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Hypervalent iodine-mediated oxygenative phenol dearomatization reactions

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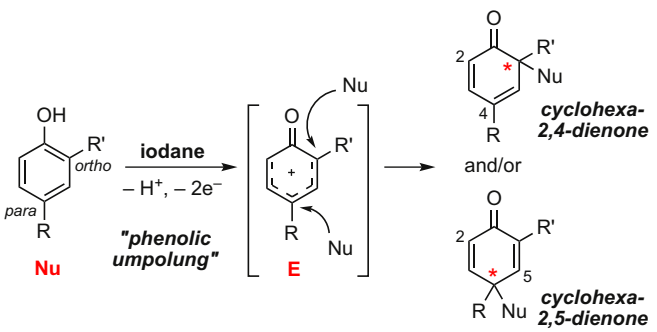
ABSTRACT

Both λ^3- and λ^5-iodanes have proven to be useful reagents in the oxygenative dearomatization of phenols, and exploitations of their chemistry in the conception of both substrate- and reagent-controlled asymmetric variants of such a transformation of great value for natural product synthesis have shown evident signs of success. Moreover, the use of stabilized IBX (i.e., SIBX) in our methodology for *O*-demethylation of 2-methoxyphenols, which relies on the same key oxygenating dearomatization event, is reported here to be much more efficacious than that of IBX itself in the chemoselective one-step conversion of homovanillyl alcohol into hydroxytyrosol, and bergenin into norbergenin.

1. Introduction

The chemistry of hypervalent (or polyvalent) iodine organic compounds, also referred to as iodanes, has experienced an impressive development starting from the early 1990s. Since 1992, four books[1] and numerous review articles[2] have been dedicated to the chemistry of hypervalent iodine-containing organic reagents and their applications in organic synthesis. This increasing interest essentially stemmed from the very useful oxidizing properties expressed by these iodanes, both as dehydrogenating and oxygenating reagents, combined with the fact that their utilization constitutes an environmentally benign alternative to that of heavy metal-based oxidizing reagents. Iodine(III) and iodine(V) derivatives, i.e., λ^3-iodanes and λ^5-iodanes, respectively, are now routinely used in organic synthesis for various selective oxidative transformations of complex organic molecules. Among the several areas of hypervalent iodine chemistry that have recently been the topic of intensive investigations, one can cite efforts aimed at expanding the scope of reactions mediated by 2-iodoxybenzoic acid (IBX) and related λ^5-iodane reagents,[3] the development of polymer-supported and recyclable λ^3- and λ^5-iodanes,[4] the development of catalytic applications of iodanes, together with the design of chiral iodane-based systems for asymmetric induction purposes,[5] and the emergence of iodane-mediated oxidative phenol dearomatization as a tactic of choice in the total synthesis of many natural products of different metabolic origins.

In this latter context, our own interest in the chemistry of cyclohexadienones as polyfunctionalized intermediates for the construction of complex natural products led us to contemplate early on the use of iodanes as mild and efficient tools to convert phenolic precursors into cyclohexa-2,4- or -2,5-dienones (Scheme 1).[6]



Scheme 1. Iodane-mediated (oxygenative) dearomatization of phenols into cyclohexadienones.

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Such transformations rely on the electrophilic character of the hypervalent iodine center and conceptually impose a reactivity switch to phenols from being nucleophiles to becoming electrophiles. This 'phenolic umpolung', also more generally first referred to as 'aromatic ring umpolung' by Canesi and co-workers,[7] then enables attack of nucleophiles at the *ortho*- or *para*-carbon centers of the starting phenol thus oxidatively activated (Scheme 1).[6] Dearomatization ensues when the reacting phenolic carbon center already bears a substituent, hence generating a possibly chiral sp^3-hybridized carbon center. Controlling the configuration of such a carbon center by iodane-based asymmetric induction means currently remains the focus of sustained efforts in several research groups worldwide, as it constitutes the last important challenge of the development of iodane-mediated phenol dearomatization reactions for organic synthesis. Besides this door open to stereoselective reactions, the duality of the reactivity expressed by phenolic species upon treatment with iodane reagents can also be exploited to transform them in remarkably useful chemo- and regioselective manners.

We wish to highlight herein some of our previous results and report previously unpublished and new observations from our investigations on iodane-mediated stereoselective oxygenative dearomatization of *ortho*-substituted phenols (see Scheme 1, Nu='oxygen') and on chemo/regioselective oxygenative *O*-demethylation of 2-methoxyphenols into catechols.[8]

2. Results and discussion

2.1. Substrate-controlled asymmetric phenol dearomatization

ortho-Quinone monoketals (**A**) and their *ortho*-quinol variants (**B**) are cyclohexa-2,4-dienone derivatives (Fig. 1) that have proven to be extremely useful in the construction of various complex natural product architectures.[6,9] Oxidative phenol dearomatization methods, and in particular those mediated by an iodane reagent, stand out among the most straightforward tactics to access these synthetically useful derivatives.[6,9] However, an ideal utilization of these cyclohexa-2,4-dienone derivatives in organic synthesis requires the stereocontrol of the sp^3-hybridized C-6 center newly created in the course of the dearomatization event. A first and obvious solution to this challenging task encompasses substrate-controlled preparations of chiral *ortho*-quinone monoketals and/or *ortho*-quinols in non-racemic form, but surprisingly, only a few examples have been reported so far.[10]

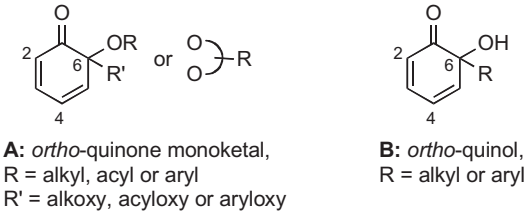
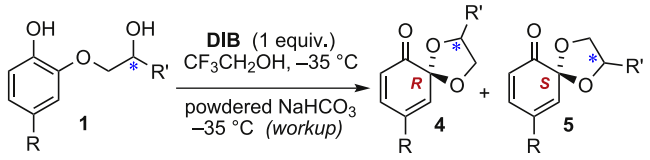


Figure 1. *ortho*-Quinone monoketal (**A**) and *ortho*-quinol (**B**) types of cyclohexa-2,4-dienone derivatives.

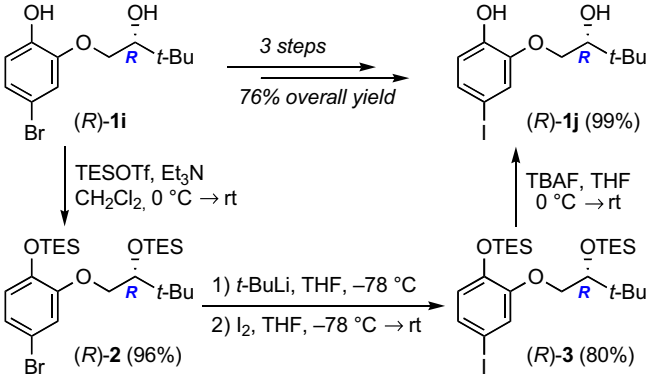
Our last contribution to the development of such substrate-controlled asymmetric preparations of *ortho*-quinone monoketals relied on the use of the λ^3-iodane (diacetoxyiodo)benzene (DIB), also referred to as phenyliodine(III) diacetate (PIDA).[8a] The starting phenols **1** bore a chiral ethanol unit *O*-tethered to the *ortho*-position of the phenolic ring (Table 1). These constructs were thus designed to permit their dearomatization into spiro-ketals of type **A** (see Fig. 1). A substituent was placed at the phenolic *para*-position to prevent or at least retard the self-dimerization of the dearomatized species through [4+2] cycloaddition events.[11] The substrates were prepared by a Williamson reaction between 5-substituted 2-benzyloxyphenols (for **1a–d** and **1f–i**) or, alternatively, 2-methoxymethylphenol (for **1e**) and enantiomerically enriched terminal epoxides generated by using the Jacobsen method.[8a] In the case of the phenolic alcohol **1j**, which was prepared in the aim of evaluating the influence of a larger halogen atom at the *para*-position on the extent of the undesired self-dimerization, a three-step sequence including a bromine exchange by iodine was implemented to transform efficiently **1i** into **1j** (Scheme 2). After silylation of (*R*)-**1i** with triethylsilyl triflate (TESOTf) in the presence of triethylamine to afford (*R*)-**2** (96% yield), a bromine/lithium exchange was performed upon treatment with *tert*-butyllithium at low temperature, and subsequent trapping with iodine furnished the iodobenzene intermediate (*R*)-**3** (80% yield), which was finally submitted to a tetrabutylammonium fluoride (TBAF)-mediated desilylation (99% yield) to afford pure (*R*)-**1j** in an overall yield of 76% (Scheme 2).

Table 1
DIB-mediated spiro-ketalization of phenolic alcohols **1** into *ortho*-quinone monoketals **4** and **5**



entry	1	R	R'	products[a]	dr[b]
1	(*R*)-**1a**	*t*-Bu	*t*-Bu	(*R*,*R*)-**4a**:(*R*,*S*)-**5a**	≥95:5
2	(*S*)-**1b**	*t*-Bu	*t*-Bu	(*S*,*R*)-**4b**:(*S*,*S*)-**5b**	≥5:95
3	(*R*)-**1c**	*t*-Bu	Et	(*R*,*R*)-**4c**:(*R*,*S*)-**5c**	60:40
4	(*S*)-**1d**	*t*-Bu	Et	(*S*,*R*)-**4d**:(*S*,*S*)-**5d**	40:60
5	(*S*)-**1e**	*i*-Pr	*t*-Bu	(*S*,*R*)-**4e**:(*S*,*S*)-**5e**	≥5:95
6	(*R*)-**1f**	OMe	*t*-Bu	(*R*,*R*)-**4f**:(*R*,*S*)-**5f**	≥95:5
7	(*S*)-**1g**	OMe	*t*-Bu	(*S*,*R*)-**4g**:(*S*,*S*)-**5g**	≥5:95
8	(*R*)-**1h**	OMe	*n*-$(CH_2)_9CH_3$	(*R*,*R*)-**4h**:(*R*,*S*)-**5h**	60:40
9	(*R*)-**1i**	Br	*t*-Bu	(*R*,*R*)-**4i**:(*R*,*S*)-**5i**[c]	≥95:5
10	(*R*)-**1j**	I	*t*-Bu	(*R*,*R*)-**4j**:(*R*,*S*)-**5j**[c]	90:10

[a] The products were isolated in quantitative combined yields.
[b] The diastereomeric ratios were determined by ^{1}H NMR spectroscopic analysis.
[c] Gradual [4+2] cyclodimerization was observed.



