Simple Synthesis of 5-Substituted Resorcinols: A Revisited Family of Interesting Bioactive Molecules†

Emma Alonso, Diego J. Ramón, and Miguel Yus*

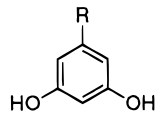
Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Apdo. 99, E-03080-Alicante, Spain

Received June 5, 1996⊗

The reaction of 3,5-dimethoxybenzyl trimethylsilyl ether (**3**) with different aldehydes (*n*-PrCHO, *n*-$C_{11}H_{23}$CHO, MeCHO, PhCHO) in the presence of lithium powder and a catalytic amount of naphthalene (4 mol %) gave, after hydrolysis, the expected alcohols **4** in moderate yields. The dehydroxylation of these compounds through the corresponding mesylates **5** or directly from benzylic derivatives by catalytic hydrogenation, afforded compounds **6**, which are finally demethylated to yield 5-alkyl-3,5-dihydroxyresorcinols, such as olivetol (**7a**), grevillol (**7b**), 1,3-dihydroxy-5-propylbenzene (**7c**), or dihydropinosilvine (**7d**). Dehydration of alcohol derivatives **4** followed by demethylation led to hydroxylated stilbene-type structures, such as pinosilvine (**9d**), resveratrol (**9e**), or piceatannol (**9f**), which in some cases can be hydrogenated to give saturated molecules such as combretastanin B-4 tetramethyl ether (**6f**) or chrysotobibenzyl (**6g**). Finally, when the naphthalene-catalyzed lithiation of compound **3** was performed in the presence of other electrophiles [Me_3SiCl, *t*-BuCHO, $CH_3(CH_2)_4CHO$, 4-$Me_3SiOC_6H_4CHO$, $(CH_2)_5CO$, PhN=C=O, PhN=CHPh], the expected reaction products **12** were isolated, after hydrolysis.

Introduction

5-Alkylresorcinols of the general type **1** are interesting naturally-occurring compounds, which have been isolated from many plants including those in the Poteaceae, Anacardiaceae, Ginkogoaceae, and Graminae families.[1] They possess a wide variety of biological activities, including fungicidal and bacteriocidal activities against numerous pathogens.[2] Recently, it was reported that this type of compound can cleave DNA at high concentrations in the presence of copper(II) chloride and oxygen.[3,4] In addition, compounds of type **1** are essential components in the synthesis of cannabinoids (2,5-disubstituted resorcinols[5]).[6] Finally, the corresponding 5-alkenyl derivatives, primarily those with a stilbene structure,[7] show interesting antileukemic properties.[8] On the other hand, we applied recently the arene-catalyzed lithiation[9,10] of *O*-silylated allylic and benzylic alcohols to the preparation of the corresponding organolithium derivatives.[11,12] In this paper we describe the application of this simple methodology to the preparation of several 5-alkyl and 5-alkenyl resorcinols, such as olivetol, grevillol, pinosilvine (and dihydropinosilvine), resveratrol, piceatannol, combretastatin B-4 tetramethyl ether, and combretastatin B-3 pentamethyl ether (chrysotobibenzyl), all of them being interesting bioactive molecules.[13]



1

Results and Discussion

Commercially available 3,5-dimethoxybenzylic alcohol (**2**) was transformed into *O*-silyl derivative **3** with chlorotrimethylsilane and triethylamine in THF.[14] Compound **3** was treated with an excess of lithium powder (1:14 molar ratio) and a catalytic amount of naphthalene (1:0.08 molar ratio, 4 mol %) in the presence of the corresponding aldehyde (1:1.2 molar ratio) in THF at −30 (for compounds **4a**, **4c** or **4d**) or 0 °C (for compound **4b**) during 2 h giving, after hydrolysis, the expected products **4** in moderate yield.[15] Compounds **4a**−**c** were transformed into their dehydroxy derivatives **6a**−**c** in a two-step process: mesylation with mesyl chloride and triethylamine in THF[16] to give compounds **5a**−**c** followed by reduction with zinc and sodium iodide under monoglyme

† This paper is dedicated to Professor Antonio González for his half-century dedication to organic chemistry.

⊗ Abstract published in *Advance ACS Abstracts,* December 15, 1996.

(1) See, for instance: Brown, G. D. *J. Nat. Prod.* **1992**, *55*, 1756.

(2) Lindenberg, B. A.; Massin, M. *J. Physiol. (Paris)* **1957**, *49*, 285.

(3) Wasser, C.; Silva, F.; Rodríguez, E. *Experientia* **1990**, *46*, 500.

(4) Lytollis, W.; Scannell, R. T.; An, H.; Murty, V. S.; Reddy, K. S.; Barr, J. R.; Hecht, S. M. *J. Am. Chem. Soc.* **1995**, *117*, 12683.

(5) For a review on cannabis, see: Mechoulam, R.; McCallum, N. K.; Burstein, S. *Chem. Rev.* **1976**, *76*, 75.

(6) See, for instance: Baek, S.-H.; Srebnik, M.; Mechoulam, R. *Tetrahedron Lett.* **1985**, *26*, 1083.

(7) Mannila, E.; Talvitie, A. *Liebigs Ann. Chem.* **1993**, 1037.

(8) Thakkar, K.; Geahlen, R. L.; Cushman, M. *J. Med. Chem.* **1993**, *36*, 2950.

