10.1071/CH14179_AC

Australian Journal of Chemistry 2014, 67(7), 1115-1118

Supplementary Material

Novel Tartrate-Based Guanidines for Enantioselective Fluorination of 1,3-Dicarbonyl and α-Cyano Carbonyl Compounds

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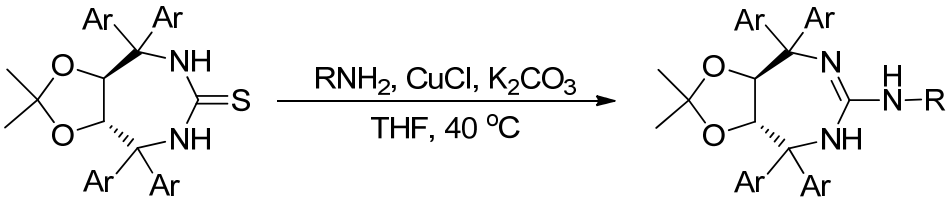
1. General information

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. All reactions were carried out in air and used undistilled solvent, without any precautions to exclude moisture unless otherwise noted. Anhydrous THF was freshly distilled from sodium and benzophenone. Column chromatography was performed on silica gel (100~200 mesh). Enantiomeric excesses (ee) were determined by HPLC using corresponding commercial chiral columns as stated at 30 °C with UV detector at 254 nm. Optical rotations were reported as follows: $[\alpha]^{T}_{D}$ (c g/100 mL, solvent). All ^{1}H NMR (400 MHz), ^{19}F NMR (376 MHz) and ^{13}C NMR (101 MHz) were recorded on a VARIAN INOVA-400 spectrometer with chemical shifts reported as ppm (in $CDCl_3$, TMS as internal standard). High resolution mass spectrometry data were obtained with an HP1100 LC/MSD mass spectrometer and an LC/Q-TOF MS spectrometer.

Chiral guanidine **3a** and **3b** were prepared according to the literature.[1] Chiral guanidine **4** was prepared from L-*tert*-leucinol according to the literature.[2] β-Ketoesters **6a-h** and **6o**,[3] *α*-cyano carbonyl compounds **6i-j**[4] and β-diketones **6k-n**[5] were prepared according to literature procedures. The racemic products were synthesized using tetramethyl guanidine (TMG) as catalyst.

2. General procedure for preparation of chiral guanidines

General method for the synthesis of guanidines 1a-k using a published procedure[6]

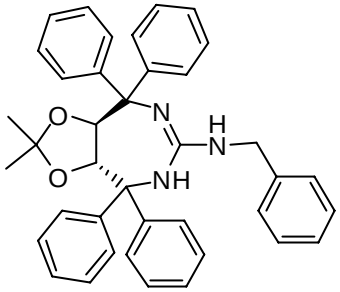


1: Yield: 60-93%

Under nitrogen atmosphere, to a suspension of K_2CO_3 (0.8 mmol, 4.0 equiv) and CuCl (0.42 mmol, 2.1 equiv) in THF (2 mL) was added thiourea (0.2 mmol, 1.0 equiv**)**. After stirring at room temperature for 10 min, amine (0.24-0.40 mmol, 1.2-2.0 equiv) was added. The resulting mixture was stirred at 40 ^oC for 4-72 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and quenched by saturated NH_4Cl aqueous solution. The pH was adjusted to 5 by the addition of 1M HCl. The mixture was extracted with dichloromethane and the combined organic layers were filtered through a pad of celite with the aid of dichloromethane. The filtrate was washed with brine and dried (Na_2SO_4). After evaporation of the solvent, the crude residue was purified by column chromatography on silica gel (dichloromethane/methanol = 50/1-20/1) to give guanidine hydrochloride salt as a solid.

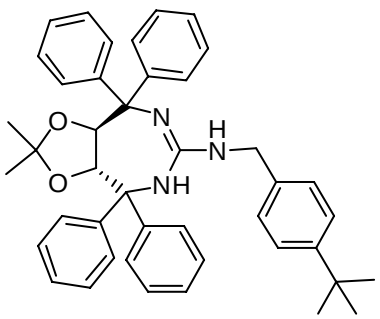
Generation of the free guanidine: To the guanidine hydrochloride salt dissolved in dichloromethane (20 mL) was added 2 M NaOH (4 mL) and stirred until the basification was finished (2 h). The aqueous phase was extracted with dichloromethane, washed with brine, dried (K_2CO_3) and the solvent was removed under reduced pressure to yield the free guanidine as a solid.

Characterization Data of 1a-k



1a

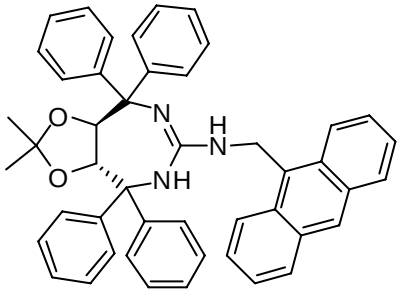
Yield: 90%; White solid; mp 103.7-105.7 ^oC; $[\alpha]_D^{21}$ = -166.9 (*c* 0.26, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.16 (m, 25H), 4.71 (brs, 2H), 4.46 (d, *J* = 14.7 Hz, 1H), 4.28 (d, *J* = 14.7 Hz, 1H), 1.00 (brd, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.3, 143.6, 141.9, 140.5, 129.8, 129.5, 128.7, 128.5, 128.0, 127.8, 127.7, 127.4, 127.3, 127.0, 126.9, 126.4, 110.5, 80.3, 78.7, 67.2, 66.2, 48.1, 27.0, 26.8; IR (KBr): 3406, 3057, 3026, 2984, 2930, 1665, 1599, 1493, 1445, 1379, 1370, 1242, 1169, 1093, 1051, 1030, 750, 698 cm^{-1}; HRMS (ESI) Calcd. for $C_{39}H_{38}N_3O_2$ ($[M+H]^+$) 580.2964, Found 580.2965.



1b

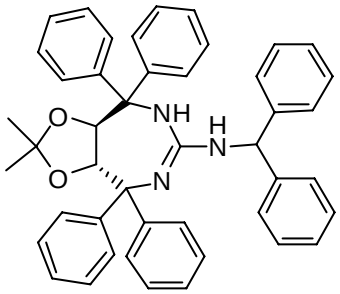
Yield: 90%; White solid; mp 106.7-108.4 ^oC; $[\alpha]_D^{24}$ = -130.8 (*c* 0.27, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.18 (m, 24H), 4.71 (s, 2H), 4.43 (d, *J* = 14.5 Hz, 1H), 4.27 (d, *J* = 14.5 Hz, 1H), 1.30 (s, 9H), 1.01 (brd, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.8, 146.3, 141.8, 137.3, 129.7, 129.5, 128.7, 128.0, 127. 8, 127.6, 127.4, 127.0, 126.4, 125.4, 110.4, 80.2,

78. 6, 67.3, 66.1, 47.6, 34.5, 31.4, 27.0, 26.8; IR (KBr): 3413, 3057, 2962, 2866, 1662, 1634, 1370, 1242, 1170, 1095, 751, 699 cm^{-1}; HRMS (ESI) Calcd. for $C_{43}H_{46}N_3O_2$ ($[M+H]^+$) 636.3590, Found 636.3582.



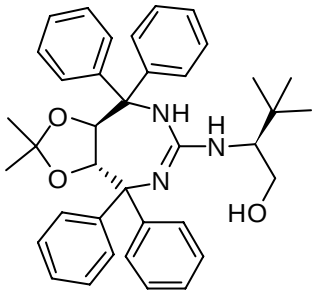
1c

Yield: 60%; Yellow solid; mp 136.0-137.4 ^oC; $[\alpha]_D^{20}$ = -182.3 (*c* 0.14, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.35-8.32 (m, 2H), 8.00-7.97 (m, 2H), 7.81-7.03 (m, 25H), 5.39 (s, 2H), 4.80 (d, J = 8.8 Hz, 1H), 4.70 (d, J = 8.4 Hz, 1H), 1.06 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.0, 143.8, 141.9, 134.1, 131.6, 130.4, 130.0, 129.5, 129.1, 128.6, 128.3, 127.8, 127.4, 127.2, 126.2, 125.1, 124.6, 110.2, 80.2, 80.1, 78.8, 66.2, 39.6, 27.0; IR (KBr): 3408, 3057, 2984, 2928, 1655, 1493, 1169, 1096, 751, 700 cm^{-1}; HRMS (ESI) Calcd. for $C_{47}H_{42}N_3O_2$ ($[M+H]^+$) 680.3277, Found 680.3266.



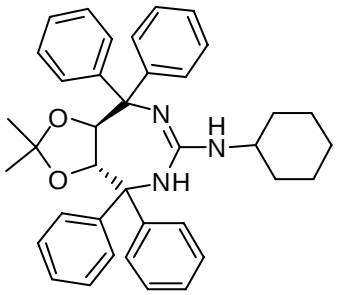
1d

Yield: 83%; White solid; mp 135.6-137.2 ^oC; $[\alpha]_D^{23}$ = -173.8 (*c* 0.18 CH_2Cl_2) ^1H NMR (400 MHz, $CDCl_3$) δ 7.49-7.12 (m, 30H), 5.67 (brs, 1H), 4.69-4.62 (m, 2H), 4.24 (s, 1H), 1.06 (brs, 3H), 0.97 (brs, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.1, 144.6, 143.8, 142.9, 141.7, 129.6, 129.4, 128.6, 128.5, 128.4, 127.9, 127.8, 127.7, 127.4, 127.3, 127.1, 126.9, 126.7, 126.6, 110.6, 80.9, 79.0, 66.3, 27.0, 26.8; IR (KBr): 3408, 3058, 3026, 2985, 2931, 1669, 1623, 1380, 1371, 1242, 1170, 1093, 751, 699 cm^{-1}; HRMS (ESI) Calcd. for $C_{45}H_{42}N_3O_2$ ($[M+H]^+$) 656.3277, Found 656.3258.



1e

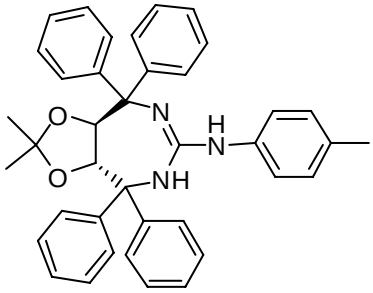
Yield: 73%; White solid; mp 207.0-208.4 ^oC; $[\alpha]_D^{22}$ = -152.6 (*c* 0.21, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 -7.15 (m, 20H), 4.57 (s, 2H), 4.48 (brs, 1H), 3.87 (d, J = 10 Hz, 1H), 3.77 (d, J = 8.4 Hz, 1H), 3.49 (t, J = 9.6 Hz, 1H), 1.19 (brs, 3H), 1.06 (brs, 3H), 0.97 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.6, 129.5, 128.5, 127.9, 127.3, 126.8, 109.9, 79.8, 78.9, 66.4, 63.2, 33.2, 27.3, 27.0; IR (KBr): 3391, 3349, 3089, 3062, 2983, 2967, 1635, 1519, 1494, 1446, 1371, 1249, 1168, 1089, 1022, 754, 699 cm^{-1}; HRMS (ESI) Calcd. for $C_{38}H_{44}N_3O_2$ ($[M+H]^+$) 590.3383, Found 590.3401.



1f

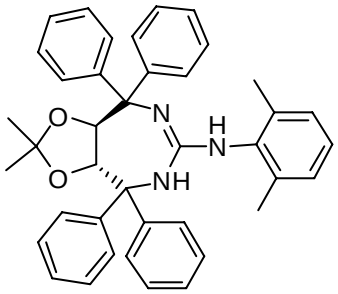
Yield: 78%; White solid; mp 109.7-111.9 ^oC; $[\alpha]_D^{21}$ = -160.8 (*c* 0.18, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.65-6.13 (m, 20H), 4.78-7.74 (m, 1H), 4.67-4.60 (m, 1H), 3.36 (brs, 1H), 2.06-184 (m, 1H), 1.65-1.55 (m, 4H), 1.07-1.22 (m, 5H), 0.95 (brs, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5, 146.5, 144.1, 142.1, 129.9, 129.6, 128.7, 128.1, 127.6, 127.3, 126.8, 126.2, 110.3, 80.0, 78.2, 67.8, 66.0, 51.7, 34.2, 33.9, 26.9, 25.9, 25.2; IR (KBr): 3412, 3058, 3032, 2929, 2852, 1659, 1632, 1493, 1446, 1382, 1371, 1244, 1170, 1091, 750, 670 cm^{-1}; HRMS (ESI) Calcd. for $C_{38}H_{42}N_3O_2$

([M+H]$^+$) 572.3277, Found 572.3280.



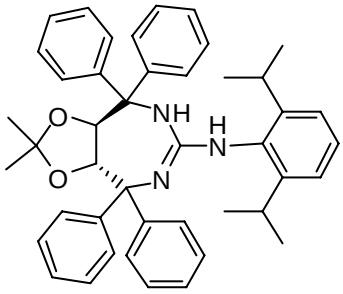
1g

Yield: 64%; Yellow solid; mp 194.1-195.4 ^{o}C; $[\alpha]_D^{20}$ = -152.7 (*c* 0.38, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.4 Hz, 2H), 7.55-6.99 (m, 22H), 6.78 (d, *J* = 8.0 Hz, 2H), 4.90 (brs, 1H), 4.77-4.67 (m, 2H), 2.23 (s, 3H), 1.29 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8, 145.9, 145.5, 145.2, 142.1, 141.7, 132.2, 130.3, 129.4, 129.0, 128.6, 128.0, 127.8, 127.7, 127.6, 127.4, 123.2, 110.6, 81.6, 79.8, 66.7, 65.8, 27.3, 26.8, 21.0; IR (KBr): 3395, 1627, 1600, 1399, 1094, 820, 751, 702 cm^{-1}; HRMS (ESI) Calcd. for $C_{39}H_{37}N_3O_2$ ([M+H]$^+$) 580.2964, Found 580.2974.



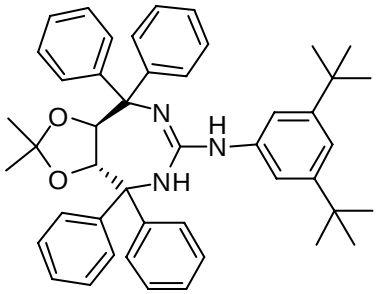
1h

Yield: 64%; Yellow solid; mp 187.8-190.2 ^{o}C; $[\alpha]_D^{19}$ = -181.1 (*c* 0.30, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-6.78 (m, 23H), 5.26 (d, *J* = 9.2 Hz, 1H), 5.02 (d, *J* = 9.2 Hz, 1H), 4.62 (s, 1H), 1.86 (brd, 6H), 1.00 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5, 145.7, 145.4, 144.7, 142.0, 141.5, 129.2, 128.9, 128.5, 128.3, 127.7, 127.5, 127.5, 127.4, 127.3, 126.8, 123.0, 111.8, 80.9, 79.1, 67.2, 66.7, 26.8, 26.4, 18.4, 18.0; IR (KBr): 3362, 3060, 2986, 2934, 1638, 1395, 1381, 1095, 698 cm^{-1}; HRMS (ESI) Calcd for $C_{40}H_{39}N_3O_2Na$([M+Na]$^+$) 616.2940, Found 616.2938.



1i

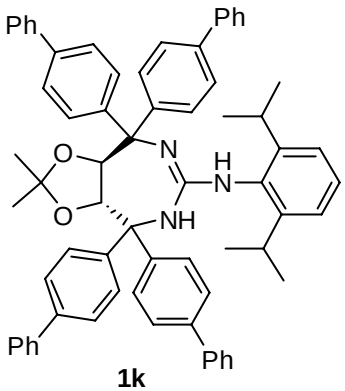
Yield: 87%; White solid; mp 229.2-230.5 ^{o}C; $[\alpha]_D^{23}$ = -110.4 (*c* 0.20, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.8 Hz, 2H), 7.33-6.85 (m, 21H), 4.89 (d, *J* = 9.1 Hz, 1H), 4.72 (d, *J* = 9.2 Hz, 1H), 4.43 (s, 1H), 3.31-3.25 (m, 1H), 2.83-2.77 (m, 1H), 1.28-1.25 (m, 6H), 1.08-1.05 (m, 6H), 0.94 (s, 3H), 0.48 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6, 145.9, 145.5, 142.4, 141.5, 141.3, 141.1, 129.8, 129.3, 128.6, 128.6, 127.8, 127.6, 127.4, 127.3, 127.1, 123.5, 123.4, 110.7, 81.5, 79.0, 67.1, 66.0, 28.1, 27.9, 27.3, 26.7, 25.1, 24.7, 23.3, 22.1; IR (KBr): 3382, 3064, 2991, 2960, 1628, 1589, 1380, 1371, 1244, 1091, 758, 701 cm^{-1}; HRMS (ESI) Calcd. for $C_{44}H_{48}N_3O_2$ ([M+H]$^+$) 650.3747, Found 650.3759.



1j

Yield: 93%; White solid; mp 114.7-117.3^{o}C; $[\alpha]_D^{19}$ = -121.3 (c 0.16, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 6.2 Hz, 2H), 7.53 (d, *J* = 6.8 Hz, 2H), 7.41- 6.98 (m, 17H), 6.78 (s, 2H), 5.09 (brs, 1H), 4.73 (d, *J* = 8.8 Hz, 1H), 4.65 (d, *J* = 8.8 Hz, 1H), 1.30-1.16 (m, 24H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.6, 152.1, 147.8, 145.4, 142.0, 141.4, 129.0, 128.4, 127.8, 127.6, 127.5, 127.1, 117.3, 116.8, 110.2, 81.4, 80.2, 66.2, 65.6, 34.8, 31.4, 27.0, 26.7; IR (KBr): 3385, 2963, 2866, 1625, 1588,

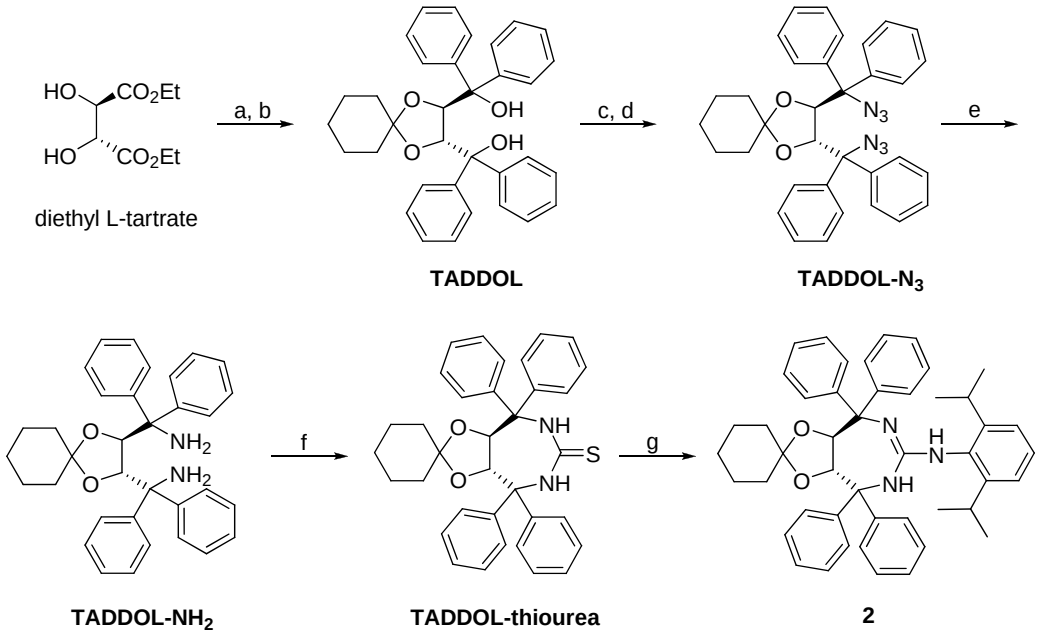
1380, 1372, 1094, 699 cm^{-1}; HRMS (ESI) Calcd. for $C_{46}H_{51}N_3O_2Na$ ($[M+Na]^+$) 700.3879, Found 700.3864.



1k

Yield: 80%; Yellowish solid; mp 163.4-165.7 °C; $[\alpha]_D^{25}$ = -109.9 (c 0.22, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.2 Hz, 2H), 7.72-7.29 (m, 33H), 7.08 (d, J = 8.1 Hz, 3H), 6.96-6.89 (m, 2H), 5.06 (d, J = 9.2 Hz, 1H), 4.88 (d, J = 9.2 Hz, 1H), 4.56 (s, 1H), 3.36-3.29 (m,1H), 3.00-2.81 (m, 1H), 1.35-1.26 (m, 6H), 1.12-1.05 (m, 9H), 0.58 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5, 144.7, 144.5, 142.3, 141.5, 141.3, 141.1, 140.7, 140.6, 140.4, 140.3, 140.2, 130.2, 129.8, 139.0, 128.2, 127.6, 127.2, 126.5, 125.9, 123.7, 123.6, 123.5, 111.0, 81.5, 79.3, 66.8, 65.8, 28.1, 28.0, 27.4, 26.8, 25.1, 24.8, 23.4, 22.2; IR (KBr): 1178, 3029, 2958, 1625, 1487, 1398, 1087, 764, 697 cm^{-1}; HRMS (ESI) Calcd. for $C_{68}H_{64}N_3O_2$ ($[M+H]^+$) 954.4954, Found 954.4999.

Synthesis of chiral guanidine 2



Reagents and conditions: (a) cyclohexanone, PTSA, $ZnCl_2$, benzene, reflux, 18 h; (b) bromobenzene, Mg, THF, reflux, 1.5 h, 75% (2 steps); (c) $SOCl_2$, Et_3N, CH_2Cl_2, reflux, 3 h; (d) NaN_3, DMF, 80 ºC, 72 h, 71% (2 steps); (e) $LiAlH_4$, THF, 0 ºC, 4 h, 1 M NaOH, 2 h, 84%; (f) CS_2, pyridine, 60 ºC, 83%; (g) 2,6-diisopropylaniline, CuCl, K_2CO_3, THF, 40 ºC, 48 h, 64 %.

Synthesis of TADDOL according to the literature procedure[7]

Cyclohexanone (2.4 g, 2.5 mL, 24 mmol, 1.5 equiv) was added to a solution of diethyl L-tartrate (3.3 g, 16 mmol), $ZnCl_2$ (0.1 g) and *p*TsOH (0.1 g) in dry benzene (60 mL) and the reaction mixture was refluxed for 18 h with Dean-Stark removal of MeOH. After cooling to room temperature, $NaHCO_3$ (0.4 g) was added and the mixture was stirred for 15 min. Water (25 mL)

was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (30 mL×2). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated to give (2*R*,3*R*)-dioxaspiro [4,5] decane-2,3-dicarboxyl-diethylester (4.6 g, quantitative) as a yellow oil. The crude product obtained was used for subsequent reaction without further purification.

Under nitrogen atmosphere, to the Grignard reagent in tetrahydrofuran (60 mL) obtained from bromobenzene (12.6 g, 80 mmol, 5.0 equiv) and magnesium powder (2.1 g, 88 mmol, 5.5 equiv) was added, with ice cooling bath, a solution of (2*R*,3*R*)-dioxaspiro [4,5] decane-2,3-dicarboxyl-diethylester (4.6 g, 16 mmol) in tetrahydrofuran (5 mL). After completion of the addition, the reaction mixture was heated at reflux for 1.5 h, then cooled to room temperature. An aqueous saturated ammonium chloride solution (80 mL) was added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (80 mL×1, 40 mL×2). The combined organic layers were washed with brine, dried (Na_2SO_4). After evaporation of the solvent, the crude residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to give **TADDOL** (6.1 g, 75%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.47 (m, 4H), 7.39-7.21 (m, 16H), 4.55 (s, 2H), 3.73 (brs, 2H), 1.50-1.31 (m, 4H), 1.31-1.07 (m, 6H).

Synthesis of TADDOL-N_3.

Under nitrogen atmosphere, to a solution of **TADDOL** (1.520 g, 3 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added thionyl chloride (1.071 g, 9 mmol, 3.0 equiv) at room temperature. The resulting solution was then heated under reflux while a solution of triethylamine (1.821 g, 18 mmol, 6.0 equiv) in CH_2Cl_2 (20 mL) was introduced over a period of 3 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction was cooled to room temperature and concentrated to give a brown solid. The crude product obtained was used for subsequent reaction without further purification. To a solution of the crude product in DMF (12 mL) was added NaN_3 (0.780 g, 12 mmol, 4.0 equiv). The reaction mixture was stirred at 80 ^{o}C for 72 h. After cooling to room temperature, the reaction mixture was poured into water (100 mL), then extracted with ether (100 mL×1, 60 mL×2). The combined organic layers were washed with water (50 mL×3) and dried (Na_2SO_4). After evaporation of the solvent, the crude residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 50/1) to give a yellowish solid. The crude residue was crystallized from ethanol to give **TADDOL-N_3** (1.187 g, 71%) as a white solid. mp 162.1-163.7 ^{o}C; $[\alpha]_D^{16}$ = 6.6 (*c* 0.49, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.18 (m, 20H), 4.90 (s, 2H), 1.49-1.39 (m, 4H), 1.30-1.22 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0, 140.2, 129.6, 128.3, 128.1, 127.8, 127.7, 127.6, 110.7, 80.0, 73.2, 36.7, 25.0, 24.1; IR (KBr): 3446, 3060, 2929, 2853, 2120, 1376, 1366, 1267, 1107, 756, 737, 698 cm^{-1}; HRMS (ESI) Calcd. for $C_{34}H_{32}N_6O_2Na([M+Na]^+)$ 579.2484, Found 579.2473.

Synthesis of TADDOL-NH_2.

To an ice-water cooled suspension of $LiAlH_4$ (0.455 g, 12 mmol, 6.0 equiv) in THF (15 mL) was added, dropwise, a solution of **TADDOL-N_3** (1.113 g, 2 mmol, 1.0 equiv) in THF (15 mL). The reaction mixture was stirred at 0 ^{o}C for 4 h. Progress of the reaction was monitored by TLC. After completion of the reaction, 1 M NaOH (8 mL) was added carefully. The mixture was diluted with ether (15 mL) and Na_2SO_4 (8.0 g) was added. After stirring for a further 2 h at room

temperature, the mixture was filtered through a pad of celite with the aid of ether. The filtrate was dried over K_2CO_3. After evaporation of the solvent, the crude residue was purified by column chromatography on silica gel (dichloromethane/methanol = 20/1) to give **TADDOL-NH$_2$** (0.851 g, 84%) as a white solid. mp 228.4-231.7^{o}C; $[\alpha]_D^{17}$ = -43.3 (*c* 0.27, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.50 (m, 4H), 7.35-7.29 (m, 6H), 7.24-7.10 (m, 10H), 4.20 (s, 2H), 2.21 (brs, 4H), 1.51-1.36 (m, 4H), 1.28-1.22 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.2, 143.9, 129.4, 128.1, 127.8, 127.4, 127.1, 126.9, 126.5, 108.0, 81.5, 62.8, 36.7, 25.3, 24.1. IR (KBr): 3359, 2942, 2858, 1493, 1367, 1352 1123, 767, 740, 704 cm^{-1}; HRMS (ESI) Calcd. for $C_{34}H_{37}N_2O_2$([M+H]$^+$) 505.2855, Found 505.2863.

Synthesis of TADDOL-thiourea:

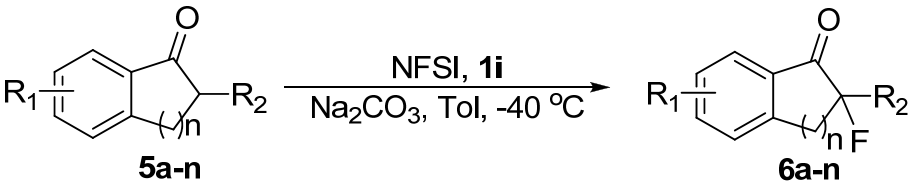
Under nitrogen atmosphere, carbon disulfide (204 μL, 3.4 mmol, 2.0 equiv) was added to a solution of the diamine **1a** (0.850 g, 1.7 mmol) in pyridine (3 mL). The reaction mixture was stirred at 60 ^{o}C for 7 h. After cooling to room temperature, to the reaction mixture was added CH_2Cl_2 (30 mL) and water (10 mL). The pH was adjusted to 2-3 by the addition of a 1 M HCl solution. The mixture was extracted with dichloromethane (20 mL×3) and the combined organic layers were washed with 1M NaOH (20 mL×1), brine (20 mL×1) and dried (Na_2SO_4). After evaporation of the solvent, the crude residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to give **TADDOL-thiourea** (762 mg, 83%) as a white solid. Mp 258.3-261.2 ^{o}C; $[\alpha]_D^{24}$ = -197.5 (*c* 0.11, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.57 (m, 4H), 7.44-7.34 (m, 6H), 7.29-7.26 (m, 6H), 7.20-7.11 (m, 4H), 6.87 (s, 2H), 4.58 (s, 2H), 1.55-1.22 (m, 10H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.7, 143.6, 139.8, 129.3, 128.8, 128.4, 128.0, 127.9, 127.7, 111.3, 77.3, 70.7, 36.3, 24.9, 23.7; IR (KBr): 3378, 3058, 2935, 1635, 1447, 1366, 1119, 755, 699 cm^{-1}; HRMS (ESI) Calcd. for $C_{35}H_{34}N_2O_2SNa$([M+Na]$^+$) 569.2239, Found 569.2216.

