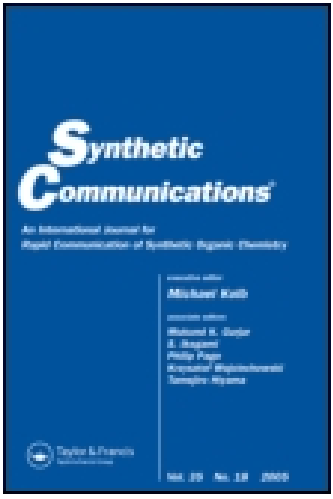

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 23 Aug 2006.

To cite this article: Adrian J. Fisher & Frank Kerrigan (1998) A New Convenient Synthesis of 1-(3-Hydroxy-4-Methoxyphenyl)Ethane-1,2-Diol (iso-Mhpg) and its Enantiomers, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 28:16, 2959-2968, DOI: 10.1080/00397919808004875

To link to this article: http://dx.doi.org/10.1080/00397919808004875

SYNTHETIC COMMUNICATIONS, 28(16), 2959-2968 (1998)

A NEW CONVENIENT SYNTHESIS OF 1-(3-HYDROXY-4-METHOXYPHENYL)ETHANE-1,2-DIOL (*iso*-MHPG) AND ITS ENANTIOMERS.

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Abstract: A safe and efficient process has been developed for the multigram synthesis of 1-(3-hydroxy-4-methoxyphenyl)ethane-1,2-diol (*iso*-MHPG) **2**, *via* osmium-catalysed dihydroxylation of 3-benzyloxy-4-methoxystyrene **5**, and subsequent debenzylation. The methodology has been extended to an asymmetric synthesis of both enantiomers.

1-(4-Hydroxy-3-methoxyphenyl)ethane-1,2-diol, also commonly known as (3-methoxy-4-hydroxyphenyl)ethyleneglycol (MHPG) **1**, is the major metabolite of noradrenaline in the mammalian central nervous system.[1] The rate of excretion of MHPG in human urine has been used as a predictive tool in the diagnosis of depressive disorders,[2] and in animal models brain MHPG levels have been used as an index of noradrenaline turnover and presynaptic α_2-adrenoceptor function.[3] The HPLC techniques employed in the analysis of MHPG require the

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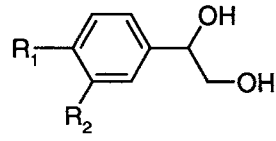
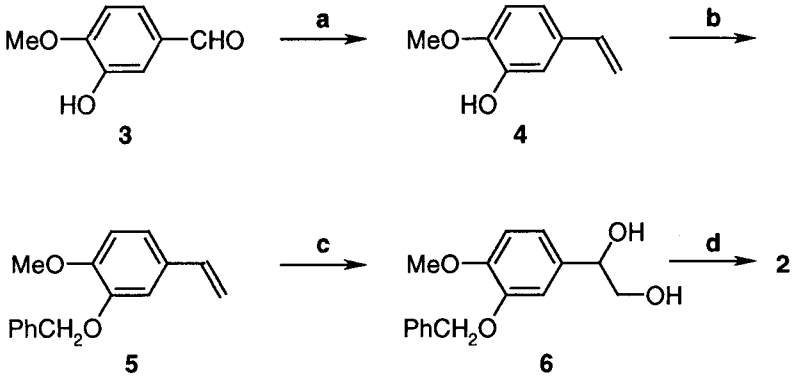
use of 1-(3-hydroxy-4-methoxyphenyl)ethane-1,2-diol (*iso*-MHPG) **2** as an internal standard.[3,4] Reported small-scale syntheses of *iso*-MHPG, by the reduction of 3-hydroxy-4-methoxymandelic acid, require the use of a large excess of lithium aluminium hydride.[4,5] In our hands this proved unsatisfactory for multigram syntheses, being extremely hazardous during aqueous work-up, and requiring extensive HPLC purification of the crude product. In this communication we wish to report a new, facile process for the synthesis of *iso*-MHPG which overcomes the limitations of the reported method.



