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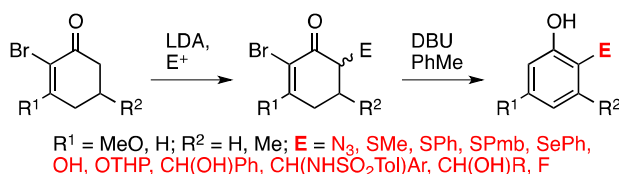
# A Family of Routes to Substituted Phenols, including *meta*-Substituted Phenols

Wenjie Shao and Derrick. L. J. Clive\*

Chemistry Department, University of Alberta, Edmonton, Alberta T6G 2G2, Canada

derrick.clive@ualberta.ca

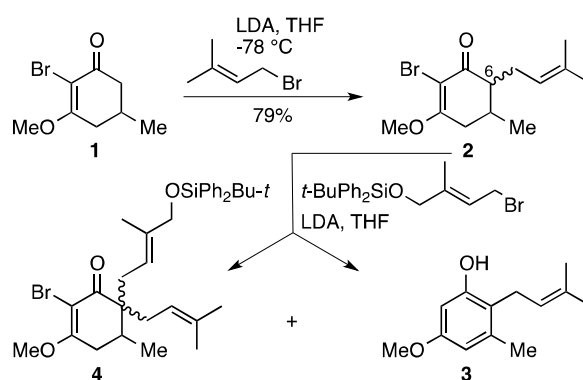
**ABSTRACT:** A new family of routes to substituted phenols has been developed. 2-Bromo-3-methoxycyclohex-2-en-1-ones are readily deprotonated at C-6 and the resulting anions react smoothly with a variety of electrophiles; treatment with DBU in PhMe at room temperature then results in efficient aromatization to benzene derivatives of regiochemically defined substitution pattern. This sequence affords phenolic azides ( $\text{ArN}_3$ ), sulfides ( $\text{ArSR}$ ,  $\text{ArSAr'}$ ), selenides ( $\text{ArSePh}$ ), alcohols [ $\text{ArCH(OH)R}$ ], amino derivatives [ $\text{ArCH(NHSO}_2\text{Ar')R}$ ], and 1,2-benzenediols. A complementary set of substitution patterns is obtained by DIBAL-H reduction or reaction with a Grignard reagent before aromatization; the latter process gives compounds in which the newly-introduced substituent is *meta* to the phenolic hydroxyl.



## INTRODUCTION

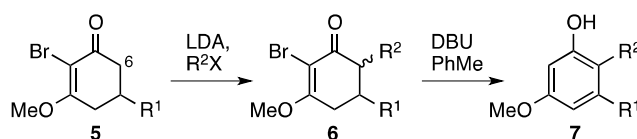
A recent report<sup>1</sup> from this laboratory described how attempts to alkylate the bromoketone **2** (Scheme 1) led to the unexpected formation of phenol **3** rather than the desired dialkylated product **4**. The formation of **3** was then developed into a general procedure (Scheme 2, R<sup>1</sup> = Me, Et) that affords alkyl-substituted resorcinol monomethyl ethers (**5**→**6**→**7**) under very

**SCHEME 1.** Discovery of the aromatization process.



straightforward conditions—simple C-6 alkylation of a bromoketone of type **5** (R<sup>1</sup> = Me, Et), followed by treatment with DBU in PhMe at room temperature. The yields in the alkylation step (**5**→**6**) were in the range 70-91% (average 74.8%) and for the aromatization (**6**→**7**) the yields were 82-92%.

**SCHEME 2.** Routes to alkyl-substituted phenols.



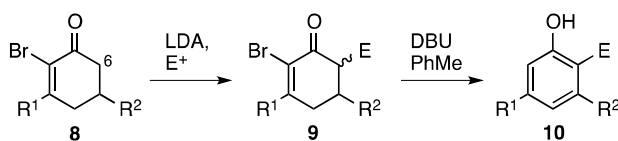
$R^1 = \text{H, Me, Et; } R^2 = \text{allyl, propargyl, benzyl, Me, CH}_2\text{CO}_2\text{Bu-}t$ .

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## RESULTS AND DISCUSSION

Our experiments were limited to *alkylation* and we found that only reactive halides such allylic, benzylic and propargylic halides,  $\alpha$ -halo esters and methyl iodide were suitable. However, we have since examined the possibility of using other electrophiles and we find that the alkylations shown generically in Scheme 2 represent only one type of example of a new family of routes to phenols; the generation of this family is summarized in Scheme 3 where E denotes a wide variety of groups easily installed with electrophilic reagents. So far, we have examined compounds of type **8** in which  $R^1$  is MeO or H, and  $R^2$  is H or Me.

**SCHEME 3.** General family of routes to substituted phenols.



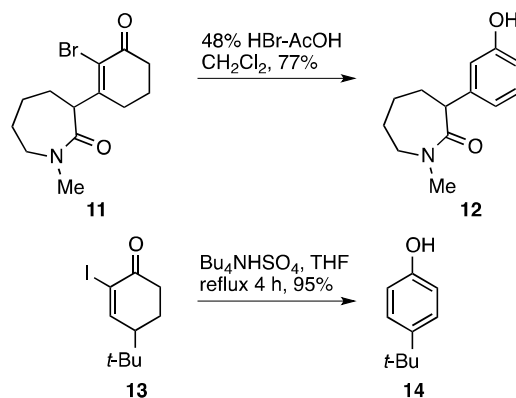
$R^1 = \text{H, OMe; } R^2 = \text{H, Me, } E = \text{N}_3, \text{SMe, SPh, SPmb, SePh, OH, OTHP, CH(OH)Ph, CH(NHSO}_2\text{Tol)Ar, CH(OH)R, F. Pmb = } p\text{-methoxybenzyl.}$

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The closest precedents we can find for the aromatization step are the reports summarized in Scheme 4, which shows that aromatization of a bromoenone (**11**→**12**) was induced with 40% HBr-AcOH in  $\text{CH}_2\text{Cl}_2$ .<sup>2, 3</sup> There is also the incidental observation, made during studies on the

preparation of (benzoyloxy)enones, that treatment of iodoenone **13** with  $\text{Bu}_4\text{NHSO}_4$  in refluxing THF (4 h) gives phenol **14**.<sup>4,5</sup>

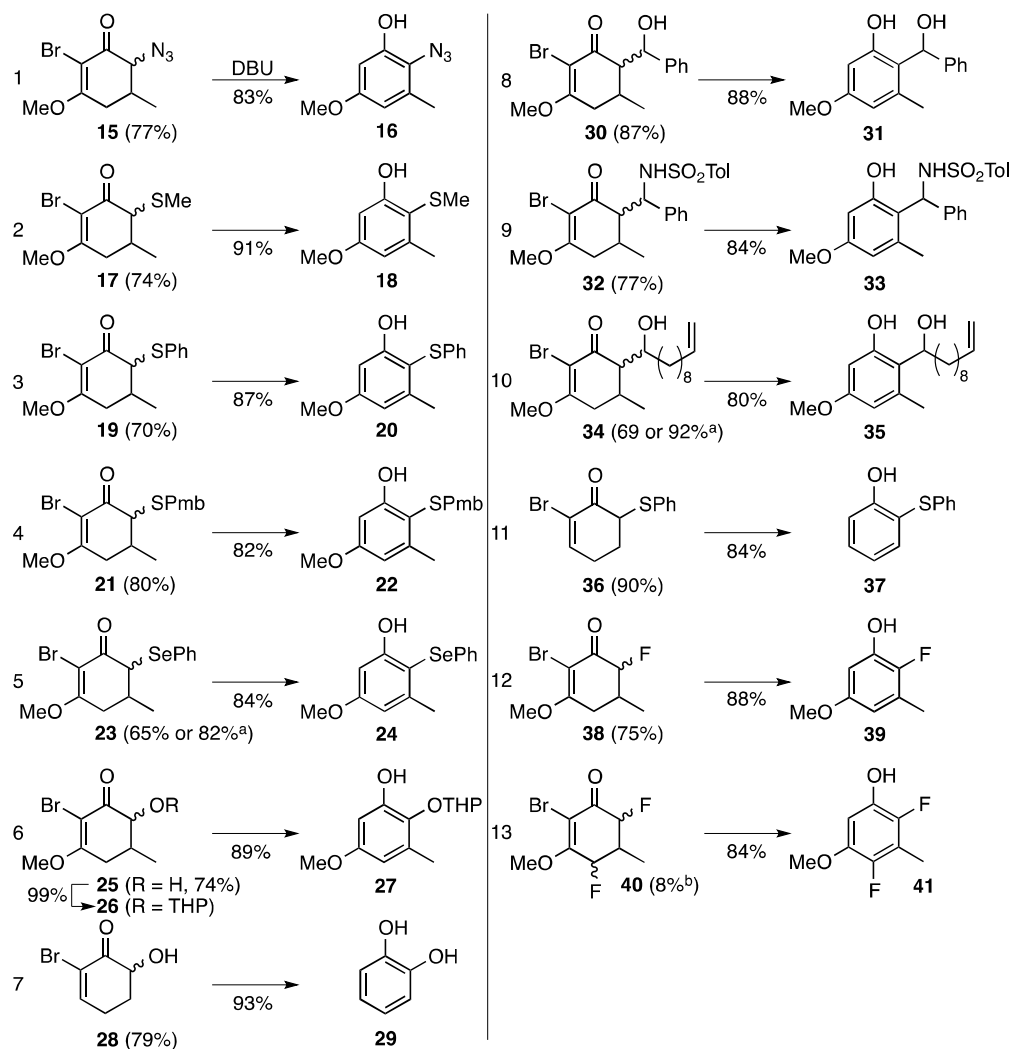
**SCHEME 4.** Acid-mediated aromatization of  $\alpha$ -haloenones.