Synthesis of 2:

Under nitrogen atmosphere, to a suspension of K_2CO_3 (55.3 mg, 0.4 mmol, 4.0 equiv) and CuCl (20.8 mg, 0.21 mmol, 2.1 equiv) in THF (1 mL) was added **TADDOL-thiourea** (54.7 mg, 0.1 mmol, 1.0 equiv**)**. After stirring at room temperature for 10 min, 2,6-diisopropylaniline (24.2 mg, 0.2 mmol, 2.0 equiv) was added. The resulting mixture was stirred at 40 ^{o}C for 48 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and quenched by saturated NH_4Cl (15 mL) aqueous solution. The pH was adjusted to 5 by the addition of 1M HCl. The mixture was extracted with dichloromethane (20 mL×3) and the combined organic layers were filtered through a pad of celite with the aid of dichloromethane. The filtrate was washed with brine and dried (Na_2SO_4). After evaporation of the solvent, the crude residue was purified by column chromatography on silica gel (dichloromethane/methanol = 20/1) to give guanidine hydrochloride salt as a solid (143.1 mg). The guanidine hydrochloride salt was dissolved in dichloromethane (20 mL) , then added 2 M NaOH (4 mL) and stirred until the basification was finished (2 h). The aqueous phase was extracted with dichloromethane washed with brine, dried (K_2CO_3) and the solvent was removed under reduced pressure to yield the free guanidine **2** (44.2 mg, 64%) as a white solid. mp 117.2-118.6 ^{o}C; $[\alpha]_D^{23}$ = -118.2 (*c* 0.28, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.0 Hz, 2H), 7.43-6.81 (m, 21H), 4.85 (d, *J* = 9.2 Hz, 1H), 4.71 (d, *J* = 9.2 Hz, 1H), 4.46 (s, 1H),

3.28 (dt, J = 13.5, 6.7 Hz, 1H), 2.82 (dt, J = 13.6, 6.8 Hz, 1H), 1.55-1.06 (m, 19H), 0.48 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6, 149.5, 145.9, 145.9, 145.5, 142.4, 142.2, 141.4, 141.3, 141.1, 129.6, 129.2, 128.4, 128.4, 127.7, 127.6, 127.5, 127.4, 127.2, 127.0, 127.0, 123.4, 123.3, 123.3, 111.0, 80.6, 78.3, 67.0, 65.9, 36.7, 35.9, 27.9, 27.7, 25.0, 24.9, 24.5, 23.9, 23.6, 23.1, 21.9; IR (KBr): 3376, 3059, 2933, 1624, 1447, 1398, 1109, 755, 699 cm^{-1}; HRMS (ESI) Calcd. for $C_{47}H_{52}N_3O_2$ ([M+H]$^+$) 690.4060, Found 690.4029.

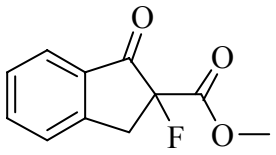
3. General procedure for fluorination of 1,3-dicarbonyl and *α*-cyano carbonyl compounds



5a-n **6a-n**

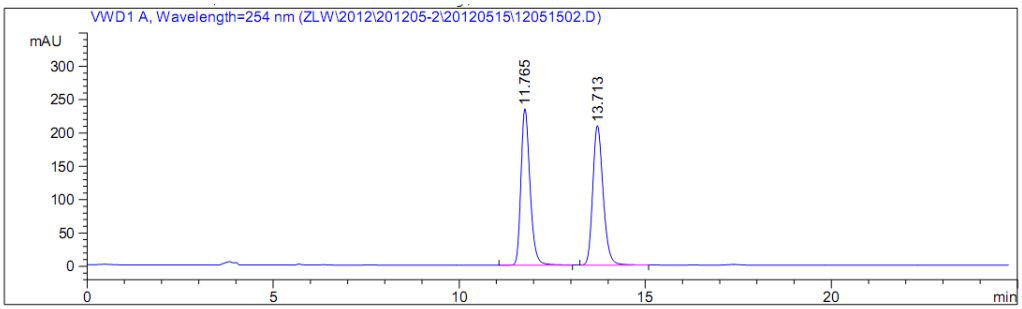
To a Schlenk tube equipped with a magnetic stir bar and charged with compound **5** (0.2 mmol) was added toulene (2 mL), followed by the **1i** (0.02 mmol), and the mixture was stirred at r.t. for 5 min before cooling to -40 ºC. Then to this mixture was added NFSI. After stirring at -40 ºC for another 10 min, to the resulting solution was added Na_2CO_3 (0.22 mmol). The resulting solution was stirred at -40 ºC until complete consumption of **5**. The temperature was raised to room temperature. The solution of the crude product was concentrated in vacuo and the residue was purified by column chromatography on silica gel(petroleum ether/ethyl acetate) to give the product **6**.

Methyl 2-fluoro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate[8]

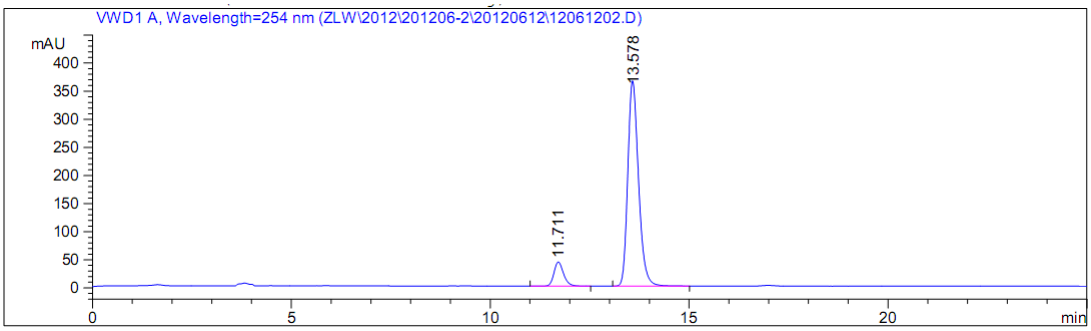


6a

Prepared according to the general procedure with a reaction time of 5 d as white solid (99% yield) after silica gel chromatography (EtOAc/petroleum ether). mp 78.2-80.3 °C (lit.,[8] 79-81 °C); $[\alpha]_D^{26}$ = 22.8 (c 0.20, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 7.7 Hz, 1H), 7.74-7.70 (m, 1H), 7.52-7.46 (m, 2H), 3.82 (s, 3H), 3.85-3.78 (m, 1H), 3.45 (dd, J = 23.3, 17.7 Hz, 1H). Enantiomeric excess was determined to be 81% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 9/1, λ = 254 nm, 30 °C, 0.8 mL/min, t_{minor} = 11.8 min, t_{major} = 13.7 min).

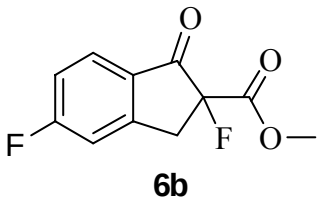


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.765	BB	0.2600	3965.55493	234.35696	49.4367
2	13.713	BB	0.2993	4055.91870	208.94138	50.5633



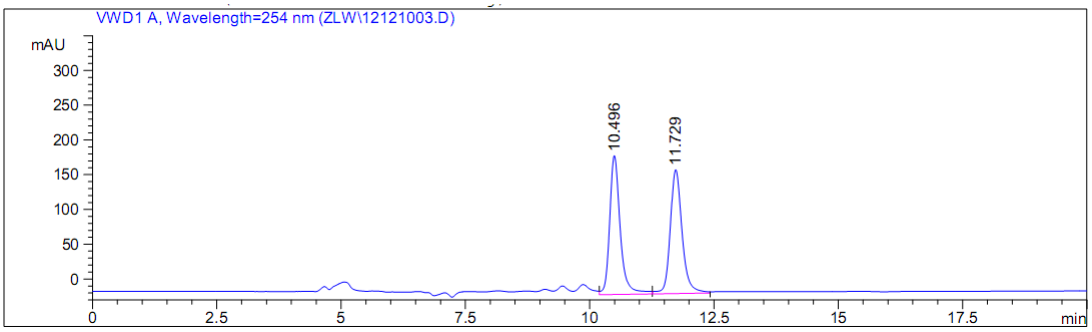
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.711	VB	0.2580	725.16272	42.97733	9.5779
2	13.578	BB	0.2887	6846.06250	365.09793	90.4221

Methyl 2,5-difluoro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate

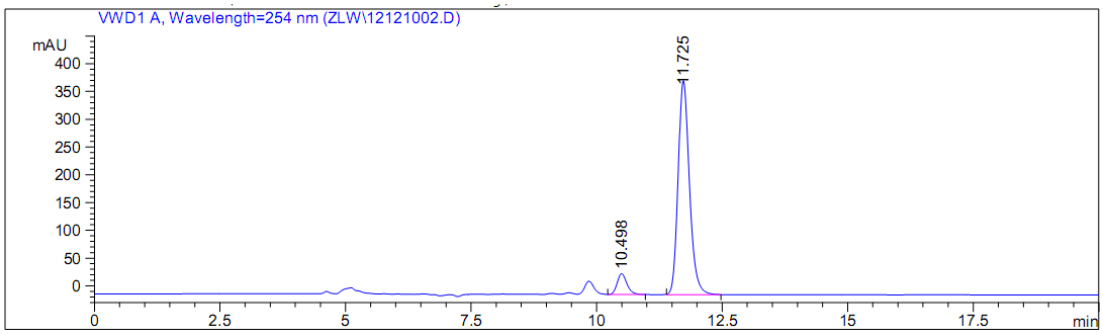


6b

Prepared according to the general procedure with a reaction time of 6 d as white solid (99% yield) after silica gel chromatography (EtOAc/petroleum ether). mp 89.8-90.8 ^{o}C; $[\alpha]_D^{19}$ = 20.2 (*c* 0.46, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 9.1, 5.3 Hz, 1H), 7.20-7.16 (m, 2H), 3.83 (s, 3H), 3.83-3.76 (m, 1H),3.43 (dd, *J* = 22.8, 17.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.2 (d, *J* = 18.3 Hz), 168.2 (d, *J* = 261.4), 167.4 (d, *J* = 27.9), 153.8 (dd, *J* = 10.8, 3.9 Hz), 129.6, 128.3 (d, *J* = 10.1 Hz), 117.2 (d, *J* = 23.7 Hz), 113.6 (d, *J* = 23.8 Hz), 94.6 (d, *J* = 202.5 Hz), 53.4, 38.1 (dd, *J* = 24.3, 2.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -98.1, -163.8; IR (KBr): 3077, 2969, 1767, 1729, 1263, 1206, 1087, 648 cm^{-1}; HRMS (ESI) Calcd. for $C_{11}H_8O_3F_2Na$ ($[M+Na]^+$) 249.0339, Found 249.0336. Enantiomeric excess was determined to be 84% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 9/1, λ = 254 nm, 30 ^{o}C, 0.6 mL/min, t_{minor} = 10.5 min, t_{major} = 11.7 min).

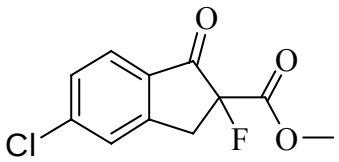


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.496	VV	0.2237	2981.79932	199.69307	50.3051
2	11.729	VV	0.2484	2945.63159	177.99185	49.6949



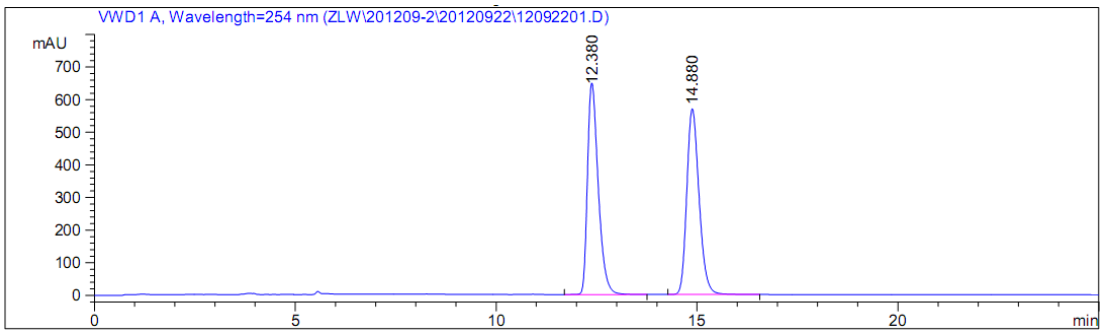
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.498	VB	0.2083	511.56195	37.58287	7.8509
2	11.725	BB	0.2403	6004.39648	384.81897	92.1491

Methyl 5-chloro-2-fluoro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate[8]

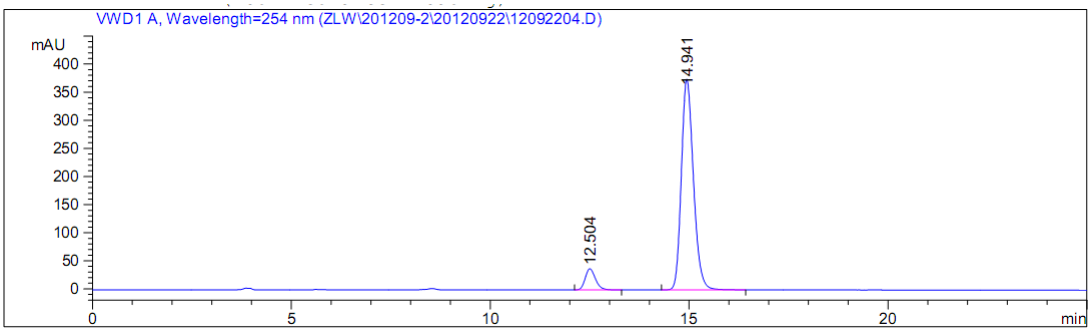


6c

Prepared according to the general procedure with a reaction time of 6 d as yellowish solid (99% yield) after silica gel chromatography (EtOAc/petroleum ether). mp 88.7-91.4°C (lit.,[8] 89-91 °C); $[\alpha]_D^{25}$ = 17.8 (*c* 0.25, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 1H), 7.51 (d, *J* = 0.8 Hz, 1H), 7.47-7.44 (m, 1H), 3.82 (s, 3H), 3.82-3.75 (m, 1H), 3.42 (dd, *J* = 22.9, 17.8 Hz, 1H). Enantiomeric excess was determined to be 84% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 9/1, λ = 254 nm, 30 °C, 0.8 mL/min, t_{minor} = 12.4 min, t_{major} = 14.9 min).

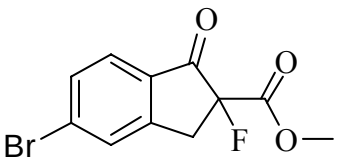


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	12.380	VB	0.2875	1.21034e4	648.88141	49.9329
2	14.880	BB	0.3273	1.21359e4	569.35748	50.0671



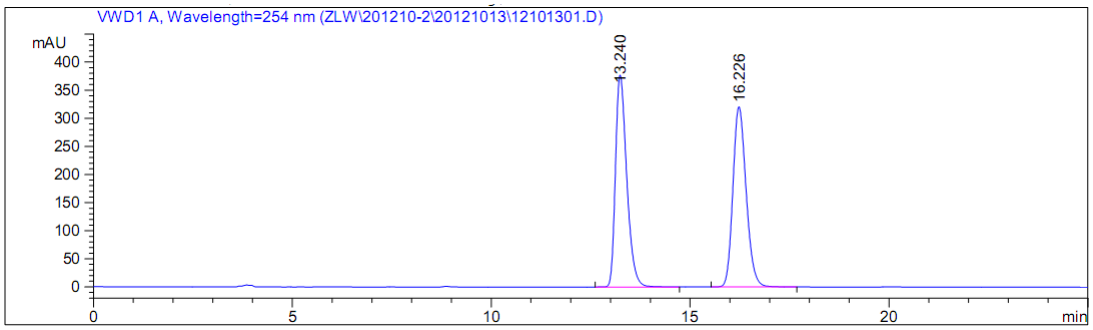
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	12.504	VB	0.2773	684.04297	37.95286	7.9515
2	14.941	BB	0.3279	7918.65967	375.01346	92.0485

Methyl 5-bromo-2-fluoro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate[8]

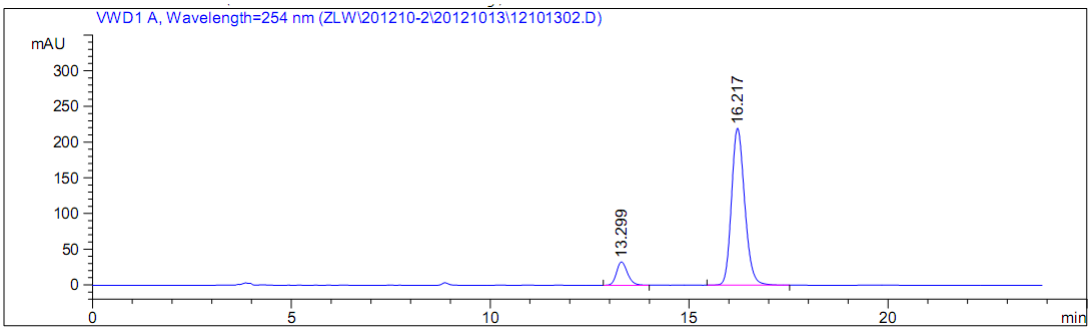


6d

Prepared according to the general procedure with a reaction time of 7 d as white solid (99% yield) after silica gel chromatography (EtOAc/petroleum ether). mp 87.6-90.1 °C (lit.,[8] 88-90 °C); $[\alpha]_D^{19}$ = 57.4 (*c* 0.50, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.69 (m, 2H), 7.62 (dd, *J* = 8.3, 0.7 Hz, 1H), 3.82 (s, 3H), 3.82-3.75 (m, 1H), 3.43 (dd, *J* = 22.9, 17.8 Hz, 1H). Enantiomeric excess was determined to be 78% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 9/1, λ = 254 nm, 30 °C, 0.8 mL/min, t_{minor} = 13.2 min, t_{major} = 16.2 min).

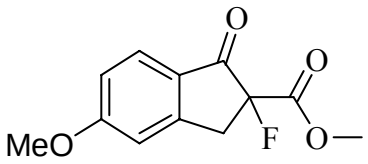


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	13.240	BB	0.3028	7438.05176	377.25070	50.0126
2	16.226	BB	0.3607	7434.29395	320.67545	49.9874



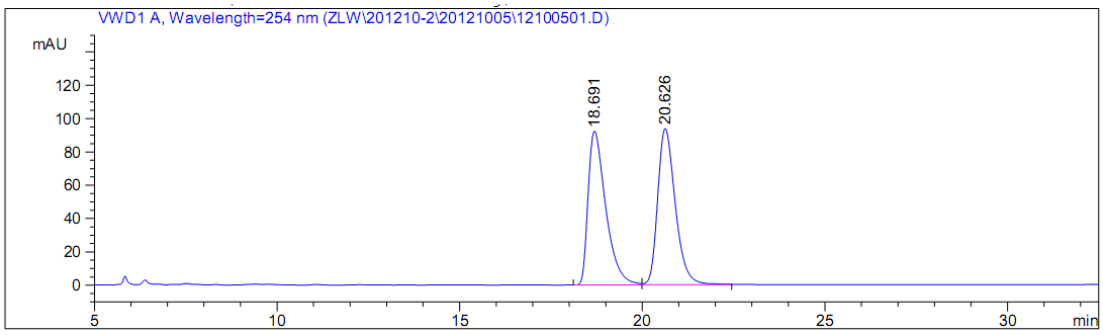
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	13.299	PB	0.2947	626.25610	32.71204	10.9760
2	16.217	BB	0.3570	5079.43701	219.73856	89.0240

Methyl 2-fluoro-5-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate

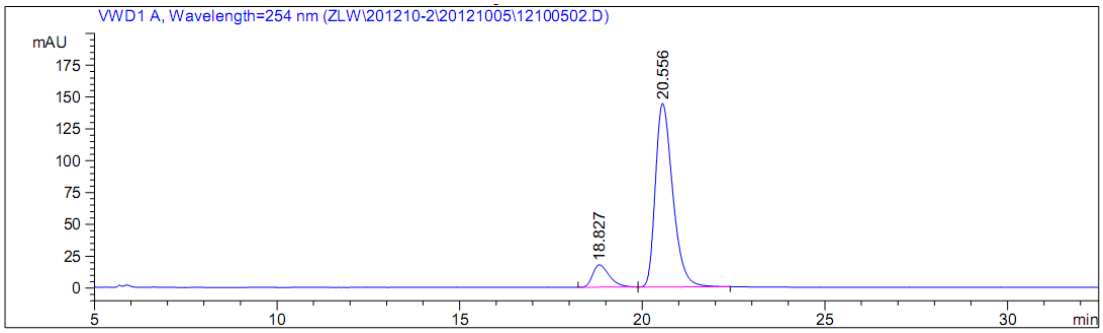


6e

Prepared according to the general procedure with a reaction time of 7 d as white solid (98% yield) after silica gel chromatography (EtOAc/petroleum ether). mp 106.4-107.7 °C; $[\alpha]_D^{19}$ = 69.6 (*c* 0.41, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.6 Hz, 1H), 6.98 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.91 (s, 1H), 3.92 (s, 3H), 3.82 (s, 3H), 3.75 (dd, *J* = 17.6, 11.1 Hz, 1H), 3.38 (dd, *J* = 23.0, 17.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.9 (d, *J* = 18.4 Hz), 168.0 (d, *J* = 27.9 Hz), 166.9, 154.0 (d, *J* = 4.0 Hz), 127.6, 126.3, 116.8, 109.8, 95.1 (d, *J* = 201.2 Hz), 55.9, 53.2, 38.2 (d, *J* = 24.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -163.5; IR (KBr): 3019, 2959, 1764, 1712, 1271, 1206, 1102, 649 cm^{-1}; HRMS (ESI) Calcd. for $C_{12}H_{11}O_4FNa$ ($[M+Na]^+$) 261.0539 Found 261.0549. Enantiomeric excess was determined to be 79% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 9/1, λ = 254 nm, 30 °C, 0.8 mL/min, t_{minor} = 18.7 min, t_{major} = 20.6 min).

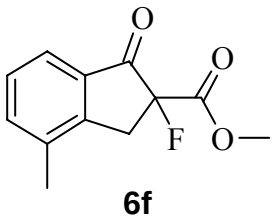


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	18.691	PV	0.5115	3102.56934	92.30386	49.6963
2	20.626	VB	0.5163	3140.49023	93.68258	50.3037



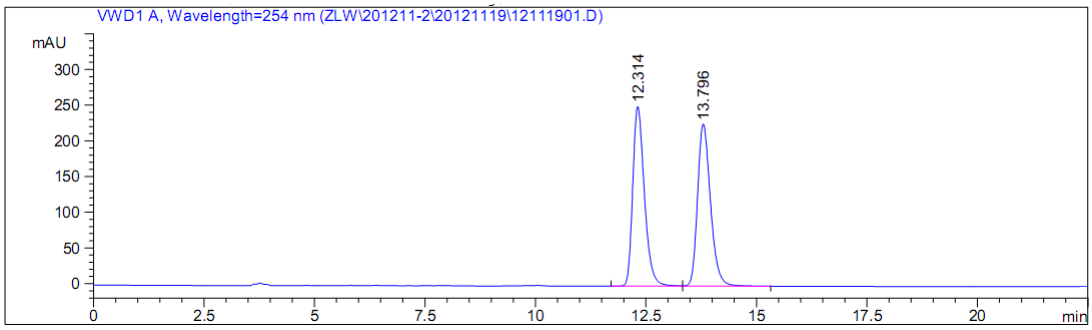
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	18.827	PV	0.4920	558.64551	17.49272	10.4814
2	20.556	VB	0.5116	4771.24805	144.06799	89.5186

Methyl 2-fluoro-4-methyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate

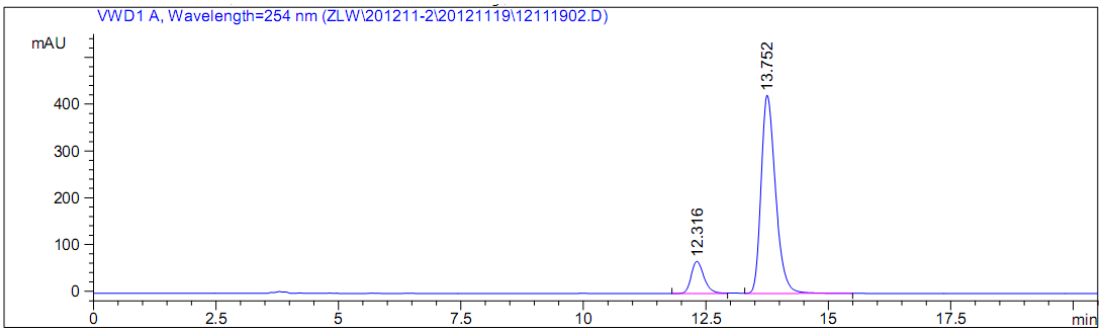


6f

Prepared according to the general procedure with a reaction time of 10 d as white solid (93% yield) after silica gel chromatography (EtOAc/petroleum ether). mp 126.1-127.6 °C; $[\alpha]_D^{17}$ = 36.2 (*c* 0.37 , CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.7 Hz, 1H), 7.52 (d, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 3.82 (s, 3H), 3.70 (dd, *J* = 17.7, 11.6 Hz, 1H), 3.31 (dd, *J* = 23.6, 17.7 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4 (d, *J* = 17.9 Hz), 167.9 (d, *J* = 27.9 Hz), 149.9 (d, *J* = 3.5 Hz), 137.3, 136.0, 133.0, 128.8, 123.0, 94.6 (d, *J* = 201.1 Hz), 53.2, 37.2(d, *J* = 23.8 Hz), 17.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -164.1; IR (KBr): 3074, 2961, 2920, 1765, 1722, 1270, 1205, 1086, 775, 674 cm^{-1}; HRMS (ESI) Calcd. for $C_{12}H_{11}O_3FNa$ ($[M+Na]^+$) 245.0590, Found 245.0586. Enantiomeric excess was determined to be 75% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 9/1, λ = 254 nm, 30 °C, 0.8 mL/min, t_{minor} = 12.3 min, t_{major} = 13.7 min).

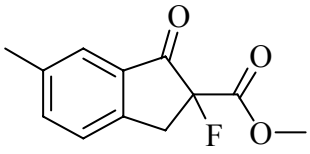


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	12.314	VV	0.2814	4620.47314	251.37808	49.9621
2	13.796	VB	0.3135	4627.48242	226.99458	50.0379



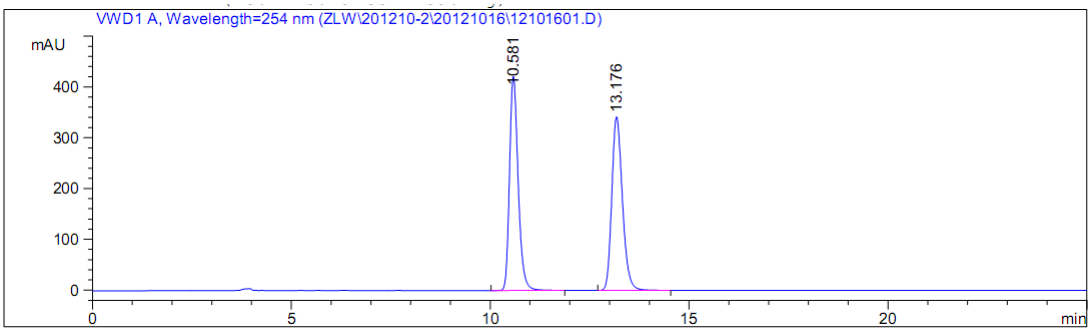
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	12.316	BV	0.2791	1243.15759	68.36427	12.4872
2	13.752	VB	0.3157	8712.32422	423.61823	87.5128

Methyl 2-fluoro-6-methyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate[8]

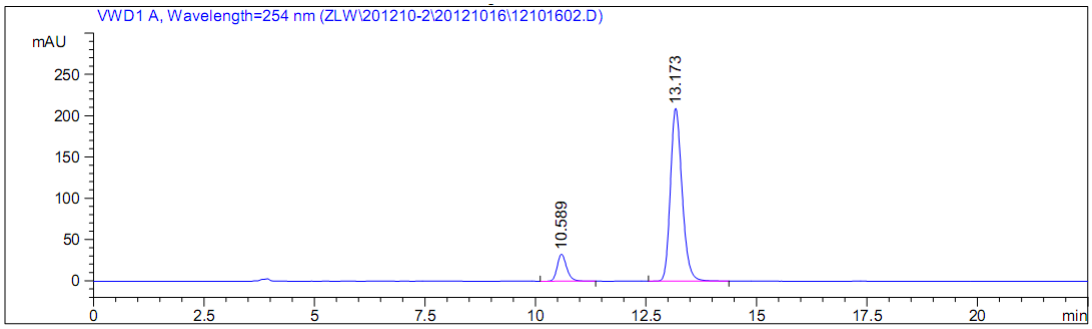


6g

Prepared according to the general procedure with a reaction time of 8 d as white solid (98% yield) after silica gel chromatography (EtOAc/petroleum ether). mp 117.1-118.4 °C (lit.,[8] 101-104 °C); $[\alpha]_D^{19}$ = 16.2 (*c* 0.39, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 7.9 Hz, 1H), 3.81 (s, 3H), 3.75 (dd, *J* = 17.5, 11.0 Hz, 1H), 3.39 (dd, *J* = 23.2, 17.5 Hz, 1H), 2.43 (s, 3H). Enantiomeric excess was determined to be 78% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 9/1, λ = 254 nm, 30 °C, 0.8 mL/min, t_{minor} = 10.6 min, t_{major} = 13.2 min).

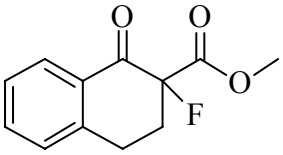


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.581	BB	0.2297	6347.83447	421.20309	50.0137
2	13.176	PB	0.2867	6344.36133	341.42920	49.9863



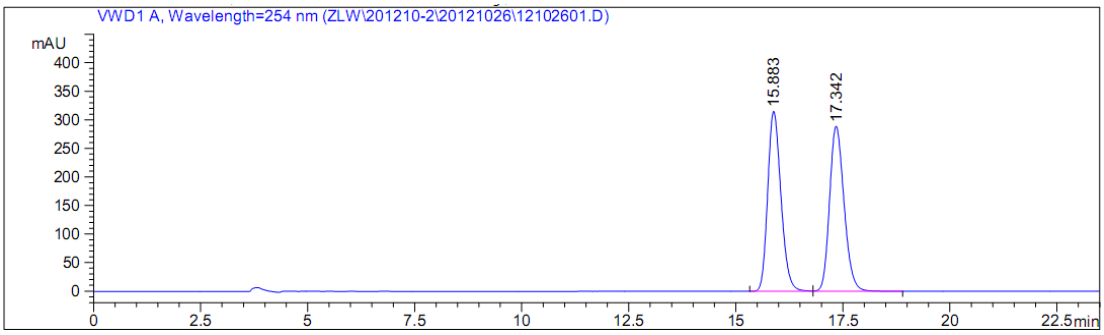
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.589	VB	0.2270	484.39337	32.64612	11.1743
2	13.173	VB	0.2819	3850.47852	209.02850	88.8257

Methyl 2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate[8]

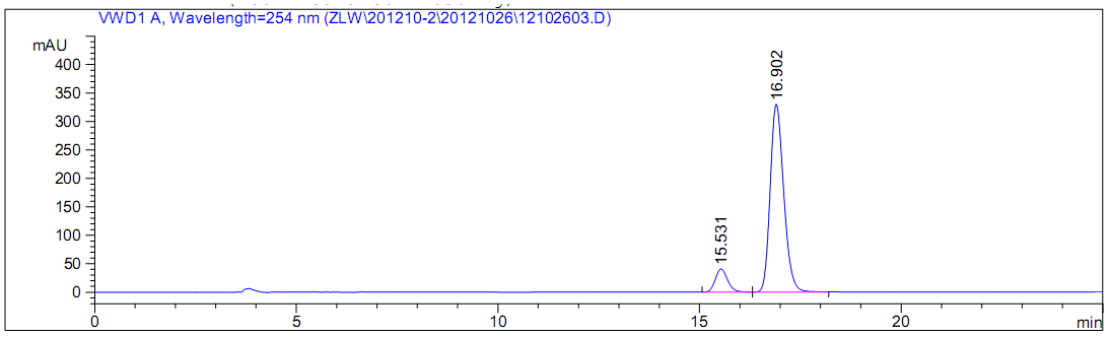


6h

Prepared according to the general procedure with a reaction time of 10 d as colourless oil (90% yield) after silica gel chromatography (EtOAc/petroleum ether); $[\alpha]_D^{17} = 3.5$ (*c* 0.32, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, $J = 7.9$, 1.1 Hz, 1H), 7.56 (td, $J = 7.5$, 1.4 Hz, 1H), 7.38 (dt, J = 7.8, 3.9 Hz, 1H), 7.28 (m, 1H), 3.84 (s, 3H), 3.23-3.16 (m, 1H), 3.13-3.05 (m, 1H), 2.8.-2.68 (m, 1H), 2.60-2.51(m, 1H). Enantiomeric excess was determined to be 80% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 95/5, λ = 254 nm, 30 °C, 0.8 mL/min, t_{minor} = 15.9 min, t_{major} = 17.3 min).