1 : $R_1 = OH$; $R_2 = OMe$
2 : $R_1 = OMe$; $R_2 = OH$

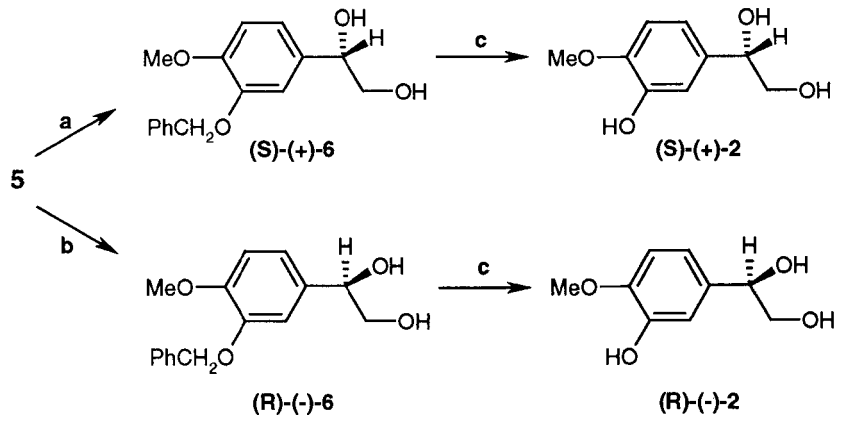
Our initial approach to *iso*-MHPG was to attempt the oxidation of the unprotected styrene **4**, obtained in 100% yield *via* a Wittig reaction of isovanillin **3** with methyltriphenylphosphonium iodide and potassium *tert*-butoxide.[6] However, oxidation of **4** with *N*-methylmorpholine-*N*-oxide (NMO)/OsO_4 [7] or formic acid/H_2O_2 [8] resulted in the formation of complex mixtures of products from which none of the required *iso*-MHPG could be isolated. We believed that the problem with the oxidation of **4** lay in the propensity for the phenol to undergo oxidative side-reactions. Consequently we decided to protect this functionality as a benzyl ether prior to the oxidation reaction. Benzylation of **4** proceeded smoothly under standard conditions, [9] giving the benzyl ether **5** in 89% yield. It is interesting to note that this route to **5** is more efficient than the



Reagents and conditions: **a)** $MePPh_3I$, $KOBu^t$, THF, 20°C, 18h, 100%. **b)** $PhCH_2Br$, K_2CO_3, Me_2CO, reflux, 48h, 89%. **c)** $K_2Os_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, Bu^tOH, H_2O, 20°C, 65h, 70%. **d)** H_2 (1 atm), Pd-C, industrial methylated spirit, 20°C, 1h, 100%.

alternative Wittig reaction on *O*-benzylisovanillin, which proceeded in only 70% yield. Initial attempts at oxidation of styrene **5** with formic acid/H_2O_2 gave only 31% conversion into the diol **6**. The yield was improved to 53% by using NMO/OsO_4(3 mol.%), but optimum results (70%) were obtained with potassium osmate dihydrate/potassium ferricyanide/potassium carbonate. Finally, the diol **6** was deprotected by palladium-catalysed hydrogenolysis under standard conditions [10] to give *iso*-MHPG **2** in 100% yield. The overall synthesis of *iso*-MHPG **2** from isovanillin **3** proceeds in 62% yield, whereas in our hands the reduction of 3-hydroxy-4-methoxymandelic acid with lithium aluminium hydride gave only a 26% yield.

