JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

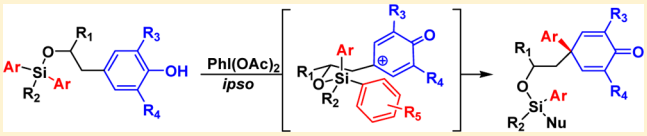
Oxidative *ipso*-Rearrangement Performed by a Hypervalent Iodine Reagent and Its Application

Guillaume Jacquemot and Sylvain Canesi*

Laboratoire de Méthodologie et Synthèse de Produits Naturels, Université du Québec à Montréal, C.P. 8888, Succ. Centre-Ville, Montréal, H3C 3P8 Québec, Canada

Supporting Information

ABSTRACT: An oxidative *ipso*-rearrangement mediated by a hypervalent iodine reagent that enables rapid generation of a functionalized dienone system containing a quaternary carbon center connected to several sp^2 centers has been developed. The process occurs through transfer of an aryl group from a silyl segment present on the lateral chain. As an illustration of the potential of this transformation, a total synthesis of sceletenone, a small alkaloid, is described.



INTRODUCTION

Structures containing a quaternary carbon center connected to an aryl group and including a cyclohexanone derivative have attracted substantial interest due to the large number of bioactive natural products containing a similar motif, including Amaryllidaceae alkaloids such as *O*-methylsceletenone **1a**, isolated from *Aptenia Cordifolia*[1] in South Africa, and its *O*-demethylated analogue sceletenone, isolated from the phenolic alkaloid fraction of *Sceletium strictum*.[1] Both of these compounds are potent serotonin reuptake inhibitors. Other examples include narwedine[2] **2** and vindoline **3**, which is an important moiety of vincristine, a mitotic inhibitor isolated from *catharanthus roseus*[3] and used in cancer chemotherapy (Figure 1).

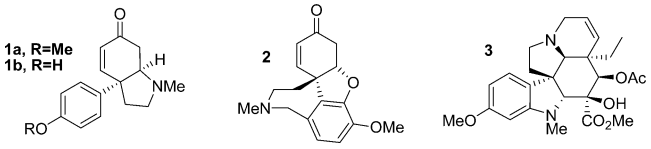


Figure 1. Natural alkaloids containing quaternary carbon centers.

To generate these structures, we have developed an approach involving a hypothetical intramolecular "oxidative *ipso*-rearrangement" promoted by subsequent oxidation of a substituted phenol containing a preactivated migrating group and connected to a silicon atom on the lateral chain. We assume that this process occurs via a chairlike transition state **5** leading to compound **6** (Figure 2).

In this paper, we describe an oxidative *ispo*-shift process occurring in electron-rich aromatic compounds and leading to the formation of a prochiral dienone system containing a quaternary carbon center connected to several sp^2 centers. The method is then applied to the total syntheses of *O*-methylsceletenone and sceletenone, two natural alkaloids.

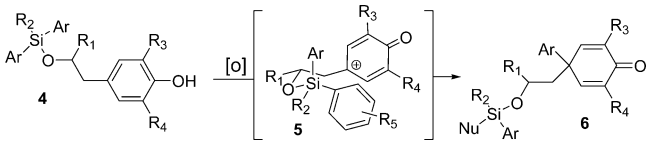


Figure 2. Oxidative *ipso*-rearrangement pathway.

RESULTS AND DISCUSSION

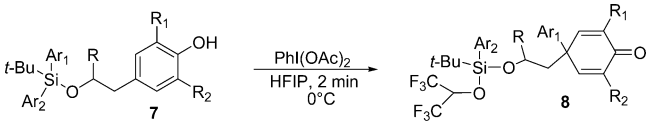
The approach requires activation to transform the electron-rich phenol into an electrophilic species susceptible to trapping by the silyl-aryl group. When the process involves an intermediate such as **5** it may be termed "aromatic ring umpolung".[4] Although electron-rich aromatic systems such as **4** normally react as nucleophiles, oxidative activation converts them into highly electrophilic species that may then be intercepted with appropriate nucleophiles. This umpolung activation is mediated by hypervalent iodine reagents such as iodobenzene diacetate (DIB) or equivalent mild oxidizing agents. The potential of this environmentally benign reagent was made evident in the pioneering work of Kita.[5] In particular, DIB promotes oxidative transformation of phenols[6,7] in a manner consistent with recent requirements for green chemical processes. As observed by Kita and co-workers,[8] DIB reactions generally occur best in non-nucleophilic highly polar solvents such as trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP). In this paper, we propose an unprecedented *ipso*-rearrangement initiated by a hypervalent iodine reagent to form a functionalized dienone system containing a quaternary carbon center connected to several sp^2 atoms including an aromatic moiety, a structural feature present in a large number of bioactive natural products. Our first attempts to verify the feasibility of this transformation were undertaken using a simple TBDPS (or a derivative)-

Received: July 5, 2012
Published: August 6, 2012

   dx.doi.org/10.1021/jo301408j | J. Org. Chem. 2012, 77, 7588−7594

protected alcohol functionality easily accessible on a large scale by protection of inexpensive starting materials **7** (Table 1).

Table 1. Oxidative *ipso*-shift process



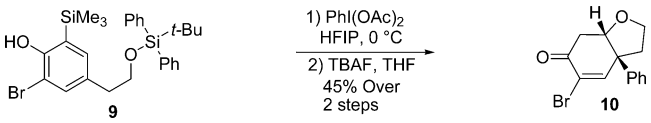
7 8

entry	Ar_1	Ar_2	R	R_1	R_2	yield (%)
a	Ph	Ph	H	H	H	40
b	*p*-anisole	*p*-anisole	H	H	H	74
c	*p*-toluene	*p*-toluene	H	H	H	51
d	Ph	OH	Me	H	H	37[a]
e	Ph	Ph	H	Br	*t*-Bu	62
f	Ph	Ph	H	*t*-Bu	*t*-Bu	85[a]
g	Ph	Ph	H	OMe	H	44[a]

[a]A minor amount of $OCH(CF_3)_2$ has been substituted by an acetate or an hydroxyl

It should be stressed that the reaction occurs in moderate to good yield (37−85%) with a simple benzene derivative; however, the one-step transformation of the simple and easily accessible starting material **7** in a highly functionalized core **8** would provide even more favorable results in terms of global yield and number of steps than traditional methodologies. As expected with *p*-toluene and *p*-anisole derivatives (entries **7c** and **7b**), the reaction occurs in higher yield compared to entry **7a** due to the presence of an electron-donating methyl or methoxy group in the *para* position. As previously observed in similar transformations, the reaction occurs in greater yields (up to 85%, entries **7e** and **7f**) when the phenol moiety is substituted with a *tert*-butyl group.[4d] This can be rationalized by considering the *tert*-butyl group as an electron donor stabilizing the electrophilic species **5**, enabling the *ipso* rearrangement and limiting alternate reaction pathways such as elimination of a benzilic hydrogen. A surprising aspect of this process is the nucleophilic addition of HFIP to the nascent asymmetric silicon center, sometimes accompanied by a small amount of acetate (∼10%) released from the hypervalent iodine reagent. HFIP is a weakly reactive nucleophile and is normally considered an inert solvent. Further treatment of the resulting dienone system with TBAF furnishes oxygenated versions of bicyclic systems similar to the natural products illustrated in Figure 1. For example, oxidation of compound **9** followed by direct treatment of the crude mixture with TBAF leads to the bicyclic system **10** in 45% yield over two steps (Scheme 1).

