nitrobenzoate) as a yellow solid (88 mg, 49%): mp 148–150 °C; $[\alpha]^{25}_D$ −13.6° (c 0.22, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.20–8.34 (m, 8 H), 5.67 (quint, J = 5.4 Hz, 1 H), 4.82 (dd, J = 4.4, 12.7 Hz, 1 H), 4.70 (dd, J = 5.6, 12.7 Hz, 1 H), 3.10 (dd, J = 6.0, 16.8 Hz, 1 H), 2.97 (dd, J = 4.8, 16.8 Hz, 1 H): IR (Nujol) 2930, 2860, 1740, 1730, 1610, 1540, 1460, 1415, 1380, 1355, 1280, 1260, 1105, 1095, 1015, 880, 850, 725, 720 cm^{-1}. Anal. Calcd for $C_{18}H_{13}N_3O_8$ (1,2-bis(p-nitrobenzoate)): C, 54.14; H, 3.28; N, 10.52. Found: C, 53.99; H, 3.41; N, 10.40.

Reaction of Glycidyl p-Nitrobenzoate with Et_2AlCN.[10] To a solution of glycidyl p-nitrobenzoate (34 mg, 0.15 mmol, racemic mixture) in toluene (5 mL) was added Et_2AlCN (1.5 M solution in toluene, Alfa, 0.1 mL, 0.15 mmol) at room temperature. After 5 min, the homogeneous yellow solution was diluted with ether (30 mL) and then washed with 10% H_2SO_4, saturated $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4) and concentrated to yield pure 3-cyano-1,2-propanediol 1-O-p-nitrobenzoate (27 mg, 71%). The product was characterized as described above.

Reaction of Glycidyl p-Nitrobenzoate with PhSH in Et_3N. A solution of glycidyl p-nitrobenzoate (56 mg, 0.25 mmol, racemic mixture) and PhSH (56 mg, 0.5 mmol) in Et_3N (3 mL) was stirred at room temperature overnight. It was concentrated and the residue was chromatographed (2:1 hexane–EtOAc) to yield 84 mg (100%) of a 4:1 mixture of 3-(phenylthio)-1,2-propanediol 1-O-p-nitrobenzoate and 3-(phenylthio)-1,2-propanediol 2-O-p-nitrobenzoate as a solid. The product was characterized as described below.

Reaction of Glycidyl p-Nitrobenzoate with PhSH in Pyridine. A solution of glycidyl p-nitrobenzoate (45 mg, 0.2 mmol, racemic mixture) and PhSH (0.04 mL, 44 mg, 0.4 mmol) in pyridine (1 mL) was stirred at room temperature overnight. It was concentrated (0.5 mm at room temperature) and the residue was chromatographed (2:1 hexane–EtOAc) to yield 65 mg (97%) of a yellow solid which was characterized by ^1H NMR as a 14:1 mixture of 3-(phenylthio)-1,2-propanediol 1-O-p-nitrobenzoate and 3-(phenylthio)-1,2-propanediol 2-O-p-nitrobenzoate. Data for the mixture: mp 97.5–100 °C; ^1H NMR ($CDCl_3$) δ 8.19–8.39 (m, 4 H), 7.23–7.47 (m, 5 H), 5.32 (m, 0.07 H), 4.53 (dd, J = 2.6, 9.9 Hz, 0.93 H), 4.43 (dd, J = 5.6, 9.0 Hz, 0.93 H), 4.10 (m, 0.93 H), 4.0 (m, 0.14 H), 3.39 (dd, J = 6.8, 14.3 Hz, 0.07 H), 3.33 (dd, J = 6.4, 14.3 Hz, 0.07 H), 3.24 (dd, J = 4.9, 13.5 Hz, 0.93 H), 3.01 (dd, J = 6.9, 13.5 Hz, 0.93 H), 2.78 (d, J = 3.7 Hz, 0.93 H), 1.93 (br, 0.07). Anal. Calcd for $C_{16}H_{15}NO_5S$: C, 57.65; H, 4.54; N, 4.20. Found: C, 57.59; H, 4.47; N, 4.05.

