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Selective Hydrolysis of Methanesulfonate Esters

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Abstract:

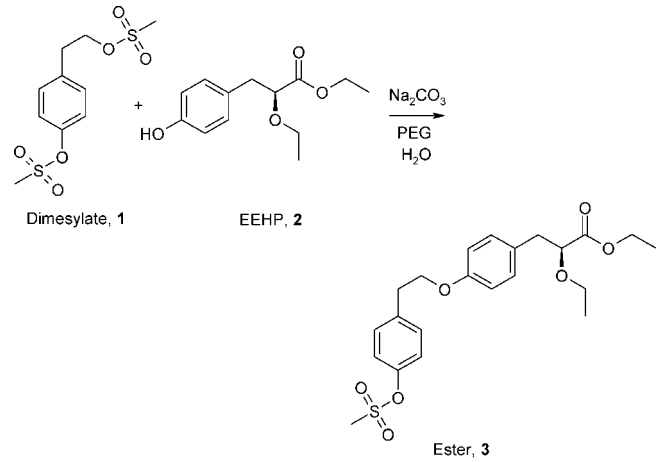
The pH dependence of the hydrolysis of 4-{2-[(methylsulfonyl)oxy]ethyl}phenyl methanesulfonate, 1, and two carboxylate esters, ethyl 2(*S*)-ethoxy-3-(4-hydroxyphenyl)propionate, 2 and (2*S*)-2-ethoxy-3-[4-(2-{4-[(methylsulfonyl)oxy]phenyl}ethoxy)phenyl]propanoate, 3, has been studied with a view to the selective removal of any remaining 1, following coupling with 2 to generate 3 in water at 95 °C (Scheme 1). It is shown that reduction of pH from that of the reaction conditions (pH ≈ 10) to pH 7–8 has little effect on the hydrolysis of 1, which is dominated by the water rate over this pH range, but reduces the rate of hydrolysis of the carboxylate ester group by 3 orders of magnitude (pH 7). This very strong quantitative difference in the response of the two types of ester group to pH change allows complete removal of 1 at low pH without measurable loss to the product ester, 3. The conclusions should be generally applicable to the removal of potentially genotoxic alkyl esters of methane sulfonic acid in the presence of carboxylic esters and other base-sensitive groups.

Introduction

The synthesis of the ester **3**, (2*S*)-2-ethoxy-3-[4-(2-{4-[(methylsulfonyl)oxy]phenyl}ethoxy)phenyl]propanoate, from dimesylate **1**, 4-{2-[(methylsulfonyl)oxy]ethyl}phenyl methanesulfonate, and ethyl 2(*S*)-ethoxy-3-(4-hydroxyphenyl)propionate (EEHP), **2**, proceeds very efficiently in a biphasic mixture with aqueous sodium carbonate at reflux (ca. 100 °C) for about 4–5 h, in the presence of a phase-transfer catalyst, PEG-400, Scheme 1.

In order to maximise the efficiency of the reaction with respect to EEHP, **2**, usage, the reaction is typically run with an excess of dimesylate **1**, (up to 1.6 mol eq). It was necessary, however, to reduce the level **1** at the end of this stage to <0.03 area % by HPLC in order to meet later-stage product specifications for this potentially genotoxic mesylate ester. Thus, although typically the coupling reaction itself is complete in about 4–5 h, an additional 3–4 h at reflux is required to degrade any excess **1**. During this prolonged heating period the ester group of the product, **3**, although partially protected by its low water solubility, is also susceptible to hydrolysis. Losses may be significant on extended heating; complete hydrolysis of the product under reaction conditions occurs after about 16 h. One important development target was the minimisation of the competing hydrolysis of EEHP, **2**, during coupling, through optimisation of the levels and mode of addition of carbonate base, thereby enabling a reduction in the excess of the dimesylate, **1**. However, the very low final levels of **1** required for product specification meant that in spite of this, it was not possible to avoid a subsequent prolonged hydrolysis, with its potential for yield losses. We therefore, wished to explore conditions under which it might be possible to achieve a more selective hydrolysis of **1** in the presence of the carboxylate ester **3**, recognising also that the selective hydrolysis of base-sensitive group is an issue of general importance.