Having successfully achieved an efficient synthesis of *iso*-MHPG, we decided to extend the methodology to asymmetric synthesis of its enantiomers *via* Sharpless asymmetric dihydroxylation (AD) [11] of **5**. Of the commercially-



Reagents and conditions: a) $(DHQ)_2$-PHAL, $K_2Os_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, Bu^tOH, H_2O, 0°C, 6h, 92%. **b)** $(DHQD)_2$-PHAL, $K_2Os_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, Bu^tOH, H_2O, 0°C, 6h, 95%. **c)** H_2 (1 atm), Pd-C, industrial methylated spirit, 20°C, 1h, 92-94%.

available AD ligands, the phthalazines, $(DHQ)_2$-PHAL and $(DHQD)_2$-PHAL, are reported to be superior for the oxidation of aromatic olefins.[12] In our hands, oxidation of **5** with potassium osmate dihydrate, potassium ferricyanide and potassium carbonate, using $(DHQ)_2$-PHAL as the chiral ligand, gave **(S)-(+)-6** in 92% yield and >99% enantiomeric excess (ee) (stereochemistry assigned by analogy with the oxidation of styrene [11]). Debenzylation of **(S)-(+)-6** using the conditions described for the racemate gave **(S)-(+)-2** in 92% yield and >99% ee. **(R)-(-)-2** was obtained in 95% yield and >99% ee in an analogous manner using $(DHQD)_2$-PHAL as the chiral ligand.

Experimental

Melting points were recorded on a Griffin MFB 590 010T apparatus and are uncorrected. ^1H spectra were obtained at 250 MHz on a Bruker AC spectrometer.

Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. Elemental analyses were conducted with a Carlo Erba model CE 1106 analyser. All solvent extracts were washed with water, dried over $MgSO_4$, and concentrated at reduced pressure. THF was dried over 4Å molecular sieves. SFC refers to supercritical fluid chromatography.

3-Hydroxy-4-methoxystyrene 4: A suspension of methyltriphenylphosphonium iodide (15.0g, 37.1 mmol) and potassium *tert*-butoxide (4.55g, 40.6 mmol) in dry THF (60 cm^3) was stirred at ambient temperature under argon for 1h, then isovanillin **3** (2.06g, 13.6 mmol) was added, and the mixture was stirred at ambient temperature for 24h. Saturated aqueous ammonium chloride solution (60 cm^3) was added, the mixture was concentrated *in vacuo* to remove THF, and the product was extracted into dichloromethane (3 x 50 cm^3). The washed and dried extract was concentrated *in vacuo*, and the residue was purified by flash chromatography over silica (dichloromethane-hexanes 75:25) to give **4** as a white solid (2.04g; 100%); mp 57-58°C, (lit. [6] 55-56°C). ^1H NMR (DMSO-d_6) δ: 8.97 (s, 1H), 6.91-6.80 (m, 3H), 6.57 (dd, 1H, *J* 17.6 and 10.9 Hz), 5.56 (dd, 1H, *J* 17.6 and 1.1 Hz), 5.07 (dd, 1H, *J* 10.9 and 1.0 Hz), 3.76 (s, 3H). Anal. - Calcd. for $C_9H_{10}O_2$: C, 72.0; H, 6.7%. Found: C, 72.0; H, 6.7%.

3-Benzyloxy-4-methoxystyrene 5: A stirred mixture of **4** (1.0g, 6.66 mmol), benzyl bromide (1.25g, 7.33 mmol), potassium carbonate (1.01g, 7.33 mmol) and acetone (50 cm^3) was heated under reflux for 48h, cooled, and filtered. The solvent was removed *in vacuo,* and the residue was purified by flash

chromatography over silica (hexanes-ethyl acetate 90:10) to give **5** as a white solid (1.42g; 89%); mp 67-69°C. ^{1}H NMR (DMSO-d_6) δ: 7.49-7.29 (m, 5H), 7.20 (d, 1H, *J* 1.7 Hz), 7.00-6.92 (m, 2H), 6.62 (dd, 1H, *J* 17.6 and 10.9 Hz), 5.67 (dd, 1H, *J* 17.6 and 1.0 Hz), 5.14-5.09 (m, 3H), 3.77 (s, 3H). Anal. - Calcd. for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7%. Found: C, 80.1; H, 6.9%.

