Supplementary data

Fused-ring structure of decahydroisoquinolin as a novel scaffold for SARS 3CL protease inhibitors

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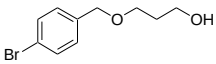
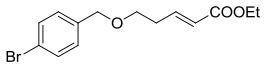
(1) Synthesis of (*E*)-ethyl 5-((4-bromobenzyl)oxy)pent-2-enoate, starting compound for the synthesis of 31



3-[(4-bromobenzyl)oxy]propan-1-ol S1

To a solution of NaH [60% in mineral oil (1.76 g, 44.0 mmol) in DMF (60 mL) 1,3-propanediol (3.06 g, 40.2 mmol) was added drop-wise at 0 ^{o}C. After being stirred for 30 min, *p*-bromobenzyl bromide (10.0 g, 40.0 mmol) was added drop-wise to the mixture at 0 ^{o}C. The resultant mixture was stirred for 16 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl and the whole was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt = 3:1) to give **S1** (6.12 g, 62%) as a colorless oil. ^{1}H NMR (400 MHz): δ = 7.48-7.46 (m, 2H), 7.21-7.19 (m, 2H), 4.47 (s, 2H), 3.79 (t, *J* = 5.8 Hz, 2H), 3.65 (t, *J* = 5.8 Hz, 2H), 2.17 (brs, 1H), 1.87 (quint., *J* = 5.8 Hz, 2H); ^{13}C NMR (100 MHz): δ = 137.1, 131.6, 129.2, 121.6, 72.5, 69.4, 61.8, 32.1; HRMS (EI) Calcd. For $C_{10}H_{13}BrO_2$ $[M]^+$: 244.0099. Found: 244.0094.



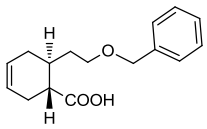
(*E*)-ethyl 5-[(4-bromobenzyl)oxy]pent-2-enoate S2

To a solution of PCC (16.1 g, 74.7 mmol) and celite (16.1 g) in CH_2Cl_2 (300 mL) was added **S1** (6.12 g, 24.9 mmol). The temperature was gradually raised up to room temperature. After being stirred for 5 h at the same temperature, the reaction mixture was filtered through silica layer and the filtrate was concentrated. This compound was immediately used for the next step without purification. Triethylphosphonoacetate (5.5 mL, 27.4 mmol) was added to a suspension of NaH [60 % in mineral oil (1.20 g, 29.9 mmol)] in THF (30 mL) at 0 ^{o}C under an argon gas atmosphere and the mixture was stirred for 0.5 h. The crude product in THF (30 mL) was added to the resultant mixture at –20 ^{o}C. After being stirred for 1.5 h at –20 ^{o}C, the reaction was quenched with saturated aqueous NH_4Cl, and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt = 20:1) to give **S2** (4.99 g, 64%, 2 steps) as a yellow pale oil. ^{1}H NMR (400 MHz): δ = 7.47 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.97 (td, *J* = 15.6, 6.8 Hz, 1H), 5.89 (d, *J* = 15.6 Hz, 1H), 4.47

(s, 2H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.58 (t, *J* = 6.6 Hz, 2H), 2.51 (ddd, *J* = 13.2, 6.4, 1.2 Hz, 2H), 1.29 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ = 166.4, 145.3, 137.1, 131.5, 129.2, 123.0, 121.5, 72.3, 68.4, 60.2, 32.6, 14.3; HRMS (EI) Calcd. For $C_{14}H_{17}BrO_3$ $[M]^+$: 312.0361. Found: 312.0365.

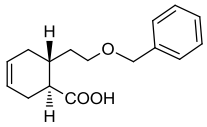
(2) Synthesis of 27 and 28

Starting from **7**, title compounds were synthesized according to the same route as the synthesis of **30** and **31**.



(1*R*,6*S*)-6-[2-(benzyloxy)ethyl]cyclohex-3-enecarboxylic acid 27

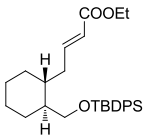
Colorless oil; yield 4.5% (50% max.): $[\alpha]^{25}_{D}$ +52 (*c* 0.83, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.35-7.32 (m, 4H), 7.29-7.23 (m, 1H), 5.67-5.61 (m, 2H) 4.49 (dd, *J* = 18.8, 12.0 Hz, 2H), 3.55-3.49 (m, 2H), 2.44-2.20 (m, 4H), 2.11-2.05 (m, 1H), 1.92-1.84 (m, 1H), 1.78-1.72 (m, 1H), 1.57-1.48 (m, 1H); ^{13}C NMR (100 MHz): δ = 181.6, 138.1, 128.3, 127.6, 127.5, 125.6, 124.4, 72.8, 67.7, 45.0, 33.5, 31.9, 29.4, 27.6; HRMS (EI) Calcd. For $C_{16}H_{20}O_3$ $[M]^+$: 260.1413. Found: 260.1417.



(1*S*,6*R*)-6-[2-(benzyloxy)ethyl]cyclohex-3-enecarboxylic acid 28

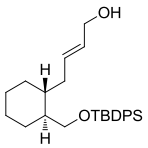
Colorless oil; yield 2.3% (50% max.): $[\alpha]^{28}_{D}$ −54.5 (*c* 0.155, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.34-7.31 (m, 4H), 7.30-7.27 (m, 1H), 5.68-5.62 (m, 2H) 4.50 (dd, *J* = 18.0, 12.0 Hz, 2H), 3.59-3.51 (m, 2H), 2.47-2.21 (m, 4H), 2.12-2.08 (m, 1H), 1.92-1.86 (m, 1H), 1.81-1.75 (m, 1H), 1.60-1.52 (m, 1H); ^{13}C NMR (100 MHz): δ = 181.4, 138.2, 128.4, 127.7, 127.6, 125.7, 124.5, 72.9, 67.8, 45.0, 33.7, 32.1, 29.5, 27.7; HRMS (EI) Calcd. For $C_{16}H_{20}O_3$ $[M]^+$: 260.1410. Found: 260.1417.

(3) Intermediates for the synthesis of 40



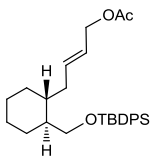
(*E*)-ethyl 4-[(1*R*,2*S*)-2-{[(*tert*-butyldiphenylsilyl)oxy]methyl}cyclohexyl]but-2-enoate S3

Colorless oil; yield 98% (2 steps): $[\alpha]^{28}_{D}$ +11 (*c* 0.60, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.67-7.64 (m, 4H), 7.44-7.36 (m, 6H), 6.91 (ddd, *J* = 15.4, 8.6, 6.6 Hz, 1H), 5.72 (d, *J* = 15.6Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.61-3.60 (m, 2H), 2.33 (m, 1H), 1.97 (td, *J* = 14.3, 8.6 Hz, 1H), 1.80-1.69 (m, 4H), 1.54-1.49 (m, 1H), 1.35-1.18 (m, 4H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.05 (s, 9H), 1.00-0.97 (m, 1H); ^{13}C NMR (100 MHz): δ = 166.6, 148.2, 135.62, 135.61, 133.82, 133.80, 129.59, 129.55, 127.62, 127.59, 122.4, 66.2, 60.1, 43.9, 37.8, 36.4, 31.9, 30.0, 26.9, 26.1, 26.0, 19.3, 14.3; HRMS (FAB) Calcd. For $C_{29}H_{40}NaO_3Si$ $[M+Na]^+$: 487.2644. Found: 487.2649.



(*E*)-4-[(1*R*,2*S*)-2-{[(*tert*-butyldiphenylsilyl)oxy]methyl}cyclohexyl]but-2-en-1-ol S4

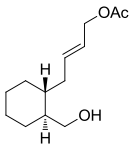
Colorless oil; yield 98%: $[\alpha]^{28}_{D}$ +8.3 (*c* 0.23, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.68-7.65 (m, 4H), 7.44-7.36 (m, 6H), 5.64-5.48 (m, 2H), 4.04 (d, *J* = 5.2 Hz, 2H), 3.66 (dd, *J* = 10.2, 3.2 Hz, 1H), 3.59 (dd, *J* = 10.2, 5.4 Hz, 1H), 2.22-2.18 (m, 1H), 1.87-1.79 (m, 2H), 1.72-1.69 (m, 3H), 1.37 (m, 1H), 1.30-1.18 (m, 4H), 1.05 (s, 9H), 1.00-0.95 (m, 1H); ^{13}C NMR (100 MHz): δ = 135.64, 135.62, 134.0, 131.6, 130.2, 129.52, 129.50, 127.58, 127.55, 66.3, 63.8, 43.8, 38.1, 36.2, 31.7, 30.0, 26.9, 26.2, 26.1, 19.4; HRMS (FAB) Calcd. For $C_{27}H_{38}NaO_2Si$ $[M+Na]^+$: 445.2539. Found: 445.2534.



(*E*)-4-[(1*R*,2*S*)-2-{[(*tert*-butyldiphenylsilyl)oxy]methyl}cyclohexyl]but-2-en-1-yl acetate 33

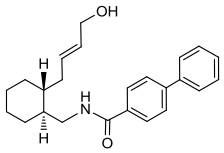
Colorless oil; yield 88%: $[\alpha]^{27}_{D}$ +11 (*c* 0.65, $CHCl_3$); ^{1}H NMR (400 MHz): δ =

7.67-7.64 (m, 4H), 7.44-7.36 (m, 6H), 5.71-5.64 (m, 1H), 5.48-5.42 (m, 1H), 4.47 (d, *J* = 6.4 Hz, 2H), 3.65 (dd, *J* = 10.0, 2.8 Hz, 1H), 3.57 (dd, *J* = 10.0, 5.2 Hz, 1H), 2.23-2.19 (m, 1H), 2.05 (s, 3H), 1.88-1.79 (m, 2H), 1.71-1.68 (m, 3H), 1.40-1.38 (m, 1H), 1.30-1.18 (m, 4H), 1.05 (s, 9H), 1.00-0.94 (m, 1H); ^{13}C NMR (100 MHz): δ = 170.9, 135.63, 135.61, 134.8, 133.944, 133.935, 129.53, 129.51, 127.58, 127.56, 125.0, 66.3, 65.3, 43.8, 38.0, 36.3, 31.7, 30.0, 26.9, 26.2, 26.1, 21.0, 19.3; HRMS (FAB) Calcd. For $C_{29}H_{40}NaO_3Si$ $[M+Na]^+$: 487.2644. Found: 487.2641.



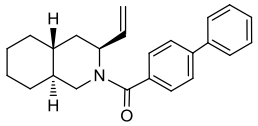
(*E*)-4-[(1*R*,2*S*)-2-(hydroxymethyl)cyclohexyl]but-2-en-1-yl acetate S5

Colorless oil; yield 92%: $[\alpha]^{28}_D$ +20.2 (*c* 1.03, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 5.76 (ddd, *J* = 15.1, 8.1, 6.9 Hz, 1H), 5.60-5.53 (m, 1H), 4.51 (d, *J* = 6.4 Hz, 2H), 3.69 (dd, *J* = 10.6, 2.4 Hz, 1H), 3.57 (dd, *J* = 10.6, 5.8 Hz, 1H), 2.33-2.27 (m, 1H), 2.06 (s, 3H), 2.00-1.93 (m, 1H), 1.85-1.67 (m, 4H), 1.34-1.14 (m, 5H), 1.05-0.96 (m, 1H); ^{13}C NMR (100 MHz): δ = 170.9, 134.5, 125.3, 65.5, 65.2, 43.8, 38.0, 36.3, 31.7, 29.5, 26.0, 25.8, 21.0; HRMS (FAB) Calcd. For $C_{13}H_{22}NaO_3$ $[M+Na]^+$: 249.1467. Found: 249.1469.



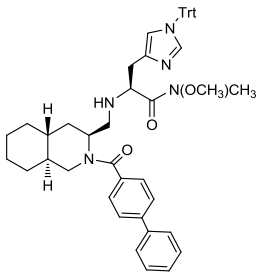
***N*-({(1*S*,2*R*)-2-[(*E*)-4-hydroxybut-2-en-1-yl]cyclohexyl}methyl)-[1,1'-biphenyl]-4-carboxamide 34**

Colorless oil; yield 53% (3 steps): $[\alpha]^{28}_D$ +13 (*c* 0.41, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.84-7.82 (d, *J* = 8.4 Hz, 2H), 7.66-7.64 (d, *J* = 8.0 Hz, 2H), 7.62-7.60 (m, 2H), 7.48-7.45 (m, 2H), 7.41-7.37 (m, 1H), 6.24 (m, 1H), 5.79-5.64 (m, 2H), 4.11 (d, *J* = 4.4 Hz, 2H), 3.79 (ddd, *J* = 13.5, 5.9, 3.7 Hz, 1H), 3.21 (ddd, *J* = 13.6, 8.0, 5.8 Hz, 1H), 2.31-2.27 (m, 1H), 2.19-2.12 (m, 1H), 1.88-1.84 (m, 1H), 1.75-1.72 (m, 3H), 1.52-1.44 (m, 1H), 1.32-1.05 (m, 5H); ^{13}C NMR (100 MHz): δ = 167.2, 144.2, 140.0, 133.3, 131.2, 130.5, 128.9, 128.0, 127.3, 127.24, 127.19, 63.8, 43.3, 41.1, 39.6, 36.5, 31.9, 30.6, 26.1, 25.7; HRMS (EI) Calced. For $C_{24}H_{29}NO_2$ $[M]^+$:363.2198. Found: 363.2191.



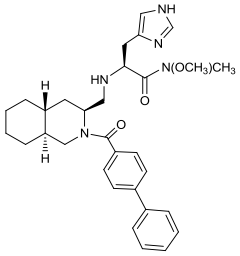
(1,1'-biphenyl)-4-yl[(3*S*,4a*R*,8a*S*)-3-vinyloctahydroisoquinolin-2(1*H*)-yl]methanone 36

Colorless oil; yield 64%: $[\alpha]^{28}_{D}$ -19 (*c* 0.87, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.64-7.58 (m, 4H), 7.49-7.43 (m, 4H), 7.38-7.35 (m, 1H), 5.87 (ddd, *J* = 17.4, 10.6, 3.8 Hz, 0.4H), 5.78 (ddd, *J* = 17.4, 10.7 3.6 Hz, 0.6H), 5.55 (brs, 0.4H), 5.31-5.28 (m, 1H), 5.23-5.16 (m, 1H), 4.53 (brs, 0.6H), 4.49 (dd, *J* = 13.2, 3.6 Hz, 0.6H), 3.49 (dd, *J* = 13.4, 3.8 Hz, 0.4H), 2.89-2.82 (m, 0.4H), 2.64-2.57 (m, 0.6H), 1.84-1.52 (m, 5H), 1.47-1.12 (m, 5.4H), 1.00-0.98 (m, 1H), 0.87-0.84 (m, 0.6H); ^{13}C NMR (100 MHz): δ = 171.1, 170.4, 142.3, 142.2, 140.3, 137.1, 136.7, 135.4, 128.8, 127.68, 127.66, 127.4, 127.1, 126.8, 116.6, 116.1, 57.2, 50.8, 49.7, 43.5, 42.8, 41.9, 37.5, 36.8, 35.9, 32.9, 29.9, 29.7, 26.2, 26.1, 25.8, 25.7; HRMS (EI) Calcd. For $C_{24}H_{27}NO$ $[M]^+$: 345.2093. Found: 345.2091.



