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Synthesis of Aromatic Bisabolene Natural Products via Palladium-Catalyzed Cross-Couplings of Organozinc Reagents†

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Aromatic bisabolene derivatives were prepared by two methods involving cross-coupling of organozinc reagents. The first synthesis of (±)-glandulone A (**10**), as well as syntheses of (±)-curcuhydroquinone (**8**) and (±)-curcuquinone (**9**), were accomplished via coupling of a secondary alkyl zinc reagent (1,5-dimethyl-4-hexenylzinc halide, **18**) to protected bromohydroquinones using $Pd(dppf)Cl_2$ as catalyst. Coupling of arylzinc halides with alkenyl triflate **16** using $Pd(PPh_3)_4$ catalyst provided a number of bisabolene derivatives and led to syntheses of dehydro-α-curcumene (**2**), (±)-curcuphenol (**3**), and (±)-elvirol (**13**). A high-yield synthesis of the (±)-heliannuol D precursor **29** is also reported using this method.

Introduction

Aromatic bisabolene natural products have been popular synthetic targets for 30 years[1] and continue to be a proving ground for the development of synthetic methods.[2] Typified by the parent hydrocarbons (+)-α-curcumene (**1a**)[3] and dehydro-α-curcumene (**2**),[4] aromatic bisabolenes are components of many plant essential oils. Some aromatic bisabolenes, such as (+)-nuciferal (**1b**)[5] and (+)-turmerone (**5a**),[6] possess side chains that are more highly oxidized than those present in curcumene and dehydrocurcumene. Phenolic aromatic bisabolenes include (−)-curcuphenol (**3**),[7] (+)-xanthorrhizol (**4**),[8] turmeronol B (**5b**),[9] allylic alcohols **6** and **7**,[10] and the rearranged bisabolene elvirol (**13**).[11] More highly oxidized

† Dedicated to Professor Stephen K. Taylor on the occasion of his 60th birthday.

‡ Henry Dreyfus Teacher-Scholar 2003

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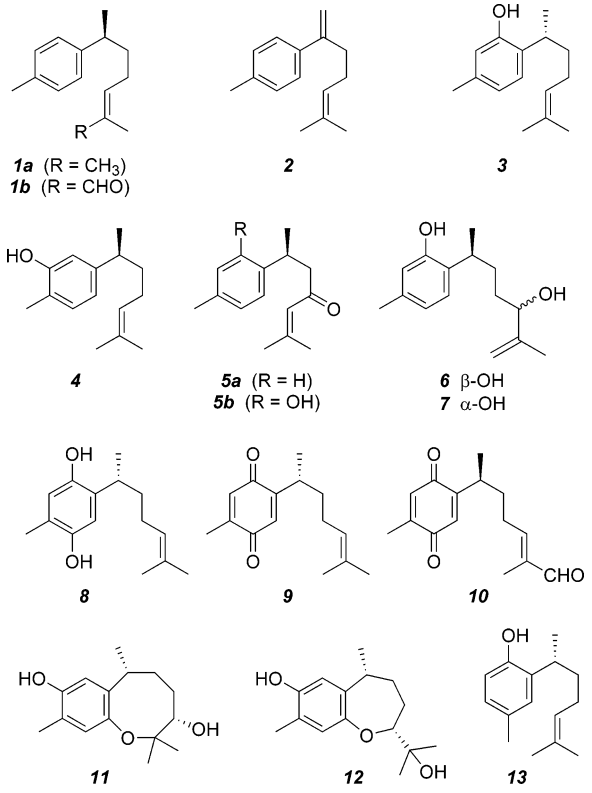
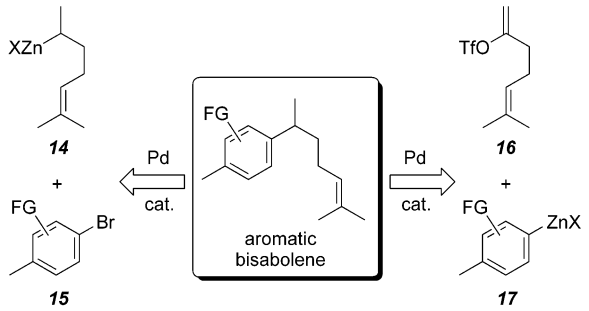
aromatic bisabolenes include (−)-curcuhydroquinone (**8**),[7] (−)-curcuquinone (**9**),[7] and glandulone A (**10**).[12] It is interesting to note that both enantiomers of curcuphenol are naturally occurring: (−)-curcuphenol (**3**) is produced by terrestrial plants and soft corals and (+)-curcuphenol (*ent*-**3**) is isolated from marine sponges.[7,10,13] (−)-Curcuphenol (**3**) has antibiotic activity,[7a] while (+)-curcuphenol (*ent*-**3**) exhibits cytotoxicity against murine and human tumors[7c,14] and inhibits H,K-ATPase.[7b] Xanthorrhizol (**4**) and its derivatives display antifungal and antitumor properties as well as inhibition of COX-2.[8]



We became interested in the preparation of functionalized aromatic bisabolenes as part of our continuing program targeting the total synthesis of the heliannuols.[15] Exemplified by heliannuols A and D (**11** and **12**, respectively), the heliannuols are a novel family of twelve allelochemicals[16] isolated from the sunflower *Helianthus annuus*.[17] The unusual benzoxocane and benzoxepane structures of the heliannuols have attracted significant attention from synthetic chemists.[15,18] The biosynthesis of the heliannuols is thought to involve **8** or **9** as an intermediate.[17b,e]

We sought short, efficient methods for preparing the aromatic bisabolene skeleton that would be useful in the synthesis of the heliannuols as well as unnatural analogues. More specifically, we desired an approach that would permit the use of a common aromatic unit that could be coupled to varying side chains to allow the preparation of the heliannuols and related compounds in a divergent manner. Thus, we envisioned two distinct ways to assemble the bisabolene skeleton by attaching the 6-methyl-5-heptenyl side chain to the aromatic core via Pd-catalyzed couplings of organozinc reagents (Scheme 1).[19] The first involved the attachment of secondary organozinc halide **14** to aryl bromide **15**. The second strategy utilized coupling alkenyl triflate **16** to arylzinc halide **17**.[20] Herein we report our results from both types of couplings and elaboration of the products thus obtained to produce natural products **2**, **3**, **8**−**10**, and **13**. We also report an improved preparation of **29**, a key intermediate in the synthesis of heliannuol D (**12**).[15a]

