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Controlled Access to C_1-Symmetrical Cyclotriveratrylenes (CTVs) by Using a Sequential Barluenga Boronic Coupling (BBC) Approach

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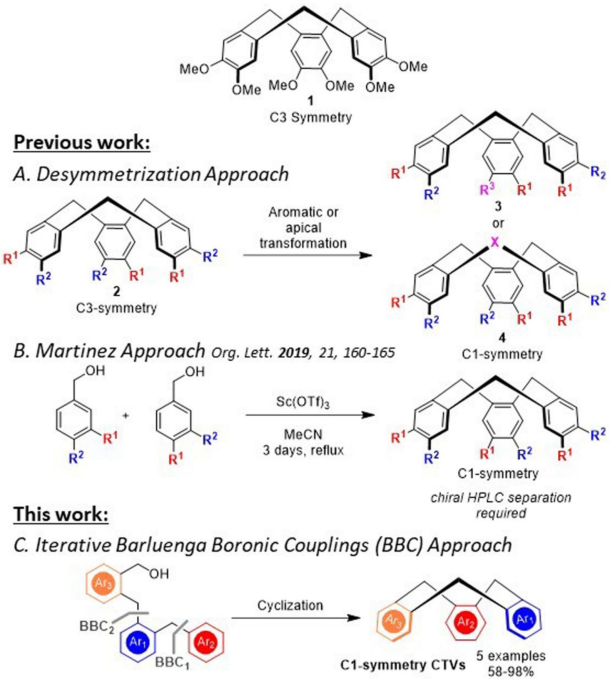
Abstract: We describe here a controlled approach to C_1-symmetrical cyclotriveratrylenes (CTVs). In this approach dimers are synthesized through Barluenga boronic coupling (BBC) and after borylation, the last aromatic ring is introduced by a second BBC. After functional transformations of the trimers, the CTVs are formed using intramolecular SEAr.

Keywords: Crown compounds; Cyclotriveratrylene; Supramolecular chemistry; Synthetic methods

Cyclotriveratrylene or CTV **1** (Figure 1) is a bowl-shaped achiral macrocyclic trimer of veratrole presenting a C_3-symmetry. CTVs derivatives have found many applications as molecular platforms in the fields of host-guest chemistry, supramolecular chemistry and soft materials.[1] Indeed, when two different substituents are introduced on the aromatic rings, the obtained derivatives **2** become chiral while still presenting a C_3-symmetry. Modifications brought to one of the aromatic rings or one of the apical positions give rise to C_1-symmetrical CTVs (**3**, **4**).

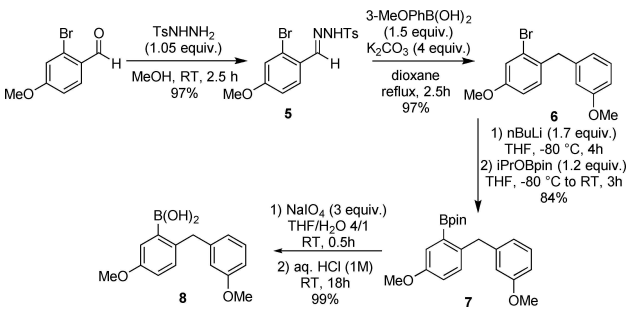
C_3-Symmetrical CTVs have found a wide variety of uses as ion or organic molecule sensors[2,3] building blocks for liquid crystals[3] or purification devices.[4–6] CTVs are also known to be precursors in supramolecular assemblies such as capsules,[7–9] cryptophanes[10–18] and hemicryptophanes.[19–26] To date, most of these applications are based on the use of C_3-symmetrical CTVs and, for decades, C_3-symmetrical CTVs have been synthesized from the corresponding substituted benzylic alcohols through cyclotrimerization using acidic conditions such as perchloric acid in methanol,[27] sulfuric acid in acetic acid,[10] formic acid[28] or scandium triflate.[29] This approach can be applied only to specific substrates (e.g. arenes bearing electron-donating groups in *para* position) and affords products with poor to moderate yields. Whereas the synthesis and the utility of C_3-symmetrical CTVs are well defined in the literature, the preparation and uses of C_1-symmetrical derivatives have been less studied. To date, the most efficient approach to access C_1-symmetrical CTVs is to desymmetrize C_3-symmetrical CTVs (Scheme 1, A) either by performing direct halogenation[18] or by modifying the nature of a substituent on one of the aromatic rings.[30,31] Using the same strategy, modification of the apical positions has also been described through an oxidation to the corresponding ketone[32] followed by further transformations such as Beckmann rearrangement.[33] Recently, another interesting approach has been reported in the literature by Martinez *et al.* (Scheme 1, B).[34] In this paper, the authors propose the optimized preparation of mixture of C_1- and C_3-symmetrical CTVs, starting from a 1:1 ratio of benzylic alcohol position isomers. The obtained stereoisomers were separated by chiral HPLC.



