Synthesis of a Potent hNK-1 Receptor Antagonist via an $S_N^2$ Reaction of an Enantiomerically Pure $\alpha$-Alkoxy Sulfonate

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Supporting Information

Experimental procedures and characterization data for compounds 1, (R)-13, 15, 16, 18, 21, 23, and 24.

General Methods. LCAP refers to HPLC area percent, LCWP refers to HPLC weight percent and GCAP refers to GC area percent.
Tosylate \([(R)-13]\):

\[
\begin{align*}
\text{(R)-10} + \text{[PMP-OH]} & \xrightarrow{\text{K}_2\text{CO}_3, \text{CH}_3\text{CN}} \text{(R)-12} \\
\text{(R)-12} & \xrightarrow{\text{TsCl, DABCO, EtOAc}} \text{(R)-13}
\end{align*}
\]

A mixture of epoxide \((R)-10\) (3583 g, 20.1 mol), \(\text{K}_2\text{CO}_3\) (4186 g, 30.3 mol, 1.5 eq), and 4-methoxyphenol (5014 g, 40.4 mol, 2.0 eq) in \(\text{CH}_3\text{CN}\) (7.2 L) was heated to 81-83 °C for 9 h (99% HPLC conversion). This was cooled to room temperature and diluted with MTBE (30 L) and 1N NaOH (22.2 L). The organic phase was separated and washed with 1N NaOH (22 L) and water (16.5 L). [HPLC assay yield was 91% (5520 g, 18.3 mol)]. The solvent was removed in vacuo to afford crude \((R)-12\), which was diluted with dry EtOAc to a final weight of 7.97 kg (at 67.4 wt%, KF = 200 ppm water). This material was further diluted with EtOAc (45.5 L) and then DABCO (3590 g, 32.0 mol, 1.80 eq) was added. After cooling to 2 °C, TsCl (4909 g, 25.8 mol, 1.45 eq) was slowly added (the internal temperature was maintained at < 20 °C). The resulting white suspension was aged at room temperature for 3 hrs. Water (15 L) was added and the mixture was heated to 35 °C and the two phase system was separated. The organic portion was washed with water (15 L) at 38 °C and then concentrated in vacuo (the resulting crystalline tosylate \((R)-13\) was slurried with a mixture of EtOAc (8 L) and hexane (30 L). This was filtered and washed [20 L hexane/EtOAc (4:1)] to afford 7450 g [16.3 mol, 99.9 LCWP, 100.0 LCAP, 81% yield from epoxide \((R)-10\)] of tosylate \((R)-13\) as a colorless, crystalline solid; mp 93.5-93.8 °C; \([\alpha]_D^{20} + 14.1^\circ\) (c 0.91 CH2Cl2); \(^1\text{H}\) NMR (400 MHz, CDCl3) \(\delta\) 7.81 (m, 2H), 7.38-7.25 (m, 7H), 6.78 (m, 2H), 6.65 (m, 2H), 5.03 (m, 1H), 4.42 (d, \(J = 12.0\) Hz, 1H), 4.39 (d, \(J = 12.0\) Hz, 1H), 4.03 (m, 2H), 3.77 (s, 3H) 3.58 (m, 1H), 3.49 (m, 1H), 2.41 (s, 3H), 2.12 (m, 2H), \(^{13}\text{C}\) NMR (100 MHz, CDCl3) \(\delta\) 154.0, 152.2, 144.5, 138.0, 133.9, 129.6, 128.3, 127.8, 127.5, 127.5, 115.4, 114.4, 78.5, 72.9, 69.5, 65.4, 55.6, 31.9, 21.5. Anal. Calcd for C25H28O6S: C, 65.77; H, 6.18. Found: C, 65.70; H, 6.10.
(3R,4R)-3-phenyl-4-[phenyl-[p-(methoxy)-phenoxy]methyl]-5,6-dihydropyran-2-one [(15)]:

