washed with brine, dried over Na_2SO_4, evaporated to dryness, and purified by silica-gel chromatography (5% EtOAc/hexanes) to yield 1,2,4-trimethoxybenzene (**3**) as an oil (97%); IR (KBr, cm^{-1}): 3081, 2998, 2938, 2908, 2834, 1230 (**C-O-C**), 1027 (**C-O-C**), 834; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.79 (d, $J = 8$ Hz, 1H, **H**-Ar); 6,52 (d, $J = 3$ Hz, 1H, **H**-Ar); 6.39 (dd, $J = 3$ Hz, $J = 8$ Hz, 1 H, **H**-Ar), 3.86 (s, 3H, O**CH$_3$**), 3.83 (s, 3H, O**CH$_3$**), 3.77 (s, 3H, O**CH$_3$**); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 154.4 (**C**-OCH_3), 150.0 (**C**-OCH_3), 143.6 (**C**-OCH_3), 112.0 (H-**C**$_{ar}$), 103.0 (H-**C**$_{ar}$), 100.5 (H-**C**$_{ar}$), 56.6 (O**C**H_3), 55.9 (O**C**H_3), 55.8 (O**C**H_3); HRMS *m/z* (%): 168.078550 (68.4). Calc. for $C_{10}H_{14}O_3$: 168.078644.

Synthesis of 1,2,4-Trimethoxybenzene C-3 Derivatives (7a–j)

General Procedure

n-Butyl lithium in hexanes 1.1 eq, (2.5 M) was added dropwise to a solution of 1,2,4–trimethoxybenzene (**5**) (400 mg, 0.36 mL, 2.38 mmol, mol wt. 168.19 g/mol; d = 1.126 g/mL) in anhydrous ether (15 mL) at −10°C under an argonium atmosphere. A white precipitate was formed. The reaction mixture was stirred additionally for 1.5 h at room temperature. Then, 1.1 eq of electrophilus (2.62 mmol) dissolved in anhydrous ether (5 mL) was added dropwise at −10°C under an argonium atmosphere, and the mixture was allowed to stir overnight. The reaction was extracted with EtOAc (3×15 mL) and saturated NH_4Cl solution (3×10 mL) or 10% $NaHSO_3$ solution (derivatives **7c** and **7h**) until complete neutralization. The total organic layer was washed with brine (3×10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain a crude residue, which was subjected to silica-gel chromatography (EtOAC/hexanes).

Preparation of 1,2,4-Trimethoxy-3-methylbenzene (**7a**)

From **3** and CH_3I (328 mg, 0.15 mL, 2.62 mmol, mol. wt. 144.92 g/mol; d = 2.26 g/mL) to yield **7a** as a white solid, after silica-gel chromatography (EtOAc 5%–hexanes): 325.00 mg, 75%; mp: 29–31°C; IR (KBr, cm^{-1}): 2995, 2937, 2859, 2833, 1257 (**C-O-C**), 1026 (**C-O-C**); ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.71 (d, $J = 8$ Hz, 1H, **H**-Ar), 6.55 (d, $J = 8$ Hz, 1H, **H**-Ar), 3.83 (s, 3, O**CH$_3$**), 3.81 (s, 3 H, O**CH$_3$**), 3.79 (s, 3H, O**CH$_3$**), 2.18 (s, 3H, C**H$_3$**); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 152.6 (**C**-OCH_3), 148.3 (**C**-OCH_3), 147.3 (**C**-OCH_3), 121.3 (**C**-CH_3), 109.4 (H-**C**$_{ar}$), 105.3 (H-**C**$_{ar}$), 60.5 (O**C**H_3), 56.3 (O**C**H_3), 56.0 (O**C**H_3), 9.1 (**C**H_3); HRMS m/z (%): 182.094154 (100.0). Calc. for $C_{10}H_{14}O_3$: 182.094294.

