Practical and Scalable Synthesis of a Selective CCK₁ Receptor Antagonist

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Supporting information

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2) Experimental
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**General experimental methods:**

Proton and carbon NMR spectra were recorded at 400, 500, or 600 MHz NMR spectrometers. Flash column chromatography was performed using Merck silica gel 60. HRMS (ESI) was performed on a μTof apparatus. Melting points were determined using an electrothermal apparatus and are uncorrected. Unless specified, all the reagents and solvents were purchased from commercial sources and used without further purification.

**Experimental Section:**

The Still-Gennari phosphonate was prepared in a 3-step sequence.

![Chemical Reaction Diagram]

(3-Chloro-benzyl)-phosphonic acid diethyl ester: To a 500-mL, round-bottomed flask was added 1-bromomethyl-3-chloro-benzene (50.0 g, 0.24 mol, 1.0 equiv) and P(OEt)₃ (119.0 g, 0.72 mol, 3.0 equiv.). The flask was fitted with a reflux condenser and the mixture was heated to 150 °C for 20 h. The reflux condenser was removed and the flask was fitted with a short path distillation apparatus. The oil bath temperature was raised to 170 °C to distill off the excess P(OEt)₃ under vacuum. The residual colorless liquid was the title compound (63.0 g, 0.24 mol, 99%), which was used in the next step without further purification. ¹H NMR (600 MHz, CDCl₃) δ 7.29 (d, J = 1.9 Hz, 1H), 7.27 – 7.17 (m, 3H), 4.10 – 3.96 (m, 4H), 3.12 (d, J = 21.7 Hz, 2H), 1.26 (t, J = 7.1 Hz, 6H). ¹³C NMR (151 MHz, CDCl₃) δ 134.3 (d, J = 3.5 Hz), 133.7 (d, J = 9.1 Hz), 129.8 (d, J = 6.7 Hz), 129.7 (d, J = 3.0 Hz), 128.0 (d, J = 6.5 Hz), 127.1 (d, J = 3.6 Hz),
62.3 (d, \( J = 6.8 \) Hz), 33.5 (d, \( J = 138.5 \) Hz), 16.4 (d, \( J = 6.0 \) Hz). HRMS-ESI (m/z): [M+H]\(^+\) calcd for C\(_{11}\)H\(_{17}\)ClO\(_3\)P 263.0598; found, 263.0602.

(3-Chloro-benzyl)-phosphonic acid bis-(2,2,2-trifluoro-ethyl) ester: A 500-mL, round-bottomed flask equipped with a magnetic stir bar was charged with (3-chloro-benzyl)-phosphonic acid diethyl ester (50 g, 190 mmol, 1.0 equiv.) and solid PCl\(_5\) (99.0 g, 475 mmol, 2.5 equiv.) was added in one portion at 0 °C. The resulting viscous suspension was stirred at 0 °C for 0.5 h and then at room temperature for 1 h. The reaction mixture was then stirred at 75 °C for 24 h.\(^1\) The solid PCl\(_5\) slowly dissolved to form a clear, slightly yellow solution overnight. The reaction flask was then fitted with a short-path distillation apparatus. Byproduct POCl\(_3\) and excess PCl\(_5\) was distilled off under vacuum. The reaction flask was cooled to 0 °C and then anhydrous toluene (120 mL), diisopropylethyl amine (49.2 g, 380 mmol, 2.0 equiv.) and trifluoroethanol (27.7 mL, 380 mmol, 2.0 equiv.) were added sequentially.\(^2\) The reaction mixture was stirred at 0 °C for 0.5 h and then at room temperature for 16 h. Et\(_2\)O (~150 mL) was added and the precipitated white solid was filtered off and washed with Et\(_2\)O. The filtrate solution was washed with H\(_2\)O, and then brine (250 mL each). The combined aqueous layers were back-extracted with Et\(_2\)O (100 mL). The organic layers were combined, dried over Na\(_2\)SO\(_4\), filtered and concentrated. The crude product was purified via column chromatography with EtOAc/Hexanes as the eluents to afford the title compound (31.0 g, 84 mmol, 44%) as a waxy solid. \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 7.34 – 7.24 (m, 3H), 7.23 – 7.14 (m, 1H), 4.38 – 4.18 (m, 18H).

\(^1\) Gas evolution was observed during the first hour of heating.

\(^2\) The addition of trifluoroethanol was highly exothermic. The addition rate was controlled that the internal temperature did not exceed 10 °C.
4H), 3.30 (d, J = 22.4 Hz, 2H). $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 134.8 (d, J = 3.9 Hz), 131.1 (d, J = 9.7 Hz), 130.1 (d, J = 3.4 Hz), 129.9 (d, J = 7.1 Hz), 128.06 (d, J = 4.0 Hz), 128.00 (d, J = 6.9 Hz), 122.5 (qd, J = 277.6, 7.7 Hz), 62.4 (qd, J = 38.0, 6.4 Hz), 33.1 (d, J = 140.7 Hz). HRMS-ESI (m/z): [M+H]$^+$ calcd for C$_{11}$H$_{11}$ClF$_6$O$_3$P 371.0033; found, 371.0048.