A solution of phenylacetic acid (2400 g, 17.6 mol, 1.15 eq) and dry THF (44.0 L) was cooled to -58 °C under N₂ and a solution of n-BuLi (22.7 L of 1.6 M solution in hexane, 35.26 mol) was added dropwise via addition funnel so that the internal temperature was maintained below 0 °C. The resultant slurry was aged for one hour at 0 °C and then DMPU (1.06 L, 8.80 mol, 0.6 eq) was added. The resultant light orange solution was aged for an additional hour at 0 °C and then tosylate (R)-13 (6982 g, 15.3 mol) was added. As the solid tosylate dissolved, the reaction became bright yellow and the reaction was allowed to warm to room temperature and aged overnight. The resultant white slurry was quenched with 2 N HCl (18.0 L). After separation, the organic portion was washed with saturated sodium bicarbonate solution (2 x 18.0 L), 1 N HCl (18.0 L) and water (18.0 L). The crude stream of carboxylic acid 14 (>97 LCAP) was concentrated to 17.1 L (ca. 358 g/L) and was used without further purification. Two portions of this solution (2400 g HPLC assay @ 6.7 L volume, 5.71 mol) were each diluted with EtOAc (5.3 L) and hydrogenated with 10% Pd/C (240 g) at 40 psig and 55 °C overnight [overall, 78% of the crude acid stream was carried on]. These two crude hydrogenation reaction mixtures were combined (rinsed with 2 L EtOAc), diluted with CH₂Cl₂ (10 L) and dried over MgSO₄ (1280 g) for 1 h. To this was added EDC (1260 g, 60 mol%). After lactonization, the slurry was allowed to settle and the solution was decanted and filtered through a plug of solka floc (571 g) under an inert atmosphere. The wet MgSO₄–Pd/C residue was swished with 5 L of 4:1 (EtOAc/CH₂Cl₂). The slurry was again allowed to settle and the solution was decanted and filtered through the solka floc plug under an inert atmosphere. Caution: The Pd/C must remain wet and kept under an inert atmosphere. To the resulting light yellow solution was added DBU (340 mL, 20 mol%) and stirred overnight at room temperature. The reaction was washed with 2 N HCl (8.8 L) and separated. The organic phase was diluted with hexane and washed with 1 N HCl (9.0 L). The solvent was concentrated in vacuo to obtain a total EtOAc volume of 5.6 L. Hexane (2.8 L) was added to the slurry, the product filtered, and washed twice with 1:1
EtOAc/hexane (4 L) to afford 2276 g (7.29 mol, 61% yield from tosylate 13) of lactone 15 as a colorless solid. m.p. 109-110 °C; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.37-7.22 (m, 5H), 6.83-6.74 (m, 4H), 4.62-4.57 (m, 1H) 4.52.4.46 (m, 1H), 3.88 (d, \(J = 10.9\) Hz, 1H), 3.82 (dd, \(J = 9.2, 3.1\) Hz, 1H), 3.77 (s, 3H), 3.67 (dd, \(J = 9.2, 5.0\) Hz, 1H), 2.57-2.53 (m, 1H), 2.30-2.24 (m, 1H), 2.20-2.13 (m, 1H), \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 172.6, 154.1, 152.6, 137.4, 129.0, 128.7, 127.5, 115.4, 114.6, 69.4, 67.7, 55.6, 49.0, 39.1, 26.4; IR (thin film) 3030, 2910, 1736 cm\(^{-1}\); Anal. Calcd for C\(_{19}\)H\(_{20}\)O\(_4\): C, 73.06; H, 6.45. Found: C, 72.92; H, 6.37.
3-phenyl-4-\([p\text{-methoxy}]\)-phenoxy methyl]-5,6-dihydropyran-2-ol \([16]\): 

\[
\begin{align*}
\text{MeO} & & \text{O} & & \text{Ph} \\
\text{O} & & \text{O} & & \text{MeO} \\
\end{align*}
\]

