

Enantioselective synthesis of trifluoromethyl substituted cyclohexanones *via* organocatalytic cascade Michael/Aldol reaction

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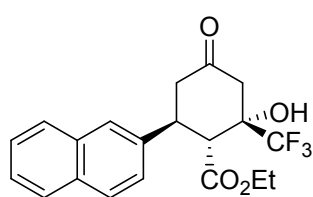
1. General methods

^1H and ^{13}C NMR spectra were recorded on Varian 400 MHz spectrometers. Chemical shifts (δ) are reported in ppm downfield from CDCl_3 ($\delta = 7.26$ ppm) for ^1H NMR and relative to the central CDCl_3 resonance ($\delta = 77.0$ ppm) for ^{13}C NMR spectroscopy. Coupling constants (J) are given in Hz. ESI-HRMS spectrometer was measured with a Thermo Scientific LTQ Orbitrap XL mass spectrometer. Enantiomeric excess was determined by HPLC analysis on Chiralpak AS-H, AD-H, OD-H and OJ-H columns in comparison with the authentic racemates. Optical rotation data were recorded on Rudolph Autopol I automatic polarimeter. Commercial grade solvents were dried and purified by standard procedures as specified in Purification of Laboratory Chemicals, 4th Ed (Armarego, W. L. F.; Perrin, D. D. Butterworth Heinemann: 1997).

Primary amines **C1-C4** were prepared according to literature procedures.¹

2. General procedure for the cascade Michael/aldol reaction

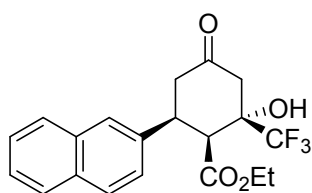
Ethyl 4,4,4-trifluoroacetoacetate **2a** (19.0 μL , 0.13 mmol), β -naphthyl-substituted cinnamone **1a** (19.6 mg, 0.1 mmol), primary amine **C3** based on quinidine (6.5 mg, 0.02 mmol) and benzoic acid (3.7 mg, 0.03 mmol) were stirred in redistilled 1,2-dichloroethane (1 mL) at room temperature. After due reaction time, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (EtOAc/petroleum ether) to afford the desired adduct. Notably, all these diastereomers were readily separable *via* flash chromatography.



Ethyl (1R, 2S, 6S)-2-hydroxy-6-(naphthalen-2-yl)-4-oxo-2-(trifluoromethyl)cyclohexane-1-carboxylate (3aa) (less polar):

White solid; 47% yield purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.86-7.79 (m, 3H), 7.68 (s, 1H), 7.51-7.49 (m, 2H), 7.39 (d, $J = 8.4$ Hz, 1H), 4.96 (br s, 1H), 3.82-3.69 (m, 3H), 3.40 (d, $J = 12.0$ Hz, 1H), 2.87 (d, $J = 14.8$ Hz, 1H), 2.84-2.73 (m, 2H), 2.68 (d, $J = 14.8$ Hz, 1H), 0.62 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 202.7, 173.5, 136.0, 133.3, 132.9, 128.8, 127.7, 127.6, 126.9, 126.5, 126.3, 124.7, 124.5 (q, $^1J_{\text{C-F}} = 285.2$ Hz), 76.5 (q, $^2J_{\text{C-F}} = 29.0$ Hz), 61.7, 49.2, 47.1, 44.8, 43.1, 13.2; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.3; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{20}\text{F}_3\text{O}_4$ 381.1308, found 381.1309; 95% ee was determined by HPLC on

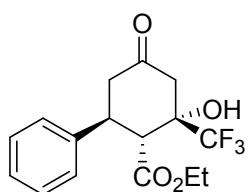
AS-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 210 nm, $t_{\text{major}} = 12.747$ min, $t_{\text{minor}} = 19.527$ min; $[\alpha]_{\text{D}}^{25} = -26.6^\circ$ ($c = 0.218$, CHCl_3).



Ethyl (1*S*, 2*S*, 6*S*)-2-hydroxy-6-(naphthalen-2-yl)-4-oxo-2-(trifluoromethyl)cyclohexane-1-carboxylate (3aa') (more polar):

White solid; 47% yield purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm):

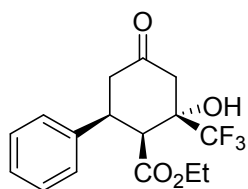
7.82-7.78 (m, 3H), 7.63 (s, 1H), 7.49-7.47 (m, 2H), 7.36 (d, $J = 8.4$ Hz, 1H), 4.07 (dt, $J = 13.6, 4.4$ Hz, 1H), 3.92-3.84 (m, 1H), 3.82-3.74 (m, 1H), 3.69 (d, $J = 14.4$ Hz, 1H), 3.57 (d, $J = 14.8$ Hz, 1H), 3.38 (d, $J = 4.0$ Hz, 1H), 3.25 (br s, 1H), 2.74-2.65 (d, $J = 14.4$ Hz, 2H), 0.76 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 205.5, 169.5, 136.8, 133.0, 132.2, 128.0, 127.8, 127.4, 126.3, 126.1, 126.0, 126.0 (q, $^1J_{\text{C-F}} = 285.1$ Hz), 125.4, 75.3 (q, $^2J_{\text{C-F}} = 28.8$ Hz), 60.3, 49.8, 42.3, 40.4, 38.6, 13.4; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.5; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{20}\text{F}_3\text{O}_4$ 381.1308, found 381.1305; 99% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (90/10), 1.0 mL/min, UV 210 nm, $t_{\text{major}} = 15.757$ min, $t_{\text{minor}} = 21.817$ min; $[\alpha]_{\text{D}}^{25} = -53.8^\circ$ ($c = 0.346$, CHCl_3).



Ethyl (1*R*, 2*S*, 6*S*)-2-hydroxy-4-oxo-6-phenyl-2-(trifluoromethyl)cyclohexane-1-carboxylate (3ab) (less polar): White solid; 45% yield

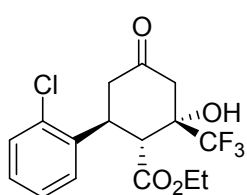
purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm): $\delta = 7.36$ -7.29 (m, 3H), 7.24 (d, $J = 6.8$

Hz, 2H), 4.90 (d, $J = 2.0$ Hz, 1H), 3.85 (q, $J = 7.2$ Hz, 2H), 3.57 (dt, $J = 11.6, 8.8$ Hz, 1H), 3.25 (d, $J = 12.0$ Hz, 1H), 2.83 (d, $J = 15.2$ Hz, 1H), 2.69 (d, $J = 9.6$ Hz, 2H), 2.63 (dd, $J = 15.0, 2.2$ Hz, 1H), 0.80 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 Hz, CD_3COCD_3) δ (ppm): 204.2, 174.3, 141.6, 130.2, 129.6, 129.2, 126.7 (q, $^1J_{\text{C-F}} = 284.9$ Hz), 78.2 (q, $^2J_{\text{C-F}} = 28.6$ Hz), 62.6, 50.8, 48.2, 46.5, 44.5, 14.5; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.4; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{18}\text{F}_3\text{O}_4$ 331.1152, found 331.1150; 96% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 210 nm, $t_{\text{major}} = 9.830$ min, $t_{\text{minor}} = 14.350$ min; $[\alpha]_{\text{D}}^{25} = 21.3^\circ$ ($c = 0.280$, CHCl_3).



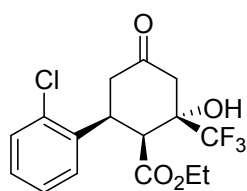
Ethyl (1*S*, 2*S*, 6*S*)-2-hydroxy-4-oxo-6-phenyl-2-(trifluoromethyl)cyclohexane-1-carboxylate (3ab') (more polar): White solid; 53% yield purified by flash column chromatography (EtOAc/petroleum ether); ^1H

NMR (400 MHz, CDCl₃) δ (ppm): 7.33 (t, $J = 7.2$ Hz, 2H), 7.27 (t, $J = 7.2$ Hz, 1H), 7.21 (d, $J = 6.8$ Hz, 2H), 3.96-3.83 (m, 3H), 3.57 (t, $J = 14.0$ Hz, 1H), 3.52 (t, $J = 14.4$ Hz, 1H), 3.44 (br s, 1H), 3.24 (d, $J = 4.4$ Hz, 1H), 2.64 (d, $J = 14.8$ Hz, 1H), 2.56 (dd, $J = 14.4, 4.0$ Hz, 1H), 0.92 (t, $J = 7.0$ Hz, 3H); ¹³C NMR (100 Hz, DMSO-d₆) δ (ppm): 205.5, 169.5, 139.2, 128.5, 127.31, 127.28, 124.9 (q, ¹ $J_{C-F} = 285.1$ Hz), 75.2 (q, ² $J_{C-F} = 28.7$ Hz), 60.3, 49.7, 42.2, 40.3, 38.5, 13.5; ¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -81.4; ESI-HRMS: [M+H]⁺ calcd. for C₁₆H₁₈F₃O₄ 331.1152, found 331.1158; 99% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 210 nm, $t_{\text{major}} = 6.897$ min, $t_{\text{minor}} = 18.483$ min; $[\alpha]_{\text{D}}^{25} = 56.5^\circ$ ($c = 0.278$, CHCl₃).



Ethyl (1R, 2S, 6S)-6-(2-chlorophenyl)-2-hydroxy-4-oxo-2-(trifluoromethyl)cyclohexane-1-carboxylate (3ac) (less polar): White solid; 51% yield purified by flash column chromatography (EtOAc/petroleum ether);

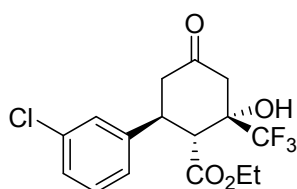
¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 7.65 (d, $J = 6.4$ Hz, 1H), 7.41 (d, $J = 8.0$ Hz, 1H), 7.36 (t, $J = 7.4$ Hz, 1H), 7.25 (t, $J = 7.4$ Hz, 1H), 6.71 (br s, 1H), 4.21 (t, $J = 12.0$ Hz, 1H), 3.81-3.76 (m, 3H), 3.07 (d, $J = 14.0$ Hz, 1H), 2.70 (t, $J = 14.0$ Hz, 1H), 2.57 (d, $J = 14.0$ Hz, 1H), 2.34 (d, $J = 13.2$ Hz, 1H), 0.84 (t, $J = 7.0$ Hz, 3H); ¹³C NMR (100 Hz, DMSO-d₆) δ (ppm): 203.9, 169.5, 138.3, 133.0, 129.5, 128.7, 128.4, 127.6, 124.9 (q, ¹ $J_{C-F} = 285.5$ Hz), 75.8 (q, ² $J_{C-F} = 28.5$ Hz), 60.0, 48.6, 46.1, 45.9, 36.6, 13.4; ¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -81.3; ESI-HRMS: [M+H]⁺ calcd. for C₁₆H₁₇³⁵ClF₃O₄ 365.0762, found 365.0765; calcd. for C₁₆H₁₇³⁷ClF₃O₄ 367.0732, found 367.0734; 97% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 210 nm, $t_{\text{minor}} = 10.863$ min, $t_{\text{major}} = 12.037$ min; $[\alpha]_{\text{D}}^{25} = 22.9^\circ$ ($c = 0.188$, CHCl₃).



Ethyl (1S, 2S, 6S)-6-(2-chlorophenyl)-2-hydroxy-4-oxo-2-(trifluoromethyl)cyclohexane-1-carboxylate (3ac') (more polar): White solid; 46% yield purified by flash column chromatography (EtOAc/petroleum ether);

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.43 (dd, $J = 5.2, 3.6$ Hz, 1H), 7.26-7.24 (m, 2H), 7.18-7.15 (m, 1H), 4.38 (dt, $J = 14.0, 4.2$ Hz, 1H), 3.98-3.77 (m, 2H), 3.59 (t, $J = 14.0$ Hz, 1H), 3.50 (d, $J = 14.8$ Hz, 1H), 3.42 (d, $J = 3.2$ Hz, 1H), 2.67 (d, $J = 14.4$ Hz, 1H), 2.48 (dd, $J = 14.6, 3.4$ Hz, 1H), 0.91 (t, $J = 7.0$ Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 206.8, 169.7, 135.8, 134.0, 130.0, 128.9, 127.5, 127.0, 124.3 (q, ¹ $J_{C-F} = 283.9$ Hz), 76.5 (q, ² $J_{C-F} = 29.9$ Hz), 61.0, 47.0,

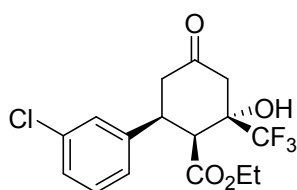
43.3, 40.6, 36.1, 13.6; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.4; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{17}^{35}\text{ClF}_3\text{O}_4$ 365.0762, found 365.0766; calcd. for $\text{C}_{16}\text{H}_{17}^{37}\text{ClF}_3\text{O}_4$ 367.0732, found 367.0744; 99% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (90/10), 1.0 mL/min, UV 210 nm, $t_{\text{major}} = 7.360$ min, $t_{\text{minor}} = 9.787$ min; $[\alpha]_{\text{D}}^{25} = 87.8^\circ$ ($c = 0.368$, CHCl_3).



Ethyl (1R, 2S, 6S)-6-(3-chlorophenyl)-2-hydroxy-4-oxo-2-(trifluoromethyl)cyclohexane-1-carboxylate (3ad) (less polar): White

solid; 48% yield purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm):

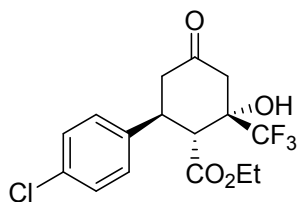
7.34-7.27 (m, 2H), 7.26 (s, 1H), 7.14-7.12 (m, 1H), 4.84 (d, $J = 2.0$ Hz, 1H), 3.97-3.85 (m, 2H), 3.56 (td, $J = 12.2, 5.6$ Hz, 1H), 3.24 (d, $J = 12.0$ Hz, 1H), 2.84 (d, $J = 15.2$ Hz, 1H), 2.71-2.59 (m, 3H), 0.87 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 202.2, 173.2, 140.7, 134.7, 130.2, 128.2, 127.7, 125.9, 124.4 (q, $^1J_{\text{C-F}} = 285.3$ Hz), 76.4 (q, $^2J_{\text{C-F}} = 29.1$ Hz), 61.9, 49.1, 46.8, 44.7, 42.5, 13.4; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.3; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{17}^{35}\text{ClF}_3\text{O}_4$ 365.0762, found 365.0765; calcd. for $\text{C}_{16}\text{H}_{17}^{37}\text{ClF}_3\text{O}_4$ 367.0732, found 367.0734; 95% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 210 nm, $t_{\text{minor}} = 7.777$ min, $t_{\text{major}} = 10.957$ min; $[\alpha]_{\text{D}}^{25} = 20.4^\circ$ ($c = 0.186$, CHCl_3).



Ethyl (1S, 2S, 6S)-6-(3-chlorophenyl)-2-hydroxy-4-oxo-2-(trifluoromethyl)cyclohexane-1-carboxylate (3ad') (more polar): White

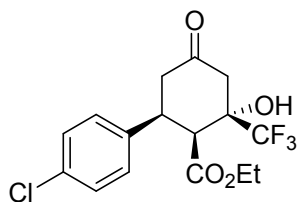
solid; 48% yield purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm):

7.31-7.24 (m, 2H), 7.22 (s, 1H), 7.14-7.10 (m, 1H), 3.95 (q, $J = 7.2$ Hz, 2H), 3.87 (dt, $J = 14.0, 4.6$ Hz, 1H), 3.52 (t, $J = 14.4$ Hz, 1H), 3.51 (d, $J = 14.8$ Hz, 1H), 3.44 (br s, 1H), 3.23 (d, $J = 4.4$ Hz, 1H), 2.65 (d, $J = 14.8$ Hz, 1H), 2.55 (dd, $J = 14.6, 4.2$ Hz, 1H), 0.98 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 207.4, 169.7, 140.8, 134.6, 129.9, 127.9, 127.6, 125.6, 124.3 (q, $^1J_{\text{C-F}} = 283.9$ Hz), 76.4 (q, $^2J_{\text{C-F}} = 29.9$ Hz), 61.2, 49.8, 43.2, 40.9, 39.4, 13.6; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.4; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{17}^{35}\text{ClF}_3\text{O}_4$ 365.0762, found 365.0769; calcd. for $\text{C}_{16}\text{H}_{17}^{37}\text{ClF}_3\text{O}_4$ 367.0732, found 367.0740; 99% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (90/10), 1.0 mL/min, UV 210 nm, $t_{\text{major}} = 8.640$ min, $t_{\text{minor}} = 22.067$ min; $[\alpha]_{\text{D}}^{25} = -56.1^\circ$ ($c = 0.180$, CHCl_3).



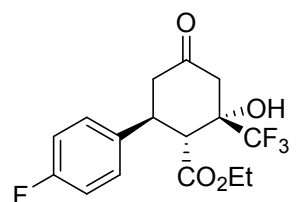
Ethyl (1R, 2S, 6S)-6-(4-chlorophenyl)-2-hydroxy-4-oxo-2-(trifluoromethyl)cyclohexane-1-carboxylate (3ae) (less polar): White

solid; 49% yield purified by flash column chromatography (EtOAc/petroleum ether); ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.32 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 4.81 (d, *J* = 2.0 Hz, 1H), 3.88 (q, *J* = 7.2 Hz, 2H), 3.56 (td, *J* = 12.0, 6.0 Hz, 1H), 3.21 (d, *J* = 12.0 Hz, 1H), 2.82 (d, *J* = 14.8 Hz, 1H), 2.68-2.57 (m, 3H), 0.87 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 202.3, 173.2, 137.2, 133.9, 129.1, 128.9, 124.4 (q, ¹*J*_{C-F} = 285.1 Hz), 76.4 (q, ²*J*_{C-F} = 28.9 Hz), 61.9, 49.3, 46.9, 44.7, 42.3, 13.4; ¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -81.3; ESI-HRMS: [M+H]⁺ calcd. for C₁₆H₁₇³⁵ClF₃O₄ 365.0762, found 365.0767; calcd. for C₁₆H₁₇³⁷ClF₃O₄ 367.0732, found 367.0734; 96% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 210 nm, *t*_{minor} = 10.110 min, *t*_{major} = 13.047 min; [α]_D²⁵ = 21.4° (*c* = 0.154, CHCl₃).



Ethyl (1S, 2S, 6S)-6-(3-chlorophenyl)-2-hydroxy-4-oxo-2-(trifluoromethyl)cyclohexane-1-carboxylate (3ae') (more polar):

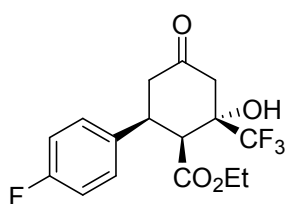
White solid; 49% yield purified by flash column chromatography (EtOAc/petroleum ether); ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.31 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 4.00-3.79 (m, 4H), 3.55 (d, *J* = 14.0 Hz, 1H), 3.48 (d, *J* = 14.4 Hz, 1H), 3.22 (d, *J* = 4.0 Hz, 1H), 2.61 (d, *J* = 14.8 Hz, 1H), 2.53 (dd, *J* = 14.2, 3.4 Hz, 1H), 0.97 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 207.2, 169.7, 137.2, 133.5, 128.9, 128.7, 124.2 (q, ¹*J*_{C-F} = 283.9 Hz), 76.4 (q, ²*J*_{C-F} = 29.8 Hz), 61.1, 49.9, 43.3, 41.0, 39.1, 13.6; ¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -81.4; ESI-HRMS: [M+H]⁺ calcd. for C₁₆H₁₇³⁵ClF₃O₄ 365.0762, found 365.0765; calcd. for C₁₆H₁₇³⁷ClF₃O₄ 367.0732, found 367.0734; 99% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (70/30), 1.0 mL/min, UV 210 nm, *t*_{major} = 5.430 min, *t*_{minor} = 9.880 min; [α]_D²⁵ = 58.0° (*c* = 0.262, CHCl₃).



Ethyl (1R, 2S, 6S)-6-(4-fluorophenyl)-2-hydroxy-4-oxo-2-(trifluoromethyl)cyclohexane-1-carboxylate (3af) (less polar): White

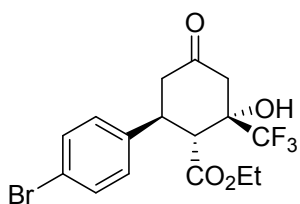
solid; 49% yield purified by flash column chromatography (EtOAc/petroleum ether); ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.22 (dd, *J* = 8.4, 5.2 Hz, 2H), 7.04 (t, *J* = 8.6 Hz, 2H), 4.83 (d, *J* = 1.6 Hz, 1H), 3.87 (q, *J* = 7.2 Hz, 2H),

3.57 (td, $J = 12.2, 5.6$ Hz, 1H), 3.20 (d, $J = 12.0$ Hz, 1H), 2.83 (d, $J = 14.8$ Hz, 1H), 2.69-2.57 (m, 3H), 0.87 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 202.4, 173.3, 162.3 (d, $^1J_{\text{C-F}} = 245.9$ Hz), 134.5 (d, $^4J_{\text{C-F}} = 3.3$ Hz), 129.2 (d, $^3J_{\text{C-F}} = 8.0$ Hz), 124.5 (q, $^1J_{\text{C-F}} = 285.1$ Hz), 115.8 (q, $^2J_{\text{C-F}} = 21.4$ Hz), 76.4 (q, $^2J_{\text{C-F}} = 29.0$ Hz), 61.9, 49.5, 47.2, 44.7, 42.2, 13.4; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.4, -113.8; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{17}\text{F}_4\text{O}_4$ 349.1057, found 349.1057; 96% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 210 nm, $t_{\text{minor}} = 10.943$ min, $t_{\text{major}} = 14.413$ min; $[\alpha]_{\text{D}}^{25} = 18.1^\circ$ ($c = 0.574$, CHCl_3).



Ethyl (1*S*, 2*S*, 6*S*)-6-(4-fluorophenyl)-2-hydroxy-4-oxo-2-(trifluoromethyl)cyclohexane-1-carboxylate (3af') (more polar):

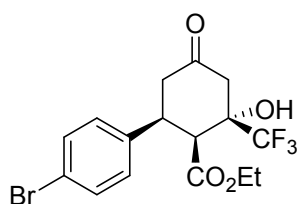
White solid; 49% yield purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.18 (dd, $J = 8.4, 5.2$ Hz, 2H), 7.02 (t, $J = 8.6$ Hz, 2H), 3.97-3.86 (m, 3H), 3.71 (br s, 1H), 3.52 (t, $J = 13.8$ Hz, 1H), 3.48 (d, $J = 14.8$ Hz, 1H), 3.22 (d, $J = 4.4$ Hz, 1H), 2.66 (d, $J = 14.8$ Hz, 1H), 2.53 (dd, $J = 14.4, 3.6$ Hz, 1H), 0.94 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 207.2, 169.7, 162.1 (d, $^1J_{\text{C-F}} = 245.2$ Hz), 134.5 (d, $^4J_{\text{C-F}} = 3.2$ Hz), 128.9 (d, $^3J_{\text{C-F}} = 8.0$ Hz), 124.3 (q, $^1J_{\text{C-F}} = 283.9$ Hz), 115.6 (q, $^2J_{\text{C-F}} = 21.3$ Hz), 76.4 (q, $^2J_{\text{C-F}} = 29.9$ Hz), 61.1, 50.1, 43.3, 41.2, 39.0, 13.6; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.5, -114.7; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{17}\text{F}_4\text{O}_4$ 349.1057, found 349.1055; 99% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (70/30), 1.0 mL/min, UV 210 nm, $t_{\text{major}} = 5.930$ min, $t_{\text{minor}} = 13.833$ min; $[\alpha]_{\text{D}}^{23} = -21.5^\circ$ ($c = 0.130$, CHCl_3).



Ethyl (1*R*, 2*S*, 6*S*)-6-(4-bromophenyl)-2-hydroxy-4-oxo-2-(trifluoromethyl)cyclohexane-1-carboxylate (3ag) (less polar):

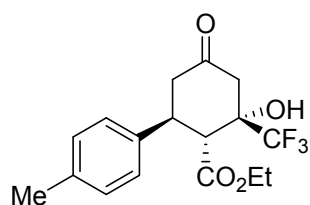
White solid; 44% yield purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.48 (d, $J = 8.4$ Hz, 2H), 7.12 (d, $J = 8.4$ Hz, 2H), 4.81 (d, $J = 2.0$ Hz, 1H), 3.89 (q, $J = 7.2$ Hz, 2H), 3.55 (td, $J = 12.0, 5.6$ Hz, 1H), 3.21 (d, $J = 12.0$ Hz, 1H), 2.82 (d, $J = 15.2$ Hz, 1H), 2.68-2.58 (m, 3H), 0.88 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 202.2, 173.2, 137.7, 132.0, 129.3, 124.4 (q, $^1J_{\text{C-F}} = 285.0$ Hz), 121.9, 76.4 (q, $^2J_{\text{C-F}} = 29.0$ Hz), 61.9, 49.2, 46.9, 44.7, 42.3, 13.4; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.4; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{17}^{79}\text{BrF}_3\text{O}_4$

409.0257, found 409.0255; calcd. for $C_{16}H_{17}^{81}BrF_3O_4$ 411.0236, found 411.0233; 96% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 210 nm, $t_{\text{minor}} = 10.237$ min, $t_{\text{major}} = 13.597$ min; $[\alpha]_D^{25} = -25.8^\circ$ ($c = 0.260$, $CHCl_3$).



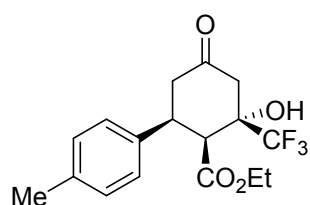
Ethyl (1*S*, 2*S*, 6*S*)-6-(4-bromophenyl)-2-hydroxy-4-oxo-2-(trifluoromethyl)cyclohexane-1-carboxylate (3ag') (more polar):

White solid; 53% yield purified by flash column chromatography (EtOAc/petroleum ether); 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.47 (d, $J = 8.8$ Hz, 2H), 7.10 (d, $J = 8.4$ Hz, 2H), 4.01-3.81 (m, 3H), 3.51 (t, $J = 14.2$ Hz, 1H), 3.49 (d, $J = 15.2$ Hz, 1H), 3.20 (d, $J = 4.8$ Hz, 1H), 2.83 (s, 1H), 3.60 (d, $J = 14.8$ Hz, 1H), 2.53 (dd, $J = 14.4$, 4.0 Hz, 1H), 0.98 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 207.6, 169.7, 137.7, 131.8, 129.0, 124.3 (q, $^1J_{C-F} = 283.8$ Hz), 121.6, 76.4 (q, $^2J_{C-F} = 29.8$ Hz), 61.2, 49.8, 43.2, 40.9, 39.2, 13.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -81.4; ESI-HRMS: $[M+H]^+$ calcd. for $C_{16}H_{17}^{79}BrF_3O_4$ 409.0257, found 409.0261; calcd. for $C_{16}H_{17}^{81}BrF_3O_4$ 411.0236, found 411.0256; 99% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (90/10), 1.0 mL/min, UV 210 nm, $t_{\text{major}} = 10.280$ min, $t_{\text{minor}} = 20.227$ min; $[\alpha]_D^{25} = 64.4^\circ$ ($c = 0.246$, $CHCl_3$).



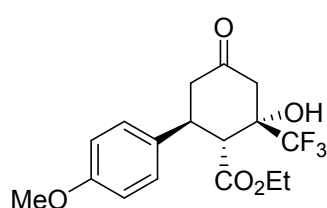
Ethyl (1*R*, 2*S*, 6*S*)-2-hydroxy-4-oxo-6-(*p*-tolyl)-2-(trifluoromethyl)cyclohexane-1-carboxylate (3ah) (less polar):

White solid; 45% yield purified by flash column chromatography (EtOAc/petroleum ether); 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.14 (d, $J = 8.4$ Hz, 2H), 7.11 (d, $J = 8.4$ Hz, 2H), 4.89 (br s, 1H), 3.86 (q, $J = 7.2$ Hz, 2H), 3.52 (td, $J = 12.0$, 8.8 Hz, 1H), 3.22 (d, $J = 12.0$ Hz, 1H), 2.81 (d, $J = 14.8$ Hz, 1H), 2.66 (d, $J = 9.2$ Hz, 2H), 2.61 (d, $J = 15.2$ Hz, 1H), 2.33 (s, 3H), 0.83 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 202.9, 173.5, 137.8, 135.7, 129.5, 127.4, 124.5 (q, $^1J_{C-F} = 285.2$ Hz), 76.5 (q, $^2J_{C-F} = 29.0$ Hz), 61.7, 49.5, 47.2, 44.7, 42.5, 21.0, 13.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -81.4; ESI-HRMS: $[M+H]^+$ calcd. for $C_{17}H_{20}F_3O_4$ 345.1308, found 345.1304; 96% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 210 nm, $t_{\text{minor}} = 9.570$ min, $t_{\text{major}} = 13.937$ min; $[\alpha]_D^{25} = -30.7^\circ$ ($c = 0.296$, $CHCl_3$).



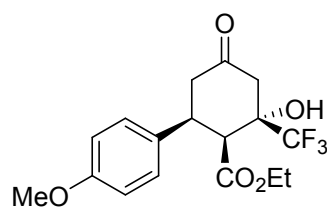
Ethyl (1*S*, 2*S*, 6*S*)-2-hydroxy-4-oxo-6-(*p*-tolyl)-2-(trifluoromethyl)cyclohexane-1-carboxylate (3ah') (more polar):

yield purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.12 (d, $J = 8.0$ Hz, 2H), 7.08 (d, $J = 8.0$ Hz, 2H), 3.98-3.80 (m, 4H), 3.56 (d, $J = 14.4$ Hz, 1H), 3.49 (d, $J = 14.4$ Hz, 1H), 3.23 (d, $J = 4.0$ Hz, 1H), 2.65 (d, $J = 14.8$ Hz, 1H), 2.53 (dd, $J = 14.4, 3.6$ Hz, 1H), 2.32 (s, 3H), 0.94 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 207.8, 169.9, 137.3, 135.7, 129.3, 127.2, 124.4 (q, $^1J_{\text{C-F}} = 284.2$ Hz), 76.5 (q, $^2J_{\text{C-F}} = 30.0$ Hz), 60.9, 50.2, 43.3, 41.3, 39.4, 21.0, 13.6; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.4; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{17}\text{H}_{20}\text{F}_3\text{O}_4$ 345.1308, found 345.1309; 99% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (90/10), 1.0 mL/min, UV 210 nm, $t_{\text{major}} = 9.607$ min, $t_{\text{minor}} = 20.573$ min; $[\alpha]_{\text{D}}^{25} = 65.4^\circ$ ($c = 0.246$, CHCl_3).



Ethyl (1R, 2S, 6S)-2-hydroxy-6-(4-methoxyphenyl)-4-oxo-2-(trifluoromethyl)cyclohexane-1-carboxylate (3ai) (less polar):

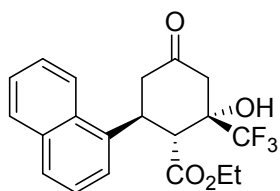
White solid; 41% yield purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.15 (d, $J = 8.8$ Hz, 2H), 6.86 (d, $J = 8.4$ Hz, 2H), 4.87 (d, $J = 2.0$ Hz, 1H), 3.87 (q, $J = 7.2$ Hz, 2H), 3.79 (s, 3H), 3.52 (dt, $J = 11.6, 6.4$ Hz, 1H), 3.19 (d, $J = 12.0$ Hz, 1H), 2.82 (d, $J = 15.2$ Hz, 1H), 2.69-2.58 (m, 3H), 0.86 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 202.9, 173.5, 159.2, 130.7, 128.6, 124.5 (q, $^1J_{\text{C-F}} = 285.2$ Hz), 114.2, 76.4 (q, $^2J_{\text{C-F}} = 28.8$ Hz), 61.7, 55.3, 49.6, 47.4, 44.7, 42.1, 13.4; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.4; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{17}\text{H}_{20}\text{F}_3\text{O}_5$ 361.1257, found 361.1258; 98% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 210 nm, $t_{\text{minor}} = 13.100$ min, $t_{\text{major}} = 23.867$ min; $[\alpha]_{\text{D}}^{25} = -31.1^\circ$ ($c = 0.254$, CHCl_3).



Ethyl (1S, 2S, 6S)-2-hydroxy-6-(4-methoxyphenyl)-4-oxo-2-(trifluoromethyl)cyclohexane-1-carboxylate (3ai') (more polar):

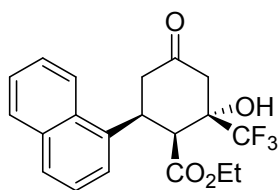
White solid; 41% yield purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.13 (d, $J = 8.8$ Hz, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 3.98-3.81 (m, 3H), 3.79 (s, 3H), 3.52 (t, $J = 14.0$ Hz, 1H), 3.49 (d, $J = 14.8$ Hz, 1H), 3.20 (d, $J = 4.0$ Hz, 1H), 3.16 (br s, 1H), 2.61 (d, $J = 14.4$ Hz, 1H), 2.53 (dd, $J = 14.4, 4.4$ Hz, 1H), 0.97 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 207.9, 169.9, 158.9, 130.7, 128.3, 124.3 (q, $^1J_{\text{C-F}} = 284.9$ Hz), 114.0, 76.4 (q, $^2J_{\text{C-F}} = 28.7$

Hz), 61.0, 55.3, 50.2, 43.3, 41.4, 39.0, 13.6; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.5; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{17}\text{H}_{20}\text{F}_3\text{O}_5$ 361.1257, found 361.1256; 95% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 210 nm, $t_{\text{major}} = 10.553$ min, $t_{\text{minor}} = 14.653$ min; $[\alpha]_{\text{D}}^{25} = 59.5^\circ$ ($c = 0.242$, CHCl_3).



Ethyl (1R, 2S, 6S)-2-hydroxy-6-(naphthalen-1-yl)-4-oxo-2-(trifluoromethyl)cyclohexane-1-carboxylate (3aj) (less polar):

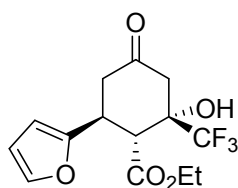
White solid; 59% yield purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.07 (d, $J = 8.4$ Hz, 1H), 7.86 (d, $J = 8.0$ Hz, 1H), 7.80 (d, $J = 8.4$ Hz, 1H), 7.61 (d, $J = 6.8$ Hz, 1H), 7.56-7.49 (m, 3H), 4.95 (d, $J = 2.0$ Hz, 1H), 4.63 (td, $J = 12.6, 4.4$ Hz, 1H), 3.69 (q, $J = 7.0$ Hz, 2H), 3.54 (d, $J = 12.0$ Hz, 1H), 2.92 (dd, $J = 15.0, 1.8$ Hz, 1H), 2.81 (ddd, $J = 15.0, 4.2, 2.0$ Hz, 1H), 2.72 (dd, $J = 14.8, 2.4$ Hz, 1H), 2.70 (d, $J = 13.6$ Hz, 1H), 0.61 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 202.9, 173.3, 135.1, 133.9, 130.9, 128.8, 128.3, 127.4 (q, $^1J_{\text{C-F}} = 285.4$ Hz), 126.7, 126.0, 125.1, 124.3, 122.3, 76.7 (q, $^2J_{\text{C-F}} = 28.9$ Hz), 61.8, 48.8, 47.7, 44.8, 35.8, 13.1; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.3; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{20}\text{F}_3\text{O}_4$ 381.1308, found 381.1309; 92% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 210 nm, $t_{\text{major}} = 8.283$ min, $t_{\text{minor}} = 11.070$ min; $[\alpha]_{\text{D}}^{25} = 6.4^\circ$ ($c = 0.264$, CHCl_3).



Ethyl (1S, 2S, 6S)-2-hydroxy-6-(naphthalen-1-yl)-4-oxo-2-(trifluoromethyl)cyclohexane-1-carboxylate (3aj') (more polar):

White solid; 40% yield purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.07 (d, $J = 8.4$ Hz, 1H), 7.89 (d, $J = 8.0$ Hz, 1H), 7.80 (d, $J = 8.4$ Hz, 1H), 7.58 (t, $J = 7.6$ Hz, 1H), 7.52 (t, $J = 7.4$ Hz, 1H), 7.42 (t, $J = 7.6$ Hz, 1H), 7.29 (d, $J = 7.2$ Hz, 1H), 4.80 (dt, $J = 13.6, 4.0$ Hz, 1H), 3.90-3.74 (m, 4H), 3.65 (d, $J = 14.8$ Hz, 2H), 3.48 (d, $J = 3.6$ Hz, 1H), 2.75 (dd, $J = 14.8, 1.6$ Hz, 1H), 2.60 (dd, $J = 14.0, 3.6$ Hz, 1H), 0.77 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 208.6, 169.8, 134.2, 133.9, 130.9, 129.1, 128.3, 126.9, 125.8, 125.0, 124.4 (q, $^1J_{\text{C-F}} = 283.8$ Hz), 123.5, 122.2, 76.7 (q, $^2J_{\text{C-F}} = 29.8$ Hz), 60.8, 48.5, 43.9, 41.4, 34.7, 13.5; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.3; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{20}\text{F}_3\text{O}_4$ 381.1308, found 381.1307; 95% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 210 nm, t_{major}

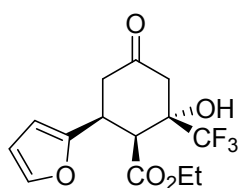
= 5.920 min, $t_{\text{minor}} = 7.757$ min; $[\alpha]_{\text{D}}^{25} = -121.6^{\circ}$ ($c = 0.334$, CHCl_3).



Ethyl (1R, 2S, 6S)-6-(furan-2-yl)-2-hydroxy-4-oxo-2-(trifluoromethyl)cyclohexane-1-carboxylate (3ak) (less polar): White solid; 46% yield

purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.39 (d, $J = 1.2$ Hz, 1H), 6.29 (dd, $J =$

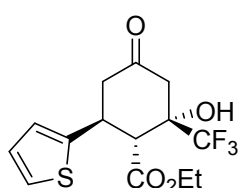
3.2, 2.0 Hz, 1H), 6.12 (d, $J = 3.2$ Hz, 1H), 4.86 (d, $J = 2.4$ Hz, 1H), 4.03 (q, $J = 7.2$ Hz, 2H), 3.71 (dt, $J = 12.4, 4.4$ Hz, 1H), 3.31 (d, $J = 12.0$ Hz, 1H), 2.84-2.77 (m, 2H), 2.70 (ddd, $J = 15.2, 4.6, 2.0$ Hz, 1H), 2.58 (dd, $J = 15.2, 2.8$ Hz, 1H), 1.07 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 202.3, 173.6, 151.7, 142.7, 124.4 (q, $^1J_{\text{C-F}} = 285.2$ Hz), 110.2, 107.3, 76.1 (q, $^2J_{\text{C-F}} = 29.0$ Hz), 62.0, 47.8, 44.6, 44.2, 36.5, 13.6; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.3; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_{16}\text{F}_3\text{O}_5$ 321.0944, found 321.0948; 96% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (90/10), 1.0 mL/min, UV 210 nm, $t_{\text{minor}} = 10.600$ min, $t_{\text{major}} = 12.030$ min; $[\alpha]_{\text{D}}^{25} = -37.7^{\circ}$ ($c = 0.236$, CHCl_3).



Ethyl (1S, 2S, 6S)-6-(furan-2-yl)-2-hydroxy-4-oxo-2-(trifluoromethyl)cyclohexane-1-carboxylate (3ak') (more polar): White solid; 50% yield

purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.36 (app s, 1H), 6.30 (t, $J = 2.0$ Hz,

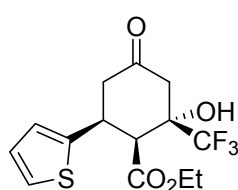
1H), 6.09 (d, $J = 3.2$ Hz, 1H), 4.01 (q, $J = 7.2$ Hz, 2H), 3.94 (dt, $J = 13.6, 4.4$ Hz, 1H), 3.47 (d, $J = 15.2$ Hz, 1H), 3.43 (dd, $J = 4.8$ Hz, 1H), 3.33 (d, $J = 14.4$ Hz, 1H), 3.29 (d, $J = 14.4$ Hz, 1H), 2.63 (d, $J = 14.8$ Hz, 2H), 1.08 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 206.5, 169.7, 152.8, 142.1, 124.3 (q, $J_{\text{C-F}} = 283.4$ Hz), 110.2, 106.4, 76.2 (q, $J_{\text{C-F}} = 31.5$ Hz), 61.2, 47.4, 43.3, 40.0, 34.1, 13.7; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.5; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_{16}\text{F}_3\text{O}_5$ 321.0944, found 321.0947; 99% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (90/10), 1.0 mL/min, UV 210 nm, $t_{\text{minor}} = 4.810$ min, $t_{\text{major}} = 6.150$ min; $[\alpha]_{\text{D}}^{25} = -60.4^{\circ}$ ($c = 0.264$, CHCl_3).



Ethyl (1R, 2S, 6S)-2-hydroxy-4-oxo-6-(thiophen-2-yl)-2-(trifluoromethyl)cyclohexane-1-carboxylate (3al) (less polar): White

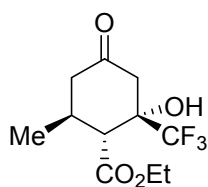
solid; 44% yield purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.26 (d, J

= 4.4 Hz, 1H), 6.94 (dd, $J = 4.8, 3.6$ Hz, 1H), 6.89 (d, $J = 3.6$ Hz, 1H), 4.84 (d, $J = 2.4$ Hz, 1H), 4.02-3.90 (m, 3H), 3.19 (d, $J = 12.0$ Hz, 1H), 2.87-2.81 (m, 2H), 2.70 (d, $J = 14.0$ Hz, 2H), 2.61 (dd, $J = 15.2, 2.4$ Hz, 1H), 0.97 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 201.8, 173.3, 142.3, 126.7, 125.7, 125.0, 124.3 (q, $^1J_{\text{C-F}} = 285.2$ Hz), 76.1 (q, $^2J_{\text{C-F}} = 29.2$ Hz), 61.9, 51.0, 48.0, 44.6, 38.3, 13.4; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.2; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_{16}\text{F}_3\text{O}_4\text{S}$ 337.0716, found 337.0718; 94% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 210 nm, $t_{\text{minor}} = 12.353$ min, $t_{\text{major}} = 14.537$ min; $[\alpha]_{\text{D}}^{25} = -15.6^\circ$ ($c = 0.256$, CHCl_3).



Ethyl (1*S*, 2*S*, 6*S*)-2-hydroxy-4-oxo-6-(thiophen-2-yl)-2-(trifluoromethyl)cyclohexane-1-carboxylate (3al') (more polar): White solid; 44% yield purified by flash column chromatography (EtOAc/petroleum ether);

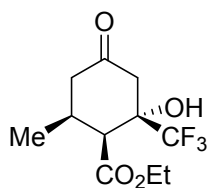
^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.22 (d, $J = 5.2$ Hz, 1H), 6.95 (t, $J = 4.4$ Hz, 1H), 6.89 (d, $J = 2.8$ Hz, 1H), 4.14 (td, $J = 13.2, 4.6$ Hz, 1H), 4.03-3.96 (m, 2H), 3.55-3.44 (m, 3H), 3.35 (d, $J = 3.6$ Hz, 1H), 2.71 (dd, $J = 14.4, 3.6$ Hz, 1H), 2.62 (d, $J = 13.4$ Hz, 1H), 1.04 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 207.0, 169.8, 142.3, 126.8, 124.7, 124.5, 124.2 (q, $^1J_{\text{C-F}} = 284.0$ Hz), 76.2 (q, $^2J_{\text{C-F}} = 30.0$ Hz), 61.3, 50.3, 43.1, 42.7, 35.6, 13.6; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.4; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_{16}\text{F}_3\text{O}_4\text{S}$ 337.0716, found 337.0719; 98% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (90/10), 1.0 mL/min, UV 210 nm, $t_{\text{minor}} = 5.110$ min, $t_{\text{major}} = 5.883$ min; $[\alpha]_{\text{D}}^{25} = 33.2^\circ$ ($c = 0.226$, CHCl_3).



Ethyl (1*R*, 2*S*, 6*S*)-2-hydroxy-6-methyl-4-oxo-2-(trifluoromethyl)cyclohexane-1-carboxylate (3am) (less polar): White solid; 45% yield purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR

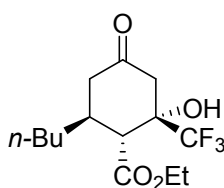
(400 MHz, CDCl_3) δ (ppm): 4.68 (d, $J = 2.8$ Hz, 1H), 4.32-4.24 (m, 2H), 2.74-2.69 (m, 2H), 2.55-2.43 (m, 3H), 2.13 (t, $J = 14.8$ Hz, 1H), 1.33 (t, $J = 7.0$ Hz, 3H), 1.07 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 203.3, 174.3, 124.5 (q, $^1J_{\text{C-F}} = 285.2$ Hz), 76.5 (q, $^2J_{\text{C-F}} = 28.8$ Hz), 62.1, 49.8, 47.5, 44.6, 31.7, 19.5, 13.9; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.4; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{11}\text{H}_{16}\text{F}_3\text{O}_4$ 269.0995, found 269.0991; after derivation to compound **6m**, 99% ee was determined by HPLC on IC-H column, hexane/*i*-propanol (90/10), 1.0 mL/min, UV 210 nm, $t_{\text{major}} = 7.023$ min, $t_{\text{minor}} = 11.190$ min; $[\alpha]_{\text{D}}^{25} = 12.1^\circ$

($c = 0.240$, CHCl_3).



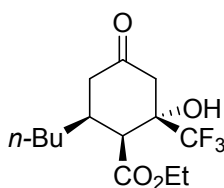
Ethyl (1S, 2S, 6S)-2-hydroxy-6-methyl-4-oxo-2-(trifluoromethyl)cyclohexane-1-carboxylate (3am') (more polar): White solid; 50% yield

purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm): 4.19 (q, $J = 6.8$ Hz, 2H), 4.04 (br s, 1H), 3.29 (d, $J = 14.8$ Hz, 1H), 2.97 (d, $J = 3.6$ Hz, 1H), 2.78-2.62 (m, 2H), 2.53 (d, $J = 14.8$ Hz, 1H), 2.27 (d, $J = 12.0$ Hz, 1H), 1.28 (t, $J = 7.2$ Hz, 3H), 1.02 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 208.1, 170.4, 124.4 (q, $^1J_{\text{C-F}} = 283.8$ Hz), 76.4 (q, $^2J_{\text{C-F}} = 29.7$ Hz), 61.2, 48.5, 44.1, 42.9, 29.5, 18.2, 14.0; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.7; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{11}\text{H}_{16}\text{F}_3\text{O}_4$ 269.0995, found 269.0996; after derivation to compound **6m'**, 99% ee was determined by HPLC on OD-H column, hexane/*i*-propanol (95/5), 1.0 mL/min, UV 210 nm, $t_{\text{minor}} = 6.243$ min, $t_{\text{major}} = 12.167$ min; $[\alpha]_{\text{D}}^{25} = -7.6^\circ$ ($c = 0.170$, CHCl_3).



Ethyl (1R, 2S, 6S)-6-butyl-2-hydroxy-4-oxo-2-(trifluoromethyl)cyclohexane-1-carboxylate (3an) (less polar): White solid; 47% yield

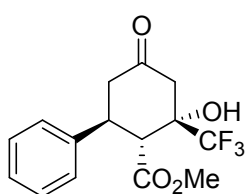
purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm): 4.66 (br s, 1H), 4.27 (q, $J = 7.2$ Hz, 2H), 2.82 (d, $J = 11.6$ Hz, 1H), 2.70 (d, $J = 14.8$ Hz, 1H), 2.60 (dd, $J = 14.4, 2.4$ Hz, 1H), 2.46 (d, $J = 15.2$ Hz, 1H), 2.41-2.38 (m, 1H), 2.07 (t, $J = 13.8$ Hz, 1H), 1.37-1.24 (m, 9H), 0.88 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 203.7, 174.4, 124.5 (q, $^1J_{\text{C-F}} = 285.2$ Hz), 76.5 (q, $^2J_{\text{C-F}} = 28.7$ Hz), 62.0, 48.5, 44.7, 44.5, 35.9, 33.0, 27.4, 22.4, 13.8, 13.7; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.4; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_{22}\text{F}_3\text{O}_4$ 311.1465, found 311.1469; after derivation to compound **6n**, 95% ee was determined by HPLC on IC-H column, hexane/*i*-propanol (90/10), 1.0 mL/min, UV 210 nm, $t_{\text{major}} = 5.743$ min, $t_{\text{minor}} = 9.017$ min; $[\alpha]_{\text{D}}^{25} = -7.0^\circ$ ($c = 0.242$, CHCl_3).



Ethyl (1S, 2S, 6S)-6-butyl-2-hydroxy-4-oxo-2-(trifluoromethyl)cyclohexane-1-carboxylate (3an') (more polar): White solid; 52% yield

purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm): 4.21 (q, $J = 7.2$ Hz, 2H), 3.56 (br s, 1H), 3.34 (d, $J = 14.8$ Hz, 1H), 3.06 (d, $J = 4.0$ Hz, 1H), 2.73 (t, $J = 13.8$ Hz, 1H), 2.55-2.49 (m, 2H),

2.35 (dd, $J = 15.0, 4.2$ Hz, 1H), 1.35-1.25 (m, 9H), 0.89 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 208.2, 170.4, 124.5 (q, $^1J_{\text{C-F}} = 284.0$ Hz), 76.4 (q, $^2J_{\text{C-F}} = 29.7$ Hz), 61.1, 47.0, 43.3, 42.8, 34.6, 32.8, 28.8, 22.5, 14.0, 13.8; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.6; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_{22}\text{F}_3\text{O}_4$ 311.1465, found 311.1466; after derivation to compound **6n'**, 99% ee was determined by HPLC on OD-H column, hexane/*i*-propanol (95/5), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 5.090$ min, $t_{\text{major}} = 10.680$ min; $[\alpha]_{\text{D}}^{25} = -4.9^\circ$ ($c = 1.072$, CHCl_3).



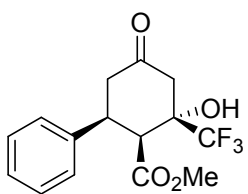
Methyl (1R, 2S, 6S)-2-hydroxy-4-oxo-6-phenyl-2-(trifluoromethyl)

cyclohexane-1-carboxylate (3bb) (less polar): White solid; 58% yield

purified by flash column chromatography (EtOAc/petroleum ether); ^1H

NMR (400 MHz, CDCl_3) δ (ppm): 7.36-7.29 (m, 3H), 7.22 (d, $J = 7.2$ Hz,

2H), 4.77 (br s, 1H), 3.61-3.54 (m, 1H), 3.37 (s, 3H), 3.27 (d, $J = 12.0$ Hz, 1H), 2.83 (d, $J = 14.8$ Hz, 1H), 2.69 (d, $J = 9.2$ Hz, 2H), 2.63 (dd, $J = 14.8, 2.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 214.0, 202.8, 138.7, 129.4, 128.3, 127.5, 124.7 (q, $^1J_{\text{C-F}} = 285.4$ Hz), 77.6 (q, $J = 28.8$ Hz), 53.9, 46.8, 45.1, 43.7, 33.4; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.5; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{15}\text{H}_{16}\text{F}_3\text{O}_4$ 317.0995, found 317.0999; 94% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 210 nm, $t_{\text{minor}} = 12.403$ min, $t_{\text{major}} = 18.223$ min; $[\alpha]_{\text{D}}^{25} = -41.3^\circ$ ($c = 0.092$, CHCl_3).



Ethyl (1S, 2S, 6S)-2-hydroxy-4-oxo-6-phenyl-2-(trifluoromethyl)

cyclohexane-1-carboxylate (3bb') (more polar): White solid; 41% yield

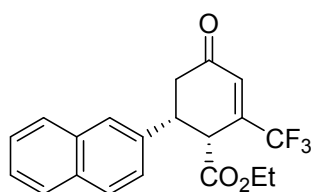
purified by flash column chromatography (EtOAc/petroleum ether); ^1H

NMR (400 MHz, CDCl_3) δ (ppm): 7.34 (t, $J = 7.2$ Hz, 2H), 7.29 (t, $J = 7.2$

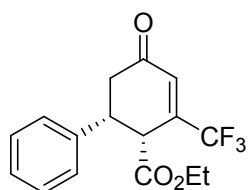
Hz, 1H), 7.20 (d, $J = 7.6$ Hz, 2H), 3.88 (dt, $J = 14.0, 4.4$ Hz, 1H), 3.56 (t, $J = 14.2$ Hz, 2H), 3.50 (d, $J = 14.8$ Hz, 1H), 3.43 (s, 3H), 3.26 (d, $J = 4.0$ Hz, 1H), 2.65 (d, $J = 14.8$ Hz, 1H), 2.55 (dd, $J = 14.4, 4.0$ Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 205.3, 170.1, 139.3, 128.6, 127.4, 127.1, 124.9 (q, $^1J_{\text{C-F}} = 285.1$ Hz), 75.2 (q, $^2J_{\text{C-F}} = 28.6$ Hz), 51.7, 49.9, 42.2, 40.4, 38.6; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.7; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{15}\text{H}_{16}\text{F}_3\text{O}_4$ 317.0995, found 317.0998; 98% ee was determined by HPLC on AS-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 210 nm, $t_{\text{major}} = 8.377$ min, $t_{\text{minor}} = 17.613$ min; $[\alpha]_{\text{D}}^{25} = 71.2^\circ$ ($c = 0.198$, CHCl_3).

3. General procedure for the cascade Michael/aldol condensation

Ethyl 4,4,4-trifluoroacetoacetate **2a** (19.0 μ L, 0.13 mmol), β -naphthyl-substituted cinnamone **1a** (19.6 mg, 0.1 mmol), quinine-derived **C1** (6.5 mg, 0.02 mmol) and trifluoroacetic acid (3.0 μ L, 0.04 mmol) were successively added to a 4 mL vial. After dissolved in toluene (1 mL), the resulting mixture was stirred at 40 $^{\circ}$ C for due time, and then the reaction mixture was directly subjected to flash column chromatography on silica gel (EtOAc/petroleum ether) to afford the corresponding products **3** and **4**.

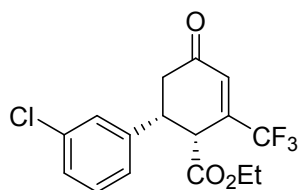


Ethyl (1R, 6R)-6-(naphthalen-2-yl)-4-oxo-2-(trifluoromethyl)cyclohex-2-ene-1-carboxylate (4aa): Colourless oil; 52% yield purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.87-7.80 (m, 3H), 7.63 (s, 1H), 7.53-7.48 (m, 2H), 7.36 (dd, $J = 8.4, 1.8$ Hz, 1H), 6.65 (s, 1H), 3.91-3.83 (m, 1H), 3.78-3.70 (m, 1H), 3.62 (dd, $J = 16.6, 14.2$ Hz, 1H), 2.78 (dd, $J = 16.8, 3.6$ Hz, 1H), 0.71 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 197.2, 168.2, 143.0 (q, $^2J_{\text{C-F}} = 31.0$ Hz), 135.8, 133.2, 132.8, 130.4 (q, $^3J_{\text{C-F}} = 4.8$ Hz), 128.5, 127.8, 127.6, 126.5, 126.3, 125.7, 125.3, 122.5 (q, $^1J_{\text{C-F}} = 272.9$ Hz), 62.8, 61.6, 46.1, 42.6, 37.6, 13.4; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -69.4; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{18}\text{F}_3\text{O}_3$ 363.1203, found 363.1206; 89% ee was determined by HPLC on OD-H column, hexane/*i*-propanol (70/30), 1.0 mL/min, UV 254 nm, $t_{\text{major}} = 8.450$ min, $t_{\text{minor}} = 21.387$ min; $[\alpha]_{\text{D}}^{25} = -30.6^{\circ}$ ($c = 0.098$, CHCl_3).

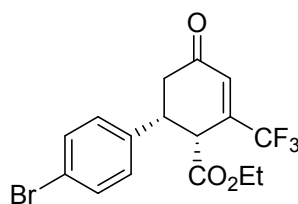


Ethyl (1R, 2R)-5-oxo-3-(trifluoromethyl)-1,2,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate (4ab): Colourless oil; 58% yield purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.39-7.30 (m, 3H), 7.22 (d, $J = 6.8$ Hz, 2H), 6.61 (s, 1H), 3.97-3.89 (m, 2H), 3.87-3.79 (m, 1H), 3.76-3.69 (m, 2H), 3.53-3.44 (m, 1H), 2.67 (dd, $J = 16.8, 3.6$ Hz, 1H), 0.89 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 197.2, 168.1, 142.9 (q, $^2J_{\text{C-F}} = 31.8$ Hz), 138.3, 130.3 (q, $^3J_{\text{C-F}} = 4.8$ Hz), 128.7, 128.0, 127.1, 122.4 (q, $^1J_{\text{C-F}} = 272.9$ Hz), 61.5, 46.2, 42.4, 37.4, 13.5; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -69.5; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{16}\text{F}_3\text{O}_3$ 313.1046, found 313.1048; 92% ee was determined by HPLC on OD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 210 nm, $t_{\text{major}} = 7.876$ min, $t_{\text{minor}} =$

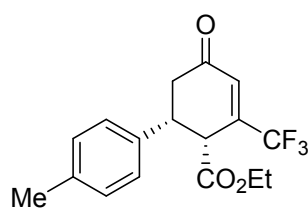
12.867 min; $[\alpha]_{\text{D}}^{25} = -15.9^\circ$ ($c = 0.434$, CHCl_3).



Ethyl (1R, 2R)-3'-chloro-5-oxo-3-(trifluoromethyl)-1,2,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate (4ad): Colourless oil; 51% yield purified by flash column chromatography (EtOAc/petroleum ether); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ (ppm): 7.31 (d, $J = 4.8$ Hz, 2H), 7.21 (s, 1H), 7.14-7.09 (m, 1H), 6.61 (s, 1H), 4.01-3.95 (m, 1H), 3.93-3.86 (m, 1H), 3.72-3.66 (m, 2H), 3.47-3.38 (m, 1H), 2.66 (dd, $J = 16.6, 3.4$ Hz, 1H), 0.95 (t, $J = 7.0$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ (ppm): 196.5, 167.9, 142.7 ($q, {}^2J_{\text{C-F}} = 32.0$ Hz), 140.4, 134.7, 130.3 ($q, {}^3J_{\text{C-F}} = 4.8$ Hz), 130.1, 128.2, 127.4, 125.4, 122.3 ($q, {}^1J_{\text{C-F}} = 273.0$ Hz), 61.8, 45.9, 42.1, 37.3, 13.6; $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ (ppm): -69.4; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{15}^{35}\text{ClF}_3\text{O}_3$ 347.0656, found 347.0659; calcd. for $\text{C}_{16}\text{H}_{15}^{37}\text{ClF}_3\text{O}_3$ 349.0627, found 347.0629; 96% ee was determined by HPLC on OJ-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 210 nm, $t_{\text{major}} = 7.760$ min, $t_{\text{minor}} = 10.320$ min; $[\alpha]_{\text{D}}^{25} = -31.8^\circ$ ($c = 0.088$, CHCl_3).

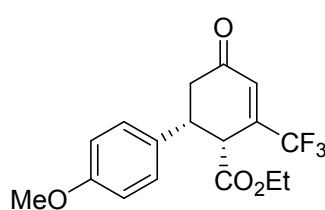


Ethyl (1R, 2R)-4'-bromo-5-oxo-3-(trifluoromethyl)-1,2,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate (4ag): Colourless oil; 55% yield purified by flash column chromatography (EtOAc/petroleum ether); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ (ppm): 7.50 (d, $J = 8.4$ Hz, 2H), 7.10 (d, $J = 8.4$ Hz, 2H), 6.60 (s, 1H), 4.01-3.93 (m, 1H), 3.90-3.82 (m, 1H), 3.71-3.65 (m, 2H), 3.47-3.38 (m, 1H), 2.64 (dd, $J = 16.0, 3.2$ Hz, 1H), 0.95 (t, $J = 7.2$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ (ppm): 196.6, 167.9, 142.8 ($q, {}^2J_{\text{C-F}} = 32.0$ Hz), 137.4, 131.9, 130.3 ($q, {}^3J_{\text{C-F}} = 4.7$ Hz), 128.8, 122.3 ($q, {}^1J_{\text{C-F}} = 273.0$ Hz), 122.0, 61.8, 45.9, 41.9, 37.3, 13.6; $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ (ppm): -69.4; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{15}^{79}\text{BrF}_3\text{O}_3$ 391.0151, found 391.0154; calcd. for $\text{C}_{16}\text{H}_{15}^{81}\text{BrF}_3\text{O}_3$ 393.0131, found 313.0135; 96% ee was determined by HPLC on OD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 210 nm, $t_{\text{major}} = 7.737$ min, $t_{\text{minor}} = 10.890$ min; $[\alpha]_{\text{D}}^{25} = 21.6^\circ$ ($c = 0.278$, CHCl_3).



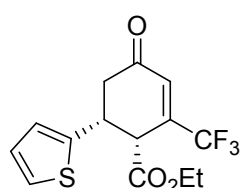
Ethyl (1R, 2R)-4'-methyl-5-oxo-3-(trifluoromethyl)-1,2,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate (4ah): Colourless oil; 55% yield purified by flash column chromatography (EtOAc/petroleum ether); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ (ppm): 7.17 (d, $J = 8.0$ Hz,

2H), 7.10 (d, $J = 8.0$ Hz, 2H), 6.60 (s, 1H), 3.99-3.91 (m, 1H), 3.89-3.81 (m, 1H), 3.70-3.65 (m, 2H), 3.50-3.41 (m, 1H), 2.67-2.62 (m, 1H), 2.35 (s, 3H), 0.92 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 197.4, 168.2, 143.0 (q, $^2J_{\text{C-F}} = 31.8$ Hz), 137.7, 135.3, 130.3 (q, $^3J_{\text{C-F}} = 4.8$ Hz), 129.4, 126.9, 122.4 (q, $^1J_{\text{C-F}} = 272.9$ Hz), 61.6, 46.2, 42.1, 37.5, 21.0, 13.5; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -69.5; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{17}\text{H}_{18}\text{F}_3\text{O}_3$ 327.1203, found 327.1203; 92% ee was determined by HPLC on OD-H column, hexane/*i*-propanol (90/10), 1.0 mL/min, UV 210 nm, $t_{\text{major}} = 8.197$ min, $t_{\text{minor}} = 11.483$ min; $[\alpha]_{\text{D}}^{25} = -29.7^\circ$ ($c = 0.232$, CHCl_3).



Ethyl (1*R*, 2*R*)-4'-methoxy-5-oxo-3-(trifluoromethyl)-1,2,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate (4ai): Colourless oil; 69% yield purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm):

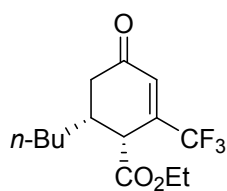
7.13 (d, $J = 8.8$ Hz, 2H), 6.89 (d, $J = 8.8$ Hz, 2H), 6.59 (s, 1H), 4.01-3.93 (m, 1H), 3.90-3.82 (m, 1H), 3.81 (s, 3H), 3.69-3.62 (m, 2H), 3.47-3.39 (m, 1H), 2.66-2.61 (m, 1H), 0.95 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 197.4, 168.3, 159.2, 143.0 (q, $^2J_{\text{C-F}} = 31.8$ Hz), 130.4, 130.3 (q, $^3J_{\text{C-F}} = 4.7$ Hz), 128.2, 122.5 (q, $^1J_{\text{C-F}} = 272.8$ Hz), 114.1, 61.6, 55.3, 46.4, 41.8, 37.8, 13.7; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -69.4; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{17}\text{H}_{18}\text{F}_3\text{O}_4$ 343.1152, found 343.1152; 91% ee was determined by HPLC on OD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 210 nm, $t_{\text{minor}} = 8.010$ min, $t_{\text{major}} = 9.170$ min; $[\alpha]_{\text{D}}^{25} = -29.7^\circ$ ($c = 0.564$, CHCl_3).



Ethyl (1*R*, 6*R*)-4-oxo-6-(thiophen-2-yl)-2-(trifluoromethyl)cyclohex-2-ene-1-carboxylate (4al): Colourless oil; 49% yield purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.28 (dd, $J = 5.2, 1.2$ Hz, 1H), 7.00 (dd, $J = 5.2, 3.6$ Hz,

1H), 6.93 (d, $J = 3.2$ Hz, 1H), 6.60 (s, 1H), 4.05-3.91 (m, 3H), 3.80 (d, $J = 5.2$ Hz, 1H), 3.42 (dd, $J = 17.2, 14.4$ Hz, 1H), 2.81 (dd, $J = 17.2, 4.0$ Hz, 1H), 1.01 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 196.2, 167.9, 142.6 (q, $^2J_{\text{C-F}} = 32.1$ Hz), 141.7, 130.3 (q, $^3J_{\text{C-F}} = 4.8$ Hz), 126.9, 124.88, 124.85, 122.3 (q, $^1J_{\text{C-F}} = 272.9$ Hz), 61.9, 46.6, 38.9, 38.1, 13.6; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -69.4; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_{14}\text{F}_3\text{O}_3\text{S}$ 319.0610, found 319.0611; 84% ee was determined by HPLC on OD-H column, hexane/*i*-propanol (90/10), 1.0

mL/min, UV 210 nm, $t_{\text{minor}} = 7.697$ min, $t_{\text{major}} = 8.257$ min; $[\alpha]_{\text{D}}^{25} = -20.0^\circ$ ($c = 0.170$, CHCl_3).



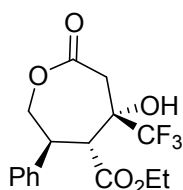
Ethyl (1R,6R)-6-butyl-4-oxo-2-(trifluoromethyl)cyclohex-2-ene-1-carboxylate (4an): Colourless oil; 45% yield purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm): 6.49 (s, 1H), 4.22 (q, $J = 7.2$ Hz, 2H), 3.52 (d, $J = 2.0$ Hz, 1H), 2.63

(t, $J = 16.0$ Hz, 1H), 2.46 (d, $J = 17.6$ Hz, 1H), 2.36-2.33 (m, 1H), 1.48-1.33 (m, 6H), 1.27 (t, $J = 7.2$ Hz, 3H), 0.91 (t, $J = 6.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 197.7, 168.5, 143.6 (q, $^2J_{\text{C-F}} = 31.6$ Hz), 130.2 (q, $^3J_{\text{C-F}} = 5.2$ Hz), 122.5 (d, $^1J = 272.8$ Hz), 61.8, 43.2, 39.4, 37.7, 32.9, 28.5, 22.5, 14.1, 13.9; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -69.8; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_{20}\text{F}_3\text{O}_3$ 293.1359, found 293.1354; 90% ee was determined by HPLC on IC-H column, hexane/*i*-propanol (95/5), 1.0 mL/min, UV 210 nm, $t_{\text{minor}} = 5.760$ min, $t_{\text{major}} = 7.067$ min; $[\alpha]_{\text{D}}^{25} = 21.8^\circ$ ($c = 0.752$, CHCl_3).

4. General procedure for the syntheses of 5 and 5'

m-CPBA (20.4 mg, 0.8 mmol) was added to a solvent of **3ab** (66.1 mg, 0.2 mmol) in DCE (2 mL). The mixture was stirred at 60 °C for 120 h and then cooled to room temperature. The residue was purified by flash chromatography on silica gel (EtOAc/petroleum ether) to afford the desired lactone **5**.

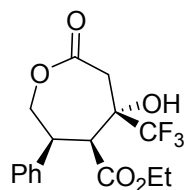
Ethyl (3R, 4R, 5R)-5-hydroxy-7-oxo-3-phenyl-5-(trifluoromethyl)oxepane-4-carboxylate (5) :



White solid; 50% yield purified by flash column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.36-7.31 (m, 3H), 7.16 (d, $J = 8.0$ Hz, 2H), 5.18 (s, 1H), 4.57 (dd, $J = 13.2, 9.6$ Hz, 1H), 4.28 (dd, $J = 13.6, 1.2$ Hz, 1H), 3.80-3.72 (m, 2H), 3.54 (t, $J = 10.6$ Hz, 1H), 3.28 (d, $J =$

14.0 Hz, 1H), 3.19 (d, $J = 12.4$ Hz, 2H), 0.74 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 173.2, 167.9, 137.1, 129.1, 128.4, 127.7, 124.8 (q, $^1J_{\text{C-F}} = 286.6$ Hz), 73.1 (q, $^2J_{\text{C-F}} = 28.2$ Hz), 70.5, 61.8, 52.6, 45.4, 38.0, 13.1; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -80.7; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{18}\text{F}_3\text{O}_5$ 347.1101, found 347.1107; 97% ee was determined by HPLC on OD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 210 nm, $t_{\text{major}} = 7.843$ min, $t_{\text{minor}} = 9.650$ min; $[\alpha]_{\text{D}}^{25} = -45.4^\circ$ ($c = 0.438$, CHCl_3).

Ethyl (3R, 4S, 5R)-5-hydroxy-7-oxo-3-phenyl-5-(trifluoromethyl)oxepane-4-carboxylate (5') :



White solid; 45% yield purified by flash column chromatography

(EtOAc/petroleum ether); ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.32-7.26 (m,

3H), 7.06 (d, $J = 6.8$ Hz, 2H), 5.68 (dd, $J = 12.8, 10.0$ Hz, 1H), 4.69 (br s, 1H), 4.38

(d, $J = 12.8$ Hz, 1H), 4.27 (d, $J = 14.4$ Hz, 1H), 3.95-3.77 (m, 3H), 3.28 (d, $J = 4.0$

Hz, 1H), 3.03 (dd, $J = 14.4, 1.2$ Hz, 1H), 0.90 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ

(ppm): 170.8, 170.3, 138.5, 128.8, 127.6, 127.4, 124.5 (q, $^1J_{\text{C-F}} = 285.4$ Hz), 72.2 (q, $^2J_{\text{C-F}} = 29.2$

Hz), 67.2, 61.0, 51.7, 41.7, 36.8, 13.4; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.4; ESI-HRMS:

$[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{18}\text{F}_3\text{O}_5$ 347.1101, found 347.1109; 99% ee was determined by HPLC on

OD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 210 nm, $t_{\text{minor}} = 4.883$ min, $t_{\text{major}} =$

5.740 min; $[\alpha]_{\text{D}}^{25} = -99.7^\circ$ ($c = 0.302$, CHCl_3).

