Asymmetric Synthesis of 1,2,3-Trisubstituted Cyclopentanes and Cyclohexanes as Key Components of Substance P Antagonists

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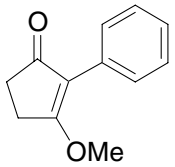
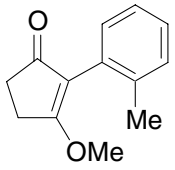
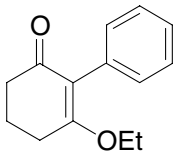
General Procedure for Suzuki-Cross Coupling of 2-Bromo-3-alkoxy-cyclopenten-1-ones and 2-Bomo-3-alkoxy-cyclohexen-1-ones with Arylboronic Acids. To a solution of the appropriate bromide (10 mmol), K_2CO_3 (20 mmol), and the appropriate arylboronic acid (13 mmol) was added $Pd_2(dba)_3$ (0.10 mmol) and PPh_3 (0.20 mmol). The resulting mixture was heated at reflux for 12 h, cooled to 20 •C, and then washed with 25 mL of 0.33 M K_3PO_4. The resulting toluene layer was concentrated under reduced pressure and the residue was purified by flash silica gel chromatography.



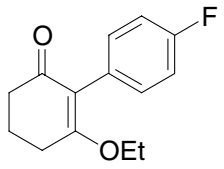
3-Methoxy-2-phenyl-2-cyclopenten-1-one. Colorless solid (82%): mp 83-83 •C (MTBE/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.59 (m, 2H), 2.80 (m, 2H), 4.00 (s, 3H), 7.27 (m, 1H), 7.37 (m, 2H), 7.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.7, 33.8, 57.0, 118.8, 127.1, 128.0, 128.5, 132.1, 184.7, 203.0; Anal. Calcd. For $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.19; H, 6.37.



3-Methoxy-2-(2-tolyl)-2-cyclopenten-1-one. Colorless solid (99%): mp 87-88 •C (MTBE/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.19 (s, 3H), 2.63 (m, 2H), 2.81 (m, 2H), 3.82 (s, 3H), 7.21 (m, 1H), 7.27 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.2, 26.0, 33.9, 57.8, 120.7, 125.6, 128.1, 130.2, 130.7, 132.2, 137.4, 184.4, 203.5; Anal. Calcd. For $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.01; H, 6.93.

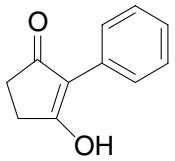


3-Ethoxy-2-phenyl-2-cyclohexen-1-one. Colorless solid (65%): mp 83-84 •C (MTBE/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (t, 3H, *J* = 7.0 Hz), 2.10 (m, 2H), 2.50 (m, 2H), 2.70 (t, 2H, *J* = 6.3 Hz), 3.96 (q, 2H, *J* = 7.0 Hz), 7.19 (m, 2H), 7.26 (m, 1H), 7.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.0, 20.6, 26.3, 36.8, 64.4, 120.5, 126.5, 127.6, 130.7, 133.5, 172.5, 197.5; Anal. Calcd. For $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.41; H, 7.42.

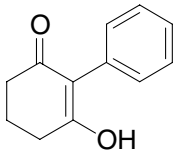


3-Ethoxy-2-(4-fluorophenyl)-cyclohexen-1-one. Colorless solid (76%): mp 87-88 •C (MTBE/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (t, 3H, *J* = 7.0 Hz), 2.09 (m, 2H), 2.48 (t, 2H, *H* = 6.7 Hz), 2.70 (t, 2H, *J* = 6.2 Hz), 4.00 (q, 2H, *J* = 7.0 Hz), 7.01 (m, 2H), 7.16 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.2, 20.8, 26.4, 37.0, 64.5, 114.5 (d, *J* = 20 Hz), 119.8, 129.3, 132.5, 161.6 (d, *J* = 240 Hz), 172.4, 197.3; Anal. Calcd. For $C_{14}H_{15}FO_2$: C, 71.78; H, 6.45. Found: C, 71.48; H, 6.40.

