Synthesis of substituted resorcinol monomethyl ethers from 2-bromo-3-methoxycyclohex-2-en-1-ones

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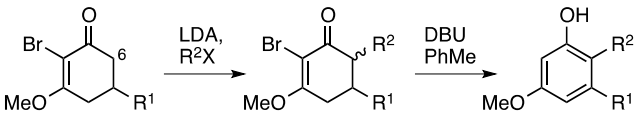
ABSTRACT: 2-Bromo-3-methoxycyclohex-2-en-1-ones are readily alkylated at C-6 with reactive halides, and then treatment with DBU (2 equiv) in PhMe at room temperature results in smooth loss of bromide and aromatization to resorcinol (δmonomethyl ethers of defined substitution pattern.

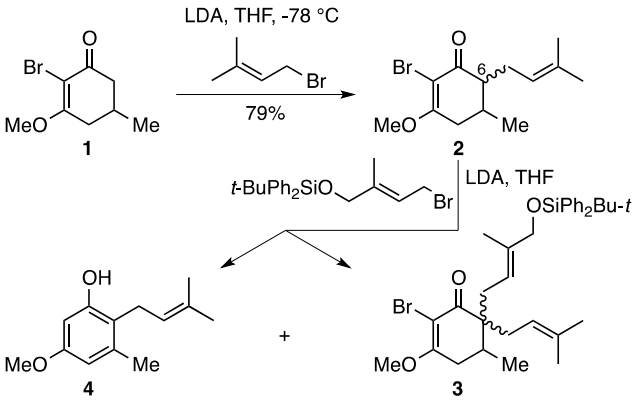


INTRODUCTION

During synthetic work related to coleophomone B[1] we alkylated the bromide **1** with prenyl bromide (**1**→**2**) under standard conditions (LDA, THF, –78 °C) and then tried to carry out a second alkylation at C-6 with a different allylic halide (**2**→**3**), again using LDA at a low temperature. However, we found that very little alkylation occurred unless the temperature was

raised to 0 °C, at which point we did obtain a somewhat larger proportion of the desired product (**3**) as a mixture of diastereoisomers, together with a small amount of the monomethyl ether **4**.

SCHEME 1. Dialkylation studies on 2-bromo-3-methoxy-5-methylcyclohex-2-en-1-one



In attempting to improve the second alkylation step (**2**→**3**) we tried to generate the required enolate with $(Me_3Si)_2NK$ in THF at -78 °C and, after an arbitrary period of 30 min, we quenched the mixture with very dilute hydrochloric acid, hoping to establish — through recovery of **2** — that the desired enolate was stable at a low temperature. However, very little of **2** was recovered and **4** was the major isolable product.

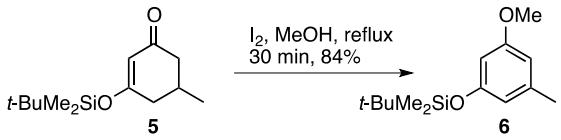
Further experiments showed that the *trans* isomer of **2** (*trans*-**2**), whose structure was verified by single crystal X-ray analysis, could be alkylated (*trans*-**2**→**3**) in 28% yield (71% corrected for recovered **2**, which was now a 10:1 *cis*-*trans* mixture). In contrast, *cis*-**2** could not be alkylated to any significant extent, using the bases we tried [LDA, $(Me_3Si)_2NK$, $(Me_3Si)_2NLi$, NaH], and we suspect that the preferred conformation is such that the α-hydrogen at C-6 is not

collinear with the *p*-orbital of the adjacent carbonyl group, so that deprotonation is difficult. Attempts to epimerize cis-**2** by heating in PhMe at 70 °C with 1 equiv of DBU[2] led cleanly to **4**.

The transformation **2**→**4** represents a regiocontrolled method for making alkylated monomethyl ethers of resorcinol and we have refined it to a general procedure.

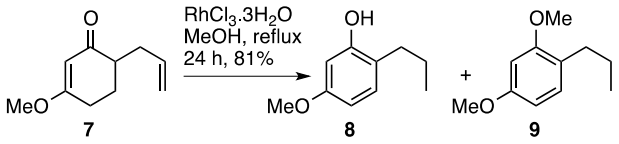
There are several corresponding methods described in the literature: The use of DDQ in refluxing dioxane for dehydrogenation of 3-alkoxycyclohex-2-en-1-ones appears to give poor yields (29-38%)[3] and sometimes fails altogether.[4] Likewise, dehydrogenation with Pd-black in refluxing cymene is also not reliable,[4] but use of $Hg(OAc)_2$ in refluxing acetic acid did work well (e.g. 84% yield) in a case where experiments with DDQ and Pd-black were unsuccessful.[4,5] Treatment of the silyl ether **5** with I_2 in refluxing MeOH gave the silyl ether **6** in 84% yield.[6] In principle, one would expect desilylation of **6** to be easy, so that this method should also provide a route to resorcinol monomethyl ethers.

SCHEME 2. An iodine-mediated aromatization



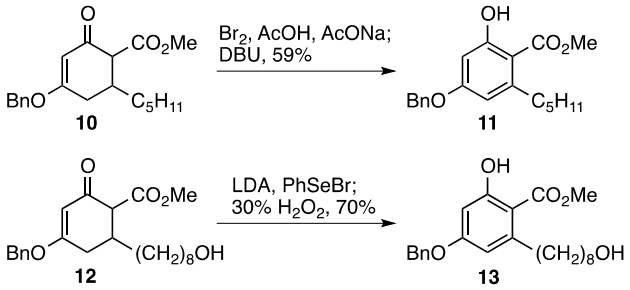
In certain highly specific cases, in the presence of Rh^{+3}, a pendant double bond has been isomerized into a six-membered ring to effect aromatization to a mixture (ca 1:1, 81% yield) of mono- and dimethyl ethers (**7** → **8** + **9**), with the ratio being sensitive to the experimental conditions.[7]

SCHEME 3. A rhodium-mediated aromatization



Finally, bromination[8,9] (e.g. **10** → **11**) or corresponding selenation[10,11] (e.g. **12** → **13**) have also been used.