5. General procedure for the syntheses of 6 and 6'

After **3am** (53.6 mg, 0.2 mmol) and malononitrile (16.5 mg, 0.25 mmol) were dissolved in

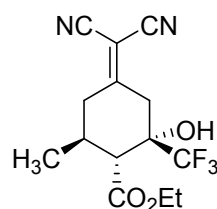
MeOH (1 mL), DABCO (4.5 mg, 0.04 mmol) was added in one portion at room temperature.

Once **3am** was completely consumed as detected by TLC after 20 h, the reaction mixture was

concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel

(EtOAc/petroleum ether) to afford the desired adduct.

Ethyl (1R, 2R, 6R)-4-(dicyanomethylene)-2-hydroxy-6-methyl-2-(trifluoromethyl) cyclo-



hexane-1-carboxylate (6m): White solid; 53% yield purified by flash

column chromatography (EtOAc/petroleum ether); ^1H NMR (400 MHz,

CDCl_3) δ (ppm): 4.75 (s, 1H), 4.31-4.23 (m, 2H), 3.31 (dd, $J = 14.4, 1.6$ Hz,

1H), 3.13-3.08 (m, 1H), 2.60 (d, $J = 11.6$ Hz, 1H), 2.43 (d, $J = 14.4$ Hz, 1H),

2.34-2.23 (m, 1H), 2.11 (t, $J = 13.4$ Hz, 1H), 1.31 (t, $J = 7.2$ Hz, 3H), 1.12 (d, $J = 6.4$ Hz, 3H); ^{13}C

NMR (100 MHz, CDCl_3) δ (ppm): 174.0, 173.6, 124.4 (q, $^1J_{\text{C-F}} = 285.6$ Hz), 110.9, 110.7, 87.5,

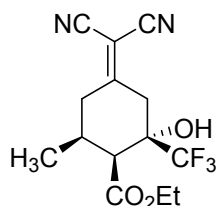
75.9 (q, $^2J_{\text{C-F}} = 28.6$ Hz), 62.4, 49.8, 40.2, 37.6, 33.1, 19.3, 13.9; ^{19}F NMR (376 MHz, CDCl_3) δ

(ppm): -81.3; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_{16}\text{F}_3\text{N}_2\text{O}_3$ 317.1108, found 317.1109; 99% ee

was determined by HPLC on IC-H column, hexane/*i*-propanol (90/10), 1.0 mL/min, UV 210 nm,

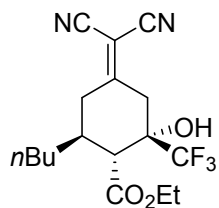
$t_{\text{major}} = 7.023$ min, $t_{\text{minor}} = 11.190$ min; $[\alpha]_{\text{D}}^{25} = -43.6^\circ$ ($c = 0.762$, CHCl_3).

Ethyl (1S, 2R, 6R)-4-(dicyanomethylene)-2-hydroxy-6-methyl-2-(trifluoromethyl)cyclohexane-1-carboxylate (6m'): White solid; 60% yield purified by flash column chromatography (EtOAc/petroleum ether); ¹H NMR (400 MHz, CDCl₃) δ (ppm): 4.23-4.16 (q, *J* = 8.2 Hz, 2H), 3.44 (br, 1H), 3.32 (d, *J* = 14.4 Hz, 1H), 3.10 (d, *J* = 14.8 Hz, 1H), 2.92-2.80 (m, 3H), 2.55-2.44 (m, 1H), 1.29

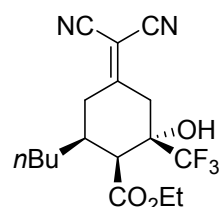


(t, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 178.7, 170.0, 124.3 (q, ¹*J*_{C-F} = 284.2 Hz), 111.2, 111.0, 86.2, 75.7 (q, ²*J*_{C-F} = 29.6 Hz), 61.5, 48.6, 36.5, 35.4, 30.4, 18.1, 14.0; ¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -81.3; ESI-HRMS: [M+H]⁺ calcd. for C₁₄H₁₆F₃N₂O₃ 317.1108, found 317.1106; 99% ee was determined by HPLC on OD-H column, hexane/*i*-propanol (95/5), 1.0 mL/min, UV 210 nm, *t*_{minor} = 6.243 min, *t*_{major} = 12.167 min; [α]_D²⁵ = -1.5° (*c* = 0.522, CHCl₃).

Ethyl (1R, 2R, 6R)-6-butyl-4-(dicyanomethylene)-2-hydroxy-2-(trifluoromethyl)cyclohexane-1-carboxylate (6n): White solid; 55% yield purified by flash column chromatography (EtOAc/petroleum ether); ¹H NMR (400 MHz, CDCl₃) δ (ppm): 4.73 (d, *J* = 2.0 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 3.30 (d, *J* = 14.4 Hz, 1H), 3.19-3.15 (m, 1H), 2.71 (d, *J* = 11.6 Hz, 1H), 2.43 (dd, *J* = 14.4,



0.8 Hz, 1H), 2.25-2.17 (m, 1H), 2.07 (t, *J* = 13.4 Hz, 1H), 1.47-1.23 (m, 9H), 0.90 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 174.5, 173.7, 124.4 (q, ¹*J*_{C-F} = 285.6 Hz), 110.9, 110.8, 87.5, 76.0 (q, ²*J*_{C-F} = 28.6 Hz), 62.4, 48.3, 37.8, 37.6, 37.4, 32.7, 27.3, 22.5, 13.8, 13.7; ¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -81.3; ESI-HRMS: [M+H]⁺ calcd. for C₁₇H₂₂F₃N₂O₃ 359.1577, found 359.1583; 95% ee was determined by HPLC on IC-H column, hexane/*i*-propanol (90/10), 1.0 mL/min, UV 210 nm, *t*_{major} = 5.743 min, *t*_{minor} = 9.017 min; [α]_D²⁵ = -30.6° (*c* = 1.104, CHCl₃).

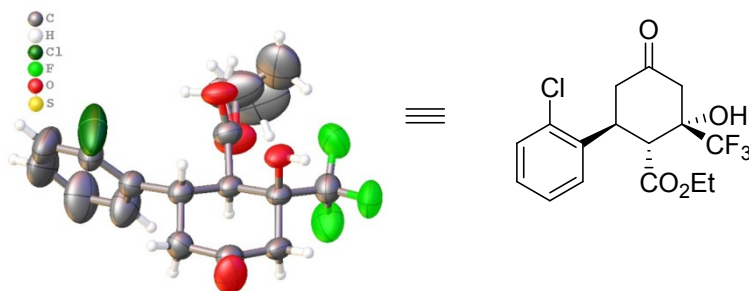


Ethyl (1S, 2R, 6R)-6-butyl-4-(dicyanomethylene)-2-hydroxy-2-(trifluoromethyl)cyclohexane-1-carboxylate (6n'): White solid; 66% yield purified by flash column chromatography (EtOAc/petroleum ether); ¹H

NMR (400 MHz, CDCl₃) δ (ppm): 4.19 (q, *J* = 7.2 Hz, 2H), 3.63-3.56 (m, 1H), 3.33 (d, *J* = 14.8 Hz, 1H), 3.10 (d, *J* = 14.8 Hz, 1H), 2.98 (d, *J* = 4.0 Hz, 1H), 2.92 (dd, *J* = 15.0, 4.2 Hz, 1H), 2.82 (t, *J* = 13.6 Hz, 1H), 2.34-2.29 (m, 1H), 1.34-1.24 (m, 9H), 0.89 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 179.1, 170.1, 124.4 (q, ¹*J*_{C-F} = 284.4 Hz), 111.2, 111.0,

86.1, 75.6 (q, $^2J_{C-F} = 29.7$ Hz), 61.4, 46.8, 35.7, 35.5, 35.3, 32.6, 28.6, 22.4, 13.9, 13.8; ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -81.3; ESI-HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{17}\text{H}_{22}\text{F}_3\text{N}_2\text{O}_3$ 359.1577, found 359.1570; 99% ee was determined by HPLC on OD-H column, hexane/*i*-propanol (95/5), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 5.090$ min, $t_{\text{major}} = 10.680$ min; $[\alpha]_{\text{D}}^{25} = -11.4^\circ$ ($c = 0.140$, CHCl_3).

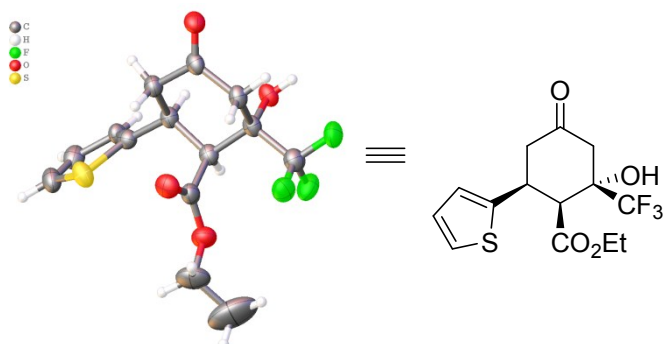
6. X-ray crystallographic analysis of 3ac (CCDC 1973697)



Identification code	lq-0903-2
Empirical formula	$\text{C}_{16}\text{H}_{16}\text{ClF}_3\text{O}_4$
Formula weight	364.74
Temperature/K	297.60(10)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
$a/\text{\AA}$	5.6493(2)
$b/\text{\AA}$	14.4444(7)
$c/\text{\AA}$	21.6781(9)
$\alpha/^\circ$	90
$\beta/^\circ$	90
$\gamma/^\circ$	90
Volume/ \AA^3	1768.95(14)
Z	4
$\rho_{\text{calc}}/\text{g/cm}^3$	1.370
μ/mm^{-1}	2.351
$F(000)$	752.0
Crystal size/ mm^3	$0.7 \times 0.5 \times 0.4$

Radiation	CuK α ($\lambda = 1.54184$)
2 Θ range for data collection/ $^{\circ}$	10.204 to 144.884
Index ranges	$-4 \leq h \leq 6$, $-16 \leq k \leq 17$, $-25 \leq l \leq 26$
Reflections collected	9792
Independent reflections	3423 [$R_{\text{int}} = 0.0337$, $R_{\text{sigma}} = 0.0281$]
Data/restraints/parameters	3423/0/240
Goodness-of-fit on F^2	1.034
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0765$, $wR_2 = 0.1951$
Final R indexes [all data]	$R_1 = 0.0830$, $wR_2 = 0.2084$
Largest diff. peak/hole / $e \text{ \AA}^{-3}$	0.48/-0.80
Flack parameter	0.012(12)

7. X-ray crystallographic analysis of 3al' (CCDC 1973712)



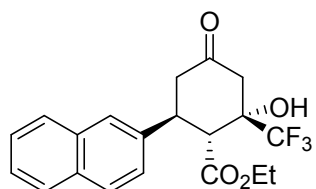
Identification code	lq-1d-150k
Empirical formula	$C_{14}H_{15}F_3O_4S$
Formula weight	336.32
Temperature/K	157(10)
Crystal system	monoclinic
Space group	I2
a/ \AA	17.4373(11)
b/ \AA	5.6433(3)
c/ \AA	16.0752(9)

$\alpha/^\circ$	90
$\beta/^\circ$	103.086(6)
$\gamma/^\circ$	90
Volume/ \AA^3	1540.78(16)
Z	4
$\rho_{\text{calc}}/\text{g}/\text{cm}^3$	1.450
μ/mm^{-1}	2.323
F(000)	696.0
Crystal size/ mm^3	$0.5 \times 0.4 \times 0.2$
Radiation	CuK α ($\lambda = 1.54184$)
2Θ range for data collection/ $^\circ$	8.504 to 146.662
Index ranges	$-21 \leq h \leq 21, -6 \leq k \leq 6, -19 \leq l \leq 19$
Reflections collected	8038
Independent reflections	2763 [$R_{\text{int}} = 0.0615, R_{\text{sigma}} = 0.0476$]
Data/restraints/parameters	2763/1/201
Goodness-of-fit on F^2	1.052
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0831, wR_2 = 0.2220$
Final R indexes [all data]	$R_1 = 0.0851, wR_2 = 0.2261$
Largest diff. peak/hole / $e \text{\AA}^{-3}$	0.59/-0.51
Flack parameter	0.02(3)

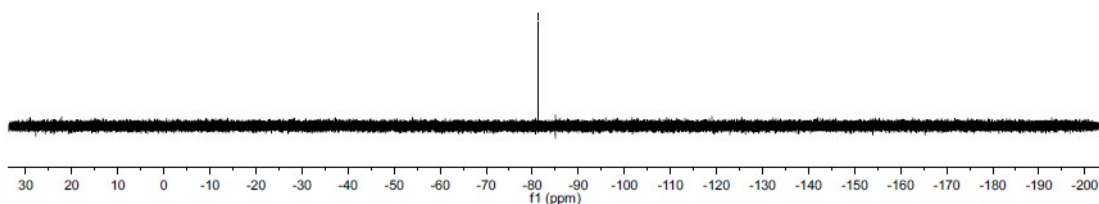
8. Reference

1. B. Vakulya, S. Varga, A. Csámpai and T. Soós, *Org. Lett.*, 2005, **7**, 1967.

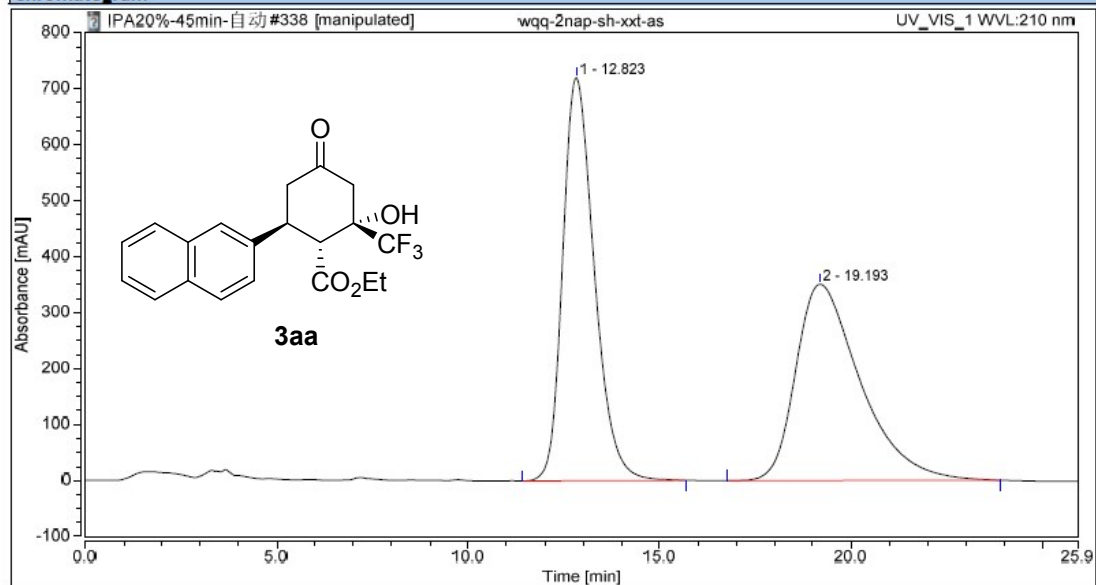
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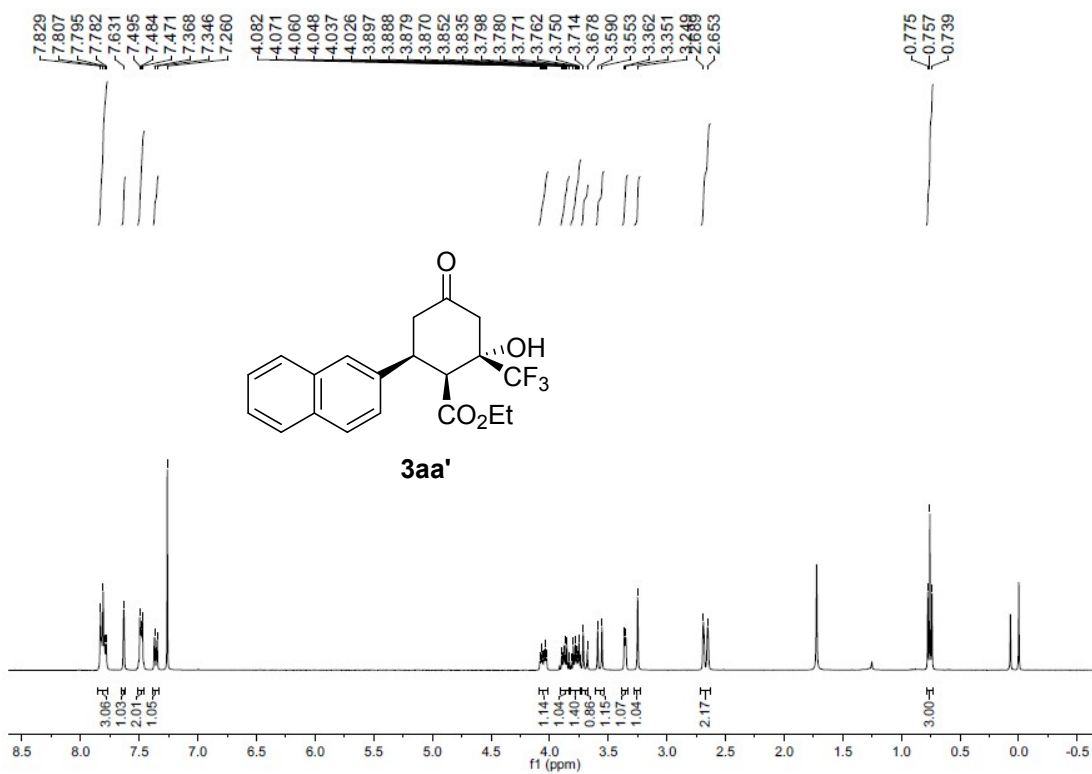
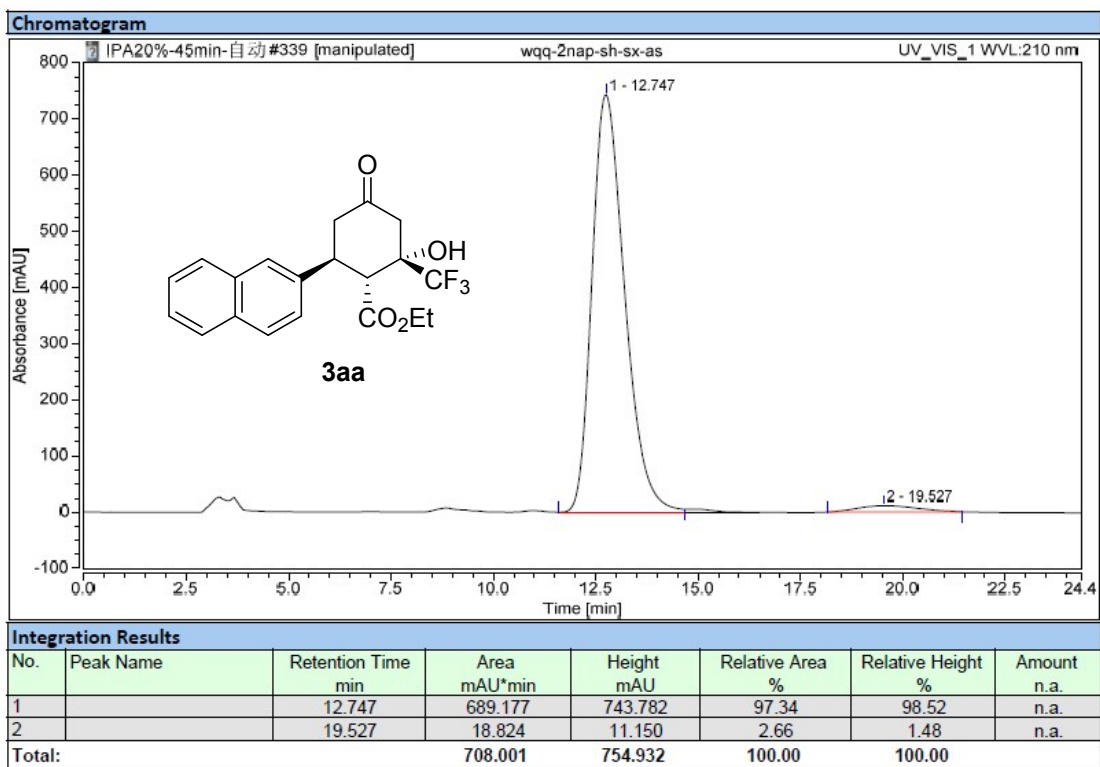
3aa

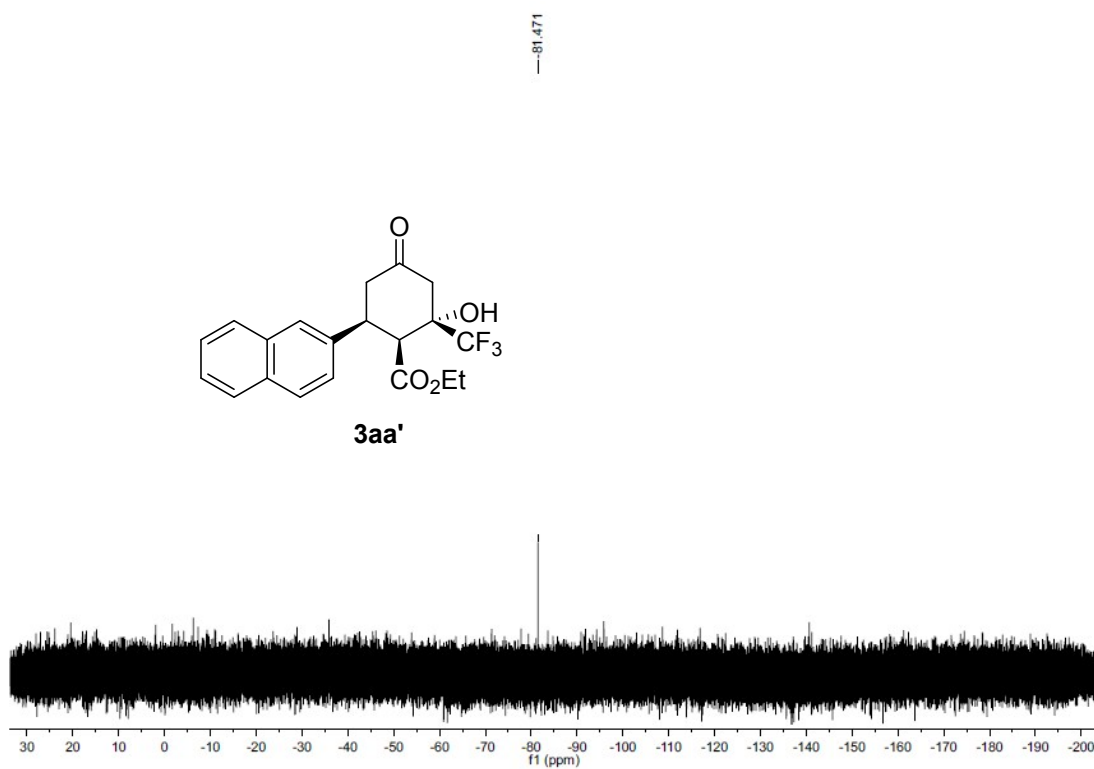
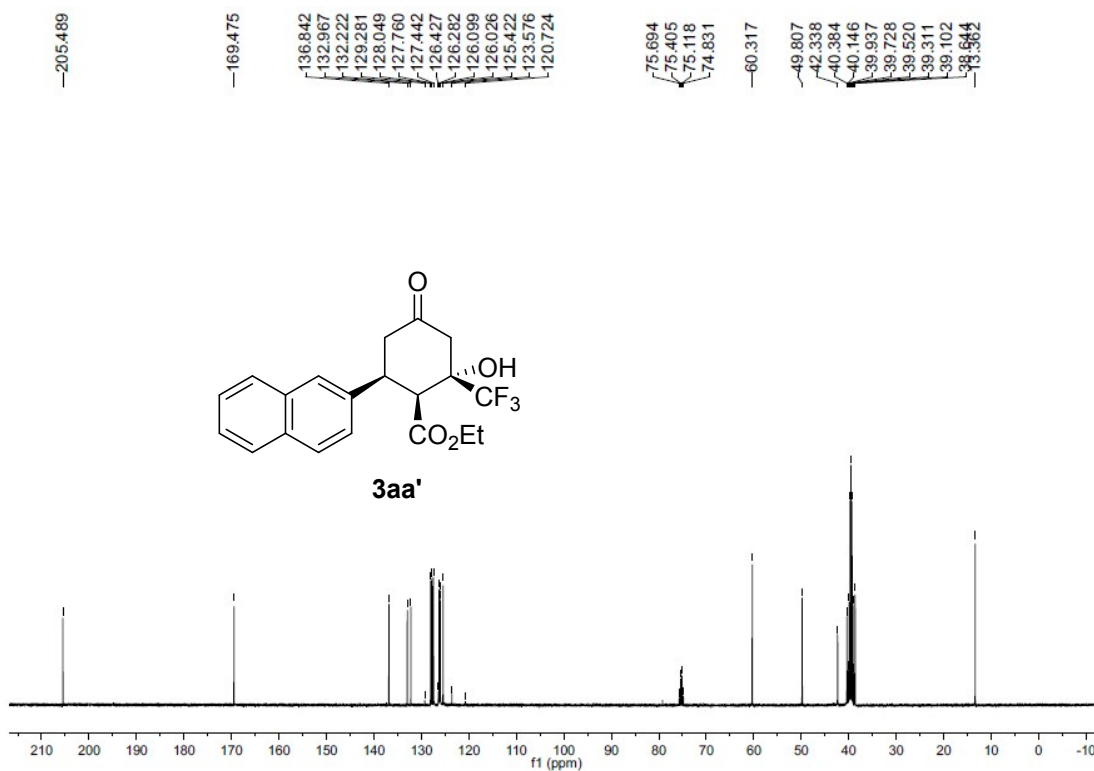


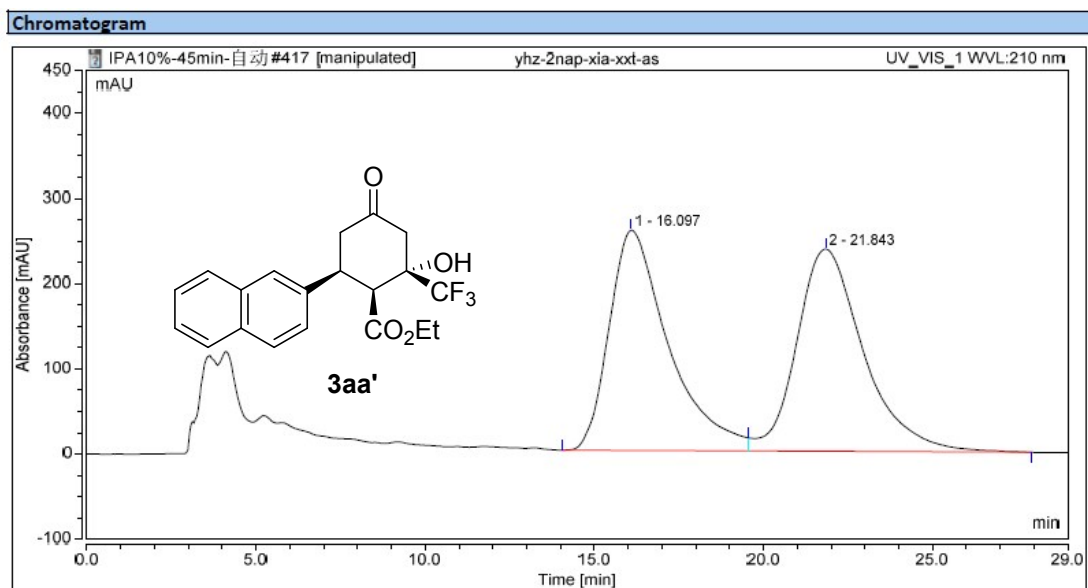
Chromatogram



Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		12.823	688.692	720.386	50.10	67.26	n.a.
2		19.193	685.981	350.619	49.90	32.74	n.a.
Total:			1374.673	1071.005	100.00	100.00	

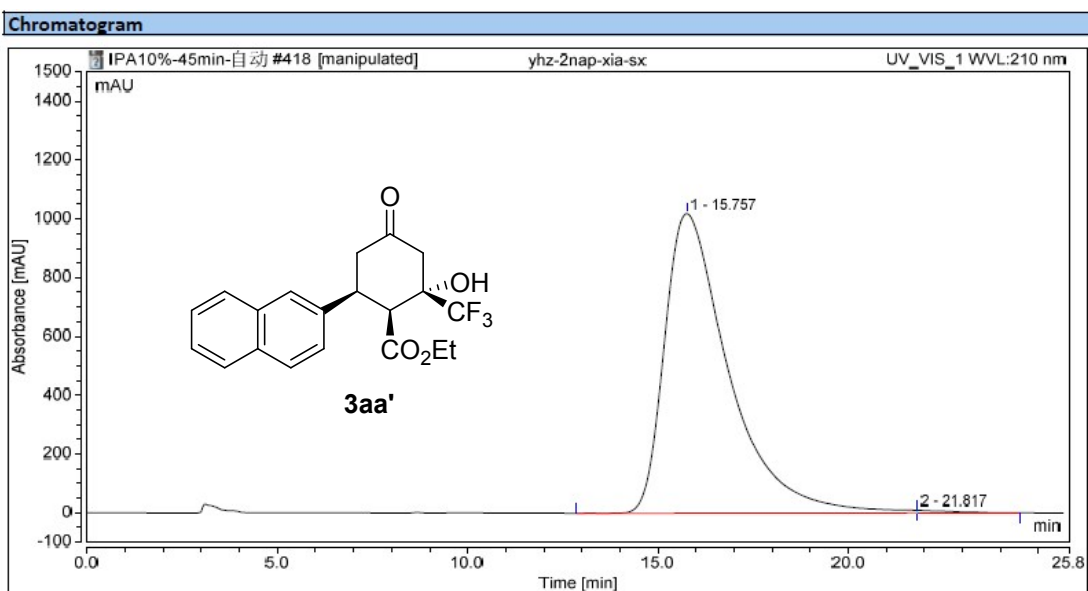






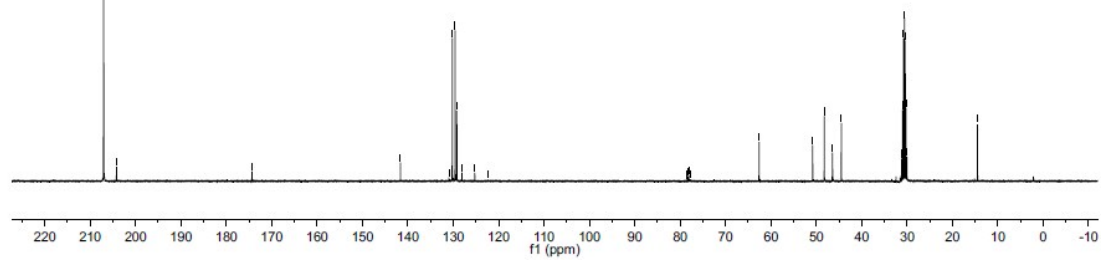
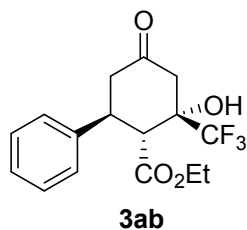
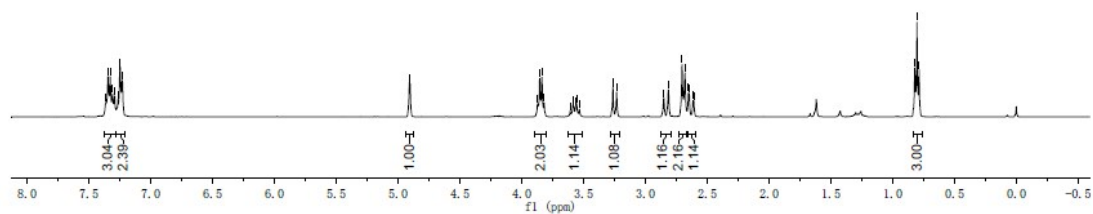
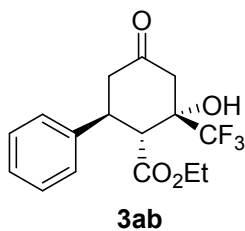
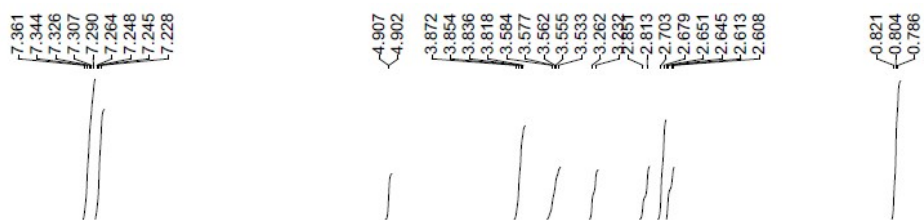
Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		16.097	525.627	258.600	49.14	52.14	n.a.
2		21.843	543.979	237.400	50.86	47.86	n.a.
Total:			1069.606	496.000	100.00	100.00	

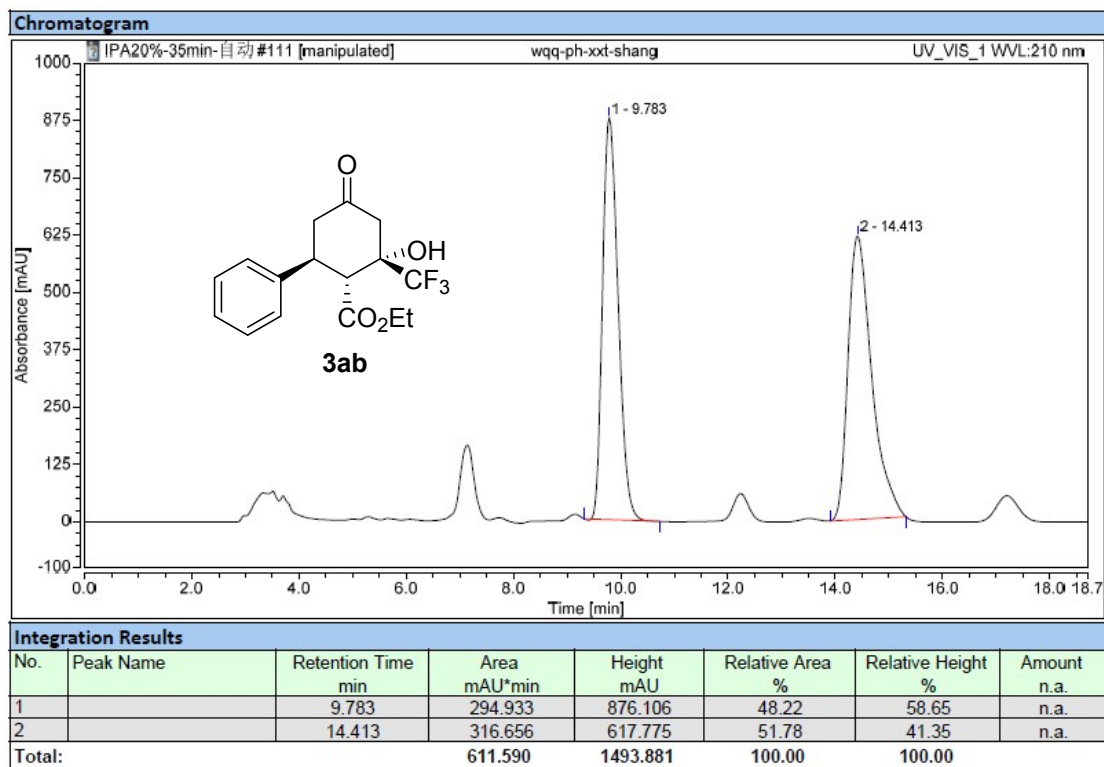
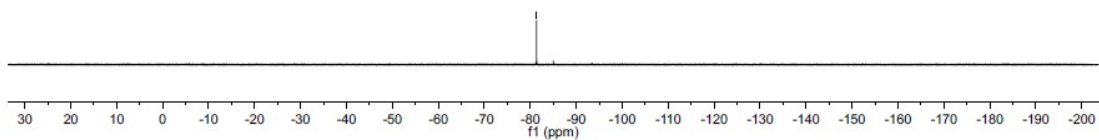
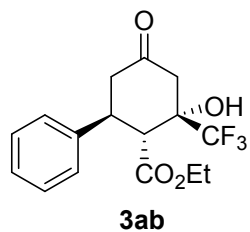


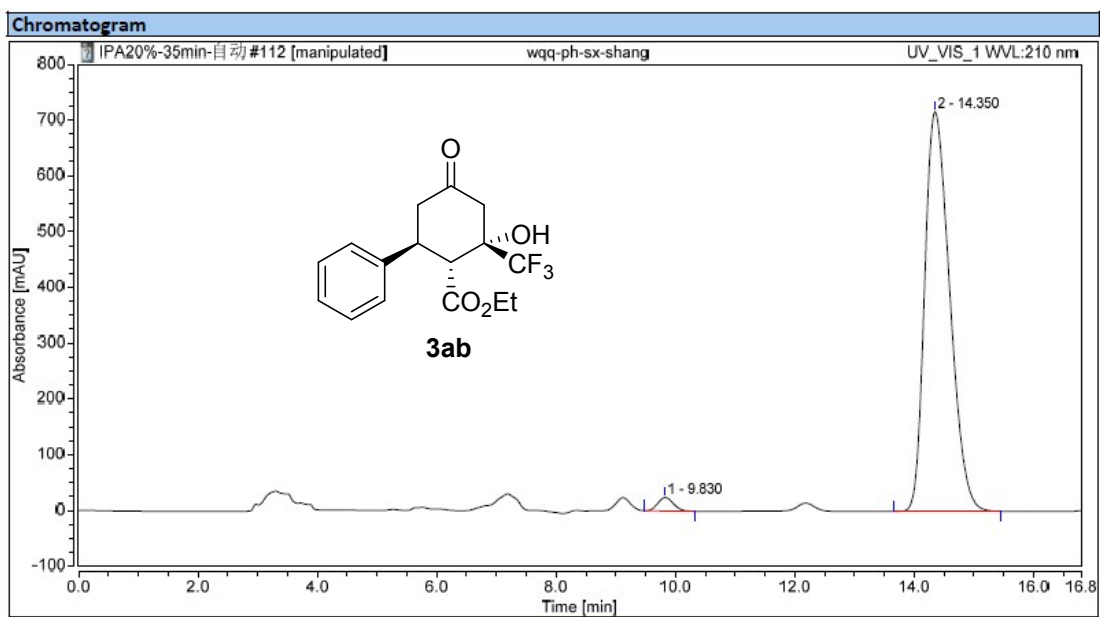
Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		15.757	1992.206	1019.377	99.50	99.12	n.a.
2		21.817	10.026	9.101	0.50	0.88	n.a.
Total:			2002.232	1028.478	100.00	100.00	



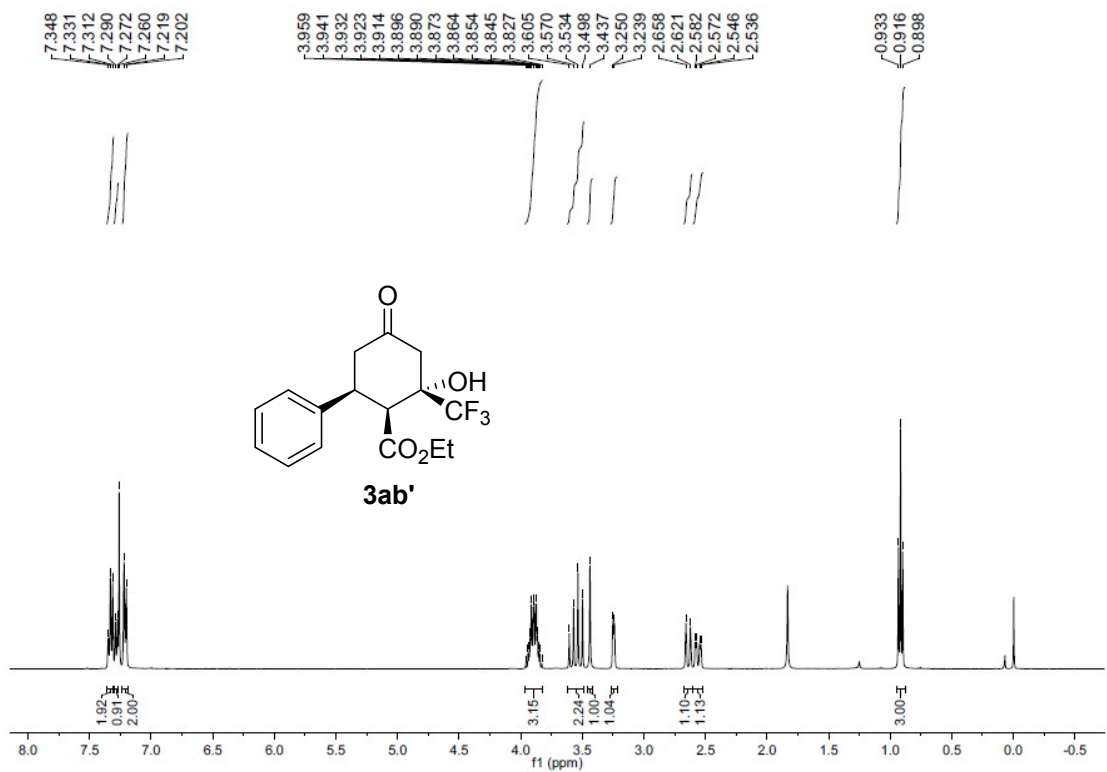
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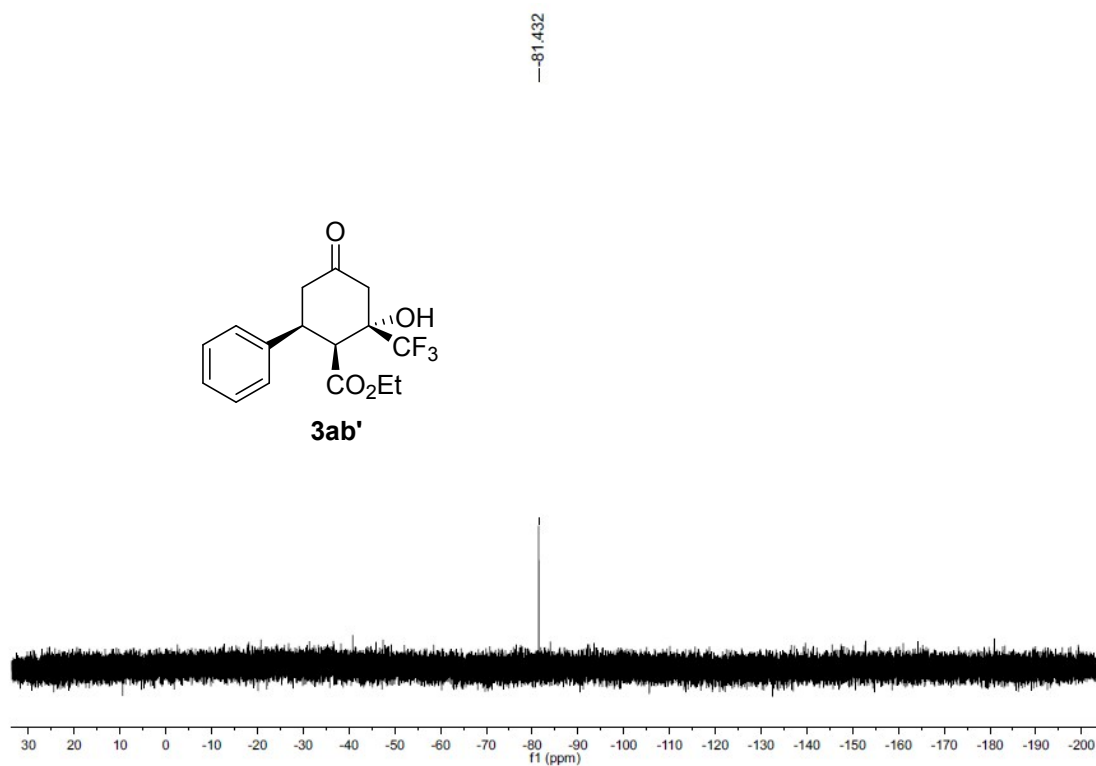
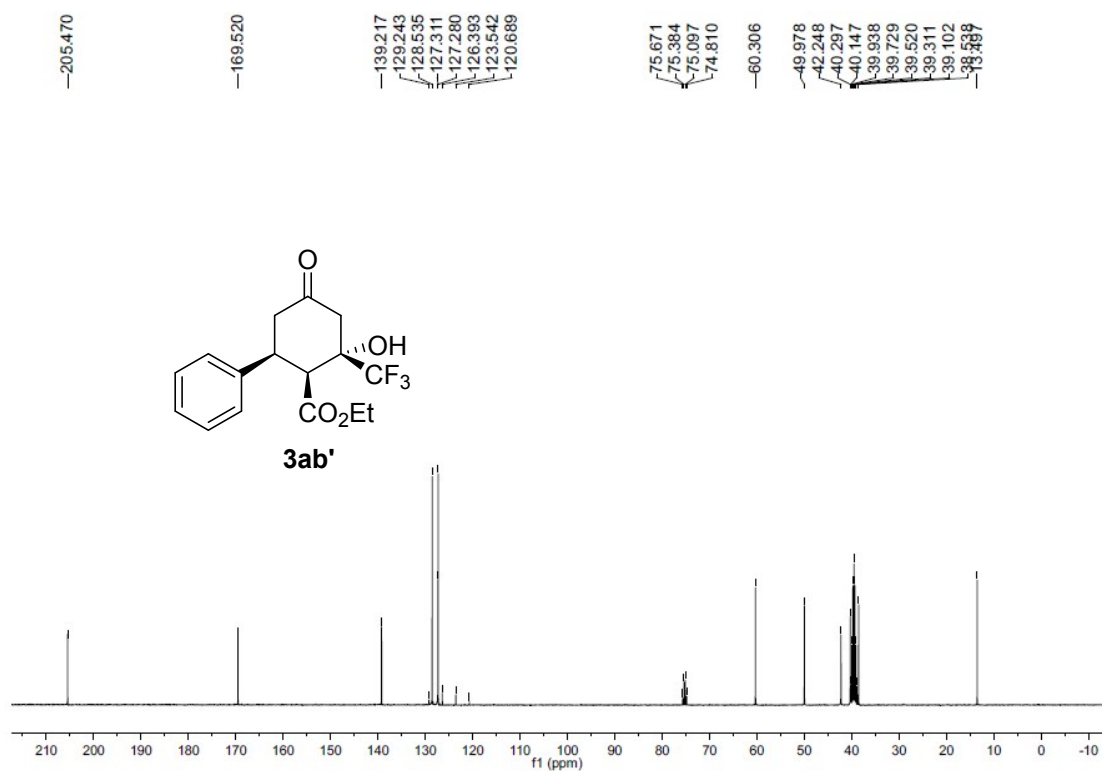


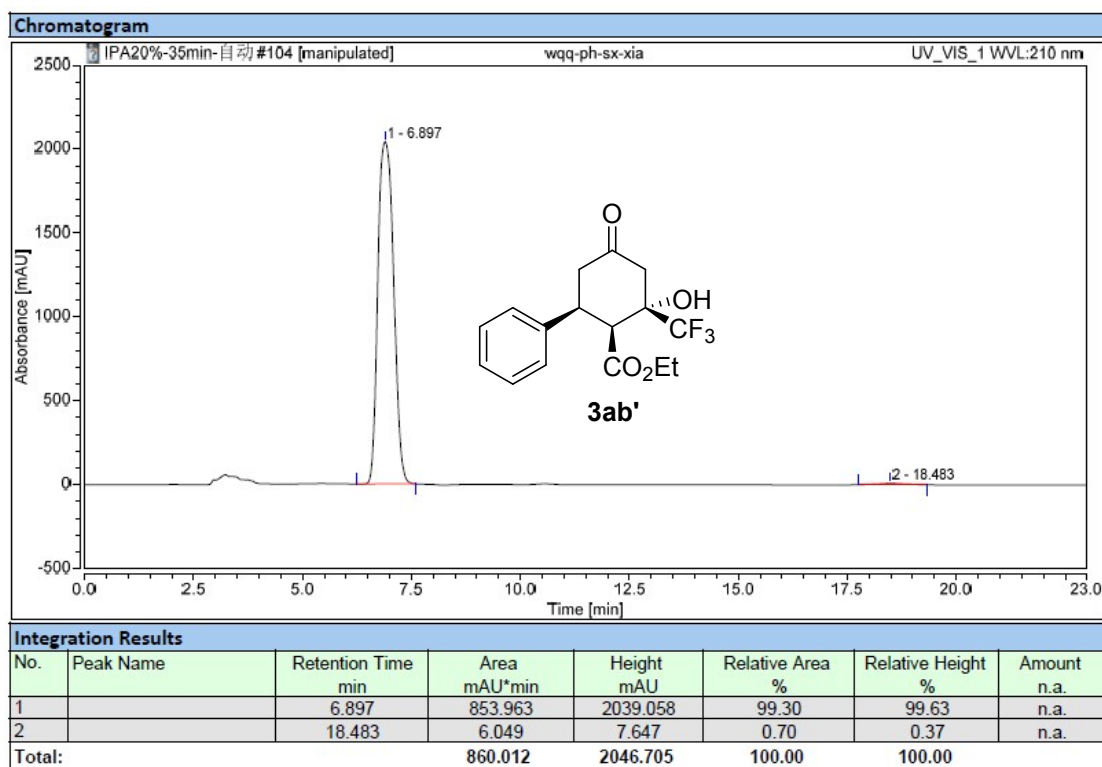
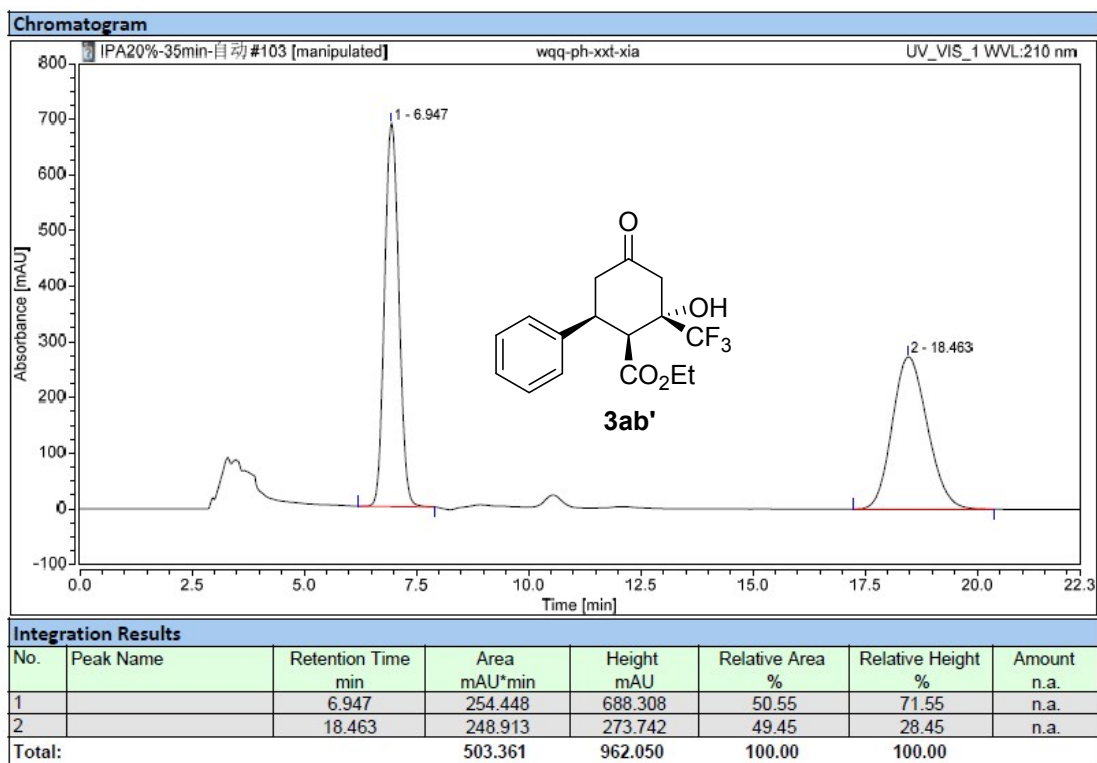


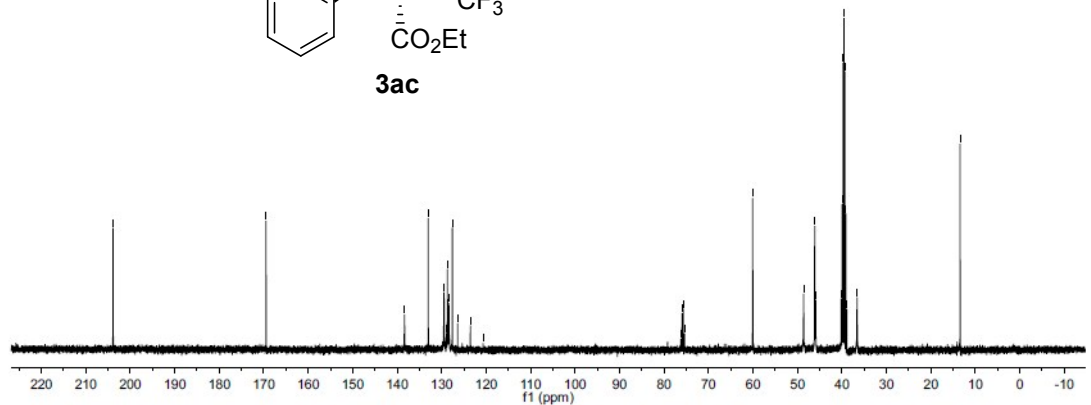
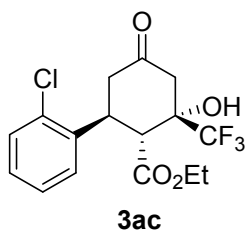
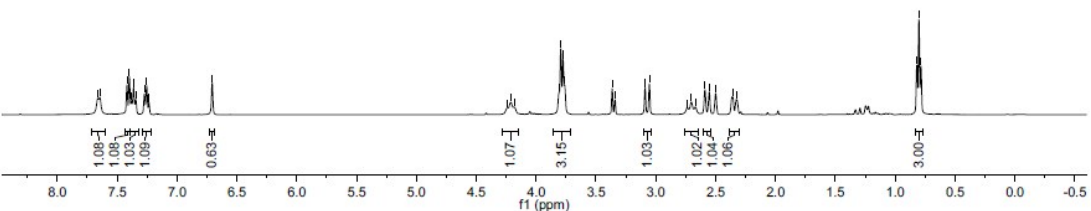
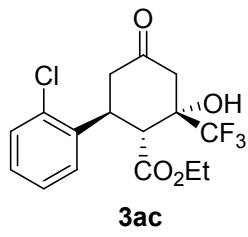
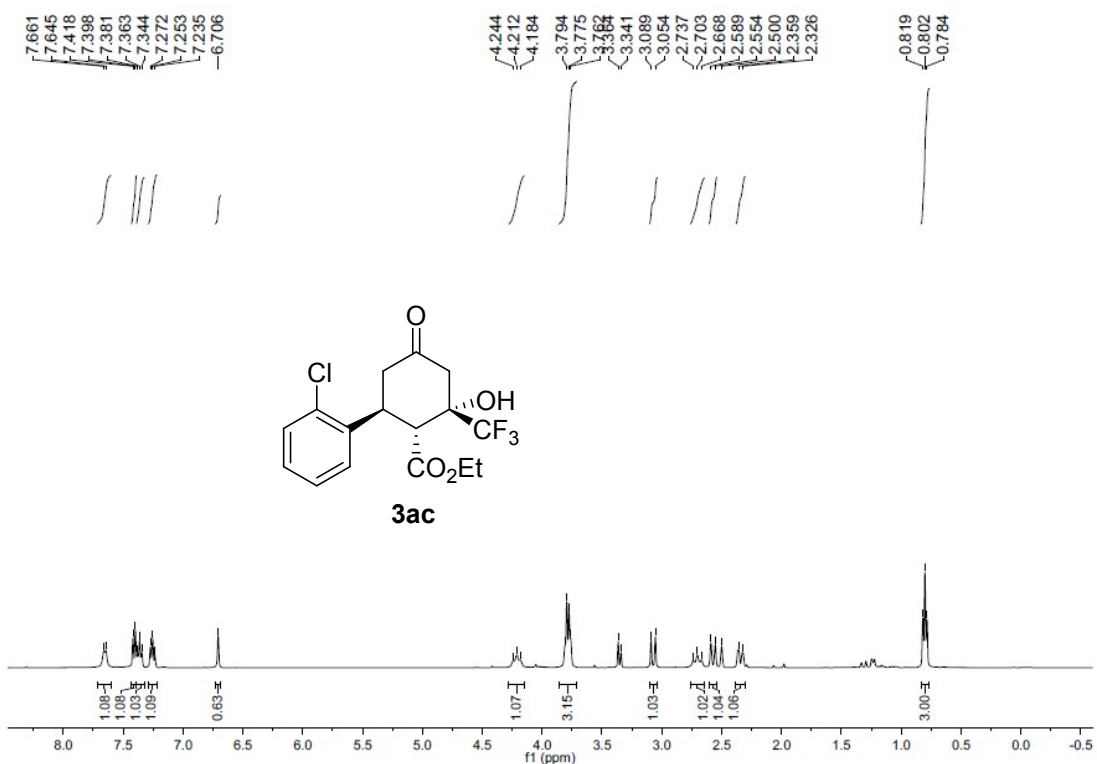
Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		9.830	7.251	24.227	2.04	3.27	n.a.
2		14.350	347.341	716.512	97.96	96.73	n.a.
Total:			354.592	740.739	100.00	100.00	

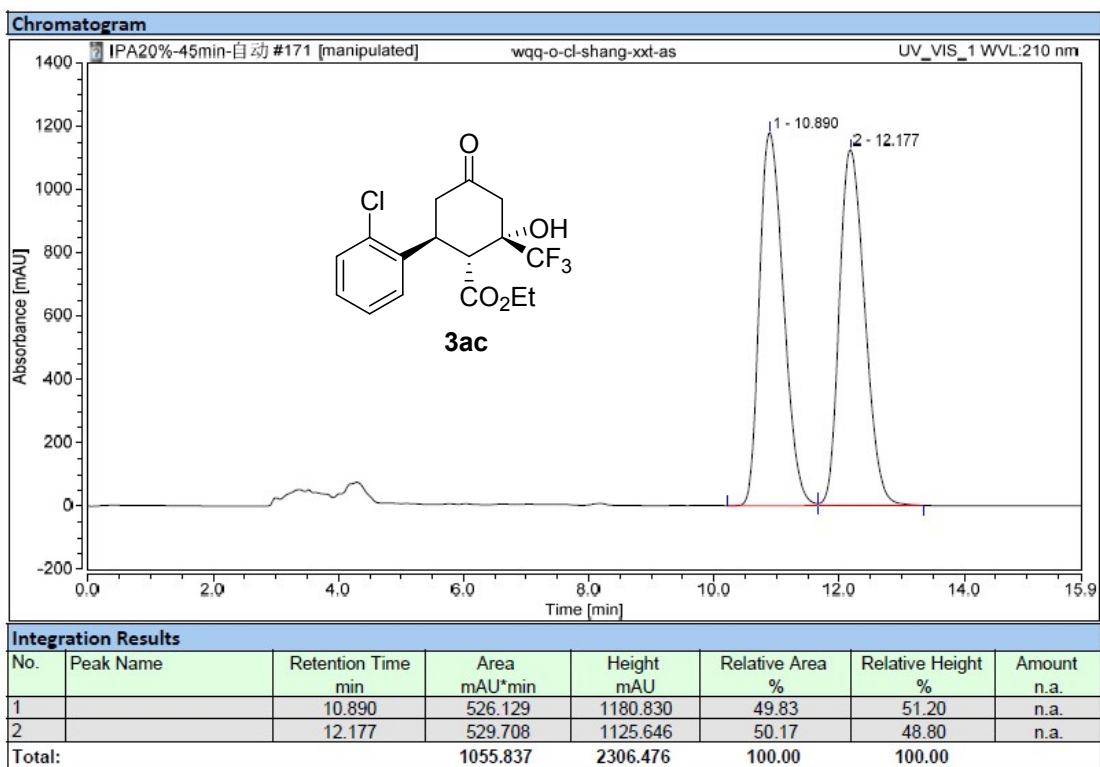
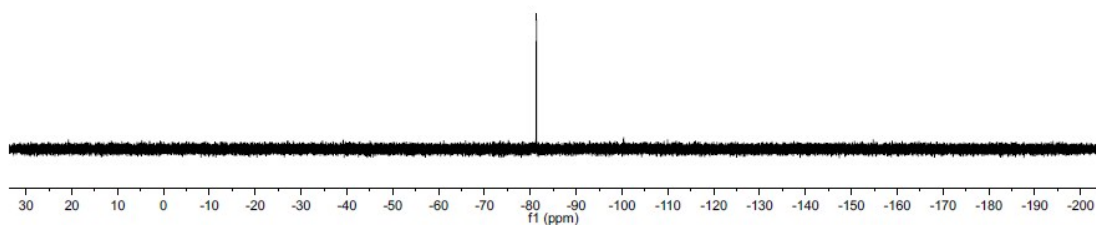
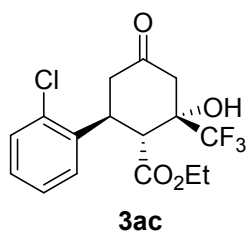


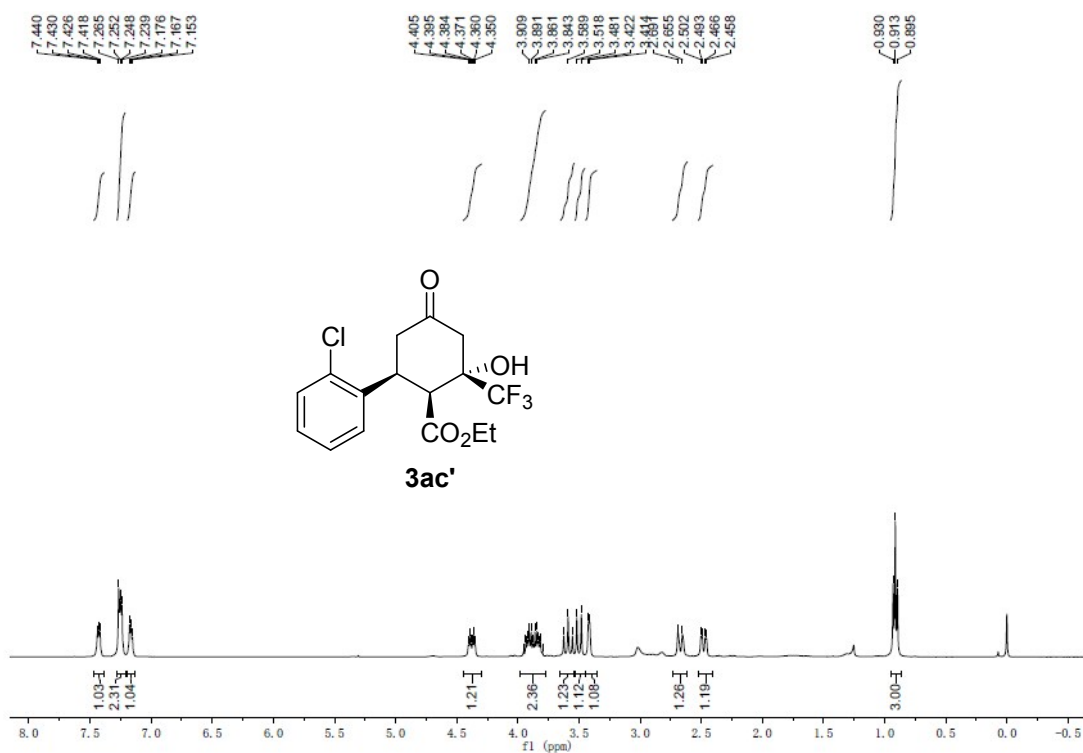
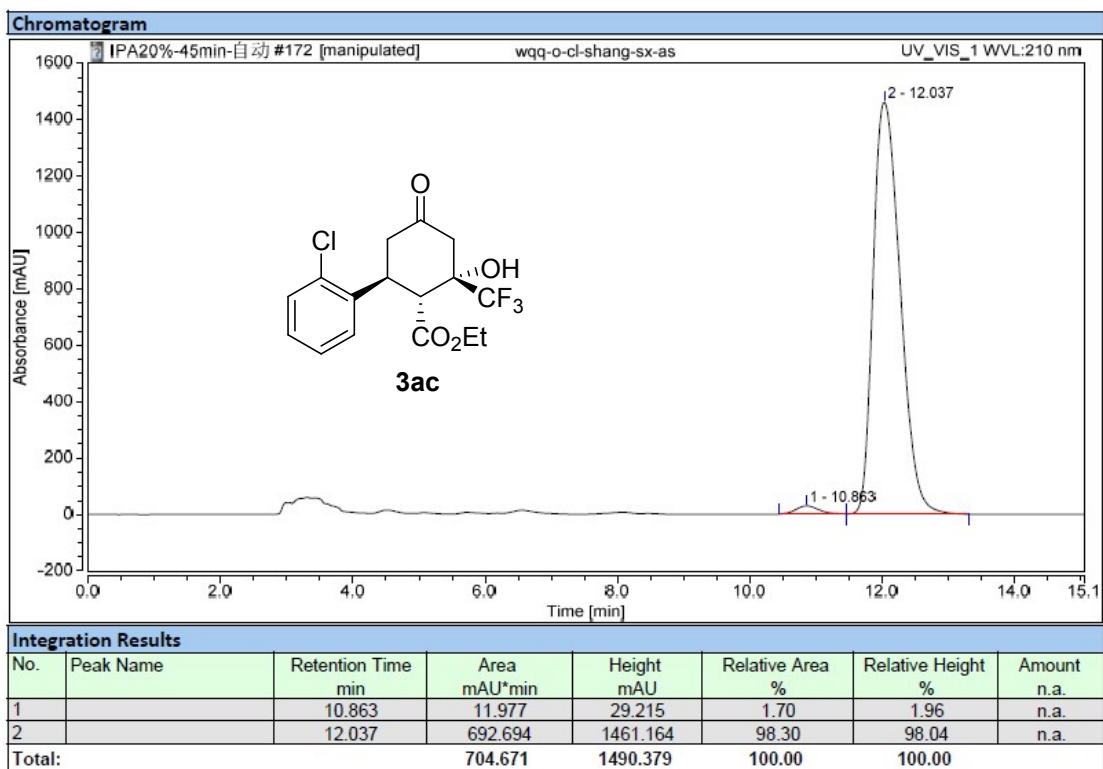




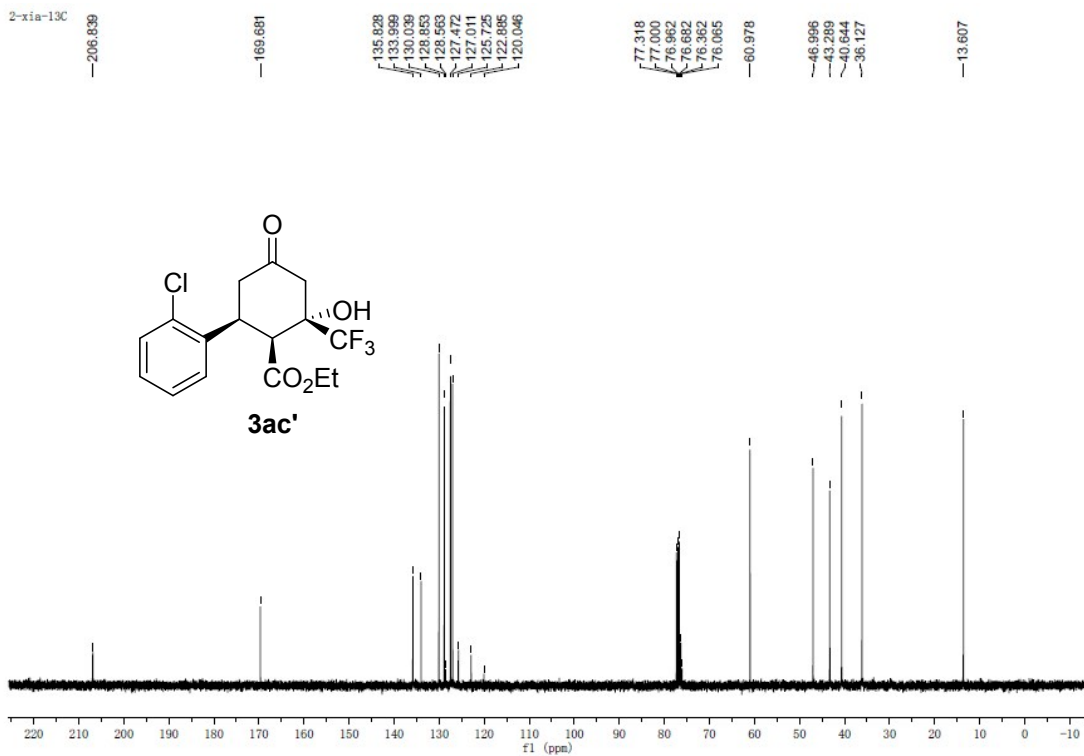


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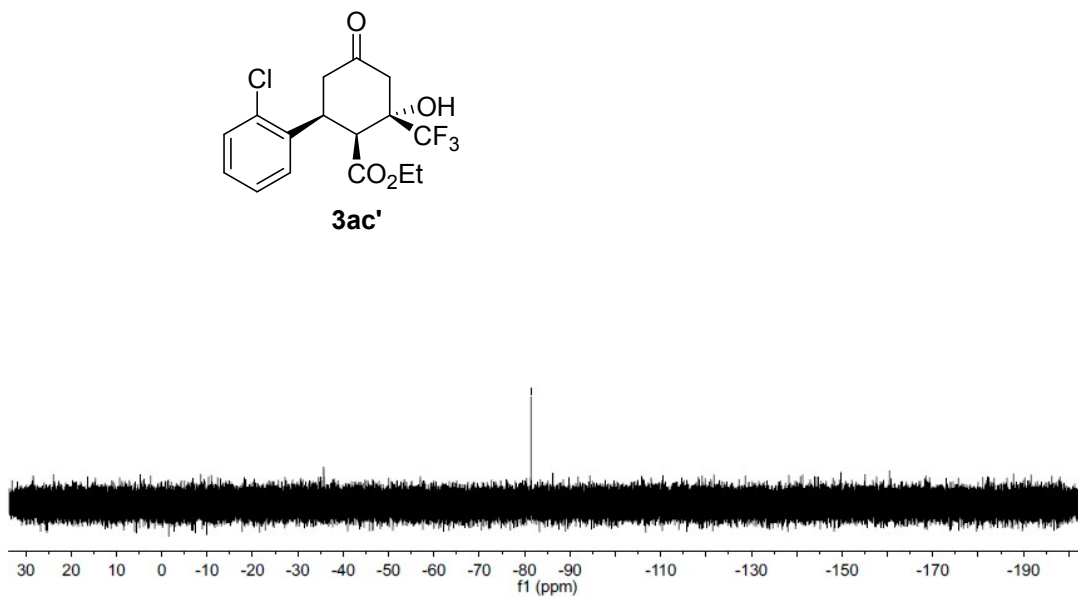