Scheme 1. **Formation of ester 3**



The rate law for hydrolysis of a substrate, S, under basic conditions at fixed pH has the form shown in eqs 1 and 2.

$$-\frac{\mathrm{d[S]}}{\mathrm{d}t} = k_e[\mathrm{S}] \tag{1}$$

where

$$k_e = k_o + k_{OH}[\mathrm{OH^-}] \tag{2}$$

In eqs 1 and 2, k_e is the observed first-order rate constant, k_o the rate constant for the uncatalysed (water) rate, and k_{OH} the rate constant for the hydroxide reaction. In an important paper, King and co-workers[1] pointed out that the relative values of k_o and k_{OH} are very substrate dependent, and introduced the concept of pH_i, the pH at which the water and hydroxide rates are equal (i.e., $k_o = k_{OH}[OH^-]$ at pH_i). In particular, it is noticeable that hydrolyses of methanesulfonate and carboxylate esters have very different pH dependences. The hydrolysis of simple methansulfonate esters, such as ethyl methanesulfonate,

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(1) King, I. F.; Rathore, R.; Lam, J. Y. L.; Guo, Z. R.; Klassen, D.F. *J Am. Chem. Soc.* **1992**, *114*, 3028.

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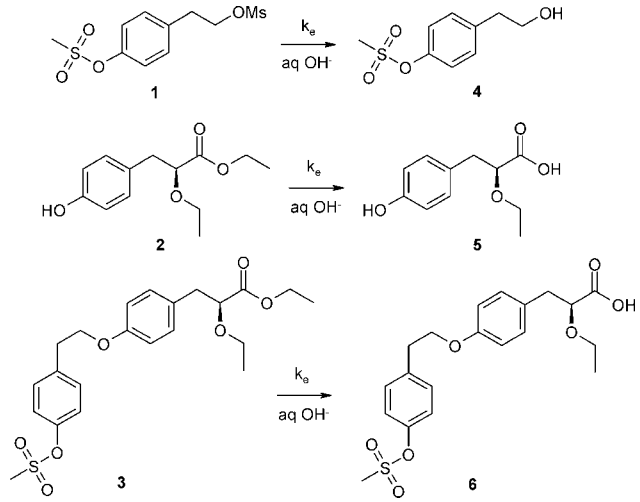
Scheme 2. **Rates of hydrolysis investigated**



is dominated by the water rate until high pH values ($pH_i \approx 12$). Carboxylate ester hydrolysis on the other hand typically shows low water rates but very high rate constants for acid- and base-catalysed reactions; typically, the hydrolysis rates depend directly on the hydroxide concentration from pH ≈ 5 onwards.[2,3] The two processes are, therefore, in principle separable, and lower pH values should strongly favour methanesulfonate hydrolysis relative to carboxylate hydrolysis.

In view of the above, the hydrolysis rates for **1**−**3** (Scheme 2), at different pH values were investigated as part of process optimisation for this system.

Under strongly basic conditions, there is also the possibility that hydrolysis of the arylsulfonate ester group in **4** would give the corresponding phenol.

Results

Dimesylate 1. The hydrolysis of dimesylate, **1**, was investigated at 95 °C at pH 6, 8, and 10. The temperature of 95 °C was chosen to allow a conveniently high reaction rate, without the complications arising from sampling at reflux. Reaction concentrations (Scheme 1, with initial concentrations $c = 0.3$ M) are such that **1** is only partially miscible with water; it forms a second phase at the beginning of the reaction, but as the amount of **1**, is reduced the system becomes homogeneous partway through the hydrolysis. There are, thus, two kinetic regimes during the hydrolysis, as follows:

(i) An initial two-phase reaction in which the aqueous concentration of **1** remains constant at its solubility, S_o, with a zero-order rate law for the formation of product alcohol, 4-(2-hydroxyethyl)phenyl methanesulfonate, **4**, eq 3.

$$\frac{d[4]}{dt} = k_e S_o \qquad (3)$$

(ii) A homogeneous reaction, that occurs once the total amount of **1** is reduced such that $[\mathbf{1}] \leq S_o$, with a first-order rate law, eq 4.