(*S*)-2-({[(3*S*,4a*R*,8a*S*)-2-[(1,1'-biphenyl)-4-carbonyl]decahydroisoquinolin-3-yl]methyl}amino)-*N*-methoxy-*N*-methyl-3-(1-trityl-1*H*-imidazol-4-yl)propanamide 38

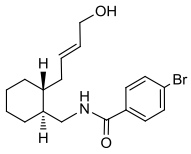
Colorless oil; yield 50% (3 steps): $[\alpha]^{29}_{D}$ -21 (*c* 0.49, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.59-7.53 (m, 4H), 7.48-7.40 (m, 4H), 7.36-7.28 (m, 11H), 7.14-7.09 (m, 6H), 6.62 (brs, 0.6H), 6.56 (brs, 0.4H), 4.91 (m, 0.6H), 4.42 (dd, *J* = 13.6, 3.2 Hz, 0.4H), 4.13 (m, 0.4H), 3.93 (brs, 1H), 3.67 (s, 1.8H), 3.49 (s, 1.2H), 3.40 (dd, *J* = 13.0, 3.4 Hz, 0.6H), 3.14 (s, 1.8H), 3.08 (s, 1.2H), 2.87-2.83 (m, 2.4H), 2.72-2.66 (m, 2H), 2.49-2.43 (m, 0.6H), 1.80-1.70 (m, 3H), 1.61-1.55 (m, 1H), 1.39-1.26 (m, 6H), 1.05-0.83 (m, 2H); ^{13}C NMR (100 MHz): δ = 175.5, 175.2, 171.3, 170.5, 142.5, 142.4, 141.88, 141.86, 140.44, 140.37, 138.2, 138.1, 137.7, 137.2, 135.9, 135.8, 129.73, 129.67, 129.3, 128.8, 128.7, 127.91, 127.87, 127.55, 127.47, 127.4, 127.2, 127.1, 127.05, 127.00, 119.2, 115.6, 77.2, 75.02, 75.01, 61.6, 61.5, 57.8, 57.5, 55.5, 49.5, 48.3, 47.1, 46.6, 43.1, 42.6, 42.1, 36.4, 36.2, 34.5, 33.0, 32.9, 32.6, 32.3, 32.0, 29.9, 29.7, 26.2, 26.1, 25.8, 25.7; HRMS (EI) Calcd. For $C_{50}H_{53}N_5O_3$ $[M]^+$: 771.4148. Found: 771.4154.



(*S*)-2-({[(3*S*,4a*R*,8a*S*)-2-[(1,1'-biphenyl)-4-carbonyl]decahydroisoquinolin-3-yl]methyl}amino)-3-(1H-imidazol-4-yl)-*N*-methoxy-*N*-methylpropanamide S6

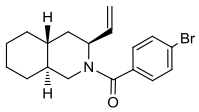
TFA/CH_2Cl_2/TIS/H_2O (10:10:1.0:1.0, 11 mL) was added **38** (120 mg, 0.155 mmol). The mixture was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 10:1) to give a title compound (60.0 mg, 73%) as a colorless oil. $[\alpha]^{28}_D$ −62 (*c* 0.085, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.68-7.36 (m, 10H), 6.84 (m, 0.6H), 6.82 (m, 0.4H), 5.03 (brs, 0.4H), 4.30-4.27 (m, 0.6H), 4.15-4.11 (m, 0.6H), 3.87-3.85 (m, 0.4H), 3.73 (s, 1.2H), 3.66 (s, 1.8H), 3.54-3.51 (m, 1H), 3.25 (s, 1.2H), 3.19 (s, 1.8H), 2.99-2.86 (m, 1H), 2.75-2.62 (m, 2H), 2.56-2.44 (m, 2H), 1.77-1.56 (m, 5H), 1.48-1.39 (m, 2H), 1.31-1.19 (m, 3H), 1.14-1.12 (m, 0.4H), 1.03-1.02 (m, 1H), 0.88-0.84 (m, 0.6H); ^{13}C NMR (100 MHz): δ = 174.4, 171.0, 143.0, 142.4, 140.2, 140.1, 135.7, 135.3, 135.2, 134.8, 128.84, 128.83, 128.2, 127.8, 127.7, 127.5, 127.19, 127.17, 127.14, 127.08, 77.2, 61.7, 59.8, 58.4, 55.7, 49.6, 49.4, 48.6, 48.1, 43.4, 42.6, 42.0, 36.6, 34.2, 34.0, 33.0, 32.9, 32.2, 30.0, 29.6, 26.2, 26.0, 25.8, 25.6; HRMS (EI) Calcd. For $C_{31}H_{39}N_5O_3$ $[M]^+$: 529.3053. Found: 529.3051.

(4) Intermediates for the synthesis of 41



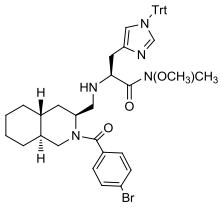
4-bromo-*N*-({(1*S*,2*R*)-2-[(*E*)-4-hydroxybut-2-en-1-yl]cyclohexyl}methyl)benzamide 35

Colorless oil; yield 55% (3 steps): $[\alpha]^{27}_{D}$ +17 (*c* 0.51, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.63-7.61 (m, 2H), 7.57-7.55 (m, 2H), 6.16 (brs, 1H), 5.77-5.66 (m, 2H), 4.10 (d, *J* = 4.4 Hz, 2H), 3.76 (ddd, *J* = 13.6, 6.0, 3.6 Hz, 1H), 3.16 (ddd, *J* = 13.8, 8.3, 6.0 Hz, 1H), 2.29-2.25 (m, 1H), 2.17-2.11 (m, 1H), 2.02 (brs, 1H), 1.84-1.80 (m, 1H), 1.73-1.71 (m, 3H), 1.49-1.41 (m, 1H), 1.28-1.01 (m, 5H); ^{13}C NMR (100 MHz): δ = 166.5, 133.5, 131.8, 131.2, 130.4, 128.5, 126.1, 63.8, 43.3, 41.0, 39.6, 36.4, 31.9, 30.5, 26.0, 25.7; HRMS (EI) Calcd. For $C_{18}H_{24}BrNO_2$ $[M]^+$ 365.0990. Found 365.0997.



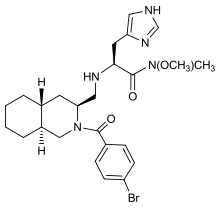
(4-bromophenyl)[(3*S*,4a*R*,8a*S*)-3-vinyloctahydroisoquinolin-2(1*H*)-yl]methanone 37

Colorless oil; yield 63%: $[\alpha]^{28}_{D}$ –10 (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.55 (d, *J* = 8.4 Hz, 0.8H), 7.51 (d, *J* = 8.4 Hz, 1.2H), 7.29-7.27 (m, 2H), 5.84 (ddd, *J* = 17.4, 10.6, 4.0 Hz, 0.4H), 5.75 (ddd, *J* = 17.5, 10.9, 3.7 Hz, 0.6H), 5.49 (brs, 0.4H), 5.29-5.26 (m, 1H), 5.19-5.11 (m, 1H), 4.44 (dd, *J* = 13.2, 4.0 Hz, 0.6H), 4.38 (brs, 0.6H), 3.33 (dd, *J* = 13.2, 4.0 Hz, 0.4H), 2.85-2.79 (m, 0.4H), 2.60-2.54 (m, 0.6H), 1.82-1.49 (m, 5H), 1.43-1.19 (m, 5H), 1.10-1.07 (m, 0.4H), 0.99-0.96 (m, 1H), 0.88-0.83 (m, 0.6H); ^{13}C NMR (100 MHz): δ = 170.2, 169.6, 136.9, 136.5, 135.4, 131.7, 131.6, 128.6, 128.0, 123.7, 123.6, 116.7, 116.2, 57.2, 50.8, 49.6, 43.5, 42.7, 41.8, 37.5, 36.7, 35.9, 32.8, 29.9, 29.6, 26.1, 26.0, 25.7, 25.6; HRMS (EI) Calcd. For $C_{18}H_{22}BrNO$ $[M]^+$: 347.0885. Found: 347.0891.



(*S*)-2-({[(3*S*,4a*R*,8a*S*)-2-(4-bromobenzoyl)decahydroisoquinolin-3-yl]methyl}amino)-*N*-methoxy-*N*-methyl-3-(1-trityl-1*H*-imidazol-4-yl)propanamide 39

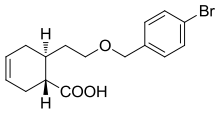
Colorless oil; yield 58% (3 steps): $[\alpha]^{28}_{D}$ –17 (*c* 0.67, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.47 (d, *J* = 8.4 Hz, 1.2H), 7.44 (d, *J* = 8.4 Hz, 0.8H), 7.35-7.29 (m, 10.8H), 7.22 (d, *J* = 8.4 Hz, 1.2H), 7.14-7.11 (m, 6H), 6.60 (s, 0.6H), 6.55 (s, 0.4H), 4.87 (m, 0.6H), 4.37 (dd, *J* = 13.4, 3.8 Hz, 0.4H), 4.10 (brs, 0.6H), 3.90 (brs, 0.4H), 3.78 (brs, 0.6H), 3.64 (s, 1.8H), 3.51 (s, 1.2H), 3.24 (dd, *J* = 13.2, 3.6 Hz, 0.6H), 3.13 (s, 1.8H), 3.09 (s, 1.2H), 2.91-2.79 (m, 2.4H), 2.73-2.63 (m, 2H), 2.46-2.40 (m, 0.4H), 1.76-1.71 (m, 3.4H), 1.60-1.54 (m, 1.6H), 1.37-1.26 (m 5H), 1.00-0.82 (m, 2H); ^{13}C NMR (100 MHz): δ = 175.4, 175.1, 170.4, 169.6, 142.46, 142.41, 138.2, 138.1, 137.6, 137.2, 135.9, 135.8, 131.50, 131.46, 129.73, 129.70, 128.7, 128.4, 127.92, 127.89, 123.21, 123.18, 119.23, 119.22, 77.2, 75.0, 61.6, 61.5, 57.8, 57.5, 55.5, 49.4, 48.3, 47.1, 46.6, 43.1, 42.5, 42.0, 36.4, 36.2, 34.5, 33.0, 32.9, 32.7, 32.3, 32.0, 29.9, 29.7, 26.1, 26.0, 25.8, 25.6; HRMS (EI) Calcd. For $C_{44}H_{48}BrN_5O_3$ $[M]^+$: 773.2941. Found: 773.2949.



(*S*)-2-({[(3*S*,4a*R*,8a*S*)-2-(4-bromobenzoyl)decahydroisoquinolin-3-yl]methyl}amino)-3-(1*H*-imidazol-4-yl)-*N*-methoxy-*N*-methylpropanamide S7

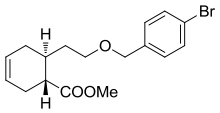
Colorless oil; yield 74%: $[\alpha]^{28}_{D}$ –36 (*c* 0.28, $CHCl_3$) ^{1}H NMR (400 MHz): δ = 7.65 (brs, 0.6H), 7.55-7.52 (m, 2H), 7.39 (m, 0.4H), 7.32 (d, *J* = 7.6 Hz, 1.2H), 7.18 (d, *J* = 8.4 Hz, 0.8H), 6.82 (s, 0.6H), 6.80 (s, 0.4H), 4.95 (brs, 0.4H), 4.25 (d, *J* = 12.0 Hz, 0.6H), 3.98 (brs, 0.6H), 3.86-3.80 (m, 0.4H), 3.71 (s, 1.2H), 3.65 (s, 1.8H), 3.54-3.53 (m, 0.6H), 3.35-3.27 (m, 0.4H), 3.23 (s, 1.2H), 3.20 (s, 1.8H), 2.99-2.82 (m, 2H), 2,71-2.60 (m, 2H), 2.51-2.42 (m, 2H), 1.76-1.58 (m, 4H), 1.47-1.24 (m, 6H), 1.05-0.83 (m, 2H); ^{13}C NMR (100 MHz): δ = 174.2, 173.4, 170.1, 135.6, 135.4, 135.3, 134.7, 131.9, 131.7, 129.3, 128.3, 124.4, 123.6, 77.2, 61.7, 59.7, 58.2, 55.7, 49.5, 49.3, 48.5, 47.9, 43.4, 42.5, 41.9, 36.5, 34.2, 33.9, 32.9, 32.8, 32.2, 29.9, 29.6, 26.1, 25.9, 25.7, 25.5; HRMS (EI) Calcd. For $C_{25}H_{34}BrN_5O_3$ $[M]^+$: 531.1845. Found: 531.1849.

(5) Intermediates for the synthesis of 44 and 45



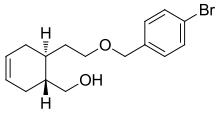
(1*R*,6*S*)-6-{2-[(4-bromobenzyl)oxy]ethyl}cyclohex-3-enecarboxylic acid 30

Colorless oil; yield 20% (50% max): $[\alpha]^{29}_{D}$ –33.2 (*c* 1.16, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.46 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 5.66 (m, 2H) 4.44 (dd, *J* = 17.2, 12.0 Hz, 2H), 3.55-3.52 (m, 2H), 2.46-2.22 (m, 4H), 2.12-2.07 (m, 1H), 1.91-1.86 (m, 1H), 1.80-1.74 (m, 1H), 1.57-1.51 (m, 1H); ^{13}C NMR (100 MHz): δ = 181.9, 137.3, 131.4, 129.2, 125.6, 124.4, 121.4, 72.1, 67.9, 45.0, 33.5, 31.9, 29.5, 27.7; HRMS (EI) Calcd. For $C_{16}H_{19}BrO_3$ $[M]^+$: 338.0518. Found: 338.0511.



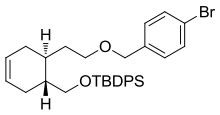
(1*R*,6*S*)-methyl 6-{2-[(4-bromobenzyl)oxy]ethyl}cyclohex-3-enecarboxylate S8

Colorless oil; yield 20%: $[\alpha]^{28}_{D}$ –40 (*c* 0.78, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.46 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 5.67-5.61 (m, 2H), 4.43 (dd, *J* = 18.0, 12.0 Hz, 2H), 3.68 (s, 3H), 3.54-3.46 (m, 2H), 2.43-2.19 (m, 4H), 2.10-2.02 (m, 1H), 1.80-1.72 (m, 2H), 1.53-1.44 (m, 1H); ^{13}C NMR (100 MHz): δ = 176.2, 137.5, 131.4, 129.2, 125.7, 124.7, 121.3, 72.1, 68.1, 51.5, 45.2, 33.8, 32.4, 29.9, 28.1; HRMS (EI) Calcd. For $C_{17}H_{21}BrO_3$ $[M]^+$: 352.0674. Found: 352.0681.



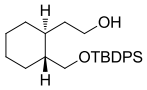
[(1*R*,6*S*)-6-{2-[(4-bromobenzyl)oxy]ethyl}cyclohex-3-en-1-yl]methanol S9

Colorless oil; yield 73%: $[\alpha]^{29}_{D}$ –20 (*c* 0.80, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.46 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 5.65-5.58 (m, 2H), 4.45 (s, 2H), 3.68 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.61 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.58-3.47 (m, 2H), 2.15-2.09 (m, 2H), 2.00-1.76 (m, 4H), 1.66-1.62 (m, 1H), 1.57-1.50 (m, 1H); ^{13}C NMR (100 MHz): δ = 137.3, 131.5, 129.3, 125.8, 125.5, 121.4, 72.3, 68.7, 65.0, 39.7, 32.9, 31.1, 29.5, 26.6; HRMS (EI) Calcd. For $C_{16}H_{21}BrO_2$ $[M]^+$: 324.0725. Found: 324.0723.