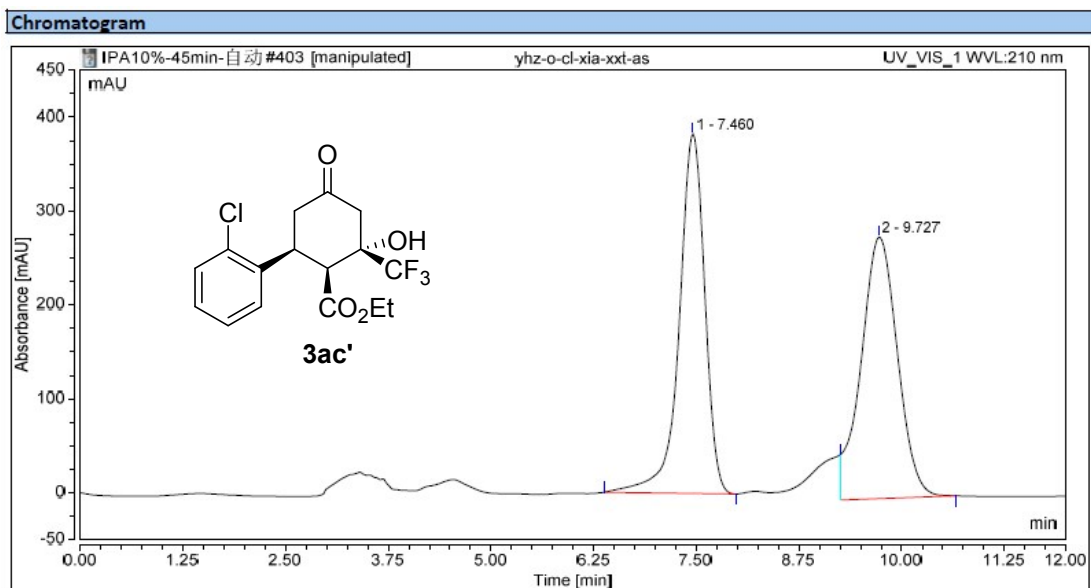


2-xia-13C



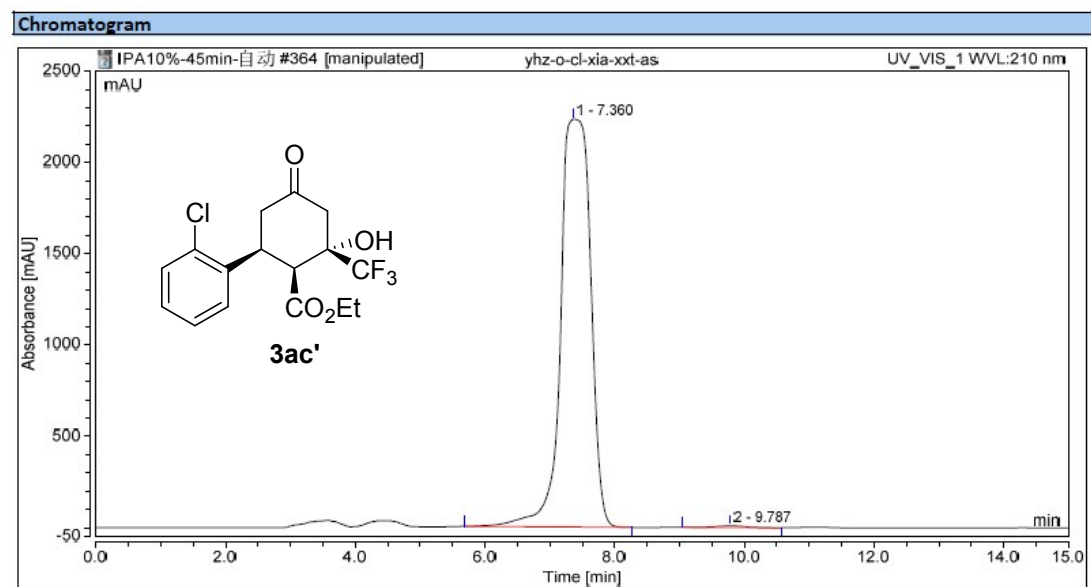
81.437





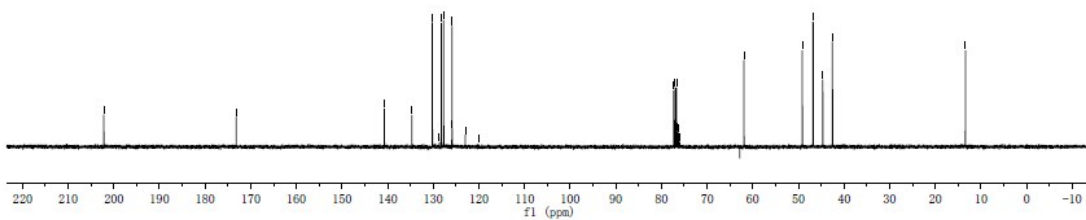
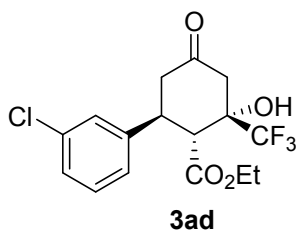
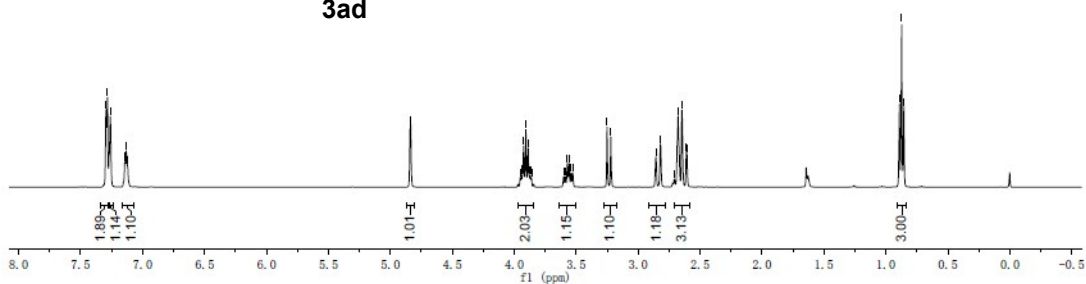
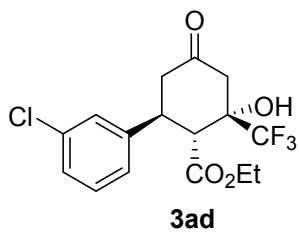
Integration Results

No.	Peak Name	Retention Time [min]	Area [mAU*min]	Height [mAU]	Relative Area [%]	Relative Height [%]	Amount
1		7.460	138.157	382.854	49.17	57.88	n.a.
2		9.727	142.802	278.552	50.83	42.12	n.a.
Total:			280.960	661.406	100.00	100.00	

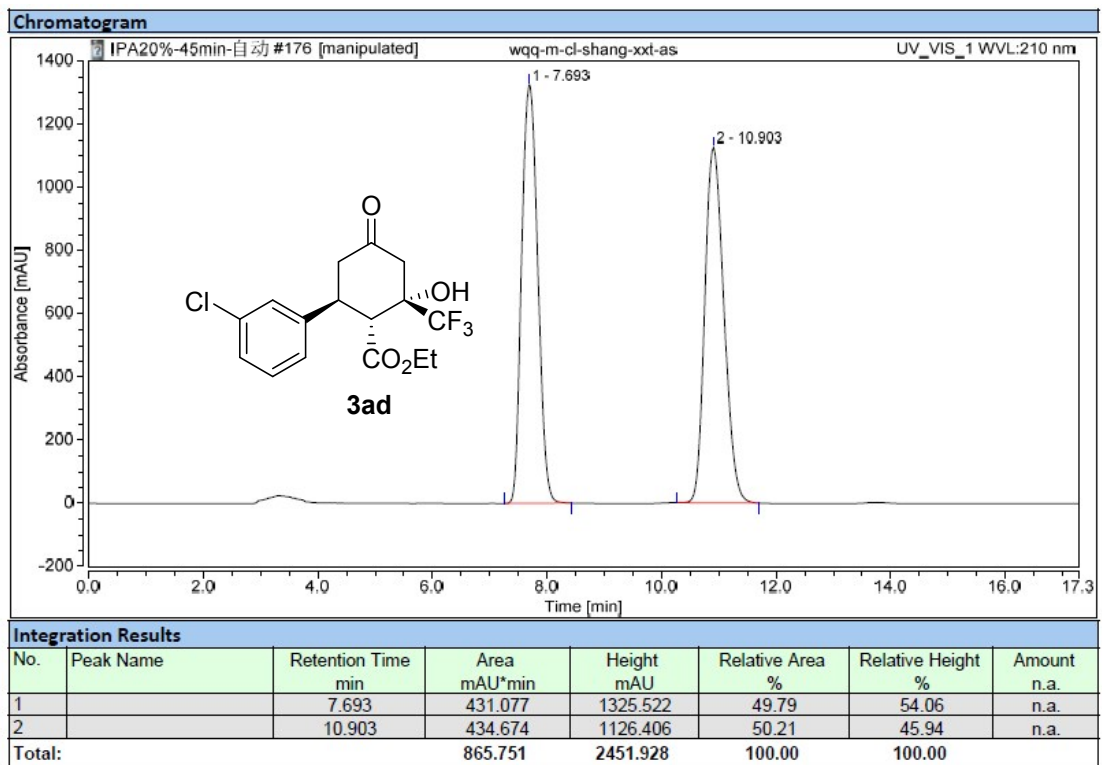
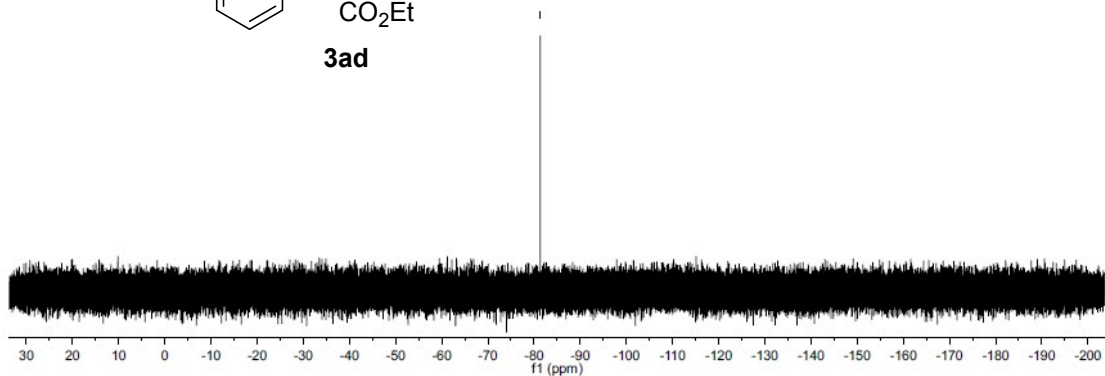
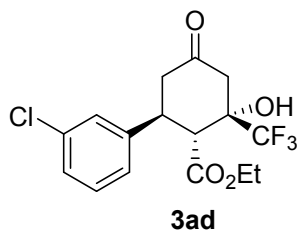


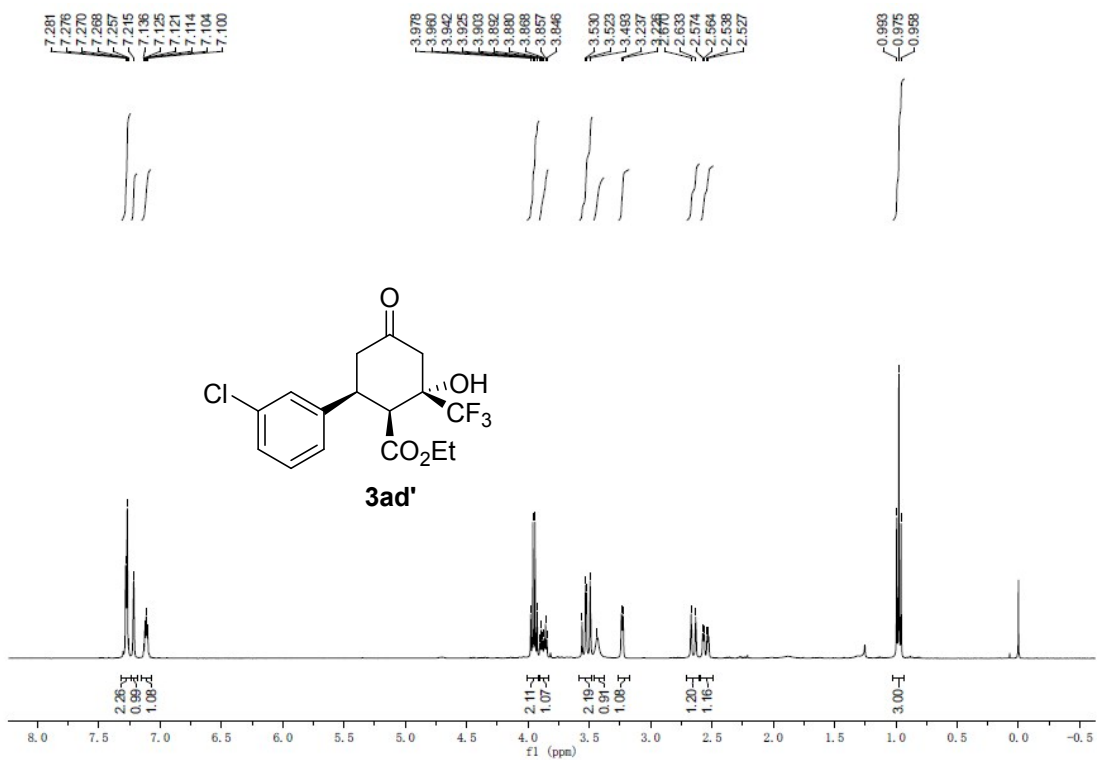
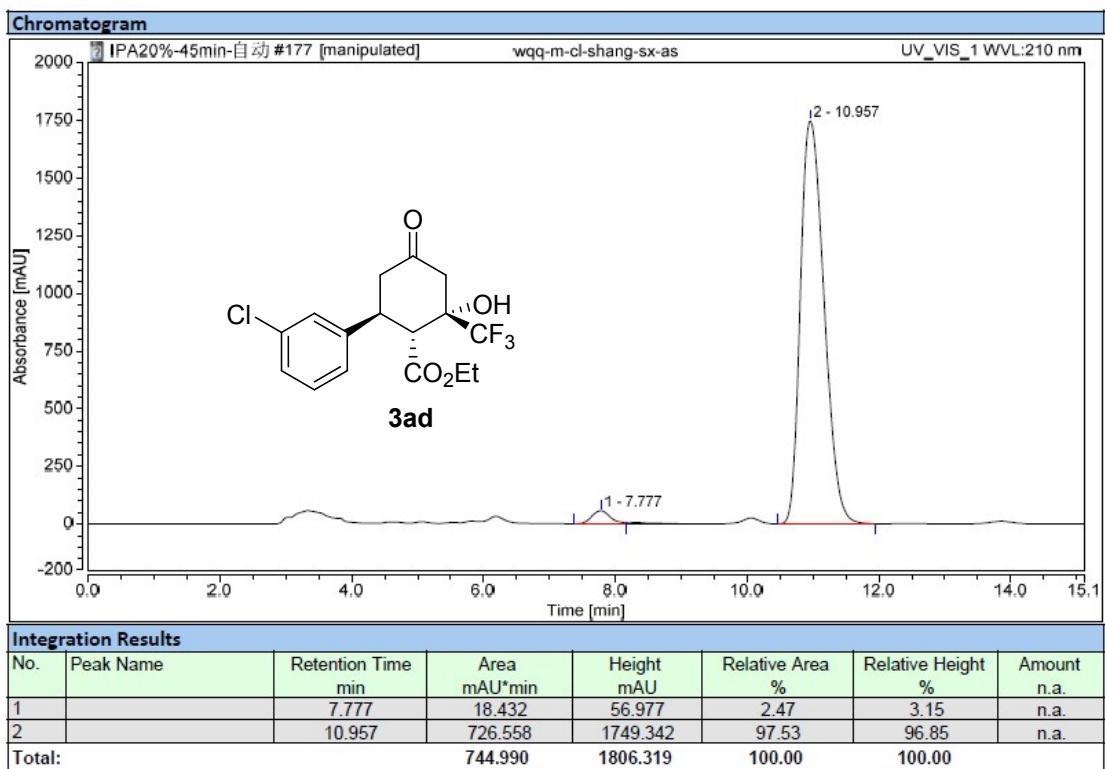
Integration Results

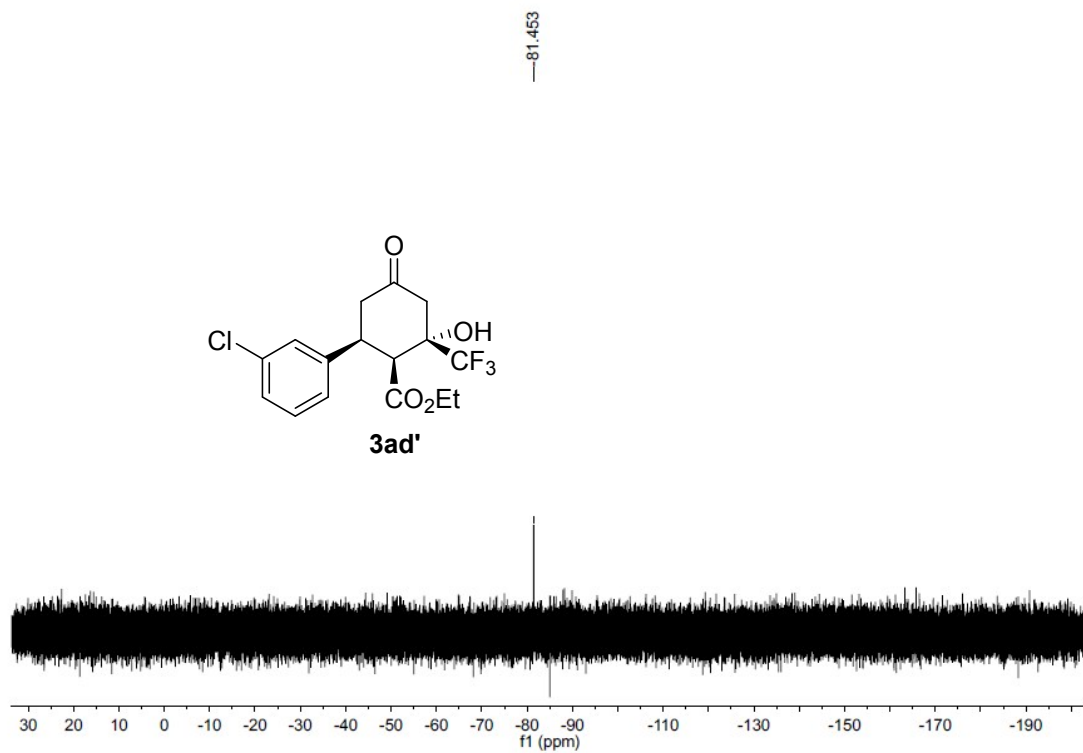
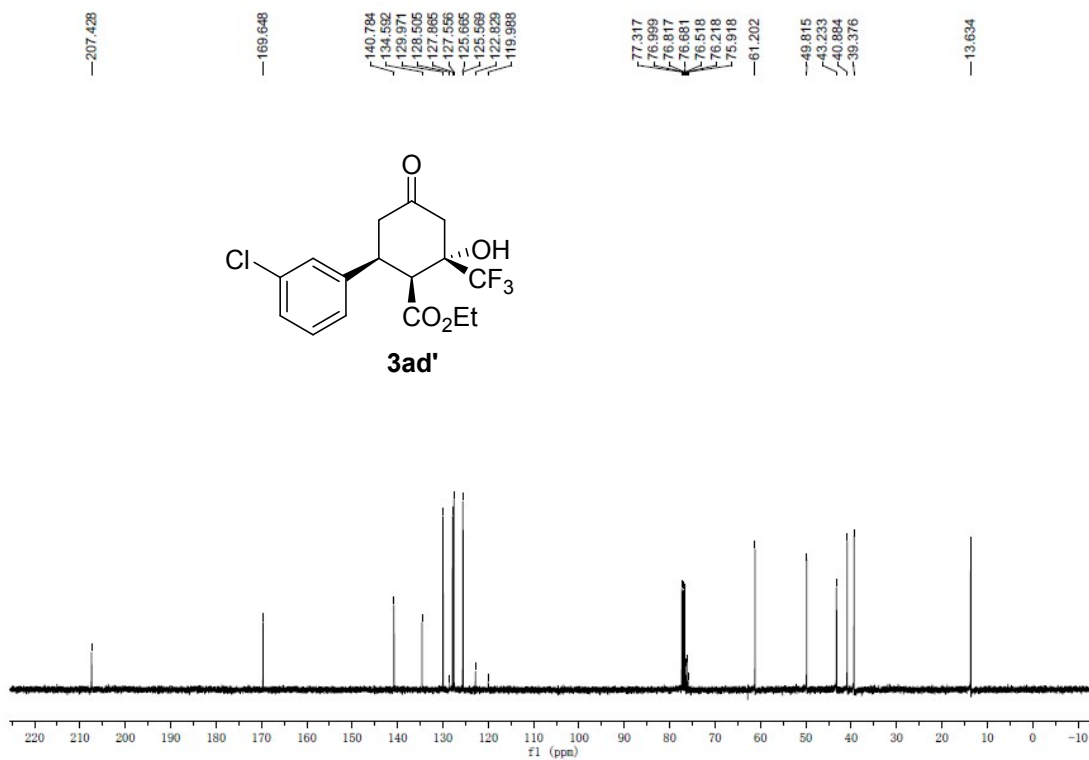
No.	Peak Name	Retention Time [min]	Area [mAU*min]	Height [mAU]	Relative Area [%]	Relative Height [%]	Amount
1		7.360	1202.179	2235.219	99.58	99.57	n.a.
2		9.787	5.022	9.682	0.42	0.43	n.a.
Total:			1207.201	2244.902	100.00	100.00	

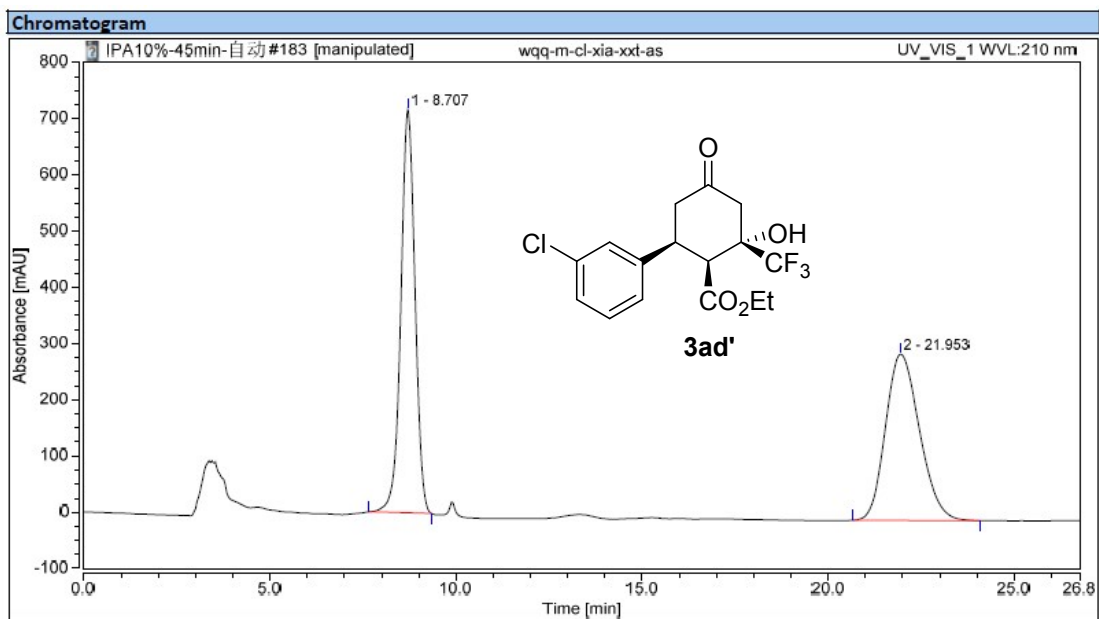


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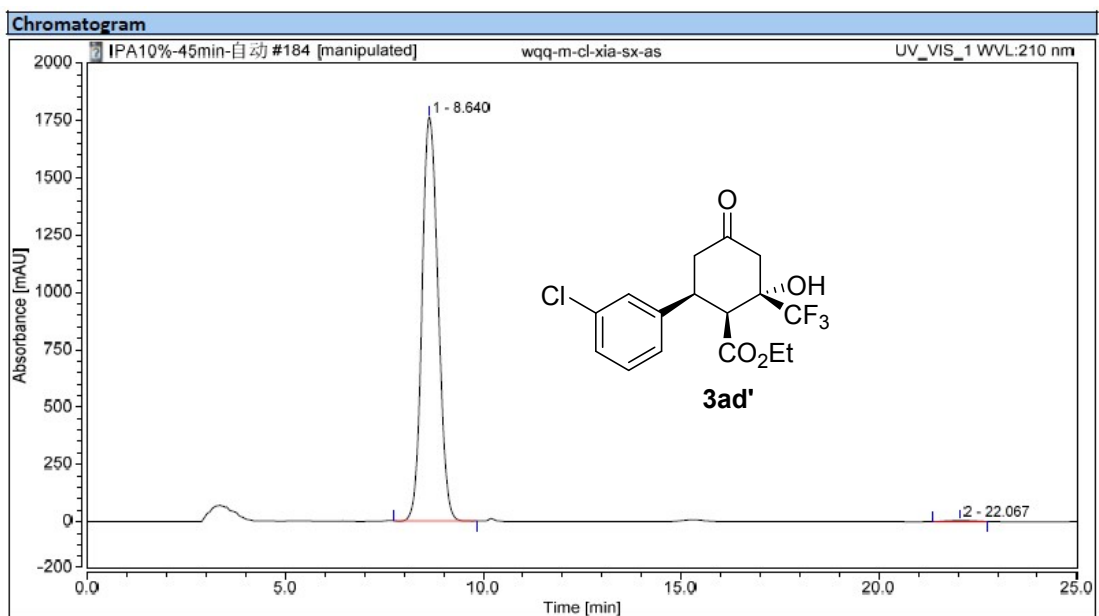






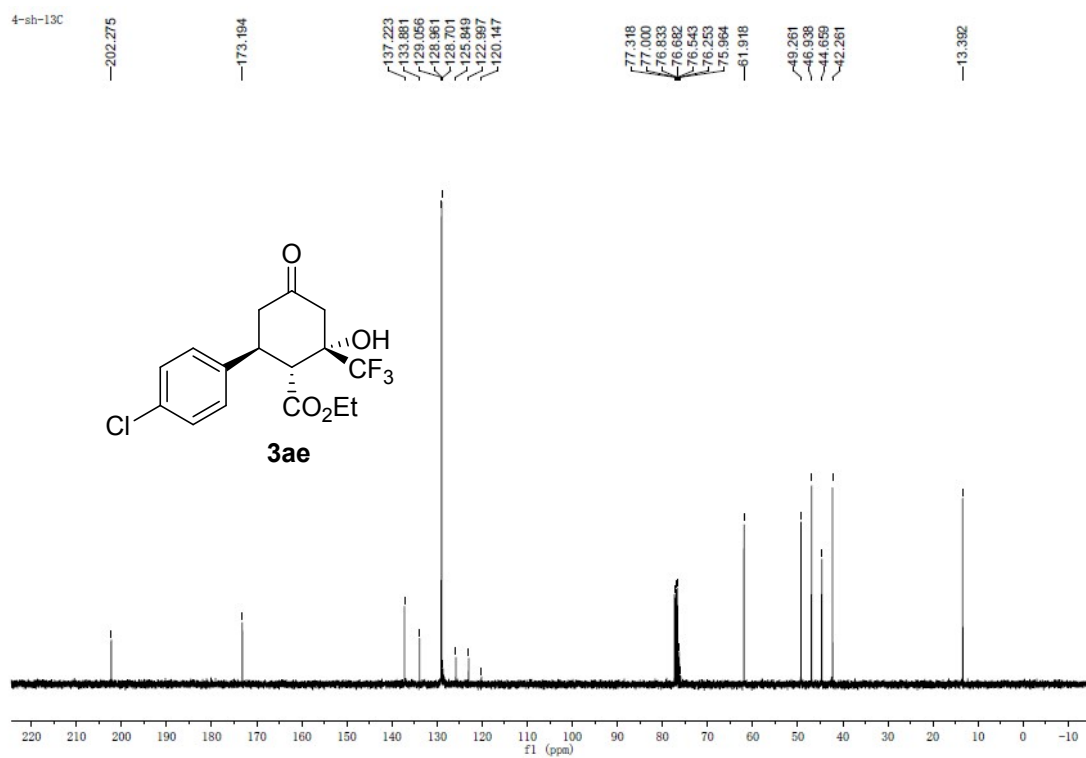
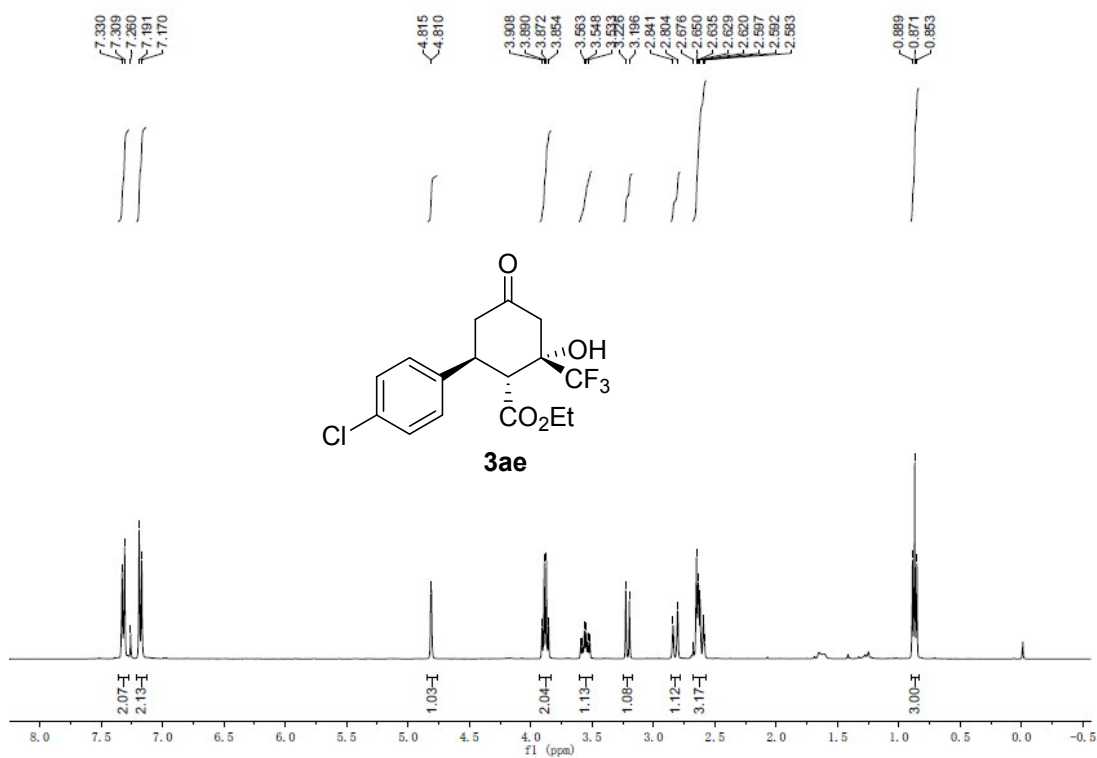
Integration Results

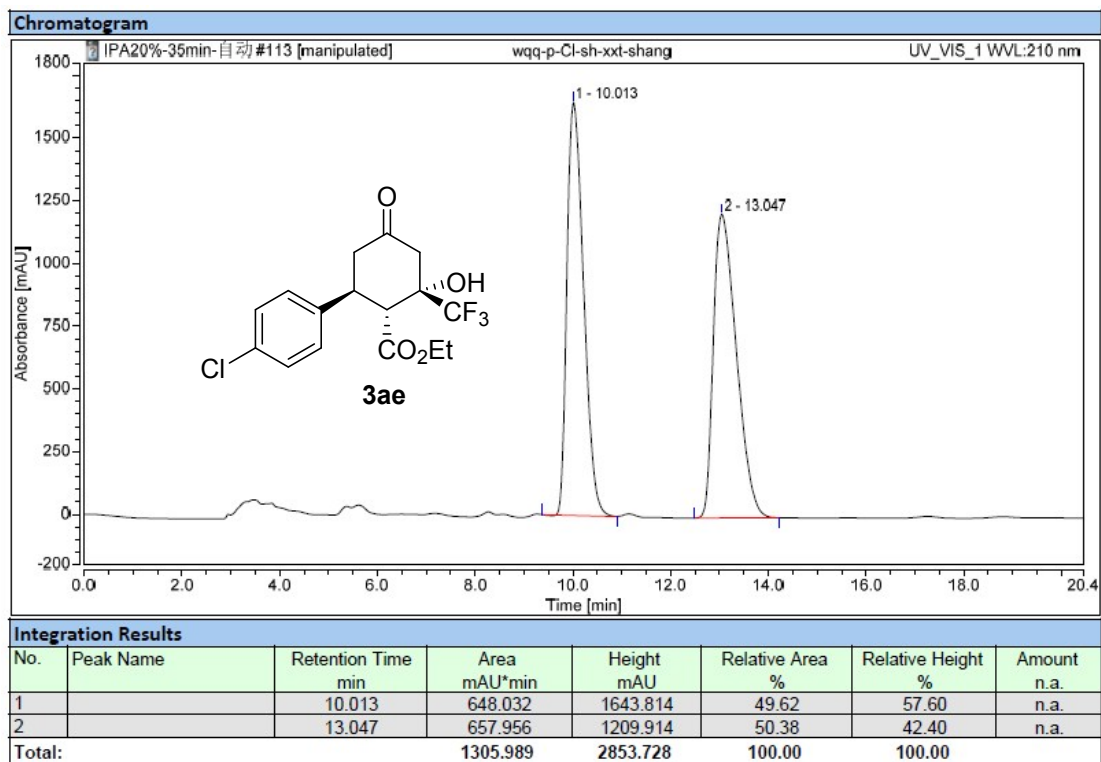
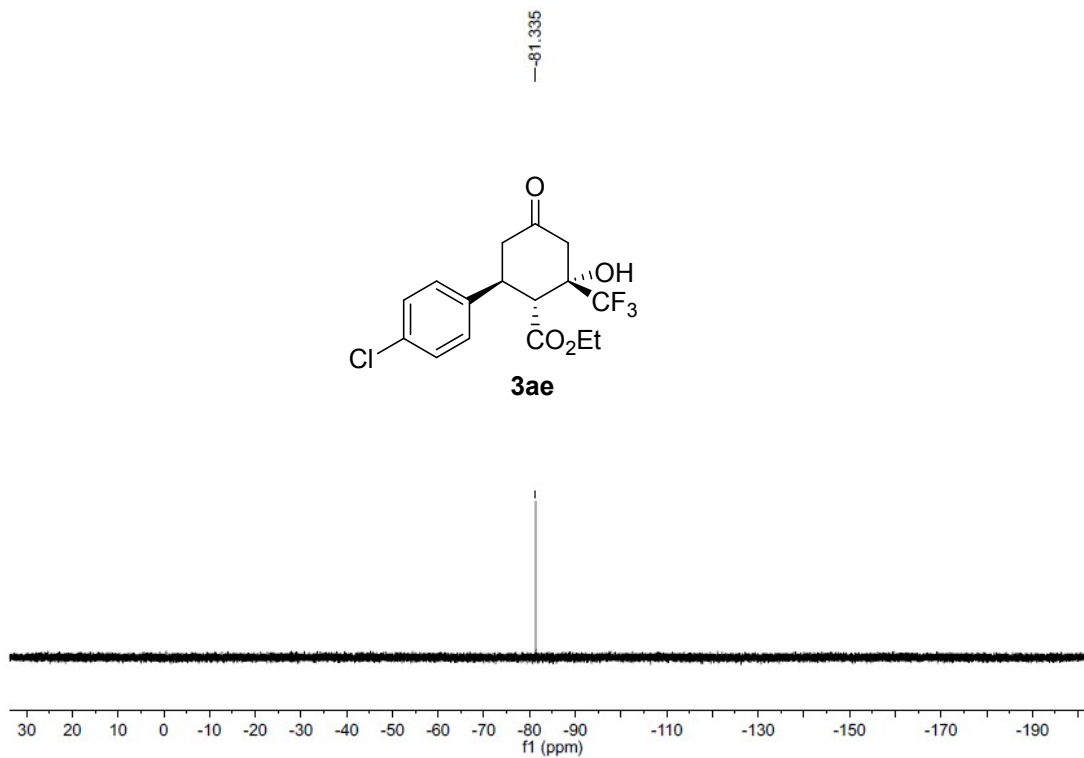
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		8.707	316.606	717.271	50.31	70.82	n.a.
2		21.953	312.710	295.602	49.69	29.18	n.a.
Total:			629.316	1012.873	100.00	100.00	

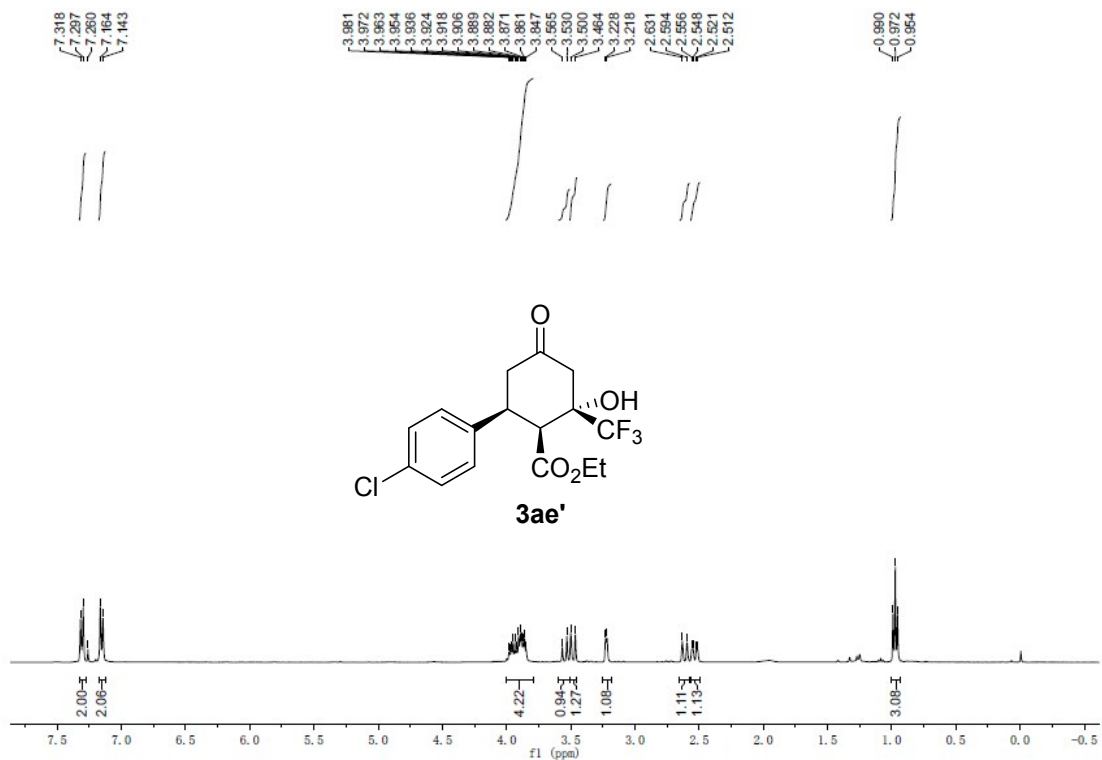
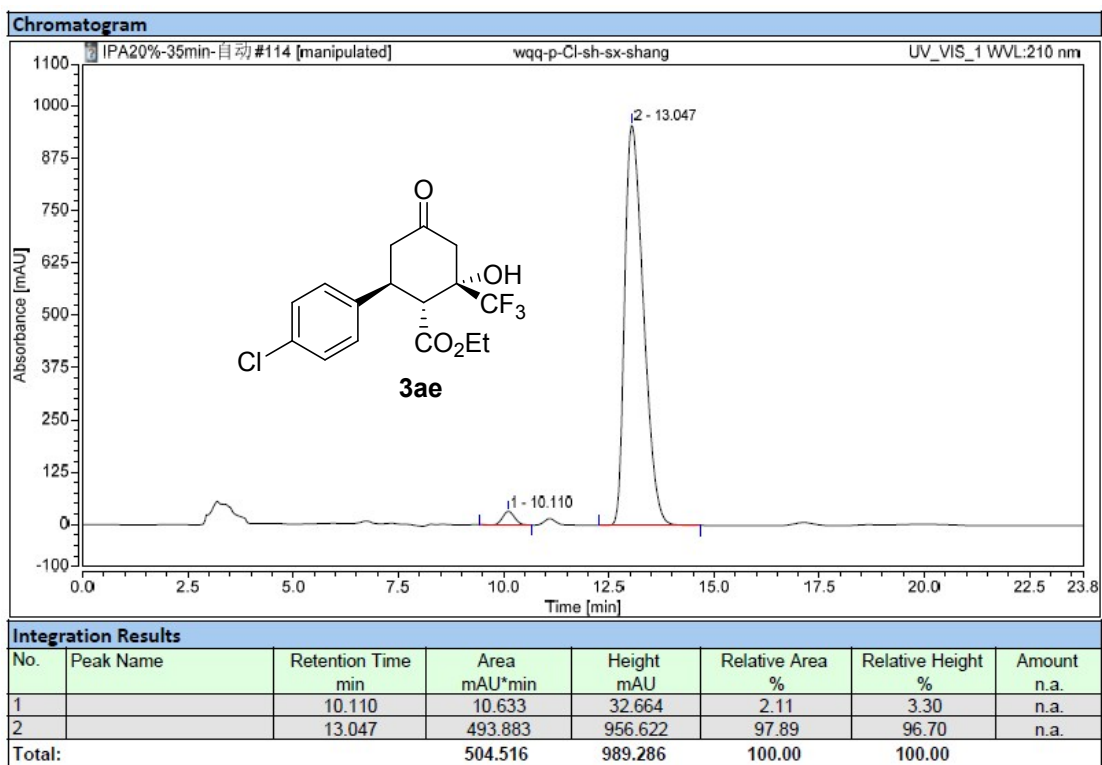


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		8.640	827.101	1760.904	99.54	99.72	n.a.
2		22.067	3.806	5.003	0.46	0.28	n.a.
Total:			830.907	1765.907	100.00	100.00	







4-xis-13C
—207.181

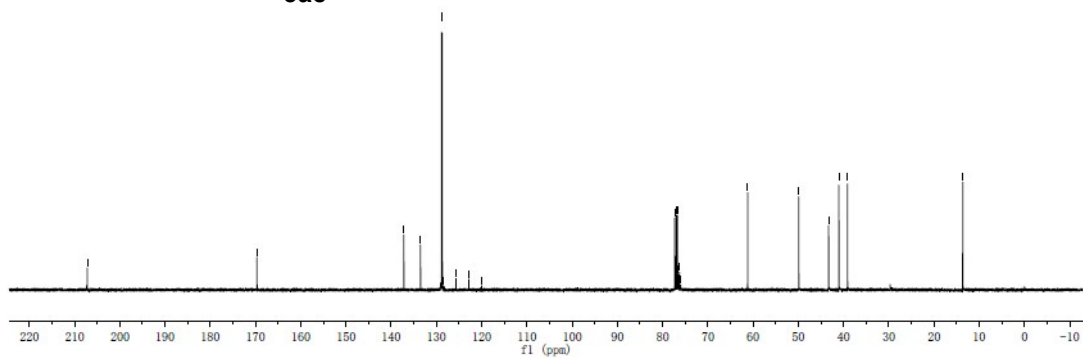
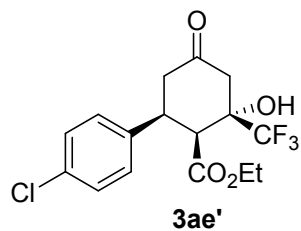
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128.703
128.508
125.669
122.831
119.990

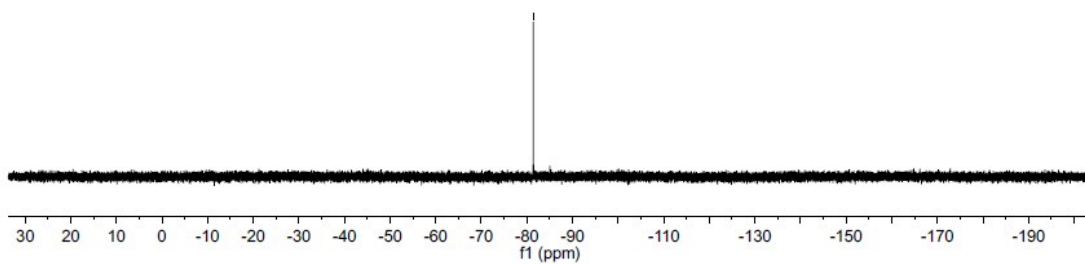
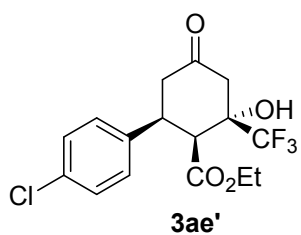
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75.983
—61.178

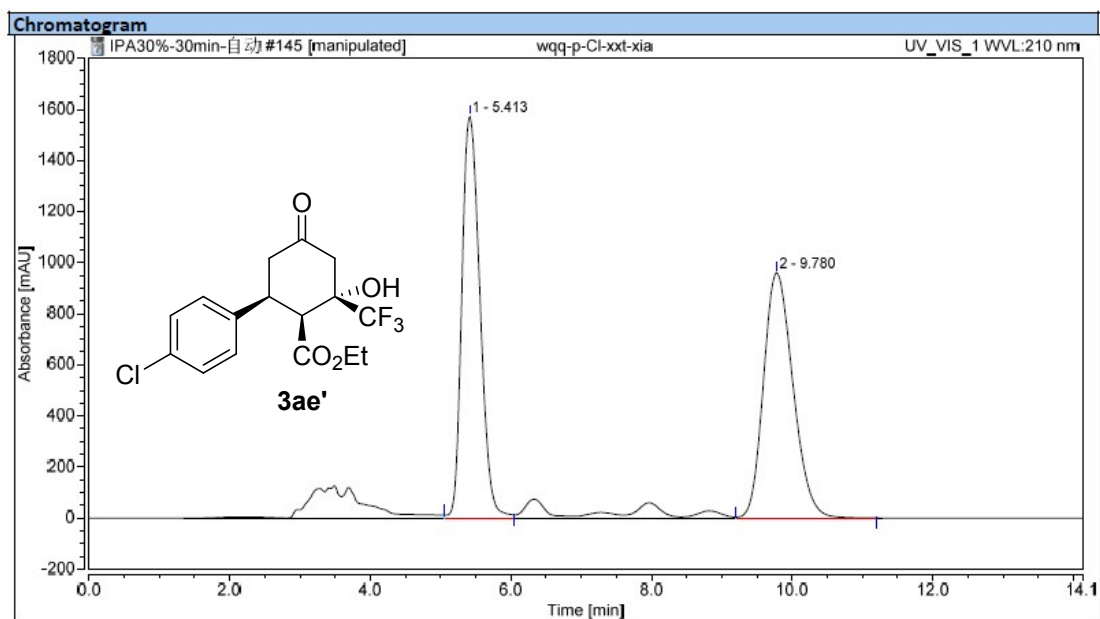
49.888
43.283
41.011
38.126

—13.632



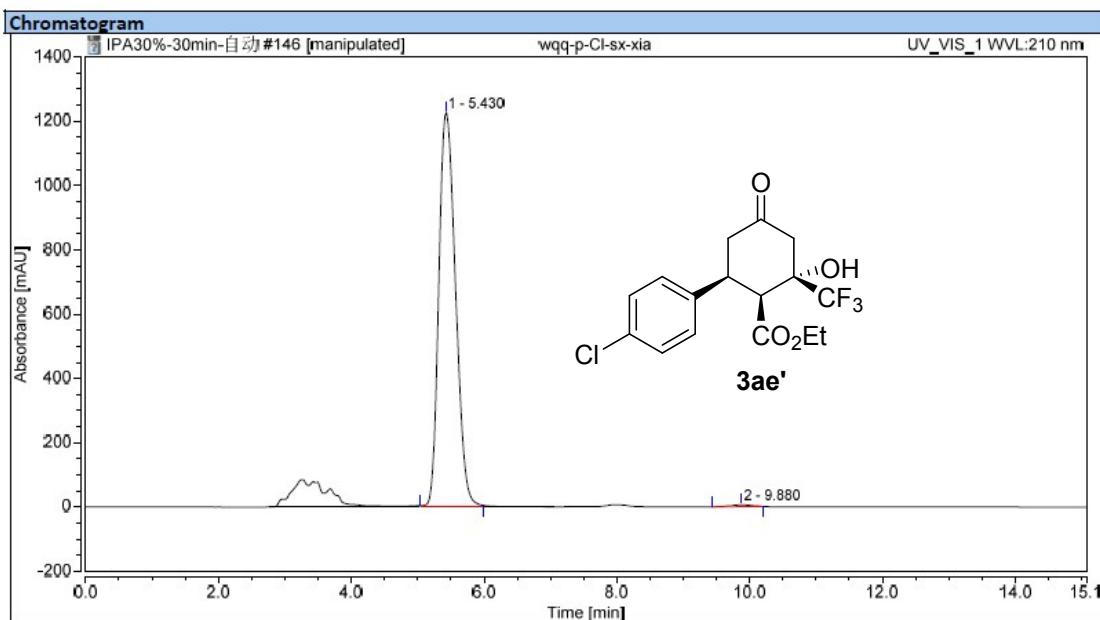
—81.430





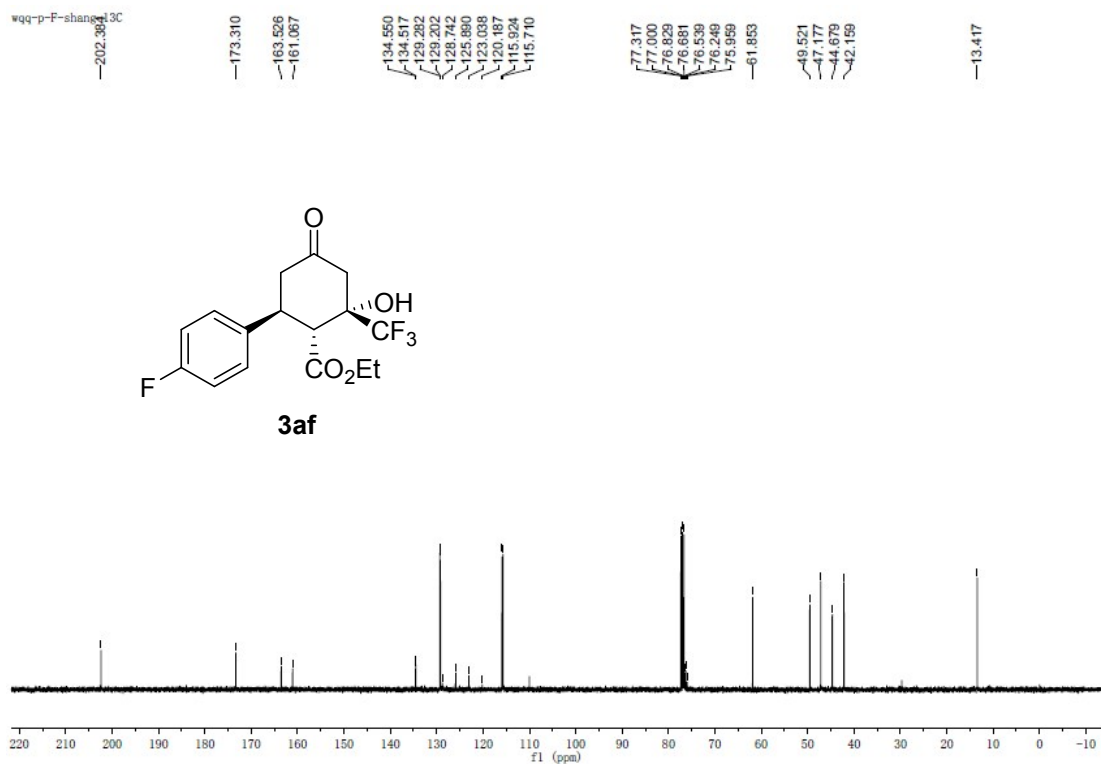
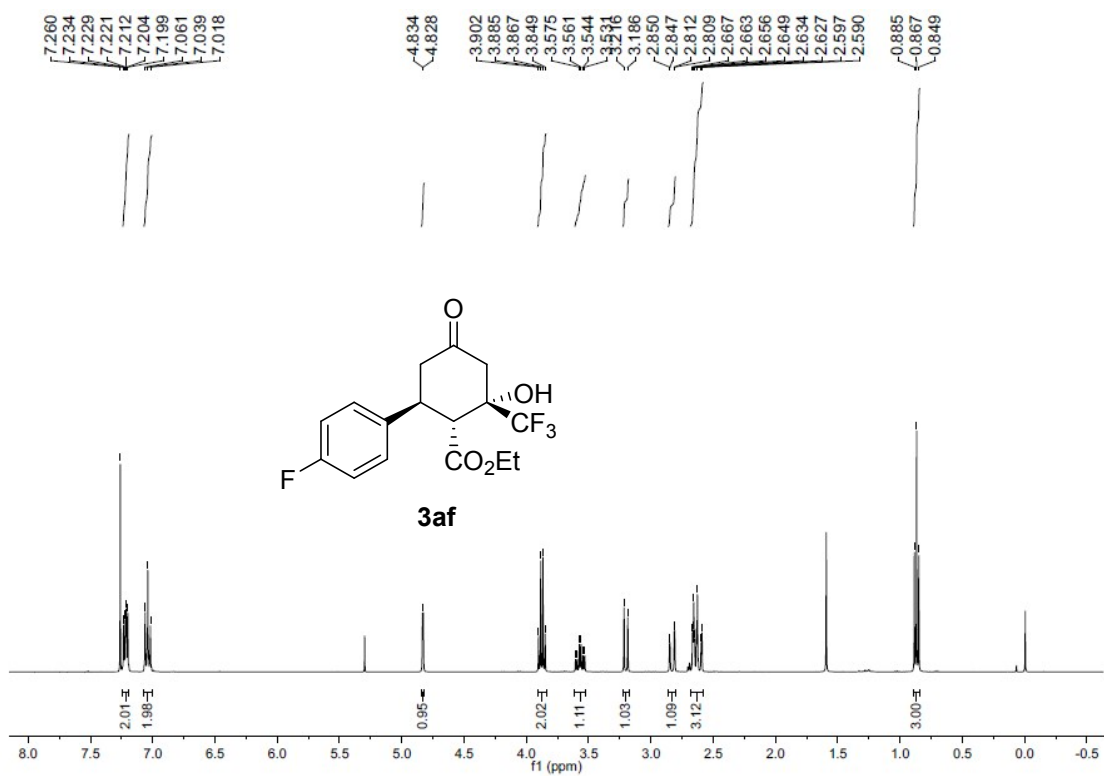
Integration Results

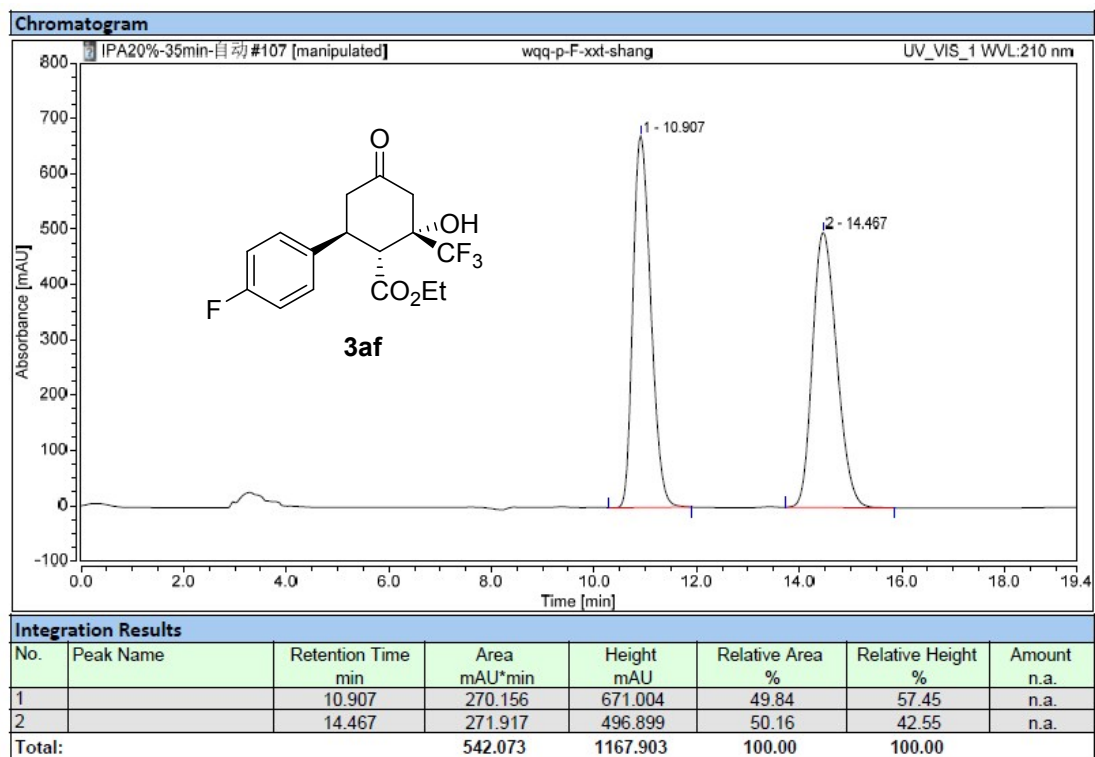
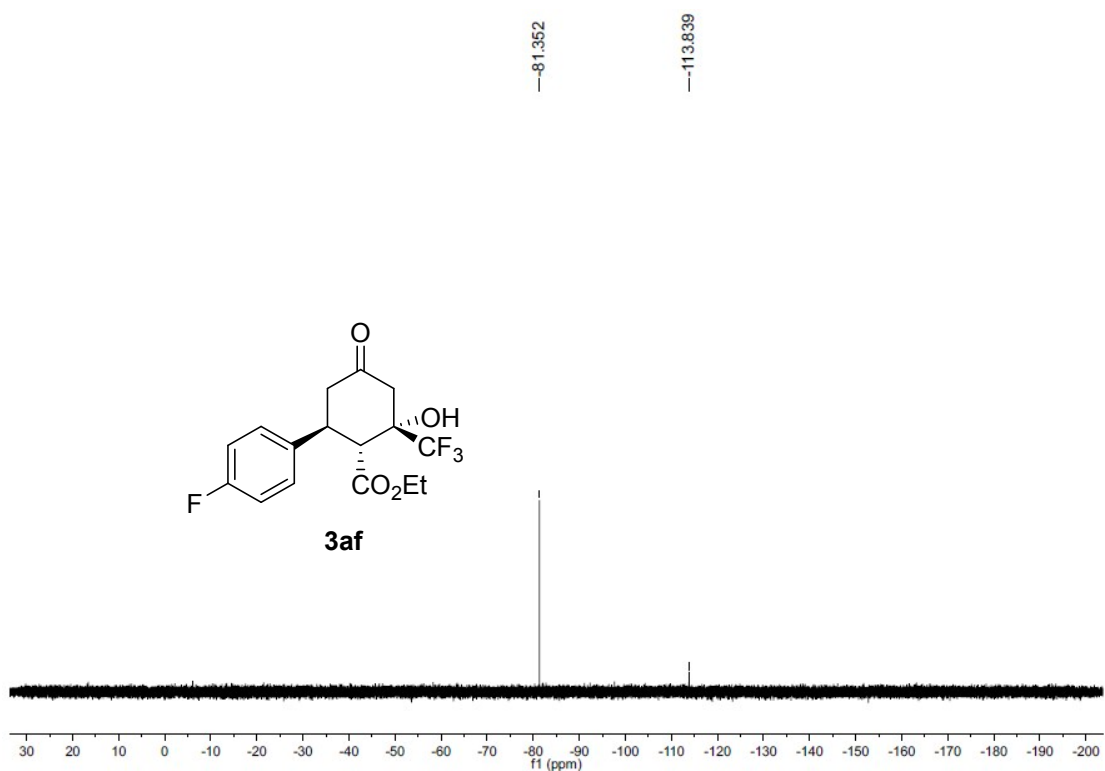
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		5.413	466.895	1573.380	50.06	62.10	n.a.
2		9.780	465.817	960.250	49.94	37.90	n.a.
Total:			932.711	2533.630	100.00	100.00	

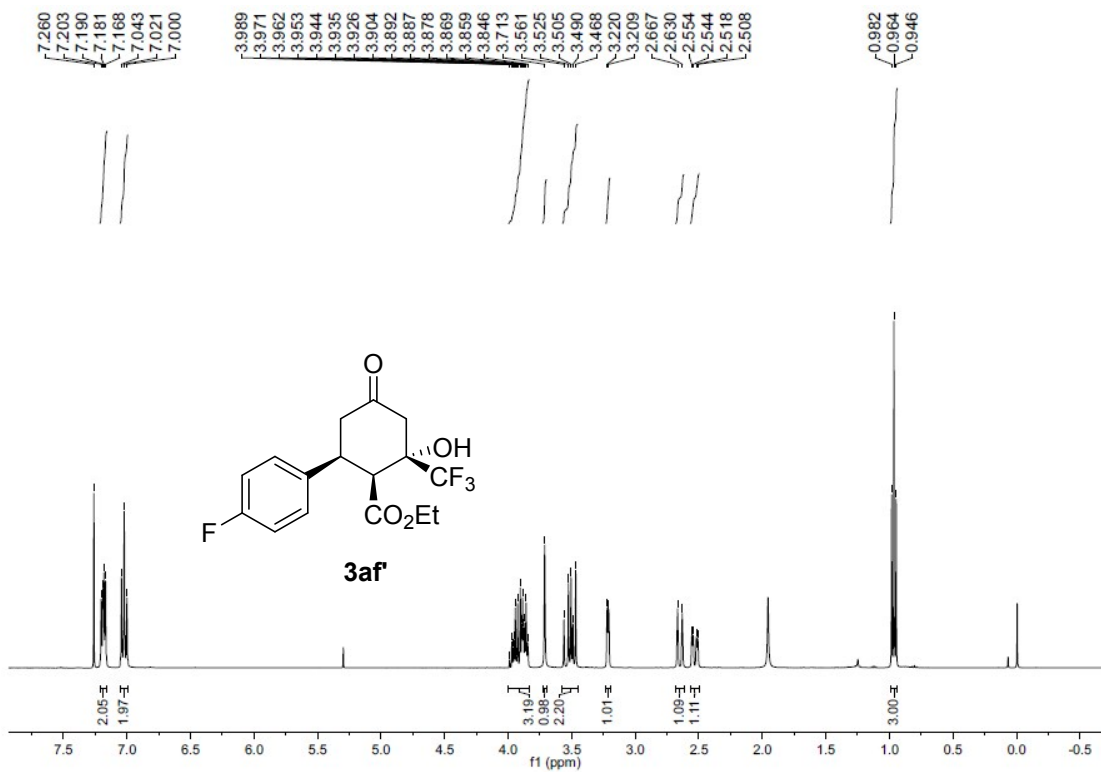
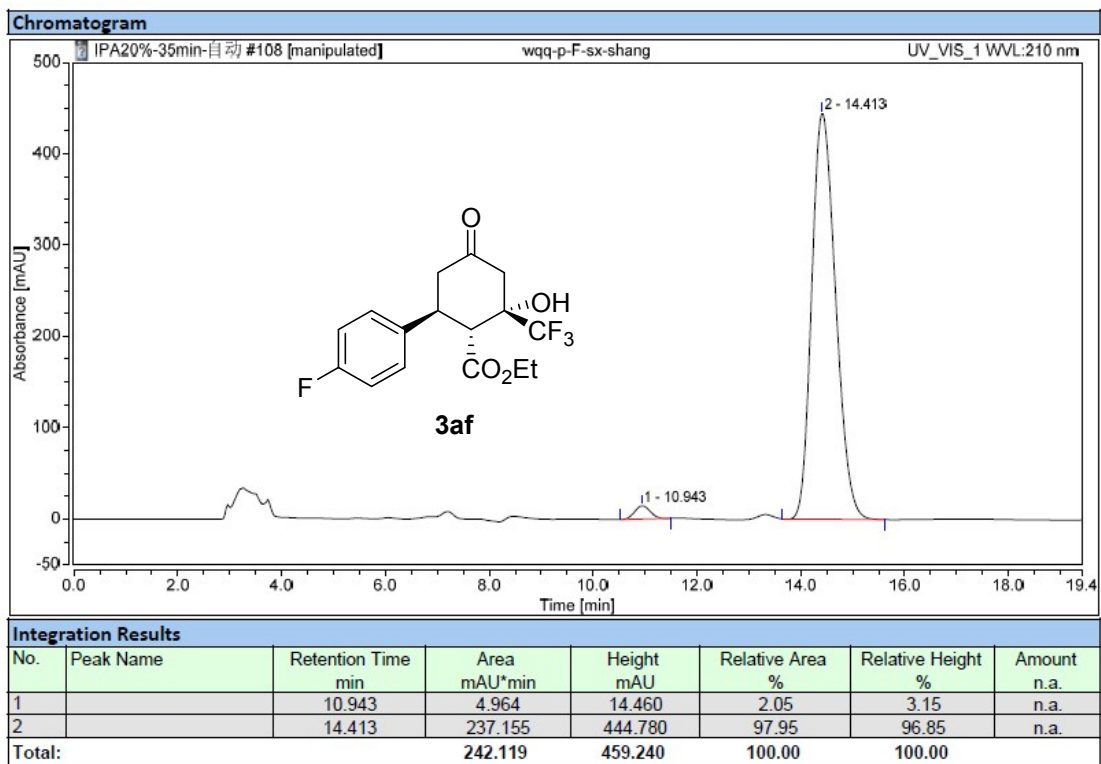


