Reaction of Bis[2-hydroxy-1-(2,6-dimethyl-4-methoxyphenyl)ethyl] Ethers with Tosyl Chloride

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In the reaction with tosyl chloride in pyridine, the meso isomer (**2a**) of bis[2-hydroxy-1-(2,6-dimethyl-4-methoxyphenyl)ethyl] ether rearranged to give arylacetaldehyde (**3**) and 2-arylmethyl-4-aryl-1,3-dioxolane (**4**), and the racemic isomer (**2b**) afforded **3**, **4**, and 2,6-diaryl-1,4-dioxane. The aryl migration in this reaction has been confirmed by the use of the deuterated compounds, **2a-D** and **2b-D**, respectively, substituted with deuteriums at the 2,2-positions.

The meso (**1a**) and racemic (**1b**) isomers of bis(2-hydroxy-1-mesitylethyl) ether gave the corresponding tosylates with tosyl chloride in pyridine at 80 °C in high yields, respectively.[1] The reaction of the *p*-methoxy compounds, **2a** and **2b**, with the same reagent, on the contrary, gave no tosylate. At 80 °C or higher, these compounds afforded the rearranged products, in which migration of a *p*-anisyl group was observed. Under reflux, **1a** and **1b** were also observed to give results similar to those of **2a** and **2b**, except for the formation of the tosylates. The reaction of **2a** and **2b** with tosyl chloride by a mechanism similar to that reported by earlier investigators for the solvolysis of *p*-methoxyneophyl tosylate will be reported.[3i]

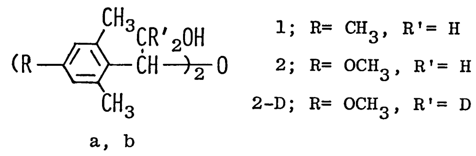


Fig. 1.

Results and Discussion

Synthesis of Bis[2-hydroxy-1-(2,6-dimethyl-4-methoxyphenyl)ethyl] Ethers (2). The meso **2a** and racemic compound **2b** have been synthesized from 2,6-dimethyl-4-methoxybenzaldehyde[2] by a method similar to the synthesis of bis(2-hydroxy-1-mesitylethyl) ethers (**1a** and **1b**).[1] Deuterated compounds **2a-D** and **2b-D** were prepared by the reduction of *meso-* and *dl*-bis(α-methoxycarbonyl-2,6-dimethyl-4-methoxybenzyl) ethers with lithium aluminium deuteride. With a large excess of the deuteride, 3,3,5,5-tetradeuterio-2,6-bis(2,6-dimethyl-4-methoxyphenyl)-1,4-dioxanes (**5a-D** and **5b-D**) were obtained as by-products, respectively. From a comparison of the PMR spectra of **2a** and **2b** with those of the *p*-methyl compounds, **1a** and **1b**, it became clear that the low-melting isomer, **2a**, is meso and the high-melting one, **2b**, is racemic.

Reaction of Bis[2-hydroxy-1-(2,6-dimethyl-4-methoxyphenyl)ethyl] Ethers (2) with Tosyl Chloride in Pyridine. The mild refluxing of **2a** with five equivalents of tosyl chloride in pyridine afforded 2,6-dimethyl-4-methoxyphenylacetaldehyde (**3**) in a 57% yield, and 2-(2,6-dimethyl-4-methoxyphenylmethyl)-4-(2,6-dimethyl-4-methoxyphenyl)-1,3-dioxolane (**4**) in a 42% yield. A similar treatment of the racemic isomer **2b** gave **3**(5%), **4**(24%) and 2,6-bis(2,6-dimethyl-4-methoxyphenyl)-1,4-dioxane (**5**) in a 42% yield. The IR spectrum of **3** shows the presence of a formyl group (1716, 2720, and 2830 cm^{-1}) and the PMR spectrum the presence of two benzyl protons (δ 3.55 ppm) coupling (2 Hz) to a formyl proton (δ 9.60 ppm).