![Structural formula of the compound](image)

[Bis-(2,2,2-trifluoro-ethoxy)-phosphoryl]-3-chloro-phenyl)-acetic acid methyl ester: A 500-mL, three-necked, round-bottomed flask was charged with anhydrous THF (56 mL) and LiHMDS (1 mol/L solution in THF, 56.7 mL, 2.1 equiv.). At -78 °C, a solution of (3-chlorobenzyl)-phosphonic acid bis-(2,2,2-trifluoro-ethyl) ester (10.0 g, 27.0 mmol, 1.0 equiv.) and methyl chloroformate (2.6 g, 27.5 mmol, 1.0 equiv.) in anhydrous THF (30 mL) was added over 30 minutes. The reaction mixture was allowed to warm to ambient temperature over 16 h. HCl aqueous solution (6 mol/L) was slowly added at 0 °C to adjust pH = 4 and H$_2$O (50 mL) was added. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 50 mL). The organic layers were combined, dried over Na$_2$SO$_4$, filtered and concentrated to afford the title compound as a slightly orange oil (11.4 g, 26.5 mmol, 98% crude yield), which was used in the next step without further purification. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.44 (d, J = 1.3 Hz, 1H), 7.39 – 7.29 (m, 3H), 4.48 – 4.31 (m, 4H), 4.10 – 4.23 (m, 1H), 3.79 (s, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 166.8 (d, J = 1.8 Hz), 134.9 (d, J = 2.9 Hz), 130.9 (d, J = 8.8 Hz), 130.2 (d, J = 2.7 Hz), 129.5 (d, J = 6.8 Hz), 129.1 (d, J = 3.2 Hz), 127.6 (d, J = 6.6 Hz), 122.3 (dd, J = 269.3, 10.2 Hz), 63.0 (ddd, J = 38.2, 9.0, 6.1 Hz), 53.5 (d, J = 0.7 Hz), 51.4 (d, J = 143.0 Hz). HRMS-ESI (m/z): [M+H]$^+$ calcd for C$_{13}$H$_{13}$ClF$_6$O$_3$P 429.0088; found, 429.0106.
5-(3-Chloro-phenyl)-2,2-dimethyl-[1,3]dioxolan-4-one (5): To a 500-mL, one-necked, round-bottomed flask, equipped with a magnetic stir-bar was added (R)-3-chloromandelic acid (24 g, 0.13 mol, 1.0 equiv.), 2,2-dimethoxypropane (16.1 g, 0.15 mol, 1.2 equiv.), and 250 mL of anhydrous toluene. The flask was fitted with a Dean-Stark condenser and heated to reflux for 18 h. Evaporation of the solvent under reduced pressure provided the title compound as a white solid (29.5 g, 0.13 mol, 100%), which was used as such in the next step without further purification. mp: 144 – 145 °C.  

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.47 (m, 1H), 7.35 (m, 3H), 5.36 (s, 1H), 1.73 (s, 3H), 1.68 (s, 3H).  

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 170.7, 136.3, 134.7, 130.0, 129.1, 126.3, 124.4, 111.3, 75.0, 27.2, 26.2. HRMS-ESI (m/z): [M+Na]$^+$ calcd for C$_{11}$H$_{11}$ClO$_3$Na, 249.0294; found, 249.0283.

5-(3-Chloro-phenyl)-2,2-dimethyl-[1,3]dioxolan-4-one (6): In a 1-L, three-necked, round-bottomed flask fitted with nitrogen inlet and magnetic stir bar, 5-(3-chlorophenyl)-2,2-dimethyl-[1,3]dioxolan-4-one (5) (22.5 g, 0.1 mol, 1.0 equiv.) was dissolved in anhydrous THF (300 mL). At -78 °C under N$_2$, LiHMDS (1M solution in THF, 110 mL, 1.1 equiv.) was added via a syringe. After stirring for about 1 h, propargyl bromide (80% wt% in toluene, 16.25 g, 0.11 mol, 1.1 equiv.) was added drop wise via a syringe. The reaction mixture
was stirred at -78 °C for 1 h and then slowly warmed to room temperature overnight. Saturated 
NH_{4}Cl aqueous solution (100 mL) and EtOAc (200 mL) were added to quench the reaction. The 
organic layer was washed with brine, dried over MgSO_{4}, filtered and concentrated. The crude 
product was passed through a short pad of silica-gel with 10% EtOAc in hexanes as the eluents 
to afford 6 as pale yellow oil (23.8 g, 0.09 mol, 90%). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.66 (m, 
1H), 7.56 (m, 1H), 7.32 (m, 2H), 2.93 (dd, \(J = 13.6, 2.0\) Hz, 1H), 2.74 (dd, \(J = 13.6, 2.0\) Hz, 1H), 
2.11 (t, \(J = 2.0\)Hz, 1H), 1.78 (s, 3H), 1.46 (s, 3H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 171.1, 140.5, 
134.7, 129.9, 128.9, 125.2, 123.0, 111.1, 81.9, 78.2, 71.8, 32.4, 27.9, 27.4. HRMS-ESI (m/z): 
[M+Na]^+ calcd for C\(_{14}\)H\(_{13}\)ClO\(_3\)Na, 287.0451; found, 287.0439.

