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Hydroxyl-Directed Regioselective Monodemethylation of Polymethoxyarenes

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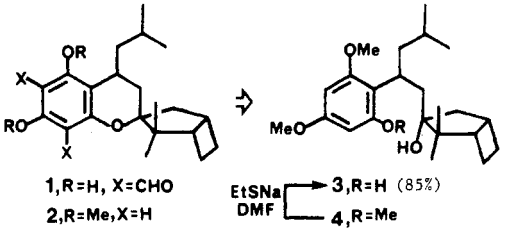
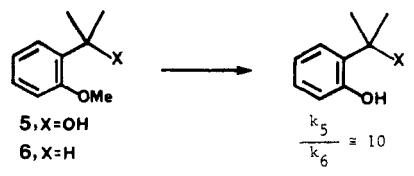
Methoxyl groups ortho to β-hydroxyethyl or γ-hydroxypropyl substituents in polymethoxybenzene derivatives were regioselectively demethylated with sodium thioethoxide in *N,N*-dimethylformamide. Methoxydihydrobenzofurans or methoxychromans were produced by cyclization of the monodemethylated β-hydroxyethyl or γ-hydroxypropyl derivatives, respectively.

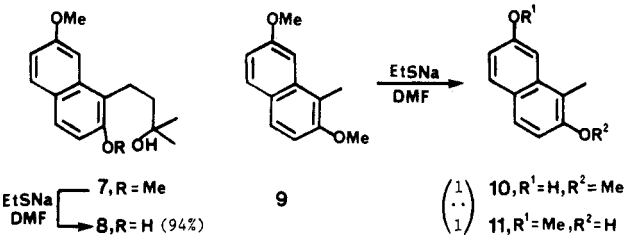
We recently achieved total syntheses of dialdehydes of structure **1**[1] which had been presumed[2] to correspond to robustadials, natural products isolated from *Eucalyptus robusta*. Our syntheses involved cyclization of phenol **3** to provide chroman intermediate **2**. Fortunately we found that monodemethylation of the trimethoxybenzene precursor **4** with sodium thioethoxide in *N,N*-dimethylformamide[3] was highly regioselective. Although a statistical



advantage of 66:33 for demethylation of a methoxyl ortho vs. para to the alkyl side chain could be anticipated, ortho demethylation product **4** was isolated in 85% yield. This favorable selectivity appeared to result from the regiodirecting influence of the remote hydroxyl group of the ortho hydroxyalkyl substituent. Previously, an ortho hydroxyalkyl substituent in **5** was shown to accelerate demethylation under these conditions by a factor of about 10 relative to demethylation of **6**.[4] Even more pertinent is the regioselective demethylation of dimethoxynaphthalene **7**



which produces **8** in 94% isolated yield.[5] The crucial role of the remote hydroxyl group in **7** was underscored by the demethylation of **9** under the same reaction conditions that nonselectively generates equal amounts of the isomeric mononaphthols **10** and **11**.[5] Since methyl ethers are important protecting groups,[6] a new general approach to regiocontrolled monodemethylation of polymethoxyarenes would be valuable for organic synthesis. We now report that such regiodirecting effects of remote hydroxyl groups are quite general.



Results and Discussion

Dimethoxybenzenes. The (polymethoxyaryl)alkanols **4** and **7** both incorporate tertiary hydroxyl groups appended to the arene ring by a three-carbon bridge. The (dimethoxyphenyl)alkanols **12d-14d** were prepared by reduction of the corresponding (dimethoxyphenyl)alkanoic acids with lithium aluminum hydride (see Experimental Section) to determine whether a primary hydroxyl group can exert a similar regiodirecting influence. In each case monodemethylation of these (dimethoxyphenyl)alkanols with sodium thioethoxide in *N,N*-dimethylformamide provided mixtures of monophenols in which demethylation of the methoxy group ortho to the alkanol substituent predominates. This regioselectivity was confirmed by conversion of each of the major demethylation products **12o-14o** into the corresponding cyclic ethers **12c-14c** by

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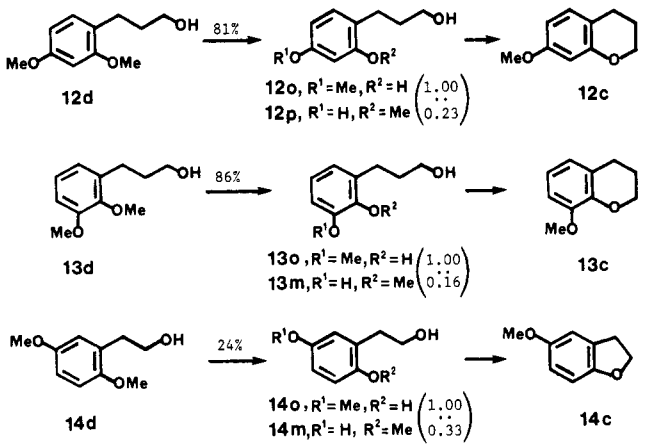
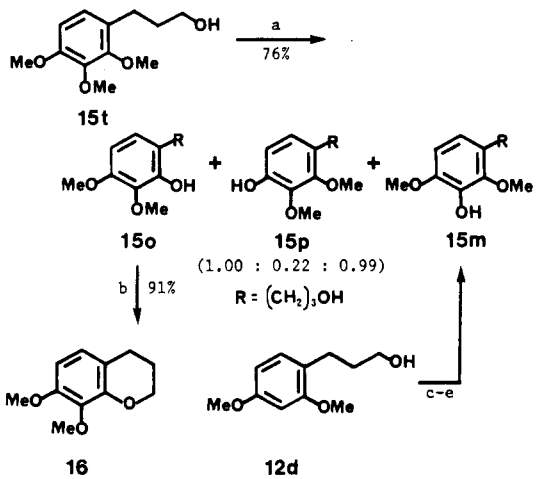


treatment with diethyl azodicarboxylate and triphenylphosphine.[7] Thus, a primary hydroxyl group appended to the benzene ring by a three-carbon chain favors demethylation of the ortho over the para methoxy group in **12d** by more than 4 to 1, and demethylation of the ortho over the meta methoxy group in **13d** by more than 6 to 1. A primary hydroxyl group appended to the benzene ring by a two-carbon chain favors demethylation of the ortho over the meta methoxy group in **14d** by 3:1.

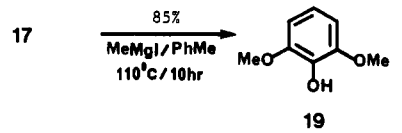
Trimethoxybenzenes. A more complex situation is encountered with the unsymmetrical trimethoxybenzene derivative **15t**. Treatment of **15t** with sodium thioethoxide in *N,N*-dimethylformamide produces three monophenols.



