Stereoselective Synthesis of 1-Aryl-4a-methyloctahydrophenanthrenes *via* Cyclization Reactions Initiated by Benzylic Cations

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Introduction

The use of polyolefin cyclizations for the synthesis of complex molecules has attracted the attention of organic chemists since the 1950s.[1] The stereoselective formation of multiple rings and stereogenic centers in one step from acyclic precursors makes this methodology highly appealing as a synthetic tool. As a result, numerous groups have devoted considerable effort toward understanding the stereochemical outcome, studying the use of different cyclization initiators and terminators, and exploring substituent effects on these reactions. As a result, polyolefin cyclizations have been exploited in the synthesis of natural products.

The cyclization initiator must be selectively activated to provide a reactive cationic intermediate without affecting the cyclization terminator. Early observations on these cyclizations showed that the initiating group played a crucial role on the efficiency of the cyzlizations.[1] To our knowledge, benzylic cations have been overlooked as initiators for these types of multiring forming cyclizations. Previous results from our laboratory have shown that quinone methides and benzylic alcohols are highly efficient cyclization initiators that participate in monocyclization reactions with a wide range of cyclization terminators.[2] It seemed likely these benzylic cation precursors might also serve as initiators for cyclizations in which more than one ring is formed. Furthermore, one might expect a high degree of stereoselectivity in the formation of the new benzylic stereogenic center due to conformational biases introduced by the aryl ring in the transition state.

We report here the results of a brief study to determine the suitability of benzylic cations as initiators for cyclizations in which more than one ring is formed in a single step. The chemistry developed provides easy access to substituted 4a-methyloctahydrophenanthrenes, a skeleton common to many natural products.[3] In addition, substituted octahydrophenanthrenes have been used as advanced intermediates in the synthesis of natural products.[3]

Design of Substrates. We elected to use a benzylic cation with a *p*-hydroxy group to form a decalin ring system. The Stork–Eschenmoser postulate[4] predicts that *E*-alkenes afford *trans*-fused decalins and *Z*-alkenes give rise to *cis*-fused rings in polyolefin cyclizations. Thus, an *E*-alkene was chosen to link the terminator and initiator so that this known preference for formation of *trans*-ring junctions could be used to provide products of known relative stereochemistry at these stereogenic centers. The choice of cyclization terminator was defined by the need to have an electron-rich group that upon cyclization would limit the number of regioisomers formed. Consequently, a 3,5-dimethoxy-substituted aryl ring was the terminator of choice.

Results and Discussion

Synthesis of Substrates. Aldehyde **1** was readily prepared from ethyl 3,5-dimethoxycinnamate[5] in 60% yield. Condensation of aldehyde **1** with 2-propenylmagnesium bromide[6] afforded allylic alcohol **2** in 67% yield (Scheme I). Allylic alcohol **2** was converted to ester **3** in 82% yield via a Johnson–orthoester–Claisen rearrangement.[7] Reduction of **3** with $LiAlH_4$ followed by treatment of the resulting alcohol with triphenylphosphine and carbon tetrabromide afforded bromide **4** in 68% yield. Nitrile **5** was obtained in 88% yield by treatment of **4** with sodium cyanide and dimethyl sulfoxide.[8] Reduction of nitrile **5** with diisobutylaluminum hydride[9] afforded aldehyde **6** in 63% yield. Treatment of aldehyde **6** with the desired aryllithium afforded **7** and **8**. Desilylation of **7** and **8** with tetrabutylammonium fluoride afforded substrates **9** and **10** in 98% and 92% yields, respectively, from **6**.

Cyclization Studies. Initially, we examined the cyclization in which the benzylic cation was derived by treatment of a benzylic alcohol with a Lewis acid. Treatment of **9** with $TiCl_4$ at 0 °C afforded octahydrophenanthrene **11** in 46% yield (Scheme II). Carrying out the reaction at room temperature increased the yield to 82%. In addition to **11**, only traces of what appear to be uncyclized or monocyclized products were observed in the ^1H NMR spectrum of the crude reaction mixture. No other diastereomeric cyclized products were observed. The reason for the higher yield at room temperature is not clear at this time. Similarly, treatment of **10** with $TiCl_4$ at 0 °C afforded octahydrophenanthrenes **12** and **13** as a 9.5:1 mixture (^1H NMR) in 78% yield (Scheme II).

In order to determine whether or not the source of the cation (benzylic alcohol vs quinone methide) had an effect

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(2) For previous work from our laboratory on monocyclization reactions of quinone methides, see: (a) Angle, S. R.; Turnbull, K. D. *J. Am. Chem. Soc.* **1989**, *111*, 1136. (b) Angle, S. R. Louie, M. S.; Mattson, H. L.; Yang, W. *Tetrahedron Lett.* **1989**, *30*, 1193. (c) Angle, S. R.; Frutos, R. P. *J. Chem. Soc., Chem. Commun.* **1993**, 171. (d) Angle, S. R.; Frutos, R. P. *J. Org. Chem.* **1993**, *58*, 5135. For previous work from our laboratory on monocyclization reactions of benzylic cations, see: (e) Angle, S. R., Louie, M. S. *J. Org. Chem.* **1991**, *56*, 2853. (f) Angle, S. R.; Louie, M. S. *Tetrahedron Lett.* **1989**, *30*, 5741.

(3) For an example of a similar reaction used for the total synthesis of (±)-triptonide and (±)-triptolide, see: van Tamelen, E. E.; Leiden, T. M. *J. Am. Chem. Soc.* **1982**, *104*, 1785. For other examples of compounds with this skeleton, see: Hanson, J. R. in *Terpenoids and Steroids*, Vol. 12; The Royal Society of Chemistry: London, 1983, and previous volumes in this series.

(4) (a) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. (b) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1957**, *38*, 1890.

(5) (a) Klemm, L. H.; Klemm, R. A.; Santhanam, P. S.; White, D. V. *J. Org. Chem.* **1971**, *36*, 1971. (b) 3,5-Dimethoxycynammic acid is commercially available and could probably be used in place of the ethyl ester.

(6) Rieke, R. D.; Bales, S. E. *J. Am. Chem. Soc.* **1974**, *96*, 1775.