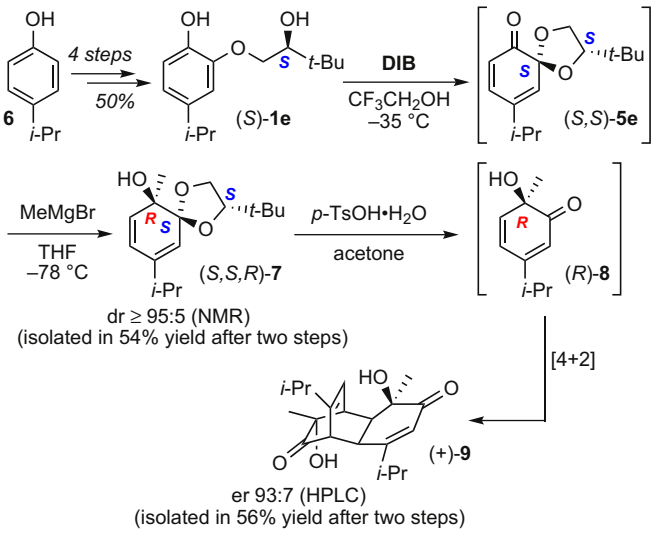
Scheme 2. Preparation of chiral phenolic alcohol **1j** from its brominated analogue **1i**.

The desired oxidative dearomatization of phenols **1** into *ortho*-

quinone monoketals **4** and **5** was then performed using the DIB reagent (Table 1). Our initial studies were carried out in CH_2Cl_2, at either room temperature or −78 °C, and furnished complex mixtures in which only undesired *ortho*-quinol acetate derivatives, resulting from the competitive attack of the acetoxy DIB ligands,[12] could be identified by ^{1}H NMR analysis. When pure dichloromethane was changed to solvent mixtures, such as CH_2Cl_2/CH_3CN (4:1) at −78 °C or CH_2Cl_2/CF_3CH_2OH (8:1) at −60 °C, the expected spiro-ketals were formed as evidenced by ^{1}H NMR detection of their diagnostic ethylenic signals, but with substantial amounts of impurities that could not be separated. These preliminary observations prompted us to further investigate the use of 2,2,2-trifluoroethanol (CF_3CH_2OH, TFE) as a polar and poorly nucleophilic solvent.[13] Reactions were thus performed in TFE at −35 °C, and worked up using saturated aqueous $NaHCO_3$, to give the expected spiro-ketals that could this time be further purified by column chromatography and isolated, albeit in moderate yields ranging from 20 to 50%. After extensive experimentations on both reaction and workup conditions, it was found that yields drastically improved when the use of DIB (1.0 equiv) in TFE (ca. 0.04 M) at −35 °C was followed by quenching of the released acetic acid with powdered $NaHCO_3$ at the same low temperature without addition of any water.[8a] All ten phenolic alcohols **1a**–**j** were thus successfully converted into the desired spiro-ketals **4** and **5**, which were isolated in a quantitative combined yield with an excellent level of purity through a simple filtration/evaporation procedure (Table 1). Although further purification of these products was not necessary before their use in subsequent reactions, they were separated by column chromatography for the characterization of each diastereomer, and their stereochemistry was unambiguously established by NOESY experiments.[8a]

Phenolic alcohols **1** with a *tert*-butyl group on the chiral sidechain (Table 1, entries 1, 2, 5–7, and 9) underwent a highly diastereoselective transformation, in contrast to those with an ethyl or *n*-decanyl group at the same position (Table 1, entries 3, 4, and 8). One can note that the iodide substrate **1j** bearing a *tert*-butyl substituent gave the expected *ortho*-quinone monoketals **4j**/**5j**, but with a surprising (slightly) lower diastereocontrol, especially when compared to the result obtained with its bromide counterpart **1i** (Table 1, entries 10 and 9). In all cases, the configuration of the starting alcohol dictated which isomer formed as the major diastereomer: reactions with enantiomers (*R*)-**1** and (*S*)-**1** furnished (*R*,*R*)-**4** and (*S*,*S*)-**5** as the major product, respectively. These *ortho*-quinone monoketals were isolated as monomers, despite the tendency of such systems to participate in [4+2] cyclodimerization.[11] The only exceptions were the unexpected gradual dimerizations of the halogenated (*R*,*R*)-**4i** and (*R*,*R*)-**4j** that were clearly observed even during the duration of NMR analyses. Typically, cyclohexa-2,4-dienone **4i** started to transform into its cyclodimer during ^{13}C NMR data acquisition, and proton NMR monitoring of the resulting orange oily mixture in a $CDCl_3$ solution (ca. 0.3 M) indicated that the quasi complete [4+2] cyclodimerization of **4i** was achieved after 15 days at room temperature, which allowed isolation of the pure dimer in 54% yield.[8a] In the case of cyclohexa-2,4-dienone **4j**, the cyclodimerization event was even faster, since the ^{1}H NMR spectrum of the 90:10 diastereomeric mixture of **4j** also revealed traces of its dimer (see the Supplementary data). However, instead of evolving to a complete conversion of **4j** into its cyclodimer, degradation of the mixture was observed after a few days (see the Supplementary data). In any event, our initial expectation of better blocking the self-dimerization process observed with **4i** by having a bulkier halogen atom at the *para*-position of the starting phenol was obviously not met. These unexpected Diels–Alder cyclodimerizing events of both **4i** and **4j** are still under investigation in the aim of gaining further insight into the cycloaddition behavior of these two halogen-substituted spiro-ketals vis-à-vis our recently proposed single all-embracing rationale of the regio-, site-, *endo*-, and π-facial selectivities of this [4+2] dimerization process involved in the biosynthetic elaboration of many natural products.[11d,14]

The process leading to the non-dimerizing alkyl-substituted spiro-ketals was further studied to better understand the mechanism underlying such a highly diastereoselective λ^3-iodane-mediated transformation in view of applying it to the synthesis of natural products. DFT calculations were thus performed on the reaction leading to *ortho*-quinone spiro-ketals (*R*,*R*)-**4a** and (*R*,*S*)-**5a**, and led to the identification of conceivable six-membered cyclic iodine(III)-containing intermediates, from which we could propose a stereocontrol rationale on the basis of the stereodifferentiating ability of these intermediates in ligand coupling reactions.[8a] Next, this methodology was successfully applied to the enantioselective synthesis of the bis(monoterpene) (+)-biscarvacrol (**9**) from 4-*iso*-propylphenol (**6**) (Scheme 3). After a four-step conversion of **6** into the phenolic alcohol (*S*)-**1e**,[8a] our DIB-mediated oxygenative dearomatization allowed the generation of the requisite spiro-ketal (*S*,*S*)-**5e** (see Table 1), which was treated immediately with methylmagnesium bromide (MeMgBr) to furnish the tertiary alcohol (*S*,*S*,*R*)-**7** with a high level of diastereoselectivity (Scheme 3). Other substrates and organometallic reagents are currently under investigation to examine the scope of this asymmetric two-step sequence. The synthesis of (+)-**9** was then simply completed by an acidic cleavage of the ketal moiety to furnish the *ortho*-quinol (*R*)-**8**,



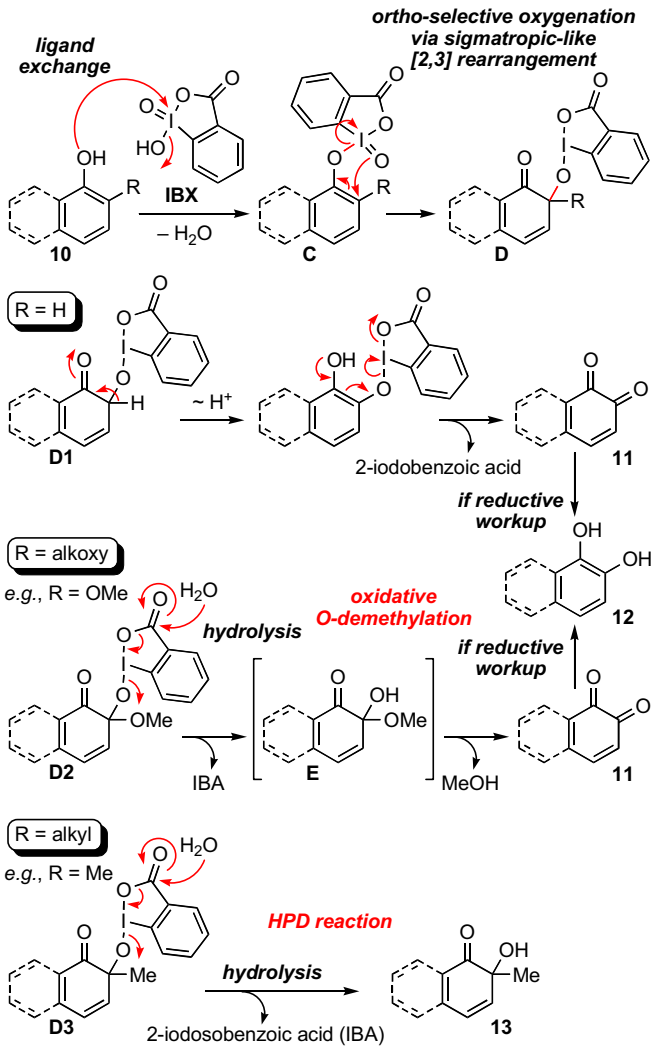
Scheme 3. Enantioselective synthesis of (+)-biscarvacrol (**9**).[8a]

which spontaneously underwent the expected cyclodimerization into (+)-**9** as the major stereoisomer (Scheme 3).[8a]