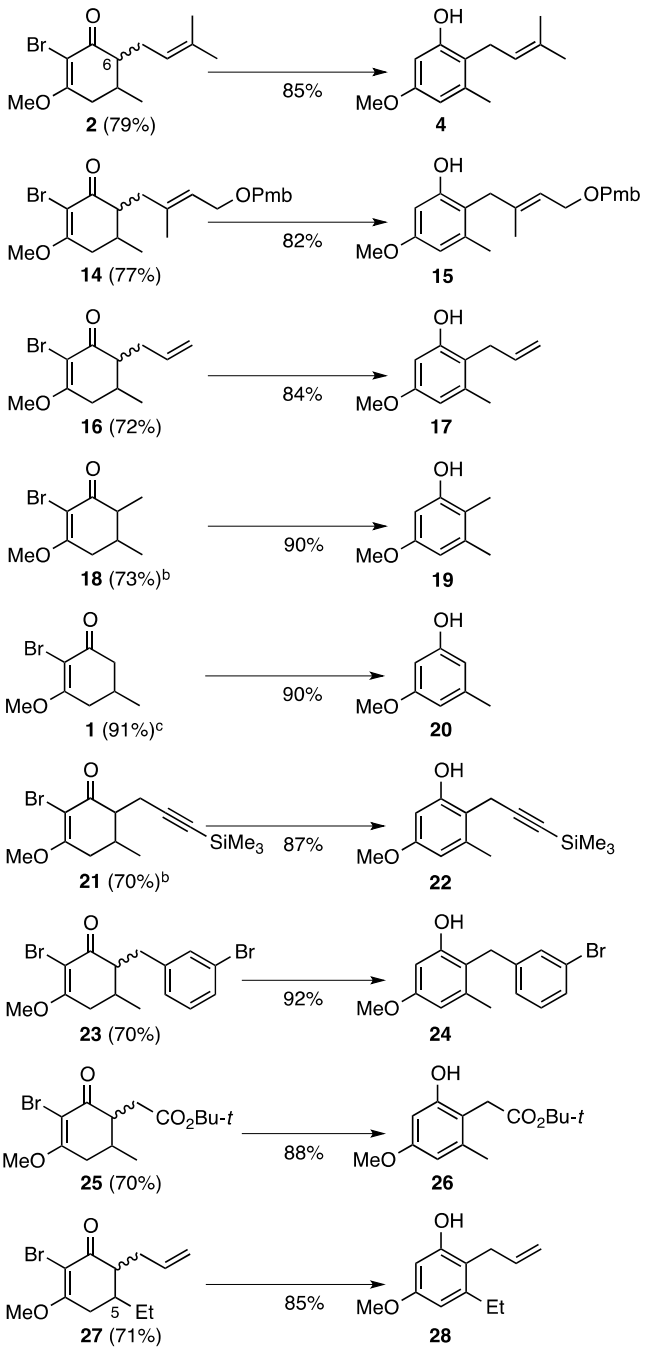
SCHEME 4. Bromination and selenenylation methods for aromatization



RESULTS AND DISCUSSION

The present method is experimentally straightforward: One alkylates a 2-bromo-3-methoxycyclohex-2-en-1-one (e.g. **1** → **2**) and adds 2 equiv of DBU to a room temperature solution of the alkylation product in PhMe. Using as a test case compound **18** (see Table 1), the only one whose aromatization we monitored, we found that the reaction is over within 5 h at 50 °C but it is more convenient to carry out the aromatizations at room temperature for an overnight period. The reactions are all very clean and Table 1 lists our results.

TABLE 1. Yields for alkylation and aromatization[a]



Footnote to Table. [a]Yields in first column are for alkylation of the parent 2-bromo-5-methyl-(or ethyl)-3-methoxycyclohex-2-en-1-one. All aromatizations at room temperature for an overnight

period. [b]Stereochemistry not determined. [c]Yield for bromination of 3-methoxy-5-methylcyclohex-2-en-1-one.

The starting 2-bromo-3-methoxycyclohex-2-en-1-one (**1**) is easily prepared by bromination[12] (NBS, 91% yield) of 3-methoxy-5-methylcyclohex-2-en-1-one, itself available by the classical procedure of Michael addition of ethyl acetoacetate to methyl crotonate in the presence of EtONa (54%), followed by heating with acid at pH 1[13] and *O*-methylation with $(MeO)_3CH$ (91%).[14] This synthetic route is general,[15] and compound **27** was made analogously from methyl (*E*)-pent-2-enoate.[16]

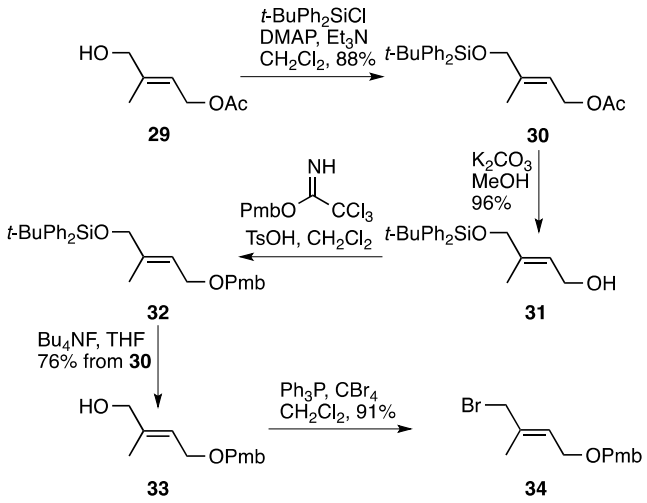
The alkylation step to attach the C-6 chain (LDA, alkyl halide, THF, -78 °C) gave the yields indicated in the Table. All the alkylations were done with an alkyl bromide, except for the preparation of **18**, where methyl iodide was used.

The last entry in the Table (**27**→**28**) shows that, as expected, the method is not limited to *methyl* substitution at C-5.

Allylic, propargylic and benzylic bromides are suitable alkylating agents, and we have also used an α-bromoester (to prepare **25**). Attempts to use butyl bromide or iodide for the alkylation step were unsuccessful, but all the activated bromides we used and methyl iodide worked satisfactorily, giving yields of at least 70% without any attempt at optimization.

The alkyl bromides used are all known compounds, except for that needed to make **14**; it was prepared by the method summarized in Scheme 5.