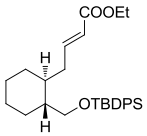
([(1*R*,6*S*)-6-{2-[(4-bromobenzyl)oxy]ethyl}cyclohex-3-en-1-yl]methoxy)(*tert*-butyl)diphenylsilane S10

Colorless oil; yield 88%: $[\alpha]^{28}_{D}$ −19.5 (*c* 1.15, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.67-7.64 (m, 4H), 7.45-7.34 (m, 8H), 7.18 (d, *J* = 8.0 Hz, 2H), 5.63-5.54 (m, 2H), 4.41 (dd, *J* = 15.2, 12.0 Hz, 2H), 3.68 (dd, *J* = 9.8, 5.4 Hz, 1H), 3.62 (dd, *J* = 10.0, 6.8 Hz, 1H), 3.53-3.44 (m, 2H), 2.16-1.96 (m, 3H), 1.88-1.80 (m, 2H), 1.73-1.68 (m, 2H), 1.50-1.44 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (100 MHz): δ = 137.7, 135.61, 135.60, 133.94, 133.92, 131.4, 129.5, 129.1, 127.6, 125.8, 125.3, 121.2, 72.1, 68.7, 65.9, 39.6, 32.9, 30.8, 29.0, 26.9, 26.7, 19.3; HRMS (FAB) Calcd. For $C_{32}H_{40}BrO_5$ $[M+H]^+$: 563.1981. Found: 563.1976.



2-[(1*S*,2*R*)-2-{[(*tert*-butyldiphenylsilyl)oxy]methyl}cyclohexyl]ethanol S11

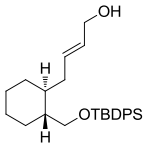
Colorless oil; yield 84%: $[\alpha]^{28}_{D}$ −9.4 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.68-7.65 (m, 4H), 7.45-7.36 (m, 6H), 3.68-3.54 (m, 4H), 1.78-1.66 (m, 5H), 1.37-1.18 (m, 6H), 1.06 (s, 9H), 1.02-0.97 (m, 1H); ^{13}C NMR (100 MHz): δ = 135.68, 135.66, 133.91, 133.89, 129.55, 129.54, 127.60, 127.57, 66.6, 61.0, 44.5, 36.5, 35.5, 31.9, 30.0, 26.9, 26.1, 26.0, 19.3; HRMS (FAB) Calcd. For $C_{25}H_{37}O_2Si$ $[M+H]^+$: 397.2563. Found: 397.2560.



(*E*)-ethyl
4-[(1*S*,2*R*)-2-{[(*tert*-butyldiphenylsilyl)oxy]methyl}cyclohexyl]but-2-enoate S12

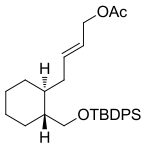
Colorless oil; yield 98% (2 steps): $[\alpha]^{28}_{D}$ −8.54 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.67-7.64 (m, 4H), 7.44-7.36 (m, 6H), 6.91 (ddd, *J* = 15.5, 8.7, 6.7 Hz, 1H), 5.72 (d, *J* = 15.6 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.64-3.58 (m, 2H), 2.38-2.32 (m, 1H), 2.00-1.93 (m, 1H), 1.79-1.69 (m, 4H), 1.54-1.49 (m, 1H), 1.35-1.18 (m, 4H), 1.28 (t, *J* = 7.0 Hz, 3H), 1.05 (s, 9H), 1.03-0.97 (m, 1H); ^{13}C NMR (100 MHz): δ = 166.6, 148.2, 135.62, 135.61, 133.83, 133.80, 129.6, 129.5, 127.62, 127.59, 122.4, 66.3, 60.1, 43.9, 37.8, 36.4, 31.9, 30.0, 26.9, 26.1, 26.0, 19.3, 14.3; HRMS (FAB) Calcd. For

$C_{29}H_{40}NaO_3Si$ $[M+Na]^+$: 487.2644. Found: 487.2640.



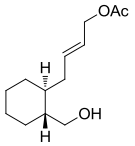
(*E*)-4-[(1*S*,2*R*)-2-{[(*tert*-butyldiphenylsilyl)oxy]methyl}cyclohexyl]but-2-en-1-ol S13

Colorless oil; yield 94%: $[\alpha]^{28}_D$ −14 (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.68-7.65 (m, 4H), 7.44-7.36 (m, 6H), 5.64-5.48 (m, 2H), 4.04 (d, *J* = 5.2 Hz, 2H), 3.66 (dd, *J* = 10.0, 2.8 Hz, 1H), 3.58 (dd, *J* = 9.8, 5.4 Hz, 1H), 2.21-2.18 (m, 1H), 1.87-1.79 (m, 2H), 1.72-1.69 (m, 3H), 1.42-1.33 (m, 1H), 1.30-1.18 (m, 4H), 1.05 (s, 9H), 1.00-0.95 (m, 1H); ^{13}C NMR (100 MHz): δ = 135.66, 135.64, 134.0, 131.6, 130.2, 129.55, 129.52, 127.60, 127.58, 66.3, 63.8, 43.9, 38.1, 36.2, 31.7, 30.0, 26.9, 26.2, 26.1, 19.4; HRMS (FAB) Calcd. For $C_{27}H_{38}NaO_2Si$ $[M+Na]^+$: 445.2539. Found: 445.2534.



(*E*)-4-[(1*S*,2*R*)-2-{[(*tert*-butyldiphenylsilyl)oxy]methyl}cyclohexyl]but-2-en-1-yl acetate S14

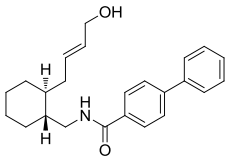
Colorless oil; yield 92%: $[\alpha]^{28}_D$ −16.2 (*c* 1.38, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.67-7.64 (m, 4H), 7.44-7.36 (m, 6H), 5.71-5.64 (m, 1H), 5.49-5.42 (m, 1H), 4.47 (d, *J* = 6.4 Hz, 2H), 3.65 (dd, *J* = 10.0, 3.2 Hz, 1H), 3.57 (dd, *J* = 10.0, 5.2 Hz, 1H), 2.23-2.19 (m, 1H), 2.05 (s, 3H), 1.88-1.79 (m, 2H), 1.71-1.68 (m, 3H), 1.40-1.38 (m, 1H), 1.30-1.18 (m, 4H), 1.05 (s, 9H), 1.00-0.94 (m, 1H); ^{13}C NMR (100 MHz): δ = 170.9, 135.63, 135.61, 134.8, 133.95, 133.94, 129.53, 129.51, 127.58, 127.56, 125.0, 66.3, 65.3, 43.8, 38.0, 36.3, 31.7, 30.0, 26.9, 26.2, 26.1, 21.0, 19.3; HRMS (FAB) Calcd. For $C_{29}H_{40}NaO_3Si$ $[M+Na]^+$: 487.2644. Found: 487.2644.



(*E*)-4-[(1*S*,2*R*)-2-(hydroxymethyl)cyclohexyl]but-2-en-1-yl acetate S15

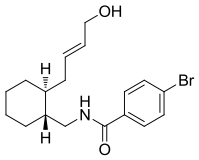
Colorless oil; yield 88%: $[\alpha]^{28}_D$ −26.5 (*c* 1.06, $CHCl_3$); ^{1}H NMR (400 MHz): δ =

5.80-5.72 (m, 1H), 5.60-5.53 (m, 1H), 4.51 (d, *J* = 6.4 Hz, 2H), 3.69 (brd, *J* = 10.0 Hz, 1H), 3.57 (dd, *J* = 10.2, 5.0 Hz, 1H), 2.32-2.28 (m, 1H), 2.06 (s, 3H), 2.00-1.93 (m, 1H), 1.81-1.71 (m, 4H), 1.41 (brs, 1H), 1.33-1.29 (m, 1H), 1.25-1.14 (m, 4H), 1.05-0.96 (m, 1H); ^{13}C NMR (100 MHz): δ = 170.9, 134.5, 125.3, 65.5, 65.2, 43.8, 38.0, 36.3, 31.7, 29.5, 26.0, 25.8, 21.0; HRMS (FAB) Calcd. For $C_{13}H_{22}NaO_3$ $[M+Na]^+$: 249.1467. Found: 249.1468.



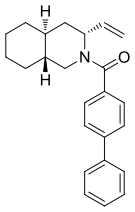
_N_-({(1_R_,2_S_)-2-[(_E_)-4-hydroxybut-2-en-1-yl]cyclohexyl}methyl)-(1,1'-biphenyl)-4-carboxamide S16

Colorless oil; yield 50%: $[\alpha]^{28}_D$ –9.1 (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.84-7.82 (m, 2H), 7.66-7.60 (m, 4H), 7.48-7.45 (m, 2H), 7.41-7.37 (m, 1H), 6.25 (m, 1H), 5.79-5.68 (m, 2H), 4.10 (d, *J* = 4.4 Hz, 2H), 3.79 (ddd, *J* = 13.5, 6.2, 3.7 Hz, 1H), 3.21 (ddd, *J* = 13.8, 8.2, 5.8 Hz, 1H), 2.31-2.27 (m, 1H), 2.19-2.12 (m, 2H), 2.08 (brs, 1H), 1.88-1.84 (m, 1H), 1.75-1.72 (m, 3H), 1.52-1.43 (m, 1H), 1.32-1.21 (m, 3H), 1.19-1.04 (m, 1H); ^{13}C NMR (100 MHz): δ = 167.2, 144.2, 140.0, 133.3, 131.2, 130.5, 128.9, 128.0, 127.3, 127.24, 127.18, 63.8, 43.3, 41.1, 39.6, 36.5, 31.9, 30.6, 26.1, 25.7; HRMS (EI) Calcd. For $C_{24}H_{29}NO_2$ $[M]^+$: 363.2198. Found: 363.2204.



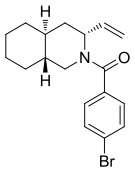
4-bromo-_N_-({(1_R_,2_S_)-2-[(_E_)-4-hydroxybut-2-en-1-yl]cyclohexyl}methyl)benzamide S17

Colorless oil; yield 52%: $[\alpha]^{28}_D$ –6.9 (*c* 0.38, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.63-7.61 (m, 2H), 7.59-7.55 (m, 2H), 6.15 (m, 1H), 5.78-5.66 (m, 2H), 4.10 (d, *J* = 4.4 Hz, 2H), 3.76 (ddd, *J* = 13.5, 5.9, 3.9 Hz, 1H), 3.16 (ddd, *J* = 13.7, 8.1, 5.9 Hz, 1H), 2.29-2.25 (m, 1H), 2.17-2.11 (m, 2H), 1.84-1.80 (m, 1H), 1.73-1.71 (m, 3H), 1.60 (brs, 1H), 1.50-1.41 (m, 1H), 1.30-1.20 (m, 4H), 1.18-1.02 (m, 1H); ^{13}C NMR (100 MHz): δ = 166.5, 133.5, 131.8, 131.2, 130.4, 128.5, 126.1, 63.8, 43.3, 41.0, 39.6, 36.4, 31.9, 30.5, 26.0, 25.7; HRMS (EI) Calcd. For $C_{18}H_{24}BrNO_2$ $[M]^+$: 365.0990. Found: 365.0987.



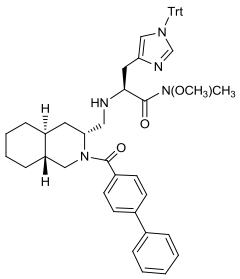
(1,1'-biphenyl)-4-yl[(3*R*,4a*S*,8a*R*)-3-vinyloctahydroisoquinolin-2(1*H*)-yl]methanone S18

Colorless oil; yield 58%: $[\alpha]^{29}_{D}$ +29 (*c* 0.80, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.64-7.58 (m, 4H), 7.49-7.43 (m, 4H), 7.38-7.35 (m, 1H), 5.87 (ddd, *J* = 17.4, 10.6, 3.6 Hz, 0.4H), 5.78 (ddd, *J* = 17.5, 10.7, 3.5 Hz, 0.6H), 5.55 (brs, 0.4H), 5.31-5.28 (m, 1H), 5.23-5.16 (m, 1H), 4.54 (brs, 0.6H), 4.49 (dd, *J* = 13.2, 3.6 Hz, 0.6H), 3.49 (dd, *J* = 12.8, 3.6 Hz, 0.4H), 2.86 (dd, *J* = 13.2, 11.6 Hz, 0.4H), 2.61 (dd, *J* = 13.2, 11.6 Hz, 0.6H), 1.84-1.52 (m, 5H), 1.47-1.18 (m, 5H), 1.15-0.98 (m, 1.4H), 0.89-0.81 (m, 0.6H); ^{13}C NMR (100 MHz): δ = 171.1, 170.4, 142.3, 142.2, 140.4, 137.1, 136.7, 135.4, 128.8, 127.7, 127.4, 127.1, 126.8, 116.6, 116.1, 57.2, 50.8, 49.7, 43.5, 42.8, 41.9, 37.5, 36.8, 35.9, 32.9, 29.9, 29.7, 26.2, 26.1, 25.8, 25.7; HRMS (EI) Calcd. For $C_{24}H_{27}NO$ $[M]^+$: 345.2093. Found: 345.2091.



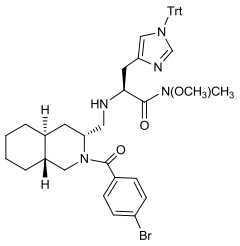
(4-bromophenyl)[(3*R*,4a*S*,8a*R*)-3-vinyloctahydroisoquinolin-2(1*H*)-yl]methanone S19

Colorless oil; yield 52%: $[\alpha]^{28}_{D}$ +22 (*c* 0.59, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.56-7.50 (m, 2H), 7.29-7.27 (m, 2H), 5.84 (ddd, *J* = 17.3, 10.7, 3.9 Hz, 0.4H), 5.75 (ddd, *J* = 17.2, 10.8, 3.6 Hz, 0.6H), 5.49 (brs, 0.4H), 5.29-5.26 (m, 1H), 5.19-5.10 (m, 1H), 4.44 (dd, *J* = 13.2, 4.0 Hz, 0.6H), 4.38 (brs, 0.6H), 3.33 (dd, *J* = 13.2, 3.6 Hz, 0.4H), 2.82 (dd, *J* = 13.0, 11.4 Hz, 0.4H), 2.57 (dd, *J* = 13.0, 11.4 Hz, 0.6H), 1.82-1.49 (m, 5H), 1.43-1.15 (m, 5H), 1.13-1.04 (m, 0.4H), 1.02-0.90 (m, 1H), 0.89-0.79 (m, 0.6H); ^{13}C NMR (100 MHz): δ = 170.2, 169.6, 136.9, 136.5, 135.4, 131.7, 131.6, 128.6, 128.0, 123.7, 123.6, 116.6, 116.2, 57.2, 50.8, 49.6, 43.5, 42.7, 41.8, 37.4, 36.7, 35.9, 32.8, 29.9, 29.7, 26.1, 26.0, 25.7, 25.6; HRMS (EI) Calcd. For $C_{18}H_{22}BrNO$ $[M]^+$: 347.0885. Found: 347.0891.



(*S*)-2-[({(3*R*,4a*S*,8a*R*)-2-[(1,1'-biphenyl)-4-carbonyl]decahydroisoquinolin-3-yl}methyl)amino]-*N*-methoxy-*N*-methyl-3-(1-trityl-1*H*-imidazol-4-yl)propanamide 42

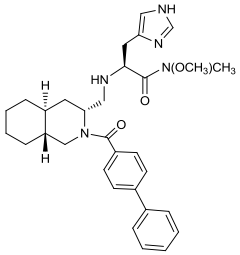
Colorless oil; yield 66%: $[\alpha]^{28}_{D}$ +58 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.58-7.24 (m, 19H), 7.13-7.07 (m, 6H), 6.57 (brs, 0.4H), 6.55 (m, 0.6H), 5.00-4.98 (m, 0.4H), 4.46 (dd, *J* = 13.2, 3.6 Hz, 0.6H), 4.13-4.11 (m, 0.4H), 3.94 (m, 1H), 3.65 (s, 1.2H), 3.62-3.58 (m, 0.6H), 3.50 (s, 1.8H), 3.44 (dd, *J* = 13.6, 3.2 Hz, 0.4H), 3.14 (s, 1.2H), 3.11 (s, 1.8H), 3.01-2.93 (m, 1H), 2.88-2.77 (m, 2H), 2.65 (dd, *J* = 12.0, 6.4 Hz, 0.4H), 2.55-2.43 (m, 1.2H), 1.71-1.69 (m, 3H), 1.60-1.52 (m, 2H), 1.45-1.19 (m, 5H), 1.05-0.83 (m, 2H); ^{13}C NMR (100 MHz): δ = 175.7, 175.4, 171.1, 170.8, 142.5, 142.4, 142.0, 141.9, 140.5, 140.3, 138.2, 138.1, 137.5, 137.4, 135.7, 129.8, 129.7, 128.8, 128.7, 127.9, 127.54, 127.47, 127.12, 127.11, 127.08, 127.00, 119.5, 119.3, 77.2, 75.1, 62.0, 61.6, 57.7, 57.6, 55.5, 49.3, 48.4, 47.5, 47.3, 43.0, 42.9, 42.1, 36.7, 36.6, 34.6, 33.5, 33.1, 33.0, 32.3, 32.1, 29.9, 29.73, 29.67, 26.2, 26.1, 25.9, 25.7; HRMS (EI) Calcd. For $C_{50}H_{53}N_5O_3$ $[M]^+$: 771.4148. Found: 771.4154.