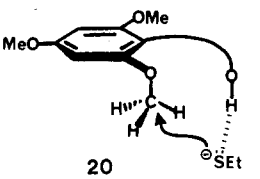
(a) EtSNa/DMF 115 °C/4 h; (b) DEAD/Ph_3P/THF; (c) DHP/PPTS/CH_2Cl_2; (d) BuLi/TMEDA/Et_2O, then $B(OMe)_3$, then H_2O_2/HOAc; (e) PPTS/EtOH

The structure of the product of ortho demethylation, **15o**, was established by cyclization to dimethoxychroman **16** upon treatment with diethyl azodicarboxylate and triphenylphosphine.[7] The structure of the other major demethylation product was shown to be **15m** by unambiguous synthesis from the dimethoxybenzene **12d**. Thus, **12d** was lithiated regioselectively[8] and the resulting aryllithium employed to arylate methyl borate.[9] Oxidative cleavage of the carbon–boron bond provided monophenol **15m**. The only remaining dimethoxy phenol structure, **15p**, is assigned to the minor demethylation product from **15t**. Thus, as for dimethoxybenzene **12d** above, a primary hydroxyl group appended to the benzene ring by a three-carbon chain favors demethylation of the ortho over the para methoxy group in **15t** by more than 4:1. However, the meta methoxy substituent in **15t** exhibits an abnormal proclivity toward demethylation compared with the meta methoxy substituent in the dimethoxybenzene **13d**. Previously, 1,2,3-trimethoxybenzene (**17**) was shown to readily

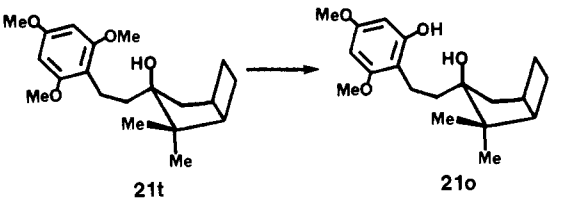
undergo bisdemethoxylation, affording a high yield of **18** upon treatment with sodium thioethoxide in *N,N*-dimethylformamide.[3b] There is precedent for an abnormal proclivity for the central methoxyl group in **17** toward nucleophilic attack resulting in demethylation. Thus, a high yield of monophenol **19** is produced upon treatment of **17** with methylmagnesium iodide in boiling toluene.[10] Perhaps the phenolate anion corresponding to **19** is an especially good nucleofuge owing to the relief of strain which accompanies its generation by cleavage of a C–O bond in 17.



Presumably a remote hydroxyl group directs the attack by a thioethoxide nucleophile by hydrogen bonding as suggested in **20**. Of course, there is also a 2:1 statistical



preference for ortho demethylation of symmetrical trimethoxybenzenes such as **21t** which in combination with the regiodirecting influence of a remote hydroxyl group can result in highly regioselective demethylations. Our synthesis of **21t** is described in the Experimental Section. Treatment of **21t** with sodium thioethoxide in *N,N*-dimethylformamide afforded monodemethylation product **21o** in 93% isolated yield. The operation of the statistical factor is clearly evident in the demethylation of **22t** which lacks a stereodirecting hydroxyl group. The products **22o** and **22p** of ortho and para demethylation are produced in exactly the 2:1 ratio expected statistically. In dramatic contrast, incorporation of a hydroxyl group at the remote end of the ethyl substituent of **22t** as in **23t** results in isolation of ortho demethylation product **23o** in 96% yield. No para demethylation product **23p** was isolated, and its yield must be less than 4%. Even a hydroxyl group separated from the aromatic ring by a four-carbon chain may exert a regiodirecting effect on demethylations with sodium



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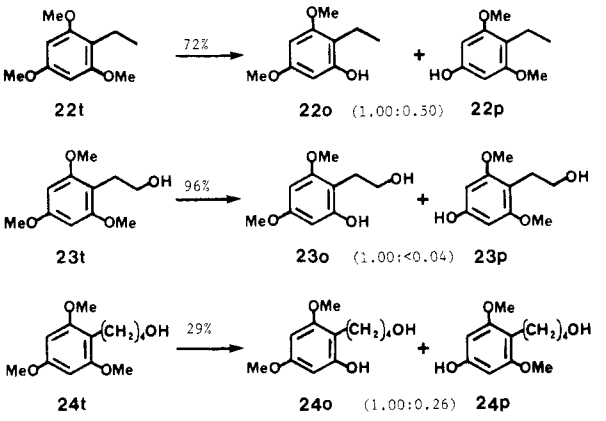
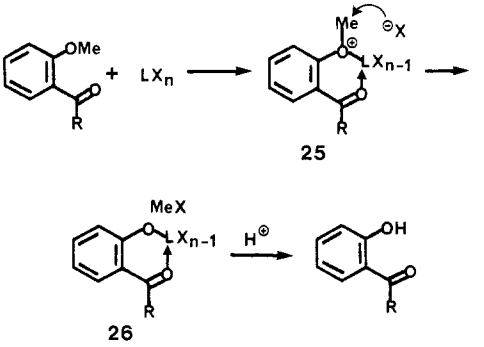


thioethoxide. The yield of ortho demethylation product **24o** was four times the yield of para demethylation product **24p** upon treatment of **24t** with sodium thioethoxide in *N,N*-dimethylformamide.

Regioselective demethylation of polymethoxyarenes is an important process for organic synthesis, and several regiodirecting substituent effects have been identified. As mentioned above, the central methoxyl group in 1,2,3-trimethoxybenzene derivatives can be selectively demethylated with methylmagnesium iodide.[10] Similarly regioselective demethylations, which occur under the influence of either protic[11] or Lewis acids,[12] have been attributed to "the enhanced basicity of the central methoxyl as it is sterically twisted out of the plane of the benzene ring".[11e] Methoxyl groups flanked by one methoxyl and one alkyl substituent show a similar proclivity toward demethylation with iodotrimethylsilane[13a,c] or boron trichloride.[13b] Selective demethylation of the most sterically crowded methoxyl group by protic acids may also account for the behavior of several complex systems containing acyl[14] or imino[15] (i.e., isoquinolines, dihydroisoquinolines) as well as several adjacent methoxyl substituents. For less crowded systems a para alkoxy substituent may decrease the basicity of a methoxyl oxygen, thus favoring demethylation of a meta methoxyl group with iodotrimethylsilane.[16]

A more complicated situation is encountered with the effects of acyl substituents. Several examples suggest that a conjugated (e.g., ortho or para) carbonyl[17] or imino[18] substituent *decreases* the reactivity of a methoxyl group toward demethylation by *protic acids* although this substituent effect has exceptions[19] especially if the methoxyl group para to the acyl substituent is flanked by two methoxyl groups.[14a,c] In remarkable contrast, a conjugated para carbonyl substituent can favor demethylation of a methoxyl group by *Lewis acids*,[20] but this regioselectivity can be reversed by changing the substrate–Lewis acid ratio.[20b,c] The most widely exploited substituent effect for selective demethylation of polymethoxybenzene derivatives is the ortho-directing influence of acyl substituents in demethylations induced by Lewis acid.[21] This regiodirecting influence is considered to depend upon coordination of $^{+}LX_{n-1}$ with two oxygen atoms in a six-membered ring as in **25**. With most Lewis acids, i.e., $AlCl_3$, MgI_2,



BCl_3, and BBr_3, the putative intermediate **26** is not isolated. With $BF_3{\cdot}OEt_2$, difluoroboron chelates **26** can be readily isolated and converted into phenols by brief treatment with hot methanol.[21u,v] Selective demethylation by boron trichloride of methoxyl groups adjacent to a phenolic substituent[22] probably involves initial formation of phenoxyborane **27**. Selective demethylation is then fostered by coordination of boron with two oxygen atoms in a five-membered ring as in **28**, leading to catechol borane intermediate **29** which affords a catechol upon protonolytic workup.