SCHEME 5. Preparation of bromide **34**

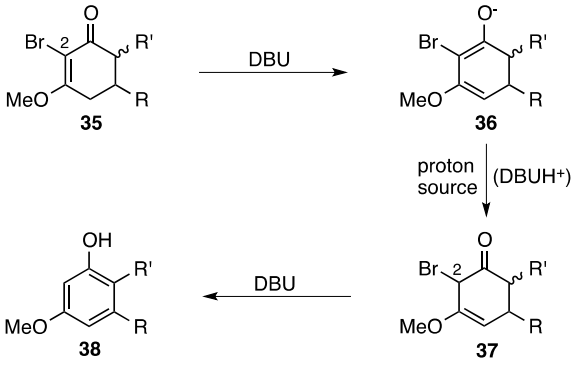


With the exception of **18** and **21**, the alkylation products (see Table 1) were inconsequential mixtures of chromatographically inseparable diastereoisomers, with one predominating, and it was sometimes difficult to decide if some of the minor signals in the NMR spectra represented the minor isomer or an impurity. If the latter, the amount must have been very small because the pure aromatization products were isolated in high yield (average yield 87% for nine examples).

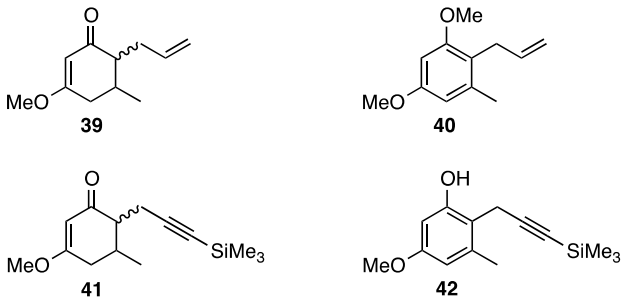
We assume that the mechanism involves migration of the initial double bond, as summarized in Scheme 6. Besides DBU we examined the use of pyridine and triethylamine with

compound **2**, but these two bases were ineffective, at least at room temperature, and the bromide starting material remained unchanged.

SCHEME 6. Suggested mechanism



For comparison purposes compound **39** was subjected to the action of I_2 in refluxing MeOH[6] but we obtained a complex mixture and very little, if any (^{1}H NMR), of the desired dimethoxy product **40**. Similarly, the use of $Hg(OAc)_2$[4,5] was shown to be incompatible with the presence of a triple bond, as compound **41** gave none (^{1}H NMR) of the desired **42**, either at the reflux temperature[4,5] or at room temperature. While the first of these experiments (I_2/MeOH) was expected to produce a bis-ether, instead of a mono ether, as in our method, both experiments serve the purpose of showing that certain side-chain functionality is incompatible with the I_2/MeOH or $Hg(OAc)_2$/AcOH reagent systems, both of which appear from the literature to be the best of the prior methods.



CONCLUSION

Our procedure for making differentially protected resorcinol derivatives is very simple. It accommodates functionality in the side chain that is added in the first step; this functionality renders the final products readily amenable to further manipulation. The alkylation yields are ≥70% provided that the alkylating agent is activated (the halide should be allylic, propargylic or benzylic, or in the form of an α-haloester, or methyl iodide), and the aromatization occurs at room temperature in yields of 82-92% for the examples we have studied. Our control experiments with the model substrates **39** and **40** show that the present method has a number of advantages over existing procedures.

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). Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. The symbols s, d, t and q used for ^{13}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.

2-Bromo-3-methoxy-5-methylcyclohex-2-en-1-one (1). NBS (4.35 g, 24.4 mmol) was added in one portion to a stirred and cooled (0 °C) solution of 3-methoxy-5-methycyclohex-2-en-1-one[13,14] (2.85 g, 20.3 mmol) in CH_2Cl_2 (14 mL). Stirring at 0 °C was continued for 2 h with protection from light. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Crystallization of the residue from MeOH gave **1** (4.05 g, 91%) as a white solid: 97-100 °C; FTIR ($CDCl_3$, cast) 1653, 1615 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.17 (d, J = 6.5 Hz, 3 H), 2.21-2.33 (m, 3 H), 2.65-2.69 (m, 1 H), 2.78-2.85 (m, 1 H), 3.97 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.8 (q), 28.1 (d), 34.7 (t), 44.8 (t), 56.3 (q), 102.7 (s), 172.1 (s), 190.9 (s); exact mass (electron ionization) m/z calcd for $C_8H_{11}{}^{79}BrO_2$ $(M)^+$ 217.9942, found 217.9941.

2-Bromo-3-methoxy-5-methyl-6-(3-methylbut-2-en-1-yl)cyclohex-2-ene-1-one (2). *n*-BuLi (2.50 M in hexanes, 2.60 mL, 6.50 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (0.93 mL, 6.64 mmol) in THF (10 mL). Stirring at -78 °C was continued for 30 min and then a solution of **1** (1.10 g, 5.02 mmol) in THF (5 mL) was added dropwise. The cold bath was not recharged so that the temperature rose to 0 °C over 2 h. The mixture was then recooled to –78 °C and a solution of prenyl bromide (2.24 mL, 19.4 mmol) in THF (5 mL) was added dropwise. The cold bath was left in place, but not recharged, and stirring was continued for 6 h. The reaction mixture was diluted with saturated aqueous NH_4Cl 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 (3 x 15 cm), using 1:4 EtOAc-hexanes, gave **2** (1.14 g, 79%) as a pale yellow solid: FTIR ($CDCl_3$, cast) 1659, 1592

cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (major isomer) 1.13 (d, *J* = 6.5 Hz, 3 H), 1.65 (s, 3 H), 1.69 (s, 3 H), 2.17-2.27 (m, 2 H), 2.32-2.41 (m, 2 H), 2.48-2.59 (m, 1 H), 2.83 (dd, *J* = 17.5, 5.0 Hz, 1 H), 3.95 (s, 3 H) 5.02-5.06 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 17.8 (q), 17.9 (q), 25.8 (q), 27.0 (t), 30.1 (d), 33.0 (t), 52.6 (d), 56.1 (q), 102.2 (s), 120.7 (d), 133.5 (s), 170.3 (s), 192.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{19}{}^{79}BrNaO_2$ $(M + Na)^+$ 309.0461, found 309.0457.