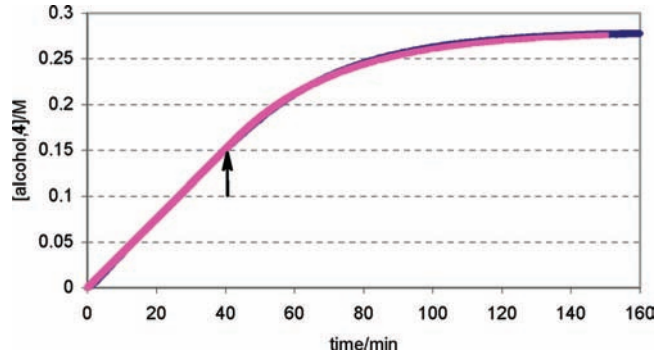


Figure 1. **Reaction profile for hydrolysis of dimesylate 1, at pH 6: ♦ (black) observed concentration of product, 4; ♦ (pink) calculated concentration, eqs 3 and 4: $k_e = 5.35 \times 10^{-4}$ s^{-1}; S_o, = 0.12 M. The arrow denotes the point at which the system becomes homogeneous.**

Table 1. **Hydrolysis of dimesylate 1, in aqueous solution at 95 °C**

pH	$[OH^-]$/M[a]	$10^4\ k_e$/s^{-1}	S_o/M
6.0	6.8×10^{-7}	5.3_5	0.12
8.0	6.8×10^{-5}	5.4_8	0.11
10.0	6.8×10^{-3}	7.3_0[b]	0.11

[a] $K_w = 6.76 \times 10^{-13}$ M^2 ($pK_w = 12.17$) at 95 °C.[4] [b] Relatively slow ($k_e = 5.5 \times 10^{-5}$ s^{-1}) hydrolysis of the aryl mesylate group of **1** and **4** is also observed at pH = 10.

$$\frac{d[4]}{dt} = k_e[1] \qquad (4)$$

By fitting the observed reaction profile to a combination of eqs 3 and 4, it was possible to determine k_e and S_o simultaneously. Figure 1 shows such a profile for reaction at pH 6, with an initial $[\mathbf{1}] = 0.27$ M. The calculated curve (pink) has been obtained from eqs 3 and 4 with values for k_e and S_o of: $k_e = 5.35 \times 10^{-4}$ s^{-1}; $S_o = 0.12$ M.

It may be seen from Figure 1 that there is an initial linear increase in the product alcohol formation until the mixture becomes homogeneous at $[\mathbf{1}] = 0.12$ M ($[\mathbf{4}] = 0.15$ M), beyond which there is an exponential change in concentration with time.

Table 1 lists the observed rate constants and solubility at the different pH values.

It is clear from the results in Table 1, which show no change in k_e between pH 6 and pH 8, and a modest increase at pH 10, that the water rate (k_o, eq 2) is dominant until around pH 10, when the hydroxide reaction begins to become important (see Discussion below). Analysing the rate constant at pH 10 in terms of eq 2, using $k_o = 5.4 \times 10^{-4}$ s^{-1} and $[OH^-] = 6.8 \times 10^{-3}$ M (Table 1), gives $k_{OH} = 2.8 \times 10^{-2}$ M^{-1} s^{-1} at 95 °C. These k_o and k_{OH} values may be used to estimate the pH at which the rates of the water and hydroxide rates are equal, pH_i: $k_o = k_{OH}[OH]^-$ at $[OH^-] = 2 \times 10^{-2}$ M, i.e., $pH_i = 10.5$ at 95 °C. This is somewhat lower than the value of $pH_i \approx 12.5$ for simple alkyl methanesulfonates at 25 °C.[1] This difference, however, is mainly a reflection of the temperature dependence of K_w, as pK_w decreases from 14.00 at 25 °C to 12.17 at 95 °C.

(2) Bamford, C. H.; *Ester Formation and Hydrolysis and Related Reactions*; Tipper, C. F. H., Eds.; Chemical Kinetics, Vol. 10; Elsevier: Amsterdam, 1972.
(3) Robertson, R. E. *Prog. Phys. Org. Chem.* **1967**, *4*, 213.

Table 2. **Hydrolysis of EEHP, 2, in aqueous solution at 95 °C**

pH	$[OH^-]/M^a$	$10^5\ k_e/s^{-1}$	% ionisation of phenolic group
8.0	6.8×10^{-5}	5.68	2.0
9.0	6.8×10^{-4}	69.2	18.9
10.0[b]	6.8×10^{-3}	>311	68

[a] $K_w = 6.76 \times 10^{-13}$ M^2 ($pK_w = 12.17$) at 95 °C.[4] [b] Reaction limited by rate of dissolution of **2** and instrument response time.