\((R,R)-15\)  CH\(_2\)Cl\(_2\), -30 °C  \[91\%\]  \[
\begin{align*}
\text{MeO} & & \text{O} & & \text{Ph} \\
\text{O} & & \text{OH} & & \end{align*}
\]

A solution of lactone 15 (3600 g, 11.5 mol) in CH\(_2\)Cl\(_2\) (21.6 L) was cooled under N\(_2\) to -60 ± 5 °C. DIBAL-H (7.9 L, 1.45 M in toluene) was added at such a rate to maintain the reaction temperature at < -30 °C. After the reaction was complete (typical time is 30 min), 2 N HCl (11 L) was added to the reaction mixture, diluted with CH\(_2\)Cl\(_2\) (13.0 L) and allowed to warm to room temperature. After separation, the organic portion was washed with 2 M HCl (11 L) and then concentrated in vacuo and the residue was crystallized from toluene/hexane to afford 3305 g of lactol 16 (10.5 mol, 91% yield) as a colorless solid. mp 127–128 °C; \((2R)\)-trans-16 \[(R,R)-15\]: \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.29–7.38 (m, 3H), 7.25–7.28 (m, 2H), 6.77–6.81 (m, 2H), 6.68–6.72 (m, 2H), 4.86 (dd, \(J = 5.5\) Hz, 8.4 Hz, 1H), 4.20 (ddd, \(J = 1.5\) Hz, 4.7 Hz, 11.8 Hz, 1H), 3.77–3.90 (m, 1H), 3.76 (s, 3H), 3.68 (dd, \(J = 3.1\) Hz, 9.2 Hz, 1H), 3.54 (dd, \(J = 7.3\) Hz, 9.2 Hz, 1H), 3.18 (d, \(J = 5.4\) Hz, 1H), 2.60 (dd, \(J = 8.4\) Hz, 11.3 Hz, 1H), 2.30–2.37 (m, 1H), 1.97–2.00 (m, 1H), 1.76–1.87 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 153.7, 152.9, 139.1, 128.7, 127.1, 115.3, 114.55 (2C), 99.2, 70.2, 65.3, 55.7, 52.0, 40.4, 28.9; \((2S)\)-cis-16 \[(R,R)-15\]: \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.29–7.38 (m, 3H), 7.25–7.28 (m, 2H), 6.77–6.81 (m, 2H), 6.68–6.72 (m, 2H), 5.22 (t, \(J = 3.1\) Hz, 1H), 4.24–4.29 (m, 1H), 3.77–3.90 (m, 1H), 3.76 (s, 3H), 3.73–3.75 (m, 1H), 3.50 (dd, \(J = 7.3\) Hz, 9.0 Hz, 1H), 2.95 (dd, \(J = 2.1\) Hz, 12.1Hz, 1H), 2.80–2.87 (m, 1H), 2.70 (dd, \(J = 1.2\) Hz, 3.1 Hz, 1H), 2.00–2.08 (m, 1H), 1.76–1.87 (m, 1H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 153.1, 139.0, 129.3, 128.3, 127.0, 115.4, 114.52 (2C), 93.9, 71.0, 59.0, 55.7, 49.6, 32.9, 29.4; Anal. Calcd for C\(_{19}\)H\(_{22}\)O\(_4\): C, 72.59; H, 7.05. Found: C, 72.54; H, 6.96.
(3R,4R)-3-phenyl-4-[(p-methoxy)-phenoxy)methyl]-5,6-dihydropyran-2-[1-[(3,5-bistrifluoromethyl)phenylethylether] [(18)]:

A solution of the lactol 16 (3300 g, 10.5 mol) in CH₂Cl₂ (25.2 L) was cooled to -10 °C and 4-DMAP (13 g) and Et₃N (1610 mL, 11.55 mol) were added. Next, 4-nitrobenzoyl chloride (1988, 10.7 mol) was charged to the reaction portionwise at such a rate to maintain the reaction temperature at < +5 °C. The reaction was stirred overnight at +5 °C, quenched with water (19.8 L), and warmed to room temperature. The aqueous layer was removed and the organic portion was washed with 1 N NaOH (16.5 L), 2 N HCl (16 L), and 10% brine (16 L). The organic layer, which contained 17, was concentrated in vacuo, diluted with CH₂Cl₂ (46 L), cooled to -31 °C, and charged with chiral alcohol (R)-2 (2710 g, 10.5 mol). Next BF₃·OEt₂ (133 mL, 1 mol%) was slowly added while maintaining the internal temperature at < -27 °C (1.5 h addition time). After 2 hr, 1 N NaOH (30 L) was added and the resultant mixture was allowed to warm to room temperature. The organic layer was separated, washed with 10% brine (20 L), concentrated and then crystallized from EtOH/water to afford 4631 g (8.35 mol, 80% yield) of acetal 18. mp 68-69 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.67 (s, 1H, Ar-H), 7.20-7.24 (5H, m, C₆H₅), 7.03-7.06 (2H, m, Ar-H), 6.74-6.76 (m, 2H, Ar-H), 6.63-6.66 (2H, m, Ar-H), 4.99 (q, J = 6.6 Hz, 13.1 Hz, CH₂OAr), 4.29 (d, 1H, J = 6.6 Hz, 13.1 Hz, CH₂Ar), 3.73 (s, 3H, OC₃H₃), 3.56-3.63 (m, 2H, CH₂OCH and CH₂C₆H₅), 3.48 (m, 1H, C₆H₂OAr), 2.71 (dd, J = 8.4 Hz, 11.7 Hz, 1H, CH₂OAr), 2.18–2.22 (m, 1H, CH₂CH₂Ar), 1.92–1.96 (m, 1H, C₆H₂CH₂), 1.77–1.82 (m, 1H, CH₂CH₂), 1.38 (d, J = 6.6 Hz, 3H, CH₃); ¹³C NMR (CDCl₃, 100 MHz) δ 153.7, 152.8, 145.7, 138.5, 131.3 (q, J = 30 Hz), 128.4, 127.9, 127.1, 126.2, 123.0 (q, J = 272 Hz), 121.3, 115.2, 114.4, 102.5, 73.6, 70.0, 65.0, 55.6, 50.2, 40.2, 28.8, 24.4. Anal. Calcd. for C₂₉H₂₈F₆O₄: C, 62.81; H, 5.09. Found C, 62.82; H, 5.01
To a solution of acetal 18 (2267 g, 4.09 mol) in 4:1 acetonitrile (36.3 L) and water (9.0 L) at 0 °C was added cerium(IV) ammonium nitrate (CAN, 5603 g, 10.2 mol). Clean deprotection occurred in <1 h (HPLC) and the reaction was diluted with MTBE (17.9 L) and 26% NaCl (27.2 L). The aqueous layer (bottom) was cut and discarded and the remaining organic portion was diluted hexanes (17.9 L) and water (27.2 L). The three phase system was allowed to settle and the aqueous layer (bottom most) was removed. The remaining two-phase organic system was sequentially washed with water (27.2 L), 1 M NaOH (2 x 13.6 L), and water (27.2 L) [The addition of the caustic wash resulted in the aqueous portion immediately turning black]. The resultant organic stream was then concentrated and dissolved in dry EtOAc (14.5 L) to bring the final volume to 18.3 L, which resulted in a solution of alcohol 19 (HPLC assay yield = 93%, 1715 g, 3.82 mol).