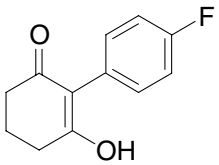
General Procedure for Coupling of 1,3-Cyclopentanediones and 1,3-Cyclohexanediones with Aryl Chlorides. Method A in 1,4-dioxane. To a 100 mL round bottom flask was sequentially added $Pd(OAc)_2$ (0.25 mmol), 2-(di-*t*-butylphosphino)biphenyl (0.55 mmol), the appropriate 1,3-dione (25.24 mmol), and powdered K_3PO_4 (50.5 mmol). The resulting mixture was degassed (3X) by vacuum/N_2 back fills. The vessel was then charged with 26 mL of 1,4-dioxane and the appropriate aryl chloride (32.78 mmol). The vessel was degassed (3X) with vacuum/N_2 back fills. The resulting slurry was heated to reflux for 12 h, cooled to rt, and water (75 mL) was added. To the homogeneous solution was added 6N HCl to adjust the pH to 1 and the slurry aged for 2.5 h. The slurry was then filtered and the cake washed with 1 bed volume of water and 1 bed volume of toluene. The solid was then dried under vacuum at 60 •C for 48 h. An analytical sample was obtained by recrystallization from acetone/hexane.



2-Phenyl-1,3-cyclopentanedione. White solid (96%); mp: 233 •C (decomp, acetone/hexane); ^{1}H NMR (d_5-py, 400 MHz) δ 2.54 (s, 4H), 7.31 (m, 1H), 7.51 (m, 2H), 8.54 (m, 2H), 12.5 (br s, 1H); ^{13}C NMR (d_5-py, 100 MHz) δ 32.2, 116.0, 127.3, 129.1, 129.3, 134.5, 195.5; Anal. Calcd. For $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.49; H, 5.86.



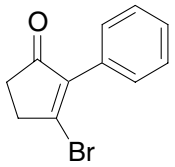
2-Phenyl-1,3-cyclohexanedione. White solid (65%); mp: 147-148 •C (acetone/hexane); ^{1}H NMR (d_5-py, 400 MHz) δ 1.93 (m, 2H), 2.64 (t, 4H, J = 6.3 Hz), 7.26 (m, 1H), 7.43 (m, 2H), 7.71 (m, 2H), 11.90 (br s, 1H); ^{13}C NMR (d_5-py, 100 MHz) δ 21.6, 34.6, 118.5, 127.0, 128.0, 131.0, 185.1; Anal. Calcd. For $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.24; H, 6.42.



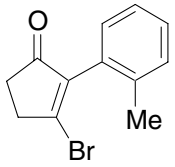
2-(4-fluorophenyl)-1,3-cyclohexanedione. White Solid (75%); mp: 203-205 •C (acetone/hexane); ^{1}H NMR (d_5-py, 400 MHz) δ 1.93 (m, 2H), 2.64 (m, 4H), 7.20 (m, 2H), 7.65 (m, 2H), 12.1 (br s, 1H); ^{13}C NMR (d_5-py, 100 MHz) δ 22.0, 34.9, 115.5 (d, J =

20 Hz), 117.7, 132.3, 134.6, 162.7 (d, J = 240 Hz), 185.7; Anal. Calcd. For $C_{12}H_{11}FO_2$: C, 69.89; H, 5.38. Found: C, 69.81; H, 5.15.

General Procedure for Bromination of 3-Alkoxy-2-substituted-cyclopenten-1-ones and 3-Alkoxy-2-substituted-cyclohexen-1-ones. To a solution of the appropriate 3-alkoxy-2-substituted-cyclopenten-1-one or cyclohexen-1-one (10 mmol) in 25 mL of 1,2-dichloroethane was added PBr_3 (15 mmol). The resulting mixture was heated to reflux for 1 h, cooled to 20 •C, and poured over cracked ice. The organic layer was separated, washed with sat. aqueous $NaHCO_3$, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified over a plug of silica gel.

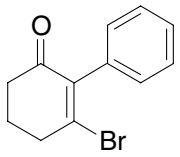


3-Bromo-2-phenyl-2-cyclopenten-1-one. White solid (65%): mp 39-40 •C (MTBE/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.73 (m, 2H), 3.11 (m, 2H), 7.46 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.8, 36.4, 128.3, 128.8, 129.0, 130.1, 143.2, 156.0, 202.3; Anal. Calcd. For $C_{11}H_9BrO$: C, 55.72; H, 3.83. Found: C, 55.63; H, 3.71.

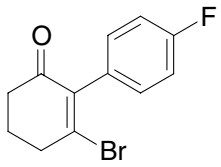


3-Bromo-2-(2-tolyl)-2-cyclopenten-1-one. White solid (62%); mp 59-60 •C (MTBE/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.18 (s, 3H), 2.75 (m, 2H), 3.14 (m, 2H), 7.05 (d, 1H, J = 7.5 Hz), 7.27 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.0, 35.9, 36.6,

125.9, 129.1, 129.5, 130.5, 130.7, 136.8, 158.0, 202.4; Anal. Calcd. For $C_{12}H_{11}BrO$: C, 57.39; H, 4.42. Found: C, 57.08, H, 4.37.