2.2. SIBX-mediated oxidative *O*-demethylation and hydroxylative phenol dearomatization (HPD)

Our interest in hypervalent iodine-based reagents as efficient tools to promote oxygenative transformations of phenols also led us to consider the use of the λ^5-iodanes 2-iodoxybenzoic acid (IBX) and its non-explosive formulation (SIBX, for Stabilized IBX).[8c,14,15] Indeed, both of these iodine(V) reagents have proven their capability to deliver *ortho*-selectively an oxygen atom during phenol dearomatization processes,[8c,14,15] as first described by Pettus' and

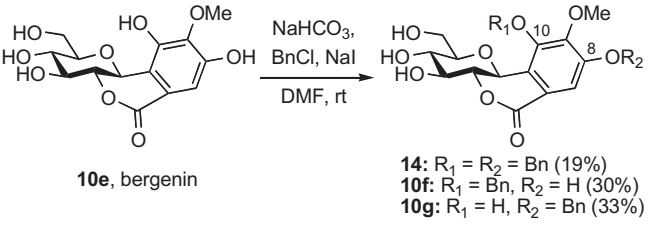
Nicolaou's groups (Scheme 4).[3a,16] An arenol of type **10** can react with IBX, presumably through an initial ligand-exchange step with elimination of water, to give rise to an aryloxy-λ^5-iodane of type **C**. This species can then rearrange in a sigmatropic-like fashion by forming regioselectively a single oxygen–carbon bond at one of the *ortho*-carbon centers of the aryloxy unit, with concomitant two-electron reduction of the iodine(V) atom leading to a λ^3-iodanyl species of type **D**. This species can then evolve differently depending on the substitution pattern of the starting arenol **10**. For example, if the *ortho*-position does not bear any substituent (i.e., R=H, Scheme 4), it can be argued that **D1** will first rearomatize by prototropy before reductive elimination of the λ^3-iodanyl moiety drives the reaction toward the generation of an *ortho*-quinonoid product of type **11**, valuable either as such or as its catecholic analogue **12** easily obtained after a reductive workup.[8c,16,17] Both **11** and **12** are also accessible if an alkoxy substituent occupies the *ortho*-position that has been oxygenated (e.g., R=OMe, Scheme 4), for the λ^3-iodanyl moiety of **D2** can be released by hydrolysis to give 2-iodosobenzoic acid (IBA) and an hemiketal product **E**, which then eliminates methanol to furnish **11**, and possibly **12**. This transformation constitutes a valuable means to cleave *ortho*-phenolic methyl aryl ether bonds[8c] and has found pertinent applications in natural products synthesis (vide infra).[6d] The outcome of this IBX-mediated *ortho*-oxygenative reaction is even different when the *ortho*-position bears an alkyl group (e.g., R=Me, Scheme 4), in which case hydrolysis of the λ^3-iodanyl moiety of **D3** furnishes IBA and an *ortho*-quinol product **13**. We refer to this transformation as the Hydroxylative Phenol Dearomatization (HPD) reaction.[6c,14b]



Scheme 4. Plausible mechanisms of the IBX-mediated *ortho*-selective oxygenative dearomatization of arenols.

2.2.1. SIBX-mediated oxidative O-demethylation. Our development, in partnership with the company Simafex, of stabilized IBX (i.e., SIBX) for safe dehydrogenative oxidation of alcohols included the aforementioned oxygenative *O*-demethylation of phenolic methyl aryl ethers.[8c] Thus, 2-methoxyphenols were conveniently converted into their corresponding catechols using SIBX, which is today commercially available. The *ortho*-selectivity of the oxygenating process is a remarkable asset of this reaction, but we were also curious to examine its chemoselectivity when using 2-methoxyphenols bearing alcoholic functions, and to compare the performances of both SIBX and IBX reagents in such scenarios. Commercially available eugenol (**10a**), vanillyl alcohol (**10b**), *iso*-vanillyl alcohol (**10c**), homovanillyl alcohol (**10d**), the *C*-galloyl-glucoside (−)-bergenin (**10e**), and its synthetic monobenzylated derivatives **10f**/**g** (vide infra) were thus selected for this study in the aim of preparing in one single step their corresponding catechols.

The selection of (−)-bergenin (**10e**) and its benzylated derivatives **10f**/**g** was driven by our current interest in delineating the mechanism of action of **10e** as a selective inhibitor of human DNA topoisomerase II.[18a] Monobenzylation of the phenolic functions[18b] of **10e** was achieved upon treatment with benzyl chloride in the presence of sodium bicarbonate ($NaHCO_3$) and sodium iodide (NaI) in freshly distilled dimethylformamide (DMF) at room temperature (Scheme 5). After 2 days, the reaction was worked up and afforded a small amount of 8,10-di-*O*-benzylbergenine (**14**, 19%), decent amounts of the expected 10-*O*-benzylbergenine (**10f**, 30%) and 8-*O*-benzylbergenine (**10g**, 33%), as well as some recovered starting material (**10e**, 17%). The regiochemistry of the two monobenzylated

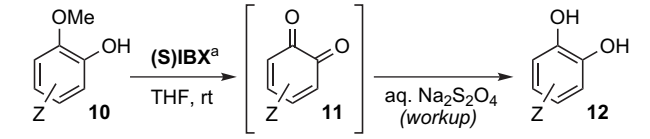


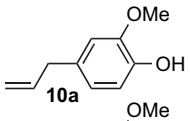
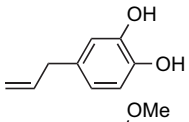
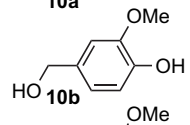
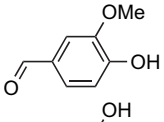
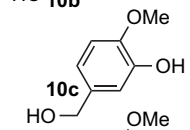
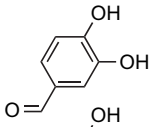
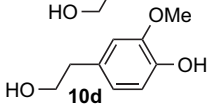
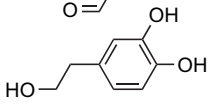
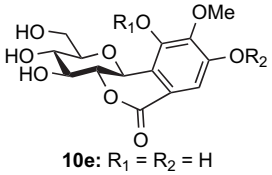
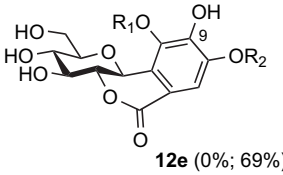
Scheme 5. Monobenzylation of (−)-bergenin (**10e**).

bergenins **10f** and **10g** was unambiguously determined by a delayed $^1H-^1H$ COSY analysis using a fixed delay of 300 ms, which permitted the observation of a 5-bond correlation between the benzyloxy protons resonating at 5.15 ppm and the aromatic singlet H-7 at 7.21 ppm in the case of **10g** (see the Supplementary data).

All seven 2-methoxyphenols **10a**–**g** were then subjected to our oxidative *O*-demethylation reaction conditions using either IBX or SIBX (Table 2). Treatment of eugenol (**10a**) with 1.1 equiv of the λ^5-iodane reagent in THF at room temperature, followed by reductive workup of the presumed *ortho*-quinonoid intermediate product of type **11** with a freshly prepared aqueous solution of sodium dithionite ($Na_2S_2O_4$), furnished the expected catechol **12a**. Both IBX and SIBX led to very good yields of 67 and 77%,[8c] respectively, with very similar times of reaction (12 and 16 h, respectively). When vanillyl alcohol (**10b**) was submitted to these same experimental conditions, vanillin (**12b**) was isolated in good yields of 60 and 51%,[19] respectively (Table 2). The absence of catechol products results from the deactivation of the phenol function by the *para*-positioned electron-withdrawing aldehyde group,[8c,d,16] which is competitively generated by the facile λ^5-iodane-mediated dehydrogenative oxidation of the benzylic

Table 2
SIBX versus IBX-mediated oxidative *O*-demethylation of 2-methoxyphenols **10** into catechols **12**[a]



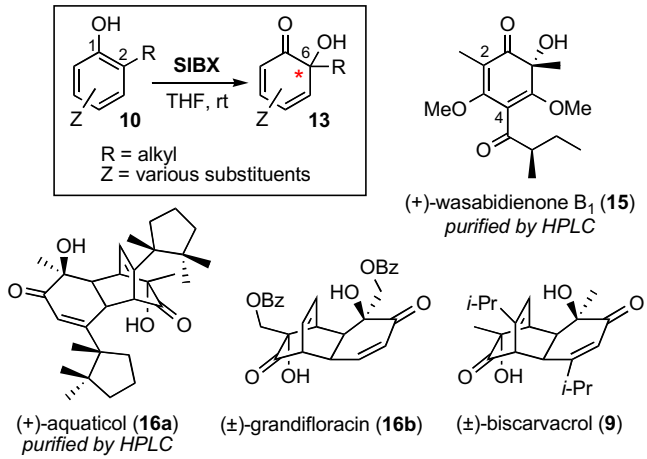
entry	10	12	yield (IBX; SIBX)
1	 **10a**		**12a** (67%; 77%)
2	 **10b**		**12b** (60%; 51%)
3	 **10c**		**12c** (56%; 52%)[b]
4	 **10d**		**12d** (16%; 42%)[c]
5	 **10e:** $R_1 = R_2 = H$		**12e** (0%; 69%)[c]
6	**10f:** R_1 = Bn, R_2 = H		**12f** (0%; 20%)[c]
7	**10g:** R_1 = H, R_2 = Bn		**12g** (0%; 21%)[c]

[a] Reactions were carried out with 1.1 equiv of (S)IBX[8c].
[b] 2.2 equiv of (S)IBX were necessary to achieve complete conversion of **10c**.
[c] The reaction was conducted in acetone/water (9:1, v/v).