Scheme 1. Structure of CTV **1**, new and previously described approaches toward C_1-symmetrical CTVs.

In this work, we propose a new strategy to prepare C_1-symmetrical CTVs using the Barluenga boronic coupling (BBC) in an iterative and controlled approach (Scheme 1, C). This reaction, described in 2009, allows the formation of methylene bridges between two arenes in very mild conditions from widely available starting building blocks (hydrazones and boronic acids) using a metal free reductive cross-coupling.[35] Since then, many applications of this protocol have been described in the literature, expanding the scope of C–C bond formation.[36–38] In order to obtain C_1-symmetrical CTVs using this reaction, we planned to synthesize an open trimer bearing a benzylic alcohol which could be obtained from two iterative BBCs. Once the trimer was obtained, a cyclization in acidic conditions will allow access to C_1-symmetrical CTVs while controlling the introduction and position of the new substituents during the iterative BBCs process.

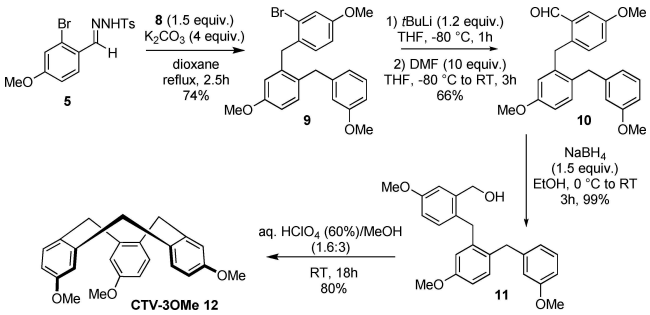
To set-up our synthetic strategy, we choose to prepare a C_3-symmetrical CTV, CTV-3OMe **12**, known in the literature as the key intermediate in the synthesis of cryptophane-111 (Scheme 2).[12,39] As mentioned by Miller *et al.*,[40] the steric hindrance of the boronic acid coupling partner in BBC can be deleterious for the reaction. A quick study of the substituents tolerated on the coupling partners (see supporting information) suggested that the coupling of hydrazone **5** and 3-methoxyphenylboronic acid would give the best results. Accordingly, tosylhydrazone **5** was prepared from 2-bromo-4-methoxybenzaldehyde and *para*-tol-



Scheme 2. Synthesis of boronic dimer **8**.

uenesulfonyl hydrazide in 97% yield. The following BBC allowed the formation of compound **6** in 97% yield. In order to perform a second BBC, we tried to synthesize boronic acid **8** through direct metal-halogen exchange followed by electrophilic trapping with trimethyl- or triisopropyl borate. Despite many attempts, the preparation of **8** using this synthetic route was not possible leading each time to complex mixtures. However, when isopropoxypinacolborane was used as the electrophile under the same metalation conditions, we were pleased to isolate the corresponding boronic ester **7** in 84% yield. As we found that boronic ester **7** was nearly unreactive in BBC attempts, the boronic acid **8** was synthesized after hydrolysis of **7** with sodium periodate in 99% yield.