We have applied the principle expressed in Scheme 3 to the preparation of a number of phenols. Our results are listed in Table 1 which also includes the outcome of a modification (entry 6) that extends the approach to 1,2-benzenediols. The significance of the overall process

is that it directly links the ability to functionalize a cyclohexenone-like structure  $\alpha$  to the carbonyl on the one hand with the correspondingly substituted benzene ring, and does this reliably and in good yield under mild conditions.

**Table 1.** Aromatization products and yields.



<sup>a</sup>Yield corrected for recovered starting 3-methoxybromoenone. <sup>b</sup>Yield deliberately suppressed; the compound is a byproduct when using only 1.05 equiv of fluorinating agent.

The starting bromoenones such as **8** are readily made by bromination<sup>6</sup> of 3-methoxycyclohexenones or cyclohexenones, which are themselves available by several straightforward classical procedures.<sup>7</sup>

Sulfonylation of 2-bromo-3-methoxycyclohex-2-en-1-one (entries 2—4) is easily achieved by deprotonation of the parent carbonyl compound (**1**, LDA) and quenching with a reagent of the type  $\text{RSSO}_2\text{Tol}$  ( $\text{R} = \text{Me}, \text{Ph}, \text{Pmb}$ ).<sup>8</sup> Likewise, phenylselenation is

straightforward (LDA, PhSeCl). All of the enone sulfur derivatives, irrespective of whether the substituent on the chalcogen is aromatic or aliphatic, undergo efficient aromatization (yields 82-91%) on treatment with DBU in PhMe at room temperature. For selenium we have examined only a phenyl substituent. These reactions are quite fast, being complete within 20 min to 2 h. In contrast, the azide **15** (entry 1), which is readily prepared by treating the appropriate enolate (generated with LDA) with 2,4,6-tri-isopropylbenzenesulfonyl azide<sup>9</sup> requires about 5 h.

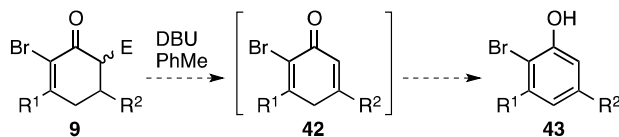
It is noteworthy that the aldol products (entries 8 and 10) do not suffer dehydration. In the case of the benzaldehyde adduct **30**, it is evident that base-induced dehydration, which would be facilitated by the presence of conjugation in the resulting product, is not a significant pathway, if it occurs at all, so that entry 8 represents the result of a demanding test for the intrusion of this undesired reaction.

The sulfonamide **32** (entry 9), easily made by enolate condensation with *N*-(toluenesulfonyl)benzaldimine<sup>10</sup> is also aromatized smoothly, but slowly; it was generated in an overnight reaction period in 84% yield.

Where the substituent introduced at the beginning is an oxygen atom [Table 1, entries 6 and 7; use of 2-(4-methylbenzenesulfonyl)-3-phenyloxaziridine<sup>11</sup>] we found that for the simple enone **28** aromatization proceeded normally, but for the 3-methoxyenone (**25**) protection of the hydroxyl is required, and a THP ether was found to be suitable.

When E<sup>+</sup> (see Scheme 3) is a heteroatom there is the potential for elimination within the six-membered ring (Scheme 5, **9**→**42**→**43**). Fortunately, for all the sulfur, selenium and oxygen

#### SCHEME 5. Potential side reaction.



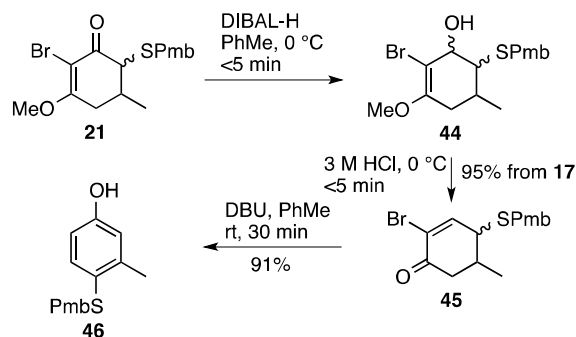
substituents we have examined, such elimination does not occur; however, it does occur with bromine (E = Br), but not with fluorine. Surprisingly, the fluoro compound **38** (entry 12) was aromatized rather slowly and was best generated by overnight exposure to DBU (PhMe, room temperature). We noticed that the difluoro compound **40** was always formed as a byproduct in the generation<sup>12</sup> of **38** but the amount could be suppressed to a level of 8% by using no more than 1.05 equiv of the commercial fluorinating reagent [FN(SO<sub>2</sub>Ph)<sub>2</sub>] and, with this stoichiometry, the yield of the monofluoride **38** was 75%. The use of a very slight excess of the fluorinating reagent, rather than exactly 1 equiv, gives a better result.

The substitution pattern of the final aromatic product can easily be modified by DIBAL-H reduction of the penultimate bromoenone.<sup>13</sup> For example, bromoenone **21** was reduced (1 equiv DIBAL-H in PhMe at 0 °C, <5 min), treated briefly (<5 min) with 3 M hydrochloric acid at 0 °C and, after product isolation, exposed to the action of DBU in PhMe. These operations served to convert **21** into **46** (Scheme 6). 3-Alkoxy-2-halocyclohex-2-en-1-ones do not appear to have been reduced before with hydride reagents, and we find that DIBAL-H in PhMe gives a much better result than DIBAL-H in CH<sub>2</sub>Cl<sub>2</sub> or LiAlH<sub>4</sub> in Et<sub>2</sub>O. The example shown in Scheme 6 was chosen as a demanding test because there again exists the potential for elimination of the PmbS group but, in the event, this does not occur and the overall transformation is extremely efficient in removing the methoxy group and affording a different regiochemical pattern to that resulting directly from **21** itself.



As illustrated by entries 7 and 11, the presence of the C-3 methoxy group is not required for the aromatization but it does play a subtle role in the first step (cf **5**→**6**) because, in its absence, that first step does not work if there is a substituent at C-5.

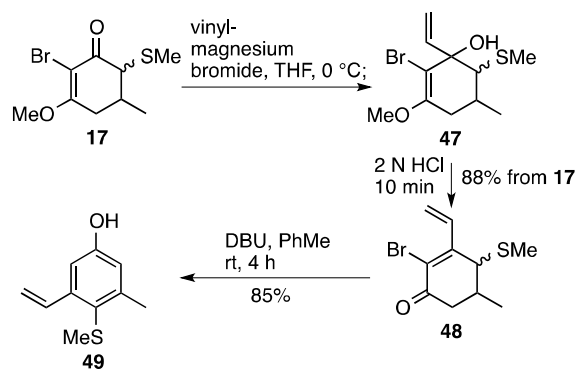
**SCHEME 6.** Modification of the substitution pattern.



Pmb = *p*-methoxybenzyl.

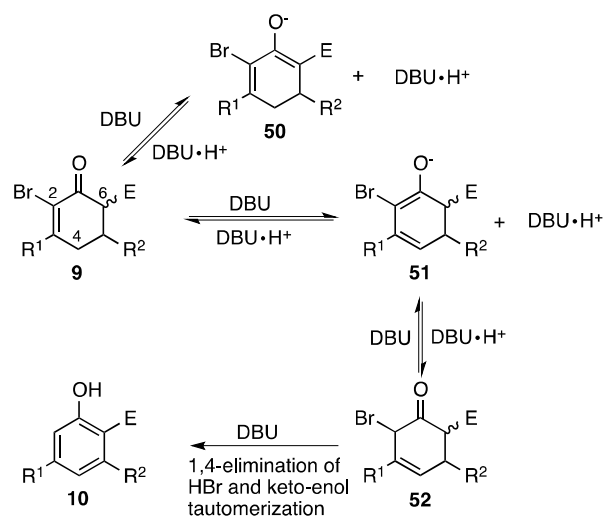
In a process analogous to the conversion of **21** to **46**, reaction of **17** with a Grignard reagent (we used vinylmagnesium bromide), mild acid hydrolysis and aromatization with DBU generates phenol **49** (Scheme 7), in which the noteworthy feature is that the new substituent has been introduced *meta* to the hydroxyl—an orientation that is complementary to that provided by classical electrophilic substitution of phenol derivatives.