primary alcohol function of **10b**. In support of this explanation is the fact that addition of another equivalent of IBX or SIBX did not allow any *O*-demethylation of vanillin (**12b**). Moreover, *iso*-vanillyl alcohol (**10c**) also showed oxidation of its benzylic alcohol group, but the *O*-demethylation was concomitantly operational. A single equivalent of λ^5-iodane clearly afforded a mixture of *iso*-vanillin and its demethylated analogue, i.e., protocatechualdehyde (**12c**). The aldehyde function *meta*-positioned in *iso*-vanillin does not affect the capability of the nucleophilic phenol function to engage the λ^5-iodane reagent, and a second equivalent of IBX or SIBX then allowed complete conversion of **10c** into **12c**, which was isolated in moderate yields of 56 or 52%, respectively (Table 2). We next turned our attention to 2-methoxyphenolic alcohols exempt from any benzylic alcohol function in the aim of further evaluating the chemoselective potential of IBX versus SIBX in oxidative *O*-demethylation reactions. Homovanillyl alcohol (**10d**) was thus selected as a precursor of hydroxytyrosol (**12d**), a naturally occurring catecholic compound exhibiting outstanding antioxidant properties.[20] After a couple of unsatisfactory attempts run in THF, the solvent system was changed to acetone/water (9:1), in which the solubility of the starting material **10d** was much better. Treatment of **10d** with 1.1 equiv of IBX over 12 h led to the successful isolation of **12d**, but in a low yield of 16%. Under the same experimental conditions, the use of SIBX proved to be much more promising, since **12d** was in this case isolated in a decent, not optimized but reproducible, yield of 42% (Table 2). The chemoselectivity thus observed in favor of the *ortho*-oxygenation of the phenol function over the dehydrogenation of the primary alcohol function of **10d** might be attributed to a preference of the iodine(V) center of IBX for reacting with the softer phenolic oxygen atom rather than with the harder primary alcoholic oxygen atom during the initial ligand-exchange step of our proposed mechanistic description (see Scheme 4). However, the reason(s) of the better performance of SIBX over that of IBX in this reaction remains obscure. In any event, it is worth noting that this one-step SIBX-mediated access to hydroxytyrosol (**12d**) from homovanillyl alcohol (**10d**) constitutes a valuable alternative to recently reported methods relying on IBX-mediated hydroxylation or demethylation of carboxymethylated derivatives of tyrosol and **10d**.[21]

In the same vein of our investigations, the *C*-galloylglucoside (−)-bergenin (**10e**) and its monobenzylated derivatives **10f**/**g** were also chemoselectively *O*-demethylated upon treatment with SIBX in acetone/water (9:1) at room temperature. The aqueous $Na_2S_2O_4$-based reductive workup was followed by either Sephadex® LH-20 or semi-preparative reverse phase HPLC purification (see Experimental section) to furnish (−)-norbergenin (**12e**) and its monobenzylated catecholic derivatives **12f**/**g** in respective yields of 69, 20, and 21% (Table 2). This fairly efficient one-step preparation of norbergenin (**12e**), a plant metabolite that has shown an in vitro *anti*-HIV activity by inhibiting the gp120/CD4 interaction,[22a] compares favorably with the previously reported three-step sequence (71% overall yield) relying on classical protection/deprotection and Lewis acid (BCl_3)-mediated demethylation.[22b] Surprisingly, the starting bergenins **10e**–**g** fully degraded upon exposure to IBX. The resulting intractable mixtures thus obtained led us to think that the glucose core of these compounds did not resist IBX oxidation, and furthermore that the benzoic and isophthalic acids present in the SIBX formulation must play a determining role in modulating the reactivity of IBX, hence making it a milder reagent with an enhanced chemoselectivity potential.

2.2.2. SIBX-mediated hydroxylative phenol dearomatization (HPD). We also exploited the capacity of SIBX to oxygenate phenols in an *ortho*-selective manner in the synthesis of cyclohexa-2,4-dienones of the *ortho*-quinol type (see **B** in Fig. 1, and Scheme 4, R=alkyl). This led us to develop what we referred to as the HPD reaction for hydroxylative phenol dearomatization,[14b] which we then applied to



Scheme 6. Examples of natural non-dimerizing *ortho*-quinol and *ortho*-quinol-derived [4+2] cyclodimers synthesized via our SIBX-mediated HPD reaction.

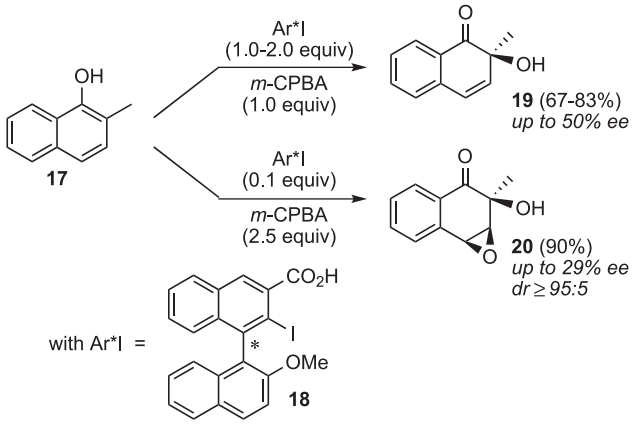
the (biomimetic) synthesis of several natural products either featuring an *ortho*-quinol motif, such as (+)-wasabidienone B_1 (**15**)[15b] or derived from the dimerization of such motifs, such as (+)-aquaticol (**16a**), *rac*-grandifloracin (**16b**), and *rac*-biscarvacrol (**9**) (Scheme 6).[14]

Access to the above natural products in enantiomerically enriched forms, using SIBX in the key step of their construction, relied on separation of racemic intermediates or diastereomeric products by (chiral) liquid chromatography techniques. Although

we developed an efficient substrate-controlled methodology for the asymmetric synthesis of such natural products, as exemplified by the synthesis (+)-**9** (see Section 2.1 and Scheme 3), we were also particularly interested in developing a reagent-controlled approach using a chiral analogue of IBX in order to limit both the number of chemical and separation steps in such synthesis endeavors.

2.3. Reagent-controlled asymmetric phenol dearomatization

This aim of developing an asymmetric route to *ortho*-quinol systems relying on the use of a chiral oxygenating IBX-like reagent turned out to be much more difficult than we initially anticipated. We soon realized that the development of chiral iodanes capable of efficacious inductions of asymmetry was like the search for the Holy Grail of hypervalent iodine chemistry. Indeed, despite unremitting efforts on the part of several research groups over the last thirty years or so, no fully satisfactory solution had been found, and like the others, we stumbled upon many difficulties in trying to design and prepare chiral λ^5-iodane reagents for asymmetric oxygenative phenol dearomatization reactions. However, significant and highly promising progresses have been made over the last two years.[23] In 2008, Kita's group reported on a chiral bis-λ^3-iodane spirobiindane-based reagent for intramolecular dearomatizing spirolactonization of a series of naphthol derivatives in enantiomeric excesses (ee's) up to 86%.[23a] A catalytic version of this reaction using 0.15 equiv of their bisiodoarene precursor and *m*-CPBA as a co-oxidant enabled spirolactonization in up to 69% ee.[23a] Inspired by this work, Ishihara's group reported this year on the same reaction using 15 mol% of a C_2-symmetric bis(*N*-mesityl amide)-based iodoarene derived from 2-iodoresorcinol and chiral lactate units, and oxidized in situ into the corresponding λ^3-iodane using *m*-CPBA, to reach enantioselectivities up to 92% ee.[23c] In February 2009, Birman's group described the stoichiometric use of chiral oxazoline-containing λ^5-iodanes in HPD reactions with enantioselectivities up to 77% ee, albeit in only moderate to good yields (29–65%).[23b] In May 2009 was published our own contribution, which involved the use of a presumed λ^5-iodane generated in situ from the chiral iodobinaphthyle derivative **18** and *m*-CPBA (Scheme 7).[8b] A twofold excess of **18** led to a HPD of naphthol **17** into the *ortho*-quinol **19** in 83% yield and 50% ee. The organocatalytic version of this reaction using 0.1 equiv of **18** and 2.5 equiv of *m*-CPBA



Scheme 7. Asymmetric HPD reactions through in situ generation of an iodane from a chiral iodoarene (Ar*I) and *m*-CPBA.[8b]

enables subsequent epoxidation of **19** in a diastereoselective fashion to furnish the *ortho*-quinol epoxide **20** in an excellent yield, but in only 29% ee (Scheme 7).[8b] Even though the resulting enantioselectivities are still moderate, these last examples constitute the first cases of reagent-controlled asymmetric iodane-mediated HPD reactions using an external oxygenating species derived from a chiral iodoarene.

3. Conclusion

There are unarguably more improvements to come in the still developing field of hypervalent iodine chemistry in general, and in particular, in its utilization in phenol dearomatization processes. These highlights of our own contributions and those of others to the development of substrate-controlled and, most notably, reagent-controlled iodane-mediated stereoselective oxygenative dearomatization of phenols attest to the interest that such a transformation has recently raised in the field and underline its tremendous potential for natural product synthesis. Iodanes, and especially IBX and IBX-like λ^5-iodanes, have clearly emerged as useful external sources of oxygen in oxygenative phenol dearomatization reactions. In this context and on the basis of the new results reported herein, we would like to emphasize the benefits of using SIBX in place of IBX in the exploitation of this transformation of phenols in the chemo- and regioselective oxygenating *O*-demethylation of 2-methoxyphenols into catechols. For example, the milder SIBX reagent thus enabled *O*-demethylation of substrates, such as homovanillyl alcohol (**10d**) or (−)-bergenin (**10e**) in decent to good yields without prior protection of their alcoholic functions, whereas IBX failed to exert the same level of chemoselectivity.