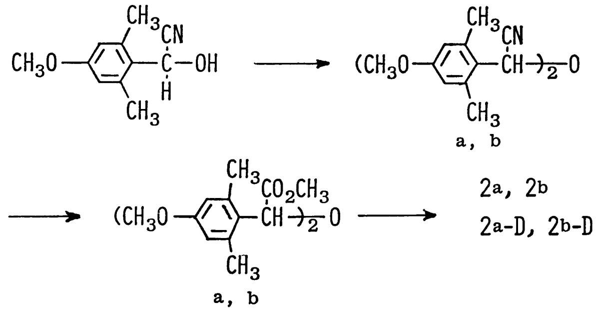


Fig. 2.

Since the IR spectra of **4** and **5** show no absorption band attributable to hydroxyl and carbonyl groups, the oxygen atoms are probably present as ether linkages. The PMR spectrum of **4** revealed the acetal moiety. The signal (δ 5.00 ppm) for the proton at C-2 is coupled (4 Hz) to the benzyl protons (δ 3.10 ppm), whereas the C-4 proton (δ 5.28 ppm) is coupled (each 8 Hz) to C-5 protons (δ 3.75 and 3.99 ppm) which are coupled (8 Hz) to each other. These nuclear spin-spin interactions have been confirmed by spin-decoupling techniques. Treatment of **4** with hydrochloric acid gave **3**. The PMR spectrum of **5** shows a overlapped ABX system for the protons on C-3 and C-5 (AB part), and C-2 and C-6 (X part) (see Experimental) which led to the tentative assignment of the 2,6-diarylsubstituted-1,4-dioxane structure, **5**. This structure was confirmed by the reaction of **2b** with concd hydrochloric acid to give **5**

The route to **3** and **4** must involve a *p*-anisyl migration to the adjacent carbon atom, and this assumption has been proved by the use of deuterated compounds, **2a-D** (meso) and **2b-D** (racemic). The reaction of **2a-D** with tosyl chloride gave a mixture of two aldehydes (the ratio of **3-D-1** and **3-D-2** was 1 : 1); **3-D-1** [PMR: δ 9.97 ppm (br s, Ar–CD$_2$C$\underline{H}$O)] and **3-D-2** [PMR: δ 3.55 (br s, Ar–C$\underline{H}$D–CDO)], a 1,3-dioxolane **4-D** and a small amount of tosylate (7%) with a composition of $C_{36}H_{38}D_4O_9S_2$, mp 118 °C. The reaction of **2b-D** also afforded **3-D-1**, **3-D-2**, **4-D**, and a tosylate (14%), mp 115 °C, but did not give **5-D**. Compared with the reaction of

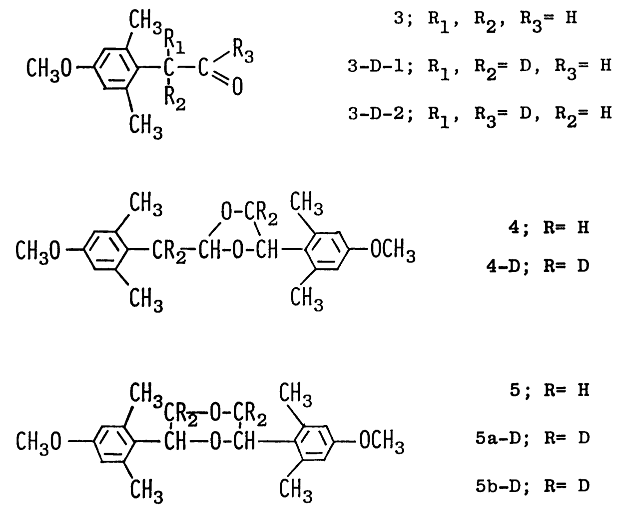
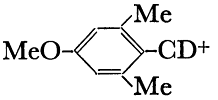
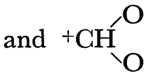


Fig. 3.