(9) (a) Yus, M.; Ramón, D. J. *J. Chem. Soc., Chem. Commun.* **1991**, 5398. (b) For a review, see: Yus, M. *Chem. Soc. Rev.* **1996**, 155. (c) For the last paper on an arene-catalyzed lithiation from our laboratory, see: Almena, J.; Foubelo, F.; Yus, M. *J. Org. Chem.* **1996**, *61*, 1859.

(10) Naphthalene or 4,4′-di-*tert*-butylbiphenyl (DTBB) are the most usual arene as electron transfer catalysts. For a comparative study on the use of both arenes, see: Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924.

(11) Alonso, E.; Guijarro, D.; Yus, M. *Tetrahedron* **1995**, *51*, 11457.

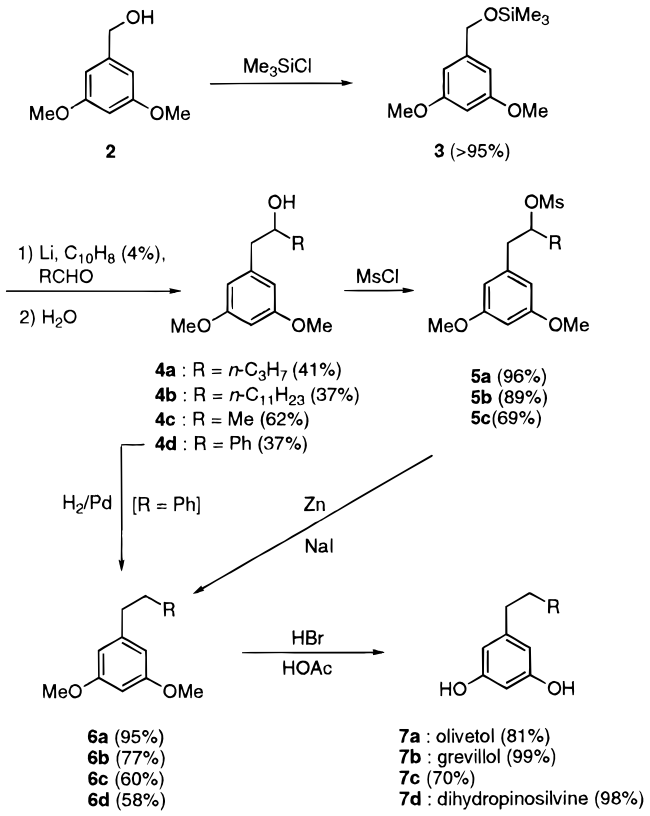
(12) Conventional methods involving halogen−lithium interchange are not useful for the preparation of allylic or benzylic lithium reagents due to the almost exclusive formation of Wurtz-type products. (a) See, for instance: Wakefield, B. J. *Organolithium Methods*; Academic Press: London, 1988; p 38. (b) For an alternative method using allylic or benzylic mesylates, see: Guijarro, D.; Mancheño, B.; Yus, M. *Tetrahedron* **1992**, *48*, 4593.

(13) For synthesis of 5-alkylresorcinols by construction of the aromatic ring,[13a−d] using 3,5-dimethoxybenzaldehyde[13e,f] or a Claisen rearrangement[13g] see, for example: (a) Marmor, R. S. *J. Org. Chem.* **1972**, *37*, 2901. (b) Foucla, A.; Teitel, S.; Prossi, A. *J. Org. Chem.* **1977**, *42*, 3456. (c) Stone, M. J.; Maplestone, R. A.; Rahman, S. K.; Williams, D. H. *Tetrahedron Lett.* **1991**, *32*, 2663. (d) Kotnis, A. S. *Tetrahedron Lett.* **1991**, *32*, 3441. (e) Krishnamurty, H. G.; Prasad, J. S. *Tetrahedron Lett.* **1975**, 2511. (f) See also refs 4 and 8. (g) Shono, T.; Matsumura, Y.; Tsubata, k.; Sugihara, Y. *J. Org. Chem.* **1979**, *44*, 4508.

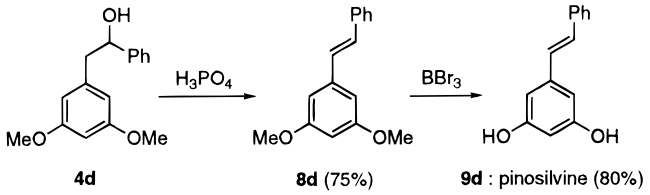
(14) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549.

S0022-3263(96)01062-6 CCC: $14.00

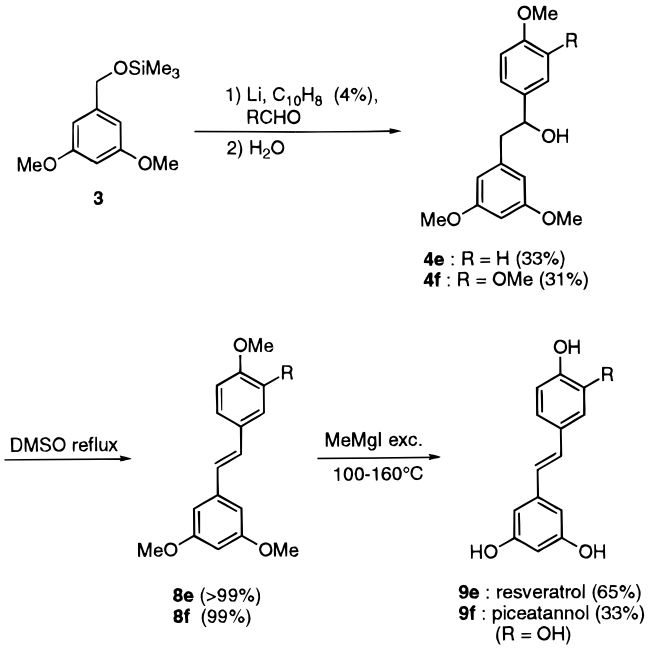
Scheme 1



Scheme 2



Scheme 3



reflux.[17] In the case of compound **4d**, the formation of the corresponding derivative **6d** was achieved by palladium-catalyzed hydrogenation in a mixture of methanol−water.[18] The last step (**6** → **7**) was performed by means of 45% hydrobromic acid and acetic acid under reflux[19] (Scheme 1).