5-Methoxy-3-methyl-2-(3-methylbut-2-en-1-yl)phenol (4).[1b] DBU (304 mg, 2.00 mmol) was added to a stirred solution of **2** (287 mg, 1.00 mmol) in PhMe (2 mL). Stirring was continued overnight and the mixture was diluted with hydrochloric acid (5%) and extracted thoroughly with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 10 cm), using 1:3 EtOAc-hexanes, gave **4** (175 mg, 85%) as a thick oil: FTIR ($CDCl_3$, cast) 3419, 1614, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.74 (s, 3 H), 1.81 (s, 3 H), 2.27 (s, 3 H), 3.30 (d, *J* = 8.5 Hz, 2 H), 3.75 (s, 3 H), 5.12 (s, 1 H), 5.13-5.17 (m, 1 H), 6.28 (d, *J* = 3.0 Hz, 1 H), 6.35 (d, *J* = 3.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.8 (q), 20.3 (q), 25.2 (t), 25.7 (q), 55.2 (q), 99.5 (d), 108.5 (d), 117.8 (s), 122.1 (d), 133.8 (s), 138.1 (s), 155.2 (s), 158.4 (s); exact mass (electron ionization) *m*/*z* calcd for $C_{13}H_{18}O_2$ $(M)^+$ 206.1306, found 206.1304.

2-Bromo-3-methoxy-6-[(2*E*)-4-[4(methoxyphenyl)methoxy]-2-methylbut-2-en-1-yl]-5-methylcyclohex-2-en-1-one (14). The procedure for compound **2** was followed, using *n*-BuLi (2.50 M in hexanes, 0.28 mL, 0.70 mmol), *i*-Pr_2NH (0.12 mL, 0.85 mmol) in THF (2 mL), a solution of **1** (138 mg, 0.63 mmol) in THF (2 mL) and a solution of **34** (468 mg, 1.64 mmol) in THF (2 mL). The mixture was left overnight after the addition of **34** and then worked up. Flash chromatography of the residue over silica gel (1.8 x 10 cm), using 1:4 EtOAc-hexanes, gave **14**

(205 mg, 77%) as a colorless oil: FTIR ($CDCl_3$, cast) 1659, 1611, 1589 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (major isomer) 1.11 (d, *J* = 7.0 Hz, 3 H), 1.63 (s, 3 H), 2.14-2.26 (m, 1 H), 2.29-2.47 (m, 4 H), 2.84 (dd, *J* = 18, 5.5 Hz, 1 H), 3.80 (s, 3 H), 3.93 (s, 3 H), 4.01 (s, 2 H) 4.42 (s, 2 H), 5.40-5.43 (m, 1 H), 6.87 (d, *J* = 9.0 Hz, 2 H), 7.26 (d, *J* = 8.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 16.1 (q), 20.0 (q), 29.1 (d), 31.2 (t), 40.1 (t), 50.5 (d), 55.2 (q), 56.2 (q), 66.2 (t), 71.9 (t), 101.2 (s), 113.7 (d), 124.2 (d), 129.4 (d), 130.4 (s), 137.0 (s), 159.2 (s), 169.7 (s), 192.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{21}H_{28}{}^{79}BrO_4$ $(M + H)^+$ 423.1165, found 423.1166.

5-Methoxy-2-[(2*E*)-4-[(4-methoxyphenyl)methoxy]-2-methylbut-2-en-1-yl]-3-methyl-phenol (15). The procedure for **4** was followed, using DBU (151 mg, 0.993 mmol) and a solution of **14** (200 mg, 0.473 mmol) in PhMe (1.5 mL). Workup and flash chromatography of the residue over silica gel (1.8 x 10 cm), using 1:3 EtOAc-hexanes, gave **15** (133 mg, 82%) as a thick oil: FTIR ($CDCl_3$, cast) 3353, 1613, 1589 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.67 (s, 3 H), 2.23 (s, 3 H), 3.32 (s, 2 H), 3.74 (s, 3 H), 3.80 (s, 3 H), 4.01 (d, *J* = 3.0 Hz, 2 H), 4.40 (s, 2 H), 5.13 (s, 1 H), 5.32-5.36 (m, 1 H), 6.26 (d, *J* = 3.0 Hz, 1 H), 6.35 (d, *J* = 3.0 Hz, 1 H), 6.86 (d, *J* = 6.0 Hz, 2 H), 7.24 (d, *J* = 6.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.7 (q), 20.2 (q), 35.5 (t), 55.1 (q), 55.2 (q), 66.1 (t), 71.7 (t), 99.5 (d), 108.5 (d), 113.7 (d), 115.6 (s), 121.7 (d), 129.4 (d), 130.4 (s), 138.6 (s), 139.1 (s), 155.5 (s), 158.7 (s), 159.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{21}H_{25}O_4$ $(M - H)^-$ 341.1758, found 341.1761.

2-Bromo-3-methoxy-5-methyl-6-(prop-2-en-1-yl)cyclohex-2-ene-1-one (16). The procedure for compound **2** was followed, using *n*-BuLi (2.50 M in hexanes, 0.60 mL, 1.50 mmol), *i*-Pr_2NH (0.25 mL, 1.78 mmol) in THF (6 mL), a solution of **1** (293 mg, 1.35 mmol) in THF (3 mL) and a solution of allyl bromide (0.40 ml, 4.63 mmol) in THF (3 mL). The mixture

was left overnight after the addition of the allyl bromide and then worked up. Flash chromatography of the residue over silica gel (1.8 x 13 cm), using 1:5 EtOAc-hexanes, gave **16** (249 mg, 72%) as a thick oil: FTIR ($CDCl_3$, cast) 3076, 1649, 1587 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (major isomer) 1.13 (d, *J* = 6.5 Hz, 3 H), 2.17-2.27 (m, 2 H), 2.33-2.39 (m, 2 H), 2.66-2.70 (m, 1 H), 2.82 (dd, *J* = 17.5, 5.0 Hz, 1 H), 3.93 (s, 3 H), 5.02-5.10 (m, 2 H), 5.67-5.75 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 19.4 (q), 30.0 (d), 32.4 (t), 33.3 (t), 51.7 (d), 56.1 (q), 102.3 (s), 117.2 (t), 135.0 (d), 170.5 (s), 192.0 (s); exact mass (electron ionization) *m*/*z* calcd for $C_{11}H_{15}{}^{79}BrO_2$ $(M)^+$ 258.0255, found 258.0257.