Reaction of Glycidyl p-Nitrobenzoate with Acetone in the Presence of Acid Catalyst. To a solution of (2R)-glycidyl p-nitrobenzoate (56 mg, 0.25 mmol, 92% ee) in acetone (5 mL) was added a drop of concentrated H_2SO_4, and the solution was stirred at room temperature overnight. The reaction mixture was diluted with ether (30 mL) and washed with saturated $NaHCO_3$ (15 mL). The aqueous layer was extracted with ether (2 × 10 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated. Flash chromatography (4:1 hexane–EtOAc) afforded 1,2-O-isopropylideneglycerol p-nitrobenzoate as an oil (54 mg, 76%): ^1H NMR ($CDCl_3$) δ 8.23–8.30 (m, 4 H), 4.47–4.55 (m, 2 H), 4.40 (dd, J = 6.7, 11.3 Hz, 1 H), 4.19 (dd, J = 6.2, 9.0 Hz, 1 H), 3.90 (dd, J = 4.9, 9.0 Hz, 1 H), 1.47 (s, 3 H), 1.41 (s, 3 H); IR (neat) 3110, 3080, 3055, 2990, 2940, 2890, 1720, 1605, 1525, 1450, 1410, 1380, 1370, 1350, 1320, 1275, 1220, 1160, 1120, 1100, 1080, 1055, 1015, 975, 875, 855, 845, 785, 720 cm^{-1}.

The ^1H NMR in the presence of a chiral shift reagent, Eu(hfc)$_3$, indicated that the enantiomeric purity of the product was 62% ee.

The product 1,2-O-isopropylideneglycerol p-nitrobenzoate (45 mg, 0.16 mmol, 62% ee, obtained from above) was treated with 60% aqueous acetic acid (5 mL) at room temperature overnight. Dilution with EtOAc (30 mL) was followed by washing with saturated $NaHCO_3$ (30 mL). The aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to yield (R)-glycerol mono-p-nitrobenzoate as a yellow solid (34 mg, 88%): mp 77–82 °C; $[\alpha]^{25}_D$ −7.80° (c 1.77, EtOH) [lit.[14] mp 88–89 °C; $[\alpha]^{25}_D$ −17.1° (EtOH)].

(14) Fischer, H. O. L.; Baer, E. *Chem. Rev.* **1941**, *29*, 287.
(15) The R,S assignments are based on the stereochemical consequences of the presumed reaction mechanisms.

(2R)-Glycidyl p-nitrobenzoate (45 mg, 0.2 mmol) was similarly treated with acetone in the presence of concentrated H_2SO_4 catalyst at −20 °C. After 14 days, it was worked up as previously described to afford the (2R)-solketal p-nitrobenzoate (37 mg, 67%). The ^1H NMR in the presence of Eu(hfc)$_3$ indicated that the product was of 77% ee.

Acknowledgment. We are grateful to the National Institutes of Health (GM28384) and Eli Lilly and Company for financial support. H.M. thanks Merck and Company for a postdoctoral fellowship.

Supplementary Material Available: The experimental procedures and spectroscopic data not described in the Experimental Section (7 pages). Ordering information is given on any current masthead page.

(16) Karpyshev, N. N.; Bushnev, A. S.; Polystyanov, A. E.; Zvonkova, E. N.; Evstigneeva, R. P. *Bioorg. Khim.* **1979**, *5*, 238; *Chem. Abstr.* **1979**, *90*, 167984u.
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Further Studies on Sodium Borohydride–Polyethylene Glycol 400 as a Novel Reducing System

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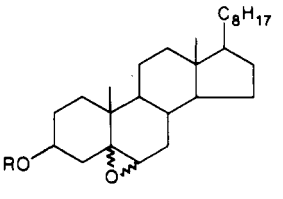
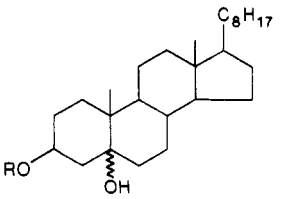
We have previously described the reaction of sodium borohydride with excess PEG (polyethylene glycol) 400 at 80 °C, the ratio 2:1 representing the stoichiometry of the reaction, suggesting that the active species could have the simplified formula $Na[(OCH_2CH_2)_nOH]_2BH_2$ (n = 8,9), $Na(PEG)_2BH_2$, not excluding other reactive species.[1,2] Several substrates were efficiently reduced by using $NaBH_4$ in PEG 400 or 0.5–0.6 M solutions of $Na(PEG)_2BH_2$ in THF.[2] We present now our most recent results of additional studies on $Na(PEG)_2BH_2$ reactivity.