Regioselective demethylations have been achieved by using sulfur,[3-5,23] selenium,[24] nitrogen,[25] hydride,[26] or

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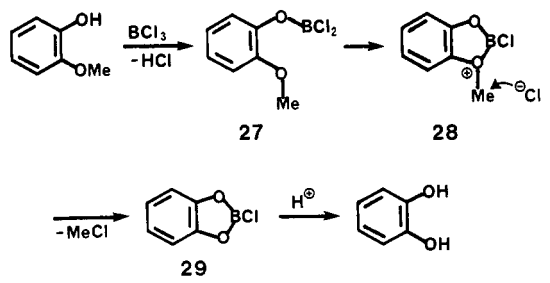

cyanide[27] nucleophiles. The regiodirecting influence of ortho hydroxyalkyl substituents on thioethoxide-induced demethylations seems most closely related to the effects of ortho acyl or phenol substituents on Lewis acid induced demethylations. These processes involve a temporary bridge between the regiodirecting and methoxyl substituents. The present study shows that the regiodirecting influence of ortho hydroxyalkyl substituents is remarkably versatile. While high regioselectivity is found with ortho β-hydroxyethyl or γ-hydroxypropyl substituents, some selectivity is engendered even with a δ-hydroxybutyl substituent. It seems reasonable to anticipate that a remote hydroxyl group could direct the attack by other nucleophiles, especially selenides, in a similar fashion as that envisioned by **20** for thioethoxide.

Experimental Section

All reactions were run under an atmosphere of dry nitrogen or argon. Reactions requiring anhydrous conditions were performed in flame-dried glassware which was cooled under nitrogen. The organic extracts were dried over anhydrous $MgSO_4$. Thin layer chromatography (TLC) and preparative TLC were performed on glass plates coated with 0.25 mm, 0.5 mm, or 2.0 mm of silica gel (Kieselgel $60F_{254}$, E. Merck). Flash chromatography was performed on 230–400-mesh silica gel 60. Preparative high performance liquid chromatography (HPLC) was performed by using a Waters system consisting of a Waters M-6000A or 590 solvent delivery system and a Waters U6K injector. Column elutants were monitored with a Waters differential refractometer R401. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on an Varian XL-200 spectrometer in $CDCl_3$ solutions unless otherwise noted. Chemical shifts are reported in units, parts per million (ppm) on the δ scale relative to chloroform (δ 7.236). Splitting patterns are designated as s (singlet); d (doublet), t (triplet), q (quartet), br (broad), and quin (quintet). Coupling constants are reported in hertz (Hz). Mass spectra were obtained on an AEI MS30 double beam mass spectrometer at an ionizing current of 3 A and ionizing voltage of 30–45 eV. Microanalyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, MI.

Preparation of (Hydroxyalkyl)polymethoxybenzene Derivatives. 3-(2,4-Dimethoxyphenyl)propanol (12d). A solution of 2,4-dimethoxycinnamic acid (525 mg, 2.52 mmol) in EtOH (25 mL) was hydrogenated by using 5% Pd/C (100 mg) as catalyst. The catalyst was filtered off and EtOH was removed under reduced pressure to afford 3-(2,4-dimethoxyphenyl)propionic acid (520 mg), which without further characterization was reduced further. A solution of $LiAlH_4$ in Et_2O (3 mL of 1 M, 3 mmol) was added dropwise to a magnetically stirred solution of the above acid (520 mg, 2.47 mmol) in THF (6 mL). The reaction mixture was stirred at room temperature for 1 h and then quenched by adding successively H_2O (120 μL), 15% aqueous NaOH (120 μL), and H_2O (360 μL) with vigorous stirring and cooling. The granular white precipitate, after filtration, was washed throughly with THF. The combined filtrate and washings were dried. Removal of solvent followed by flash chromatography (10% 2-propanol in hexane) afforded **12d** (436 mg, 88%): ^{1}H NMR δ 1.80 (2 H, m), 2.64 (2 H, t, J = 7.4 Hz), 3.58 (2 H, t, J = 6.1 Hz), 3.78 (3 H, s), 3.80 (3 H, s), 6.41 (0.5 H, d, J = 2.4 Hz), 6.45 (1.5 H, s), 7.03 (H, d, J = 8.6 Hz).

3-(2,3-Dimethoxyphenyl)propanol (13d). A solution of 2,3-dimethoxycinnamic acid (552 mg, 2.65 mmol) in EtOAc (25 mL) was hydrogenated by using 5% Pd/C (110 mg) as catalyst to afford 3-(2,3-dimethoxyphenyl)propionic acid (513 mg), which without further characterization was reduced further. A solution of $LiAlH_4$ in Et_2O (3 mL of 1 M, 3 mmol) was added dropwise to a stirred solution of the above propionic acid (510 mg, 2.42 mmol) and stirring was continued for 1 h at room temperature. The ice-cold reaction mixture was quenched by adding successively H_2O (120 μL), 15% aqueous NaOH (120 μL), and H_2O (360 μL). The granular white precipitate, after filtration, was washed thoroughly with THF. The combined filtrate and washings were dried. Removal of solvent followed by flash chromatography (10% 2-propanol in hexane) afforded **13d** (441 mg, 85%): ^{1}H NMR δ 1.83 (2 H, quin), 2.03 (H, br s) 2.73 (2 H, t, J = 7.4 Hz), 3.57 (2 H, br s), 3.83 (3 H, s), 3.85 (3 H, s), 6.75 (H, s), 6.79 (H, s), 6.99 (H, dd, J = 8.6 and 7.1 Hz); mass spectrum, m/z obsd 196.1098 (M^+, calcd for $C_{11}H_{16}O_3$, 196.1100).

2-(2,5-Dimethoxyphenyl)ethanol (14d). A solution of $LiAlH_4$ in Et_2O (5 mL of 1 M, 5 mmol) was added dropwise to a stirred solution of 2,5-dimethoxyphenylacetic acid (0.981 g, 5 mmol) in THF (5 mL). The resulting reaction mixture, after stirring for 30 min at room temperature, was worked up as for **13d** above to afford **14d** (0.755 g, 85%): ^{1}H NMR δ 2.01 (H, br s), 2.84 (2 H, t, J = 6.4 Hz), 3.73 (3 H, s), 3.79 (2 H, t, J = 6.6 Hz), 6.74 (3 H, m); mass spectrum, m/z obsd 182.0946 (M^+, calcd for $C_{10}H_{14}O_3$, 182.0943).