1-(3-Benzyloxy-4-methoxyphenyl)ethane-1,2-diol 6: The styrene **5** (1.0g, 4.17 mmol) was added to a stirred mixture of potassium osmate dihydrate (3mg, 0.008 mmol), potassium ferricyanide (4.06g, 12.32 mmol), potassium carbonate (1.7g, 12.32 mmol), *tert*-butanol (20 cm^3) and water (20 cm^3), then the mixture was stirred at ambient temperature for 65h. Sodium sulfite (6.3g, 50 mmol) was added and the mixture was stirred for 1h at ambient temperature, then the product was extracted into ethyl acetate. The washed and dried extract was concentrated *in vacuo*, and the residue was purified by flash chromatography over silica (ethyl acetate - hexanes 50:50, then ethyl acetate) to give **6** as a white solid (0.8g; 70%); mp 92-93°C. ^{1}H NMR ($CDCl_3$) δ: 7.46-7.26 (m, 5H), 6.92-6.84 (m, 3H), 5.14 (s, 2H), 4.72-4.66 (m, 1H), 3.87 (s, 3H), 3.70-3.52 (m, 2H), 2.58-2.56 (m, 1H), 2.16-2.11 (m, 1H). Anal. - Calcd. for $C_{16}H_{18}O_4$: C, 70.1; H, 6.6%. Found: C, 70.0; H, 6.8%.

(S)-(+)-1-(3-Benzyloxy-4-methoxyphenyl)ethane-1,2-diol (S)-(+)-6: A stirred mixture of AD-mix-α (5.8g),[13] *tert*-butanol (20 cm^3) and water (20 cm^3) was cooled to 0°C whereupon some of the dissolved salts began to precipitate. The styrene **5** (1.0g, 4.17 mmol) was added without delay, and the mixture was stirred

at 0°C for 6h. Sodium sulfite (6.3g, 50 mmol) was added and the mixture was stirred for 1h at ambient temperature, then the product was extracted into ethyl acetate. The washed and dried extract was concentrated *in vacuo*, and the residue was purified by flash chromatography over silica (ethyl acetate - hexanes 50:50, then ethyl acetate) to give **(S)-(+)-6** as a white solid (1.05g; 92%); mp 86-87°C. ^{1}H NMR ($CDCl_3$) δ: 7.46-7.26 (m, 5H), 6.93-6.85 (m, 3H), 5.15 (s, 2H), 4.74-4.68 (m, 1H), 3.88 (s, 3H), 3.71-3.53 (m, 2H), 2.43-2.42 (m, 1H), 2.04-1.97 (m, 1H). Anal. - Calcd. for $C_{16}H_{18}O_4$: C, 70.1; H, 6.6%. Found: C, 70.1; H, 6.6%. $[\alpha]_D$ = +22.3° (C = 1.289; methanol). HPLC [Chiralcel OJ using *iso*-hexane/propan-2-ol/diethylamine (49.95:49.95:0.1) as eluant at a flow rate of 0.5 $cm^3min.^{-1}$] - 100% at 17.8 min.

(R)-(-)-1-(3-Benzyloxy-4-methoxyphenyl)ethane-1,2-diol (R)-(-)-6: Procedure as above, but using AD-mix-β (5.8g),[13] to give **(R)-(-)-6** as a white solid (1.08g; 95%); mp 86-87°C. ^{1}H NMR ($CDCl_3$) δ: 7.46-7.26 (m, 5H), 6.93-6.85 (m, 3H), 5.15 (s, 2H), 4.72-4.68 (m, 1H), 3.88 (s, 3H), 3.71-3.53 (m, 2H), 2.46-2.45 (m, 1H), 2.04-2.00 (m, 1H). Anal. - Calcd. for $C_{16}H_{18}O_4$: C, 70.1; H, 6.6%. Found: C, 70.0; H, 6.5%. $[\alpha]_D$ = -22.4° (C = 0.9725; methanol). HPLC [Chiralcel OJ using *iso*-hexane/propan-2-ol/diethylamine (49.95:49.95:0.1) as eluant at a flow rate of 0.5 $cm^3min.^{-1}$] - 100% at 14.5 min.