(*S*)-2-({[(3*R*,4a*S*,8a*R*)-2-(4-bromobenzoyl)decahydroisoquinolin-3-yl]methyl}amino)-*N*-methoxy-*N*-methyl-3-(1-trityl-1*H*-imidazol-4-yl)propanamide 43

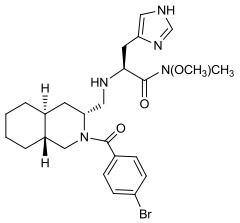
Colorless oil; yield 66%: $[\alpha]^{28}_{D}$ +8.1 (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.47-7.31 (m, 14H), 7.12-7.11 (m, 6H), 6.55 (brs, 1H), 4.94 (m, 0.4H), 4.40 (dd, *J* = 13.4, 3.4 Hz, 0.6H), 4.10 (brs, 0.4H), 3.91 (brs, 0.6H), 3.80 (m, 0.6H), 3.63 (s, 1.8H), 3.54 (s, 1.6H), 3.27 (dd, *J* = 13.0, 3.4 Hz, 0.4H), 3.12 (s, 1.8H), 3.11 (s, 1.2H), 2.98-2.91 (m, 1H), 2.86-2.73 (m, 2.6H), 2.61 (dd, *J* = 11.6, 6.0 Hz, 0.6H), 2.47-2.41 (m, 1.4H), 1.68-1.66 (m, 3H), 1.59-1.47 (m, 2H), 1.38-1.18 (m, 5H), 0.99-0.88 (m, 2H); ^{13}C NMR (100 MHz): δ = 175.6, 175.3, 170.3, 170.0, 142.5, 142.4, 138.2, 138.1, 137.4,

137.3, 135.8, 135.7, 131.50, 131.49, 129.8, 129.7, 128.9, 128.7, 127.9, 123.33, 123.28, 119.5, 119.3, 77.2, 75.1, 75.0, 61.6, 57.8, 57.5, 55.5, 49.2, 48.5, 47.4, 47.2, 42.9, 42.8, 42.0, 36.7, 36.5, 34.7, 33.5, 33.0, 32.9, 32.3, 32.1, 29.9, 29.7, 26.2, 26.0, 25.8, 25.7; HRMS (EI) Calcd. For $C_{44}H_{48}BrN_5O_3$ $[M]^+$: 773.2941. Found: 771.2935.



(*S*)-2-[({(3*R*,4a*S*,8a*R*)-2-[(1,1'-biphenyl)-4-carbonyl]decahydroisoquinolin-3-yl}methyl)amino]-3-(1*H*-imidazol-4-yl)-*N*-methoxy-*N*-methylpropanamide S20

Colorless oil; yield 84%: $[\alpha]^{28}_D$ –30.7 (*c* 1.25, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.65-7.60 (m, 4H), 7.55 (s, 1H), 7.49-7.44 (m, 4H), 7.40-7.36 (m, 1H), 6.79 (s, 1H), 5.23-5.21 (m, 0.75H), 4.53-4.51 (m, 0.25H), 4.13 (m, 0.25H), 3.90-3.88 (m, 0.75H), 3.67 (s, 2.25H), 3.67-3.65 (m, 0.75H), 3.57 (s, 0.75H), 3.57-3.53 (m, 0.75H), 3.28-3.26 (m, 0.25H), 3.26 (s, 2.25H), 3.22 (s, 0.75H), 3.12-3.06 (m, 0.25H), 2.97 (dd, *J* = 15.4, 3.4 Hz, 0.75H), 2.86 (dd, *J* = 13.4, 11.8 Hz, 0.75H), 2.62-2.53 (m, 1.5H), 2.36 (dd, *J* = 12.4, 4.4 Hz, 1H), 1.73 (m, 2H), 1.62-1.41 (m, 4H), 1.30-1.22 (m, 4H), 1.15-1.12 (m, 0.75H), 0.97-0.88 (m, 1.25H); ^{13}C NMR (100 MHz): δ = 175.0, 171.6, 171.0, 142.5, 140.2, 135.6, 135.4, 135.2, 134.4, 129.0, 128.9, 127.7, 127.4, 127.3, 127.2, 127.1, 127.0, 77.2, 61.7, 58.6, 55.5, 49.5, 49.1, 47.5, 42.8, 42.3, 37.0, 36.8, 35.2, 34.3, 33.1, 33.0, 32.3, 29.9, 29.7, 29.6, 29.2, 26.2, 26.0, 25.8, 25.6; HRMS (EI) Calcd. For $C_{31}H_{39}N_5O_3$ $[M]^+$: 529.3053. Found: 529.3061.

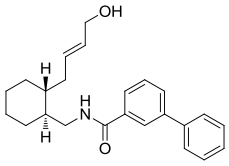


(*S*)-2-({[(3*R*,4a*S*,8a*R*)-2-(4-bromobenzoyl)decahydroisoquinolin-3-yl]methyl}amino)-3-(1*H*-imidazol-4-yl)-*N*-methoxy-*N*-methylpropanamide S21

Colorless oil; yield 85%: $[\alpha]^{28}_D$ –26 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.56-7.47 (m, 3H), 7.31-7.28 (m, 2H), 6.78 (s, 0.25H), 6.77 (s, 0.75H), 5.16-5.13 (m, 0.75H), 4.44 (dd, *J* = 13.4, 3.8 Hz, 0.25H), 3.89-3.87 (m, 1H), 3.66 (s, 2.25H), 3.58 (s,

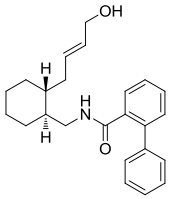
0.75H), 3.38 (dd, *J* = 13.6, 3.6 Hz, 0.75H), 3.24 (s, 2.25H), 3.20 (s, 0.75H), 3.18-3.15 (m, 0.75H), 3.03 (dd, *J* = 11.6, 9.6 Hz, 0.25H), 2.98-2.88 (m, 1H), 2.82 (dd, *J* = 13.4, 11.8 Hz, 0.75H), 2.70-2.48 (m, 1.5H), 2.38 (dd, *J* = 12.2, 4.6 Hz, 0.75H), 2.31 (dd, *J* = 11.8, 5.4 Hz, 0.25H), 1.72-1.67 (m, 2H), 1.60-1.37 (m, 5H), 1.30-1.21 (m, 5H), 1.11-1.05 (m, 0.75H), 0.97-0.83 (m, 1.25H); ^{13}C NMR (100 MHz): δ = 174.8, 170.6, 170.2, 135.6, 135.3, 135.2, 134.6, 131.7, 131.6, 128.8, 128.4, 123.7, 123.4, 77.2, 61.7, 58.4, 57.9, 55.4, 49.4, 49.1, 47.5, 47.3, 42.8, 42.7, 42.1, 36.8, 36.7, 35.0, 34.2, 33.0, 32.9, 32.3, 29.8, 29.5, 29.3, 26.1, 25.9, 25.8, 25.5; HRMS (EI) Calcd. For $C_{25}H_{34}BrN_5O_3$ $[M]^+$: 531.1845. Found: 531.1837.

(6) Intermediates for the synthesis of 46 to 49



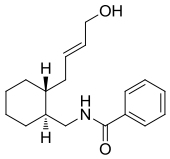
***N*-({(1*S*,2*R*)-2-[(*E*)-4-hydroxybut-2-en-1-yl]cyclohexyl}methyl)-(1,1'-biphenyl)-3-carboxamide S22**

Colorless oil; yield 45%: $[\alpha]^{21}_{D}$ +7.7 (*c* 0.60, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.98-7.97 (m, 1H), 7.73-7.69 (m, 2H), 7.64-7.58 (m, 2H), 7.52-7.43 (m, 3H), 7.40-7.35 (m, 1H), 6.25 (m, 1H), 5.79-5.67 (m, 2H), 4.10 (d, *J* = 4.4 Hz, 2H), 3.80 (ddd, *J* = 13.6, 6.0, 3.6 Hz, 1H), 3.20 (ddd, *J* = 13.7, 8.1, 5.9 Hz, 1H), 2.31-2.27 (m, 1H), 2.19-2.12 (m, 1H), 2.02 (brs, 1H), 1.87-1.83 (m, 1H), 1.71 (m, 3H), 1.58-1.43 (m, 1H), 1.30-1.01 (m, 5H); ^{13}C NMR (100 MHz): δ = 167.5, 141.8, 140.2, 135.3, 131.2, 130.5, 130.1, 129.0, 128.9, 127.8, 127.2, 125.8, 125.4, 63.8, 43.3, 41.1, 39.6, 36.5, 31.9, 30.6, 26.0, 25.7; HRMS (EI) Calcd. For $C_{24}H_{29}NO_2$ $[M]^+$: 363.2198. Found: 363.2193.



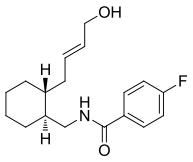
***N*-({(1*S*,2*R*)-2-[(*E*)-4-hydroxybut-2-en-1-yl]cyclohexyl}methyl)-(1,1'-biphenyl)-2-carboxamide S23**

Colorless oil; yield 55%: $[\alpha]^{28}_{D}$ +19.4 (*c* 1.58, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.72 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.49-7.35 (m, 7H), 7.33 (dd, *J* = 7.4, 1.0 Hz, 1H), 5.68-5.53 (m, 2H), 5.29 (m, 1H), 4.06 (d, *J* = 5.6 Hz, 2H), 3.46 (ddd, *J* = 13.6, 6.0, 3.2 Hz, 1H), 2.88 (ddd, *J* = 13.5, 7.6, 5.7 Hz, 1H), 2.11-2.06 (m, 2H), 1.95-1.88 (m, 2H), 1.61-1.58 (m, 1H), 1.51-1.48 (m, 1H), 1.10-0.91 (m, 5H), 0.57-0.48 (m, 1H); ^{13}C NMR (100 MHz): δ = 169.4, 140.4, 139.3, 135.7, 131.0, 130.4, 130.3, 130.0, 128.9, 128.74, 128.72, 127.7, 127.6, 63.7, 43.0, 40.6, 38.8, 36.3, 31.7, 30.0, 25.8, 25.7; HRMS (EI) Calcd. For $C_{24}H_{29}NO_2$ $[M]^+$: 363.2198. Found: 363.2193.



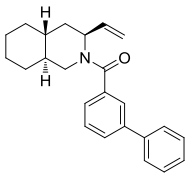
***N*-({(1*S*,2*R*)-2-[(*E*)-4-hydroxybut-2-en-1-yl]cyclohexyl}methyl)benzamide S24**

Colorless oil; yield 56%: $[\alpha]^{28}_{D}$ +17 (*c* 0.60, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.76-7.74 (m, 2H), 7.52-7.48 (m, 1H), 7.45-7.41 (m, 2H), 6.19 (brs, 1H), 5.78-5.66 (m, 2H), 4.10 (d, *J* = 4.4 Hz, 2H), 3.77 (ddd, *J* = 13.5, 5.9, 3.7 Hz, 1H), 3.19 (ddd, *J* = 13.7, 8.1, 5.9 Hz, 1H), 2.32-2.26 (m, 1H), 2.18-2.11 (m, 1H), 1.85-1.82 (m, 1H), 1.73-1.71 (m, 3H), 1.51-1.41 (m, 1H), 1.32-1.03 (m, 6H); ^{13}C NMR (100 MHz): δ = 167.5, 134.7, 131.4, 131.2, 130.5, 128.6, 126.8, 63.8, 43.2, 41.1, 39.6, 36.5, 31.9, 30.6, 26.0, 25.7; HRMS (EI) Calcd. For $C_{18}H_{25}NO_2$ $[M]^+$: 287.1885. Found: 287.1889.



4-fluoro-*N*-({(1*S*,2*R*)-2-[(*E*)-4-hydroxybut-2-en-1-yl]cyclohexyl}methyl)benzamide S25

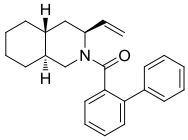
Colorless oil; yield 54%: $[\alpha]^{28}_{D}$ +15.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.78-7.75 (m, 2H), 7.12-7.08 (m, 2H), 6.25 (brs, 1H), 5.77-5.65 (m, 2H), 4.09 (d, *J* = 4.4 Hz, 2H), 3.75 (ddd, *J* = 13.4, 5.8, 3.8 Hz, 1H), 3.16 (ddd, *J* = 13.7, 8.1, 5.9 Hz, 1H), 2.29-2.24 (m, 1H), 2.17-2.10 (m, 1H), 1.84-1.71 (m, 4H), 1.49-1.41 (m, 1H), 1.28-1.05 (m, 5H); ^{13}C NMR (100 MHz): δ = 166.5, 164.6 (d, *J* = 250.4 Hz), 131.1, 130.8 (d, *J* = 3.2 Hz), 130.4, 129.2, 129.1, 115.7, 115.4, 63.7, 43.3, 41.0, 39.5, 36.4, 31.9, 30.5, 26.0, 25.7; HRMS (EI) Calcd. For $C_{18}H_{24}FNO_2$ $[M]^+$: 305.1791. Found: 305.1787.



(1,1'-biphenyl)-3-yl[(3*S*,4a*R*,8a*S*)-3-vinyloctahydroisoquinolin-2(1*H*)-yl]methanone S26

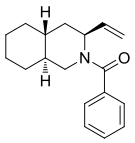
Colorless oil; yield 55%: $[\alpha]^{28}_{D}$ –29 (*c* 0.90, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.63-7.56 (m, 4H), 7.49-7.42 (m, 3H), 7.39-7.36 (m, 2H), 5.87 (ddd, *J* = 17.4, 10.6, 3.8 Hz, 0.4H), 5.77 (ddd, *J* = 17.6, 10.8 3.6 Hz, 0.6H), 5.56 (brs, 0.4H), 5.30-5.27 (m, 1H),

5.23-5.15 (m, 1H), 4.50 (d, *J* = 12.4, 3.6 Hz, 0.6H), 4.49 (brs, 0.6H), 3.44 (dd, *J* = 13.4, 3.8 Hz, 0.4H), 2.84 (dd, *J* = 13.2, 11.6 Hz, 0.4H), 2.61 (dd, *J* = 13.2, 11.2 Hz, 0.6H), 1.84-1.52 (m, 5H), 1.46-1.19 (m, 5.4H), 1.00-0.97 (m, 1H), 0.88-0.82 (m, 0.6H); ^{13}C NMR (100 MHz): δ = 171.1, 170.5, 141.5, 141.4, 141.41, 140.36, 137.2, 137.15, 137.11, 136.7, 128.9, 128.11, 128.06, 127.62, 127.59, 127.2, 127.1, 125.54, 125.48, 125.0, 124.9, 116.6, 116.1, 77.2, 57.2, 50.7, 49.6, 43.4, 42.8, 41.9, 37.4, 36.8, 36.7, 35.9, 32.8, 29.9, 29.7, 26.1, 26.0, 25.8, 25.6; HRMS (EI) Calcd. For $C_{24}H_{27}NO_2$ $[M]^+$: 345.2093. Found: 345.2090.