3-(2,3,4-Trimethoxyphenyl)propanol (15t). A solution of $LiAlH_4$ in Et_2O (4 mL of 1 M, 4 mmol) was added dropwise to a stirred solution of 3-(2,3,4-trimethoxyphenyl)propionic acid (0.961 g, 4 mmol) in anhydrous THF (6 mL). The resulting solution was stirred at room temperature for 30 min followed by successive addition of H_2O (150 μL), 15% aqueous NaOH (150 μL), and water (450 μL) to the cooled reaction mixture. The white precipitate, after filtration, was washed thoroughly with EtOAc. The combined filtrate and washings were washed with H_2O and dried. Solvent was removed to afford **15t** (0.76 g, 84%): ^{1}H NMR δ 1.76 (2 H, quin, J = 6.8 Hz), 2.25 (H, s), 2.62 (2 H, t, J = 7.3 Hz), 3.54 (2 H, t, J = 6.2 Hz), 3.79 (3 H, s), 3.82 (3 H, s), 3.84 (3 H, s), 6.58 (H, d, J = 8.4 Hz), 6.79 (H, d, J = 8.4 Hz). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.39; H, 8.19.

3-(2,4,6-Trimethoxyphenyl)-3-hydroxypropionitrile (21a). To a stirred solution of n-butyllithium (8.0 mL of 2.5 M in hexanes, 20 mmol) in anhydrous THF (100 mL) at −78 °C under argon was added acetonitrile (1.05 mL, 0.82 g, 20.1 mmol) over 5 min. After stirring for 30 min at −78 °C, solid 2,4,6-trimethoxybenzaldehyde (3.28 g, 16.72 mmol) was added. The resulting suspension was stirred for 1 h after which the aldehyde had dissolved. The cold bath was removed and the solution was allowed to warm and stirred for 10 min. It was poured into a mixture of ice (50 g), water (25 mL), and HCl (5 mL, 37%) and then extracted with ether (3 × 50 mL). The combined organic extracts were washed with water (3 × 10 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue thus obtained was purified by flash chromatography (50% ethyl acetate in hexanes) to give 1,3,5-trimethoxybenzaldehyde (0.35 g) and **21a** (3.4 g, 97% based on consumed trimethoxybenzaldehyde) which crystallized from CH_2Cl_2–hexanes, mp 92–3 °C: ^{1}H NMR δ 2.73 (H, dd, J = 6.2, 16.4 Hz), 2.88 (H, dd, J = 7.4, 16.6 Hz), 3.79 (3 H, s), 3.82 (6 H, s), 4.09 (H, d, J = 11.2 Hz), 5.39 (H, m), 6.11 (2 H, s). Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37. Found: C, 60.88; H, 6.35.

3-(2,4,6-Trimethoxyphenyl)propionitrile (21b). Trifluoroacetic acid (6.62 mL, 9.80 g, 86.0 mmol) was added to a stirring solution of **21a** (3.40 g, 14.3 mmol) and triethylsilane (5.73 mL, 4.17 g, 35.9 mmol) in anhydrous CH_2Cl_2 (36 mL) at −78 °C under argon over 5 min. The cold bath was removed, and the reaction mixture was allowed to come to room temperature over a period of 1 h and then stirred at room temperature for 30 min. After careful neutralization with saturated aqueous $NaHCO_3$ solution, the mixture was extracted with ether (3 × 25 mL). The combined organic extracts were washed with water (3 × 5 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under

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reduced pressure. The residue thus obtained was rinsed with hexanes to remove silanes, leaving **21b** as yellowish white crystals (3.07 g, 97%), which crystallized from CH_2Cl_2–hexanes, mp 91–92 °C (lit.[28] mp 92–93 °C); ^1H NMR δ 2.45 (2 H, t, J = 7.6 Hz), 2.92 (2 H, t, J = 7.6 Hz), 3.80 (9 H, s), 6.10 (2 H, s). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83. Found: C, 65.18; H, 6.79.

1-(2,4,6-Trimethoxyphenyl)-4,4-dimethylhex-5-en-3-one (21c). Isopentenylmagnesium chloride, prepared from 1-chloro-3-methyl-2-butene and Mg turnings in THF (30 mL of 0.5 M in THF, 15 mmol), was added dropwise to a stirring solution of **21b** (2.21 g, 10 mmol) in anhydrous THF (20 mL) at −20 °C under argon over a period of 30 min. The reaction mixture was stirred for an additional 30 min and then the reaction was quenched with 10% HCl. The pale yellow solution thus formed was boiled under reflux with stirring for 30 min. The cooled reaction mixture was diluted with water (100 mL) and then extracted with ether (3 × 25 mL). The combined organic extracts were washed with water (3 × 5 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue thus obtained was purified by flash chromatography (10% ethyl acetate in hexanes) to give **21c** (2.70 g, 92%) as a syrup: ^1H NMR δ 1.21 (6 H, s), 2.57 (2 H, m), 2.76 (2 H, m), 3.76 (6 H, s), 3.78 (3 H, s), 5.09 (2 H, m), 5.92 (H, m), 6.11 (2 H, s). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.92; H, 8.16.

1-(2,4,6-Trimethoxyphenyl)-3-allyl-4,4-dimethylhex-5-en-3-ol (21d). Allylmagnesium bromide (16.9 mL of 0.8 M in ether, 13.5 mmol), freshly prepared from allyl bromide and Mg turnings in ether, was added dropwise to a stirring solution of **21c** (3.60 g, 12.3 mmol) in anhydrous ether (25 mL) at −20 °C under argon over a period of 30 min. The reaction mixture was stirred for 30 min and then hydrolyzed with saturated aqueous NH_4Cl solution (20 mL) and extracted with ether (3 × 20 mL). The combined organic extracts were washed with water (3 × 5 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue thus obtained was purified by flash chromatography (5% ethyl acetate in hexanes) to give **21d** (3.70 g, 90%) as a syrup: ^1H NMR δ 1.09 (H, s), 1.10 (3 H, s), 1.70 (2 H, m), 1.84 (H, s), 2.44 (2 H, d, J = 7.4 Hz), 2.66 (2 H, J = 8.2 Hz), 3.80 (9 H, s), 5.07 (4 H, m), 6.08 (2 H, m), 6.12 (2 H, s); ^{13}C NMR δ 17.57, 22.02, 22.46, 34.90, 40.06, 44.79, 54.76, 55.14, 75.97, 90.24, 111.33, 111.87, 116.87, 135.69, 145.79, 158.13, 158.90. Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.88; H, 9.03.