3-Bromo-2-phenyl-2-cyclohexen-1-one. Colorless solid (64%); mp 77-78 •C (MTBE/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.15 (m, 2H), 2.61 (t, 2H, *J* = 6.8 Hz), 3.07 (t, 2H, *J* = 6.2 Hz), 7.20 (d, 2H, *J* = 6.7 Hz), 7.40 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.9, 37.7, 38.0, 127.9, 128.0, 129.5, 136.1, 142.0, 148.2, 194.6; Anal. Calcd. For $C_{12}H_{11}BrO$: C, 57.40; H, 4.42. Found: C, 57.09; H, 4.27.



3-Bromo-2-(4-fluorophenyl)-2-cyclohexen-1-one. Colorless solid (66%); mp 76-77 •C (MTBE/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.17 (m, 2H), 2.62 (t, 2H, *J* = 6.8 Hz), 3.07 (t, 2H, *J* = 6.1 Hz), 7.10 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz)) δ 23.0, 37.8, 38.2, 115.2 (d, *J* = 20 Hz), 131.6, 132.0, 162.6 (d, *J* = 250 Hz), 194.7; Anal. Calcd. For $C_{12}H_{10}BrFO$: C, 53.56; H, 3.75. Found: C, 53.58; H, 3.43.

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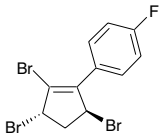

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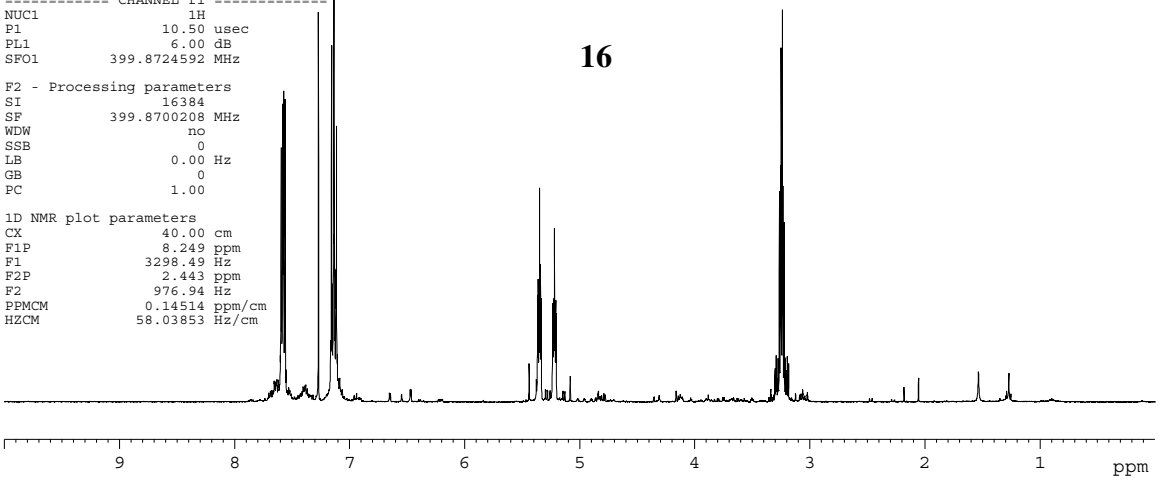