SCHEME 1



Results and Discussion

We first examined the reactions of secondary alkylzinc reagents **14** because it provided the most direct route to the desired bisabolene skeleton via formation of an sp^2-sp^3 C−C bond. The alkylzinc reagents employed in the first part of the study were prepared by reaction of the corresponding halides **18** with Rieke zinc in tetrahydrofuran (Scheme 2). The bromide **18a** generally gave a cleaner conversion to the organozinc reagent **14a** as determined by GC analysis. Iodide **18b** produced a significant amount of 2,6,7,11-tetramethyl-2,10-dodeca-

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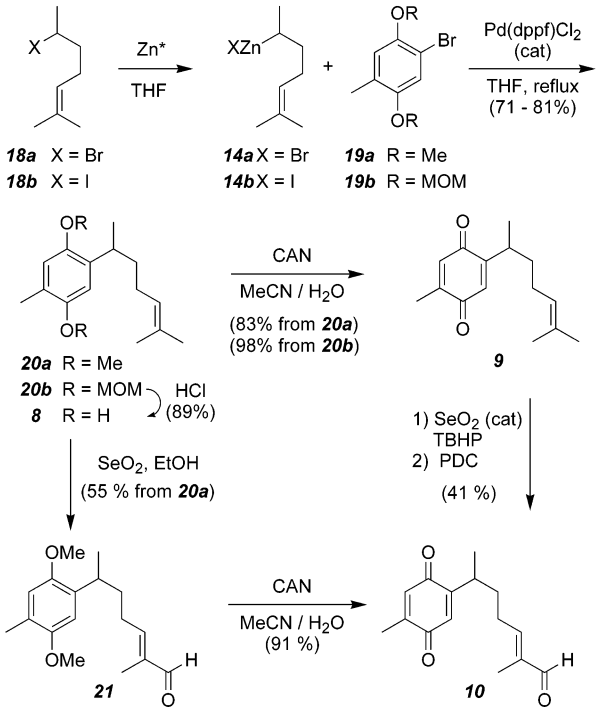
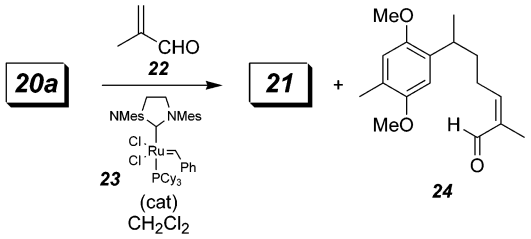
SCHEME 2



diene[21] during the reaction with activated zinc, thereby reducing the amount of **14b** available for subsequent coupling. The alkylzinc halides **14** were coupled to aryl bromides **19a** and **19b** using $Pd(dppf)Cl_2$ as catalyst to produce aromatic bisabolenes **20a** and **20b** in good yield (Scheme 2). In both cases use of alkylzinc reagent **14b** instead of **14a** resulted in a slightly lower yield (8% on average) of **20** from the coupling reaction.

Despite reports to the contrary,[22] cleavage of the methyl ethers in **20a** with boron tribromide was unsuccessful in our hands, yielding a mixture of mono-deprotected compounds and side products arising from Friedel–Crafts-type alkylation of the trisubstituted olefin of the side chain.[2a,i,23] Methoxymethyl protected **20b**, on the other hand, was easily deprotected under acidic conditions to provide (±)-curcuhydroquinone (**8**) in excellent yield. Hydroquinone **8** was prone to air oxidation, however, leading us to convert both **20a** and **20b** to (±)-curcuquinone (**9**) through oxidative deprotection with ceric ammonium nitrate (CAN)[24] (Scheme 2). Allylic oxidation of **9** to install the α,*β*-unsaturated aldehyde of glandulone A (**10**) proved somewhat problematic. Reaction of **9** with a stoichiometric amount of selenium dioxide gave very low yields (12–15%) of **10**. Use of catalytic amounts of SeO_2 with *tert*-butylhydroperoxide as the stoichiometric oxidant[25] improved the yield of crude product considerably but gave a mixture of **10** and the corresponding allylic alcohol in a 3:1 ratio as determined by ^1H NMR analysis. The crude product was oxidized directly with PDC to yield (±)-glandulone A (**10**) in 41% yield for the two steps after chromatographic purification. The IR, UV–vis, and ^1H and ^{13}C NMR spectra of our synthetic **10** matched the data reported for natural glandulone A.[12]

TABLE 1. Olefin Cross Metathesis of 20a with Methacrolein



entry	equiv of **22**	equiv of **23**	temp (°C)	time (h)	yield (%)[a] **21**	yield (%)[a] **24**
1	1.0	0.02	41	19	52	25
2	5.0	0.02	41	18	32	3
3	1.2	0.02	23	18	37[b]	0

[a] Isolated yield of purified material. [b] 62% recovered **20a**.

In an attempt to improve the overall yield of **10**, we reversed the order of the allylic oxidation and the conversion to the quinone. Dimethyl ether **20a** was oxidized with SeO_2 to produce the corresponding (*E*)-α,*β*-unsaturated aldehyde **21** in modest yield, and the subsequent oxidation of **21** with ceric ammonium nitrate produced **10** in excellent yield (Scheme 2). Still frustrated by the low yield of **21** via the SeO_2 oxidation, however, we examined the olefin cross metathesis of **20a** with methacrolein (**22**) using Grubbs' second generation catalyst (**23**). Using the reported conditions,[26] **21** was produced along with the corresponding *Z*-isomer **24** in a 2:1 ratio (Table 1, entry 1). Using excess **22** at reflux resulted in a higher *E:Z* product ratio (entry 2). Running the cross metathesis at room temperature resulted in exclusive formation of *E*-isomer **21**, but at the expense of overall conversion (entry 3). Attempts to perform the olefin cross metathesis reaction on quinone **9** were unsuccessful. Thus the first synthesis of (±)-glandulone A (**10**) was accomplished in three steps from **18** (via **21**) in 41% overall yield.