2,2-Dimethyl-*exo*-3-(2-(2,4,6-trimethoxyphenyl)ethyl)bicyclo[3.2.0]heptan-3-*endo*-ol (21t). A solution of **21d** (3.60 g, 10.76 mmol) and $(CuOTf)_2{\cdot}C_6H_6$ (0.75 g) in anhydrous benzene (240 mL) was illuminated through a water-cooled quartz immersion well with a Hanovia medium pressure UV lamp under argon for 3 h. The reaction mixture was washed with aqueous NH_4OH solution (3 × 10 mL) and water (3 × 10 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue thus obtained was purified by flash chromatography (6% ethyl acetate in hexanes) to give **21t** (2.70 g, 75%) which crystallized from hexanes, mp 64–65 °C: ^1H NMR δ 0.69 (3 H, s), 0.95 (3 H, s), 1.62 (4 H, m), 1.88 (2 H, m), 2.10 (2 H, m), 2.34 (2 H, m), 2.66 (3 H, m), 3.78 (3 H, s), 3.79 (6 H, s), 6.12 (2 H, s); ^{13}C NMR δ 16.41, 17.32, 20.68, 24.72, 26.87, 34.69, 36.50, 45.31, 47.93, 51.31, 55.12, 55.54, 86.79, 90.56, 11.65, 158.39, 159.13. Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.80; H, 9.02.

2-(2,4,6-Trimethoxyphenyl)ethanol (23t). *n*-Butyllithium (8.0 mL of 2 M in hexanes, 16 mmol) was added slowly to a stirring solution of 1,3,5-trimethoxybenzene (2.50 g, 14.9 mmol) in anhydrous ether (25 mL) at 0 °C under argon. The resulting mixture was boiled under reflux for 24 h and then cooled to 0 °C. Ethylene oxide (0.88 g, 20.0 mmol) was added, and the resulting mixture was boiled under reflux for 12 h. The reaction mixture was then cooled to room temperature, poured into water (50 mL), acidified with 10% HCl (5 mL), and then extracted with ether (3 × 10 mL). The combined ether extracts were washed with water (3 × 4 mL), dried, and filtered, and the solvent was removed under reduced pressure. The residual oil was purified by flash chromatography (5% EtOAc in hexanes) to furnish 1,3,5-trimethoxybenzene (0.45 g) and **23t** (1.13 g, 65% based on consumed trimethoxybenzene), which crystallized from ether, mp 90–91 °C: ^1H NMR δ 1.81 (H, br s), 2.86 (2 H, t, J = 6.4 Hz), 3.69 (2 H, t, J = 6.4 Hz), 3.77 (6 H, s), 3.78 (3 H, s), 6.12 (2 H, s). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.24; H, 7.60. Found: C, 62.34; H, 7.65.

2-(2,4,6-Trimethoxyphenyl)ethyl Bromide (22b). A solution of **23t** (0.55 g, 2.59 mmol), triphenylphosphine (0.85 g, 3.24 mmol), and carbon tetrabromide (1.08 g, 3.26 mmol) in anhydrous CH_3CN (25 mL) was stirred at room temperature for 2 h. Solvent was removed under reduced pressure and the residual product was purified by flash chromatography (10% CH_2Cl_2 in hexanes) to give **22b** (0.63 g, 88%) which crystallized from *n*-pentane, mp 88–90 °C: ^1H NMR δ 3.10 (2 H, m), 3.39 (2 H, m), 3.77 (6 H, s), 3.78 (3 H, s), 6.08 (2 H, s). Anal. Calcd for $C_{11}H_{15}BrO_3$: C, 48.01; H, 5.49. Found: C, 48.12; H, 5.49.

(2,4,6-Trimethoxyphenyl)ethane (22t). A mixture of **22b** (0.5 g, 1.8 mmol) and Mg turnings (0.2 g, 8.3 mmol) in THF (10 mL) was boiled under reflux with stirring for 3 h. The cooled (0 °C) reaction mixture was treated with saturated aqueous NH_4Cl. THF was then removed under reduced pressure and the residue was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with water (3 × 3 mL) and dried. Removal of solvent followed by flash chromatography gave **22t** (0.21 g, 59%): ^1H NMR δ 1.07 (3 H, t, J = 7.5 Hz), 2.55 (2 H, q, J = 7.5 Hz), 3.73 (3 H, s), 6.02 (2 H, s). Anal. Calcd for $C_{11}H_{16}O$: C, 67.32; H, 8.22. Found: C, 67.41; H, 8.29.

4-Hydroxy-4-(2,4,6-trimethoxyphenyl)but-1-ene (24a). A solution of allylmagnesium bromide in Et_2O (20 mL of 0.5 M, 10 mmol) was added dropwise to a warm solution of 2,4,6-trimethoxybenzaldehyde (900 mg, 5 mmol) in THF (5 mL) with stirring. The resulting reaction mixture was stirred at room temperature for 1 h followed by addition of saturated aqueous NH_4Cl. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 30 mL). The combined organic extracts, after drying, were concentrated in vacuo. The residual liquid was flash chromatographed (25% EtOAc in hexane) to afford **24a** (416 mg, 35%): ^1H NMR δ 2.40–2.75 (2 H), 3.60 (H, m), 4.96–5.2 (3 H), 5.75–5.96 (H, m), 6.13 (2 H, s); mass spectrum, m/z obsd 221.1174 [M^+ − OH (80%), calcd for $C_{13}H_{17}O_3$, 221.1178]. No M^+ was detected.

4-(2,4,6-Trimethoxyphenyl)but-1-ene (24b). Trifluoroacetic acid (0.587 mL, 7.62 mmol) was added dropwise to a cooled (−50 °C) and magnetically stirred solution of **24a** (300 mg, 1.27 mmol) and triethylsilane (370 mg, 3.2 mmol) in CH_2Cl_2 (4 mL). After complete addition, the cooling bath was removed and the reaction mixture was stirred at room temperature for 1.5 h. After neutralization by addition of saturated aqueous $NaHCO_3$, the reaction mixture was extracted with ether (3 × 20 mL). The combined ether extracts were washed with water (3 × 10 mL) and dried. After removing solvent by rotary evaporation, the residue was flash chromatographed (50% toluene in hexane) to afford **24b** (135 mg, 48%), mp 49–52 °C; ^1H NMR δ 2.19 (2 H, m), 2.64 (2 H, m), 3.77 (6 H, s), 3.78 (3 H, s), 4.87–5.04 (2 H), 5.82–6.03 (H, m), 6.11 (2 H, s); mass spectrum, m/z obsd 222.1253 (M^+, calcd for $C_{13}H_{18}O_3$, 222.1256).

4-(2,4,6-Trimethoxyphenyl)butanol (24t). A solution of BH_3 in THF (0.493 mL of 1 M, 0.493 mmol) was added dropwise to a solution of **24b** (110 mg, 0.495 mmol) in THF (1 mL), and the reaction mixture was left at room temperature for 30 min. Water was added to decompose excess BH_3 followed by addition of aqueous NaOH (0.25 mL, 3 N) and H_2O_2 (0.235 mL, 30%) at 25–30 °C. The resulting mixture was stirred for 1 h and then extracted with Et_2O (3 × 20 mL). The organic layer was washed with brine (2 × 5 mL) and dried. Removal of solvent under reduced pressure afforded **24t** (117 mg, 98%): mp 60–62 °C; ^1H NMR δ 1.42–1.68 (5 H), 2.56 (2 H, t, J = 7.3 Hz), 3.63 (2 H, t, J = 6.5 Hz), 3.76 (6 H, s), 3.77 (3 H, s), 6.10 (2 H, s); mass spectrum, m/z obsd 240.1354 (M^+, calcd for $C_{13}H_{20}O_4$, 240.1362).