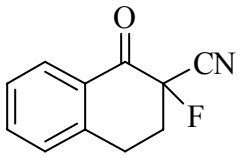


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	15.883	BV	0.3330	6797.00146	315.31500	49.9379
2	17.342	VB	0.3652	6813.90771	289.13651	50.0621



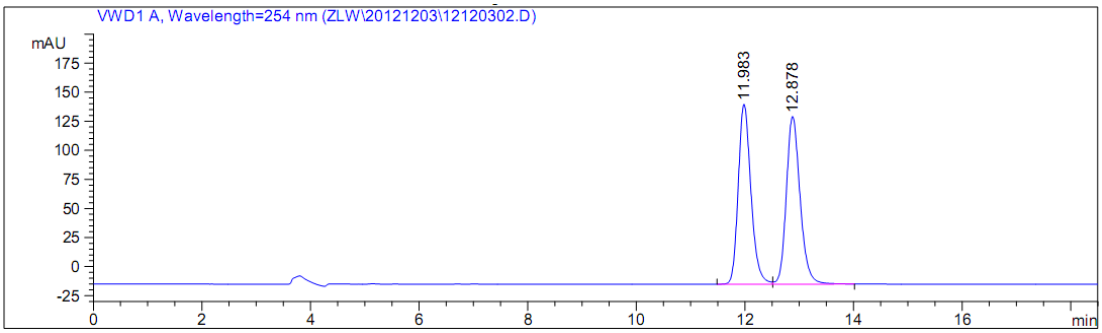
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	15.531	BV	0.3259	851.20007	40.39427	9.9563
2	16.902	VB	0.3625	7698.19629	329.88229	90.0437

2-Fluoro-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carbonitrile

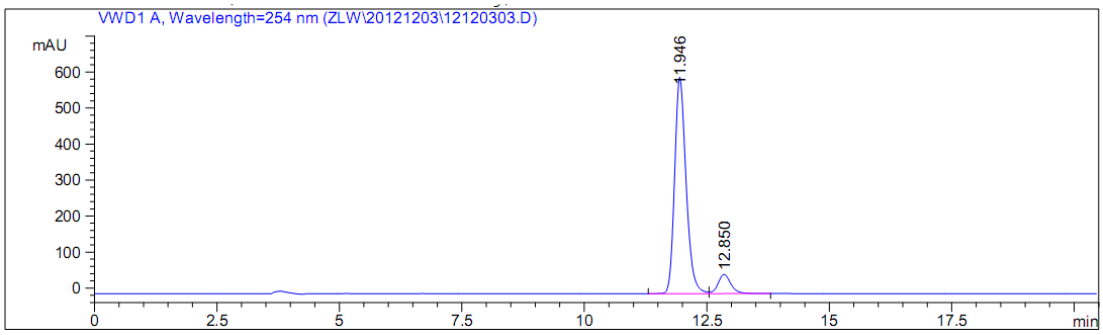


6i

Prepared according to the general procedure with a reaction time of 12 d as colourless oil (84% yield) after silica gel chromatography (EtOAc/ petroleum ether); $[\alpha]_D^{15}$ = -67.3 (*c* 0.32, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.63 (td, *J* = 7.6, 1.4 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 3.37-3.32 (m, 2H), 2.82-2.65 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.0 (d, *J* = 19.1 Hz), 142.2, 135.6, 129.3 (d, *J* = 1.3 Hz), 129.0, 128.9, 128.0, 113.7 (d, *J* = 35.2 Hz), 87.3 (d, *J* = 195.8 Hz), 33.9 (d, *J* = 21.9 Hz), 25.4 (d, *J* = 7.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -160.4; IR (Neat): 3070, 2940, 1709, 704 cm^{-1}; HRMS (ESI) Calcd. for $C_{11}H_8NOFNa$ ($[M+Na]^+$) 212.0488, Found 212.0483. Enantiomeric excess was determined to be 82% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 95/5, λ = 254 nm, 30 °C, 0.8 mL/min, t_{major} = 12.0 min, t_{minor} = 12.9 min).

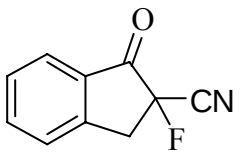


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.983	BV	0.2494	2517.39722	154.85497	49.7301
2	12.878	VB	0.2699	2544.71826	144.22397	50.2699



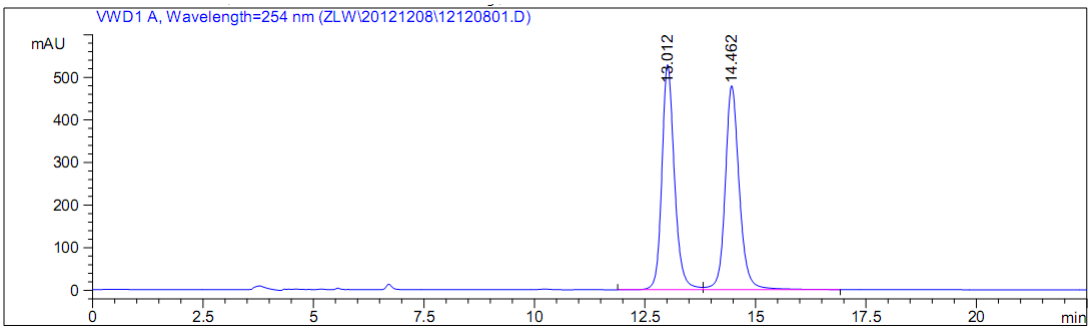
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.946	BV	0.2497	9775.35938	600.38049	91.0489
2	12.850	VB	0.2760	961.02856	52.90715	8.9511

2-Fluoro-1-oxo-2,3-dihydro-1H-indene-2-carbonitrile

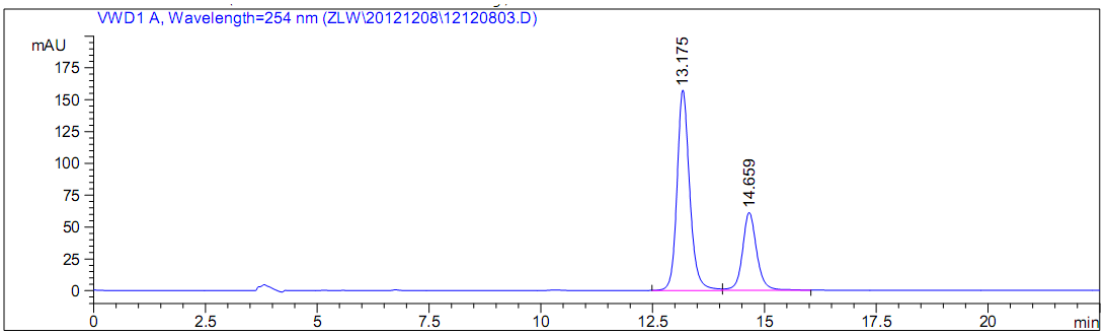


6j

Prepared according to the general procedure with a reaction time of 8 d as colourless oil (89% yield) after silica gel chromatography (EtOAc/ petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 7.7 Hz, 1H), 7.79 (td, J = 7.6, 1.1 Hz, 1H), 7.54 (t, J = 7.8 Hz, 2H), 3.94 (dd, J = 18.0, 13.3 Hz, 1H), 3.65 (dd, J = 23.0, 18.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.1 (d, J = 19.0 Hz), 148.2 (d, J = 2.9 Hz), 137.9, 131.5, 129.6, 126.9, 126.5, 114.7 (d, J = 36.1 Hz), 86.5 (d, J = 197.5 Hz), 39.3 (d, J = 24.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -158.29; IR (Neat): 3077, 2928, 1736, 736 cm^{-1}; HRMS (ESI) Calcd. for $C_{10}H_6NOFNa$ ([M+Na]$^+$) 198.0331, Found 198.0334. Enantiomeric excess was determined to be 39% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 95/5, λ = 254 nm, 30 ^{o}C, 0.8 mL/min, t_{major} = 13.0 min, t_{minor} = 14.5 min).

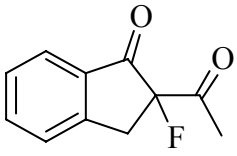


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	13.012	BV	0.2991	1.04352e4	527.90173	49.5771
2	14.462	VB	0.3346	1.06132e4	478.30350	50.4229



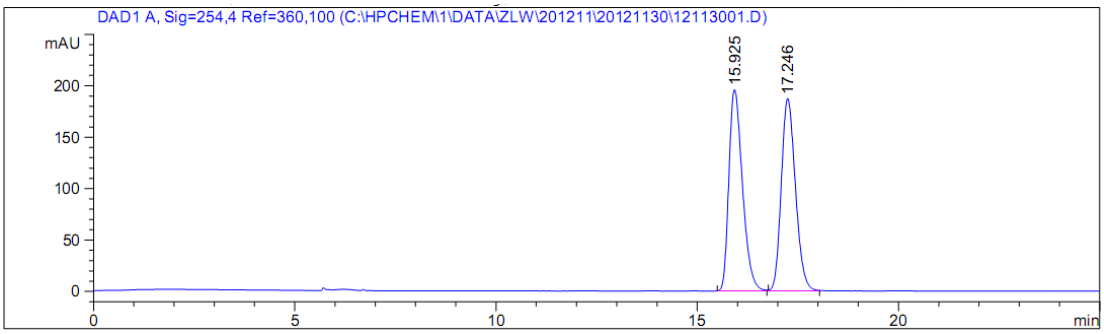
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	13.175	BV	0.2985	3102.77075	157.33357	69.5074
2	14.659	VB	0.3354	1361.17163	61.16313	30.4926

2-Acetyl-2-fluoro-2,3-dihydro-1H-inden-1-one

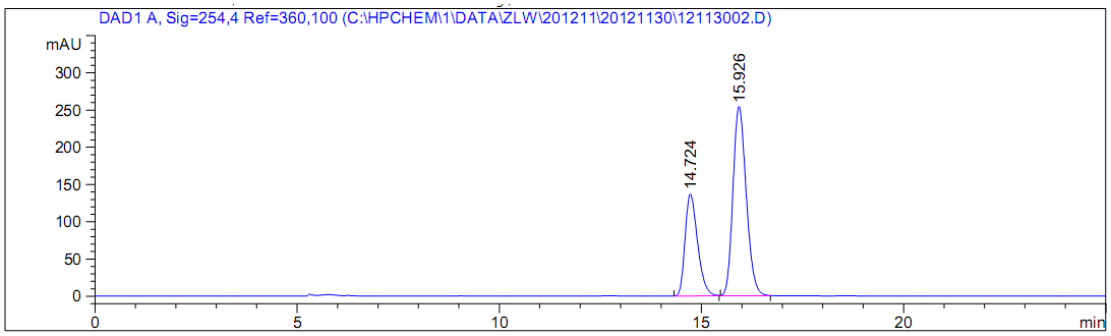


6k

Prepared according to the general procedure with a reaction time of 8 d as colourless oil (91% yield) after silica gel chromatography (EtOAc/ petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 7.7 Hz, 1H), 7.68 (t, J = 7.5 Hz, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.44 (t, J = 7.4 Hz, 1H), 3.79 (dd, J = 17.0, 9.2 Hz, 1H), 3.27 (dd, J = 22.1, 17.2 Hz, 1H), 2.48 (d, J = 5.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.0 (d, J = 30.5 Hz), 196.2 (d, J = 17.8 Hz), 151.5 (d, J = 4.7 Hz), 136.7, 132.9, 128.5, 126.5 (d, J = 1.3 Hz), 125.4, 101.5 (d, J = 201.8 Hz), 36.8 (d, J = 22.8 Hz), 26.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -162.3; IR(Neat): 2973, 2926, 1716, 1625, 734 cm^{-1}; HRMS (ESI) Calcd. for $C_{11}H_9O_2FNa$ ([M+Na]$^+$) 215.0484, Found 215.0491. Enantiomeric excess was determined to be 33% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 95/5, λ = 254 nm, 30 °C, 0.6 mL/min, t_{minor} = 15.9 min, t_{major} = 17.2 min).

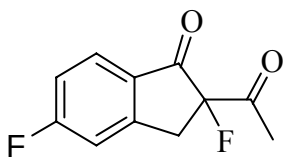


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.925	BB	0.3591	4583.34229	195.78459	50.0481
2	17.246	BB	0.3793	4574.53223	187.04327	49.9519



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.724	BB	0.3332	2939.14185	136.50108	33.5582
2	15.926	BB	0.3554	5819.19043	253.85568	66.4418

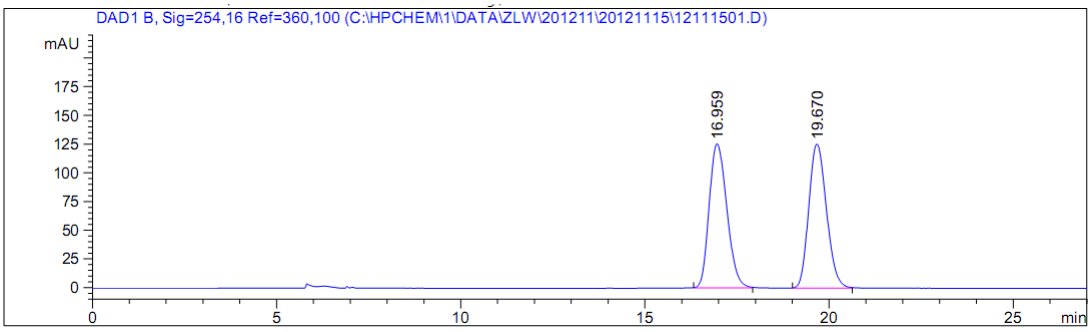
2-Acetyl-2,5-difluoro-2,3-dihydro-1H-inden-1-one



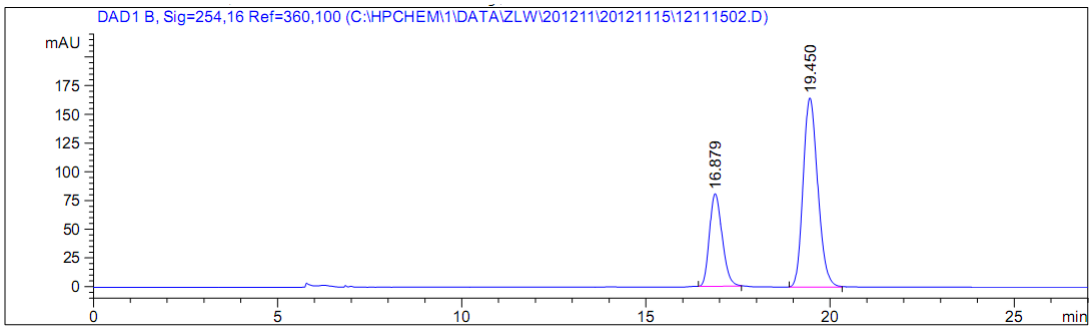
6l

Prepared according to the general procedure with a reaction time of 8 d as white solid (99% yield) after silica gel chromatography (EtOAc/petroleum ether). mp 72.1-73.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, J = 8.4, 5.3 Hz, 1H), 7.18-7.12 (m, 2H), 3.78 (dd, J = 17.4, 8.8 Hz, 1H), 3.26 (dd, J = 21.7, 17.4 Hz, 1H), 2.49 (d, J = 5.1

Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.0 (d, J = 30.4 Hz), 194.2, 168.3 (d, J = 260.2 Hz), 154.6, 129.3, 128.1 (d, J = 10.4 Hz), 117.2 (d, J = 24.0 Hz), 113.6 (d, J = 23.0 Hz), 101.6 (d, J = 202.7 Hz), 36.8 (d, J = 23.4 Hz), 26.4; ^{19}F NMR (377 MHz, $CDCl_3$) δ -98.6, -162.1; IR (KBr): 2956, 2923, 1734, 1713, 742, 687 cm^{-1}; HRMS (ESI) Calcd. for $C_{11}H_8O_2F_2Na$ ([M+Na]$^+$) 233.0390, Found 233.0391. Enantiomeric excess was determined to be 40% (determined by HPLC using chiral AS-H column, hexane/2-propanol = 95/5, λ = 254 nm, 30 °C, 0.6 mL/min, t_{minor} = 17.0 min, t_{major} = 19.7 min).

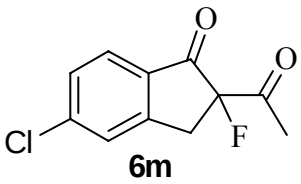


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.959	BB	0.5260	4191.00244	125.35831	49.9962
2	19.670	BB	0.5263	4191.63330	125.29539	50.0038



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.879	BB	0.3753	1945.18750	80.66766	29.9008
2	19.450	BB	0.4292	4560.27930	164.62288	70.0992

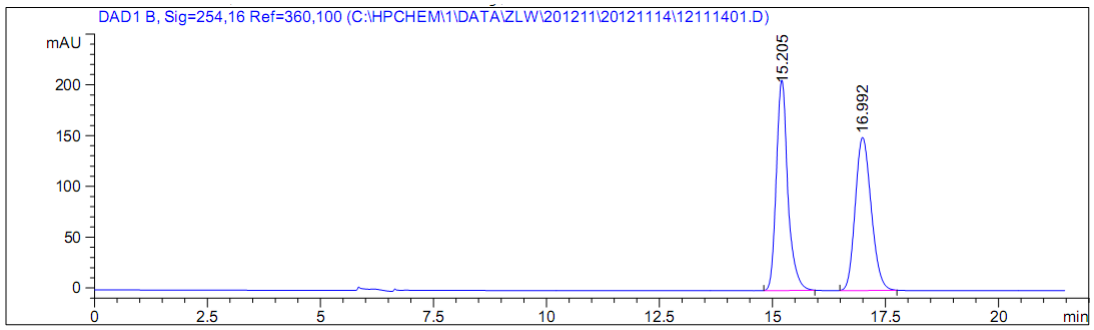
2-Acetyl-5-chloro-2-fluoro-2,3-dihydro-1H-inden-1-one



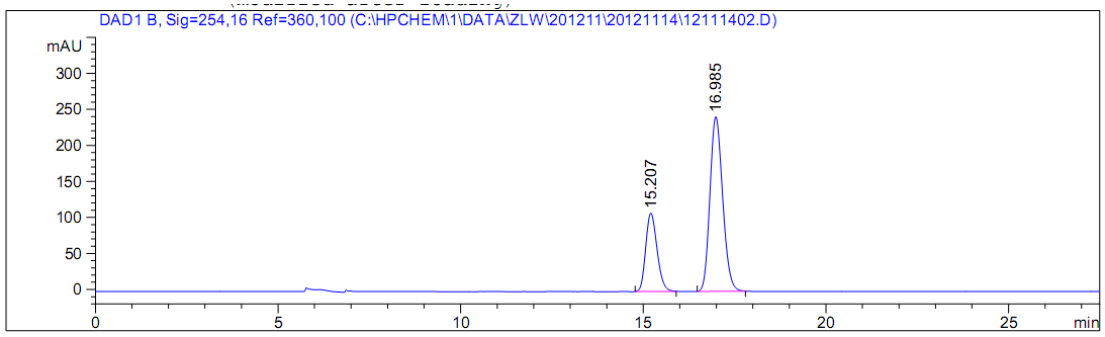
6m

Prepared according to the general procedure with a reaction time of 8 d as white solid (90% yield) after silica gel chromatography (EtOAc/petroleum ether). mp 63.8-65.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.2 Hz, 1H), 7.50 (s, 1H), 7.42 (d, J = 8.2 Hz, 1H), 3.76 (dd, J = 17.4, 8.9 Hz, 1H), 3.25 (dd, J = 21.8, 17.4 Hz, 1H), 2.48 (d, J = 5.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.7 (d, J = 30.3 Hz), 194.7 (d, J = 17.7 Hz), 152.8 (d, J = 4.8 Hz), 143.5, 131.3, 129.5, 126.8 (d, J = 1.3 Hz), 126.5, 101.4 (d, J = 203.0 Hz), 36.5 (d, J = 23.3 Hz), 26.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -161.9; IR (KBr): 2920, 2846, 1741, 1717, 821 cm^{-1}; HRMS (ESI) Calcd. for $C_{11}H_8O_2FClNa$ ([M+Na]$^+$) 249.0095, Found

249.0096. Enantiomeric excess was determined to be 43% (determined by HPLC using chiral AS-H column, hexane/2-propanol = 95/5, λ = 254 nm, 30 °C, 0.6 mL/min, t_{minor} = 15.2 min, t_{major} = 17.0 min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.205	BB	0.2713	3680.00684	207.07394	49.8538
2	16.992	BB	0.3786	3701.58545	150.68094	50.1462



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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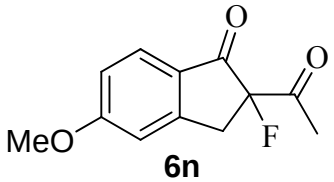
2	16.985	BB	0.3779	5895.20850	242.23814	71.3933

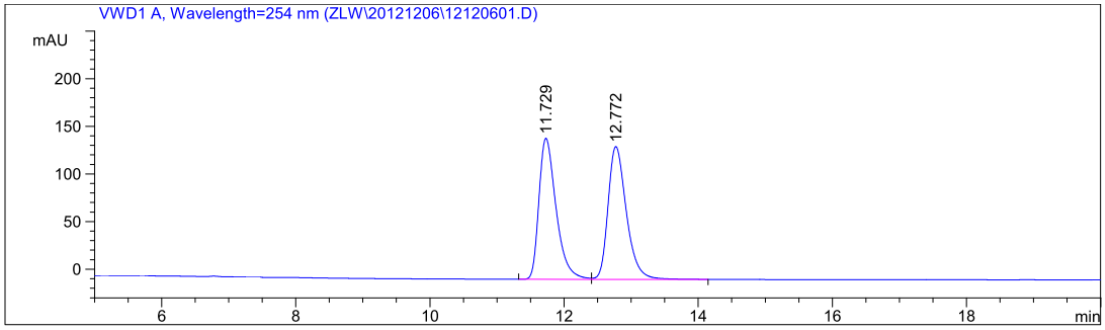
2-Acetyl-2-fluoro-5-methoxy-2,3-dihydro-1H-inden-1-one



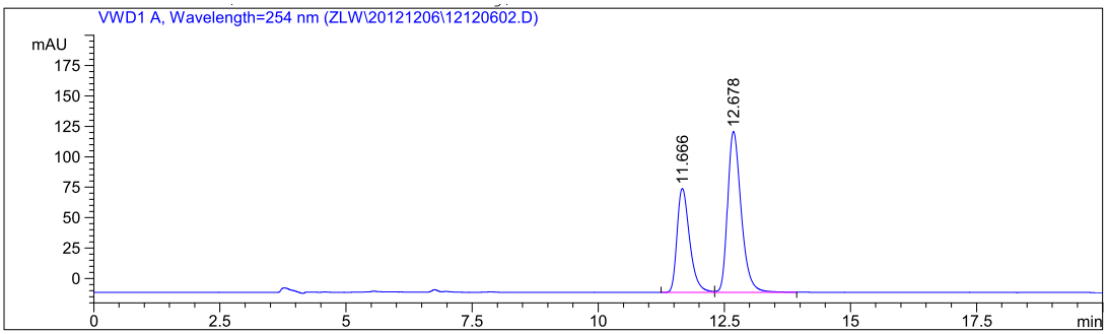
6n

Prepared according to the general procedure with a reaction time of 14 d as colourless oil (82% yield) after silica gel chromatography (EtOAc/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.6 Hz, 1H), 6.95 (dd, J = 8.6, 2.2 Hz, 1H), 6.91 (s, 1H), 3.91 (s, 3H), 3.73 (dd, J = 17.2, 8.8 Hz, 1H), 3.21 (dd, J = 21.9, 17.2 Hz, 1H), 2.47 (d, J = 5.0 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -161.4; ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.4 (d, J = 30.7 Hz), 193.9 (d, J = 17.8 Hz), 166.9, 154.6 (d, J = 4.8 Hz, 1H), 127.3, 125.9, 116.8, 109.5 (d, J = 1.3 Hz), 101.9 (d, J = 201.2 Hz), 55.9, 36.8 (d, J = 22.9 Hz), 26.3; IR(Neat): 2924, 2854, 1736, 1717, 1597, 1210, 1060, 819 cm^{-1}; HRMS (ESI) Calcd. for $C_{12}H_{11}O_3FNa$ ($[M+Na]^+$) 245.0590, Found 245.0599. Enantiomeric excess was determined to be 25% (determined by HPLC using chiral OD-H column,

hexane/2-propanol = 95/5, λ = 254 nm, 30 °C, 0.8 mL/min, t_{minor} = 11.7 min, t_{major} = 12.8 min).



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.729	VV	0.2710	2625.65698	148.02196	49.7505
2	12.772	VB	0.2918	2651.99707	139.44887	50.2495



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.666	VV	0.2634	1470.77173	85.44897	37.3455
2	12.678	VB	0.2875	2467.50952	132.29709	62.6545

4. References

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[3] For the preparation of β-ketoesters, see: (a) A. M. R. Smith, D. Billenb, K. K. Hii, *Chem. Commun.* **2009**, 3925. dio:10.1039/b907151b

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(b) M. Bella, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 5672. doi: 10.1021/ja0493594

[5] For the preparation of α-cyano carbonyl compounds see: (a) W. S. Johnson; J. M. Anderson; W. E. Shelerg, *J. Am. Chem. Soc.* **1944**, *66*, 218. doi:10.1021/ja01230a018

(b) W. S. Johnson; W. E. Sherleg, *J. Am. Chem. Soc.* **1945**, *67*, 1745. doi:10.1021/ ja01226a038