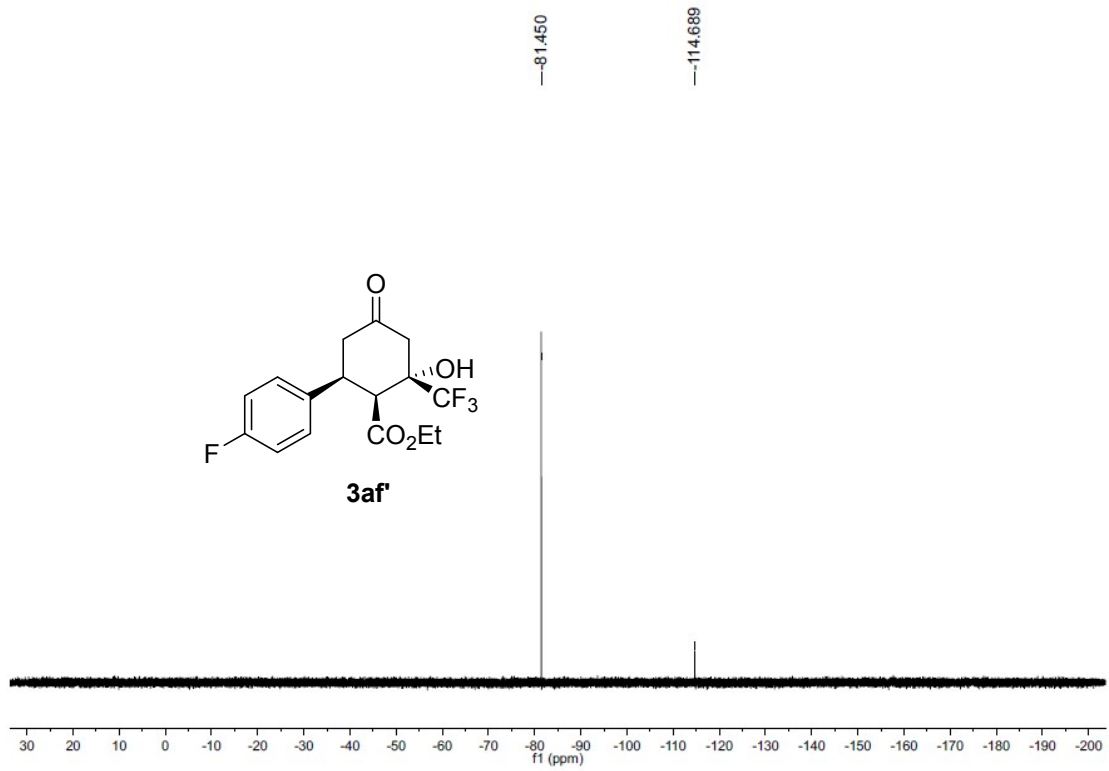
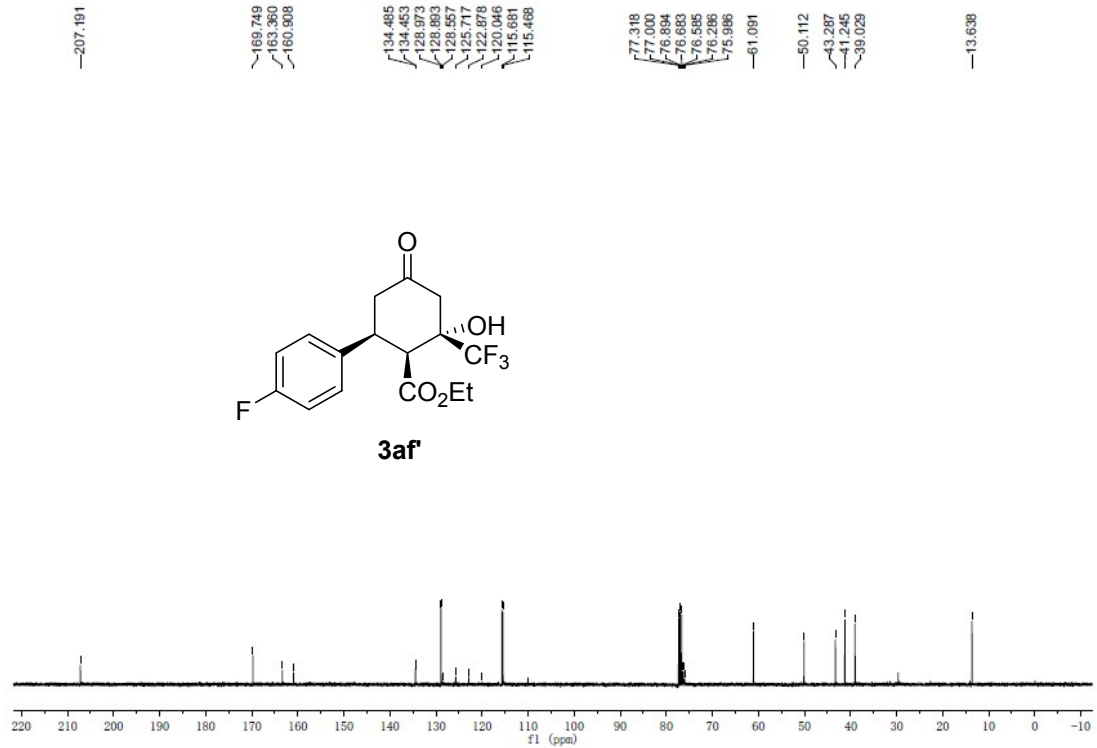
Integration Results

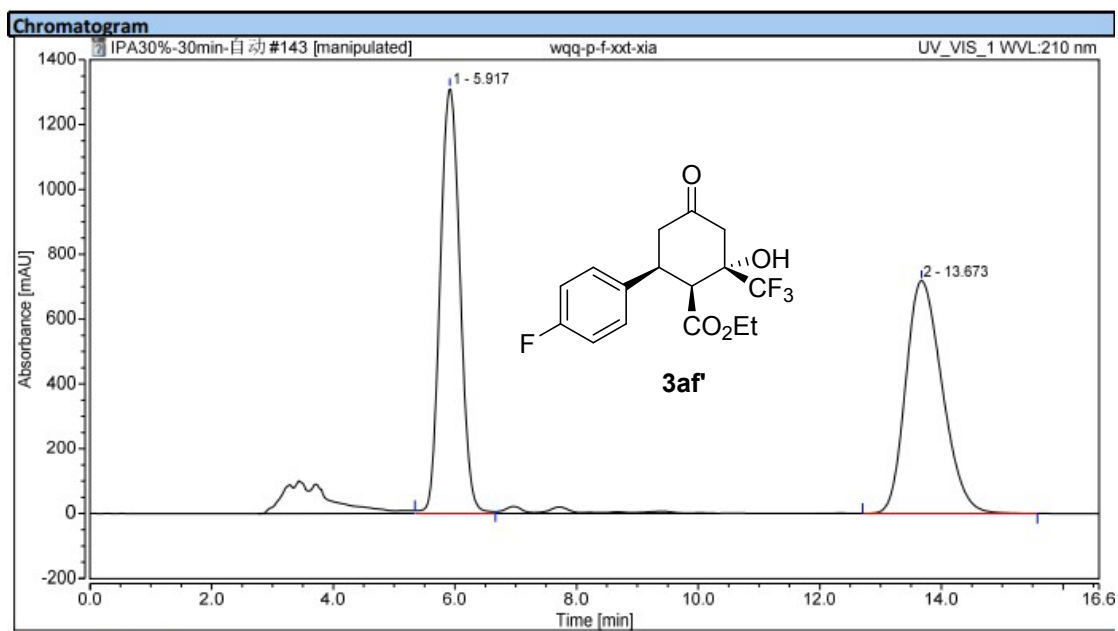
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		5.430	358.055	1226.727	99.42	99.56	n.a.
2		9.880	2.094	5.375	0.58	0.44	n.a.
Total:			360.149	1232.102	100.00	100.00	





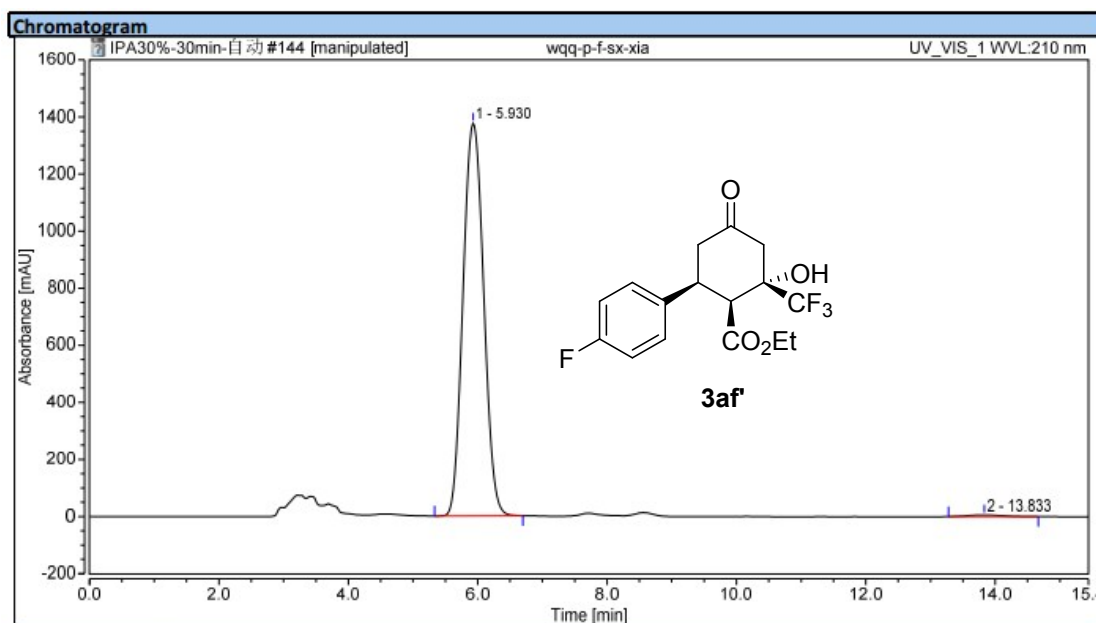






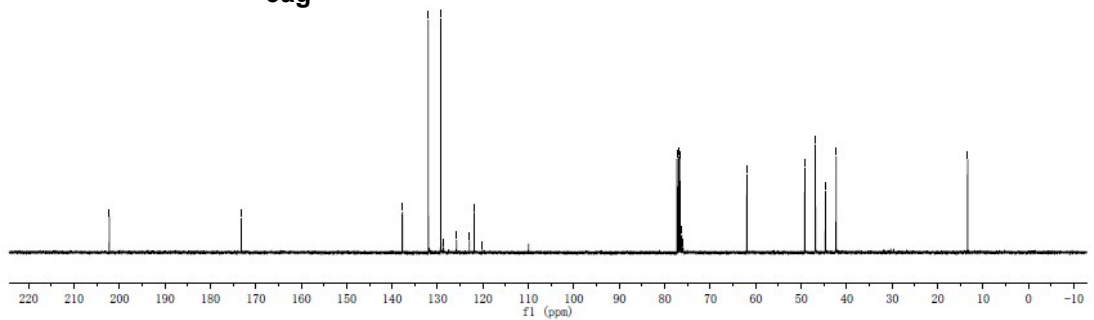
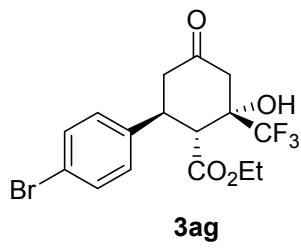
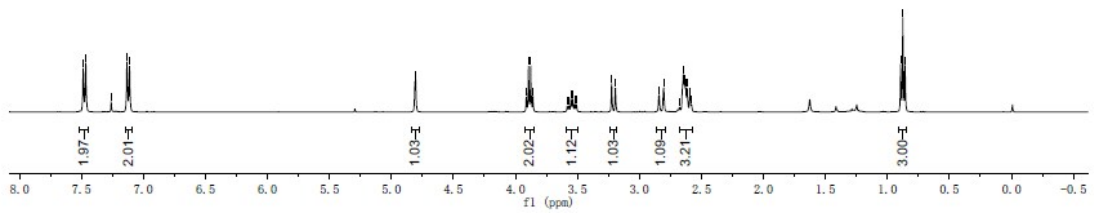
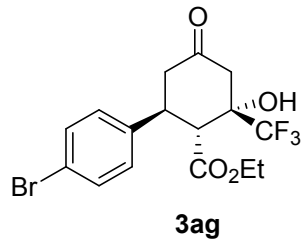
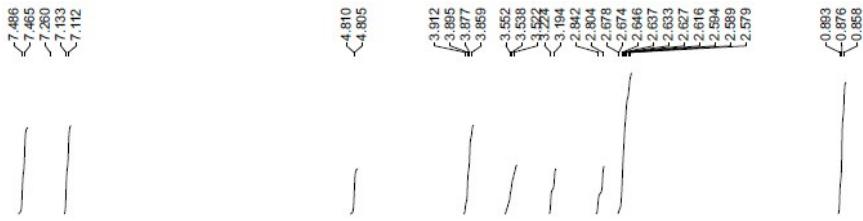
Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		5.917	494.140	1311.236	49.75	64.59	n.a.
2		13.673	499.072	718.805	50.25	35.41	n.a.
Total:			993.212	2030.041	100.00	100.00	

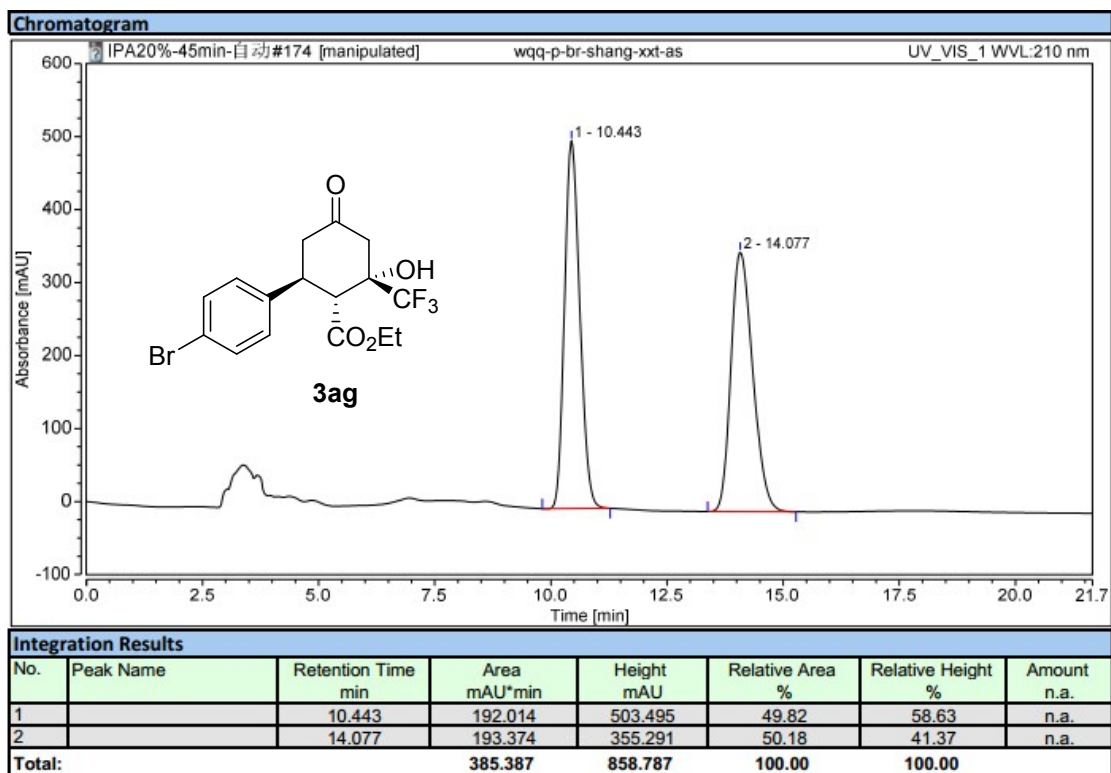
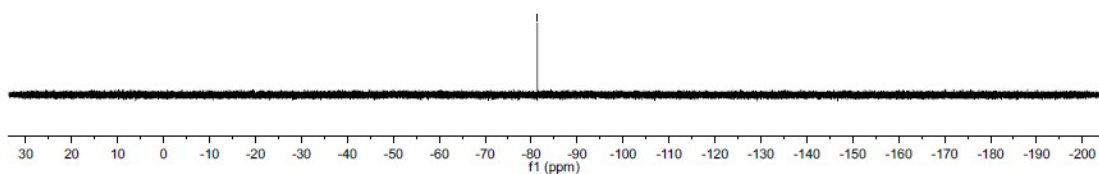
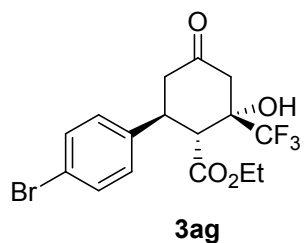


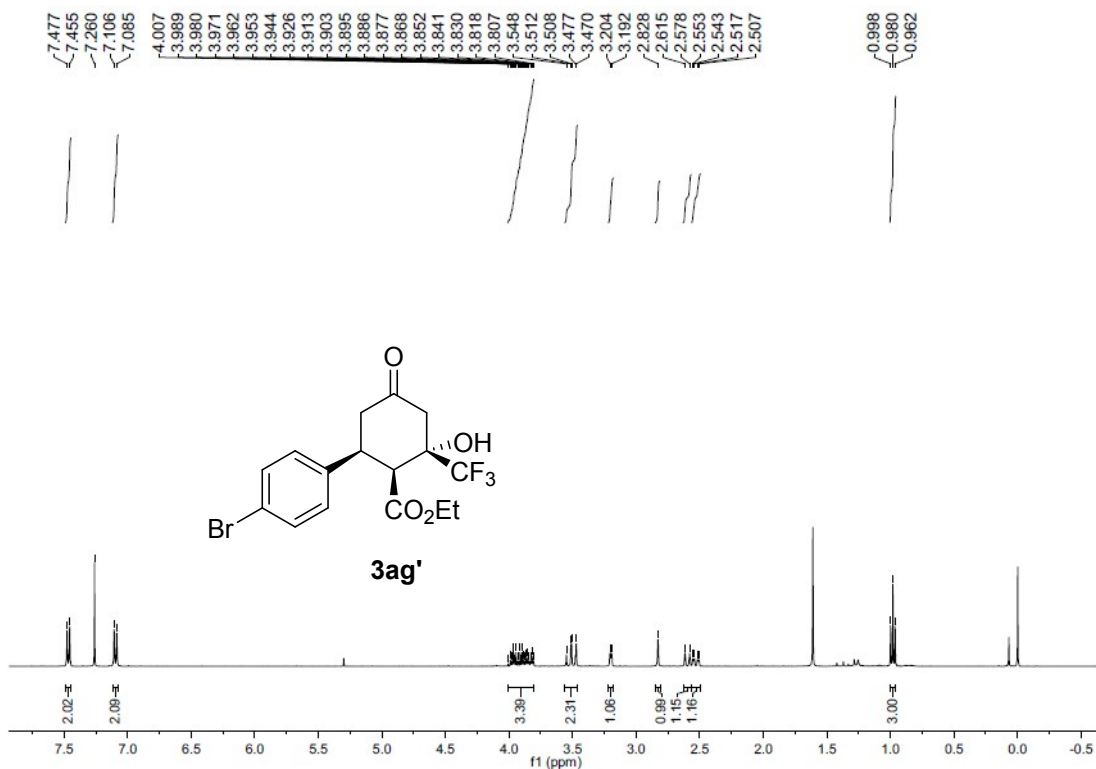
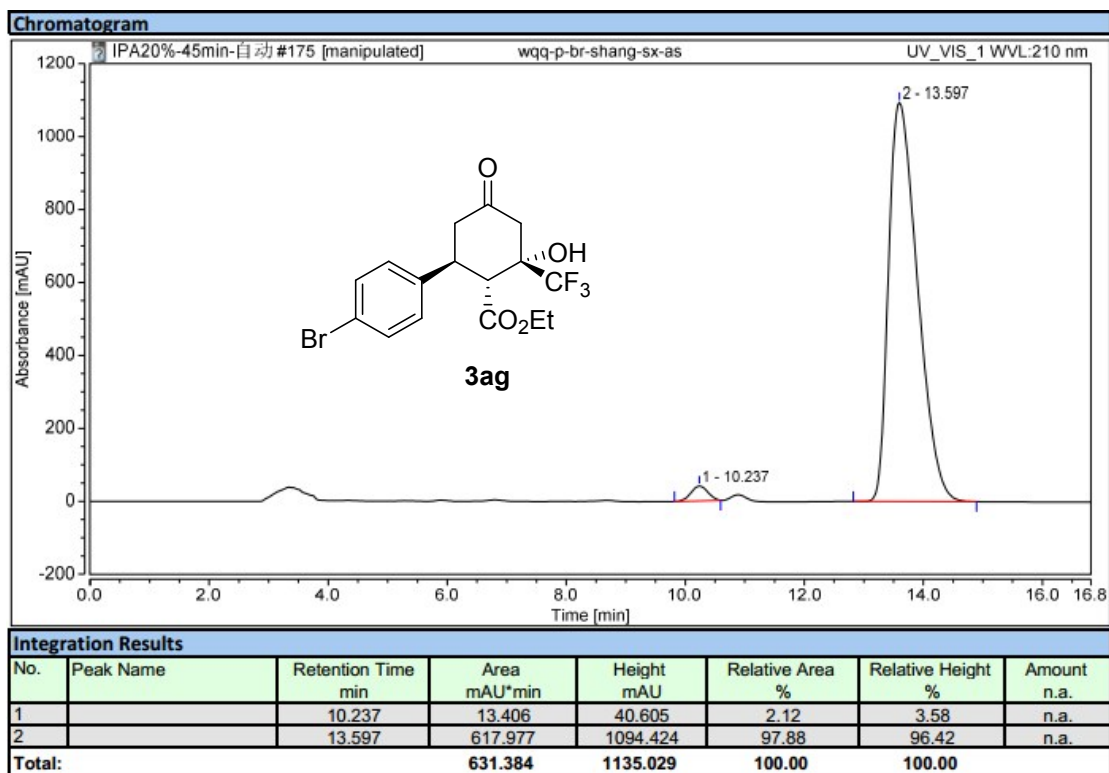
Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		5.930	506.143	1376.448	99.30	99.58	n.a.
2		13.833	3.580	5.838	0.70	0.42	n.a.
Total:			509.723	1382.285	100.00	100.00	



—81.331





—207.588

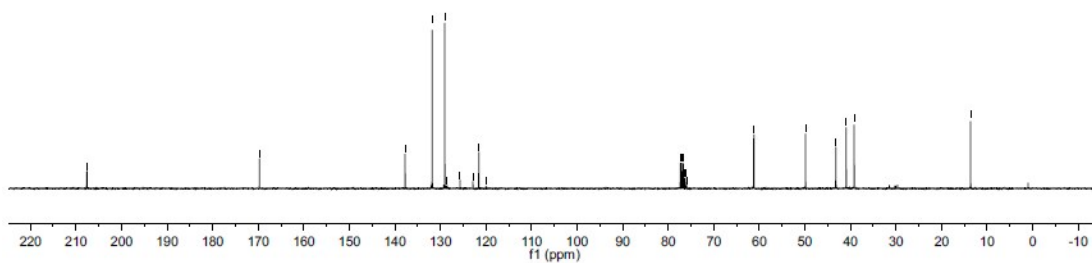
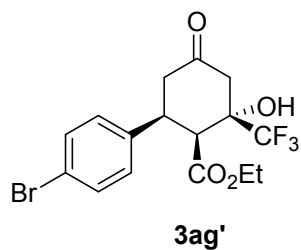
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122.854
121.570
120.014

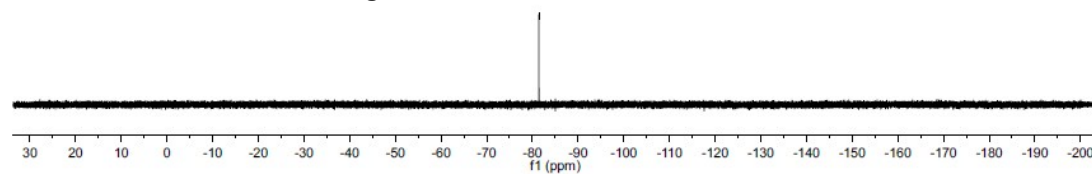
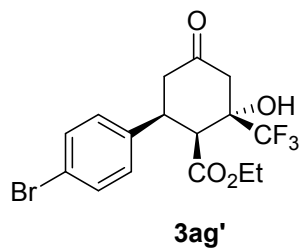
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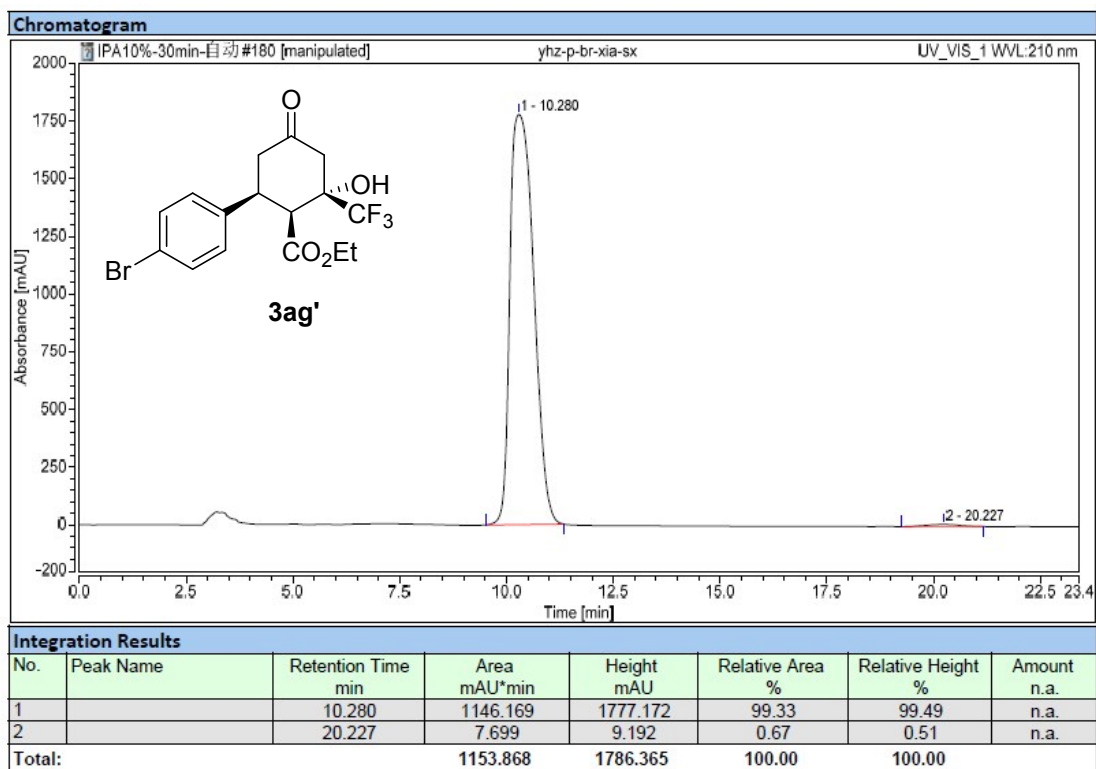
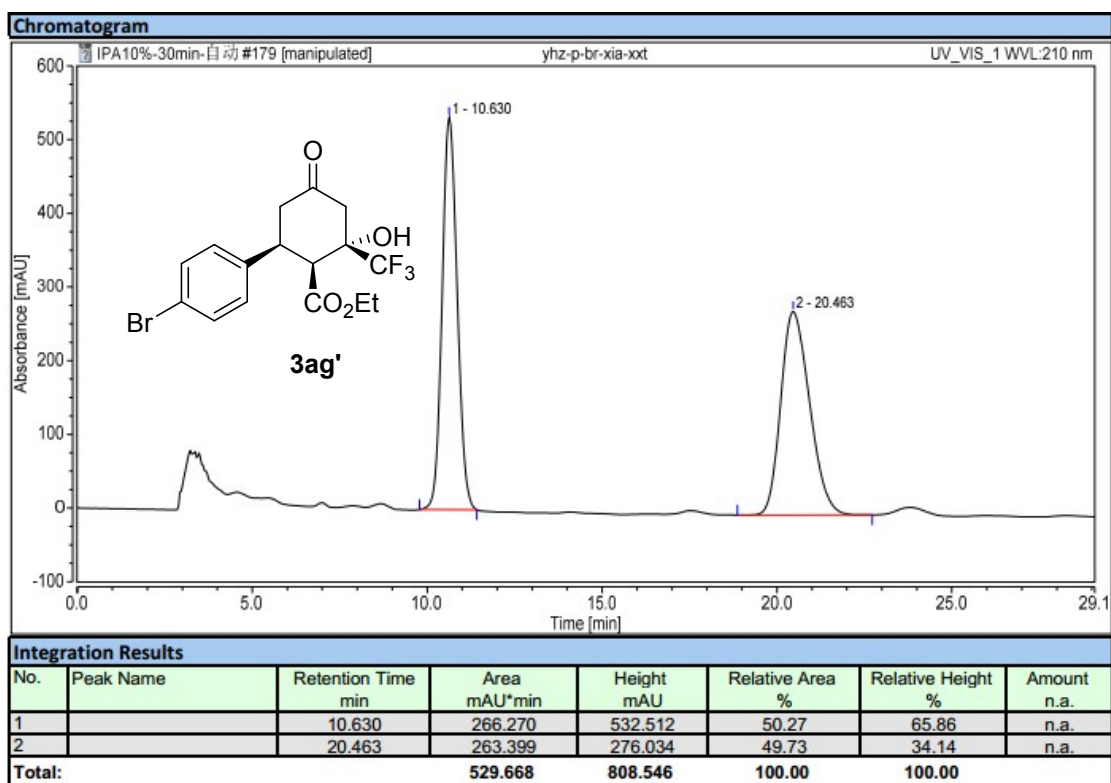
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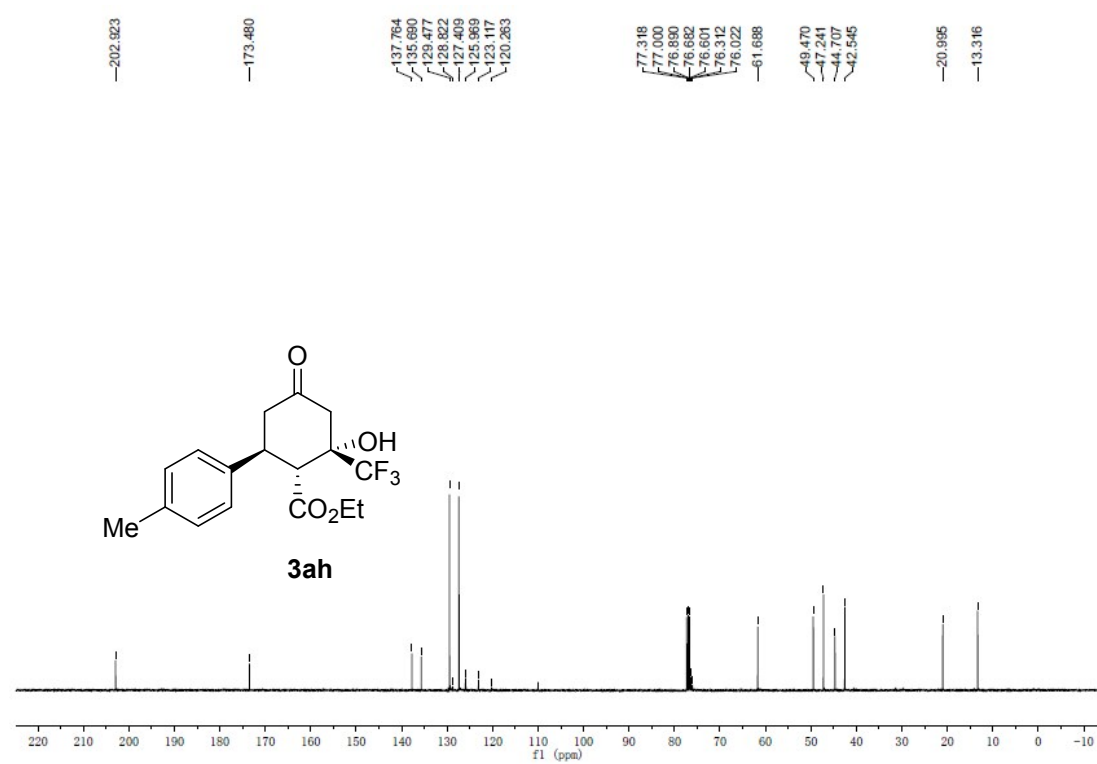
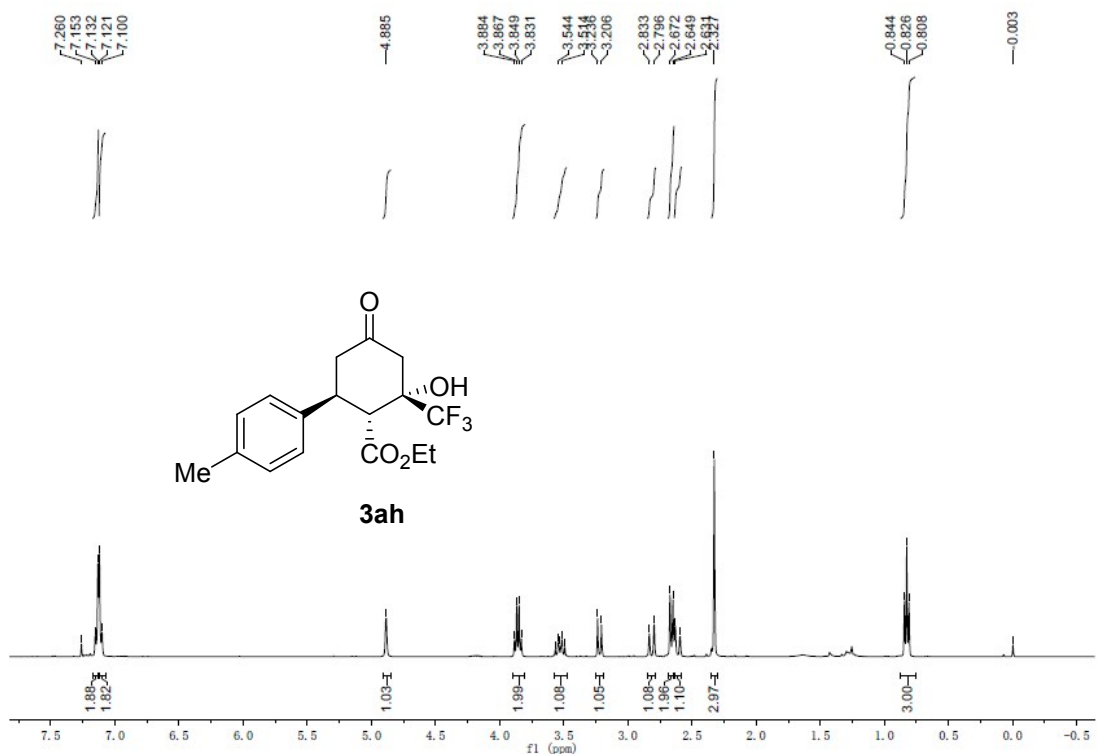
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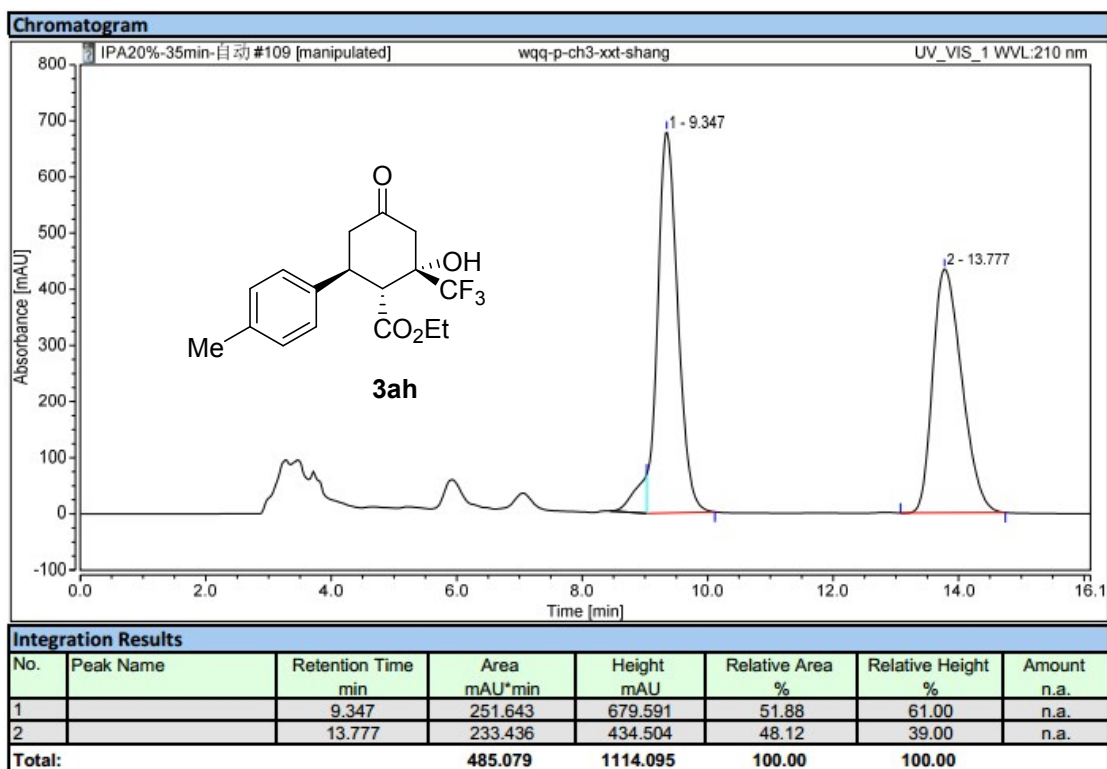
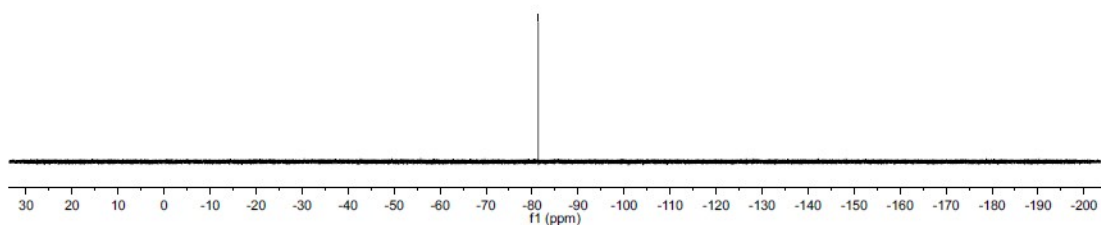
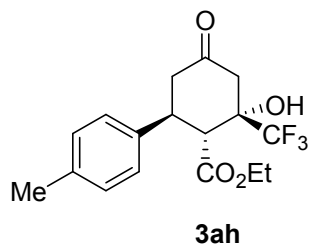
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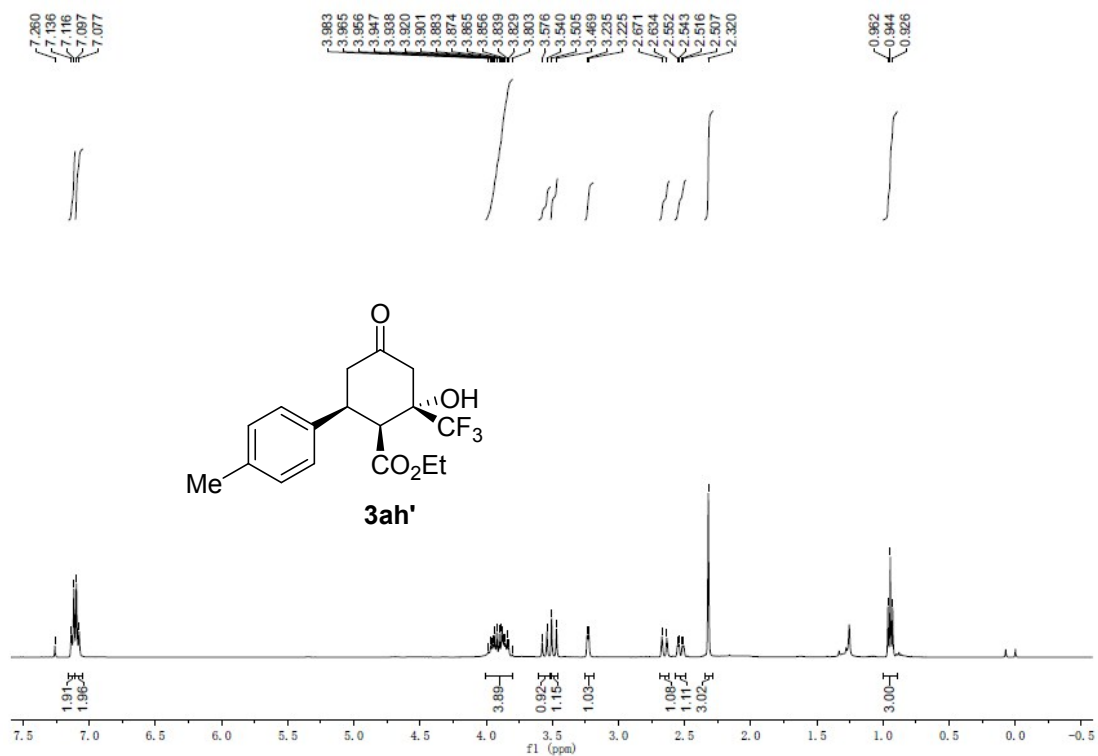
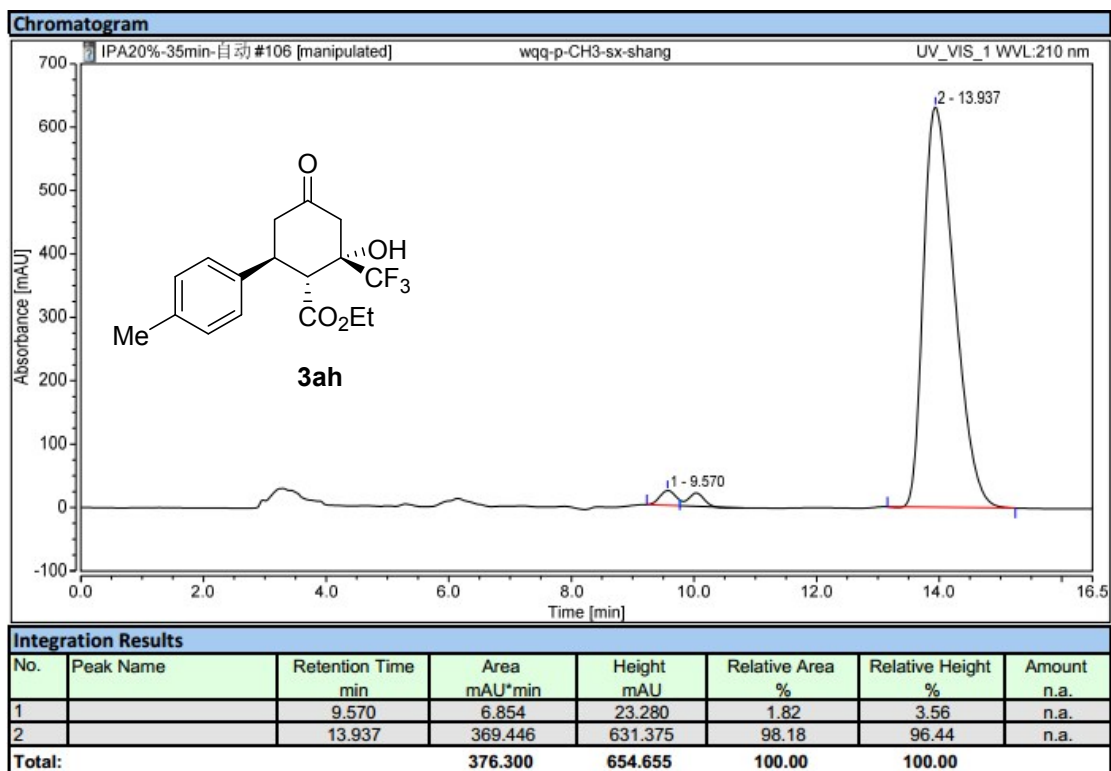






-81.359





—207.827

—169.919

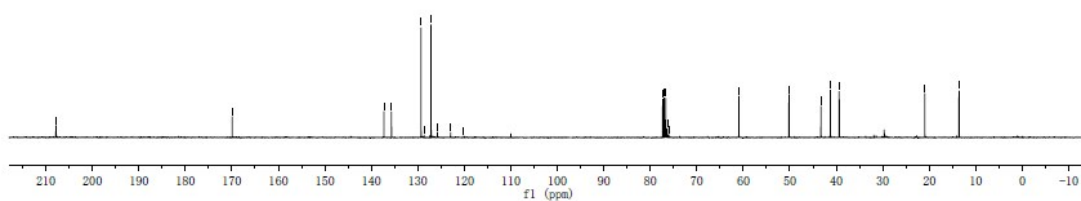
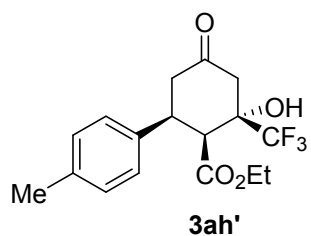
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77.000
76.910
76.682
76.607
76.009
60.944

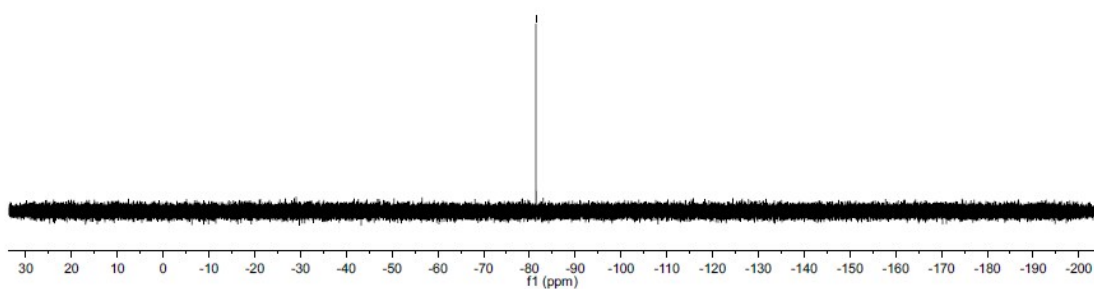
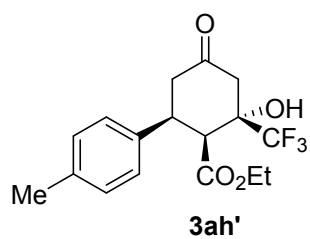
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39.363

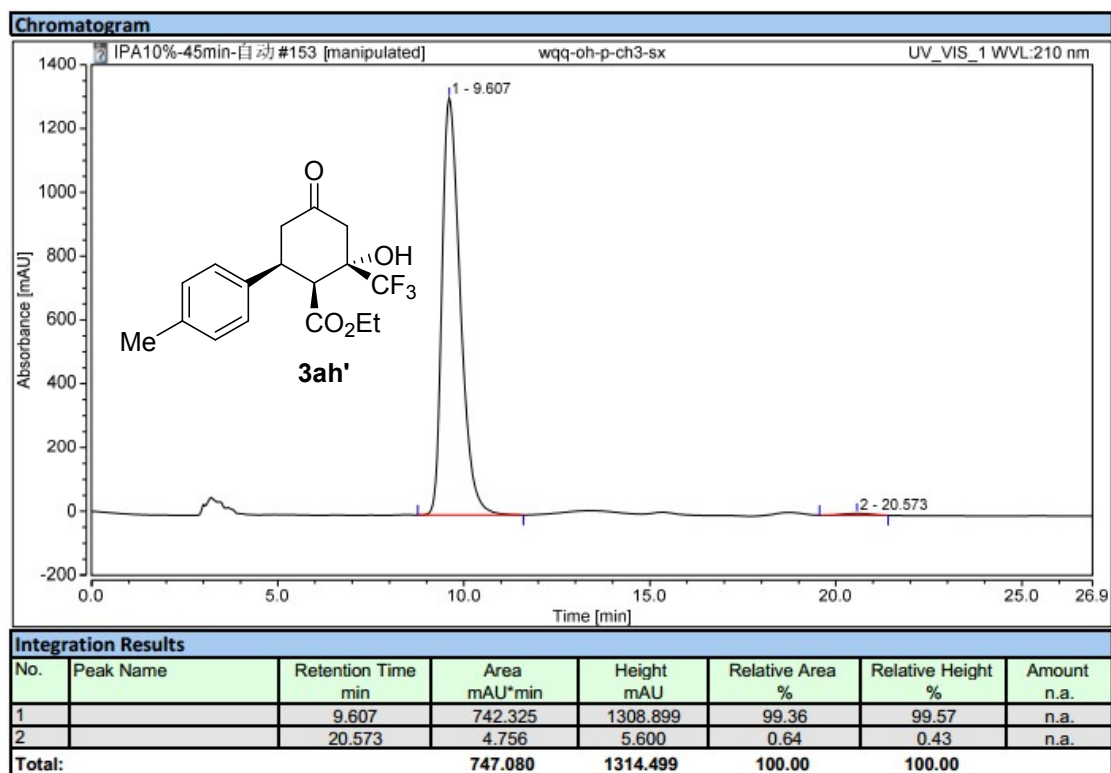
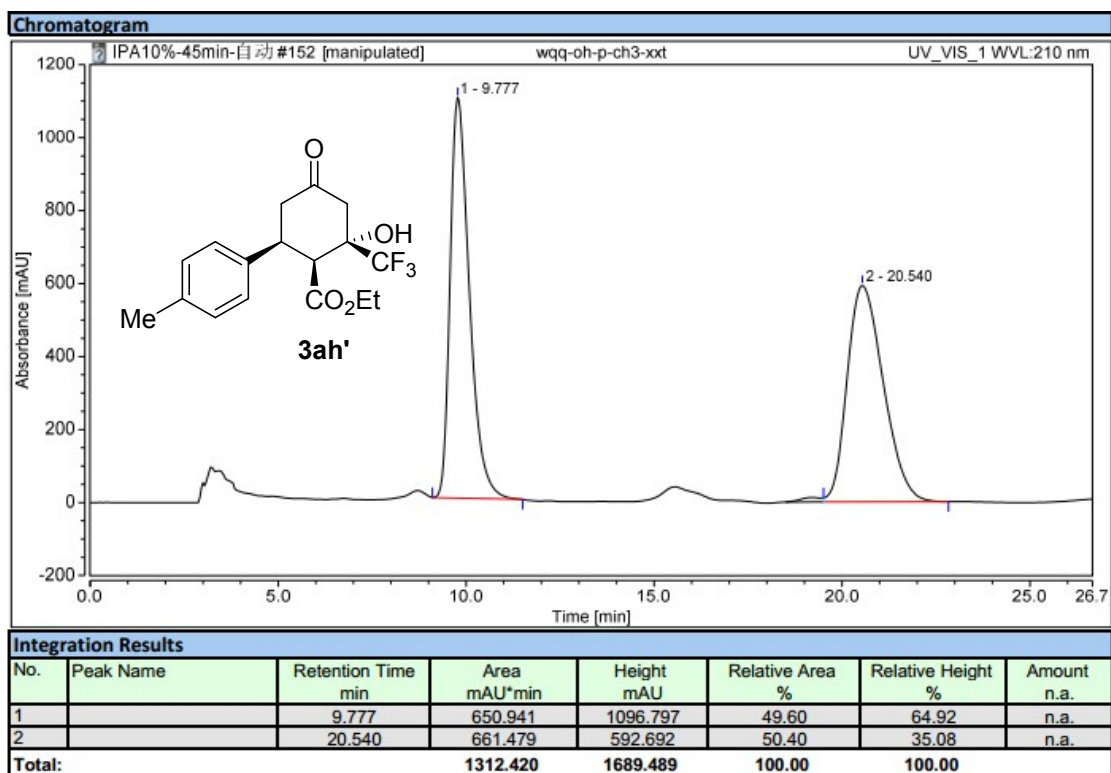
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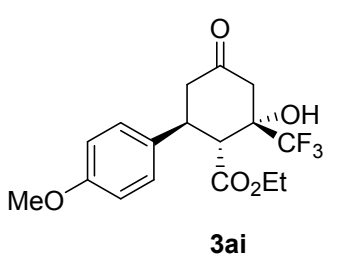
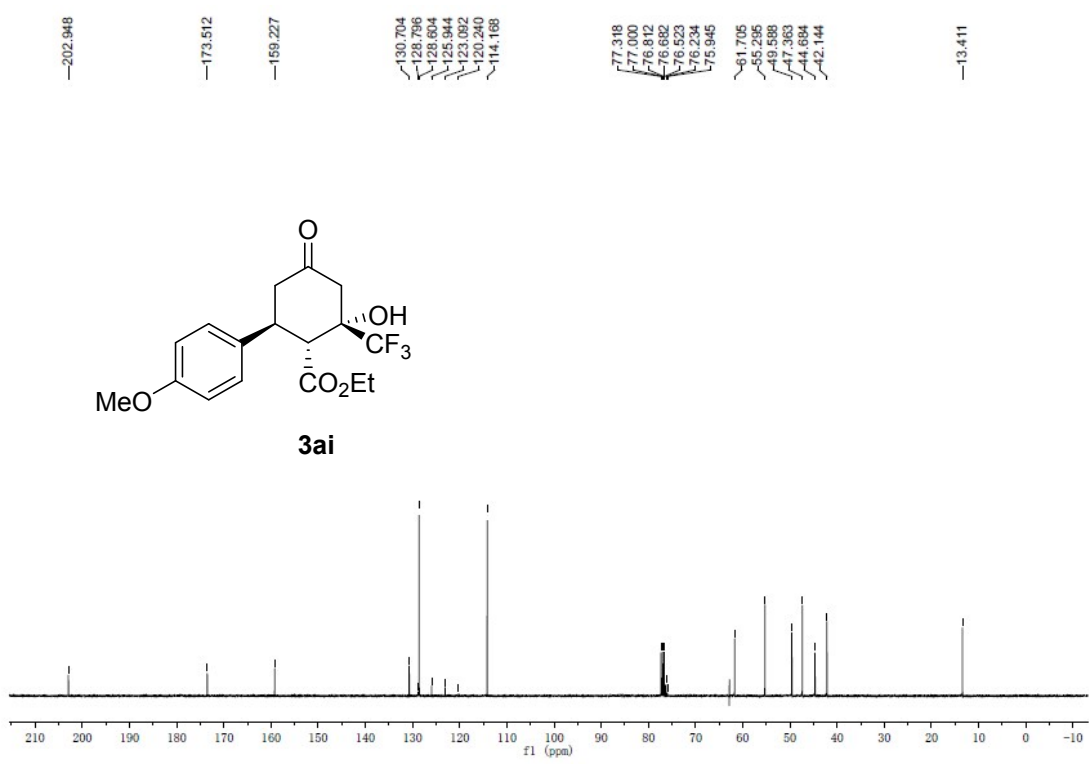
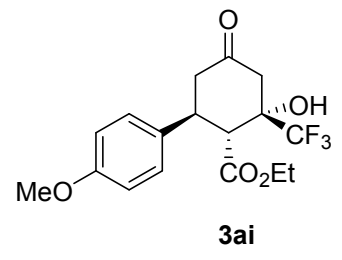
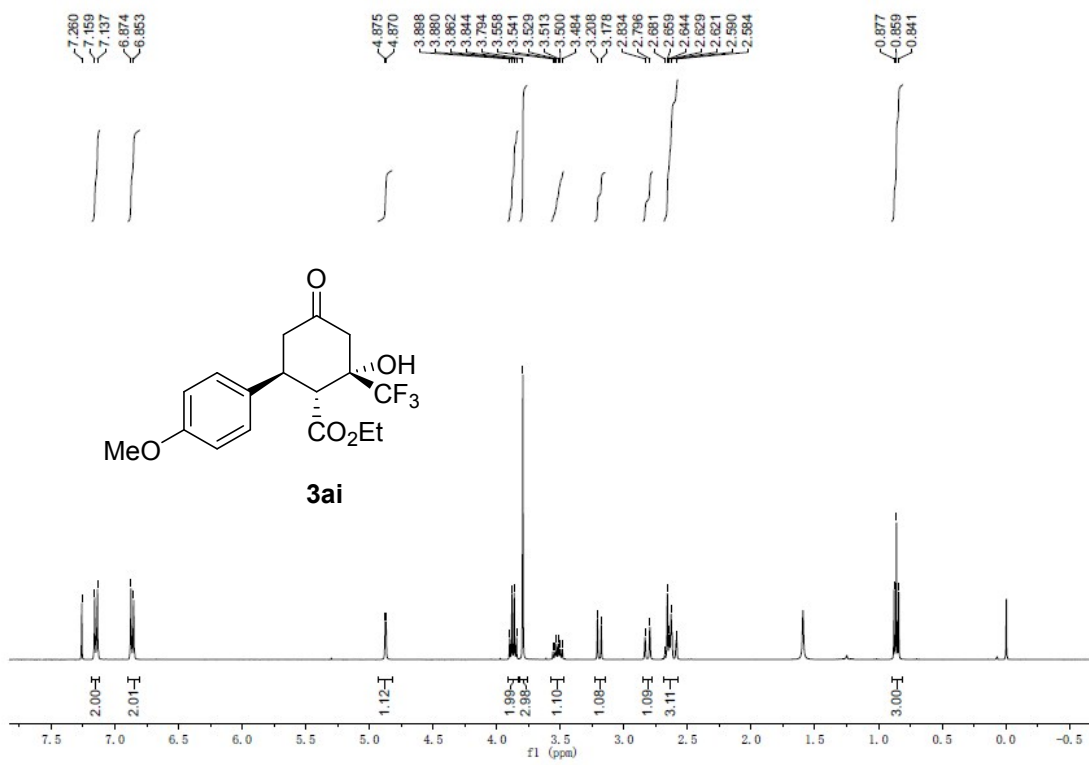
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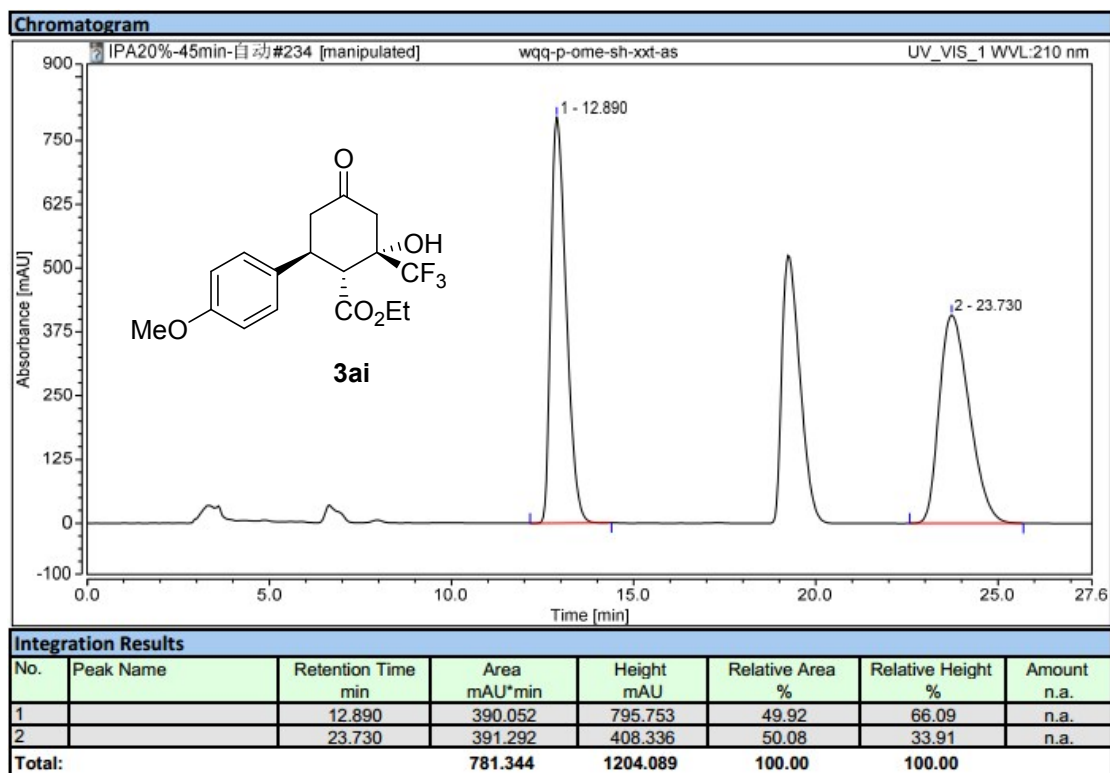
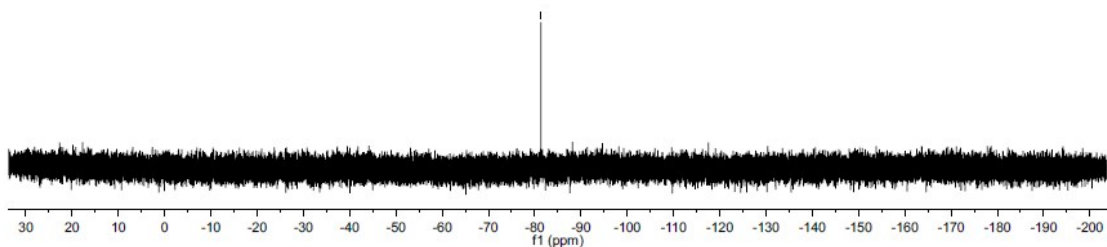
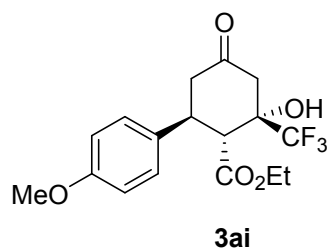
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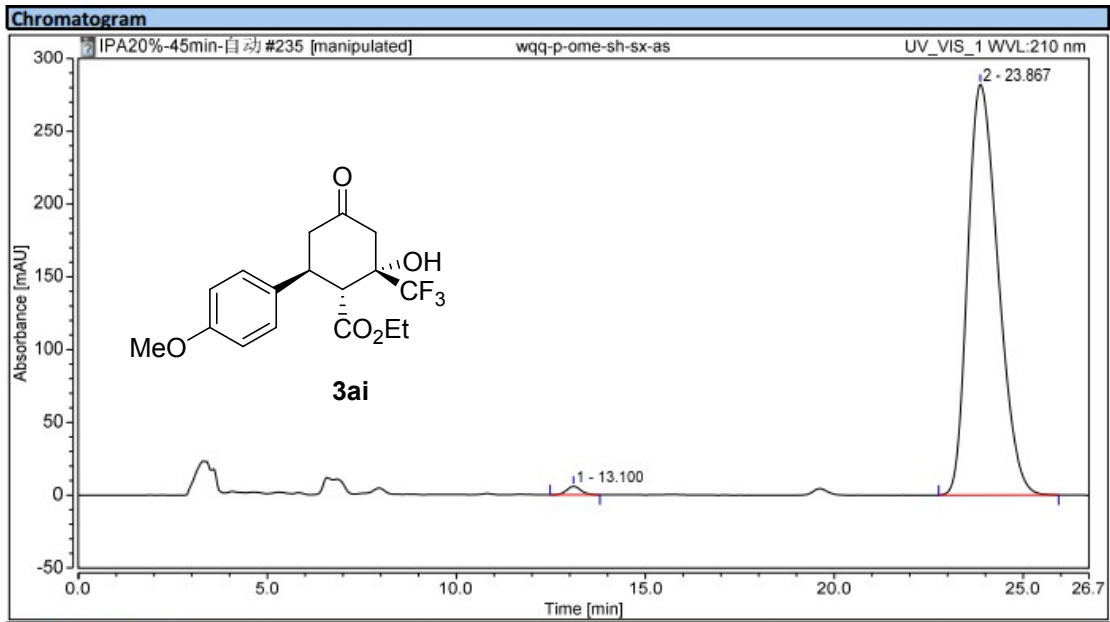






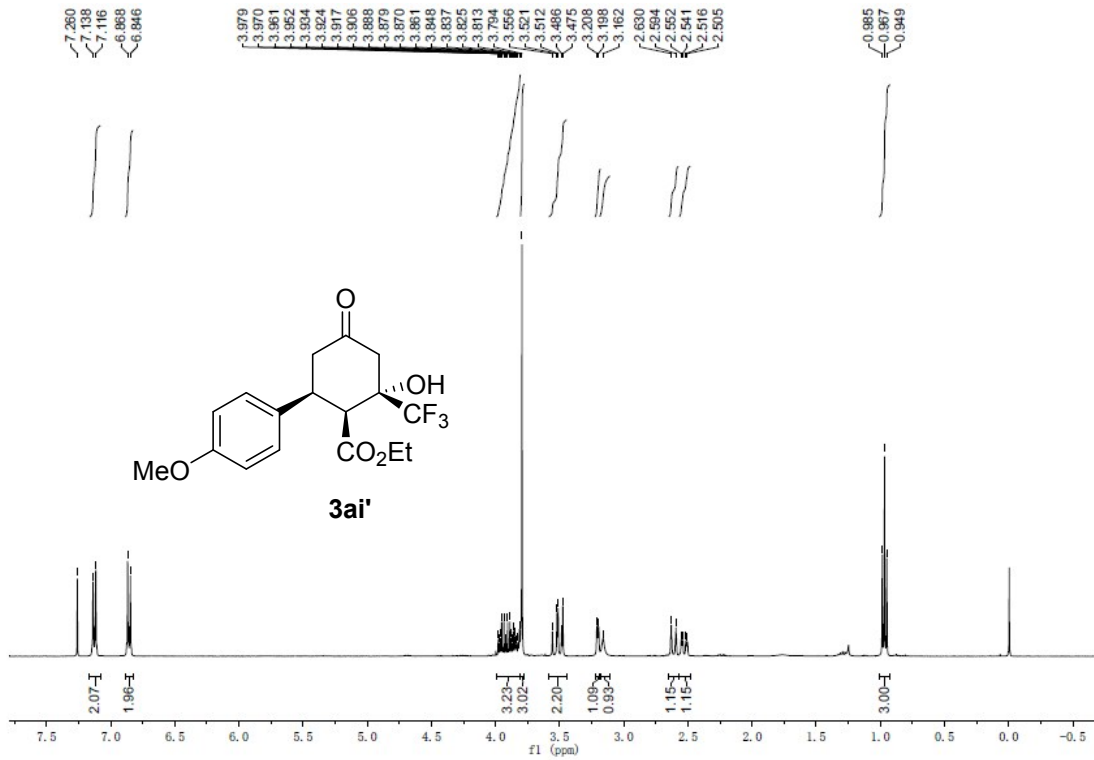
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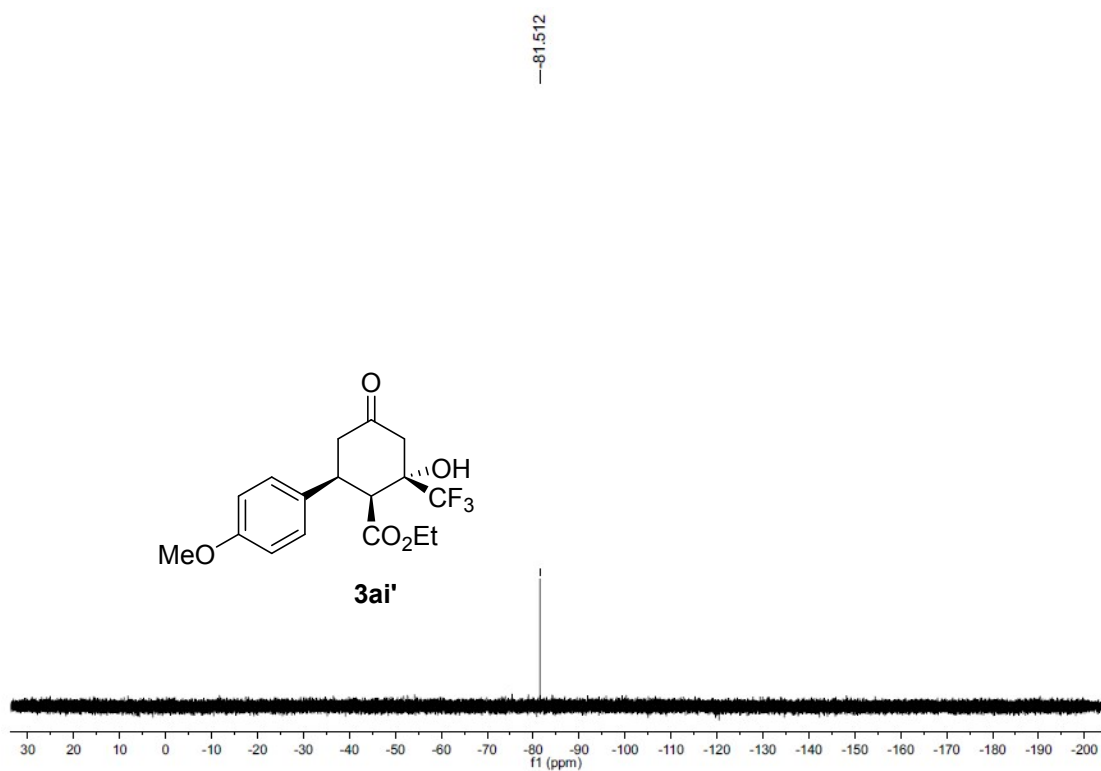
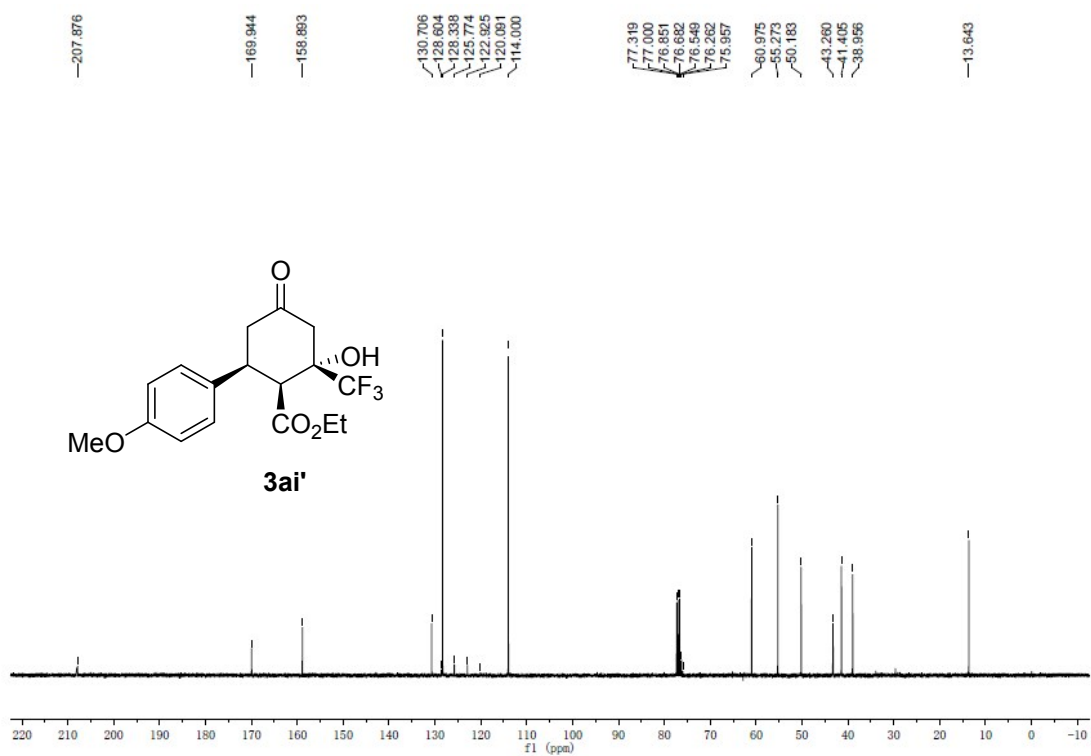