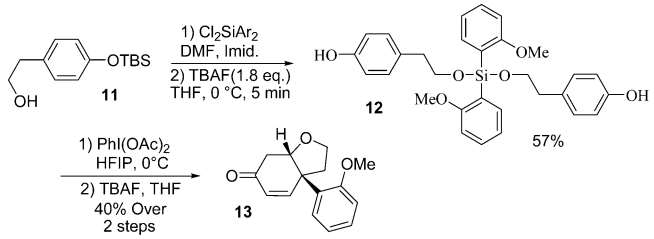
Scheme 1. Oxidative *ipso*-1,4-Conjugate Addition



9 10

In order to develop a method with favorable atom economy, dimers such as **12** containing two phenol moieties and two aromatic segments have been prepared. In this case, only one silicon atom is used as a tether to generate two dienone subunits, and subsequent treatment with TBAF produces the tricyclic core **13**. In order to generate the more elaborate quaternary carbon-connected aromatic systems found in natural products, an *o*-anisole subunit was used as a migrating group. The corresponding dimer was obtained by treatment of dichloro-diarylsilane with an *O*-TBS-protected phenol followed by a selective phenol deprotection in 57% overall yield (Scheme 2).

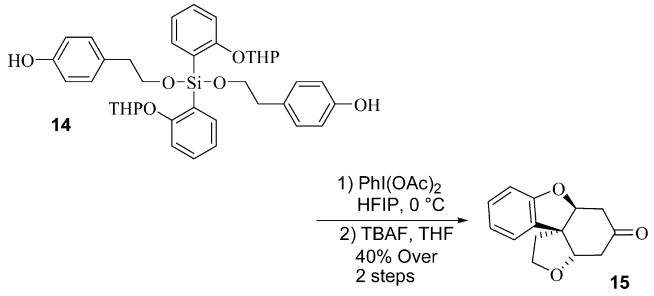
Scheme 2. Application to Dimeric Substrates



11 12 13

The potential utility of this new method is demonstrated in an expeditious two-step method to generate the tetracyclic system **15**, an oxygenated version of the main core of vindoline **3** (Figure 1). The oxidation occurs via *ipso*-rearrangement followed by a tetrahydropyran deprotection and subsequent 1,4-conjugate addition from the resulting phenol moiety, provoked by the acidity of the medium used (HFIP and acetic acid released). Further treatment with TBAF furnishes the elaborated tetracyclic core **15** in 40% overall yield from the simple dimer **14** (Scheme 3).

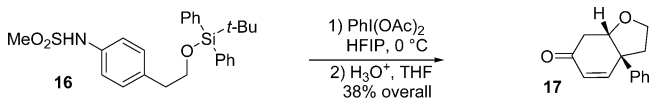
Scheme 3. Rapid Formation of Oxygenated Tetracyclic Core



14 15

The process is not restricted to phenol derivatives, as illustrated by the generation of **17** from the aniline derivative **16** under similar conditions. The reaction proceeds via formation of a sulfonyl dieniimine that is subsequently hydrolyzed under acidic conditions into dienone subunit **17** in similar yield (Scheme 4).

Scheme 4. *N*-(Sulfonyl)-aniline *ipso*-Transformation



16 17

As an initial application of the oxidative *ipso*-rearrangement, we describe the total syntheses of *O*-methylsceletenone **1a** and sceletenone **1b**.[1] These small molecules belonging to the Amaryllidaceae family are generally isolated in racemic form, most probably due to an aza-Michael/retro-Michael equilibrium. The compounds are known to have antidepressant properties and are bioprecursors to the natural analogue mesembrine.[1c,9] A retrosynthetic pathway is presented in Figure 3.

dx.doi.org/10.1021/jo301408j | J. Org. Chem. 2012, 77, 7588−7594

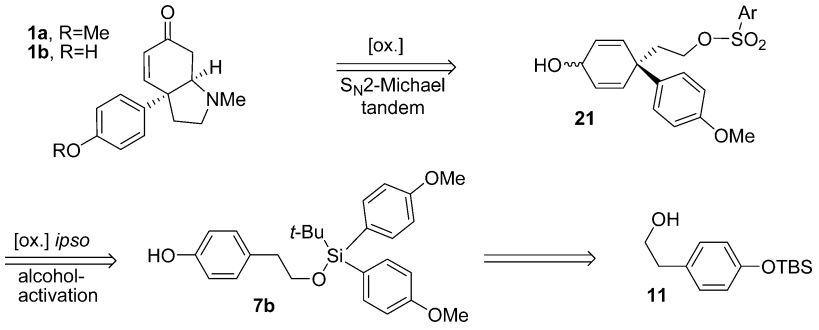
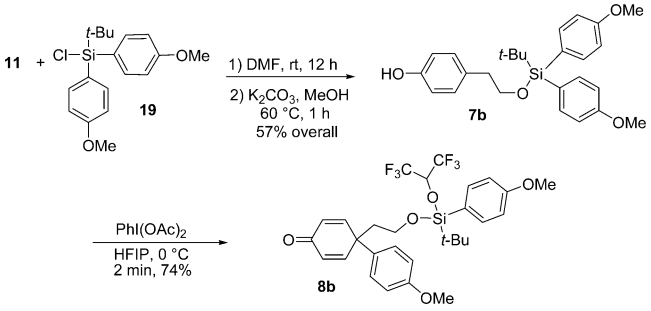


Figure 3. Retrosynthetic pathway to *O*-methylsceletenone and sceletenone.

Starting from compound **11**,[10] the primary alcohol functionality is protected with a modified *p*-methoxy-TBDPSCl segment **19** using classical conditions. The modified TBDPSCl reagent **19** is obtained by treatment of *tert*-butyltrichlorosilane with 2 equiv of the corresponding aryl-organolithium reagent **18**. Selective deprotection of the phenol group using potassium carbonate in methanol furnishes **7b** in 57% yield over two steps. At this stage, the key oxidative *ispo*-rearrangement promoted by a hypervalent iodine reagent produces the functionalized dienone system **8b** in 74% yield. It should be noted that the silicon moiety used during this transformation not only acts as a simple protecting group but also enables the formation of an important component of the target as a tether. In addition, the modified fluorinated protecting group emerging in compound **8b** remains available for further transformations (Scheme 5).

Scheme 5. Oxidative Key Step



A reduction of the ketone functionality in **8b** with DIBAL-H leads stereoselectively to the diastereoisomer **20** in a 9:1 ratio. Subsequent deprotection of the primary alcohol using TBAF produces the diol in 85% yield. A selective activation of the primary alcohol into a leaving group performed in the presence of a hindered sulfonyl moiety such as *o*-nosyl chloride furnishes compound **21** in 40% yield. Oxidation with TPAP/NMO regenerates the dienone system and further treatment of this core with methylamine via a S_N2-aza-Michael tandem process leads to the target *O*-methylsceletenone **1a** in 76% yield. Despite the fact that *O*-methylsceletenone **1a** are isolated in racemic form,[1] You and Gu[11] recently reported an asymmetric synthesis based on a sulfonamide derivative and employing a cinchonine-derived thiourea catalyst[11] to desymmetrize enantioselectively similar dienone systems. In addition, sceletenone **1b** can also be easily and quantitatively obtained from **1a** by treatment with BBr_3 (Scheme 6).

