

Total Synthesis of (–)-Bacchopetiolone via an Asymmetric Hydroxylative Phenol Dearomatization/[4+2]-Dimerization Cascade Promoted by a Novel Salen-Type Chiral Iodane

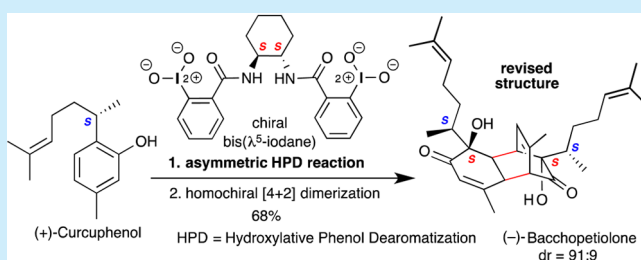
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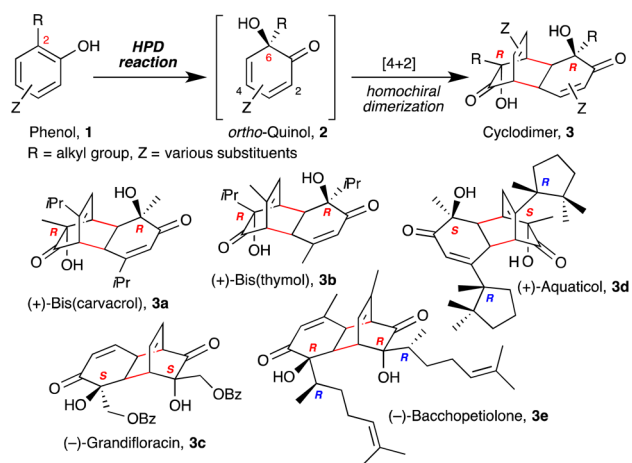
S Supporting Information

ABSTRACT: The first total and biomimetic synthesis of the natural bis(sesquiterpene) (–)-bacchopetiolone (revised structure) was completed through a highly diastereoselective hydroxylative phenol dearomatization/[4+2]-dimerization cascade conversion of (+)-curcuphenol using a novel C₂-symmetrical chiral Salen-type bis(λ^5 -iodane).



Oxidative phenol dearomatization is a powerful and often biomimetic tactic for the synthesis of complex natural products, as it allows the conversion of planar aromatic scaffolds into highly functionalized and possibly chiral cyclohexadienone-type synthons.^{1–3} Hypervalent organoiodine compounds, also referred to as iodanes, occupy a place of choice among reagents capable of such dearomative transformations, notably because these iodanes can substitute environmentally deleterious metal-based reagents and are also amenable to the introduction of chiral ligands for asymmetric reactions.^{1d,4} The hydroxylative phenol dearomatization (HPD)/[4+2]-dimerization cascade conversion of 2-alkylphenols **1** into 6-alkyl-6-hydroxycyclohexa-2,4-dienone (*o*-quinol)-derived *endo*-cyclodimers **3** is one of the archetypal reactions^{2a,5,6} that can benefit from the intervention of (chiral) iodanes (Scheme 1). The λ^5 -iodane 2-iodylbenzoic acid (IBX) or its stabilized (nonexplosive) version named SIBX⁷ mediates the regioselective dearomative hydroxylation of 2-alkylphenols into racemic *o*-quinols **2**, which usually and spontaneously cyclodimerize.^{2a,5b,d–i} Natural cyclodimers such as bis(carvacrol) **3a**, grandifloracin **3c**, and aquaticol **3d** have been synthesized in this way.^{5e–8} More recently, chiral iodanes were designed to promote asymmetric versions of some of these syntheses.^{6a–c} Our own contribution relied on the design of an axially chiral biphenylic bis(iodyl) reagent (**A**) (Scheme 3), which was used for the enantioselective syntheses of the natural bis(carvacrol) (+)-**3a** and its regioisomer bis(thymol) (+)-**3b** with enantiomeric excesses (ee) up to 94%.^{6a} This success made us turn our attention to finding a solution for the still-unachieved total synthesis of (–)-bacchopetiolone **3e**.⁸ This bis(sesquiterpene) was isolated in 1991 from *Baccharis petiolata* (Asteraceae), a Chilean shrub used in traditional medicine.^{8a} The structure of **3e** was reported as an “allR” [4+2]-cyclodimerization product of the *o*-quinol (6*R*,7*R*)-**2e** (not shown), which would be itself derived