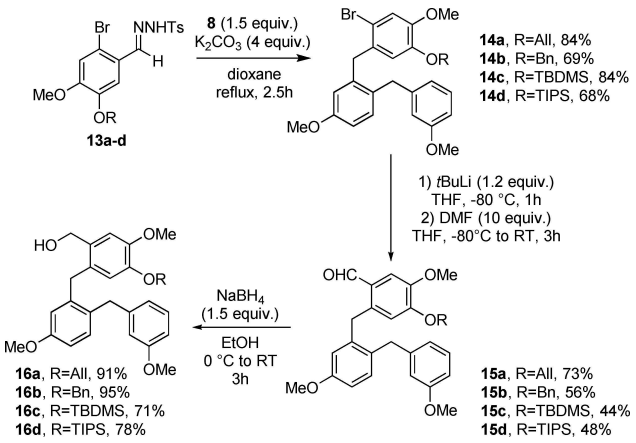
A second BBC between tosylhydrazone **5** and boronic acid dimer **8** was then performed to obtain brominated trimer **9** in 74% yield (Scheme 3). In order to reach the cyclization precursor **11**, aldehyde **10** was prepared from metal-halogen exchange followed by trapping of the lithiated species with DMF in 66% yield. Reduction of **10** with $NaBH_4$ afforded **11** in 99% yield. Cyclization was then performed using perchloric acid in excess for 18 h at room temperature and led to the expected CTV-3OMe **12** in 80% yield. Overall, the CTV-3OMe has been synthesized in 8 steps with 28% overall yield and the efficiency of an iterative BBCs approach toward the synthesis of C_3-symmetrical CTVs has been established. Even if this strategy



Scheme 3. Synthesis of CTV-3OMe **12**.

requires more synthetic steps than the most efficient CTV-3OMe synthesis,[12] a similar overall yield was observed while avoiding lengthy purification processes.

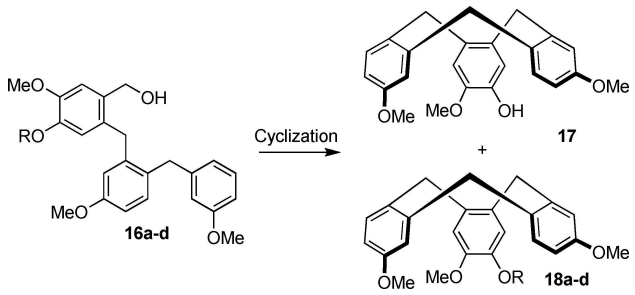
In order to produce C_1-symmetrical CTV using the same route, we investigated the preparation of C_1-symmetrical CTVs **18a–d** bearing methoxy groups, because of their usefulness as key intermediates in the design of cryptophanes. Four substituted tosylhydrazones **13a–d** were prepared from the corresponding commercially available starting materials (see supporting information) and coupled with boronic acid dimer **8** to afford brominated trimers **14a–d** in 68–84% yields (Scheme 4). Metal-halogen exchanges were performed, and trapping with DMF afforded the corresponding aldehydes **15a–d** in 44–73% yields. The reduction of **15a–d** was performed using $NaBH_4$ and afforded efficiently four cyclization precursors **16a–d** substituted with allyl-, benzyl-, TBDMS- and TIPS-protected phenol.



Scheme 4. Synthesis of trimers **16a–d**.

The cyclization step was then investigated (Table 1). First, the cyclization was evaluated from the allyl derivative **16a** using an excess of perchloric acid in methanol (entry 1). Under these conditions, the cyclization didn't occur and a complex mixture of polymerized compounds was observed. The same conditions were repeated with acetonitrile as the solvent (entry 2) affording the deprotected C_1-symmetrical CTV **17** within 20% yield along with polymers. Performing the reaction in acetonitrile for one hour at room temperature while reducing the amount of perchloric acid to 1.2 equivalents allowed us to isolate the *O*-allyl functionalized CTV **18a** in 86% yield (entry 3). The same conditions were

Table 1. Synthesis of C_1-symmetrical CTVs **18a–d**.



