Synthesis of GKA71

Methyl 3-hydroxy-5-\{phenylmethyl\}oxy\}benzoate

To a stirred solution of methyl 3,5-dihydroxybenzoate (5.95 mol) in DMF (6 L) was added potassium carbonate (9 mol), and the suspension stirred at ambient temperature under argon. To this was added benzyl bromide (8.42 mol) slowly over 1 hour, with a slight exotherm, and the reaction mixture stirred overnight at ambient temperature. The reaction was quenched cautiously with ammonium chloride solution (5 L) followed by water (35 L). The aqueous suspension was extracted with dichloromethane (DCM) (1 × 3 L and 2 × 5 L). The combined extracts were washed with water (10 L) and dried overnight (MgSO₄). The solution was evaporated in vacuo, and the crude product was purified by flash column chromatography in 3 batches (3 × 2 kg silica, eluting with a gradient consisting of hexane containing 10% DCM, to neat DCM, to DCM containing 50% ethyl acetate) to eliminate starting material. The resulting material was further purified by high pressure liquid chromatography (HPLC) in 175 g batches (Amicon HPLC, 5 kg normal-phase silica, eluting with isohexane containing 20% v/v of ethyl acetate) to afford the title compound (21% yield). ¹H NMR δ (d₆-DMSO): 3.8 (s, 3H), 5.1 (s, 2H), 6.65 (m, 1H), 7.0 (m, 1H), 7.05 (m, 1H), 7.3-7.5 (m, 5H), 9.85 (br s, 1H)

Methyl 3-\{(1S)-2-methoxy-(1-methylethyl)oxy\}-5-\{phenylmethyl\}oxy\}benzoate

To a solution of methyl 3-hydroxy-5-\{phenylmethyl\}oxy\}benzoate (77.4 mmol) in THF was added polymer-supported triphenylphosphine (51.7g of 3 mmol/g loading, 155mmol) and (R)-(−)-1-methoxy-2-propanol (102 mmol). The stirred solution was blanketed with argon and
cooled in an ice bath. A solution of diisopropylazodicarboxylate (116 mmol) was added dropwise by syringe over 10 minutes. The solution was stirred for 20 minutes and filtered, washing the residue with THF (500 mL). The filtrate and washings were combined, and evaporated to give the desired compound which was used without further purification.

\[ ^{1} \text{H NMR } \delta (d_{6}-\text{DMSO}): 3.26 (s, 3H), 3.44 (m, 2H), 3.82 (s, 3H), 4.63 (m, 1H), 5.14 (s, 2H), 6.85 (s, 1H), 7.05 (s, 1H), 7.11 (s, 1H), 7.30-7.47 (m, 5H) \]

Methyl 3-Hydroxy-5-\{(1S)-2-methoxy-(1-methylethyl)oxy\}benzoate

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\begin{array}{c}
\text{MeO} \\
\text{O} \\
\text{O} \\
\text{MeO} \\
\text{OH}
\end{array}
\]

Methyl 3-\{(1S)-2-methoxy-(1-methylethyl)oxy\}-5-\{(phenylmethyl)oxy\}benzoate (50.0 g; 0.152 mmol) was dissolved in a mixture of THF:ethanol (600 mL) and the flask evacuated and purged with nitrogen (3 times). 10% Palladium on carbon (5.0g) was added and the flask further evacuated and finally purged with hydrogen gas. The reaction mixture was stirred at ambient temperature for 20 hours until completion. The reaction mixture was evacuated and purged with nitrogen (3 times). The catalyst was filtered off, and the filtrate concentrated in vacuo to give the desired compound (36.7 g). \[ ^{1} \text{H NMR } \delta (d_{6}-\text{DMSO}): 1.2 (d, 3H), 3.25 (s, 3H), 3.44 (m, 2H), 3.82 (s, 3H), 4.55 (m, 1H), 6.6 (s, 1H), 6.9 (s, 1H), 6.95 (s, 1H), 9.8 (s, 1H) \]

Methyl 3-\{(1S)-2-methoxy-(1-methylethyl)oxy\}-5-\{4-(methylsulfonyl)phenyl\}oxy\}benzoate

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\begin{array}{c}
\text{MeO} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array}
\]