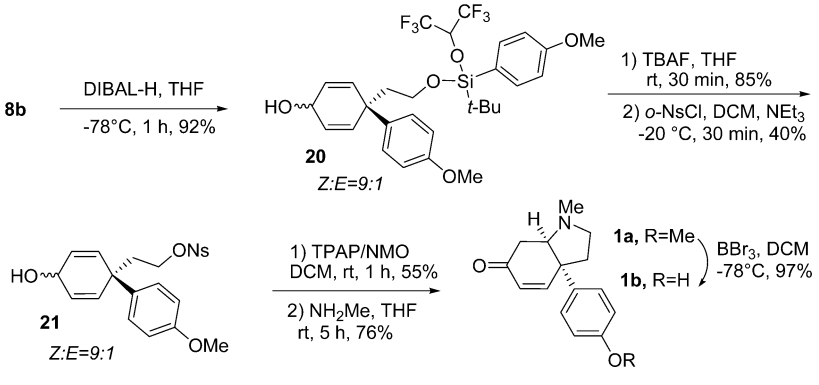
■ CONCLUSION

A practical new method for inducing intramolecular oxidative *ipso*-rearrangements is now available. The transformation provides new strategic opportunities by enabling one-step transformation of stable and simple aromatic compounds into more reactive dienone cores containing a polyfunctionalized quaternary carbon center, a prominent feature of several natural products. The utility of this method is illustrated through its application to total syntheses of *O*-methylsceletenone and sceletenone.

■ EXPERIMENTAL SECTION

Unless otherwise indicated, ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ solutions. Chemical shifts are reported in ppm on the δ scale. Multiplicities are described as s (singlet), d (doublet), dd, ddd, etc. (doublet of doublets, doublet of doublets of doublets, etc.), t (triplet), q (quartet), quin (quintuplet), m (multiplet) and further qualified as app (apparent), br (broad). Coupling constants, *J*, are reported in Hz. IR spectra (cm−1) were

Scheme 6. Syntheses of *O*-Methylsceletenone and Sceletenone



dx.doi.org/10.1021/jo301408j | J. Org. Chem. 2012, 77, 7588−7594

recorded from thin films. HRMS were measured in the electrospray (ESI) mode on a LC-MSD TOF mass analyzer.

General Procedure for the Formation of Phenols 7. To a solution of **11** (2.52 mmol, 1.0 equiv) in DMF (3.0 mL) was added imidazole (7.56 mmol, 3.0 equiv), and the solution was stirred for 5 min. TBDPS-Cl (3.78 mmol, 1.5 equiv) was then added, and the reaction mixture was stirred at room temperature. The reaction was followed by TLC. After completion, ether was added, followed by water. The aqueous phase was extracted with ether, and the organic phases were then washed with water and brine and then dried with Na_2SO_4. The solution was filtered and concentrated under vacuum, and the residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to afford the protected alcohol. The substrate was then diluted in methanol (16.0 mL), K_2CO_3 (5.04 mmol, 2.0 equiv) was added, and the solution was stirred at 60 °C. The reaction was followed by TLC. After completion, aqueous NH_4Cl was added, and the aqueous phase was extracted with DCM. The organic phases were dried with Na_2SO_4, filtered, and concentrated under vacuum. The residue was then purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give the corresponding phenol for more details.

General Procedure for the Oxidative *ipso*-Rearrangement. A solution of $PhI(OAc)_2$ ("DIB", 78 mg, 0.24 mmol, 1.2 equiv) in $(CF_3)_2CHOH$ ("HFIP", 0.35 mL) was added dropwise over 30 s to a vigorously stirred solution of phenol (0.2 mmol, 1 equiv) in HFIP (0.6 mL) at 0 °C. The mixture was then stirred for 30 s and concentrated under vacuum, and the residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane.

1-(2-((*tert*-Butyl((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)(phenyl)silyl)oxy)ethyl)-[1,1′-biphenyl]-4(1*H*)-one (8a). Pale yellow oil: 0.059 mmol, 31.9 mg, 40% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (m, 2H), 7.36 (m, 8H), 6.98 (d, 2H, J = 10.0 Hz), 6.36 (d, 2H, J = 10.7 Hz), 4.46 (hept, 1H, J = 5.8 Hz), 3.90 (m, 2H), 2.51 (t, 2H, J = 6.9 Hz), 0.98 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.0, 153.7, 153.7, 139.5, 135.7, 135.2, 131.1, 129.3, 128.7, 128.6, 128.6, 128.3, 128.0, 127.8, 126.5, 70.6 (hept, J_2 = 33.6 Hz), 60.8, 47.6, 40.1, 27.0, 26.0, 19.4; HRMS (ESI) calcd for $C_{27}H_{28}F_6O_3Si$ (M + H)$^+$ 543.1785, found 543.1776.

1-(2-((*tert*-Butyl((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)(4-methoxyphenyl)silyl)oxy)ethyl)-4′-methoxy-[1,1′-biphenyl]-4(1*H*)-one (8b). Pale yellow oil: 0.033 mmol, 20.0 mg, 74% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J = 8.6 Hz, 2H), 7.23 (t, J = 6.0 Hz, 2H), 6.93 (dt, J = 14.3, 8.5 Hz, 6H), 6.34 (d, J = 9.9 Hz, 2H), 4.43 (hept, 1H, J = 5.8 Hz), 3.90 (m, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 2.46 (t, J = 6.9 Hz, 2H), 0.97 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.1, 161.9, 159.2, 154.1, 154.1, 137.3, 136.9, 131.1, 128.3, 128.2, 127.7, 119.3, 114.7, 114.1, 70.5 (hept, J_2 = 33.6 Hz), 60.7, 55.5, 55.19, 55.1, 47.0, 40.1, 25.9, 19.5, 19.3; HRMS (ESI) calcd for $C_{29}H_{33}F_6O_5Si$ (M + H)$^+$ 603.1996, found 603.1986.

1-(2-((*tert*-Butyl((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)(*p*-tolyl)silyl)oxy)ethyl)-4′-methyl-[1,1′-biphenyl]-4(1*H*)-one (8c). Pale yellow oil: 0.021 mmol, 12.2 mg, 51% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 7.8 Hz, 2H), 7.25−7.15 (m, 6H), 6.96 (d, J = 9.6 Hz, 2H), 6.34 (d, J = 9.8 Hz, 2H), 4.43 (hept, 1H, J = 5.8 Hz), 3.87 (m, 2H), 2.47 (t, J = 6.9 Hz, 2H), 2.38 (s, 3H), 2.34 (s, 3H), 0.97 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.1, 154.0, 154.0, 141.3, 137.8, 136.4, 135.3, 130.0, 129.1, 128.5, 128.4, 126.4, 125.0, 70.5 (hept, J_2 = 33.6 Hz), 60.7, 47.4, 40.1, 26.0, 25.9, 21.7, 21.1, 19.4; IR υ (cm^{-1}) 1667, 1626, 1218, 1106; HRMS (ESI) calcd for $C_{29}H_{32}F_6NaO_3Si$ (M + Na)$^+$ 593.1917, found 593.1910.