5-Methoxy-3-methyl-2-(prop-2-en-1-yl)phenol (17).[17] The procedure for **4** was followed, using DBU (100 mg, 0.658 mmol) and a solution of **14** (81.5 mg, 0.318 mmol) in PhMe (1 mL). Workup and flash chromatography of the residue over silica gel (1 x 10 cm), using 1:3 EtOAc-hexanes, gave **17** (46.8 mg, 84%) as a thick oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 2.26 (s, 3 H), 3.36 (d, *J* = 7.5 Hz, 2 H), 3.75 (s, 3 H), 5.00-5.08 (m, 2 H), 5.90-6.00 (m, 1 H), 6.28 (d, *J* = 3.5 Hz, 1 H), 6.37 (d, *J* = 3.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.9 (q), 30.1 (t), 55.2 (q), 99.5 (d), 108.5 (d), 115.2 (t), 116.0 (s), 135.9 (d), 138.8 (s), 154.9 (s), 158.6 (s).

2-Bromo-3-methoxy-5,6-dimethylcyclohex-2-en-1-one (18). The procedure for compound **2** was followed, using *n*-BuLi (2.50 M in hexanes, 0.63 mL, 1.57 mmol), *i*-Pr_2NH (0.26 mL, 1.85 mmol) in THF (6 mL), a solution of **1** (313 mg, 1.43 mmol) in THF (3 mL) and a solution of MeI (0.20 ml, 3.21 mmol) in THF (2 mL). The mixture was left overnight after the addition of MeI and then worked up. Flash chromatography of the residue over silica gel (1.8 x 13 cm), using 1:5 EtOAc-hexanes, gave **18** (243 mg, 73%) as a white solid: FTIR ($CDCl_3$, cast) 1654, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (major isomer) 1.17 (d, *J* = 6.5 Hz, 3 H), 1.24 (d, *J* = 7.0 Hz, 3 H), 1.92-1.98 (m, 1 H), 2.12-2.18 (m, 1 H), 2.36 (dd, *J* = 17.5, 10.0 Hz, 1 H), 2.83

(dd, J = 17.5, 9.5 Hz, 1 H), 3.95 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 13.4 (q), 19.7 (q), 34.0 (d), 34.4 (t), 47.4 (d), 56.1 (q), 102.3 (s), 170.7 (s), 193.1 (s),; exact mass (electron ionization) m/z calcd for $C_9H_{13}{}^{79}BrO_2$ $(M)^+$ 232.0098, found 232.0097.

5-Methoxy-2,3-dimethylphenol (19).[18] The procedure for **4** was followed, using DBU (330 mg, 2.17 mmol) and a solution of **18** (241 mg, 1.03 mmol) in PhMe (2 mL). Workup and flash chromatography of the residue over silica gel (1.8 x 10 cm), using 1:5 EtOAc-hexanes, gave **19** (141 mg, 90%) as a white solid: mp 94-95 °C (lit.[18] 93-93.5 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.08 (s, 3 H), 2.24 (s, 3 H), 3.74 (s, 3 H), 4.64 (s, 1 H), 6.25 (d, J = 2.5 Hz, 1 H), 6.35 (d, J = 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.8 (q), 20.4 (q), 55.2 (q), 98.9 (d), 108.0 (d), 114.3 (s), 138.8 (s), 154.2 (s), 157.9 (s).

3-Methoxy-5-methylphenol (20).[19] The procedure for **4** was followed, using DBU (114 mg, 0.75 mmol) and a solution of **1** (77.2 mg, 0.357 mmol) in PhMe (1 mL). Workup and flash chromatography of the residue over silica gel (1 x 8 cm), using 1:3 EtOAc-hexanes, gave **20** (43.4 mg, 90%) as a thick oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.28 (s, 3 H), 3.77 (s, 3 H), 5.16 (br s, 1 H), 6.25 (dd, J = 2.5 Hz, 1 H), 6.28 (s, 1 H), 6.34 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.5 (q), 55.2 (q), 98.6 (d), 107.3 (d), 108.6 (d), 140.6 (s), 156.5 (s), 160.8 (s).

2-Bromo-3-methoxy-5-methyl-6-[3-(trimethylsilyl)prop-2-yn-1-yl]cyclohex-2-en-1-one (21). The procedure for compound **2** was followed, using n-BuLi (2.50 M in hexanes, 0.51 mL, 1.27 mmol), i-Pr_2NH (0.20 mL, 1.43 mmol) in THF (3 mL), a solution of **1** (257 mg, 1.17 mmol) in THF (3 mL) and a solution of propargylic bromide (750 mg, 3.93 mmol) in THF (3 mL). The mixture was left overnight after the addition of propargylic bromide and then worked up. Flash chromatography of the residue over silica gel (1.8 x 13 cm), using 1:4 EtOAc-hexanes, gave **21** (270 mg, 70%) as a white solid: FTIR ($CDCl_3$, cast) 2169, 1649, 1582 cm^{-1}; ^{1}H NMR

($CDCl_3$, 500 MHz) δ □major isomer□ 0.13 (s, 9 H), 1.23 (d, *J* = 6.5 Hz, 3 H), 2.22-2.90 (m, 1 H), 2.39-2.42 (m, 2 H), 2.65 (dd, *J* = 17.0, 4.5 Hz, 1 H), 2.86-2.91 (m, 2 H), 3.97 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 0.1 (q), 18.8 (t), 19.5 (q), 30.9 (d), 33.8 (t), 50.9 (d), 56.2 (q), 86.5 (s), 102.2 (s), 103.5 (s), 170.9 (s), 190.3 (s); exact mass (electron ionization) *m*/*z* calcd for $C_{14}H_{21}{}^{79}BrO_2Si$ $(M)^+$ 328.0494, found 328.0487.