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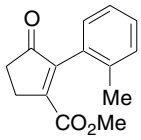
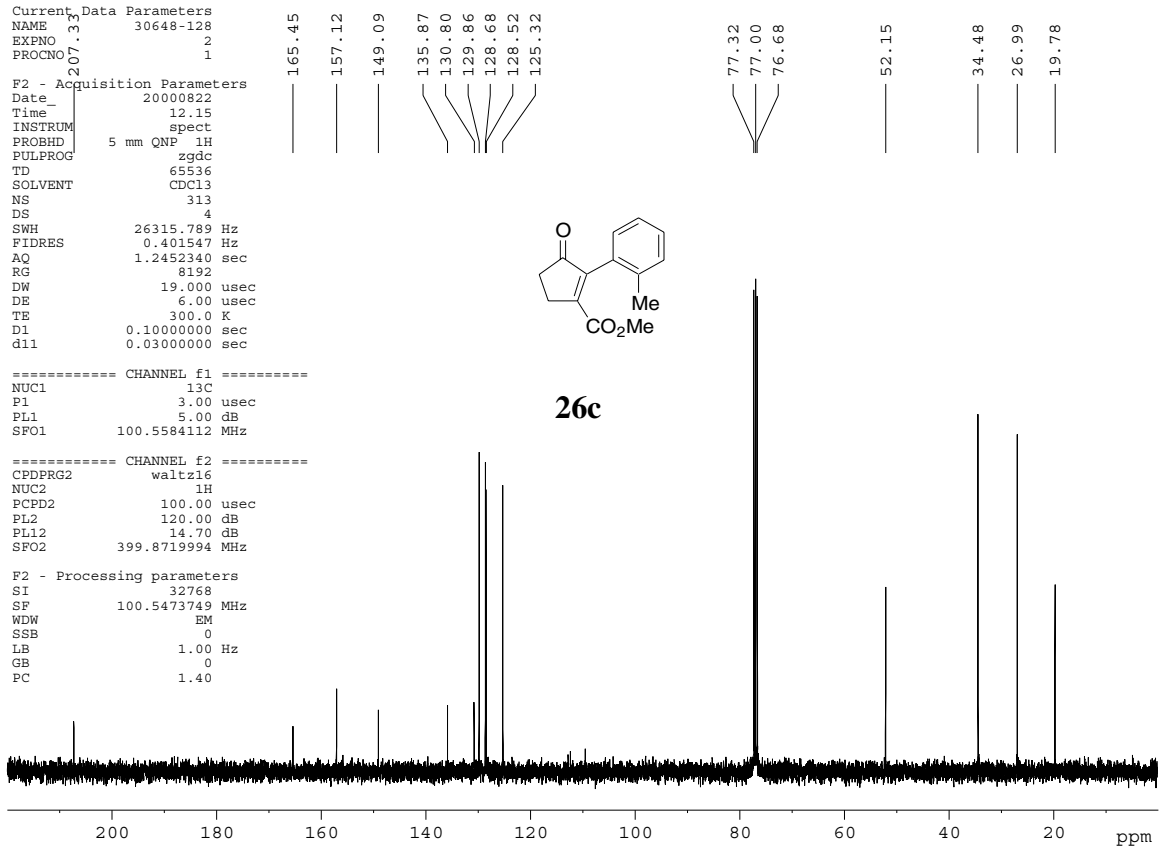