Although the secondary alkylzinc route to functionalized aromatic bisabolenes described above was successful, preparing large quantities of the alkylzinc reagents **14** presented some difficulties, including variation in the reactivity of the Rieke zinc from batch to batch and removal of the naphthalene used in the preparation of the Rieke zinc.[27]

We then turned our attention to the palladium-catalyzed coupling of arylzinc species (cf. **17**) to alkenyl triflate **16**.[28] We optimized the coupling reaction conditions using commercially available 4-methylphenylzinc

(21) Characterization data for 2,6,7,11-tetramethyl-2,10-dodecadiene (mixture of diastereomers). IR (neat, NaCl plates): 1642, 1454, 1378, 908, and 735 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.10 (m, 2H), 1.95 (m, 4H), 1.68 (br s, 6H), 1.60 (br s, 6H), 1.5–0.9 (overlapping m, 6H), 0.82 (d, J = 6.5, 3H), and 0.76 (d, J = 6.5, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 131.0, 125.1, 125.09, 37.1, 36.2, 35.0, 33.0, 31.6, 26.2, 26.1, 25.7, 17.6, 16.3, and 14.3. LRMS (EI): *m/z* (rel int) 222 (5, M^+), 137 (5), 123 (5), 109 (60), 95 (20), 82 (95), 69(95), 55 (50), and 41 (100).

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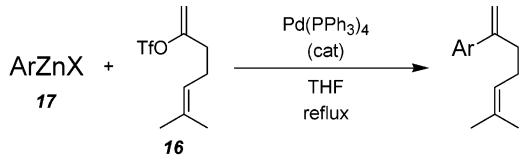
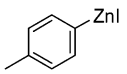
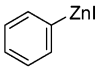
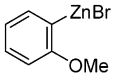
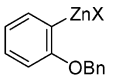
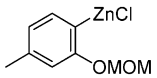
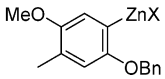
TABLE 2. Palladium-Catalyzed Couplings of Arylzinc Halides with Alkenyl Triflate 16

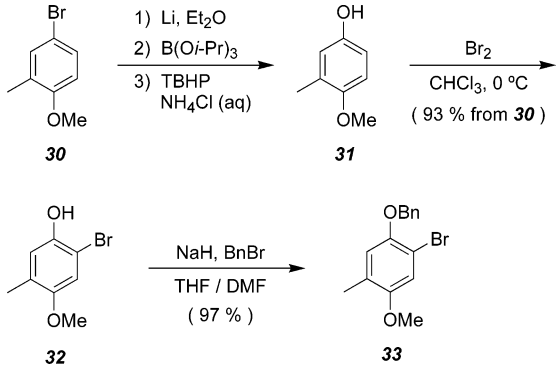


entry	aryl zinc reagent[a]	equiv 16	Pd (mol %)	product	yield (%)[b]
1		0.5	10	**2**	62
2		1.0	5		66
3		1.25	5		78
4		2.0	10		86
5		1.5	5	**25**	68
6		1.5	5	**26**	85
7		1.8	5	**27**	63
8		1.5	5	**28**	90
9		1.8	5	**29**	94

[a] 4-Methylphenylzinc iodide (entries 1−4), phenylzinc iodide (entry 5), and 2-methoxyphenylzinc bromide (entry 6) were purchased from Aldrich as 0.5 M solutions in THF. 2-Benzyloxyphenylzinc bromide (entry 7), 2-methoxymethoxy-4-methylphenyl zinc chloride (entry 8), and 2-benzyloxy-4-methoxy-3-methylphenylzinc halide (entry 9) were prepared by reaction of the corresponding aryl bromide (entries 7 and 9) or arene (entry 8) with *tert*-butyllithium followed by transmetalation with zinc chloride (see Experimental Section). [b] Isolated yield.

iodide as a test substrate to produce dehydro-α-curcumene (**2**) (Table 2, entries 1−4). Higher yields of **2** were obtained when **16** was used in slight excess (compare entry 1 to entry 4 and entry 2 to entry 3). Reducing the amount of palladium catalyst to 5 mol % lowered product yield only slightly (compare entries 3 and 4). Use of the nonaflate[29] corresponding to **16** in the cross-coupling reaction resulted in a shorter reaction time but a comparable isolated yield of the cross-coupled product. Phenylzinc, 2-methoxyphenylzinc, 2-benzyloxyphenylzinc and

SCHEME 3



2-methoxymethoxy-4-methylphenylzinc reagents all reacted with triflate **16** under the optimized conditions to produce cross-coupled products **25**−**28**, respectively, in moderate to good yields (Table 2, entries 5−8). This coupling strategy was also employed in the preparation of benzyl ether **29** in an impressive 94% yield (entry 9), considerably higher than was achieved previously in our synthesis of (±)-heliannuol D (**12**).[15]

The arylzinc reagent required for the synthesis of **29** was prepared from 4-bromo-2-methylanisole (**30**) (Scheme 3).[15] Bromide **30** was converted to the aryllithium species followed by reaction with triisopropylborate and oxidation of the resulting boronate ester with *tert*-butylhydroperoxide, which gave 3-methyl-4-methoxyphenol (**31**) in nearly quantitative yield. We have found the use of *tert*-butylhydroperoxide in aqueous ammonium chloride solution for this transformation to be superior to acidic hydrogen peroxide in some cases.[30] Phenol **31** was then brominated at the less-hindered *ortho* position and protected as the benzyl ether to provide **33**. Lithium−halogen exchange on **33** with *tert*-butyllithium followed by transmetalation with zinc chloride provided the arylzinc species for the cross-coupling with triflate **16** to yield **29** (Table 2, entry 9).

The conjugated olefin in dienes such as **2** and **25**−**29** can be selectively reduced using lithium or sodium in liquid ammonia.[7a,22] We have found it more efficient and convenient, however, to submit the crude product mixture from the cross-coupling reaction directly to the dissolving metal reduction rather than purify and characterize the dienes. This process is illustrated with syntheses of curcuphenol (**3**) and elvirol (**13**) (Scheme 4). Directed metalation of MOM-protected *m*-cresol **34**,[31,32] transmetalation with zinc chloride, palladium-catalyzed coupling of the arylzinc species to triflate **16**, and dissolving metal reduction of the crude coupling product provided **35** in 91% overall yield. Hydrolysis of the methoxymethyl ether group gave (±)-curcuphenol (**3**) in excellent yield. Aryl bromide **36** was subjected to a similar sequence of reactions to produce (±)-elvirol (**13**) in 86% overall yield.

(27) It is also possible to prepare Rieke zinc with substoichiometric amounts of naphthalene as electron carrier: Rieke, R. D.; Hanson, M. V. In *Organozinc Reagents: A Practical Approach*; Knochel, P., Jones, P. Eds.; Oxford: New York, 1999; Chapter 2. Since this portion of the work was completed, highly active Rieke zinc has become commercially available.

