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Synthesis and anti-inflammatory activity of isoquebecol

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ABSTRACT

We report here the synthesis of isoquebecol, an unprecedented constitutional isomer of quebecol, a polyphenolic compound discovered in maple syrup. The methodology used to prepare isoquebecol involves, as key steps, the formation of a dibromoalkene from an α-ketoester precursor, followed by a double Suzuki-Miyaura reaction. The anti-inflammatory activity of isoquebecol was studied on macrophage cells by monitoring its ability to inhibit LPS-induced IL-6 secretion. Results show that this new compound has an improved bioactivity over that of its natural isomer. Precursors and derivatives of quebecol, isoquebecol and model analog 2,3,3-triphenylpropanol were also prepared and tested in this study. Comparison between the three series of compounds led to establishing new SARs concerning the aryl ring substitution pattern on the triarylpropanol scaffold and substructure functionalization.

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1. Introduction

Chronic inflammatory disorders are a major contemporary concern in public health.[1–3] Although inflammation is a normal physiological response to injury, tissue ischemia, infectious agents, or an imbalance of the pro- and anti-inflammatory signals can lead to inappropriate and deleterious perpetuation of the inflammatory response.[4,5] Deregulation of inflammatory processes leads to specific pathologies including psoriasis, rheumatoid arthritis, periodontal disease, asthma and atherosclerosis. It has also been shown to be a fundamental contributor to other degenerative conditions, such as diabetes, cancer and cardiovascular diseases.[5–7] Furthermore, the inflammatory response can be identified as the major cause of damage related to autoimmune diseases.[6]

Consequently, the regulation of inflammatory processes is an essential avenue in the treatment of various pathologies. Even if many efforts have been made in this direction in past years, the search for new anti-inflammatory compounds is still an important area of research, as traditional therapies involving steroidal or non-steroidal agents are often associated with a lack of efficiency and undesirable side effects.[8]

The anti-inflammatory activity of a new compound can be studied by evaluating its effect on the inflammatory response of human macrophages, a type of leukocyte cells. These leukocytes, key members of the innate immune system, are known to play a major role in the overall inflammatory response and are also major contributors to pathologies involving chronic inflammatory disorders.[9–11] Macrophages act on the inflammation process of surrounding cells by secreting various chemical agents, including cytokines, that can amplify or reduce the inflammatory response. Inhibition of the production of those biological mediators, involved in various steps of the inflammatory processes, is a promising approach to modulate inflammation.[12] It has been previously shown that the production of pro-inflammatory mediators can be stimulated upon simulating an infection event by treating cells with bacterial lipopolysaccharides (LPS).[13,14] The activity of bacterial LPS on macrophage cells originates from their interaction with the Toll-like receptor-4 (TLR4), which results in the activation of nuclear factor-kappaB (NF-κB). This latter event then leads to increased gene expression of various cytokines.[13–15]

Plants have been used for centuries in the traditional medicine of many cultures to alleviate pain associated with inflammatory diseases.[8,16] More recently, society's interest in functional foods and nutraceuticals has driven efforts, by both academia and the food industry, to discover new bioactive molecular agents in foods.[17–22] Many familiar and traditionally used plant-sourced foodstuffs have been revisited with a molecular approach in the search for new phytochemical compounds.[23–27] As a part of this effort, the Seeram group has extensively studied Canadian maple syrup.[28–33] In 2011, they reported the isolation of a new polyphenolic compound named quebecol **1** (Fig. 1). This compound showed activity against breast and colon cancer cell lines in preliminary

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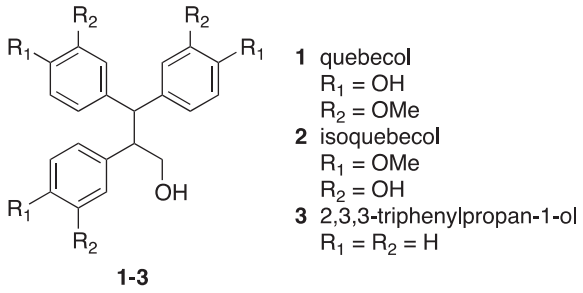


Fig. 1. Structures of quebecol (**1**), isoquebecol (**2**) and the 2,3,3-triphenylpropanol model system (**3**).

in vitro biological assays.[33–35] The study of this compound has as yet been limited by its low abundance in its primary source.

To facilitate further research on this compound by solving its availability problem, we developed a way to synthesize quebecol **1**.[36] Our synthetic approach to quebecol **1** and to the 2,3,3-triarylpropanol moiety in general is illustrated in Fig. 2. It involves, as first key step, a Wittig-like C-1 homologation to prepare a *gem*-dibromoalkene synthon from the corresponding α-ketoester compound. The second key step is the installation of the two other aryl rings, using a double Suzuki-Miyaura cross-coupling (SMC) to prepare a 2,3,3-triphenylacrylic acid ester. This key precursor scaffold then gives direct access to 2,3,3-triarylpropanol compounds by both hydrogenation and reduction of the α,β-unsaturated system.

Encouraged by the promising properties of quebecol **1** reported by Seeram,[33–35] we decided to evaluate its anti-inflammatory activity. In a previous study, we demonstrated that quebecol **1** (Fig. 1) inhibits the secretion of two pro-inflammatory cytokines (IL-6 and TNF-α) and reduces the NF-κB activation of LPS-stimulated macrophage cells, resulting in anti-inflammatory activity.[37] Precursors and compounds corresponding to substructures of **1** were also synthesized and tested. The results obtained in this previous work with those compounds allowed us to define some structure-activity relationships (SARs) and identify the most active region of **1**.

In this study, our intent was to extend the SAR studies regarding the anti-inflammatory activity of quebecol **1**, by studying the effects that structural changes in the aryl rings have on the IL-6 secretion of LPS-stimulated macrophages. More specifically, we were interested in evaluating the impact of 1) the presence of oxygenated groups and 2) the relative position of those functionalities in regard to the propanol scaffold. Novel compounds with related structures were prepared for these studies.

Herein, we report on the synthesis and evaluation of the anti-inflammatory properties of an unprecedented isomer of quebecol, which we have named isoquebecol **2** (Fig. 1). We synthesized and tested analogs and substructures of this new compound to compare their activities with the corresponding isomers related to quebecol.[37] We also prepared 2,3,3-triphenylpropan-1-ol **3** (Fig. 1) and its precursors to include in our bioassays as unfunctionalized models.

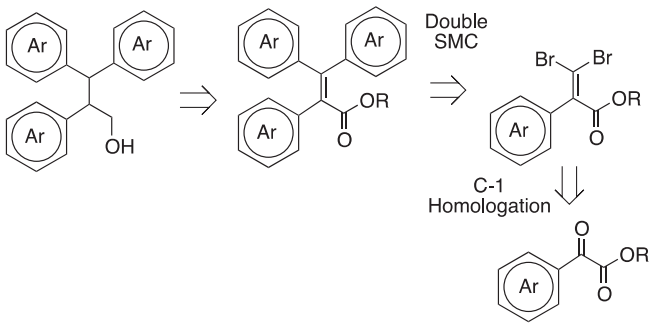


Fig. 2. Synthetic strategy designed to access the 2,3,3-triarylpropanol moiety used in the total synthesis of quebecol.

2. Compounds of interest

An overview of the molecules used in this study is shown in Fig. 3. Those compounds can be classified in three different series. *Series 1* is based on quebecol **1** and related compounds. *Series 2* includes isoquebecol **2**, its precursors and substructures. *Series 3* represents the model system and contains 2,3,3-triphenylpropanol **3** and analogs with unfunctionalized aryl rings. Table 1 presents the complete list of all 21 compounds that we evaluated for anti-inflammatory properties. The compounds are presented in Table 1 according to the above-mentioned *Series 1*, *2*, or *3*, and are also classified according to their general scaffold (*Class A* to *D*).

Firstly, in addition of quebecol **1**, isoquebecol **2** and 2,3,3-triarylpropanol **3**, we included, in our biological assays, two precursors for each *Series*: a triarylpropanoate ethyl ester (*Class C* compounds **4**–**6**) and a triarylacrylic acid ethyl ester (*Class D* compounds **7**–**9**). This allowed us to evaluate the effects of an ester or an α,β-unsaturated ester on the activities.

Secondly, as an attempt to identify an active region on the quebecol/isoquebecol scaffold, we divided, in our previous study, the structure of quebecol **1** into two substructures, denoted "South" and "North" (Fig. 3). The same approach was used in the present study for isoquebecol **2**.

A variety of compounds **10**–**19** associated with the South substructures (*Class B*) and bearing different functional groups were prepared and included in *Series 1* and *Series 2* (Table 1). Even if compounds **10**, **12**, and **14** showed no significant anti-inflammatory properties in our previous work,[37] we were interested in positively enhancing the activity of this substructure. To do so, isomers **11**, **13** and **15**, and new compounds **16**–**19** were prepared and tested to evaluate the impact of a different aryl ring substitution (*Series 1* vs *2*) and of new functionalities on this substructure.

Diarylmethanes **20** and **21**, corresponding to the exact North substructure (*Class A*) of quebecol **1** and isoquebecol **2** respectively,

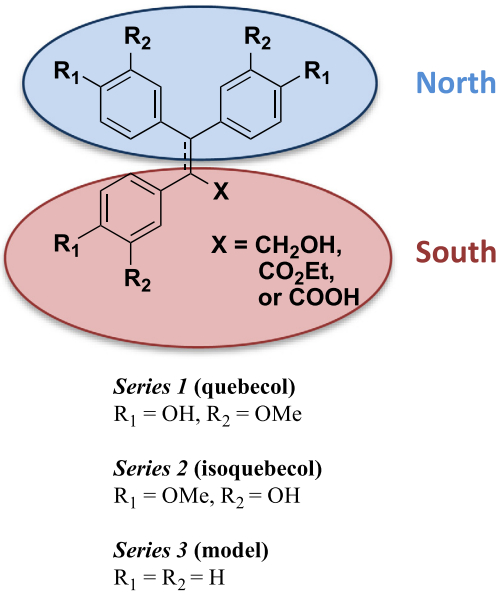
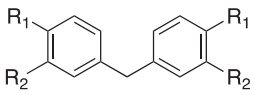
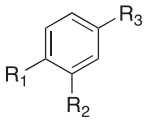
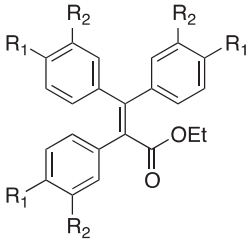
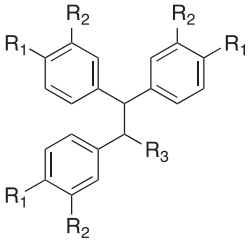


Fig. 3. Overview of the scope of compounds studied.

Table 1
Complete list of compounds included in bioassays classified by substitution pattern on the aromatic ring (*Series 1–3*) and molecular scaffold (*Class A–D*).

	Class A	*Class B*	*Class C*	*Class D*
	Class A	**Class B**	**Class C**	**Class D**
	North substructures	South substructures	Triarylethene scaffold	Triarylethane scaffold
				
Series 1 R_1 = OH, R_2 = OMe	**22**	**10** (R_3 = CH_2COOH) **12** (R_3 = CH_2COOEt) **14** (R_3 = CH_2CH_2OH) **16** (R_3 = $CH(OH)CH_2OH$) **18** (R_3 = $COCH_2OH$)	**7**	**1** (R_3 = CH_2OH) **4** (R_3 = COOEt)
Series 2 R_1 = OMe, R_2 = OMe	**23**	**11** (R_3 = CH_2COOH) **13** (R_3 = CH_2COOEt) **15** (R_3 = CH_2CH_2OH) **17** (R_3 = $CH(OH)CH_2OH$) **19** (R_3 = $COCH_2OH$)	**8**	**2** (R_3 = CH_2OH) **5** (R_3 = COOEt)
Series 3 R_1 = R_2 = H			**9**	**3** (R_3 = CH_2OH) **6** (R_3 = COOEt)

complete the list of the evaluated compounds. As compound **20** showed an anti-inflammatory activity similar to quebecol **1** in our previous study,[37] we were particularly interested in evaluating the effect of the positions of the functional groups for this particular scaffold (*Series 1 vs. 2*).