Scheme 1. HPD Reaction/[4+2]-Dimerization Cascade Conversion of 2-Alkylphenols **1** and Representative *o*-Quinol-Based Cyclodimers **3a–e**

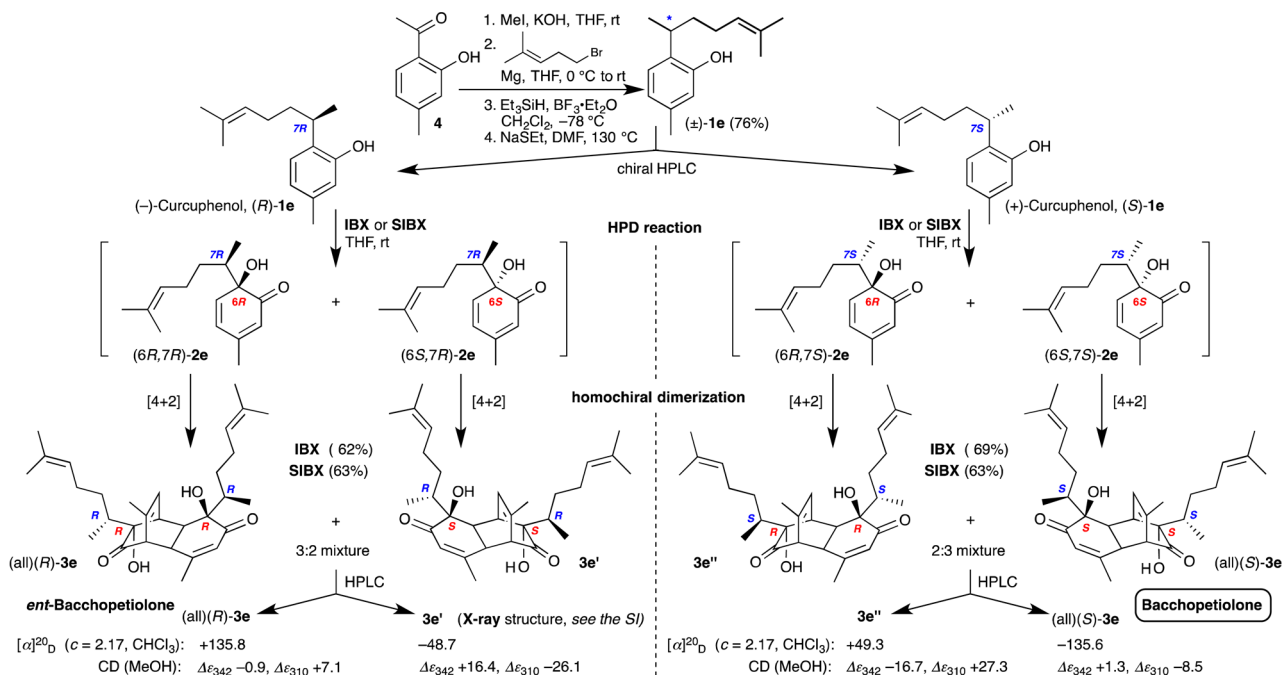


from an enantioselective biosynthetic HPD of (–)-curcuphenol (**R**)-**1e**.^{8a} We herein report the first total synthesis of (–)-bacchopetiolone that resulted from an investigation of the HPD-induced conversion of **1e** using either IBX, SIBX, previously developed chiral biaryl iodanes, or new Salen-type bis(λ^5 -iodanes).

Our synthesis began with the preparation of racemic curcuphenol **1e** starting from acetophenone **4** and using a combination of known protocols [Scheme 2 and Supporting

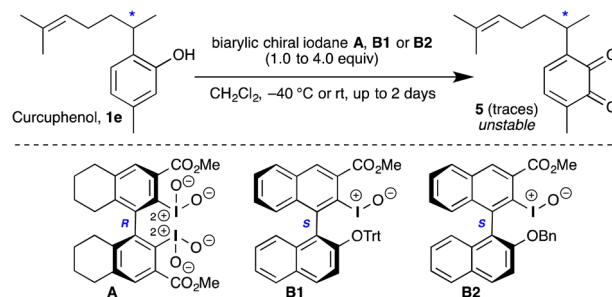
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Scheme 2. IBX- or SIBX-Mediated Synthesis of (–)-Bacchopetiolone (All)(S)-3e and Its Diastereomers