1-(2-((*tert*-Butyl((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)(phenyl)silyl)oxy)propyl)-[1,1′-biphenyl]-4(1*H*)-one (8d). Pale yellow oil: 0.012 mmol, 6.1 mg, 37% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.28 (m, 5H), 7.08−6.99 (m, 2H), 6.41 (dd, J = 10.1, 1.8 Hz, 1H), 6.30 (dd, J = 10.1, 1.8 Hz, 1H), 4.63 (h, J = 5.8 Hz, 1H), 4.10 (m, 1H), 2.48 (dd, J = 14.1, 5.6 Hz, 1H), 2.21 (dd, J = 14.1, 3.5 Hz, 1H), 1.25 (d, J = 6.1 Hz, 3H), 0.95 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.0, 155.5, 154.0, 139.9, 129.3, 128.9, 127.9, 127.5, 126.6, 70.2 (hept, J_2 = 33.6 Hz), 67.3, 48.2, 47.8, 25.8, 25.2, 17.4; IR υ (cm^{-1}) 3354, 1654, 1617, 1376, 1292, 1227, 1195, 1103; HRMS (ESI) calcd for $C_{22}H_{26}F_6NaO_4Si$ (M + Na)$^+$ 519.1397, found 519.1399.

3-Bromo-5-(*tert*-butyl)-1-(2-((*tert*-butyl((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)(phenyl)silyl)oxy)ethyl)-[1,1′-biphenyl]-4(1*H*)-one (8e). Pale yellow oil: 0.018 mmol, 12.0 mg, 62% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (m, 2H), 7.39 (m, 8H), 7.29 (d, 1H, J = 1.7 Hz), 6.71 (dd, 1H, J = 4.6, 2.8 Hz), 4.46 (hept, 1H, J = 5.8 Hz), 3.84 (m, 2H), 2.49 (m, 2H), 1.24 (s, 9H), 1.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5, 152.1, 152.1, 147.0, 146.9, 145.3, 145.19, 139.3, 139.3, 135.3, 135.2, 131.2, 129.5, 128.5, 128.4, 128.3, 128.1, 126.4, 125.7, 125.5, 70.5 (hept, J_2 = 33.6 Hz), 60.6, 49.8, 49.8, 40.2, 35.5, 29.2, 26.0, 19.4; IR υ (cm^{-1}) 1659, 1232, 1229, 1197, 1106; HRMS (ESI) calcd for $C_{31}H_{35}BrF_6NaO_3Si$ (M + Na)$^+$ 701.1320, found 701.1314.

3,5-Di-*tert*-butyl-1-(2-((*tert*-butyl((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)(phenyl)silyl)oxy)ethyl)-[1,1′-biphenyl]-4(1*H*)-one (8f). Pale yellow oil: 0.02 mmol, 13.2 mg, 85% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (m, 2H), 7.40 (m, 6H), 7.29 (m, 2H), 6.55 (m, 2H), 4.45 (hept, 1H, J = 5.8 Hz), 3.79 (ddd, 2H, J = 10.7, 5.5, 2.7 Hz), 2.48 (m, 2H), 1.21 (s, 9H), 1.19 (s, 9H), 0.99 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.2, 146.7, 146.7, 144.6, 144.5, 141.8, 135.3, 131.1, 129.1, 128.8, 128.2, 127.4, 126.3, 70.5 (hept, J_2 = 33.6 Hz), 61.1, 45.6, 39.9, 35.0, 35.0, 29.5, 29.4, 25.9, 19.4; IR υ (cm^{-1}) 1644, 1215; HRMS (ESI) calcd for $C_{35}H_{44}ClF_6O_3Si$ (M + Cl)$^-$ 689.2658, found 689.2674.

1-(2-((*tert*-Butyl((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)(phenyl)silyl)oxy)ethyl)-3-methoxy-[1,1′-biphenyl]-4(1*H*)-one (8g). Pale yellow oil: 0.012 mmol, 7.0 mg, 44% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (m, 4H), 7.40 (m, 6H), 6.82 (dd, 1H, J = 9.9, 2.1 Hz), 6.12 (d, J = 2.1 Hz 1H), 6.01 (d, 1H, J = 9.9 Hz), 5.54 (hept, 1H, J = 5.8 Hz), 3.83 (t, 2H, J = 6.0 Hz), 3.35 (s, 3H), 2.48 (t, 2H, J = 5.8 Hz), 1.03 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.9, 137.6, 135.7, 135.7, 135.1, 133.3, 133.3, 129.9, 129.6, 129.3, 128.7, 128.3, 127.9, 125.1, 124.9, 67.5 (hept, J_2 = 33.6 Hz), 62.3, 52.2, 38.4, 29.9, 26.9, 25.8, 19.2; calcd for $C_{28}H_{30}F_6O_4SiNa$ (M + Na)$^+$ 595.1170, found 595.1171.

5-Bromo-3a-phenyl-3,3a,7,7a-tetrahydrobenzofuran-6(2*H*)-one (10). Pale yellow oil: 0.018 mmol, 5.2 mg, 45% yield over 2 steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 5H), 7.19 (d, 1H, J = 2.2 Hz), 4.35 (q, 1H, J = 2.8 Hz), 4.12 (td, 1H, J = 8.8, 3.1 Hz), 3.95 (ddd, 1H, J = 9.7, 8.6, 6.8 Hz), 3.01 (ddd, 1H, J = 17.2, 3.1, 0.7 Hz), 2.74 (m, 2H), 2.36 (ddd, 1H, J = 12.9, 6.8, 3.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.6, 150.7, 138.6, 129.4, 128.1, 126.6, 124.0, 83.1, 67.1, 54.6, 40.2, 38.9; calcd for $C_{14}H_{14}O_2Br$ (M + H)$^+$ 293.0172, found 293.0171.

4,4′-(((Bis(2-methoxyphenyl)silanediyl)bis(oxy))bis(ethane-2,1-diyl))diphenol (12). To a solution of **18** (16.7 mg, 0.066 mmol, 1.0 equiv) in DMF (1.0 mL) was added imidazole (53.9 mg, 0.792 mmol, 12.0 equiv), and the solution was stirred during 5 min. The solution was then added to a solution of "dichlorosilane" (0.198 mmol, 3.0 equiv) in DMF (1.0 mL). The reaction mixture was stirred at room temperature, and the reaction was followed by TLC. After completion, ether was added, followed by water. The aqueous phase was extracted with ether, and the organic phases were then washed with water and brine and then dried with Na_2SO_4. The solution was filtered and concentrated under vacuum, and the residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to afford the protected dimer. To this dimer in THF (1.0 mL) was added TBAF (42 μL, 0.042 mmol, 1.8 equiv) at 0 °C under stirring, and the reaction was followed by TLC. After completion, aqueous NH_4Cl was added, and the aqueous phase was extracted with EtOAc. The organic phases were dried with Na_2SO_4, filtered, and concentrated under vacuum. The residue was then purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give 9.7 mg (57% over 2 steps) of a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 7.1 Hz, 2H), 7.38 (t, J = 7.8 Hz, 2H), 7.00 (d, J = 8.2 Hz, 4H), 6.94 (t, J = 7.3 Hz, 2H), 6.82 (d, J = 8.3 Hz, 2H), 6.69 (d, J = 8.3 Hz, 4H), 3.90 (t, J = 7.3 Hz, 4H), 3.64 (s, 6H), 2.80 (t, J = 7.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 153.9, 137.4, 131.9, 130.3, 122.2, 120.6, 115.1, 109.9, 64.7, 55.3, 38.4; IR υ (cm^{-1}) 3389, 1615, 1455, 1240; HRMS (ESI) calcd for $C_{30}H_{33}O_6Si$ (M + H)$^+$ 517.2041, found 517.2034.