3. Synthesis

3.1. Preparation of North substructure of isoquebecol (Class A)

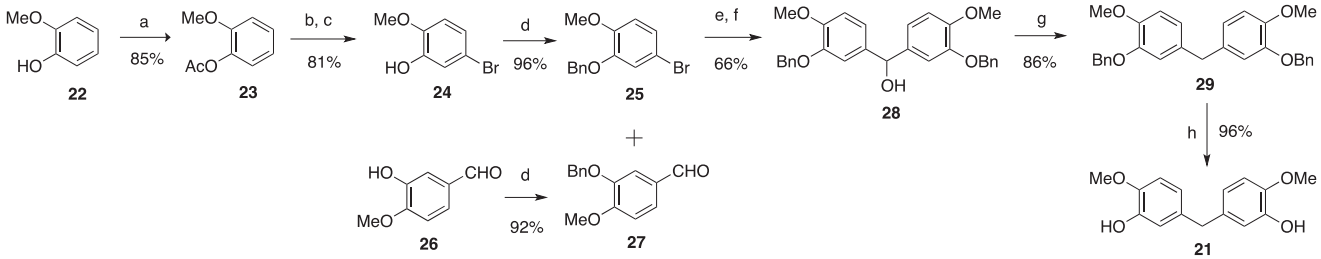
We previously reported the preparation of the North substructure of quebecol **20** by the condensation of an arylbromine with an aryldehyde followed by the reduction of the obtained benzhydrol and the deprotection of the phenol.[37] We used the same strategy to prepare the North substructure of isoquebecol and obtained the desired product **21** with good yields (Scheme 1). In this case, the needed arylbromine **24** was not commercially available. Consequently, it was prepared from guaïacol **22** by an acetylation/bromination/hydrolysis sequence.

3.2. Preparation of the South substructures of quebecol and isoquebecol (Class B)

The preparation of the South substructure compounds (*Class B*) for *Series 1* and *2* is presented in Scheme 2. Compounds **10**, **11**, **12** and **31** (Table 1) were all commercially available. We have previously reported the preparation of **14**, **30** and **32**.[36,37]

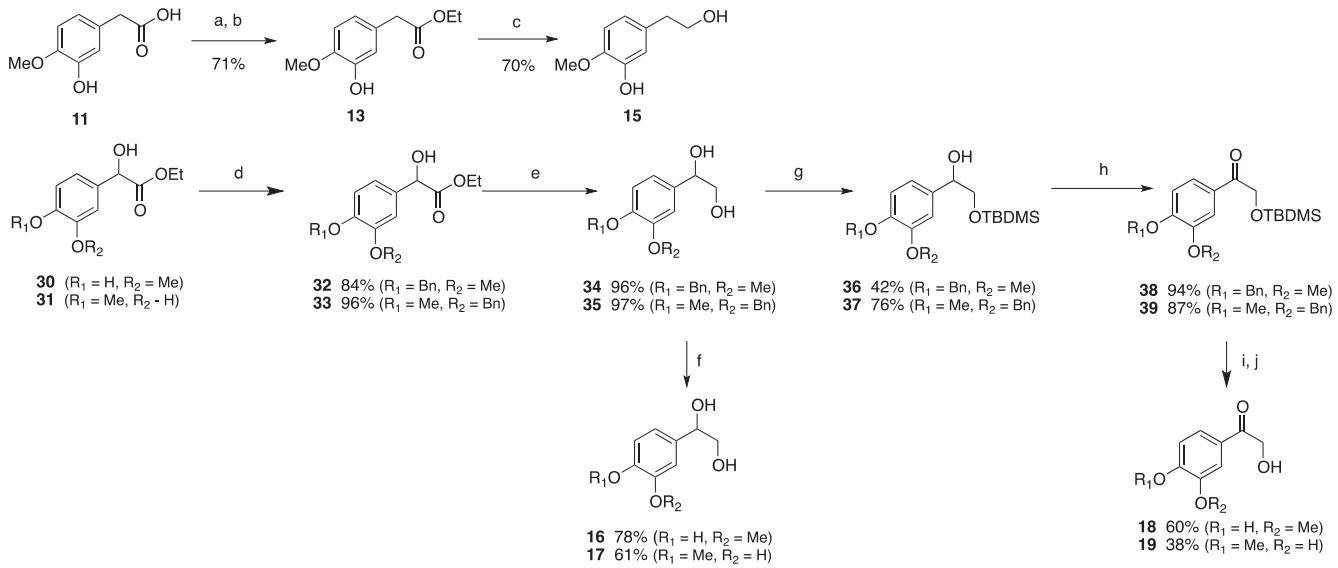
The exact substructure of isoquebecol **15** was prepared by the reduction of the corresponding ester **13**, which had been prepared from its carboxylic acid precursor **11**.

Other *Class B* compounds used in this study were prepared from compounds **30** and **31**. As previously mentioned, we were interested in furthering our previous studies on this moiety by extending the variety of functionalities explored. Compounds **32** and **33** were reduced to the corresponding diols **34** and **35**. Deprotection of the benzyl group on those two compounds gave phenolic compounds **16** and **17**, which were included in the bioassays. Further transformations were performed on **34** and **35** to access **18** and **19** with an oxidized benzylic position. First, the use of a DMAP/TBDMS protocol[38] was used for a chemoselective protection of



a) Ac_2O (1.1 equiv), Et_3N (1.5 equiv), DMAP (0.1 equiv), CH_2Cl_2, 0 °C to r.t., 20 h. b) NBS (1.1 equiv), ACN, 60 °C, 24 h. c) KOH (2 equiv), MeOH, reflux, 5 h. d) BnBr (1.7 equiv), K_2CO_3 (1.7 equiv), acetone, reflux, 5-24 h. e) n-BuLi (1.15 equiv), -78 °C, THF. f) Addition of **27** (1 equiv), -78 °C to r.t., 3 h. g) $NaBH_4$ (55 equiv), Et_2O then TFA (72 equiv), 3 h, r.t. h) H_2 (50 psi), Pd/C (10%), EtOAc, r.t., 16 h.

Scheme 1. Synthesis of **21**: North substructure of isoquebecol.



a) Cs_2CO_3, pH 7, MeOH / H_2O (10:1). b) CH_3CH_2Br (1 equiv), DMF, r.t., 72 h. c) $LiAlH_4$ (4 equiv), THF, 0 °C to reflux, 16 h. d) BnBr (1.7 equiv), acetone, reflux, 20 h. e) $LiAlH_4$ (1.5 equiv), Et_2O, r.t., 2 h. f) H_2 (50 psi), Pd/C (10%), MeOH, r.t., 2 h. g) TBDMS-Cl (1 equiv), DMAP (0.06 equiv), CH_2Cl_2, r.t., 24 h. h) Dess-Martin periodinane (2 equiv), CH_2Cl_2, 0 °C, 2 h. i) H_2 (30 psi), Pd/C (10%), MeOH, r.t. 16 h. j) TBAF (1.5 equiv), THF, 0 °C to r.t., 1 h.

Scheme 2. Preparation of *Class B* compounds: South substructures of quebecol (*Series 1*) and isoquebecol (*Series 2*).

the primary alcohol to give **36** and **37**. Secondly, those products were oxidized with the Dess Martin periodinane, yielding **38** and **39**. Sequential removal of the two protecting groups led to phenolic compounds **18** and **19**.

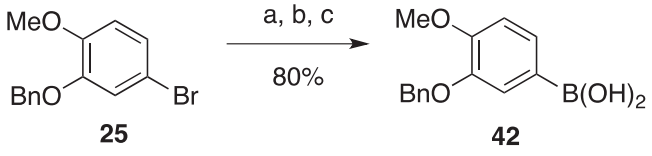
3.3. Preparation of triarylethene precursor of isoquebecol (Class C)

3.3.1. Preparation of cross-coupling partners

As previously mentioned, the strategy presented in Fig. 2 was used to prepare isoquebecol.[36]

The *gem*-dibromoalkene precursor of isoquebecol **41** was prepared in two steps from **33** (Scheme 3). First, the benzylic position was oxidized using Dess-Martin periodinane to give the α-ketoester **40**. The *gem*-dibromoalkene functionality was then installed by a Wittig-like C-1 homologation reaction. The CBr_4/PPh_3 protocol used in our previous work[36,39] led us to prepare **41** in a 72% yield.

We accessed the arylboronic acid partner **42**, corresponding to the isoquebecol aryl ring substitution pattern, from the arylbromine compound **25**. This latter compound was previously used in the synthesis of the North substructure **21** (Scheme 1). The boronic acid functionality was installed on **25**, using a lithiation/transmetallation/hydrolysis sequence. The desired compound **42** was obtained in a 80% yield (Scheme 4).

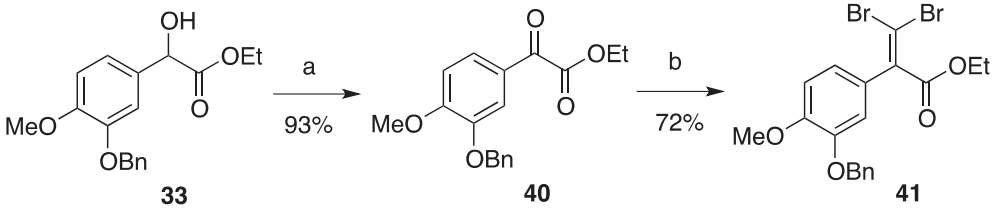


a) n-BuLi (1.1 equiv), THF, -78 °C, 30 min. b) $B(OMe)_3$ (3 equiv), -78 °C to r.t., 5 h. c) 1N HCl, -20 °C.

Scheme 4. Preparation of the boronic acid synthon **42** for the synthesis of isoquebecol.

3.3.2. Double Suzuki-Miyaura cross-coupling

As a way to give a more sustainable character to our previously reported synthesis of quebecol,[36] we were interested, while working on the synthesis of isoquebecol, to develop alternative conditions to perform the double Suzuki-Miyaura coupling (SMC) reaction in water. Additionally, having recently developed a synthetic strategy to access various 1,2,2-triarylethene compounds using SMCs on a *gem*-dibromoalkene template,[40] we were particularly interested to explore the behavior of this substrate in aqueous conditions.



a) Dess-Martin periodinane (2 equiv), CH_2Cl_2, 0 °C, 2 h. b) PPh_3 (4 equiv), CBr_4 (2 equiv), CH_2Cl_2, r.t., 12h.

Scheme 3. Preparation of *gem*-dibromoalkene precursor of isoquebecol **41**.

Interestingly, the SMC reaction is fully compatible with an aqueous system from a theoretical/mechanistic point of view.[41,42] In fact, many cases of SMCs have been shown to be promoted by the presence of water.[43,44] However, the solubility of organic species remains a major limitation to efficient coupling in aqueous media.[42,43] To overcome this obstacle, we explored the use of TPGS-750-M, a commercially available surfactant developed by Lipshutz.[45] When used as an additive, this environmentally benign amphiphile has shown to form aqueous micellar nanoparticles that can enable many metal-catalyzed cross-couplings (including SMCs) in water at ambient temperatures.[45–47]

Due to their availability in our lab from other ongoing projects, cross-coupling partners **44** and **45** (Scheme 5), associated with the synthesis of quebecol **1**, were used to investigate the extension of this double SMC reaction to aqueous solvent systems. Due to its efficiency (shown in our previous work[36,40]) for double coupling in toluene, we were interested in exploring the reactivity of the $Pd_2(dba)_3$/SPhos ligand combination in water. Many experiments, using different loading of this catalytic system, various temperatures, along with different concentrations of TPGS-750-M and Et_3N (most common base use for SMC with this surfactant), led us to establish the optimized conditions presented in Scheme 5 for the coupling of **44** and **45** (see Supplementary data for complete coupling results).

As illustrated in Scheme 5, we used those conditions to prepare **46** (the 1,2,2-triarylethene precursor of quebecol) at a gram scale with a 75% yield. Afterwards, we apply them to the coupling of **41** and **42** to give **43**, the key precursor towards the synthesis of isoquebecol **2**. It is worth noting that, in addition to the substitution of organic solvents, ligand and catalyst loadings were reduced by half (compared with our original conditions in toluene) in these conditions, without affecting coupling yields. To the best of our knowledge, these reactions are the first reported examples of SMCs on a *gem*-dibromoalkene in water.

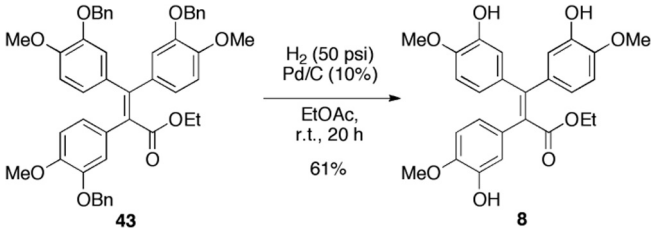
3.3.3. Deprotection

The protecting groups on the phenol functionalities of **43** had to be removed to obtain the triarylethene precursor of isoquebecol **8** (*Class C*). To prepare this derivative, we submitted **43** to the same mild hydrogenation conditions that we previously used to access **7** (Table 1) from **46** (Scheme 5).[37] Scheme 6 shows that those conditions led to the preparation of polyphenolic compound **8** in a 61% yield.