**SCHEME 7.** Introduction of a *meta* substituent.



The probable mechanism for the aromatization is shown in Scheme 8 and, on that basis, all of these transformations depend on the ability of the 2-bromocyclohex-2-en-1-one unit to undergo deconjugation (see **9**→**52**, Scheme 8) in the presence of DBU, so that elimination of HBr (**52**→**10**) can then take place. The process must involve initial removal of a C-4 hydrogen from a *non-enolized* enone system (**9**), and so the relative acidity of the C-4 and C-6 hydrogens, as well as the  $\text{pK}_{\text{a}}$  of the base (and, possibly, its steric requirements) are critical for the successful outcome. The choice of DBU was not arbitrary; when we tried pyridine with **1** there was no reaction and the compound was equally inert to  $\text{Et}_3\text{N}$ . The deconjugation is evidently easy, as the aromatization proceeds at room temperature in good yield (80-92%).

**SCHEME 8.** Mechanism of the aromatization.



## CONCLUSION

The possibility of using both kinetic enolization of bromoenone systems and more attractive conditions than those of Scheme 4 for aromatization have not been appreciated before—neither of the precedents in Scheme 4 made use of functionalization  $\alpha$  to the carbonyl but, as shown here, such an enolate-based approach opens a simple and general route to an extensive range of aromatics.

Our results establish that deprotonation of 2-bromocyclohex-2-en-1-one systems and quenching with various azido, carbonyl, fluorine, oxygen, sulfur, selenium, *N*-(sulfonyl)aldimine and alkyl<sup>1</sup> electrophiles gives the expected  $\alpha$ -substituted adducts which, in turn, undergo efficient aromatization on exposure to the action of DBU in PhMe at room temperature. The regiochemistry of the final products is established in the initial reaction  $\alpha$  to the carbonyl and is highly regiocontrolled, while the aromatic products themselves are functionalized in a way that allows further manipulation. The process is clearly general and is based on a previously

unrecognized characteristic of the 2-bromocyclohex-2-en-1-one structure—the ability to effect *irreversible* kinetic deprotonation at C-6 with LDA and then to deprotonate the system *reversibly* at C-4 with DBU. The overall procedure constitutes a new family of routes to phenolic compounds that have been functionalized in a regiocontrolled manner, and gives direct and efficient access to a wide range of phenols.<sup>14</sup> If the initial product before aromatization is reduced with DIBAL-H or treated with a Grignard reagent then the scope is enlarged to a further range of substitution patterns. When a Grignard reagent RMgX is used a noteworthy result is that the R group is *meta* to the phenolic hydroxyl in the final product. For some purposes the transition metal-free nature of the process will be an important advantage.

## EXPERIMENTAL SECTION

**General Procedures.** Solvents used for chromatography were distilled before use. Commercial thin layer chromatography plates (silica gel, Merck 60F-254) were used. Silica gel for flash chromatography was Merck type 60 (230-400 mesh). The specified solvents were the same as those used for tlc monitoring of the reactions. Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. The symbols s, d, t and q used for <sup>13</sup>C NMR spectra indicate zero, one, two, or three attached hydrogens, respectively, the assignments being made from APT spectra. Solutions were evaporated under water pump vacuum and the residue was then kept under oil pump vacuum. High resolution electrospray mass spectrometric analyses were done with an orthogonal time of flight analyzer and electron ionization mass spectra were measured with a double-focusing sector mass spectrometer.

**6-Azido-2-bromo-3-methoxy-5-methylcyclohex-2-en-1-one (15).** *n*-BuLi (2.5 M in hexanes, 0.13 mL, 0.325 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of

*i*-Pr<sub>2</sub>NH (0.05 mL, 0.357 mmol) in THF (1.5 mL). Stirring at −78 °C was continued for 30 min and then a solution of **1** (65 mg, 0.297 mmol) in THF (1.5 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, so that the temperature rose to 0 °C over 2 h. The mixture was then re-cooled to −78 °C and a solution of 2,4,6-triisopropylbenzenesulfonyl azide<sup>5</sup> (180 mg, 0.582 mmol) in THF (1.5 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, and stirring was continued for 1 h, by which point the temperature had risen to −20 °C. A solution of AcOH in THF (1 N, 0.33 mL) was added and the solvent was evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:3 EtOAc–hexanes, gave **15** (59.5 mg, 77%) as a pale yellow oil: FTIR (CDCl<sub>3</sub>, cast) 2104, 1668 cm<sup>−1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ (major isomer) 1.15 (d, *J* = 7.0 Hz, 3 H), 2.34–2.40 (m, 1 H), 2.50–2.55 (m, 1 H), 2.62–2.90 (m, 1 H), 3.97 (s, 3 H), 4.04–4.05 (m, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ (major isomer) 15.9 (q), 31.0 (t), 33.0 (d), 56.7 (d), 66.7 (q), 100.0 (s), 172.8 (s), 186.6 (s); exact mass (electron ionization) *m/z* calcd for C<sub>8</sub>H<sub>10</sub>O<sub>2</sub><sup>79</sup>BrN<sub>3</sub> (M)<sup>+</sup> 258.9956, found 258.9951.

**2-Azido-5-methoxy-3-methylphenol (16).** DBU (67 mg, 0.44 mmol) was added to a stirred solution of **15** (56.1 mg, 0.215 mmol) in PhMe (1 mL). Stirring was continued for 1 h and the reaction mixture was diluted with 5% hydrochloric acid and extracted with EtOAc. The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:5 EtOAc–hexanes, gave **16** (32.1 mg, 83%) as a pale yellow, thick oil: FTIR (CDCl<sub>3</sub>, cast) 3366, 2115, 1614 cm<sup>−1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 2.34 (s, 3 H), 3.74 (s, 3 H), 5.40 (br s, 1 H), 6.29 (d, *J* = 3.0 Hz, 1 H), 6.34 (d, *J* = 3.0 Hz, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 17.1 (q), 56.3 (q), 99.3 (d), 108.6 (d), 127.7

(s), 163.2 (s), 172.0 (s); exact mass (electrospray)  $m/z$  calcd for  $C_8H_8O_2N_3$  (M-H)<sup>-</sup> 178.0622, found 178.0621.

**2-Bromo-3-methoxy-5-methyl-6-(methylsulfanyl)cyclohex-2-en-1-one (17).** *n*-BuLi (2.5 M in hexanes, 0.13 mL, 0.325 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of *i*-Pr<sub>2</sub>NH (0.05 mL, 0.357 mmol) in THF (2.0 mL). Stirring at -78 °C was continued for 30 min and then a solution of **1** (65 mg, 0.297 mmol) in THF (2.0 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, so that the temperature rose to 0 °C over 2.5 h. The mixture was then recooled to -78 °C and a solution of TolSO<sub>2</sub>SMe<sup>8b</sup> (132 mg, 0.653 mmol) in THF (2.0 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, and stirring was continued for 4 h, during which the mixture reached room temperature. The reaction mixture was diluted with saturated aqueous NH<sub>4</sub>Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:3 EtOAc-hexanes, gave **17** (58.2 mg, 74%) as a pale yellow oil: FTIR (CDCl<sub>3</sub>, cast) 1655 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ (major isomer) 1.20 (d, *J* = 7.0 Hz, 3 H), 2.15 (s, 3 H), 2.42–3.05 (m, 3 H), 3.25–3.34 (m, 1 H), 3.93 (s, 3 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ (major isomer) 14.2 (q), 19.6 (q), 31.0 (t), 31.5 (d), 54.5 (d), 56.3 (q), 99.7 (s), 169.0 (s), 187.3 (s); exact mass (electron ionization)  $m/z$  calcd for C<sub>9</sub>H<sub>13</sub>O<sub>2</sub><sup>79</sup>BrS (M)<sup>+</sup> 263.9819, found 263.9813.

**5-Methoxy-3-methyl-2-(methylsulfanyl)phenol (18).** DBU (35.6 mg, 0.234 mmol) was added to a stirred solution of **17** (31 mg, 0.117 mmol) in PhMe (1 mL). Stirring was continued for 1 h and the reaction mixture was diluted with 5% hydrochloric acid and extracted with EtOAc. The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:4 EtOAc-hexanes, gave

**18** (19.6 mg, 91%) as a colorless oil: FTIR (CDCl<sub>3</sub>, cast) 3374, 1608 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 2.16 (s, 3 H), 2.48 (s, 3 H), 3.77 (s, 3 H), 6.40 (d, *J* = 3.0 Hz, 1 H), 6.43 (d, *J* = 3.0 Hz, 1 H), 7.14 (s, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 18.7 (q), 20.9 (q), 55.2 (q), 97.3 (d), 108.7 (d), 111.4 (s), 144.1 (s), 158.2 (s), 161.2 (s); exact mass (electrospray) *m/z* calcd for C<sub>9</sub>H<sub>11</sub>O<sub>2</sub>S (M-H)<sup>-</sup> 183.0485, found 183.0488.