Demethylation with Sodium Thioethoxide/DMF. General Procedure. A 0.5 M solution of NaSEt in DMF was prepared by adding EtSH (931 mg, 1.1 mL, 15 mmol) to an ice-cooled and magnetically stirred suspension of NaH (400 mg of a 60% oil dispersion, 10 mmol) in DMF (20 mL) under N_2 and stirring at room temperature for 15 min. Then 4–8 mL (2–4 mmol) of this solution was added to the aromatic methoxy compound (1 mmol) and the resulting solution was heated in an oil bath at 115–120 °C under N_2. The completion of the reaction in each case was

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determined by TLC. The cooled reaction mixture was then acidified with 10% aqueous HCl and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with 10% aqueous NaOH (3 × 3 mL) and H_2O (3 mL) and dried ($MgSO_4$). Removal of solvent by rotary evaporation afforded the starting material (if any), which was purified by flash chromatography. The chilled basic aqueous washings were acidified with 10% aqueous HCl and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with water (2 × 3 mL) and dried. Removal of solvent by rotary evaporation afforded the phenolic products, which were purified by flash chromatography or HPLC.

3-(2-Hydroxy-4-methoxyphenyl)propanol (12o) and 3-(4-Hydroxy-2-methoxyphenyl)propanol (12p). Demethylation of **12d** for 10 h gave a product mixture which, upon purification by flash chromatography (10% 2-propanol in hexane) afforded **12o** (66%) [^{1}H NMR δ 1.84 (2 H, m), 2.62 (H, br s), 2.72 (2 H, t, J = 6.5 Hz), 3.65 (2 H, t, J = 5.8 Hz), 3.77 (3 H, s), 6.45 (H, dd, J = 9.1 and 2.5 Hz), 6.45 (H, d, J = 2.2 Hz), 6.99 (H, d, J = 9.1 Hz), 7.4 (H, br s); mass spectrum, m/z obsd 182.0937 (M^+, calcd for $C_{10}H_{14}O_3$, 182.0943).] and **12p** (15%) [^{1}H NMR δ 1.81 (2 H, quin, J = 6.9 Hz), 2.0 (H, br s), 2.63 (2 H, t, J = 7.2 Hz), 3.60 (2 H, t, J = 6.1 Hz), 3.78 (3 H, s), 5.56 (H, br s), 6.35 (H, dd, J = 8 and 2.4 Hz), 6.40 (H, d, J = 2.3 Hz), 6.95 (H, d, J = 7.9 Hz); mass spectrum, m/z obsd 182.0940 (M^+, calcd for $C_{10}H_{14}O_3$, 182.0943).]

3-(2-Hydroxy-3-methoxyphenyl)propanol (13o) and 3-(3-Hydroxy-2-methoxyphenyl)propanol (13p). Demethylation of **13d** for 3 h afforded a mixture which after flash chromatography [2-propanol in hexane (1:9)] afforded **13o** (74%) [^{1}H NMR δ 1.87 (2 H, quin, J = 7 Hz), 2.3 (H, br s), 2.76 (2 H, t, J = 7 Hz), 3.61 (2 H, t, J = 6.1 Hz), 3.87 (3 H, s), 6.01 (H, s), 6.73–6.8 (3 H); mass spectrum, m/z obsd 182.0943 (M^+, calcd for $C_{10}H_{14}O_3$, 182.0943).] and **13p** (12%) [^{1}H NMR δ 1.87 (2 H, quin, J = 6.8 Hz), 2.01 (H, br s), 2.75 (2 H, t, J = 7.1 Hz), 3.62 (2 H, t, J = 6.1 Hz), 3.81 (3 H, s), 5.89 (H, br s), 6.70–7.01 (3 H); mass spectrum, m/z obsd 182.0945 (M^+, calcd for $C_{10}H_{14}O_3$, 182.0943).].

2-(2-Hydroxy-5-methoxyphenyl)ethanol (14o) and 2-(5-Hydroxy-2-methoxyphenyl)ethanol (14p). Demethylation of **14d** for 16 h gave a mixture which, upon purification by preparative TLC (50% EtOAc in hexane), afforded **14o** (18%) [^{1}H NMR δ 2.84 (2 H, t, J = 5.4 Hz), 2.98 (H, br s), 3.74 (3 H, s), 3.93 (2 H, t, J = 5.3 Hz), 6.62 (H, d, J = 3 Hz), 6.68 (H, dd, J = 8.5 and 3 Hz), 6.81 (H, d, J = 8.5 Hz), 7.67 (H, br s); mass spectrum, m/z obsd 168.0799 (M^+, calcd for $C_9H_{12}O_3$, 168.0786).] and **14p** (6%) [^{1}H NMR δ 1.50–1.95 (H), 2.83 (2 H, t, J = 6.3 Hz), 3.75 (3 H, s), 3.81 (2 H, t, J = 6.3 Hz), 4.90–5.25 (H), 6.61–6.91 (3 H); mass spectrum, m/z obsd 168.0784 (M^+, calcd for $C_9H_{12}O_3$, 168.0786).].

3-(2-Hydroxy-3,4-dimethoxyphenyl)propanol (15o), 3-(4-Hydroxy-2,3-dimethoxyphenyl)propanol (15p), and 3-(3-Hydroxy-2,4-dimethoxyphenyl)propanol (15m). Demethylation of **15t** for 4 h gave a mixture which upon purification by flash chromatography followed by HPLC (45% ethyl acetate in hexane) afforded **15o** (34%) [^{1}H NMR δ 1.80 (2 H, quin, J = 7 and 6.3 Hz), 2.20 (H, br s), 2.65 (2 H, t, J = 7.1 Hz), 3.58 (2 H, t, J = 6.1 Hz), 3.80 (3 H, s), 3.85 (3 H, s), 6.32 (H, br s), 6.39 (H, d, J = 8.5 Hz), 6.75 (H, d, J = 8.5 Hz). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.24; H, 7.60. Found: C, 62.29; H, 7.82.], **15p** (7.6%) [^{1}H NMR δ 1.77 (3 H, m), 2.62 (2 H, t, J = 7.3 Hz), 3.57 (2 H, t, J = 6.1 Hz), 3.83 (3 H, s), 3.88 (3 H, s), 5.65 (H, br s), 6.63 (H, d, J = 8.4 Hz), 6.76 (H, d, J = 8.3 Hz); mass spectrum, m/z obsd 212.1045 (M^+, calcd for $C_{11}H_{16}O_4$, 212.1049).], and **15m** (33.5%) [^{1}H NMR δ 1.78 (2 H, quin), 2.14 (H, br s), 2.64 (2 H, t, J = 7.4 Hz), 3.55 (2 H, t, J = 6.2 Hz), 3.82 (3 H, s), 3.84 (3 H, s), 5.75 (H, br s), 6.55 (H, d, J = 8.4 Hz), 6.61 (H, d, J = 8.4 Hz); mass spectrum, m/z obsd 212.1074 (M^+, calcd for $C_{11}H_{16}O_4$, 212.1049).].