4. Experimental section

4.1. General

All moisture and oxygen sensitive reactions were carried out in flame-dried glassware under N_2. Tetrahydrofuran (THF) was purified immediately before use by distillation from sodium/benzophenone under N_2, or by filtration through alumina under N_2. Methanol (MeOH) and dimethylformamide (DMF) were distilled under N_2 prior to use from Mg/I_2 and P_2O_5, respectively. Acetone, dichloromethane (CH_2Cl_2), ethyl acetate (EtOAc), absolute ethanol (EtOH), and *n*-butanol (*n*-BuOH), were used as received. The iodanes, i.e., (diacetoxyiodo)benzene (DIB; Simafex), 2-iodoxybenzoic acid (IBX),[24] and stabilized 2-iodoxybenzoic acid (SIBX; Simafex),[8c] were used as received. The 2-methoxyphenols **10a**–**d** were all purchased from Aldrich and used as received. (−)-Bergenin (**10e**) was isolated from the methanol extract of either the roots (ca. 9% and 2% yields from the dry methanolic extract and the dry weight material, respectively) or the stem-bark (ca. 10% and 1.2% yields from the dry methanolic extract and the dry weight material, respectively) of *Peltophorum africanum* Sond. (*Fabaceae*),[25a] or purchased from either Amfinecom Inc. (mp 236–238 °C) or Sigma–Aldrich as its monohydrate [mp 139–141 °C (lit.[25b] 140 °C)], which was further oven-dried at 60 °C overnight to ensure the use of the anhydrous compound [mp 239–240 °C (lit.[25c] 238 °C; lit.[25d] 237 °C)]. Evaporations were conducted under reduced pressure at temperatures less than 30 °C unless otherwise noted. Column chromatography was carried out under positive pressure using 40–63 μm silica gel (Merck) and the indicated solvents. Melting points were measured in open capillary tubes and are uncorrected. Optical rotations were determined on a Krüss P3001 digital polarimeter at 589 nm, and are given as $[\alpha]_D^{20}$ (concentration in g/100 mL solvent). IR spectra were recorded with a Bruker IFS55 FT-IR spectrometer. NMR spectra of samples in the indicated solvent were run at 300 MHz, and calibrated using residual solvent as an internal standard. Carbon multiplicities were determined by DEPT135 experiments. Stereochemical assignments were achieved by NOESY experiments. Diagnostic correlation information was obtained with a delayed $^1H-^1H$ correlative experiment using

a fixed delay of 300 ms. Electron impact (EIMS, 50–70 eV) and electrospray (ESIMS) low and/or high resolution (HRMS) mass spectrometric analyses were obtained from the mass spectrometry laboratory at either the Institut Européen de Chimie et Biologie (IECB), the Centre d'Etude Structurale et d'Analyse des Molécules Organiques (CESAMO, Université Bordeaux 1), or the Centre Régional de Mesures Physiques de l'Ouest (CRMPO, Université Rennes 1), France. Elemental analyses were carried out at the Service Central d'Analyses du CNRS, Vernaison, France.

*4.1.1. (R)-(+)-1-Triethylsilyloxy-2-(2-triethylsilyloxy-3,3-dimethylbutoxy)-4-bromobenzene [(R)-**2**].* To a stirred ice-cold solution of bromophenol (*R*)-**1i** (289 mg, 1.0 mmol) in dry CH_2Cl_2 (10 mL, ca. 0.1 M) were successively added Et_3N (0.84 mL, 6 mmol) and TESOTf (0.68 mL, 3 mmol). The mixture was then allowed to warm to room temperature, and was stirred for 45 min, after which time saturated aqueous NH_4Cl (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with water (15 mL), dried over $MgSO_4$, filtered, and evaporated. The resulting oily residue (658 mg) was purified by column chromatography, eluting with pure cyclohexane, to give (*R*)-**2** as a colorless oil (497 mg, 96%): $[\alpha]_D^{20}$ +10.7 (*c* 0.94, $CHCl_3$); IR (neat) 2956, 2912, 2877, 1497, 1457, 1121, 739, 462 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.63 (q, *J*=7.7 Hz, 6H), 0.74 (q, *J*=7.4 Hz, 6H), 0.91–1.00 (m, 27H), 3.70 (dd, *J*=2.9, 5.9 Hz, 1H), 3.81 (dd, *J*=6.1, 9.5 Hz, 1H), 3.97 (dd, *J*=2.8, 9.6 Hz, 1H), 6.69 (d, *J*=8.3 Hz, 1H), 6.90–6.93 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 151.3, 144.7, 123.6, 121.3, 117.1, 113.2, 78.8, 72.3, 34.9, 26.2, 7.0, 6.6, 5.1, 5.0; ESIMS *m*/*z* (rel intensity) 541 (MNa^+, 100), 539 (MNa^+, 90), 526 (3), 524 (1); HRMS (ESI) calcd for $C_{24}H_{45}{}^{79}BrNaO_3Si_2$ 539.1988, found 539.1981.

*4.1.2. (R)-(−)-1-Triethylsilyloxy-2-(2-triethylsilyloxy-3,3-dimethylbutoxy)-4-iodobenzene [(R)-**3**].* A stirred solution of bromobenzene (*R*)-**2** (444 mg, 0.86 mmol) in dry THF (10 mL, ca. 0.1 M) was cooled at −78 °C, and treated dropwise with *t*-BuLi (1.7 M in pentane, 1.06 mL, 1.8 mmol). The reaction mixture was stirred at −78 °C for 50 min, after which time a solution of I_2 (436 mg, 1.72 mmol) in dry THF (3 mL) was added dropwise. The reaction mixture was then allowed to warm to room temperature over 1 h, and further stirred for 13 h before hydrolysis with saturated aqueous NH_4Cl (10 mL), followed by extraction with EtOAc (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and evaporated. The resulting oily residue (456 mg) was purified by column chromatography, eluting with pure cyclohexane, to give the iodobenzene (*R*)-**3** as a colorless oil (386 mg, 80%): $[\alpha]_D^{20}$ −21.5 (*c* 1.07, $CHCl_3$); IR (neat) 2956, 2912, 2876, 1496, 1457, 1124, 732, 463 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.63 (q, *J*=7.7 Hz, 6H), 0.74 (q, *J*=7.4 Hz, 6H), 0.91–1.00 (m, 27H), 3.69 (dd, *J*=2.8, 5.9 Hz, 1H), 3.79 (dd, *J*=5.9, 9.5 Hz, 1H), 3.96 (dd, *J*=2.9, 9.5 Hz, 1H), 6.57 (d, *J*=8.1 Hz, 1H), 7.08–7.12 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 151.5, 145.6, 129.9, 122.8, 122.0, 83.1, 78.8, 72.2, 34.9, 26.2, 7.0, 6.6, 5.1, 5.0; ESIMS *m*/*z* (rel intensity) 587 (MNa^+, 100); HRMS (ESI) calcd for $C_{24}H_{45}INaO_3Si_2$ 587.1850, found 587.1863.

*4.1.3. (R)-(−)-2-(2-Hydroxy-3,3-dimethylbutoxy)-4-iodophenol [(R)-**1j**].* To a stirred ice-cold solution of (*R*)-**3** (375 g, 0.66 mmol) in THF (20 mL, ca. 0.03 M) was added TBAF (1.0 M in THF, 1.46 mL, 1.46 mmol). The mixture was then allowed to warm to room temperature, and was stirred for 30 min, after which time saturated aqueous $NaHCO_3$ (20 mL) was added, and the mixture was extracted with EtOAc (3×20 mL). The combined organic layers were then washed with brine (20 mL), dried over $MgSO_4$, filtered, and evaporated. The resulting oily residue (333 mg) was submitted to column chromatography, eluting with cyclohexane/acetone (9:1→4:1), to give pure phenolic alcohol (*R*)-**1j** as a yellow powder (221 mg, 99%): mp 80–81 °C; $[\alpha]_D^{20}$ −11.4 (*c* 1.14, $CHCl_3$); IR (neat) 3396, 2958, 2872, 1499, 1458, 1122, 460 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.00 (s, 9H), 3.71, (dd, *J*=2.2, 9.2 Hz, 1H), 3.84 (br t, *J*=9.5 Hz, 1H), 4.18 (dd, *J*=2.3, 9.8 Hz, 1H), 6.69 (d, *J*=8.5 Hz, 1H), 7.15 (d, *J*=1.9 Hz, 1H), 7.21 (dd, *J*=1.9, 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 147.3, 146.5, 131.1, 122.0, 117.7, 80.6, 77.8, 70.7, 33.7, 25.9; ESIMS *m*/*z* (rel intensity) 359 (MNa^+, 100); HRMS (ESI) calcd for $C_{12}H_{17}INaO_3$ 359.0120, found 359.0110.

4.2. General procedure for DIB-mediated chiral *ortho*-quinone monoketals preparation[8a]

A stirred solution of phenol **1a**–**j** (ca. 110 mg, 1.00 equiv) in CF_3CH_2OH (10 mL, ca. 0.04 M) was cooled at −35 °C, and was treated dropwise, over 5 min, with a solution of DIB (1.02 equiv) in CF_3CH_2OH (1 mL). The reaction mixture immediately became pale yellow, and then slowly changed to yellow-pink. After 20 min, TLC monitoring [hexanes/Et_2O (7:3)] indicated complete consumption of the starting material. Powdered $NaHCO_3$ was added in one portion to the reaction mixture, which was kept under stirring at −35 °C for 15 min. After CF_3CH_2OH removal in vacuo, the residue was taken up with CCl_4 (3×5 mL), filtered, and evaporated. Further drying under high vacuum allowed complete removal of the iodobenzene by-product, and afforded a diastereomeric mixture of the corresponding chiral *ortho*-quinone monoketals **4a**–**j**/**5a**–**j** (dr, i.e., diastereomeric ratios, were determined by ^1H NMR analysis; see Table 1) as yellow oils. Although further purification revealed not necessary before engaging these products in subsequent reactions, they could be separated by silica gel column chromatography for identification and characterization purposes.

*4.2.1. 2R-tert-Butyl-9-iodo-1,4-dioxaspiro[4.(5R)]deca-7,9-dien-6-one [(R,R)-**4j**].* Yellow oil (dr 90:10, quantitative crude yield), which was identified as a 9:1 mixture of (*R*,*R*)-**4j** and (*R*,*S*)-**5j**: IR (neat) 1686, 1093, 1002 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (s, 9H), 3.85 (dd, *J*=6.4, 7.4 Hz, 1H), 4.25 (br t, *J*=7.4 Hz, 1H), 4.34 (br t, *J*=6.8 Hz, 1H), 5.75 (d, *J*=10.0 Hz, 1H), 6.70 (d, *J*=1.9 Hz, 1H), 6.96 (dd, *J*=2.2, 10.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 196.5, 147.3, 147.2, 145.0, 125.5, 98.9, 92.4, 85.3, 85.2, 66.5, 66.1, 33.0, 30.0, 25.9, 25.3; ESIMS *m*/*z* (rel intensity) 357 (MNa^+, 100), 230 (6); HRMS (ESI) calcd for $C_{12}H_{15}INaO_3$ 356.9958, found 356.9971.