Reduction of Epoxides. Preliminary experiments in THF at 80 °C (ratio of $Na(PEG)_2BH_2$ to epoxide, 3:1) on the epimeric mixture of 5,6-epoxides **1a** prepared from cholesterol acetate were hampered by hydrolysis of the acetate moiety, and yields of the corresponding diol **2a** were 45%. Under the same conditions, reduction of 3β-methoxy-5,6-epoxide **1b** was cleaner and yields of **2b** were 50% along with 50% of unreacted starting material. For



1a, R = $COCH_3$
b, R = CH_3



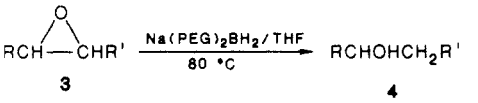
2a, R = H
b, R = CH_3

further studies, simple epoxides were examined, and we noticed that the best reproducible yields were obtained

(1) Istituto di Endocrinologia, Facoltà di Farmacia, Università di Milano.
(2) Santaniello, E.; Fiecchi, A.; Manzocchi, A.; Ferraboschi, P. *J. Org. Chem.* **1983**, *48*, 3074.

0022-3263/87/1952-0671$01.50/0

Table I. Reduction of Epoxides by $Na(PEG)_2BH_2$



epoxide	reducing agent:substrate ratio[a]	time, h	yield,[b] %
3a, R = C_6H_5, R' = H	1.5	5	95
3b, R = R' = C_6H_5	6	20	70
3c, R = $CH_3(CH_2)_5$, R' = H	5	6	75
3d, R = R' = $CH_3(CH_2)_2$	3	5	*c*
3e, R,R' = $-CH_2(CH_2)_4CH_2-$	3	20	*d*
3f, R = $CH_3(CH_2)_7$, R' = $(CH_2)_7COOCH_3$	6	1	10[e]

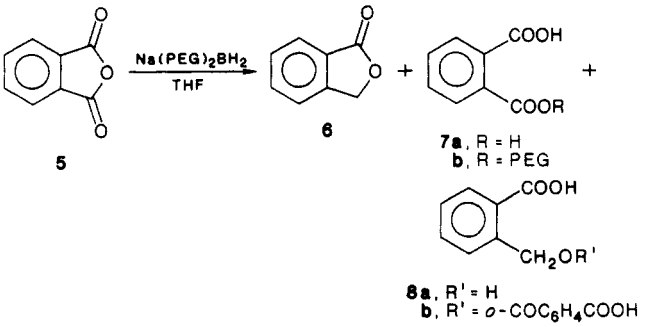
[a] Ratio 3 means that 3 mol of $NaBH_4$ are reacted with 6 mol of PEG 400 at 80 °C until 6 mol of hydrogen is formed. We consider that, at this point, 3 mol of $Na(PEG)_2BH_2$ are formed. [b] Yields refer to isolated, pure products and are not optimized. [c] Starting material present in traces, more polar product(s) prevailing. [d] Essentially starting material was recovered, along with minor amounts of more polar unidentified compounds. [e] 10% of starting material and 30% of 1,9(10)-dihydroxyoctadecane were isolated.

with unsubstituted epoxides (Table I). Stilbene oxide (**3b**) was reduced to the corresponding alcohol only when an excess of borohydride was used for longer time (30% of unreacted starting material still present). When an epoxide containing an ester group was reduced, a complex mixture of products was obtained and, as in the case of epoxide **3f**, it was rather difficult to direct the reduction toward the hydroxy ester **4f**, which was isolated in 10% yield. In the most significant experiment, products were obtained in 50% yields (10% starting material) and the main product recovered after flash chromatography[3] corresponded to the 1,9(10)-diol (30% yield). With substituted epoxides **3d** and **3e**, no product of reduction was obtained, and in the case of **3d**, low recovery of starting material was noticed. This was probably due to opening of the oxirane ring and binding of a polyethylene glycol moiety to the molecule with consequent formation of compounds of more difficult recovery.