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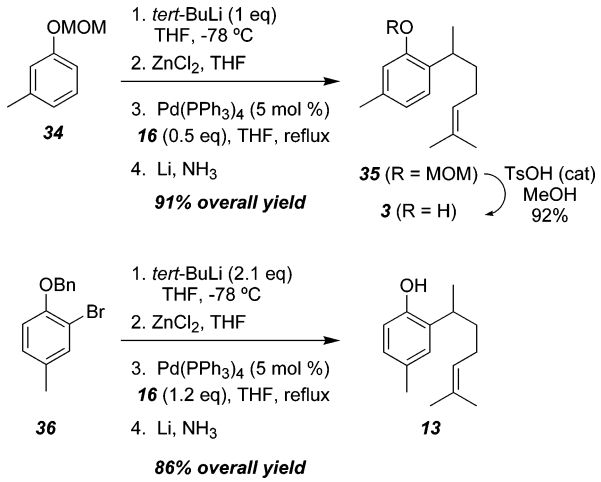
SCHEME 4



Conclusions

The assembly of the aromatic bisabolene skeleton was accomplished using two complementary strategies involving the cross-coupling of organozinc derivatives. Secondary alkylzinc halides **14** react with aryl bromides **19** using Pd(dppf)Cl_2 as catalyst to produce the cross-coupled product **20** in good yield. The side chain of bisabolene derivative **20** was elaborated through selenium dioxide oxidation and alkene cross metathesis to yield (±)-glandulone A (**10**) in high overall yield via the natural products (±)-curcuhydroquinone (**8**) and (±)-curcuquinone (**9**). Arylzinc halides react with alkenyl triflate **16** using Pd(PPh_3)$_4$ as catalyst to produce cross-coupled products in good to excellent yields. These styrene derivatives may be purified and characterized or subjected to dissolving metal reduction to saturate the conjugated olefin in the side chain. The natural products (±)-curcuphenol (**3**) and (±)-elvirol (**13**) were prepared by the latter protocol.

Experimental Section[33]

4-(1,5-Dimethyl-4-hexenyl)-2,5-dimethoxytoluene (20a).[22] A 50-mL centrifuge tube was charged with naphthalene (7.69 g, 60.0 mmol) and lithium wire (0.42 g, 60 mmol) that was hammered flat and rinsed free of mineral oil in hexanes. After an argon atmosphere was established, THF (5 mL) was added, and a dark green color was established. After disappearance of the Li (approx 2 h), $ZnCl_2$ (1.0 M in ether, 30 mL, 30 mmol) was slowly added. The mixture was then stirred for 1 h and centrifuged. The supernatant was withdrawn via syringe, and a fresh portion of dry THF (10 mL) was added. The mixture was stirred for 10 min and centrifuged, and the supernatant was withdrawn. Bromide **18a** (2.87 g, 15.0 mmol) in THF (10 mL) was added to the zinc particulate, and the mixture was stirred overnight. The zinc insertion was checked by GC analysis,[27] which showed disappearance of the halide and appearance of the corresponding alkane. When the halide was consumed, the solution was transferred via cannula to a flask containing a solution of **19a** (1.86 g, 8.00 mmol) and Pd(dppf)-Cl_2 (0.65 g, 0.80 mmol, 10 mol %) in THF (20 mL). The mixture was heated to reflux, and after 24 h the mixture was cooled, diluted with ether (100 mL), washed (10% HCl, sat. $NaHCO_3$, brine), and dried ($MgSO_4$). After solvent removal, the resulting residue was purified by MPLC (19:1 hexanes/ethyl acetate) to give **20a** as a colorless oil (1.70 g, 81%). R_f = 0.2 in 30:1 hexanes/ethyl acetate. IR (neat, NaCl plates): 1652, 1466, 1207, 1049, and 860 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.68 (s, 1H), 6.67 (s, 1H), 5.12 (t septets, J = 7.1, 1.3, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.14 (sextet, J = 7.1, 1H), 2.20 (s, 3H), 1.91 (m, 2H), 1.66 (br s, 3H), 1.70−1.49 (m, 2H), 1.54 (br s, 3H), and 1.18 (d, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 151.8, 150.8, 133.9, 131.1, 124.8, 124.1, 114.3, 109.7, 56.3, 56.1, 37.3, 31.8, 26.3, 25.7, 21.2, 17.6, and 16.0. LRMS (EI): *m*/*z* (rel int) 262 (81, M$^+$), 192 (14), 180 (34), and 170 (100).

2,5-Bis(methoxymethoxy)-4-(1,5-dimethylhex-4-enyl)-toluene (20b).[2i,34] Following the procedure used above for the preparation of **20a**, bromide **18a** (2.87 g, 15.0 mmol), aryl bromide **19b** (2.33 g, 8.00 mmol), and Pd(dppf)Cl_2 (0.65 g, 0.80 mmol, 10 mol %) yielded **20b** as a colorless oil (2.04 g, 79%) after purification by MPLC (12:1 hexanes/ethyl acetate). R_f = 0.3 in 19:1 hexanes/ethyl acetate. IR (neat, NaCl plates): 1503, 1450, 1185, 1148, 1080, and 1012 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.93 (s, 2H), 5.16 (obscured m, 1H) 5.16 (s, 2H), 5.14 (s, 2H) 3.53 (s, 6H), 3.21 (sextet, J = 7.1, 1H), 2.26 (s, 3H), 1.97 (m, 2H), 1.71 (br s, 3H), 1.75−1.55 (m, 2H), 1.58 (br s, 3H), and 1.24 (d, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.7, 149.6, 135.1, 131.2, 125.6, 124.9, 117.5, 113.8, 95.6, 95.4, 56.0, 56.0, 37.4, 32.0, 26.4, 25.8, 21.4, 17.7, and 16.3. LRMS (EI): *m*/*z* (rel int) 322 (14, M$^+$), 195 (37), 151 (13), and 45 (100).

Glandulone A (10) via SeO_2 Oxidation of Curcuquinone (9). *tert*-Butylhydroperoxide (90% solution, 0.35 mL, 3.6 equiv) was added to a solution of **9** (200 mg, 0.861 mmol), SeO_2 (10 mg, 0.086 mmol), and salicylic acid (12 mg, 0.086 mmol) in CH_2Cl_2 (20 mL). The mixture was refluxed for 2.5 h and then diluted with $CHCl_3$. The solution was washed (Na_2CO_3, brine), dried (Na_2SO_4), and concentrated. The residue was then dissolved in CH_2Cl_2 (20 mL), pyridinium dichromate (324 mg, 0.861 mmol) was added, and the mixture was stirred for 2 h. The mixture was then passed through a plug of silica, concentrated, and purified by radial chromatography (12:1 hexanes/ethyl acetate) to yield **10** (87 mg, 41%) as a yellow oil.