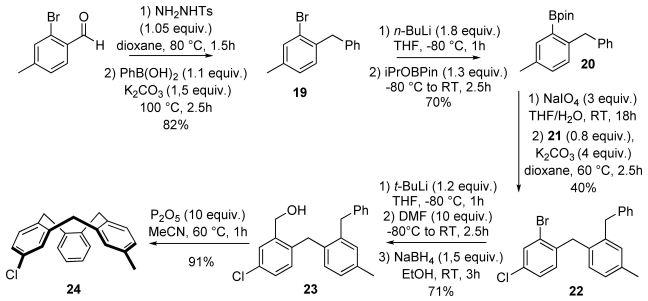
Entry	Starting material	Conditions	Results[a]
1	**16a** R = All	$HClO_4$[b]/MeOH (1.6:3) RT, 18 h	polymerisation
2	**16a** R = All	$HClO_4$[a]/MeCN (1.6:3) RT, 18 h	**17** (20%)[c]
3	**16a** R = All	$HClO_4$[b] (1.2 equiv.) MeCN, RT, 1 h	**18a** (86%)
4	**16b** R = Bn	$HClO_4$[b] (1.2 equiv.) MeCN, RT, 1 h	**18b** (91%)
5	**16c** R = TBDMS	$HClO_4$[b] (1.2 equiv.) MeCN, RT, 1 h	**17** (98%)
6	**16c** R = TBDMS	P_2O_5 (1.3 equiv.) MeCN, RT, 1 h	**17** (34%)/**18c** (58%)
7	**16d** R = TIPS	P_2O_5 (1.3 equiv.) MeCN, RT, 1 h	**18d** (84%)

[a] Isolated yields;
[b] Aqueous $HClO_4$ at 60% was used;
[c] Trace amount of **18a** were also observed on the crude ^1H NMR.

repeated starting from the *O*-benzyl precursor **16b** and the corresponding CTV **18b** was obtained in 91% yield (entry 4). The use of these conditions onto the *tert*-butyldimethylsilyl protected intermediate **16c** led quantitatively to the deprotected CTV **17** (entry 5). Replacement of perchloric acid by phosphorus pentoxide under the same conditions afforded the *O*-TBDMS functionalized CTV **18c** in 58% (entry 6) along with **17** (34%). These latter conditions were repeated with the tri-isopropylsilyl protected intermediate **16d** affording the *O*-TIPS functionalized CTV **18c** in 84% yield (entry 7).

To further demonstrate the ability of our strategy to provide efficiently C_1-symmetrical CTV, we chose to illustrate its potency and flexibility through the synthesis of a CTV containing three different aromatic rings (Scheme 5). First, compound **19** was synthesized in 82% yield starting from 2-bromo-methylbenzaldehyde through a one-pot tosylhydrazone formation followed by BBC. Metalation followed by borylation afforded boronic ester **20** from **19** within 70% yield. Boronic ester **20** was then hydrolysed and a BBC with tosylhydrazone **21** was directly initiated to provide trimer **22** in 40% yield. Compared to our previous attempts of BBC to obtain this kind of trimers, the BBC temperature had to be reduced to 60 °C in order to allow isolation of **22**. Performing the reaction under reflux afforded **22** in a higher conversion rate along with a side product co-eluting in all our purification attempts. A metalation/formylation/reduction sequence was then initiated from **22** to afford benzylic alcohol **23** in 71% yield. This latter was cyclized with an excess of P_2O_5 at 60 °C affording CTV **24** in 91% yield. Finally, compound **24** was obtained with an overall yield of 15% with this 5-steps sequence, thus demonstrating the ability of this strategy to afford diversely functionalized C_1-symmetrical CTV.

In conclusion, we have demonstrated an iterative BBC approach toward CTVs allowing their controlled preparation. This strategy has been validated in the preparation of a known C_3-symmetrical CTV, CTV-3OMe, and presents an alternative route to this compound. Moreover, our methodology can be used to prepare efficiently new C_1-symmetrical CTVs **18a–d**, inaccessible using existing procedures from the literature, while allowing the introduction of the asymmetry in the last stage of the synthesis from the common precursor **8**. The flexibility of the sequence was further illustrated in the production of the CTV **24** containing three different aromatic rings. Using this approach, the structural diversity of CTV could be considerably widen by choosing the adequate synthetic partners. This strategy paves the way to the preparation of a large amount of new CTVs with original structures thus enabling more applications with these macrocycles.



Scheme 5. Synthesis of CTV **24**.