5-Methoxy-3-methyl-2-[3-(trimethylsilyl)prop-2-yn-1-yl]phenol (22). The procedure for **4** was followed, using DBU (119 mg, 0.735 mmol) and a solution of **21** (121 mg, 0.368 mmol) in PhMe (1 mL). Workup and flash chromatography of the residue over silica gel (1 x 10 cm), using 1:5 EtOAc-hexanes, gave **22** (79.3 mg, 87%) as a thick oil: FTIR ($CDCl_3$, cast) 3444, 2170, 1615, 1592 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.15 (s, 9 H), 2.28 (s, 3 H), 3.53 (s, 2 H), 3.75 (s, 3 H), 5.88 (s, 1 H), 6.34 (d, *J* = 2.5 Hz, 1 H), 6.37 (d, *J* = 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –0.05 (q), 17.2 (t), 20.3 (q), 55.2 (q), 87.2 (s), 100.1 (d), 103.4 (s), 108.8 (d), 113.1 (s), 138.0 (s), 155.4 (s), 159.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{14}H_{19}O_2Si$ $(M - H)^-$ 247.1160, found 247.1161.

2-Bromo-6-[(3-bromophenyl)methyl]-3-methoxy-5-methylcyclohex-2-en-1-one (23). The procedure for compound **2** was followed, using *n*-BuLi (2.50 M in hexanes, 0.32 mL, 0.80 mmol), *i*-Pr_2NH (0.13 mL, 0.93 mmol) in THF (2 mL), a solution of **1** (161 mg, 0.735 mmol) in THF (2 mL) and a solution of 3-bromobenzyl bromide (550 mg, 2.20 mmol) in THF (2 mL). The mixture was left overnight after the addition of 3-bromobenzyl bromide and then worked up. Flash chromatography of the residue over silica gel (1.8 x 13 cm), using 1:4 EtOAc-hexanes, gave **23** (199 mg, 70%) as a white solid: FTIR ($CDCl_3$, cast) 1659, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ □major isomer□ 1.12 (d, *J* = 7.0 Hz, 3 H), 2.03-2.07 (m, 1 H), 2.36-2.56 (m, 2 H),

2.74-3.00 (m, 3 H), 3.93 (s, 3 H), 7.15-7.16 (m, 2 H), 7.33-7.37 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 20.0 (q), 29.6 (d), 32.6 (t), 34.4 (t), 53.8 (d), 56.3 (q), 101.9 (s), 122.4 (s), 127.9 (d), 129.4 (d), 130.0 (d), 132.1 (d), 141.6 (s), 170.4 (s), 192.0 (s); exact mass (electron ionization) *m*/*z* calcd for $C_{15}H_{16}{}^{79}Br_2O_2$ $(M)^+$ 385.9516, found 385.9522.

2-[(3-Bromophenyl)methyl]-5-methoxy-3-methylphenol (24). The procedure for **4** was followed, using DBU (150 mg, 0.987 mmol) and a solution of **23** (191 mg, 0.492 mmol) in PhMe (2 mL). Workup and flash chromatography of the residue over silica gel (1.8 x 10 cm), using 1:5 EtOAc-hexanes, gave **24** (139 mg, 92%) as a white solid: mp 115-117 °C; FTIR ($CDCl_3$, cast) 3402, 3057, 1615, 1592 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.21 (s, 3 H), 3.77 (s, 3 H), 3.95 (s, 2 H), 4.60 (s, 1 H), 6.26 (d, *J* = 2.5, 1 H), 6.38 (d, *J* = 2.5, 1 H), 7.06-7.12 (m, 2 H), 7.28-7.30 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.2 (q), 31.0 (t), 55.2 (q), 99.5 (d), 108.5 (d), 116.8 (s), 122.6 (s), 126.7 (d), 129.0 (d), 129.9 (d), 131.0 (d), 139.4 (s), 142.9 (s), 154.5 (s), 158.8 (s); exact mass (electron ionization) *m*/*z* calcd for $C_{15}H_{15}{}^{79}BrO_2$ $(M)^+$ 306.0255, found 306.0250.

***tert*-Butyl-2-(3-bromo-4-methoxy-6-methyl-2-oxocyclohex-3-en-1-yl)acetate (25).** The procedure for compound **2** was followed, using *n*-BuLi (2.50 M in hexanes, 0.30 mL, 0.75 mmol), *i*-Pr_2NH (0.12 mL, 0.856 mmol) in THF (2 mL), a solution of **1** (146 mg, 0.667 mmol) in THF (2 mL) and a solution of *tert*-butyl bromoacetate (0.31 ml, 2.10 mmol) in THF (2 mL). The mixture was left overnight after the addition of the *tert*-butyl bromoacetate and then worked up. Flash chromatography of the residue over silica gel (1.8 x 13 cm), using 1:3 EtOAc-hexanes, gave **25** (178 mg, 70%) as a thick oil: FTIR ($CDCl_3$, cast) 1726, 1664, 1593 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ □major isomer) 1.14 (d, *J* = 6.5 Hz, 3 H), 1.46 (s, 9 H), 2.15-2.20 (m, 1 H), 2.37 (dd, *J* = 17.5, 10.5 Hz, 1 H), 2.46 (dd, *J* = 11.0, 5.5, 1 H), 2.56-2.61 (m, 1 H), 2.76-2.82 (m,

1 H), 3.94 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 19.4 (q), 28.0 (q), 32.3 (d), 33.9 (t), 34.8 (t), 49.3 (d), 56.2 (q), 80.6 (s), 102.1 (s), 170.9 (s), 171.6 (s), 191.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{14}H_{22}{}^{79}BrO_4$ $(M + H)^+$ 333.0696, found 333.0690.

***tert*-Butyl 2-(2-hydroxy-4-methoxy-6-methylphenyl)acetate (26).** The procedure for **4** was followed, using DBU (155 mg, 1.02 mmol) and a solution of **25** (167 mg, 0.50 mmol) in PhMe (2 mL). Workup and flash chromatography of the residue over silica gel (1.8 x 10 cm), using 1:4 EtOAc-hexanes, gave **26** (111 mg, 88%) as an off-white solid: mp 72-74 °C; FTIR ($CDCl_3$, cast) 3411, 1732, 1702, 1616, 1594 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.45 (s, 9 H), 2.29 (s, 3 H), 3.53 (s, 2 H), 3.75 (s, 3 H), 6.35 (d, *J* = 2.5, 1 H), 6.40 (d, *J* = 2.0, 1 H), 7.44 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.3 (q), 27.9 (q), 34.2 (t), 55.1 (q), 82.4 (s), 100.7 (d), 108.9 (d), 112.5 (s), 138.3 (s), 156.5 (s), 159.3 (s), 173.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{14}H_{19}O_4$ $(M - H)^-$ 251.1289, found 251.1285.