Information (SI)].⁹ Scale-up of this four-step synthesis (76% overall yield) reproductively afforded ca. 2 g of (±)-1e, which was easily separated by chiral semipreparative HPLC. We first verified the reactivity of (–)-(R)-1e by subjecting it to our standard IBX- or SIBX-mediated HPD conditions,^{5c–h} which led to the expected *endo*-[4+2]-homodimers in ca. 60% yield as a clean 3:2 mixture of the (all)(R)-3e and its diastereomer 3e' (Scheme 2). These diastereomers were separated by HPLC, and their structures were determined by NMR spectroscopy (see the SI). In addition, an X-ray analysis of the colorless plates obtained by crystallization of 3e' from hot hexanes confirmed both the expected *endo*-cycloaddition mode and the homochiral dimerization process (CCDC-993815, see Figure S4).¹⁰ However, optical rotation and circular dichroism measurements surprisingly indicated that none of these two dimers could be identified as the natural bis(sesquiterpene) $[[\alpha]_D^{24} - 125$ (c = 2.17, CHCl_3); CD (MeOH) $\Delta\epsilon_{342} +0.2$, $\Delta\epsilon_{306} -4.6$]^{8a} and that the (all)(R)-3e dimer was in fact *ent*-bacchopetiolone. The previously proposed biosynthesis of (–)-bacchopetiolone from (R)-curcuphenol thus appeared incorrect.^{8a} Therefore, we subjected (+)-(S)-1e to the same IBX- or SIBX-mediated HPD conditions in order to obtain the other two possible diastereomers. The (all)(S)-3e dimer turned out to correspond to the known natural product (Scheme 2 and SI).

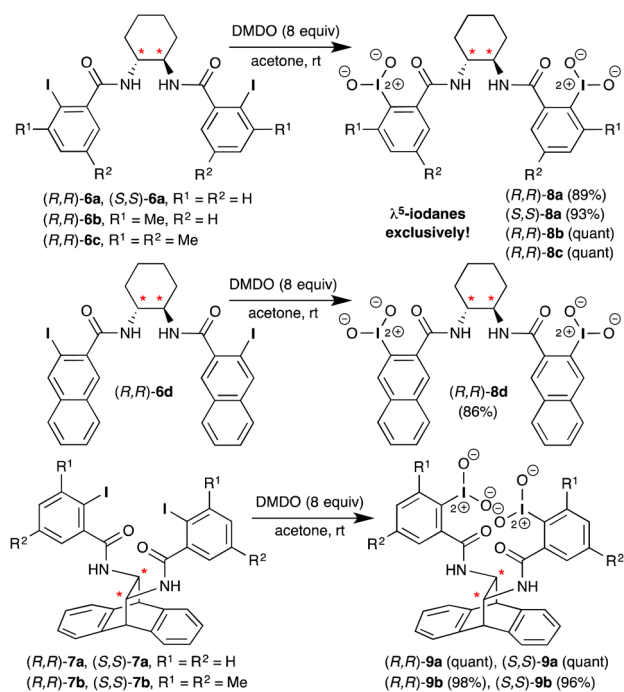
We then attempted the same transformation of 1e, but this time using our chiral biphenylic bis(λ^5 -iodane) (R)-A.^{6a} Unfortunately, the conditions tested (i.e., 1.0 to 4.0 equiv of A in CH_2Cl_2 at –40 °C or at room temperature, with reaction times up to 2 days) did not give rise to the expected cyclodimers but instead led to traces of an unstable dark yellow quinonoid product. It was identified by ¹H NMR analysis as the *o*-quinone derivative 5 that results from oxygenation at the unsubstituted *ortho*-position of 1e^{5f–h} (Scheme 3 and SI). Compound 5 was also formed when 1e was treated with the chiral alkoxyated binaphthyl λ^3 -iodanes (S)-B1 and (S)-B2,^{6a} thus indicating that the *o*-(6-methylhept-5-en-2-yl) side chain of curcuphenol

Scheme 3. Conversion of Curcuphenol 1e into the *o*-Quinone Derivative 5

impedes the desired oxygen-atom transfer regioselectivity with these probably too bulky iodanes.