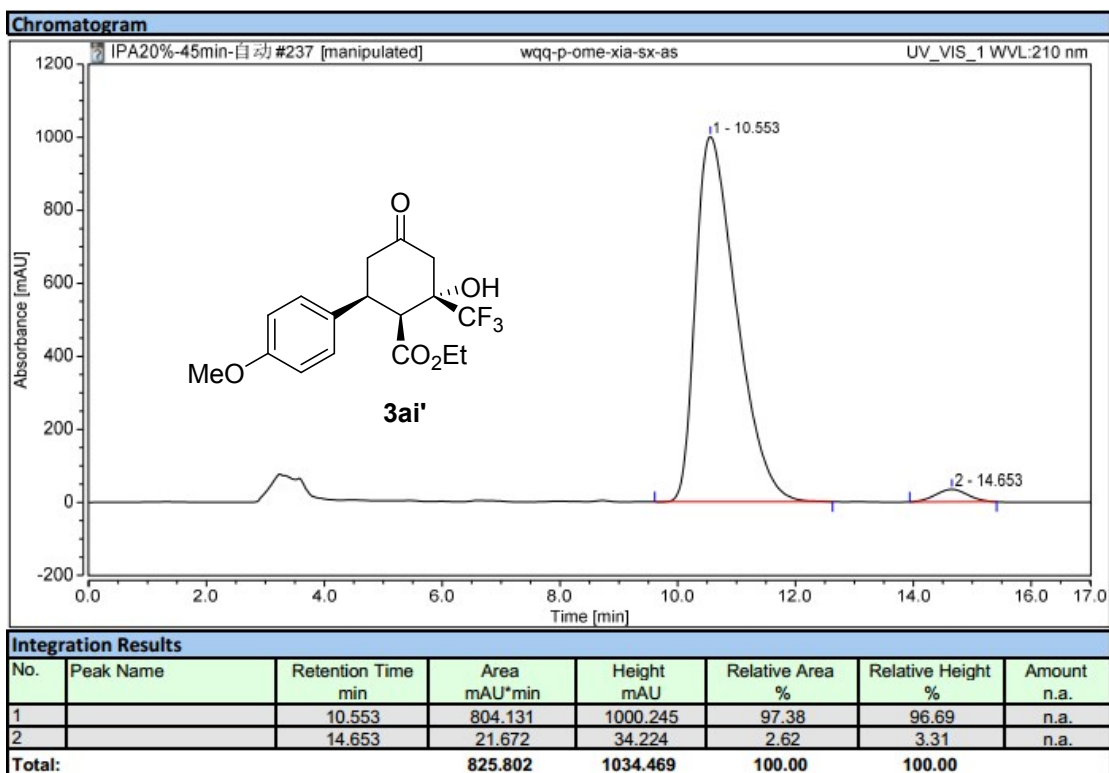
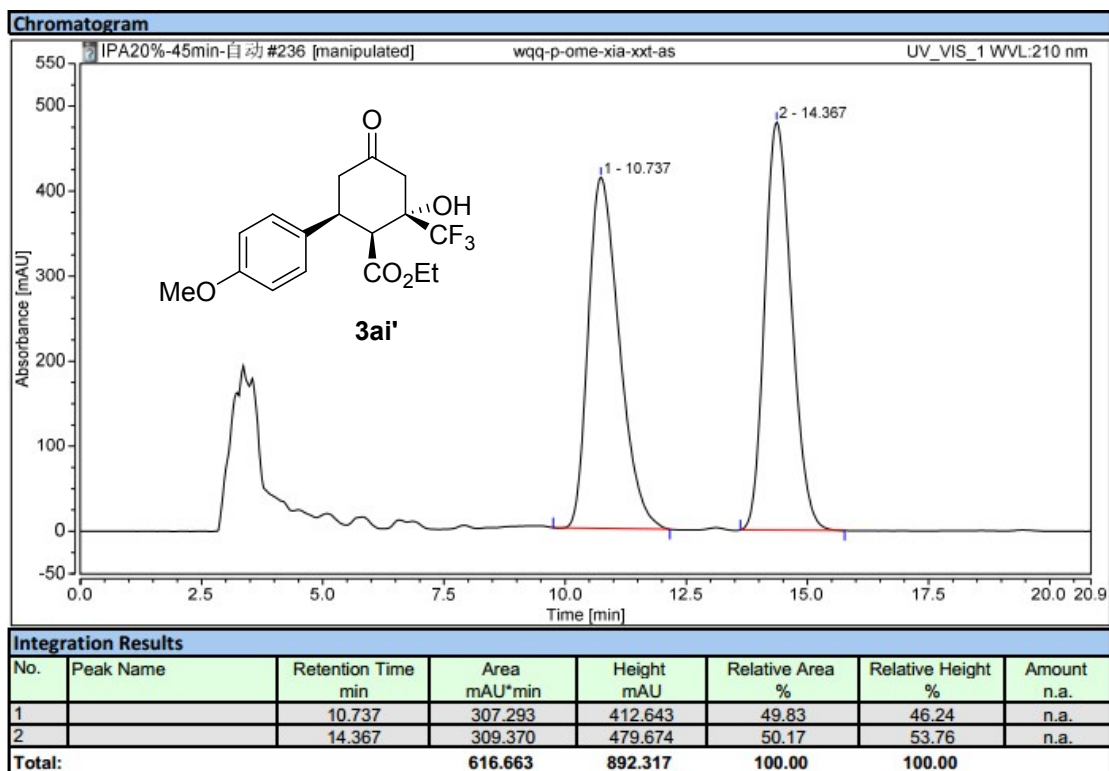


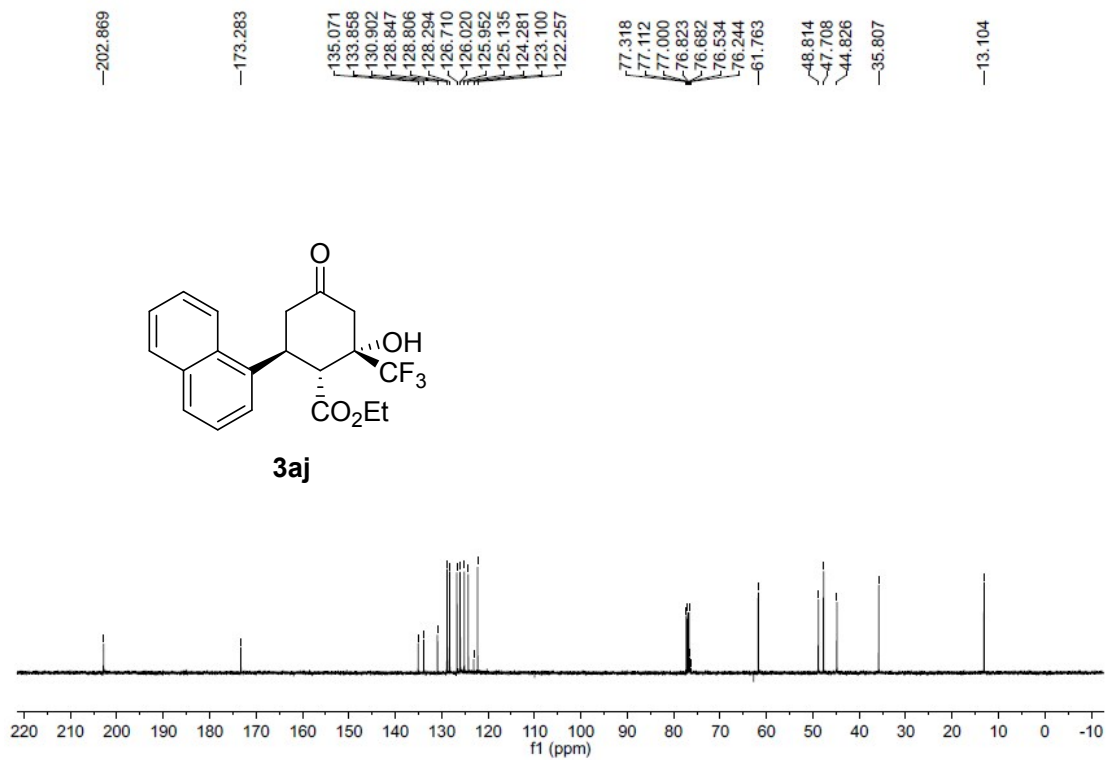
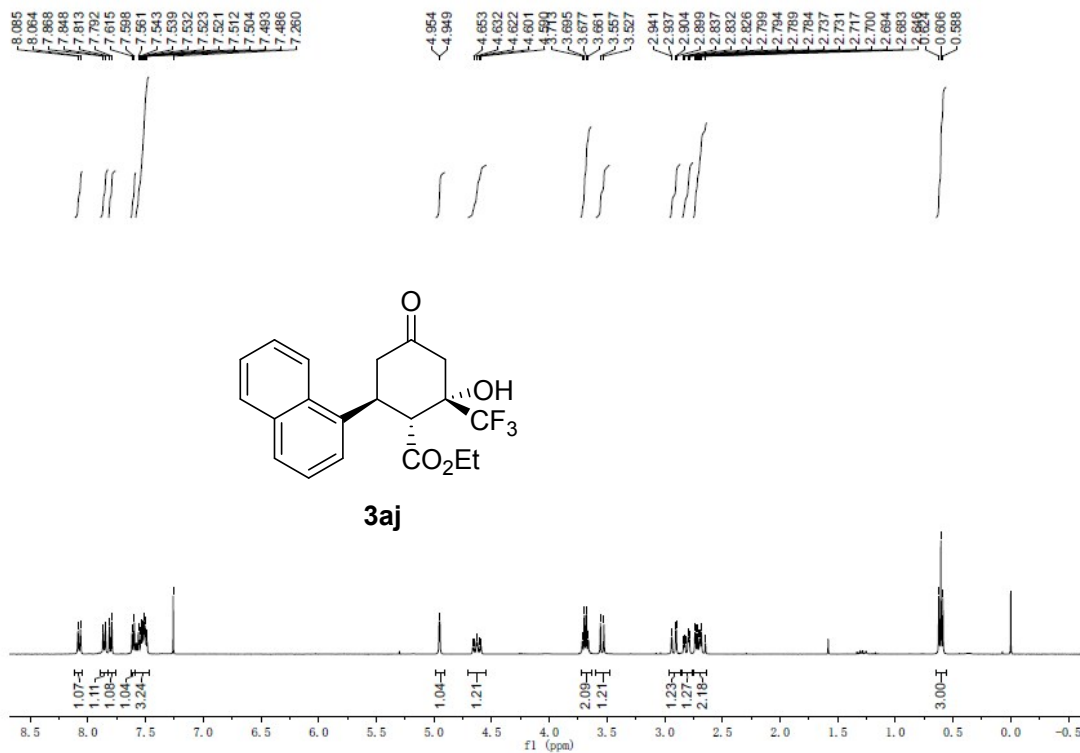
Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		13.100	2.510	5.799	0.95	2.01	n.a.
2		23.867	262.979	282.220	99.05	97.99	n.a.
Total:			265.489	288.018	100.00	100.00	

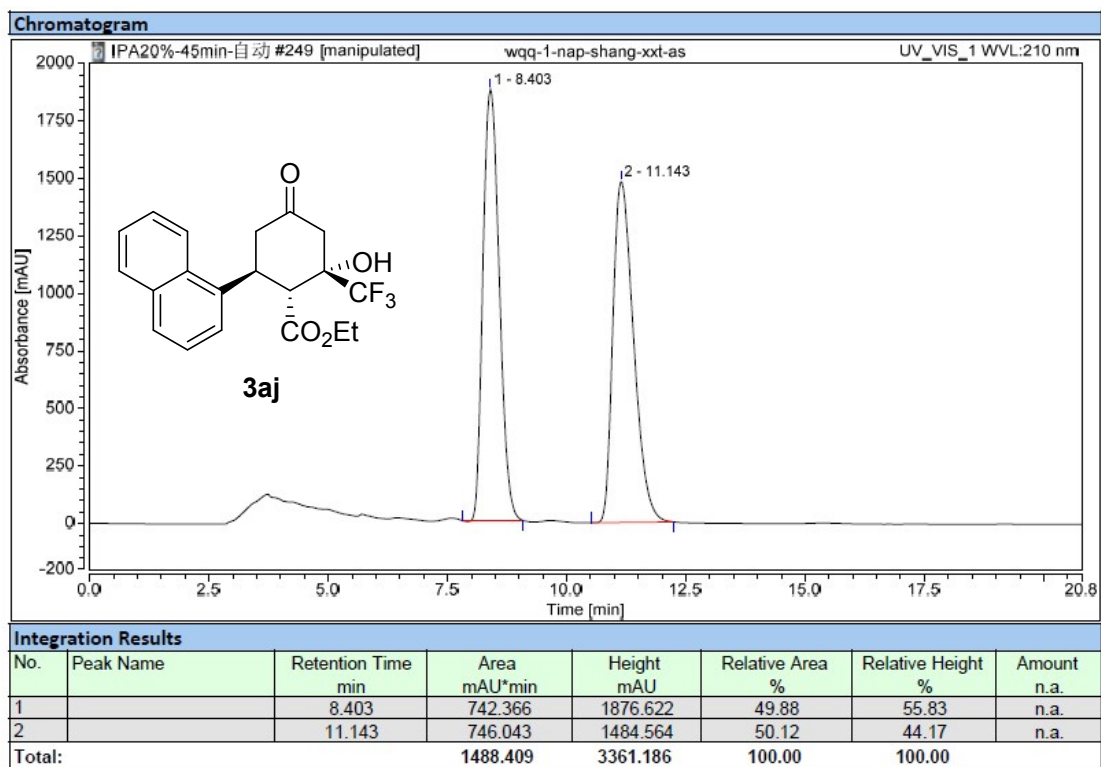
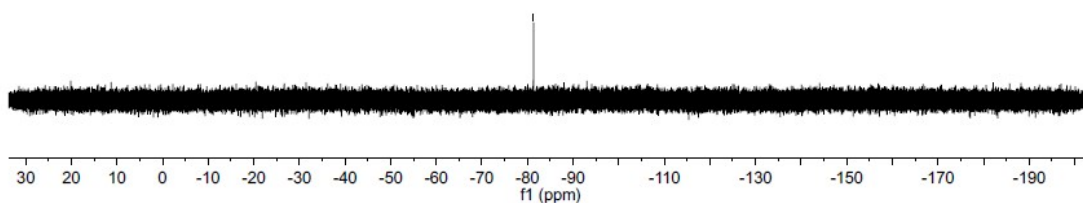
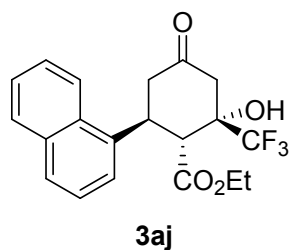


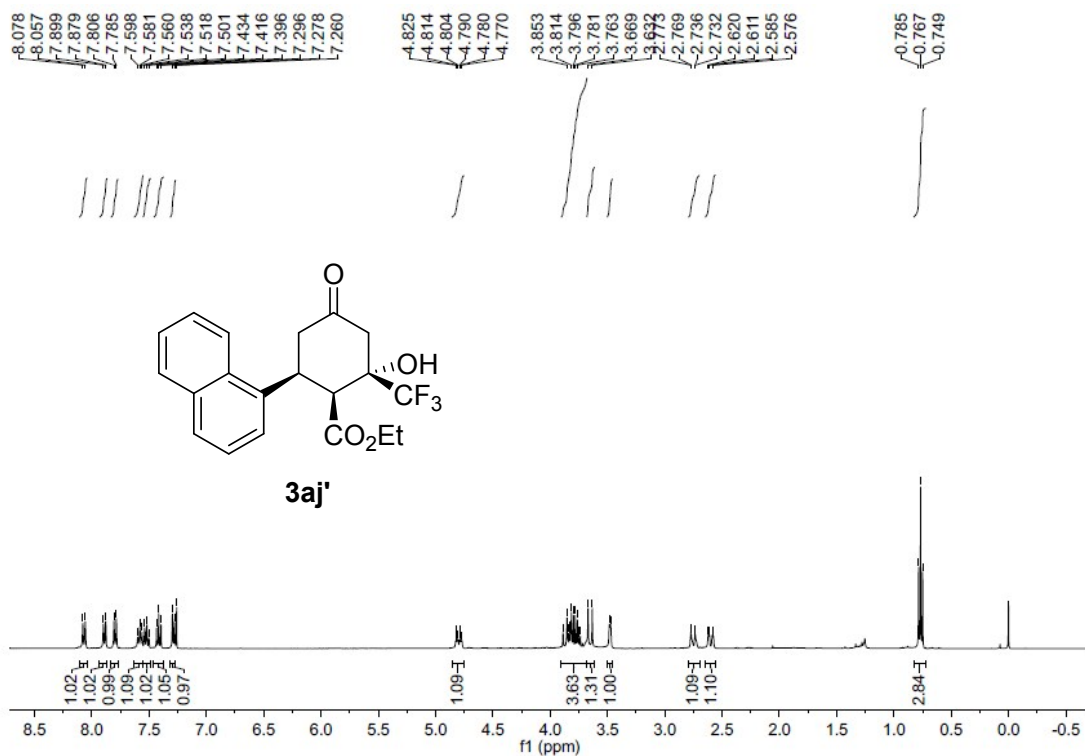
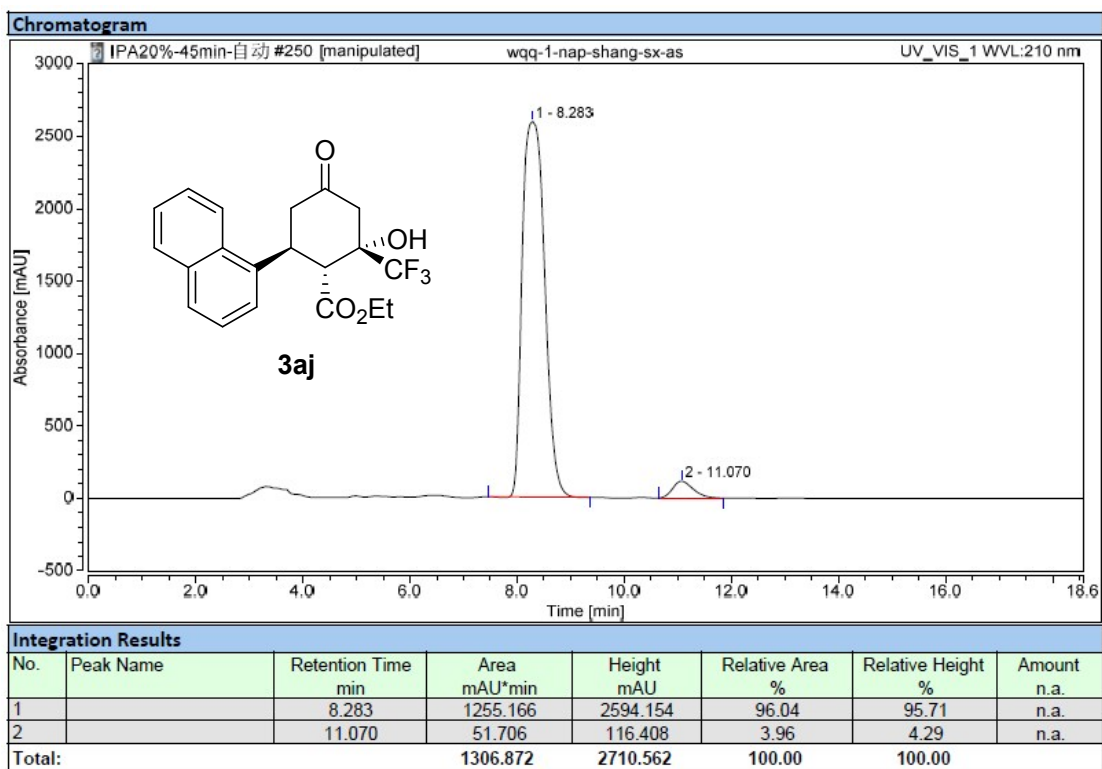


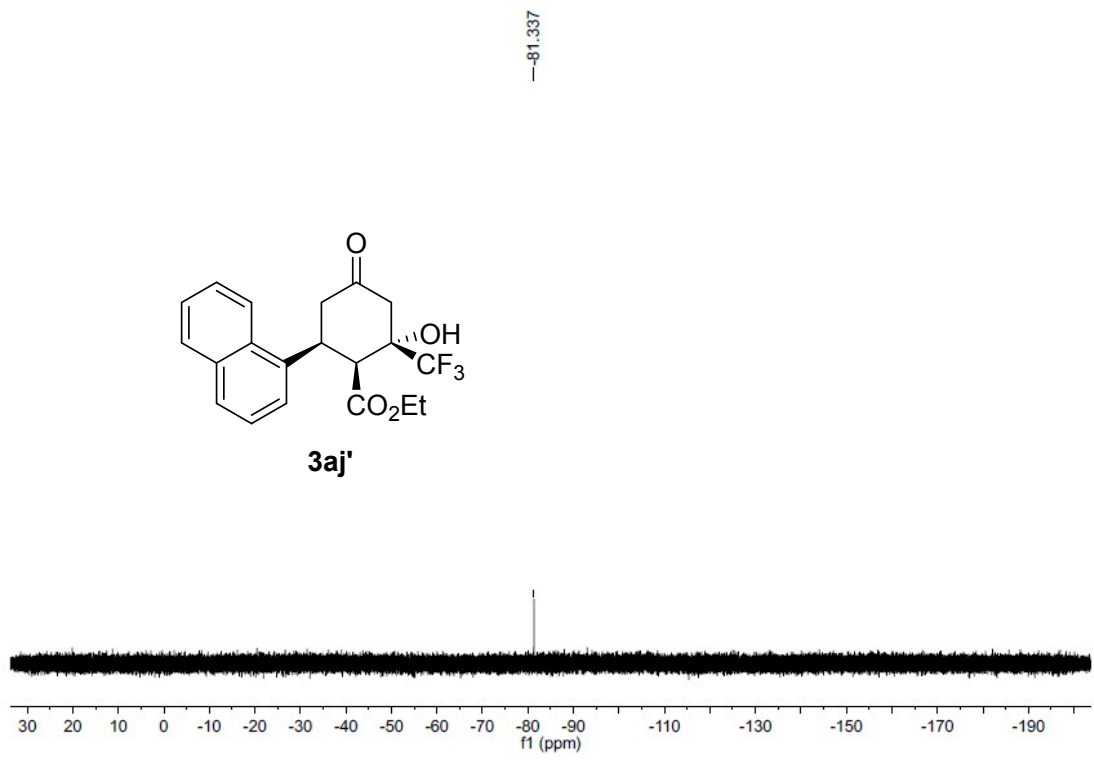
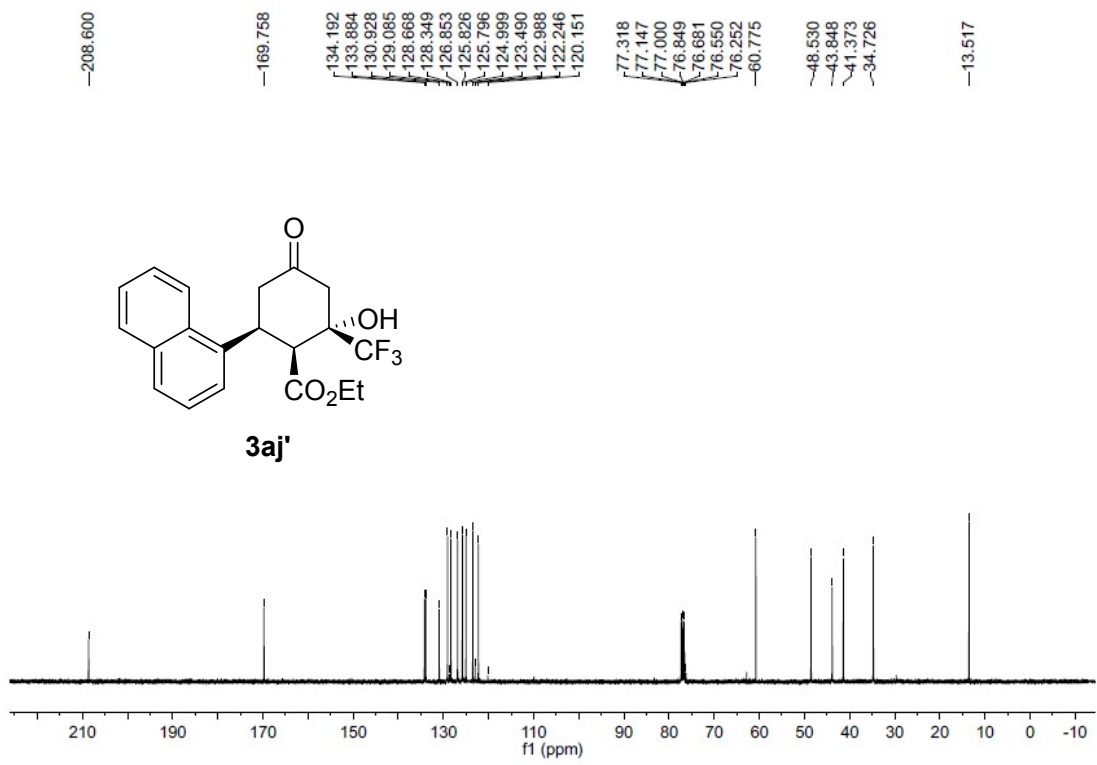


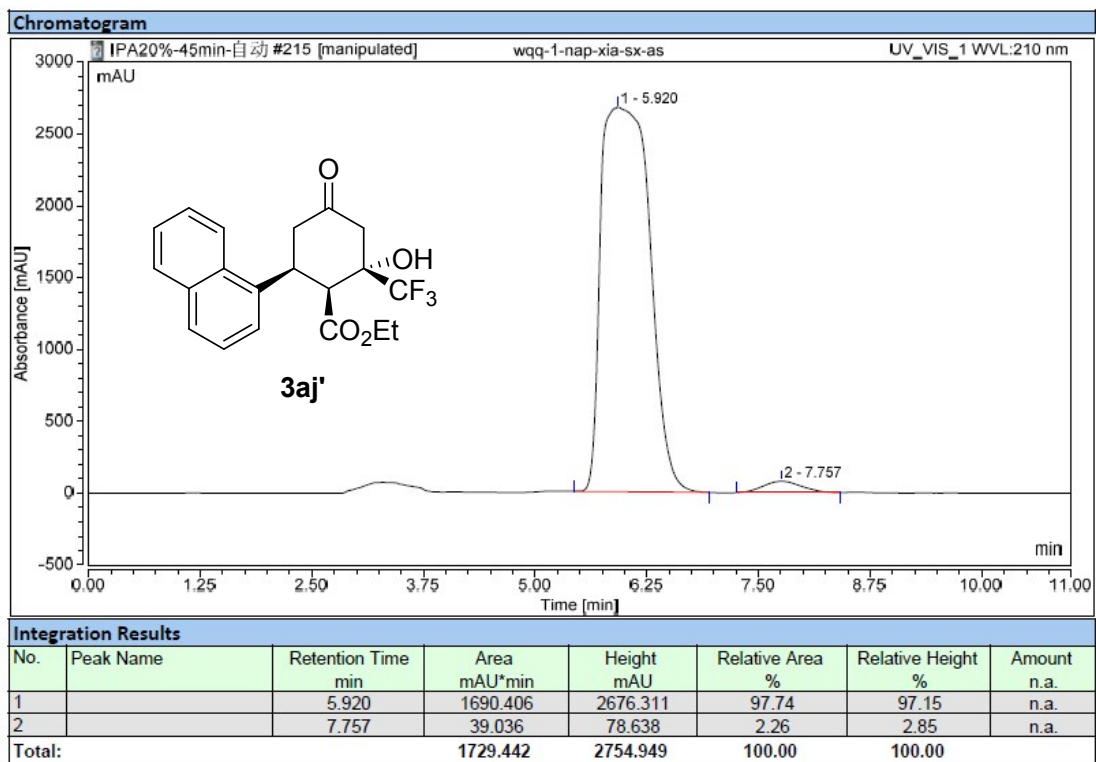
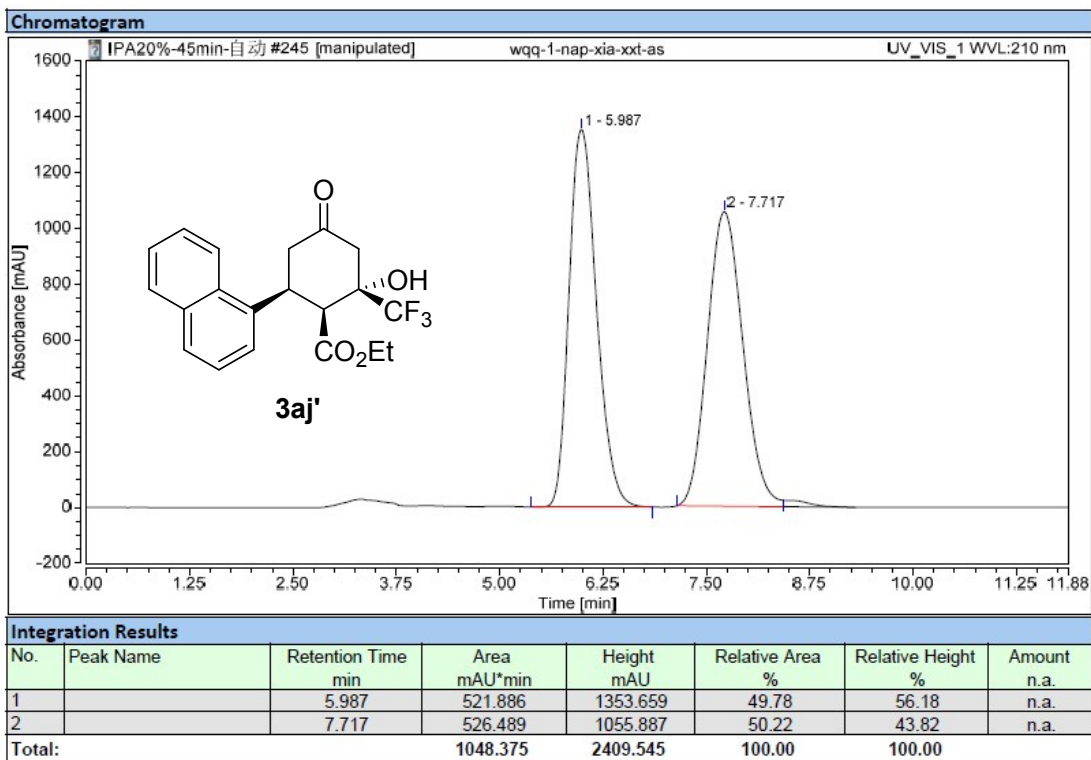


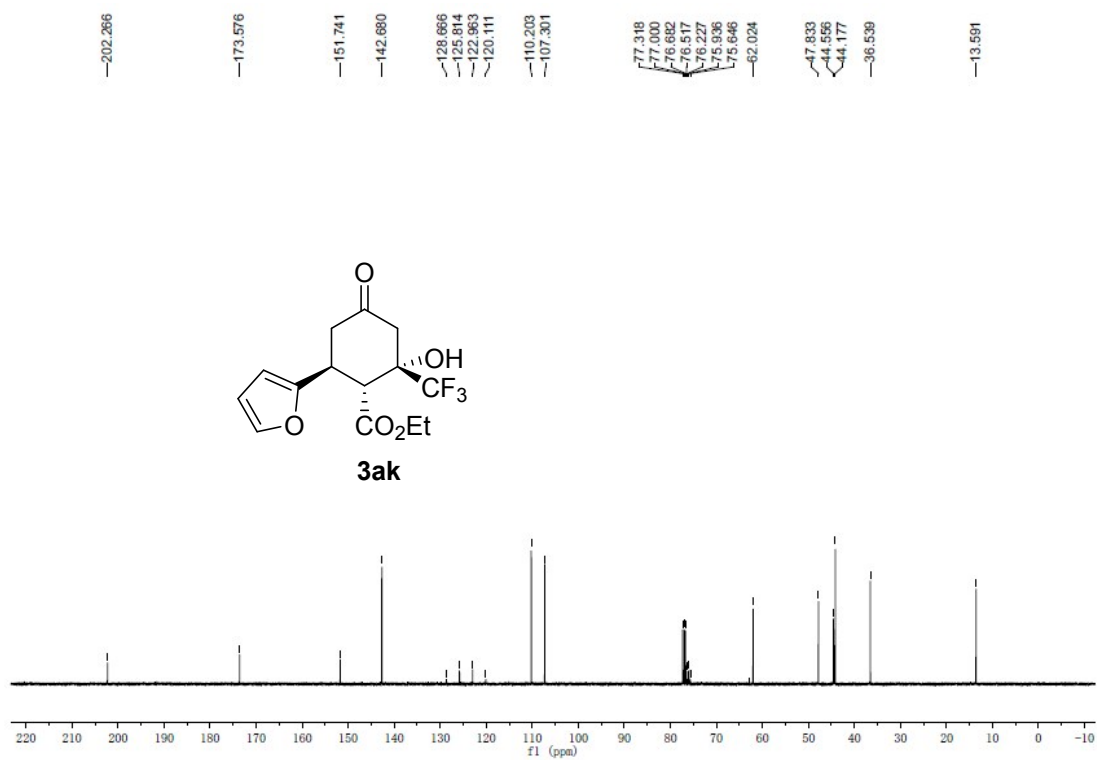
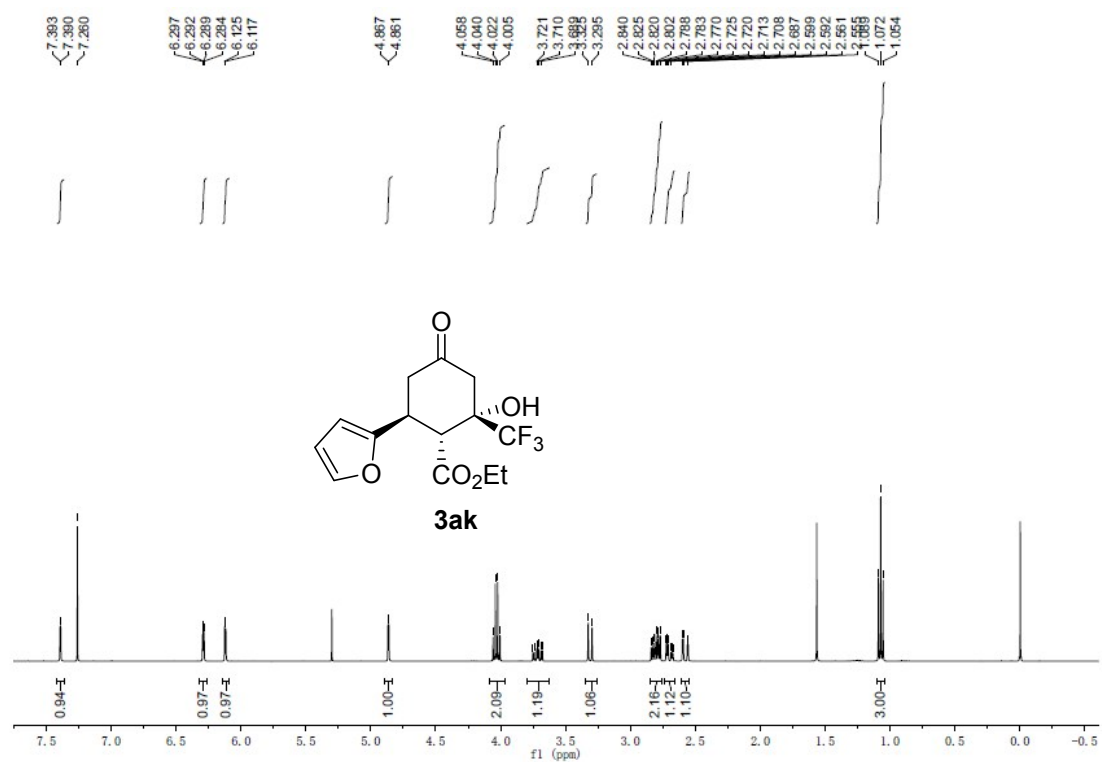
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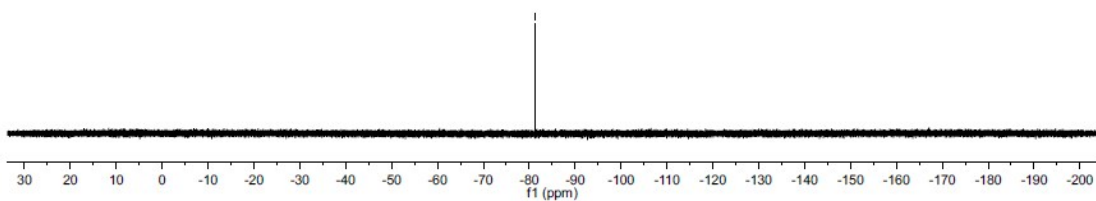
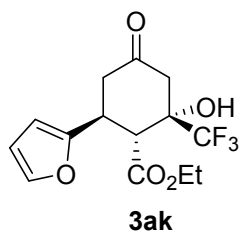




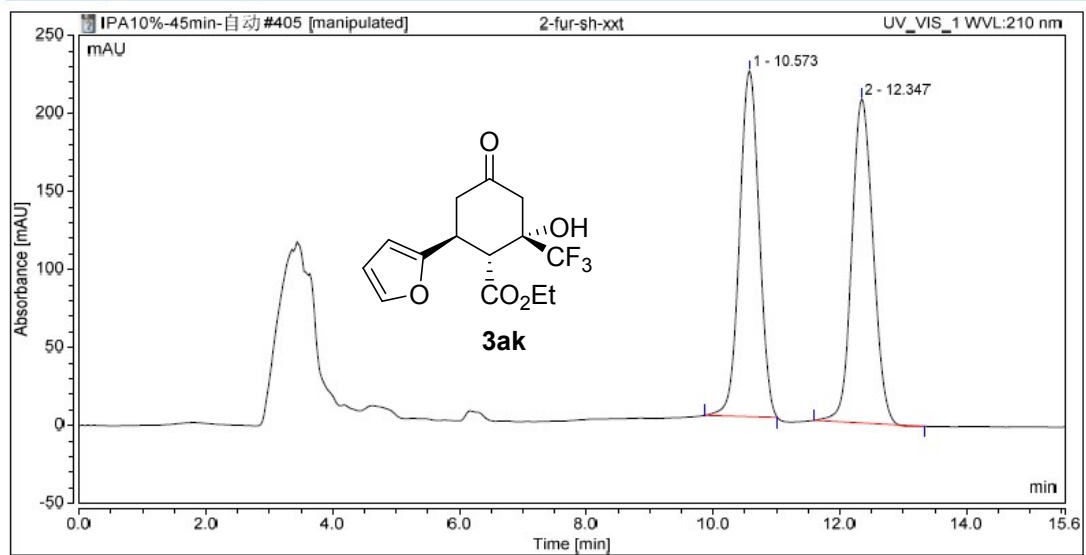




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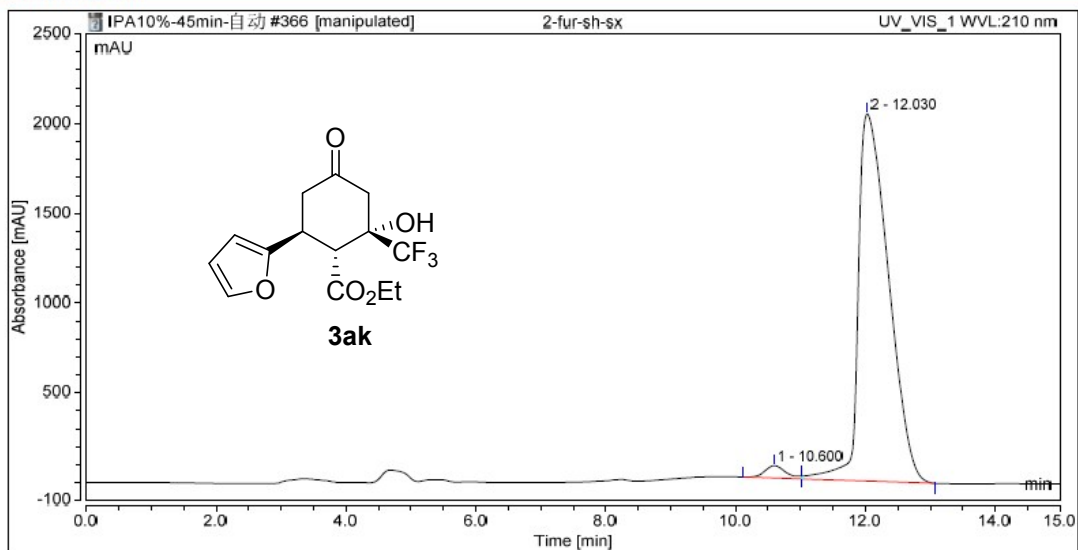


Chromatogram



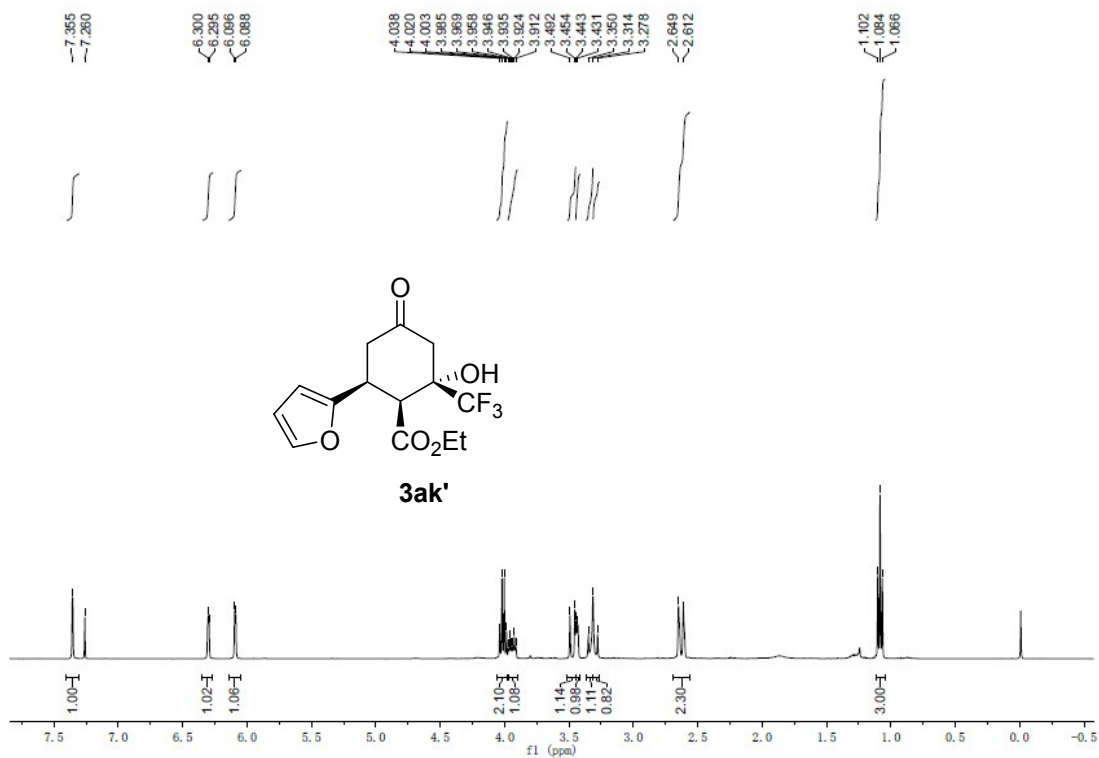
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		10.573	79.179	221.792	49.48	51.64	n.a.
2		12.347	80.834	207.677	50.52	48.36	n.a.
Total:			160.013	429.469	100.00	100.00	

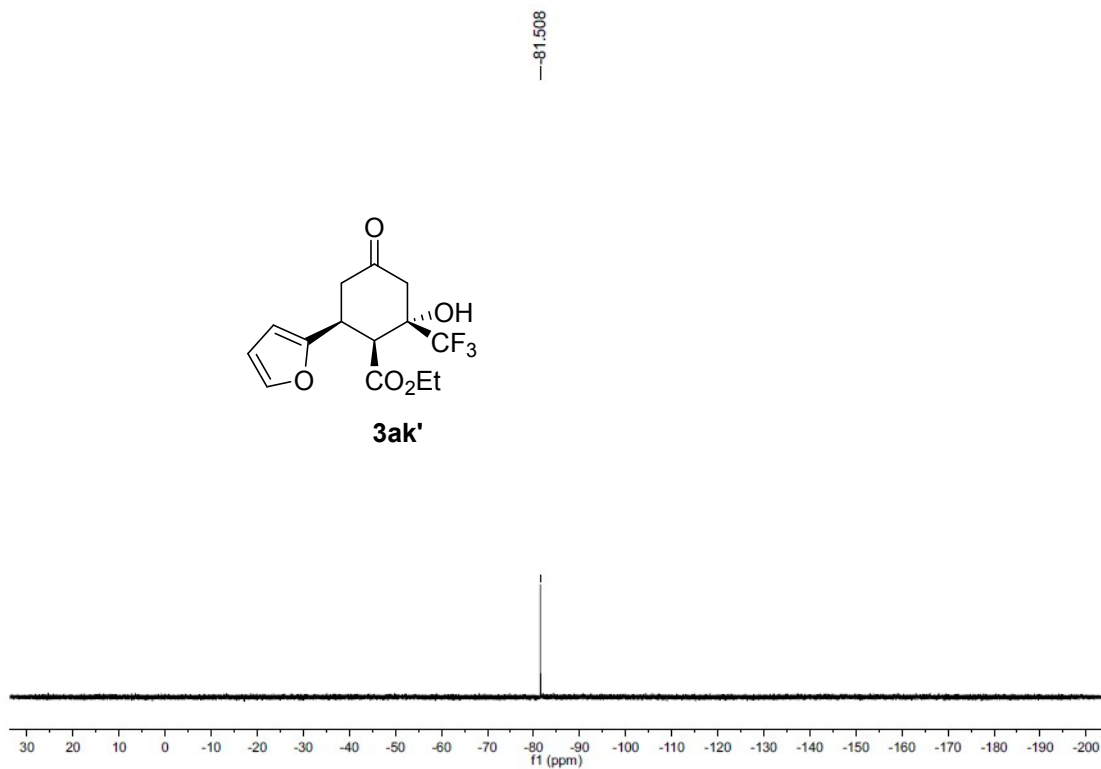
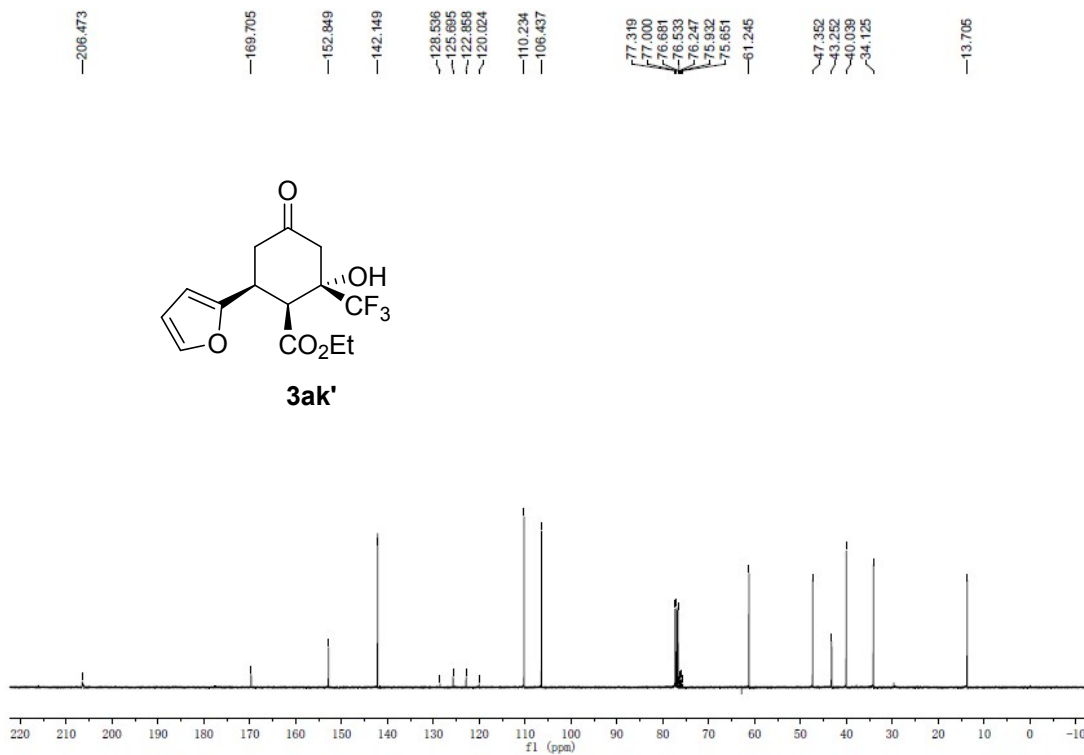
Chromatogram

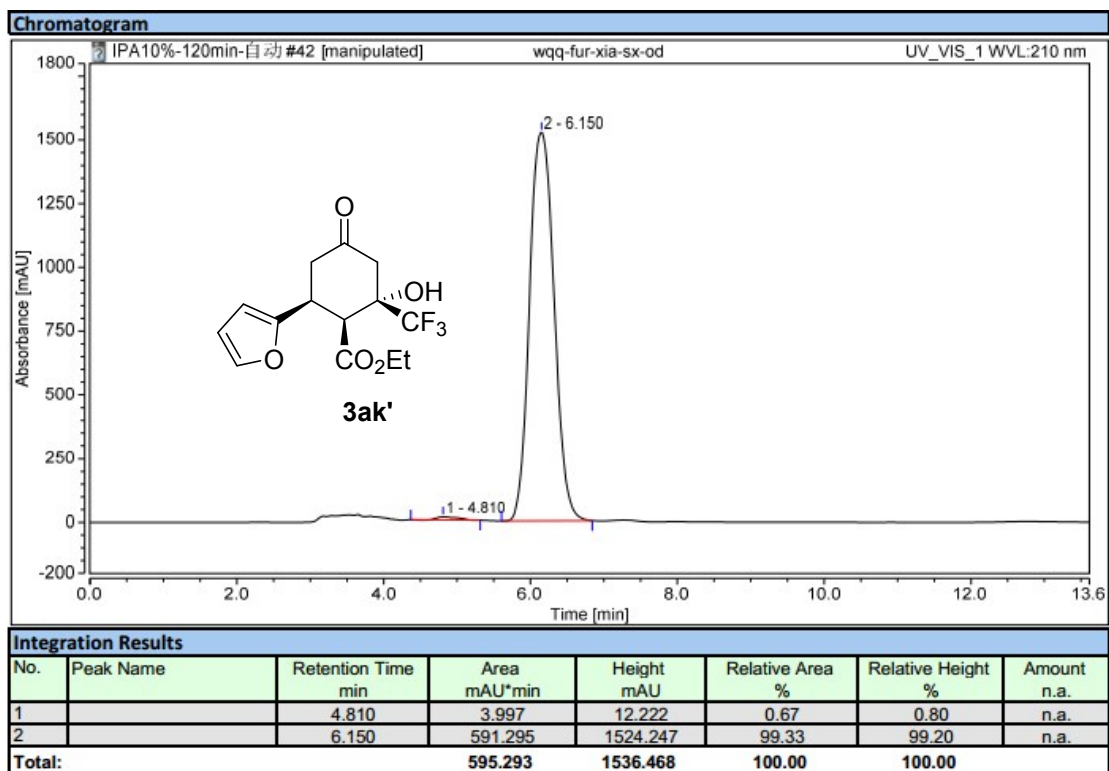
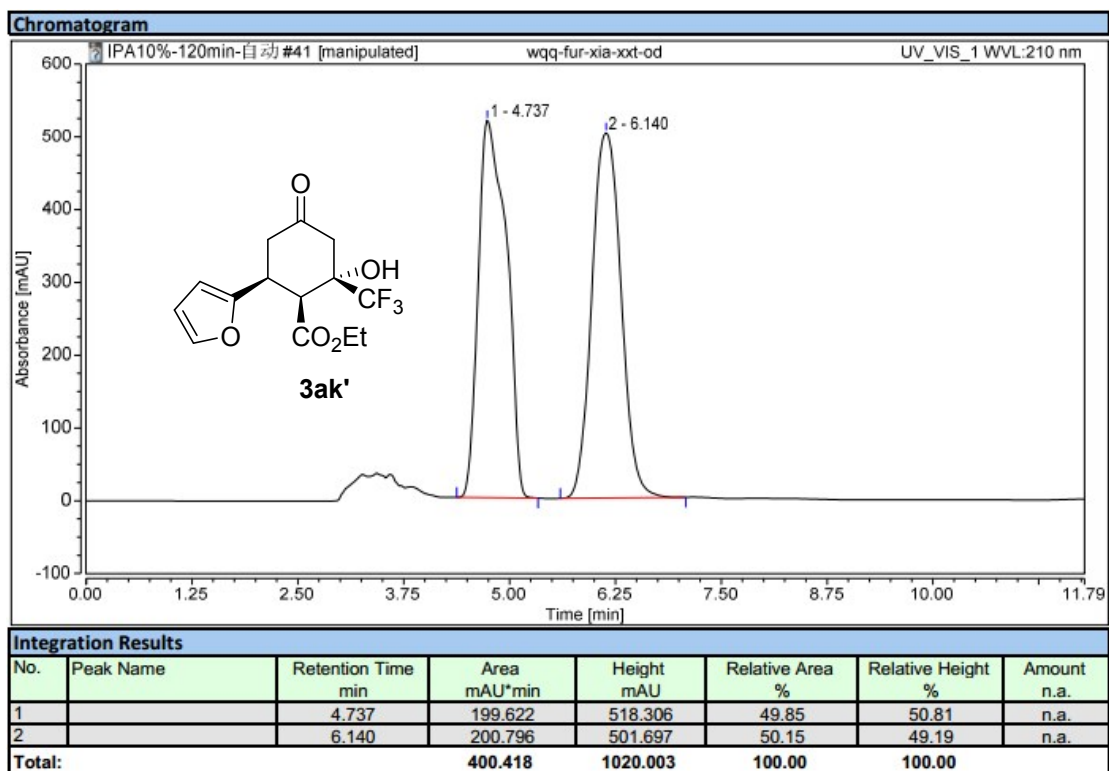


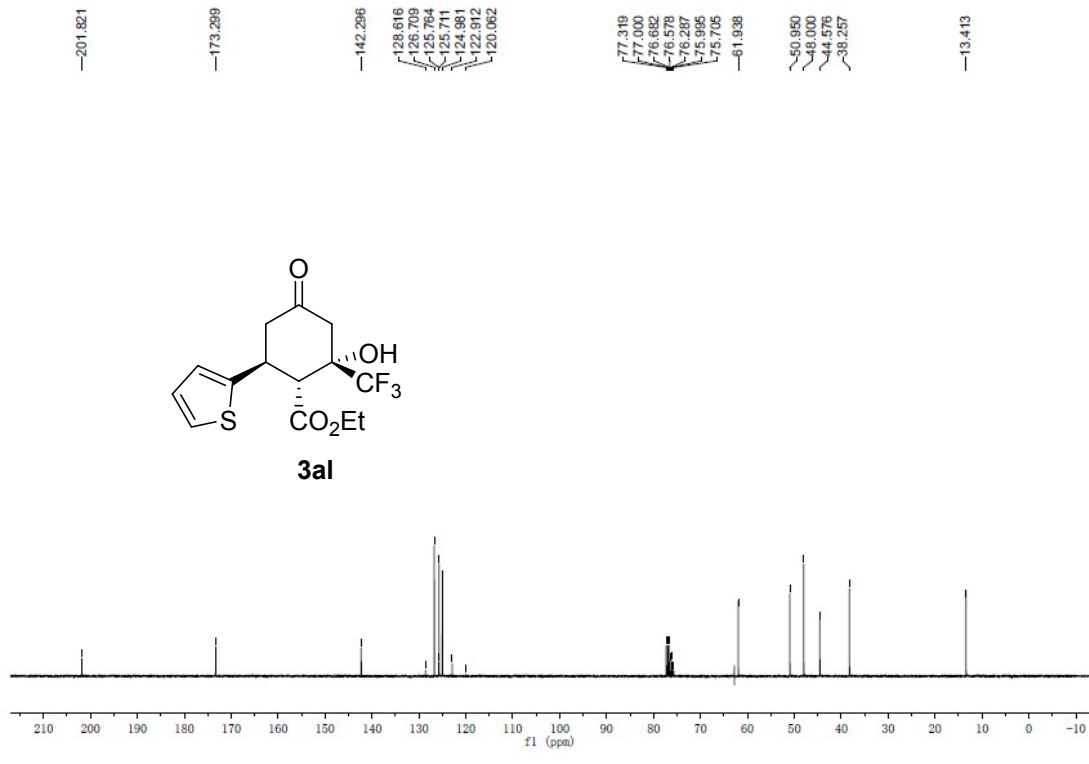
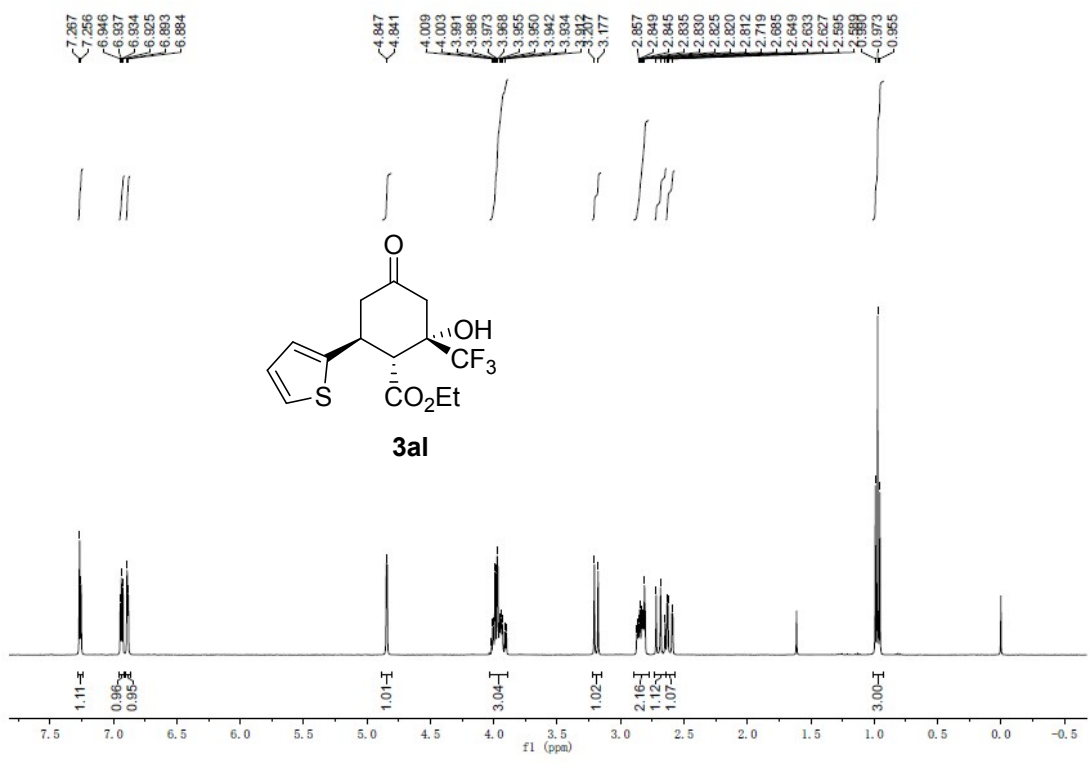
Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		10.600	25.404	68.630	2.24	3.24	n.a.
2		12.030	1108.243	2047.450	97.76	96.76	n.a.
Total:			1133.648	2116.080	100.00	100.00	

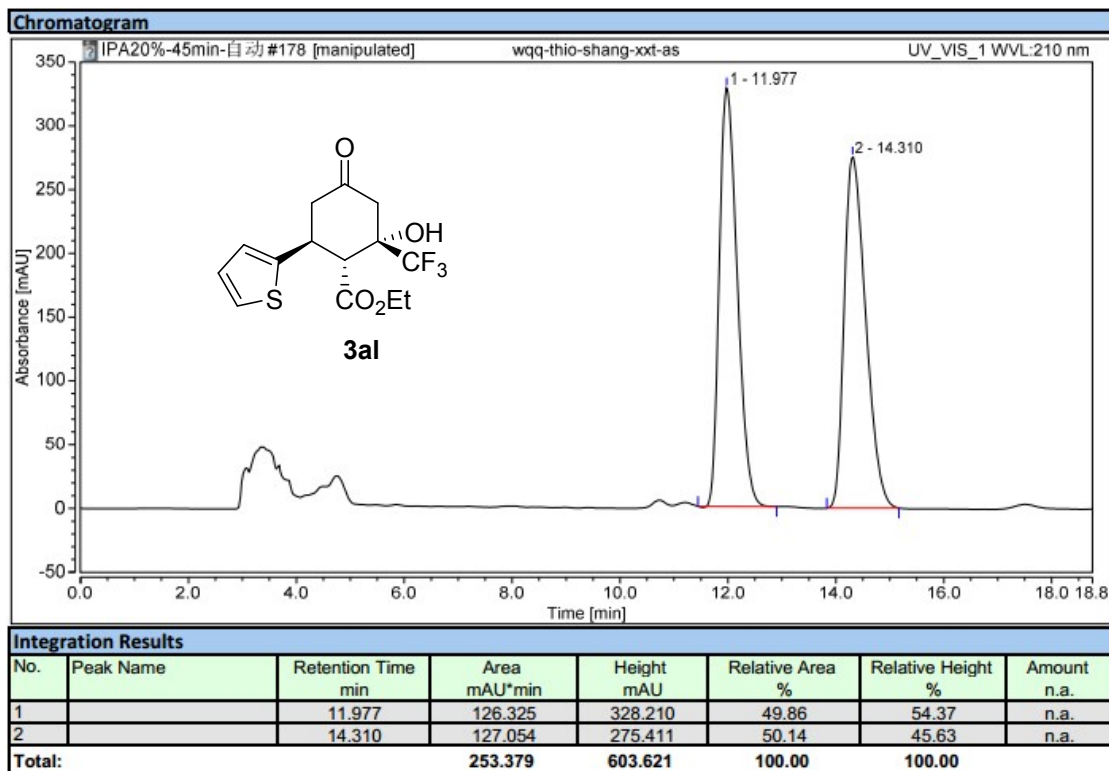
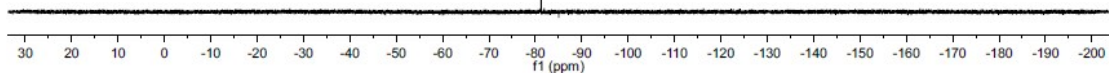
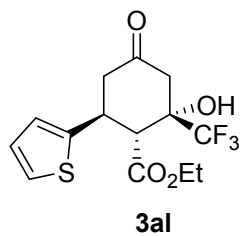


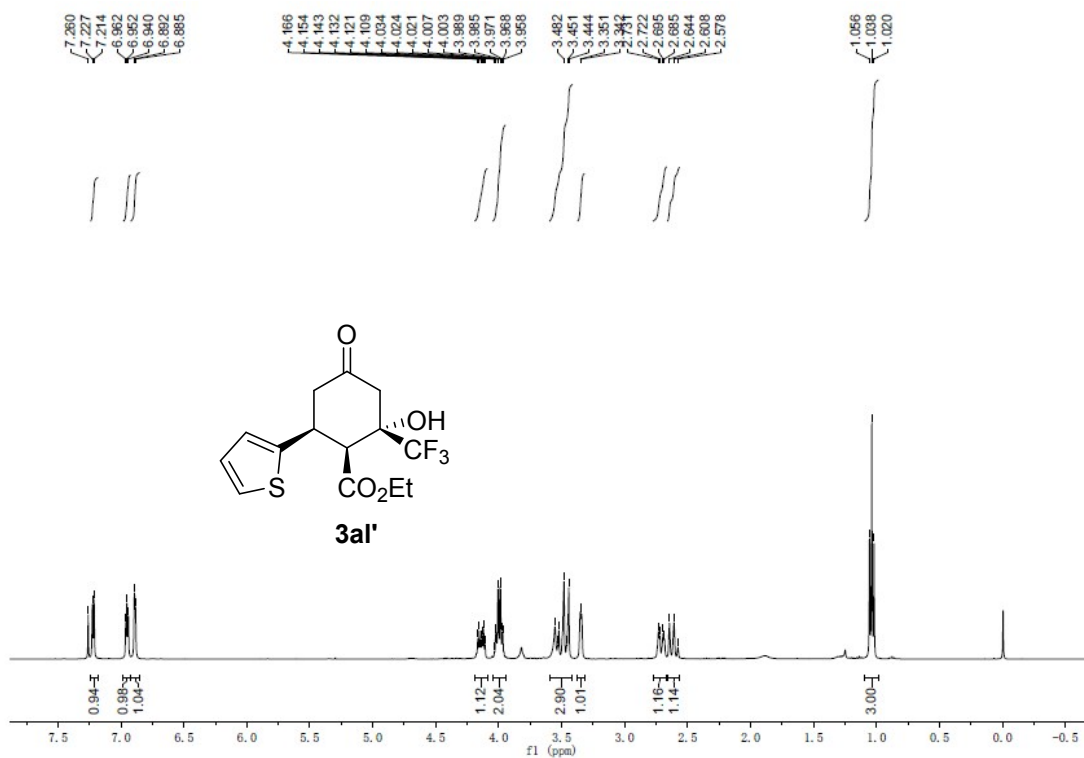
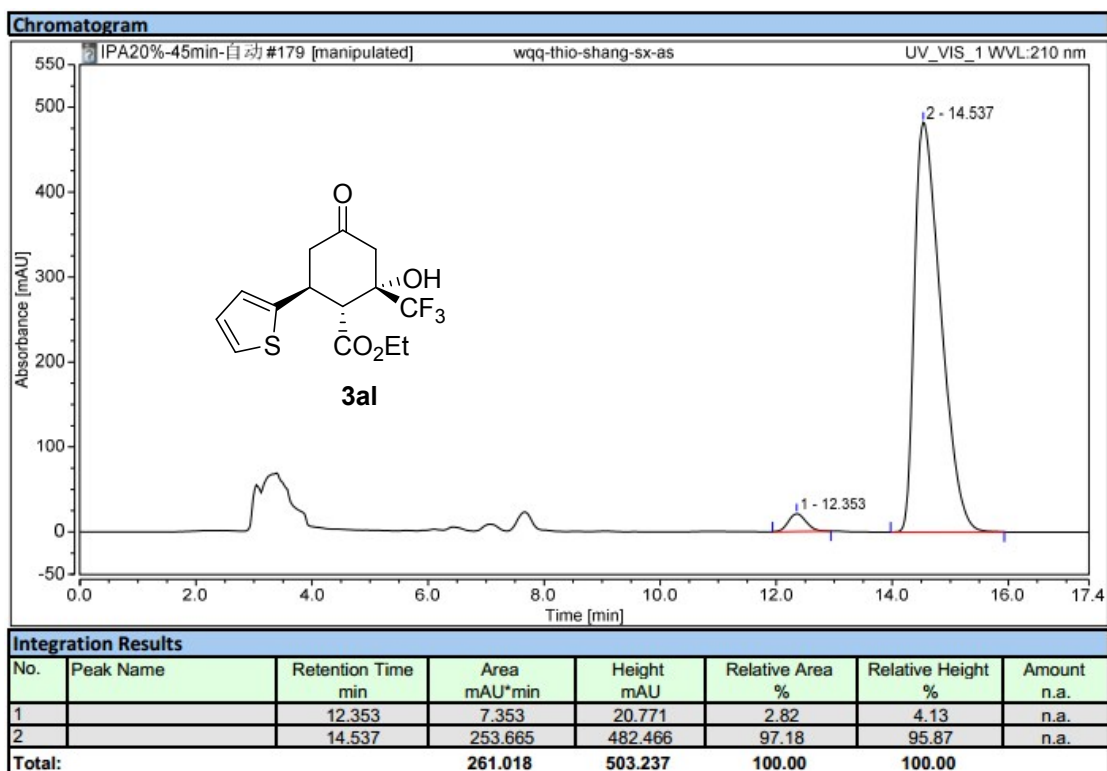