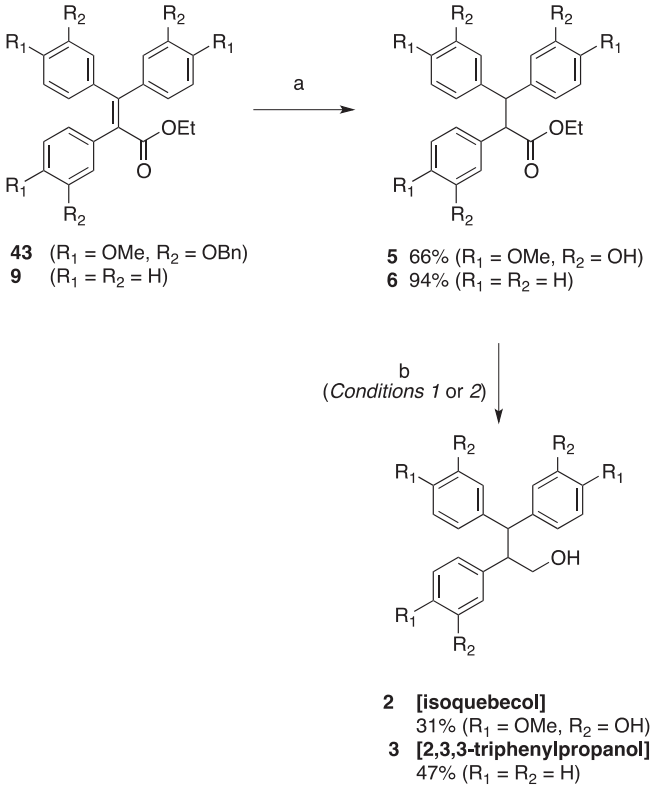
It is noteworthy that our group has already produced the model 1,2,2-triarylethene compound **9** (Table 1) with unfunctionalized aryl rings (*Series 3*), using ethyl benzoylformate and phenylboronic acid as starting materials.[40]

3.4. Preparation of isoquebecol, 2,3,3-triphenylpropanol and precursors (Class D)

The preparation of isoquebecol **2** from precursor **43** requires the reduction of the α,β-usaturated ester functionality and the deprotection of the phenolic functionalities. We have previously demonstrated, during the total synthesis of quebecol, that a hydrogenation reaction performed at high pressure can be used to reduce this type of double bond, in addition to removing the benzyl groups.[36] The same set of conditions was used on **43** to prepare isoquebecol **2** via **5**, also used in our bioassays (Scheme 7). Triarylethane compound **6** (*Series 3*) was also prepared from its triarylethene precursor **9** using this reaction.

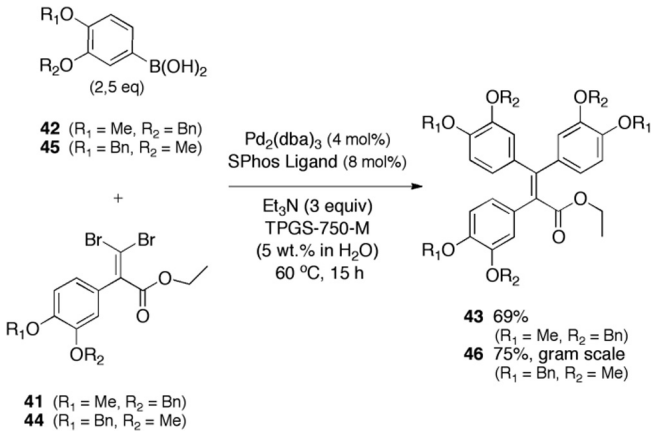


Scheme 6. Deprotection of **43** to prepare compound **8** (*Class C*).



a) H_2 (286 psi), Pd/C (10%), MeOH, 50 °C, 24 h. b) *Conditions 1*: $LiAlH_4$ (12 equiv), THF, reflux, 16 h; *Conditions 2*: $LiAlH_4$ (1.5 equiv), THF, 50 °C, 16 h.

Scheme 7. Preparation of isoquebecol **2** and 2,3,3-triphenylpropanol **3** from α,β-usaturated esters **45** and **9**.



Scheme 5. Synthesis of 1,2,2-triarylethene precursors of isoquebecol and quebecol (**43** and **46**, respectively) in a TPGS-750-M (5 wt.% in H_2O) solvent system.

The final step in the preparation of isoquebecol **2** was the reduction of the ester functionality of **5** to the corresponding alcohol. We successfully performed this transformation with a large excess of a reducing agent (12 equiv) and reflux heating, to complete the total synthesis of isoquebecol **2**. Due to the limited quantity of precursor **5** at hand, we were only able to do this reaction once. Therefore, the low yield observed for this transformation (31%, Scheme 7) could not be optimized.

The structure of isoquebecol **2** was confirmed by mass spectrometry as well as by ^{1}H and ^{13}C NMR. Slight differences were observed between the spectral signatures of quebecol **1** and isoquebecol **2**, mainly in ^{1}H NMR. Three singlets on the spectrum of isoquebecol clearly show the presence of the three methoxy groups (δ = 3.66, 3.72 and 3.78 ppm). The doublet centered at 4.18 ppm can be attributed to one of the CH groups (β from CH_2). Signals corresponding to the other CH group (α from CH_2) and to the methylene group are poorly resolved on the ^{1}H NMR spectrum of **2** and form the broad multiplet found between 3.47 and 3.63 ppm. All those assignments were confirmed by the COSY and HSQC spectra (see Supplementary data for 2D NMR).

The preparation of 2,3,3-triphenylpropanol **3** was also completed by the reduction of the corresponding ester. Milder reductive conditions were used for the reduction of non-phenolic compound **6** (Conditions 2, Scheme 7) and led us to obtain 2,3,3-triphenylpropanol **3** as unfunctionalized analog (*Series 3*) of quebecol **1** and isoquebecol **2**.

4. Biological evaluation

4.1. General remarks

The results of all bioassays for the studied compounds of *Classes A* (**20** and **21**), *B* (**10**–**19**), *C* (**7**–**9**) and *D* (**1**–**6**) are summarized in Table 2 (see Supplementary data for complete detailed results). Those assays were performed according to previously reported procedures.[37,48] Before the evaluation of their anti-inflammatory activity, the cytotoxicity of all compounds towards the macrophage cells was evaluated by an MTT [3-(4,5-diethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay.

The effect of each compound on the secretion of the pro-inflammatory cytokine IL-6 was evaluated by treating the macrophage cells with different concentrations of **1**–**21** for 2 h, prior to a 24 h stimulation with bacterial LPS. Concentrations ranging from 125 to 500 μM were evaluated for compounds of *Classes A* and *B*. A wider range of concentrations (31.25–500 μM) was considered for *Class C* and *Class D* compounds, due to their general higher cytotoxicity according to the MTT assay. The quantification of IL-6 was performed with Enzyme-linked immunosorbent assay (ELISA) kits, according to the manufacturer's protocol.

4.2. Anti-inflammatory activity of isoquebecol

A primary objective of this study was to evaluate the anti-inflammatory activity of isoquebecol **2** and compare it with quebecol **1**. First, those two compounds showed some similarities regarding their biological activity. Indeed, Table 2 shows that quebecol **1** and isoquebecol **2** have a comparable activity at their highest non-cytotoxic concentration. Furthermore, results obtained for quebecol **1** and isoquebecol **2** at different concentration showed the dose-dependent character of that inhibition. A major activity drop was also observed between 250 and 125 μM in both cases.

However, the results presented in Table 2 clearly show that isoquebecol **2**, even if showing more toxicity than quebecol **1**, has a better activity profile. Indeed, isoquebecol **2** kept significant activity at all the lower concentrations evaluated, while the activity of quebecol **1** became negligible below 125 μM. In fact, isoquebecol **2** represents the most active species at 62.5 μM and below, among all the compounds tested at those concentrations.

4.3. Aryl ring functionalization and anti-inflammatory activity

To evaluate the impact of the aryl ring functionalization on the anti-inflammatory activity of quebecol **1** and related structures, two general aspects were investigated.

Table 2
Highest non-cytotoxic concentration and inhibition of IL-6 secretion for all tested compounds (**1**–**21**).

		Compound	Highest non-cytotoxic conc. (μM)	% Inhibition of IL-6 secretion at different concentrations[a,b,c]			
				250 μM	125 μM	62.5 μM	31.25 μM
Class A	*Series 1*	**20**	500 μM	90.5 ± 2.4	27.5 ± 10.1	n/d[d]	n/d
	Series 2	**21**	500 μM	92.5 ± 0.9	50.7 ± 7.3	n/d	n/d
Class B	*Series 1*	**10**	>1000 μM	0.2 ± 0.2	0.3 ± 0.1	n/d	n/d
		12	>1000 μM	0.4 ± 0.1	0.2 ± 0.2	n/d	n/d
		14	>1000 μM	0.9 ± 0.7	1.1 ± 0.1	n/d	n/d
		16	500 μM	8.0 ± 1.4	2.1 ± 0.2	n/d	n/d
		18	500 μM	64.4 ± 2.0	4.9 ± 1.4	n/d	n/d
	Series 2	**11**	>1000 μM	2.1 ± 0.1	0.5 ± 0.5	n/d	n/d
		13	>1000 μM	3.2 ± 0.2	0.8 ± 0.1	n/d	n/d
		15	>1000 μM	2.7 ± 0.4	0.9 ± 0.1	n/d	n/d
		17	500 μM	20.9 ± 0.7	1.4 ± 0.2	n/d	n/d
		19	500 μM	24.1 ± 2.6	0.8 ± 0.5	n/d	n/d
Class C	*Series 1*	**7**	62.50 μM	100 ± 0.0	99.5 ± 0.1	11.2 ± 7.2	2.5 ± 0.1
	Series 2	**8**	62.50 μM	100 ± 0.0	97.8 ± 1.1	31.2 ± 3.5	0.8 ± 0.2
	Series 3	**9**	<15.62 μM	100 ± 0.0	11.0 ± 0.7	0.5 ± 0.3	0.5 ± 0.2
Class D	*Series 1*	**4**	250 μM	91.9 ± 0.7	34.6 ± 1.5	9.4 ± 0.3	4.0 ± 0.1
		1 [quebecol]	500 μM	84.7 ± 0.3	55.3 ± 6.2	4.7 ± 3.4	3.7 ± 0.1
	Series 2	**5**	62.50 μM	96.8 ± 0.2	41.3 ± 0.5	5.9 ± 0.3	3.0 ± 0.8
		2 [isoquebecol]	250 μM	96.9 ± 0.2	48.3 ± 0.5	43.3 ± 3.3	34.5 ± 3.8
	Series 3	**6**	62.50 μM	85.3 ± 3.4	2.0 ± 0.4	0.4 ± 0.2	0.2 ± 0.1
		3 [2.3.3-triphenylpropanol]	31.25 μM	100 ± 0.0	100 ± 0.0	15.6 ± 2.6	1.4 ± 0.9

[a] PMA-differentiated U937 macrophages.
[b] The means ± standard deviations of triplicate assays were calculated; statistically different from control at $p < 0.01$.
[c] See Supplementary data for % inhibition evaluated at 500 μM.
[d] n/d: not determined.

4.3.1. Presence of oxygenated functions [Series 1 and 2 vs. Series 3]

Comparison between compounds of *Series 3* with their corresponding analogs belonging to *Series 1* and *2* established that an increase of toxicity could generally be associated with the absence of the functional groups on the aryl rings of *Class C* and *Class D* compounds (Table 2). Indeed, 2,3,3-triphenylpropanol **3** shows a far greater toxicity in the MTT assay than quebecol **1** and isoquebecol **2**. Same thing could be observed with **9** when compared to its functionalized analogs **7** and **8**. Finally, compound **6** also showed a greater toxicity than it's analog from *Series 1* (**4**).

4.3.2. Position of oxygenated functions [Series 1 vs. Series 2]

As expected, the impact on the biological activity of the position of the oxygenated functions on the aryl ring (*Series 1* vs. *Series 2*).

As discussed earlier, inverting the hydroxy and the methoxy group from quebecol **1** (*Series 1*) to isoquebecol **2** (*Series 2*) is accompanied by an increase in toxicity and an improvement of the anti-inflammatory activity, particularly at lower concentrations. Similar behavior concerning toxicity was observed when comparing compounds **4** and **5**, the other pair of isomers of *Class D*.

Results obtained for compounds **7** and **8** (*Class C*) showed that the functional groups position does not affect toxicity in the case of this α,β-unsaturated ester scaffold. On the other hand, a slightly better anti-inflammatory activity was observed at 62.5 μM for **8** (*Series 2*).

Comparison between compounds of *Series 1* and *Series 2* for quebecol and isoquebecol substructures (*Class A* and *B* respectively) shows that all pairs of isomers share the same cytotoxicity. No particular tendency regarding biological activity while was observed. The only pairs of isomers of *Class B* (South substructure) for which a meaningful difference in anti-inflammatory activity was noted were **16**–**17** and **18**–**19**. In the first case, compound **17** with the substitution pattern of isoquebecol (*Series 2*) demonstrated a better inhibition of IL-6 secretion than **16**. In the latter case, **18** (belonging to *Series 1*) was three times more active than **19**. Concerning the *Class A* compounds (North substructures), **21** (*Series 2*) was about twice as active as its isomer **20** (*Series 1*) at the lowest tested concentration (125 μM).