Therefore, we decided to continue our exploration of novel chiral organoiodane structures capable of promoting asymmetric HPD/[4+2]-cascade conversion of 2-alkylphenols, with the added specific aim of finding a suitable reagent for the transformation of (+)-(S)-1e into (–)-bacchopetiolone 3e. The main prerequisite for this search of novel chiral organoiodanes was the utilization of readily accessible chiral motifs on which iodoaryl units can be easily installed. We thus considered the synthesis of the chiral bis(amidoiodoarenes) 6 and 7 with structures based on C_2 -symmetrical Salen-type scaffolds, whose design was inspired by that of the diphenylphosphinobenzoic acid (DPPBA)-based ligands used in asymmetric transition-metal-catalyzed reactions (Scheme 4).¹¹ We expected that the resulting iodanes could benefit from stabilizing interactions between their amide functions and hypervalent iodine centers.¹² The diiodo compounds 6 and 7 were synthesized in a high-yielding one-step process through coupling of a C_2 -symmetrical chiral diamine with an *o*-iodinated benzoic acid (see Scheme S2). The *trans*-1,2-diaminocyclohexane-based bis(iodoarene) (R,R)-6a was selected to identify suitable conditions for conversion into its corresponding bis(iodane). A screening of oxidizing systems among those classically used in hypervalent iodine chemis-

Scheme 4. DMDO-Mediated Oxygenation of C_2 -Symmetrical Salen-Type Bis(iodoarenes) **6a–d and **7a/b** into Bis(λ^5 -iodanes) **8a–d** and **9a/b****



try^{4c,6a,12b} revealed that effective oxygenation of **6a** could be achieved only with DMDO (Scheme 4).^{6a,c,12b} Using 8 equiv of freshly prepared DMDO at room temperature for 24 h, a single iodane precipitated from the reaction mixture. It was identified as the bis(iodyl) derivative (*R,R*)-**8a** and isolated in 89% yield by simple filtration (see the SI). ¹³C NMR analysis was used to confirm the oxidation state of its iodine centers on the basis of the chemical shift of the aromatic *ipso* carbons ($C_{ipso}-I^V$) at 148.8 ppm in DMSO- d_6 .¹³ No iodosyl variant (i.e., any λ^3 -iodane with $C_{ipso}-I^{III}$ resonating at 110–120 ppm) was detected.

This selective DMDO-mediated oxygenation was successfully applied to other *trans*-diaminocyclohexane- and *trans*-11,12-diamino-9,10-dihydro-9,10-ethanoanthracene-based bis(iodoarenes) **6b–d** and **7a/b** to furnish the bis(λ^5 -iodanes) **8b–d** and **9a/b** in high yields (Scheme 4). These new bis(iodyl) compounds were obtained as stable amorphous powders, but the dimethylated bis(iodylaryl) and the bis(iodylnaphthyl) derivatives **8c**, **9b**, and **8d** were found to be unstable in solution, as they slowly degraded during the acquisition of their ¹³C NMR

spectrum in DMSO- d_6 .¹⁴ Their insolubility in most common solvents is probably due to their arrangement in polymeric structures.^{4c,12b} DFT calculations (B3LYP/6-31G** for C,H,O,N and Stuttgart–Dresden (SDD) pseudopotential for I; see the SI) were performed on (*R,R*)-**8a** to examine this structural hypothesis. Indeed, strong secondary I...O bonding interactions between neighboring molecules of the calculated “dimer” and “trimer” of **8a** (average interatomic distances of 2.8 Å) were highlighted (see the SI), together with the expected intramolecular contacts of the I^V centers with the oxygen atom of each amide group (ca. 2.7 Å), in agreement with reported X-ray crystallographic data on a 2-iodylbenzamide tetramer.^{12b}