Preparation of 2,3,6-Trimethoxybenzaldehyde (**7b**)

From **3** and dimethylformamide (192 mg; 0.20 mL, 2.62 mmol, mol. wt. 73.09 g/mol; d = 0.95 g/mL) to yield **7b** as an orange oil, after gradient silica-gel chromatography (EtOAc 5–20%/hexanes): 285.00 mg; 61%; IR (KBr, cm^{-1}): 3094, 3001, 2941, 2838, 2765 (O=**C**-**H**), 1692 (**C**=**O**), 1260 (**C**-**O**-**C**), 1069 (**C**-**O**-**C**); ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 10.43 (s, 1H, C-CO**H**), 7.07 (d, $J = 10$ Hz, 1H, **H**-Ar), 6.63 (d, $J = 10$ Hz, 1H, **H**-Ar), 3.91 (s, 3H, O**CH$_3$**), 3.83 (s, 6H, O**CH$_3$**); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 189.8 (**C**=O), 155.0 (**C**-OCH_3), 152.2 (**C**-OCH_3), 146.9 (**C**-OCH_3), 119.8 (**C**-CHO), 119.3 (H-**C**$_{ar}$), 106.5 (H-**C**$_{ar}$), 62.1 (O**C**H_3), 56.8 (O**C**H_3), 56.3 (O**C**H_3); HRMS m/z (%): 196.073196 (100.0). Calc. for $C_{10}H_{12}O_4$: 196.073559.

Preparation of 2-Bromo-1,3,4-trimethoxybenzene (**7c**)

From **3** and CBr_4 (869 mg, 2.62 mmol, mol. wt. 331.65 g/mol) to yield **7c** as yellow solid, after silica-gel chromatography (EtOAc 5%-hexanes): 527 mg; 89.6%; mp: 69–71°C; IR (KBr, cm^{-1}): 3092, 3061, 3004, 2955, 2934, 2907, 2870, 2833, 1256 (**C-O-C**), 1040 (**C-O-C**), 651 (**C-Br**); ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.83 (d, $J = 10$ Hz, 1H, **H**-Ar), 6.62 (d, $J = 10$ Hz, 1H, **H**-Ar), 3.87 (s, 3H, O**CH$_3$**), 3.85 (s, 3H, O**CH$_3$**), 3.84 (s, 3H, O**CH$_3$**); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 151.1 (**C**-OCH_3), 148.1 (**C**-OCH_3), 147.9 (**C**-OCH_3), 111.7 (H-**C**$_{ar}$), 108.4 (**C**-Br), 106.8 (H-**C**$_{ar}$), 60.6 (O**C**H_3), 56.9 (O**C**H_3), 56.8 (O**C**H_3); HRMS m/z (%): 245.988557 (100.0), 247.986838 (94.5). Calc. for $C_9H_{11}O_3Br$: 245.988119, 247.987109.

Preparation of 2,3,6-Trimethoxybenzoic Acid (**7d**)

From **3** and solid CO_2 (excess) to yield **7d** as a white solid, after acid–base extraction: (406.20 mg; 81%); mp: 143–145°C; IR (KBr, cm^{-1}): 3300–2500 (broad, **O-H**), 3020, 3004, 2979, 2964, 2945, 2843, 1724 (**C=O**), 1253 (**C-O-C**), 1061 (**C-O-C**); ^{1}H NMR (DMSO-d_6, 200 MHz) δ: 7.01 (d, $J = 10$ Hz, 1H, **H**-Ar), 6.73 (d, $J = 10$ Hz, 1H, **H**-Ar), 3.76 (s, 3H, O**C**$\mathbf{H_3}$), 3.72 (s, 3H, O**C**$\mathbf{H_3}$), 3.70 (s, 3H, O**C**$\mathbf{H_3}$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 166.8 (**C**OOH), 149.8 (**C**-OCH_3), 146.9 (**C**-OCH_3), 145.8 (**C**-OCH_3), 121.1 (**C**-COOH), 114.2 (H-**C**$_{ar}$), 107.2 (H-**C**$_{ar}$), 61.3 (O**C**H_3), 56.7 (O**C**H_3), 56.5 (O**C**H_3); HRMS m/z (%): 212.068211 (100.0). Calc. for $C_{10}H_{12}O_5$: 212.068474.