Overall, no dominant trend could be identified from our biological results regarding the substitution pattern of the oxygenated functions on the aryl ring. In many cases, pair of isomers showed the same toxicity and similar anti-inflammatory activity, when comparing between *Series 1* and *Series 2*. However, compounds with the aryl ring substitution pattern of isoquebecol (*Series 2*) were generally better inhibitors when a difference was observed between the two isomers.

4.4. Anti-inflammatory activity of quebecol and isoquebecol precursors (Class C and D)

We demonstrated in our previous study that the alcohol functionality on the propanol core of quebecol **1** could be modified to an ester or to α,β-unsaturated ester without altering the anti-inflammatory activity.[37] However, this introduction of an electrophilic function considerably increased the toxicity of the scaffold of interest.[37] Similar trends were observed in the present study for both *Series 1* and *Series 2* (Table 2).

Indeed, as shown in Table 2 for *Series 1*, the anti-inflammatory activity of **1** and **4** were comparable at 250 μM, while the activity profile shown by **7** was mostly attributable to toxicity. Furthermore, comparison between the *Class D* compounds **1** and **4** (*Series 1*) showed that the ester precursor **4** was twice more toxic than quebecol **1**. The introduction of a conjugated α,β-unsaturated system between structures **4** (*Class D*) and **7** (*Class C*) resulted in another increase in toxicity, **7** being the most toxic of all *Series 1* compounds tested.

Similar results were obtained for *Series 2* when comparing isoquebecol **2** and its analogs **5** and **8**, except that a more drastic rise of toxicity was observed between **2** and **5** compared with the one between **1** and **4** (Table 2). Also, we observed in the case of *Series 2* that the ester **5** (*Class D*) and the α,β-unsaturated ester **8** (*Class C*) have equivalent toxicities.

4.5. Anti-inflammatory activity of quebecol and isoquebecol substructures (Class a and B)

We were demonstrated in our previous work that the North substructure **20** of quebecol had an anti-inflammatory activity, while the South substructures studied were inactive.[37] Along the same line, substructures **10**, **12**, **14** and **20** of *Series 1* were tested again in this study and compared with **11**, **13**, **15** and **21**, their corresponding isomers of *Series 2*. Results presented in Table 2 illustrate that structures related to isoquebecol (*Series 2*) showed the same behavior as the substructures of quebecol (*Series 1*), concerning the relation between the North and South substructures.

Firstly, compound **15** corresponding to the exact South substructure of isoquebecol (*Class B*) showed no toxicity, as well as no inhibition of the secretion of IL-6 by macrophages. The same behavior was observed with analogs **11** and **13**, which bear different functionalities.

Secondly, as observed with *Series 1*, the diarylmethane compound **21** corresponding to the North substructure (*Class A*) of **2** (*Series 2*) showed an anti-inflammatory activity comparable to the complete structure (**2**) at the studied concentrations (125–500 μM), suggesting that the anti-inflammatory activity of **2** comes also from this structural subunit. This result is even more interesting in the case of *Series 2* (vs. *Series 1*), considering the drop of toxicity observed between the North substructure **21** and the full structure **2**. Furthermore, compound **21** (*Series 2*) showed a better anti-inflammatory activity than its isomer **20** (*Series 1*) at 125 μM, the lowest studied concentration (50.7% for **21** vs. 27.5% for **20**).

We were also interested in evaluating the biological activity of new compounds associated with the South substructure of quebecol **1** (*Class B*), even if this moiety had been so far mostly inactive in our previous study.[37] Hence, compounds **16** and **18** (*Series 1*), as well as **17** and **19** (*Series 2*), were included as new analogs of the quebecol and isoquebecol South substructures. Interestingly, **16**–**19** showed an improved anti-inflammatory activity over the other *Class B* compounds tested for both *Series 1* and *Series 2*, while maintaining a low toxicity (Table 2). First, **16** and **17** with an ethanediol moiety showed a low but higher inhibition of IL-6 secretion than the one observed in our previous study for compounds **10**, **12** and **14**.[37] The introduction of the carbonyl function at the benzylic position gave a similar result for **19** in *Series 2*, but led to an important increase in activity for **18** (*Series 1*). While moderate, the observed activity of **18** illustrates that simple modifications on the South substructure can have an impact on its inhibition potential. This shows that anti-inflammatory activity can be tuned on this moiety and eventually on more complex analogs bearing the quebecol/isoquebecol scaffold.

5. Conclusion

In summary, we synthesized an unprecedented constitutional isomer of quebecol, which we named isoquebecol **2**. We also developed aqueous conditions to efficiently perform the key step of the double Suzuki-Miyaura cross-coupling in our synthetic strategy towards quebecol **1** and isoquebecol **2**.

Isoquebecol **2** showed an overall improved biological activity over quebecol **1** in the present study. Indeed, **2** presented a slightly higher toxicity than quebecol **1**, but a better activity

profile on the LPS-induced IL-6 secretion at low concentrations, making it a potential anti-inflammatory compound to be investigated further.

A series of isoquebecol analogs and substructures (*Series 2*) were prepared and tested in our bioassays, along with their corresponding isomers derived from quebecol (*Series 1*). 2,3,3-triphenylpropanol **3** and two of its precursors (*Series 3*) were also included in our biological assays to serve as a model for the quebecol/isoquebecol scaffold. The cytotoxicity and inhibition of IL-6 secretion were studied for a total of 21 compounds, allowing us to establish some structure-activity relationships (SARs). Comparison between phenolic compounds (*Series 1* and *2*) and unfunctionalized systems (*Series 3*) showed that the oxygenated substituents are essential for anti-inflammatory activity and cell viability, considering the important toxicity evaluated for all compounds lacking those functionalities (*Series 3*). On the other hand, no definitive trends could be underlined regarding the substitution pattern on the aryl rings and biological activity (*Series 1* vs. *2*), even if compounds associated with isoquebecol (*Series 2*) showed in general more activity where a difference was observed between two isomers.

The studies of isoquebecol substructures clearly demonstrated that, as previously observed with quebecol,[37] the anti-inflammatory activity of this compound originates from its North portion **21** (*Class A*). We established, in our precedent study, that the diarylmethane scaffold **20** related to quebecol is a promising moiety to investigate in the search for new anti-inflammatory compounds, considering its structural simplicity and easy synthetic access.[37] Interestingly, the present study showed that compound **21** has an anti-inflammatory activity twice as high as its isomer **20** (at 125 μM), making **21** a better candidate as a leading moiety to a new class of anti-inflammatory compounds inspired from quebecol **1**.

Finally, analogs of the South substructure (*Class B*) bearing previously unstudied functionalities were prepared (**16**–**19**) and showed enhanced activity towards the inhibition of IL-6 secretion, thus demonstrating that the South region of the quebecol/isoquebecol scaffold could be used as a fine-tuning tool to modulate and enhance the activity of future analogs. Based on those results we are currently exploring the preparation of new quebecol analogs, as well as additional diarylmethane derivatives. The investigation of the activity of quebecol **1** and isoquebecol **2** on other biological processes is also currently underway.

6. Experimental section

6.1. Chemical synthesis

6.1.1. General information

Unless otherwise indicated, all starting materials were purchased from commercial sources (Sigma-Aldrich) and used without further purification. Solvents were dried and purified by distillation under inert atmosphere before use. All reagents and solvents were assembled under an inert atmosphere. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 MHz or an Agilent DD2 500 MHz spectrometer. The coupling constants are reported in hertz (Hz) and the splitting patterns are designated as: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), br (broad singlet) and m (multiplet). All melting points were taken using a Standford Research Systems OptiMelt MPA 100 instrument. Mass spectra were obtained on an Agilent 6210 LC Time of Flight Mass Spectrometer in direct injection mode. IR spectra were taken on a Bomem MB-Series Arid-Zone spectrometer (NaCl windows) or a Thermo Nicolet 380 (ATR, ZnSe).

6.1.2. Preparation of Class A compounds (North substructures)

Our group has already reported on the preparation and complete characterization of **20** (the North substructure of quebecol).[37]

*6.1.2.1. (2-Methoxy)phenyl acetate (**23**).* Guaiacol **22** (40.3 mmol, 5.00 g) was dissolved in dried CH_2Cl_2 (50 mL) in a round-bottom flask. Triethylamine (60.42 mmol, 8.42 mL) and 4-dimethylaminopyridine (4.03 mmol, 0.49 g) were added to the mixture. The temperature was cooled to 0 °C and acetic anhydride (44.3 mmol, 4.19 mL) was added dropwise. The mixture was stirred at room temperature for 24 h and then washed several times using the following sequence: saturated $NaHCO_3$, water, HCl 2 N, water and brine. The remaining organic layer was dried with $MgSO_4$ and concentrated *in vacuo*, giving **23** without the need for further purification in a 85% yield (34.2 mmol, 5.66 g). Transparent oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.21 (1H, ddd, J = 8.2, 7.4, 1.7), 7.06–7.02 (1H, m), 7.00–6.92 (2H, m), 3.84 (3H, s), 2.32 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 169.3, 151.3, 140.0, 127.1, 123.0, 121.0, 112.6, 56.0, 20.9. IR (ATR, ZnSe): ν_{max} 1759, 1498, 1367, 1254, 1192, 1168, 1108, 903, 745 cm^{-1}. HRMS (ESI-TOF, m/z): calcd for $C_9H_{11}O_3$ $(M+H)^+$ = 167.0703, found 167.0707. This compound has been also previously reported.[49]

*6.1.2.2. 5-Bromo-2-methoxyphenol (**24**).* (2-Methoxy)phenyl acetate **23** (62.92 mmol, 10.46 g) was dissolved in anhydrous acetonitrile (110 mL) in an oven-dried three-neck flask under nitrogen. N-Bromosuccinimide (94.39 mmol, 16.80 g) was added to the mixture and stirred at 60 °C for 24 h or until completion was observed by TLC (60:40 hexanes/CH_2Cl_2). The solution was then diluted with EtOAc (150 mL) and water (150 mL). The aqueous layer was extracted three times with EtOAc. The organic layers were combined and washed with saturated Na_2SO_3, water and brine. The solution was dried with $MgSO_4$ and concentrated *in vacuo*. The resulting crude product [(5-bromo-2-methoxy)phenyl acetate] was used further purification and dissolved in dried MeOH (50 mL) in a three-neck flask under argon. A solution of KOH (134.37 mmol, 7.52 g) in 100 mL of MeOH was added to the mixture and stirred for 5 h at reflux or until completion was observed by TLC (80:20 hexanes/EtOAc). The solution was then diluted with EtOAc (150 mL) and 150 mL of water. HCl (6 N, 60 mL) was added to the reaction mixture and the aqueous layer was extracted three times with CH_2Cl_2. The organic layers were combined, washed with water and brine, dried with $MgSO_4$ and concentrated *in vacuo*, giving **24** as a brownish solid in a 81% yield (50.95 mmol, 10.34 g). mp = 62–66 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.07 (1H, d, J = 2.4), 6.97 (1H, dd, J = 8.6, 2.4), 6.71 (1H, d, J = 8.6), 3.87 (1H, s). ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 146.7, 146.1, 123.0, 118.0, 113.5, 112.0, 56.3. IR (ATR, ZnSe): ν_{max} 3386, 2930, 2840, 1589, 1494, 1433, 1213, 1124, 1022, 854, 796 cm^{-1}. This compound has been also previously reported.[49]

*6.1.2.3. 1-Benzyloxy-5-bromo-2-methoxybenzene (**25**).* 5-Bromo-2-methoxyphenol **24** (14.84 mmol, 3.01 g) was dissolved in anhydrous acetone (50 mL) in an oven-dried three-neck flask under argon. K_2CO_3 (29.69 mmol, 4.10 g) was then added and the mixture was stirred for 5 min before the addition of benzyl bromide (17.81 mmol, 2.12 mL). The reaction was refluxed for 5 h or until completion was shown by TLC (20:80 EtOAc/hexanes) (up to 24 h). The reaction mixture was cooled down to room temperature. Water (15 mL) was added to the reaction mixture which was extracted three times with EtOAc (3 × 30 mL). The organic layers were combined, washed with saturated K_2CO_3, water and brine, dried with $MgSO_4$, concentrated *in vacuo* and purified by silica gel column chromatography (100% hexanes), giving **25** as a white solid in a 96% yield. mp = 106–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.47–7.29 (5H, m), 7.07–7.01 (2H, m), 6.77 (1H, d, J = 8.3), 5.12

(1H, s), 3.86 (1H, s). ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 149.2, 136.6, 128.9, 128.3, 127.6, 124.2, 117.4, 113.3, 112.8, 71.4, 56.4. IR (ATR, ZnSe): ν_{max} 1455, 1246, 1213, 1185, 1159, 1128, 1000, 919, 838, 773, 698 cm^{-1}. HRMS (ESI-TOF, *m*/*z*): calcd for $C_{14}H_{17}BrNO_2$ (M +NH_4)$^+$ = 310.0437, found 310.0440. This compound has been also previously reported.[50]