**2-Bromo-3-methoxy-5-methyl-6-(phenylsulfanyl)cyclohex-2-en-1-one (19).** *n*-BuLi (2.5 M in hexanes, 0.13 mL, 0.325 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of *i*-Pr<sub>2</sub>NH (0.05 mL, 0.357 mmol) in THF (2.0 mL). Stirring at -78 °C was continued for 30 min and then a solution of **1** (65 mg, 0.297 mmol) in THF (1.5 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, so that the temperature rose to 0 °C over 2.5 h. The mixture was then re-cooled to -78 °C and a solution of TolSO<sub>2</sub>SPh<sup>8b</sup> (123 mg, 0.442 mmol) in THF (1.5 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, and stirring was continued for 3 h, during which the mixture reached room temperature. The reaction mixture was diluted with saturated aqueous NH<sub>4</sub>Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:5 EtOAc-hexanes, gave **19** (67.8 mg, 70%) as a pale yellow oil: FTIR (CDCl<sub>3</sub>, cast) 1664 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ (major isomer) 1.12 (d, *J* = 7.0 Hz, 3 H), 2.38–2.42 (m, 1 H), 2.51–2.53 (m, 1 H), 3.18–3.22 (m, 1 H), 3.96–3.72 (m, 1 H), 4.18 (s, 3 H), 7.36–7.38 (m, 3 H), 7.46–7.48 (m, 2 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ (major isomer) 19.4 (q), 33.0 (d), 39.5 (t), 50.7 (d), 56.6 (q), 104.8 (s), 128.9 (d), 129.6 (d), 132.5 (s), 132.8 (d), 167.1 (s), 189.5 (s); exact mass (electron ionization) *m/z* calcd for C<sub>14</sub>H<sub>15</sub>O<sub>2</sub><sup>79</sup>BrS (M)<sup>+</sup> 325.9976, found 325.9973.

**5-Methoxy-3-methyl-2-(phenylsulfanyl)phenol (20).** DBU (61.6 mg, 0.405 mmol) was added to a stirred solution of **19** (60.3 mg, 0.184 mmol) in PhMe (1 mL). Stirring was continued for 2 h and the reaction mixture was diluted with 5% hydrochloric acid and extracted with EtOAc. The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and evaporated. Flash chromatography of the residue over silica gel (0.8 × 10 cm), using 1:4 EtOAc-hexanes, gave **20** (39.5 mg, 87%) as a white solid: mp 102–104 °C; FTIR (CDCl<sub>3</sub>, cast) 3359 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 2.37 (s, 3 H), 3.78 (s, 3 H), 4.83 (br s, 1 H), 6.38 (d, *J* = 2.5 Hz, 1 H), 6.44 (d, *J* = 2.5 Hz, 1 H), 6.96–6.98 (m, 2 H), 7.02–7.06 (m, 1 H), 7.15–7.18 (m, 2 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 21.4 (q), 56.2 (q), 97.4 (d), 109.7 (d), 110.2 (s), 124.4 (d), 125.5 (d), 128.6 (d), 138.6 (s), 146.6 (s), 157.6 (s), 162.2 (s); exact mass (electrospray) *m/z* calcd for C<sub>14</sub>H<sub>13</sub>O<sub>2</sub>S (M–H)<sup>-</sup> 245.0642, found 245.0640. Anal. Calcd for C<sub>14</sub>H<sub>14</sub>O<sub>2</sub>S: C, 68.26; H, 5.73; S, 13.02. Found: C, 68.47; H, 5.73; S, 12.88.

**2-Bromo-3-methoxy-6-[(4-methoxyphenyl)methyl]sulfanyl-5-methylcyclohex-2-en-1-one (21).** *n*-BuLi (2.5 M in hexanes, 0.13 mL, 0.325 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr<sub>2</sub>NH (0.05 mL, 0.357 mmol) in THF (2.0 mL). Stirring at –78 °C was continued for 30 min and then a solution of **1** (65 mg, 0.297 mmol) in THF (1.5 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, so that the temperature rose to 0 °C over 3.5 h. The mixture was then re-cooled to –78 °C and a solution of TolSO<sub>2</sub>SPmb<sup>8c</sup> (113 mg, 0.387 mmol) in THF (1.5 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, and stirring was continued for 1 h, by which point the temperature had risen to –20 °C. The reaction mixture was diluted with saturated aqueous NH<sub>4</sub>Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using



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3 1:3 EtOAc–hexanes, gave **21** (84.3 mg, 80%) as a colorless oil: FTIR (CDCl<sub>3</sub>, cast) 1657, 1609  
4 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ (major isomer) 1.12 (d, *J* = 6.8 Hz, 3 H), 2.32–2.57 (m, 2  
5 H), 2.93–2.99 (m, 1 H), 3.21–3.28 (m, 1 H), 3.68–3.84 (m, 5 H), 3.91 (s, 3 H), 6.82–6.85 (m, 2  
6 H), 7.29–7.32 (m, 2 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ (major isomer) 19.7 (q), 31.1 (t), 31.9 (d),  
7 H 34.1 (t), 51.5 (d), 55.3 (q), 56.4 (q), 99.9 (s), 113.8 (d), 129.4 (s), 130.4 (d), 158.7 (s), 169.1 (s),  
8 187.7 (s); exact mass (electrospray) *m/z* calcd for C<sub>16</sub>H<sub>20</sub>O<sub>3</sub><sup>79</sup>BrS (M+H)<sup>+</sup> 371.0311, found  
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20 **5-Methoxy-2-[[4-methoxyphenyl)methyl]sulfanyl]-3-methylphenol (22).** DBU (50.9  
21 mg, 0.335 mmol) was added to a stirred solution of **21** (58.0 mg, 0.163 mmol) in PhMe (1 mL).  
22 Stirring was continued for 2 h and the reaction mixture was diluted with 5% hydrochloric acid  
23 and extracted with EtOAc. The combined organic extracts were washed with brine, dried  
24 (MgSO<sub>4</sub>) and evaporated. Flash chromatography of the residue over silica gel (0.8 × 10 cm),  
25 using 1:4 EtOAc-hexanes, gave **22** (36.7 mg, 82%) as a white solid: mp 48–50 °C; FTIR  
26 (CDCl<sub>3</sub>, cast) 3377, 1614 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 2.25 (s, 3 H), 3.67 (s, 2 H), 3.77  
27 (s, 3 H), 3.78 (s, 3 H), 6.35 (dd, *J* = 3.0, 0.5 Hz, 1 H), 6.38 (dd, *J* = 3.0, 0.5 Hz, 1 H), 6.77–6.78  
28 (m, 2 H), 6.93 (s, 1 H), 6.97–6.99 (m, 2 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 21.1 (q), 39.7 (t),  
29 55.2 (q), 55.3 (q), 97.2 (d), 108.6 (d), 109.4 (s), 113.9 (d), 129.7 (s), 129.9 (d), 144.9 (s), 158.7  
30 (s), 158.9 (s), 161.4 (s); exact mass (electrospray) *m/z* calcd for C<sub>16</sub>H<sub>17</sub>O<sub>3</sub>S (M–H)<sup>–</sup> 289.0904,  
31 found 289.0902.  
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49 **2-Bromo-3-methoxy-5-methyl-6-(phenylselenenyl)cyclohex-2-en-1-one (23).** *n*-BuLi  
50 (2.5 M in hexanes, 0.13 mL, 0.325 mmol) was added dropwise to a stirred and cooled (–78 °C)  
51 solution of *i*-Pr<sub>2</sub>NH (0.05 mL, 0.357 mmol) in THF (2.0 mL). Stirring at –78 °C was continued  
52 for 30 min and then a solution of **1** (65 mg, 0.297 mmol) in THF (2.0 mL) was added dropwise  
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over < 1 min. The cold bath was left in place, but not recharged, so that the temperature rose to 0 °C over 2.5 h. The mixture was then re-cooled to –78 °C and a solution of PhSeCl (113 mg, 0.590 mmol) in THF (2.0 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, and stirring was continued for 4 h, during which the mixture reached room temperature. The reaction mixture was diluted with saturated aqueous NH<sub>4</sub>Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:3 EtOAc–hexanes, gave **23** [72.1 mg, 65%, or 82% corrected for recovered **1** (11.1 mg)] as a pale yellow oil: FTIR (CDCl<sub>3</sub>, cast) 1657 cm<sup>–1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ (major isomer) 1.17 (d, *J* = 7.0 Hz, 3 H), 2.42–3.01 (m, 3 H), 3.87–3.91 (m, 4 H), 7.26–7.33 (m, 3 H), 7.59–7.61 (m, 2 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ (major isomer) 19.9 (q), 31.2 (t), 32.4 (d), 52.0 (d), 56.4 (q), 100.7 (s), 127.6 (s), 128.6 (d), 129.2 (d), 135.5 (d), 171.1 (s), 187.5 (s); exact mass (electron ionization) *m/z* calcd for C<sub>14</sub>H<sub>15</sub>O<sub>2</sub><sup>79</sup>Br<sup>80</sup>Se (M)<sup>+</sup> 373.9421, found 373.9420.