2a and **2b**, there may be present the isotope effect of deuterium in these reactions, but no conclusion may be drawn from these experimental results. The hydrolysis of dioxane **4-D** with concd hydrochloric acid in methanol afforded a mixture of the aldehydes(the ratio of **3-D-1** and **3-D-2** was 1: 1), 2,2-dideuterio-2-(2,6-dimethyl-4-methoxyphenyl)ethanal dimethyl acetal (**6**), and 1,1-dideuterio-2-methoxy-2-(2,6-dimethyl-4-methoxyphenyl)ethanol (**7**). The mass spectrum of the mixture of **3-D-1** and **3-D-2** showed a molecular ion peak at *m*/*e* 180 and these ratios of the **3-D-1** and **3-D-2** aldehydes were established by estimating the peak areas of the signals due to benzyl and formyl protons in the PMR spectra. Structure **6** and **7** have been assigned on the basis of the spectral data. The mass spectrum of **6** displayed fragment peaks which have been assigned to



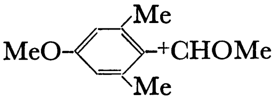
(*m*/*e* 151) and



$^{+}CH(OMe)_2$

(*m*/*e* 75).

The PMR spectrum showed the proton (δ 4.50 ppm) at C-1 and two equivalent methoxyl groups (δ 3.39 ppm) in the dimethyl acetal moiety, but did not show a benzyl proton. The mass spectrum of **7** however showed a fragment peak which has been assigned to



(*m*/*e* 179) and the PMR spectrum showed one benzyl proton (δ 4.86 ppm). This structure has been confirmed by direct comparison with a specimen synthesized by an established route. The tosylate of **2b-D** afforded a mixture of the aldehydes (the ratio of **3-D-1** and **3-D-2** was *ca.* 1: 1) in pyridine under reflux.

Many studies have been reported on the aryl migration in the solvolysis of tosylates.[3] Winstein *et al.*[3i] investigated the solvolysis rates of *p*-methoxyneophyl tosylate on various solvents and established that it underwent ionization in pyridine to give a rearranged product. In these experiments, it may be assumed that the tosylate formed from **2** undergoes ionization followed by the migration of the *p*-anisyl group to the adjacent carbon atom to give the rearranged products, **3** and **4**. Although there may be several mechanisms by which the formation of **3**, **4**, and **5** can be explained, Scheme 1 is the simplest.

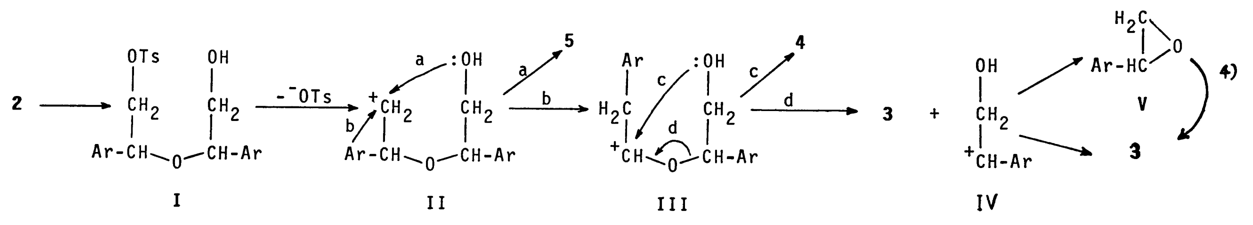
Experimental

All the melting points are uncorrected. IR and UV spectra were recorded with Shimadzu IR-27C and Shimadzu UV-210A spectrophotometers. PMR spectra were measured with JEOL JNM 60 and JNM 100 apparatus (with TMS as an internal standard).