(1,1'-biphenyl)-2-yl[(3*S*,4a*R*,8a*S*)-3-vinyloctahydroisoquinolin-2(1*H*)-yl]methanone S27

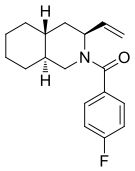
Colorless oil; yield 55%: ^{1}H NMR (400 MHz): δ = 7.55-7.53 (m, 2H), 7.48-7.33 (m, 7H), 5.72 (ddd, *J* = 17.5, 10.7, 3.7 Hz, 0.38H), 5.49 (ddd, *J* = 17.3, 10.5 3.7 Hz, 0.38H), 5.43 (brs, 0.38H), 5.28 (ddd, *J* = 17.8, 10.6 3.7 Hz, 0.24H), 5.21-5.19 (m, 0.38H), 5.09 (s, 0.38H), 5.06-5.04 (m, 0.38H), 4.94-4.90 (m, 0.38H), 4.88-4.85 (m, 0.24H), 4.74 (m, 0.24H), 4.38 (dd, *J* = 12.6, 4.2 Hz, 0.38H), 4.34 (m, 0.38H), 4.01 (brs, 0.24H), 3.89 (brs, 0.38H), 2.90 (dd, *J* = 13.0, 3.8 Hz, 0.24H), 2.80 (dd, *J* = 13.4, 3.4 Hz, 0.38H), 2.44 (t, *J* = 12.4 Hz, 0.38H), 2.37 (t, *J* = 12.4 Hz, 0.38H), 2.21 (t, *J* = 12.4 Hz, 0.24H), 2.00 (m, 0.24H), 1.67-1.52 (m, 4.38H), 1.39-0.82 (m, 5H), 0.59-0.47 (m, 1.24H), –0.02-–0.84 (m, 0.38H), –0.77-–0.86 (m, 0.38H); ^{13}C NMR (100 MHz): δ = 170.6, 170.1, 140.1, 140.0, 139.8, 138.8, 138.3, 138.1, 138.0, 136.8, 136.5, 136.3, 136.2, 136.0, 135.9, 129.6, 129.3, 129.2, 129.13, 129.06, 129.0, 128.94, 128.86, 128.6, 128.5, 128.4, 128.2, 128.0, 127.8, 127.7, 127.63, 127.59, 127.5, 127.4, 126.6, 115.9, 115.8, 115.7, 56.0, 50.4, 50.0, 48.6, 48.4, 42.9, 42.4, 40.7, 40.6, 36.4, 36.1, 35.9, 35.7, 35.6, 35.4, 32.8, 32.7, 32.6, 29.73, 29.68, 29.6, 29.3, 26.0, 25.9, 25.7, 25.6, 25.4; HRMS (EI) Calcd. For $C_{24}H_{27}NO_2$ $[M]^+$: 345.2093. Found: 345.2096.



Phenyl[(3*S*,4a*R*,8a*S*)-3-vinyloctahydroisoquinolin-2(1*H*)-yl]methanone S28

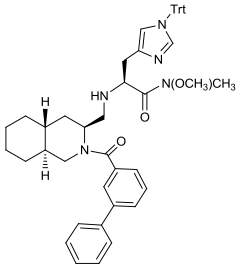
Colorless oil; yield 55%: $[\alpha]^{28}_D$ −12 (*c* 0.45, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.40-7.37 (m, 5H), 5.85 (ddd, *J* = 17.5, 10.7, 3.7 Hz, 0.4H), 5.75 (ddd, *J* = 17.4, 10.6 3.6

Hz, 0.6H), 5.53 (brs, 0.4H), 5.29-5.26 (m, 1H), 5.21-5.11 (m, 1H), 4.47 (dd, *J* = 13.2, 4.0 Hz, 0.6H), 4.43 (brs, 0.6H), 3.39 (dd, *J* = 13.4, 3.4 Hz, 0.4H), 2.81 (dd, *J* = 13.0, 11.8 Hz, 0.4H), 2.58 (dd, *J* = 12.8, 11.6 Hz, 0.6H), 1.83-1.50 (m, 5H), 1.44-1.18 (m, 5H), 1.14-1.06 (m, 0.4H), 0.99-0.97 (m, 1H), 0.88-0.82 (m, 0.6H); ^{13}C NMR (100 MHz): δ = 171.2, 170.6, 137.1, 136.7, 136.6, 129.4, 129.3, 128.41, 128.38, 126.8, 126.2, 116.5, 116.0, 57.1, 50.7, 49.6, 43.4, 42.7, 41.9, 37.4, 36.7, 35.9, 32.9, 29.9, 29.6, 26.2, 26.1, 25.8, 25.7; HRMS (EI) Calcd. For $C_{18}H_{23}NO$ $[M]^+$: 296.1780. Found: 296.1784.



(4-fluorophenyl)[(3*S*,4a*R*,8a*S*)-3-vinyloctahydroisoquinolin-2(1*H*)-yl]methanone S29

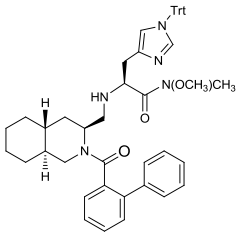
Colorless oil; yield 58%: $[\alpha]^{28}_D$ −8.9 (*c* 0.77, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.43-7.40 (m, 2H), 7.12-7.04 (m, 2H), 5.85 (ddd, *J* = 17.5, 10.7, 3.7 Hz, 0.4H), 5.76 (ddd, *J* = 17.4, 10.6 3.6 Hz, 0.6H), 5.50 (brs, 0.4H), 5.30-5.27 (m, 1H), 5.20-5.12 (m, 1H), 4.44 (dd, *J* = 13.2, 4.0 Hz, 0.6H), 4.43 (brs, 0.6H), 3.37 (dd, *J* = 13.4, 3.4 Hz, 0.4H), 2.83 (dd, *J* = 13.0, 11.8 Hz, 0.4H), 2.58 (dd, *J* = 12.8, 11.6 Hz, 0.6H), 1.83-1.49 (m, 5H), 1.44-1.17 (m, 5H), 1.14-1.05 (m, 0.4H), 0.99-0.95 (m, 1H), 0.89-0.80 (m, 0.6H); ^{13}C NMR (100 MHz): δ = 170.3, 169.7, 163.3 (d, *J* = 247.3 Hz), 163.2 (d, *J* = 247.8 Hz), 137.0, 136.6, 132.6 (d, *J* = 3.4 Hz), 129.1, 129.0, 128.6, 128.5, 116.6, 116.1, 115.6, 115.5, 115.4, 115.3, 57.3, 50.9, 49.7, 43.6, 42.8, 41.8, 37.5, 36.7, 35.9, 32.8, 29.9, 29.6, 26.1, 26.0, 25.8, 25.6; HRMS (EI) Calcd. For $C_{18}H_{22}FNO$ $[M]^+$: 287.1685. Found: 287.1689.



(*S*)-2-[({(3*S*,4a*R*,8a*S*)-2-[(1,1'-biphenyl)-3-carbonyl]decahydroisoquinolin-3-yl}methyl)amino]-*N*-methoxy-*N*-methyl-3-(1-trityl-1*H*-imidazol-4-yl)propanamide S30

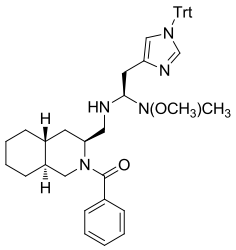
Colorless oil; yield 65%: $[\alpha]^{28}_D$ −18 (*c* 0.67, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.60-7.53 (m, 4H), 7.45-7.29 (m, 15H), 7.14-7.08 (m, 6H), 6.61 (brs, 0.55H), 6.53 (brs,

0.45H), 4.91 (m, 0.55H), 4.43 (dd, *J* = 13.4, 3.8 Hz, 0.45H), 4.13-4.11 (m, 0.45H), 3.90 (m, 1H), 3.67 (s, 1.65H), 3.45 (s, 1.35H), 3.37 (dd, *J* = 13.4, 3.8 Hz, 0.55H), 3.13 (s, 1.65H), 3.04 (s, 1.35H), 2.90-2.76 (m, 2.55H), 2.73-2.64 (m, 2H), 2.48-2.42 (m, 0.45H), 1.82-1.52 (m, 4.55H), 1.35-1.19 (m, 5.45H), 1.04-0.78 (m, 2H); ^{13}C NMR (100 MHz): δ = 175.4, 175.1, 171.3, 170.6, 142.52, 142.45, 141.34, 141.31, 140.5, 140.4, 138.2, 138.1, 137.69, 137.65, 137.58, 137.3, 129.8, 129.7, 127.93, 127.89, 127.8, 127.7, 127.5, 127.4, 127.2, 127.1, 125.6, 125.45, 125.37, 125.3, 119.2, 77.2, 75.04, 75.02, 61.7, 61.4, 57.9, 57.4, 55.5, 49.6, 48.2, 47.1, 46.5, 43.0, 42.6, 42.3, 42.1, 36.4, 36.2, 34.5, 33.0, 32.9, 32.5, 32.3, 32.0, 30.0, 29.7, 26.2, 26.1, 25.9, 25.7; HRMS (EI) Calcd. For $C_{50}H_{53}N_5O_3$ $[M]^+$: 771.4148. Found: 771.4141.



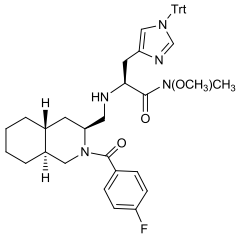
(*S*)-2-[({(3*S*,4a*R*,8a*S*)-2-[(1,1'-biphenyl)-2-carbonyl]decahydroisoquinolin-3-yl}methyl)amino]-*N*-methoxy-*N*-methyl-3-(1-trityl-1*H*-imidazol-4-yl)propanamide S31

Colorless oil; yield 62%: ^{1}H NMR (400 MHz): δ = 7.52-7.48 (m, 1.4H), 7.45-7.29 (m, 17.6H), 7.14-7.12 (m, 6H), 6.60 (brs, 0.6H), 6.55 (brs, 0.3H), 6.51 (brs, 0.1H), 4.93-4.91 (m, 0.3H), 4.87-4.84 (m, 0.1H), 4.78 (dd, *J* = 13.2, 7.2 Hz, 0.6H), 4.72-4.70 (m, 0.3H), 4.46-4.43 (m, 0.1H), 4.39 (dd, *J* = 13.6, 4.0 Hz, 0.6H), 4.07 (m, 0.6H), 4.01 (m, 0.4H), 3.82-3.76 (m, 0.6H), 3.69 (s, 1.8H), 3.64 (s, 0.9H), 3.61 (s, 0.6H), 3.33-3.30 (m, 0.1H), 3.27-3.22 (m, 0.3H), 3.18 (s, 0.9H), 3.14 (s, 1.8H), 2.97-2.95 (m, 0.3H), 2.88-2.67 (m, 2H), 2.55-2.44 (m, 1H), 2.38-1.83 (m, 2.7H), 1.66-1.50 (m, 2H), 1.35-1.03 (m, 3H), 0.89-0.81 (m, 2H), 0.69 (td, *J* = 12.8, 5.5 Hz, 0.6H), 0.59-0.36 (m, 1.4H), –0.23 (td, *J* = 13.1, 5.7 Hz, 0.1H), –0.35 (td, *J* = 12.7, 5.5 Hz, 0.3H), –0.73-–0.89 (0.6H, m); ^{13}C NMR (100 MHz): δ = 175.5, 170.3, 169.9, 142.54, 142.52, 142.48, 140.1, 139.93, 139.85, 138.3, 138.2, 138.1, 137.81, 137.76, 137.3, 136.4, 136.2, 129.8, 129.7, 129.1, 128.9, 128.85, 128.76, 128.73, 128.66, 128.52, 128.47, 128.4, 128.3, 128.03, 127.96, 127.93, 127.90, 127.87, 127.7, 127.5, 127.4, 119.2, 119.1, 77.2, 75.0, 62.6, 61.7, 61.5, 61.4, 61.0, 57.8, 57.5, 57.4, 54.5, 51.1, 48.8, 48.6, 48.5, 47.8, 47.5, 47.4, 46.4, 42.4, 41.9, 40.59, 40.56, 40.2, 35.96, 35.94, 35.5, 35.4, 33.0, 32.80, 32.78, 32.7, 32.32, 32.26, 32.1, 32.0, 31.6, 29.8, 29.6, 29.4, 29.3, 25.99, 25.97, 25.84, 25.78, 25.6, 25.46, 25.38; HRMS (EI) Calcd. For $C_{50}H_{53}N_5O_3$ $[M]^+$: 771.4148. Found: 771.4154.



{(3*S*,4a*R*,8a*S*)-3-[({(*R*)-1-[methoxy(methyl)amino]-2-(1-trityl-1*H*-imidazol-4-yl)ethyl}amino)methyl]octahydroisoquinolin-2(1*H*)-yl}(phenyl)methanone S32

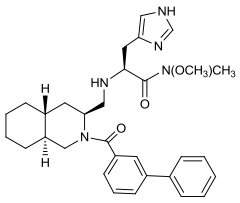
Colorless oil; yield 55%: $[\alpha]^{28}_{D}$ –23 (*c* 0.12, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.31 (brs, 15H), 7.11 (brs, 6H), 6.61 (brs, 0.6H), 6.54 (brs, 0.4H), 4.89 (brs, 0.6H), 4.41 (d, *J* = 10.8 Hz, 0.4H), 4.12 (brs, 0.6H), 3.90 (brs, 0.4H), 3.82 (brs, 0.4H), 3.66 (s, 1.8H), 3.50 (s, 1.2H), 3.30 (d, *J* = 10.8 Hz, 0.6H), 3.13 (s, 1.8H), 3.08 (s, 1.2H), 2.87-2.80 (m, 2.6H), 2.66-2.61 (m, 2H), 2.43 (t, *J* = 12.0 Hz, 0.4H), 1.79-1.69 (m, 3H), 1.60-1.53 (m, 2H), 1.35-1.26 (m, 5H), 1.03-0.80 (m, 2H); ^{13}C NMR (100 MHz): δ = 175.5, 175.3, 171.4, 170.7, 142.5, 142.4, 138.2, 138.1, 137.7, 137.3, 137.1, 137.0, 129.75, 129.70, 129.01, 128.96, 128.33, 128.29, 127.93, 127.88, 126.7, 126.6, 119.2, 77.2, 75.0, 61.7, 61.5, 57.9, 57.4, 55.4, 49.4, 48.2, 47.1, 46.5, 43.0, 42.5, 42.1, 36.4, 36.2, 34.4, 33.0, 32.9, 32.6, 32.3, 32.1, 29.9, 29.7, 26.2, 26.1, 25.8, 25.7; HRMS (EI) Calcd. For $C_{44}H_{49}N_5O_3$ $[M]^+$: 695.3835. Found: 695.3829.