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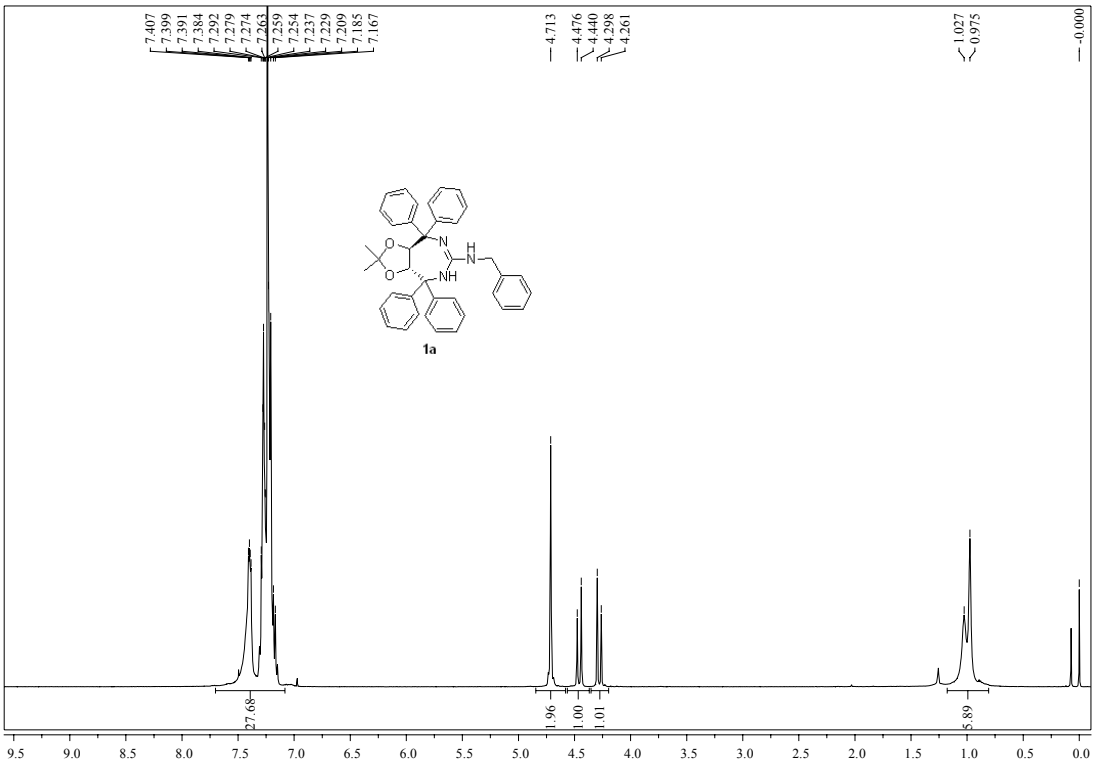
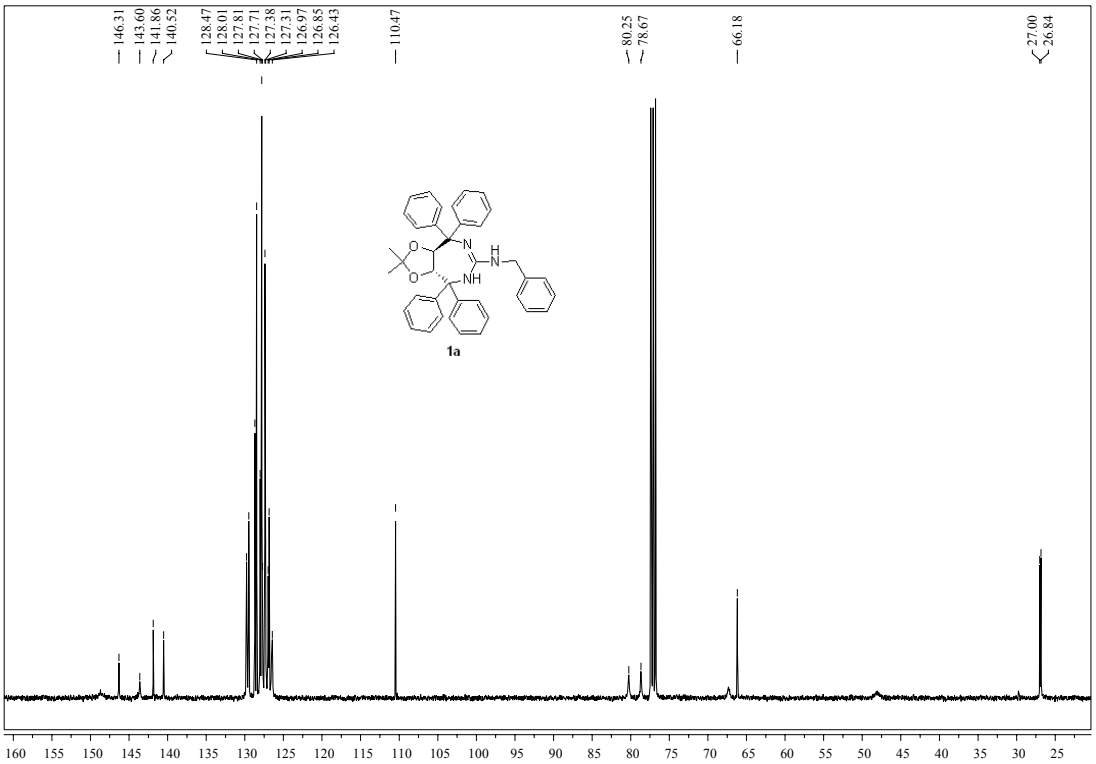
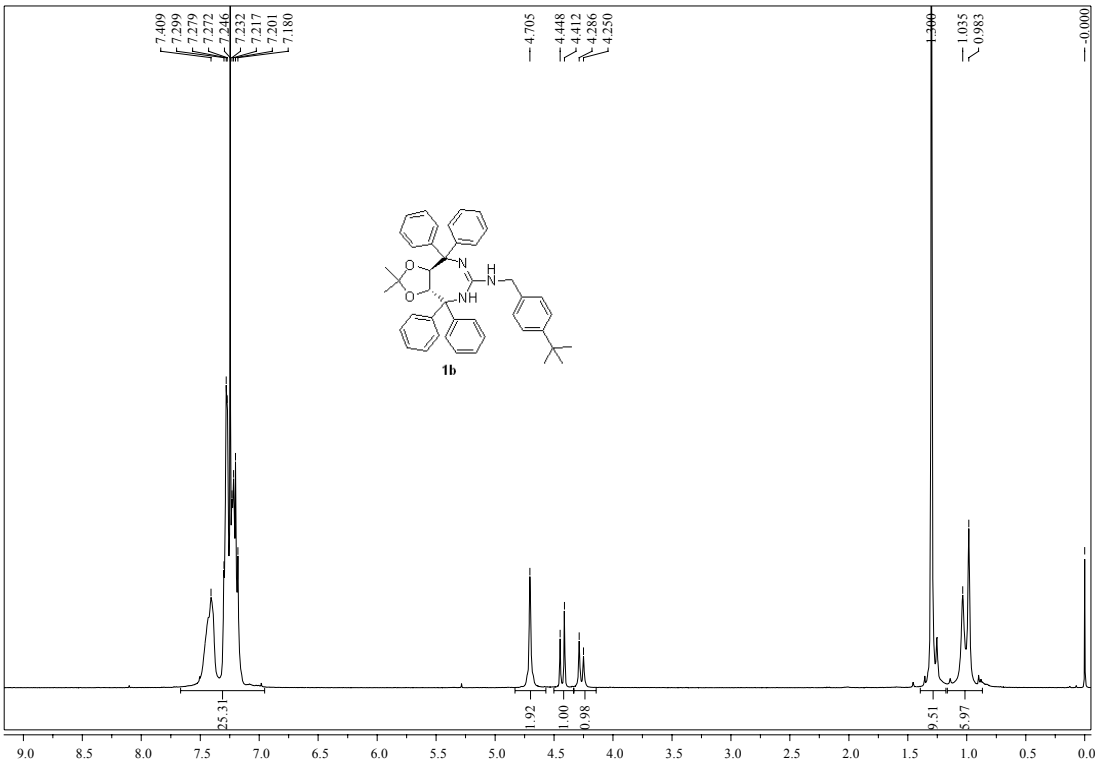
[8] J. Xu, Y. Hu, D. Huang, K.-H. Wang, C. Xu, T. Niu, *Adv. Synth. Catal.* **2012**, *354*, 515. doi:10.1002/adsc.201100660