(7) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

(8) Friedman, L.; Shechter, H. *J. Org. Chem.* **1960**, *25*, 877.

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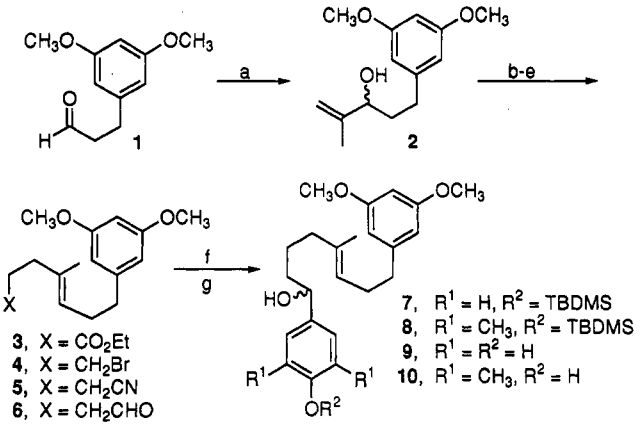
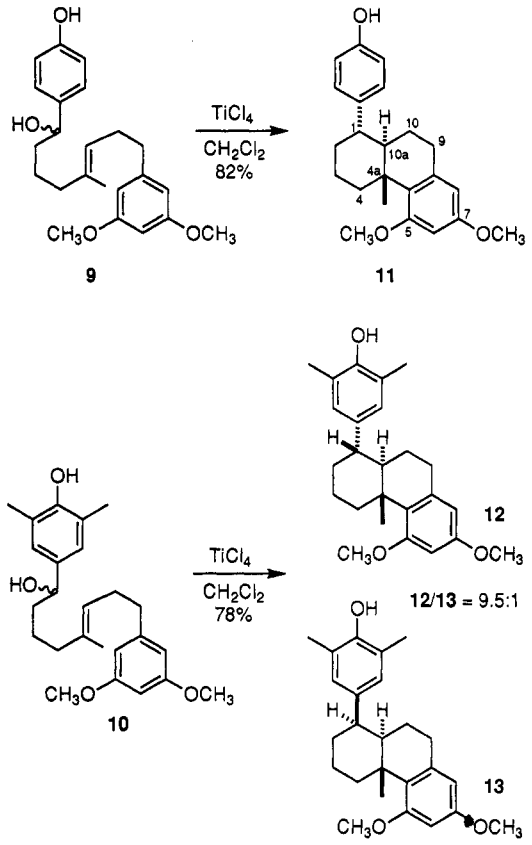
Scheme I[a]



[a] Reagents: (a) CH_2=$C(CH_3)MgBr$, 67%; (b) $CH_3C(OEt)_3$, $CH_3CH_2CO_2H$, 140 °C, 82%; (c) $LiAlH_4$; Ph_3P, CBr_4, 68%; (d) NaCN, DMSO, 88%; (e) DIBAI-H, 63%; (f) aryllithium, (99%, 7), (96%, 8); (g) *n*-Bu_4F, (99%, 9), (96%, 10).

Scheme II

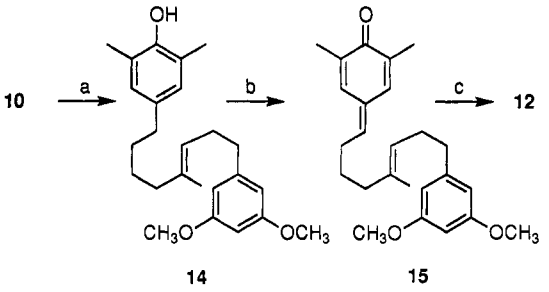


on the cyclization, quinone methide **15** was prepared from phenol **10** (Scheme III). Benzylic alcohol **10** was converted into its bis-methanesulfonate derivative and reduced with $LiAlH_4$. Hydrolysis of the resulting aryl methanesulfonate ester with KOH afforded phenol **14** in an unoptimized 39% yield. Oxidation of **14** with Ag_2O[10] afforded quinone methide **15**. Treatment of **15** with $TiCl_4$ at 0 °C afforded **12** in 78% yield. Diastereomer **13** could not be detected in the ^1H NMR spectrum of the crude reaction mixture. The yield of the cyclization was identical for the benzylic alcohol and quinone methide; however, the diastereoselectivity for the quinone methide was noticeably higher.

Overall, these benzylic cation initiated cyclizations produced two rings and three new stereogenic centers with

(10) Dyall, L. K.; Winstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 2196.

Scheme III[a]



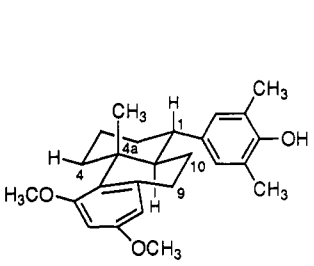
[a] Reagents: (a) MsCl, Et_3N, Et_2O; $LiAlH_4$; KOH, EtOH, 39%; (b) Ag_2O, $CDCl_3$; (c) $TiCl_4$, CH_2Cl_2, 78% (2 steps).

excellent stereoselectivity. The yields were comparable or higher than those obtained with tertiary carbocation and activated ketone initiators and higher than that seen for a similar cyclization reaction in which an epoxide initiator was used.[11] In addition, the diastereoselectivity in the formation of the new benzylic stereogenic center was excellent.