(*S*)-2-({[(3*S*,4a*R*,8a*S*)-2-(4-fluorobenzoyl)decahydroisoquinolin-3-yl]methyl}amino)-*N*-methoxy-*N*-methyl-3-(1-trityl-1*H*-imidazol-4-yl)propanamide S33

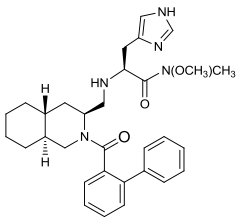
Colorless oil; yield 55%: $[\alpha]^{28}_{D}$ –17 (*c* 0.65, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.42-7.39 (m, 1.2H), 7.36-7.31 (m, 10.8H), 7.12-7.10 (m, 6H), 7.04-6.97 (m, 2H), 6.60 (brs, 0.6H), 6.55 (brs, 0.4H), 4.89-4.87 (m, 0.6H), 4.37 (dd, *J* = 13.2, 3.6 Hz, 0.4H), 4.11 (brs, 0.4H), 3.91 (m, 0.4H), 3.82 (m, 0.6H), 3.65 (s, 1.8H), 3.52 (s, 1.2H), 3.28 (d, *J* = 13.2, 3.6 Hz, 0.6H), 3.13 (s, 1.8H), 3.09 (s, 1.2H), 2.91-2.80 (m, 2.6H), 2.73-2.63 (m, 2H), 2.46-2.40 (m, 0.4H), 1.77-1.66 (m, 3H), 1.60-1.52 (m, 2H), 1.36-1.24 (m, 5H), 1.03-0.82 (m, 2H); ^{13}C NMR (100 MHz): δ = 175.5, 175.2, 170.6, 169.8, 163.0 (d, *J* = 247.2 Hz), 162.9 (d, *J* = 246.9 Hz), 142.5, 142.4, 138.2, 138.1, 137.6, 137.2, 133.1 (d, *J*

= 3.4 Hz), 133.0 (d, *J* = 3.5 Hz), 129.73, 129.70, 129.2, 129.1, 128.9, 128.8, 127.92, 127.89, 119.24, 119.22, 115.4, 115.2, 77.2, 75.0, 61.6, 61.5, 57.9, 57.5, 55.6, 49.5, 48.4, 47.2, 46.6, 43.2, 42.6, 42.0, 36.4, 36.2, 34.5, 33.0, 32.9, 32.7, 32.3, 32.0, 29.9, 29.7, 26.1, 26.0, 25.8, 25.7; HRMS (EI) Calcd. For $C_{44}H_{48}FN_5O_3$ $[M]^+$: 713.3741. Found: 771.3748.



(*S*)-2-[({(3*S*,4a*R*,8a*S*)-2-[(1,1'-biphenyl)-3-carbonyl]decahydroisoquinolin-3-yl}methyl)amino]-3-(1*H*-imidazol-4-yl)-*N*-methoxy-*N*-methylpropanamide S34

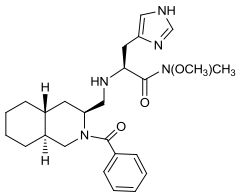
Colorless oil; yield 78%: $[\alpha]^{28}_D$ −35 (*c* 0.27, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.66-7.63 (d, *J* = 9.6 Hz, 2H), 7.58-7.55 (m, 2H), 7.50-7.41 (m, 3.6H), 7.39-7.35 (m, 1.4H), 7.26 (s, 1H), 6.84 (s, 0.6H), 6.83 (s, 0.4H), 5.03-5.01 (m, 0.4H), 4.32 (dd, *J* = 13.2, 3.2 Hz, 0.6H), 4.13-4.11 (m, 0.6H), 3.88-3.86 (m, 0.4H), 3.72 (s, 1.2H), 3.64 (s, 1.8H), 3.57-3.55 (m, 0.6H), 3.48 (dd, *J* = 13.0, 3.4 Hz, 0.4H), 3.24 (s, 1.2H), 3.18 (s, 1.8H), 3.00-2.86 (m, 1H), 2.73-2.62 (m, 2H), 2.55-2.44 (m, 2H), 1.79-1.68 (m, 3H), 1.64-1.44 (m, 2H), 1.41-1.19 (m, 5H), 1.14-0.82 (m, 2H); ^{13}C NMR (100 MHz): δ = 174.3, 171.1, 141.7, 141.6, 140.3, 140.2, 137.2, 137.0, 135.6, 134.8, 129.3, 128.89, 128.87, 128.2, 127.69, 127.65, 127.2, 127.1, 126.5, 126.1, 125.29, 125.27, 77.2, 61.7, 59.8, 58.4, 55.7, 49.5, 49.4, 48.5, 48.0, 43.4, 42.6, 42.0, 36.65, 36.58, 34.3, 34.0, 33.0, 32.9, 32.2, 30.0, 29.6, 26.2, 26.0, 25.8, 25.6; HRMS (EI) Calcd. For $C_{31}H_{39}N_5O_3$ $[M]^+$: 529.3053. Found: 529.3057.



(*S*)-2-[({(3*S*,4a*R*,8a*S*)-2-[(1,1'-biphenyl)-2-carbonyl]decahydroisoquinolin-3-yl}methyl)amino]-3-(1*H*-imidazol-4-yl)-*N*-methoxy-*N*-methylpropanamide S35

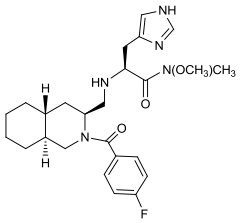
Colorless oil; yield 84%: ^{1}H NMR (400 MHz): δ = 7.65 (brs, 1H), 7.52-7.30 (m, 9H), 6.83 (m, 0.9H), 6.75 (brs, 0.1H), 5.14-5.12 (m, 0.1H), 4.92 (brs, 0.6H), 4.78-4.76 (m, 0.3H), 4.46-4.43 (m, 0.1H), 4.37 (dd, *J* = 13.2, 3.6 Hz, 0.6H), 3.80 (m, 1H), 3.71 (s,

0.9H), 3.67 (s, 0.3H), 3.62 (s, 1.8H), 3.50 (m, 0.4H), 3.38 (m, 0.6H), 3.25 (m, 0.3H), 3.23 (s, 0.9H), 3.18 (s, 1.8H), 2.99-2.86 (m, 2.3H), 2.74-2.54 (m, 2H), 2.47-1.97 (m, 2H), 1.66-1.53 (2H, m), 1.43-1.02 (4H, m), 0.86 (2H, m), 0.59-0.38 (m, 1.4H), –0.21 (brs, 0.3H), –0.78-–0.86 (m, 0.3H); ^{13}C NMR (100 MHz): δ = 174.3, 172.0, 170.6, 170.1, 140.2, 139.9, 139.8, 138.8, 138.4, 138.1, 137.9, 137.8, 136.3, 136.0, 135.9, 135.5, 134.7, 134.4, 129.6, 126.5, 129.4, 129.12, 129.08, 129.0, 128.9, 128.7, 128.6, 128.5, 128.2, 127.8, 127.7, 127.64, 127.58, 127.42, 127.38, 126.5, 77.2, 61.7, 59.6, 58.4, 57.7, 55.3, 54.3, 48.9, 48.8, 48.4, 48.3, 48.1, 47.8, 45.7, 42.5, 41.8, 40.5, 40.4, 36.0, 35.7, 33.3, 32.8, 32.7, 32.6, 32.2, 29.7, 29.6, 29.5, 29.3, 26.0, 25.9, 25.7, 25.5, 25.3; HRMS (EI) Calcd. For $C_{31}H_{39}N_5O_3$ $[M]^+$: 529.3053. Found: 529.3046.



(*S*)-2-({[(3*S*,4a*R*,8a*S*)-2-benzoyldecahydroisoquinolin-3-yl]methyl}amino)-3-(1*H*-imidazol-4-yl)-*N*-methoxy-*N*-methylpropanamide S36

Colorless oil; yield 74%: $[\alpha]^{28}_D$ –45 (*c* 0.29, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.67 (brs, 0.6H), 7.43-7.40 (m, 4.4H), 7.33-7.31 (m, 1H), 6.83 (s, 0.6H), 6.81 (s, 0.4H), 5.00 (m, 0.4H), 4.28 (brd, *J* = 12.0 Hz, 0.6H), 4.07 (brs, 0.6H), 3.84-3.81 (m, 0.4H), 3.72 (s, 1.2H), 3.66 (s, 1.8H), 3.51 (brs, 0.6H), 3.43 (d, *J* = 11.2 Hz, 0.4H), 3.24 (s, 1.2H), 3.19 (s, 1.8H), 2.99-2.84 (m, 1.4H), 2.72-2.59 (m, 2H), 2.48-2.42 (m, 1.6H), 1.77-1.58 (m, 4H), 1.46-1.21 (m, 6H), 1.13-0.94 (m, 1.4H), 0.90-0.81 (m, 0.6H); ^{13}C NMR (100 MHz): δ = 174.3, 171.2, 136.6, 136.5, 135.8, 134.8, 130.1, 129.5, 128.7, 128.5, 127.6, 126.6, 125.7, 77.2, 61.7, 59.9, 58.5, 55.6, 49.3, 48.6, 43.4, 42.6, 42.0, 36.6, 34.2, 33.0, 32.9, 32.2, 30.0, 29.6, 26.2, 26.0, 25.8, 25.6; HRMS (EI) Calcd. For $C_{25}H_{35}N_5O_3$ $[M]^+$: 453.2740. Found: 453.2744.

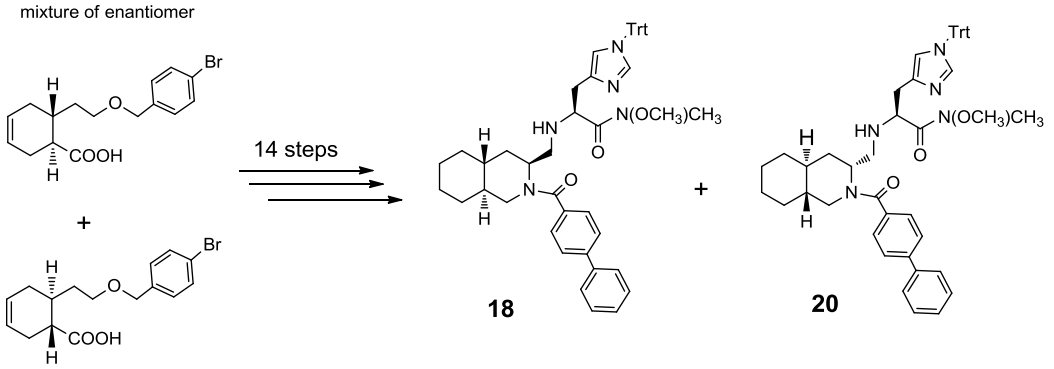


(*S*)-2-({[(3*S*,4a*R*,8a*S*)-2-(4-fluorobenzoyl)decahydroisoquinolin-3-yl]methyl}amino)-3-(1*H*-imidazol-4-yl)-*N*-methoxy-*N*-methylpropanamide S37

Colorless oil; yield 78%: $[\alpha]^{28}_{D}$ –35 (*c* 0.41, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.75-7.69 (m, 0.4H), 7.66 (s, 0.6H), 7.48-7.44 (m, 1.2H), 7.37 (s, 0.4H), 7.34-7.30 (m, 1H), 7.12-7.06 (m, 1.4H), 6.83 (s, 0.6H), 6.81 (s, 0.4H), 4.98-4.96 (m, 0.4H), 4.24 (dd, *J* = 13.2, 3.2 Hz, 0.6H), 4.05-4.02 (m, 0.6H), 3.86-3.84 (m, 0.4H), 3.72 (s, 1.2H), 3.66 (s, 1.8H), 3.56-3.54 (m, 0.4H), 3.39 (dd, *J* = 13.4, 3.4 Hz, 0.4H), 3.24 (s, 1.2H), 3.20 (s, 1.8H), 2.95-2.83 (m, 1.2H), 2.72-2.64 (m, 2H), 2.50-2.43 (m, 2H), 1.76-1.36 (m, 5H), 1.33-1.25 (m, 5H), 1.06-0.97 (m, 1.4H), 0.89-0.83 (m, 0.6H); ^{13}C NMR (100 MHz): δ = 174.3, 173.3, 170.2, 163.6 (d, *J* = 249.1 Hz), 163.2 (d, *J* = 248.1 Hz), 135.6, 134.7, 132.6 (d, *J* = 3.4 Hz), 132.5 (d, *J* = 3.4 Hz), 130.0, 129.9, 128.9, 128.82, 128.78, 127.5, 127.3, 127.0, 115.9, 115.71, 115.65, 115.4, 77.2, 61.7, 59.7, 58.3, 55.8, 49.6, 49.4, 48.6, 48.0, 43.6, 42.6, 42.0, 36.6, 34.2, 34.0, 33.0, 32.8, 32.2, 29.9, 29.6, 26.1, 26.0, 25.8, 25.6; HRMS (EI) Calcd. For $C_{25}H_{34}FN_5O_3$ $[M]^+$: 471.2646. Found: 471.2644.

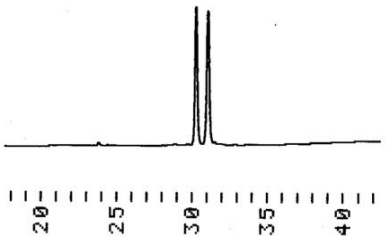
(7) Figure S-1: Separation of diastereomer mixture on a reversed-phase HPLC

(a) Separation of **18** and **20**

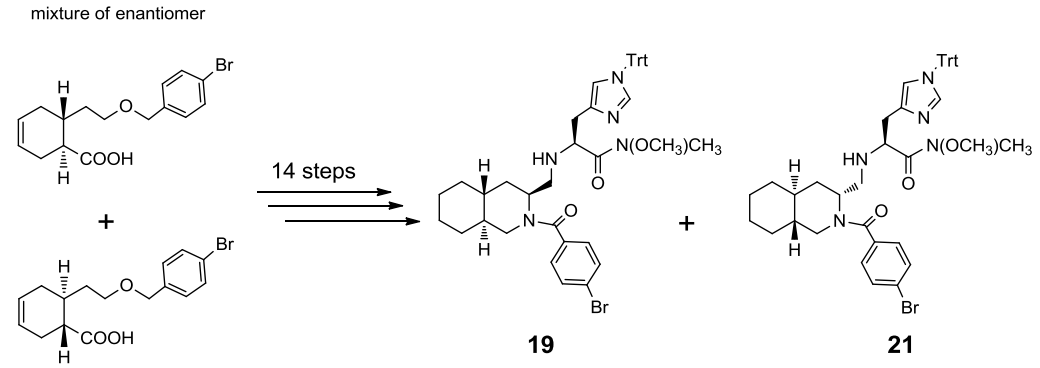


CH_3CN 0-100%/40 min, detected at 254 nm, flow: 0.9 mL/min,

YMC Pack ODS (4.6×150 mm); t_R 30.22 min, 31.02 min

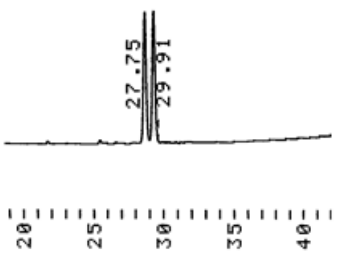


(b) Separation of **19** and **21**



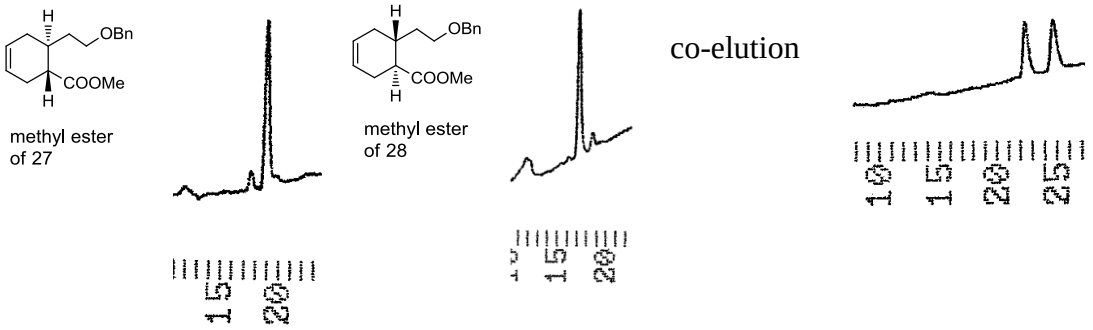
CH_3CN 0-100%/40 min, detected at 254 nm, flow: 0.9 mL/min,