**5-(4-Benzol[1,3]dioxol-5-yl-4-oxo-but-2-ynyl)-5-(3-chloro-phenyl)-2,2-dimethyl-
[1,3]dioxolan-4-one** 7: In a 500-mL, three-necked, round-bottomed flask fitted with a magnetic 
stir-bar was charged Pd(PPh\(_3\))Cl\(_2\) (0.38 g, 0.54 mmol, 0.01 equiv.), Cul (0.21 g, 1.1 mmol, 0.02 
equiv.), and THF (150 mL) under N\(_2\). The solution was degassed with a stream of N\(_2\) for 5 min. 
Under N\(_2\), N-methylmorpholine (7.26 mL, 66 mmol, 1.2 equiv), benzo[1,3]dioxole-5-carbonyl 
chloride (10.1 g, 55.0 mmol, 1.0 equiv.) and the solution of 5-(3-chloro-phenyl)-2,2-dimethyl-5-
prop-2-ynyl-[1,3]dioxolan-4-one (6, 16.0 g, 60.5 mmol, 1.1 equiv.) in toluene (150 mL) were 
added successively. After the addition, the reaction mixture was degassed with a stream of N\(_2\) 
for 5 min. The reaction was then stirred under N\(_2\) at room temperature for 16 h. The white
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Precipitate was filtered off and washed with toluene (100 mL). The combined filtrates were washed with water (2 x 200 mL), brine (200 mL), dried over MgSO₄, filtered, and evaporated under reduced pressure to yield crude 7 (22.6 g, 55 mmol). The crude product was obtained as a brown solid, which was used on the next reaction without further purification. mp: 128 – 130 °C.

¹H NMR (500 MHz, CDCl₃): δ 7.74-7.70 (m, 1 H), 7.69-7.64 (m, 1 H), 7.63-7.58 (m, 1 H), 7.50-7.45 (m, 1 H), 7.40-7.35 (m, 2 H), 6.86 (d, J = 8.1 Hz, 1 H), 6.07 (s, 2 H), 3.19 (d, J = 17.4 Hz, 1 H), 3.10 (d, J = 17.4 Hz, 1 H), 1.77 (s, 3 H), 1.48 (s, 3 H). ¹³C NMR (126 MHz, CDCl₃) δ 175.5, 170.9, 153.0, 148.3, 140.0, 134.9, 131.7, 130.1, 129.2, 127.5, 125.2, 123.1, 111.6, 108.2, 108.0, 102.1, 87.9, 81.7, 81.4, 33.1, 27.8, 27.6. HRMS-ESI (m/z): [M+Na]⁺ calcd for C₂₂H₁₇ClO₆Na, 435.0611; found, 435.0616.
(3-Chloro-benzyl)-phosphonic acid diethyl ester, CDCl₃, 600 MHz, ¹H NMR

1H NMR, CDCl₃, 600 MHz
(3-Chloro-benzyl)-phosphonic acid diethyl ester, CDCl₃, 600 MHz, $^{13}$C NMR

13C NMR, CDCl₃, 600 MHz
(3-Chloro-benzyl)-phosphonic acid bis-(2,2,2-trifluoro-ethyl) ester, CDCl$_3$, 600 MHz, $^1$H NMR
(3-Chloro-benzyl)-phosphonic acid bis-(2,2,2-trifluoro-ethyl) ester, CDCl₃, 600 MHz, \(^{13}\)C NMR
[Bis-(2,2,2-trifluoro-ethoxy)-phosphoryl]-(3-chloro-phenyl)-acetic acid methyl ester, CDCl₃, 600 MHz, ¹H NMR
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[Bis-(2,2,2-trifluoro-ethoxy)-phosphoryl]-(3-chloro-phenyl)-acetic acid methyl ester, CDCl₃, 600 MHz, ¹³C NMR
Compound 5, $^1$H NMR, 500 MHz, CDCl$_3$
Compound 5, $^{13}$C NMR, 600 MHz, CDCl$_3$
Compound 6, $^1$H NMR, 500 MHz, CDCl$_3$
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Compound 6, $^{13}$C NMR, 500 MHz, CDCl$_3$
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Compound 7, $^1$H NMR, 500 MHz, CDCl$_3$
Compound 7, $^{13}$C NMR, 500 MHz, CDCl$_3$
Compound 8, $^1$H NMR, 500 MHz, CDCl$_3$
Supporting Information

Compound 8, $^{13}$C NMR, 500 MHz, CDCl$_3$
Compound 4, $^1$H NMR, 400 MHz, CDCl$_3$
Compound 4, $^{13}$C NMR, 400 MHz, CDCl$_3$
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Compound (Z)-3, $^1$H NMR, 600 MHz, CDCl$_3$
Compound (Z)-3, $^{13}$C NMR, 600 MHz, CDCl$_3$
Compound (Z)-1, $^1$H NMR, 400 MHz, CDCl$_3$
Compound (Z)-1, $^{13}$C NMR, 400 MHz, CDCl$_3$