Reduction of Phthalic Anhydride. The tetrahydrofuran solution of $Na(PEG)_2BH_2$ was tested for selective reduction of phthalic anhydride (**5**) to phthalide (**6**). Indeed, an intriguing situation was evident from the results of this reduction by means of $Na(PEG)_2BH_2$ at different temperatures (Table II). At room temperature, no formation of phthalide (**6**) was observed and a mixture of phthalic acid (**7a**) (identified as its dimethyl ester, 34%) and a monoester of phthalic acid with PEG (compound **7b**, 22% yield assigning to this monoester an average molecular weight of 565) could be isolated and identified. It is noteworthy that PEG monoester **7b** was actually a mixture of esters of different oligomers, since treatment of **7b** with diazomethane afforded a mixture of different esters, as shown by TLC analysis. At 0 °C, a mixture of the hydroxy acid **8a** and the product of alcoholysis of phthalic anhydride (**5**) with **8a** itself, namely, ester **8b**, was formed. Also the previously described ester of phthalic acid with PEG, **7b** (9%), was formed in the reduction at 0 °C. For determination of the relative proportions of **8a** and **8b**, some chemical work was still necessary. Thus, the residue from reduction was partially soluble in chloroform, and this portion consisted of a mixture of hydroxy acid **8a** (cyclized to **6** by acidic treatment, 22%) and PEG ester **7b** (identified by ^1H NMR and GC–MS of its acetate, 9%).

(3) Still, W. C.; Kahn. M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Table II. Reduction of Phthalic Anhydride (5)



$NaBH_4$–PEG 400 (mol)	*T*, °C	time, h	yields of **6**, %[a]	yields of **7b**, %[b]	yields of **8b**, %
1:3	25	1		22[c]	
1:3	0	0.5	40	9	18
1:3	−10	1	54	9	19
1:3	−20	1	75	6	21

[a] Yields of phthalide are referred to as overall yields, occurring from hydroxy acid **8a** recovered as such from the mixture and from **8b**. [b] Pure and isolated products. [c] Phthalic acid (**7a**) (34%) was also isolated.

The residue insoluble in chloroform was **8b**, identified by its dimethyl ester, and corresponded to 18% of the reaction mixture, thus bringing to 40% the overall yield of phthalide (**6**) from reduction of **5** at 0 °C. At −10 °C, yields of phthalide (**6**) were slightly improved (54% overall, 35% as **8a** and 19% as free **8b**), together with **7b** (9%). The best yields in the reduction product expressed as percentage of phthalide (**6**) were obtained at −20 °C (75% overall, 54% as **8a** and 21% as **8b**), along with 6% of **7b**. We conclude that at room temperature reaction of PEG itself with phthalic anhydride (**5**) is faster than reduction by means of $Na(PEG)_2BH_2$. On the contrary, at lower temperatures alcoholysis of **5** by PEG is limited in extent, the main reaction being reduction of the anhydride moiety, eventually accompanied by reaction of the formed 2-(hydroxymethyl)benzoic acid (**8a**) with the anhydride **5**.

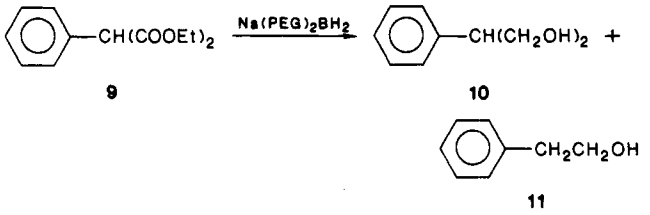
Reduction of Diethyl Phenylmalonate.[4] Initially phenylmalonate **9** was reacted under conditions suitable for ester reduction by $NaBH_4$–PEG 400,[5] but, to our surprise, the diol **10** was not the main product. Instead, 2-phenylethanol (**11**) was obtained in substantial amounts, and after investigation of this reduction, we found that yields depended on the solvent used (Table III). Attempts to direct the reduction toward diol **10** by use of lower temperature or reduced ratio of the borohydride slowed the reaction too much and was not convenient with respect to yields of products. In Table III are presented the optimized conditions for this unusual reduction, which could be rationalized as a dealkoxycarbonylation followed by reduction of the formed ethyl phenylacetate. On the other hand, it is well-known that dealkoxycarbonylation can be effected by heating with lithium halides or sodium cyanide in solvents such as hexamethylphosphoric triamide, dimethyl sulfoxide, or dimethylformamide.[6] We attempted dealkoxycarbonylation of phenylmalonate **9** in PEG 400 in the presence of a variety of inorganic salts. The only appreciable result was that at 180–210 °C in the presence