Via CAN Oxidation of Aldehyde 21. A solution of ceric ammonium nitrate (1.10 g, 2.00 mmol dissolved in 5 mL water) was added dropwise to a solution of aldehyde **21** (276 mg, 1.00 mmol) in acetonitrile (5 mL). After the addition was complete, the mixture was stirred an additional 5 min before transferring the solution to a separatory funnel. The solution was extracted with CH_2Cl_2, and the organic phase was dried over Na_2SO_4. Solvent removal yielded spectroscopically pure **10** (224 mg, 91%) as a yellow oil. R_f = 0.42 in 6:1 hexanes/ethyl acetate. UV−vis: λ_{max} 232 nm (log ϵ = 4.53), 252, and 262 (sh). IR (neat, NaCl plates): 2922, 2852, 2710, 1719, 1682, 1650, and 1611 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.40 (s, 1H), 6.61 (q, J = 1.5, 1H), 6.54 (d, J = 0.9, 1H), 6.45 (app. tq, J = 7.3, 1.3, 1H), 2.97 (sextet, J = 6.8, 1H), 2.34 (app qd, J = 7.3, 1.1, 2H), 2.05 (d, J = 1.5, 3H), 1.8−1.5 (m, 2H), 1.72 (d, J = 1.1, 3H), and 1.18 (d, J = 6.8, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 195.1, 188.2, 187.2, 153.3, 153.1, 145.4, 139.8, 133.7, 131.4, 34.4, 31.3, 26.8, 19.1, 15.4, and 9.2. Anal. Calcd for C_{15} $H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 72.83; H, 7.17.

(*E*)-6-(2,5-Dimethoxy-4-methylphenyl)-2-methyl-2-heptenal (21) and (*Z*)-6-(2,5-Dimethoxy-4-methylphenyl)-2-methyl-2-heptenal (24) via Cross Metathesis of 20a. Grubbs' catalyst **23** (25 mg, 0.03 mmol, 2 mol %) was placed in a 25-mL two-necked flask fitted with a condenser under argon. Dry CH_2Cl_2 (5 mL) was added, followed by **20a** (394 mg, 1.50 mmol) and freshly distilled methacrolein (105 mg, 1.50 mmol). The mixture was refluxed overnight, concentrated on a rotary evaporator, and passed through a small silica plug (12:1 hexanes/ethyl acetate). The filtrate was concentrated and purified by MPLC (19:1 hexanes/ethyl acetate) to yield **21** (218 mg, 52%) and **24** (103 mg, 25%) as yellow oils. **Data for 21.**

(33) General experimental procedures may be found in Supporting Information.

(34) Ono, M.; Yamamoto, Y.; Todoriki, R.; Akita, H. *Heterocycles* **1994**, *37*, 181−185.

IR (neat, NaCl plates): 2830, 2710, 1685, 1642, 1505, 1466, 1400, 1209, 1049 and 861 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 9.35 (s, 1H), 6.68 (s, 1H), 6.65 (s, 1H), 6.47 (app td, J = 7.3, 1.5, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.19 (sextet, J = 6.8, 1H), 2.27 (m, 2H), 2.21 (s, 3H), 1.77 (m, 2H), 1.66 (br s, 3H), and 1.23 (d, J = 6.8, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 195.4, 155.3, 151.8, 150.8, 139.1, 132.4, 124.8, 114.1, 109.7, 56.2, 56.1, 35.8, 31.9, 27.3, 21.1, 16.1 and 9.1. LRMS (EI): *m/z* (rel int) 276 (45, M^+), 192 (15), and 179 (100). Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.85; H, 9.04. **Data for 24.** IR (neat, NaCl plates): 2852, 1676, 1503, 1208, and 1047 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 9.90 (s, 1H), 6.66 (s, 1H), 6.61 (s, 1H), 6.47 (app tq, J = 8.2, 1.5, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 3.19 (sextet, J = 6.7, 1H), 2.40 (m, 2H), 2.20 (s, 3H), 1.75 (m, 2H), 1.72 (q, J = 1.2, 3H), and 1.22 (d, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 191.3, 151.9, 150.7, 150.0, 135.8, 132.2, 124.8, 114.1, 109.6, 56.2, 56.1, 37.2, 31.6, 25.0, 21.4, 16.4 and 16.1. Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.68; H, 8.71.

(*E*)-6-(2,5-Dimethoxy-4-methylphenyl)-2-methyl-2-heptenal (21) via SeO_2 Oxidation of 20a. A mixture of alkene **20a** (122 mg, 0.465 mmol) and SeO_2 (102 mg, 0.919 mmol) in ethanol (25 mL) was heated to reflux for 2 days. At that time a small amount of $NaHSO_3$ was added, and the solvent was removed by evaporation. The residue was dissolved in CH_2Cl_2, washed with 10% HCl and brine, dried over Na_2SO_4, and concentrated. Purification by radial chromatography (9:1 hexanes/ethyl acetate) gave **21** (70 mg, 55%) as a yellow oil.

General Procedure for Reaction of Arylzinc Reagents with Alkenyl Triflate 16. 4-(5-Methyl-1-methylene-4-hexenyl)toluene (dehydro-α-curcumene) (2, Table 2, entry 4).[35] Triflate **16** (0.515 g, 1.99 mmol) was added to a mixture of $Pd(PPh_3)_4$ (0.118 g, 0.102 mmol, 10 mol %) in THF (20 mL) under argon. 4-Methylphenylzinc iodide (2.0 mL, 0.5 M in THF, 1.0 mmol) was added, and the solution was heated at reflux for 6 h. The solution was then cooled and partitioned between hexanes and water. The layers were separated, and the aqueous phase was extracted with ether. The combined organic layers were washed (3 M NaOH, brine), dried (Na_2SO_4), and concentrated. Radial chromatography (hexanes) provided **2** (0.172 g, 86%) as a pale yellow oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.31 (app d, J = 8.0, 1H), 7.13 (app d, J = 8.0, 1H), 5.25 (d, J = 1.4, 1H), 5.12 (t septets, J = 7.0, 1.4, 1H), 5.01 (br q, J = 1.4, 1H), 2.50 (t, J = 7.5, 2H), 2.35 (s, 3H), 2.13 [br dt (app q), J = 7.5, 2H], 1.67 (br s, 3H), and 1.55 (br s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 148.1, 138.3, 136.9, 131.7, 128.9, 125.9, 123.9, 111.4, 35.4, 27.0, 25.7, 21.1, and 17.7.