*6.1.2.4. 3-Benzyloxy-4-methoxybenzaldehyde (**27**).* Isovanillin **26** (46 mmol, 7.00 g) was dissolved in anhydrous acetone (50 mL) in an oven-dried three-neck flask under argon. K_2CO_3 (78.2 mmol, 10.81 g) was then added and the mixture was stirred for 5 min before the addition of benzyl bromide (78.2 mmol, 9.30 mL). The reaction was refluxed for 24 h or until completion was shown by TLC (EtOAc/hexanes 30:70). The reaction mixture was allowed to warm to room temperature, poured into saturated K_2CO_3 and extracted three times with EtOAc. The organic layers were combined, washed with brine, dried with $MgSO_4$, concentrated *in vacuo* and purified by silica gel column chromatography (30:70 EtOAc/hexanes), giving **27** as a white solid in a 92% yield (41.2 mmol, 10.17 g). mp = 61–63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.82 (1H, s), 7.49–7.45 (4H, m), 7.41–7.30 (3H, m), 7.01–6.98 (1H, m), 5.19 (2H, s), 3.96 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 191.1, 155.3, 149.0, 136.5, 130.2, 128.9, 128.4, 127.8, 127.7, 127.1, 111.6, 111.0, 71.1, 56.4. IR (NaCl): ν_{max} 2839, 1685, 1596, 1584, 1510, 1434, 1268, 1283, 1134, 1018, 738 cm^{-1}. HRMS (ESI-TOF, *m*/*z*): calcd for $C_{15}H_{15}O_3$ (M+H)$^+$ = 243.1016, found 243.1027. This compound has been also previously reported.[51]

*6.1.2.5. Bis(3-benzyloxy-4-methoxyphenyl)methanol (**28**).* At room temperature, 1-benzyloxy-3-bromo-2-methoxybenzene **25** (21.52 mmol, 6.31 g) was dissolved in freshly distilled THF (90 mL) in an oven-dried three-neck flask under argon. The temperature was cooled to −78 °C and *n*-BuLi (1.6 M in hexanes, 24.75 mmol, 15.5 mL) was added dropwise. The reaction mixture was stirred for 1 h at this temperature and a solution of **27** (21.52 mmol, 5.21 g) in THF (30 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 1.5 h, allowed to warm to room temperature and stirred for another 2 h. Water (300 mL) was slowly added to the mixture, which was then extracted three times with EtOAc. The organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was dissolved in a minimum of EtOAc and 250 mL of hexanes were added to precipitate the desired product. After 12 h at 0 °C, the precipitate was filtered, lightly washed with cold EtOAc and dried *in vacuo*, giving **28** as a white solid in a 66% yield (14.20 mmol, 6.45 g). mp = 110–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.42–7.25 (10H, m), 6.88–6.78 (6H, m), 5.64 (1H, s), 5.07 (4H, s), 3.88 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 149.2, 148.3, 137.2, 136.7, 128.7, 128.0, 127.7, 119.6, 112.6, 111.7, 75.7, 71.1, 56.3. IR (NaCl): ν_{max} 2932, 2835, 1511, 1256, 1227, 1134, 1024, 738, 697 cm^{-1}. HRMS (ESI-TOF, *m*/*z*): calcd for $C_{29}H_{27}O_4$ (M-H_2O+H)$^+$ = 439.1904, found 439.1938. This compound has been also previously reported.[52]

*6.1.2.6. Bis(3-benzyloxy-4-methoxyphenyl)methane (**29**).* At room temperature, **28** (0.438 mmol, 0.20 g) and $NaBH_4$ (55.4 mmol, 0.917 g) were dissolved in freshly distilled Et_2O. Trifluoroacetic acid (31.54 mmol, 2.43 mL) was added dropwise during a period of 1.5 h. After the addition, the mixture was stirred for 0.5 h. A solution of $NaHCO_3$ 10% (12 mL) was slowly added to the mixture and after 30 min of stirring, the mixture was extracted 3 times with Et_2O. The organic layers were combined, dried with Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography (50:50 EtOAc/hexanes), giving **29** as a white solid in a 86% yield (0.377 mmol, 0.165 g). mp = 114–118 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.42–7.27 (10H, m), 6.81 (2H, d, *J* = 8.1), 6.70–6.66 (4H, m), 5.06 (4H, s), 3.88 (2H, s), 3.77 (2H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 148.2, 137.4, 134.1, 128.8, 128.7, 128.0, 127.7, 127.6, 121.5, 115.1, 112.1, 71.1, 56.4, 41.0. IR (ATR, ZnSe): ν_{max} 2931, 1585, 1509, 1379, 1229, 1129, 1008, 838, 795, 696 cm^{-1}. HRMS (ESI-TOF, *m*/*z*): calcd for $C_{29}H_{32}NO_4$ (M +NH_4)$^+$ = 458.2326, found 458.2346.

*6.1.2.7. Bis(3-hydroxy-4-methoxyphenyl)methane (**21**).* Bis(3-benzyloxy-4-methoxyphenyl)methane **29** (0.340 mmol, 0.150 g) was dissolved in EtOAc (7 mL) in a high-pressure hydrogenation vessel. Pd/C 10% (0.04 g) was then added. The vessel was installed in the reactor and, after 4 purges, the H_2 pressure was set to 50 psi. After 3 h, the reaction was stopped. After cooling, the mixture was filtered on a Celite® pad. The filtrate was concentrated *in vacuo* and the crude product was purified by silica gel column chromatography (50:50 EtOAc/hexanes) giving **21** as a white solid in a 96% yield (0.326 mmol, 0.085 g). mp = 138–143 °C. ^{1}H NMR (500 MHz, CD_3OD): δ_H 6.79 (2H, d, *J* = 8.1), 6.63–6.57 (4H, m), 4.89 (2H, s), 3.79 (6H, s), 3.69 (2H, s). ^{13}C NMR (125 MHz, CD_3OD): δ_C 145.9, 145.9, 134.7, 119.6, 115.5, 111.3, 55.0, 40.1. IR(NaCl): ν_{max} 3412, 3031, 2962, 2836, 1587, 1511, 1435, 1356, 1268, 1127, 1029, 964, 791 cm^{-1}. HRMS (ESI-TOF, *m*/*z*): calcd for $C_{15}H_{20}O_4$ (M +NH_4)$^+$ = 278.1387, found 278.1374.

6.1.3. Preparation and/or characterization of Class B compounds (South substructures)

Compounds **10** and **12** were purchased from Sigma-Aldrich [products 71639 and 197971]. Characterization of those commercial products was made prior to the biological assays and have been previously reported by our group.[37] We have previously reported the synthesis and complete characterization of compound **14**,[37] as well as **30** and **32**.[36]

*6.1.3.1. 3-Hydroxy-4-methoxyphenyl acetic acid (**11**).* 3-Hydroxy-4-methoxyphenyl acetic acid **11** was purchased from Sigma-Aldrich (product 716391). Characterization of this commercial product was made prior to the biological assays. White powder. mp = 129–131 °C. ^{1}H NMR (500 MHz, CD_3OD): δ_H 6.84 (1H, d, *J* = 8.2), 6.75 (1H, d, *J* = 2.1), 6.70 (1H, dd, *J* = 8.2, 2.2), 3.82 (3H, s), 3.46 (2H, s). ^{13}C NMR (125 MHz, CD_3OD): δ_C 176.0, 148.1, 147.5, 128.8, 121.6, 117.3, 112.7, 56.4, 41.3. IR (ATR, ZnSe): ν_{max} 3373, 2910, 1687, 1512, 1270, 1229, 1152, 1025, 758, 685 cm^{-1}. HRMS (ESI-TOF, *m*/*z*): calcd for $C_9H_{10}NaO_4$ (M+Na)$^+$ = 205.0471, found 205.0466.

*6.1.3.2. Ethyl 3-hydroxy-4-methoxyphenylacetate (**13**).* 3-Hydroxy-4-methoxyphenyl acetic acid **11** (2.75 mmol, 0.500 g) was dissolved in 2.5 mL of a (10:1) MeOH/H_2O mixture and then treated with 20% aqueous Cs_2CO_3 to adjust the pH to 7. After removal of the solvent, 5 mL of DMF was added to the dry residue. After 5 min, ethylbromide (3.02 mmol, 225 µL) was added and the mixture was stirred for 72 h. HCl 1 N was then added and the product was extracted with 3 portions of EtOAc. The organic layers were combined, washed with brine, dried with Na_2SO_4 and concentrated *in vacuo*, giving an oil which was purified by flash chromatography (50:50 EtOAc/hexanes), yielding **13** as a colorless oil in a 71% yield (1.95 mmol, 0.408 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 6.86 (1H, d, *J* = 2.1), 6.79 (1H, d, *J* = 8.2), 6.75 (1H, dd, *J* = 8.2, 2.1), 5.75 (1H, s), 4.14 (2H, q, *J* = 7.1), 3.85 (3H, s), 3.51 (2H, s), 1.25 (3H, t, *J* = 7.1). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 171.9, 145.7, 145.6, 127.3, 120.8, 115.6, 110.7, 60.8, 55.9, 40.8, 14.2. IR (NaCl): ν_{max} 3437, 2981, 1731, 1592, 1513, 1442, 1274, 1212, 1029, 761 cm^{-1}. HRMS (ESI-TOF, *m*/*z*): calcd for $C_{11}H_{15}O_4$ (M+H)$^+$ = 211.0965, found 211.0979. This compound has been also previously reported.[53]

*6.1.3.3. 2-(3-Hydroxy-4-methoxyphenyl)ethanol (**15**).* Ethyl 3-hydroxy-4-methoxyphenylacetate **13** (1.19 mmol, 0.250 g) was

dissolved in freshly distilled anhydrous THF (5 mL) in an oven-dried three-neck flask under argon. The temperature was cooled to 0 °C and $LiAlH_4$ (1 N in THF, 4.75 mmol, 4.75 mL) was added dropwise. The mixture was allowed to warm to room temperature and the reaction was refluxed for 3 h or until completion was shown by TLC (EtOAc/hexanes 50:50). The reaction mixture was cooled to 0 °C and HCl 1 N was added dropwise until pH 2–3. The mixture was extracted three times with EtOAc. The organic layers were combined, dried with $MgSO_4$, concentrated *in vacuo* and purified by silica gel column chromatography (EtOAc/hexanes 50:50), giving **15** as a white solid in a 70% yield (0.832 mmol, 0.140 g). mp = 79–82 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 6.82–6.78 (2H, m), 6.70 (1H, dd, J = 8.1, 2.1), 3.86 (3H, s), 3.81 (2H, t, J = 6.6), 2.77 (2H, t, J = 6.6). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 145.7, 145.3, 131.6, 120.5, 115.2, 110.8, 63.7, 56.0, 38.5. IR (NaCl): ν_{max} 3380, 2938, 1591, 1514, 1441, 1272, 1131, 1024, 804, 761 cm^{-1}. HRMS (ESI-TOF, m/z): calcd for $C_9H_{11}O_2$ (M-H_2O+H)$^+$ = 151.0754, found 151.0760. This compound has been also previously reported.[54]

*6.1.3.4. Ethyl 3-hydroxy-4-methoxymandelate (**31**).* Ethyl 3-hydroxy-4-methoxymandelate **31** was purchased from Sigma-Aldrich (product 78814). Characterization of this commercial product was made, prior to biological assays. White powder. mp = 125–126 °C. ^{1}H NMR (500 MHz, CD_3OD): δ_H 6.92–6.85 (3H, m), 5.03 (1H, s), 4.22–4.07 (2H, m), 3.84 (3H, s), 1.20 (3H, t, J = 7.1). ^{13}C NMR (125 MHz, CD_3OD): δ_C 173.2, 147.7, 146.2, 131.8, 118.0, 113.4, 111.0, 72.6, 60.8, 55.0, 13.0. IR (ATR, ZnSe): ν_{max} 3415, 3178, 1742, 1444, 1368, 1192, 1080, 1023, 811, 745 cm^{-1}. HRMS (ESI-TOF, m/z): calcd for $C_{11}H_{13}O_4$ (M-H_2O +H)$^+$ = 209.0808, found 209.0804.