Cyanohydrin of 2,6-Dimethyl-4-methoxybenzaldehyde. A mixture of 2,6-dimethyl-4-methoxybenzaldehyde[2] (2 g) and anhydrous HCN (2 ml) was kept with CaO (400 mg) in a sealed tube at 50 °C for 2 h. The reaction mixture was acidified with dil H_2SO_4 followed by extraction with ether to give the cyanohydrin (1.8 g, 79%) as needles, mp 122—123 °C (acetone–petroleum ether). Found: C, 69.23; H, 6.91; N, 7.30%. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33% IR (Nujol); 3380 and 2250 cm^{-1}. PMR ($CDCl_3$); δ 2.53 (6H, s, Ar–C$\underline{H}_3$), 3.02 (1H, s, –O$\underline{H}$), 3.82 (3H, s, –OC$\underline{H}_3$), 5.83 (1H, s, –$\overset{|}{C}\underline{H}$OH), and 6.60 ppm (2H, s, Ar–$\underline{H}$). From the mother liquor, yellow crystals were obtained in a 2% yield, mp 215 °C. Found: C, 66.11; H, 5.66; N, 22.23%. Calcd for $C_{14}H_{14}N_4O$: C, 66.12; H, 5.55; N, 22.04%. IR (Nujol): 3580, 3400, 2360, and 2306 cm^{-1}. UV $(EtOH)_{max}$: 251.5 (ε 13500), 260 (15900), and 277 nm (18900). PMR (DMSO): δ 2.50 (6H, s), 3.43 (2H, br), 3.82 (4H, s), 6.72 (2H, s), and 7.35 ppm (2H, br).

Bis(α-cyano-2,6-dimethyl-4-methoxybenzyl) Ethers. The cyanohydrin (2 g) was refluxed with a catalytic amount of TsOH in dry benzene (500 ml) for 6 h. The crude product gave a mixture of ethers in a 65% yield (the ratio of meso and racemic forms was 5: 7), which was recrystallized from EtOH to give the racemic isomer as plates, mp 132—133 °C. Found: C, 72.74; H, 6.58; N, 7.97%. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69%. IR (Nujol): 1378, 1140, and 1050 cm^{-1}. PMR ($CDCl_3$): δ 2.38 (12H, s, Ar–C$\underline{H}_3$), 3.80 (6H, s, –OC$\underline{H}_3$), 5.75 (2H, s, –$\overset{|}{C}\underline{H}$–O–), and 6.59 ppm (4H, s, Ar–$\underline{H}$).

meso- *and* dl-*Bis(α-methoxycarbonyl-2,6-dimethyl-4-methoxybenzyl) Ethers.* Into a mixture of the above ethers (2 g) in abs EtOH (100 ml), dry HCl gas was passed for 5 h at 45—50 °C. The solvent was removed *in vacuo*, and the residue hydrolyzed with 30% aq KOH in ethylene glycol for 3 h. After acidification with dil HCl, the reaction mixture was extracted with ether and the ether extract methylated with



Scheme 1.

diazomethane. The crude product was chromatographed over silica gel. Elution with $CHCl_3$ containing acetone (0.5% v/v) gave a meso ester (1.3 g, 52%) as prisms from EtOH, mp 123—124 °C. Found: C, 66.79; H, 7.08%. Calcd for $C_{24}H_{30}D_7$: C, 66.96; H, 7.02%. IR (Nujol): 1765, 1745, 1380, 1200, 1140, and 1070 cm^{-1}. PMR ($CDCl_3$): δ 2.16 (12H, s, $Ar-C\underline{H}_3$), 3.71 (6H, s, $-CO_2C\underline{H}_3$), 3.77 (6H, s, $Ar-OC\underline{H}_3$), 5.45 (2H, s, $Ar-\overset{|}{C}\underline{H}-O-$), and 6.54 ppm (4H, s, $Ar-\underline{H}$). Further elution with $CHCl_3$ containing acetone (3% v/v) gave the racemic isomer (0.9 g, 39%) as prisms from EtOH, mp 173—174 °C. Found: C, 67.04; H, 7.13%. IR (Nujol): 1750, 1380, 1220, 1190, 1140, and 1065 cm^{-1}. PMR ($CDCl_3$): δ 2.19 (12H, s, $Ar-C\underline{H}_3$), 3.68 (6H, s, $-CO_2C\underline{H}_3$), 3.79 (6H, s, $Ar-OCH_3$), 5.24 (2H, s, $Ar-\overset{|}{C}\underline{H}-O-$), and 6.56 ppm (4H, s, $Ar-\underline{H}$).