6-Methyl-2-phenyl-1,5-heptadiene (25).[36] The general procedure for the preparation of **2** was followed. Triflate **16** (0.777 g, 3.01 mmol), $Pd(PPh_3)_4$ (0.120 g, 0.104 mmol, 5 mol %) and phenylzinc iodide (4.0 mL, 0.5 M in THF, 2.0 mmol) yielded **25** (0.252 g, 68%) as a pale yellow oil after purification by radial chromatography. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.5−7.2 (m, 5H), 5.28 (d, J = 1.4, 1H), 5.12 (m, 1H), 5.06 (q, J = 1.4, 1H), 2.52 (t, J = 7.5, 2H), 2.13 [br dt (app q), J = 7.3, 2H], 1.68 (br s, 3H), and 1.55 (br s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 148.3, 141.3, 131.8, 128.2, 127.2, 126.1, 123.8, 112.2, 35.4, 26.9, 25.7, and 17.7.

2-(5-Methyl-1-methylene-4-hexenyl)anisole (26). The general procedure for the preparation of **2** was followed. Triflate **16** (1.89 g, 7.31 mmol), $Pd(PPh_3)_4$ (0.339 g, 0.293 mmol), and 2-methoxyphenylzinc bromide (10.0 mL, 0.5 M in THF, 5.00 mmol) yielded **26** (0.920 g, 85%) as a colorless oil after purification by radial chromatography. IR (neat, NaCl plates): 3074, 1629, 1596, 1576, 1489, 1240, 1029, 897, and 750 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.24 (td, J = 8.0, 1.8, 1H), 7.12 (dd, J = 7.4, 1.8, 1H), 6.90 (td, J = 7.4, 1.0, 1H), 6.86 (br d, J = 8.0, 1H), 5.12 (overlapping m, 2H), 5.00 (d, J = 2.0, 1H), 3.81 (s, 3H), 2.49 (t, J = 7.4, 2H), 2.03 [br dt (app q), J = 7.3, 2H], 1.66 (br s, 3H), and 1.53 (br s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.5, 149.0, 132.1, 131.4, 130.2, 128.2, 124.2, 120.4, 114.0, 110.5, 55.4, 36.3, 26.8, 25.7, and 17.6. Anal. Calcd for $C_{15}H_{20}O$: C, 83.29; H, 9.32. Found: C, 83.13; H, 9.53.

1-Benzyloxy-2-(5-methyl-1-methylene-4-hexenyl)-benzene (27). 2-Benzyloxyphenylzinc bromide was prepared by adding an ethereal solution of benzyl 2-bromophenyl ether[37] (1.43 g, 5.43 mmol) to a cold (−78 °C) solution of *t*-BuLi (7.0 mL, 1.7 M in pentane, 11.9 mmol) in ether (5 mL). The solution was warmed to 0 °C over 1 h and then recooled to −78 °C. A solution of anhydrous $ZnCl_2$ (5.7 mL, 1.0 M in THF, 5.7 mmol) was added, and the resulting solution was stirred 1 h as it warmed to room temperature. In a separate flask, triflate **16** (2.47 g, 9.55 mmol) was added to a mixture of $Pd(PPh_3)_4$ (0.356 g, 0.308 mmol) in THF (25 mL). The arylzinc reagent prepared above was then cannulated into this flask and the mixture heated to reflux for 2 h, stirred overnight at room temperature, and heated to reflux again for 5 h. The reaction mixture was partitioned between hexanes and 10% HCl solution. The layers were separated, and the aqueous phase was extracted with hexanes three times. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated. Purification by radial chromatography (gradient elution, hexanes to 12:1 hexanes/ethyl acetate) gave **27** (1.00 g, 63%) as a colorless oil. IR (neat, NaCl plates): 3069, 3030, 1627, 1596, 1578, 1488, 1232, 1020, 899, 749, and 694 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.38 (m, 5H), 7.18 (m, 2H), 6.91 (br t, J = 7.5, 2H), 6.86 (br d, J = 8.0, 1H), 5.14 (m, 1H), 5.08 (s, 2H), 5.04 (d, J = 2.0, 1H), 2.53 (t, J = 7.5, 2H), 2.03 [br dt (app q), J = 7.5, 2H], 1.64 (d, J = 1.0, 3H), and 1.50 (br s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.6, 148.7, 137.3, 132.6, 131.4, 130.3, 129.5, 128.4, 127.7, 127.1, 124.2, 120.8, 114.2, 112.3, 70.2, 36.4, 26.8, 25.7, and 17.6. Anal. Calcd for $C_{21}H_{24}O$: C, 86.26; H, 8.27. Found: C, 86.12; H, 8.38.

2-Methoxymethoxy-4-methyl-1-(5-methyl-1-methylene-4-hexenyl)-benzene (28). The procedure used for the preparation of **2** was followed. The arylzinc reagent was prepared from methoxymethyl ether **34**[32] (0.832 g, 5.46 mmol), *t*-BuLi (3.53 mL, 1.7 M in pentane, 6.00 mmol), and anhydrous $ZnCl_2$ (0.774 g, 5.46 mmol dissolved in dry THF). The resulting solution was added to a mixture of triflate **16** (2.25 g, 8.19 mmol) and $Pd(PPh_3)_4$ (0.314 g, 0.273 mmol, 5 mol %) in THF (30 mL). The mixture was heated to reflux for 2 h and worked up as described above to give **28** (1.28 g, 90%) as a colorless oil after flash chromatography (50:1 hexanes/ethyl acetate). IR (neat, NaCl plates): 3069, 3030, 1611, 1569, 1503, 1154, 1073, 1016, 926, 898, and 818 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.00 (d, J = 7.6, 1H), 6.98 (br s, 1H), 6.76 (br d, J = 7.6, 1H), 5.15 (s, 2H), 5.11 (m, 1H), 5.08 (m, 1H), 4.98 (d, J = 2.0, 1H), 3.47 (s, 3H), 2.48 (t, J = 8.0, 2H), 2.33 (s, 3H), 2.03 [br dt (app q), J = 7.5, 2H], 1.66 (br s, 3H), and 1.53 (br s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.2, 148.8, 138.5, 131.6, 130.3, 130.2, 124.5, 122.7, 115.6, 114.2, 94.8, 56.4, 37.1, 27.3, 26.1, 21.8, and 18.1. LRMS (EI): *m/z* (rel int) 260 (5, M^+), 217 (65), 185 (53), 173 (16), 159 (30), 145 (45), 69 (43), and 45 (100). Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.05; H, 9.61.