5. NMR spectra for compounds:



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0.000
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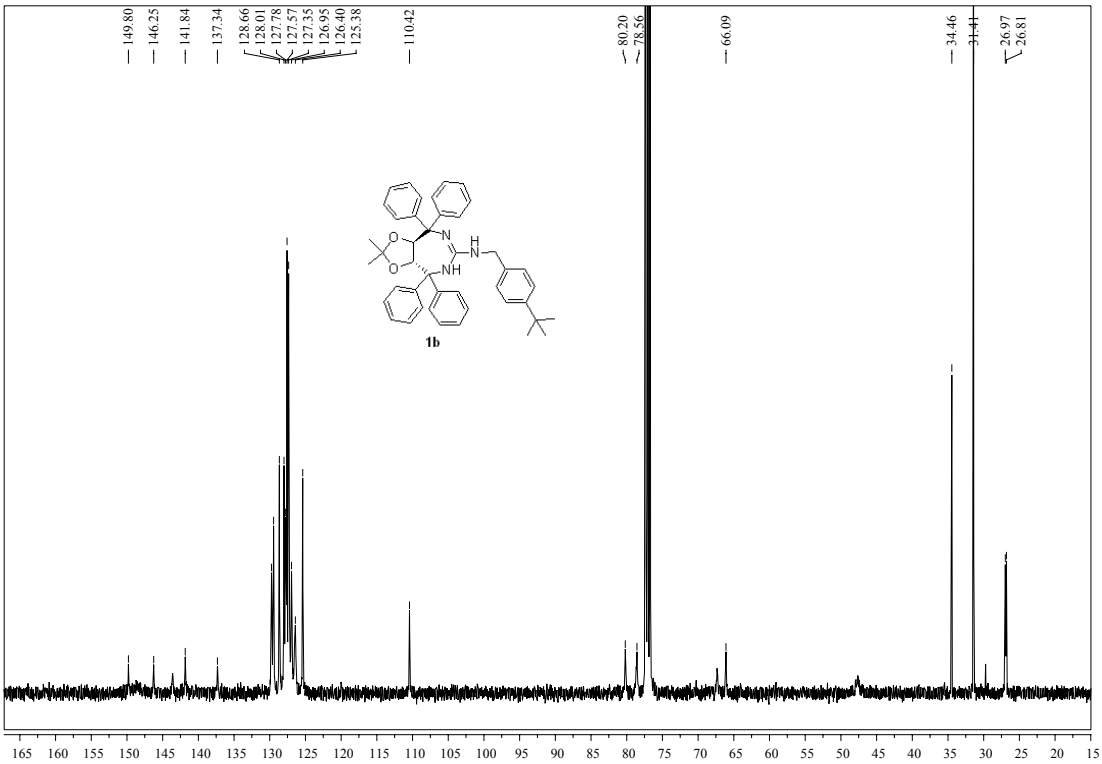
1.00
0.98
9.51
5.97
1b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26.97
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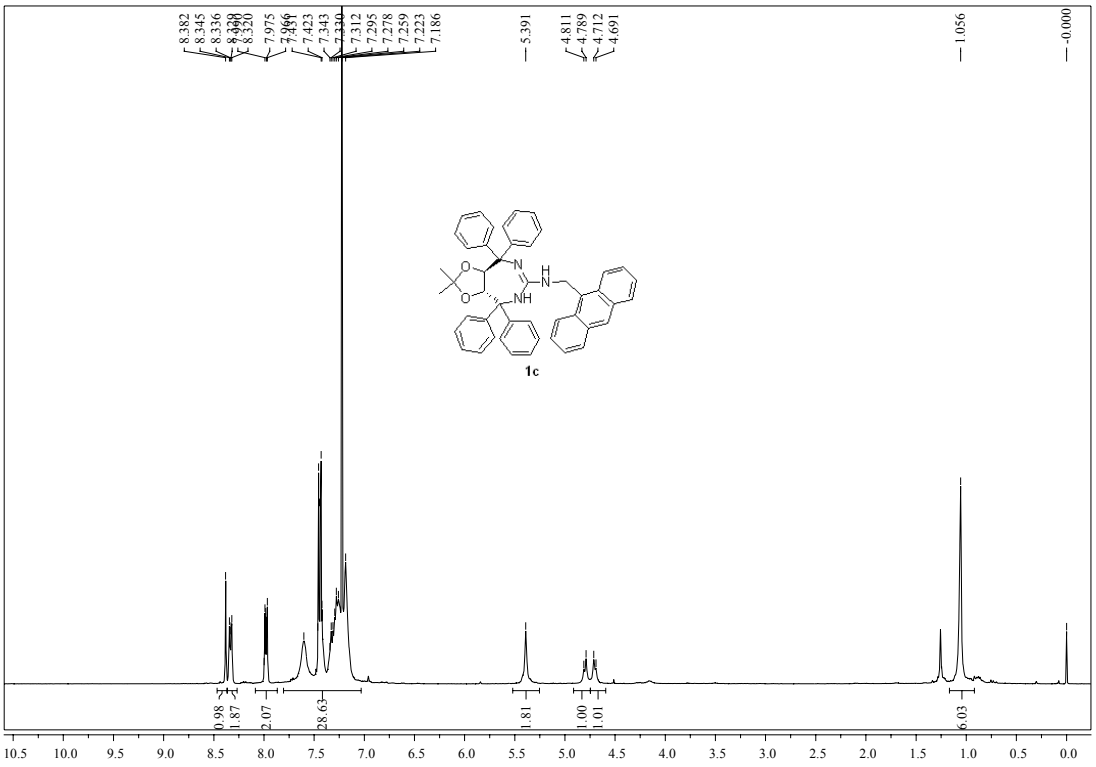
1b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4.712
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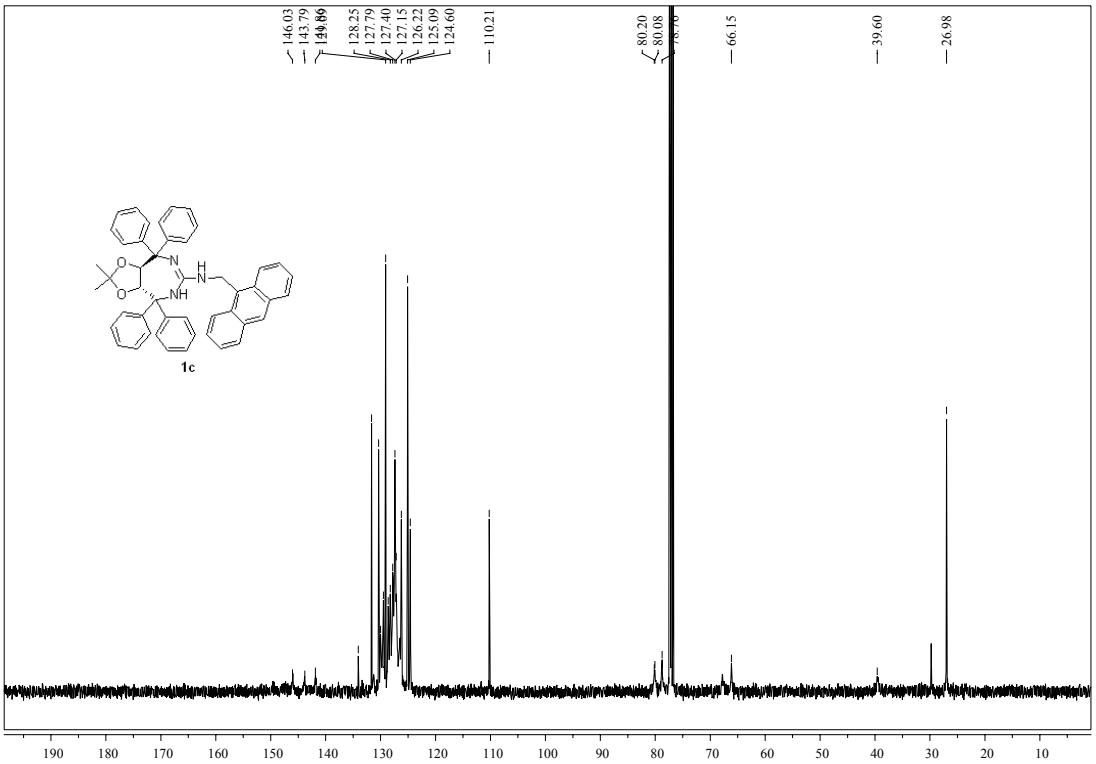
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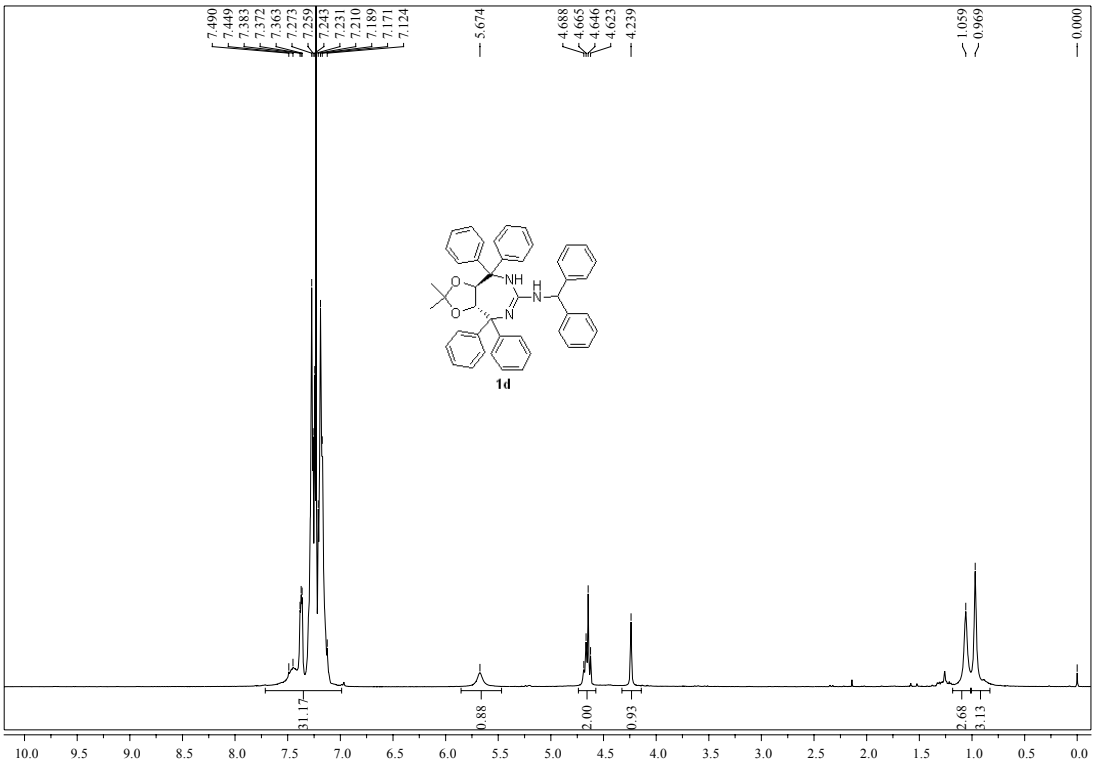
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4.623
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0.000
1d
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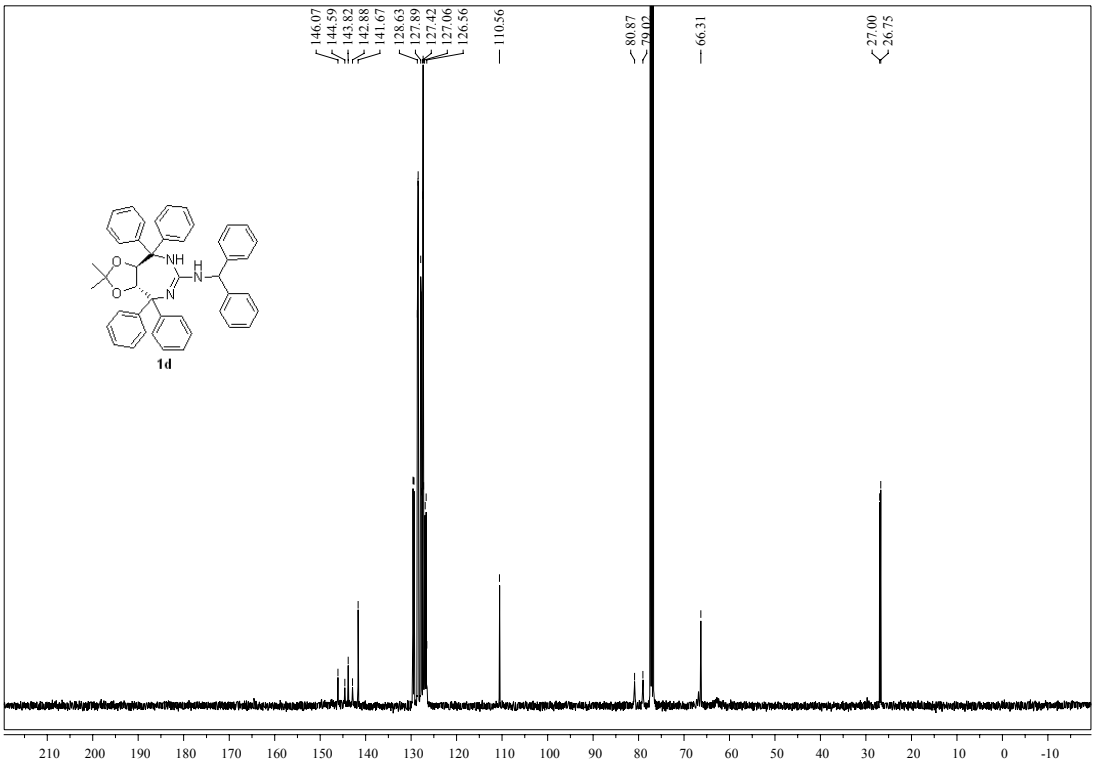
0.93
2.68
3.13
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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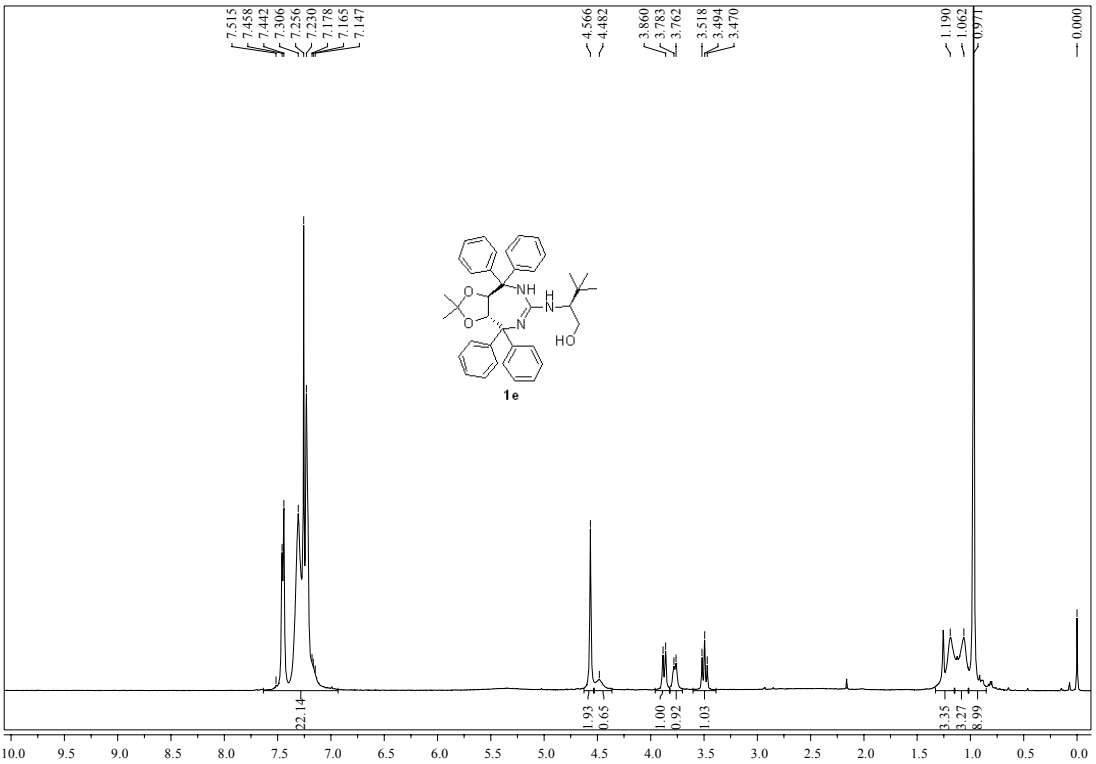
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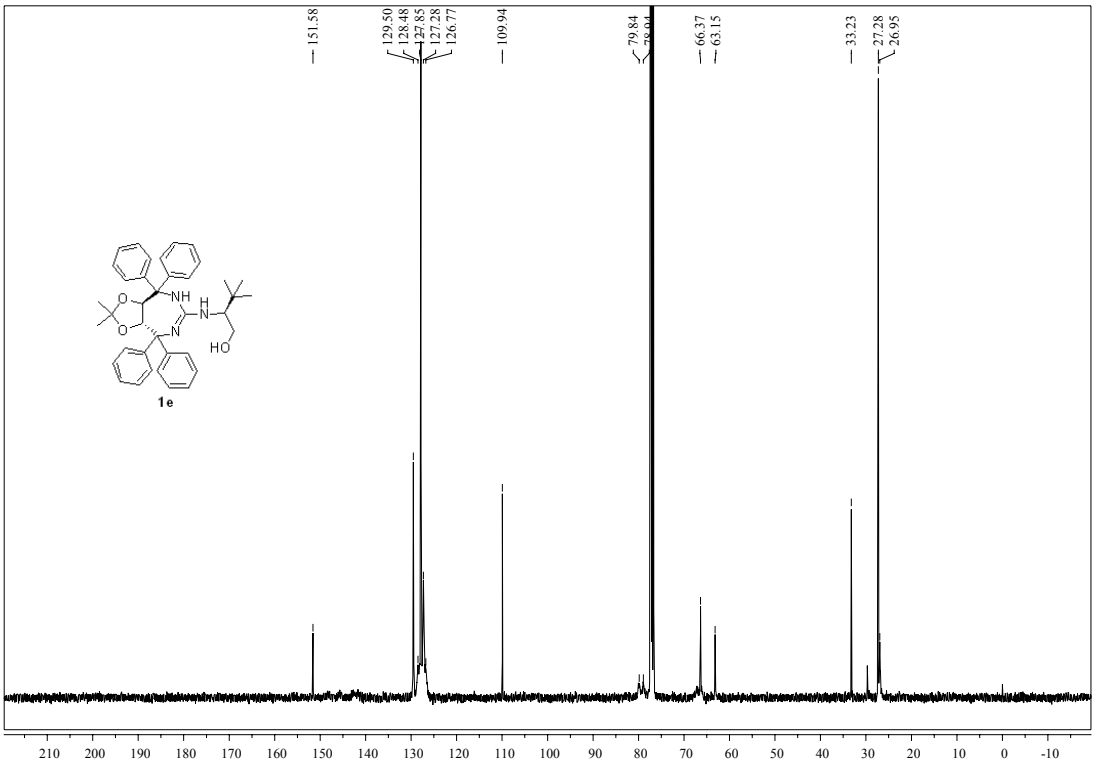
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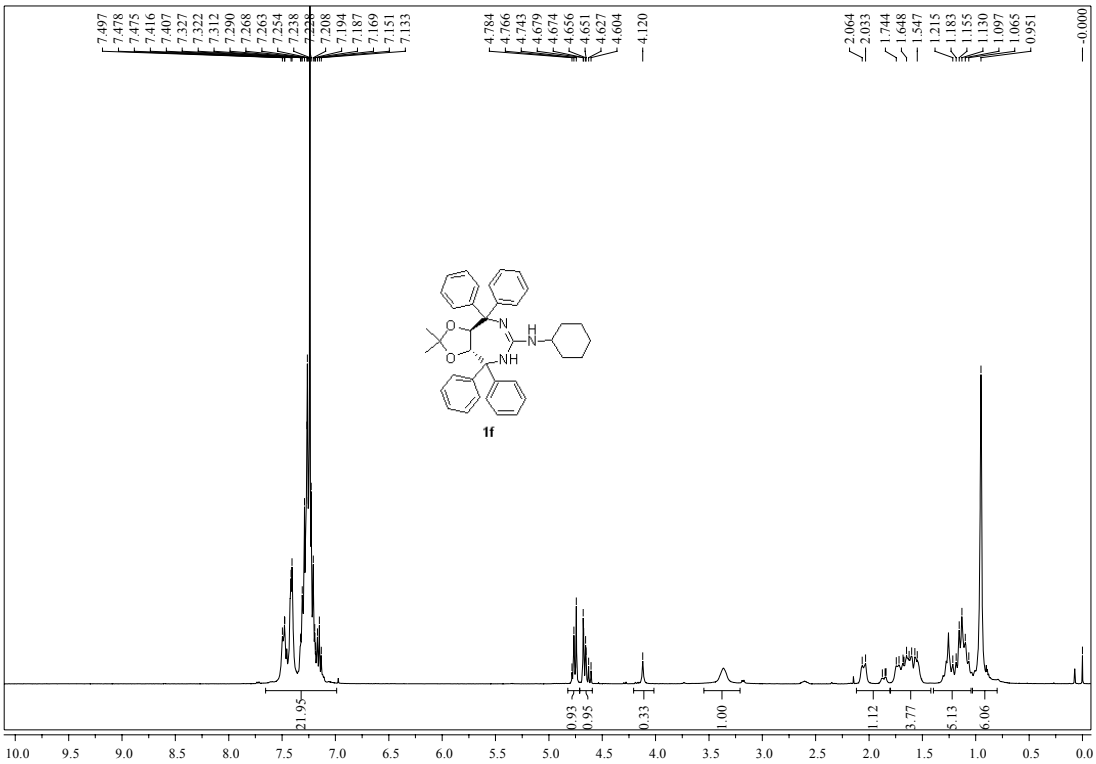
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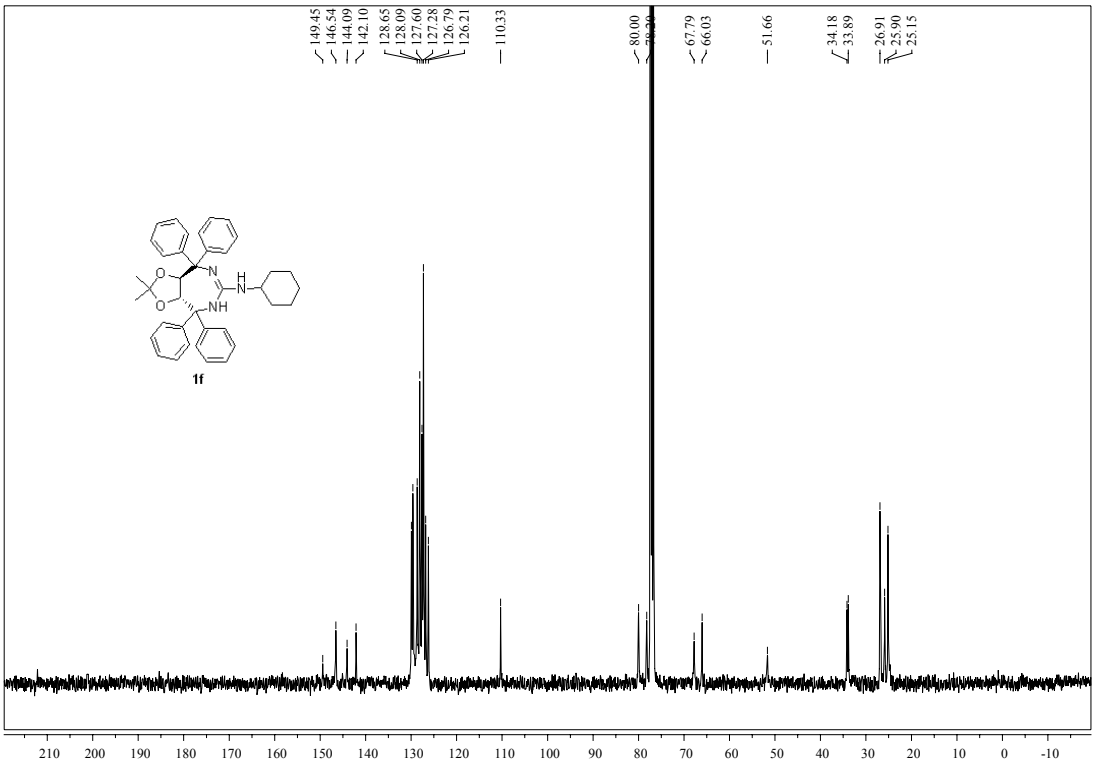
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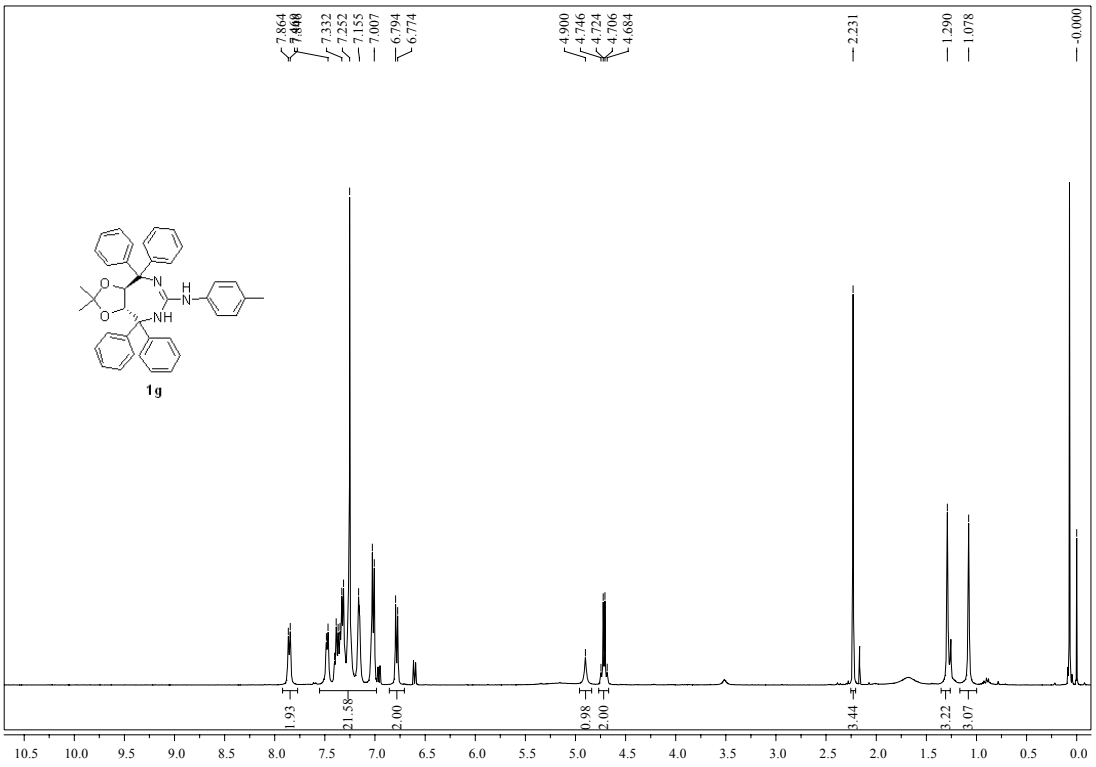
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3.22
3.07
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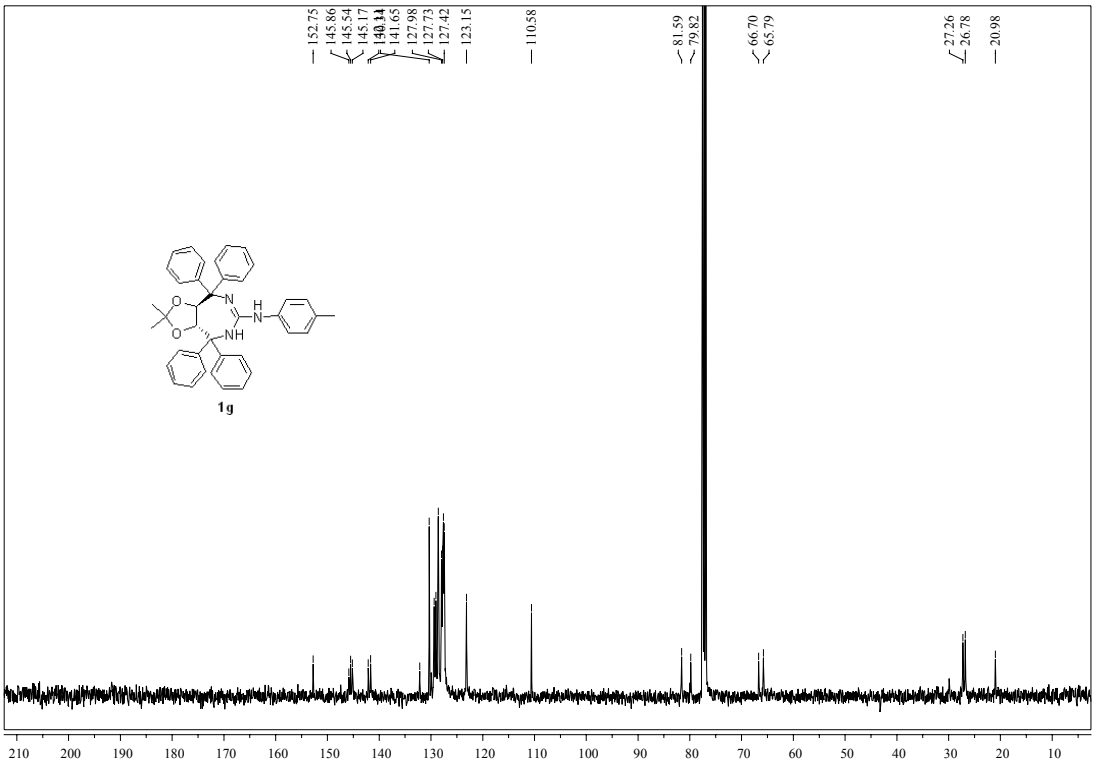
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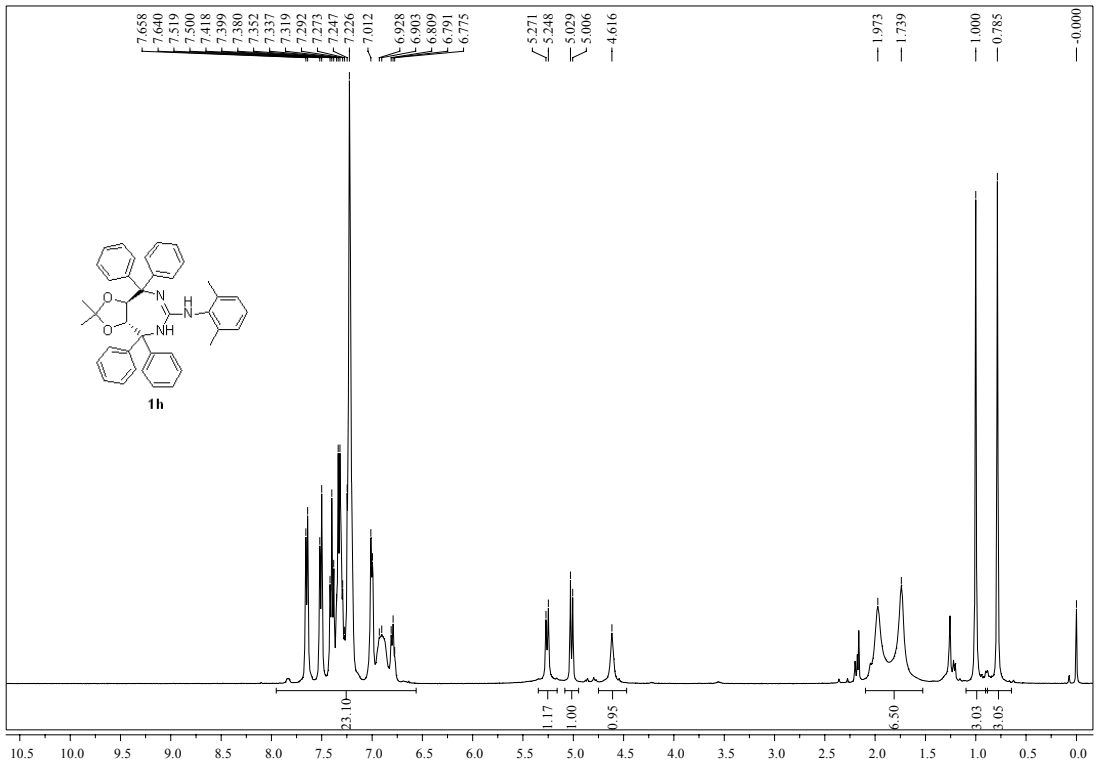
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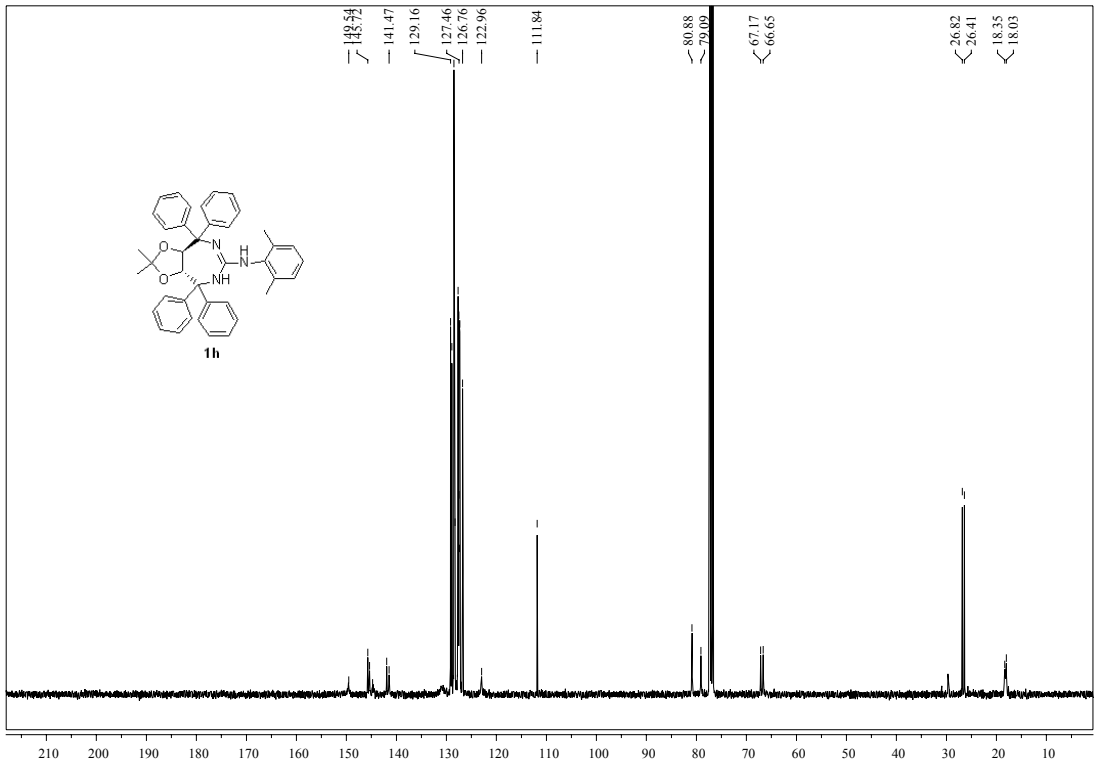
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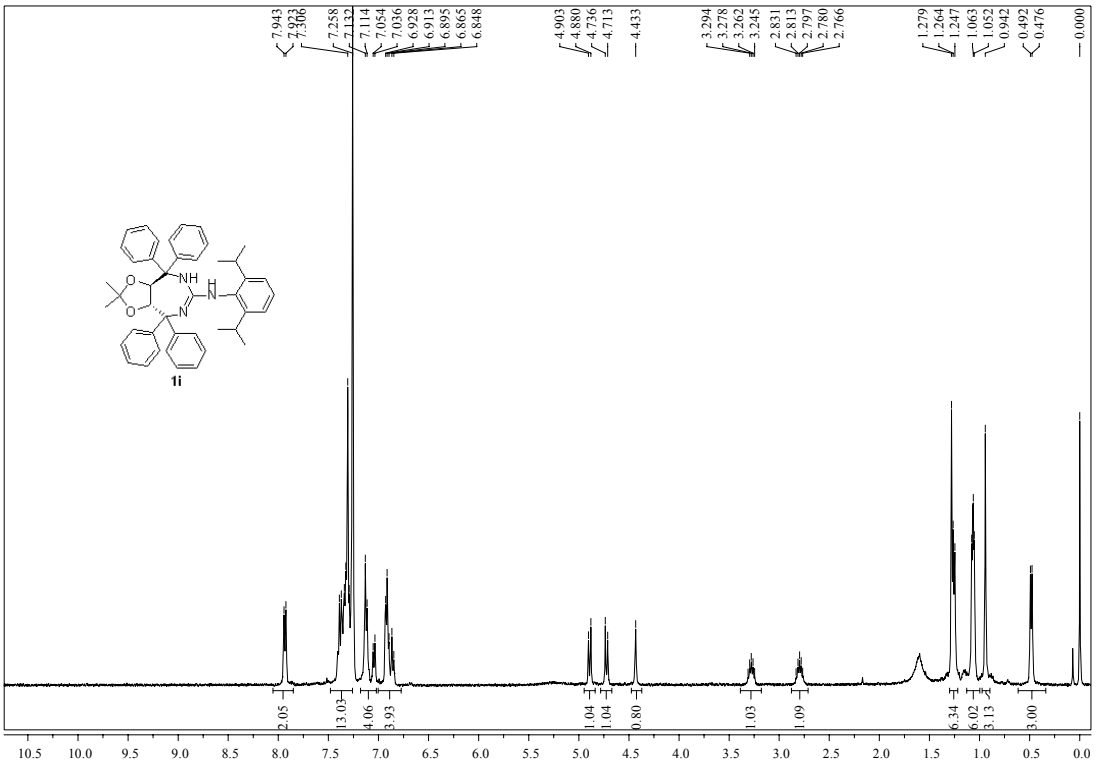
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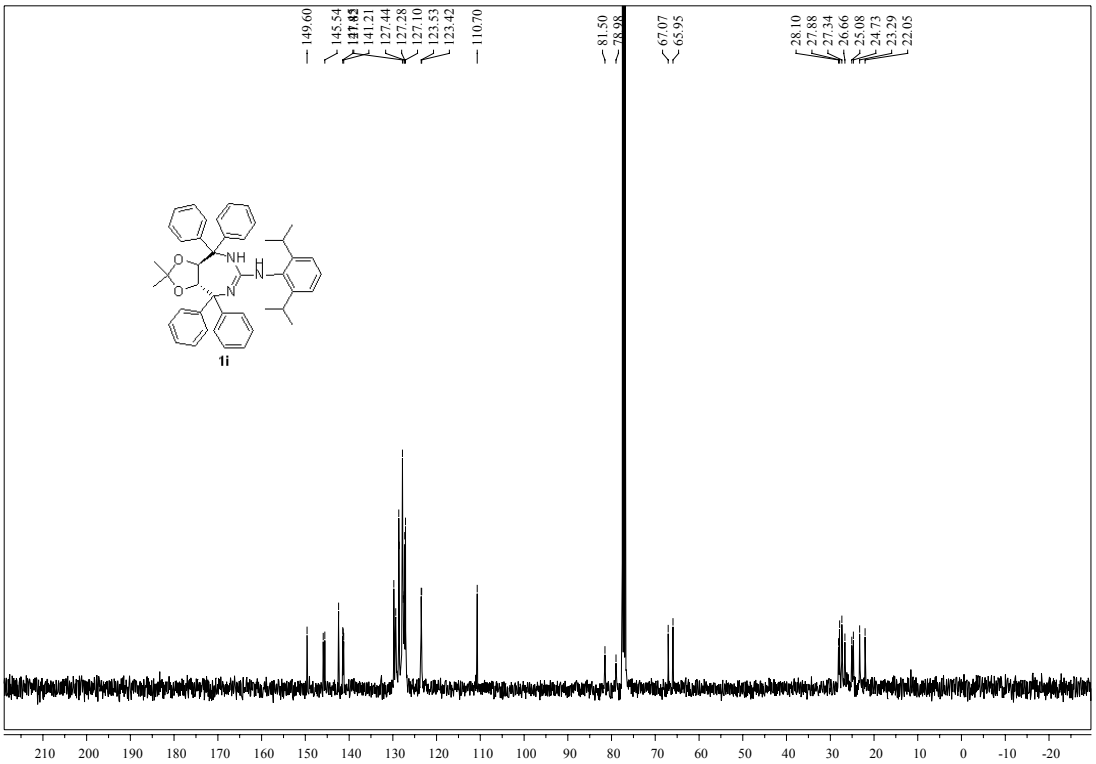
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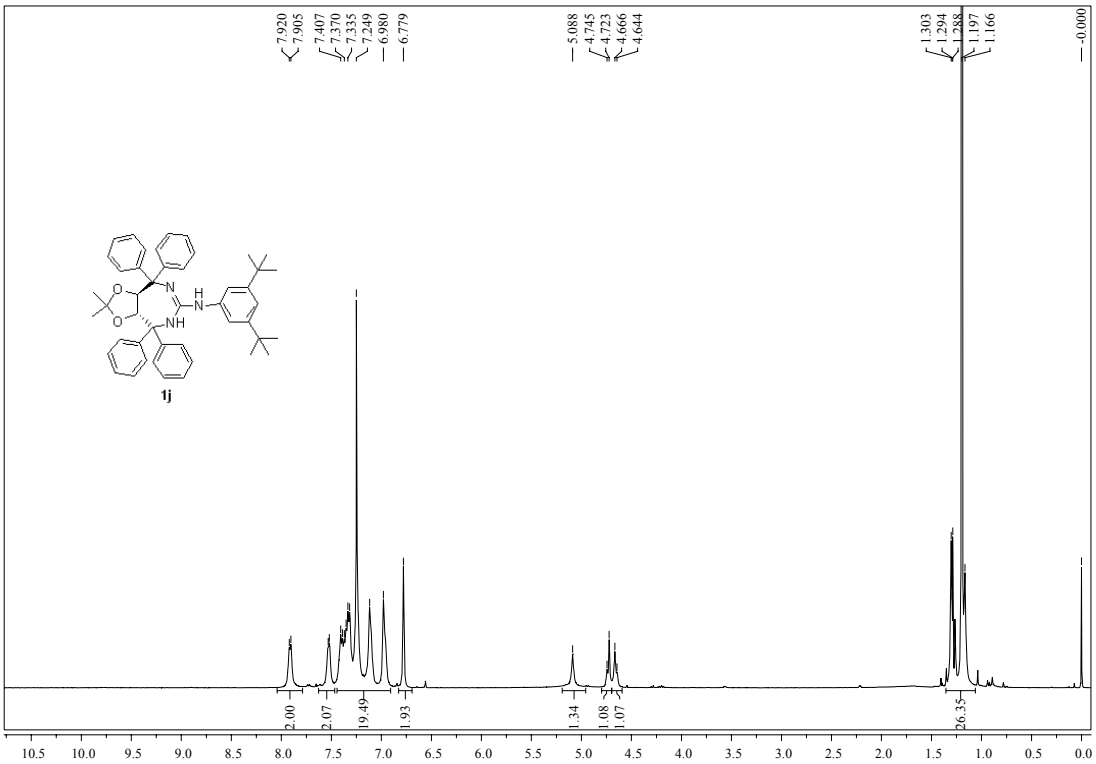
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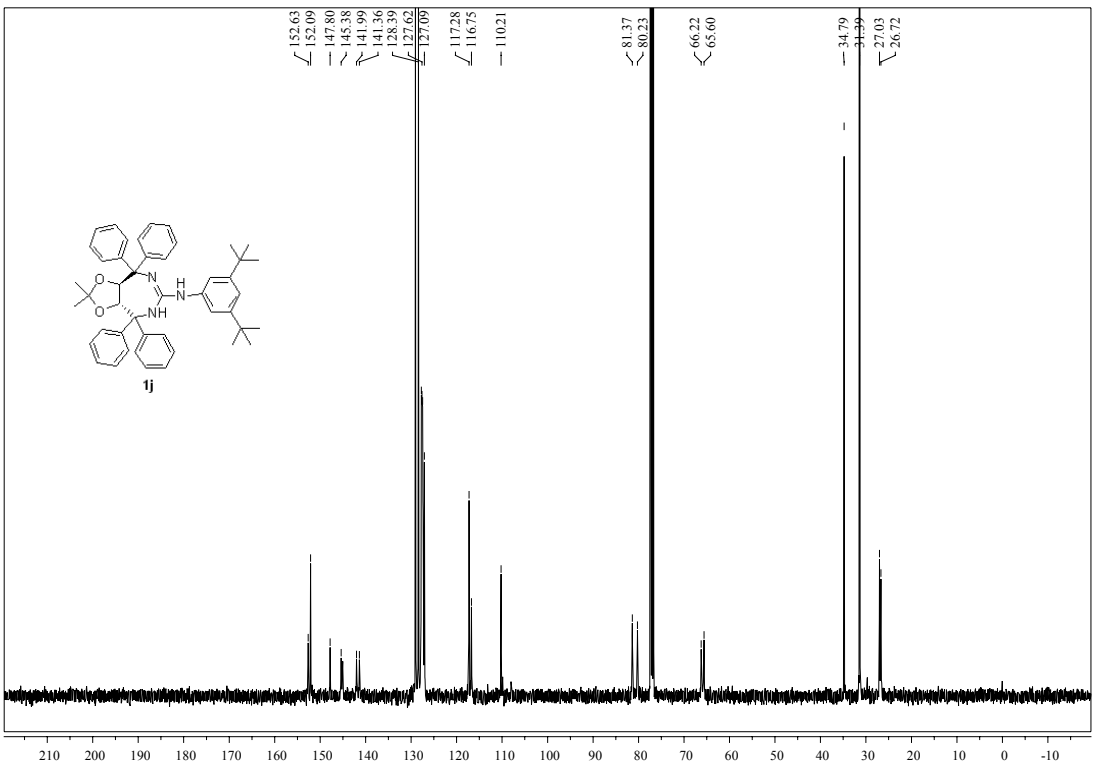
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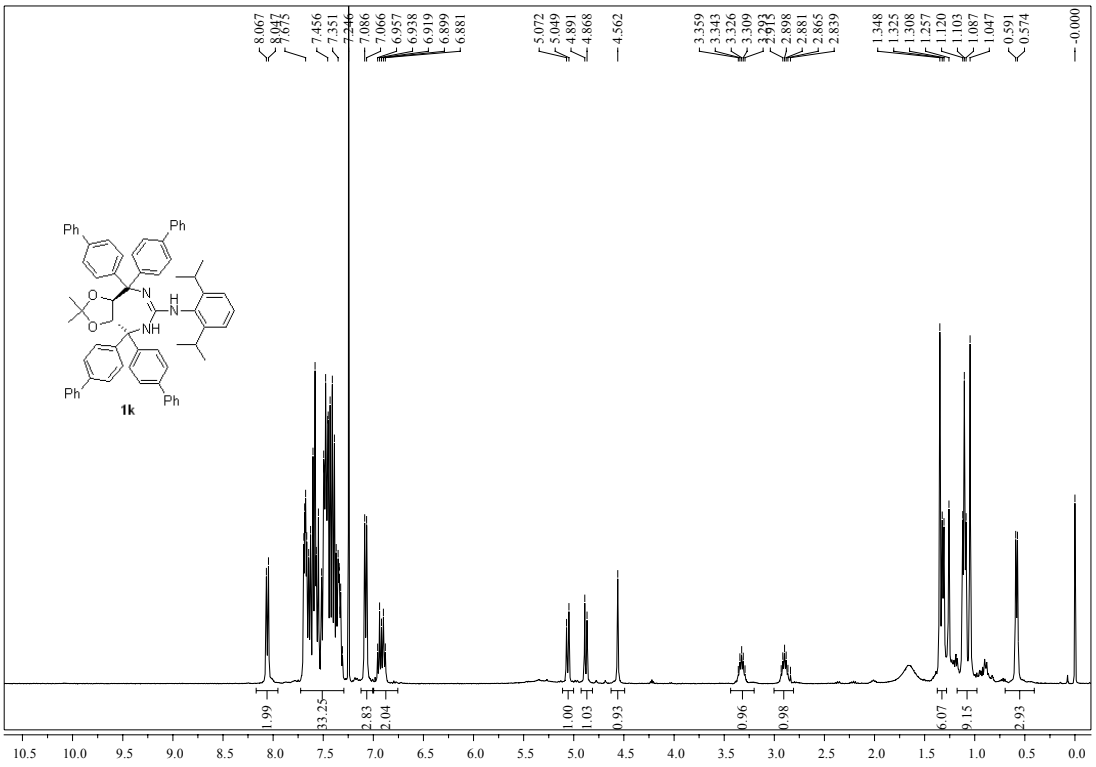
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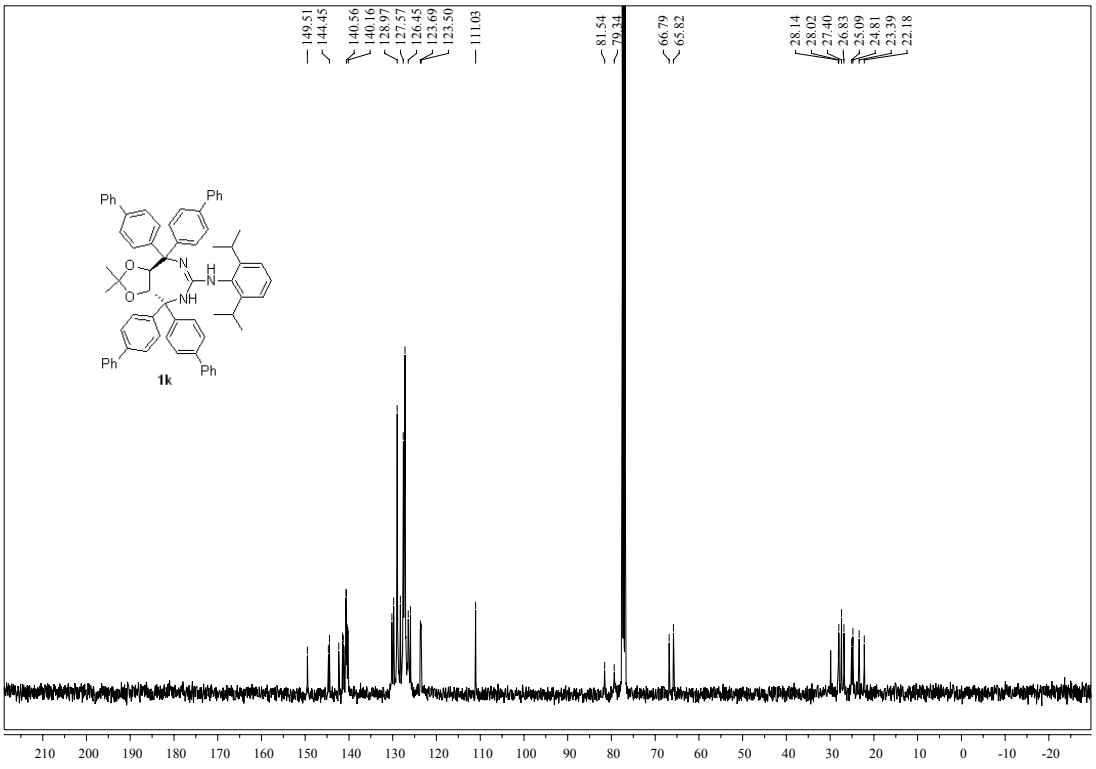
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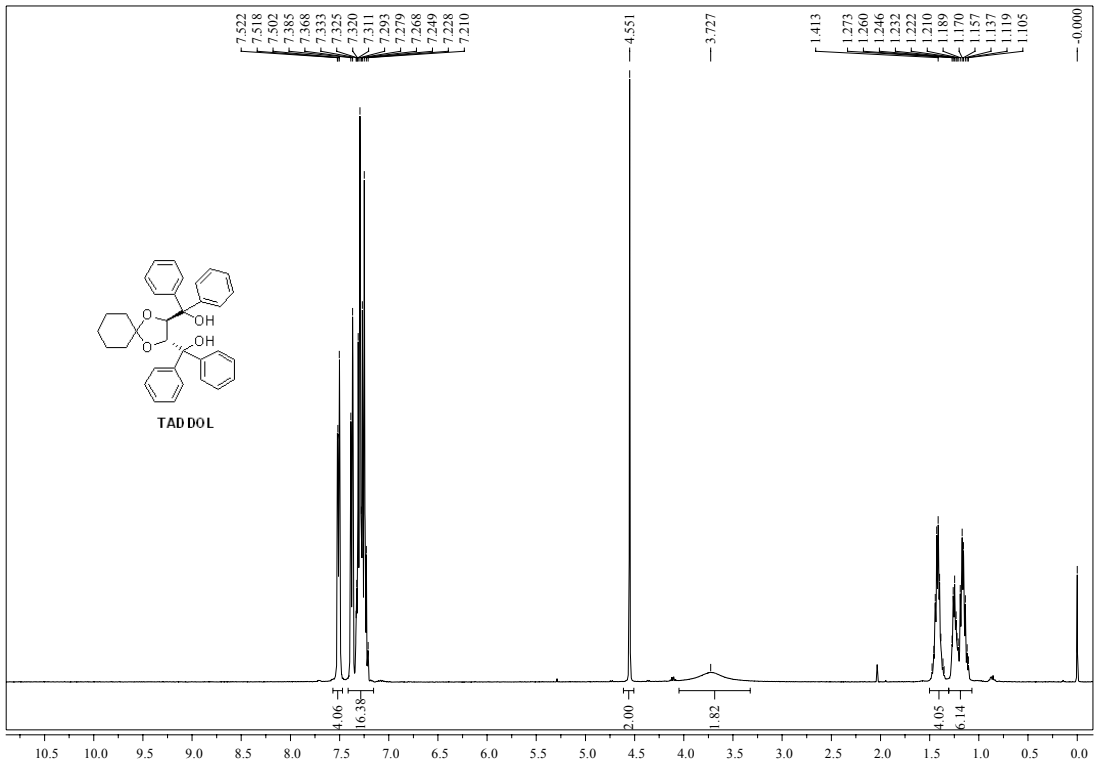