Pinosilvine (**9d**) was prepared from compound **4d** by dehydration with 85% phosphoric acid under toluene reflux,[20] to give pinosilvine dimethyl ether (**8d**), which was demethylated by means of boron tribromide−dimethyl sulfide complex under 1,2-dichloroethane reflux[21] (Scheme 2).

Resveratrol and piceatannol were prepared starting from the same common material **3** using 4-methoxybenzaldehyde and 3,4-dimethoxybenzaldehyde, respectively, as electrophiles during the lithiation/condensation step at 0 °C, so the expected compounds **4e** and **4f** were isolated in moderate yield, after hydrolysis. These alcohols were dehydrated under DMSO reflux,[22] giving the corresponding *trans*-olefins **8e** and **8f**, respectively, which after final full demethylation with an excess of methylmagnesium iodide[23] (1:20 molar ratio) under heating at 100−160 °C gave resveratrol (**9e**) and piceatannol (**9f**) (Scheme 3).

Finally, we prepared combretastatin B-4 tetramethyl ether (**6f**) and combretastatin B-3 pentamethyl ether (**6g**) starting from the corresponding alkenes **8f** (see Scheme 3) and **8g** [prepared from commercially available 3,4,5-trimethoxybenzyl alcohol (**10**) by silylation (to give *O*-silyl alcohol **11**) followed by naphthalene-catalyzed lithiation in the presence of 3,4-dimethoxybenzaldehyde and final hydrolysis], respectively, by palladium-catalyzed hydrogenation in the presence of anhydrous ammonium formate under methanol reflux[24] (Scheme 4). The demethylation of compounds **6f** and **6g** tried by the different methods used in this work failed.[25]

Lastly, we applied the methodology described here to prepare other dimethylated 5-substituted resorcinols from the starting material **3**. Thus, when the naphthalene-catalyzed lithiation of compound **3** was carried out in the presence of Me_3SiCl, *t*-BuCHO, $CH_3(CH_2)_4CHO$, $4\text{-}Me_3SiOC_6H_4CHO$, $(CH_2)_5CO$, PhNCO, or PhCH=NPh under the reaction conditions described above for compound **4a**, the expected products **12a**−**g** were isolated after hydrolysis (Scheme 5 and Table 1).

In conclusion, the chemistry described in this paper offers an easy and versatile approach to a biologically

(15) Some attemps to improve yields [varying reaction temperature or a different catalyst (4,4'-di-*tert*-butylbiphenyl)] were unsuccessful. As side products we obtained in all reactions variable amounts (<30%) of the corresponding "reduced" system (3,5-dimethoxytoluene), resulting from a proton abstraction of the benzylic organolithium intermediate from the reaction medium (see, for instance: Bates, R. B.; Kroposki, L. M.; Potter, D. E. *J. Org. Chem.* **1972**, *37*, 560 as well as ref 12b). Concerning a possible *O*- to *C*-anionic silyl migration in the starting material **3**, we observed only in a few cases a small amount (<5%) of either the correponding alcohol **2** or the sililated species **12a** (we thank a referee for calling our attention to this possibility).

(16) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.

(17) Fujimoto, Y.; Tatsuno, T. *Tetrahedron Lett.* **1976**, 3325.

(18) Blaser, H. U. Reaction at Surfaces: Opportunities and Pitfalls for the Organic Chemist. In *Modern Synthetic Methods 1995*; Ernst, B., Leumann, C., Eds.; VCH: Weinheim, 1995; pp 181−257.

(19) Doxsee, K. M.; Feigel, M.; Stewart, K. D.; Canary, J. W.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1987**, *109*, 3098.

(20) Gil, J. F.; Ramón, D. J.; Yus, M. *Tetrahedron* **1994**, *50*, 7307.

(21) Williard, P. G.; Fryhle, C. B. *Tetrahedron Lett.* **1980**, *21*, 3731.

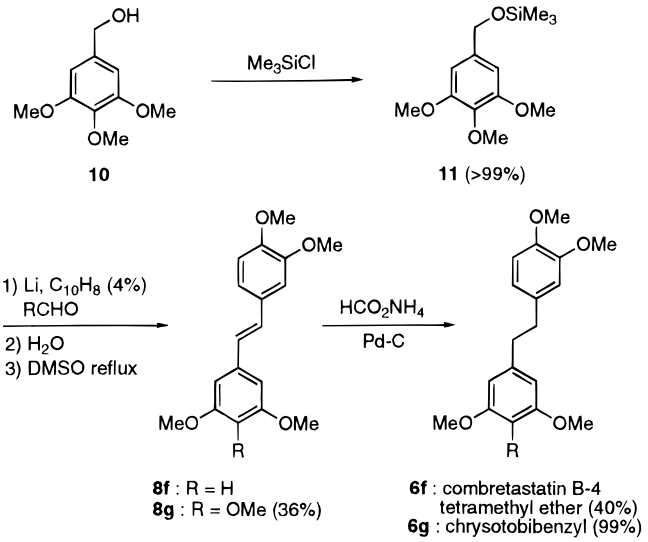
(22) Traynelis, V. J.; Hergenrother, W. L.; Livingston, J. R.; Valicenti, J. A. *J. Org. Chem.* **1962**, *27*, 2377.