(4) We thank Dr. Fiamma Ronchetti (Dipartimento di Chimica Organica e Industriale, University of Milan) for preliminary reactions on phenylmalonate.

(5) Santaniello, E.; Ferraboschi, P.; Sozzani, P. *J. Org. Chem.* **1981**, *46*, 4584.

(6) Krapcho, A. P. *Synthesis* **1982**, 805, 983.

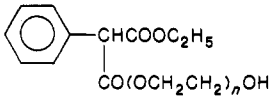
Table III. Reduction of Diethyl Phenylmalonate (9)



$NaBH_4$–PEG 400 (mol)	T, °C	time, h	solvent	yields of 10,[a] %	yields of 11,[a] %
1:10	80	1	PEG 400	4	44
1:2	80	5	THF	15	45[b]

[a] Yields of pure and isolated products. [b] Starting material **9** (12%) was recovered, along with $C_6H_5CH_2COOC_2H_5$ (12%) and transesterification product **12b**.

of water the process of dealkoxycarbonylation is limited in extent (10–20%), the main product being unreacted malonate. When water was omitted, the main product obtained arose from a transesterification with PEG 400, namely ester **12a**. However, again a complication arises



12a, n = 8,9 (av)
b, n = 4

from the facts that PEG 400 consists of a mixture of oligomers (400 corresponds only to the molecular average weight) and a depolymerization of PEG 400 at the adopted temperatures cannot be excluded. Consequently, the transesterification product(s) **12a** show several spots of close R_f by TLC analysis. Therefore, in order to prepare and characterize a standard of transesterification, we reacted malonate **9** with tetraethyleneglycol (TEG), a purified oligomer that can be roughly compared to PEG 200. The ester **12b** was obtained in 30% yields of isolated product (180 °C, 0.5 h), whereas no transesterification with PEG 400 or TEG was observed when ethyl phenylacetate was heated in the same conditions as above also for a longer period (4 h). It is also worthy of note that when reduction of malonate **9** with $Na(PEG)_2BH_2$ was performed in THF, some transesterification product of the malonate ester with PEG (**12a**, 7% yields) was also isolated.

Experimental Section

Infrared spectra were recorded for solutions in chloroform or Nujol mulls. NMR spectra were taken on a Varian EM 360 L as chloroform-*d* solutions. The mass spectra were determined on a LKB 2091 mass spectrometer by direct inlet methods or by GC with a 1% OV 17 column and helium as carrier. The progress of all reactions was monitored by TLC on silica gel (HF_{254}) plates or by GC analyses on a 2-m silanized column of 1% SE-30 on Gas Chrom Q, operating at 70–200 °C. Distillations were performed with a Büchi 500 glass oven.

Preparation of $Na(PEG)_2BH_2$. The alkoxyborohydride $Na(PEG)_2BH_2$ was prepared as described[2] and used after the evolution of 2 molar equiv of hydrogen. Freshly prepared dialkoxyborohydride was used for the reduction of different substrates in tetrahydrofuran.

Reductions of Epoxides with $Na(PEG)_2BH_2$ in Tetrahydrofuran. Typical Procedure: Reduction of Epoxide 3a. A solution of **3a** (0.12 g, 1 mmol) in tetrahydrofuran (2 mL) was added to freshly prepared $Na(PEG)_2BH_2$ (1.5 mmol) and the temperature raised to 80 °C. Additional THF was added (2 mL) in order to dissolve the viscous solid formed, and when the reaction was complete, the reaction mixture was cooled to room temperature. It was poured into water, and 0.1 M HCl was added to pH 5 and the solvent removed under reduced pressure. Extractions with diethyl ether and usual workup furnished 1-phenylethanol (**4a**) (0.116 g, 95%), essentially pure: ^1H NMR δ 1.45 (d, 3 H), 2.20 (s, exchangeable with ^2H_2O), 4.75 (q, 1 H), 7.20 (complex, 5 H).