Preparation of Trimethyl(2,3,6-trimethoxyphenyl)silane (**7e**)

From **3** and chlorotrimethylsilane 98% (285 mg, 0.34 mL, 2.62 mmol, mol. wt. 108.64 g/mol; d = 0.856 g/mL) to yield **7e** as a pale yellow oil, after silica-gel chromatography (EtOAc 5%–hexanes): 521.70 mg, 91.20 %; IR (KBr, cm^{-1}): 3073, 2952, 2939, 2900, 2832, 1463 (**Si-C**H_3), 1249 (**C-O-C**), 1089 (**C-O-C**); ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.90 (d, $J = 8$ Hz, 1H, **H**-Ar), 6.56 (d, $J = 8$ Hz, 1H, **H**-Ar), 3.84 (s, 3H, O**C**$\mathbf{H_3}$), 3.82 (s, 3H, O**C**$\mathbf{H_3}$), 3.75 (s, 3H, O**C**$\mathbf{H_3}$), 0.350 (s, 3H, **C**$\mathbf{H_3}$), 0.333 (s, 3H, **C**$\mathbf{H_3}$), 0.283 (s, 3H, **C**$\mathbf{H_3}$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 158.6 (**C**-OCH_3), 154.6 (**C**-OCH_3), 147.0 (**C**-OCH_3), 121.2 (Si-**C**$_{ar}$), 114.54 (H-**C**$_{ar}$), 105.4 (H-**C**$_{ar}$), 60.9 (O**C**H_3), 56.3 (O**C**H_3), 55.6 (O**C**H_3), 1.4 (**C**$\mathbf{H_3}$); HRMS m/z (%): 240.118123 (100.0). Calc. for $C_{12}H_{20}O_3Si$: 240.118173.

Preparation of 3-D-1,2,4-Trimethoxybenzene (**7f**)

From **3** and D_2O (excess) to yield **7f** as a pale yellow liquid, after silica-gel chromatography (EtOAc 5%-hexanes): 221.20 mg, 55%; IR (KBr, cm^{-1}): 3081, 2998, 2938, 2908, 2834, 1229 (**C-O-C**), 1026 (**C-O-C**); **^{1}**H NMR ($CDCl_3$, 200 MHz) δ: 6.78 (d, $J = 8$ Hz, 1H, **H**-Ar), 6.39 (d, $J = 8$ Hz, 1H, **H**-Ar), 3.85 (s, 3H, O**C**$\mathbf{H_3}$), 3.83 (s, 3H, O**C**$\mathbf{H_3}$), 3.76 (s, 3H, O**C**$\mathbf{H_3}$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 154.3 (**C**-OCH_3), 150.0 (**C**-OCH_3), 143.5 (**C**-OCH_3), 111.9 (H-**C**$_{ar}$), 103.0 (H-**C**$_{ar}$), 100.2 (**C**-D), 56.5 (O**C**H_3), 55.9 (O**C**H_3), 55.7 (O**C**H_3). HRMS m/z (%): 169.08520 (10.5). Calc. for $C_9H_{11}DO_3$: 169.084921.

Preparation of N,N-Diethyl-2,3,6-trimethoxybenzamide (**7g**)

From **3** and diethylcarbamic chloride (355 mg, 0.33 mL, 2.62 mmol, mol. wt. 135.59 g/mol; d = 1.070 g/mL) to yield **7 g** as a yellow solid, after gradient silica-gel chromatography (EtOAc 10–50%/hexanes): 381.3 mg, 60%; mp: 73–75°C, IR (KBr, cm^{-1}): 3100, 3068, 2980, 2970, 2938, 2906, 2839, 1633 (**C=O**), 1258 (**C-O-C**), 1061 (**C-O-C**); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.83 (d, $J = 9$ Hz, 1H, **H**-Ar), 6.58 (d, $J = 9$ Hz, 1H, **H**-Ar), 3.86 (s, 3H, O**CH$_3$**), 3.83 (s, 3H, O**CH$_3$**), 3.76 (s, 3H, O**CH$_3$**), 3.60 (q, $J = 7$ Hz, 2H, **CH$_2$**), 3.14 (q, $J = 5{,}4$ Hz, $J = 1{,}8$ Hz, 2H, **CH$_2$**), 1.25 (t, $J = 7$ Hz, 3H, **CH$_3$**), 1.03 (t, $J = 7$ Hz, 3H, **CH$_3$**); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 165.5 (**C**=O), 149.6 (**C**-OCH$_3$), 146.8 (**C**-OCH$_3$), 145.6 (**C**-OCH$_3$), 121.9 (**C**-CON-), 112.3 (H-**C**$_{ar}$), 105.9 (H-**C**$_{ar}$), 61.3 (O**C**H$_3$), 56.1 (O**C**H$_3$), 55.8 (O**C**H$_3$), 42.6 (**C**H$_2$), 38.5 (**C**H$_2$), 13.6 (**C**H$_3$), 12.6 (**C**H$_3$); HRMS m/z (%): 267.146886 (100.0). Calc. for $C_{14}H_{21}O_4N$: 267.147058.