(23) Wilds, A. L.; McCormack, W. B. *J. Am. Chem. Soc.* **1948**, *70*, 4127.

(24) Boyle, P. H.; Davis, A. P.; Dempsey K. J.; Hosken, G. D. *Tetrahedron: Asymmetry* **1995**, *6*, 2819.

(25) This behavior has been already observed in the demethylation of several compounds of type **6** or **7**: see, for instance, refs 4 and 8.

Scheme 4



Scheme 5

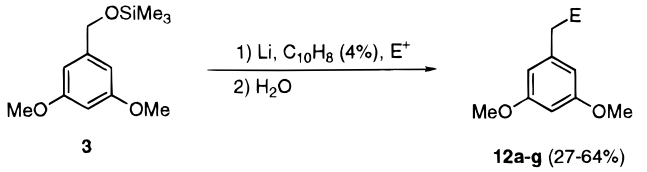
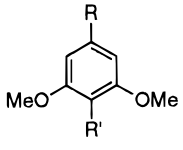


Table 1. Preparation of Compounds 12a−g

		product		
entry	electrophile E^+	no.	E	yield (%)[a]
1	Me_3SiCl	**12a**	Me_3Si	64
2	Bu^tCHO	**12b**	Bu^tCHOH	55
3	$Me(CH_2)_4CHO$	**12c**	$Me(CH_2)_4CHOH$	41
4	4-$Me_3SiOC_6H_4CHO$	**12d**	4-$Me_3SiOC_6H_4CHOH$	43
5	$(CH_2)_5CO$	**12e**	$(CH_2)_5COH$	52
6	PhNCO	**12f**	PhNHCO	27
7	PhCH=NPh	**12g**	PhCHNHPh	44

[a] Isolated yield after flash chromatography (silica gel, hexane/ethyl acetate).

interesting family of compounds, namely 5-substituted resorcinols. We are now studying the possibility of *o*-lithiation of compounds of type **6**[26] in order to prepare molecules of the general fomula **13**, which show high antibiotic activity.[27]



13

Experimental Section

General Methods. For general information see ref 28. Benzylideneaniline[29] and 4-(trimethylsiloxy)benzaldehyde[30] were prepared according to the literature procedure. ^1H and ^{13}C NMR spectra were recorded using $CDCl_3$ as solvent (unless otherwise stated). High resolution mass spectra were performed at the corresponding service at the University of Zaragoza. Compounds **11**,[31] **4e**,[7] **4f**,[7] **12a**,[32] **6a**,[13b] **6b**,[4] **6c**,[26a] **6d**,[26b] **7a**,[13d,e] **7b**,[4] **7c**,[26a] **7d**,[26b] **8d**,[35] **9d**,[8] **8e**,[7] **8f**,[7] **8g**,[34] **9e**,[8] **9f**,[8] **6f**[35] and **6g**,[36] which are partially described in the literature were fully characterized by spectroscopic means (IR, ^1H and ^{13}C NMR, and MS) and are included as supporting information.

General Procedure for the Preparation of *O*-Silylated Alcohols 3 and 11. To a solution of the corresponding alcohol (10 mmol) and triethylamine (20 mmol) in THF (20 mL) was dropwise added chlorotrimethylsilane (10 mmol) at 0 °C. After 1 h stirring at temperatures ranging between 0 and 20 °C the resulting mixture was hydrolyzed with water (10 mL) and extracted with ether (2 × 20 mL). The organic layer was washed with water (1 × 10 mL) and dried over anhyd Na_2SO_4. Solvents were evaporated (15 Torr), and the resulting residue contained the title compounds **3** and **11** (>95% yield; >90% pure by 300 MHz ^1H-NMR) were submitted to the lithiation/condensation step without further purification.

[(3,5-Dimethoxybenzyl)oxy]trimethylsilane (3): oil, R_f = 0.56 (hexane/ethyl acetate 6/1); t_R = 11.78 min; IR (film) 1610, 1461, 1250, 1155, 1100, 1054 cm^{-1}; ^1H NMR δ 0.16 (s, 9H), 3.78 (s, 6H), 4.64 (s, 2H), 6.35 (t, J = 2.4, 1H), 6.49 (d, J = 2.4, 2H); ^{13}C NMR δ −0.4, 55.25, 64.55, 99.05, 104.2, 143.5, 160.8; MS m/z 240 (M^+, 75%), 151 (100).

General Procedure for the Preparation of Compounds 4 and 12. To a green suspension of lithium powder (100 mg, 14 mmol) and naphthalene (10 mg, 0.08 mmol) in THF (5 mL) was added a solution of the corresponding *O*-silylated alcohol **3** or **11** (1 mmol) and the electrophile (1.2 mmol) in THF (2 mL) at −30 or 0 °C (see text) under argon for 5 min. Stirring was continued for 2 h, allowing the temperature to rise to 0 °C. The resulting mixture was then hydrolyzed with water (5 mL) and extracted with diethyl ether (2 × 20 mL) and the organic layer dried over anhyd Na_2SO_4. Solvents were evaporated (15 Torr), and the resulting residue was chromatographied (silica gel, hexane/ethyl acetate) to afford pure title compounds **4** and **12**. Yields are included in Scheme 1 and Table 1; analytical and spectroscopic data follow.