dx.doi.org/10.1021/jo301408j | *J. Org. Chem.* 2012, 77, 7588−7594

3a-(2-Methoxyphenyl)-3,3a,7,7a-tetrahydrobenzofuran-6(2*H*)-one (13). Pale yellow oil: 0.034 mmol, 8.3 mg, 40% yield over 2 steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (t, 1H, J = 7.8 Hz), 7.19 (d, 1H, J = 7.6 Hz), 6.96 (d, 2H, J = 7.9 Hz), 6.92 (s, 1H), 6.09 (d, 1H, J = 10.3 Hz), 4.73 (d, 1H, J = 2.6 Hz), 3.98 (m, 2H), 3.88 (s, 3H), 2.79 (m, 2H), 2.65 (dd, 1H, J = 17.2, 3.2 Hz), 2.38 (dt, 1H, J = 12.7, 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 157.8, 151.7, 129.0, 128.7, 128.0, 127.6, 121.0, 111.9, 79.3, 66.7, 55.3, 49.8, 39.4, 38.7; IR υ (cm^{-1}) 1684, 1490, 1240, 1215; HRMS (ESI) calcd for $C_{15}H_{17}O_3$ (M + H)$^+$ 245.1172, found 245.1167.

4,4′-(((Bis(2-((tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)-silanediyl)bis(oxy))bis(ethane-2,1-diyl))diphenol (14). To a solution of **11** (283 mg, 1.12 mmol, 2.0 equiv) in DMF (1.0 mL) was added imidazole (115 mg, 1.69 mmol, 3.0 equiv), and the solution was stirred during 5 min. The solution was then added to a solution of the corresponding "diaryldichlorosilane" (0.56 mmol, 1.0 equiv) in DMF (1.0 mL). The reaction mixture was stirred at room temperature, and the reaction was followed by TLC. After completion, ether was added, followed by water. The aqueous phase was extracted with ether, and the organic phases were then washed with water and brine and then dried with Na_2SO4. The solution was filtered and concentrated under vacuum, and the residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane (1:4) to afford the protected dimer. The substrate was diluted in THF (1.0 mL), TBAF (569 μL, 1.8 equiv) was added at 0 °C under stirring, and the reaction was followed by TLC. After completion, aqueous NH_4Cl was added, and the aqueous phase was extracted with EtOAc. The organic phases were dried with Na_2SO_4, filtered, and concentrated under vacuum. The residue was then purified by silica gel chromatography with a mixture of ethyl acetate/hexane (2:3) to give the corresponding dimeric substrate 94 mg (32% overall) as a pale oil in a diastereomeric mixture (1:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 7.2 Hz, 2H), 7.34−7.27 (m, 2H), 7.04−6.94 (m, 8H), 6.69 (d, J = 8.2 Hz, 4H), 5.23 (d, J = 13.2 Hz, 2H), 3.93−3.80 (m, 4H), 3.56 (t, J = 10.5 Hz, 1H), 3.49−3.38 (m, 3H), 2.83−2.72 (m, 4H), 1.68−1.06 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 161.9, 154.2, 137.0, 131.7, 131.1, 130.2, 122.6, 122.6, 121.2, 121.1, 115.2, 112.8, 112.6, 95.8, 95.6, 64.7, 64.3, 61.3, 61.1, 38.4, 30.7, 25.3, 19.2, 17.8, 13.8; HRMS (ESI) calcd for $C_{38}H_{45}O_8Si$ (M + H)$^+$ 657.2878, found 657.2871.

Tetracyclic Compound (15). Pale yellow oil: 0.057 mmol, 13.1 mg, 40% yield over 2 steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (m, 2H), 6.98 (t, 1H, J = 7.5 Hz), 6.83 (d, 1H, J = 8.4 Hz), 4.78 (d, 1H, J = 3.2 Hz), 4.09 (m, 2H), 3.93 (d, 1H, J = 3.2 Hz), 2.80 (dd, 1H, J = 17.9, 3.0 Hz). 2.77 (m, 2H), 2.72 (dd, 1H, J = 17.8, 3.0 Hz), 2.26 (dd, 1H, J = 17.8, 3.0 Hz), 2.23 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.9, 159.6, 129.7, 129.5, 123.2, 121.7, 110.4, 87.9, 83.7, 67.4, 52.9, 39.8, 39.4, 38.8; IR υ (cm^{-1}) 1652, 1215; HRMS (ESI) calcd for $C_{14}H_{15}O_3$ (M + H)$^+$ 231.1016, found 231.1017.

***N*-(4-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)phenyl)-methanesulfonamide (16).** To a solution of *N*-(4-(2-hydroxyethyl)-phenyl)methanesulfonamide (25.7 mg, 0.12 mmol, 1.0 equiv) in DMF (1.0 mL) was added imidazole (24.4 mg, 0.36 mmol, 3.0 equiv), and the solution was stirred during 5 min. TBDPS-Cl (49.2 mg, 0.18 mmol, 1.5 equiv) was then added, and the reaction mixture was stirred at room temperature. The reaction was followed by TLC. After completion, ether was added, followed by water. The aqueous phase was extracted with ether, and the organic phases were then washed with water and brine and then dried with Na_2SO_4. The solution was filtered and concentrated under vacuum, and the residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane (1:3) to afford **16** in 95% (51.2 mg, 0.11 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J = 7.7 Hz, 4H), 7.44−7.31 (m, 6H), 7.15 (s, 4H), 6.79 (s, 1H), 3.83 (t, J = 6.7 Hz, 2H), 2.97 (s, 3H), 2.83 (t, J = 6.7 Hz, 2H), 1.02 (s, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.0, 135.7, 134.8, 133.8, 130.6, 129.8, 127.8, 121.4, 65.0, 39.2, 38.7, 26.93, 25.8, 19.3; HRMS (ESI) calcd for $C_{25}H_{32}NO_3SSi$ (M + H)$^+$ 454.1867, found 454.1871.

3a-Phenyl-3,3a,7,7a-tetrahydrobenzofuran-6(2*H*)-one (17). Pale yellow oil: 0.025 mmol, 5.3 mg, 38% yield over 2 steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 4.3 Hz, 4H), 7.23−7.15 (m, 1H), 6.60 (dd, J = 10.2, 2.3 Hz, 1H), 6.11 (d, J = 10.2 Hz, 1H), 4.23 (dd, J = 5.4, 2.9 Hz, 1H), 3.98 (td, J = 8.7, 3.0 Hz, 1H), 3.79 (ddd, J = 9.8, 8.5, 6.8 Hz, 1H), 2.71−2.58 (m, 2H), 2.44 (dd, J = 17.3, 3.0 Hz, 1H), 2.16 (ddd, J = 12.7, 6.6, 2.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 150.6, 139.6, 129.7, 129.2, 127.8, 126.7, 83.3, 67.0, 51.0, 40.1, 38.6; HRMS (ESI) calcd for $C_{14}H_{15}O_2$ (M + H)$^+$ 215.1067, found 215.1073.