Hence for a given pH at 95 °C the hydroxide concentration is almost 2 orders of magnitude higher than at the corresponding pH at 25 °C; indeed the $[OH^-]$ at which $k_o = k_{OH}$ for this ester at 95 °C (2×10^{-2} M) is very similar to that for ethyl methanesulfonate at 25 °C (3×10^{-2} M).[1]

EEHP, 2. The kinetics of this reaction showed simple first-order behaviour, eq 5, for the rate of formation of the acid, ethyl (2*S*)-2-ethoxy-3-(4-hydroxyphenyl)propanoic acid, **5**, as expected, because **2** is soluble as a phenol/phenolate mixture at reaction concentrations.

$$\frac{d[5]}{dt} = k_e[2] \qquad (5)$$

The reaction was studied at pH values 8, 9, and 10, and the results are listed in Table 2. Also included in Table 2 is the % ionisation of the phenolic group, determined from the total hydroxide uptake (mol OH^- consumed/mol **2** = 1 + fraction of phenolic group of **2/5** ionised).

In this case, as expected, the rate constants for hydrolysis of the ester group increase strongly with pH. At pH 10 the rate constant would be expected to be around 6×10^{-3} s^{-1} (half-life ≈ 2 min), based on extrapolation from values at pH 8 and pH 9, but under these conditions the reaction is partially limited by the rate of dissolution of **2**. The percentage ionisation at the different pH values may also be determined from the total amount of hydroxide consumed during reaction, and the observed values (Table 2) correspond to $pK_a = 9.6 \pm 0.1$ for the phenolic groups of ethyl ester **2,** and its hydrolysis product, **5**, assuming these to be closely similar.

Ester, 3. The pH-rate profile for ester **3** in homogeneous solution should be very similar to that of **2**. The very low water solubility of **3**, however, means that at higher levels of **3** the resulting two-phase system will hydrolyse much more slowly due its low availability in the aqueous phase. Reactions were studied at pH = 9 and 10. At pH 9 the observed reaction, as measured by hydroxide uptake and HPLC analysis, shows a zero-order rate of product (2*S*)-2-ethoxy-3-[4-(2-{4-[(methylsulfonyl)oxy]phenyl}ethoxy)phenyl] propanoic acid, **6**), formation, eq 6, with $k_eS_o = 1.04 \times 10^{-7}$ M s^{-1} at 95 °C.

$$\frac{d[6]}{dt} = k_eS_o \qquad (6)$$

It is therefore not possible to determine separately k_e and the solubility S_o directly from the kinetic measurements. We can, however, estimate S_o if we assume that k_e has the same value as that for the ester group in EEHP, **2**, i.e., $k_e = 6.9 \times 10^{-4}$ s^{-1}: this corresponds to a solubility of **3** in water at 95 °C, of $S_o = 1.5 \times 10^{-4}$ M. At pH 9, the above rate shows that complete reaction would require ca. 250 h.

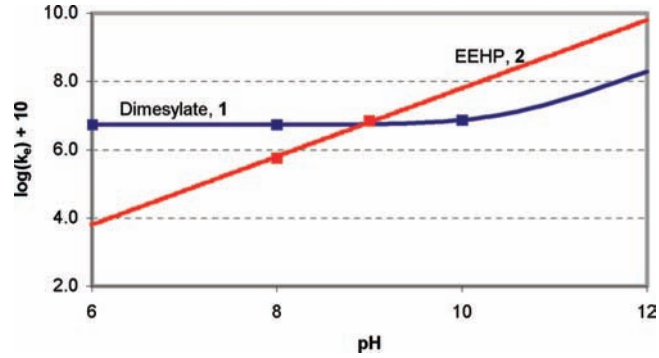


Figure 2. **pH Dependence of the hydrolysis of dimesylate (1) and EEHP (2) at 95 °C.**

The reaction at pH 10 was significantly faster than at pH 9 (hydroxide consumption and HPLC analysis), as expected. The reaction was, however, difficult to analyse quantitatively without further assumptions because of some accompanying hydrolysis of the aryl sulfonate group of the (soluble) product, **6**, which is manifested as accelerating hydroxide consumption as the reaction proceeds. The hydrolysis of aryl sulfonate esters has been previously shown to be base catalysed.[5,6]

Discussion

The present kinetic data are limited, but the implications for process development are clear. The conclusions that the rate of hydrolysis of the carboxylic ester group of **2** and **3** in the range studied is directly proportional to the hydroxide concentration, whereas that of the alkyl mesylate ester of **1** is independent of pH below pH ≈ 10 at 95 °C are consistent with expectations based on simple carboxylate and methylsulfonate ester hydrolysis. Furthermore, the contrasting behaviour of the carboxylate ester of **2** and the alkylsulfonate ester of **1**, illustrated in Figure 2, point immediately to a solution to the issue of selective removal of **1** in the presence of product ester, **3**, namely the use of near-neutral pH conditions.