1,3-Dimethoxy-5-(2′-hydroxypentyl)benzene (4a): oil, R_f = 0.30 (hexane/ethyl acetate 2/1); t_R = 13.81 min; IR (film) 3403, 1606, 1463, 1206, 1151, 1066 cm^{-1}; ^1H NMR δ 0.94 (t, J = 6.7, 3H), 1.37−1.68 (m, 4H), 2.04 (br s, 1H), 2.57 (dd, J = 13.4, 8.5, 1H), 2.77 (dd, J = 13.4, 3.9, 1H), 3.72−3.86 (m with s, 7H), 6.35 (t, J = 2.1, 1H), 6.38 (d, J = 2.1, 2H); ^{13}C NMR δ 14.05, 18.95, 38.95, 44.4, 55.25, 72.2, 98.4, 107.35, 140.95, 160.9; MS m/z 224 (M^+, 21%), 152 (100); HRMS calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1395.

1,3-Dimethoxy-5-(2′-hydroxytridecyl)benzene (4b): oil, R_f = 0.18 (hexane/ethyl acetate 6/1); t_R = 18.96 min; IR (film) 3414, 3004, 1606, 1464, 1206, 1152, 1069 cm^{-1}; ^1H NMR δ 0.88 (t, J = 6.7, 3H), 1.26−1.53 (m, 20H), 2.56 (dd, J = 13.4, 8.7, 1H), 2.75 (dd, J = 13.4, 4.0, 1H), 3.78 (m with s, 7H), 6.34 (t, J = 2.1, 1H), 6.37 (d, J = 2.1, 2H); ^{13}C NMR δ 14.1, 22.7, 25.75, 29.35, 29.6, 29.65, 31.9, 36.85, 44.4, 55.25, 72.5, 98.4, 107.3, 141.0, 160.9; MS m/z 336 (M^+, 3%), 152 (100); HRMS calcd for $C_{21}H_{36}O_3$ 336.2664, found 336.2648.

1,3-Dimethoxy-5-(2′-hydroxypropyl)benzene (4c): oil, R_f = 0.31 (hexane/ethyl acetate 2/1); t_R = 11.81 min; IR (film) 3416, 1608, 1461, 1206, 1150, 1069 cm^{-1}; ^1H NMR δ 1.25 (d, J

(26) (a) Durrani, A. A.; Tyman, J. H. P. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1658. (b) Eicher, T.; Tiefensee, K.; Döing, R.; Rigobert, P. *Synthesis* **1991**, 98.
(27) Mitscher, L. A.; Park, Y. H.; Al-Shamma, A.; Hudson, P. B.; Haas, T. *Phytochemistry* **1981**, *21*, 781.
(28) Almena, J.; Foubelo, F.; Yus, M. *J. Org. Chem.* **1994**, *59*, 3210.
(29) Sandler, S. R.; Karo, W. *Organic Functional Group Preparation*; Academic Press: New York, 1971; Vol. 12-II, p 255.
(30) Kim, H. J.; Jackson, W. R. *Tetrahedron: Asymmetry* **1994**, *5*, 1541.
(31) Midgley, J. M.; Millership, J. S.; Whalley, W. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1384.
(32) Ali, A. S.; Liepa, A. J.; Thomas, M. D.; While, J. S.; Winzenberg, K. N. *Aust. J. Chem.* **1994**, *47*, 1205. *Chem. Abstr.* **1994**, *121*, 133567d.
(33) Yasuda, M.; Isami, T.; Kubo, J.; Mizutani, M.; Yamashita, T.; Shima, K. *J. Org. Chem.* **1992**, *57*, 1351.
(34) Lin, C. M.; Singh, S. B.; Chu, P. S.; Dempcy, R. O.; Schmidt, J. M.; Pettit, G. R.; Hamel, E. *Mol. Pharmacol.* **1988**, *34*, 200. *Chem. Abstr.* **1989**, *110*, 68959q.
(35) Talvitie, A.; Mannila, E.; Kolehmainen, E. *Liebigs. Ann. Chem.* **1992**, 399.
(36) (a) Ma, G. X.; Xu, L. S.; Wang, Z. T.; Kickuchi, T. *Yaoxue Xuebao* **1994**, *29*, 763. *Chem. Abstr.* **1995**, *112*, 209764j. (b) Medarde, M.; Pelaez-Lamamie de Clairac, R.; Ramos, A. C.; Caballero, E.; Lopez, J. L.; Gravalos, D. G.; San Feliciano, A. *Med. Chem. Lett.* **1995**, *5*, 229. *Chem. Abstr.* **1995**, *122*, 239431r.

= 6.1, 3H), 2.61 (dd, J = 13.2, 8.2, 1H), 2.74 (dd, J = 13.2, 4.6, 1H), 3.78 (s, 6H), 3.96−4.05 (m, 1H), 6.34−6.37 (m, 3H); ^{13}C NMR δ 22.75, 46.1, 55.25, 68.7, 98.45, 107.3, 140.8, 160.9; MS m/z 196 (M^+, 41%), 152 (100); HRMS calcd for $C_{11}H_{16}O_3$ 196.1099, found 196.1095.