***tert*-Butylchlorobis(4-methoxyphenyl)silane (19).** To a solution of 4-bromoanisole (1.12 g, 6.0 mmol, 3.0 equiv) in THF (6.0 mL) at −78 °C was added ^{t}BuLi (7.3 mL, 12.4 mmol, 6.2 equiv) dropwise. The solution was stirred during 5 min, and a solution of ^{t}BuSiCl$_3$ (383.2 mg, 2.0 mmol, 1.0 equiv) in THF (2.0 mL) was added at 0 °C via a cannula. The solution was then stirred at room temperature, and the reaction was followed by NMR. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 8.6 Hz, 4H), 6.94 (d, J = 8.5 Hz, 4H), 3.83 (s, 6H), 1.11 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 137.0, 136.5, 113.7, 55.2, 26.6, 20.9; HRMS (ESI) calcd for $C_{18}H_{25}O_3Si$ (M − Cl + H_2O)$^+$ 317.1567, found 317.1582.

4-(2-((*tert*-Butylbis(4-methoxyphenyl)silyl)oxy)ethyl)phenol (7b). To a solution of **18** (161.5 mg, 0.64 mmol, 1.0 equiv) in DMF (1.0 mL) was added imidazole (272.3 mg, 4.0 mmol, 6.0 equiv), and the solution was stirred during 5 min. The solution was then added to a solution of silane **19** (2.0 mmol, 3.0 equiv) in DMF (2.0 mL). The reaction mixture was stirred at room temperature, and the reaction was followed by TLC. After completion, ether was added, followed by water. The aqueous phase was extracted with ether, and the organic phases were then washed with water and brine and then dried with Na_2SO_4. The solution was filtered and concentrated under vacuum, and the residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to afford the protected alcohol along with the corresponding silanol. To this mixture in methanol (3.0 mL) was added K_2CO_3 (157.3 mg, 1.14 mmol, 2.0 equiv), and the solution was stirred at 60 °C. The reaction was followed by TLC. After completion, aqueous NH_4Cl was added, and the aqueous phase was extracted with DCM. The organic phases were dried with Na_2SO_4, filtered, and concentrated under vacuum. The residue was then purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give 159.2 mg (57% over 2 steps) of a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J = 8.6 Hz, 4H), 7.01 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.6 Hz, 4H), 6.72 (d, J = 8.4 Hz, 2H), 4.53 (s, 1H), 3.83 (s, 6H), 3.75 (t, J = 6.9 Hz, 2H), 2.76 (t, J = 6.9 Hz, 2H), 1.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 154.3, 137.2, 130.9, 130.3, 125.0, 115.1, 113.4, 65.3, 60.8, 54.9, 38.4, 26.9, 21.1, 19.2, 14.1; IR υ (cm^{-1}) 1664, 1228, 1197, 1107; HRMS (ESI) calcd for $C_{26}H_{31}O_4Si$ (M − H)$^-$ 435.1997, found 435.2002.

1-(2-((*tert*-Butyl((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)(4-methoxyphenyl)silyl)oxy)ethyl)-4′-methoxy-1,4-dihydro-[1,1′-biphenyl]-4-ol (20). To a solution of **8b** (169.1 mg, 0.28 mmol, 1.0 equiv) in THF (3.0 mL) at −78 °C was added DIBAL-H (421 μL, 0.42 mmol, 1.5 equiv) dropwise under stirring. The reaction was followed by TLC. After completion, aqueous Rochelle salt was added, and the aqueous phase was extracted with EtOAc. The organic phases were dried with Na_2SO_4, filtered, and concentrated under vacuum. The residue was then purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give 159.6 mg (94%) of a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 5.97 (dd, J = 10.7, 2.9 Hz, 2H), 5.86 (dd, J = 8.6, 6.4 Hz, 2H), 4.49 (m, 2H), 3.89 (t, J = 6.4 Hz, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 2.24 (t, J = 6.0 Hz, 2H), 0.98 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 158.3, 137.3, 137.3, 137.0, 135.6, 135.5, 135.3, 135.2, 127.6, 127.4, 127.1, 126.9, 126.8, 126.72, 119.9, 114.1, 113.9, 70.5 (hept, J_2 = 33.6 Hz), 62.2, 61.9, 55.4, 55.2, 42.8, 41.3, 40.8, 29.8, 27.0, 25.9, 19.5; IR υ (cm^{-1}) 3408, 1218, 1105; HRMS (ESI) calcd for $C_{29}H_{34}F_6NaO_5Si$ (M + Na)$^+$ 627.1972, found 627.1971.

1-(2-Hydroxyethyl)-4′-methoxy-1,4-dihydro-[1,1′-biphenyl]-4-ol (20bis). To a solution of **20** (159.6 mg, 0.26 mmol, 1.0 equiv) in THF (2.5 mL) at 0 °C was added TBAF (396 μL, 0.40 mmol, 1.5 equiv) dropwise under stirring. The reaction was followed by TLC.

dx.doi.org/10.1021/jo301408j | J. Org. Chem. 2012, 77, 7588−7594

After completion, the solution was directly purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give 55.1 mg (85%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, J = 8.6 Hz, 2H), 6.85 (dd, J = 8.7, 3.1 Hz, 2H), 5.99 (d, J = 10.2 Hz, 2H), 5.87 (d, J = 9.7 Hz, 2H), 4.57 (s, 1H), 3.78 (s, 3H), 3.73 (t, J = 6.4 Hz, 2H), 2.16 (t, J = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 137.6, 136.8, 135.8, 127.6, 127.4, 126.9, 114.0, 61.9, 60.5, 60.2, 55.4, 43.2, 41.7, 41.0, 20.4, 13.7; HRMS (ESI) calcd for $C_{15}H_{18}NaO_3$ $(M + Na)^+$ 269.1148, found 269.1145.

2-(4-Hydroxy-4′-methoxy-1,4-dihydro-[1,1′-biphenyl]-1-yl)-ethyl 2-nitrobenzenesulfonate (21). To a solution of "diol" (33.9 mg, 0.14 mmol, 1.0 equiv) in DCM (2.0 mL) at −20 °C was added Et_3N (27.8 mg, 0.28 mmol, 2.0 equiv), followed by DMAP (8.4 mg, 0.07 mmol, 0.5 equiv) and NsCl (33.5 mg, 0.15 mmol, 1.1 equiv). The reaction was followed by TLC. After completion, the solution was directly purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give 23.1 mg (40%) of a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 7.2 Hz, 1H), 7.85−7.72 (m, 4H), 7.16 (d, J = 8.9 Hz, 2H), 6.84 (d, J = 8.9 Hz, 2H), 6.01 (dd, J = 10.2, 3.2 Hz, 2H), 5.78 (dd, J = 10.2, 1.6 Hz, 2H), 4.54 (s, 1H), 4.34 (t, J = 6.7 Hz, 2H), 3.77 (s, 3H), 2.34 (t, J = 6.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 136.6, 135.0, 133.9, 132.4, 131.3, 129.5, 128.2, 127.3, 124.8, 114.2, 70.1, 61.9, 55.4, 42.8, 36.9; HRMS (ESI) calcd for $C_{21}H_{21}NNaO_7S$ $(M + Na)^+$ 454.0931, found 454.0930.