To 27.5 L of alcohol 19 solution (2550 assay g, 5.69 mol) in EtOAc at -12 °C was added 1,4-diazabicyclo[2.2.2]octane (1020 g, 9.10 mol). After dissolution, benzenesulfonyl chloride (1016 mL, 7.96 mol) was added slowly via an addition funnel while maintaining the internal temperature between -10 and 15 °C. The resulting slurry was warmed to room temperature and then quenched with water (25.5 L) and stirred for 90 min. When the hydrolysis of residual benzenesulfonyl chloride was confirmed by HPLC, the aqueous layer was removed and the organic layer was washed sequentially with 1 N HCl (26 L) and 0.5 N NaHCO₃ (26 L). The solvent was removed in vacuo and the crude benzenesulfonate 20 was dissolved in acetonitrile (23 L). (R)-Ethyl-3-methyl-piperidine-3-carboxylate (2) (1217 g, 7.11 mol, 1.25 eq) and powdered sodium carbonate (904 g, 8.53 mol) were added to this solution and the resulting suspension was heated at reflux overnight. The reaction was cooled to room temperature, diluted with isopropyl acetate (33 L) and then extracted sequentially with water (33 L), 10 % ammonium chloride (33
L), and 5% sodium carbonate (33 L). The organic layer was concentrated in vacuo and
diluted to a final volume of isopropyl acetate (23 L). The solution was heated to 50 °C
and 2.5 L of a solution prepared from p-toluenesulfonic acid monohydrate (1050 g, 5.52
mol) in IPAC (20 L) was added. After crystallization, the volume of the resulting slurry
was reduced to 23 L by vacuum distillation. Heptane (10.0 L) was added slowly at 21
°C. Filtration of the slurry (rinse with 1:1 IPAC/heptane) afforded 3995 g (5.16 mol,
91% yield from 19) of penultimate 21 tosylate salt as a white solid; mp 163.3-163.7 °C;
¹H NMR (400 MHz, CD₃OD) δ 7.71 (s, 1H), 7.68 (m, 2H), 7.31 (s, 2H), 7.28-7.21 (m,
3H), 7.20 (m, 2H), 7.14 (m, 2H), 5.01 (q, J = 6.5 Hz, 1H), 4.41 (d, J = 7.8 Hz, 1H), 4.21
(m, 2H), 4.11 (m, 1H), 3.66 (m, 1H), 3.52 (brd, J = 12.5 Hz, 1H), 3.24 (brd, J =11.7 Hz,
1H), 3.03 (dd, J = 13.2, 9.2, Hz, 1H), 2.78 (d, J = 12.6 Hz, 1H), 2.70 (d, J =13.7 Hz,
1H), 2.56-2.42 (m, 3H), 2.34 (s, 3H), 2.07 (brd, J = 13.3Hz, 2H), 1.73 (m, 1H), 1.65-
1.54 (m, 2H), 1.38 (brtd, J = 13.7, 3.9 Hz, 1H), 1.32 (d, J = 6.5 Hz, 3H), 1.24 (t, J = 7.2
Hz, 3H), 1.15 (s, 3H); ¹³C NMR (100 MHz, CD₃OD) δ 176.9, 147.9, 144.0, 139.4, 132.7 (q,
JCF 33.2 Hz), 130.2, 130.0, 129.7, 128.9, 127.7, 127.1, 124.8 (q, JCF
272.0 Hz), 122.3, 103.9, 75.4, 65.3, 63.8, 63.4, 61.7, 54.6, 53.1, 43.9, 37.2, 32.3, 31.3,
24.9, 23.9, 22.0, 21.4, 14.4; IR (thin film) 3458, 1731 cm⁻¹. Anal. Calcd for
C₃₈H₄₅F₆NO₇S: C, 58.98; H, 5.86; F, 14.73; N, 1.81. Found: C, 58.82; H, 5.71; F,
14.56; N, 1.61.
(+)-[2R,3R,4R,8R,9(3'R)-2-{1-[1(3,5-bis(trifluoromethyl)phenyl]-ethyl}oxy]-4(-3-carboxy-3-methylpiperidin-1-yl)-3-phenyl-methyltetrahydropyran: [1]