Bis[2-hydroxy-1-(2,6-dimethyl-4-methoxyphenyl)ethyl] Ethers (2a and 2b). The meso and racemic ethers (1 g) were reduced with $LiAlH_4$ (0.5 g) in ether to give **2a** (760 mg, 87%) and **2b** (810 mg, 93%) respectively as needles from acetone–hexane. **2a**; mp 114—115 °C. Found: C, 70.31; H, 8.20%. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08%.

IR (Nujol): 3300, 1195, 1145, 1100, and 1067 cm^{-1}. PMR ($CDCl_3$): δ 2.20 (12H, br s, $Ar-C\underline{H}_3$), 2.92 (2H, br s, $-O\underline{H}$), 3.63 (2H, dd, J=4.5 and 12 Hz, $-CH-\overset{\underline{H}}{\underset{H}{C}}-OH$), 3.72 (6H, s, $-OC\underline{H}_3$), 4.15 (2H, dd, J=9 and 12 Hz, $-CH-\overset{H}{\underset{\underline{H}}{C}}-OH$), 5.07 (2H, dd, J=4.5 and 9 Hz, $Ar-C\underline{H}\begin{smallmatrix}\diagup CH_2-\\ \diagdown O-\end{smallmatrix}$), and 6.43 ppm (4H, s, $Ar-\underline{H}$). **2b**; mp 167—168 °C. Found: C, 70.51; H, 8.12%. IR (Nujol): 3250, 1310, 1196, 1140, 1090, 1068, and 1045 cm^{-1}. PMR ($CDCl_3$): δ 1.50 (6H, br s, $Ar-C\underline{H}_3$), 2.51 (6H, br s, $Ar-C\underline{H}_3$), 2.17 (2H, br s, $-O\underline{H}$), 3.66 (2H, dd, J=5 and 11.5 Hz, $-CH-\overset{\underline{H}}{\underset{H}{C}}-OH$), 3.72 (6H, s, $-OC\underline{H}_3$), 4.05 (2H, dd, J=9 and 11.5 Hz, $-CH-\overset{H}{\underset{\underline{H}}{C}}-OH$), 4.70 (2H, dd, J=5 and 9 Hz, $Ar-C\underline{H}\begin{smallmatrix}\diagup CH_2-\\ \diagdown O-\end{smallmatrix}$), and 6.53 ppm (4H, br s, $Ar-\underline{H}$).

Reduction of meso- *and* dl-*Bis(α-methoxycarbonyl-2,6-dimethyl-4-methoxybenzyl) Ethers with Lithium Aluminium Deuteride.* i) The meso and racemic ethers (430 mg, 1 mmol) were reduced with $LiAlD_4$ (76 mg, 2 mmol) in ether under reflux to give **2a-D** (352 mg, 93%) and **2b-D** (349 mg, 92%), respectively. **2a-D**; mp 114—115 °C. PMR ($CDCl_3$): δ 2.20 (12H, br s, $Ar-C\underline{H}_3$), 2.75 (2H, br s, $-O\underline{H}$), 3.73 (6H, s, $-OC\underline{H}_3$), 5.09 (2H, s, $Ar-C\underline{H}\begin{smallmatrix}\diagup CD_2-\\ \diagdown O-\end{smallmatrix}$), and 6.52 ppm (4H, s, $Ar-\underline{H}$). **2b-D**; mp 166—167 °C. PMR ($CDCl_3$): δ 1.57 (6H, br s, $Ar-C\underline{H}_3$), 2.27 (1H, s, $-O\underline{H}$), 2.57 (1H, s, $-O\underline{H}$), 2.58 (6H, br s, $Ar-C\underline{H}_3$), 3.75 (6H, s, $-OC\underline{H}_3$), 4.74 (2H, s, $Ar-C\underline{H}\begin{smallmatrix}\diagup CD_2-\\ \diagdown O-\end{smallmatrix}$), and 6.58 ppm (4H, br s, $Ar-\underline{H}$).