2-(4′-Methoxy-4-oxo-1,4-dihydro-[1,1′-biphenyl]-1-yl)ethyl 2-nitrobenzenesulfonate (21bis). To a solution of **21** (22.8 mg, 0.05 mmol, 1.0 equiv) and molecular sieves 4Å in DCM (2.0 mL) at 0 °C was added TPAP (1.8 mg, 0.005 mmol, 0.1 equiv) under stirring, followed by NMO (18.6 mg, 0.16 mmol, 3.0 equiv). The reaction was followed by TLC. After completion, the reaction mixture was diluted with ethyl acetate, filtered through a pad of Celite, and concentrated under vacuum. The residue was then purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give 12.4 mg (55%) of a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 7.6 Hz, 1H), 7.86−7.71 (m, 2H), 7.18 (d, J = 8.9 Hz, 2H), 6.87 (d, J = 9.3 Hz, 4H), 6.27 (d, J = 10.1 Hz, 2H), 4.25 (t, J = 6.9 Hz, 2H), 3.79 (s, 3H), 2.62 (t, J = 6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.4, 159.4, 152.7, 135.2, 132.5, 131,3, 130.2, 129.3, 128.9, 127.5, 124.9, 114.8, 68.5, 55.5, 46.6, 36.3; IR υ (cm^{-1}) 1667, 1543, 1511, 1255, 1369, 1214; HRMS (ESI) calcd for $C_{21}H_{19}NNaO_7S$ $(M + Na)^+$ 452.0774, found 452.0772.

3a-(4-Methoxyphenyl)-1-methyl-3,3a,7,7a-tetrahydro-1*H*-indol-6(2*H*)-one, *O*-Methylsceletenone (1a). To a solution of "dienone" (11.5 mg, 0.027 mmol, 1.0 equiv) in THF (1.0 mL) at room temperature was added aqueous $MeNH_2$ (8.3 mg, 0.27 mmol, 10.0 equiv) under stirring. The reaction was followed by TLC. After completion, water was added to the solution. The phases were separated and the aqueous phase was extracted with EtOAc. The organic phases were dried with Na_2SO_4, filtered, and concentrated under vacuum. The residue was then purified by silica gel chromatography with a mixture of ethyl acetate/methanol to afford *O*-methylsceletenone **1** in 76% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.72 (dd, J = 10.1, 1.7 Hz, 1H), 6.10 (d, J = 10.1 Hz, 1H), 3.81 (s, 3H), 3.31 (t, J = 7.9 Hz, 1H), 2.68−2.37 (m, 5H), 2.32 (s, 3H), 2.26−2.13 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 158.7, 153.9, 135.3, 127.9, 126.6, 114.3, 73.9, 56.2, 55.5, 50.8, 40.2, 38.8, 36.3; IR υ (cm^{-1}) 1649, 1216; HRMS (ESI) calcd for $C_{16}H_{20}NO_2$ $(M + H)^+$ 258.1489, found 258.1488.

Sceletenone (1b). To a solution of **1a** (4.2 mg, 0.016 mmol, 1.0 equiv) in DCM (1.0 mL) at 0 °C under argon was added BBr_3 (12.3 mg, 0.049 mmol, 3.0 equiv) under stirring. The reaction was followed by TLC. After completion, $NaHCO_3$ was added to the solution. The phases were separated, and the aqueous phase was extracted with DCM. The organic phases were dried with Na_2SO_4, filtered, and concentrated under vacuum. The residue was then purified by silica gel chromatography with a mixture of DCM/methanol to afford **1b** in quantitative yield. ^{1}H NMR (300 MHz, CDCl3) δ 7.22 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 6.72 (d, J = 10.1 Hz, 1H), 6.10 (d, J = 10.1 Hz, 1H), 3.31 (t, J = 7.9 Hz, 1H), 2.63 (d, J = 7.6 Hz, 1H), 2.47 (ddd, J = 21.7, 14.2, 10.1 Hz, 4H), 2.32 (s, 3H), 2.26−2.13 (m,1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 154.9, 154.1, 135.2, 128.1, 126.7, 115.8, 73.9, 56.2, 50.8, 40.2, 38.7, 36.2; IR υ (cm^{-1}) 3403, 1648, 1215; HRMS (ESI) calcd for $C_{15}H_{17}NO_2Na$ $(M + Na)^+$ 266.1151, found 266.1147.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: canesi.sylvain@uqam.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are very grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC), the Canada Foundation for Innovation (CFI), the provincial government of Quebec (FQRNT and CCVC) and Boehringer Ingelheim (Canada) Ltd. for their precious financial support in this research.

■ REFERENCES

(1) (a) Jeffs, W.; Capps, T. M.; Johnson, D. B.; Karle, J. M.; Martin, N. H.; Rauckman, B. *J. Org. Chem.* **1974**, *39*, 2703. (b) Sanchez, I. H.; Larraza, M. I.; Flores, H. J.; Rojas, I.; Alcala, R. *Synth. Commun.* **1983**, *13*, 35. (c) Jeffs, P. W.; Karle, J. M.; Martin, N. H. *Phytochemistry* **1978**, *17*, 719. (d) Gaffney, C. D. Dissertation, University of Johannesburg, 2008.

(2) (a) Bazhenova, E. D.; Aliev, Kh. U.; Zakirov, U. B. *Farmakol. Alkaloidov Ikh. Proizvod.* **1972**, 74. (b) Shieh, W. C.; Carlson, J. A. *J. Org. Chem.* **1994**, *59*, 5463.

(3) Gorman, M.; Neuss, N.; Biemann, K. *J. Am. Chem. Soc.* **1962**, *84*, 1058.

(4) (a) Guérard, K. C.; Sabot, C.; Racicot, L.; Canesi, S. *J. Org. Chem.* **2009**, *74*, 2039. (b) Sabot, C.; Guérard, K. C.; Canesi, S. *Chem. Commun.* **2009**, 2941. (c) Guérard, K. C.; Chapelle, C.; Giroux, M. A.; Sabot, C.; Beaulieu, M. A.; Achache, N.; Canesi, S. *Org. Lett.* **2009**, *11*, 4756. (d) Guérard, K. C.; Sabot, C.; Beaulieu, M. A.; Giroux, M. A.; Canesi, S. *Tetrahedron* **2010**, *66*, 5893. (e) Andrez, J. A.; Giroux, M. A.; Lucien, J.; Canesi, S. *Org. Lett.* **2010**, *12*, 4368. (f) Beaulieu, M. A.; Sabot, C.; Achache, N.; Guérard, K. C.; Canesi, S. *Chem.—Eur. J.* **2010**, *16*, 11224. (g) Desjardins, S.; Andrez, J. A.; Canesi, S. *Org. Lett.* **2011**, *13*, 3406. (h) Beaulieu, M. A.; Guérard, K. C.; Maertens, G.; Sabot, C.; Canesi, S. *J. Org. Chem.* **2011**, *76*, 9460. (i) Guérard, K. C.; Guerinot, A.; Bouchard-Aubin, C.; Ménard, M. A.; Lepage, M.; Beaulieu, M. A.; Canesi, S. *J. Org. Chem.* **2012**, *77*, 2121.