Penultimate tosylate salt 21 (3735 g, 4.83 mol) was suspended in ethanol (11.5 L), heated to 50 °C, and aqueous 2.0 N sodium hydroxide was added (3.9 L, 19.3 mol). The resulting suspension was heated for 2 d at 50 °C. The clear solution was cooled to room temperature and diluted with water (37.5 L). Phosphoric acid (94 mL, 1.38 mol) was added and the solution was adjusted from pH 12.7 to pH 7.0 with 2.0 N HCl (6.2 L). The resulting solution was extracted with dichloromethane (2 x 17 L) and the combined extracts were washed with water (7.5 L). The solvent was removed in vacuo and the product was dissolved in isooctane (29 L) at 50 °C. This was slowly cooled to 0 °C, filtered, and rinsed with isooctane (12 L) to afford 2588 g (4.51 mol, 93% yield) of 1 as a colorless solid; mp 105.8-106.5 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.68 (s, 1H), 7.26 (m, 2H), 7.17 (s, 1H), 7.02 (m, 2H), 4.96 (q, J = 6.6 Hz, 1H), 4.22 (d, J = 8.3 Hz, 1H), 4.18 (ddd, J = 12.0, 4.7, 1.5 Hz, 1H), 3.56 (td, J = 12.1, 2.2 Hz 1H), 2.91 (m, 1H), 2.76 (d, J = 11.7 Hz, 1H), 2.39 (dd, J = 11.2, 8.3 Hz, 1H), 2.24-2.07 (m, 3H), 1.52 (qd, J = 12.0, 4.5 Hz, 1H), 1.36 (d, J = 6.6 Hz, 3H), 1.13 (m, 1H), 1.10 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 177.6, 145.7, 138.4, 131.5 (q, J_CF 33.1 Hz), 128.8, 127.9, 127.4, 126.3, 123.2 (q, J_CF = 272.8 Hz), 121.4 (m), 102.4, 73.8, 64.9, 63.8, 61.5, 52.5, 50.8, 41.7, 37.1, 34.8, 30.3, 24.4, 22.9, 22.0; IR (thin film) 3435, 1718 cm⁻¹. Anal. Calcd for C₂₉H₃₃F₆NO₄:  C, 60.73; H, 5.80; F, 19.87; N, 2.44. Found:  C, 60.53; H, 5.62; F, 19.45; N, 2.36.
Olefin 23:

An authentic sample of the elimination by-product 23 was isolated from the mother liquor of the acetalization reaction. m.p. 97-99 °C; $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.25-7.18 (m, 4H), 7.17-7.10 (m, 1H), 6.76 (d, $J = 1.3$ Hz, 1H), 6.72-6.65 (m, 4H), 4.11-4.06 (m, 1H), 3.90 (app dt, $J = 11.5$, 2.4 Hz, 1H), 3.80 (ddd, $J = 9.6$, 3.4, 0.9 Hz, 1H), 3.66 (s, 3H), 3.60 (app t, $J = 9.8$ Hz, 1H), 3.17-3.12 (m, 1H), 2.19-2.13 (m, 1H), 2.05-1.96 (m, 1H); $^{13}$C NMR (CDCl$_3$ 100 MHz) δ 153.8, 152.8, 144.2, 138.3, 128.5, 126.2, 125.4, 115.4, 114.5, 113.2, 69.5, 62.1, 55.6, 31.5, 24.3; IR (thin film) 2990, 1625, 1512, cm$^{-1}$; Anal. Calcd for C$_{19}$H$_{20}$O$_3$: C, 77.00; H, 6.80. Found: C, 76.89; H, 6.85.
(R)-Ethyl-3-methylpiperidine-3-carboxylate di-p-toluoyl-d-tartrate [24]:

A solution of 4000 g of ethyl nipecotate and 20 L of toluene was cooled to -20 to -35 °C and NaHMDS (14.5 L, 40 wt% in THF) was slowly added via addition funnel. The internal temperature was maintained at -20 to -10 °C during the addition. After complete addition, the slurry was aged for 30 min at -20 °C and then methyl iodide (3610 g) was slowly added, giving initially a clear yellow solution, then a precipitate. The internal temperature was maintained between -20 and -10 °C during the addition (>98 GCAP). The reaction was then warmed to room temperature and quenched with water (4 L). The layers were separated and the organic layer was washed with water (4 L). To the cloudy organic layer was added ethanol (4 L) in order to clarify the solution. The solution was distilled at atmospheric pressure to a final volume of 10 L. This was diluted with 20 L ethanol and redistilled to a final volume of 10 L, and the process was repeated. [this process removed toluene and silyl residues]. The ethanol was removed and the residue was dissolved in ethyl acetate to a final volume of 25.2 L (target < 1 % GC v/v EtOH). The solution was then cooled to 50 °C and diluted with 15.2 L ethyl acetate (92% assay yield). The solution was maintained at 50 °C while 10 to 15% of a solution was di-p-toluoyl-D-tartaric acid (2700 g) in ethyl acetate (10 L) was added. The remaining acid solution was added over 2 h via addition funnel to the 50 °C slurry. The resulting slurry was cooled to ambient temperature, filtered, and rinsed with ethyl acetate to afford 2.6 kg [28% (56 % of theoretical), >98 % d.e.] of nipecotate-di-toluoyl tartrate salt 24 as a colorless solid; mp 158-159 °C; 1H NMR (400 MHz, CD3OD integrations listed as 1 amine to ½ tartrate) δ 8.04 (app d, J = 8.3 Hz, 2H), 7.27 (app d, J = 8.3 Hz, 2H), 5.83 (s, 1H), 4.24-4.12 (m, 2H), 3.42 (brd, J = 13.0 Hz, 1H), 3.12 (m, 1H), 2.83 (td, J = 12.2, 3.4 Hz, 1H), 2.71 (d, J = 13.0 Hz, 1H), 2.39 (s, 3H), 2.08 (m, 1H), 1.73 (m, 1H), 1.55-1.40 (m, 2H), 1.24 (t, J = 7.2 Hz, 3H), 1.13 (s, 3H); 13C NMR (100 MHz, CD3OD) δ 176.3, 174.2, 168.1, 145.1, 131.3, 130.2, 129.4, 77.0, 62.8, 50.8, 44.7, 42.4, 33.1, 23.9, 21.8, 21.2, 14.5; IR (thin film) 3426, 1723, 1705 cm⁻¹. Anal. Calcd for C19H26NO6: C, 62.62; H, 7.19; N, 3.84. Found: C, 62.83; H, 7.11; N, 3.84. GC conditions: RTX-1701 column, 60 m x 0.32, injector temp. 150 °C, oven temp. 50-120 °C (ramp at 10 °C/min then 120 to 140 °C @ 1 °C/min then 140 to 220 °C @ 20 °C/min, detector temp. 250 °C; helium flow 3 mL/min, 1mL injections with 1:1 split ratio.
(R)-Ethyl 3-methylpiperidine-3-carboxylate [(R)-4]:

![Chemical Structure](image)

(**Method A**): A mixture of amine salt 24 (2596 g, 7.1 mol), water (26 L), and sodium carbonate (1562 g, 14.7 mol) were stirred at room temperature. After dissolution, the solution was extracted with MTBE (17 L) five times. The MTBE layers were combined and concentrated to an oil via rotary evaporation that afforded 1143 g of amine (R)-4 (6.67 mol, 94% yield, 1.1 wt% MTBE by 1H NMR). This was used in the alkylation reaction without further purification.

(**Method B**): Amine salt 24 (10.09 g, 27.7 mmol) and cyclohexane (100 mL) were rapidly stirred and sodium hydroxide (5 N, 6.1 mL) was charged in one portion to the slurry and the mixture was stirred for 1 hour. The slurry was transformed to a water-white supernatant with white tacky agglomerated solids. The batch was diluted with 90 mL cyclohexane and atmospherically distilled to a volume of 100 mL in order to remove excess water. The solids turned-over to small pellets, which were then filtered and washed (2 X 50 mL cyclohexane). The batch and washes were combined and concentrated in vacuo to afford 4.73 g (27.6, 100% yield, >97 GCWP) of amine (R)-4 as an oil.