Reduction of Phthalic Anhydride (5). A. At Room Temperature. $Na(PEG)_2BH_2$ was prepared by heating at 80 °C $NaBH_4$ (128 mg, 3.37 mmol) and PEG 400 (4.04 g, 10.11 mmol) until 148 mL of hydrogen was formed. The solution was cooled to room temperature, and a solution of **5** (1 g, 6.75 mmol) in tetrahydrofuran (17 mL) was added to the borohydride with stirring. After 1 h, 1 N HCl was added to acidic pH, the solvent was removed under reduced pressure, and after usual workup, a residue was obtained (1.18 g), which was only partially soluble in chloroform. The insoluble solid was filtered off and identified as phthalic acid (0.382 g, 34%) by mixed melting point with authentic acid and identification of its dimethyl ester. The organic solution (0.841 g) was further examined, and the ^1H NMR spectrum of this compound suggested a structure of monoester PEG–phthalic acid **7b** (22% yield): δ 3.75 (br), 4.50 (br t), 7.70 (br). Acetylation of part of the above compound (70 mg) with acetic anhydride (0.2 mL) and pyridine (0.2 mL) afforded after workup a residue, which was examined by GC–MS (OV 17, 1% *T* 210 °C): MS, m/z M^+ absent, 280, 207, 192, 163, 149 (100%), 133, 105.

B. At −20 °C. $Na(PEG)_2BH_2$ was prepared as above from $NaBH_4$ (128 mg, 3.37 mmol) and PEG 400 (4.04 g, 10.11 mmol). The solution was cooled to room temperature and then brought to −20 °C, and a solution of **5** (1 g, 6.75 mmol) in tetrahydrofuran (17 mL) was added to the borohydride with stirring. After 1 h, 1 N HCl was added to acidic pH, the solvent was removed under reduced pressure, and after usual workup, a residue was obtained (1.29 g), which was taken up with chloroform. The organic solution (0.782 g) consisted of a mixture of hydroxy acid **8a** and the monoester PEG–phthalic acid **7b** as suggested by the ^1H NMR spectrum of this mixture: δ 3.75 (br), 4.50 (br t), 5.3 (s), 7.70 (br). In order to evaluate the relative proportions of **8a** and **7b**, which presented the same R_f by TLC, 156 mg of the above mixture was treated with 4 N HCl (3 mL) and refluxed (4 h). After cooling at room temperature, the solid formed was filtered off and identified as phthalic acid. Extraction with diethyl ether (3 × 5 mL) and usual workup afforded a residue of essentially pure phthalide (**6**) (98 mg, 0.73 mmol). Acetylation of the above mixture of **7b** and **8a** (156 mg) with acetic anhydride (0.4 mL) and pyridine (0.4 mL) afforded after workup a residue, which was examined by GC–MS, and the peak identical with the acetate of **7b** isolated from the reduction at room temperature was present. The amount of **7b** in the reaction mixture was therefore roughly estimated to be 0.228 g (6% yield). An aliquot (85 mg) of the solid residue after treatment of the initial crude reaction mixture with chloroform (0.425 g, 21%) was dissolved in methanol and treated with an ethereal solution of diazomethane and consisted of essentially pure dimethyl ester of **8b**: IR ν_{max} 1760, 1720 cm^{-1}; ^1H NMR δ 3.80 (s, 3 H), 3.90 (s, 3 H), 5.65 (s, 2 H), 7.30–8.00 (br, 8 H); MS, m/z 328, 263, 207, 163, 149, 133, 119, 105.