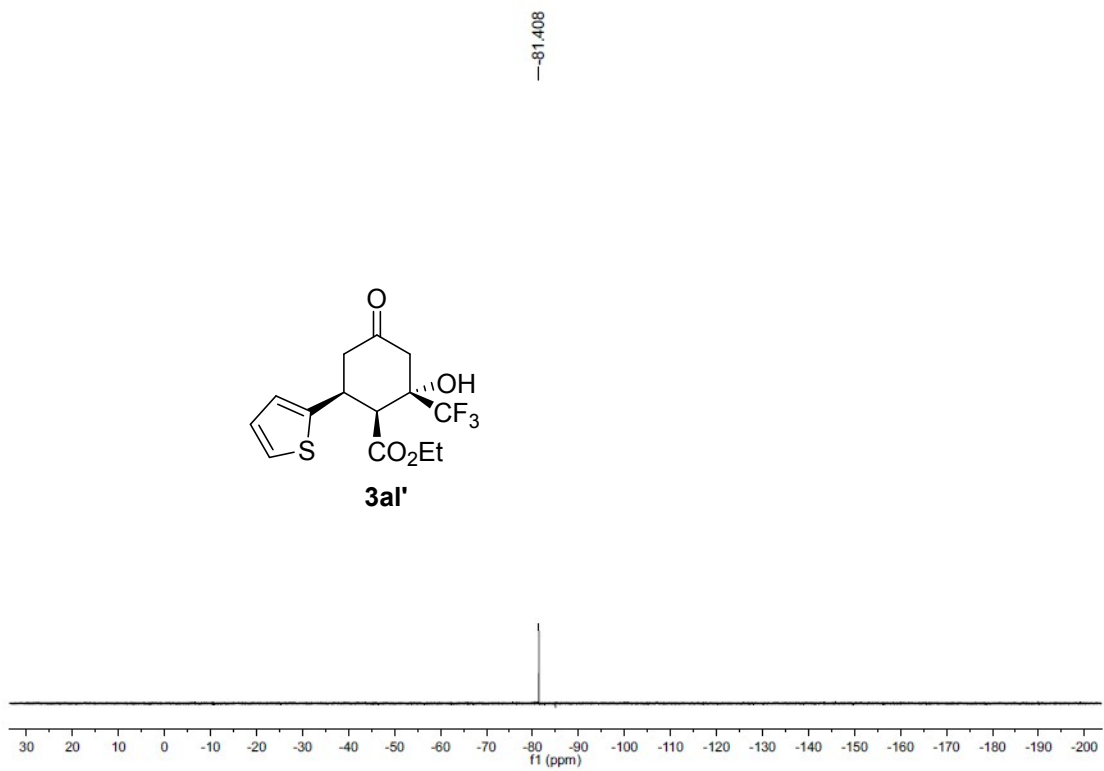
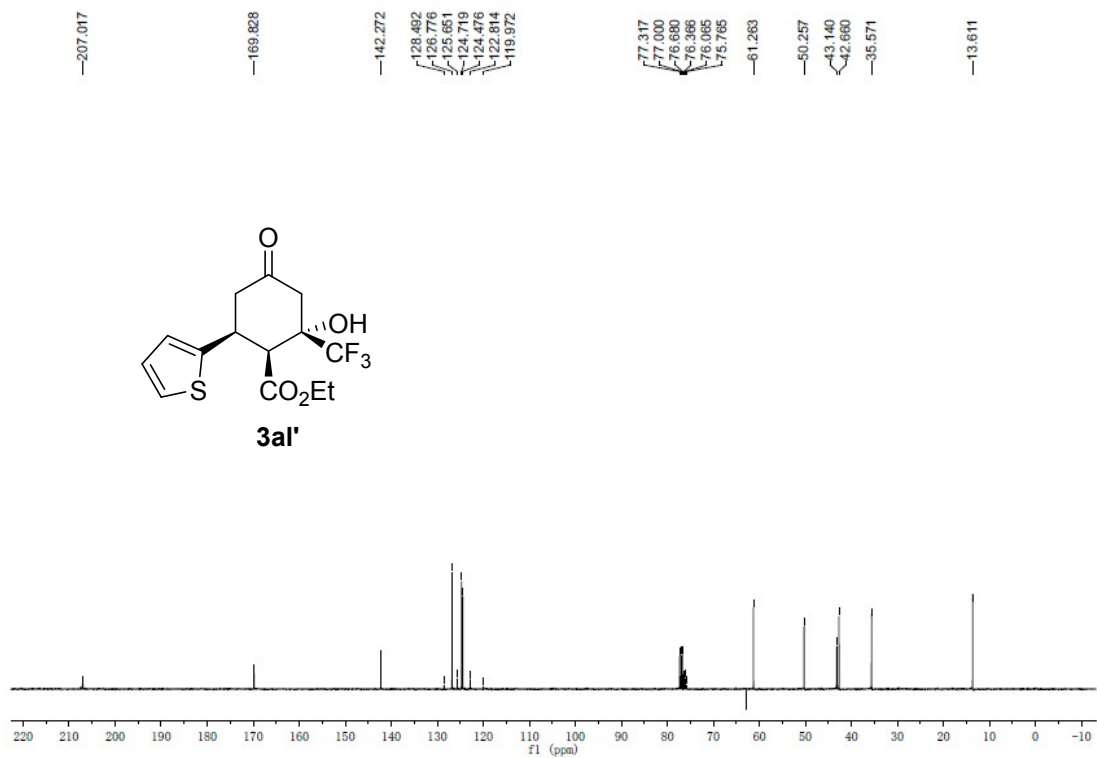


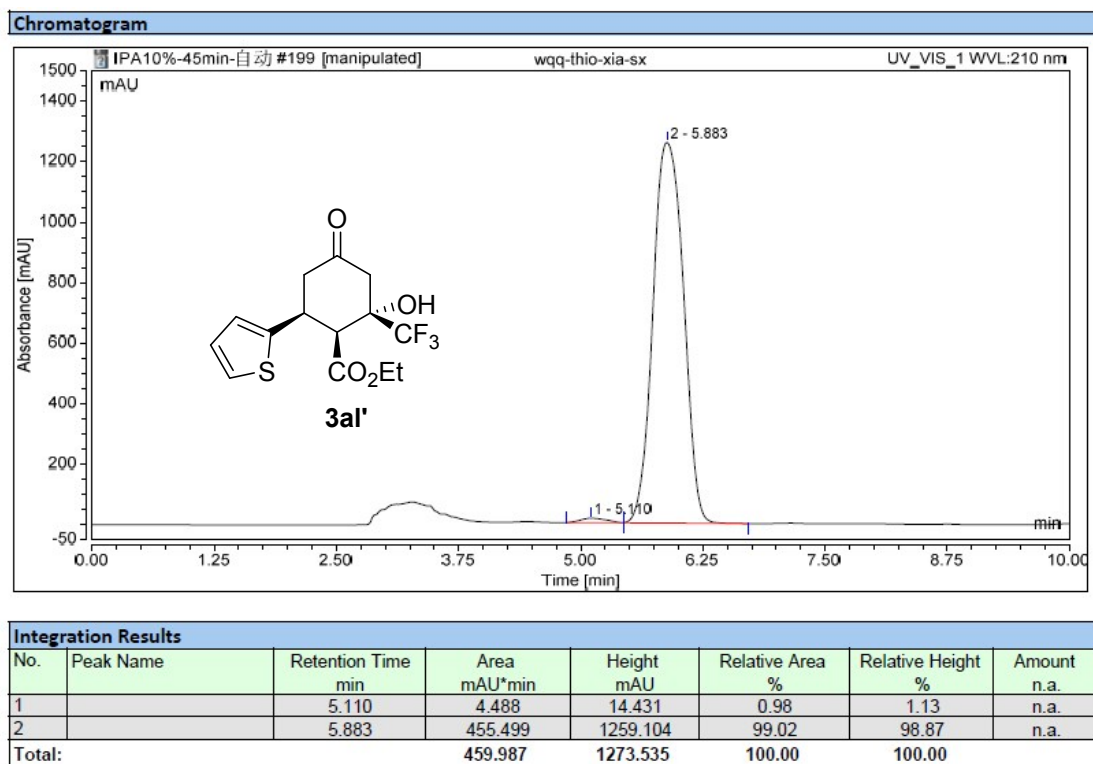
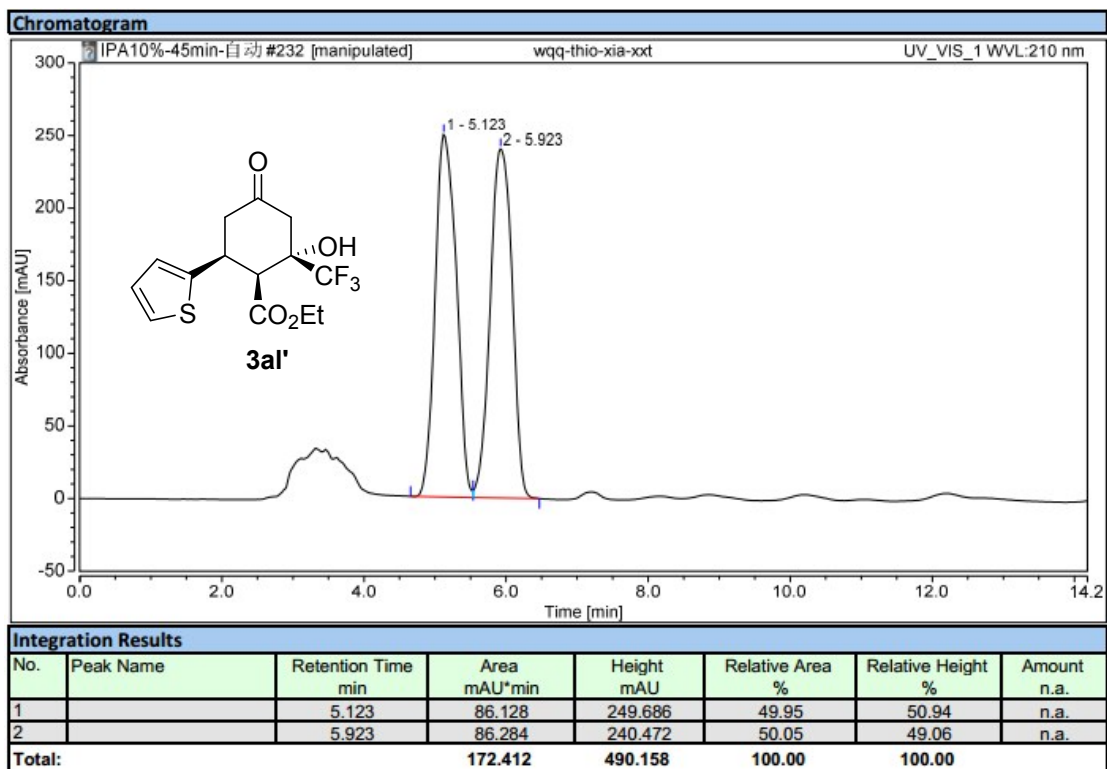


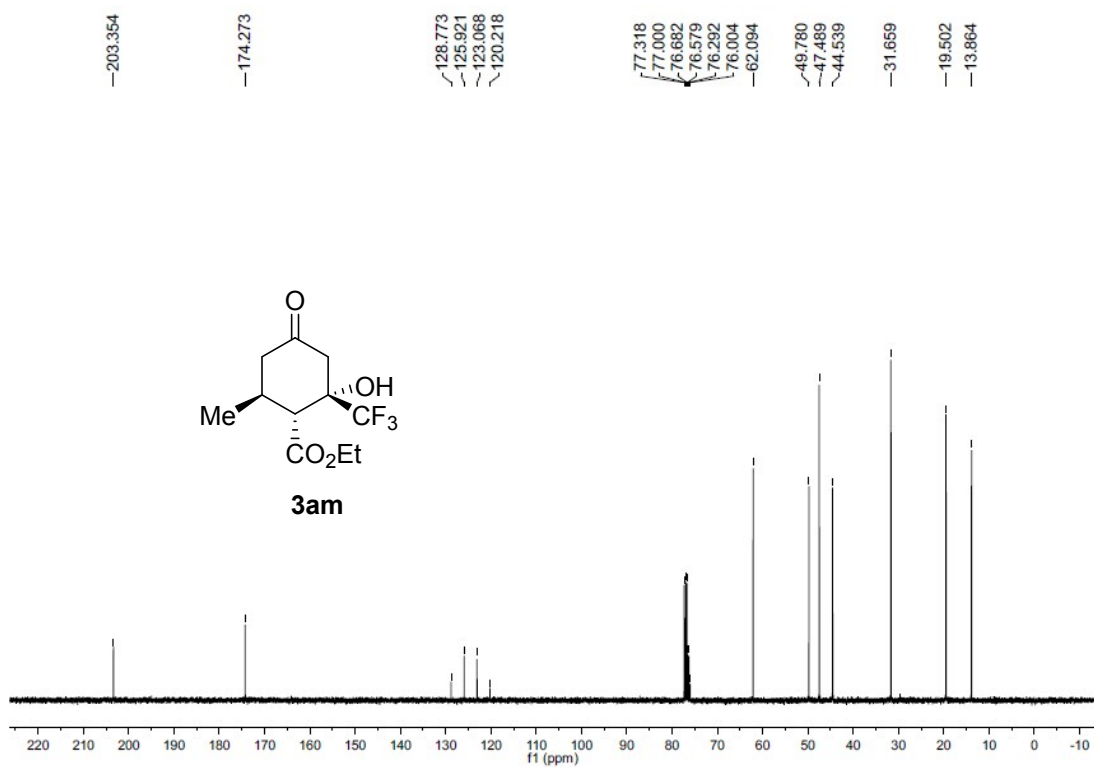
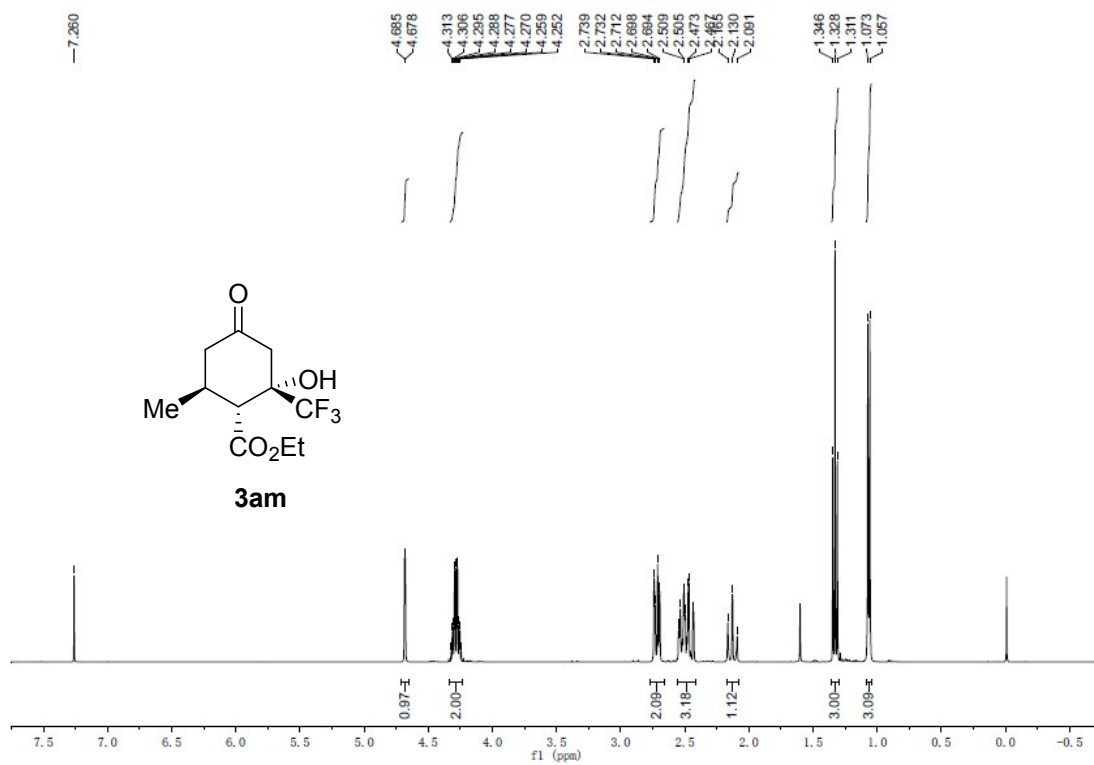
--81.238



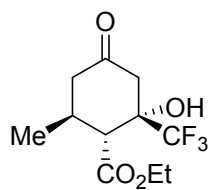




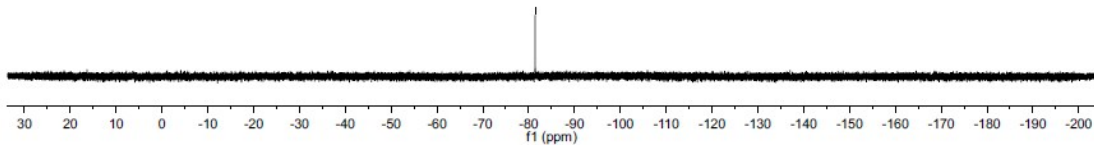




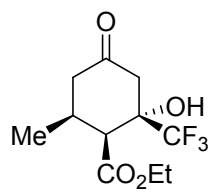
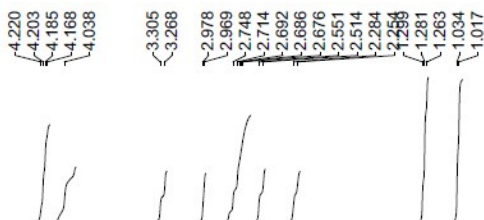
-81.429



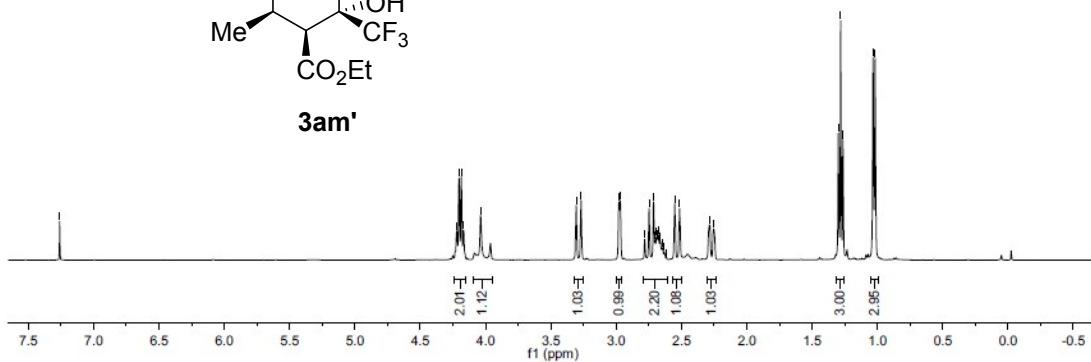
3am



-7.260



3am'



—208.115

—170.367

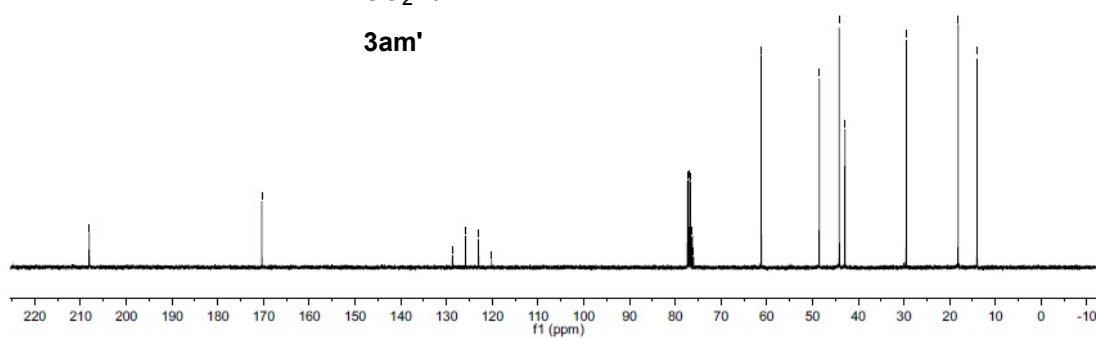
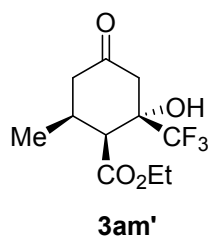
128.684
125.846
123.007
120.169

77.318
77.000
76.858
76.682
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76.265
75.969
61.196

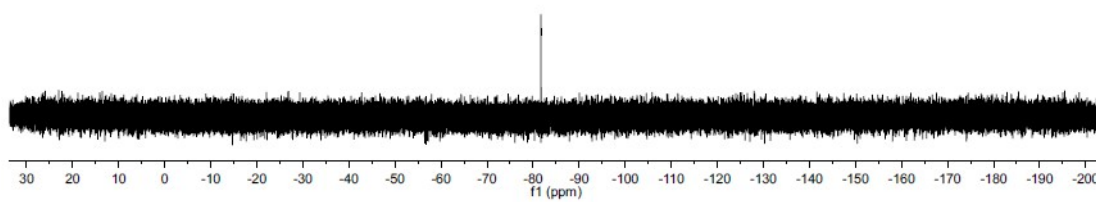
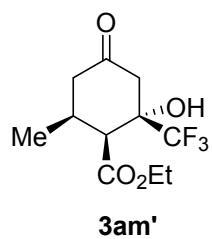
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44.131
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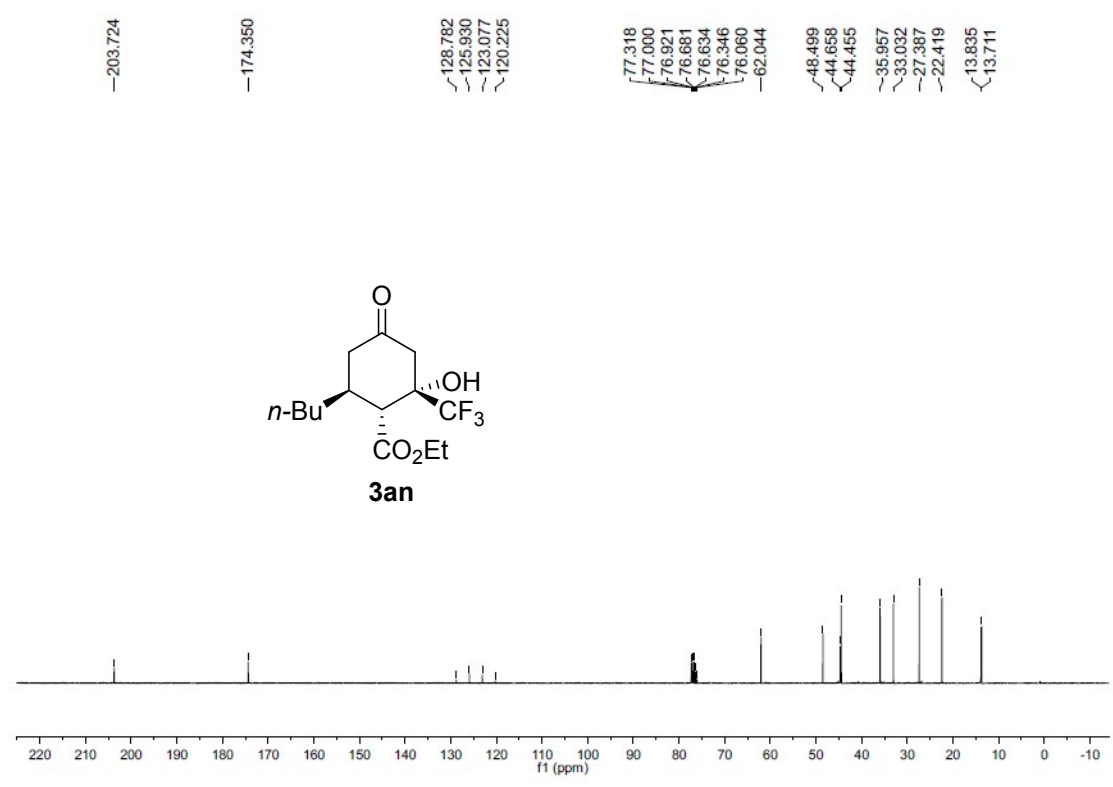
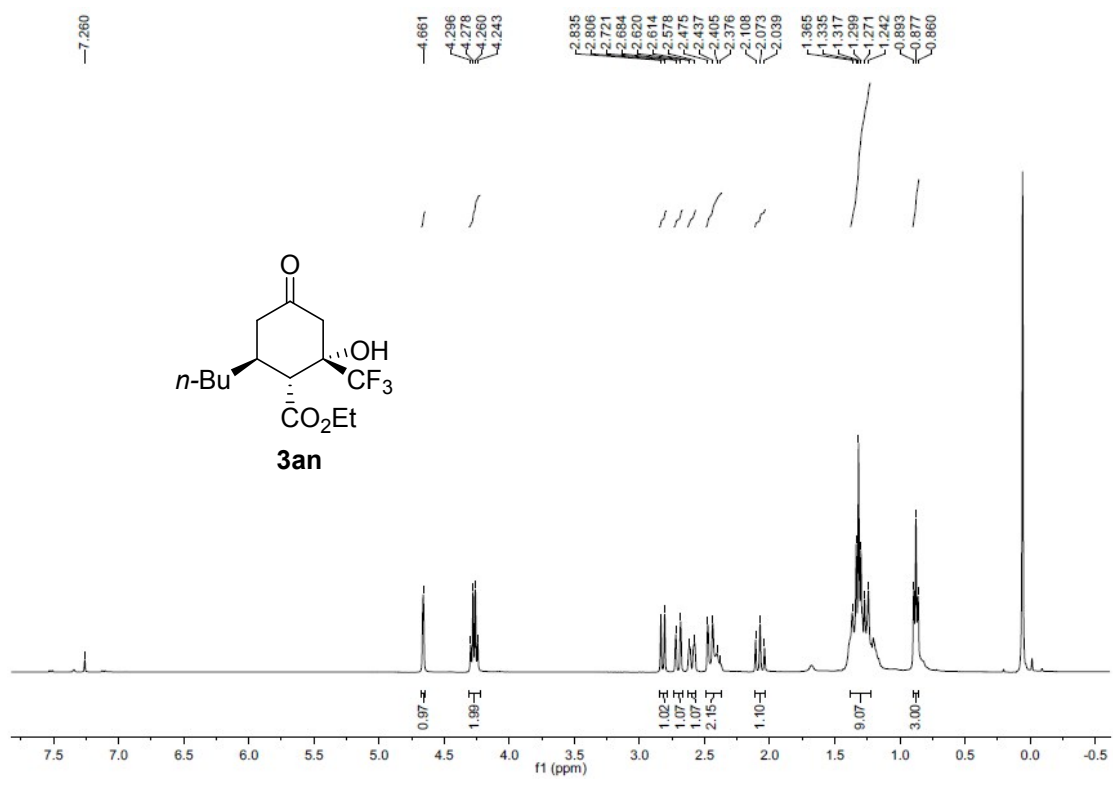
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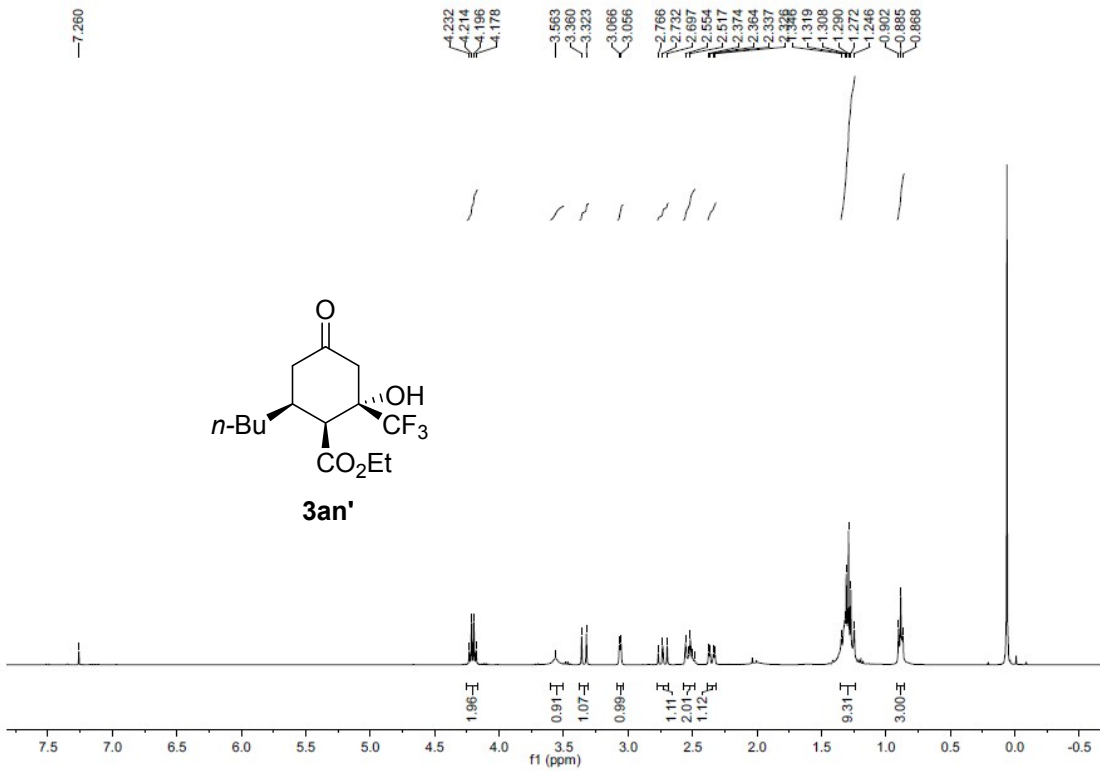
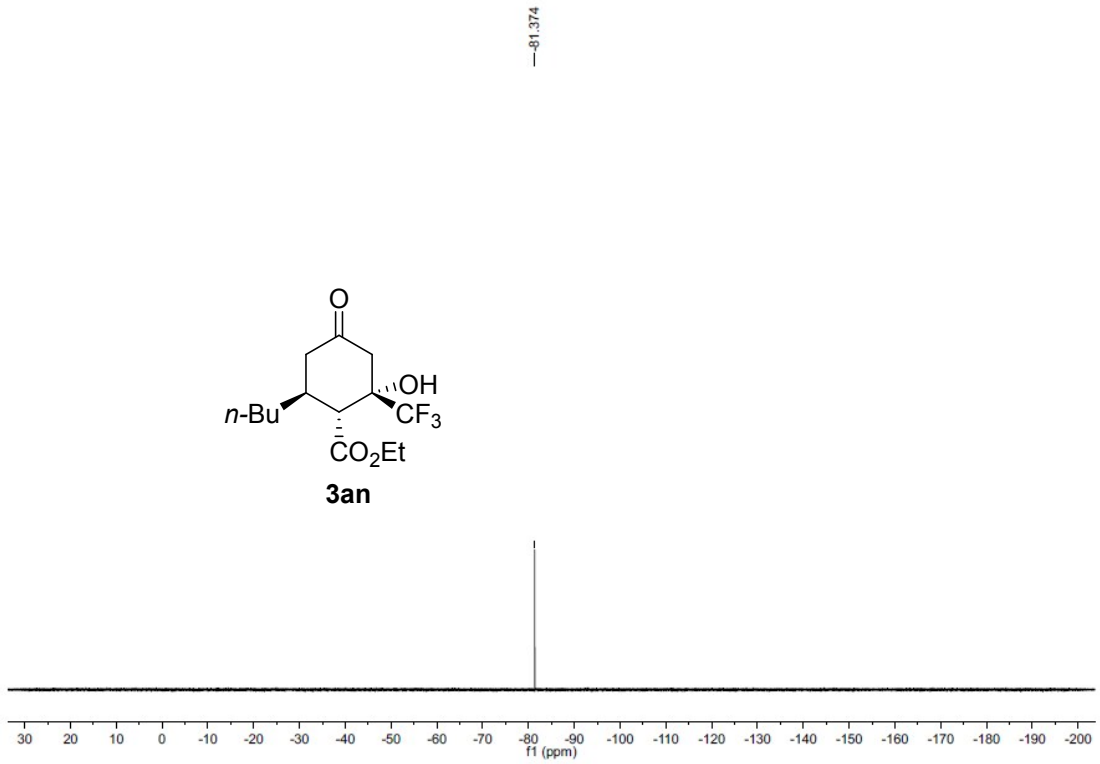
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—14.000



—81.713







—208.221

—170.423

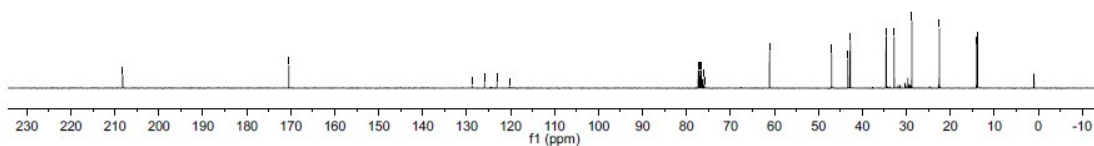
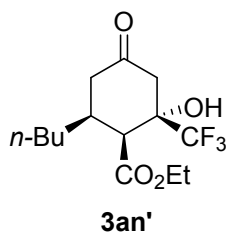
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—120.242

—77.319
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—75.924
—61.112

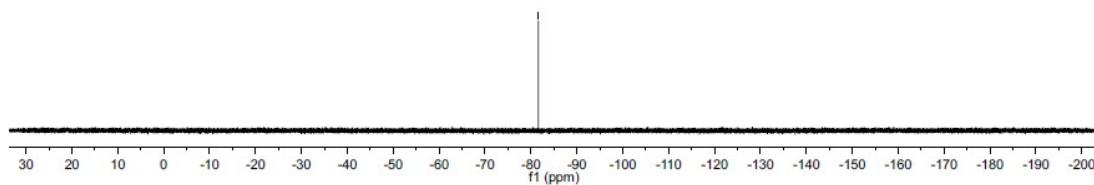
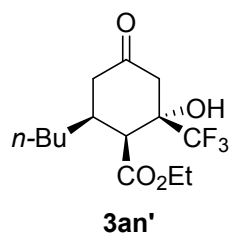
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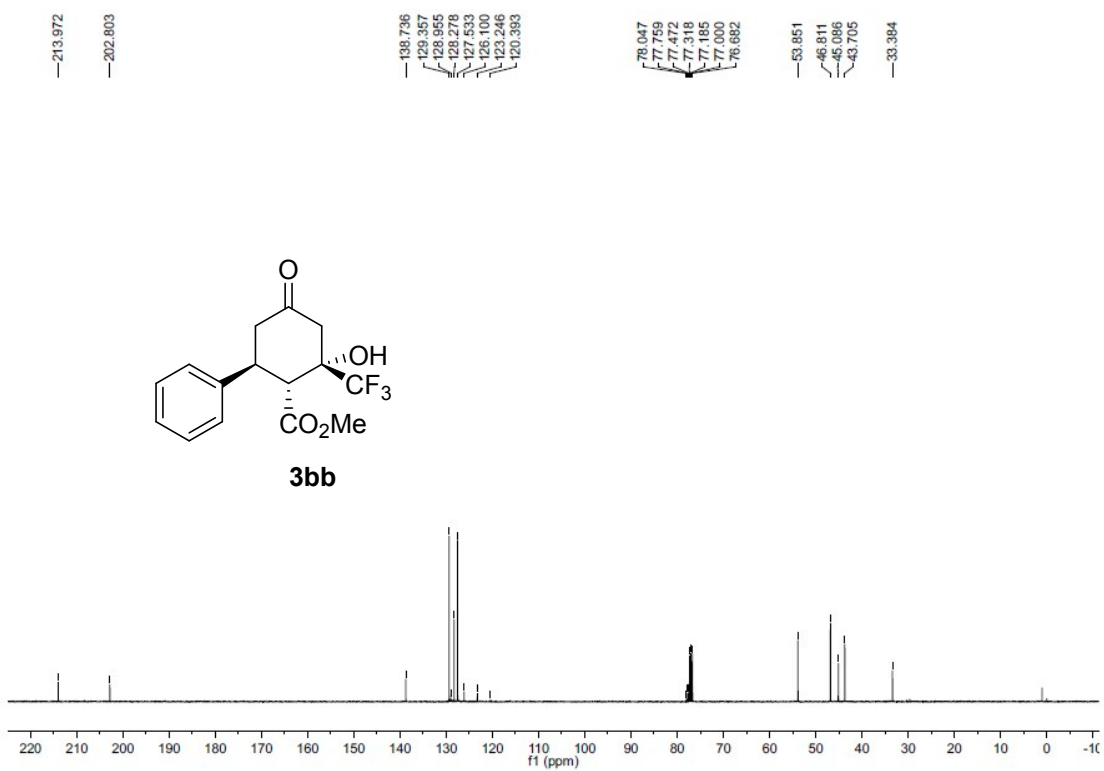
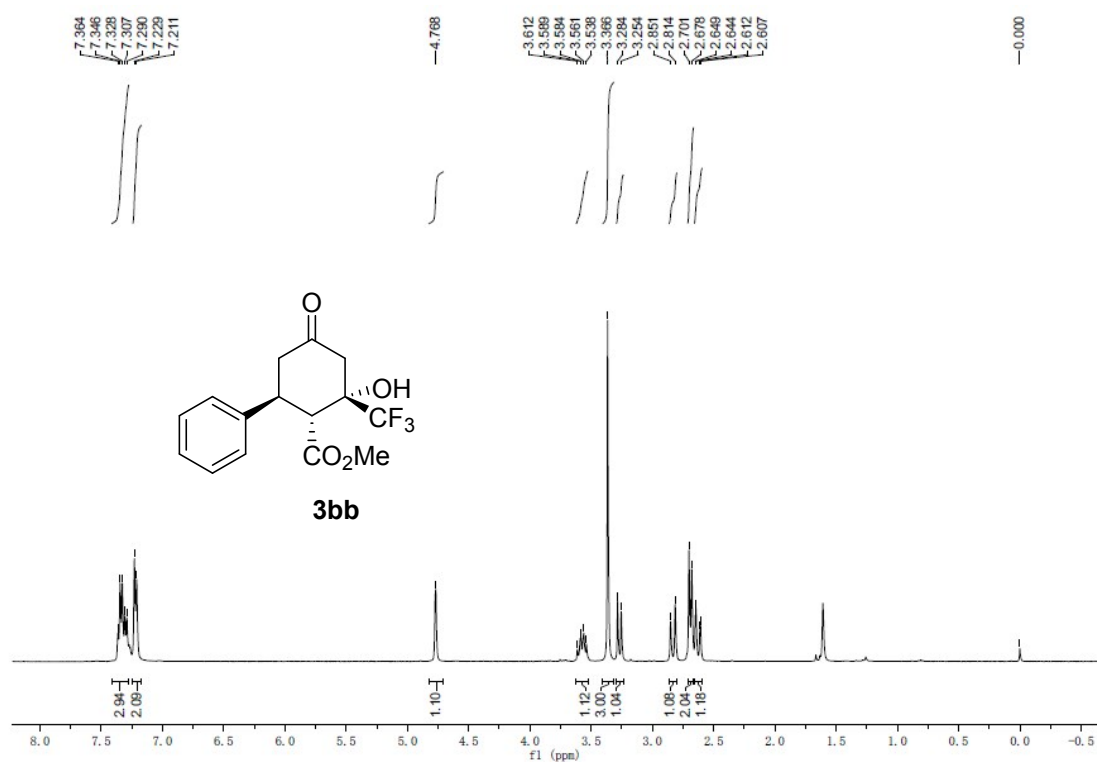
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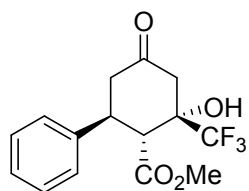


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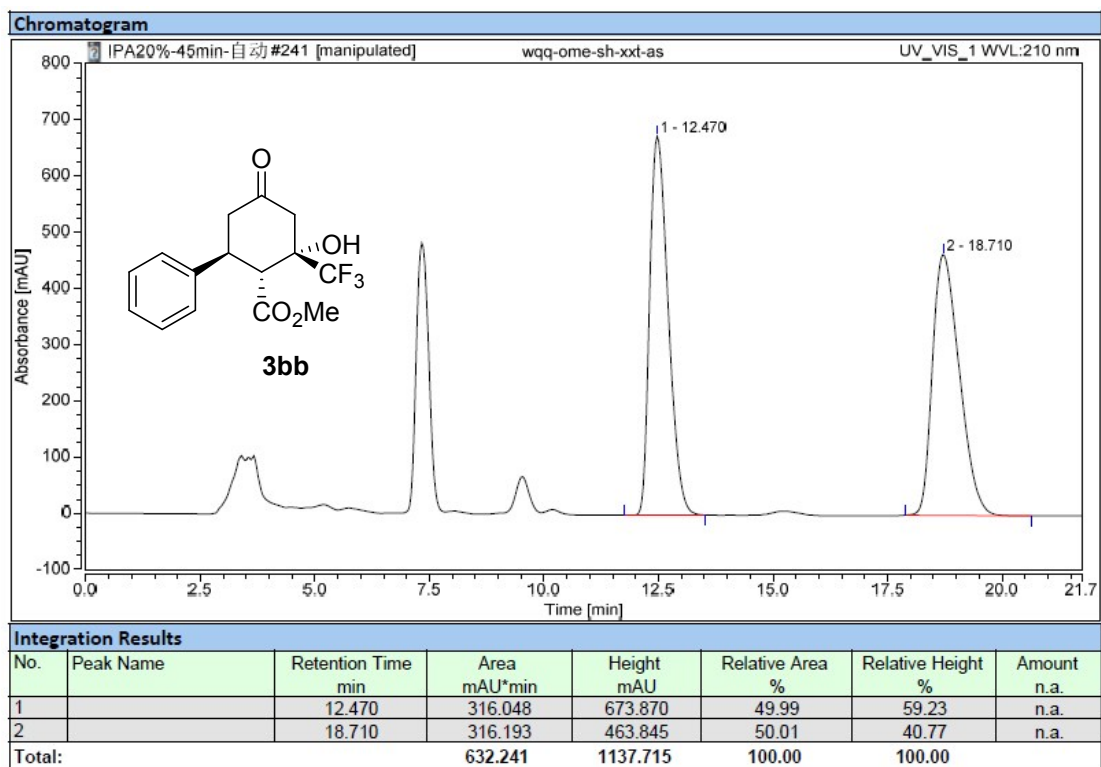
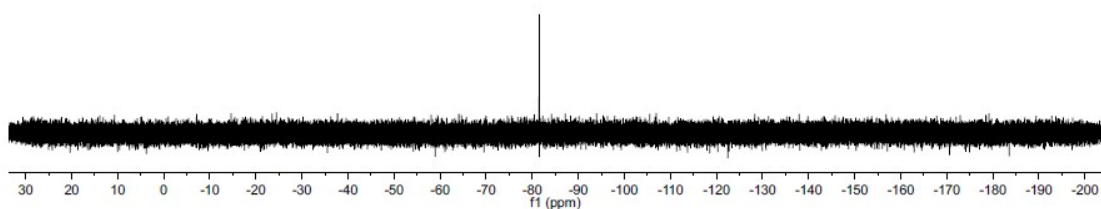


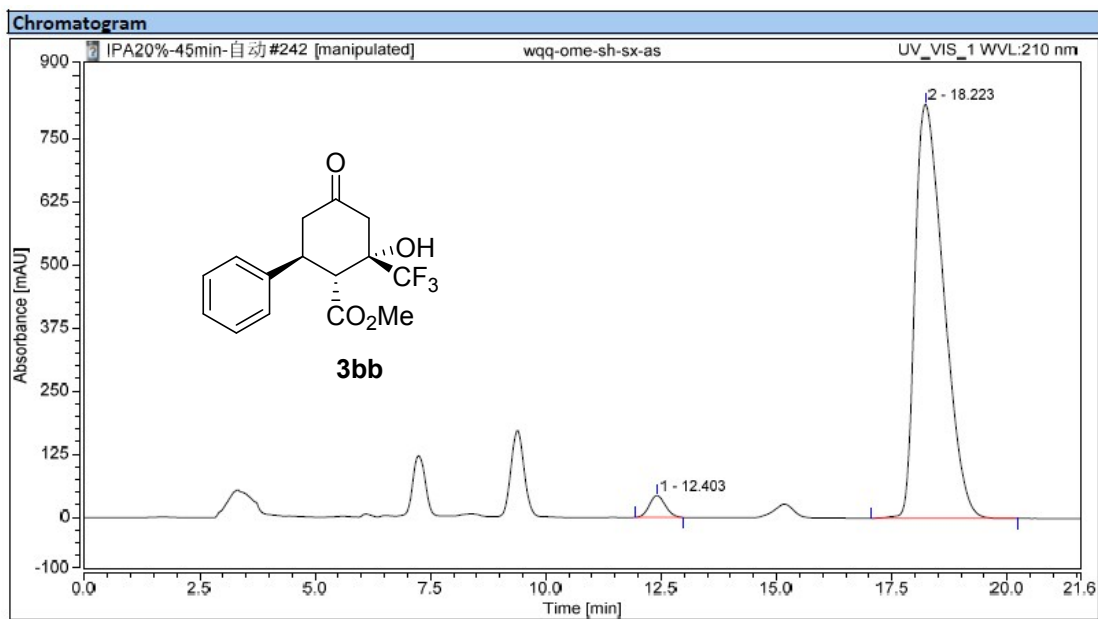


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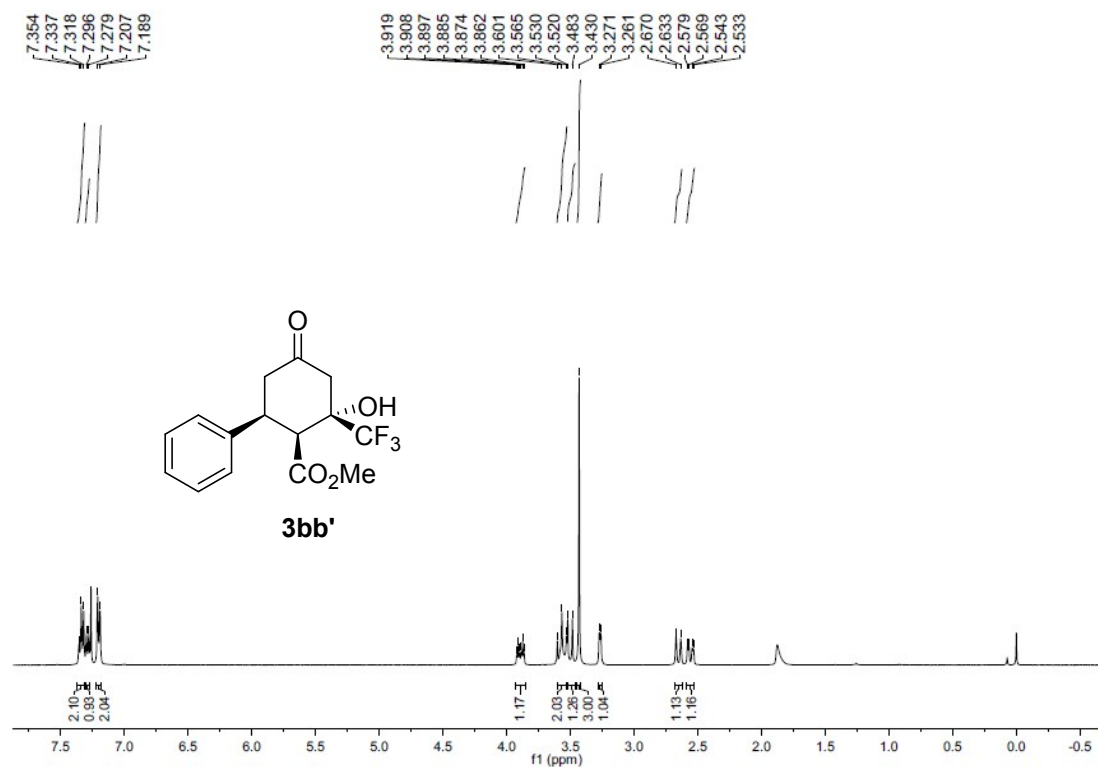
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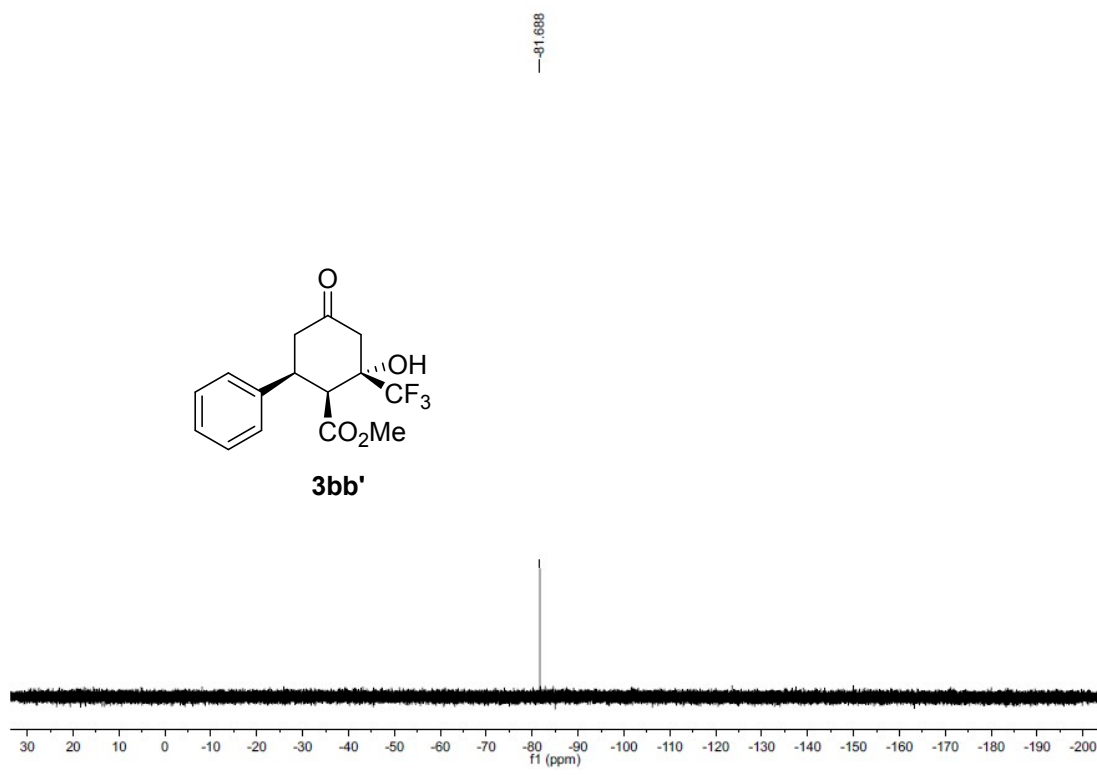
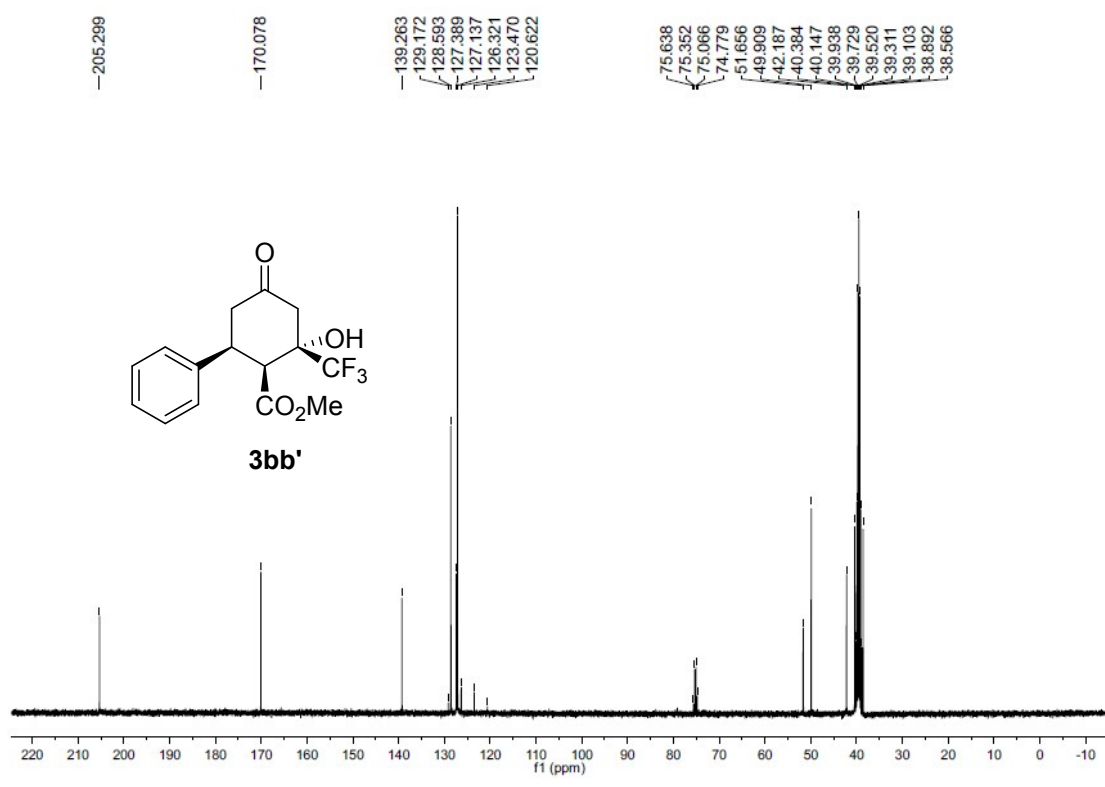


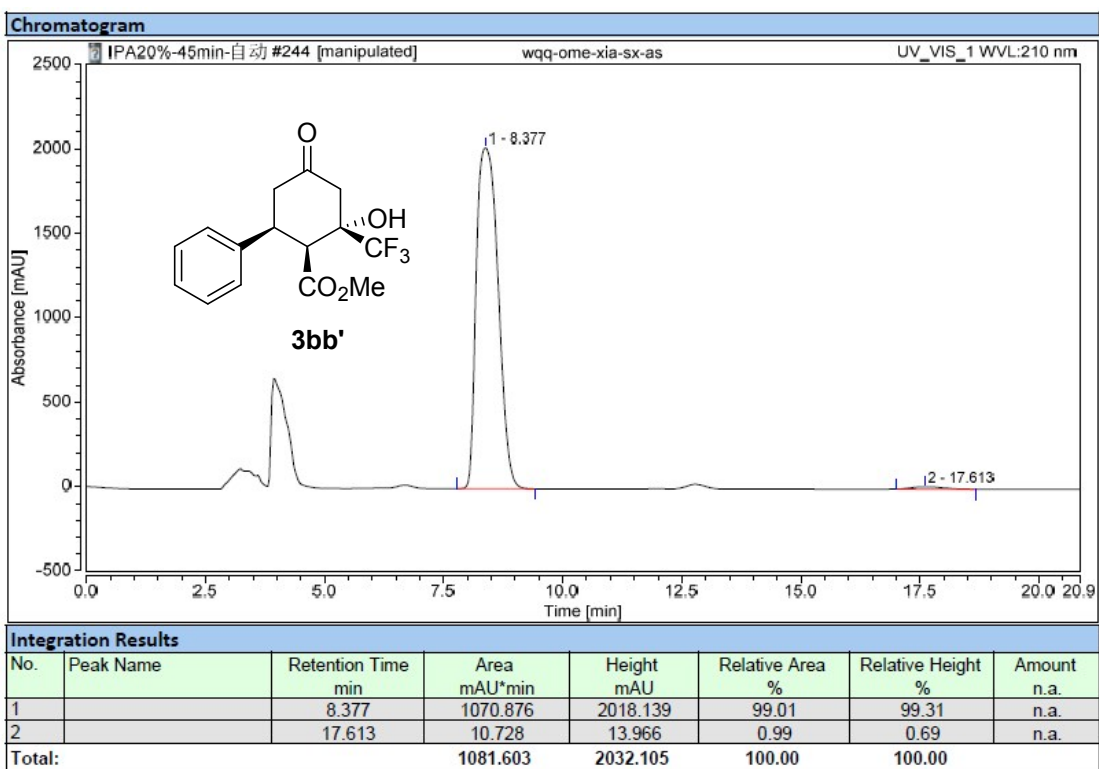
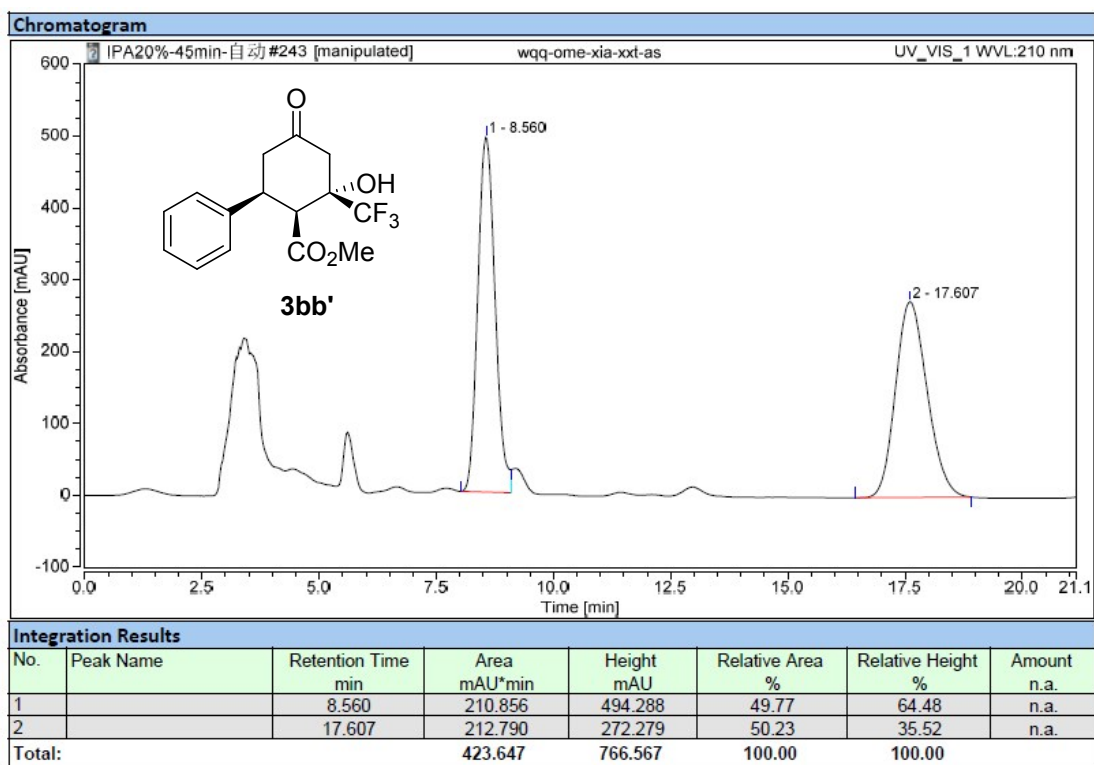


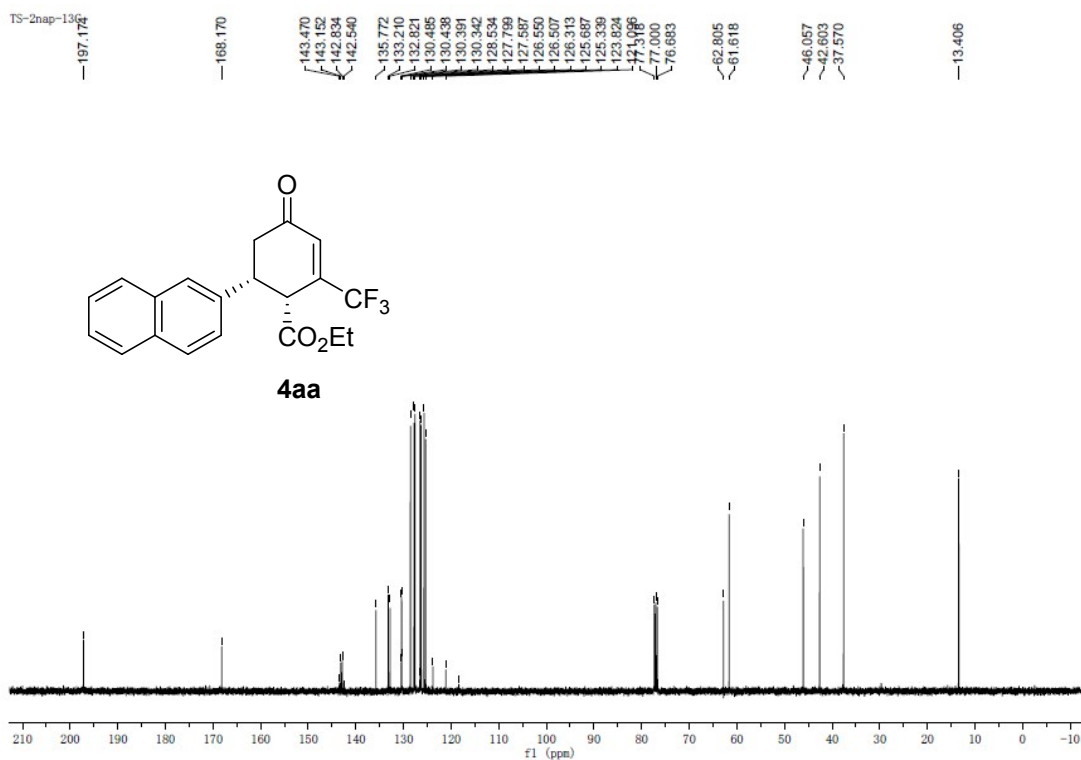
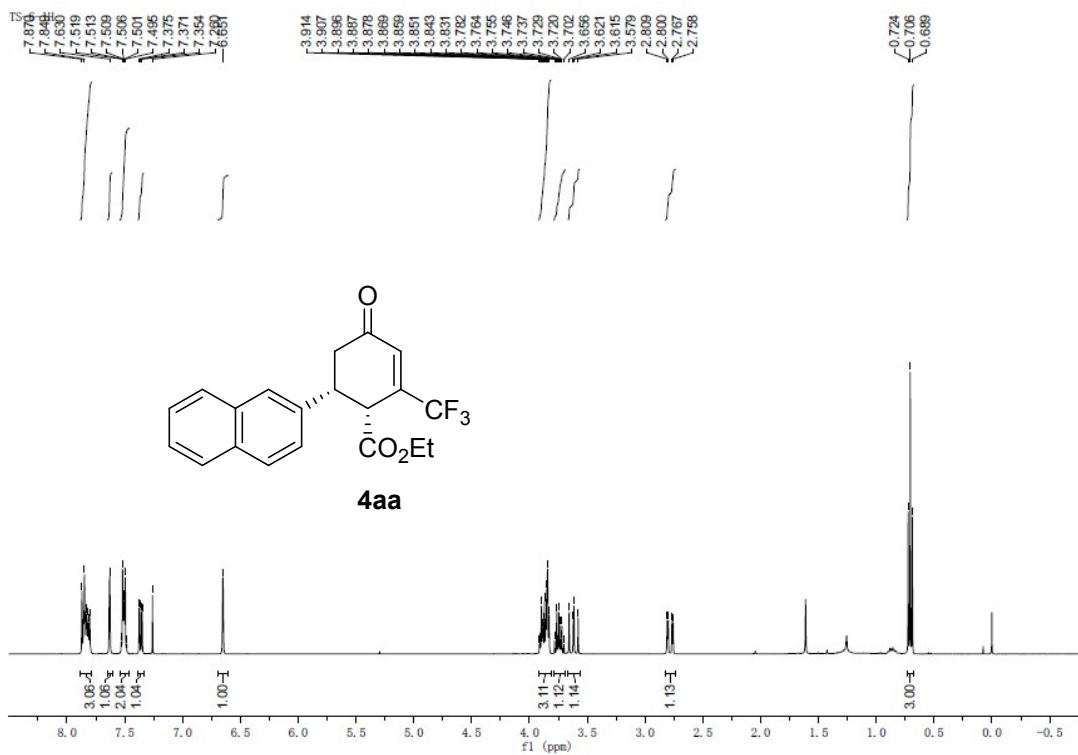
Integration Results

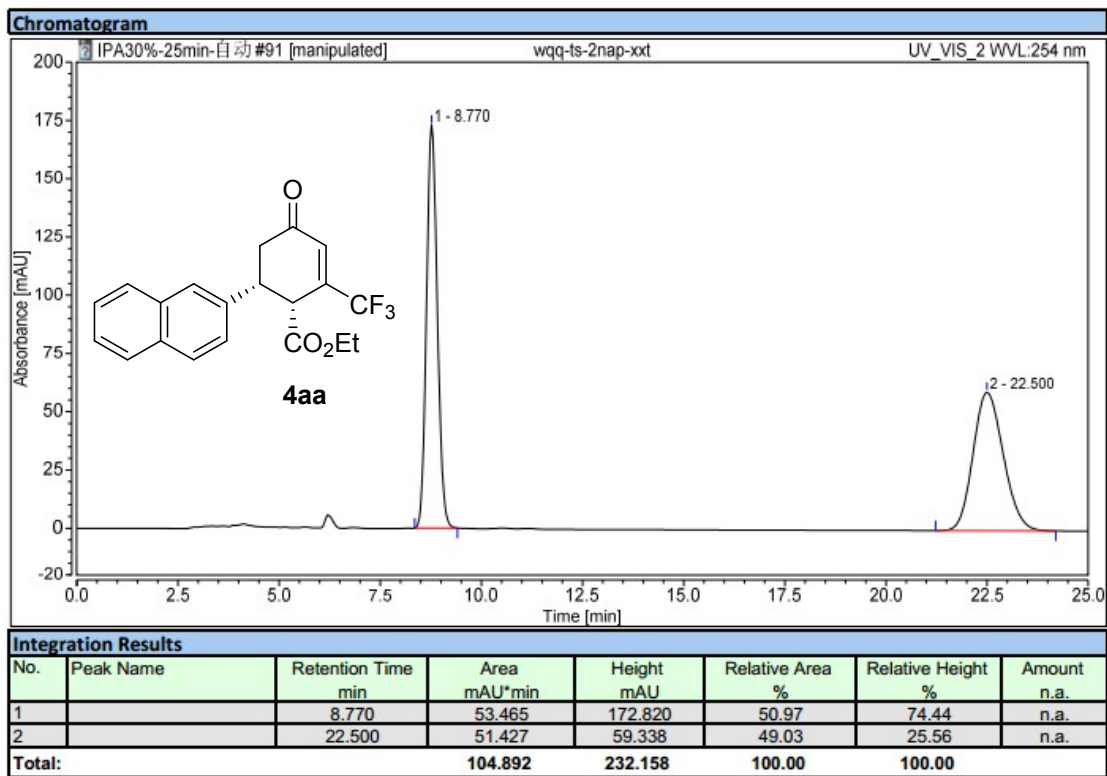
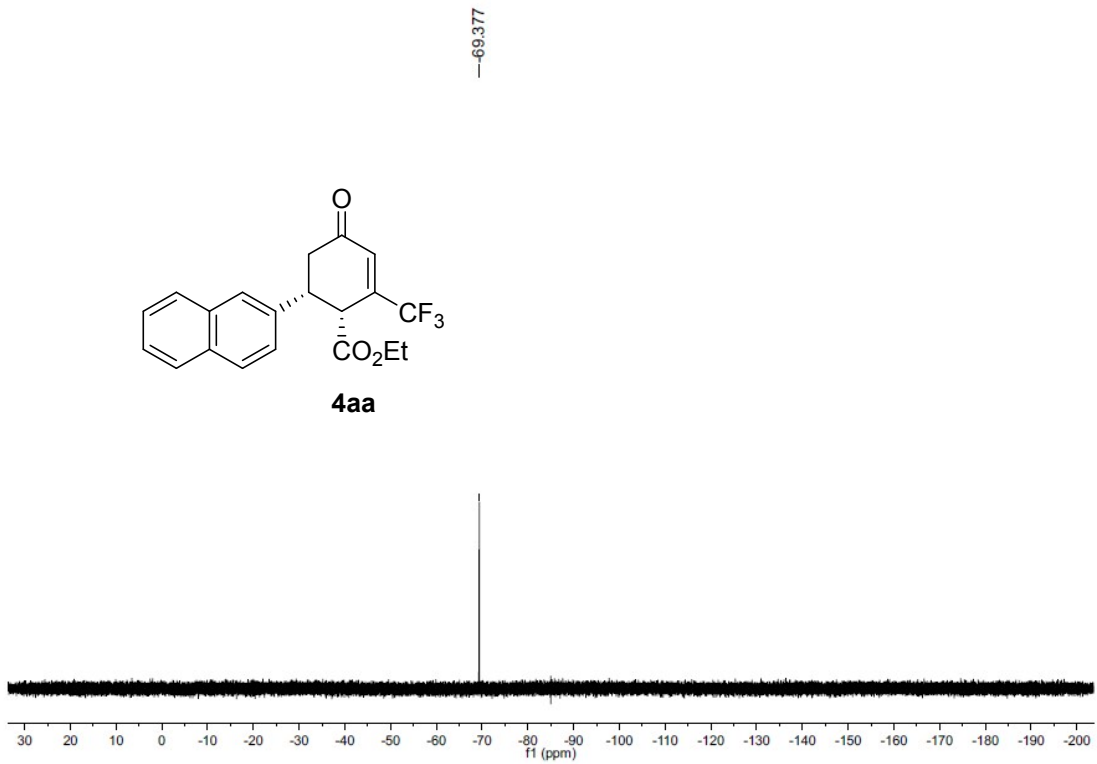
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		12.403	17.349	43.227	2.86	5.01	n.a.
2		18.223	588.560	819.183	97.14	94.99	n.a.
Total:			605.910	862.410	100.00	100.00	