1,3-Dimethoxy-5-(2′-hydroxy-2′-phenylethyl)benzene (4d): oil, R_f = 0.29 (hexane/ethyl acetate 2/1); t_R =15.88 min; IR (film) 3439, 3085, 3061, 3028, 1597, 1461, 1205, 1151, 1067 cm^{-1}; ^{1}H NMR δ 2.18 (s, 1H), 2.89 (dd, J = 13.6, 8.2, 1H), 2.97 (dd, J = 13.6, 4.9, 1H), 3.72 (s, 6H), 4.86 (dd, J = 8.2, 4.9, 1H), 6.33, 7.33−7.39 (s and m respectively, 3H and 5H, respectively); ^{13}C NMR δ 46.35, 55.2, 75.0, 98.7, 107.4, 125.85, 127.55, 128.35, 140.25 143.7, 160.8; MS m/z 258 (M^+, 10%), 152 (100); HRMS calcd for $C_{16}H_{18}O_3$ 258.1256, found 258.1260.

1,3-Dimethoxy-5-(2′,2′-dimethyl-3′-hydroxybutyl)benzene (12b): oil, R_f = 0.29 (hexane/ethyl acetate 4/1); t_R = 13.46 min; IR (film) 3551, 1607, 1463, 1206, 1153, 1069 cm^{-1}; ^{1}H NMR δ 0.99 (s, 9 H), 2.40 (dd, J = 13.4, 10.8, 1H), 2.85 (dd, J = 13.4, 1.5, 1H), 3.43 (m, 1H), 3.77 (s, 6 H), 6.33 (t, J = 2.2, 1H), 6.39 (d, J = 2.2, 1H); ^{13}C NMR δ 25.8, 34.7, 38.75, 55.2, 80.3, 98.35, 107.15, 142.2, 160.9; MS m/z 238 (M^+, 40%), 152 (100); HRMS calcd for $C_{14}H_{22}O_3$ 238.1569, found 238.1570.

1,3-Dimethoxy-5-(2′-hydroxyheptyl)benzene (12c): oil, R_f = 0.17 (hexane/ethyl acetate 6/1); t_R = 14.66 min; IR (film) 3420, 1596, 1463, 1206, 1151, 1069 cm^{-1}; ^{1}H NMR δ 0.89 (t, J = 6.7, 3H), 1.26−1.66 (m, 9H), 2.56 (dd, J = 13.4, 8.5, 1H), 2.77 (dd, J = 13.4, 4.0, 1H), 3.78 (m, 7H), 6.34 (t, J = 2.1, 1H), 6.37 (d, J = 2.1, 2H); ^{13}C NMR δ 13.95, 22.55, 25.35, 31.75, 36.7, 44.3, 55.1, 72.4, 98.25, 107.25, 140.95, 160.75; MS m/z 252 (M^+, 33%), 152 (100); HRMS calcd for $C_{15}H_{24}O_3$ 252.1725, found 252.1735.

2-(3,5-Dimethoxyphenyl)-1-(4-hydroxyphenyl)ethanol (12d): white solid, R_f = 0.32 (hexane/ethyl acetate 1/1); mp 148−149 °C (hexane/MeOH); t_R = 18.44 min; IR (KBr) 3416, 3198, 1606, 1517, 1202, 1143, 1067 cm^{-1}; ^{1}H NMR δ (CD_3COCD_3) 2.81−2.95 (m, 2H), 3.71 (s, 6H), 4.04 (d, J = 3.7, 1H), 4.77−4.82 (m, 1H), 6.28, 6.35 (t and d respectively, J = 2.0 Hz, 1H and 2H, respectively), 6.76, 7.18 (2d, J = 8.5, 4H), 8.18 (br s, 1H); ^{13}C NMR δ (CD_3COCD_3) 47.35, 55.35, 75.15, 98.7, 108.35, 115.5, 128.1, 137.3, 142.35, 157.2, 161.45; MS m/z 256 (M^+ −18, 100%). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.04; H, 6.62. Found: C, 69.59; H, 6.68.

1-(3,5-Dimethoxybenzyl)cyclohexanol (12e): oil, R_f = 0.29 (hexane/ethyl acetate 4/1); t_R = 14.97 min; IR (film) 3504, 1596, 1462, 1205, 1150, 1062 cm^{-1}; ^{1}H NMR δ 1.21−1.75 (m, 11H), 2.68 (s, 2H), 3.78 (s, 6H), 6.37 (s, 3H); ^{13}C NMR δ 22.1, 25.75, 37.35, 48.95, 55.2, 71.0, 98.3, 108.6, 139.35, 160.5; MS m/z 250 (M^+, 12%), 152 (100); HRMS calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1570.

(3,5-Dimethoxyphenyl)-*N*-phenylacetamide (12f): oil, R_f = 0.39 (hexane/ethyl acetate 1/1); t_R = 17.31 min; IR (film) 3303, 1662, 1597, 1205, 1154, 1066 cm^{-1}; ^{1}H NMR δ 3.67 (s, 2H), 3.80 (s, 6H), 6.43, 6.47 (2m, 1H and 2H, respectively), 7.28−7.53 (m, 5H); ^{13}C NMR δ 45.2, 55.4, 99.6, 107.5, 119.8, 124.45, 128.95, 136.5, 137.55, 161.45, 168.75; MS m/z 271 (M^+, 68%), 152 (100); HRMS calcd for $C_{16}H_{17}NO_3$ 271.1208, found 271.1205.