2-Bromo-5-ethyl-3-methoxy-6-(prop-2-en-1-yl)cyclohex-2-ene-1-one (27).

(a) Preparation of 5-ethyl-3-methoxycyclohex-2-en-1-one. EtONa was prepared by dissolving Na (150 mg, 6.52 mmol) in ice-cold EtOH (7 mL). Then ethyl acetoacetate (0.84 mL, 860 mg, 6.61 mmol) and methyl 2-pentenoate (846 mg, 6.61 mmol) were added by syringe to the resulting stirred solution. The mixtures was refluxed for 6 h (N_2 atmosphere) and then evaporated. The residue was dissolved in water (4 ml) and KOH (730 mg, 13.0 mmol) was added. The solution was refluxed for 1 h and then cooled. Concentrated H_2SO_4 was added carefully to adjust the pH to 1. The solution was refluxed for 2 h, cooled to room temperature, and extracted thoroughly with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was dissolved in MeOH (5 mL) and $(MeO)_3CH$ (0.72 mL, 700 mg, 6.61 mmol) was added. The solution was stirred for 24 h at room

temperature and then evaporated. Flash chromatography of the residue over silica gel (1.8 x 12 cm), using 2:3 EtOAc-hexanes, gave 5-ethyl-3-methoxycyclohex-2-en-1-one (350 mg, 41% over two steps) as a colorless, thick oil: FTIR ($CDCl_3$, cast) 1734, 1655, 1609 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.95 (t, *J* = 9.5 Hz, 3 H), 1.40-1.47 (m, 2 H), 2.01-2.20 (m, 3 H), 2.42-2.50 (m, 2 H), 3.70 (s, 3 H), 5.37 (d, *J* = 1.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.1 (q), 28.0 (t), 34.9 (t), 35.4 (d), 43.0 (t), 55.7 (q), 102.1 (s), 178.2 (s), 199.7 (s); exact mass (electron ionization) *m*/*z* calcd for $C_9H_{14}O_2$ $(M)^+$ 154.0993, found 154.0995.

(b) Preparation of 2-bromo-5-ethyl-3-methoxycyclohex-2-en-1-one. NBS (166 mg, 0.932 mmol) was added in one portion to a stirred and cooled (0 °C) solution of 5-ethyl-3-methoxycyclohex-2-en-1-one (120 mg, 0.779 mmol) in CH_2Cl_2 (4 mL). Stirring at 0 °C was continued for 3.5 h with protection from light and the mixture was then diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 12 cm), using 2:3 EtOAc-hexanes, gave 2-bromo-5-ethyl-3-methoxycyclohex-2-en-1-one (165 mg, 91%) as a white solid: mp 100-103 °C; FTIR ($CDCl_3$, cast) 1733, 1662, 1585 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.98 (t, *J* = 7.5 Hz, 3 H), 1.48-1.52 (m, 2 H), 2.04-2.12 (m, 1 H), 2.21 (dd, *J* = 16.0, 12.5 Hz, 1 H), 2.32 (dd, *J* = 17.0, 10.0 Hz, 1 H), 2.69-2.85 (m, 2 H), 3.97 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.1 (q), 28.0 (t), 32.7 (t), 34.5 (d), 42.6 (t), 56.3 (q), 102.6 (s), 172.4 (s), 191.0 (s); exact mass (electron ionization) *m*/*z* calcd for $C_{15}H_{15}{}^{79}BrO_2$ $(M)^+$ 306.0255, found 306.0250.

(c) 2-Bromo-5-ethyl-3-methoxy-6-(prop-2-en-1-yl)cyclohex-2-ene-1-one (27). The procedure for compound **2** was followed, using *n*-BuLi (2.50 M in hexanes, 0.20 mL, 0.50 mmol), *i*-Pr_2NH (0.08 mL, 0.57 mmol) in THF (2 mL), 2-bromo-5-ethyl-3-methoxycyclohex-2-en-1-one (103

mg, 0.442 mmol) in THF (2 mL) and allyl bromide (267 mg, 2.20 mmol) in THF (1 mL). The mixture was left overnight after the addition of allyl bromide and then worked up. Flash chromatography of the residue over silica gel (1 x 12 cm), using 1:3 EtOAc-hexanes, gave **27** (85.6 mg, 71%) as a white solid which was a mixture of diastereoisomers: FTIR ($CDCl_3$, cast) 3075, 1646, 1613, 1587 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ□ □major isomer□ 0.95 (t, *J* = 7.5 Hz, 3 H), 1.59-1.64 (m, 2 H), 2.01-2.04 (m, 1 H), 2.37-2.49 (m, 3 H), 2.52-2.58 (m, 1 H), 2.83 (dd, *J* = 17.5, 5.5, 1 H), 3.96 (s, 3 H), 5.05-5.11 (m, 2 H), 5.71-5.76 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 10.9 (q), 25.3 (t), 29.2 (t), 33.2 (t), 35.7 (d), 49.8 (d), 56.1 (q), 101.7 (s), 117.2 (t), 135.2 (d), 170.4 (s), 192.5 (s); exact mass (electron ionization) *m*/*z* calcd for $C_{12}H_{17}{}^{79}BrO_2$ $(M)^+$ 272.0412, found 272.0408.

3-Ethyl-5-methoxy-2-(prop-2-en-1-yl)phenol (28). The procedure for **4** was followed, using DBU (91.3 mg, 0.60 mmol) and **27** (82.0 mg, 0.30 mmol) in PhMe (1 mL). Workup and flash chromatography of the residue over silica gel (1 x 10 cm), using 1:6 EtOAc-hexanes, gave **28** (49.0 mg, 85%) as a thick oil: FTIR ($CDCl_3$, cast) 3431, 3077, 3001, 1636, 1616, 1589 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.18 (t, *J* = 9.0 Hz, 3 H), 2.59 (q, *J* = 7.5 Hz, 2 H), 3.37 (dt, *J* = 6.0, 1.5 Hz, 2 H), 3.76 (s, 3 H), 4.88 (s, 1 H), 5.03-5.10 (m, 2 H), 5.98 (ddt, *J* = 17.0, 10.0, 6.0 Hz, 1 H), 6.29 (□, *J* = 2.5 Hz, 1 H), 6.39 (□, *J* = 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.3 (q), 26.5 (t), 29.7 (t), 55.2 (q), 99.4 (d), 107.1 (d), 115.1 (s), 115.6 (s), 136.5 (d), 144.8 (s), 155.2 (s), 159.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{12}H_{15}O_2$ $(M)^+$ 191.1078, found 191.1079.