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1.105
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OH
OH
TADDOL
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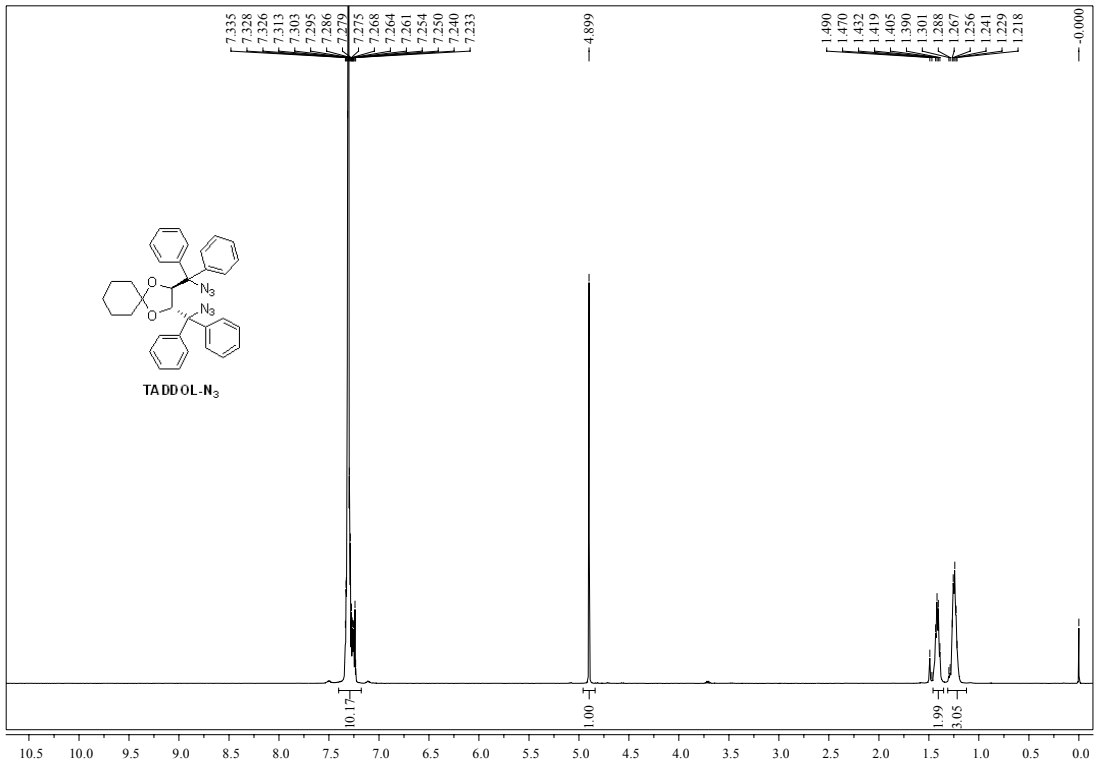
16.38
2.00
1.82
4.05
6.14
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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7.254
7.250
7.240
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1.432
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1.405
1.390
1.301
1.288
1.267
1.256
1.241
1.229
1.218
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N3
N3
TADDOL-N3
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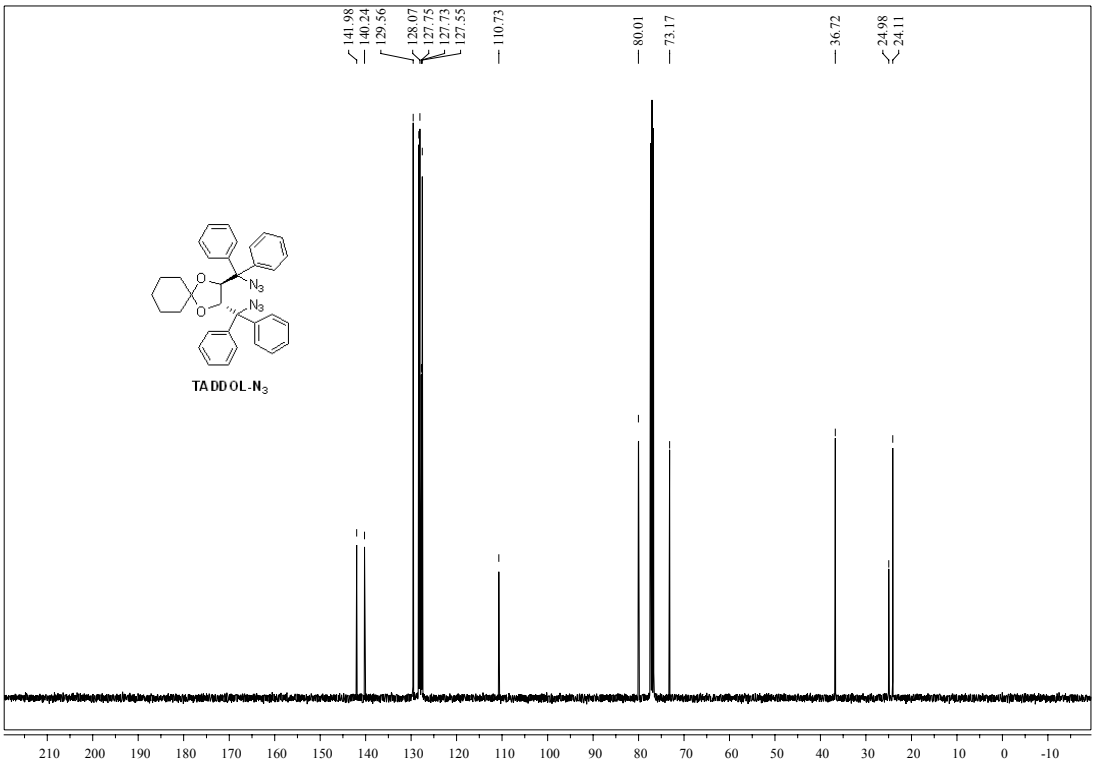
1.00
1.99
3.05
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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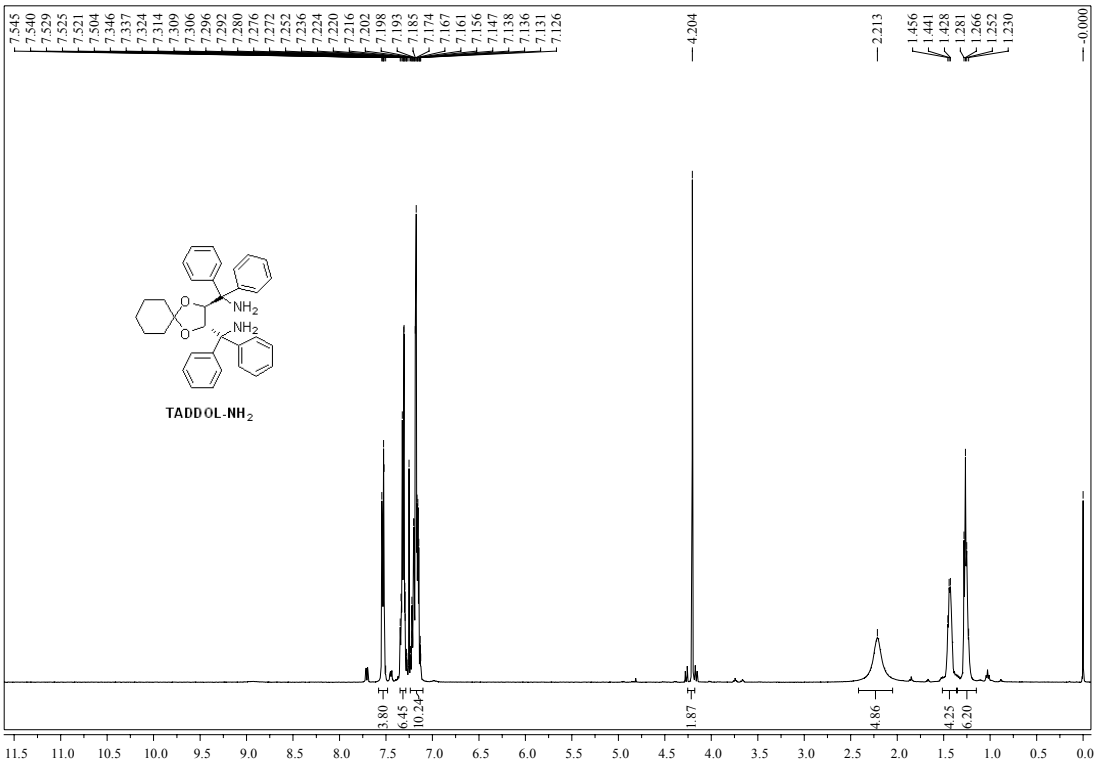
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7.292
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7.272
7.252
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7.224
7.220
7.216
7.202
7.198
7.193
7.185
7.174
7.167
7.161
7.156
7.147
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7.136
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2.213
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1.428
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1.252
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NH2
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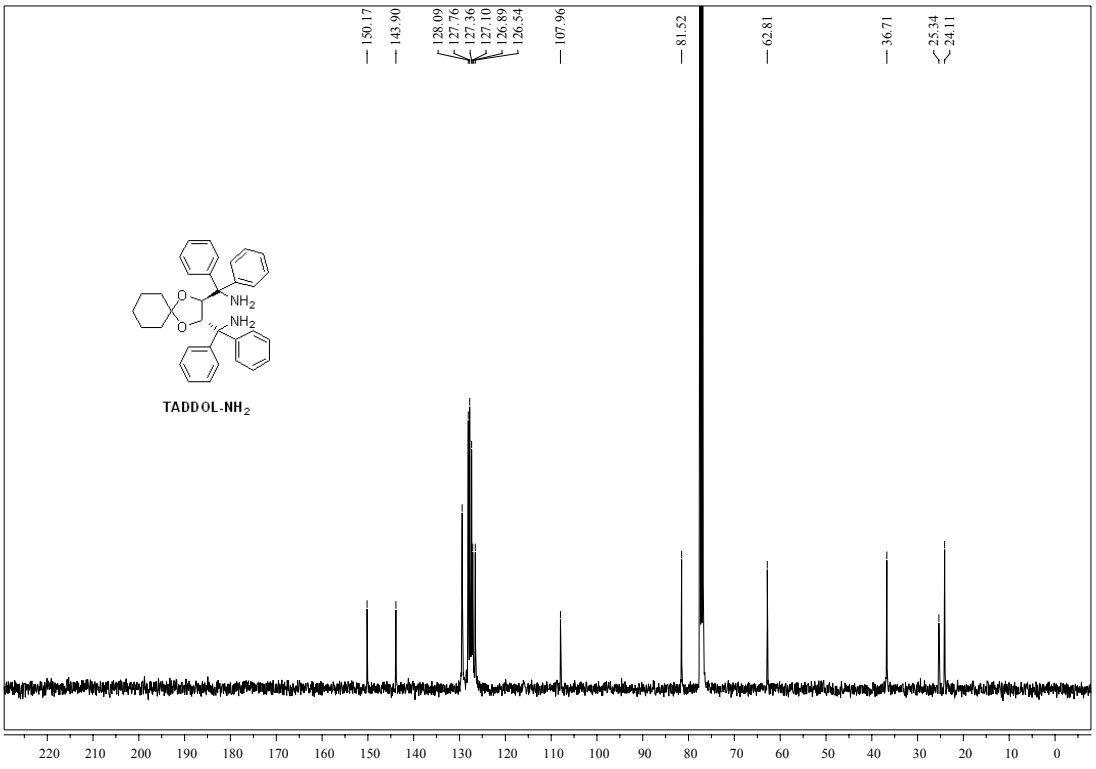
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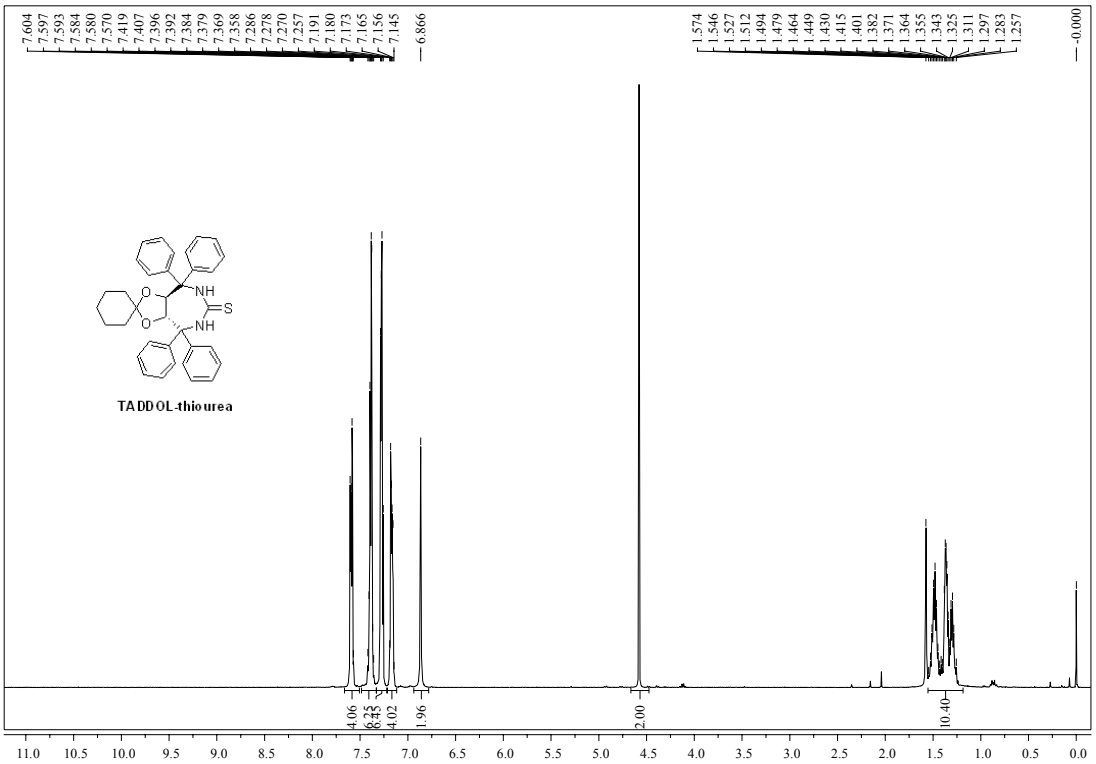
NH2
TADDOL-NH2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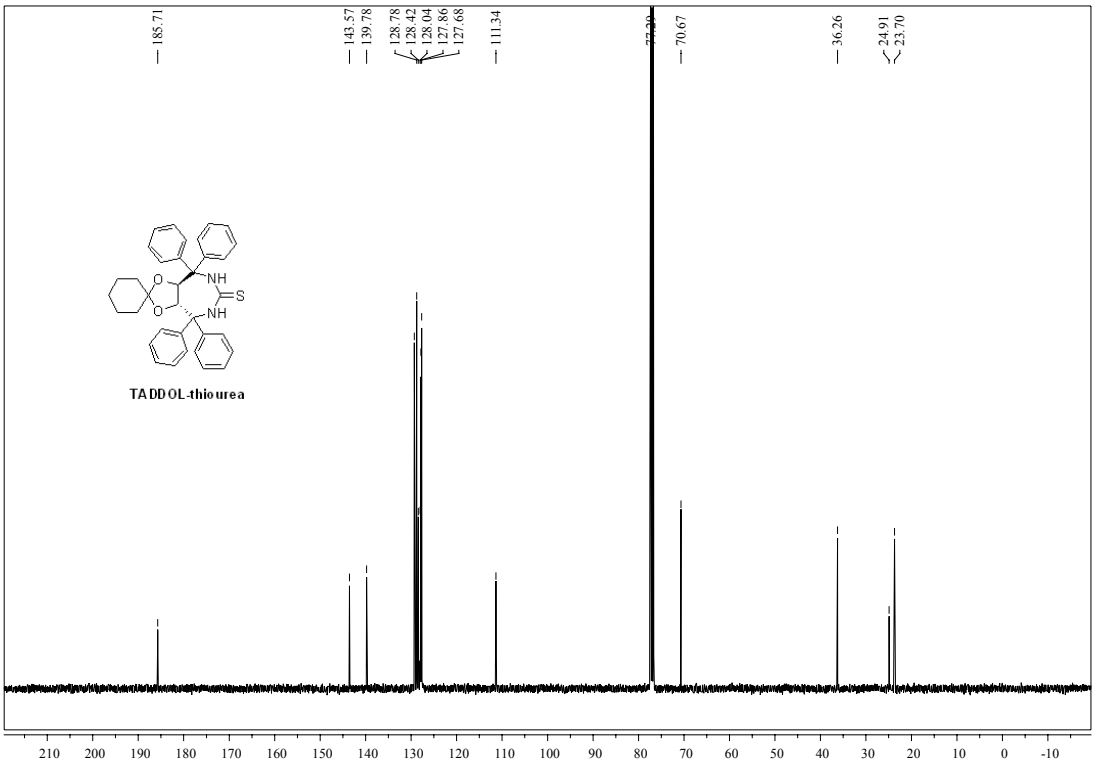
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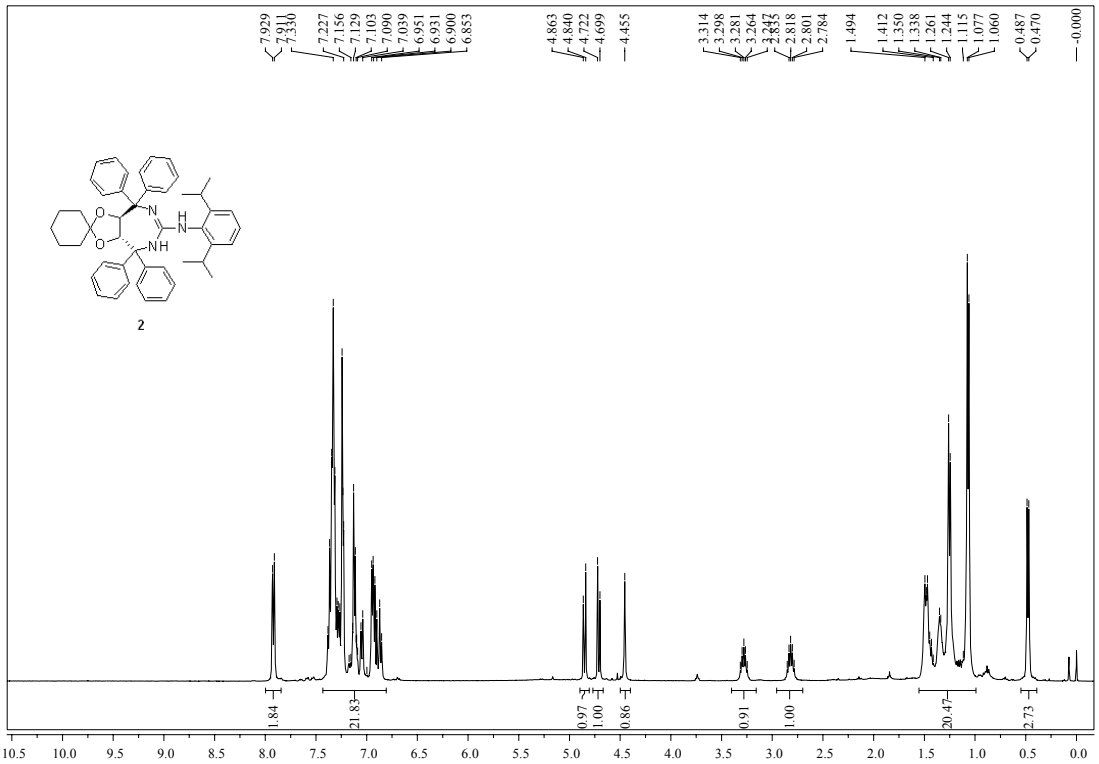
S
NH
TADDOL-thiourea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3.281
3.264
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2.801
2.784
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1.412
1.350
1.338
1.261
1.244
1.115
1.077
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0.470
-0.000
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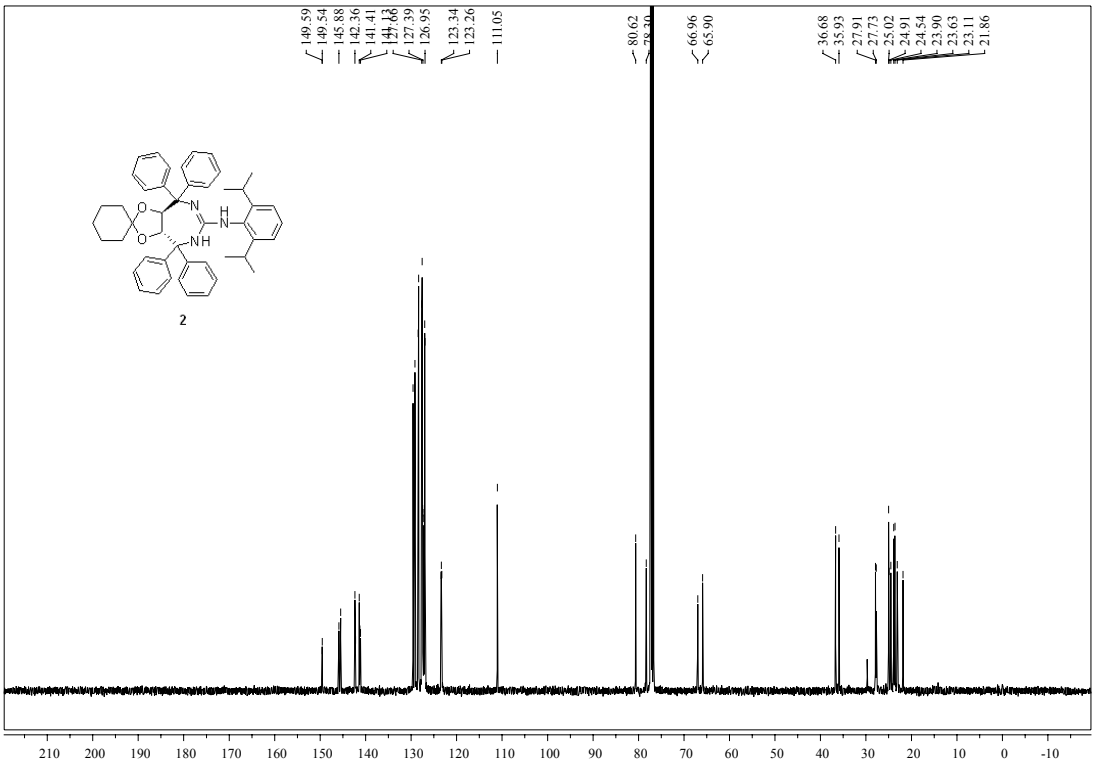
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23.11
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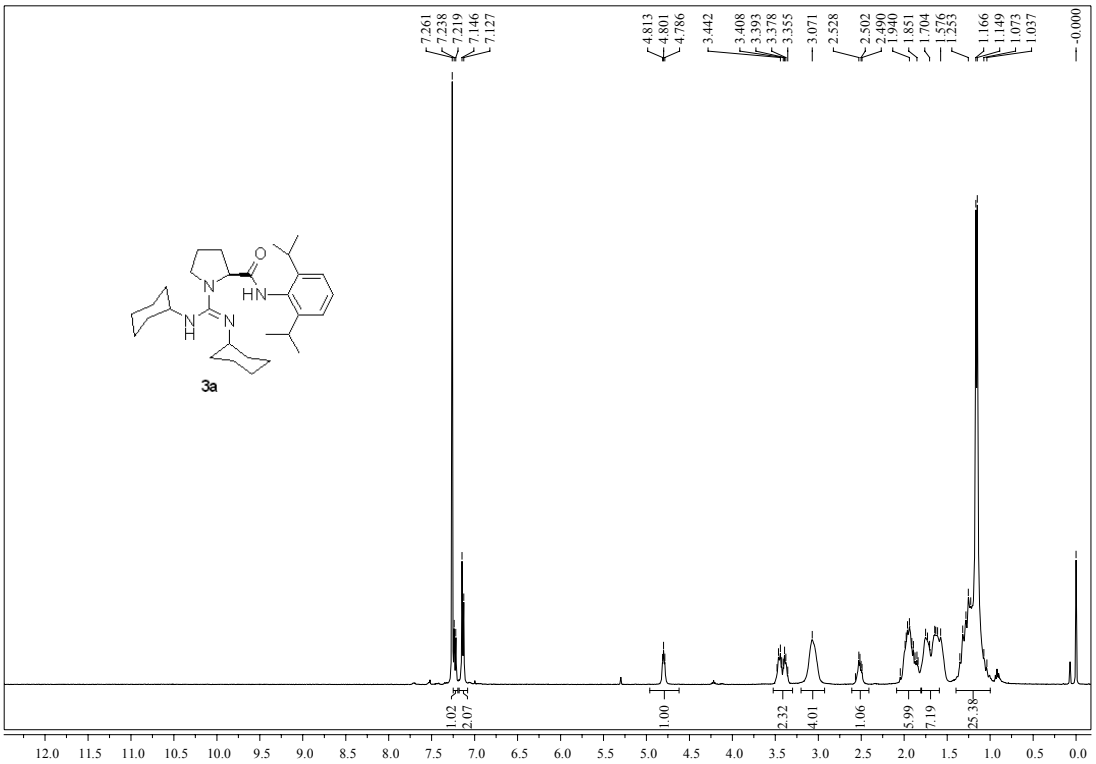