YMC Pack ODS (4.6×150 mm); t_R 27.75 min, 29.91 min



(8) Figure S-2: Separation of enantiomer on a chiral column

(a) Separation of **27** and **28** as the corresponding methyl ester

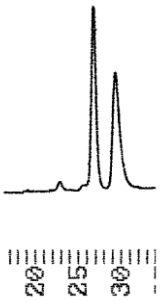


2-propanol:hexane=1:560, detected at 254nm, flow: 1 mL/min, YMC CHIRAL Amylose-C (4.6×250 mm)

(b) Separation of **30** and **31** as the corresponding methyl ester

From the minor peak in front of the major peak, no mass-value related to 30/31 was observed

co-elution



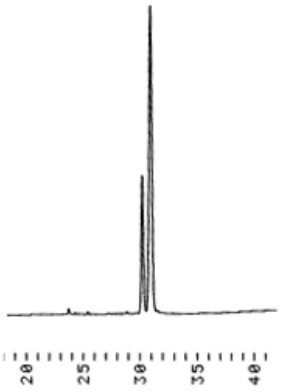
2-propanol:hexane=1:560, detected at 254 nm, flow: 1 mL/min, YMC CHIRAL Amylose-C (4.6×250 mm)

(9) Figure S-3: Elution profiles of 38 and 42 on a reversed-phase HPLC

CH_3CN 0-100%/40 min, detected at 254 nm, flow: 0.9 mL/min, YMC Pack ODS (4.6×150 mm)

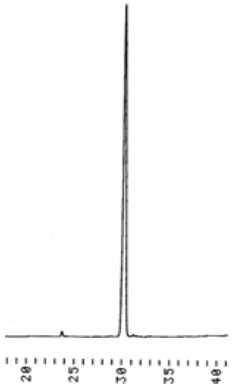
(a) Profile of **38** (t_R 30.86 min**)**

(b) Co-eluted with **18** and **20**

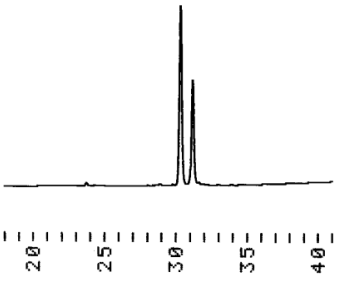


t_R 30.16 min, 30.88 min

(c) Profile of **42** (t_R 29.99 min**)**



(d) Co-eluted with **18** and **20**

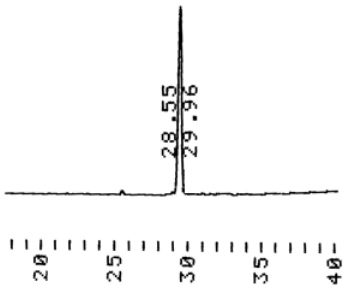


t_R 30.27 min, 31.15 min

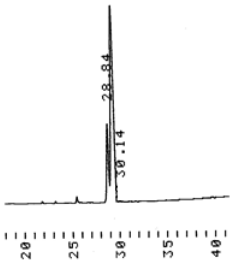
(10) Figure S-4: Elution profiles of 39 and 43 on a reversed-phase HPLC

CH_3CN 0-100%/40 min, detected at 254nm, flow : 0.9 mL/min, YMC Pack ODS (4.6×150 mm)

(a) Profile of **39** (t_R 29.30 min**)**

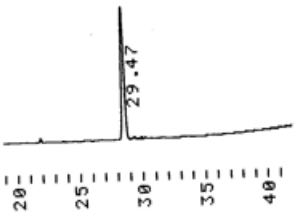


(b) Co-eluted with **19** and **21**

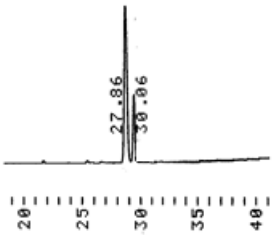


t_R 28.84 min, 29.31min

(c) Profile of **43** (t_R 28.68 min**)**



(d) Co-eluted with **19** and **21**

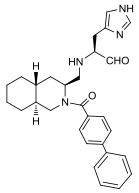


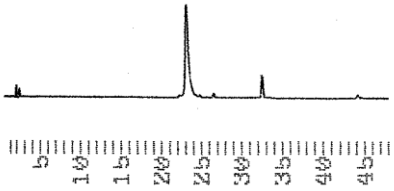
t_R 28.67 min, 29.42 min

(11) Figure S-5: HPLC profiles of 40, 41, and 44-49

YMC Pack ODS (4.6×150 mm), detected at 254 nm, flow: 0.9 mL/min,
Elution condition A; CH_3CN 25-45%/40 min
B; CH_3CN 20-40%/40 min
C; CH_3CN 15-35%/40 min

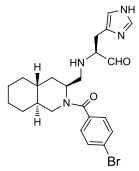
40

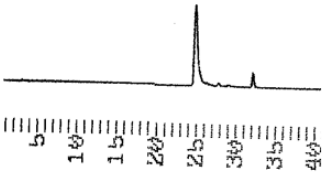




Condition A
t_R 23.14 min

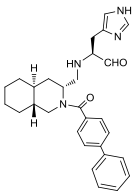
41

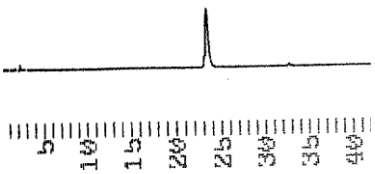




Condition B
t_R 23.93 min

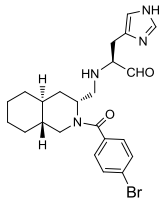
44

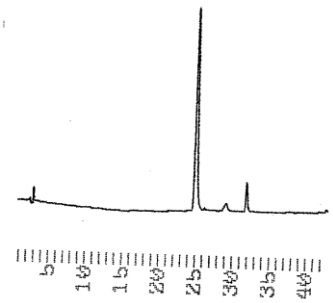




Condition A
t_R 23.16 min

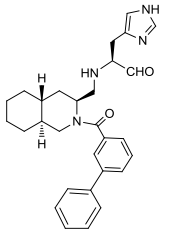
45

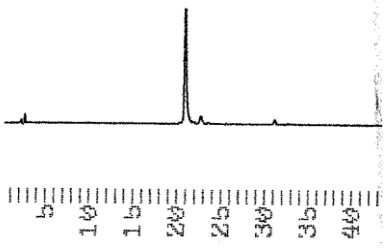




Condition B
t_R 25.49 min

46

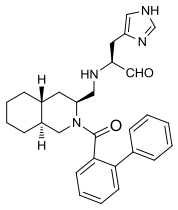


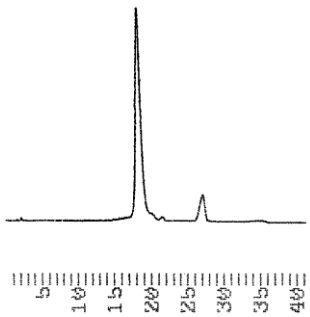


Condition A

t_R 20.52 min

47

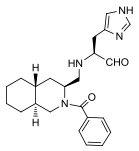


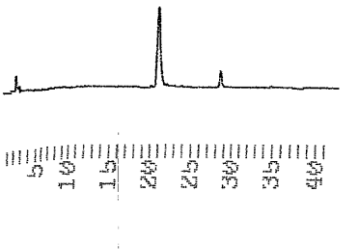


Condition A

t_R 18.14 min

48

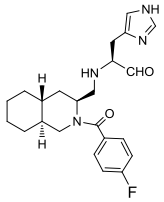


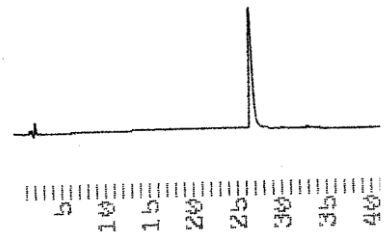


Condition C

t_R 19.90 min

49

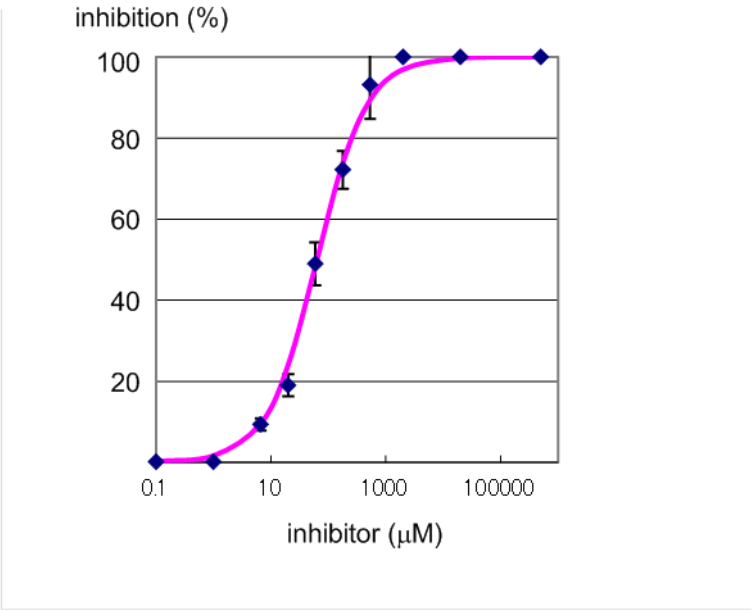




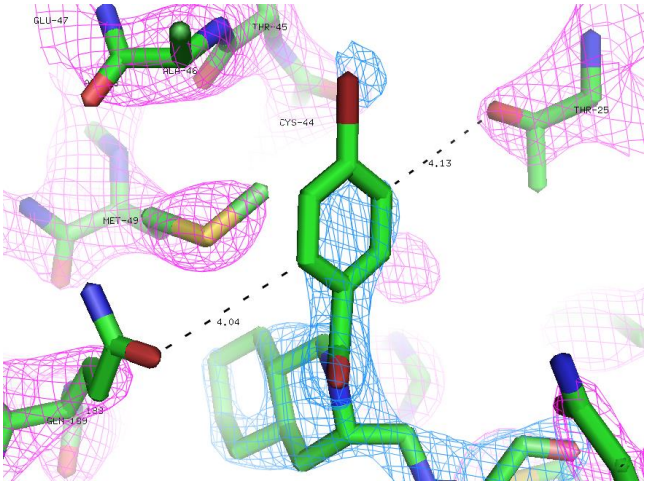
Condition B

t_R 26.88 min

(12) Figure S-6: IC_{50} values of 41 (63 μM) obtained from sigmoidal curve

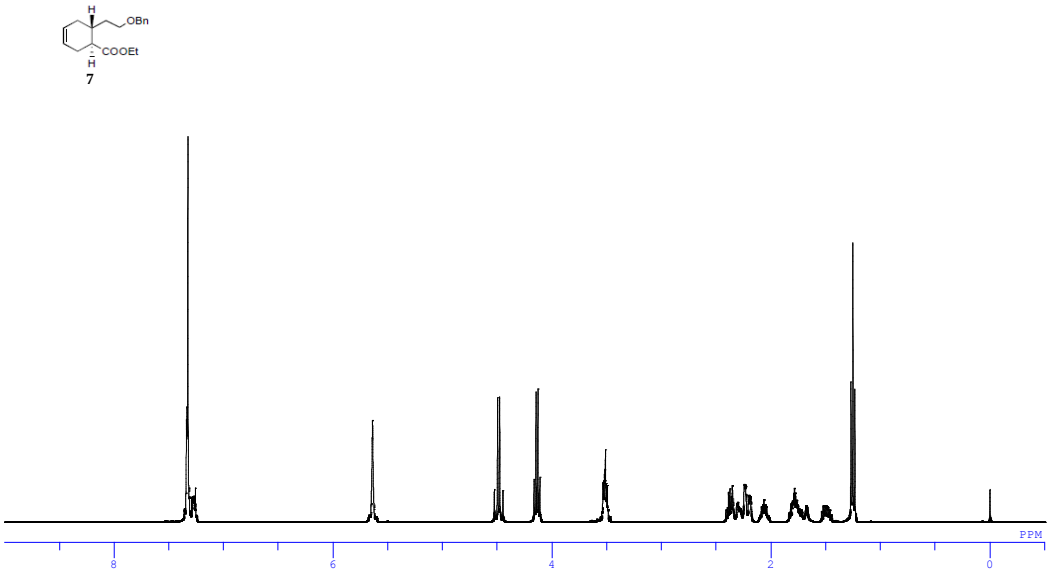


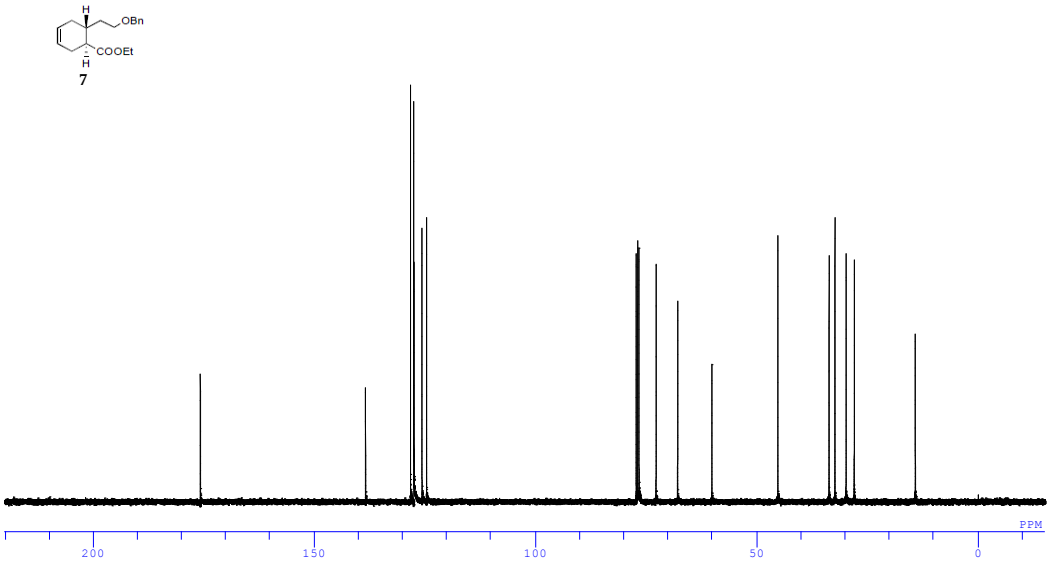
(13) Figure S-7: Possible interactions at the *N*-substituent