**5-Methoxy-3-methyl-2-(phenylselenyl)phenol (24).** DBU (45 mg, 0.296 mmol) was added to a stirred solution of **23** (50.3 mg, 0.134 mmol) in PhMe (1 mL). Stirring was continued for 8 h and the reaction mixture was diluted with 5% hydrochloric acid and extracted with EtOAc. The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and evaporated. Flash chromatography of the residue over silica gel (0.8 × 10 cm), using 1:10 EtOAc–hexanes, gave **24** (33.3 mg, 84%) as a white solid: mp 74–76 °C; FTIR (CDCl<sub>3</sub>, cast) 3384, 1602 cm<sup>–1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 2.41 (s, 3 H), 3.81 (s, 3 H), 6.49 (d, *J* = 3.0 Hz, 1 H), 6.52 (d, *J* = 3.0 Hz, 1 H), 6.79 (s, 1 H), 7.12–7.21 (m, 5 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 23.6 (q), 55.3 (q), 97.3 (d), 107.1 (s), 109.1 (d), 126.4 (d), 128.5 (d), 129.4 (d), 131.1 (s), 145.2 (s), 158.4 (s), 162.3 (s); exact mass (electrospray) *m/z* calcd for C<sub>14</sub>H<sub>13</sub>O<sub>2</sub><sup>80</sup>Se (M–H)<sup>–</sup> 293.0086, found 293.0091. A

sample was recrystallized from hexane for combustion analysis. Anal. Calcd for C<sub>14</sub>H<sub>14</sub>O<sub>2</sub>Se: C, 57.37; H, 4.81. Found: C, 57.25; H, 4.82. Another sample was crystallized from hexane-CH<sub>2</sub>Cl<sub>2</sub> for X-ray analysis (see Supporting Information).

**2-Bromo-6-hydroxy-3-methoxy-5-methylcyclohex-2-en-1-one (25).** *n*-BuLi (2.5 M in hexanes, 0.26 mL, 0.65 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of *i*-Pr<sub>2</sub>NH (0.10 mL, 0.713 mmol) in THF (3.0 mL). Stirring at −78 °C was continued for 30 min and then a solution of **1** (130 mg, 0.594 mmol) in THF (3.0 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, so that the temperature rose to 0 °C over 3.5 h. The mixture was then re-cooled to −78 °C and a solution of 2-(4-methylbenzenesulfonyl)-3-phenyloxaziridine<sup>11</sup> (250 mg, 0.909 mmol) in THF (3.0 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, and stirring was continued for 4 h, during which the mixture reached room temperature. The reaction mixture was diluted with saturated aqueous NaHCO<sub>3</sub> and extracted with EtOAc. The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:1 EtOAc-hexanes, gave **25** (103.3 mg, 74%) as a colorless oil: FTIR (CDCl<sub>3</sub>, cast) 3346, 1666 cm<sup>−1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 1.00 (d, *J* = 7.0 Hz, 3 H), 2.71–2.75 (m, 2 H), 2.92 (dd, *J* = 18.0, 5.5 Hz, 1 H), 3.75 (br s, 1 H), 3.99 (s, 3 H), 4.31 (d, *J* = 5.0 Hz, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 11.9 (q), 32.4 (d), 32.6 (t), 56.6 (q), 74.5 (d), 97.8 (s), 171.1 (s), 191.9 (s); exact mass (electrospray) *m/z* calcd for C<sub>8</sub>H<sub>10</sub>O<sub>3</sub><sup>79</sup>Br (M–H)<sup>−</sup> 232.9819, found 232.9816.

**2-Bromo-3-methoxy-5-methyl-6-(oxan-2-yloxy)cyclohex-2-en-1-one (26).** 3,4-Dihydropyran (20 mg, 0.208 mmol) and pyridinium *p*-toluenesulfonate (0.8 mg, 0.0032 mmol) were added to a stirred solution of **25** (40.1 mg, 0.171 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL). Stirring was

continued for 5 h and the reaction mixture was then diluted with saturated aqueous NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and evaporated to give **26** (55.9 mg, ca 99%) as an oil that was a mixture of isomers (<sup>1</sup>H NMR) which was used directly in the next step.

**5-Methoxy-3-methyl-2-(oxan-2-yloxy)phenol (27).** DBU (111 mg, 0.730 mmol) was added to a stirred solution of **26** (55.9 mg, ca 0.171 mmol) in PhMe (1 mL). Stirring was continued overnight and the reaction mixture was diluted with ice-cold saturated aqueous NH<sub>4</sub>Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and evaporated. Flash chromatography of the residue over silica gel (0.8 × 10 cm), using 1:10 EtOAc-hexanes, gave **27** (37.9 mg, 89%) as a colorless, thick oil: FTIR (CDCl<sub>3</sub>, cast) 3327, 1620 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 1.55–2.06 (m, 6 H), 2.19 (s, 3 H), 3.55–3.60 (m, 1 H), 3.73 (s, 3 H), 4.14–4.16 (m, 1 H), 4.64 (dd, *J* = 8.5, 2.5 Hz, 1 H), 6.24 (d, *J* = 2.5 Hz, 1 H), 6.38 (d, *J* = 3.0 Hz, 1 H), 7.91 (s, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 16.6 (q), 21.4 (t), 24.7 (t), 31.4 (t), 55.4 (q), 66.4 (t), 100.1 (d), 104.9 (d), 107.2 (d), 132.0 (s), 138.1 (s), 150.3 (s), 156.7 (s); exact mass (electrospray) *m/z* calcd for C<sub>13</sub>H<sub>17</sub>O<sub>4</sub> (M–H)<sup>–</sup> 237.1132, found 237.1130.

**2-Bromo-6-hydroxycyclohex-2-en-1-one (28).** *n*-BuLi (2.5 M in hexanes, 0.21 mL, 0.525 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr<sub>2</sub>NH (0.09 mL, 0.642 mmol) in THF (3.0 mL). Stirring at –78 °C was continued for 30 min and then a solution of 2-bromocyclohex-2-en-1-one<sup>6b</sup> (85.2 mg, 0.487 mmol) in THF (3.0 mL) was added dropwise over < 1 min. Stirring at –78 °C was continued for 1 h and oxaziridine 2-(4-methylbenzenesulfonyl)-3-phenyloxaziridine<sup>11</sup> (102 mg, 0.584 mmol) in THF (3.0 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, and stirring was continued for 4 h, during which the mixture reached room temperature. The reaction

mixture was diluted with saturated aqueous  $\text{NH}_4\text{Cl}$  and extracted with EtOAc. The combined organic extracts were washed with ice-cold aqueous 0.1%w/v NaOH and brine, dried ( $\text{MgSO}_4$ ) and evaporated. Flash chromatography of the residue over silica gel ( $1 \times 15$  cm), using 1:3 EtOAc–hexanes, gave **28** (73.4 mg, 79%) as a colorless oil: FTIR ( $\text{CDCl}_3$ , cast)  $3482\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  1.94–2.04 (m, 1 H), 2.40–2.46 (m, 1 H), 2.55–2.58 (m, 2 H), 3.57 (d,  $J = 2.0$  Hz, 1 H), 4.30 (ddd,  $J = 13.5, 5.5, 1.5$  Hz, 1 H), 7.40–7.42 (m, 1 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  26.7 (t), 30.7 (t), 73.3 (d), 120.2 (s), 152.2 (d), 193.9 (s); exact mass (electron ionization)  $m/z$  calcd for  $\text{C}_6\text{H}_7\text{O}_2^{79}\text{Br}(\text{M})^+$  189.9629, found 189.9629.

**Benzene-1,2-diol (29).**<sup>15</sup> DBU (120 mg, 0.789 mmol) was added to a stirred solution of **28** (69.9 mg, 0.366 mmol) in PhMe (1 mL). Stirring was continued overnight and the reaction mixture was diluted with a few (5–6) drops of AcOH. The PhMe and excess of AcOH were evaporated, and flash chromatography of the residue over silica gel ( $0.8 \times 10$  cm), using 1:1 EtOAc–hexanes, gave **29** (37.4 mg, 93%) as an off-white solid: mp  $102\text{--}104\text{ }^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  5.09 (s, 2 H), 6.81–6.83 (m, 2 H), 6.87–6.88 (m, 2 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  115.5 (d), 121.3 (d), 143.5 (s).