4-Benzyloxy-2-methyl-5-(5-methyl-1-methylene-4-hexenyl)anisole (29). The procedure used for the preparation of **27** was followed. The arylzinc reagent was prepared from bromide **33** (1.69 g, 5.50 mmol), *tert*-BuLi (7.0 mL, 1.7 M in pentane, 11.9 mmol), and anhydrous $ZnCl_2$ (5.5 mL, 1.0 M in THF, 5.5 mmol). The resulting solution was added to a mixture of triflate **16** (2.58 g, 10.0 mmol) and $Pd(PPh_3)_4$ (0.326 g, 0.282 mmol) in THF (25 mL). The mixture was heated to reflux for

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12 h and worked-up as described above to give **29** (1.75 g, 94%) as a light brown oil that was spectroscopically pure and used in subsequent reactions. An analytical sample was prepared by flash chromatography (19:1 hexanes/ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37 (m, 5H), 6.75 (br s, 1H), 6.65 (br s, 1H), 5.13, (d, J = 2.0, 1H), 5.08 (obscured m, 1H), 5.05 (d, J = 2.0, 1H), 5.00 (s, 2H), 3.80 (s, 3H), 2.53 (t, J = 7.5, 2H), 2.19 (s, 3H), 2.05 (m, 2H), 1.65 (br s, 3H), and 1.51 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 151.8, 149.3, 148.8, 137.6, 131.3, 130.7, 128.4, 127.6, 127.2, 126.0, 124.3, 116.5, 113.9, 112.5, 71.5, 55.9, 36.5, 26.8, 25.7, 17.7, and 16.1. Anal. Calcd for $C_{23}H_{28}O_2$: C, 82.10; H, 8.39. Found: C, 81.84; H, 8.23.

4-Methoxy-3-methylphenol (31).[38] 4-Bromo-2-methylanisole (**30**)[39] (20.2 g, 0.100 mol) was charged to a dry 500-mL three-necked flask equipped with an efficient reflux condenser and a large magnetic stir bar. The vessel was placed under argon and dry ether (200 mL) was added via syringe. Lithium wire (1.62 g, 0.233 mol) was cut into ~1 cm pieces, hammered flat, rinsed with hexanes to remove mineral oil, and added to the reaction flask under a positive flow of argon. The reaction mixture began to spontaneously reflux. Reflux was maintained with a heating mantle until the lithium was nearly consumed. A small (0.7 mL) aliquot was removed via syringe, quenched with saturated NH_4Cl solution, and extracted with ether (2 mL), and the ether layer was passed through a plug of anhydrous $MgSO_4$. Analysis by GC indicated 97% 2-methylanisole (from protonation of the aryllithium species) and 3% **30**. The flask was cooled with a dry ice/2-propanol bath, triisopropylborate (30 mL, 0.130 mol) was added via syringe, and the mixture was allowed to warm to room temperature. A large amount of white solid formed. The reaction mixture was transferred to a 1-L Erlenmeyer flask with the aid of additional ether. At this point the remaining pieces of lithium were carefully removed and quenched with ethanol. *tert*-Butylhydroperoxide (90% solution, 15 mL) was added **CAUTIOUSLY** with vigorous stirring, followed by saturated NH_4Cl solution (~100 mL). Two clear layers formed during this process. The light brown mixture was transferred to a separatory funnel, and the aqueous phase was acidified (pH ~4) with 10% HCl. The layers were separated, and the aqueous phase was extracted with ether (100 mL). The combined ether layers were washed [sat. $NaHSO_3$, sat. $NaHCO_3$ (**CAUTION**-frothing!), and brine] and dried over anhydrous Na_2SO_4. Removal of solvent gave **31** (15.9 g, 115% crude mass recovery) as a light brown oil. The crude phenol was >95% pure by GC analysis (the main contaminant was *tert*-butyl alcohol) and was used without further purification. IR (neat, NaCl plates): 3294 (br), 949, 861, 802, 751 and 721 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.69 (d, J = 8.5, 1H), 6.66 (d, J = 3.0, 1H), 6.61 (dd, J = 8.5, 3.0, 1H), 4.29 (s, OH), 3.78 (s, 3H), and 2.19 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 151.8, 148.9, 128.0, 118.0, 112.6, 111.6, 56.1, and 16.1.

2-Bromo-4-methoxy-5-methylphenol (32). The crude phenol **31** prepared above was dissolved in $CHCl_3$ (125 mL), and the solution was cooled in an ice bath. Bromine (5.0 mL, 16 g, 0.10 mol) was dissolved in $CHCl_3$ (75 mL) and added via an addition funnel over 3 h. The reaction was quenched with sat. $NaHSO_3$ solution and transferred to a separatory funnel. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed (water, sat. $NaHCO_3$, brine), dried (Na_2SO_4), and concentrated to yield **32** (20.1 g, 93%) as a tan solid of sufficient purity to be used in subsequent reactions. An analytical sample was recrystallized (mp 76−78 °C) from light petroleum ether. IR (film deposited from $CDCl_3$): 3140 (br), 1200, 859, 824, 787, and 728 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.86 (s, 1H), 6.82 (s, 1H), 5.11 (s, OH), 3.76 (s, 3H), and 2.14 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 152.0, 145.8, 128.1, 117.9, 113.3, 105.8, 56.0, and 16.0. Anal. Calcd for $C_8H_9BrO_2$: C, 44.27; H, 4.18. Found: C, 44.27; H, 4.17.