*6.1.3.5. Ethyl 3-benzyloxy-4-methoxymandelate (**33**).* Ethyl 3-hydroxy-4-methoxymandelate **31** (17.7 mmol, 4.00 g) was dissolved in 60 mL of anhydrous acetone in an oven-dried three-neck flask under argon. Potassium carbonate (30.1 mmol, 4.16 g) was added. After 5 min, benzyl bromide (30.1 mmol, 3.57 mL) was added and the reaction was refluxed for 24 h or until completion was shown by TLC (50:50 EtOAc/hexanes). The reaction mixture was allowed to cool at room temperature, poured into saturated K_2CO_3 and extracted three times with EtOAc. The organic layers were combined, washed with brine, dried with $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (50:50 EtOAc/hexanes), giving **33** as a white solid in a 96% yield (16.9 mmol, 5.35 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.46–7.28 (5H, m), 7.00–6.96 (2H, m), 6.88 (1H, d, J = 8.1), 5.15 (2H, s), 5.05 (1H, s), 4.26–4.17 (1H, m), 4.15–4.06 (1H, m), 3.88 (3H, s), 3.09 (1H, br), 1.18 (3H, t, J = 7.2). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 174.0, 150.0, 148.4, 137.2, 131.1, 128.8, 128.1, 127.6, 119.9, 112.4, 111.8, 72.8, 71.2, 62.4, 56.3, 14.3. IR (NaCl): ν_{max} 3465, 1732, 1514, 1262, 1231, 1156, 1138, 1081, 1023, 740, 697 cm^{-1}. HRMS (ESI-TOF, m/z): calcd for $C_{18}H_{19}O_4$ (M-H_2O+H)$^+$ = 299.1278, found 299.1289.

*6.1.3.6. 1-(4-Benzyloxy-3-methoxyphenyl)ethane-1,2-diol(**34**).* At room temperature, **32** (3.57 mmol, 1.13 g) was dissolved in freshly distilled Et_2O (27 mL) in an oven-dried three-neck flask under argon. A solution of $LiAlH_4$ (1 M in THF, 5.37 mmol, 5.37 mL) was added dropwise. After the addition, the mixture was refluxed until completion was shown by TLC (50:50 EtOAc/hexanes). The mixture was then cooled to 0 °C and a solution on HCl 1 N was added. Three extractions with EtOAc were performed. The organic layers were combined, washed with brine, dried with $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (50:50 EtOAc/hexanes), yielding **34** as a white solid in a 96% yield (3.43 mmol, 0.940 g). mp = 67–73 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.38 –7.20 (5H, m), 6.89 (1H, d, J = 1.9), 6.79 (1H, d, J = 8.2), 6.74 (1H, dd, J = 8.2, 1.9), 5.05 (2H, s), 4.60 (1H, dd, J = 8.4, 3.5), 3.81 (3H, s), 3.61–3.47 (4H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 149.5, 147.5, 137.0, 134.2, 128.4, 127.8, 127.2, 118.4, 113.9, 109.9, 74.2, 71.0, 67.8, 55.8. IR (ATR, ZnSe): ν_{max} 3308, 2930, 2870, 1589, 1514, 1228, 1134, 1027, 847, 739, 694 cm^{-1}. HRMS (ESI-TOF, m/z): calcd for $C_{16}H_{17}O_3$ (M-H_2O+H)$^+$ = 257.1172, found 257.1181.

*6.1.3.7. 1-(3-Benzyloxy-4-methoxyphenyl)ethane-1,2-diol (**35**).* 1-(3-Benzyloxy-4-methoxyphenyl)ethane-1,2-diol **35** was prepared using the same procedure described above for **34**, using **33** (15.8 mmol, 5.00 g). Product **35** was obtained as a white solid in a 97% yield (15.3 mmol, 4.14 g). mp = 68–75 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.42–7.26 (5H, m), 6.89–6.83 (3H, m), 5.12 (2H, s), 4.66 (1H, dd, J = 3.6, 8.2), 3.85 (3H, s), 3.64–3.52 (2H, m), 2.77 (2H, br). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 149.6, 148.4, 137.2, 133.3, 128.8, 128.2, 127.7, 119.2, 112.3, 111.9, 74.6, 71.3, 68.3, 56.3. IR (NaCl): ν_{max} 3319, 2934, 1516, 1262, 1233, 1159, 1137, 11061, 1025 cm^{-1}. HRMS (ESI-TOF, m/z): calcd for $C_{16}H_{17}O_3$ (M-H_2O+H)$^+$ = 257.1172, found 257.1190. This compound has been also previously reported.[55]

*6.1.3.8. 1-(4-Hydroxy-3-methoxyphenyl)ethane-1,2-diol (**16**).* 1-(4-Benzyloxy-3-methoxyphenyl)ethane-1,2-diol **34** (0.106 mmol, 0.029 g) was dissolved in MeOH (2 mL) in a high-pressure hydrogenation vessel. Pd/C 10% (0.019 g) was then added. The vessel was installed in the reactor and, after 4 purges, the H_2 pressure was set to 50 psi. After 2 h, the reaction was stopped and the mixture was filtered on a Celite® pad. The filtrate was concentrated *in vacuo* and the crude product was purified by silica gel column chromatography (100% EtOAc), yielding **16** as a brownish solid in a 78% yield (0083 mmol, 0.015 g). ^{1}H NMR (400 MHz, CD_3OD): δ_H 6.96 (1H, d, J = 1.7), 6.79 (1H, dd, J = 8.2, 1.6), 6.76 (1H, d, J = 8.1), 4.60 (1H, t, J = 6.1), 3.85 (3H, s), 3.59 (2H, d, J = 6.2). ^{13}C NMR (101 MHz, CD_3OD): δ_C 148.8, 147.0, 134.8, 120.2, 115.9, 111.0, 75.8, 68.8, 56.3. IR (NaCl): ν_{max} 3341, 2933, 1604, 1518, 1274, 1153, 1126, 1078, 1031, 877 cm^{-1}. HRMS (ESI-TOF, m/z): calcd for $C_9H_{11}O_3$ (M-H_2O+H)$^+$ = 167.0703, found 167.0713. This compound has been also previously reported.[56]

*6.1.3.9. 1-(3-Hydroxy-4-methoxyphenyl)ethane-1,2-diol (**17**).* 1-(3-Hydroxy-4-methoxyphenyl)ethane-1,2-diol **17** was prepared using the same procedure described above for **16**, using **35** (0.106 mmol, 0.029 g). Product **17** was obtained as a brownish solid in 61% yield (0.065 mmol, 0.012 g). mp = 87–91 °C. ^{1}H NMR (500 MHz, CD_3OD): δ_H 6.84 (1H, d, J = 8.3), 6.81 (1H, d, J = 2.0), 6.76 (1H, dd, J = 8.3, 2.0), 4.53 (1H, t, J = 6.1), 3.79 (3H, s), 3.54–3.52 (2H, m). ^{13}C NMR (125 MHz, CD_3OD): δ_C 147.1, 146.0, 134.8, 117.4, 113.1, 111.1, 74.2, 67.3, 55.0. IR (NaCl): ν_{max} 3347, 2935, 1594, 1512, 1440, 1273, 1219, 1130, 1025, 877, 762 cm^{-1}. HRMS (ESI-TOF, m/z): calcd for $C_9H_{11}O_3$ (M-H_2O+H)$^+$ = 167.0703, found 167.0716. This compound has been also previously reported.[55]

*6.1.3.10. 1-(4-Benzyloxy-3-methoxyphenyl)-2-(tert-butyldimethylsilyloxy)ethanol (**36**).* At room temperature, **34** (3.26 mmol, 0.891 g), *tert*-butyldimethylsilyl chloride (3.58 mmol, 0.538 g) and DMAP (0.06 mmol, 0.024 g) were dissolved in CH_2Cl_2 (7 mL) in an oven-dried flask under argon. Freshly distilled Et_3N was added (3.58 mmol, 0.500 mL) and the mixture was stirred for 16 h at room temperature under argon. The solution was then diluted with CH_2Cl_2, washed with water, washed with a saturated NH_4Cl solution, dried with Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography (29:70:1 EtOAc/hexanes/Et_3N), yielding **36** as a transparent oil in a 42% yield (1.36 mmol, 0.531 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.49–7.22 (5H, m), 6.99 (1H, d, J = 1.9), 6.86 (1H, d, J = 8.2), 6.82 (1H, dd, J = 8.2, 1.9), 5.16 (2H, s),

4.69 (1H, dd, J = 8.6, 2.8), 3.92 (3H, s), 3.74 (1H, dd, J = 10.1, 3.6), 3.55 (1H, dd, J = 10.1, 8.7), 2.97 (1H, d, J = 1.7), 0.93 (9H, s, J = 3.0), 0.08 (6H, d, J = 0.9). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 149.7, 147.7, 137.2, 133.5, 128.5, 127.8, 127.2, 118.5, 113.9, 109.9, 74.1, 71.1, 68.9, 56.0, 25.9, 18.3, −5.3, −5.4. IR (ATR, ZnSe): ν_{max} 3501, 2927, 2854, 1510, 1462, 1251, 1103, 1004, 833, 774, 694 cm^{-1}. HRMS (ESI-TOF, m/z): calcd for $C_{22}H_{31}O_3Si$ (M-H_2O +H)$^+$ = 371.2037, found 371.2041.

*6.1.3.11. 1-(3-Benzyloxy-4-methoxyphenyl)-2-(tert-butyldimethyl-silyloxy)ethanol (**37**).* 1-(3-Benzyloxy-4-methoxyphenyl)-2-(*tert*-butyldimethyl-silyloxy)ethanol **37** was prepared using the same procedure described above for **36**, using **35** (17.7 mmol, 4.85 g). Product **37** was obtained as a yellowish solid in 76% yield (13.5 mmol, 5.21 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.48–7.28 (5H, m), 6.98–6. 86 (3H, m), 5.16 (2H, s), 4.65 (1H, dd, J = 8.8, 3.6), 3.87 (3H, s), 3.66 (1H, dd, J = 3.6, 10.3), 3.46 (1H, dd, J = 8.8, 10.3), 0.92 (9H, s), 0.07 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 149.6, 148.3, 137.4, 133.0, 128.8, 128.1, 127.8, 119.4, 112.5, 111.8, 74.3, 71.3, 69.2, 56.3, 26.2, 18.6, −5.1. IR (NaCl): ν_{max} 3487, 2953, 2928, 2857, 1516, 1259, 1136, 1107, 1026, 837, 778 cm^{-1}. HRMS (ESI-TOF, m/z): calcd for $C_{22}H_{31}O_3Si$ (M-H_2O +H)$^+$ = 371.2037, found 371.2044.

*6.1.3.12. 1-(4-Benzyloxy-3-methoxyphenyl)-2-(tert-butyl-dimethyl-silyloxy)ethanone (**38**).* At room temperature, **36** (1.05 mmol, 0407 g) was dissolved in anhydrous CH_2Cl_2 (58 mL) in an oven-dried three-neck flask under argon. The temperature was cooled to 0 °C and the Dess-Martin periodinane (2.09 mmol, 0.894 g) was added. The mixture was stirred at 0 °C for 1 h or until completion was observed by TLC (30:69:1 EtOAc/hexanes/Et_3N). The solution was then diluted with CH_2Cl_2 (50 mL) and 50 mL of a solution 50% $NaHSO_3$. The organic layer was extracted, washed with saturated $NaHCO_3$, dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified with silica gel column chromatography (30:70 EtOAc/hexanes), giving **38** as a white solid in a 94% yield (0.95 mmol, 0.277 g). mp = 48–55 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.58 (1H, d, J = 2.0), 7.51 (1H, dd, J = 8.4, 2.0), 7.46–7.30 (5H, m), 6.91 (1H, d, J = 8.4), 5.22 (2H, s), 4.85 (2H, s), 3.94 (3H, s), 0.95 (9H, s), 0.14 (6H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 195.9, 152.7, 149.8, 136.4, 128.6, 128.0, 127.2, 122.2, 112.7, 111.4, 71.0, 67.3, 56.1, 25.8, 18.4, −5.3. IR (ATR, ZnSe): ν_{max} 2927, 2854, 1691, 1584, 1509, 1251, 1163, 1014, 880, 776, 698 cm^{-1}. HRMS (ESI-TOF, m/z): calcd for $C_{22}H_{31}O_4Si$ (M+H)$^+$ = 387.1986, found 387.1996.

*6.1.3.13. 1-(3-Benzyloxy-4-methoxyphenyl)-2-(tert-butyl-dimethyl-silyloxy)ethanone (**39**).* 1-(3-benzyloxy-4-methoxyphenyl)-2-(*tert*-butyl-dimethyl-silyloxy)ethanone **39** was prepared using the same procedure described above for **38**, using **37** (0.820 mmol, 0.318 g). Product **39** was obtained as a yellowish solid in a 87% yield (0.713 mmol, 0.277 g). mp = 39–47 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.60–7.56 (2H, m), 7.48–7.29 (5H, m), 6.90 (2H, d, J = 8.9), 5.18 (2H, s), 4.84 (2H, s), 3.94 (3H, s), 0.93 (9H, s), 0.12 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 196.1, 154.3, 148.4, 136.7, 128.9, 128.3, 128.1, 127.8, 122.9, 113.0, 110.7, 71.2, 67.4, 56.3, 26.1, 18.8, −5.1. IR (NaCl): ν_{max} 2953, 2929, 2856, 1694, 1595, 1516, 1426, 1267, 1136, 1022, 838, 778 cm^{-1}. HRMS (ESI-TOF, m/z): calcd for $C_{22}H_{31}O_4Si$ (M+H)$^+$ = 387.1986, found 387.2017.