4.3. Monobenzylation of bergenin

To a stirred solution of bergenin (**10e**, 300 mg, 0.915 mmol) in dry DMF (12 mL) were added powdered $NaHCO_3$ (154 mg, 1.83 mmol), benzyl chloride (116 μL, 0.915 mmol), and NaI as a catalyst (30 mg). The resulting mixture was stirred at room temperature for 48 h, after which time DMF was removed under high vacuum. The oily residue was dissolved with EtOAc (50 mL) and washed with brine (2×15 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated. The resulting brown oil was then submitted to column chromatography, eluting with CH_2Cl_2/MeOH (40:1), to furnish a small amount of dibenzylated bergenin **14** (87 mg, 19%), a ca. 1:1 mixture of the two monobenzylated compounds **10f** and **10g** (245 mg, 64%), and some recovered starting material **10e** (52 mg, 17%), which could be recycled. The **10f**/**10g** mixture was separated by semi-preparative reverse phase HPLC, which was performed on a Varian ProStar system equipped with a Merck Lichrospher® RP-18 column (250×25 mm I.D., 5 μm), eluting with A/B (75:25) [solvent A=H_2O/HCO_2H (99:1); solvent B=CH_3CN/HCO_2H (99:1)] at a flow rate of 16 mL/min. Column effluent was monitored by UV detection at 280 nm using a ProStar

320 UV-visible detector [retention time=16.5 min for **10f**, and 19.5 min for **10g**] (see the Supplementary data). Both pure **10f** (115 mg, 30%) and **10g** (126 mg, 33%) were obtained as white amorphous solids.

*4.3.1. (−)-2-β-D-Glucopyranosyl-(8,10-di-O-benzyl-4-O-methyl)gallic acid δ-lactone (**14**; 8,10-di-O-benzylbergenin).* White amorphous solid (19% yield after SiO_2 column chromatography): mp 182–183 °C; $[\alpha]_D^{20}$ −68.7 (*c* 0.50, MeOH); UV (MeOH) λ_{max} (log ϵ) 268 (2.42), 312 (2.35) nm; IR (neat) 3327, 2929, 1739, 1334, 1133, 1038 cm^{-1}; ^1H NMR [acetone-d_6/D_2O (9:1), 300 MHz] δ 3.45–3.49 (m, 1H), 3.60 (br t, *J*=9.2 Hz, 1H), 3.74–3.84 (m, 3H), 3.86 (s, 3H), 4.02 (br t, *J*=9.8 Hz, 1H), 4.62 (d, *J*=10.2 Hz, 1H), 5.02 (d, *J*=11.5 Hz, 1H), 5.07 (d, *J*=11.3 Hz, 1H), 5.20 (s, 2H), 7.30–7.49 (m, 11H); ^{13}C NMR [acetone-d_6/D_2O (9:1), 75.5 MHz] δ 165.9, 153.7, 151.0, 150.3, 138.5, 137.7, 129.9, 129.7, 129.5, 129.4, 128.9, 128.4, 120.2, 112.8, 82.1, 81.5, 76.9, 75.4, 72.9, 72.0, 70.9, 62.1, 61.8; EIMS *m*/*z* (rel intensity) 508 (M^+, 1.8), 417 (1), 209 (1.6), 208 (1.3), 91 (100); ESIMS *m*/*z* (rel intensity) 531 (MNa^+, 15), 509 (MH^+, 100), 508 (M^+, 1.5); HRMS (ESI) calcd for $C_{28}H_{28}NaO_9$ 531.1631, found 531.1627.

*4.3.2. (−)-2-β-D-Glucopyranosyl-(10-O-benzyl-4-O-methyl)gallic acid δ-lactone (**10f**; 10-O-benzylbergenin).* White amorphous solid (30% yield after SiO_2 column chromatography, followed by semi-preparative HPLC): mp 203–204 °C; $[\alpha]_D^{20}$ −41.7 (*c* 0.50, MeOH); UV (MeOH) λ_{max} (log ϵ) 267 (2.75), 309 (2.33) nm; IR (neat) 3381, 2942, 1713, 1341, 1097, 1024 cm^{-1}; ^1H NMR [acetone-d_6/D_2O (9:1), 300 MHz] δ 3.43–3.49 (m, 1H), 3.60 (br t, *J*=9.2 Hz, 1H), 3.73–3.85 (m, 3H), 3.87 (s, 3H), 4.00 (br t, *J*=9.9 Hz, 1H), 4.57 (d, *J*=10.4 Hz, 1H), 5.04 (s, 2H), 7.30–7.46 (m, 6H); ^{13}C NMR [acetone-d_6/D_2O (9:1), 75.5 MHz] δ 166.0, 152.4, 150.9, 148.7, 138.6, 129.7, 129.6, 129.5, 126.4, 120.3, 115.3, 82.1, 81.6, 76.7, 75.4, 73.0, 70.9, 61.9, 61.8; EIMS *m*/*z* (rel intensity) 418 (M^+, 4), 209 (3), 208 (7), 91 (100); ESIMS *m*/*z* (rel intensity) 419 (MH^+, 100); HRMS (ESI) calcd for $C_{21}H_{22}NaO_9$ 441.1162, found 441.1147. Anal. Calcd for $C_{21}H_{22}O_9$: C, 60.28; H, 5.30; O, 34.42. Found: C, 60.41; H, 5.41.

*4.3.3. (−)-2-β-D-Glucopyranosyl-(8-O-benzyl-4-O-methyl)gallic acid δ-lactone (**10g**; 8-O-benzylbergenin).* White amorphous solid (33% yield after SiO_2 column chromatography, followed by semi-preparative HPLC): mp 193–194 °C; $[\alpha]_D^{20}$ −36.3 (*c* 0.50, MeOH); UV (MeOH) λ_{max} (log ϵ) 275 (2.84), 312 (2.48) nm; IR (neat) 3371, 2930, 1681, 1209, 1144, 1031 cm^{-1}; ^1H NMR [acetone-d_6/D_2O (9:1), 300 MHz] δ 3.48 (br t, *J*=9.1 Hz, 1H), 3.64–3.76 (m, 2H), 3.84 (s, 3H), 3.89 (br t, *J*=9.1 Hz, 1H), 4.06 (br t, *J*=10.4 Hz, 1H), 4.09 (br t, *J*=10.0 Hz, 1H), 4.99 (d, *J*=10.4 Hz, 1H), 5.15 (s, 2H), 7.21 (s, 1H), 7.26–7.57 (m, 5H); ^{13}C NMR [acetone-d_6/D_2O (9:1), 75.5 MHz] δ 165.4, 153.9, 149.8, 143.9, 138.1, 129.9, 129.5, 128.9, 119.5, 108.8, 83.1, 81.3, 75.4, 73.9, 72.0, 71.9, 62.7, 61.5; EIMS *m*/*z* (rel intensity) 418 (M^+, 43), 208 (16), 91 (100); ESIMS *m*/*z* (rel intensity) 441 (MNa^+, 10), 419 (MH^+, 100), 408 (M^+, 1); HRMS (ESI) calcd for $C_{21}H_{22}NaO_9$ 441.1162, found 441.1144. Anal. Calcd for $C_{21}H_{22}O_9$: C, 60.28; H, 5.30; O, 34.42. Found: C, 60.13; H, 5.41.

4.4. General procedure for the (*S*)IBX-mediated oxidative *O*-demethylation[8c] of the 2-methoxyphenols 10a–d

To a stirred solution of 2-methoxyphenol **10a–d** (ca. 150 mg, 1.00 equiv) in dry THF (20 mL, ca. 0.05 M) was added IBX (1.1 equiv) or SIBX (2.2 equiv) in one portion. The reaction mixture became immediately bright yellow, and the resulting suspension was stirred vigorously at room temperature in the dark for ca. 16–24 h, after which time it was treated with an aqueous solution (2 mL) of $Na_2S_2O_4$ (3.0 equiv) and further vigorously stirred in the dark for 30 min. After discarding the solid IBA by-product by filtration, the filtrate was evaporated. The resulting crude product was then either directly submitted to column chromatography (when using IBX), or, prior to purification, dissolved in EtOAc (50 mL), washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried over $MgSO_4$, filtered, and evaporated in order to remove the stabilizing agents (when using SIBX).

*4.4.1. 4-Allylcatechol (**12a**).* SiO_2 column chromatography, eluting with hexane/Et_2O (1:2), furnished pure **12a** as an orange syrup (67 or 77% yield using IBX or SIBX, respectively): IR (neat) 3369, 1618 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 3.22 (d, *J*=6.8 Hz, 2H), 3.77–3.84 (m, 1H), 4.94–5.06 (m, 2H), 5.84–5.98 (m, 1H), 6.51 (dd, *J*=2.1, 8.1 Hz, 1H), 6.66–6.74 (m, 2H), 7.67 (br s, 1H); ^{13}C NMR (acetone-d_6, 75.5 MHz) δ 145.8, 144.1, 139.2, 132.5, 120.6, 116.4, 116.0, 115.2, 40.2; EIMS *m*/*z* (rel intensity) 150 (M^+, 100), 149 (15), 123 (40).

*4.4.2. 4-Hydroxy-3-methoxybenzaldehyde (**12b**; vanillin).* SiO_2 column chromatography, eluting with hexane/Et_2O (1:2), afforded pure vanillin **12b** as a white solid (60 or 51% yield using IBX or SIBX, respectively): mp 80–81 °C (lit.[8c] 79–80 °C); IR (neat) 3192, 1669 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.90 (s, 3H), 6.70 (br s, 1H), 7.00 (d, *J*=8.5 Hz, 1H), 7.37–7.40 (m, 2H), 9.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 191.0, 151.8, 147.2, 129.6, 127.4, 114.4, 108.8, 55.9; EIMS *m*/*z* (rel intensity) 152 (M^+, 64), 151 (76), 137 (5), 123 (12), 81 (100).