**2-Bromo-6-[hydroxy(phenyl)methyl]-3-methoxy-5-methylcyclohex-2-en-1-one (30).**  $n\text{-BuLi}$  (2.5 M in hexanes, 0.26 mL, 0.650 mmol) was added dropwise to a stirred and cooled ( $-78\text{ }^\circ\text{C}$ ) solution of  $i\text{-Pr}_2\text{NH}$  (0.10 mL, 0.714 mmol) in THF (3.0 mL). Stirring at  $-78\text{ }^\circ\text{C}$  was continued for 30 min and then a solution of **1** (131 mg, 0.598 mmol) in THF (3.0 mL) was added dropwise over  $< 1$  min. The cold bath was left in place, but not recharged, so that the temperature rose to  $0\text{ }^\circ\text{C}$  over 3.5 h. The mixture was then re-cooled to  $-78\text{ }^\circ\text{C}$  and PhCHO (0.24 mL, 2.39 mmol) was added dropwise over  $< 1$  min. Stirring was continued for 20 min at  $-78\text{ }^\circ\text{C}$ . A solution of AcOH in THF (1 N, 0.65 mL) was added and the solvent was evaporated. The

residue was partitioned between water and EtOAc and the combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:3 EtOAc–hexanes, gave **30** (143 mg, 87%) as a white solid: FTIR (CDCl<sub>3</sub>, cast) 3438, 1652 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ (major isomer) 1.07 (d, *J* = 7.0 Hz, 3 H), 2.03–2.40 (m, 2 H), 2.66–2.90 (m, 2 H), 3.16 (br s, 1 H), 3.94 (s, 3 H), 4.81–5.08 (m, 1 H), 7.26–7.37 (m, 5 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ (major isomer) 20.6 (q), 28.0 (d), 31.8 (t), 56.4 (d), 59.5 (q), 74.7 (d), 101.4 (s), 126.5 (d), 128.1 (d), 128.7 (d), 141.7 (s), 171.2 (s), 192.6 (s); exact mass (electron ionization) *m/z* calcd for C<sub>15</sub>H<sub>17</sub>O<sub>3</sub><sup>79</sup>Br (M)<sup>+</sup> 324.0361, found 324.0356.

**2-[Hydroxy(phenyl)methyl]-5-methoxy-3-methylphenol (31).** DBU (0.10 mL, 0.696 mmol) was added to a stirred solution of **30** (113 mg, 0.348 mmol) in PhMe (1.5 mL). Stirring was continued overnight and the reaction mixture was diluted with 5% hydrochloric acid and extracted with EtOAc. The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 1:4 EtOAc–hexanes, gave **31** (74.6 mg, 88%) as a white solid: mp 113–115 °C; FTIR (CDCl<sub>3</sub>, cast) 3319, 1623 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 2.15 (s, 3 H), 2.72 (d, *J* = 3.0 Hz, 1 H), 3.77 (s, 3 H), 6.17 (d, *J* = 2.5 Hz, 1 H), 6.29 (dd, *J* = 2.5, 1.0 Hz, 1 H), 6.38 (d, *J* = 2.5 Hz, 1 H), 7.30–7.37 (m, 5 H), 8.59 (s, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 19.9 (q), 55.2 (q), 74.6 (d), 100.7 (d), 108.6 (d), 116.4 (s), 127.1 (d), 128.3 (d), 128.8 (d), 136.8 (s), 141.2 (s), 157.7 (s), 160.1 (s); exact mass (electrospray) *m/z* calcd for C<sub>15</sub>H<sub>15</sub>O<sub>3</sub> (M–H)<sup>–</sup> 243.1027, found 243.1026. A sample was recrystallized from hexane for combustion analysis. Anal. Calcd for C<sub>15</sub>H<sub>16</sub>O<sub>3</sub>: C, 73.75; H, 6.60. Found: C, 73.38; H, 6.56.

***N*–[(3-Bromo-4-methoxy-6-methyl-2-oxocyclohex-3-en-1-yl)(phenyl)methyl]-4-methylbenzene-1-sulfonamide (32).** *n*-BuLi (2.5 M in hexanes, 0.26 mL, 0.650 mmol) was

added dropwise to a stirred and cooled ( $-78\text{ }^{\circ}\text{C}$ ) solution of *i*-Pr<sub>2</sub>NH (0.10 mL, 0.714 mmol) in THF (3.0 mL). Stirring at  $-78\text{ }^{\circ}\text{C}$  was continued for 30 min and then a solution of **1** (130 mg, 0.598 mmol) in THF (3.0 mL) was added dropwise over  $< 1$  min. The cold bath was left in place, but not recharged, so that the temperature rose to  $0\text{ }^{\circ}\text{C}$  over 3.5 h. The mixture was then recooled to  $-78\text{ }^{\circ}\text{C}$  and a solution of *N*-(toluenesulfonyl)benzaldimine<sup>10</sup> (300 mg, 1.16 mmol) in THF (2.0 mL) was added dropwise over  $< 1$  min. The cold bath was left in place, but not recharged, and stirring was continued for 1 h, by which point the temperature had risen to  $-20\text{ }^{\circ}\text{C}$ . The reaction mixture was diluted with saturated aqueous NaHCO<sub>3</sub> and extracted with EtOAc. The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and evaporated. Flash chromatography of the residue over silica gel (1  $\times$  15 cm), using 1:1 EtOAc–hexanes, gave **32** (218.5 mg, 77%) as a colorless oil: FTIR (CDCl<sub>3</sub>, cast) 3358, 1657 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  (major isomer) 1.26 (d, *J* = 6.5 Hz, 3 H), 2.41–2.39 (m, 5 H), 2.57 (dd, *J* = 8.5, 5.0 Hz, 1 H), 2.83 (dd, *J* = 8.5, 5.0 Hz, 1 H), 3.94 (s, 3 H), 4.67 (dd, *J* = 8.0, 5.0 Hz, 1 H), 5.78 (d, *J* = 8.0 Hz, 1 H), 7.04–7.11 (m, 7 H), 7.44–7.45 (m, 2 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  (major isomer) 19.9 (q), 21.4 (q), 29.3 (d), 33.3 (t), 56.4 (d), 56.5 (q), 58.9 (d), 101.6 (s), 126.9 (d), 127.0 (d), 127.1 (d), 128.2 (d), 129.2 (d), 137.6 (s), 139.5 (s), 142.9 (s), 171.4 (s), 191.4 (s); exact mass (electrospray) *m/z* calcd for C<sub>22</sub>H<sub>25</sub>O<sub>4</sub><sup>79</sup>BrNS (M+H)<sup>+</sup> 478.0682, found 478.0687.

*N*-[(2-hydroxy-4-methoxy-6-methylphenyl)(phenyl)methyl]-4-methylbenzene-1-sulfonamide (**33**). DBU (148 mg, 0.966 mmol) was added to a stirred solution of **32** (210 mg, 0.439 mmol) in PhMe (3 mL). Stirring was continued overnight and the reaction mixture was diluted with 5% hydrochloric acid and extracted with EtOAc. The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and evaporated. Flash chromatography of the residue over silica gel (1  $\times$  10 cm), using 1:5 EtOAc–hexanes, gave **33** (147 mg, 84%) as a white solid:

mp 58–60 °C; FTIR (CDCl<sub>3</sub>, cast) 3326, 1614 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 2.11 (s, 3 H), 2.32 (s, 3 H), 3.69 (s, 3 H), 5.68 (s, 1 H), 5.76 (d, *J* = 9.5 Hz, 1 H), 6.00 (d, *J* = 2.5 Hz, 1 H), 6.17 (d, *J* = 2.5 Hz, 1 H), 6.25 (d, *J* = 9.5 Hz, 1 H), 7.04 (d, *J* = 8.0 Hz, 2 H), 7.22–7.26 (m, 5 H), 7.52–7.54 (m, 2 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 20.1 (q), 21.4 (q), 55.2 (q), 55.4 (d), 100.5 (d), 108.4 (d), 117.0 (s), 126.6 (d), 126.8 (d), 127.3 (d), 128.4 (d), 129.1 (d), 137.2 (s), 138.3 (s), 140.1 (s), 142.9 (s), 154.3 (s), 159.6 (s); exact mass (electrospray) *m/z* calcd for C<sub>22</sub>H<sub>22</sub>NO<sub>4</sub>S (M–H)<sup>–</sup> 396.1275, found 396.1282.