ii) The meso ether (200 mg, 0.47 mmol) was allowed to react with $LiAlD_4$ (180 mg, 4.7 mmol) in ether under reflux and the complex decomposed with dil HCl to give **2a-D** (163 mg, 91%) and **5a-D** (8 mg, 5%). **5a-D**; mp 243—244 °C. Found: C, 73.52; H, 7.77%. Calcd for $C_{22}H_{24}D_4O_4$: C, 73.31; H, 8.03%. IR (Nujol): 1306, 1280, 1142, 1100, and 1060 cm^{-1}. MS: *m/e* (rel intensity) 360 (M^+, 1), 164 (100), 148 (18), 135 (23), 121 (29), 105 (25), and 91 (35). The racemic isomer (200 mg, 0.47 mmol) was treated with $LiAlD_4$ (180 mg, 4.7 mmol) in a manner similar to that described above to give **2b-D** (142 mg, 72%) and **5b-D** (37 mg, 22%). **5b-D**; mp 252—253 °C. Found: C, 73.35; H, 7.71%. IR (Nujol): 1306, 1280, 1150, 1135, 1090, 1062, and 1000 cm^{-1}. MS: *m/e* (rel intensity) 360 (M^+, 4), 180 (1), 164 (100), 148 (13), 135 (17), 121 (23), 105 (14), and 91 (25).

Reaction of Bis[2-hydroxy-1-(2,6-dimethyl-4-methoxyphenyl)ethyl] Ethers (2a and 2b) with Tosyl Chloride. i) The ether **2a** (110 mg, 0.29 mmol) was mildly refluxed with tosyl chloride (550 mg, 2.3 mmol) in pyridine (10 ml) for 1 h. The reaction mixture was poured into ice water and extracted with ether. The ether layer was washed with dil HCl and water, and dried. The crude product afforded an oily **3** (29 mg, 56%) and **4** (43 mg, 42%), mp 113—114 °C. **3**; IR ($CHCl_3$): 2830, 2720, 1716, 1200, 1140, and 1060 cm^{-1}. PMR ($CDCl_3$): δ 2.17 (6H, s), 3.55 (2H, d, J=2 Hz), 3.64 (3H, s), 6.49 (2H, s), and 9.6 ppm (1H, t, J=2 Hz). 2,4-Dinitrophenylhydrazone of **3**; mp 168—169 °C. Found; C, 56.91; H, 5.04; N, 15.61%. Calcd for $C_{17}H_{18}N_4O_5$: C, 56.98; H, 5.06; N, 15.64%. Oxidation of **3** with chromium(VI) oxide in acetic acid gave 2,6-dimethyl-4-methoxy-phenylacetic acid, mp 144—145 °C. Found: C, 68.13; H, 6.55%. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 6.74%. **4**; Found: C, 74.23; H, 8.09%. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92%. IR ($CHCl_3$): 1180, 1140, 1118, and 1040 cm^{-1}. MS: *m/e* (rel intensity) 356 (M^+, 2), 207 (25), 179 (28), 162 (10), 149 (100), 138 (11), 119 (18), 105 (8), and 91 (18). PMR ($CDCl_3$): δ 2.39 (12H, s), 3.10 (2H, d, J=4 Hz), 3.75 (1H, t, J=8 Hz), 3.78 (6H, s), 3.99 (1H, t, J=8 Hz), 5.00 (1H, t, J=4 Hz), 5.28 (1H, t, J=8 Hz), and 6.68 ppm (4H, br s). Both evaporation to dryness of the water layer and acetylation of the residue did not give any isolable product.