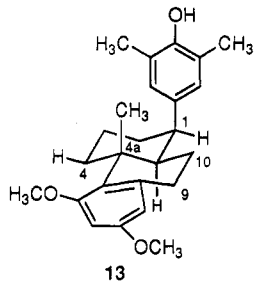
Assignment of Relative Stereochemistry for the Cycloadducts. The relative stereochemistry of the cyclization products was assigned on the basis of ^1H NMR spectral data, difference NOE experiments and comparison with spectral data of similar compounds of known structure,[11-13] and precedent for the formation of *trans*-decalins from similar cyclizations with *E*-alkenes and stabilized carbocation initiators.[4,11] Assignment of the signal for the C(1)-hydrogen of **12** in the ^1H NMR spectrum was based on a 2D-COSY spectrum and NOE experiments. Irradiation of the signal at δ 6.79 for the *ortho* hydrogen on the 3,5-dimethyl-4-hydroxyphenyl substituent caused a 4.8% enhancement of the signal for the C(1)-hydrogen at δ 2.56 (ddd, J = 4, 12, 12 Hz). No other signals in the δ 2–3 region of the spectrum showed an enhancement. The axial orientation of the C(1)-hydrogen was apparent from the two large axial–axial (12 Hz) coupling constants and one small (4 Hz) coupling constant. This places the adjacent C(10a)-hydrogen in an axial orientation ($J_{H(10a)-H(1)}$ = 12 Hz). At first glance, the downfield shift of the signal for the C(4a)-angular methyl group in the ^1H NMR spectrum of **12** at δ 1.31 appeared inconsistent with a *trans*-ring junction. The ^1H NMR signal for the angular methyl group in *trans*-fused octahydrophenanthrenes is normally observed at δ 1.06–1.08, whereas in a *cis*-fused systems the signal for this methyl is usually observed at δ 1.20–1.35.[13] However, similar deshielding effects on the angular methyl group and one of the C(4)-hydrogens by a methoxy group at C(5) on related systems has been reported.[11,12] In support of this, the signal for the C(4)-equatorial hydrogen at δ 3.13 (apparent broad d, J = 13 Hz), also exhibiting a downfield shift due to the C(5)-methoxy group. The assigned *trans*-decalin structure is consistent with all the spectra data.

The axial orientation of the C(1)-aryl group in the minor diastereomer **13** was also deduced by difference NOE experiments and coupling constant information. Irradi-

(11) Goldsmith, D. J.; Phillips, C. F. *J. Am. Chem. Soc.* **1969**, *91*, 5862.
(12) Nasipuri, D.; Chaudhuri, S. R. R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 262.
(13) (a) Wenkert, E.; Afonso, A.; Beak, P.; Carney, W. J.; Jeffs, P. W.; McChesney, J. D. *J. Org. Chem.* **1965**, *30*, 713. (b) Campbell, A. L.; Leader, H. N.; Sierra, M. G.; Spencer, C. L.; McChesney, J. D. *J. Org. Chem.* **1979**, *44*, 2755. (c) Sierra, M. G.; Leader, H. N.; McChesney, J. D. *J. Org. Chem.* **1985**, *50*, 4450. (d) Vila, A. J.; Spanevello, R. A.; Olivieri, A. C.; Sierra, M. G.; McChesney, J. D. *Tetrahedron* **1989**, *45*, 4951.



12



13

ation of the signal at δ 7.10 for the *ortho* hydrogens on the 3,5-dimethyl-4-hydroxyphenyl substituent caused a 2.8% enhancement of the signal for the C(4a)-angular methyl group at δ 0.91 and a 1.1% enhancement of the signal for the C(1)-hydrogen. This places the C(1)-aryl substituent and the C(4a)-angular methyl syn-diaxial to each other. The signals for the C(1)-hydrogen and the C(4)-equatorial hydrogen come together at δ 3.14–3.06 as a multiplet. In the NOE experiment above, there is no enhancement for the C(4)-equatorial hydrogen and the coupling constants for the C(1)-hydrogen can be clearly observed (δ 3.12, triplet, J = 5.1 Hz). These coupling constants are consistent with an equatorial hydrogen coupled to two vicinal axial hydrogens with the 5-Hz coupling constant and a small, <1 Hz, coupling constant to the one equatorial hydrogen. The upfield shift of the signal for the C(4a)-angular methyl group in **13** is consistent with a shielding effect by the axial C(1)-aryl substituent.

The stereochemistry of **11** was assigned on the basis of the similarity to the spectrum for **12**. In particular, the aliphatic region of the spectrum was nearly identical to that of **12**.

Conclusion

Benzylic cations are excellent cyclization iniatiors, offering the advantages of both high yield and high stereoselectivity. The aryl ring might be further functionalized, or oxidatively degraded to a variety of functional groups.[14] These initiators could clearly find application to the construction of functionalized polycyclic compounds. Exploitation of this chemistry for natural product synthesis is currently under investigation.

Experimental Section[15a]

General Information. NMR spectra were recorded on a General Electric QE-300 or GN-500 NMR instrument; coupling constants (J) are reported in hertz and refer to apparent peak multiplicities and may not necessarily be true coupling constants. Abbreviations used are as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, br = broad. Mass spectra are reported as relative intensity to the parent peak. The molarities indicated for alkyllithiums were established by titration with 2,5-dimethoxybenzyl alcohol.[15b] In cases where products were isolated by "aqueous workup (solvent, drying agent)", the procedure was to dilute the reaction mixture with water, extract the aqueous layer several times with the indicated organic solvent, wash the combined organic layers with brine, dry over the indicated drying agent, and concentrate the reaction mixture. "Concentration" in the experimental procedures refers to isolation of product(s) from a solvent/product mixture by removal of the solvent under reduced pressure (water aspirator) with a rotary evaporator. Unless stated otherwise, all reactions were run under an atmosphere of nitrogen or argon in oven-dried glassware.