Experimental Section

Preparation of C_1-CTV 24

1-Benzyl-2-bromo-4-methylbenzene 19

p-Toluenesulfonyl hydrazide (985 mg, 5.27 mmol) was added to a solution of 2-bromo-4-methylbenzaldehyde (1 g, 5.02 mmol) in dioxane (25 mL) and the mixture was stirred at 80 °C for 1.5 h. Potassium carbonate (1.04 g, 7.53 mmol) and phenylboronic acid (673 mg, 5.52 mmol) were added and the solution was refluxed for 2.5 h. The resulting mixture was evaporated to dryness, dissolved in ethyl acetate, washed with an aqueous saturated solution of sodium bicarbonate and brine, dried over $MgSO_4$, filtrated and evaporated under vacuum. Purification over silica gel (Cyclohexane/AcOEt 99/1) afforded the product as a colorless oil (1.07 g, 82%).[1] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.42 (s, 1H), 7.34–7.24 (m, 2H), 7.26–7.16 (m, 3H), 7.08–6.99 (m, 2H), 4.09 (s, 2H), 2.31 (s, 3H).[13] **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 140.0, 138.0, 137.3, 133.4, 130.9, 129.1 (2C), 128.6 (2C), 128.4, 126.3, 124.7, 41.4, 20.7. **HRMS-ASAP** calculated for $C_{14}H_{13}Br$ [$M^{+\cdot}$] 260.0201, found 260.0203.

2-(2-Benzyl-5-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 20

n-BuLi 2.5 M in n-hexane (1.47 mL, 3.65 mmol) was added to a solution of **19** (530 mg, 2.03 mmol) in 8 mL of dry THF at −78 °C. The solution was stirred for 1 hour and *i*PrOBPin (0.54 mL, 2.64 mmol) was added. The mixture was stirred at −78 °C for 2 h and subsequently warm to room temperature over 1 hour. The reaction was quenched with water and extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification over silica gel (Cyclohexane/AcOEt 98/2) afforded the product as a yellow oil (436 mg, 70%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.63 (d, J = 2.1 Hz, 1H), 7.25–7.20 (m, 2H), 7.18–7.11 (m, 4H), 7.06 (d, J = 7.8 Hz, 1H), 4.29 (s, 2H), 2.32 (s, 3H), 1.27 (s, 12H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 144.5, 142.9, 136.7 (2C), 134.8, 131.9, 130.2, 129.1 (2C), 128.2 (2C), 125.6, 83.6 (2C), 40.6, 24.9 (4C), 21.0. **HRMS-ESI** calculated for $C_{20}H_{25}BO_2$ [$M+H^+$] 309.2026, found 309.2039.

N′-[(Z)-(2-Bromo-4-chlorophenyl)methylidene]-4-methylbenzene-1-sulfonohydrazide 21

In a round bottom flask, *p*-toluenesulfonyl hydrazide (892 mg, 4.79 mmol) was solubilized in methanol (4 mL/g). 2-bromo-4-chlorobenzaldehyde (1 g, 4.56 mmol) was added to the solution, the resulting mixture was stirred for 2.5 h. The resulting mixture was evaporated to dryness, dissolved in a small portion of diethyl ether. The solid was filtered, and the expected product was obtained as a white powder (1.72 g, 98%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.05 (s, 1H), 7.90 (s, 1H), 7.88–7.85 (m, 2H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.29 (dd, *J* = 8.6, 2.0 Hz, 1H), 2.42 (s, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$): δ = 144.7, 136.9, 135.2, 132.8 (2C), 130.8, 130.0 (2C), 128.6, 128.3, 128.1 (2C), 124.2, 21.8. **Melting Point**: 185–187 °C. **HRMS-ESI** calculated for $C_{14}H_{13}BrClN_2O_2S$ [M + H$^+$] 386.9570, found 386.9753.

1-[(2-Benzyl-4-methylphenyl)methyl]-2-bromo-4-chlorobenzene 22

To a solution of **20** (314 mg, 1.4 mmol) in a mixture of THF (12 mL) and H_2O (5 mL) at room temperature, $NaIO_4$ (895 mg, 4.2 mmol) was added. The solution was stirred at room temperature, under air for 30 minutes. Aqueous 1 M HCl (2.1 mL, 2.1 mmol) was then added to the reaction mixture and the solution was stirred at room temperature for 18 h, over which time a white solid precipitated. The reaction mixture was quenched with H_2O and extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under vacuum to afford the product as an oil.