2,2-Dimethyl-3-(2-(2-hydroxy-4,6-dimethoxyphenyl)-ethyl)bicyclo[3.2.0]heptan-3-ol (21o). Ethanethiol (1.38 mL, 1.16 g, 18.7 mmol) was added to a suspension of sodium hydride (0.45 g, 18.8 mmol, 0.75 g of 60% oil dispersion) in anhydrous DMF (20 mL) under argon. The solution was stirred for 5 min before a solution of **21t** (2.50 g, 7.47 mmol) in anhydrous DMF (15 mL) was added. The resulting solution was then heated under reflux for 2 h (150 °C oil bath temperature). The cooled mixture was acidified with 10% HCl, diluted with water (50 mL), and extracted with ether (3 × 30 mL). The combined ether extracts were washed with water (3 × 5 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue thus obtained was crystallized from CH_2Cl_2–hexanes to give **21o** (2.23 g, 93%), mp 157–158 °C: ^{1}H NMR δ 0.71 (3 H, s), 0.93 (3 H, s), 2.40 (H, m), 2.67 (3 H, m), 3.74 (3 H, s), 3.75 (3 H, s), 6.04 (H, d, J = 2.4 Hz), 6.11 (H, d, J = 2.4 Hz), 7.54 (H, br s). Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.39; H, 8.75.

2-Ethyl-3,5-dimethoxyphenol (22o) and 4-Ethyl-3,5-dimethoxyphenol (22p). Demethylation of **22t** for 16 h afforded a mixture which, after preparative TLC (25% EtOAc in hexane), gave **22o** (48%) [^{1}H NMR δ 1.07 (3 H, t, J = 7.5 Hz), 2.55 (2 H, q, J = 7.5 Hz), 3.72 (3 H, s), 3.76 (3 H, s), 4.85 (H, s), 6.01 (H, d, J = 2.3 Hz), 6.07 (H, d, J = 2.3 Hz); mass spectrum, m/z obsd 182.0951 (M^+, calcd for $C_{10}H_{14}O_3$, 182.0943).] and **22p** (24%) [^{1}H NMR δ 0.74 (3 H, t, J = 7.4 Hz), 2.25 (2 H, q, J = 7.4 Hz), 3.48 (3 H, s), 5.82 (2 H); mass spectrum, m/z obsd 182.0937 (M^+, calcd for $C_{10}H_{14}O_3$, 182.0943).

2-(2-Hydroxy-4,6-dimethoxyphenyl)ethanol (23o). Demethylation of **23t** for 3 h gave **23o** in 93% yield as a crystalline solid, mp 79–80 °C (from EtOAc–hexane): ^{1}H NMR δ 2.85 (2 H, t, J = 5.4 Hz), 3.73 (6 H, s), 3.85 (2 H, t, J = 5.3 Hz), 6.05 (H, d, J = 2.3 Hz), 6.13 (H, d, J = 2.4 Hz), 7.91 (H, br s). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.67; H, 7.11.

4-(2-Hydroxy-4,6-dimethoxyphenyl)butanol (24o) and 4-(4-Hydroxy-2,6-dimethoxyphenyl)butanol (24p). Demethylation of **24t** for 7 h gave a mixture which, after flash chromatography (40% EtOAc in hexane) followed by preparative TLC (10% 2-propanol in toluene), afforded the recovered starting material **24t** (23%) and the phenols **24o** (23%) [mp 109–110 °C; ^{1}H NMR δ 2.53–1.66 (5 H), 2.62 (2 H, t, J = 7 Hz), 3.73 (3 H, s), 3.74 (3 H, s), 3.76 (2 H, t, J = 5.7 Hz), 6.04 (2 H, s); mass spectrum, m/z obsd 226.1204 (M^+, calcd for $C_{12}H_{18}O_4$, 226.1205).] and **24p** (6%) [^{1}H NMR δ 1.47–1.60 (5 H), 2.55 (2 H, t, J = 7 Hz), 3.65 (2 H, t, J = 6.2 Hz), 3.73 (3 H, s), 6.03 (2 H, s); mass spectrum, m/z obsd 226.1202 (M^+, calcd for $C_{12}H_{18}O_4$, 226.1205).].

Structure Confirmation by Cyclization or Unambiguous Synthesis. 7-Methoxychroman (12c).[29] A solution of **12o** (14 mg, 0.077 mmol) in THF (1 mL) was stirred at room temperature with triphenylphosphine (PPh_3) (26.2 mg, 0.099 mmol) and diethyl azodicarboxylate (DEAD) (17.39 mg, 0.099 mmol) for 1 h. The residue, after removal of THF, was flash chromatographed (10% Et_2O in hexane) to afford **12c** (6 mg, 48%); ^{1}H NMR δ 1.97 (2 H, m), 2.71 (2 H, t, J = 6.3 Hz), 3.74 (3 H, s), 4.16 (2 H, t, J = 5.3 Hz), 6.35 (H, d, J = 2.5 Hz), 6.43 (H, dd, J = 8.4 and 2.5 Hz), 6.92 (H, d, J = 8.3 Hz); mass spectrum, m/z obsd 164.0834 (M^+, calcd for $C_{10}H_{12}O_2$, 164.0837).

8-Methoxychroman (13c). A solution of **13o** (12.5 mg, 0.068 mmol) in THF (1 mL) was stirred at room temperature with PPh_3 (23.4 mg, 0.089 mmol) and DEAD (15.5 mg, 0.089 mmol) for 1 h. The residue, after removal of THF, was flash chromatographed (10% 2-propanol in hexane) to afford **13c** (5 mg, 44%): ^{1}H NMR δ 1.99 (2 H, m), 2.77 (2 H, t, J = 6.3 Hz), 3.84 (3 H, s), 4.25 (2 H, t, J = 5.3 Hz), 6.70 (3 H, m); mass spectrum, m/z obsd 164.0835 (M^+, calcd for $C_{10}H_{12}O_2$, 164.0837).