**2-Bromo-6-(1-hydroxyundec-10-en-1-yl)-3-methoxy-5-methylcyclohex-2-en-1-one**

**(34).** *n*-BuLi (2.5 M in hexanes, 0.13 mL, 0.325 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr<sub>2</sub>NH (0.05 mL, 0.357 mmol) in THF (1.5 mL). Stirring at –78 °C was continued for 30 min and then a solution of **1** (65 mg, 0.298 mmol) in THF (1.5 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, so that the temperature rose to 0 °C over 4.5 h. The mixture was then re-cooled to –78 °C and a solution of undec-10-enal (74.8 mg, 0.445 mmol) in THF (1.5 mL) was added dropwise over < 1 min. The cold bath was left in place, and stirring at –78 °C was continued for 10 min. A solution of AcOH in THF (1 N, 0.33 mL) was added and the solvent was evaporated. The residue was partitioned between water and EtOAc and the combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:3 EtOAc–hexanes, gave **34** [79.3 mg, 69% or 92% corrected for recovered **1** (14.8 mg)] as a colorless oil: FTIR (CDCl<sub>3</sub>, cast) 3485, 1653 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 1.18 (d, *J* = 6.4 Hz, 3 H), 1.25–1.79 (m, 14 H), 2.00–2.24 (m, 4 H), 2.36–2.43 (m, 2 H), 2.87–2.90 (m, 1 H), 3.82 (br s, 1 H), 3.94 (s, 3 H), 4.90–5.00 (m, 2 H), 5.75–5.85 (m, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 20.3 (q), 26.1 (t), 28.9 (t), 29.1 (t), 29.4 (t), 29.5 (t), 29.6 (t), 29.9 (d), 33.8 (t), 33.8 (t),



36.4 (t), 56.3 (d), 57.2 (q), 71.4 (d), 102.3 (s), 114.1 (t), 139.2 (d), 171.4 (s), 192.7 (s); exact mass (electron ionization)  $m/z$  calcd for  $C_{19}H_{31}O_3^{79}Br (M)^+$  386.1456, found 386.1450.

**2-(1-Hydroxyundec-10-en-1-yl)-5-methoxy-3-methylphenol (35).** DBU (17.8 mg, 0.117 mmol) was added to a stirred solution of **34** (22.7 mg, 0.0587 mmol) in PhMe (2 mL). Stirring was continued overnight and the reaction mixture was diluted with 5% hydrochloric acid and extracted with EtOAc. The combined organic extracts were washed with brine, dried ( $MgSO_4$ ) and evaporated. Flash chromatography of the residue over silica gel ( $0.8 \times 10$  cm), using 1:4 EtOAc-hexanes, gave **35** (14.3 mg, 80%) as a thick oil: FTIR ( $CDCl_3$ , cast) 3435, 3177, 1627  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 500 MHz)  $\delta$  1.26–1.37 (m, 12 H), 1.62–1.72 (m, 1 H), 1.88–2.60 (m, 3 H), 2.19 (s, 3 H), 2.36 (d,  $J = 3.0$  Hz, 1 H), 3.75 (s, 3 H), 4.92–5.00 (m, 2 H), 5.08–5.10 (m, 1 H), 5.78–5.84 (m, 1 H), 6.24 (d,  $J = 2.5$  Hz, 1 H), 6.32 (d,  $J = 2.5$  Hz, 1 H), 8.49 (s, 1 H);  $^{13}C$  NMR ( $CDCl_3$ , 125 MHz)  $\delta$  19.8 (q), 26.0 (t), 28.9 (t), 29.1 (t), 29.4 (t), 29.4 (t), 29.5 (t), 33.8 (t), 36.3 (t), 55.2 (q), 72.7 (d), 100.6 (d), 108.3 (d), 114.1 (t), 118.3 (s), 135.8 (s), 139.2 (d), 157.5 (s), 159.6 (s); exact mass (electrospray)  $m/z$  calcd for  $C_{19}H_{29}O_3 (M-H)^-$  305.2122, found 305.2123.

**2-Bromo-6-(phenylsulfanyl)cyclohex-2-en-1-one (36).**  $n$ -BuLi (2.5 M in hexanes, 0.26 mL, 0.650 mmol) was added dropwise to a stirred and cooled ( $-78$  °C) solution of  $i$ -Pr $_2$ NH (0.10 mL, 0.714 mmol) in THF (3.0 mL). Stirring at  $-78$  °C was continued for 30 min and then a solution of 2-bromocyclohex-2-enone<sup>6b</sup> (96 mg, 0.548 mmol) in THF (3.0 mL) was added dropwise over  $< 1$  min. The cold bath was left in place, but not recharged, so that the temperature rose to  $0$  °C over 3.5 h. The mixture was then re-cooled to  $-78$  °C and PhCHO (0.24 mL, 2.39 mmol) was added dropwise over  $< 1$  min. The cold bath was left in place, but not recharged, and stirring was continued for 4 h, during which the mixture reached room

temperature. The reaction mixture was diluted with saturated aqueous  $\text{NH}_4\text{Cl}$  and extracted with EtOAc. The combined organic extracts were washed with brine, dried ( $\text{MgSO}_4$ ) and evaporated. Flash chromatography of the residue over silica gel ( $1 \times 15$  cm), using 1:8 EtOAc–hexanes, gave **36** (139.5 mg, 90%) as a colorless oil: FTIR ( $\text{CDCl}_3$ , cast)  $1684\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  2.28–2.32 (m, 1 H), 2.46–2.49 (m, 2 H), 2.71–2.77 (m, 1 H), 4.04 (dd,  $J = 4.5$  Hz, 1 H), 7.32–7.37 (m, 4 H), 7.48–7.50 (m, 2 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  25.9 (t), 28.7 (t), 53.2 (d), 122.1 (s), 128.4 (d), 129.2 (d), 132.2 (s), 133.5 (d), 149.5 (d), 186.9 (s); exact mass (electron ionization)  $m/z$  calcd for  $\text{C}_{12}\text{H}_{11}\text{O}^{79}\text{BrS}(\text{M})^+$  281.9714, found 281.9716.

**2-(Phenylsulfanyl)phenol (37).**<sup>16</sup> DBU (89 mg, 0.585 mmol) was added to a stirred solution of **36** (83.4 mg, 0.293 mmol) in PhMe (2 mL). Stirring was continued for 30 min and the reaction mixture was diluted with 5% hydrochloric acid and extracted with EtOAc. The combined organic extracts were washed with brine, dried ( $\text{MgSO}_4$ ) and evaporated. Flash chromatography of the residue over silica gel ( $0.8 \times 10$  cm), using 1:15 EtOAc–hexanes, gave **37** (50.3 mg, 84%) as a pale yellow oil: FTIR ( $\text{CDCl}_3$ , cast)  $3424, 1595\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  6.50 (s, 1 H), 6.96 (ddd,  $J = 7.5, 1.5$  Hz, 1 H), 7.06–7.10 (m, 3 H), 7.14–7.17 (m, 1 H), 7.22–7.25 (m, 3 H), 7.36–7.40 (m, 1 H), 7.53 (dd,  $J = 7.5$  Hz, 1.5 Hz, 1 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  115.6 (d), 116.3 (s), 121.3 (d), 126.2 (d), 126.9 (d), 129.2 (d), 132.3 (d), 135.9 (s), 136.9 (d), 157.3 (s); exact mass (electrospray)  $m/z$  calcd for  $\text{C}_{12}\text{H}_9\text{OS}(\text{M}-\text{H})^-$  201.0380, found 201.0387.

**2-Bromo-6-fluoro-3-methoxy-5-methylcyclohex-2-en-1-one (38) and 2-Bromo-4,6-difluoro-3-methoxy-5-methylcyclohex-2-en-1-one (40).** *n*-BuLi (2.5 M in hexanes, 0.26 mL, 0.65 mmol) was added dropwise to a stirred and cooled ( $-78\text{ }^\circ\text{C}$ ) solution of *i*-Pr<sub>2</sub>NH (0.10 mL, 0.713 mmol) in THF (3.0 mL). Stirring at  $-78\text{ }^\circ\text{C}$  was continued for 30 min and then a solution

of **1** (130 mg, 0.594 mmol) in THF (3.0 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, so that the temperature rose to 0 °C over 3.5 h. The mixture was then recooled to -78 °C and a solution of commercial *N*-fluorobenzenesulfonimide (196 mg, 0.622 mmol) in THF (3.0 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, and stirring was continued for 4 h, during which the mixture reached room temperature. The reaction mixture was diluted with saturated aqueous NaHCO<sub>3</sub> and extracted with EtOAc. The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:3 EtOAc–hexanes, gave **38** (105 mg, 75%) and **40** (12 mg, 8%) as colorless oils: Compound **38** had: FTIR (CDCl<sub>3</sub>, cast) 1677 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 1.22 and 1.29 (d, *J* = 7.0 Hz, integration together 3 H), 2.37–2.96 (m, 3 H), 3.98 and 3.99 (s, integration together 3 H), 4.59 (dd, *J* = 48.5, 11.5 Hz) and 4.82 (dd, *J* = 49.5, 3.0 Hz) integration together 1 H; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ (major isomer) 14.6 (q), 30.8 (t), 32.3 (d), 56.7 (q), 91.1 (d), 100.2 (s), 171.9 (s), 185.6 (s); exact mass (electron ionization) *m/z* calcd for C<sub>8</sub>H<sub>10</sub>O<sub>2</sub><sup>79</sup>BrF (M)<sup>+</sup> 235.9848, found 235.9852; Compound **40** had: FTIR (CDCl<sub>3</sub>, cast) 1698 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ (major isomer) 1.13 (d, *J* = 7.0 Hz, 3 H), 2.54–3.00 (m, 1 H), 4.12 (s, 3 H), 4.91–5.41 (m, 2 H); the <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) was too complicated to be informative; exact mass (electron ionization) *m/z* calcd for C<sub>8</sub>H<sub>9</sub>O<sub>2</sub><sup>79</sup>BrF<sub>2</sub> (M)<sup>+</sup> 253.9754, found 253.9753.