Reduction of Diethyl Phenylmalonate (9). A. In PEG 400 as Solvent. To a mixture of title ester **9** (1.18 g, 5 mmol) in PEG 400 (50 mL) was added sodium borohydride (0.567 g, 15 mmol) at room temperature with stirring, and the temperature was raised to 80 °C, during which evolution of hydrogen was observed. The solution was kept at 80 °C for 1 h and cooled to room temperature, and water was added (30 mL) and then 2 N HCl to acidic pH. The solution was extracted with diethyl ether (3 × 50 mL), and the organic solution was washed with water (3 × 30 mL) and dried (Na_2SO_4). Evaporation of solvent at reduced pressure left a residue (0.410 g). After flash chromatography[3] (petroleum ether–ethyl acetate, 6:4), phenylethanol **11** was obtained (0.27 g, 44%). Yield of diol **10** (eluted with petroleum ether–ethyl acetate, 3:7) was 4% (30 mg, 0.2 mmol). Compound **11**: ^1H NMR δ 1.60 (s, 1 H exchangeable with ^2H_2O), 2.80 (t, 2 H), 3.85 (t, 2 H), 7.25 (br, 5 H). Compound **10**, ^1H NMR δ 3.20 (m, 1 H), 3.70 (br, 2 H), 4.10 (d, 4 H), 7.25 (complex, 5 H).

B. In Tetrahydrofuran. A solution of the malonate **9** (1.05 g, 4.44 mmol) in tetrahydrofuran (20 mL) was added to freshly

prepared $Na(PEG)_2BH_2$ (12 mmol) and the temperature raised to 80 °C. During the time of reaction (4 h), the formation of a viscous solid was observed, which made the stirring difficult. Tetrahydrofuran (10 mL) was therefore added in order to make the mixture homogeneous, and after cooling to room temperature, water and 1 N HCl solution to acidic pH were sequentially added and the solvent was removed under reduced pressure. Extractions and usual workup furnished a residue (0.77 g), which was purified by flash chromatography as above. Phenylethanol **11** was obtained (0.244 g, 2 mmol, 45%) along with diol **10** (0.101 g, 0.66 mmol, 15%). Also a mixture of starting malonate **9** (0.125 g, 0.53 mmol, 12%), phenylacetate $C_6H_5CH_2COOC_2H_5$ (0.088 g, 0.53 mmol, 12%), and transesterification product(s) (0.182 g, 0.31 mmol assuming as average molecular weight 590, 7% yield) were obtained.

Transesterification of Malonate 9 with Tetraethylene Glycol (TEG) (12b). In a round-bottom flask equipped with magnetic stirrer and reflux condenser, a mixture of malonate **9** (0.937 g, 3.95 mmol) and tetraethylene glycol (TEG) (3.85 g, 19.8 mmol) was kept at 180 °C for 0.5 h. After cooling, brine was added (40 mL, pH 5), and products were recovered by extractions with diethyl ether (6 × 20 mL) (0.750 g). Flash chromatography (dichloromethane–acetone, 8:2) gave starting material **9** (0.216 g, 0.914 mmol, 23%) and **12b** (0.36 g, 0.937 mmol, 24%): MS, m/z 384 (M^+); IR ν_{max} 1750, 1730 cm^{-1}; ^1H NMR δ 1.2 (t, 3 H), 3.0 (br, 1 H exchangeable with ^2H_2O), 3.40–3.75 (14 H), 3.90–4.35 (m, 4 H), 4.58 (s, 1 H), 7.30 (complex, 5 H).

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Directed Hydroxylation of Aromatics

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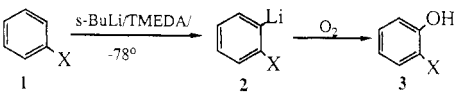
Although there are a number of mechanistically diverse methods which result in the hydroxylation of an aromatic ring,[1] it is often difficult to effect the transformation in a direct and regiospecific fashion. A potentially versatile class of procedures, the oxidation of aryl organometallics, is well-known;[2] however, examples of directed hydroxylation by application of this strategy are few.[3]

Studies on the chemical synthesis of phenolic natural products led us to investigate the oxygenation of aryllithium species which had been prepared by functional group-directed metalation (**1**[4,5] → **2** → **3**,[5] Scheme I). The one-pot lithiation/oxygenation sequence described here (*sec*-BuLi, TMEDA; then O_2) affords moderate yields of regiospecifically monohydroxylated products. Our experiments are summarized in Table I.