3-(3,5-Dimethoxyphenyl)propanal (1). $LiAlH_4$ (3.11 g, 83.8 mmol) was slowly added to a solution of ethyl *trans*-3,5-dimethoxycinnamate (6.02 g, 25.5 mmol)[5] and THF (200 mL) at 0 °C. The mixture was allowed to reach room temperature and then refluxed for 6 h. The reaction mixture was then cooled to 0 °C and treated sequentially with H_2O (3.11 mL), 15% NaOH (3.11 mL), and H_2O (9.33 mL). The resulting suspension was filtered, dried ($MgSO_4$), and concentrated to afford 5.01 g of crude alcohol. The resulting crude alcohol was then oxidized using the general procedure of Swern, Mancuso, and Huang.[16] A solution of DMSO (6.0 mL, 84.6 mmol) and CH_2Cl_2 (19.0 mL) was added dropwise to a stirred solution of oxalyl chloride (20.0 mL of a 2 M solution in CH_2Cl_2, 40.0 mmol) and CH_2Cl_2 (70 mL) at –60 °C. The resulting solution was stirred for 2 min and then a solution of the above alcohol (5.01 g) and CH_2Cl_2 (25 mL) was added dropwise. The resulting solution was stirred for an additional 15 min and then triethylamine (18.0 mL, 129 mmol) was added dropwise. After the solution was stirred for 5 min, the cold bath was removed and the reaction mixture was allowed to warm to room temperature. Aqueous workup (CH_2Cl_2, $MgSO_4$) afforded 5.38 g of crude **1** as a yellow oil. Flash chromatography (9:1 hexane/ethyl acetate) afforded 2.94 g (60%) of **1** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H, CHO), 6.34 (d, J = 2.1 Hz, 2H, ArH), 6.31 (t, J = 2.1 Hz, 1H, ArH), 3.76 (s, 6H, $Ar(CH_3)_2$), 2.88 (dd, J = 7.5, 6.9 Hz, 2H), 2.74 (dd, J = 7.5, 6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 160.8, 142.6, 106.2, 98.0, 55.1, 44.9, 28.3; IR ($CDCl_3$) 2840, 1725, 1607, 1206 cm^{-1}; MS (EI, 70 eV) m/z 194 (M^+, 26), 166 (100), 83 (34): HRMS calcd for $C_{11}H_{14}O_3$ 194.0943, found 194.0938.

(±)-5-(3,5-Dimethoxyphenyl)-2-methyl-1-penten-3-ol (2). Using a modification of the procedure described by Rieke and Bales,[6] a suspension of freshly cut potassium (154 mg, 3.94 mmol), $MgCl_2$ (207 mg, 2.18 mmol), and THF (5.0 mL) was refluxed for 2 h. The resulting dark gray suspension was allowed to cool to room temperature and stirred for 30 min. 2-Bromopropene (100 μL, 1.13 mmol) was slowly added, and after 10 min the mixture was cooled to 0 °C. A solution of 3-(3,5-dimethoxyphenyl)-propanal (**1**; 133 mg, 0.686 mmol) and THF (1.0 mL) was slowly added *via* cannula to the reaction mixture. The resulting mixture was allowed to warm up to room temperature, stirred for 35 min at room temperature, and poured into aqueous NH_4Cl solution. Aqueous workup (ethyl acetate, $MgSO_4$) afforded 165 mg of a yellow oil. Flash chromatography (9:1 hexane/ethyl acetate) afforded 109 mg (67%) of **2** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (d, J = 2.1 Hz, 2H, ArH), 6.31 (t, J = 2.1 Hz, 1H, ArH), 4.97 (s, 1H, C*H*H=C), 4.86 (apparent, d, J = 1.5 Hz, 1H, CH*H*=C), 4.08 (t, J = 6.5 Hz, 1H, C*H*OH), 3.77 (s, 6H, Ar-$(OCH_3)_2$), 2.74–2.51 (m, 2H, $ArCH_2$), 2.11 (br s, 1H, OH), 1.89–1.82 (m, 2H, $ArCH_2CH_2$), 1.74 (s, 3H, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 147.3, 144.3, 111.1, 106.4, 97.7, 75.0, 55.1, 36.2, 32.1, 17.5; IR ($CDCl_3$) 3608, 2942, 1597, 1206, 1155 cm^{-1}; MS (EI, 50 eV) m/z 236 (M^+, 43), 165 (61), 152 (100); HRMS calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1418.

(*E*)-Ethyl 7-(3,5-Dimethoxyphenyl)-4-methylhept-4-enoate (3). Using a modification of the procedure described by Johnson and co-workers,[7] a stirred mixture of allylic alcohol **2** (329 mg, 1.39 mmol), triethyl orthoacetate (1.80 mL, 9.82 mmol), and propionic acid (6.0 μL) was heated to 140 ± 5 °C for 3 h. The mixture was allowed to reach room temperature and unreacted orthoacetate was removed by vacuum distillation (0.5 mmHg, 60 °C) to afford 427 mg of a yellow oil. Flash chromatography (15:1 hexane/ethyl acetate) afforded 348.2 mg (82%) of **3** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.34 (d, J = 2.1 Hz, 2H, ArH), 6.30 (t, J = 2.1 Hz, 1H, ArH), 5.21 (t, J = 9 Hz, 1H, C*H*OH), 4.11 (q, J = 6.9 Hz, 2H, OCH_2CH_3), 3.78 (s, 6H, $Ar(OCH_3)_3$), 2.57 (t, J = 7.2 Hz, 2H), 2.41–2.36 (m, 2H), 2.32–2.24 (m, 4H), 1.59 (s, 3H, CH_3), 1.24 (t, J = 6.9 Hz, 3H, OCH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 160.6, 144.4, 134.0, 124.2, 106.4, 97.6, 60.1, 55.0, 36.1, 34.5, 33.1, 29.5, 15.8, 14.1; IR ($CDCl_3$) 2941, 1727, 1596, 1206, 1156 cm^{-1}; MS (CI, NH_3) m/z 307 (MH^+, 100), 99 (6); HRMS calcd for $C_{18}H_{27}O_4$ (M^+H) 307.1909, found 307.1901.

(14) Mander, L. N. *Syn. Lett.* **1991**, 134.

