SYNTHESIS
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A Simple Synthesis of Potassium (±)-3-Methoxy-4-hydroxyphenylethyleneglycol-4-sulfate

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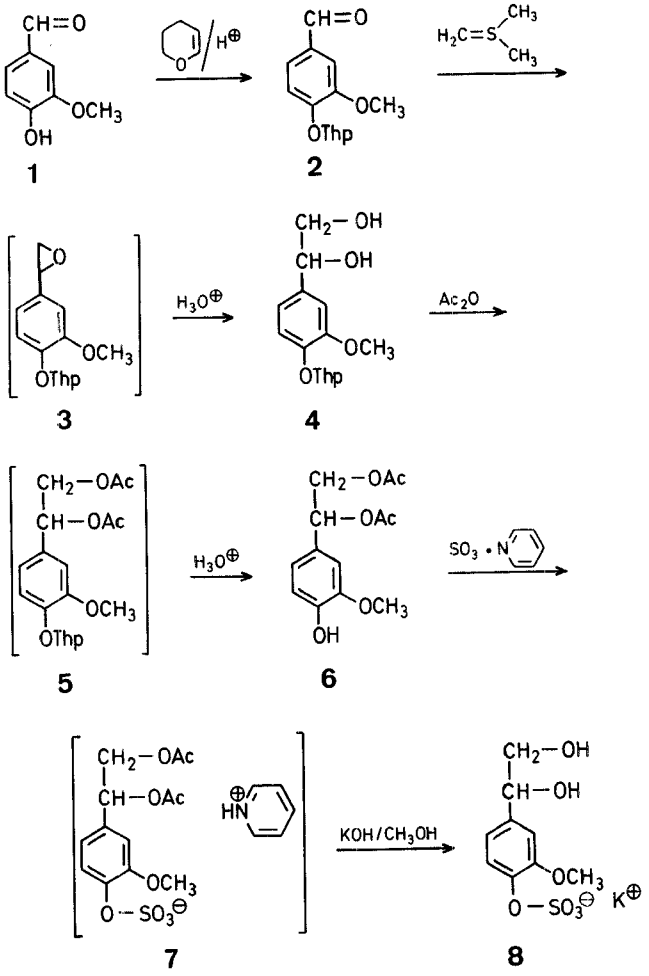
Potassium 3-methoxy-4-hydroxyphenylethyleneglycol-4-sulfate **(8)** is a major metabolite of noradrenaline in the mammalian brain[1]. Synthetic **8** is useful as a standard in the assay of naturally occurring **8**[2]. Compound **8** has previously been prepared by a lengthy and laborious procedure[3]. We describe here an improved economical synthesis of this metabolite from vanillin, in seven steps. This entire sequence can be performed in five days and is suitable for the preparation of multigram quantities of **8**[4].

The synthesis begins with the protection of the phenolic hydroxy function of vanillin **(1)** with the tetrahydropyranyl (Thp) group[5]. This apparently simple transformation turned out to be very sensitive to the conditions employed, giving variable yields of **2** until the optimized procedure was developed (see experimental). This optimized procedure consistantly gives good yields of **2**. This protected vanillin derivative **2**, was then transformed into the homologous epoxide **3**, by treatment with dimethylsulfonium methylide in dimethyl sulfoxide[6]. We have found that this sulfur ylid is conveniently prepared by treating a suspension of trimethylsulfonium iodide in dimethyl sulfoxide with an equivalent of potassium *t*-butoxide. The acid sensitive epoxide **3** was selectively hydrolysed with dilute aqueous acid in tetrahydrofuran to produce the crystalline diol **4** in 65% yield. This observed selectivity is possible because of the facile ring opening of the epoxide, which is in turn due to the involvement of the stabilized benzylic carbonium-ion intermediate. The diol **4** is then transformed into the diacetate **6**, in a single reaction vessel, via the presumed intermediate **5**, in an overall yield of 95%.