ii) The racemic isomer **2b** (110 mg, 0.29 mmol) was treated with tosyl chloride (550 mg, 2.3 mmol) in a manner similar to that described above to give **3** (5 mg, 10%), **4** (24 mg, 23%) and **5** (43 mg, 42%). **5**; mp 244 °C. Found: C, 73.96; H, 7.86%. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92%. IR ($CDCl_3$): 1190, 1177, 1148, 1100, and 1065 cm^{-1}. MS: *m/e* (rel intensity) 356 (M^+, 15), 178 (14), 163 (34), 162 (100), 149 (88), 105 (6), and 91 (13). PMR ($CDCl_3$): δ 2.46 (12H, s), 3.66 (6H, s), 3.79 and 3.88 (4H, AB in ABX, $J_{AX}=10$, $J_{BX}=6$ Hz, $J_{AB}\simeq 0$), 4.99 (2H, X in ABX, $J_{AX}=10$ and $J_{BX}=6$ Hz), and 6.46 ppm (4H, s).

Reaction of Bis[2,2-dideuterio-2-hydroxy-1-(2,6-dimethyl-4-methoxyphenyl)ethyl] Ethers (2a-D and 2a-D) with Tosyl Chloride.

i) The meso compound, **2a-D** (210 mg, 0.56 mmol), was allowed to react with tosyl chloride (1.1 g, 4.6 mmol) in pyridine (20 ml) for 1 h. After the usual work-up, when the crude product was dissolved in a solution of benzene–hexane (1:1), a tosylate (28 mg, 8%) precipitated, mp 128 °C from EtOH. Found: C, 63.31; H, 6.39%. Calcd for $C_{36}H_{38}D_4O_9S_2$: C, 62.94; H, 6.29%. PMR ($CDCl_3$): δ 1.94 (6H, br s, $Ar-C\underline{H}_3$), 2.04 (6H, br s, $Ar-C\underline{H}_3$), 2.48 (6H, s, $Ar-C\underline{H}_3$), 3.78 (6H, s, $-OC\underline{H}_3$), 5.20 (2H, s, $Ar-C\underline{H}-O-$), 6.57 (4H, br s, $Ar-\underline{H}$), 7.58 (4H, d, J=9 Hz, $Ar-\underline{H}$), and 8.05 ppm (4H, d, J=9 Hz, $Ar-\underline{H}$). The mother liquor afforded a mixture (79 mg) of **3-D-1** and **3-D-2**, and **4-D** (42 mg, 21%). The mixture of **3-D-1** and **3-D-2**; PMR ($CDCl_3$): δ 2.27 (6H, s), 3.55 (0.5H, br s), 3.79 (3H, s), 6.71 (2H, s), and 9.97 ppm (0.5H, s). **4-D**; PMR ($CDCl_3$): δ 2.41 (12H, s), 3.80 (6H, s), 5.13 (1H, s), 5.42 (1H, s), and 6.73 ppm (2H, s).

ii) The racemic isomer **2b-D** (214 mg, 0.57 mmol) afforded a mixture (50 mg) of **3-D-1** and **3-D-2** (1:1), **4-D** (52 mg, 26%), and a tosylate (55 mg, 15%), mp 115 °C. Found:

C, 62.77; H, 6.03%. PMR ($CDCl_3$): δ 1.47 (6H, br s, Ar–C$\underline{H}_3$), 2.38 (6H, br s, Ar–C$\underline{H}_3$), 2.43 (6H, br s, Ar–C$\underline{H}_3$), 3.77 (6H, s, –OC$\underline{H}_3$), 4.70 (2H, s, Ar–C$\underline{H}$–O–), 6.50 (2H, br d, J=2 Hz, Ar–$\underline{H}$), 6.59 (2H, br d, J=2 Hz, Ar–$\underline{H}$), 7.40 (4H, d, J=8.5 Hz, Ar–$\underline{H}$), and 7.80 ppm (4H, d, J=8.5 Hz, Ar–$\underline{H}$).