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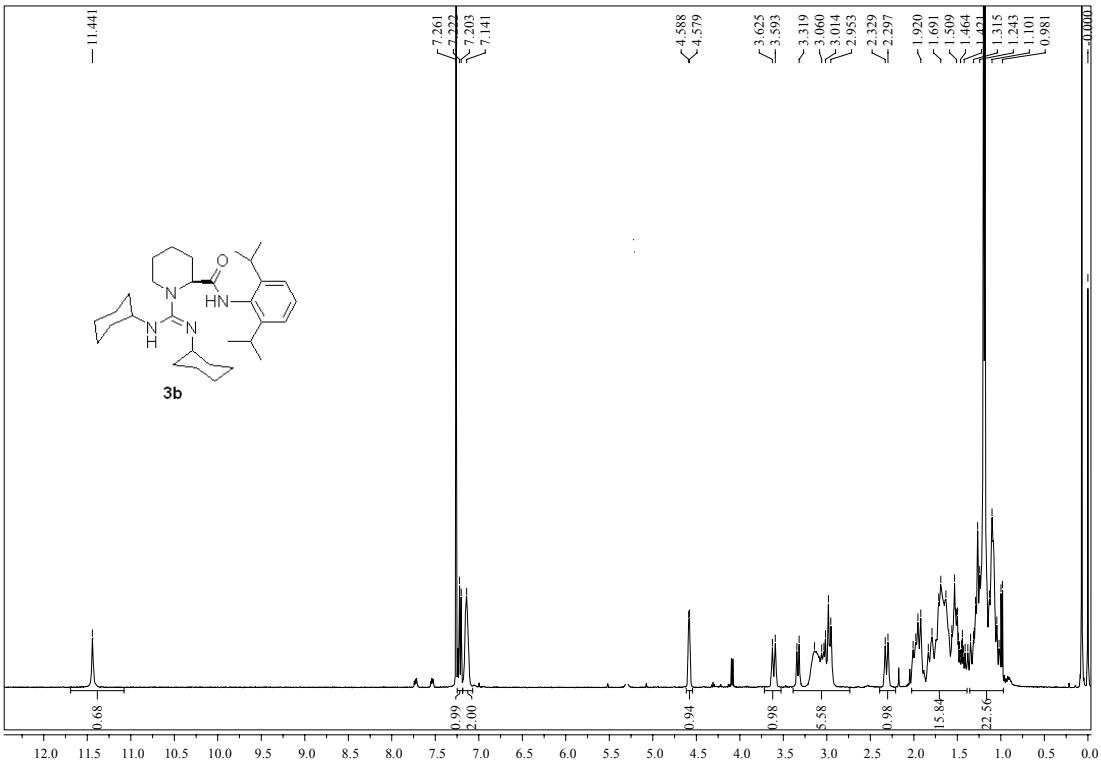
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1.243
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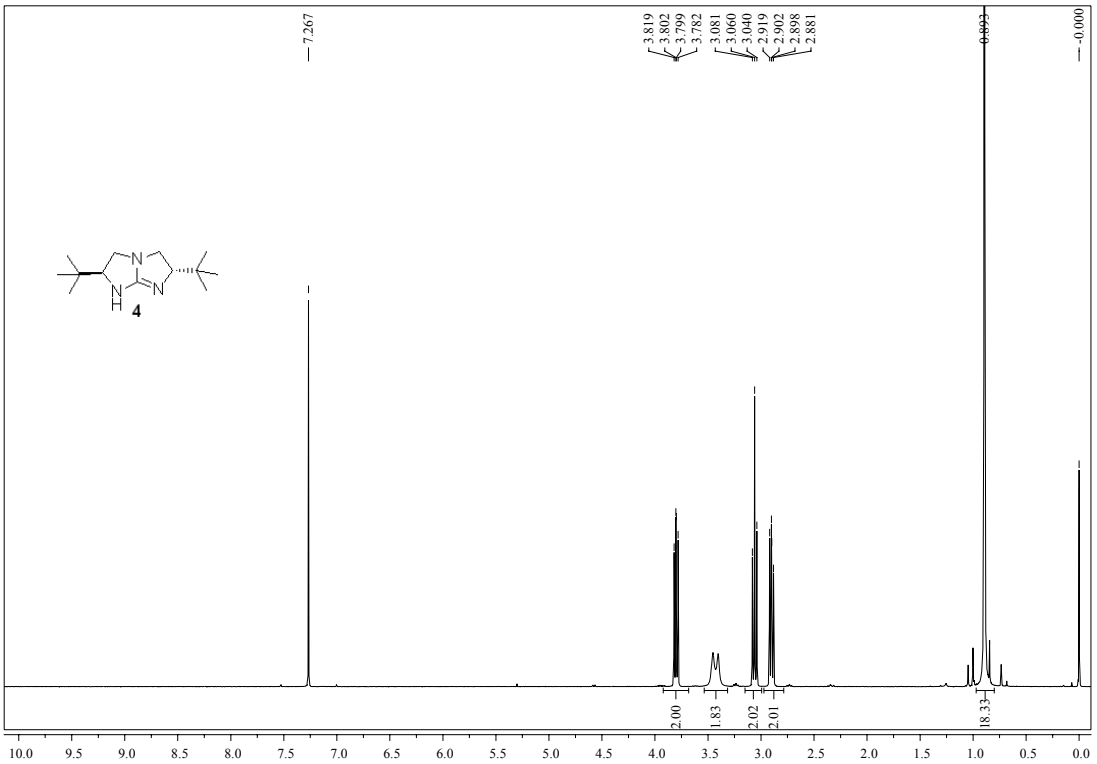
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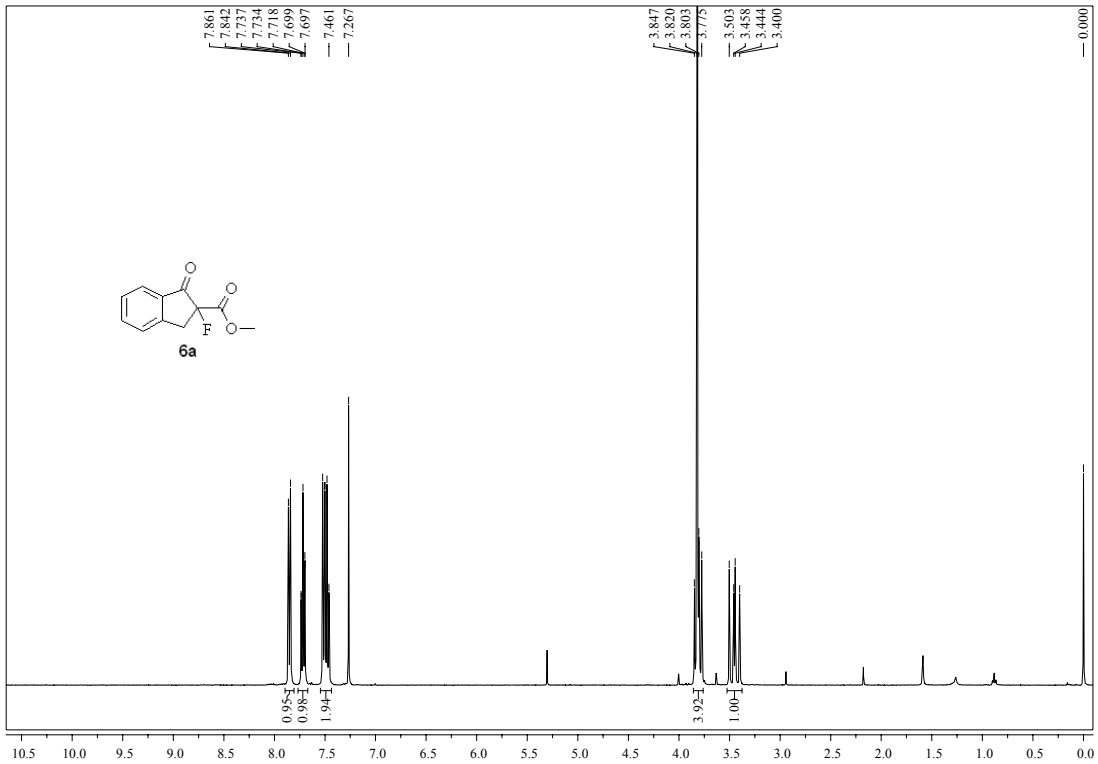
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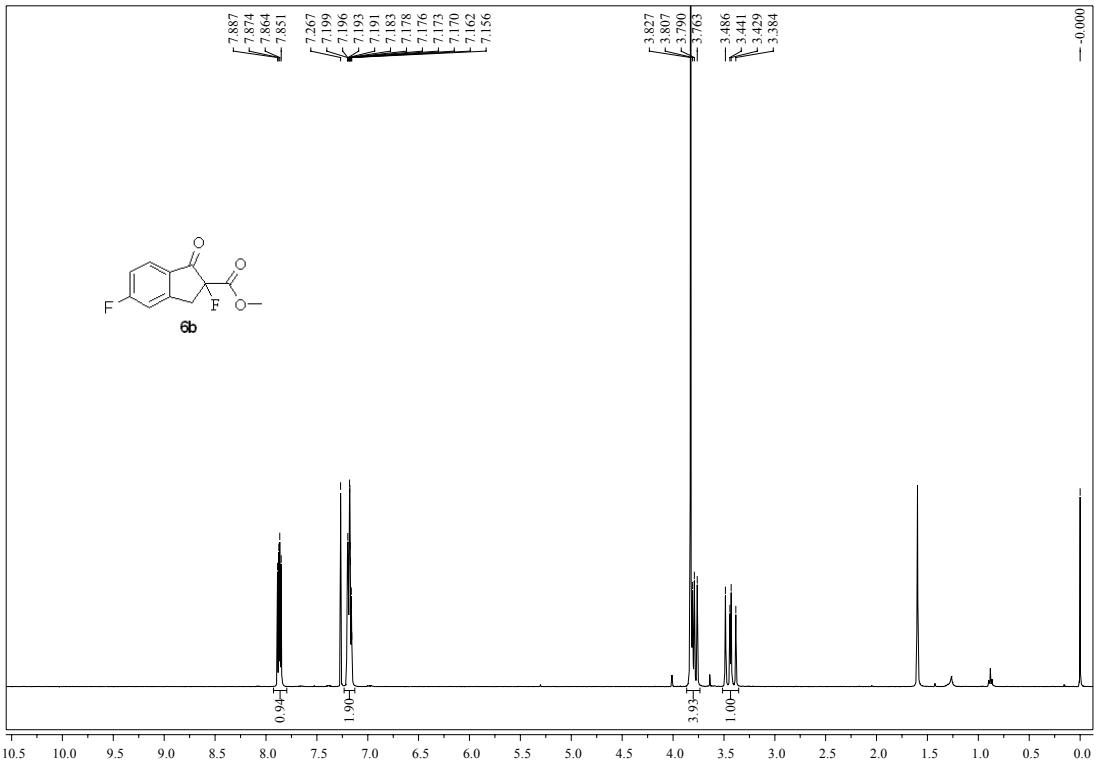
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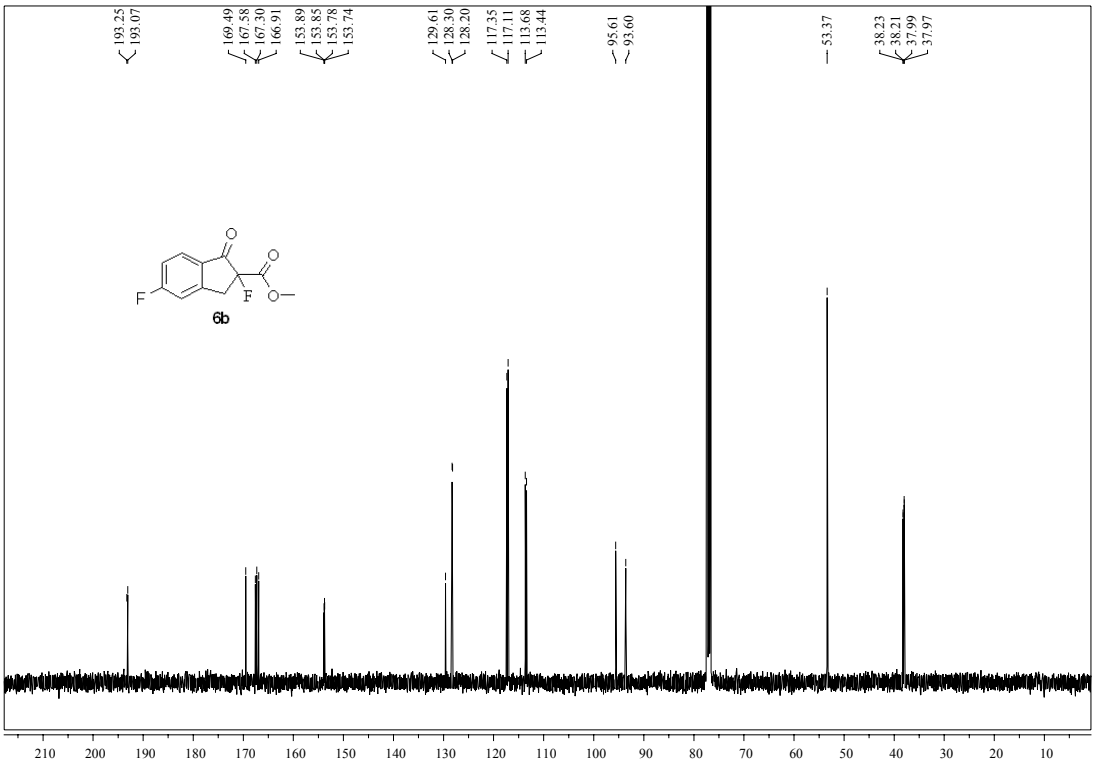
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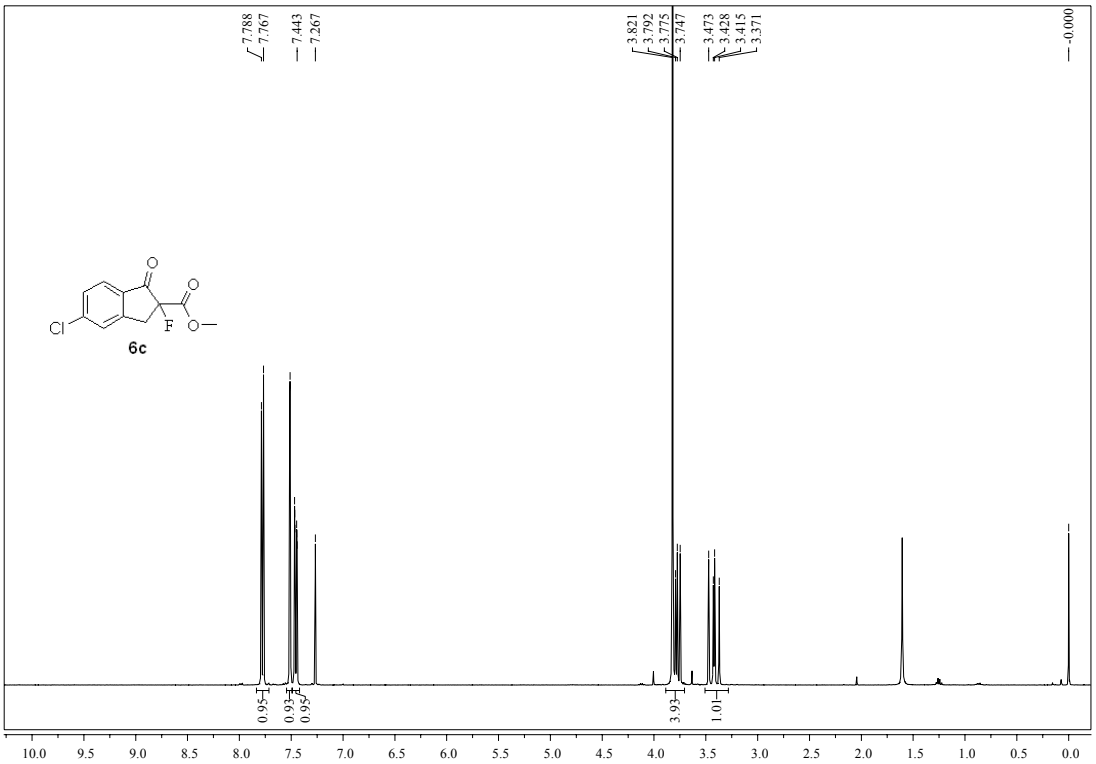
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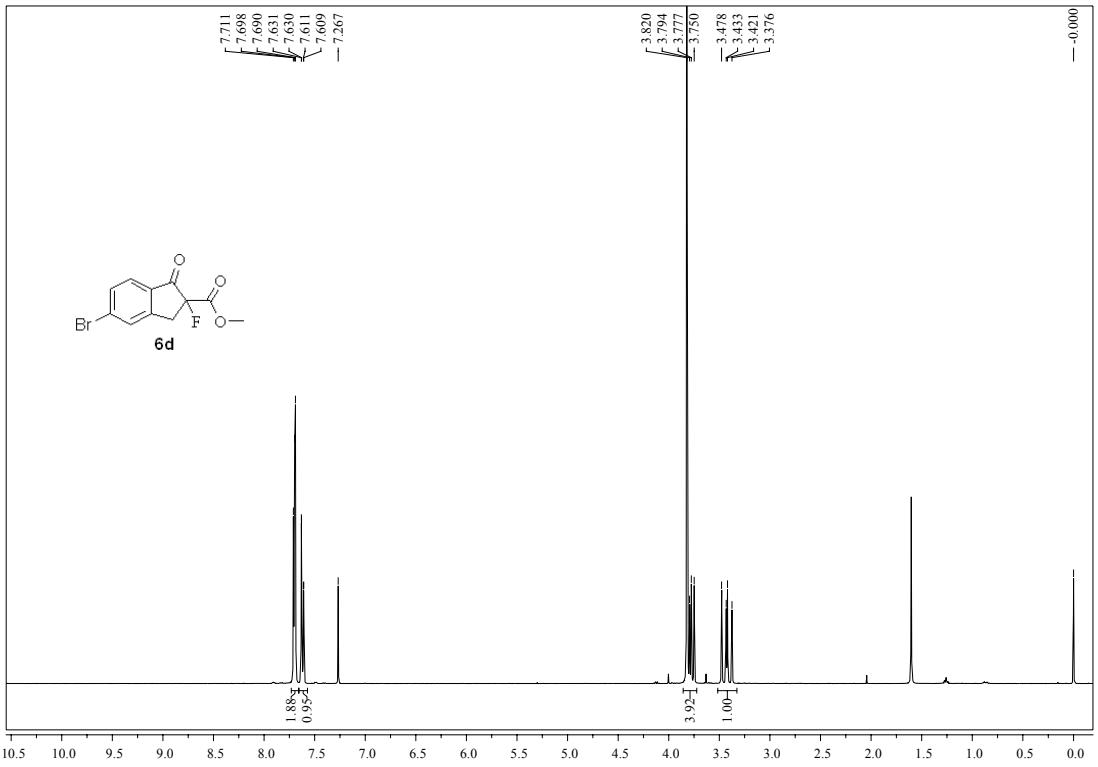
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3.376
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Br
O
O
F
O
6d
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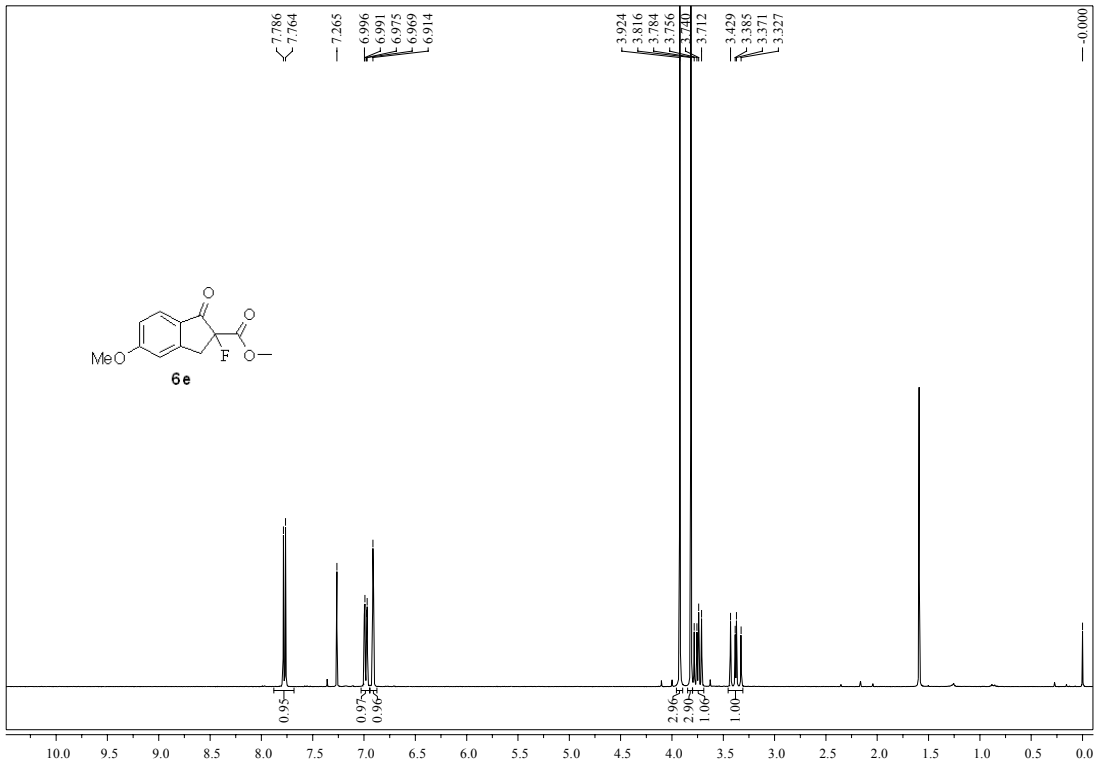
0.95
3.92
1.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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MeO
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O
F
O
6e
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0.97
0.96
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2.90
1.06
1.00
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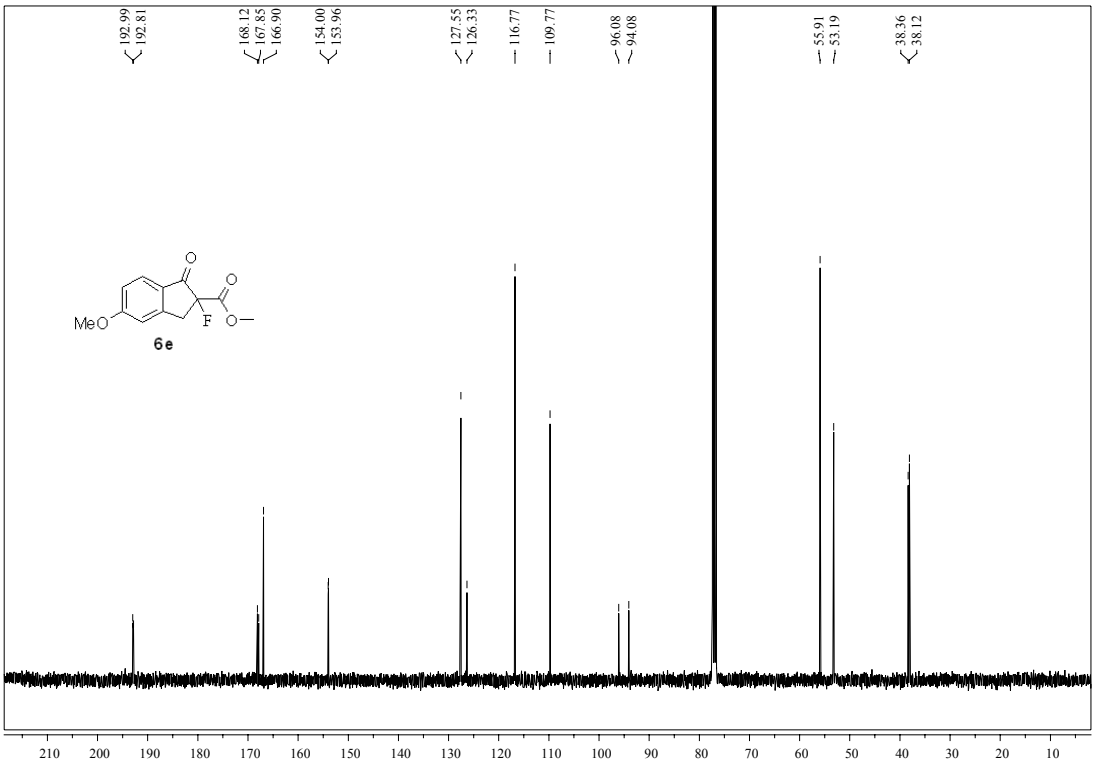
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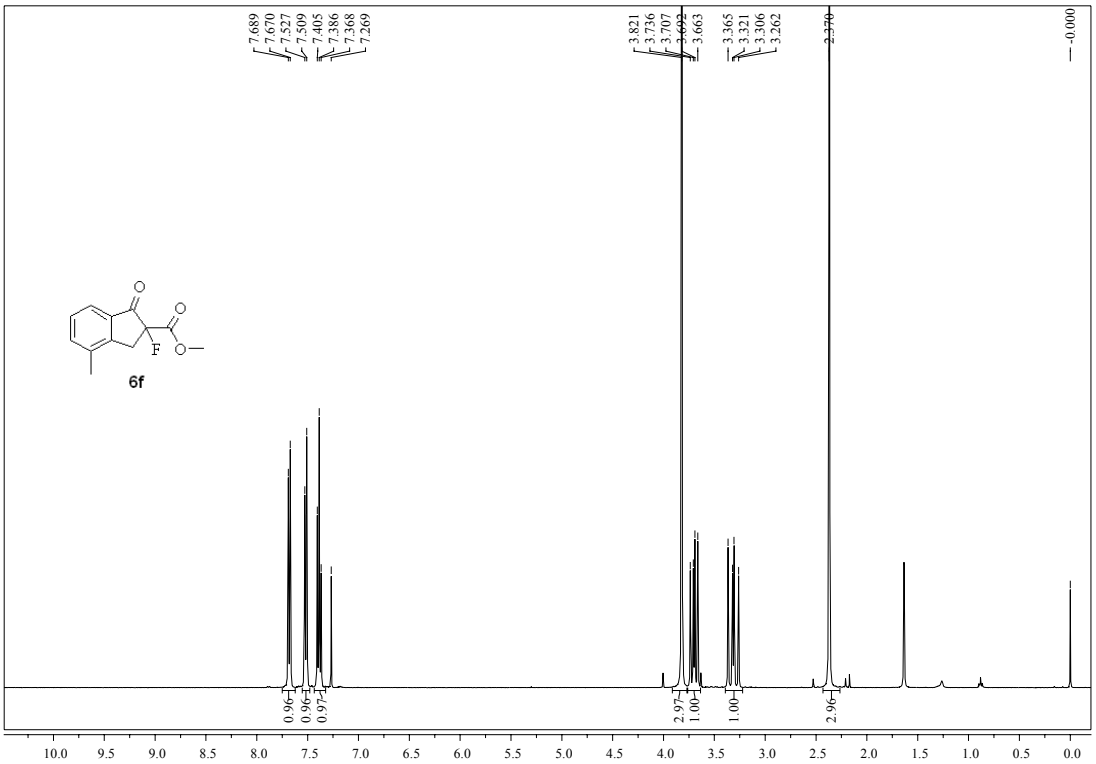
MeO
F
O
6e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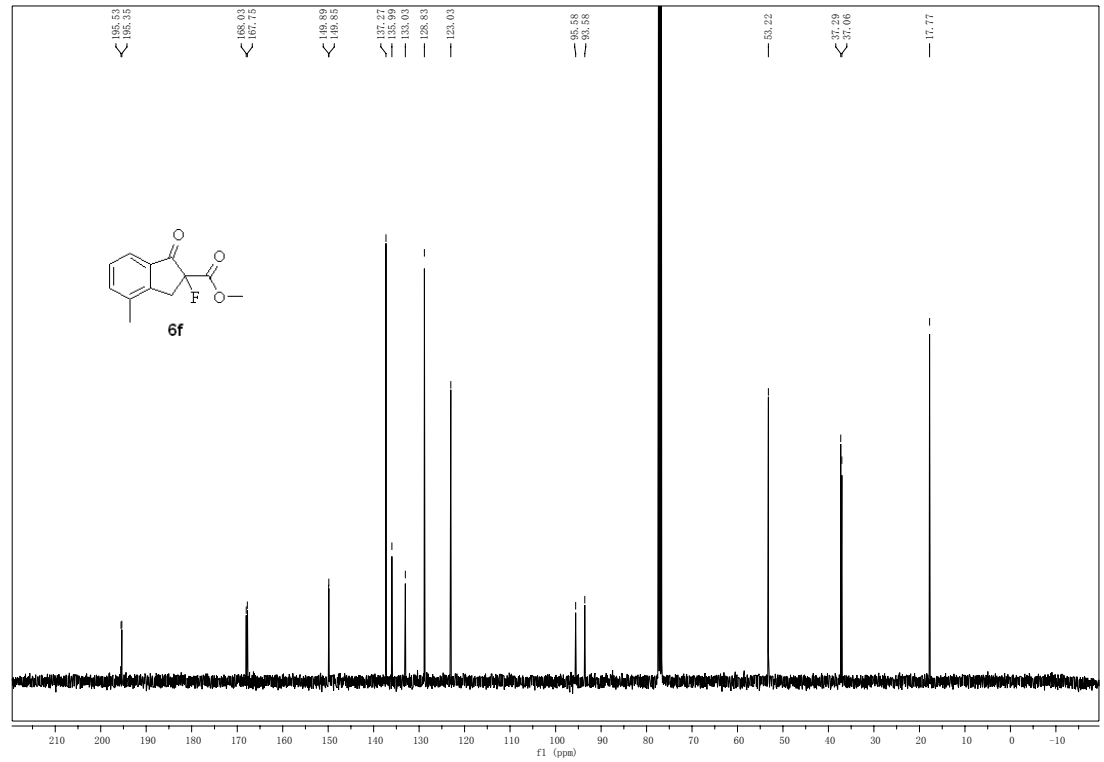
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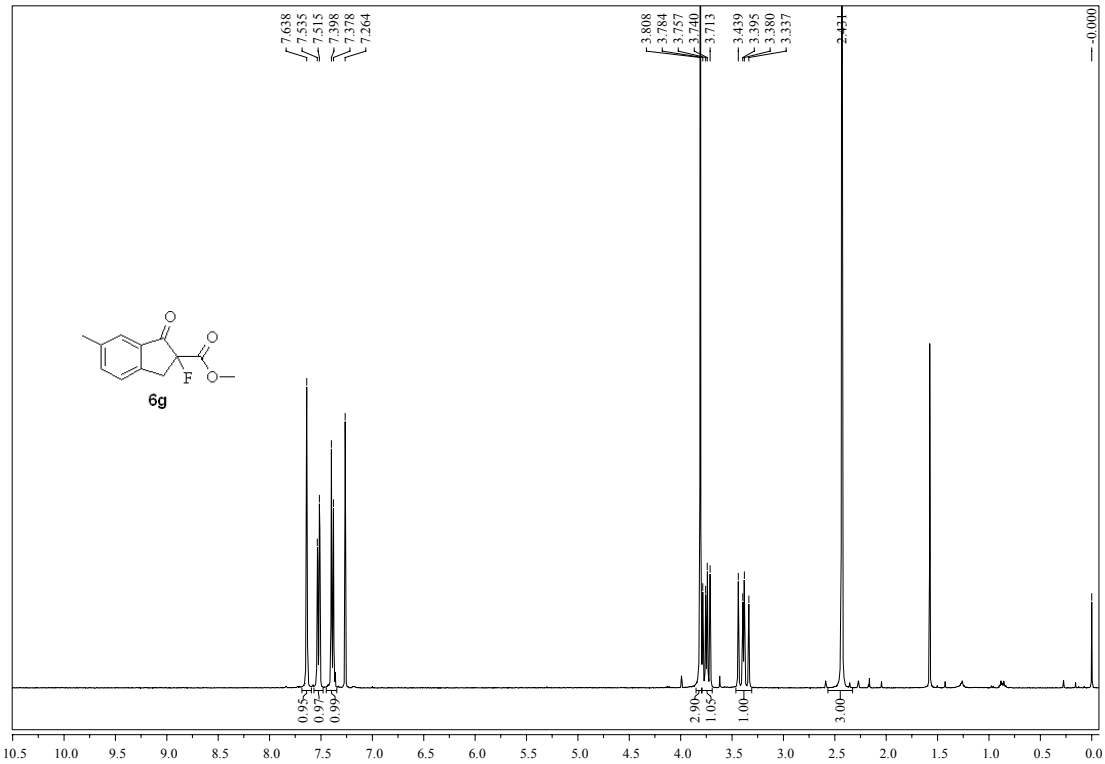
f1 (ppm)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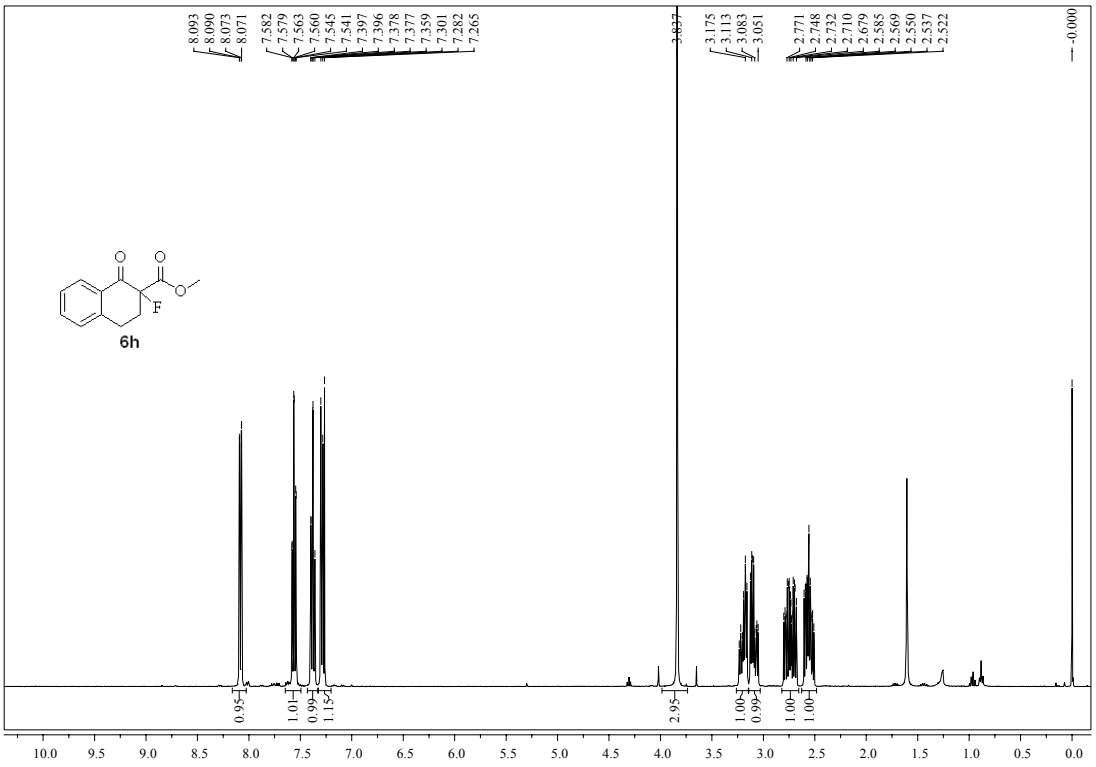
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O
O
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0.99
1.15
2.95
1.00
0.99
1.00
1.00
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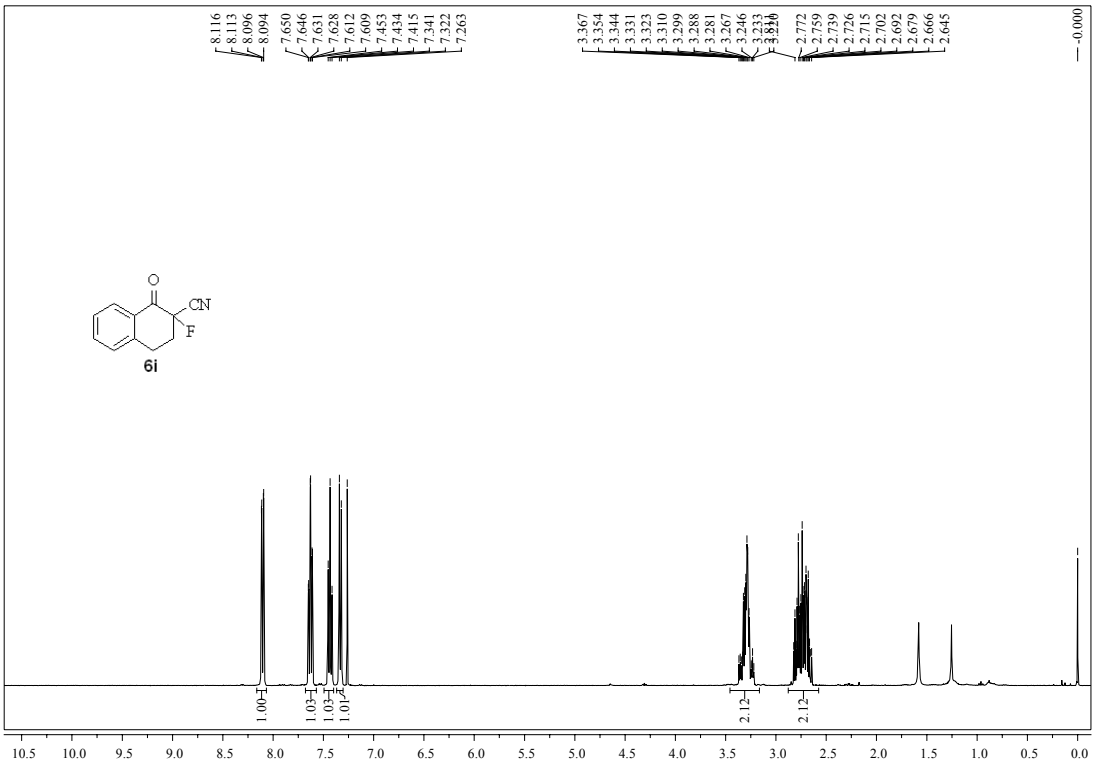
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1.03
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2.12
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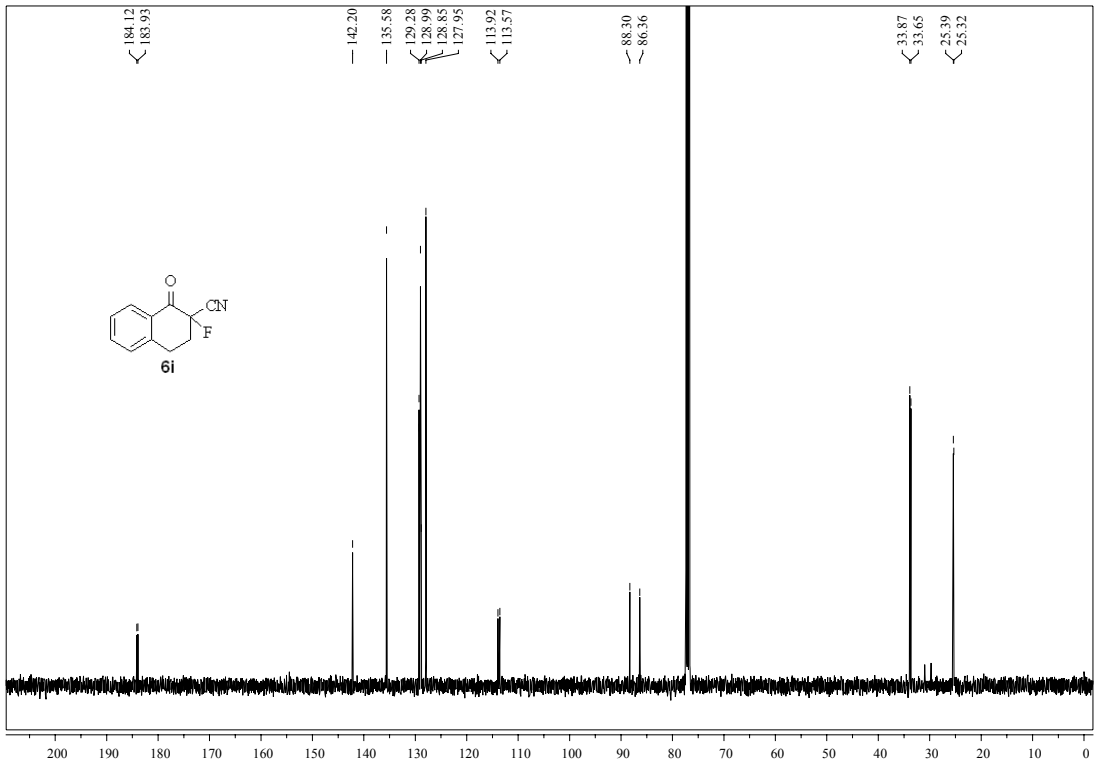
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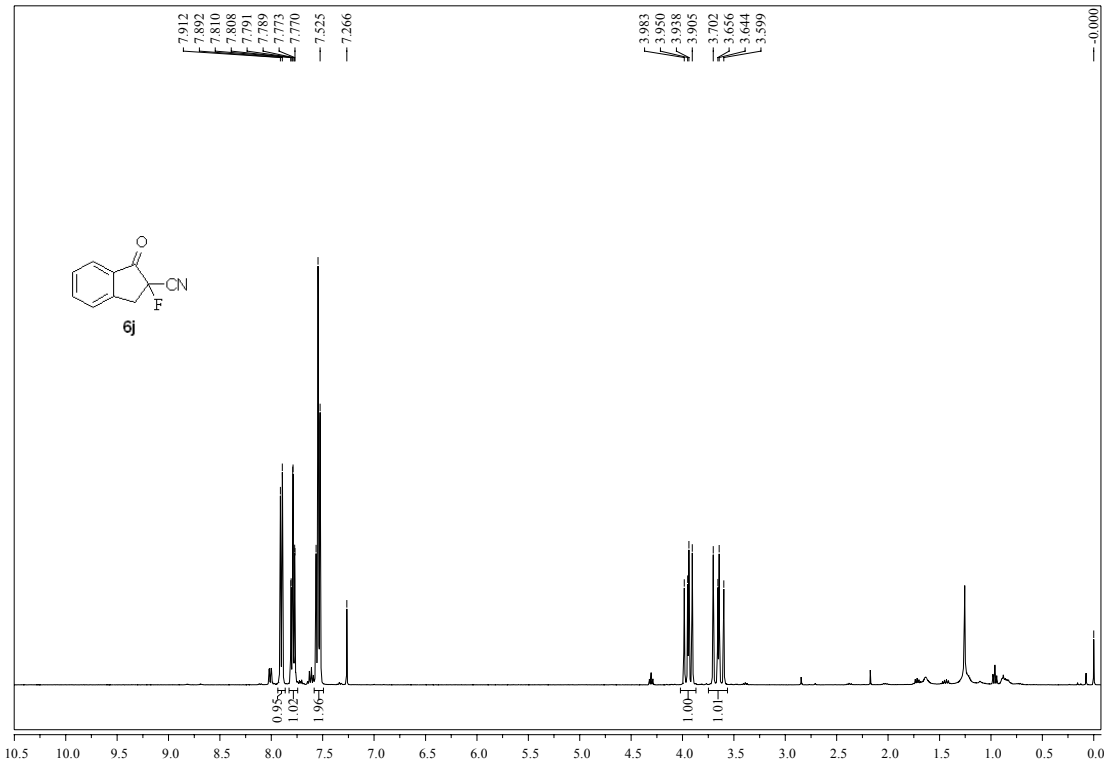
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CN