2-(3,5-Dimethoxyphenyl)-*N*,1-diphenylethylamine (12g): oil, R_f = 0.56 (hexane/ethyl acetate 2/1); t_R = 19.91 min; IR (film) 3404, 3052, 3023, 1601, 1505, 1204, 1151, 1067 cm^{-1}; ^{1}H RMN δ 2.93 (dd, J = 13.8, 8.2, 1H), 3.08 (dd, J = 13.8, 5.8, 1H), 3.71 (s, 6H), 4.16 (br s, 1H), 4.56 (dd, J = 8.2, 5.8, 1H), 6.25 (d, J = 2.1, 2H), 6.32 (t, J = 2.1, 1H), 6.46 (d, J = 7.6, 2H), 6.60 (t, J = 7.6, 1H), 7.05 (t, J = 7.6, 2H), 7.23−7.36 (m, 5H); ^{13}C NMR δ 45.35, 55.15, 58.95, 98.7, 107.2, 113.6, 117.4, 126.45, 127.0, 128.5, 128.95, 139.8, 143.35, 147.2, 160.75; MS m/z 333 (M^+, 1%), 182 (100); HRMS calcd for $C_{22}H_{23}NO_2$ 333.1729, found 333.1722.

General Procedure for the Preparation of Mesylates 5. To a solution of the corresponding alcohol **4** (1 mmol) and triethylamine (1.25 mmol) in THF (5 mL) at 0 °C was dropwise added methanesulfonyl chloride (1.2 mmol) over a period of 5 min. Stirring for additional 60 min completed reaction. The reaction mixture was hydrolyzed with water (10 mL) and extracted with ether (2 × 20 mL). The organic layer was washed with water (1 × 10 mL) and dried over anhyd Na_2SO_4. Solvents were evaporated (15 Torr), and the resulting residue contained the title compounds **5** (>90% pure by 300 MHz ^{1}H-NMR) which were submitted to the next step. Yields are included in Scheme 1; analytical and spectroscopic data follow.

1,3-Dimethoxy-5-[2′-(methanesulfonyloxy)pentyl]benzene (5a): oil, R_f = 0.34 (hexane/ethyl acetate 2/1); IR (film) 1596, 1463, 1350, 1206, 1172, 1152, 1059 cm^{-1}; ^{1}H NMR δ 0.95 (t, J = 7.2, 3H), 1.39−1.75 (m, 4H), 2.60 (s, 3H), 2.91 (d, J = 6.4, 2H), 3.78 (s, 6H), 4.80−4.89 (m, 1H), 6.35 (t, J = 2.1, 1H), 6.39 (d, J = 2.1, 2H); ^{13}C NMR δ 13.75, 18.45, 36.95, 38.0, 41.45, 55.35, 84.7, 98.85, 107.65, 139.1, 160.95; MS m/z 302 (M^+, 55%), 152 (100).

1,3-Dimethoxy-5-[2′-(methanesulfonyloxy)tridecyl]benzene (5b): oil, R_f = 0.68 (hexane/ethyl acetate 2/1); IR (film) 1597, 1465, 1351, 1206, 1174, 1064 cm^{-1}; ^{1}H NMR δ 0.88 (t, J = 6.7, 3H), 1.25−1.49, 1.63−1.88 (2m, 20H and 2H, respectively), 2.59 (s, 3H), 2.91 (d, J = 6.7, 2H), 3.78 (s, 6H), 4.78−4.87 (m, 1H), 6.33−6.40 (m, 3H); ^{13}C NMR δ 14.1, 22.65, 25.05, 29.3, 29.4, 29.5, 29.55, 31.85, 34.85, 37.95, 41.3, 45.75, 55.25, 55.3, 85.0, 98.8, 107.6, 139.1, 160.9; MS m/z 414 (M^+, 12%), 152 (100); HRMS calcd for $C_{22}H_{38}O_5S$ 414.2440, found 414.2454.

1,3-Dimethoxy-5-[2′-(methanesulfonyloxy)propyl]benzene (5c): white solid, R_f = 0.31 (hexane/ethyl acetate 2/1); mp 44−45 °C (hexane/ether); IR (KBr) 3016, 1597, 1469, 1345, 1204, 1174, 1155, 1063 cm^{-1}; ^{1}H NMR δ 1.45 (d, J = 6.1, 3H), 2.62 (s, 3H), 2.82 (dd, J = 14.0, 5.5, 1H), 2.94 (dd, J = 14.0, 7.8, 1H), 3.77 (s, 6H), 4.85−4.96 (m, 1H), 6.35 (t, J = 2.2, 1H), 6.38 (d, J = 2.2, 2H); ^{13}C NMR δ 21.35, 37.75, 43.1, 55.2, 81.0, 98.75, 107.45, 138.85, 160.85; MS m/z (M^+, 66%), 178 (100), 151 (100). Anal. Calcd for $C_{12}H_{18}O_5S$: C, 52.54; H, 6.62; S, 11.66. Found: C, 53.20; H, 6.73; S, 10.69.

General Procedure for the Preparation of Compounds 6a−c. A mixture of mesylate **5** (1 mmol), sodium iodide (5 mmol), zinc powder (10 mmol), and glyme (10 mL) under argon atmosphere was refluxed for 8 h. The reaction mixture was filtered to remove excess sodium iodide and zinc powder. Then, the filtrate was poured into water (10 mL) and extracted with ether (2 × 20 mL). The organic layer was washed with brine, dried over sodium sulfate, and concentrated under reduced pressure (15 Torr). The residual oil was chromatographed (silica gel, hexane/ethyl acetate) to afford pure title compounds **6a−c**. Yields are included in Scheme 1.