*Hydrolysis of Acetal (**4-D**) with Hydrochloric Acid in Methanol.* Acetal **4-D** (30 mg) was refluxed with 4 M HCl (6 ml) in MeOH (10 ml) for 1 h. The crude product afforded a mixture (7 mg) of **3-D-1** and **3-D-2**, and an oil **6** (8 mg) and **7** (15 mg). **6**; Found: C, 68.72; H, 8.80%. Calcd for $C_{13}H_{18}D_2O_2$: C, 69.00; H, 9.06%. MS: *m*/*e* (rel intensity) 226 (M^+, 2), 151 (9), and 75 (100). IR ($CHCl_3$): 1315, 1180, 1145, 1130, 1065, and 1000 (sh) cm^{-1}. PMR ($CDCl_3$): δ 2.38 (6H, s), 3.39 (6H, s), 3.83 (3H, s), 4.50 (1H, br s), and 6.74 ppm (2H, s). **7**; Found: C, 67.52; H, 8.53%. Calcd for $C_{12}H_{16}D_2O_3$: C, 67.90; H, 8.70%. MS: *m*/*e* (rel intensity) 213 ($M+1^+$, 2), and 179 (100). IR ($CHCl_3$): 3580, 3460, 1305, 1140, 1095, 1085, 1000, and 963 cm^{-1}. PMR ($CDCl_3$): δ 2.33 (1H, br s), 2.42 (6H, s), 3.30 (3H, s), 3.83 (3H, s), 4.86 (1H, s), and 6.72 ppm (2H, s).

*Preparation of 1,1-Dideuterio-2-methoxy-2-(2,6-dimethyl-4-methoxyphenyl)ethanol (**7**).* α-Cyano-2,6-dimethyl-4-methoxybenzylalcohol (1.3 g) was refluxed with a catalytic amount of TsOH in abs MeOH for 12 h. The crude product gave 0.72 g (52%) of α-cyano-2,6-dimethyl-4-methoxybenzyl methyl ether, bp 204—206 °C/27 mmHg. Found: C, 70.19; H, 7.39; N, 7.17%. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82%. PMR ($CDCl_3$): δ 2.45 (6H, s), 3.48 (3H, s), 3.76 (3H, s), 5.41 (1H, s), and 6.69 ppm (2H, s). The methyl ether (500 mg) was hydrolyzed in abs EtOH (50 ml) with dry HCl at 50 °C for 3 h. The crude product gave 420 mg (75%) of α-methoxy-(2,6-dimethyl-4-methoxyphenyl)-acetamide, mp 156—157 °C from benzene. Found: C, 64.59; H, 7.70; N, 6.16%. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.68; N, 6.27%. IR (Nujol): 3350, 3130, and 1675 cm^{-1}. PMR ($CDCl_3$): δ 2.38 (6H, s), 3.30 (3H, s), 3.83 (3H, s), 5.20 (1H, s), 6.74 (2H, s), and 6.5—7.1 ppm (2H, br s, –N$\underline{H}_2$). The amide (240 mg) was hydrolyzed in ethylene glycol (10 ml) with aq 30% KOH to give α-methoxy-(2,6-dimethyl-4-methoxyphenyl)acetic acid, mp 101—102 °C from benzene–hexane. Found: C, 64.12; H, 7.21%. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19%. IR (Nujol): 3300—2200 and 1718 cm^{-1}. PMR ($CDCl_3$): δ 2.00—2.40 (1H, –O$\underline{H}$), 2.40 (6H, s), 3.37 (3H, s), 3.82 (3H, s), 5.30 (1H, s), and 6.73 ppm (2H, s). The carboxylic acid (85 mg) was reduced with $LiAlD_4$ (40 mg) in ether to give 68 mg (81%) of **7**.

Treatment of the tosylate of **2b-D** in pyridine. The tosylate (70 mg) of **2b-D** was boiled in pyridine (10 ml) for 4 h and gave a mixture (17 mg) of **3-D-1** and **3-D-2** (54:46).

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