F
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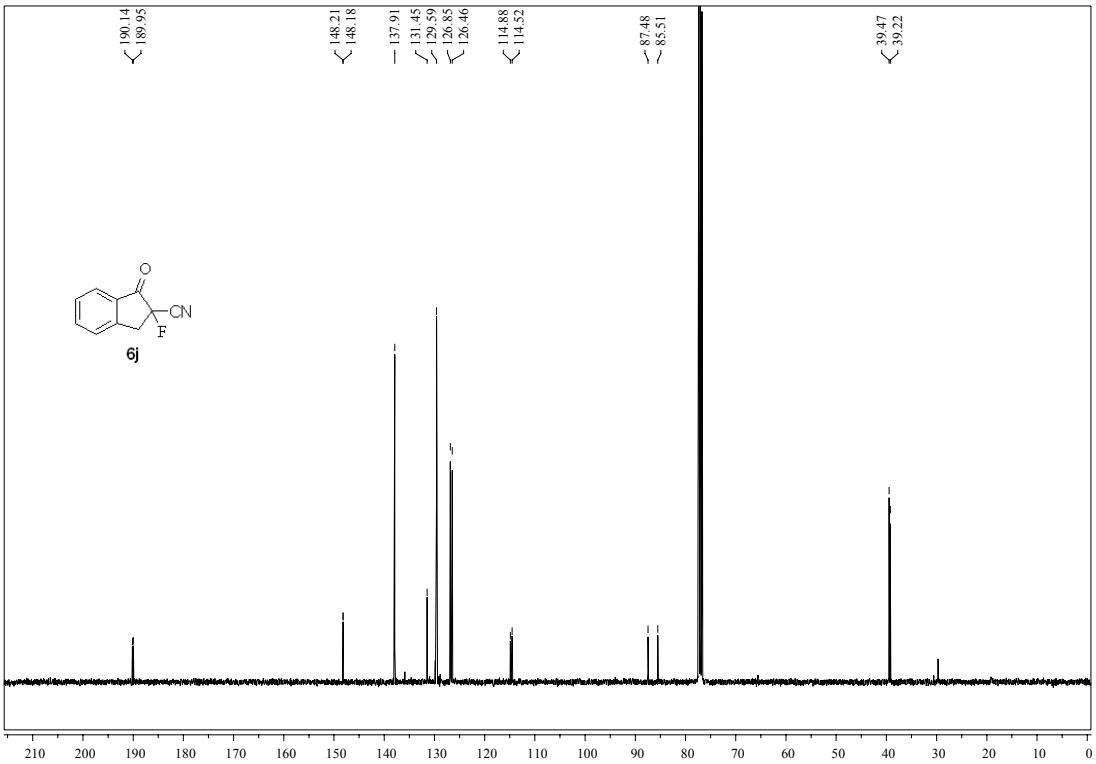
1.02
1.96
1.00
1.01
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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CN
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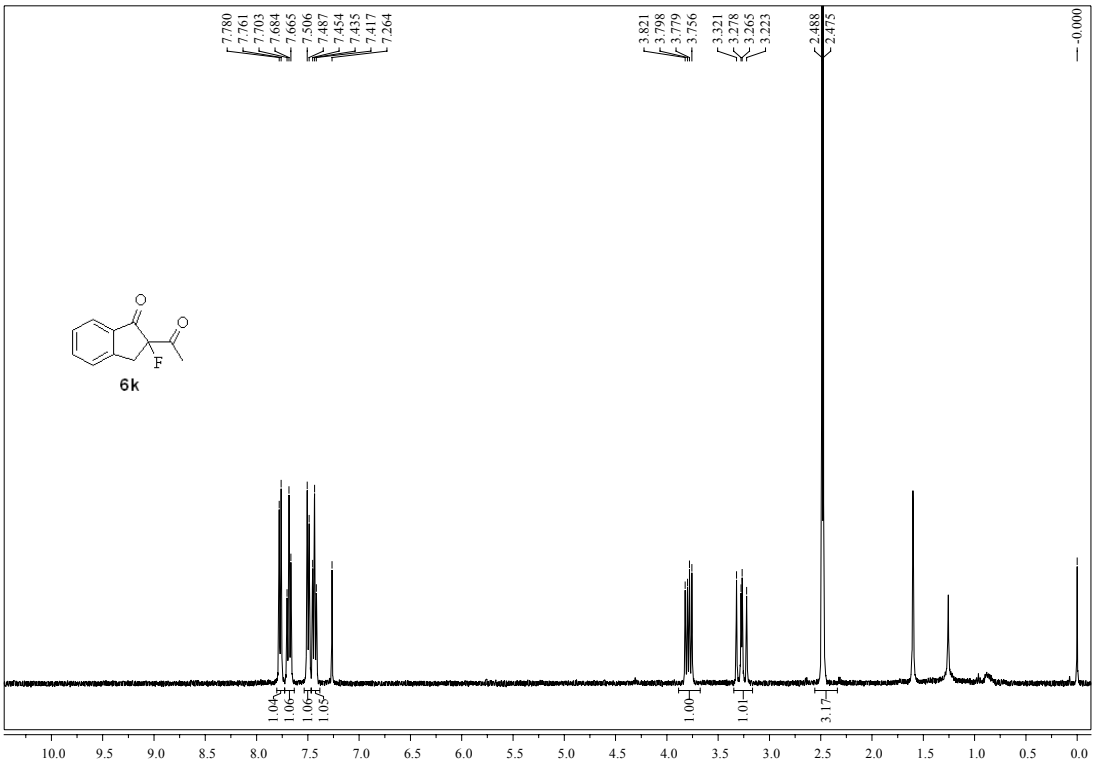
6j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7.454
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7.264
3.821
3.798
3.779
3.756
3.321
3.278
3.265
3.223
2.488
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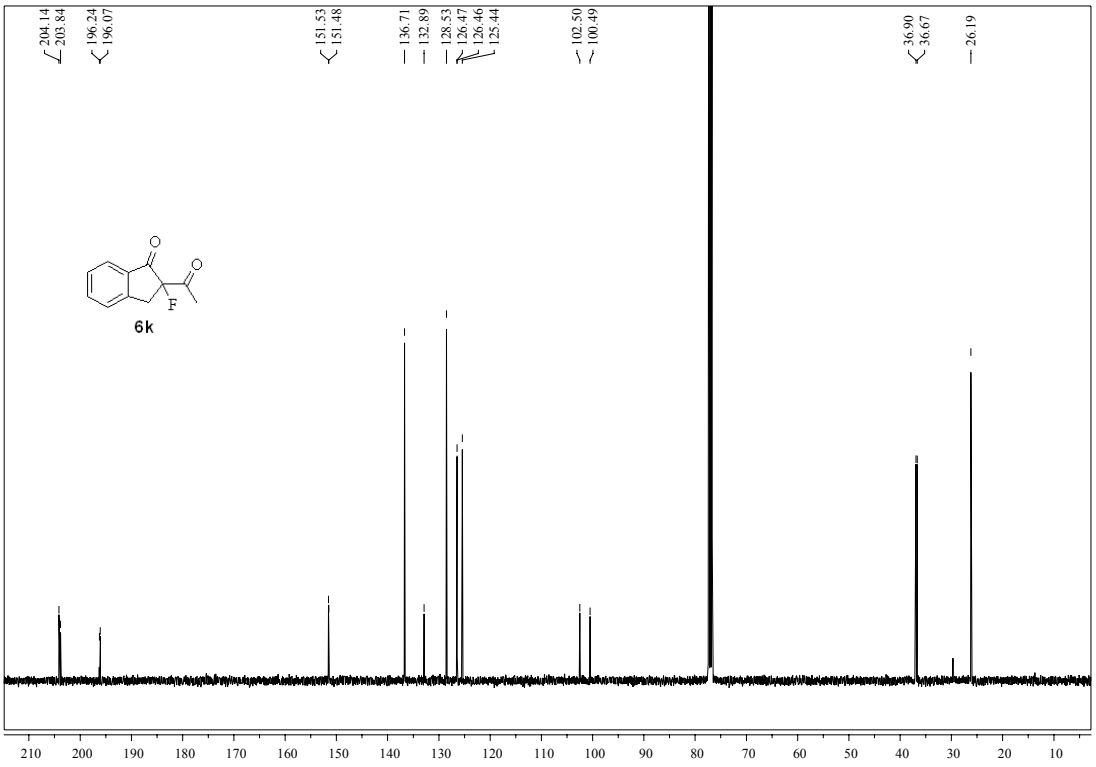
O
O
F
6k
1.04
1.06
1.06
1.05
1.00
1.01
3.17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196.24
196.07
151.53
151.48
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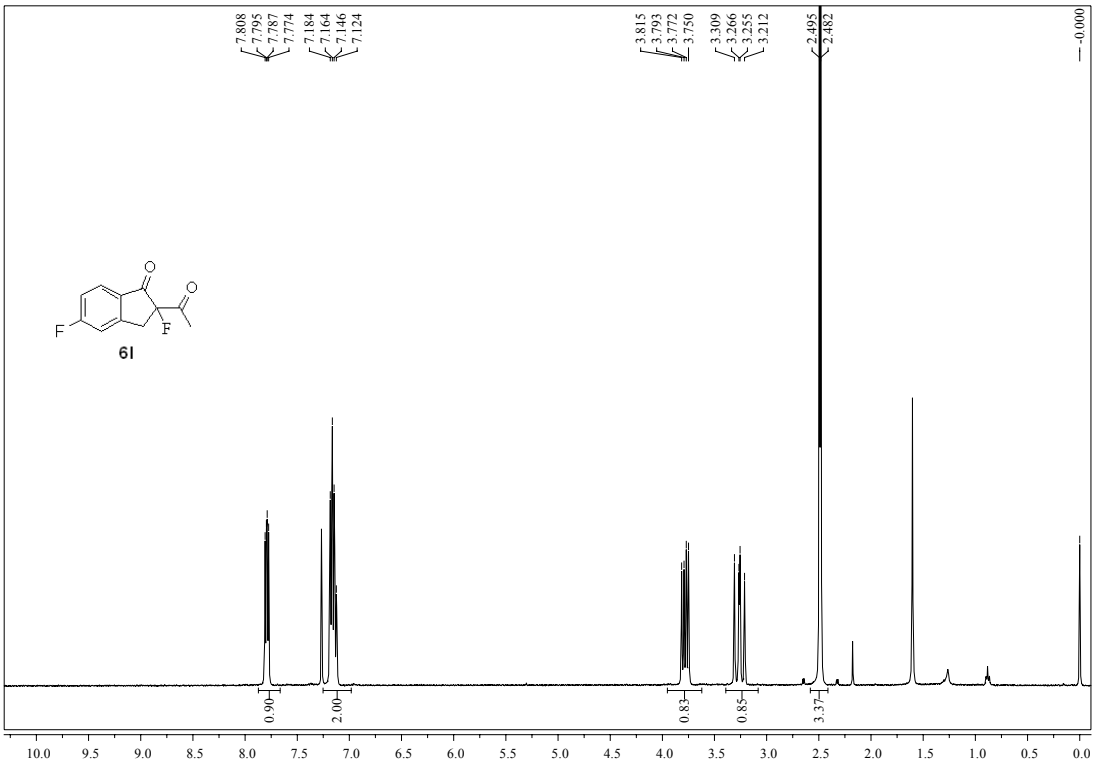
128.53
126.47
126.46
125.44
102.50
100.49
36.90
36.67
26.19
6k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3.793
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3.750
3.309
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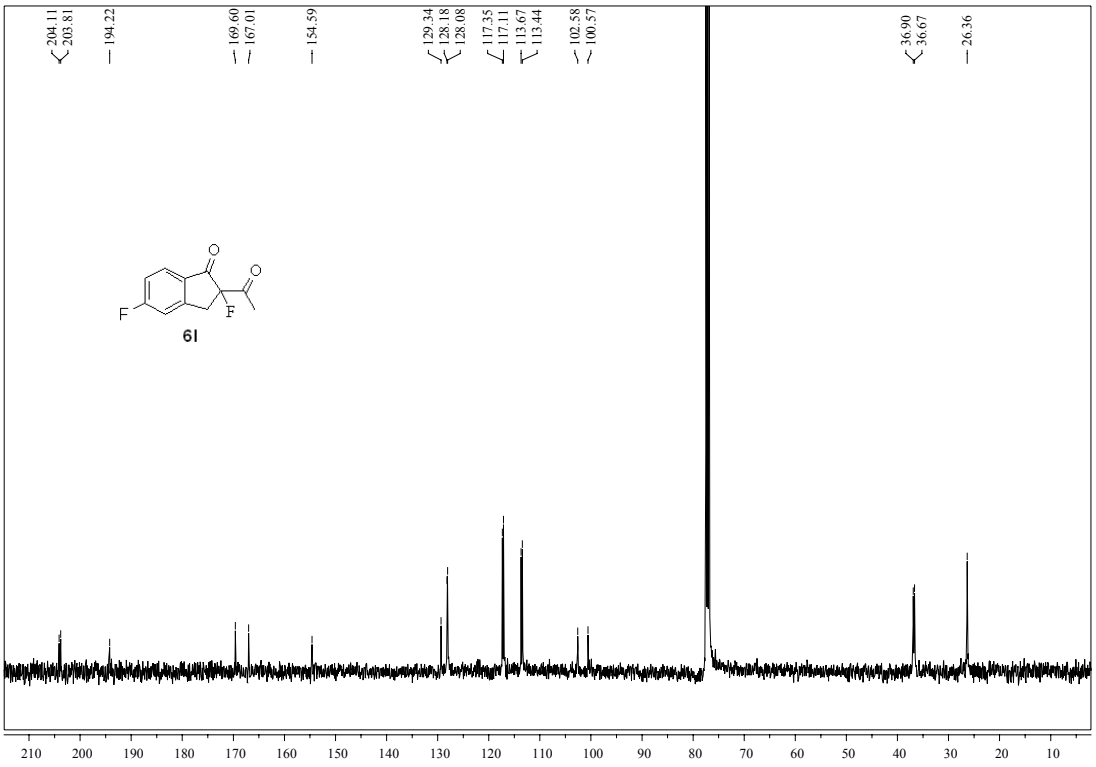
2.00
0.83
0.85
3.37
6l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154.59
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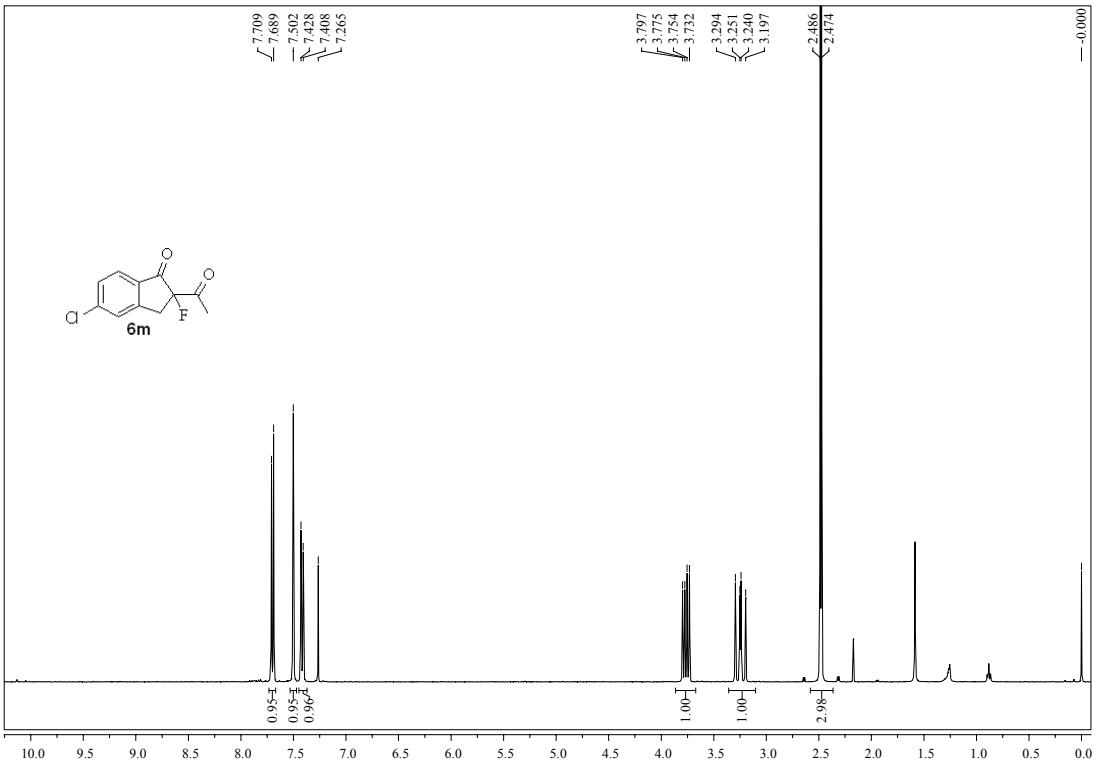
113.67
113.44
102.58
100.57
36.90
36.67
26.36
6l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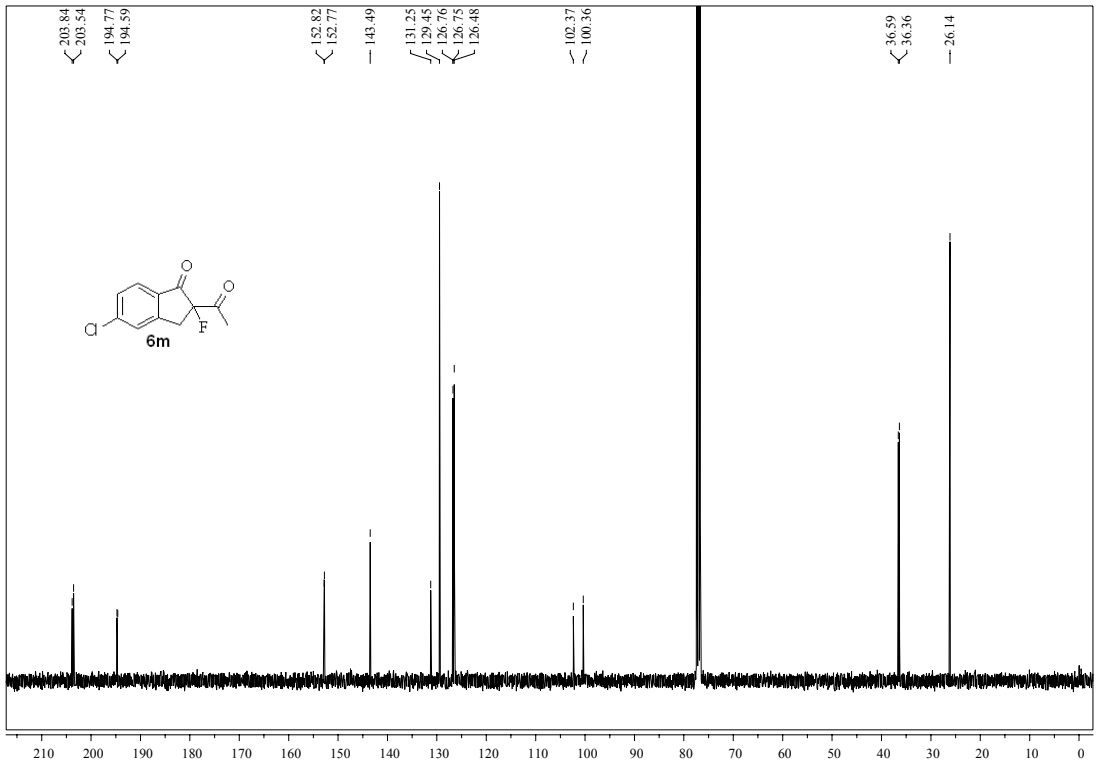
6m
0.95
0.95
0.96
1.00
1.00
2.98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131.25
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126.75
126.48
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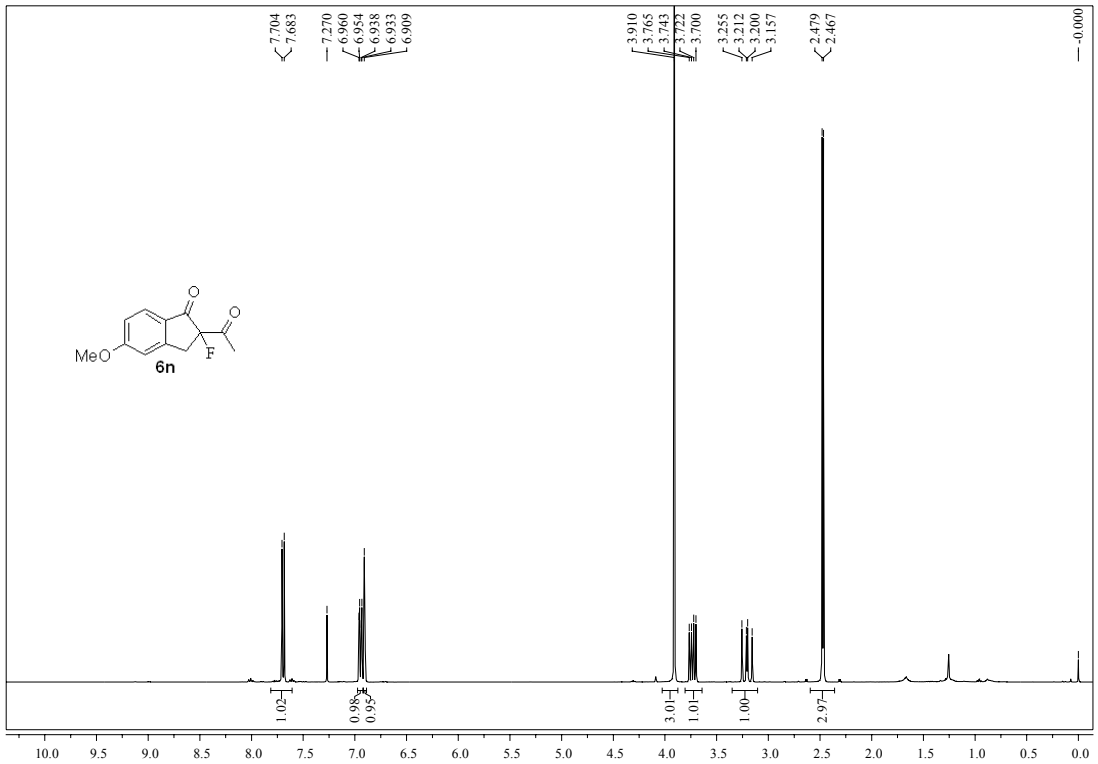
36.59
36.36
26.14
Cl
F
6m
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0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7.270
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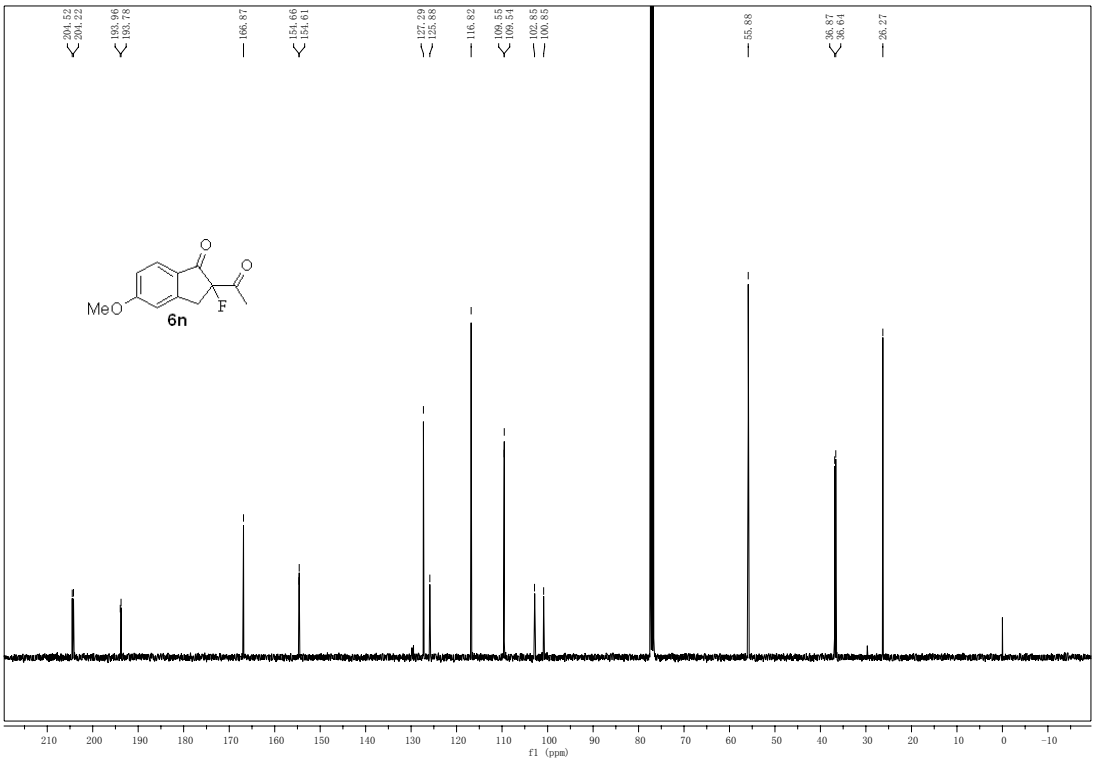
6.909
3.910
3.765
3.743
3.722
3.700
3.255
3.212
3.200
3.157
2.479
2.467
-0.000
MeO
F
6n
1.02
0.98
0.95
3.01
1.01
1.00
2.97
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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201.22
193.96
193.78
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154.61
127.29
125.88
116.82
109.55
109.54
102.85
100.85
55.88
36.87
36.64
26.27
MeO
F
6n
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)