Preparation of 1,3-Dimethoxy-5-(2′-phenylethyl)benzene (6d). A mixture of alcohol **4d** (1 mmol) and palladium on activated charcoal (60 mg) in a mixture of methanol−water (5 mL/3 mL) was stirred under atmospheric pressure of hydrogen during 36 h. The mixture was filtered through a plug of Celite with ether to remove the catalyst. Then the filtrate was poured into water (5 mL) and extracted with ether (2 × 20 mL). The organic layer was washed with brine, dried over sodium sulfate, and concentrated under reduced pressure (15 Torr). The residual oil was chromatographed (silica gel, hexane/ethyl acetate) to afford pure **6d**. Yield is included in Scheme 1.

General Procedure for the Preparation of Cathecols 7a−d. A solution of methyl ether **6** (1 mmol) in 3 mL of 45% hydrobromic acid and 3 mL of glacial acetic acid was refluxed for 3 h. The reaction mixture was hydrolyzed with water (15 mL) and extracted with ether (2 × 20 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure (15 Torr). The residual oil was chromatographed (silica gel, hexane/ethyl acetate) to afford pure title **7**. Yields are included in Scheme 1.

Preparation of 1,3-Dimethoxy-5-(2′-phenylethenyl)-benzene (8d). A mixture of compound **4d** (1 mmol) and 85% phosphoric acid 0.5 mL in toluene (5 mL) was refluxed for 2 h. The resulting mixture was extracted with diethyl ether (2 × 20 mL) and the organic layer dried over anhyd Na_2SO_4 and evaporated (15 Torr). The obtained residue was purified by column chromatography (silica gel, hexane/ethyl acetate), yielding the pure title compound **8d**. Yield is included in Scheme 2.

Preparation of (*E*)-1-(1,3-Dihydroxyphenyl)-2-phenylethene (*Pinosylvine*, 9d). To a 100 mL flask under an atmosphere of argon was added approximately 30 mL of 1,2-

dichloroethane and 7.74 mmol of boron tribromide−methyl sulfide complex. To this solution was added dimethyl ether **8d** (1 mmol). The reaction was stirred at reflux and monitored by GC. When the starting material had disappeared, the reaction mixture was hydrolyzed by adding 30 mL of water, stirring for 20 min, and diluting with ether. The organic phase was separated and washed with 1 M $NaHCO_3$, and the phenol was subsequently taken up with 1 N NaOH (3 × 20 mL). The combined NaOH washings were acidified, the product was extracted into ether and dried over anhyd Na_2SO_4, and the solvent was removed in vacuo (15 Torr). The obtained residue was purified by column chromatography (silica gel, hexane/ethyl acetate), yielding the pure title compound **9d**. Yield is included in Scheme 2.

General Procedure for the Preparation of Compounds 8e−g. A solution of corresponding alcohol **4e−g** (1 mmol) in dimethyl sulfoxide (2 mL) was heated in an oil bath at 160−185 °C under a reflux condenser for 2 h. The resulting mixture was cooled, and the olephine was isolated by distillation off DMSO (130 °C, 0.1 Torr). The residue was purified by column chromatography (silica gel, hexane/ethyl acetate), yielding the pure title compound **8e−g**. Yields are included in Schemes 3 and 4.

General Procedure for the Preparation of Phenols 9e and 9f. Methyl iodide (87.8 mmol) and magnesium (23.4 mmol) were stirred together in 24 mL of dry ether until the initial exothermic reaction had subsided. A solution containing 1 mmol of **8e** or **8f** in 24 mL of dry ether was added dropwise, and then the solution was concentrated under diminished pressure. The residue was heated to 100 °C while still under vacuum (aspirator) and was then heated at 160 °C for 15 min under argon. The cooled reaction mixture treated slowly with 20 mL of 10% aqueous NH_4Cl and extracted with three 20-mL portions of ether. The combined organic extract was washed with 20 mL of water and 20 mL of brine. The dried ($MgSO_4$) organic phase was concentrated under diminished pressure. The residue was purified by flash chromatography on a silica gel column yielding the pure title compounds **9e** or **9f**. Yields are included in Scheme 3.

General Procedure for the Preparation of Compounds 6f and 6g. Alkene **8f** or **8g** (100 mg) was added under argon to a reaction flask containing palladium on activated charcoal (100 mg) covered by anhydrous methanol (3 mL). Ammonium formate (6.9 mmol) was then added and the mixture refluxed for 2 h. The catalyst was removed by filtering off the reaction mixture through a plug of Celite and the solvent was removed under reduced pressure. The obtained residue was purified by column chromatography (silica gel, hexane/ethyl acetate) yielding the pure title compounds **6f** or **6g**. Yields are included in Schemes 3 and 4.

Acknowledgment. This work was financially supported by the DGICYT (no. PB94-1514) from the spanish Ministerio de Educación y Ciencia (MEC). D.J.R. thanks the MEC for a fellowship.

Supporting Information Available: Copies of ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra of new compounds lacking microanalysis (**3, 4a, 4b, 4c, 4d, 12b, 12c, 12e, 12f, 12g, 5a, 5b**), as well as physical and spectroscopic data for compounds **11**, **4e**, **4f**, **12a**, **6a**, **6b**, **6c**, **6d**, **7a**, **7b**, **7c**, **7d**, **8d**, **9d**, **8e**, **8f**, **8g**, **9e**, **9f**, **6f**, and **6g** (28 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.

JO9610624