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(16) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(*E*)-1-Bromo-7-(3,5-dimethoxyphenyl)-4-methyl-4-heptene (4). $LiAlH_4$ (842 mg, 22.2 mmol) was slowly added to a stirred solution of ester **3** (3.11 g, 10.2 mmol) and ether (100 mL) at 0 °C. The mixture was allowed to reach room temperature and stirred for 2 h. The reaction mixture was then cooled to 0 °C, and H_2O (840 μL), 15% NaOH (840 μL), and H_2O (2.50 mL) were added sequentially. The resulting suspension was allowed to warm to room temperature, stirred for 1 h, filtered, dried ($MgSO_4$), and concentrated to afford 2.51 g of crude alcohol as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (d, J = 2.4 Hz, 2H, ArH), 6.30 (t, J = 2.4 Hz, 1H, ArH), 5.21 (dt, J = 1.0 Hz, J = 7.1 Hz, 1H, C=CH), 3.78 (s, 6H, $Ar(OCH_3)_2$), 3.60 (t, J = 6.5 Hz, 2H, CH_2OH), 2.58 (t, J = 7.7 Hz, 2H), 2.30 (q, J = 7.4 Hz, 2H), 2.06 (t, J = 7.4 Hz, 2H), 1.70–1.61 (m, 2H), 1.58 (s, 3H, CH_3). Triphenylphosphine (5.08 g, 19.4 mmol) was added to a stirred solution of the above crude alcohol (2.51 g), CBr_4 (6.37 g, 19.2 mmol), and ether (100 mL) at room temperature. The resulting mixture was stirred for 8 h and then poured into H_2O (300 mL). Aqueous workup (ether, $MgSO_4$) afforded 11.7 g of a brown oil. Flash chromatography (20:1 hexane/ethyl acetate) afforded 2.82 g (68%) of pure **4** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (d, J = 2.1 Hz, 2H, ArH), 6.30 (t, J = 2.1 Hz, 1H, ArH), 5.22 (t, J = 6.8 Hz, 1H, C=CH), 3.78 (s, 6H, $Ar(OCH_3)_2$), 3.33 (t, J = 6.8 Hz, 2H, CH_2Br), 2.59 (t, J = 7.7 Hz, 2H), 2.31 (q, J = 7.4 Hz, 2H), 2.11 (t, J = 7.2 Hz, 2H), 1.93 (p, J = 6.9 Hz, 2H), 1.56 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 144.3, 133.6, 124.8, 106.3, 97.5, 55.0, 37.6, 36.1, 33.2, 30.7, 29.5, 15.6; IR ($CDCl_3$) 2941, 1597, 1462, 1154, 1067 cm^{-1}; MS (EI, 50 eV) m/z 328 (M^+, 6), 326 (M^+, 6), 247 (50), 152 (100), 151 (61); HRMS calcd for $C_{16}H_{23}O_2Br$ 326.0881, found 326.0866.

(*E*)-8-(3,5-Dimethoxyphenyl)-5-methyloct-5-enenitrile (5). Using a modification of the procedure described by Friedman and Shechter,[8] a solution of bromide **4** (2.82 g, 8.62 mmol) and dimethyl sulfoxide (10.0 mL) was added dropwise to a stirred solution of sodium cyanide (765 mg, 15.6 mmol) and dimethyl sulfoxide (5.0 mL) at room temperature. The reaction mixture was warmed to 50 °C and stirred for 2 h. The mixture was allowed to reach room temperature and then poured into aqueous NH_4Cl solution. Aqueous workup (ethyl acetate, $MgSO_4$) afforded 2.36 g of a brown oil. Flash chromatography (9:1 hexane/ethyl acetate) afforded 2.06 g (88%) of **5** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.34 (d, J = 1.8 Hz, 2H, ArH), 6.29 (t, J = 1.8 Hz, 1H, ArH), 5.21 (t, J = 7.1 Hz, 1H, C=CH), 3.76 (s, 6H, $Ar(OCH_3)_2$), 2.59 (t, J = 7.7 Hz, 2H), 2.31 (q, J = 7.4 Hz, 2H), 2.15 (t, J = 7.2 Hz, 2H), 2.09 (t, J = 7.2 Hz, 2H), 1.69 (p, J = 7.2 Hz, 2H), 1.53 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4, 144.1, 132.8, 125.5, 119.5, 106.2, 97.3, 54.8, 37.8, 35.7, 29.2, 23.0, 15.6, 15.2; IR($CDCl_3$) 2941, 1597, 1462, 1206, 1155 cm^{-1}; MS (EI, 30 eV) m/z 273 (M^+, 28), 152 (100), 151 (78); HRMS calcd for $C_{17}H_{23}O_2N$ 273.1729, found 273.1727.

(*E*)-8-(3,5-Dimethoxyphenyl)-5-methyl-5-octenal (6). Using a modification of the procedure described by Miller, Biss, and Schwartzman,[9] a solution of DIBAL-H (1.60 mL, 8.98 mmol) and benzene (10.0 mL) was slowly added *via* cannula to a stirred solution of nitrile **5** (2.06 g, 7.54 mmol) and benzene (20.0 mL) at room temperature. The resulting mixture was stirred for 14 h and then poured into aqueous NH_4Cl solution. Aqueous workup (ethyl acetate, $MgSO_4$) afforded 2.14 g of a yellow oil. Flash chromatography (9:1 hexane/ethyl acetate) afforded 1.30 g (63%) of pure **6** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (br s, 1H, CH=O), 6.35 (d, J = 2.1 Hz, 2H, ArH), 6.30 (t, J = 2.1 Hz, 1H, ArH), 5.17 (t, J = 6.9 Hz, 1H, C=CH), 3.78 (s, 6H, $Ar(OCH_3)_2$), 2.59 (t, J = 7.8 Hz, 2H), 2.37–2.27 (m, 4H), 2.01 (t, J = 7.2 Hz, 2H), 1.71 (p, J = 7.3 Hz, 2H), 1.55 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 160.6, 144,6, 134.5, 124.8, 106.5, 97.6, 55.2, 43.0, 38.7, 36.2, 29.5, 20.0, 15.6; IR ($CDCl_3$) 2940, 1722, 1606, 1596, 1206, 1155 cm^{-1}; MS (EI, 50 eV) m/z 276 (M^+, 10), 152 (100), 151 (45); HRMS calcd for $C_{17}H_{24}O_3$ 276.1725, found 276.1714.