*6.1.3.14. 1-(4-Hydroxy-3-methoxyphenyl)-2-hydroxyethanone (**18**).* 1-(4-Benzyloxy-3-methoxyphenyl)-2-(*tert*-butyl-dimethyl-silyloxy)ethanone **38** (0.100 mmol, 0.039 g) was dissolved in MeOH (3 mL) in a high-pressure hydrogenation vessel. Pd/C 10% (0.020 g) was then added. The vessel was installed in the reactor and, after 4 purges, the H_2 pressure was set to 30 psi. After 16 h, the reaction was stopped and filtered on a Celite® pad. The filtrate was concentrated *in vacuo* and the crude product was dissolved in THF (2 mL). The solution was cooled to 0 °C and TBAF (1 N in THF, 0.150 mmol, 0.150 mL) was added dropwise. After the addition, the reaction was allowed to warm to room temperature and stirred for 1 h or until completion was shown by TLC (100% EtOAc). Water was then added to the mixture and three extractions with EtOAc were performed. The organic layers were combined, washed with brine, dried with $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (100% EtOAc), giving **18** as a brownish solid in a 60% yield (0.060 mmol, 0.011 g). mp = 112–123 °C. ^{1}H NMR (500 MHz, CD_3OD): δ_H 7.53 (1H, d, J = 2.0), 7.50 (1H, dd, J = 8.2, 2.0), 6.87 (1H, d, J = 8.2), 4.84 (2H, s), 3.91 (3H, s). ^{13}C NMR (125 MHz, CD_3OD): δ_C 197.1, 152.3, 147.8, 126.2, 122.4, 114.6, 110.0, 64.5, 55.0. IR (NaCl): ν_{max} 3339, 2924, 2852, 1674, 1592, 1517, 1276, 1205, 1032, 875 cm^{-1}. HRMS (ESI-TOF, m/z): calcd for $C_9H_{11}O_4$ (M+H)$^+$ = 183.0652, found 183.0652. This compound has been also previously reported.[57]

*6.1.3.15. 1-(3-Hydroxy-4-methoxyphenyl)-2-hydroxyethanone (**19**).* 1-(3-Hydroxy-4-methoxyphenyl)-2-hydroxyethanone **19** was prepared using the same procedure described above for **18**, using **39** (0.258 mmol, 0.100 g). Product **19** was obtained as a brownish solid in 38% yield (0.099 mmol, 0.018 g). mp = 125–126 °C. ^{1}H NMR (500 MHz, CD_3OD): δ_H 7.50 (1H, dd, J = 8.4, 2.1), 7.40 (1H, d, J = 2.1), 7.01 (1H, d, J = 8.5), 4.82 (2H, s), 3.93 (3H, s). ^{13}C NMR (125 MHz, CD_3OD): δ_C 197.4, 152.6, 146.5, 120.6, 113.6, 110.5, 64.5, 55.0. IR (NaCl): ν_{max} 3422, 2922, 2852, 1666, 1586, 1514, 1276, 887 cm^{-1}. HRMS (ESI-TOF, m/z): calcd for $C_9H_{11}O_4$ (M+H)$^+$ = 183.0652, found 183.0648.

6.1.4. Preparation of cross-coupling partners for the synthesis of isoquebecol

*6.1.4.1. Ethyl (3-benzyloxy-4-methoxyphenyl)(oxo)acetate (**40**).* At room temperature, **33** (1.58 mmol, 0.50 g) was dissolved in anhydrous CH_2Cl_2 (86 mL) in an oven-dried three-neck flask under argon. The temperature was cooled to 0 °C and the Dess-Martin periodinane (3.16 mmol, 1.34 g) was added. The mixture was stirred at 0 °C until completion was observed by TLC (50:50 EtOAc/hexanes). The solution was then diluted with CH_2Cl_2 and 100 mL of a solution 10% $Na_2S_2O_3$ in saturated $NaHCO_3$ was added. The mixture was stirred for 15 min and the organic layer was extracted, dried with $MgSO_4$ and concentrated *in vacuo*. The crude product (yellowish solid) was purified by silica gel column chromatography (50:50 EtOAc/hexanes), yielding **40** as a brownish solid in a 93% yield (1.47 mmol, 0.462 g). mp = 54–60 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.67–7.61 (2H, m), 7.48–7.29 (5H, m), 6.94 (1H, d, J = 8.4), 5.19 (1H, s), 4.41 (2H, q, J = 7.1), 3.88 (3H, s), 1.40 (3H, t, J = 7.2). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 185.1, 164.4, 155.8, 148.7, 136.4, 128.9, 128.4, 127.8, 126.6, 125.7, 113.4, 110.9, 71.2, 62.4, 56.5, 14.4. IR (ATR, ZnSe): ν_{max} 2932, 1723, 1662, 1578, 1508, 1430, 1261, 1229, 1141, 1042, 877, 698 cm^{-1}. HRMS (ESI-TOF, m/z): calcd for $C_{18}H_{19}O_5$ (M+H)$^+$ = 315.1227, found 315.1238.

*6.1.4.2. Ethyl 3,3-dibromo-2-(3-benzyloxy-4-methoxyphenyl)propenoate (**41**).* PPh_3 (3.11 mmol, 0.818 g) was dissolved in anhydrous CH_2Cl_2 (2 mL) in an oven-dried three-neck flask under argon. The temperature was cooled to 0 °C and CBr_4 (1.56 mmol, 0.516 g) in solution in 1.5 mL of anhydrous CH_2Cl_2 was added dropwise. The mixture was stirred at 0 °C for 30 min and a solution of **40** (0.777 mmol, 0.244 g) in 1.5 mL of anhydrous CH_2Cl_2 was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 12 h or until completion was observed by TLC (20:80 Et_2O/hexanes). Pentane (50 mL) was added to the mixture, which was stirred for 30 min. After filtration, the solvent was evaporated *in vacuo* and the crude product was puri-

fied by silica gel column chromatography (20:80 Et_2O/hexanes), giving **41** as a white solid in a 72% yield (0.556 mmol, 0.261 g). mp = 66–69 °C. ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.46–7.26 (5H, m), 6.99 (1H, dd, J = 8.3, 2.1), 6.95 (1H, d, J = 2.0), 6.88 (1H, d, J = 8.4), 5.17 (2H, s), 4.23 (2H, q, J = 7.1), 3.90 (3H, s), 1.28 (3H, t, J = 7.1). ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 166.2, 150.2, 147.7, 141.1, 136.7, 128.6, 127.9, 127.6, 127.3, 121.4, 114.0, 111.3, 94.2, 70.9, 62.2, 55.9, 14.0. IR (ATR, ZnSe): ν_{max} 1716, 1509, 1245, 1217, 1191, 1164, 996, 872, 727, 700 cm^{-1}. HRMS (ESI-TOF, m/z): calcd for $C_{19}H_{22}Br_2NO_4$ $(M+NH_4)^+$ = 485.9910, found 485.9890.

*6.1.4.3. 3-Benzyloxy-4-methoxyphenylboronic acid (**42**).* 4-Bromo-3-methoxyphenol **25** (0.682 mmol, 0.200 g) was dissolved in freshly distilled THF (7 mL) in an oven-dried three-neck flask under argon. The temperature was cooled to −78 °C and the solution was stirred for 30 min before dropwise addition of *n*-BuLi (1.6 N in hexanes, 0.752 mmol, 0.470 mL). Once the addition of *n*-BuLi was completed, the mixture was stirred for another 30 min at −78 °C before the dropwise addition of trimethyl borate (2.05 mmol, 0.233 mL). The reaction mixture was allowed to warm to room temperature and stirred for 5 h. The temperature was cooled to −20 °C and HCl 1 N was slowly added to reach pH = 2–3. The reaction mixture was allowed to warm to room temperature and extracted three times with EtOAc. The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo* until precipitation occurred. Hexanes was then added to maximize precipitation. The solution was filtered and the solid was dried under vacuum. The precipitation/filtration procedure was repeated twice, giving **42** as a white solid in an 80% yield (0.543 mmol, 0.140 g). mp = 135–155 °C. ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.80 (1H, d, J = 8.0), 7.70 (1H, s), 7.58–7.29 (6H, m), 7.04 (1H, d, J = 8.0), 5.28 (2H, s), 3.99 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 153.6, 147.7, 137.2, 130.3, 128.6, 127.9, 127.5, 120.5, 111.0, 71.3, 55.9. ^{11}B NMR (160 MHz, $CDCl_3$): δ_B 28.6. IR (ATR, ZnSe): ν_{max} 1595, 1410, 1319, 1250, 1216, 1179, 1133, 1018, 740, 710 cm^{-1}. HRMS (ESI-TOF, m/z): calcd for $C_{14}H_{14}BO_3$ $(M-H_2O+H)^+$ = 241.1031, found 241.1049. This compound has been also previously reported.[58]

6.1.5. Double Suzuki-Miyaura coupling in aqueous conditions

Complete coupling results regarding the optimisation work of this reaction are presented in the Supplementary data.

*6.1.5.1. Ethyl 2,3,3-tris(3-benzyloxy-4-methoxyphenyl)propenoate (**43**).* Ethyl 3,3-dibromo-2-(3-benzyloxy-4-methoxyphenyl)propenoate **41** (0.184 mmol, 0.087 g), 4-benzyloxy-3-methoxyphenylboronic acid **42** (0.461 mmol, 0.119 g), $Pd_2(dba)_3$ (0.007 mmol, 0.007 g) and 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos ligand) (0.015 mmol, 0.006 g) were poured in an oven-dried three-neck flask under argon. Three vacuum/argon purges were made and 0.400 mL of a DL-α-tocopherol methoxypolyethylene glycol succinate solution (5 wt.% in H_2O) was added [commercially available from Sigma-Aldrich: TPGS-750-M (product 763918)]. Et_3N was also added (0.552 mmol, 0.077 mL) and the suspension was vigorously stirred at room temperature for 5 min and then at 60 °C for 20 h. After cooling to room temperature, brine was added and the reaction mixture was extracted three times with EtOAc. The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (30:70 EtOAc/hexanes), yielding **43** as an orange solid in a 69% yield (0.127 mmol, 0.094 g). ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.39–7.23 (15H, m), 6.86 (1H, dd, J = 8.3, 2.0), 6.81 (1H, d, J = 8.3), 6.75 (1H, d, J = 2.0), 6.73 (1H, d, J = 8.4), 6.67 (1H, dd, J = 8.3, 2.0), 6.65–6.61 (2H, m), 6.54–6.50 (2H, m), 5.00 (2H, s), 4.83 (2H, s), 4.74 (2H, s), 3.97 (2H, q, J = 7.1), 3.91 (3H, s), 3.84 (6H, bs), 0.99 (3H, t, J = 7.1). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 171.0, 149.6, 149.1, 148.8, 147.8, 147.6, 147.3, 144.5, 137.0, 136.9, 136.8, 135.1, 133.1, 131.6, 130.6, 128.4, 128.4, 128.4, 127.8, 127.4, 127.2, 127.2, 124.4, 122.9, 122.4, 116.7, 115.5, 115.0, 111.4, 111.0, 110.8, 70.9, 70.8, 70.7, 60.8, 56.0, 55.9, 55.8, 13.9. IR (NaCl): ν_{max} 2955, 2927, 1713, 1600 1513, 1247, 1138, 1023, 736, 697 cm^{-1}. HRMS (ESI-TOF, m/z): calcd for $C_{47}H_{45}O_8$ $(M+H)^+$ = 737.3109, found 737.3137.