The capacity of these new chiral λ^5 -iodanes to transfer their oxygen atom(s) in an asymmetric fashion was then first evaluated through the HPD/[4+2]-dimerization cascade conversion of simple achiral 2-alkylphenols, including the monoterpenes carvacrol **1a** and its 2-isopropylated regioisomer thymol **1b** (see Tables S1 and S3). For the conversion of **1a** into bis(carvacrol) **3a**,^{3c,6a} the best ee values of 60 and 68% were obtained using a slight excess (i.e., 0.65 equiv) of enantiomers of the anthracenyl-mounted bis(iodyl) **9a** either in a 85:15 CH₂Cl₂/TFE solvent mixture (TFE = 2,2,2-trifluoroethanol)¹⁵ at room temperature for 16 h or in CH₂Cl₂ with 1.0 equiv of trifluoroacetic acid^{6c,16} (TFA) at –50 °C for 2 h. This positive influence of TFA on the reaction outcome^{6c,16} might be explained by a TFA-mediated “depolymerization”¹⁶ of the hypothesized structure of our Salen-type iodanes (vide supra), thus providing the phenolic substrate with a better access to the electrophilic I^V -centers. The bis(iodyl) (*R,R*)-**9a** was then used to convert **1b** into bis(thymol) (+)-**3b**^{6a} in good to high yields with ee values up to 74%. These promising results led us to attempt the conversion of curcuphenol **1e** into bacchopetiolone **3e** using this same bis(iodyl) reagent. Unfortunately, after 2 days at room temperature in CH₂Cl₂/TFE (85:15), only the *o*-quinone **5** (see Scheme 3) was observed and isolated in 48% yield. Notwithstanding this disappointing result, we looked back at our other chiral Salen-type iodanes and were pleased to observe that the cyclohexyl-based bis(λ^5 -iodanes) **8** were capable of cleanly promoting the desired conversion of **1e** into **3e**. The bis(iodyl) **8a** turned out to be the most useful reagent (Table 1). A diastereomeric ratio (dr) of 72:28 in favor of the (all)(*R*)-**3e** dimer was obtained when (*R*)-**1e** was treated with 0.65 equiv of (*R,R*)-**8a** in CH₂Cl₂/TFE at room temperature for 16 h (Table 1, entry 1). The oxygenative dearomatization of (*S*)-**1e** showed a clear mismatch effect with (*R,R*)-**8a** under the same conditions, since it led to **3e** with a dr of 50:50 (entry 2). A decrease of the reaction temperature down to –35 °C, combined with an

Table 1. Asymmetric HPD/[4+2]-Dimerization Cascade Reaction of Curcuphenol **1e Using the Bis(λ^5 -iodane) **8a**^a**

entry	1e	8a	equiv	solvent	temp (°C)	time (h)	3e ^b (major)	yield ^c (%)	dr ^d
1	<i>R</i>	(<i>R,R</i>)	0.65	CH ₂ Cl ₂ /TFE (85:15)	rt	16	(all)(<i>R</i>)	45	72:28
2	<i>S</i>	(<i>R,R</i>)	0.65	CH ₂ Cl ₂ /TFE (85:15)	rt	16	(all)(<i>R</i>)	44	50:50
3	<i>R</i>	(<i>R,R</i>)	0.65	CH ₂ Cl ₂ /TFE (85:15)	–35	72	(all)(<i>R</i>)	43	78:22
4	<i>R</i>	(<i>R,R</i>)	1.10	CH ₂ Cl ₂ /TFE (85:15)	–35	72	(all)(<i>R</i>)	50	79:21
5	<i>S</i>	(<i>S,S</i>)	1.10	CH ₂ Cl ₂ /TFE (85:15)	–35	72	(all)(<i>S</i>)	42	80:20
6	<i>R</i>	(<i>R,R</i>)	1.10	CH ₂ Cl ₂ , TFA ^e	–45	2	(all)(<i>R</i>)	58	88:12
7	<i>S</i>	(<i>S,S</i>)	1.10	CH ₂ Cl ₂ , TFA ^e	–45	2	(all)(<i>S</i>)	68	91:9
8	<i>S</i>	(<i>S,S</i>)	1.10	CH ₂ Cl ₂ , TFA ^e	–50	1.5	(all)(<i>S</i>)	31	86:14

^aReactions run using [**1e**] = 14 mM. ^bMajor cyclodimer **3e** identified by chiral HPLC analysis and comparison with the IBX- or SIBX-synthesized cyclodimers. ^cIsolated yield. ^dDiastereomeric ratio determined by chiral HPLC analysis. ^e1.0 equiv (all)(*R*) = *ent*-bacchopetiolone, (all)(*S*) = bacchopetiolone.

increase of the amount of iodane (1.10 equiv), led to some diastereoselectivity improvement with dr values up to 80:20, but these conversions required a much longer reaction time (Table 1, entries 3–5). It is again the use of the CH₂Cl₂/TFA solvent system that gave the best results, allowing us to step up close to a dr of 90:10 (entries 6–8). In this solvent system, the HPD/[4+2]-cascade reaction of (+)-curcuphenol (S)-1e using the bis(λ^5 -iodane) (S,S)-8a was best performed at –45 °C for 2 h to furnish the natural “allS” (–)-bacchopetiolone 3e in 68% isolated yield and with an excellent dr of 91:9 (Table 1, entry 7).