5-Bromo-4-benzyloxy-2-methylanisole (33). Sodium hydride (60% dispersion in mineral oil, 3.3 g, 0.082 mol hydride) was washed thrice with hexanes and slurried in dry THF (60 mL). The flask was cooled in an ice bath, and phenol **32** (16.2 g, 0.074 mol) was added via addition funnel as a solution in THF. Benzyl bromide (9.0 mL, 13 g, 0.076 mol) was then dissolved in THF (15 mL) and added via addition funnel. When the addition was complete, the cooling bath was removed. The mixture was stirred 2 h before dry DMF (25 mL) was added and the reaction was stirred overnight. The reaction mixture was quenched by the addition of sat. NH_4Cl solution and diluted with ether. The layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with 10% NaOH solution (2×) and sat. LiCl solution before drying over $MgSO_4$. Solvent removal gave a light brown oil that was purified by Kugelrohr distillation (bp 170−180 °C at 0.1 mmHg) to yield **33** (22.2 g, 97%) as an oil that solidified on standing. An analytical sample was recrystallized (mp 43−45 °C) from light petroleum ether. IR (film deposited from CH_2Cl_2): 1208, 1028, 852, 789, 730, and 695 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.46 (br d, J = 7.5, 2H), 7.35 (m, 3H), 6.98 (s, 1H), 6.77 (s, 1H), 5.03 (s, 2H), 3.74 (s, 3H), and 2.13 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 152.6, 148.8, 136.9, 128.4, 127.8, 127.2, 126.7, 117.7, 115.1, 109.3, 72.0, 55.9 and 16.2. Anal. Calcd for $C_{15}H_{15}BrO_2$: C, 58.65; H, 4.92. Found: C, 58.81; H, 5.10.

4-(1,5-Dimethyl-4-hexenyl)-3-methoxymethoxy-toluene (35).[2f,i,j] *t*-BuLi (2.78 mL, 1.4 M in pentane, 4.00 mmol) was added over 10 min to a cold (−78 °C) solution of **34**[32] (609 mg, 4.00 mmol) in THF (10 mL). After 1 h, anhydrous $ZnCl_2$ (4.0 mL, 1.0 M in Et_2O, 4.0 mmol) was added, and the mixture was warmed to room temperature over 0.5 h. The arylzinc species was then transferred via cannula to a solution of triflate **16** (516 mg, 1.99 mmol) and $Pd(PPh_3)_4$ (115 mg, 0.10 mmol, 5 mol %) in THF (10 mL). The mixture was refluxed for 24 h, cooled, and diluted with hexanes (100 mL). The mixture was passed through silica (1 × 0.5 in.) with hexanes and concentrated to yield crude **28** that was used directly in the next step.

Ammonia (~15 mL) was condensed into a two-necked flask fitted with a dry ice coldfinger condenser and cooled in a dry ice/*i*-PrOH bath. Dry ether (10 mL) was then added followed by lithium wire (42 mg, 6.0 mmol) cut into small pieces. A dark blue color was established, and the crude **28** prepared above was added as a solution in ether (2 mL). The mixture was stirred for 0.5 h before NH_4Cl (1.5 g) was added in small portions to discharge the blue color. The ammonia was allowed to evaporate, and the residue was diluted with ether, washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography (9:1 hexanes/ethyl acetate) gave **35** (0.480 g, 91% from **16**) as a colorless oil. IR (neat, NaCl plates): 1649, 1502, 1150, 1073, 1017, 923, and 808 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.06 (d, J = 7.7, 1H), 6.88 (s, 1H), 6.79 (d, J = 7.7, 1H), 5.17 (s, 2H), 5.12 (t septets, J = 7.1, 1.3, 1H), 3.49 (s, 3H), 3.16 (sextet, J = 7.0, 1H), 2.31 (s, 3H), 1.91 (app. septet, J = 7.0, 2H), 1.7−1.4 (m, 2H), 1.66 (s, 3H), 1.57 (br s, 3H), and 1.19 (d, J = 7.1, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.5, 136.3, 133.4, 131.1, 126.7, 124.8, 124.5, 114.8, 94.5, 55.9, 37.3, 31.5, 26.3, 25.7, 21.27, 21.21, and 17.6. Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.62; H, 9.99.

2-(1,5-Dimethyl-4-hexenyl)-4-methylphenol [(±)-Elvirol] (13).[2k,v,w,11b,c] *t*-BuLi (6.12 mL, 1.7 M in pentane, 10.4 mmol) was added over 10 min to a cold (−78 °C) solution of **36** (1.37 g, 4.94 mmol) in THF (10 mL). After 1 h, anhydrous $ZnCl_2$ (5.9 mL, 1.0 M in ether, 5.9 mmol) was added, and the mixture was warmed to room temperature. The solution was then transferred via cannula to a solution of alkenyl triflate **16** (1.53 g, 5.93 mmol) and $Pd(PPh_3)_4$ (285 mg, 0.250 mmol, 5 mol %) in THF (10 mL). The mixture was refluxed for 24 h,

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cooled, and diluted with hexanes (100 mL). The mixture was washed (10% HCl, brine), dried (Na_2SO_4), and concentrated. The residue was passed through a silica plug with hexanes and concentrated to give a yellow oil (1.74 g, >100%) that was used directly in the next step.

Ammonia (~30 mL) was condensed into a two-necked flask fitted with a dry ice condenser and cooled in a dry ice/*i*-PrOH bath. Ether (30 mL) was added followed by lithium wire (225 mg, 32.4 mmol) cut in small pieces. A dark blue color was established, and the aforementioned crude alkene was added as a solution in ether. The mixture was stirred for 1.5 h before NH_4Cl (3g) was added in small portions to discharge the blue color. The mixture was diluted with ether, washed with brine, dried (Na_2SO_4), and concentrated. Purification by flash chromatography (3:1 hexanes/ethyl acetate) gave (±)-elvirol (**13**) (0.920 g, 86% from **36**) as a colorless oil. IR (neat): 3441 (br), 1609, 1258, 1200, and 810 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.95 (d, J = 1.8, 1H), 6.84 (dd, J = 8.1, 1.8, 1H), 6.64 (d, J = 8.1, 1H), 5.13 (t septets, J = 7.1, 1.3, 1H), 4.68 (s, 1H), 2.98 (sextet, J = 7.0, 1H), 2.26 (s, 3H), 1.94 (m, 2H), 1.69 (s, 3H), 1.65 (m, 2H), 1.51 (br s, 3H), and 1.23 (d, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.7, 132.8, 132.0, 130.0, 127.6, 127.0, 124.6, 115.3, 37.2, 31.6, 26.1, 25.7, 21.0, 20.7, and 17.6. Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.61; H, 10.26.

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Supporting Information Available: Experimental procedures and characterization data for **3**, **8**, **9**, **18a**, **18b**, **19b,** and **36**. This material is available free of charge via the Internet at http://pubs.acs.org.

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