(±)-(*E*)-1-[4-[(*tert*-Butyldimethylsilyl)oxy]phenyl]-8-(3,5-dimethoxyphenyl)-5-methyl-5-octen-1-ol (7). *t*-BuLi (625 μL of a 1.92 M solution in pentane, 1.20 mmol) was added dropwise to a stirred solution of 1-bromo-4-[(*tert*-butyldimethylsilyl)oxy]-benzene (182 mg, 0.632 mmol) and ether (8.0 mL) at −78 °C. The resulting solution was stirred for 45 min and then a solution of aldehyde **6** (106 mg, 0.385 mmol) and ether (2.0 mL) was slowly added *via* cannula. The resulting mixture was allowed to warm to room temperature over a period of 8 h and then poured into a rapidly stirred solution of saturated aqueous NH_4Cl solution. Aqueous workup (ethyl acetate, $MgSO_4$) afforded 230 mg of a clear oil. Flash chromatography (9:1 hexane/ethyl acetate) afforded 182 mg (97%) mg of **7** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, J = 8.4 Hz, 2H, ArH), 6.83 (d, J = 8.4 Hz, 2H, ArH), 6.39 (d, J = 2.1 Hz, 2H, ArH), 6.32 (t, J = 2.1, 1H, ArH), 5.18 (t, J = 6.6 Hz, 1H, C=CH), 4.57 (t, J = 6.6 Hz, 1H, CHOH), 3.77 (s, 6H, $Ar(OCH_3)_2$), 2.61 (t, J = 7.7 Hz, 2H), 2.32 (q, J = 7.4 Hz, 2H), 2.23 (s, 1H, OH), 2.00 (t, J = 7.2 Hz, 2H), 1.84–1.41 (m, 3H), 1.54 (s, 3H, CH_3), 1.40–1.25 (m, 1H), 1.02 (s, 9H, $C(CH_3)_3$), 0.22 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 154.8, 144.7, 137.5, 135.4, 127.0, 123.7, 119.8, 106.5, 97.6, 74.0, 55.1, 39.3, 38.3, 36.3, 29.6, 25.6, 23.8, 18.1, 15.7, −4.5; IR ($CDCl_3$) 3606, 2934, 1606, 1598, 1258 cm^{-1}; MS (CI, NH_3) 483 (M-H$^+$, 13), 476 (100), 259 (44), 152 (40); HRMS calcd for $C_{29}H_{43}O_4Si$ (M-H) 483.2931, found 483.2949.

(±)-(*E*)-1-[4-[(*tert*-Butyldimethylsilyl)oxy]-3,5-dimethylphenyl]-8-(3,5-dimethoxyphenyl)-5-methyl-5-octen-1-ol (8). The same procedure used for the preparation of **7** was carried out with 1-bromo-4-[*tert*-butyldimethylsilyl)oxy]-3,5-dimethylbenzene[17] (311 mg, 0.986 mmol) and aldehyde **6** (157 mg, 0.567 mmol) to afford 393 mg of crude product as a yellow oil. Flash chromatography (9:1 hexane/ethyl acetate) afforded 257 mg (88%) of **8** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (s, 2H, ArH), 6.36 (d, J = 2.1 Hz, 2H, ArH), 6.30 (t, J = 2.1 Hz, 1H, ArH), 5.16 (t, J = 6.6 Hz, 1H, C=CH), 4.51 (t, J = 6.6 Hz, 1H, CHOH), 3.77 (s, 6H, $Ar(OCH_3)_2$), 2.58 (t, J = 7.7 Hz, 2H), 2.28 (q, J = 7.6 Hz, 2H), 2.21 (s, 6H, $Ar(CH_3)_2$), 1.98 (t, J = 7.4 Hz, 2H), 1.83–1.43 (m, 3H), 1.52 (s, 3H, CH_3), 1.42–1.25 (m, 1H), 1.03 (s, 9H, $C(CH_3)_3$), 0.18 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 151.3, 144.7, 137.3, 135.5, 128.3, 126.3, 123.8, 106.5, 97.6, 74.2, 55.1, 39.3, 38.2, 36.3, 29.6, 26.1, 24.0, 18.7, 17.9, 15.7, −3.0; IR ($CDCl_3$) 3606, 2934, 1597, 1234, 1154 cm^{-1}; MS (FAB, CH_2Cl_2/NBA) m/z 512 (M^+, 24), 259 (80), 151 (100); HRMS calcd for $C_{31}H_{48}O_4Si$ 512.3322, found 512.3333.

(±)-(*E*)-8-(3,5-Dimethoxyphenyl)-1-(4-hydroxyphenyl)-5-methyl-5-octen-1-ol (9). *n*-Bu_4NF (180 μL of a 1 M solution in THF, 180 mmol) was added dropwise to a stirred solution of **7** (178 mg, 0.368 mmol) and THF (5.0 mL) at room temperature. The resulting solution was stirred at room temperature for 8 h and poured into saturated aqueous NH_4Cl solution. Aqueous workup (ethyl acetate, $MgSO_4$) afforded 174 mg of a brown oil. Flash chromatography (2:1 hexane/ethyl acetate) afforded 136 mg (99%) of **9** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, J = 8.4 Hz, 2H, ArH), 6.76 (d, J = 8.4 Hz, 2H, ArH), 6.36 (d, J = 2.1 Hz, 2H, ArH), 6.31 (t, J = 2.1 Hz, 1H, ArH), 5.14 (t, J = 6.8 Hz, 1H, C=CH), 4.58 (t, J = 6.8 Hz, CHOH), 3.76 (s, 6H, $Ar(OCH_3)_2$), 2.57 (t, J = 7.7 Hz, 2H), 2.28 (q, J = 7.5 Hz, 2H), 1.96 (t, J = 7.2 Hz, 2H), 1.82–1.54 (m, 2H), 1.51 (s, 3H, CH_3), 1.50–1.22 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4, 155.4, 144.8, 136.0, 135.4, 127.4, 123.8, 115.3, 106.7, 97.6, 74.4, 55.2, 39.2, 38.0, 36.2, 29.5, 23.8, 15.7; IR ($CDCl_3$) 3600, 3380, 2939, 1597, 1205, 1155 cm^{-1}; MS (EI, 20eV) m/z 370 (M^+, 4), 352 (28), 245 (78), 152 (58), 133 (100); HRMS calcd for $C_{23}H_{30}O_4$ 370.2144, found 370.2141.