In a round bottom flask, **21** (451 mg, 1.17 mmol) was solubilized in dioxane (15 mL/mmol). Potassium carbonate (4 equiv.) and crude boronic acid (1.5 equiv.) were added, and the solution was heated at reflux for 2.5 h. The resulting mixture was allowed to reach room temperature and an aqueous saturated solution of sodium bicarbonate was added (15 mL/mmol). The mixture was extracted three times with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, filtered and evaporated under vacuum. The crude mixture was purified using silica chromatography using cyclohexane/ethyl acetate (95/5) as the eluent, affording the expected product as a colorless oil (175 mg, 40%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 2.2 Hz, 1H), 7.26–7.21 (m, 2H), 7.17 (d, *J* = 7.3 Hz, 1H), 7.11–7.05 (m, 5H), 6.80 (s, 1H), 6.72 (d, *J* = 8.3 Hz, 1H), 3.94 (s, 2H), 3.88 (s, 2H), 2.30 (s, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$): δ = 140.4, 138.7, 137.0, 136.5, 136.3, 132.6, 132.2, 131.2, 131.1, 130.8, 128.9 (2C), 128.5 (2C), 127.8, 127.7, 126.1, 125.2, 38.9, 38.7, 21.2. **HRMS-ASAP** calculated for $C_{21}H_{18}BrCl$ [M$^{+\bullet}$] 384.0280, found 384.0279.

{2-[(2-Benzyl-4-methylphenyl)methyl]-5-chlorophenyl}methanol 23

Prepared from **22** (270 mg, 0.69 mmol), following general procedure C, the crude mixture was engaged without purification in the reduction reaction following general procedure D, the expected compound was obtained as a colorless oil (166 mg, 71%).**^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 2.2 Hz, 1H), 7.29–7.24 (m, 2H), 7.22–7.14 (m, 2H), 7.11–7.07 (m, 3H), 7.05–7.02 (m, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.67 (s, 1H), 4.41 (d, *J* = 5.7 Hz, 2H), 3.93 (s, 2H), 3.85 (s, 2H), 2.25 (s, 3H), 1.41 (t, *J* = 5.8 Hz, 1H).**^{13}C NMR** (100 MHz, $CDCl_3$): δ = 140.69, 140.59, 137.87, 136.61, 136.32, 135.89, 132.44, 131.38, 130.88, 130.35, 128.75, 128.59, 127.77, 127.77, 127.56, 126.22, 77.16, 62.55, 39.10, 34.88, 21.21. **HRMS-ASAP** calculated for $C_{22}H_{19}Cl$ [M-H_2O] 318.1175, found 318.1169.

C_1-CTV 24

Phosphorus pentoxide (697 mg, 2.4 mmol) was added to a solution of **23** (80 mg, 0.24 mmol) in acetonitrile (48 mL) and the mixture was stirred at 60 °C for 1 h. The reaction was quenched with an aqueous solution of saturated $NaHCO_3$, extracted with AcOEt, washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Purification over silica gel (cyclohexane/AcOEt 95/5) afforded the product as a white powder (62 mg, 91%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.31–7.26 (m, 2H), 7.25–7.15 (m, 3H), 7.06–7.01 (m, 3H), 6.98 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 4.74 (dd, *J* = 15.7, 13.7 Hz, 3H), 3.68–3.55 (m, 3H), 2.16 (s, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$): δ = 141.4, 139.9, 138.8, 138.7, 138.2, 136.7, 136.5, 132.3, 131.5, 130.6, 130.2, 130.19, 130.15, 129.9, 128.1, 127.4, 127.2, 127.1, 37.1, 36.9, 36.6, 21.1. **Melting Point**: 206–208 °C. **HRMS-ASAP** calculated for $C_{22}H_{19}Cl$ [M$^{+\bullet}$] 318.1175, found 318.1171.

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