6.1.5.2. Gram scale preparation of ethyl 2,3,3-tris(4-benzyloxy-3-methoxyphenyl)propenoate (46). Ethyl 3,3-dibromo-2-(4-benzyloxy-3-methoxyphenyl)propenoate **44** (3.19 mmol, 1.5 g), 4-benzyloxy-3-methoxyphenylboronic acid **45** (7.97 mmol, 2.06 g), $Pd_2(dba)_3$ (0.128 mmol, 0.117 g) and 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos ligand) (0.255 mmol, 0.105 g) were poured in an oven-dried three-neck flask under argon. Three vacuum/argon purges were made and 10 mL of a DL-α-tocopherol methoxypolyethylene glycol succinate solution (5 wt.% in H_2O) was added [commercially available from Sigma-Aldrich: TPGS-750-M (product 763918)]. Et_3N was also added (9.57 mmol, 1.35 mL) and the suspension was vigorously stirred at room temperature for 5 min and then at 60 °C for 15 h. After cooling to room temperature, brine was added and the reaction mixture was extracted three times with EtOAc. The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (30:70 EtOAc/hexanes), yielding **46** as an orange solid in 75% yield (2.39 mmol, 1.76 g). mp = decomp. ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.48–7.30 (15H, m), 6.86–6.52 (9H, m), 5.19 (2H, s), 5.13 (2H, s), 5.11 (2H, s), 4.04 (2H, q, J = 7.07), 3.82 (3H, s), 3.56 (3H, s), 3.50 (3H, s), 0.99 (3H, t, J = 7.16). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 171.2, 149.1, 148.2, 147.7, 147.4, 144.8, 137.0, 136.9, 135.7, 133.7, 131.9, 131.1, 128.6, 127.3, 127.9, 124.0, 122.1, 115.0, 113.9, 113.5, 113.2, 113.0, 70.8, 61.0, 56.0, 55.7, 13.9. IR (NaCl): ν_{max} 1711, 1511, 1463, 1454, 1262, 1236, 1139, 1129, 1027, 735 cm^{-1}. HRMS (ESI-TOF, m/z): calcd for $C_{47}H_{45}O_8$ $(M+H)^+$ = 731.3109, found 731.3126. We have also previously reported the preparation of this compound in toluene.[36]

6.1.6. Preparation of Class C compounds

We have previously reported the synthesis of triarylethene compound **7**,[36] as well as **9**.[40]

*6.1.6.1. Ethyl 2,3,3-tris(3-hydroxy-4-methoxyphenyl)propenoate (**8**).* 2,3,3-Tris(3-benzyloxy-4-methoxyphenyl)propenoate **43** (0.028 mmol, 0.021 g) was dissolved in EtOAc (5 mL) in a high-pressure hydrogenation vessel. Pd/C 10% (0.01 g) was then added. The vessel was installed in the reactor and, after 4 purges, the H_2 pressure was set to 50 psi at room temperature. After 20 h, the reaction was stopped and the mixture was filtered on a Celite® pad. The filtrate was concentrated *in vacuo* and the crude product was purified by silica gel column chromatography (50:50 EtOAc/hexanes), giving **8** as brownish solid in a 61% yield (0.017 mmol, 0.008 g). ^1H NMR (500 MHz, $CDCl_3$): δ_H 6.81–6.76 (3H, m), 6.71 (1H, d, J = 2.1), 6.67 (1H, d, J = 8.4), 6.63–6.59 (3H, m), 6.54 (1H, dd, J = 8.3, 2.1), 5.53 (1H, s), 5.47 (1H, s), 5.42 (1H, s), 4.06 (2H, q, J = 7.1), 3.90 (3H, s), 3.84 (3H, s), 3.83 (3H, s), 1.05 (3H, t, J = 7.1). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 170.9, 146.4, 146.0, 145.7, 145.1, 145.1, 144.8, 144.3, 136.1, 134.0, 131.9, 131.2, 123.3, 122.0, 121.3, 117.2, 115.9, 115.7, 110.3, 109.9, 109.8, 60.8, 55.9, 55.8, 55.8, 13.9. IR (NaCl): ν_{max} 3434, 2932, 2842, 1706, 1583, 1509, 1441, 1274, 1247, 1130, 1025, 734 cm^{-1}. HRMS (ESI-TOF, m/z): calcd for $C_{26}H_{27}O_8$ $(M+H)^+$ = 467.1700, found 467.1782.

*6.1.7. Preparation of Class D compounds: isoquebecol **2**, 2.3.3-triphenylpropanol **3** and precursors*

The preparation of **1** and **4** has been previously reported by our group.[36]

*6.1.7.1. Ethyl 2,3,3-tris(3-hydroxy-4-methoxyphenyl)propanoate (**5**).* Ethyl 2,3,3-tris(3-benzyloxy-4-methoxyphenyl)propenoate **43** (0.068 mmol, 0.05 g) was dissolved in freshly distilled MeOH (5 mL) in a high-pressure hydrogenation vessel. Pd/C 10% (0.03 g) was then added. The vessel was installed in the reactor and, after 4 purges, the H_2 pressure was set to 286 psi and the temperature to 50 °C. After 24 h, the reaction was stopped. The mixture was filtered on a Celite® pad. The filtrate was concentrated *in vacuo* and the crude product was purified by silica gel column chromatography (60:40 EtOAc/hexanes), giving **5** as a yellowish solid in a 66% yield (0.045 mmol, 0.017 g). ^{1}H NMR (500 MHz, CD_3OD): δ_H 6.87–6.82 (3H, m), 6.81 (1H, d, J = 8.2), 6.72 (1H, dd, J = 8.3, 1.9), 6.69 (1H, d, J = 8.3), 6.61 (1H, d, J = 2.0), 6.59 (1H, d, J = 8.3), 6.53 (1H, dd, J = 8.3, 2.1), 4.37 (1H, d, J = 12.4), 4.23 (1H, d, J = 12.3), 3.97–3.85 (2H, m), 3.79 (3H, s), 3.74 (3H, s), 3.68 (3H, s), 1.01 (3H, t, J = 7.1). ^{13}C NMR (125 MHz, CD_3OD): δ_C 173.7, 146.7, 146.2, 145.9, 145.8, 145.8, 145.5, 136.6, 135.3, 130.1, 120.1, 119.4, 118.5, 115.1, 114.9, 114.7, 111.2, 110.9, 72.1, 60.3, 56.3, 55.0, 54.8, 53.3, 12.8. IR (NaCl): ν_{max} 3445, 2949, 1718, 1593, 1510, 1439, 1274, 1131, 1026, 762 cm^{-1}. HRMS (ESI-TOF, m/z): calcd for $C_{26}H_{32}NO_8$ $(M+NH_4)^+$ = 486.2122, found 486.2117.

*6.1.7.2. Ethyl 2,3,3-triphenylpropanoate (**6**).* This compound was prepared with the same procedure described for **5**, using **9** (0.487 mmol, 0.160 g). Product **6** was obtained as a white solid in a 94% yield (0.458 mmol, 0.152 g). mp = 110–114 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.46 (2H, dd, J = 8.3, 1.1), 7.36–7.29 (4H, m), 7.24–7.14 (4H, m), 7.12–7.06 (4H, m), 7.05–6.99 (1H, m), 4.73 (1H, d, J = 12.3), 4.47 (1H, d, J = 12.3), 4.04–3.87 (2H, m), 1.01 (3H, t, J = 7.1). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 172.7, 142.9, 141.6, 137.1, 128.6, 128.6, 128.3, 128.3, 128.2, 127.8, 127.3, 126.6, 126.2, 60.7, 56.9, 54.9, 13.9. IR (NaCl): ν_{max} 3029, 2929, 1721, 1498, 1453, 1370, 1299, 1171, 1159, 1095, 697 cm^{-1}. HRMS (ESI-TOF, m/z): calcd for $C_{23}H_{23}O_2$ $(M+H)^+$ = 331.1693, found 331.1703. This compound has been also previously reported.[59]

*6.1.7.3. Preparation of isoquebecol [2,3,3-tris(3-hydroxy-4-methoxyphenyl)propan-1-ol] (**2**).* Ethyl 2,3,3-tris(3-hydroxy-4-methoxyphenyl)propanoate **5** (0.03 mmol, 0.014 g) was dissolved in freshly distilled anhydrous THF (5 mL) in an oven-dried three-neck flask under argon. The temperature was cooled to 0 °C and $LiAlH_4$ (1 N in THF, 0.358 mmol, 0.358 mL) was added dropwise. The mixture was allowed to warm to room temperature and the reaction was refluxed for 13 h. The reaction mixture was cooled to 0 °C and HCl 1 N was added dropwise until pH 2–3. The mixture was extracted three times with EtOAc. The organic layers were combined, dried with $MgSO_4$, concentrated *in vacuo* and purified by silica gel column chromatography (70:30 EtOAc/hexanes), yielding isoquebecol **2** as a white solid in a 31% yield (0.009 mmol, 0.004 g). This reaction was done only once, due to the very small quantity of **5**. The low yield is attributed to accidental loss of solvent during overnight heating. ^{1}H NMR (500 MHz, acetone-d_6): δ_H 7.44 (1H, s), 7.20 (2H, s), 6.97 (1H, d, J = 2.2), 6.91 (1H, dd, J = 8.3, 2.2), 6.87–6.84 (2H, m), 6.81 (1H, d, J = 2.2), 6.76 (1H, dd, J = 8.3, 2.1), 6.73–6.70 (2H, m), 6.63 (1H, d, J = 8.3), 4.19 (1H, d, J = 11.8), 3.80 (3H, s), 3.74 (3H, s), 3.68 (3H, s), 3.55 (5H, m). ^{13}C NMR (125 MHz, acetone-d_6): δ_C 147.3, 146.7, 146.6, 146.3, 146.0, 139.2, 138.5, 136.6, 132.7, 129.5, 121.2, 120.2, 119.8, 116.6, 116.1, 115.5, 112.4, 111.8, 111.6, 66.5, 56.3, 56.0, 53.0, 52.2. IR (NaCl): ν_{max} 2929, 1592, 1509, 1439, 1270, 1130, 1027 cm^{-1}. HRMS (ESI-TOF, m/z): calcd for $C_{24}H_{30}NO_7$ $(M+NH_4)^+$ = 444.2017, found 444.2022. COSY and HSQC NMR studies were also performed (see supplementary data).

*6.1.7.4. Preparation of 2,3,3-triphenylpropanol (**3**).* Ethyl 2,3,3-triphenylpropanoate **6** (0.242 mmol, 0.080 g) was dissolved in freshly distilled anhydrous THF (4 mL) in an oven-dried three-neck flask under argon. The temperature was cooled to 0 °C and $LiAlH_4$ (1 N in THF, 0.363 mmol, 0.363 mL) was added dropwise. The mixture was allowed to warm room temperature and the reaction was heated at 50 °C for 15 h. The reaction mixture was cooled to 0 °C and HCl 1 N was added dropwise until pH 2–3. The mixture was extracted three times with EtOAc. The organic layers were combined, dried with $MgSO_4$, concentrated *in vacuo* and purified by silica gel column chromatography (50:50 EtOAc/hexanes), yielding **3** as a gummy white solid in a 47% yield (0.114 mmol, 0.033 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.47–7.43 (2H, m), 7.37–7.31 (3H, m), 7.28–7.17 (6H, m), 7.15–7.07 (3H, m), 7.02–6.97 (1H, m), 4.36 (1H, d, J = 11.3), 3.76–3.64 (3H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 143.4, 142.9, 140.8, 128.8, 128.8, 128.5, 128.3, 128.2, 128.0, 126.7, 126.6, 125.9, 66.1, 53.7, 52.3. IR (NaCl): ν_{max} 3559, 3417, 3085, 3061, 2925, 1600, 1451, 1494, 1060, 1032, 747, 700 cm^{-1}. HRMS (ESI-TOF, m/z): calcd for $C_{21}H_{24}NO$ $(M+NH_4)^+$ = 306.1852, found 306.1905.

6.2. Investigation of biological activity of studied compounds

6.2.1. Preparation of macrophage cells

U937 human monocytes (ATCC CRL-1593.2) from the American Type Culture Collection (Manassas, VA, USA) were cultivated in RPMI-1640 supplemented with 10% fetal bovine serum (FBS) and 100 μg/mL of penicillin G/streptomycin at 37 °C in a 5% CO_2 atmosphere. The monocytes (2.5×10^5 cells/mL) were then incubated in RPMI-10% FBS containing 100 ng/mL of phorbol myristic acid [PMA, Sigma-Aldrich] for 48 h to induce differentiation into adherent macrophage-like cells. Adherent macrophage-like cells were harvested by scraping and were centrifuged at 1200*g* for 5 min. The cells were washed, suspended in RPMI-1% FBS at a concentration of 1×10^6 cells/mL, seeded into the wells of a 12-well microplate (1×10^6 cells/well) and incubated overnight at 37 °C in a 5% CO_2 atmosphere, prior of their use for the two following sets of analysis.

6.2.2. Evaluation of cytotoxicity

The above-mentioned prepared macrophage-like cells were treated with 2-fold serial dilutions of the compounds **1**–**21** (1000–7.81 μM). After 24 h, cell viability is determined with an MTT [3-(4,5-diethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay, following the manufacturer's protocol (Roche Diagnostics, Mannheim, Germany). Detailed results of those assays are presented in the Supplementary data.

6.2.3. Evaluation of IL-6 secretion by LPS-stimulated macrophages

The above-mentioned macrophage-like prepared cells were treated (2 h) with non-cytotoxic concentrations of compounds **1**–**21**, prior to being stimulated with *Aggregatibacter actinomycetemcomitans* ATCC 29522 lipopolysaccharide (LPS) at a final concentration of 1 μg/mL. After a 24 h incubation at 37 °C in a 5% CO_2 atmosphere, the culture medium supernatants were collected and stored at −20 °C until used. Cells incubated in a culture medium with or without the compounds and stimulated or not with LPS were used as controls. Enzyme-linked immunosorbent assay (ELISA) kits (eBioscience Inc., San Diego, CA, USA) were used to quantify IL-6 concentrations according to the manufacturer's protocols. Two independent experiments were performed in triplicate and a representative set of data (means ± standard deviations) was used to determine the activity of each compound. Detailed results of those assays are presented in the Supplementary data.

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A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2017.01.050.

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