In summary, we have accomplished the first total, biomimetic, and diastereoselective synthesis (in five steps with 23% overall yield from acetophenone 4) of the bis(sesquiterpene) (–)-bacchopetiolone, whose structure and biosynthetic filiation could hence be revised to the “allS” diastereomer 3e derived from (+)-curcuphenol (S)-1e. This achievement was made possible thanks to the development of readily accessible chiral Salen-type bis(λ^5 -iodanes), among which the cyclohexyl-based reagent (S,S)-8a was used to promote the focal asymmetric HPD/[4+2]-cascade step of this synthesis.

■ ASSOCIATED CONTENT

● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00224.

Experimental procedures and full compound characterization, including ¹H and ¹³C NMR spectra for all new compounds; HPLC traces; computational results (PDF) Crystallographic data of 3e' (CIF)

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Author Contributions

§R.C. and M.E.A. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) Recent reviews on dearomatization in natural product synthesis: (a) Ding, Q.; Ye, Y.; Fan, R. *Synthesis* **2012**, 45, 1. (b) Zhuo, C.-X.; Zhang, W.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, 51, 12662. (c) Roche, S. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, 50, 4068. (d) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, 66, 2235.
- (2) Selection of reviews on cyclohexadienones, see: (a) Quideau, S.; Pouységu, L.; Deffieux, D. *Synlett* **2008**, 467. (b) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, 104, 1383. (c) Liao, C.-C.; Peddinti, R. K. *Acc. Chem. Res.* **2002**, 35, 856. (d) Quideau, S.; Pouységu, L. *Org. Prep. Proced. Int.* **1999**, 31, 617.
- (3) Selected examples of nonracemic cyclohexa-2,4-dienones: (a) Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2013**, 52, 9215. (b) Dohi, T.; Takenaga, N.; Nakae, T.; Toyoda, Y.; Yamasaki, M.; Shiro, M.; Fujioka, H.; Maruyama, A.; Kita, Y. *J. Am. Chem. Soc.* **2013**, 135, 4558. (c) Pouységu, L.; Chassaing, S.; Dejuguac, D.; Lamidey, A.-M.; Miquieu, K.; Sotiropoulos, J.-M.; Quideau, S. *Angew. Chem., Int. Ed.* **2008**, 47, 3552. (d) Quideau, S.; Fabre, I.; Deffieux, D. *Org. Lett.* **2004**, 6, 4571. (e) Mejorado, L. H.; Hoarau, C.; Pettus, T. R. R. *Org. Lett.* **2004**, 6, 1535.
- (4) Recent reports on chiral iodanes: (a) Berthiol, F. *Synthesis* **2015**, 47, 587. (b) Harned, A. M. *Tetrahedron Lett.* **2014**, 55, 4681. (c) Zhdankin, V. V. *Hypervalent Iodine Chemistry – Preparation, Structure, and Synthetic Applications of Polyvalent Iodine Compounds*; Wiley: Chichester, 2013. (d) Parra, A.; Reboredo, S. *Chem. - Eur. J.* **2013**, 19, 17244. (e) Uyanik, M.; Ishihara, K. *Yuki Gosei Kagaku Kyokaiishi* **2012**, 70, 1116. (f) Liang, H.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2011**, 50, 11849. (g) Farid, U.; Wirth, T. *Stereoselective Synthesis with Hypervalent Iodine Reagents. In Asymmetry Synthesis II: More Methods and Applications*, Christmann, M., Bräse, S., Eds.; Wiley-VCH: Weinheim, 2012; p 197.