Entries 1–3 show the preparation of the predicted aryllithium[6] and its conversion to the corresponding phenol. Likewise, entries 4 and 5 show the expected phenolic products and illustrate the dominance of the tertiary amide group in determining the position of lithiation[7] and subsequent hydroxylation. Entries 1, 2, and

Scheme I



Scheme II

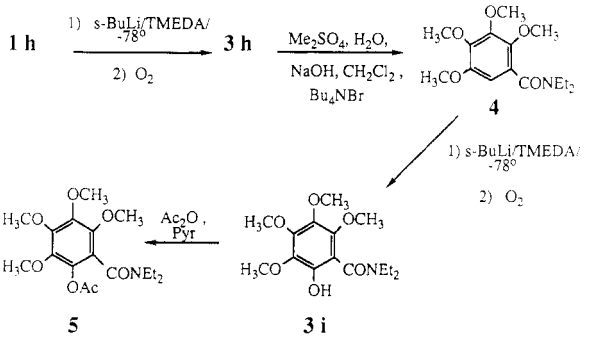
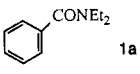
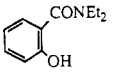
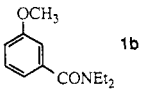
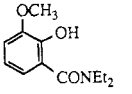
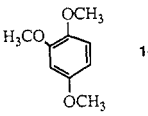
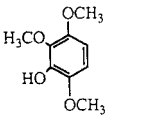
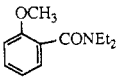
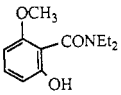
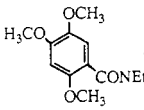
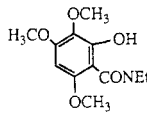
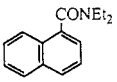
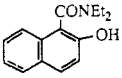
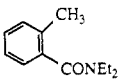
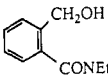
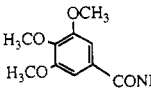
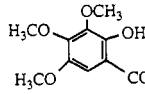


Table I

entry	starting material		reaction product		yield, %
1		1a		3a	37
2		1b		3b	51
3		1c		3c	34
4		1d		3d	46
5		1e		3e	52
6		1f		3f	34
7		1g		3g	49
8		1h		3h	48

(1) (a) For a short discussion of the problem and some key references, see: Dolson, M. G.; Swenton, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 2361. (b) For a review, see: Wedemeyer, K.-F. *Methoden der Organischen Chemie. Phenole*; Muller, E., Ed.; Georg Thieme Verlag: Stuttgart, 1976; Vol. VI/1C.

(2) (a) Garst, J. F.; Smith, C. D.; Ferrar, A. C. *J. Am. Chem. Soc.* **1972**, *94*, 7707. (b) Sosnovsky, G.; Brown, J. H. *Chem. Rev.* **1966**, *66*, 529.

(3) (a) Gilman, H.; Swiss, J.; Cheney, L. C. *J. Am. Chem. Soc.* **1940**, *62*, 1963. (b) Air oxygenation of arylcopper species prepared from aryllithium reagents has been reported: Lambert, G. J.; Duffey, R. P.; Dalzell, H. C.; Razdan, R. K. *J. Org. Chem.* **1982**, *47*, 3350. (c) A procedure involving lithiation–boration–oxidation was used for the conversion of **1a** to **3a** by: Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34. (d) The Beak procedure[3c] was applied for the ortho hydroxylation of *N,N*-dimethyl-3,4-(methylenedioxy)benzamide: Iwao, M.; Reed, J. N.; Snieckus, V. *J. Am. Chem. Soc.* **1982**, *104*, 5531.

(4) Amides **1** were prepared from the corresponding acids by the method of: McCabe, E. T.; Barthel, W. F.; Gertler, S. I.; Hall, S. A. *J. Org. Chem.* **1954**, *19*, 493.

(5) All new compounds were characterized by infrared and NMR spectroscopy and by high-resolution mass spectroscopy (satisfactory M^+).

(6) Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N. Y.)* **1979**, *26*, 1–360.

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