Thus, for example, at pH 7 the rate constant for hydrolysis of the sulfonate ester of **1** is 100 times that of the carboxylate ester, **2**, whereas it is 10 times lower at pH 10. The product ester, **3**, should similarly show a 1000-fold rate reduction relative to **1** as the pH is reduced from 10 to 7. The product is also further protected by its low solubility, as under reaction conditions only 0.2% is soluble at reaction end.

The pH of the reaction mixture (4 mol Na_2CO_3/mol **1**), Scheme 1, varies between 10.5 at the start of reaction and 9.5 at the end of the hold period. The above results suggest that losses of **3** during removal of any remaining **1** from the reaction mixture could be reduced to a negligible value by neutralising the reaction mixture to around pH 7 for the hold period once

(4) Harned, H. S.; Robinson, R. A. *Trans. Farad. Soc.* **1940**, *36*, 973.
(5) Farrar, C. R.; Williams, A. *J. Am. Chem. Soc.*, **1977**, *99*, 1912 and references therein.
(6) Laleh, A.; Ranson, R.; Tillett, J. G., *J. Chem. Soc.*, **1980**, 610 and references therein.

the coupling is complete. It was found that under such conditions, hydrolysis of remaining **1** to alcohol **4** proceeds at a rate similar to that observed in mixtures held under normal reaction conditions obtained at the end of the coupling process, but no observable loss of **3** occurred even after an additional hold time of 16 h.

Conclusion

The pH dependence of the base hydrolysis of alkyl carboxylate and methanesulfonate esters shows strong quantitative differences. The former react very slowly at low pH (5–6), but the rate increases directly as the hydroxide concentration increases (rate constant (eq 4), $k_e \propto [OH^-]$). The latter are characterised by high, uncatalysed (water) rates, but relatively lower k_{OH} values; the result is a constant rate of hydrolysis up to around pH 12 at 25 °C (pH 10 at 95 °C), above which the rate increases with $[OH^-]$. We have shown that this difference can be successfully exploited to enable selective hydrolysis of an alkyl methanesulfonate impurity in the presence of a carboxylic ester-containing product. The conclusions should be generally applicable to the removal of (potentially genotoxic) alkyl esters of methane sulfonic acid in the presence of carboxylic esters and indeed other base-sensitive groups.

Experimental Section

Materials. Inorganic chemicals and the phase-transfer catalyst, PEG-400, were high-purity commercial reagents used without further purification.

HPLC analyses were carried out using Agilent Symmetry C8 column (3.9 mm × 150 mm) with 45/55 (v/v) CH_3CN/50 mM sodium phosphate buffer and 70/30 (v/v) CH_3CN/ 50 mM sodium phosphate buffer as the mobile phases (1.0 mL/min) and detection at 220 nm wavelength.

Preparation of 4-{2-[(Methylsulfonyl)oxy]ethyl}phenyl Methanesulfonate, 1. Methanesulfonyl chloride (12.88 mL, 167 mmols, 2.30 mol equiv) was added slowly over 2−2.5 h to a cooled (−20 °C) solution of 2-(4-hydroxyphenyl)ethanol (10.0 g, 72.4 mmols, 1.0 mol equiv) and triethylamine (23.2 mL, 167 mmols, 2.3 mol equiv) in *iso*-butyl methyl ketone (MIBK) (87.0 mL, 8.7 rel vol), keeping the reaction temperature below 20 °C. The mixture was heated to 25 °C and held at 25 °C for 1 h to complete the reaction. The mixture was then warmed to 35 °C and filtered to remove the triethylamine hydrochloride. The filter cake was washed with MIBK (50.0 mL, 5.0 rel vol). The combined filtrates were washed twice with water (2 × 20.0 mL, 2.0 rel vol) at 35 °C. The MIBK solution was then concentrated under reduced vacuum to a total volume 60 mL (6.0 rel vol). The solution was cooled to 20 °C and seeded with dimesylate **(1)** (0.06 g, 0.2 mmol, 0.003 mol equiv). The solution was held at 20 °C for 1 h to effect nucleation and then cooled over 2 h to 5 °C for the crystallisation. Isooctane (25.0 mL, 2.5 rel vol) was then added slowly over 1 h, keeping the reaction temperature below 20 °C. The slurry was then cooled to 5 °C, and the solids were filtered. The solid was then slurried in ethanol (30.0 mL, 3.0 rel vol) at 20 °C to remove any residual methanesulfonyl chloride. The product was isolated by filtration and dried in vacuo at 40 °C. The yield of dimesylate **(1)** was 18.2 g (85%).