1-(3-Hydroxy-4-methoxyphenyl)ethane-1,2-diol (*iso*-MHPG) 2: A mixture of **6** (3.84g, 14.0 mmol), 10% palladium on carbon catalyst (100 mg) and industrial methylated spirit (150 cm^3) was hydrogenated at ambient temperature,

1 atmosphere, for 1h. The catalyst was removed by filtration, and the solvent was removed *in vacuo* to give **2** as a white solid (2.57g; 100%); mp 97-98°C. ^{1}H NMR (DMSO-d_6) δ: 8.81 (s, 1H), 6.84-6.66 (m, 3H), 5.04-5.02 (m, 1H), 4.64-4.59 (m, 1H), 4.41-4.35 (m, 1H), 3.72 (s, 3H), 3.37-3.32 (m, 2H). Anal. - Calcd. for $C_9H_{12}O_4$: C, 58.7; H, 6.5%. Found: C, 58.8; H, 6.6%.

(S)-(+)-1-(3-Hydroxy-4-methoxyphenyl)ethane-1,2-diol (S)-(+)-2: Procedure as above, but starting with **(S)-(+)-6** (0.6g, 2.19 mmol), to give **(S)-(+)-2** as a white solid (0.37g; 92%); mp 97-98°C. ^{1}H NMR (DMSO-d_6) δ: 8.82 (s, 1H), 6.84-6.66 (m, 3H), 5.05-5.04 (m, 1H), 4.65-4.60 (m, 1H), 4.41-4.35 (m, 1H), 3.72 (s, 3H), 3.37-3.32 (m, 2H). Anal. - Calcd. for $C_9H_{12}O_4$: C, 58.7; H, 6.5%. Found: C, 58.8; H, 6.6%. $[\alpha]_D$ = +35.8° (C = 1.0035; methanol). SFC [Chiralpak AS using carbon dioxide/propan-2-ol/diethylamine/acetic acid (91:8.3:0.5:0.2) as eluant at a flow rate of 3 $cm^3min.^{-1}$, 45°C, 2980 psi] - 100% at 15.9 min.

(R)-(-)-1-(3-Hydroxy-4-methoxyphenyl)ethane-1,2-diol (R)-(-)-2: Procedure as above, but starting with **(R)-(-)-6** (0.6g, 2.19 mmol), to give **(R)-(-)-2** as a white solid (0.38g; 94%); mp 97-98°C. ^{1}H NMR (DMSO-d_6) δ: 8.82 (s, 1H), 6.84-6.66 (m, 3H), 5.05-5.04 (m, 1H), 4.65-4.61 (m, 1H), 4.41-4.35 (m, 1H), 3.72 (s, 3H), 3.35-3.31 (m, 2H). Anal. - Calcd. for $C_9H_{12}O_4$: C, 58.7; H, 6.5%. Found: C, 58.6; H, 6.55%. $[\alpha]_D$ = -34.2° (C = 0.5375; methanol). SFC [Chiralpak AS using carbon dioxide/propan-2-ol/diethylamine/acetic acid (91:8.3:0.5:0.2) as eluant at a flow rate of 3 $cm^3min.^{-1}$, 45°C, 2980 psi] - 100% at 17.4 min.

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13. Commercially available AD-mix-α (5.8g) or AD-mix-β (5.8g), which contain

potassium osmate dihydrate (3mg, 0.008 mmol), potassium ferricyanide (4.06g, 12.32 mmol), potassium carbonate (1.7g, 12.32 mmol) and $(DHQ)_2$-PHAL (0.032g, 0.041 mmol) or $(DHQD)_2$-PHAL (0.032g, 0.041 mmol)

(Received in the USA 06 March 1998)