**2-Fluoro-5-methoxy-3-methylphenol (39).** DBU (98 mg, 0.644 mmol) was added to a stirred solution of **38** (75.4 mg, 0.318 mmol) in PhMe (1.5 mL). Stirring was continued overnight and the reaction mixture was diluted with 5% hydrochloric acid and extracted with EtOAc. The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:5 EtOAc-hexanes, gave

**39** (43.5 mg, 88%) as a colorless, thick oil: FTIR (CDCl<sub>3</sub>, cast) 3390, 1604 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 2.24 (tt, *J* = 2.5, 0.5 Hz, 3 H), 3.73 (s, 3 H), 5.02 (br s, 1 H), 6.23–6.25 (m, 2 H), 6.39–6.41 (m, 2 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 14.6 (q), 55.6 (q), 100.2 (d), 107.4 (d), 125.4 (s), 143.7 (s), 145.5 (s), 155.6 (s); exact mass (electrospray) *m/z* calcd for C<sub>8</sub>H<sub>8</sub>O<sub>2</sub>F (M–H)<sup>–</sup> 155.0514, found 155.0514.

**2,4-Difluoro-5-methoxy-3-methylphenol (41).** DBU (50.6 mg, 0.333 mmol) was added to a stirred solution of **40** (42.4 mg, 0.166 mmol) in PhMe (1 mL). Stirring was continued overnight and the reaction mixture was diluted with 5% hydrochloric acid and extracted with EtOAc. The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:5 EtOAc-hexanes, gave **41** (24.4 mg, 84%) as a colorless, thick oil: FTIR (CDCl<sub>3</sub>, cast) 3429, 1613 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 2.21 (t, *J* = 2.5 Hz, 3 H), 3.82 (s, 3 H), 4.86 (br s, 1 H), 6.50 (t, *J* = 10.0 Hz, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 7.6 (q), 56.7 (q), 99.4 (d), 114.1 (s), 138.9 (s), 142.1 (s), 143.9 (s), 145.3 (s); exact mass (electrospray) *m/z* calcd for C<sub>8</sub>H<sub>7</sub>O<sub>2</sub>F<sub>2</sub> (M–H)<sup>–</sup> 173.0420, found 173.0419.

**2-Bromo-4-[(4-methoxyphenyl)methyl]sufanyl}-5-methylcyclohex-2-en-1-one (45).** DIBAL-H (1.0 M in hexanes, 0.21 mL) was added over < 1 min to a stirred solution of **21** (74.0 mg, 0.20 mmol) in toluene at 0 °C. The mixture was stirred for 5 min, diluted at 0 °C with 3 N hydrochloric acid, stirred for 5 min and extracted with EtOAc. The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and evaporated. Flash chromatography of the residue over silica gel (0.8 × 12 cm), using 1:4 EtOAc-hexanes, gave **45** (64.4 mg, 95%) as a colorless, thick oil: FTIR (CDCl<sub>3</sub>, cast) 1678 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ (major isomer) 1.11 (d, *J* = 7.0 Hz, 3 H), 2.65–2.39 (m, 1 H), 2.49–2.92 (m, 2 H), 3.12–3.36 (m, 1 H), 3.78 (s, 2 H), 3.81

(s, 3 H), 6.86–6.89 (m, 2 H), 7.18–7.26 (m, 3 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  (major isomer) 19.2 (q), 34.9 (d), 35.3 (t), 43.6 (t), 48.9 (d), 55.3 (q), 114.2 (d), 123.4 (s), 129.1 (s), 130.1 (d), 149.3 (d), 159.1 (s), 190.5 (s); exact mass (electron ionization)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{17}\text{O}_2\text{S}^{81}\text{Br}$  ( $\text{M}$ ) $^{+}$  342.0112, found 342.0111.

**4-[(4-Methoxyphenyl)methyl]sulfanyl-3-methylphenol (46).** DBU (57.2 mg, 0.376 mmol) was added to a stirred solution of **45** (60.3 mg, 0.184 mmol) in PhMe (1 mL). Stirring was continued for 30 min and the reaction mixture was diluted with aqueous  $\text{NH}_4\text{Cl}$  and extracted with EtOAc. The combined organic extracts were washed with brine, dried ( $\text{MgSO}_4$ ) and evaporated. Flash chromatography of the residue over silica gel ( $0.8 \times 12$  cm), using 1:4 EtOAc-hexanes, gave **46** (41.6 mg, 91%) as a white solid: mp 81–83 °C; FTIR ( $\text{CDCl}_3$ , cast) 3397, 1609  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  2.28 (s, 3 H), 3.78 (s, 3 H), 3.87 (s, 2 H), 4.68 (br s, 1 H), 6.58 (ddd,  $J = 10.5, 3.5, 0.5$  Hz, 1 H), 6.67 (dd,  $J = 3.5, 0.5$  Hz, 1 H), 6.77–6.79 (m, 2 H), 7.06–7.08 (m, 2 H), 7.19 (d,  $J = 10.5$  Hz, 1 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  20.8 (q), 39.9 (t), 55.3 (q), 113.4 (d), 113.8 (d), 117.1 (d), 125.8 (s), 130.0 (d), 130.1 (s), 135.0 (d), 142.5 (s), 155.1 (s), 158.6 (s); exact mass (electrospray)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{15}\text{O}_2\text{S}$  ( $\text{M}-\text{H}$ ) $^{-}$  259.0798, found 259.0797.

**2-Bromo-3-ethenyl-5-methyl-4-(methylsulfanyl)cyclohex-2-en-1-one (48).** Vinyl-magnesium bromide solution (1.0 M in THF, 0.15 mL) was added dropwise over < 1 min to a stirred solution of **17** (26.0 mg, 0.098 mmol) in THF (2.0 mL) and stirring at 0 °C was continued for 1 h. The ice bath was left in place, but not recharged, and stirring was continued for 12 h, during which the mixture reached room temperature. The reaction mixture was diluted with 2 N hydrochloric acid, stirred for 10 min and extracted with EtOAc. The combined organic extracts were washed with brine, dried ( $\text{MgSO}_4$ ) and evaporated. Flash chromatography of the residue

over silica gel (0.5 × 10 cm), using 1:5 EtOAc-hexanes, gave **48** (22.5 mg, 88%) as a colorless, thick oil: FTIR (CDCl<sub>3</sub>, cast) 1676 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ (major isomer) 1.23 (d, *J* = 6.5 Hz, 3 H), 2.15 (s, 3 H), 2.47–3.35 (m, 3 H), 3.68–3.74 (m, 1 H), 5.74 (d, *J* = 11.0 Hz, 1 H), 5.98 (d, *J* = 17.5 Hz, 1 H), 7.13 (dd, *J* = 17.5, 11.0 Hz, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ (major isomer) 17.5 (q), 18.5 (q), 34.3 (d), 41.4 (t), 49.7 (d), 123.7 (t), 125.8 (s), 135.6 (d), 153.3 (s), 191.2 (s); exact mass (electron ionization) *m/z* calcd for C<sub>10</sub>H<sub>13</sub>OS<sup>81</sup>Br (M)<sup>+</sup> 261.9850, found 261.9852.

**3-Ethenyl-5-methyl-4-(methylsulfanyl)phenol (49).** DBU (29.3 mg, 0.192 mmol) was added to a stirred solution of **48** (25.1 mg, 0.096 mmol) in PhMe (0.5 mL). Stirring was continued for 4 h and the reaction mixture was diluted with saturated aqueous NH<sub>4</sub>Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and evaporated. Flash chromatography of the residue over silica gel (0.5 × 12 cm), using 1:5 EtOAc-hexanes, gave **49** (14.7 mg, 85%) as a white solid: mp 98-101 °C; FTIR (CDCl<sub>3</sub>, cast) 3375, 1598 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 2.16 (s, 3 H), 2.51 (s, 3 H), 4.73 (s, 1 H), 5.32 (dd, *J* = 11.2, 1.6 Hz, 1 H), 5.63 (d, *J* = 11.2, 1.6 Hz, 1 H), 6.69 (d, *J* = 2.8 Hz, 1 H), 6.89 (d, *J* = 2.8 Hz, 1 H), 7.50 (dd, *J* = 17.6, 10.8 Hz, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 19.3 (q), 21.7 (q), 110.6 (d), 115.7 (t), 116.9 (d), 126.2 (s), 136.3 (d), 143.7 (s), 144.7 (s), 155.4 (s); exact mass (electrospray) *m/z* calcd for C<sub>10</sub>H<sub>11</sub>OS (M-H)<sup>-</sup> 179.0538, found 179.0536.

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## SUPPORTING INFORMATION

Copies of NMR spectra of all compounds and X-ray data for **24**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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