^{1}H NMR ($CDCl_3$, 500 MHz, 300 K) δ 7.30−7.18 (m, 4H), 4.41 (t, J = 6.7 Hz, 2H), 3.14 (s, 3H), 3.07 (t, J = 6.7 Hz, 2H), 2.90 (s, 3H); ^{13}C (NMR ($CDCl_3$, 125 MHz, 300 K) δ 148.6, 136.3, 131.0 (2C), 122.7 (2C), 70.0, 37.9 (2C), 35.4.

MS (ES) m/z 317 (M + Na), 312 (M + NH_4^+), 295 (M + H).

Ethyl 2(*S*)Ethoxy-3-(4-hydroxyphenyl)propanoate (EEHP), 2. was supplied by Lonza AG, Switzerland, or was prepared as previously described.[7]

Preparation of Ethyl (2*S*)-2-Ethoxy-3-[4-(2-{4-[(methylsulfonyl)oxy]phenyl}ethoxy)phenyl]propanoate, 3. Concentrated hydrochloric acid (37%w/w, 1.75 mL, 0.37 mol equiv) was added to a mixture of **6** (35 g, 1.0 mol equiv) in ethanol (350 mL, 10.0 rel vol) at ambient temperature. The mixture was then heated to reflux and distilled under atmospheric pressure to effect the reaction. After 150 mL of solvent had been collected, the reaction mixture was analysed by TLC (60: 40 EtOAc/isohexane) for the presence of starting material **6**. TLC analysis indicated no starting material was left. The mixture was then cooled to room temperature and concentrated under reduced vacuum to give a pale-yellow/colourless oil (36.1 g, 96.6%).

^{1}H NMR ($CDCl_3$, 500 MHz, 300 K) δ 7.33 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 8.6 Hz, 2H), 7.14 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 4.20−4.09 (m, 4H), 3.96 (dd, J = 6.0 Hz, 1.2 Hz, 1H), 3.63−3.55 (m, 1H), 3.39−3.30 (m, 1H), 3.11 (s, 3H), 3.08 (t, J = 6.6 Hz, 2H), 2.99−2.89 (m, 2H), 1.22 (t, J = 7.0 Hz, 3H), 1.16 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz, 300 K) δ 172.5, 157.4, 147.9, 138.0, 130.6 (2C), 130.4 (2C), 129.5, 121.9 (2C), 114.3 (2C), 80.4, 68.2, 66.2, 60.8, 38.4, 37.3, 35.1, 15.1, 14.2.

MS (ES) m/z 454 (M + NH_4^+), 437 (M + H).

4-(2-Hydroxyethyl)phenyl methanesulfonate, 4. ^{1} H NMR ($CDCl_3$, 500 MHz, 300 K): δ 7.30−7.18 (m, 4H), 3.88−3.80 (m, 2H), 3.12 (s, 3H), 2.86 (t, J = 6.6 Hz, 2H), 1.74−1.68 (br s, OH); ^{13}C NMR ($CDCl_3$, 125 MHz, 300 K) δ 147.8, 138.3, 130.6 (2C), 122.0 (2C), 63.3, 38.5, 37.3.

MS (ES) m/z 234 (M + NH_4^+).

Kinetic Measurements. The hydrolysis of dimesylate, **1**, EEHP, **2**, and ester, **3**, were carried out in a 500-mL jacketed vessel, using HEL Autolab software to control and record the temperature, the pH of the experiment, and the volume of hydroxide consumed as the reactions proceeded. The vessel was equipped with a retreat-curve agitator, thermocouple, water condenser, and Frisolyt pH probe. The reaction temperature was maintained at 95 °C. Samples were also removed periodically for HPLC analysis to confirm species identity as reactions proceeded.