(2*E*)-4-[(*tert*)-Butyldiphenylsilyl)oxy]-3-methylbut-2-en-1-yl acetate (30). DMAP (1.52 g, 12.4 mmol), Et_3N (17.4 mL, 125 mmol) and *t*-$BuPh_2SiCl$ (10.7 mL, 41.7 mmol) were added to a stirred solution of **29**[20] (6.00 g, 41.7 mmol) in CH_2Cl_2 (48 mL) at room temperature.

Stirring was continued for 8 h and the mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (6 x 15 cm), using 1:6 EtOAc-hexanes, gave **30** (14.0 g, 88%) as a pale yellow oil: FTIR ($CDCl_3$, cast) 3071, 3049, 1741 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.10 (s, 9 H), 1.67 (s, 3 H), 2.09 (s, 3 H), 4.10 (s, 2 H), 4.68 (d, *J* = 2.5, 2 H), 5.73-5.76 (m, 1 H), 7.39-7.45 (m, 6 H), 7.68-7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.6 (q), 19.3 (s), 21.0 (q), 26.8 (q), 60.9 (t), 67.9 (t), 117.4 (d), 127.6 (d), 129.6 (d), 133.5 (s), 135.5 (d), 140.3 (s), 171.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{23}H_{30}NaO_3Si$ $(M + Na)^+$ 405.1856, found 405.1850.

(2*E*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-3-methylbut-2-en-1-ol (31).[21] K_2CO_3 (15.2 g, 110 mmol) was added to a stirred solution of **30** (14.0 g, 36.6 mmol) in MeOH (36 mL) at room temperature and stirring was continued for 2 h. The mixture was diluted with water and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (6 x 15 cm), using 1:5 EtOAc-hexanes, gave **31** (11.9 g, 96%) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.08 (s, 9 H), 1.63 (s, 3 H), 4.08 (s, 2 H), 4.21 (d, *J* = 2.0 Hz, 2 H), 5.73-5.76 (m, 1 H), 7.38-7.42 (m, 6 H), 7.67-7.69 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.5 (q), 19.3 (s), 26.8 (q), 59.1 (t), 68.0 (t), 122.4 (d), 127.7 (d), 129.7 (d), 133.6 (s), 135.5 (d), 137.9 (s).

***tert*-Butyl ({[(2*E*)-4-[(methoxyphenyl)methoxy]-2-methylbut-2-en-1-yl]oxy})diphenylsilane (32).** 4-Methoxybenzyl 2,2,2-trichloroacetimidate (729 mg, 2.59 mmol) in CH_2Cl_2 (3 mL) and *p*-TsOH.H_2O (41.6 mg, 0.22 mmol) were added to a stirred and cooled (0 °C) solution of **31** (735 mg, 2.16 mmol) in CH_2Cl_2 (6 mL). Stirring was continued for 4.5 h, and the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed

with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 1:5 EtOAc-hexanes, gave **32** (863 mg, ca 87%) as a colorless oil which contained a minor impurity. The material was used directly for next step.

(2*E*)-4-[(4-Methoxyphenyl)methoxy]-2-methylbut-2-en-1-ol (33).[22] Bu_4NF (1.0 M in THF, 2.20 mL, 2.20 mmol)) was added to a stirred and cooled solution of **32** (863 mg, 1.88 mmol) in THF (10 mL). Stirring was continued for 12 h, and the mixture was diluted with saturated aqueous NH_4Cl 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 (3 x 15 cm), using 1:1 EtOAc-hexanes, gave **33** (363 mg, 76% over two steps) as a colorless oil: FTIR ($CDCl_3$, cast) 3395, 1612 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.44 (br s, 1 H), 1.67 (s, 3 H), 3.80 (s, 3 H), 4.02-4.06 (m, 4 H), 4.45 (s, 2 H), 5.64-5.67 (m, 1 H), 6.88 (d, J = 9.0 Hz, 2 H), 7.27 (d, J = 9.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9 (q), 55.3 (q), 65.9 (t), 68.1 (t), 72.0 (t), 113.8 (d), 121.6 (d), 129.4 (d), 130.4 (s), 139.1 (s), 159.2 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{18}NaO_3$ $(M + Na)^+$ 245.1148, found 245.1154.

1-({[(2*E*)-4-Bromo-3-methylbut-2-en-1-yl]oxy}methyl)-4-methoxybenzene (34).[23] Ph_3P (227 mg, 0.866 mmol) and CBr_4 (240 mg, 0.723 mmol) were added to a stirred and cooled solution of **33** (160 mg, 0.723 mmol) in CH_2Cl_2 (7 mL). Stirring was continued for 3.5 h and the solvent was then evaporated. Flash chromatography of the residue over silica gel (1.8 x 15 cm), using 1:12 EtOAc-hexanes, gave **34** (187 mg, 91%) as a colorless oil: FTIR ($CDCl_3$, cast) 1612 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.78 (s, 3 H), 3.80 (s, 3 H), 3.96 (s, 2 H), 4.02 (d, J = 6.5 Hz, 2 H), 4.44 (s, 2 H), 5.78-5.80 (m, 1 H), 6.88 (d, J = 7.5 Hz, 2 H), 7.26 (d, J = 7.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.1 (q), 40.2 (t), 55.3 (q), 66.1 (t), 72.1 (t), 113.8 (d), 127.3 (d),

129.4 (d), 130.1 (s), 135.5 (s), 159.3 (s); exact mass (electron ionization) *m*/*z* calcd for $C_{13}H_{17}{}^{81}BrO_2$ $(M)^+$ 286.0391, found 286.0400.

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Supporting Information

Copies of NMR spectra and, for compound *trans*-**2**, X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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