(±)-(*E*)-8-(3,5-Dimethoxyphenyl)-1-(3,5-dimethyl-4-hydroxyphenyl)-5-methyl-5-octen-1-ol (10). The same procedure used for the preparation of **9** was carried out with **8** (66.1 mg, 0.129 mmol) to afford 64.1 mg of crude product as a brown oil. Flash chromatography (4:1 hexane/ethyl acetate) afforded 49.1 mg (96%) of **10** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (s, 2H, ArH), 6.36 (d, J = 2.1 Hz, 2H, ArH), 6.30 (t, J = 2.1 Hz, ArH), 5.16 (t, J = 6.3 Hz, 1H, C=CH), 4.65 (s, 1 H, ArOH), 4.52 (t, J = 6.6 Hz, 1H, CHOH), 3.77, (s, 6H, $Ar(OCH_3)_2$), 2.58 (t, J = 7.8 Hz, 2H), 2.36–2.16 (m, 2H), 2.24 (s, 6H, $Ar(CH_3)_2$), 1.98 (t, J = 7.2 Hz, 2H), 1.88–1.42 (m, 3H), 1.53 (s, 3H, CH_3), 1.42–1.22 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 160.5, 151.5, 144.7, 136.2, 135.5, 126.2, 123.7, 123.1, 106.5, 97.6, 74.3, 55.1, 39.3, 38.2, 36.3, 29.6, 24.0, 16.0, 15.7; IR ($CDCl_3$) 3609, 2939, 1596, 1205 cm^{-1}; MS (FAB, CH_2Cl_2/NBA) m/z 398 (M^+, 34), 381 (52), 152 (70), 151 (100); HRMS calcd for $C_{25}H_{34}O_4$ 398.2457, found 398.2460.

(17) Angle, S. R.; Rainier, J. D. *J. Org. Chem.* **1992**, *57*, 6883.

(±)-(1*S,4a*R**,10a*R**)-5,7-Dimethoxy-1-(4-hydroxyphenyl)-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (11).** $TiCl_4$ (0.40 mL of a 1 M solution in CH_2Cl_2, 0.400 mmol) was added dropwise to a stirred solution of **9** (37.5 mg, 0.101 mmol) and CH_2Cl_2 (10.0 mL) at room temperature. The mixture was stirred for 30 min and then poured into aqueous NH_4Cl solution. Aqueous workup (CH_2Cl_2, $MgSO_4$) afforded 39.8 mg of a yellow oil. Flash chromatography (9:1 hexane/ethyl acetate) afforded 29.4 mg (82%) of **11** as a white solid (mp 156–158 °C): ^1H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, J = 8.0 Hz, 2H, ArH), 6.78 (d, J = 8.0 Hz, 2H, ArH), 6.31 (d, J = 2.3 Hz, 1H, ArH), 6.18 (d, J = 2.3 Hz, 1H, ArH), 4.71 (s, 1H, OH), 3.78 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3) 3.13 (br, d, J = 12.9 Hz, 1H, C(4H)), 2.78–2.53 (m, 3H, $ArCH_2$, ArCH), 1.71–1.58 (m, 4H), 1.47 (dq, J = 4.6, 12.6 Hz, 1H), 1.32 (s, 3H, CH_3), 1.37–1.15 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 157.9, 153.5, 139.1, 139.1, 128.6, 115.2, 104.9 (br), 97.6, 55.1, 55.0, 50.5, 43.6, 38.7, 36.4, 35.9, 32.7, 22.3, 21.6, 17.7; IR ($CDCl_3$) 3600, 2930, 1604, 1513, 1158; MS (EI, 50 eV) m/z 352 (M^+, 45), 337 (100), 133 (47); HRMS calcd for $C_{23}H_{28}O_3$ 352.2038, found 352.2031.