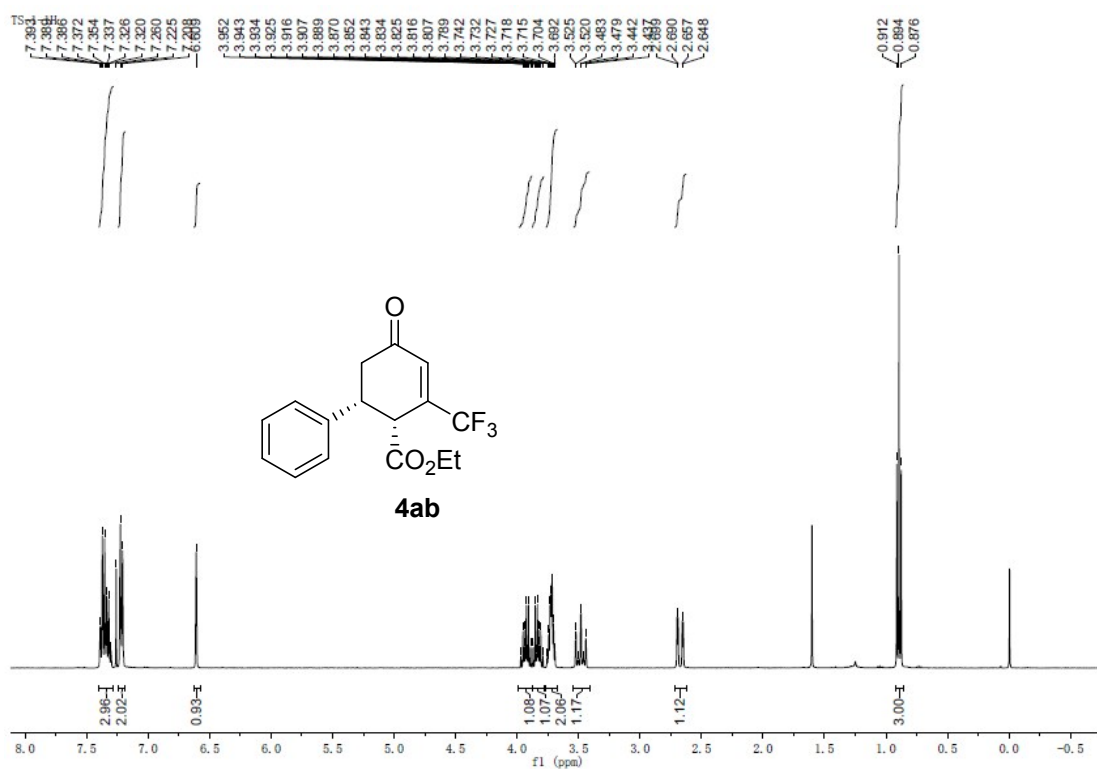
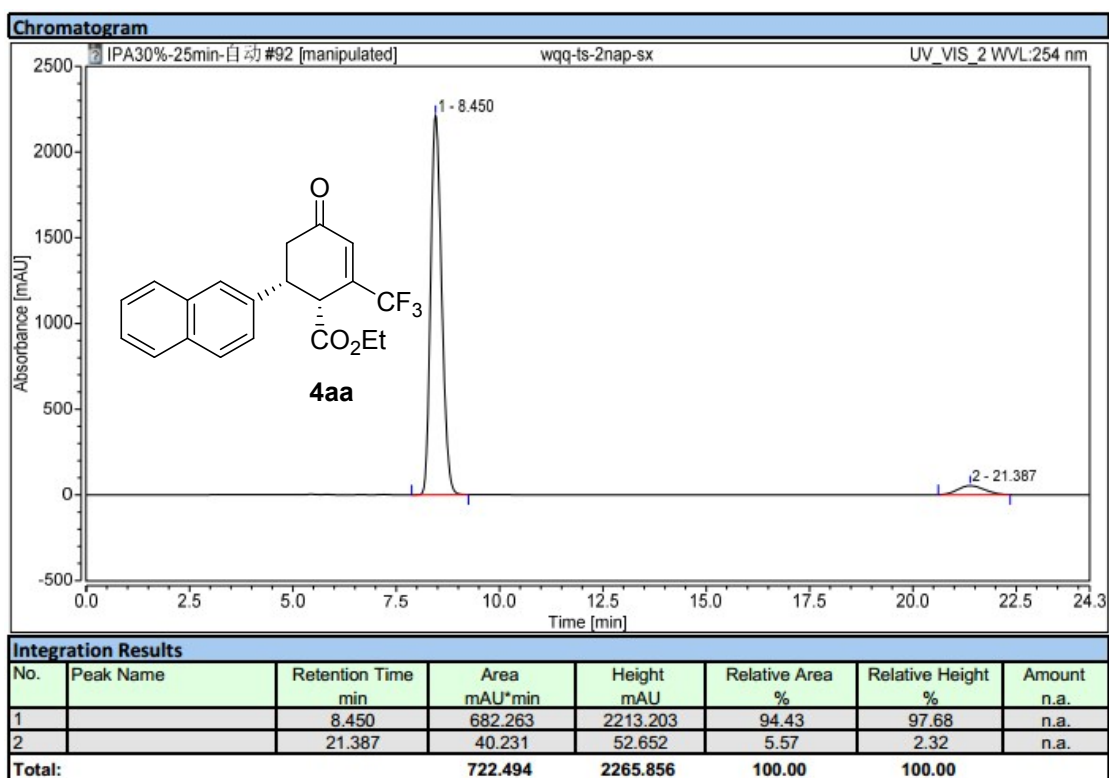












TS-Ph-13C
—197.204

—168.126

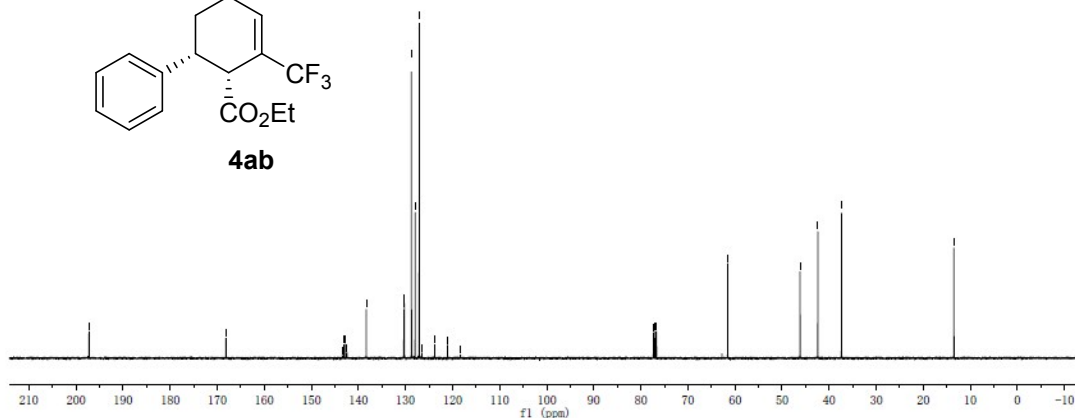
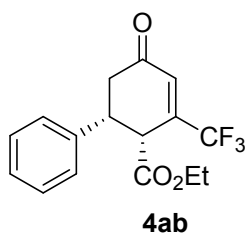
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121.050
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77.319
77.000
76.682

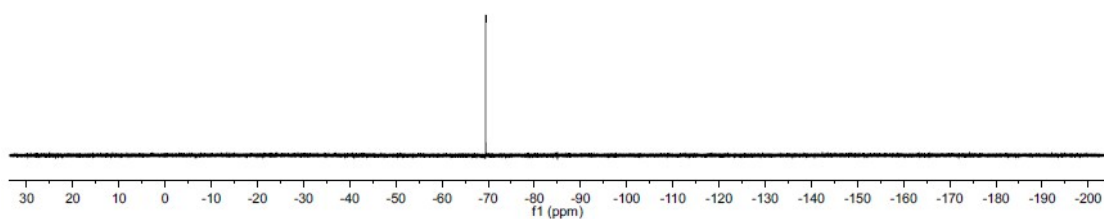
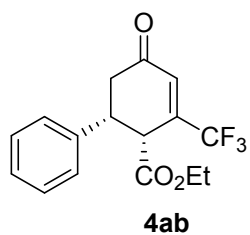
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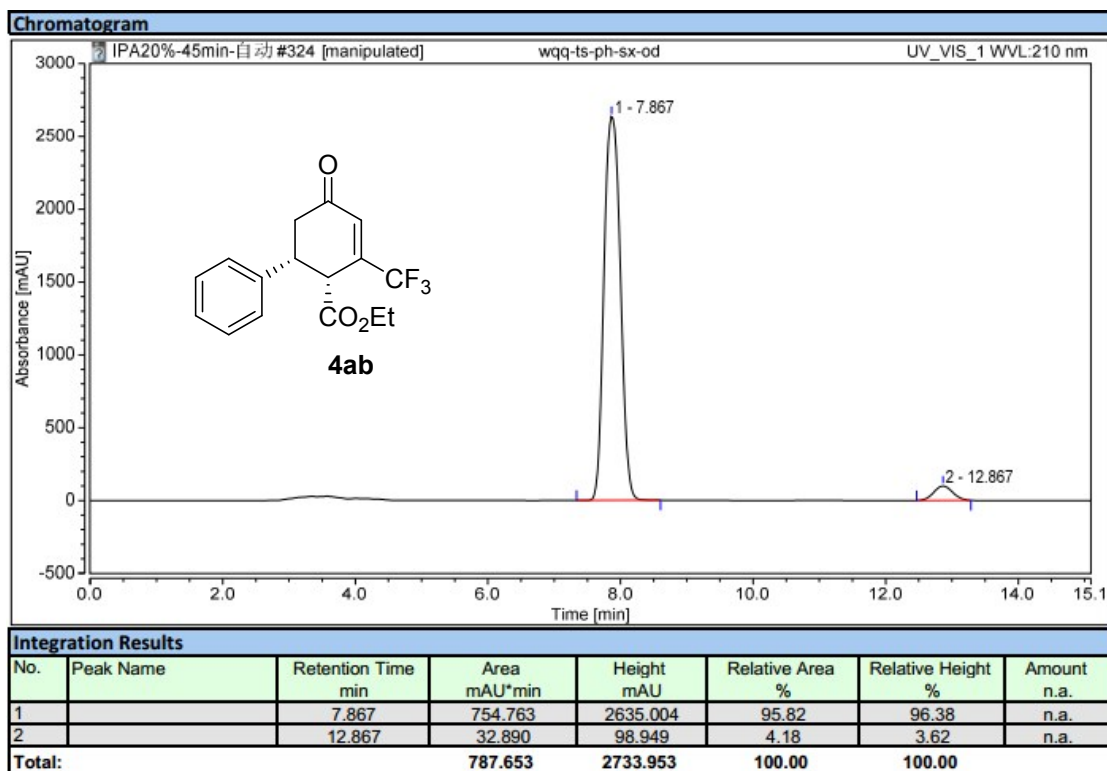
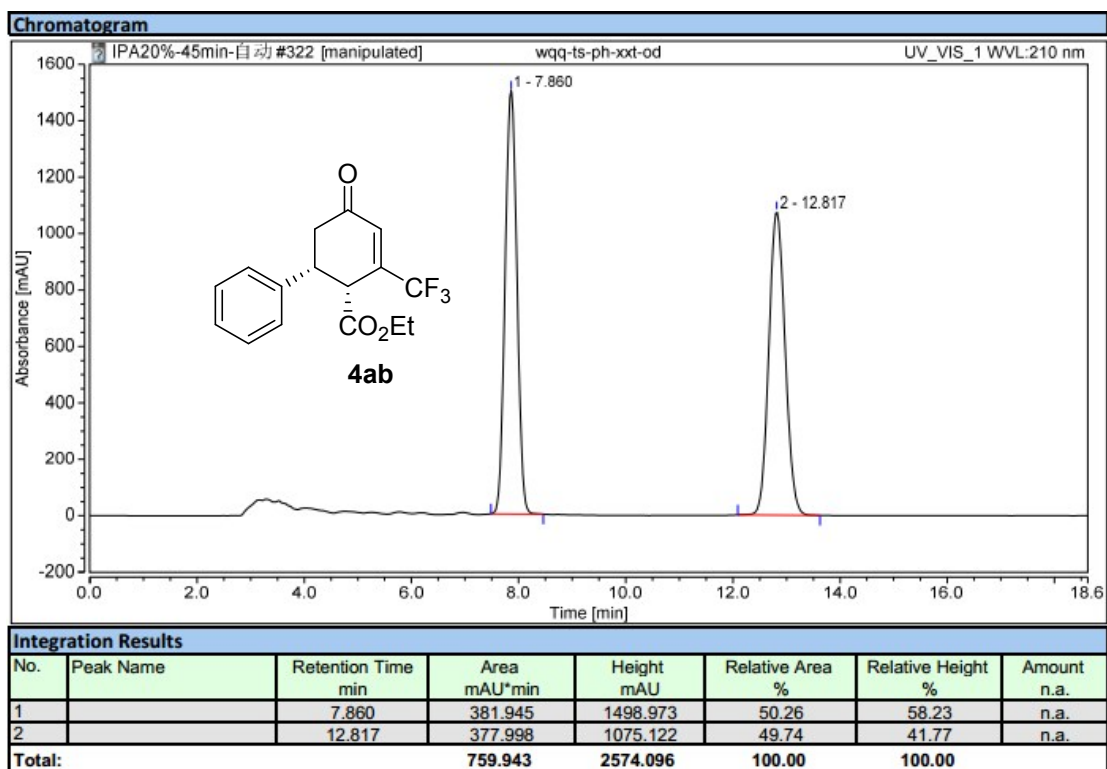
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37.361

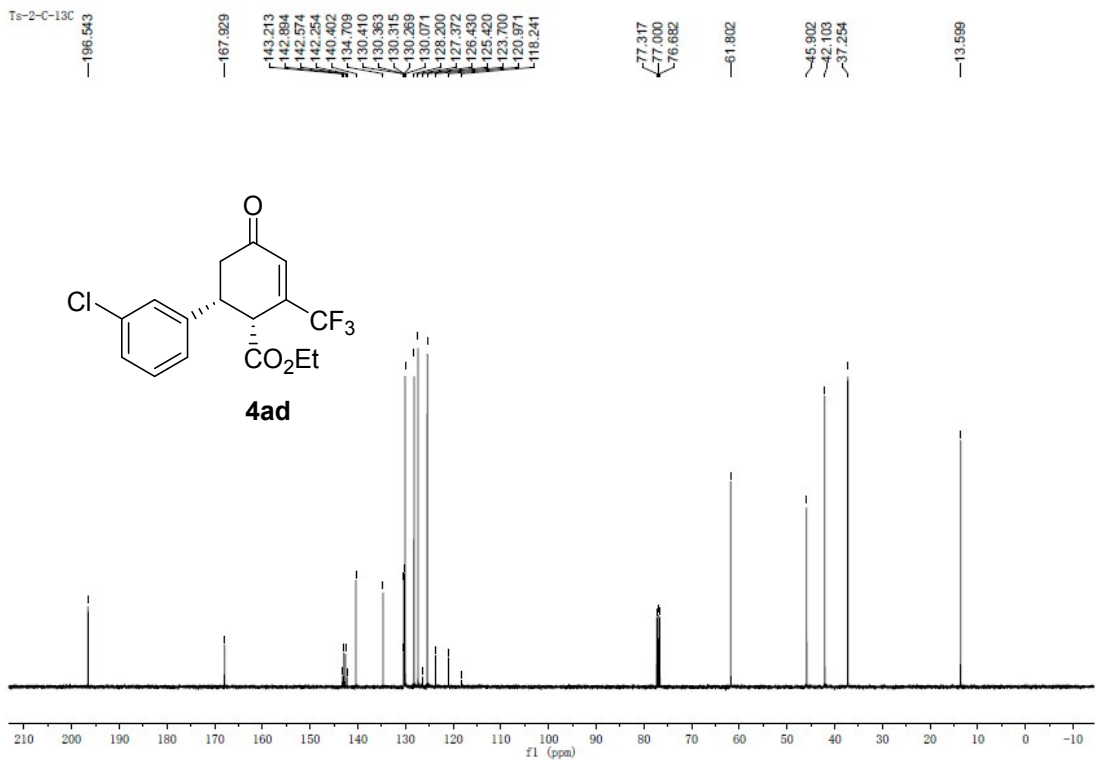
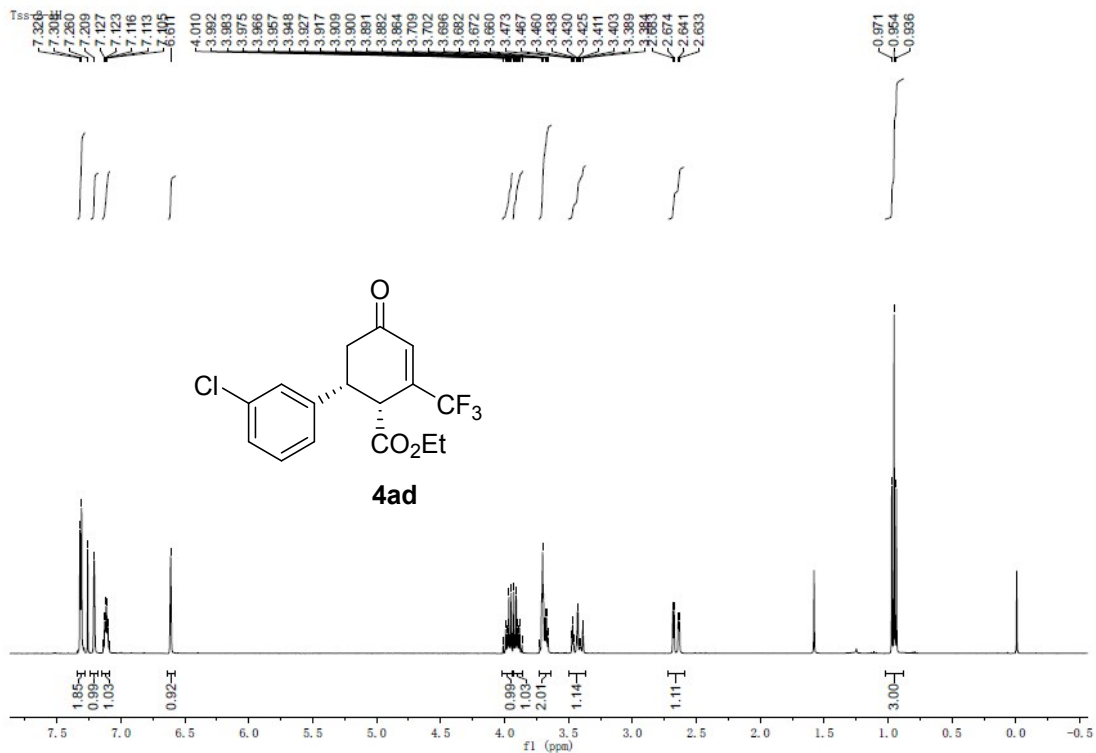
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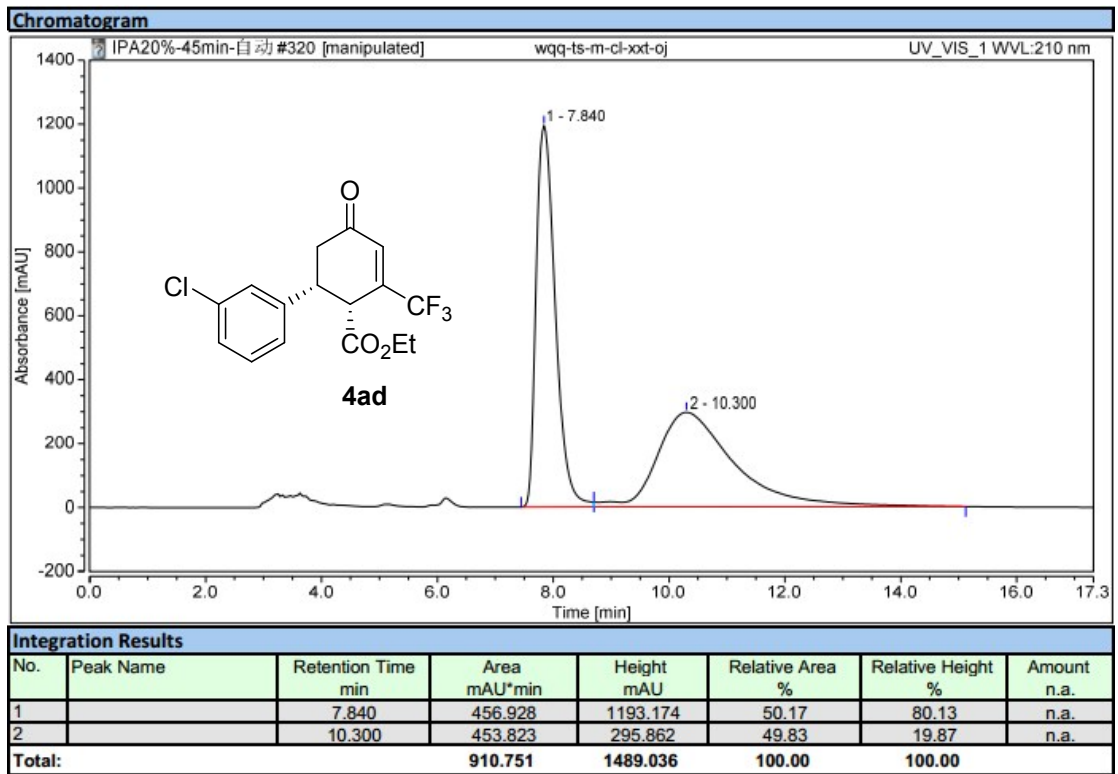
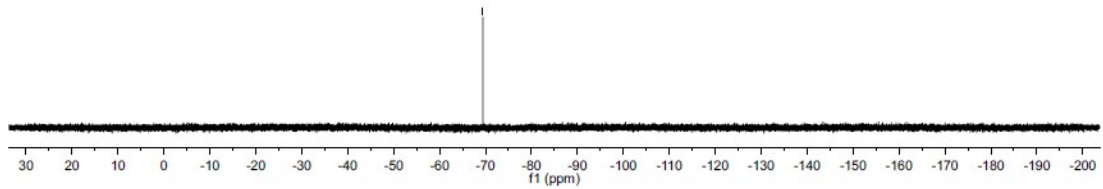
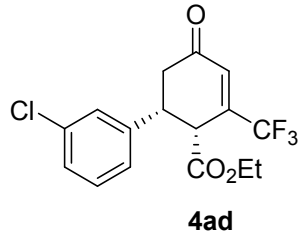
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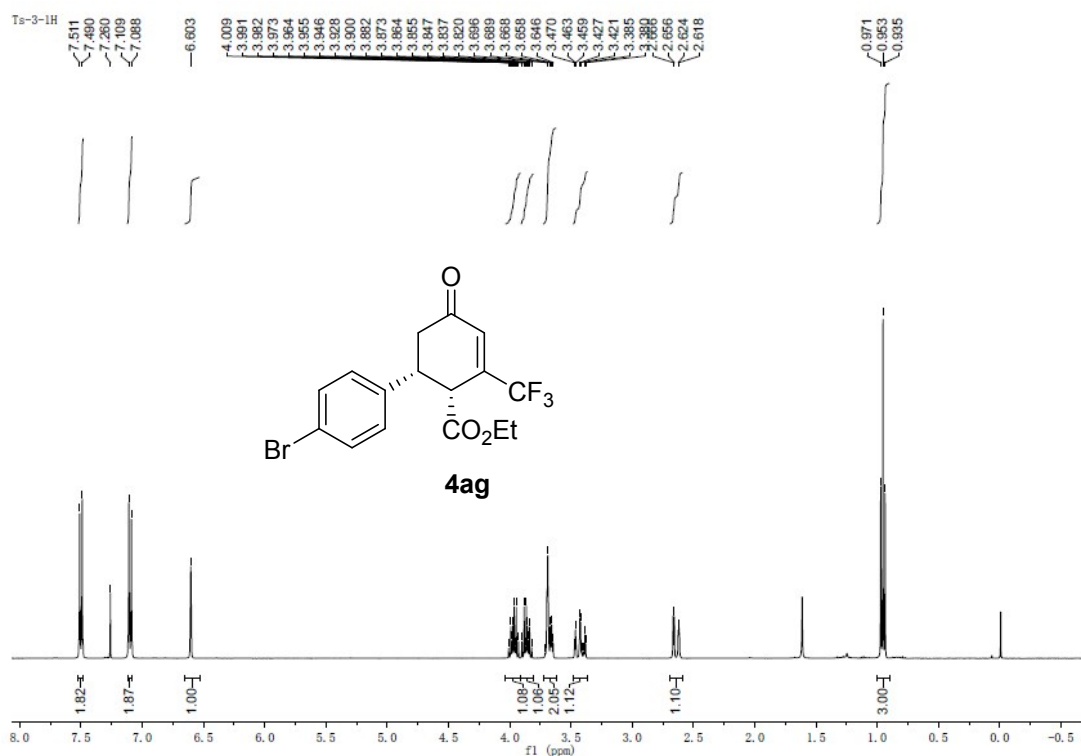
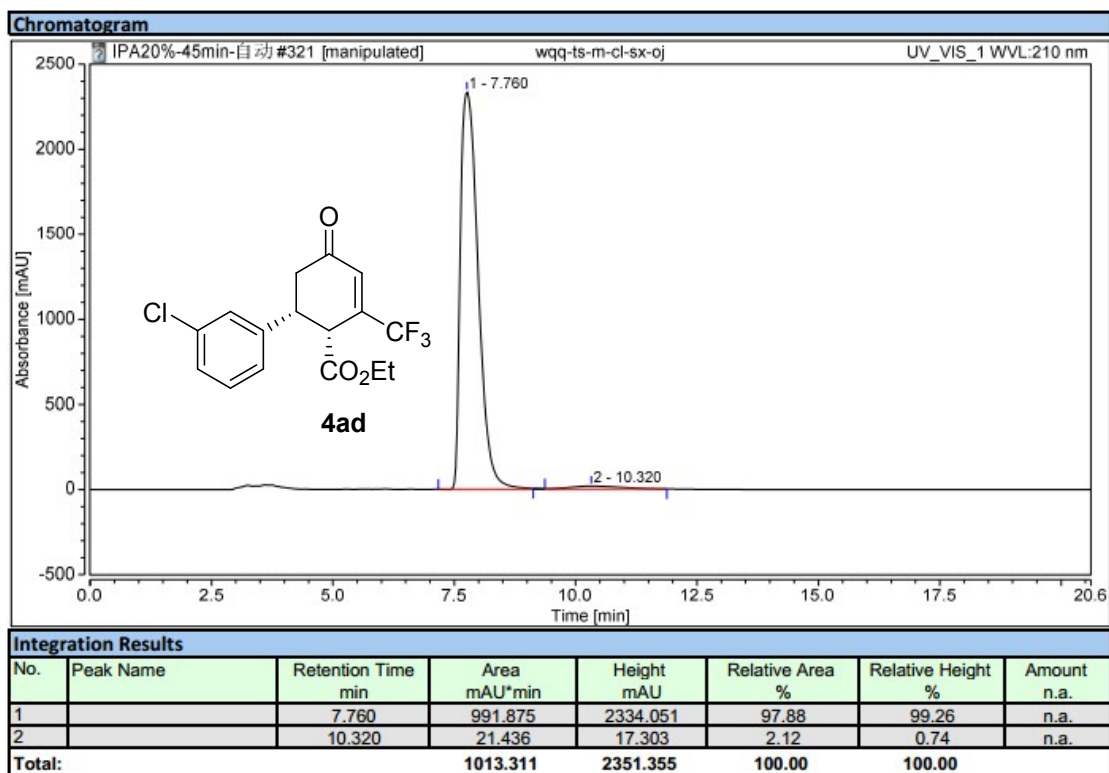


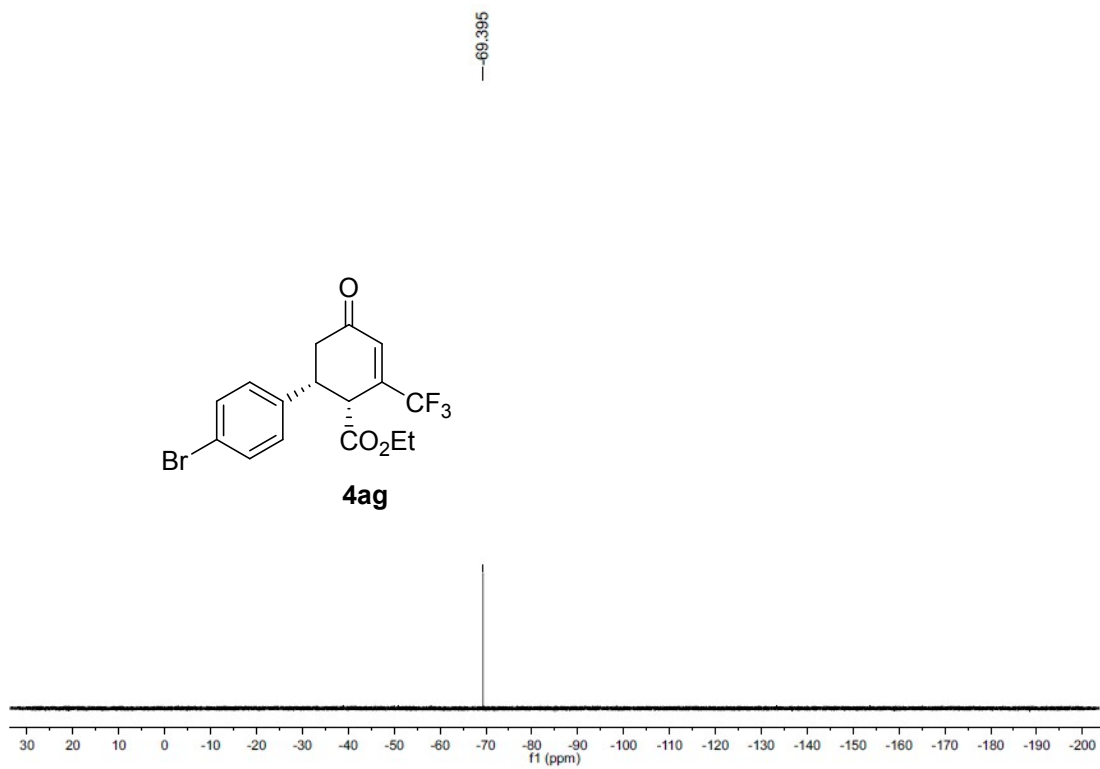
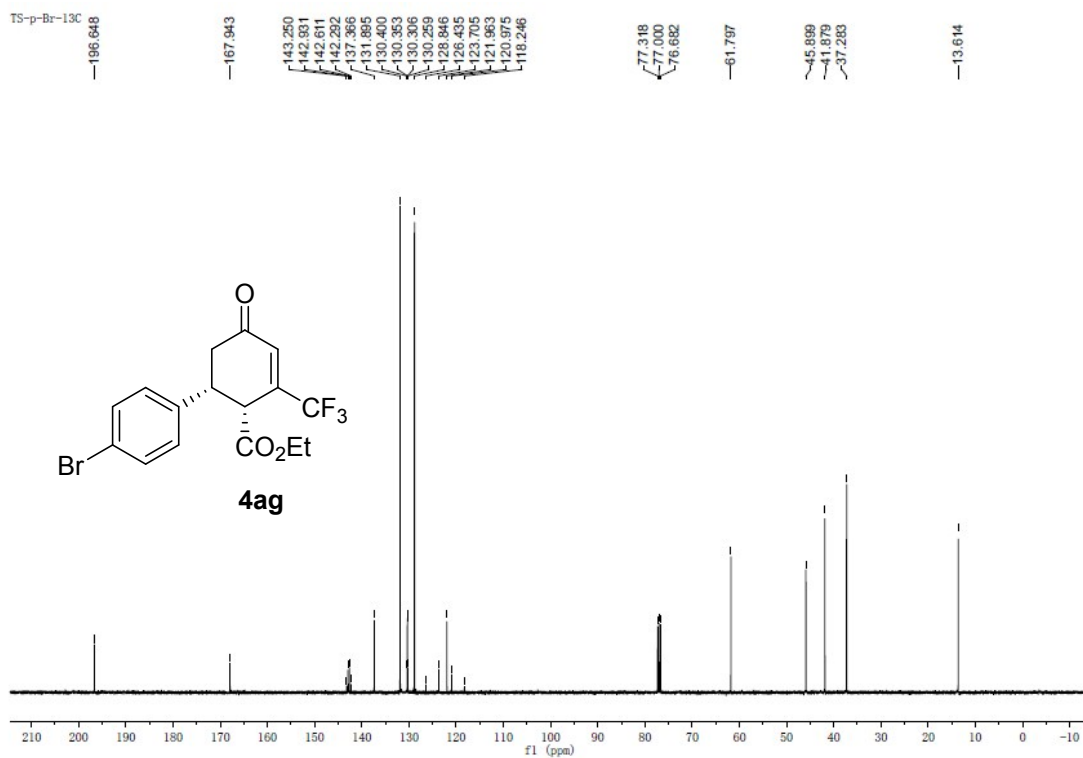


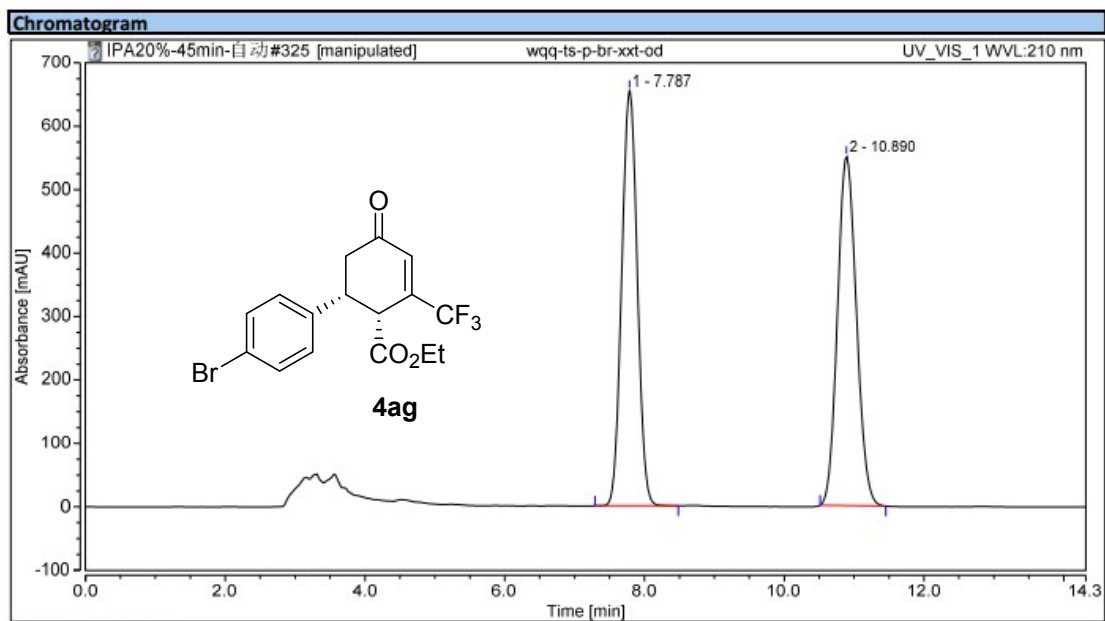


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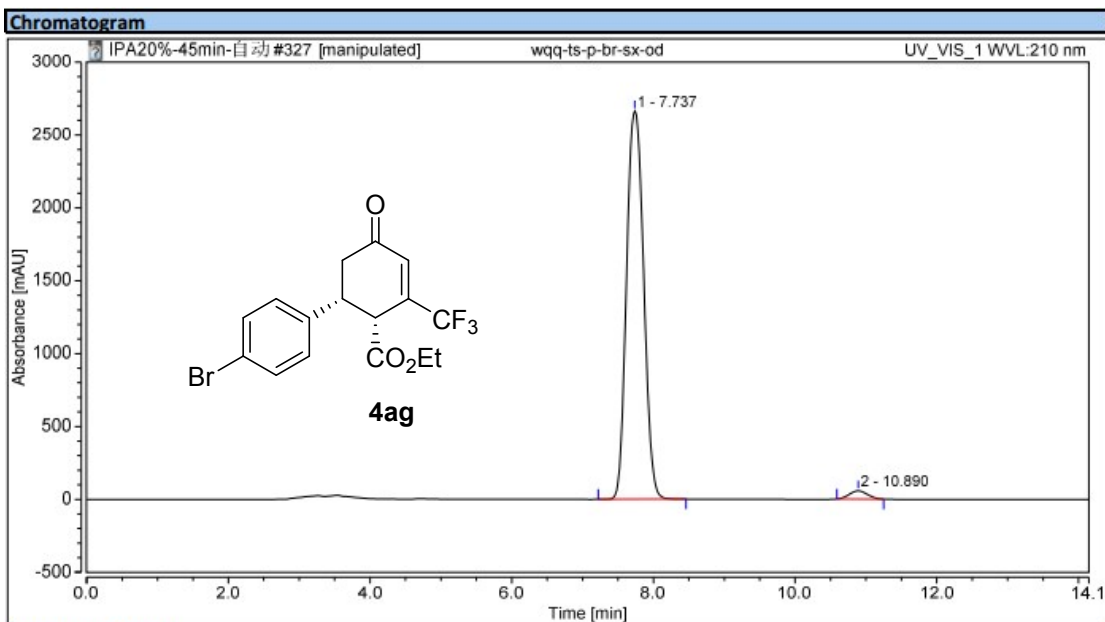






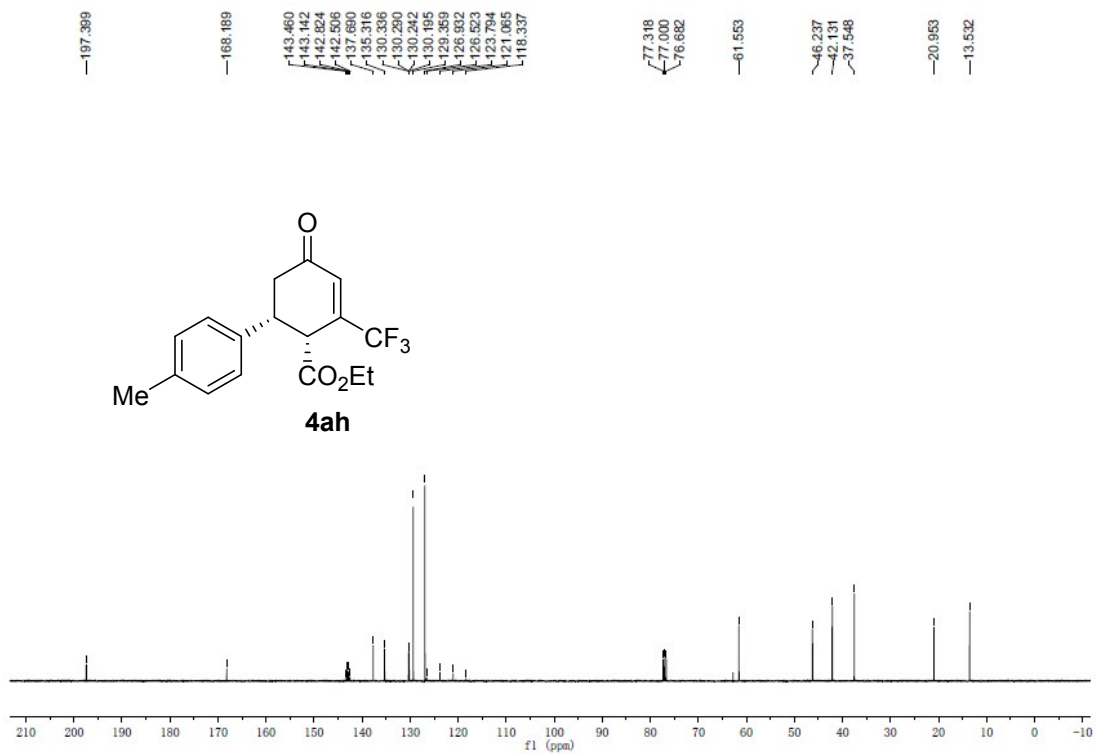
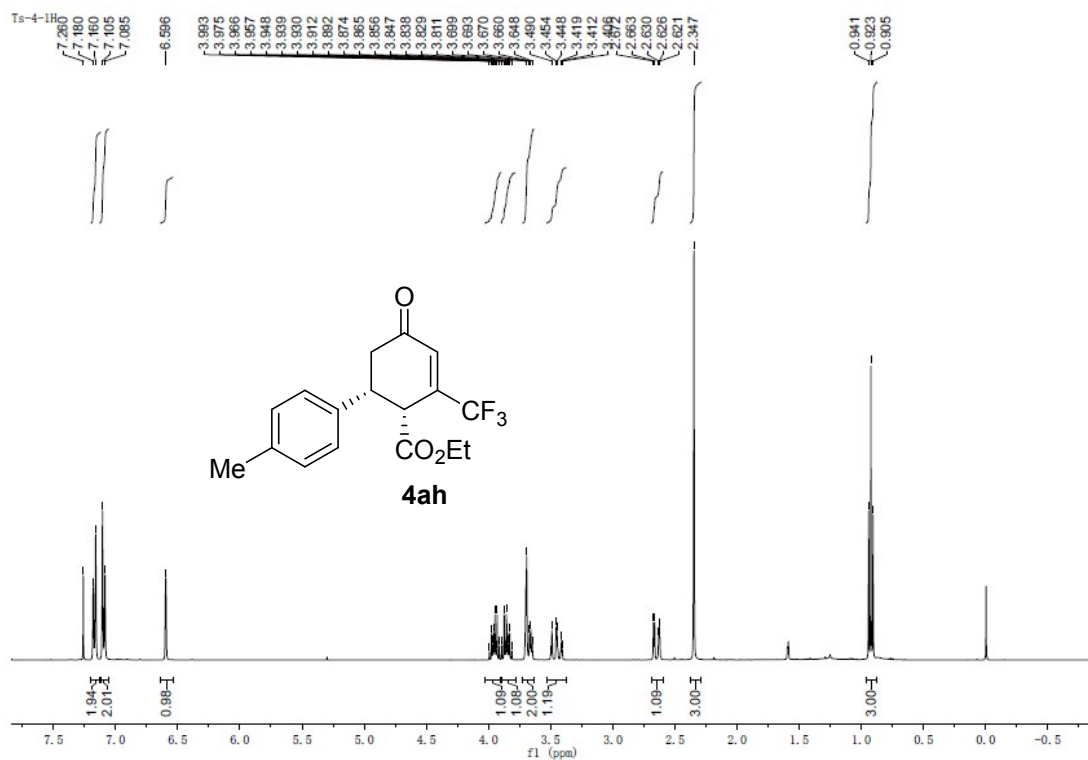
Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		7.787	168.921	655.114	49.42	54.33	n.a.
2		10.890	172.858	550.599	50.58	45.67	n.a.
Total:			341.779	1205.713	100.00	100.00	

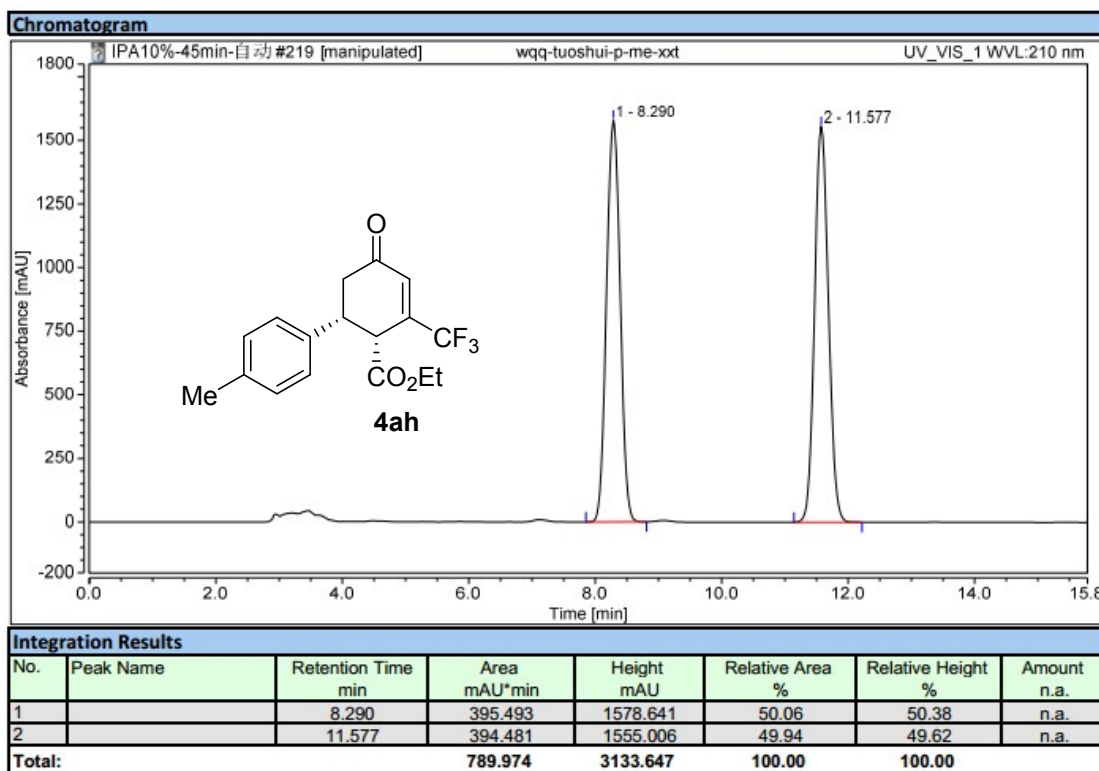
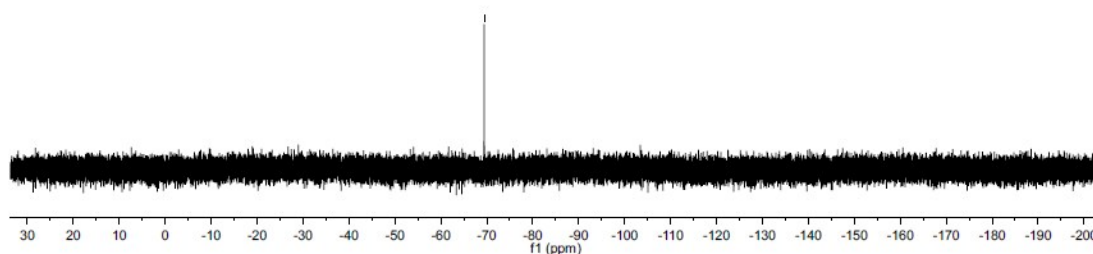
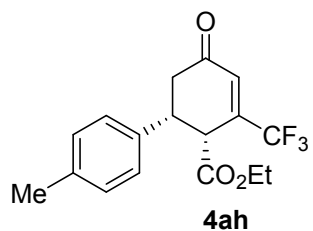


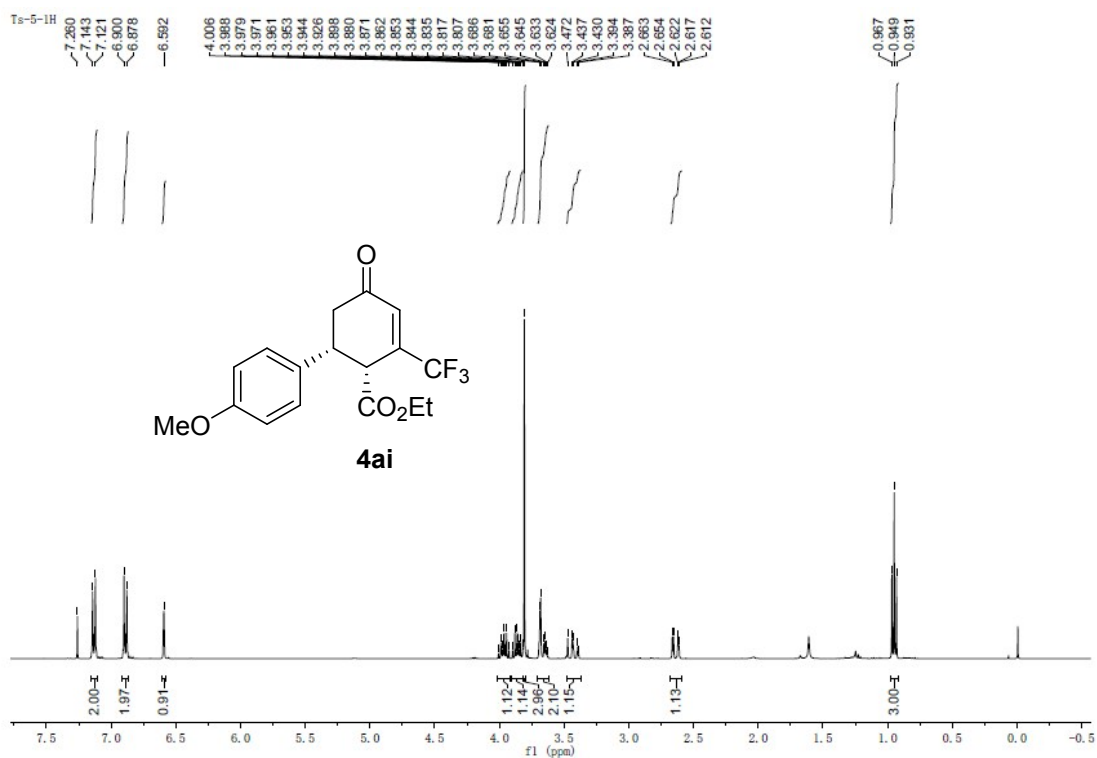
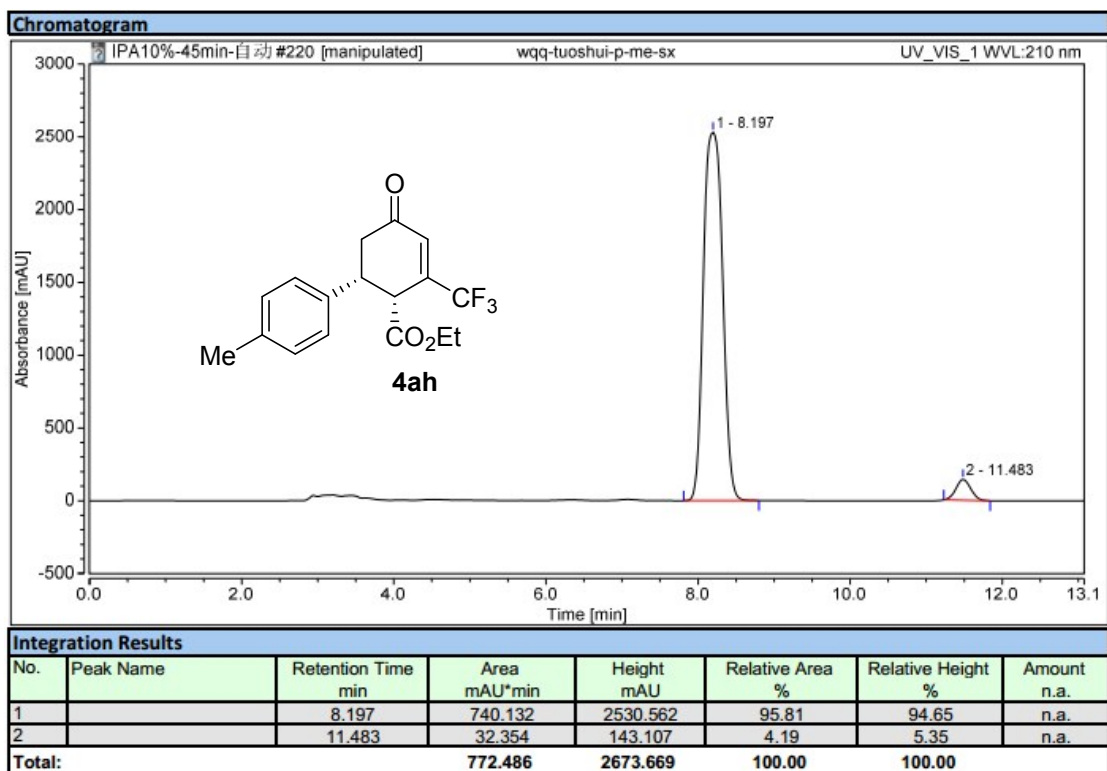
Integration Results

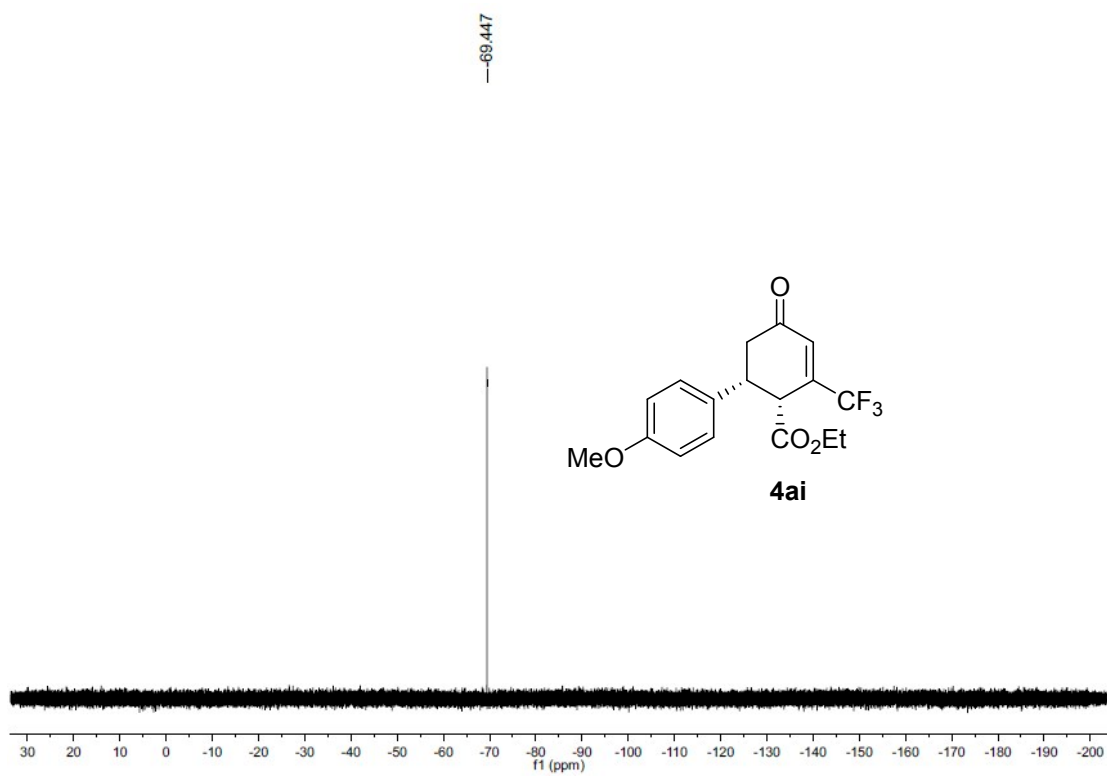
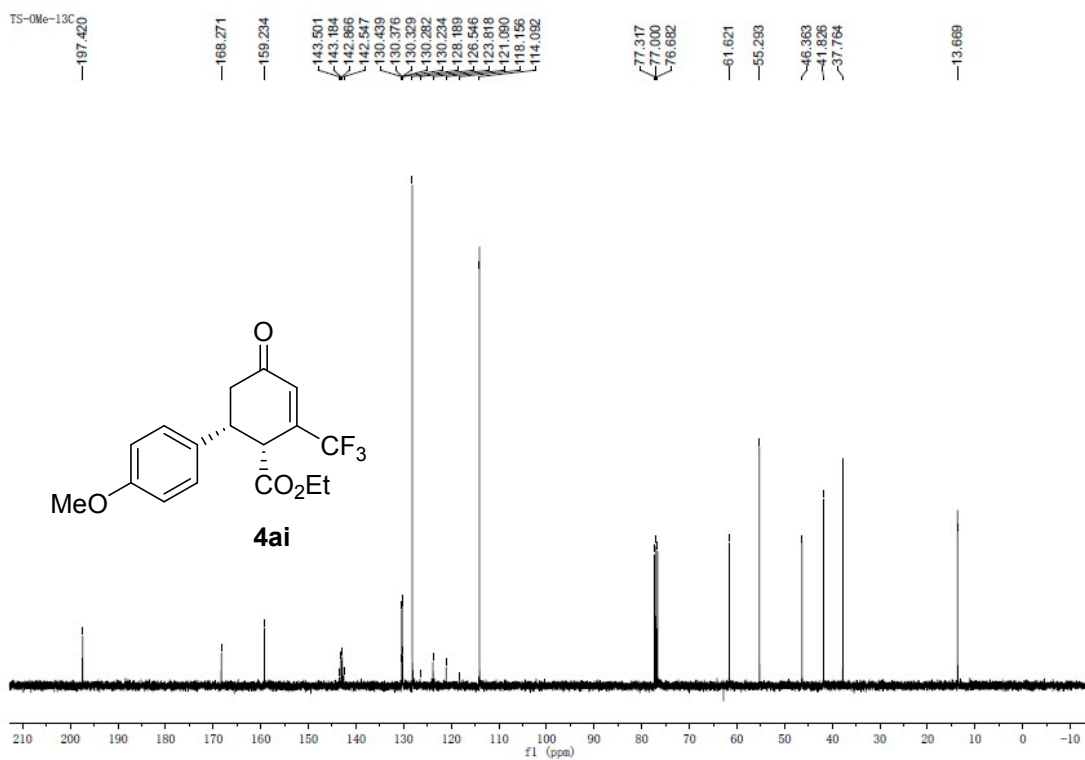
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		7.737	743.923	2665.483	97.80	97.93	n.a.
2		10.890	16.734	56.279	2.20	2.07	n.a.
Total:			760.657	2721.762	100.00	100.00	

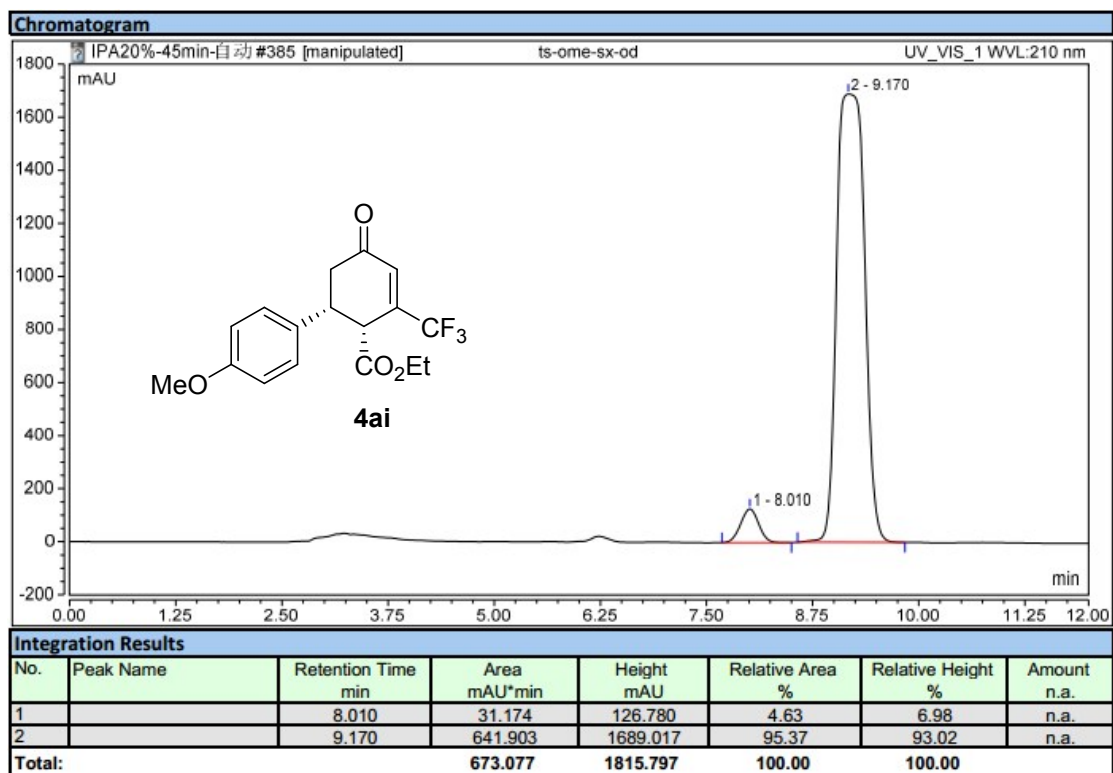
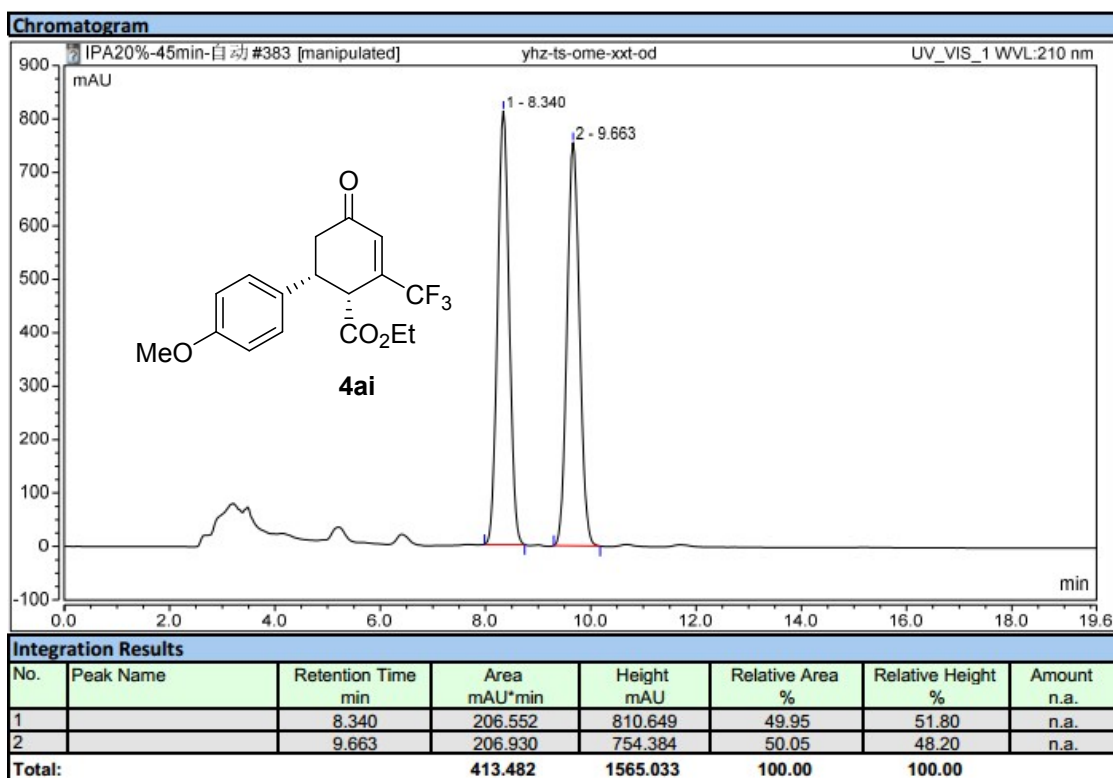


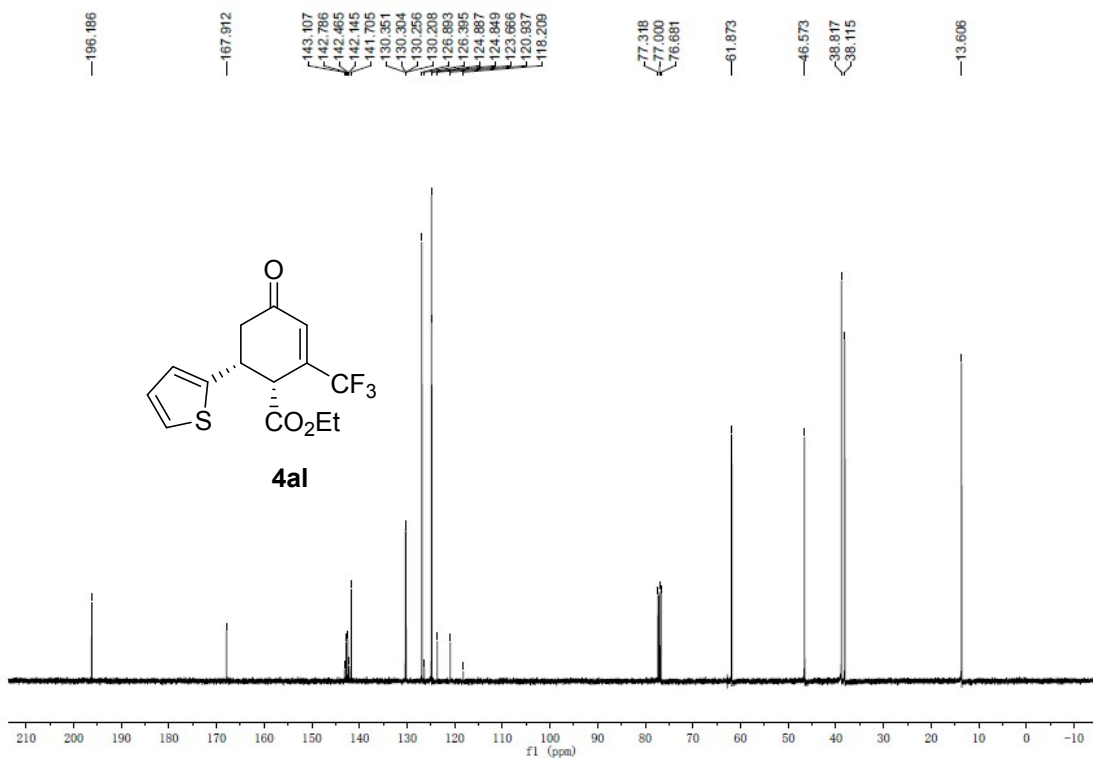
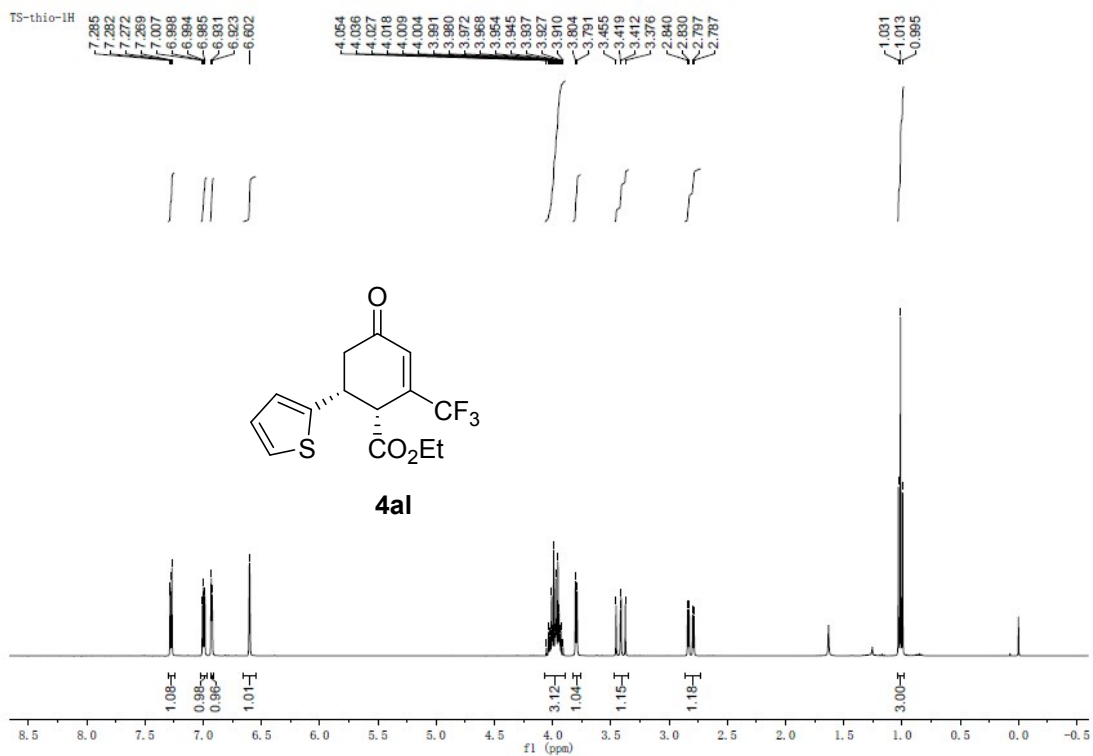
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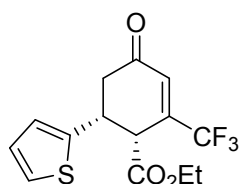




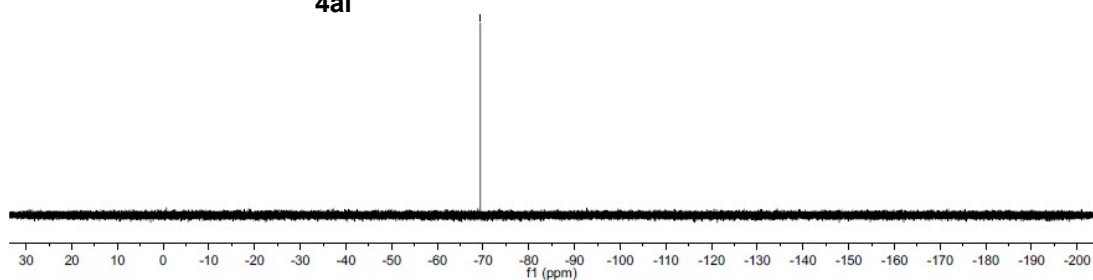




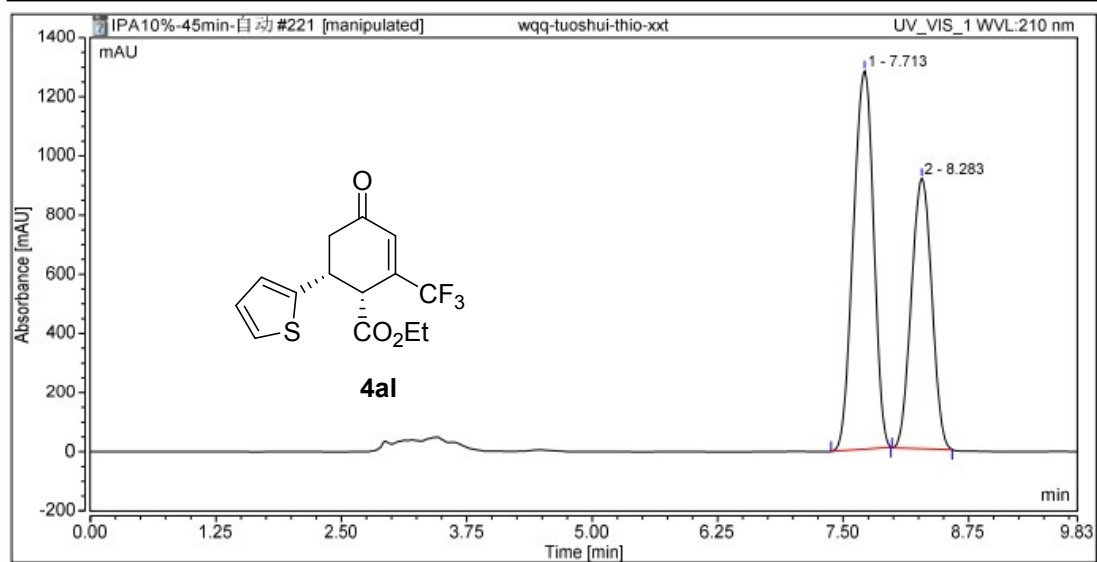
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4al