A suspension of methyl 3-hydroxy-5-\{(1S)-2-methoxy-(1-methylethyl)oxy\}benzoate (154 mmol), (4-methylsulfonylphenyl)boronic acid ( 1.1 equivalents), copper (II) acetate (1.1 equivalents), triethylamine (5 equivalents) and freshly activated 4Å molecular sieves (200 g) in DCM (500 mL) was stirred at ambient temperature and under ambient atmosphere for 2 days. The reaction mixture was filtered, the DCM removed in vacuo and the residual oil
partitioned between ethyl acetate and 1-2M hydrochloric acid. The ethyl acetate layer was separated, washed with aqueous sodium hydrogen carbonate and brine, dried (MgSO₄), and evaporated to a residue which was chromatographed on silica (with 20-60% ethyl acetate in isohexane as eluant) to give the desired ester (58% yield). 1H NMR δ (d₆-DMSO): 1.2 (d, 3H), 3.2 (s, 3H), 3.26 (s, 3H), 3.44 (m, 2H), 3.8 (s, 3H), 4.65 (m, 1H), 7.05 (s, 1H), 7.11 (s, 1H), 7.2 (d, 2H), 7.3 (s, 1H), 7.9 (d, 2H)

3-{(1S)-2-methoxy-(1-methylethyl)oxy}-5-[[4-(methylsulfonyl)phenyl] oxy]benzoic acid

A solution of methyl 3-[(1S)-2-methoxy-(1-methylethyl)oxy]-5-[[4-(methylsulfonyl)phenyl] oxy]benzoate (60.9 mmol) in THF (400 mL) was treated with a solution of 1M sodium hydroxide (125 mmol), and the reaction mixture stirred for 13 hours at ambient temperature. Most of the organic solvent was removed in vacuo, and the remaining solution was diluted with water (150 mL). The resulting aqueous solution was acidified to pH4 with 1M citric acid solution, and extracted with ethyl acetate (2 × 100 mL). The extracts were combined, washed with brine, dried (MgSO₄), and evaporated to give the desired compound (83% yield). 1H NMR δ (d₆-DMSO): 1.2 (d, 3H), 3.2 (s, 3H), 3.26 (s, 3H), 3.44 (m, 2H), 4.63 (m, 1H), 7.05 (s, 1H), 7.11 (s, 1H), 7.2 (d, 2H), 7.3 (s, 1H), 7.9 (d, 2H); m/z 479 (M-H)

GKA71 - 3-[(1S)-2-methoxy-1-methyl-ethoxy]-5-(4-methylsulfonylphenoxy)-N-(3-methyl-1,2,4-thiadiazol-5-yl)benzamide

Diisopropylethylamine (2.5 equivalents) was added to a suspension of 3-[(1S)-2-methoxy-(1-methylethyl)oxy]-5-[[4-(methylsulfonyl)phenyl] oxy]benzoic acid (1 equivalent), O-(7-
azabenzotriazol-1-yl)-N,N,N’,N’-tetramethyluronium hexafluorophosphate (1.25 equivalents) and 3-methyl-1,2,4-thiadiazol-5-amine (1.25 equivalents) in DMF (20 mL). The initial suspension dissolved into a dark orange solution. The resulting mixture was stirred at ambient temperature for 2 hours. The DMF was removed in vacuo, and the residue azeotroped with toluene. Water was added and the mixture extracted with ethyl acetate. The extracts were combined and washed sequentially with 1M hydrochloric acid, saturated sodium hydrogen carbonate solution and brine. The solution was dried (MgSO₄), filtered, and evaporated in vacuo to give the crude product which was chromatographed (50% ethyl acetate in isohexane) to give desired compound (40-70% yield). 1H NMR δ (d₆-DMSO): 1.2 (d, 3H), 2.5 (s, 3H), 3.2 (s, 3H), 3.25 (s, 3H), 3.5 (m, 2H), 4.75 (m, 1H), 7.0 (s, 1H), 7.2 (d, 2H), 7.4 (s, 1H), 7.6 (s, 1H), 7.95 (d, 2H), 13.5 (br s, 1H); m/z 478 (M+H)⁺

The material may be crystallised by allowing isohexane to vapour diffuse into a solution of the compound in ethylacetate, in a closed system, with subsequent slow evaporation of the mixture at room temperature over 4 days, mp 109-112 °C.