(±)-(1*S,4a*R**,10a*R**)- and (±)-(1*R**,4a*R**,10a*R**)-5,7-Dimethoxy-1-(3,5-dimethyl-4-hydroxyphenyl-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (12 and 13, respectively). Method A.** $TiCl_4$ (190 μL of a 1 M solution in CH_2Cl_2, 0.190 mmol) was added dropwise to a solution of **10** (18.6 mg, 0.0470 mmol) and CH_2Cl_2 (5.0 mL) at 0 °C. The resulting purple mixture was stirred for 30 min at 0 °C and then poured into saturated aqueous NH_4Cl solution. Aqueous workup (ethyl acetate, $MgSO_4$) afforded 19.8 mg of a yellow oil. Flash chromatography (9:1 hexane/ethyl acetate) afforded 14.1 mg (78%) of **12** and **13** as a 9.5:1 (**12**/**13**, ^1H NMR) mixture (clear oil). **Method B.** Ag_2O (96.7 mg, 0.417 mmol) was added to a solution of phenol **14** (14.7 mg, 0.0384 mmol) and $CDCl_3$ (1.0 mL) at room temperature. The mixture was stirred for 1 h, filtered, dried (K_2CO_3), and concentrated to afford quinone methide **15** (13.4 mg) as a bright yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (s, 1H), 6.88 (s, 1H), 6.35 (d, J = 2.1 Hz, 2H, ArH), 6.29 (t, J = 2.1 Hz, 1H, ArH), 6.33–6.25 (obscured m, 1H), 5.18 (t, J = 7.2 Hz, 1H, C=CH), 3.76 (s, 6H, $Ar(OCH_3)_2$), 2.59 (dd, J = 7.5, 8.1 Hz, 2H), 2.42 (q, J = 7.6 Hz, 2H), 2.31 (q, J = 7.5 Hz, 2H), 2.10–1.95 (partially obscured m, 2H), 2.05 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 1.70–1.55 (partially obscured m, 2H), 1.57 (s, 3H, CH_3). $TiCl_4$ (150 μL of a 1 M solution in CH_2Cl_2, 0.150 mmol) was added to a solution of crude quinone methide **15** and CH_2Cl_2 (4.0 mL) at 0 °C. The resulting dark purple mixture was stirred for 35 min at 0 °C and then poured into aqueous NH_4Cl solution. Aqueous workup (CH_2Cl_2, $MgSO_4$) afforded 14.6 mg of a crude product as a yellow oil. Flash chromatography (9:1 hexane/ethyl acetate) afforded 11.4 mg (78%) of **12**. Analytical samples of both diastereomers were obtained by HPLC (4.6 mm ID column, 8:1 hexane/ethyl acetate, 1.0 mL/min t_R (**12**) = 8.9 min, t_R (**13**) = 9.7 min) purification of the product prepared *via* method A. Major diastereomer **12** (white solid): mp 151–152 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 6.79 (s, 2H, ArH), 6.31 (d, J = 2.3 Hz, 1H, ArH), 6.18 (d, J = 2.3 Hz, 1H, ArH), 4.47 (s, 1H, OH), 3.79 (s, 3H, $ArOCH_3$), 3.76 (s, 3H, $ArOCH_3$), 3.13 (d, J = 13.0 Hz, 1H, C(4H)), 2.71 (ddd, J = 17, 11, 8 Hz, 1H, $ArCHHCH_2$), 2.60–2.58 (partially obscured m, 1H, $ArCHHCH_2$), 2.56 (partially obscured ddd, J = 4, 12, 12 Hz, 1H, ArCH), 2.24 (s, 6H, $Ar(CH_3)_2$), 1.84 (br, d, J = 6.0 Hz, 1H), 1.74 (tt, J = 4.0, 13.5 Hz, 1H), 1.68–1.59 (m, 2H), 1.48 (dq, J = 4.5 Hz, J = 13.0 Hz, 1H), 1.31 (s, 3H, CH_3), 1.34–1.22 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 55 °C) δ160.0 (c), 158.1 (C), 150.2 (C), 139.2 (C), 138.5 (C), 129.0 (br), 127.8 (br), 122.9 (C), 105.4 (CH), 97.8 (CH), 55.1 (CH_3), 55.1 (CH_3), 50.5 (CH), 43.8 (CH), 38.7 (C), 36.5 (CH_2), 36.2 (CH_2), 32.7 (CH_2), 22.5 (CH_2), 21.8 (CH_2), 17.9 (CH_3), 16.0 (CH_3); IR ($CDCl_3$) 3611, 2929, 1604, 1487, 1197, 1156 cm^{-1}; MS (EI, 30 eV) m/z 380 (M^+, 60) 365 (100), 135 (63); HRMS calcd for $C_{25}H_{32}O_3$ 380.2351, found 380.2351. Minor product **13** (white solid): mp 145–146 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.10 (s, 2H, ArH), 6.26 (d, J = 2.5 Hz, 1H, ArH), 6.19 (d, J = 2.5 Hz, 1H, ArH), 4.45 (br s, 1H, OH), 3.75 (s, 3H, $ArOCH_3$), 3.73 (s, 3H, $ArOCH_3$), 3.14–3.06 (m, 2H, ArCH, $(CH_3)CCHH$), 2.96 (ddd, J = 16.5, 12.5, 6.5 Hz, 1H, $ArCHHCH_2$), 2.81 (dd, J = 16.5, 4.5 Hz, 1H, $ArCHHCH_2$), 2.31–2.25 (m, 1H), 2.24 (s, 6H, $Ar(CH_3)_2$), 1.99 (ddd, J = 1.3, 5.0, 12 .8 Hz, 1H), 1.92 (dd, J = 6.5, 12.5, 1H), 1.88–1.77 (m, 2H), 1.73 (br m, 1H), 1.27 (dt, J = 4.2, 13.2 Hz, 1H), 0.91 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 157.7, 149.8, 138.3, 136.5, 129.3, 128.8, 121.8, 104.7, 97.6, 55.1, 54.9, 49.3, 42.1, 39.0, 36.6, 33.4, 30.8, 26.4, 20.7, 19.5. 16.2; IR ($CDCl_3$) 3610, 2938, 1604, 1463, 1198 cm^{-1}; MS (EI, 50 eV) m/z 380 (M^+, 44), 365 (68), 177 (100); HRMS calcd for $C_{25}H_{32}O_3$ 380.2351, found 380.2354.

(±)-(*E*)-1-(3,5-Dimethoxyphenyl)-8-(3,5-dimethyl-4-hydroxyphenyl)-4-methyl-3-octene (14). Methanesulfonyl chloride (25 μL, 0.323 mmol) was added dropwise to a stirred solution of **9** (49.1 mg, 0.124 mmol), triethylamine (36.0 μL, 0.258 mmol), and ether (3.0 mL) at −5 °C. The mixture was allowed to reach room temperature over a period of 10 h and $LiAlH_4$ (33.0 mg, 0.830 mmol) was slowly added. The reaction mixture was then cooled to 0 °C and H_2O (33 μL), 15% NaOH (33 μL), and H_2O (1.0 mL) were added sequentially. The resulting suspension was allowed to warm to room temperature, stirred for 1 h, filtered, dried ($MgSO_4$), and concentrated to afford 46.2 mg of crude product as a yellow oil. Ethanol (5.0 mL) and 6% KOH (5.0 mL) were added to the resulting oil and the mixture was refluxed for 10 h. The mixture was then allowed to reach room temperature and acidified to pH ~6 with dilute HCl. Aqueous workup (ethyl acetate, $MgSO_4$) afforded 50.1 mg of crude product as a yellow oil. Flash chromatography (4:1 hexane/ethyl acetate) afforded 18.4 mg (39%) of **14** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.79 (s, 2H, ArH), 6.37 (d, J = 2.1 Hz, 2H, ArH), 6.32 (t, J = 2.1 Hz, 1H, ArH), 5.19 (t, J = 7.2 Hz, 1H, C=CH), 4.49 (s, 1H, ArOH), 3.78 (s, 3H, $Ar(OCH_3)_2$), 2.59 (dd, J = 7.2, 8.4 Hz, 2H), 2.48 (dd, J = 7.2, 7.8 Hz, 2H), 2.30 (partially obscured q, J = 7.7 Hz, 2H), 2.23 (s, 6H, $Ar(CH_3)_2$), 2.00 (t, J = 7.2 Hz, 2H), 1.65–1.35 (m, 4H), 1.57 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 150.0, 144.9, 135.9, 134.4, 128.4, 123.5, 122.7, 106.5, 97.7, 55.2, 39.5, 36.5, 34.9, 31.4, 29.7, 27.6, 15.9; IR ($CDCl_3$) 3611, 2934, 1597, 1202, 1154 cm^{-1}; MS (EI, 50 eV) m/z 382 (M^+, 24), 152 (81), 135 (100); HRMS calcd for $C_{25}H_{34}O_3$ 382.2508, found 382.2520.

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Supplementary Material Available: Summary of key NOE and decoupling experiments and ^1H NMR and ^{13}C NMR spectra for new compounds (29 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.