5-Methoxy-2,3-dihydrobenzofuran (14c). A solution of **14o** (10 mg, 0.059 mmol) in THF (500 μL) was stirred at room temperature with PPh_3 (17 mg, 0.065 mmol) and DEAD (11.3 mg, 0.065 mmol) for 1 h. The residue, after removal of THF, was purified by preparative TLC (10% EtOAc in hexane) to afford **14c** (7 mg, 79%): ^{1}H NMR (CCl_4) δ 3.12 (2 H, t, J = 8.5 Hz), 3.68 (3 H, s), 4.45 (2 H, t, J = 8.5 Hz), 6.50–6.63 (3 H, m) identical with the reported ^{1}H NMR spectrum.[30]

7,8-Dimethoxychroman (16). A solution of **15o** (14 mg, 0.066 mmol) in THF (1 mL) was stirred at room temperature with PPh_3 (45 mg, 0.17 mmol) and DEAD (30 mg, 0.17 mmol) for 25 h. Removal of THF, followed by flash chromatography (15% EtOAc in hexane), afforded **16** (11.7 mg, 91%): ^{1}H NMR δ 1.97 (2 H, m), 2.74 (2 H, t, J = 6.5 Hz), 3.83 (3 H, s), 3.85 (3 H, s), 4.23 (2 H, t, J = 5.3 Hz), 6.45 (H, d, J = 8.5 Hz), 6.72 (H, d, J = 8.8 Hz); mass spectrum, m/z obsd 194.0941 (M^+, calcd for $C_{11}H_{14}O_3$, 194.0943).

1-((Tetrahydropyranyl)oxy)-3-(2,4-dimethoxyphenyl)-propane (12x). A solution of **12d** (130 mg, 0.66 mmol) in CH_2Cl_2

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(5 mL) was treated with dihydropyran (110 mg, 1.32 mmol) and pyridinium *p*-toluenesulfonate (PPTS) (33 mg, 0.13 mmol) at room temperature for 16 h. The reaction mixture was diluted with Et_2O (25 mL), washed with half-saturated brine (2 × 10 mL), and dried. Removal of solvent followed by flash chromatography (10% EtOAc in hexane) afforded **12x** (185 mg, 99.6%); ^1H NMR δ 1.48–1.93 (8 H), 2.59 (2 H, t, J = 7.6 Hz), 3.36–3.57 (2 H), 3.68–3.98 (2 H), 3.76 (6 H, s), 4.56 (H, t, J = 3.8 Hz), 6.39 (H, dd, J = 9.6 and 2.4 Hz), 6.41 (H, s), 7.01 (H, d, J = 7.9 Hz); mass spectrum, m/z obsd 280.1674 (M^+, calcd for $C_{16}H_{24}O_4$, 280.1675).

3-(3-Hydroxy-2,4-dimethoxyphenyl)propanol (15m). To an ice-cold solution of **12x** (140 mg, 0.5 mmol) in Et_2O (4 mL) containing TMEDA (226.4 μL, 1.5 mmol), was added *n*-BuLi (745 μL, 2.02 M in hexane, 1.5 mmol) dropwise with stirring under argon. After complete addition, the cooling bath was removed and the reaction mixture was stirred at room temperature for 16 h followed by boiling under reflux for 16 h during which the color turned from yellow to brown. The reaction mixture was cooled to −10 °C and to it was added a solution of $B(OMe)_3$ (171.5 mg, 1.65 mmol) in THF (1 mL) with vigorous stirring upon which a white sludge appeared. After stirring for an additional 15 min, cold HOAc (129 μL, 2.24 mmol) was added all at once followed by addition of a solution of H_2O_2 (168 μL, 30%) in H_2O (168 μL). The cooling bath was then removed. The reaction mixture was allowed to warm to room temperature, then transferred into a separatory funnel with Et_2O (5 mL), and washed with a saturated aqueous solution of $(NH_4)_2SO_4$ containing $Fe(NH_3)_2(SO_4)_2$ until no more brown precipitate was formed. The organic layer was then washed with water (3 × 3 mL) and dried. Removal of solvent by rotary evaporation afforded the starting material (89 mg). The alkaline aqueous layer was acidified (cold concentrated HCl) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried. Removal of EtOAc afforded the phenolic product (65 mg, 0.224 mmol) which, without further purification, was treated in EtOH (2 mL) solution with PPTS (5.5 mg, 0.022 mmol) at 55 °C for 2 h. Removal of EtOH followed by purification of the residue by preparative TLC (75% EtOAc–hexane) afforded **15m** [24.4 mg, 62% based on consumed **12x**]: ^1H NMR δ 1.78 (2 H, quin), 2.14 (H, br s), 2.64 (2 H, t, J = 7.4 Hz), 3.55 (2 H, t, J = 6.2 Hz), 3.82 (3 H, s), 3.84 (3 H, s), 5.75 (H, br s), 6.55 (H, d, J = 8.4 Hz), 6.61 (H, d, J = 8.4 Hz).

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Simple and Stereocontrolled Preparation of Optically Pure (*E*)- and (*Z*)-1-Alkenyl *p*-Tolyl Sulfoxides via 1-Alkynyl *p*-Tolyl Sulfoxides

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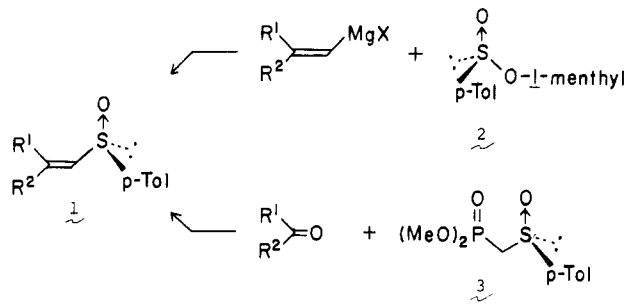
1-Alkynylmagnesium bromides react cleanly and stereospecifically with (−)-menthyl (−)-(*S*)-*p*-toluenesulfinate (**2**) in toluene to produce chiral 1-alkynyl *p*-tolyl (+)-(*S*)-sulfoxides **5a–d** in high yields. Reduction of **5a–d** with lithium aluminum hydride in THF at −90 °C proceeds stereospecifically to give (*E*)-1-alkenyl *p*-tolyl (+)-(*R*)-sulfoxides (*E*)-**7** in excellent yields, while catalytic hydrogenation of **5a–d** using Wilkinson catalyst, $RhCl(PPh_3)_3$, in benzene affords quantitatively (−)-(*R*)-*Z* isomers (*Z*)-**7**. Conjugate addition of organocopper reagents to **5** also proceeds stereoselectively.

In recent years, 1-alkenyl *p*-tolyl sulfoxides **1** with the optically active center at the sulfur atom have been used successfully in various asymmetric syntheses: the Michael reaction,[1] the Diels–Alder reaction,[2] the additive Pummerer rearrangement,[3] the sequential prototropic shift and [2,3] sigmatropic rearrangement,[4] the 1,3-dipolar cycloaddition,[5] and the reaction as the vinylic carbanion species.[3b,6] The *R* enantiomers of **1** are usually prepared by the Andersen synthesis using (−)-menthyl (−)-(*S*)-*p*-toluenesulfinate **2** and vinylic Grignard reagents[7] or by the Horner–Wittig procedure using carbonyl compounds and the anion of dimethyl ((*R*)-*p*-tolylsulfinyl)methanephosphonate **3**[8] (Scheme I). However, applicability of the former method depends on the availability of stereochemically pure 1-alkenyl halides for preparing Grignard reagents, and the latter usually leads to a mixture of (*E*)- and (*Z*)-vinylic sulfoxides. Pursuing our interest in the asymmetric synthesis of acyclic compounds using chiral

Scheme I



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