- (5) (a) Bergner, M.; Duquette, D. C.; Chio, L.; Stoltz, B. M. *Org. Lett.* **2015**, 17, 3008. (b) Ren, X.-D.; Zhao, N.; Xu, S.; Lü, H.-N.; Ma, S.-G.; Liu, Y.-B.; Li, Y.; Qu, J.; Yu, S.-S. *Tetrahedron* **2015**, 71, 4821. (c) Pouységu, L.; Marguerit, M.; Gagnepain, J.; Lyvinec, G.; Eatherton, A. J.; Quideau, S. *Org. Lett.* **2008**, 10, 5211. (d) Gagnepain, J.; Méreau, R.; Dejuguac, D.; Léger, J.-M.; Castet, F.; Deffieux, D.; Pouységu, L.; Quideau, S. *Tetrahedron* **2007**, 63, 6493. (e) Lebrasseur, N.; Gagnepain, J.; Ozanne-Beaudenon, A.; Léger, J.-M.; Quideau, S. *J. Org. Chem.* **2007**, 72, 6280. (f) Gagnepain, J.; Castet, F.; Quideau, S. *Angew. Chem., Int. Ed.* **2007**, 46, 1533. (g) Gagnepain, J.; Castet, F.; Quideau, S. *Angew. Chem., Int. Ed.* **2008**, 47, 628. (h) Quideau, S.; Pouységu, L.; Deffieux, D.; Ozanne, A.; Gagnepain, J.; Fabre, I.; Oxoby, M. *Arkivoc* **2003**, 6, 106. (i) Magdziak, D.; Rodriguez, A. A.; Van De Water, R. W.; Pettus, T. R. R. *Org. Lett.* **2002**, 4, 285.
- (6) (a) Bosset, C.; Coffinier, R.; Peixoto, P. A.; El Assal, M.; Miquieu, K.; Sotiropoulos, J.-M.; Pouységu, L.; Quideau, S. *Angew. Chem., Int. Ed.* **2014**, 53, 9860. (b) Quideau, S.; Lyvinec, G.; Marguerit, M.; Bathany, K.; Ozanne-Beaudenon, A.; Buffeteau, T.; Cavagnat, D.; Chénéde, A. *Angew. Chem., Int. Ed.* **2009**, 48, 4605. (c) Boppisetti, J. K.; Birman, V. B. *Org. Lett.* **2009**, 11, 1221. (d) Dong, S.; Zhu, J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2008**, 130, 2738.
- (7) Ozanne, A.; Pouységu, L.; Depernet, D.; François, B.; Quideau, S. *Org. Lett.* **2003**, 5, 2903.
- (8) (a) Zdero, C.; Bohlmann, F.; Niemeyer, H. M. *Phytochemistry* **1991**, 30, 1597. (b) Bérubé, A.; Drutu, I.; Wood, J. L. *Org. Lett.* **2006**, 8, 5421.
- (9) (a) Du, Z.; Li, Y.; Wang, Y.; Ding, L.; Gao, J. *Synth. Commun.* **2010**, 40, 1920. (b) Montiel, L. E.; Zepeda, L. G.; Tamariz, J. *Helv. Chim. Acta* **2010**, 93, 1261. (c) Palais, L.; Alexakis, A. *Chem. - Eur. J.* **2009**, 15, 10473.
- (10) Crystallographic data CCDC-993815 (3e') can be obtained free of charge from the Cambridge Crystallographic Data Centre.
- (11) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, 103, 2921.
- (12) (a) Zhdankin, V. V.; Protasiewicz, J. D. *Coord. Chem. Rev.* **2014**, 275, 54. (b) Zhdankin, V. V.; Kuposov, A. Y.; Netzel, B. C.; Yashin, N. V.; Rempel, B. P.; Ferguson, M. J.; Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, 42, 2194.
- (13) Katritzky, A. R.; Gallos, J. K.; Dupont Durst, H. *Magn. Reson. Chem.* **1989**, 27, 815.
- (14) In situ generation of these iodanes could bypass their lack of stability in solution, but terminal oxidants (e.g., *m*-CPBA, DMDO) commonly used in catalytic processes are not compatible with oxygenation-sensitive 2-alkylphenols; see ref 6a.
- (15) (a) Shuklov, I. A.; Dubrovina, N. V.; Börner, A. *Synthesis* **2007**, 2007, 2925. (b) Ito, M.; Ogawa, C.; Yamaoka, N.; Fujioka, H.; Dohi, T.; Kita, Y. *Molecules* **2010**, 15, 1918.
- (16) Boulangé, A.; Peixoto, P. A.; Franck, X. *Chem. - Eur. J.* **2011**, 17, 10241.