*4.4.3. 3,4-Dihydroxybenzaldehyde (**12c**; protocatechualdehyde).* SiO_2 column chromatography, eluting with cyclohexane/EtOAc (5:1), gave pure protocatechualdehyde **12c** as a pale yellow solid (56 or 52% yield using IBX or SIBX, respectively): mp 153 °C (lit.[26] 154 °C); IR (neat) 3198, 1686 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 3.01 (br s, 1H), 7.00 (d, *J*=8.1 Hz, 1H), 7.33–7.36 (m, 2H), 8.69 (br s, 1H), 9.78 (s, 1H); ^{13}C NMR (acetone-d_6, 75.5 MHz) δ 191.1, 152.3, 146.5, 131.0, 125.4, 116.2, 115.2; EIMS *m*/*z* (rel intensity) 138 (M^+, 84), 137 (100), 109 (40).

*4.4.4. 3,4-Dihydroxyphenylethanol (**12d**; hydroxytyrosol).* SiO_2 column chromatography, eluting with cyclohexane/EtOAc (5:1), gave pure hydroxytyrosol **12d** as a colorless oil (16 or 42% yield using IBX or SIBX, respectively): IR (neat) 3185, 2952 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 2.65 (t, *J*=7.1 Hz, 2H), 3.13 (br s, 1H), 3.67 (t, *J*=7.1 Hz, 2H), 6.54 (dd, *J*=1.9, 7.9 Hz, 1H), 6.69–6.72 (m, 2H), 7.67 (br s, 1H); ^{13}C NMR (acetone-d_6, 75.5 MHz) δ 145.6, 144.0, 131.9, 121.0, 116.8, 115.9, 64.2, 39.7; EIMS *m*/*z* (rel intensity) 154 (M^+, 24), 123 (100), 31 (80).

4.5. General procedure for the (*S*)IBX-mediated oxidative *O*-demethylation[8c] of the bergenin derivatives 10e–g

The reaction was conducted as described in the Section 4.4, but in acetone/H_2O (9:1) instead of THF. When IBX was used, degradation of the starting material **10e–g** was observed. When SIBX was used, after stirring the solution in the dark at room temperature for 24 h, a second portion of SIBX (1.02 equiv, ca. 0.50 equiv of IBX) was added in order to complete the consumption of **10e**, or to optimize the conversion of **10f**/**g** (see the Supplementary data). After an additional period of time (24 h for **10e**, and 4 h for **10f**/**g**), the resulting white suspension was treated according to the general procedure (see the Section 4.4). In the case of bergenin (**10e**), after evaporation of the filtrate, the resulting pale yellow solid was successively washed with *n*-BuOH (10 mL) and acetone (15 mL) to discard the stabilizing agents (i.e., isophthalic acid and benzoic acid, respectively). The resulting crude norbergenin (**12e**) was then purified by preparative gel chromatography on

Sephadex® LH-20 (ca. 15 g), packing with pure MeOH and eluting with pure H_2O (ca. 100 mL) followed by H_2O/MeOH (1:1, ca. 50 mL) and pure MeOH (ca. 150 mL), to afford pure norbergenin (**12e**). In the case of the monobenzylated bergenins **10f**/**g**, after evaporation of the filtrate, the resulting solid mixture was separated by semi-preparative reverse phase HPLC, which was performed on a Varian ProStar system equipped with a Merck Lichrospher® RP-18 column (250×25 mm I.D., 5 μm), eluting with A/B (75:25) [solvent A=H_2O/HCO_2H (99:1); solvent B=CH_3CN/HCO_2H (99:1)] at a flow rate of 16 mL/min. Column effluent was monitored by UV detection at 280 nm using a ProStar 320 UV-visible detector, and pure catechols **12f** and **12g** were isolated, respectively [retention time=14.2 min for **12f**, and 16.9 min for **12g**] (see the Supplementary data).

*4.5.1. (−)-2-β-D-Glucopyranosyl-gallic acid δ-lactone (**12e**; norbergenin).* Beige amorphous solid (69% yield after purification on Sephadex® LH-20): mp 248–249 °C (lit.[22b] 250 °C); $[\alpha]_D^{20}$ −23.3 (*c* 0.30, MeOH) [lit.[22a] $[\alpha]^{18}_D$ −22.0 (*c* 1.00, EtOH)]; UV (MeOH) λ_{max} (log ϵ) 288 (2.08) nm; IR (neat) 3383, 2924, 1700, 1319, 1238, 1087 cm^{-1}; ^1H NMR [acetone-d_6/D_2O (9:1), 300 MHz] δ 3.48 (br t, *J*=9.2 Hz, 1H), 3.65–3.79 (m, 2H), 3.89 (br t, *J*=9.1 Hz, 1H), 4.02–4.09 (m, 2H), 4.98 (d, *J*=10.6 Hz, 1H), 7.09 (s, 1H); ^{13}C NMR [acetone-d_6/D_2O (9:1), 75.5 MHz] δ 166.2, 147.1, 143.6, 141.1, 117.5, 114.5, 111.1, 82.8, 81.3, 75.3, 74.1, 71.8, 62.6; EIMS *m*/*z* (rel intensity) 314 (M^+, 32), 195 (35), 194 (100); ESIMS *m*/*z* (rel intensity) 315 (MH^+, 100); HRMS (ESI) calcd for $C_{13}H_{14}NaO_9$ 337.0536, found 337.0540.

*4.5.2. (−)-2-β-D-Glucopyranosyl-10-O-benzyl-gallic acid δ-lactone (**12f**; 10-O-benzylnorbergenin).* White amorphous solid (20% yield after HPLC purification): mp 208–209 °C; $[\alpha]_D^{20}$ −32.4 (*c* 0.50, MeOH); UV (MeOH) λ_{max} (log ϵ) 247 (2.47), 270 (2.27) nm; IR (neat) 3366, 2926, 1710, 1335, 1223, 1091 cm^{-1}; ^1H NMR [acetone-d_6/D_2O (9:1), 300 MHz] δ 3.43–3.46 (m, 1H), 3.58 (br t, *J*=9.1 Hz, 1H), 3.68–3.83 (m, 3H), 3.96 (br t, *J*=9.8 Hz, 1H), 4.50 (d, *J*=10.2 Hz, 1H), 5.03 (d, *J*=11.3 Hz, 1H), 5.09 (d, *J*=11.3 Hz, 1H), 7.29–7.46 (m, 6H); ^{13}C NMR [acetone-d_6/D_2O (9:1), 75.5 MHz] δ 166.6, 147.4, 146.9, 144.6, 138.6, 130.0, 129.6, 129.5, 126.7, 115.3, 114.3, 82.2, 81.5, 75.9, 75.5, 73.2, 71.1, 62.0; ESIMS *m*/*z* (rel intensity) 405 (MH^+, 100); HRMS (ESI) calcd for $C_{20}H_{20}NaO_9$ 427.1005, found 427.0989.

*4.5.3. (−)-2-β-D-Glucopyranosyl-8-O-benzyl-gallic acid δ-lactone (**12g**; 8-O-benzylnorbergenin).* White amorphous solid (21% yield after HPLC purification): mp 197–198 °C; $[\alpha]_D^{20}$ −27.9 (*c* 0.50, MeOH); UV (MeOH) λ_{max} (log ϵ) 248 (2.42), 276 (2.27) nm; IR (neat) 3382, 2926, 1699, 1327, 1092 cm^{-1}; ^1H NMR [acetone-d_6/D_2O (9:1), 300 MHz] δ 3.48 (br t, *J*=9.1 Hz, 1H), 3.65–3.78 (m, 2H), 3.89 (br t, *J*=8.9 Hz, 1H), 4.01–4.09 (m, 2H), 4.99 (d, *J*=10.4 Hz, 1H), 5.19 (s, 2H), 7.20 (s, 1H), 7.29–7.48 (m, 5H); ^{13}C NMR [acetone-d_6/D_2O (9:1), 75.5 MHz] δ 166.0, 148.3, 143.6, 142.6, 138.1, 129.8, 129.4, 128.9, 119.4, 114.2, 109.3, 82.8, 81.1, 75.2, 73.9, 71.9, 71.7, 62.5; ESIMS *m*/*z* (rel intensity) 427 (MNa^+, 9), 405 (MH^+, 100); HRMS (ESI) calcd for $C_{20}H_{20}NaO_9$ 427.1005, found 427.0992.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.05.078.