The diacetate **6** has been converted into **8** by chlorosulfonic acid in pyridine, followed by aqueous potassium hydroxide, and isolated by repeated ion-exchange chromatography[3]. This procedure was needlessly laborious and, in our hands, gave a very low yield of **8**. We therefore developed an alternative sulfation procedure based on the work of Tserng and Klein[7] using the sulfur trioxide/pyridine complex[8] in dimethylformamide. The analytically pure product was readily isolated by a simple precipitation procedure[7]. After deacetylation and conversion to the potassium salt, with potassium hydroxide in methanol, the product was isolated in 60% overall yield from **6**.

This synthesis represents an improved and economical preparation of **8** with a minimum of manipulations, taking advantage of the unique selectivity observed in the transformation of **3** into **4**. This type of specially tailored synthesis makes it possible to use the minimum of protection and deprotection steps. This work will make **8** readily available to those who require it for their research endeavors[4].



3-Methoxy-4-(2,3,5,6-tetrahydropyran-2-yloxy)-benzaldehyde (2): A solution of vanillin (**1**; 30.4 g, 200 mmol) in dichloromethane (150 ml) at 15°C is treated with *p*-toluenesulfonic acid monohydrate (80 mg, 0.4 mmol), followed by the rapid addition of dihydropyran (21 ml, 230 mmol). The solution rapidly turns yellow, then green and finally deep blue in about 5 min. After this time the reaction begins to warm and an ice/acetone bath is used to bring the internal temperature to ~0°C. The solution is allowed to stir at this temperature for 30 min. After this time the solution is rapidly filtered through a pad of silica gel (30 g) in a fritted funnel to give a colorless filtrate. The silica is washed with dichloromethane (60 ml) and the combined filtrate and washings are extracted with 1 molar aqueous sodium hydroxide solution (2 × 200 ml). The dichloromethane phase is dried with potassium carbonate and concentrated under vacuum, with low heat (~40°C), to give a thick syrup. The syrup is treated with hexane until slight turbility persists and then cooled to −20°C. After several hours, the crystals are collected by filtration, washed with hexane (~50 ml), and dried under vacuum to give product **2** (25.8 g). The mother liquor and washings are combined and seeded. Cooling to 0°C, filtration, and drying gives a further portion of **2** (5.2 g); total yield: 31.0 g (66%); m.p. 44–46°C.

$C_{13}H_{16}O_4$	calc.	C 66.09	H 6.83
(236.3)	found	66.32	6.81

^{1}H-N.M.R. ($CDCl_3$/TMS, 60 MHz): δ = 1.5–2.0 (m, 6H, CH_2); 3.8 (s, 3H, CH_3O—); 7.0–7.5 (m, 3 H_{arom}); 9.8 ppm (s, 1H, CHO).

1-[3-Methoxy-4-(2,3,5,6-tetrahydropyran-2-yloxy)-phenyl]-1,2-ethanediol (4):

A suspension of trimethylsulfonium iodide (61.2 g, 300 mmol) in dimethyl sulfoxide (200 ml) is treated with solid potassium *t*-butoxide (32.5 g, 290 mmol). This suspension is stirred for 30 min, then solid **2** (26 g) is added in one portion, this mixture is stirred for 2 h at 25°C. The mixture is poured into ice/water (~400 ml) and extracted with ether (3 × 300 ml). The combined ether phases are washed with water (3 × 100 ml), then concentrated to give an oil. This oil is dissolved in tetrahydrofuran (500 ml) and 0.05 molar hydrochloric acid (100 ml) is added with stirring. After 40 min, the solution is neutralized by the addition of 5% aqueous sodium hydrogen carbonate solution and extracted into dichloromethane (1000 ml). The dichloromethane phase is dried with potassium carbonate and concentrated to give crude **4**. This crude product is purified by flash chromatography on silica gel 60, eluting first with ether, to remove impurities, followed by ethyl acetate to elute the product. The ethyl acetate fractions are combined, concentrated and the product is allowed to crystallize at 5°C; yield: 16.5 g (65%); m.p. 59–61°C. This material should be carried on to **6** quickly, since it is stable only if very pure.