26c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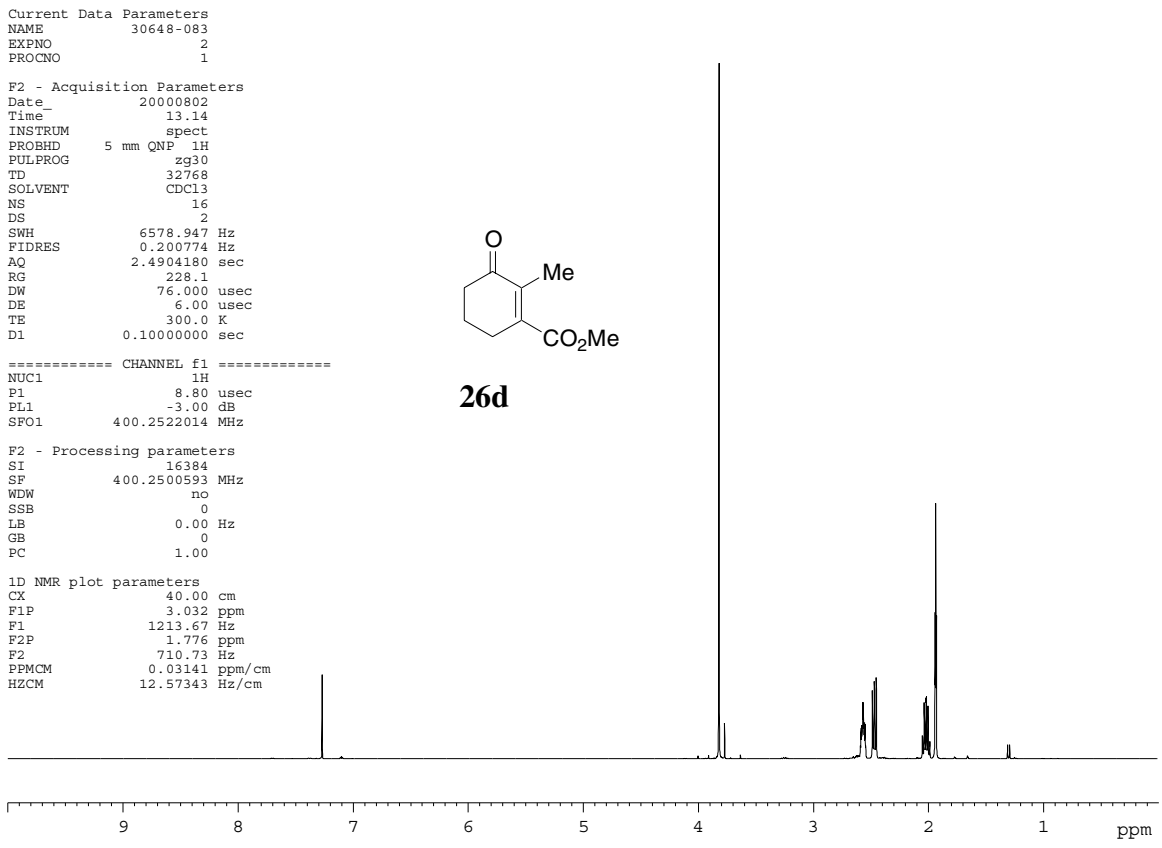
26c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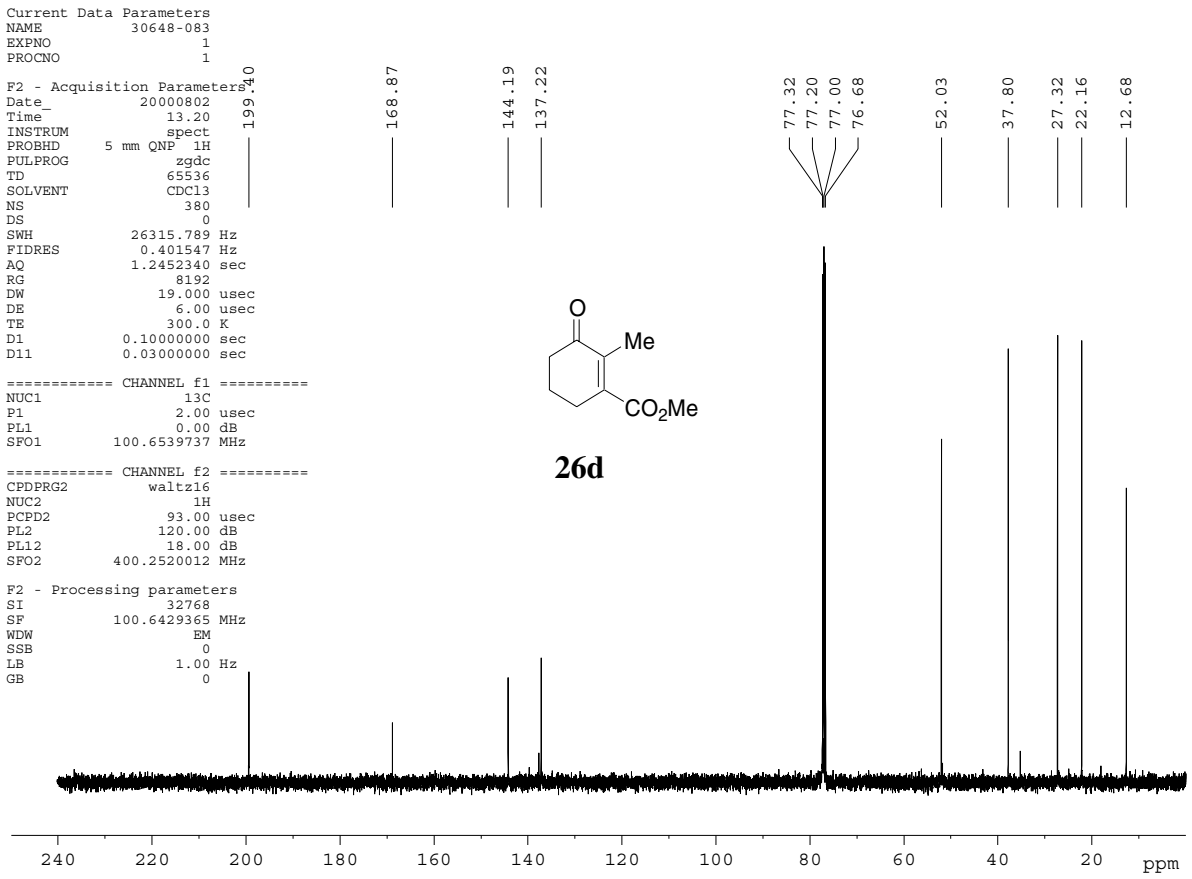
26d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