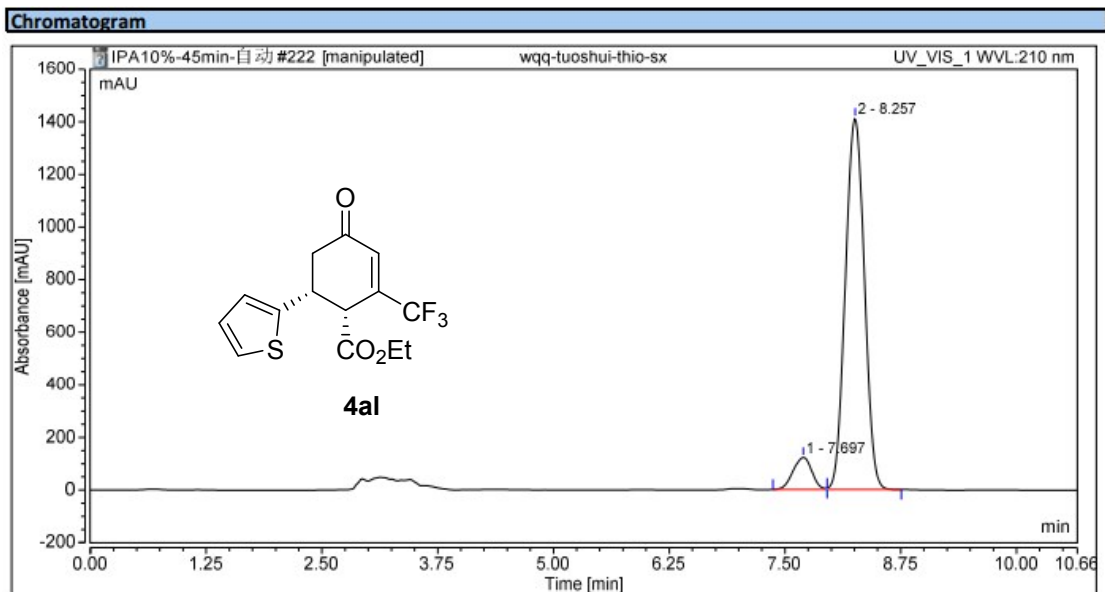


Chromatogram



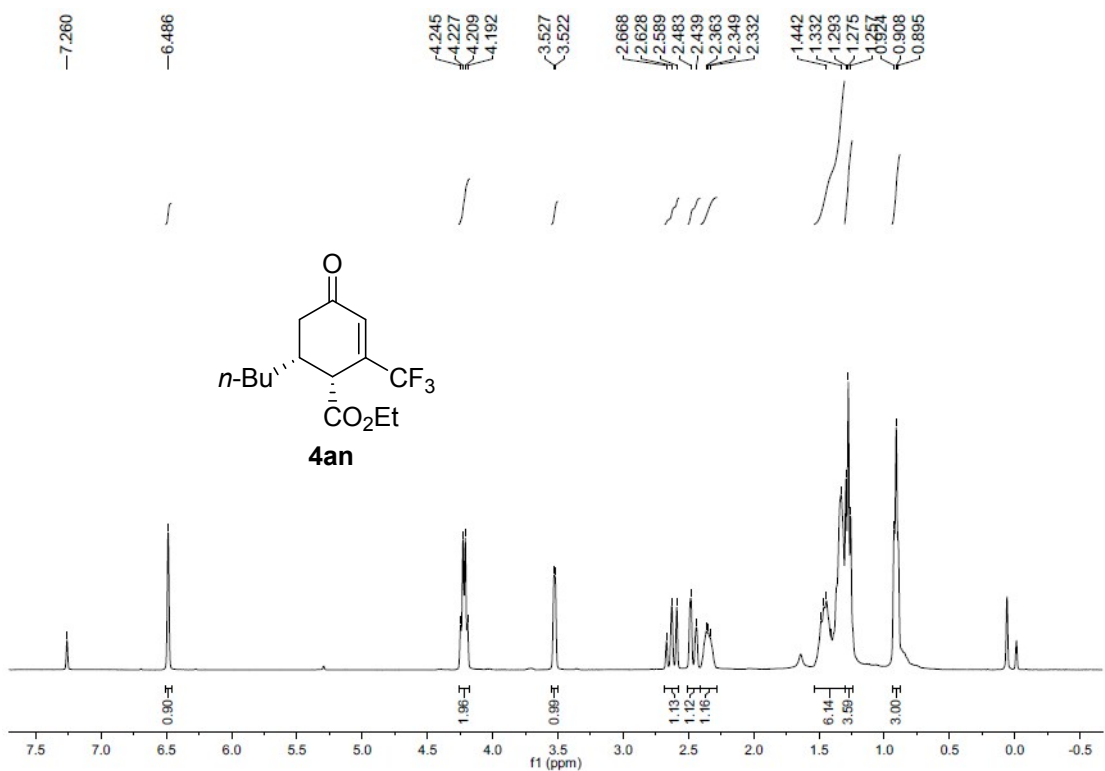
Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		7.713	298.710	1278.968	58.09	58.32	n.a.
2		8.283	215.483	913.905	41.91	41.68	n.a.
Total:			514.193	2192.873	100.00	100.00	

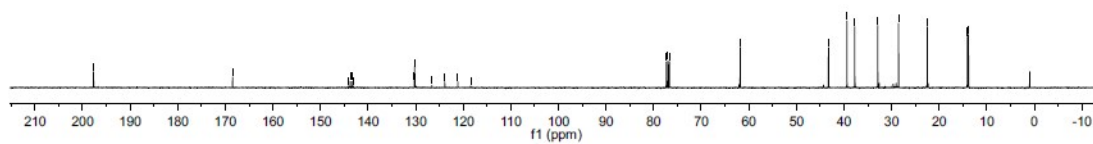
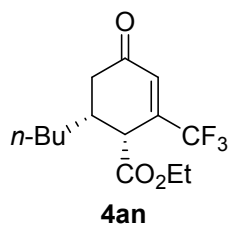


Integration Results

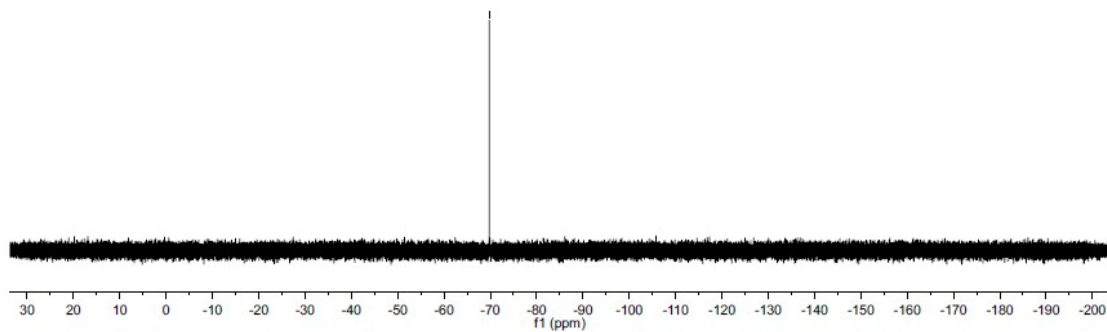
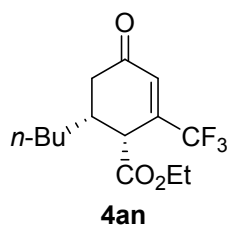
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		7.697	28.705	122.029	7.88	7.96	n.a.
2		8.257	335.510	1411.506	92.12	92.04	n.a.
Total:			364.215	1533.534	100.00	100.00	

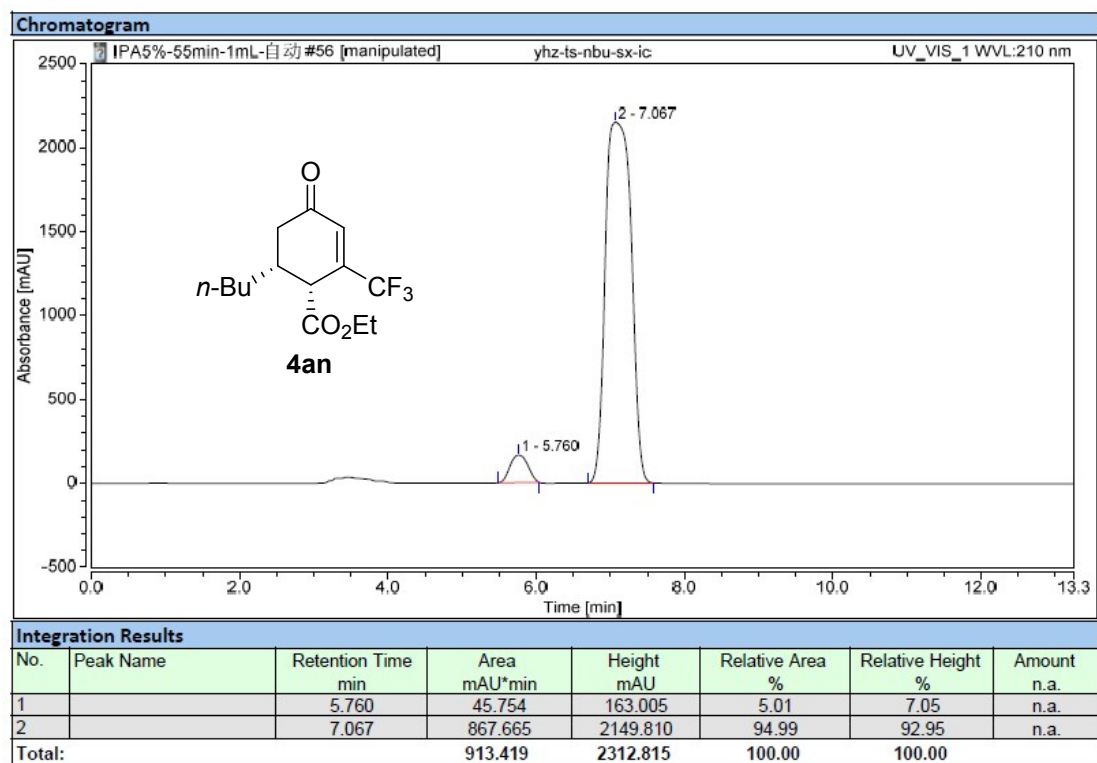
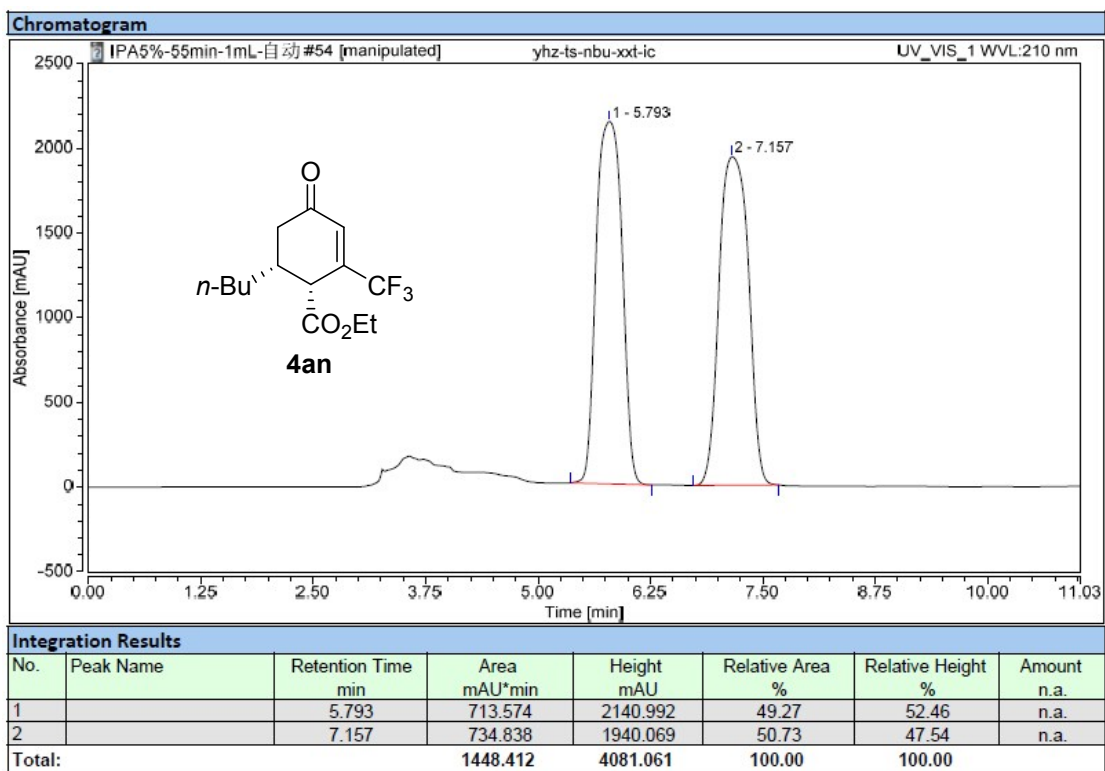


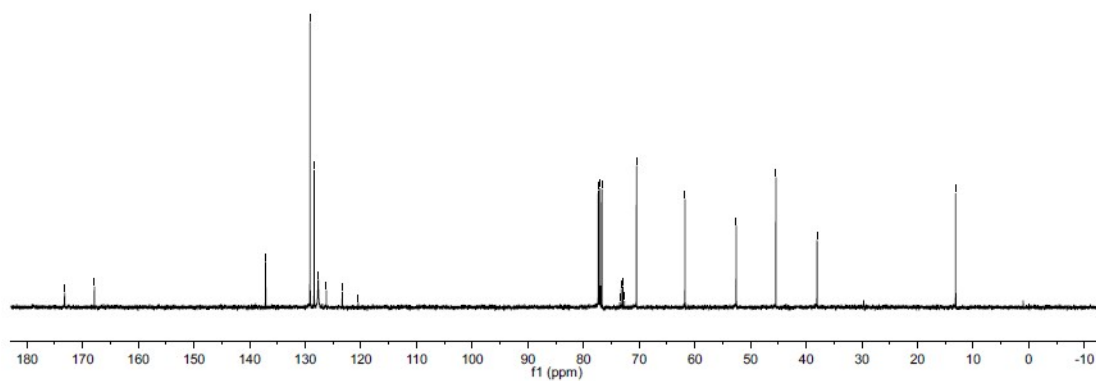
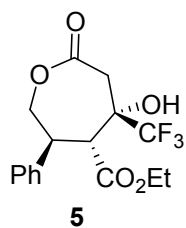
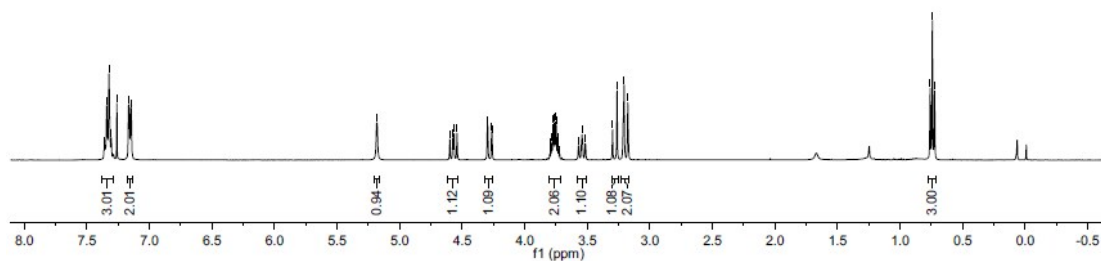
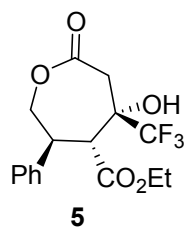
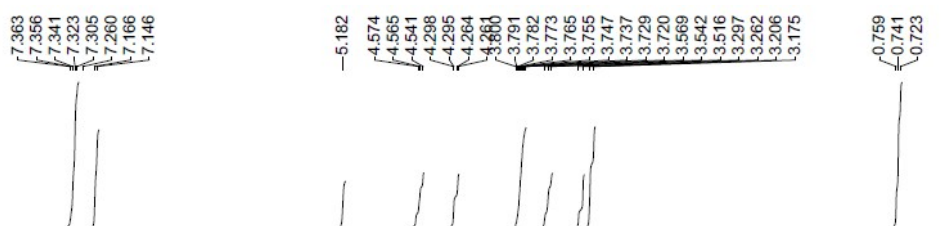
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 13.849



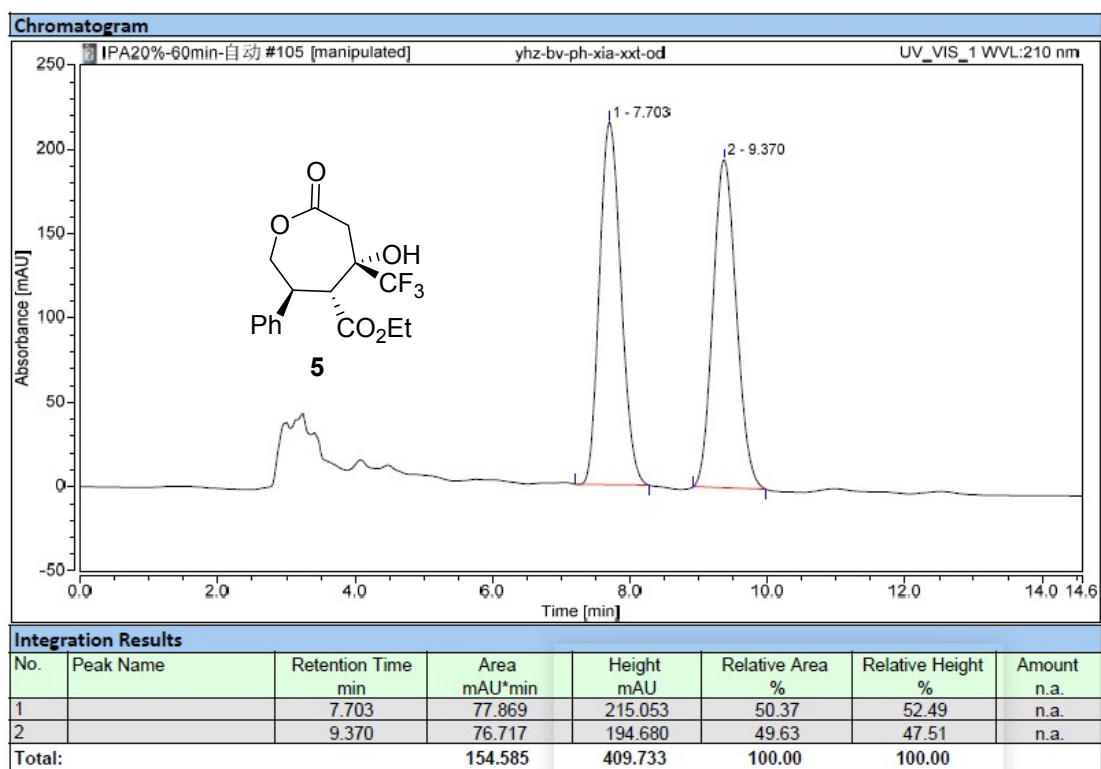
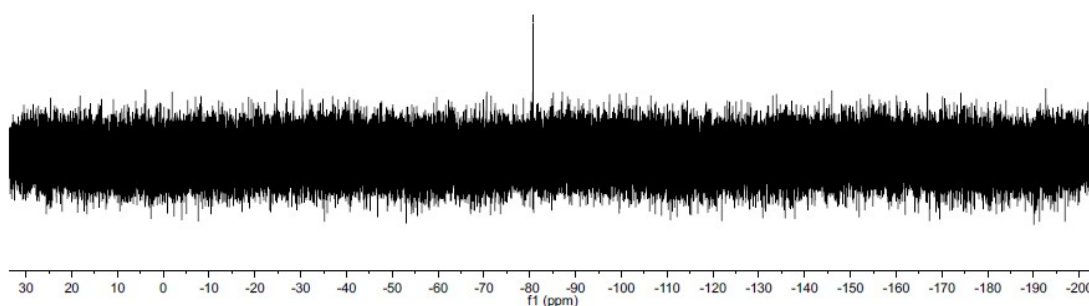
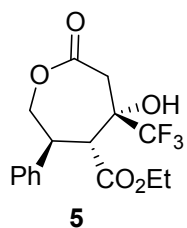
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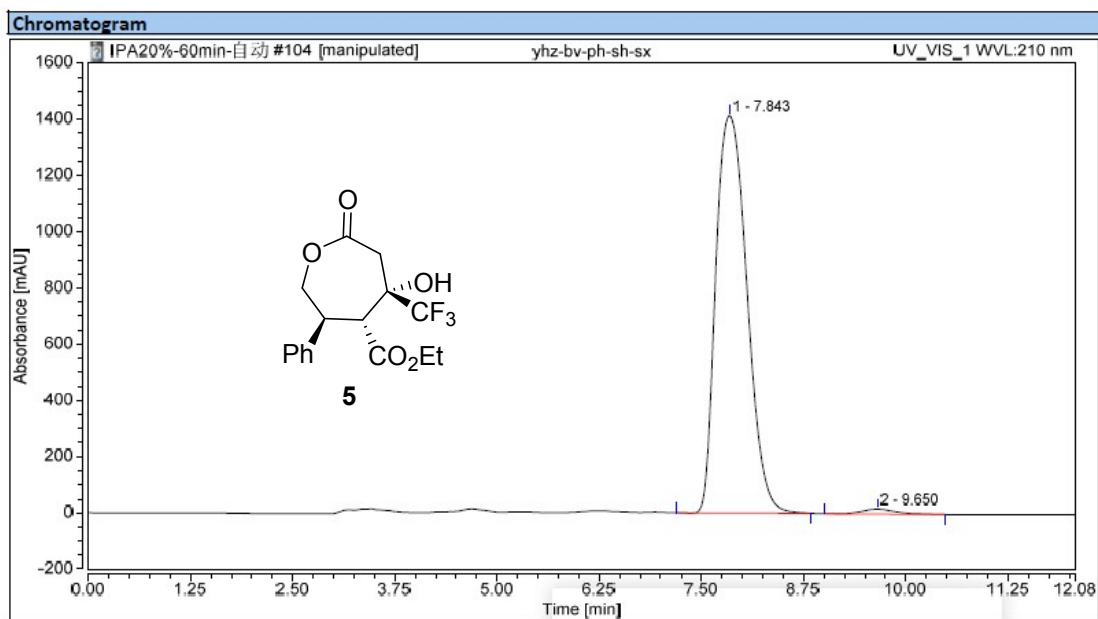






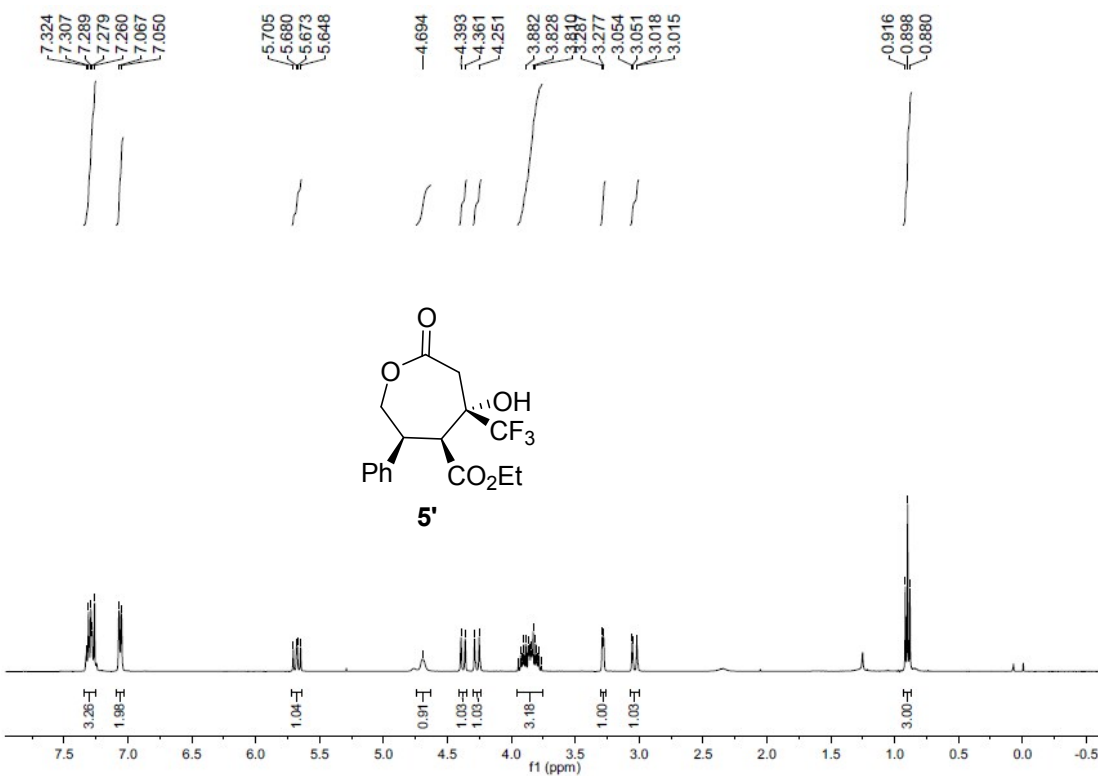
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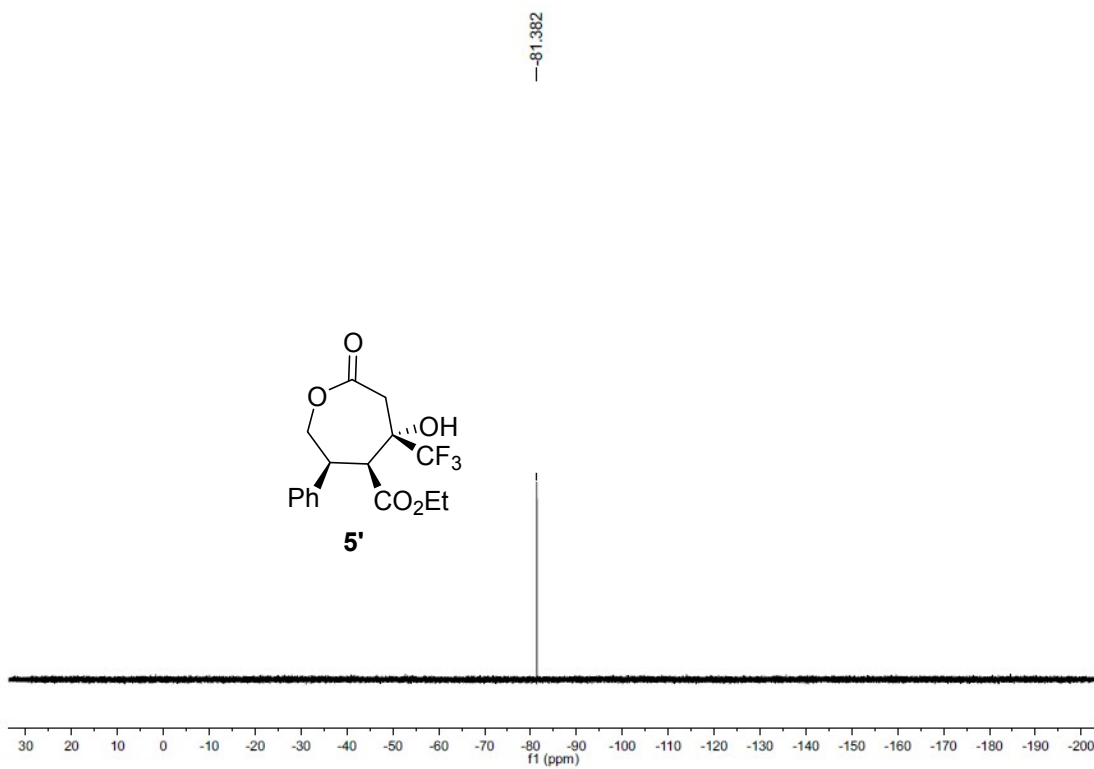
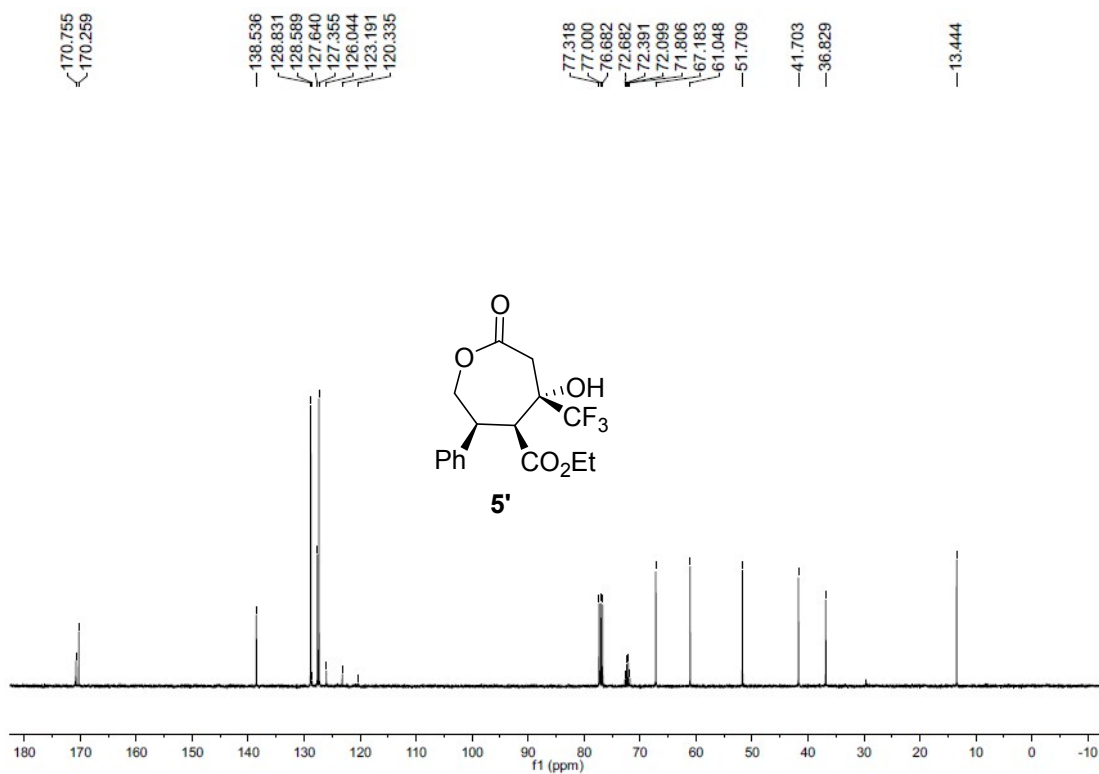


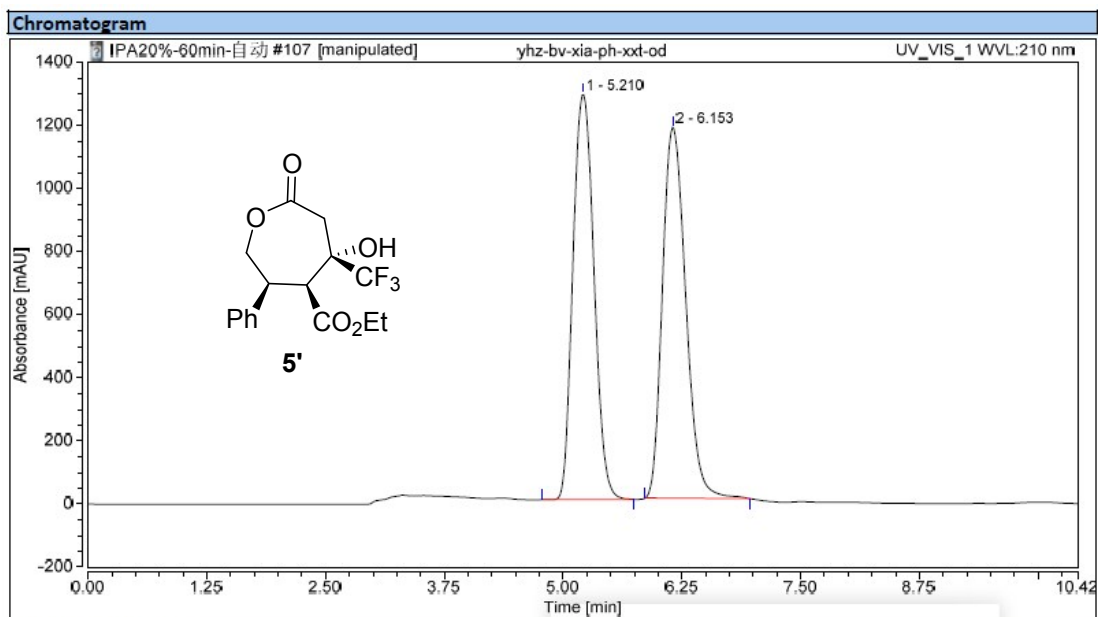


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		7.843	623.625	1414.008	98.70	98.79	n.a.
2		9.650	8.216	17.369	1.30	1.21	n.a.
Total:			631.841	1431.377	100.00	100.00	

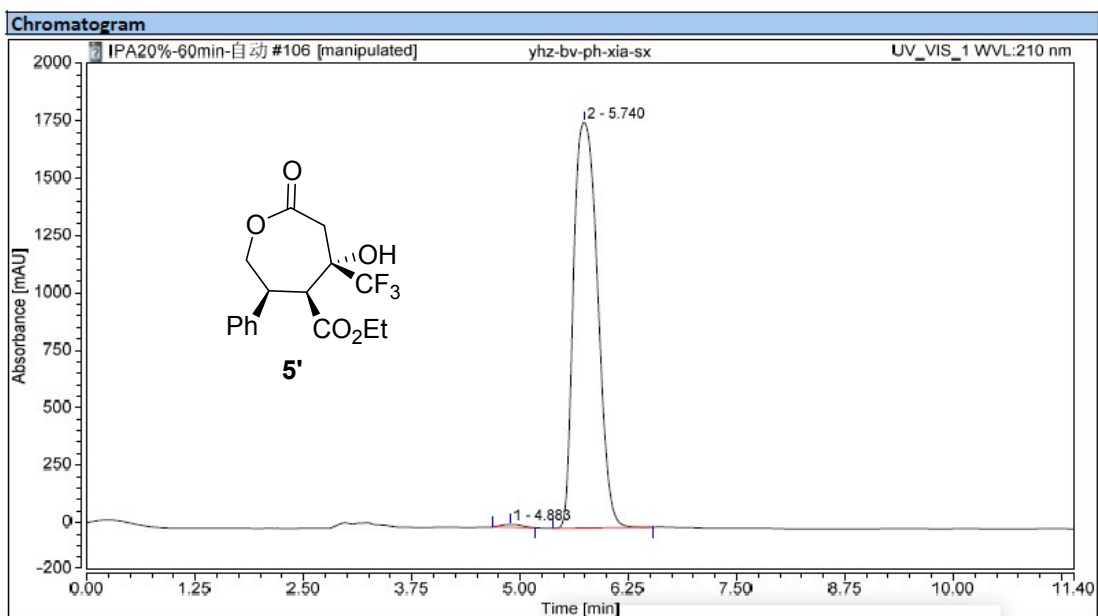






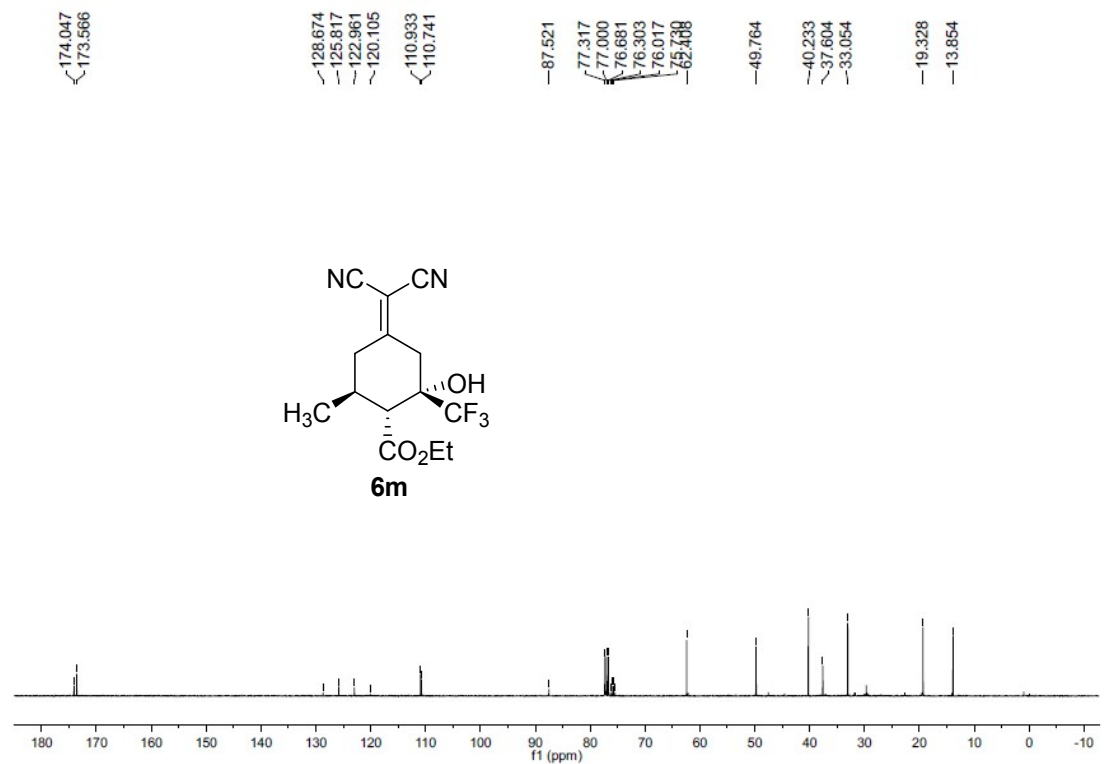
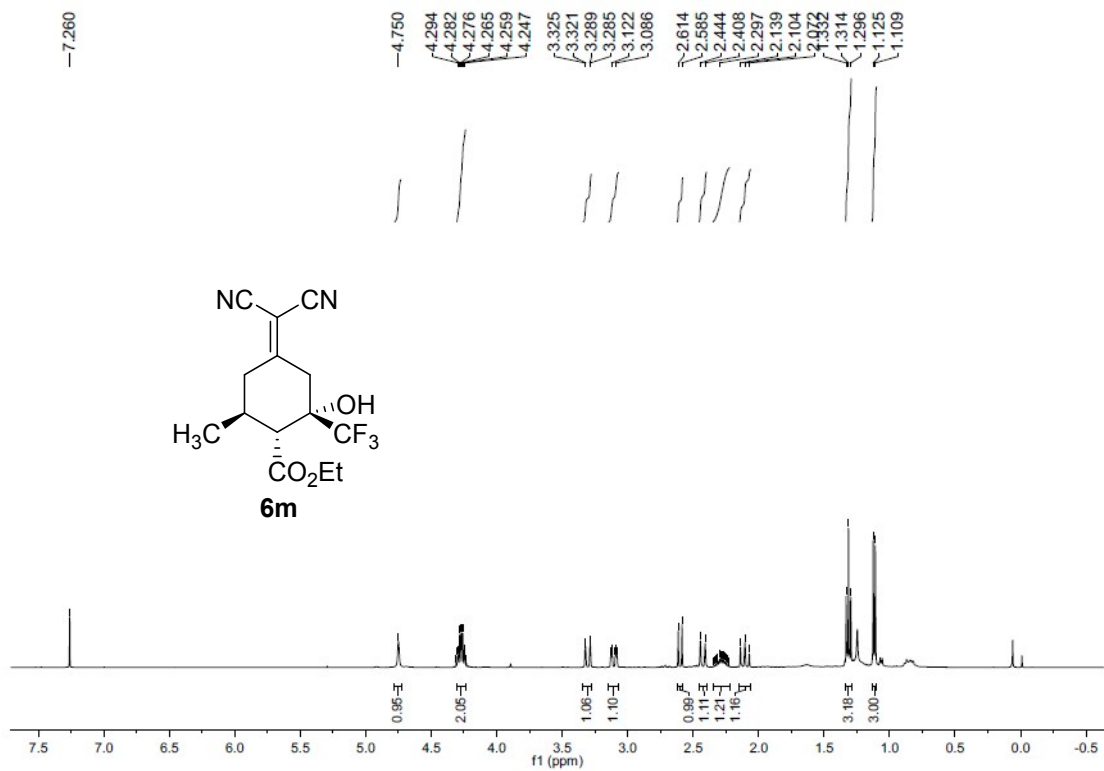
Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		5.210	329.379	1286.781	49.64	52.23	n.a.
2		6.153	334.159	1176.688	50.36	47.77	n.a.
Total:			663.538	2463.469	100.00	100.00	

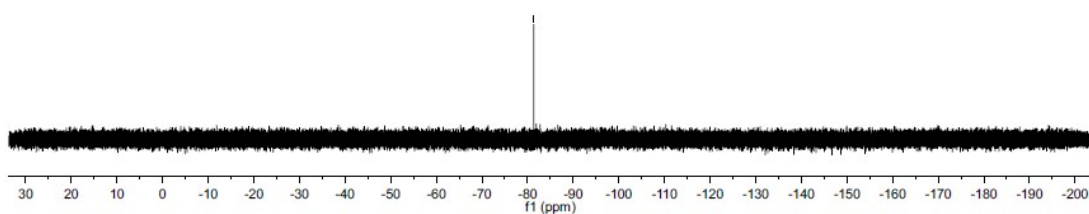
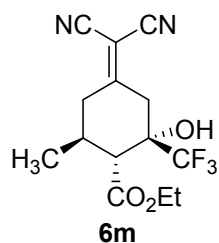


Integration Results

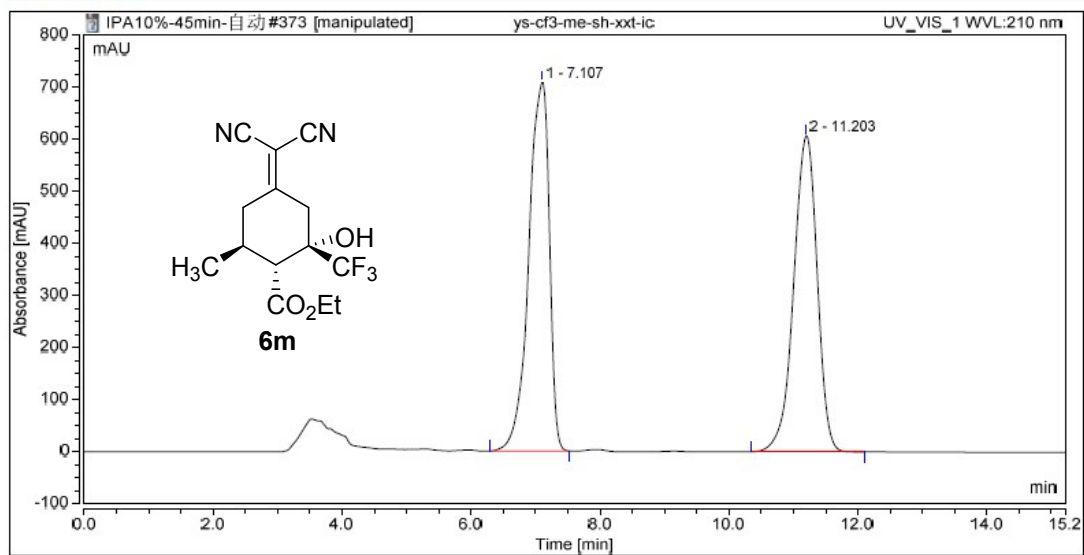
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		4.883	3.435	12.995	0.60	0.73	n.a.
2		5.740	565.251	1766.699	99.40	99.27	n.a.
Total:			568.686	1779.694	100.00	100.00	



-81.344



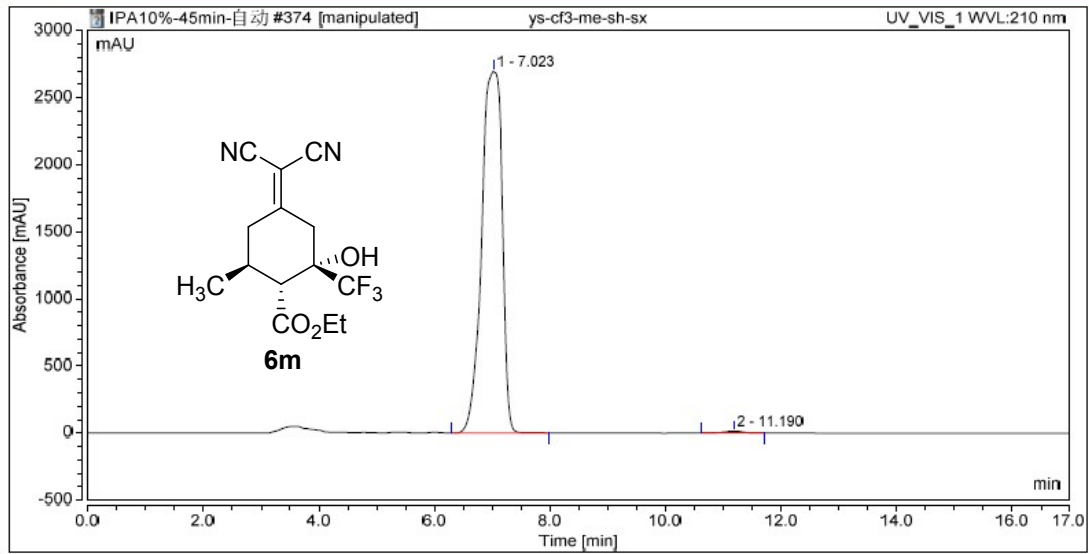
Chromatogram



Integration Results

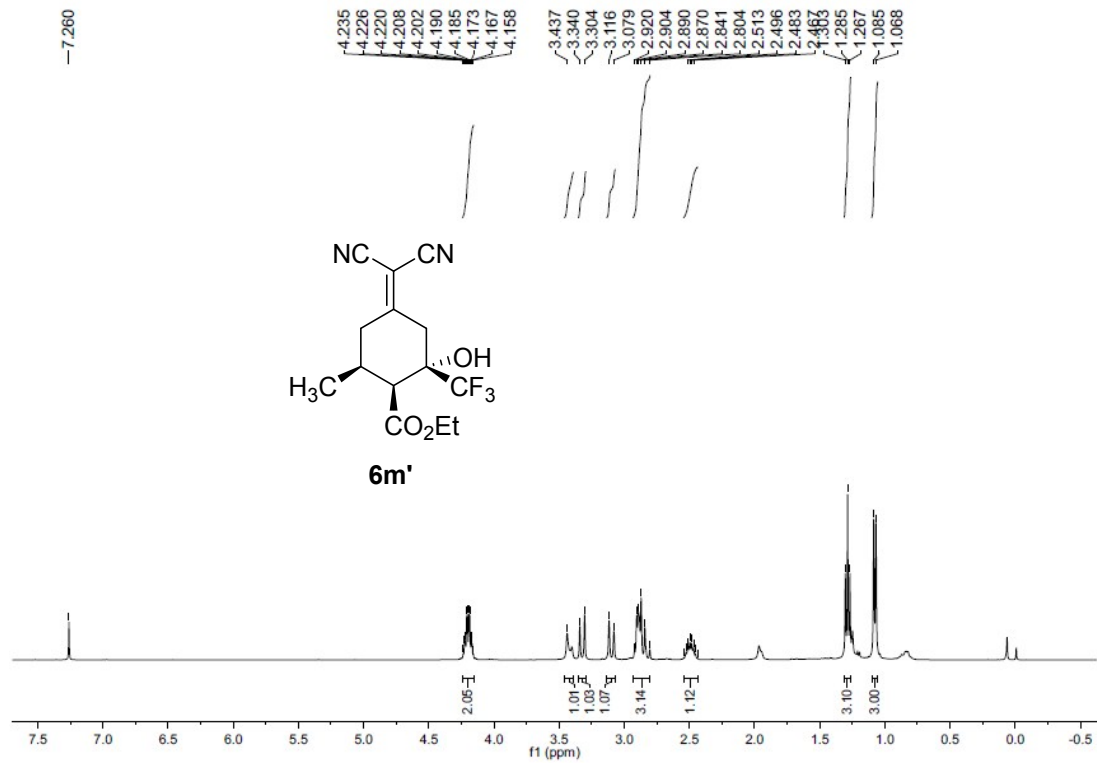
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		7.107	261.656	708.954	50.49	53.84	n.a.
2		11.203	256.619	607.863	49.51	46.16	n.a.
Total:			518.276	1316.817	100.00	100.00	

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		7.023	1107.417	2698.715	99.45	99.40	n.a.
2		11.190	6.161	16.168	0.55	0.60	n.a.
Total:			1113.577	2714.883	100.00	100.00	



—178.711
—169.998

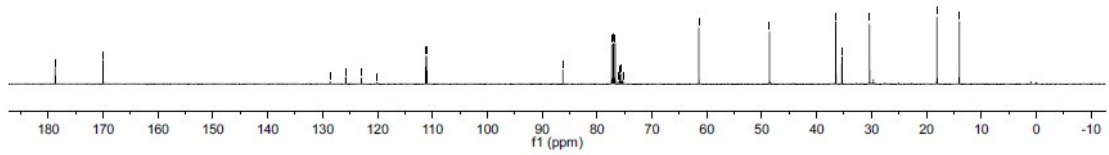
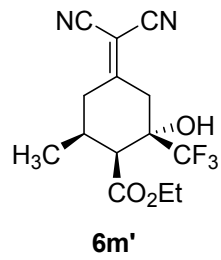
128.611
125.769
122.927
120.085
111.187
111.022

—86.214
77.318
77.000
76.683
75.845
75.550
69.754

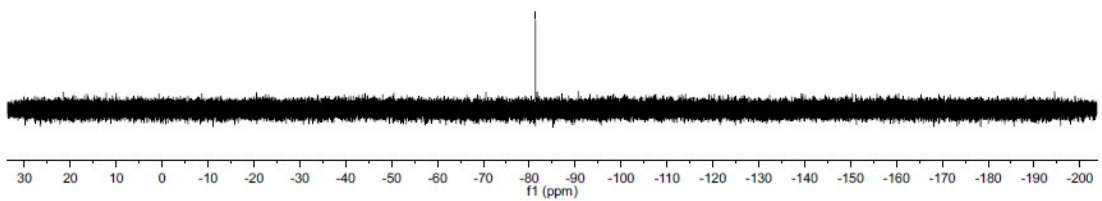
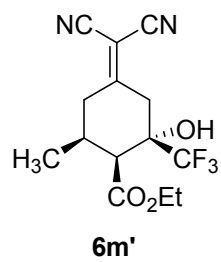
—48.575

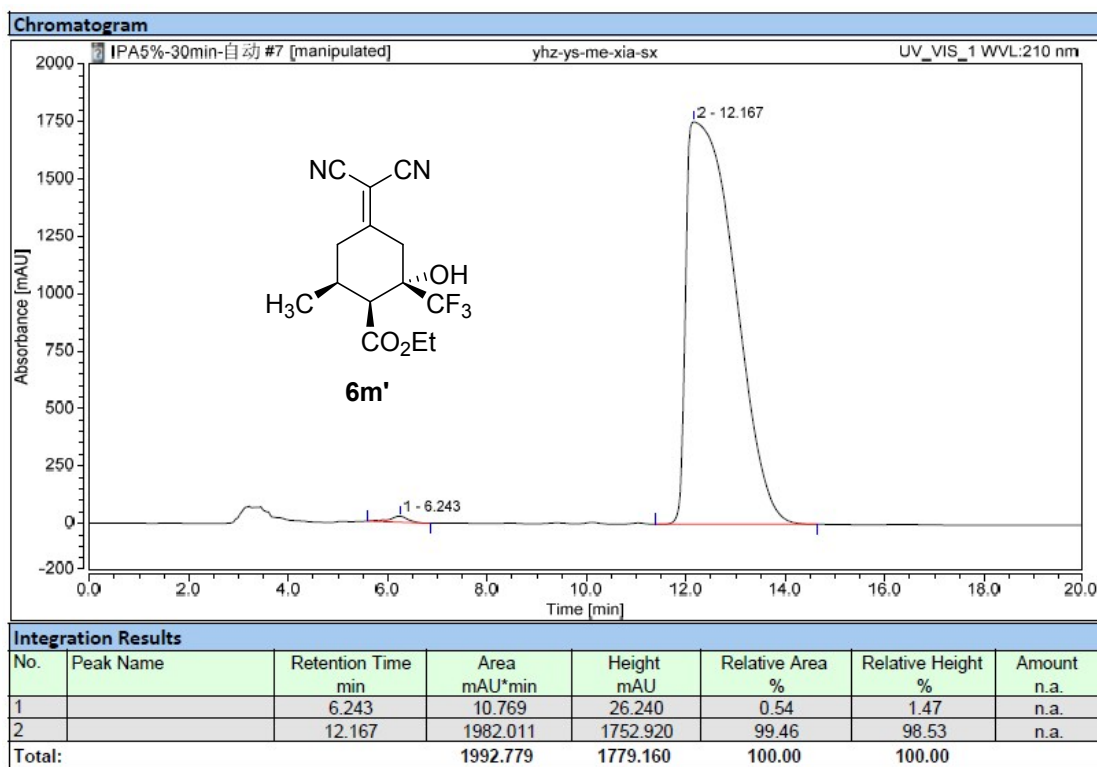
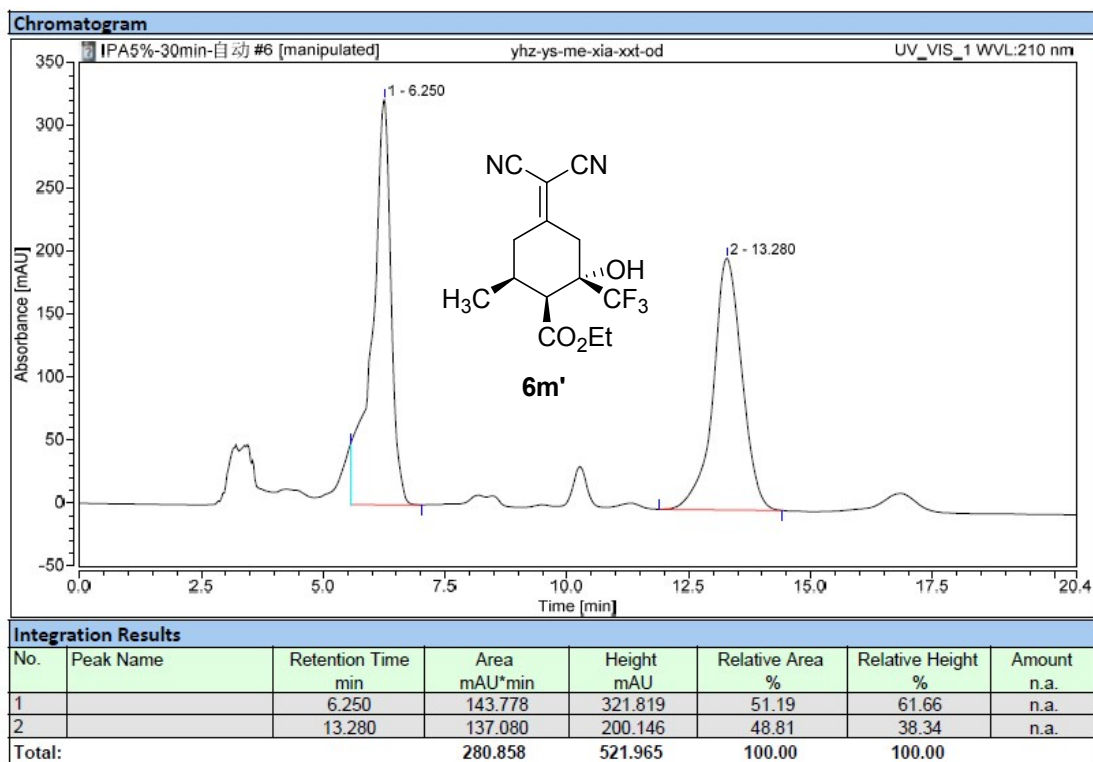
—36.500
—35.362
—30.352

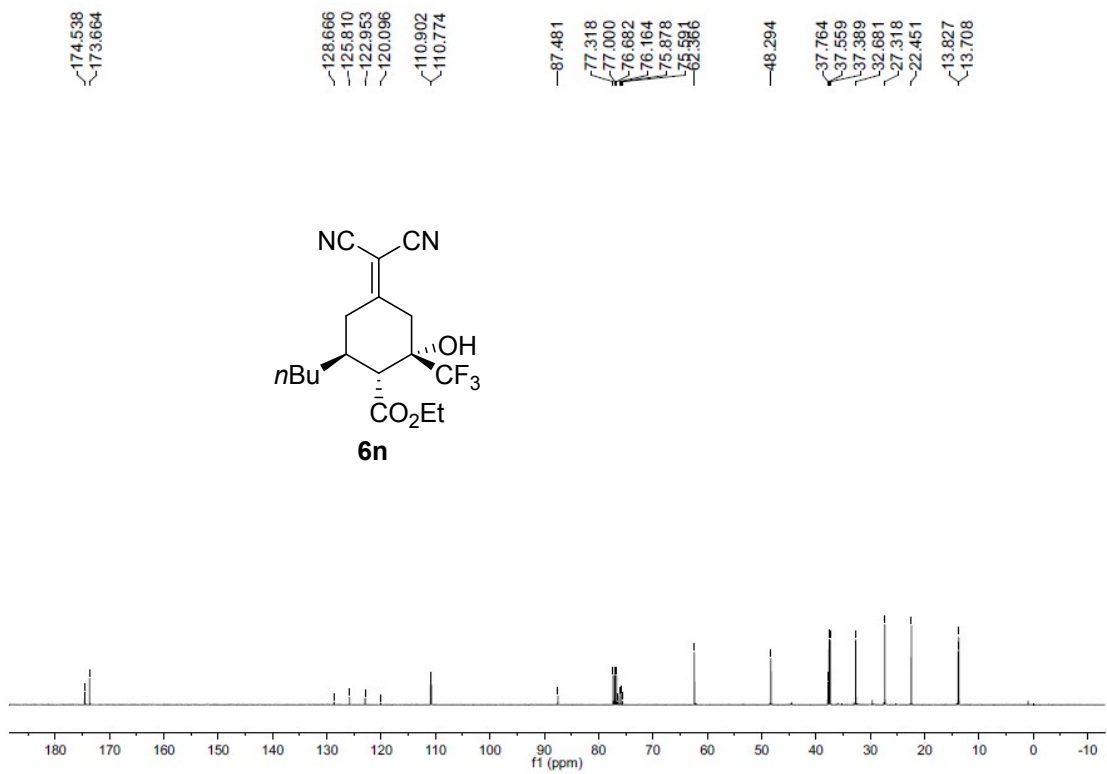
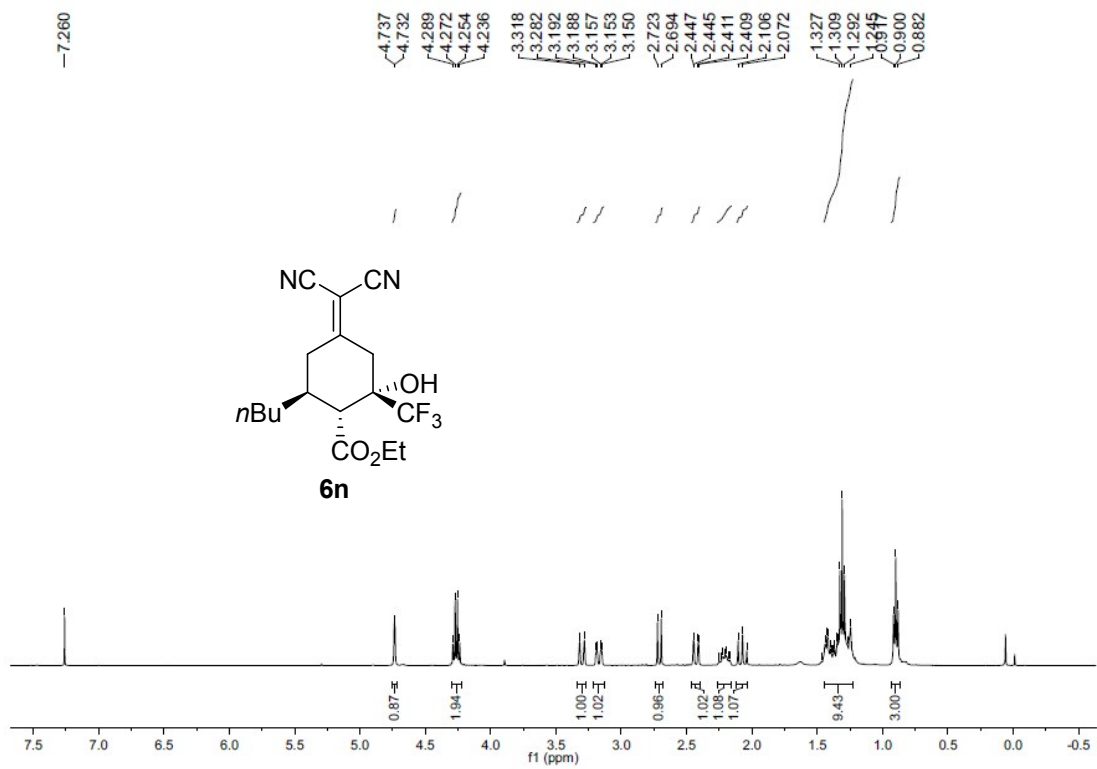
—18.062
—13.985

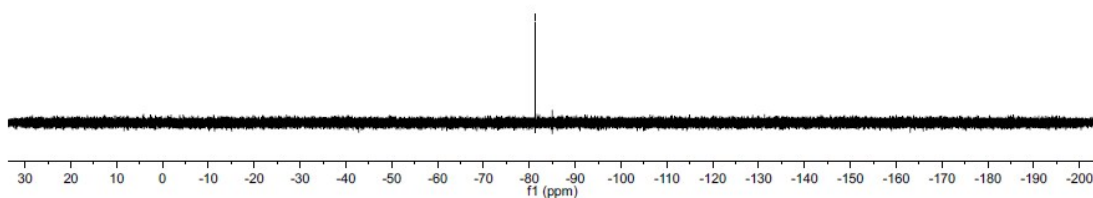
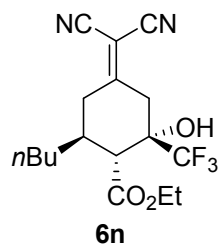


—81.342

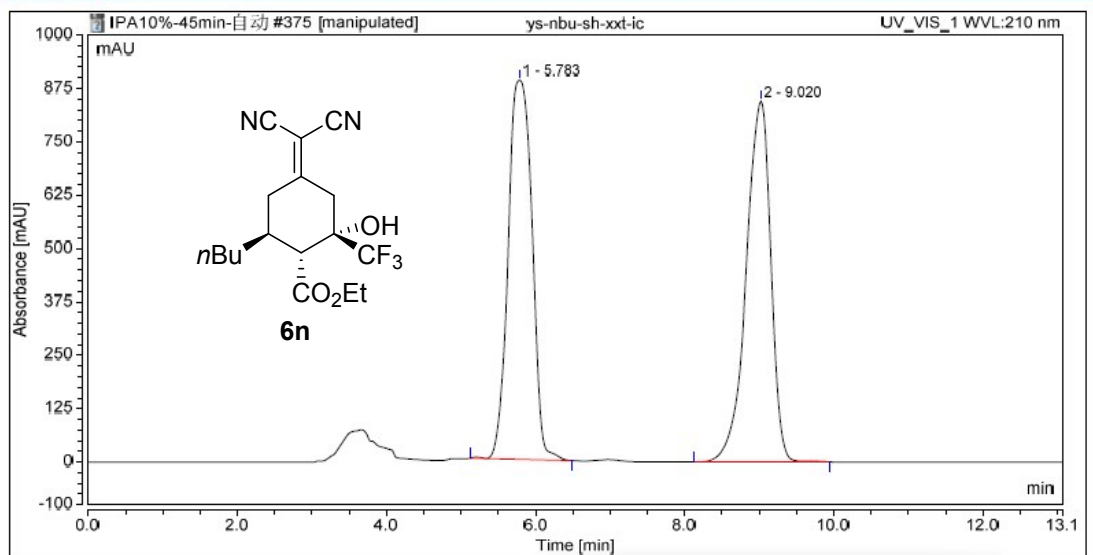




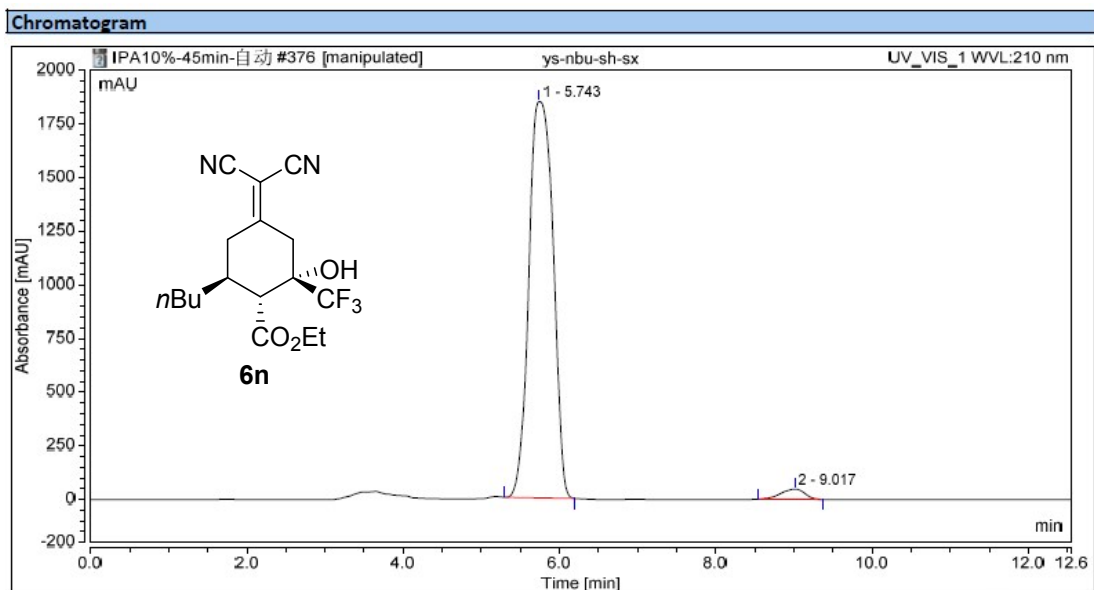




Chromatogram

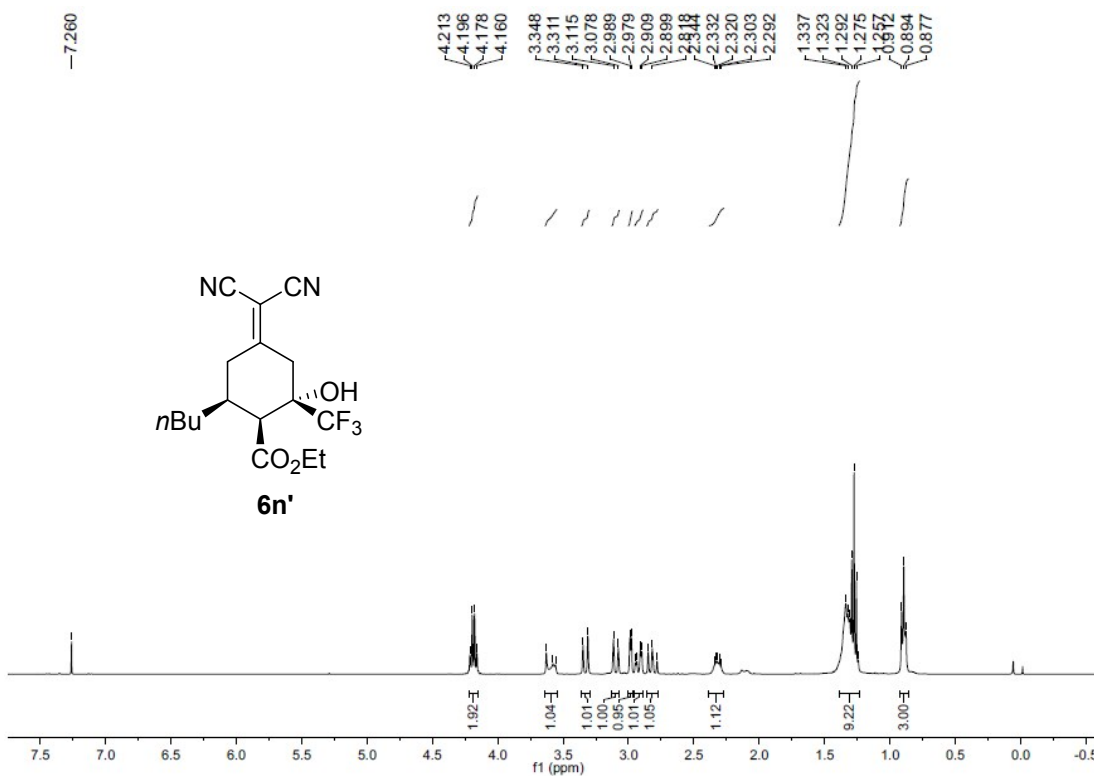


Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		5.783	329.299	888.155	50.46	51.25	n.a.
2		9.020	323.347	844.941	49.54	48.75	n.a.
Total:			652.646	1733.096	100.00	100.00	



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		5.743	662.293	1847.513	97.48	97.45	n.a.
2		9.017	17.090	48.332	2.52	2.55	n.a.
Total:			679.383	1895.845	100.00	100.00	



—179.128

—170.087

~128.650

~125.809

~122.963

~120.120

~111.152

~110.971

—86.088

~77.319

~77.000

~76.681

~75.753

~75.458

~69.395

—46.832

~35.690

~35.495

~35.325

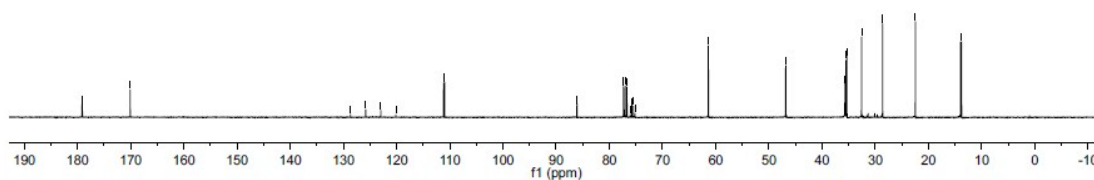
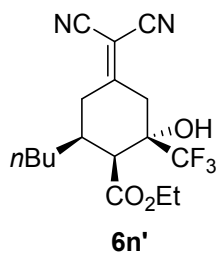
~32.560

~28.609

~22.449

~13.938

~13.770



—81.278