Preparation of Methyl 2,3,6-Trimethoxybenzoate (**7h**)

From **3** and methyl chroloformate (247 mg, 0.20 Ml, 2.62 mmol, mol. wt. 94.5 g/mol; d = 1.223 g/mL) to yield **7h** as a white solid, after gradient silica-gel chromatography (EtOAc 20–40%/hexanes): (296.00 mg, 55%); mp: 50–53°C; IR (KBr, cm^{-1}): 3104, 3068, 3015, 2987, 2970, 2948, 2841, 1735 (**C=O**), 1261 (**C-O-C**), 1061 (**C-O-C**); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.88 (d, $J = 9$ Hz, 1H, **H**-Ar), 6.59 (d, $J = 9$ Hz, 1H, **H**-Ar), 3.92 (s, 3 H, O**CH$_3$**), 3.87 (s, 3 H, O**CH$_3$**), 3.82 (s, 3H, O**CH$_3$**), 3.78 (s, 3 H, O**CH$_3$**); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.44 (**C**=O), 150.4 (**C**-OCH$_3$), 146.9 (**C**-OCH$_3$), 146.8 (**C**-OCH$_3$), 119.1 (**C**-COCH$_3$), 114.3 (H-**C**$_{ar}$), 106.1 (H-**C**$_{ar}$), 61.4 (O**C**H$_3$), 56.5 (O**C**H$_3$), 56.2 (O**C**H$_3$), 52.4 (**C**H$_3$); HRMS m/z (%): 226.084114 (100.0). Calc. for $C_{11}H_{14}O_5$: 226.084124.

Preparation of 2-Allyl-1,3,4-trimethoxybenzene (**7i**)

From **3** and allyl bromide (317 mg, 0.22 mL, 2.62 mmol, mol. wt. 120.98 g/mol; d = 1.43 g/mL) to yield **7i** as a pale yellow liquid, after gradient silica-gel chromatography (EtOAc 5–70%/hexanes): 173.30 mg, 35%; IR (KBr, cm^{-1}): 3077, 2997, 2976, 2938, 2907, 2833, 1256 (**C-O-C**), 1068 (**C-O-C**); **^{1}**H NMR ($CDCl_3$, 300 MHz) δ: 6.75 (d, $J = 9$ Hz, 1H, **H**-Ar), 6.57 (d, $J = 9$ Hz, 1H, **H**-Ar), 6.09–5.85 (m, 1 H, -C**H**=), 5.07–4.93 (m, 2 H, =C**H$_2$**), 3.83 (s, 3H, O**CH$_3$**), 3.82 (s, 3H, O**CH$_3$**), 3.78 (s, 3H,

OCH_3), 3.47–3.41 (dt, $J = 1,6$ Hz, $J = 3$ Hz, 2 H, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 152.0 (**C**-OCH_3), 147.8 (**C**-OCH_3), 147.0 (**C**-OCH_3), 136.9 (-**C**H=), 122.9 (**C**-allyl), 114.3 (=CH_2), 110.0 (H-C_{ar}), 105.4 (H-C_{ar}), 60.7 (OCH_3), 56.0 (OCH_3), 55.9 (OCH_3), 28.0 (Ar-CH_2-); HRMS m/z (%): 208.109710 (100.0). Calc. for $C_{12}H_{16}O_3$: 208.109945.