$C_{14}H_{20}O_4 \cdot H_2O$	calc.	C 62.20	H 8.20
(270.3)	found	62.37	7.80

^{1}H-N.M.R. ($CDCl_3$/TMS, 60 MHz: δ = 1.5–2.0 (m, 6H, CH_2); 3.6 (br. s, 2H, CH_2OH); 3.8 (s, 3H, CH_3O—); 6.6–7.2 ppm (m, 3 H_{arom}).

1-(4-Hydroxy-3-methoxyphenyl)-1,2-diacetoxyethane (6):

A solution of **4** (8.5 g; 31 mmol) in dry tetrahydrofuran (80 ml) is treated with 4-dimethylaminopyridine (100 mg) and acetic anhydride (8 ml). This solution is allowed to stir for 1 h at 25°C, then water (80 ml) is added followed by 88% formic acid (70 ml). This mixture is stirred for 30 min, then it is added to dichloromethane (1400 ml) and neutralized by the addition of solid sodium hydrogen carbonate. The dichloromethane phase is washed with 5% aqueous sodium hydrogen carbonate solution (200 ml), dried with potassium carbonate, and concentrated. This material distills at 190°C/0.1 torr. Despite the earlier report that this material is a solid[3], in our hands it remained an oil; yield: 7.9 g (95% based on **4**).

$C_{13}H_{16}O_6$	calc.	C 58.20	H 6.01
(268.3)	found	58.06	6.17

^{1}H-N.M.R. ($CDCl_3$/TMS, 60 MHz): δ = 1.60 (s, 3H, O—CO—CH_3); 1.65 (s, 3H, O—CO—CH_3); 3.80 (s, 3H, OCH_3); 4.35 (d, 2H, CH_2OAc); 5.95 (t, 1H, —CHOAc); 6.90 ppm (s, 3 H_{arom}).

1-(4-Hydroxy-3-methoxyphenyl)-1,2-ethanediol-4-sulfate, Potassium Salt (8):

A solution of **6** (5.0 g, 18.6 mmol) in dry dimethylformamide (35 ml) is treated with SO_3/pyridine complex (3.5 g, 22.0 mmol) and allowed to stir for 2 h at 25°C. After this time the solution is poured into dry ether (600 ml), and set for 16 h at 5°C. The supernatant is discarded and the residue suspended (the insoluble portion is potassium sulfate) in a solution of potassium hydroxide (5 g) in methanol (650 ml). After this mixture has stirred for 1 h at 25°C it is taken to pH 7–7.5 with 2 normal aqueous sulfuric acid, then filtered (to remove potassium sulfate), and washed with methanol (100 ml). The filtrate is then slowly added to ether (800 ml) with good stirring. The resulting suspension is cooled to 5°C and allowed to stir for 1 h, filtered, washed with ether, and dried under vacuum; yield: 3.6 g (64%). Despite the earlier report[3], no melting is observed below 200°C.

$C_9H_{11}O_7SK$	calc.	C 35.75	H 3.67	S 10.61	K 12.93
(302.3)	found	35.69	3.69	10.79	13.16

^{1}H-N.M.R. (D_2O/TMS_{ext}, 60 MHz): δ = 3.4 (br. s, 1H, CH—OH); 3.6 (br. s, 2H, CH_2—OH); 3.8 (s, 3H, CH_3O); 7.0–7.5 ppm (m, 3 H_{arom}).

^{13}C-N.M.R. (D_2O/TMS_{ext}, 60 MHz, ^{1}H-decoupled): δ = 57.5; 67.35; 74.7; 113.0; 120.1; 123.6 ppm.

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