(5) (a) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927. (b) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684. (c) Kita, Y.; Takada, T.; Gyoten, M.; Tohma, H.; Zenk, M. H.; Eichhorn, J. *J. Org. Chem.* **1996**, *61*, 5854. (d) Kita, Y.; Gyoten, M.; Ohtsubo, M.; Tohma, H.; Takada, T. *Chem. Commun.* **1996**, 1481. (e) Takada, T.; Arisawa, M.; Gyoten, M.; Hamada, R.; Tohma, H.; Kita, Y. *J. Org. Chem.* **1998**, *63*, 7698. (f) Arisawa, M.; Utsumi, S.; Nakajima, M.; Ramesh, N. G.; Tohma, H.; Kita, Y. *Chem. Commun.* **1999**, 469. (g) Akai, S.; Kawashita, N.; Morita, N.; Nakamura, Y.; Iio, K.; Kita, Y. *Heterocycles* **2002**, *58*, 75. (h) Dohi, T.; Maruyama, A.; Takenaga, N.; Senami, K.; Minamitsuji, Y.; Fujioka, H.; Caemmerer, S. B.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3787. (i) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073. (j) Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, Y. *Tetrahedron* **2009**, *65*, 10797.

(k) Fujioka, H.; Komatsu, H.; Nakamura, T.; Miyoshi, A.; Hata, K.; Ganesh, J.; Murai, K.; Kita, Y. *Chem. Commun.* **2010**, *46*, 4133. (l) Dohi, T.; Kato, D.; Hyodo, R.; Yamashita, D.; Shiro, M.; Kita, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 3784.

(6) (a) Vanderlaan, D. G.; Schwartz, M. A. *J. Org. Chem.* **1985**, *50*, 743. (b) Lewis, N.; Wallbank, P. *Synthesis* **1987**, 1103. (c) *Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis*; Wirth, T., Ed.; Springer: New York, 2003; Topics in Current Chemistry Vol. *224*. (d) Gates, B. D.; Dalidowicz, P.; Tebben, A.; Wang, S.; Swenton, J. S. *J. Org. Chem.* **1992**, *57*, 2135. (e) Ciufolini, M. A.; Braun, N. A.; Canesi, S.; Ousmer, M.; Chang, J.; Chai, D. *Synthesis* **2007**, *24*, 3759. (f) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (g) Quideau, S.; Looney, M. A.; Pouységu, L. *Org. Lett.* **1999**, *1*, 1651. (h) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235. (i) Liang, H.; Ciufolini, M. A. *Chem.—Eur. J.* **2010**, *16*, 13262. (j) Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7534. (k) Quideau, S.; Pouységu, L.; Oxoby, M.; Looney, M. A. *Tetrahedron* **2001**, *57*, 319. (l) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4336. (m) Quideau, S.; Pouységu, L.; Deffieux, D. *Curr. Org. Chem.* **2004**, *8*, 113. (n) Silva, L. F., Jr.; Siqueira, F. A.; Pedrozo, E. C.; Vieira, F. Y. M.; Doriguetto, A. C. *Org. Lett.* **2007**, *9*, 1433. (o) Quideau, S.; Pouységu, L.; Deffieux, D. *Synlett* **2008**, 467. (p) Liang, H.; Ciufolini, M. A. *J. Org. Chem.* **2008**, *73*, 4299. (q) Giroux, M. A.; Guérard, K. C.; Beaulieu, M. A.; Sabot, C.; Canesi, S. *Eur. J. Org. Chem.* **2009**, 3871. (r) Peuchmaur, M.; Saıdani, N.; Botté, C.; Maréchal, E.; Vial, H.; Wong, Y. S. *J. Med. Chem.* **2008**, *51*, 4870. (s) Mendelsohn, B. A.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 4736. (t) Jen, T.; Mendelsohn, B. A.; Ciufolini, M. A. *J. Org. Chem.* **2011**, *76*, 728. (u) Traoré, M.; Ahmed-Ali, S.; Peuchmaur, M.; Wong, Y. S. *J. Org. Chem.* **2011**, *76*, 1409.

(7) (a) Pelter, A.; Drake, R. A. *Tetrahedron Lett.* **1988**, *29*, 4181. (b) Quideau, S.; Looney, M. A.; Pouységu, L. *J. Org. Chem.* **1998**, *63*, 9597. (c) Ozanne-Beaudenon, A.; Quideau, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7065. (d) Ciufolini, M. A.; Canesi, S.; Ousmer, M.; Braun, N. A. *Tetrahedron* **2006**, *62*, 5318. (e) Bérard, D.; Jean, A.; Canesi, S. *Tetrahedron Lett.* **2007**, *48*, 8238. (f) Jean, A.; Cantat, J.; Bérard, D.; Bouchu, D.; Canesi, S. *Org. Lett.* **2007**, *9*, 2553. (g) Pouységu, L.; Chassaing, S.; Dejugnac, D.; Lamidey, A. M.; Miqueu, K.; Sotiropoulos, J. M.; Quideau, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3552. (h) Bérard, D.; Racicot, L.; Sabot, C.; Canesi, S. *Synlett* **2008**, 1076. (i) Pouységu, L.; Marguerit, M.; Gagnepain, J.; Lyvinec, G.; Eatherton, A. J.; Quideau, S. *Org. Lett.* **2008**, *10*, 5211. (j) Mendelsohn, B. A.; Lee, S.; Kim, S.; Teyssier, F.; Aulakh, V. S.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 1539. (k) Quideau, S.; Lyvinec, G.; Marguerit, Bathany, K.; Ozanne-Beaudenon, A.; Bufeteau, T.; Cavagnat, D.; Chenede, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4605. (l) Liang, H.; Ciufolini., M. A. *Org. Lett.* **2010**, *12*, 1760. (m) Traoré, M.; Ahmed-Ali, S.; Peuchmaur, M.; Wong, Y. S. *Tetrahedron* **2010**, *66*, 5863. (n) Liang, H.; Ciufolini, M. A. *Tetrahedron* **2010**, *66*, 5884. (o) Pouységu, L.; Sylla, T.; Garnier, T.; L. B. Rojas, L. B.; Charris, J.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 5908. (p) Dylan Turner, C.; Ciufolini, M. A. *ARKIVOC* **2011**, *1*, 410. (q) Chau, J.; Ciufolini, M. A. *Mar. Drugs* **2011**, *9*, 2016. (r) Liang, H; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 11849.

(8) Dohi, T.; Yamaoka, N.; Kita, Y. *Tetrahedron* **2010**, *66*, 5775.

(9) (a) Popelak, A.; Haack, E.; Lettenbauer, G.; Spingler, H. *Naturwissenschaften* **1960**, *47*, 156. (b) Smith, E.; Hosansky, N.; Shamma, M.; Moss, J. B. *Chem. Ind* **1961**, 402. (c) Taber, D. F.; He, Y. *J. Org. Chem.* **2005**, *70*, 7711. (d) Taber, D. F.; Neubert, T. D. *J. Org. Chem.* **2001**, *66*, 143.

(10) Nakajima, R.; Ono, M.; Aiso, S.; Akita, H. *Chem. Pharm. Bull* **2005**, *53*, 684.

(11) Gu, Q.; You, S. L. *Chem. Sci.* **2011**, *2*, 1519.