Preparation of 2,3,6-Trimethoxyphenylboronic Acid (**7j**)

From **3** and trimethylborate (272 mg, 0.30 mL, 2.62 mmol, mol. wt. 103.91 g/mol; d = 0.915 g/mL) **7j** was obtained as an oil, after gradient silica-gel chromatography (EtOAc 30–50%/hexanes): (306.30 mg, 60.7%); IR (KBr, cm^{-1}): 3474, 3088, 2998, 2942, 2838, 1329 (**B-O**), 1251 (**C-O-C**), 1087 (**C-O-C**); ^1H NMR ($CDCl_3$, 400 MHz) δ: 6.98 (d, $J = 9$ Hz, 1H, **H**-Ar), 6.66 (d, J = 9 Hz, 1 H, **H**-Ar), 3.92 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 158.0 (**C**-OCH_3), 154.9 (**C**-OCH_3), 146.7 (**C**-OCH_3), 116.0 (H-C_{ar}), 106.4 (H-C_{ar}), 61.5 (OCH_3), 56.2 (OCH_3), 56.1 (OCH_3); HRMS m/z (%): 212.085909 (100.0). Calc. for $C_9H_{13}O_5B$: 212.085604.

ACKNOWLEDGMENTS

We thank CAPES, CNPQ, FAPERJ, and FUJB for financial support and also Qiang Wang, a Postdoctoral student in Clayton H. Heathcock's research group, Department of Chemistry, University of California Berkeley, USA, for personal contributions.

REFERENCES

1. Knudsen, J. T.; Tollsten, L.; Bergstrom, L. G. Floral scents a checklist of volatile compounds isolated by head-space techniques. *Phytochemistry* **1993**, *33*, 253–280.
2. Lopes, C. C.; Alves, G. B. C.; Cardoso, J. N.; Lopes, R. S. C.; Azevedo, M. S. Total syntheses of oxygenated brazanquinones via regioselective homologous anionic Fries rearrangement of benzylic O-carbamates. *Beilstein J. Org. Chem.* **2006**, *2*, 1–4.
3. Walton, N. J.; Mayer, M. J.; Narbad, A. Vanillin. *Phytochemistry.* **2003**, *63*, 505–515.
4. Wriede, U.; Fernandez, M.; West, K. F.; Harcourt, D.; Moore, H. W. Synthesis of halodimethoxy-1,2-benzoquinones. *J. Org. Chem.* **1987**, *52*, 4485–4489.
5. Dickstein, J. S.; Mulrooney, C. A.; O'Brien, E. M.; Morgan, B. J.; Kozlowski, M. C. Development of a catalytic aromatic decarboxylation reaction. *Org. Lett.* **2007**, *9*, 2441–2444.

6. Hardegger, E.; Steiner, K.; Corrodi, W. E.; Schmidt, T.; Knoepfel, H. P.; Rieder, W.; Kugler, F.; Gempeler, H. Wilting agents and antibiotics, XXX: Starting products for the total synthesis of javanicin. *Helv. Chim. Acta.* **1964**, *47*, 1996–2017.
7. Spyer, L.; Kloc, K.; Mlochowski, J. An improved synthesis of 1,4-benzo- and 1,4-naphthoquinones bearing active substituents. *J. Prakt. Chem.* **1985**, *327*, 808–822.
8. Belleau, B.; Weinberg, N. L. Eletrochemical síntesis: The methoxylation of dimethoxybenzenes to quinones ketals and the ring fission of 1,2-dimethoxybenzene to hexamethyl cis,cis-orthomuconate. *J. Am. Chem. Soc.* **1963**, *85*, 2525–2526.
9. Brito, C. M. S.; Rêgo, M. M. C. Community of male Euglossini bees (Hymenoptera: Apidae) in a secondary forest, Alcantara, MA, Brazil. *Braz. J. Biol.* **2001**, *61*, 631–638.
10. Smith, M. B. *Organic Synthesis,* 2nd ed.; McGraw-Hill Inc., New York, 2002.
11. Snieckus, V. Directed ortho metalation: Tertiary amide carbamate directors in synthetic strategies for polysubstituted aromatics. *Chem. Rev.* **1990**, *90*, 879–933.
12. Slocum, D. W.; Dumbris, S.; Brown, S.; Jackson, G.; Lamastus, R.; Mullins, E.; Ray, J.; Shelton, P.; Walstrom, A.; Wilcox, J. M.; Holman, R. W. Metalation in hydrocarbon solvents: The mechanistic aspects of substrate-promoted ortho-metalations. *Tetrahedron* **2003**, *59*, 8275–8284.