Hydrolysis of Dimesylate, 1. In a typical procedure, water (280 mL) and PEG-400 (1.24 mL, 0.2 mol equiv) were charged into a 500-mL jacketed vessel. The mixture was stirred at 350 rpm and was heated to 95 °C. To adjust the pH of the contents to 10, 1 M NaOH was then added via solenoid pump. Dimesylate **(1)** (8.21 g, 0.0279 mol, 1.0 mol equiv) was then

(7) Linderberg, M. T.; Moge, M.; Sivadasan, S. *Org. Process Res. Dev* **2004**, *8*, 838.

added in three aliquots over 10 min, keeping the reaction temperature at 95 °C and the pH at 10. The mixture was held at 95 °C and at pH 10, and the volume of hydroxide consumed was recorded until the reaction had stopped, i.e. no more NaOH was taken up.

Hydrolysis of Ethyl Ester (2). 2[6.65 g (0.0279 mol)] was charged, and the hydrolysis was studied at pH 10, 9, and 8.

Hydrolysis of Ethyl Ester (3). In 10 mL of xylene was dissolved 10.9 g (0.023 mol) of **(3)**. The ester solution was then added to the water at 95 °C at pH 10, over 5 min. The hydrolysis of **3** was studied at pH 10 and 9.

Typical Manufacturing Process for (2*S*)-2-Ethoxy-3-[4-(2-{4-[(methylsulfonyl)oxy]phenyl}ethoxyphenyl]propanoic Acid, 6. Dimesylate, **1**, (39.53 g, 0.134 mol, 1.6 mol equiv), EEHP, **2** (20.0 g, 0.084 mol, 1.0 mol equiv), water (144 mL, 7.2 rel vol), sodium bicarbonate (35.59 g, 0.336 mol, 4.0 mol equiv), and polyethyene glycol (PEG 400) (6.71 g, 0.017 mol, 0.2 mol equiv) were heated to reflux (~102 °C) in a 500-mL jacketed vessel with vigorous stirring. The biphasic was held at reflux for 7 h. The mixture was cooled to 95 °C and the aqueous phase separated. The organic phase was cooled <55 °C, and acetone (54 mL, 2.7 rel vol) was added. The mixture was cooled to 25 °C, aqueous solution of $LiOH \cdot xH_2O$ (4.6 g, 0.109 mol, 1.3 mol equiv in water (80 mL, 4.0 rel vol)) was added, and the mixture was stirred at 25 °C for 2 h. EtOAc (10 mL, 0.5 rel vol), was added, and the mixture was stirred at 25 °C for another 45 min. The solution was then concentrated to 4.5 rel vol by vacuum distillation. EtOAc (120 mL, 6.0 rel vol) was added, and the mixture was screened at 35 °C to remove any inorganics. Water (70 mL, 3.5 rel vol) was added to the filtrates, and the mixture was extracted with EtOAc (3 × 60 mL, 3 × 3.0 rel vol) at 35 °C. The aqueous phase was then concentrated to 4.0 rel vol by vacuum distillation. Acetic acid (83.9 g, 1.398 mols, 16.65 mol equiv) and acid **6** seeds (0.1 g, 0.25 mmol, 0.003 mol equiv) were added to the mixture at 27 °C. The mixture was stirred at 27 °C for 1 h. An aqueous solution of CH_2SO_4 (3.6 mL, 0.068 mol, 0.8 mol equiv in water (92 mL, 4.6 rel vol)) was then added over 2 h, keeping the temperature of the contents at 27 °C. The slurry was cooled to −10 °C over 7 h and held at −10 °C for 2 h. The slurry was then filtered, washed with water (3 × 60 mL, 3 × 3.0 rel vol), and dried under vacuum at 40 °C to give product **6** (24.2 g, 70%).

This reaction has also been carried out on 256 mol scale on plant.

Acknowledgment

We thank Lisselotte B. Johansson (who sadly passed away in 2007) for help with analytical data.

Supporting Information Available

^1H, ^{13}C NMR and LC/MS spectra in pdf format for compounds **1**, **3**, and **4**. This information is available free of charge via the Internet at http://pubs.acs.org.

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