References and notes

1. (a) Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*; VCH: New York, NY, 1992; (b) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic: London, 1997; (c) *Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis*; Wirth, T., Ed.Topics in Current Chemistry; Springer: Berlin, Heidelberg, New York, NY, 2003; Vol. 224; (d) Moriarty, R. M.; Prakash, O. *Hypervalent Iodine in Organic Chemistry: Chemical Transformations*; Wiley-Interscience: New York, NY, 2008.
2. For examples of review articles on hypervalent iodine chemistry, see: (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123–1178; (b) Kitamura, T.; Fujiwara, Y. *Org. Prep. Proced. Int.* **1997**, *29*, 409–458; (c) Varvoglis, A. *Tetrahedron* **1997**, *53*, 1179–1255; (d) Wirth, T.; Hirt, U. H. *Synthesis* **1999**, 1271–1287; (e) Koser, G. F. *Aldrichimica Acta* **2001**, *34*, 89–102; (f) Wirth, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 2812–2814; (g) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523–2584; (h) Stang, P. J. *J. Org. Chem.* **2003**, *68*, 2997–3008; (i) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656–3665; (j) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893–2903; (k) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299–5358; (l) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052–9070; (m) Uyanik, M.; Ishihara, K. *Chem. Commun.* **2009**, 2086–2099.
3. (a) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245–2258; (b) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Barluenga, S.; Hunt, K. W.; Kranich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2233–2244; (c) Nicolaou, K. C.; Sugita, K.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2221–2232; (d) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Sugita, K. *J. Am. Chem. Soc.* **2002**, *124*, 2212–2220.
4. (a) Ley, S. V.; Thomas, A. W.; Finch, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 669–671; (b) Sorg, G.; Mengel, A.; Jung, G.; Rademann, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4395–4397; (c) Ficht, S.; Mülbaier, M.; Giannis, A. *Tetrahedron* **2001**, *57*, 4863–4866; (d) Mülbaier, M.; Giannis, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4393–4394; (e) Reed, N. N.; Delgado, M.; Hereford, K.; Clapham, B.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2047–2049; (f) Togo, H.; Sakuratani, K. *Synlett* **2002**, 1966–1975; (g) Lei, Z.; Denecker, C.; Jegasothy, S.; Sherrington, D. C.; Slater, N. K. H.; Sutherland, A. J. *Tetrahedron Lett.* **2003**, *44*, 1635–1637; (h) Chung, W.-J.; Kim, D.-K.; Lee, Y.-S. *Tetrahedron Lett.* **2003**, *44*, 9251–9254; (i) Karimov, R. R.; Kazhkenov, Z.-G. M.; Modjewski, M. J.; Peterson, E. M.; Zhdankin, V. V. *J. Org. Chem.* **2007**, *72*, 8149–8151.
5. (a) Richardson, R. D.; Wirth, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4402–4404; (b) Ochiai, M. *Chem. Rec.* **2007**, *7*, 12–23; (c) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073–2085; (d) Ngatimin, M.; Lupton, D. W. *Aust. J. Chem.* **2010**, *63*, 653–658.
6. (a) Quideau, S.; Pouységu, L. *Org. Prep. Proced. Int.* **1999**, *31*, 617–680; (b) Quideau, S.; Pouységu, L.; Deffieux, D. *Curr. Org. Chem.* **2004**, *8*, 113–148; (c) Quideau, S.; Pouységu, L.; Deffieux, D. *Synlett* **2008**, 467–495; (d) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235–2261.
7. (a) Bérard, D.; Giroux, M.-A.; Racicot, L.; Sabot, C.; Canesi, S. *Tetrahedron* **2008**, *64*, 7537–7544; (b) Sabot, C.; Bérard, D.; Canesi, S. *Org. Lett.* **2008**, *10*, 4629–4632; (c) Sabot, C.; Commare, B.; Duceppe, M.-A.; Nahi, S.; Guérard, K. C.; Canesi, S. *Synlett* **2008**, 3226–3230; (d) Guérard, K. C.; Sabot, C.; Racicot, L.; Canesi, S. *J. Org. Chem.* **2009**, *74*, 2039–2045; (e) Sabot, C.; Guérard, K. C.; Canesi, S. *Chem. Commun.* **2009**, 2941–2943.
8. (a) Pouységu, L.; Chassaing, S.; Dejugnac, D.; Lamidey, A.-M.; Miqueu, K.; Sotiropoulos, J.-M.; Quideau, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3552–3555; (b) Quideau, S.; Lyvinec, G.; Marguerit, M.; Bathany, K.; Ozanne-Beaudenon, A.; Buffeteau, T.; Cavagnat, D.; Chénedé, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4605–4609; (c) Ozanne, A.; Pouységu, L.; Depernet, D.; François, B.; Quideau, S. *Org. Lett.* **2003**, *5*, 2903–2906; (d) Quideau, S.; Pouységu, L.; Deffieux, D.; Ozanne, A.; Gagnepain, J.; Fabre, I.; Oxoby, M. *Arkivoc* **2003**, *6*, 106–119.
9. (a) Quideau, S. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, 2002; pp 539–573; (b) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383–1429; (c) Rodriguez, S.; Wipf, P. *Synthesis* **2004**, *17*, 2767–2783.
10. (a) Murakata, M.; Yamada, K.; Hoshino, O. *J. Chem. Soc., Chem. Commun.* **1994**, 443–444; (b) Myers, A. G.; Siegel, D. R.; Buzard, D. J.; Charest, M. G. *Org. Lett.* **2001**, *3*, 2923–2926; (c) Mejorado, L. H.; Hoarau, C.; Pettus, T. R. R. *Org. Lett.* **2004**, *6*, 1535–1538; (d) Quideau, S.; Fabre, I.; Deffieux, D. *Org. Lett.* **2004**, *6*, 4571–4573.
11. (a) Liao, C.-C.; Chu, C.-S.; Lee, T.-H.; Rao, P. D.; Ko, S.; Song, L.-D.; Shiao, H.-C. *J. Org. Chem.* **1999**, *64*, 4102–4110; (b) Lai, C.-H.; Shen, Y.-L.; Wang, M.-N.; Rao, K.; Liao, C.-C. *J. Org. Chem.* **2002**, *67*, 6493–6502; (c) Deffieux, D.; Fabre, I.; Titz, A.; Léger, J.-M.; Quideau, S. *J. Org. Chem.* **2004**, *69*, 8731–8738; (d) Gagnepain, J.; Méreau, R.; Dejugnac, D.; Léger, J.-M.; Castet, F.; Deffieux, D.; Pouységu, L.; Quideau, S. *Tetrahedron* **2007**, *63*, 6493–6505; (e) Surasani, S. R.; Rajora, V. S.; Bodipati, N.; Peddinti, R. K. *Tetrahedron Lett.* **2009**, *50*, 773–775.
12. (a) Quideau, S.; Pouységu, L.; Looney, M. A. *J. Org. Chem.* **1998**, *63*, 9597–9600; (b) Quideau, S.; Looney, M. A.; Pouységu, L.; Ham, S.; Birney, D. M. *Tetrahedron Lett.* **1999**, *40*, 615–618; (c) Quideau, S.; Pouységu, L.; Avellan, A.-V.; Whelligan, D. K.; Looney, M. A. *Tetrahedron Lett.* **2001**, *42*, 7393–7396;

(d) Quideau, S.; Pouységu, L.; Oxoby, M.; Looney, M. A. *Tetrahedron* **2001**, *57*, 319–329; (e) Pouységu, L.; Avellan, A.-V.; Quideau, S. *J. Org. Chem.* **2002**, *67*, 3425–3436.
13. Kita, Y.; Tohma, H.; Kikuchi, K.; Inagaki, M.; Yakura, T. *J. Org. Chem.* **1991**, *56*, 435–438.
14. (a) Gagnepain, J.; Castet, F.; Quideau, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 1533–1535 and **2008**, *47*, 628; (b) Lebrasseur, N.; Gagnepain, J.; Ozanne-Beaudenon, A.; Léger, J.-M.; Quideau, S. *J. Org. Chem.* **2007**, *72*, 6280–6283.
15. (a) Quideau, S.; Pouységu, L.; Ozanne, A.; Gagnepain, J. *Molecules* **2005**, *10*, 201–216; (b) Pouységu, L.; Marguerit, M.; Gagnepain, J.; Lyvinec, G.; Eatherton, A. J.; Quideau, S. *Org. Lett.* **2008**, *10*, 5211–5214.
16. Magdziak, D.; Rodriguez, A. A.; Van De Water, R. W.; Pettus, T. R. R. *Org. Lett.* **2002**, *4*, 285–288.
17. Wu, A.; Duan, Y.; Xu, D.; Penning, T. M.; Harvey, R. G. *Tetrahedron* **2010**, *66*, 2111–2118.
18. (a) Rojas Fermín, L.B. Doctoral Thesis, Université Bordeaux 1, France, 2005, Order No. 2983; (b) Plourde, G. L.; Spaetzel, R. R. *Molecules* **2002**, *7*, 697–705.
19. This improved yield compared to that we previously obtained [i.e., 32%, see Ref. 8c] further evidences the facility with which iodoxybenzoic acid reagents dehydrogenate benzylic alcohols.
20. Fernandez-Bolanos, J. G.; Lopez, O.; Fernandez-Bolanos, J.; Rodriguez-Gutierrez, G. *Curr. Org. Chem.* **2008**, *12*, 442–463.
21. (a) Bernini, R.; Mincione, E.; Barontini, M.; Crisante, F. *J. Agric. Food Chem.* **2008**, *56*, 8897–8904 See also: (b) Bernini, R.; Mincione, E.; Crisante, F.; Barontini, M.; Fabrizi, G. *Tetrahedron Lett.* **2009**, *50*, 1307–1310; (c) Bernini, R.; Barontini, M.; Mosesso, P.; Pepe, G.; Willför, S. M.; Sjöholm, R. E.; Eklund, P. C.; Saladino, R. *Org. Biomol. Chem.* **2009**, *7*, 2367–2377.
22. (a) Piacente, S.; Pizza, C.; De Tommasi, N.; Mahmood, N. *J. Nat. Prod.* **1996**, *59*, 565–569; (b) Takahashi, H.; Kosaka, M.; Watanabe, Y.; Nakade, K.; Fukuyama, Y. *Bioorg. Med. Chem.* **2003**, *11*, 1781–1788.
23. (a) Dohi, T.; Maruyama, A.; Takenaga, N.; Senami, K.; Minamitsuji, Y.; Fujioka, H.; Caemmerer, S. B.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3787–3790; (b) Boppisetti, J. K.; Birman, V. B. *Org. Lett.* **2009**, *11*, 1221–1223; (c) Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2175–2177.
24. Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537–4538.
25. (a) Bessong, P. O.; Obi, C. L.; Andréola, M.-L.; Rojas, L. B.; Pouységu, L.; Igumbor, E.; Meyer, J. J. M.; Quideau, S.; Litvak, S. *J. Ethnopharmacol.* **2005**, *99*, 83–91; (b) Posternak, T.; Dürr, K. *Helv. Chim. Acta* **1958**, *41*, 1159–1162; (c) Hay, J. E.; Haynes, L. J. *J. Chem. Soc.* **1958**, 2231–2238; (d) Atchuta Ramaiah, P.; Ramachandra Row, L.; Sivakumar Reddy, D.; Anjaneyulu, A. S. R.; Ward, R. S.; Pelter, A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2313–2316.
26. *Protocatechualdehyde. In The Merck Index*, 11th ed., 1989, p 1254.