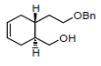


(14) NMR data of synthesized compounds

(a) Compounds included in the manuscript



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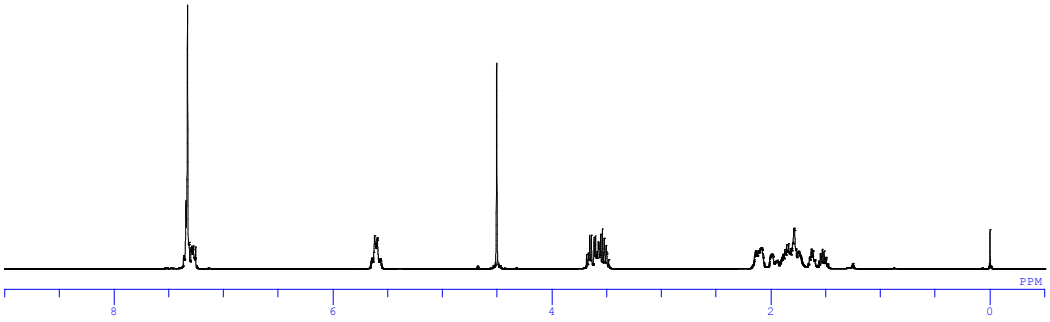
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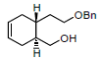
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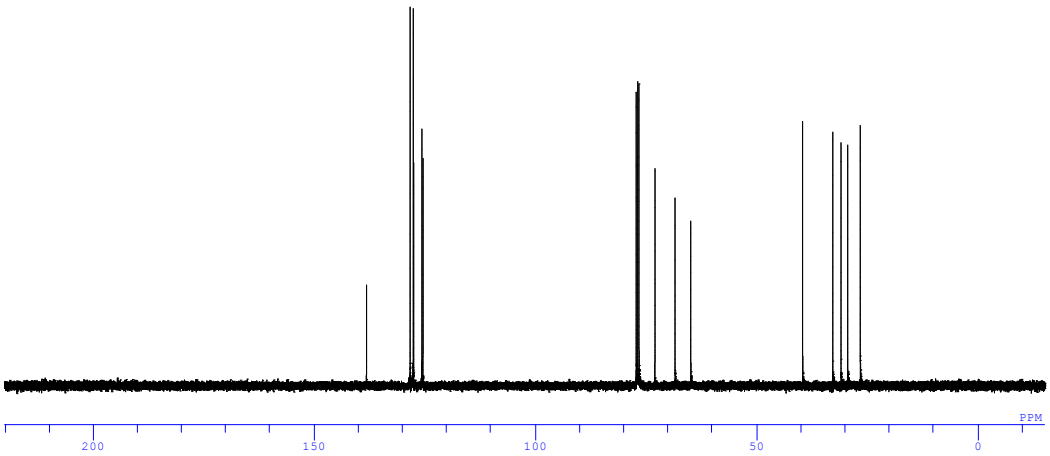
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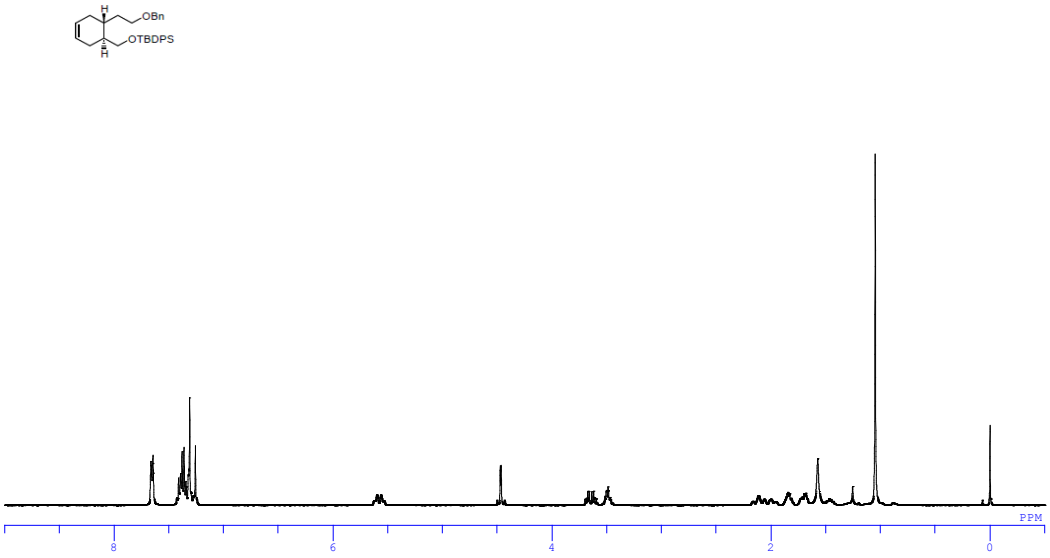
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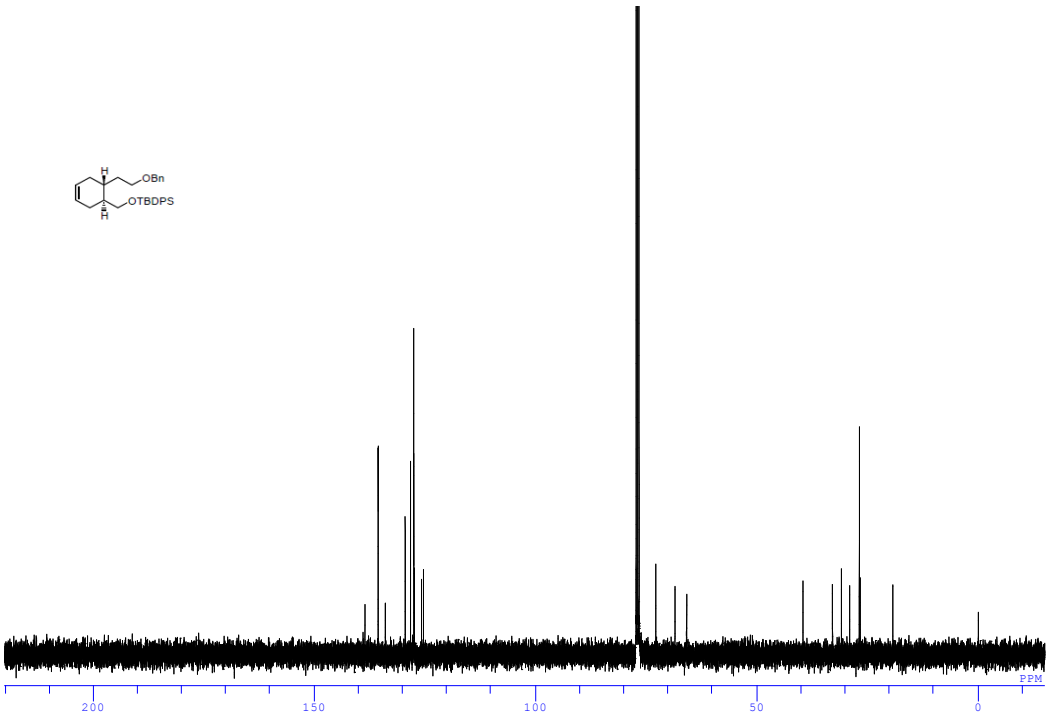
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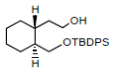

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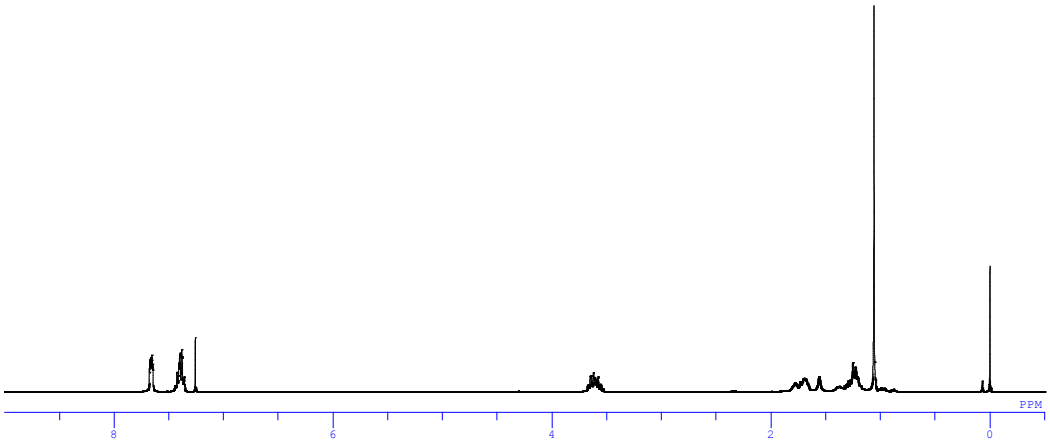

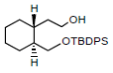

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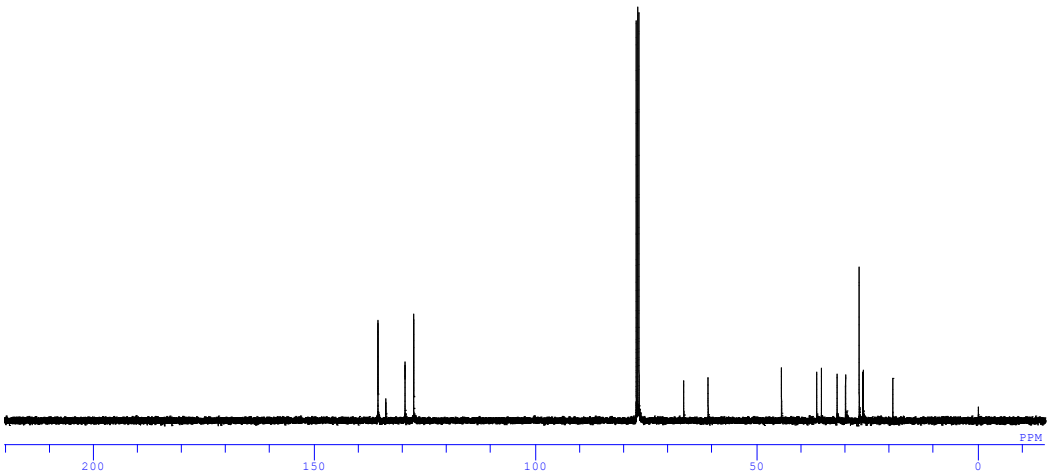

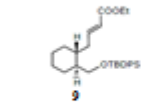

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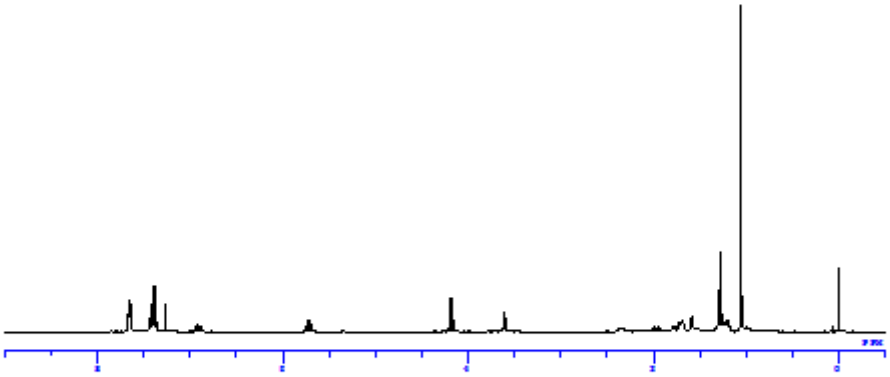

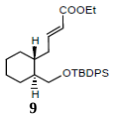

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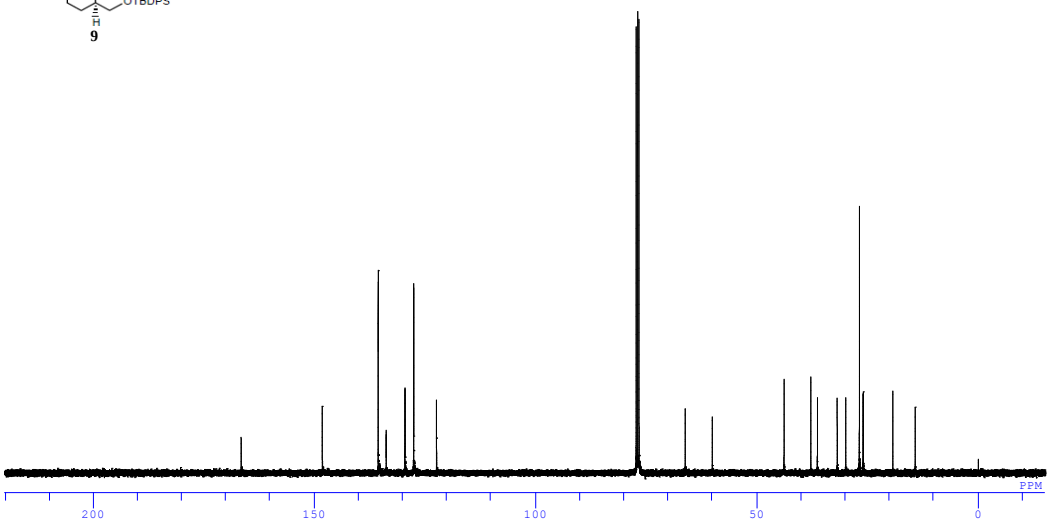

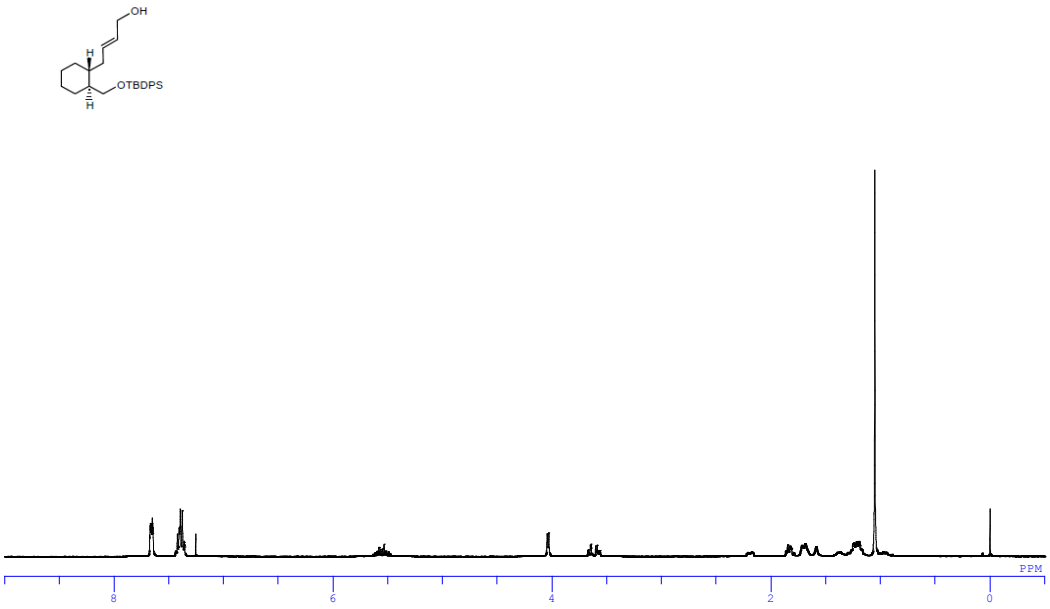
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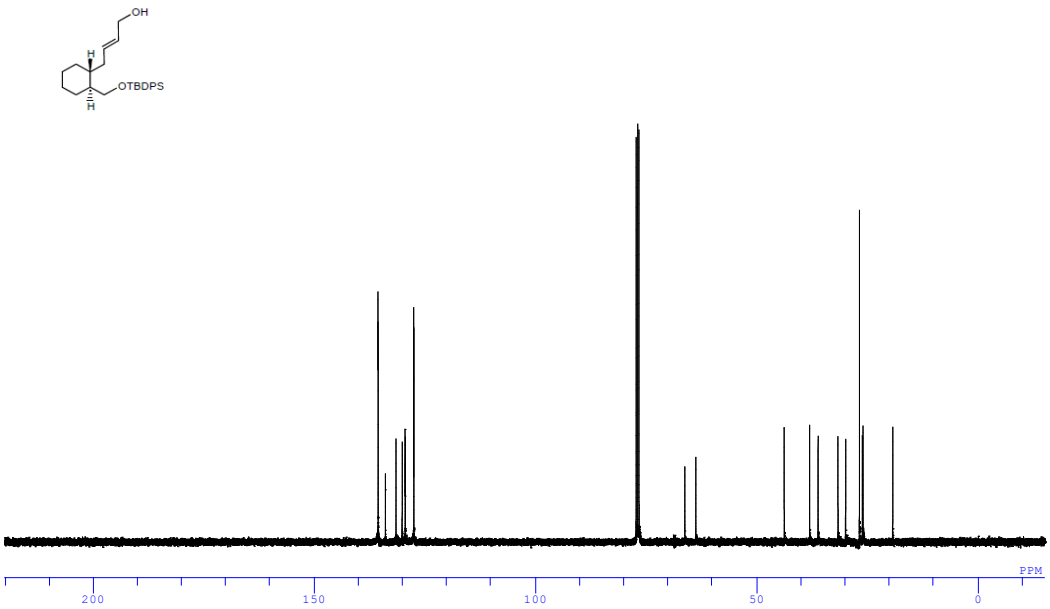
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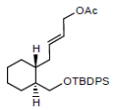

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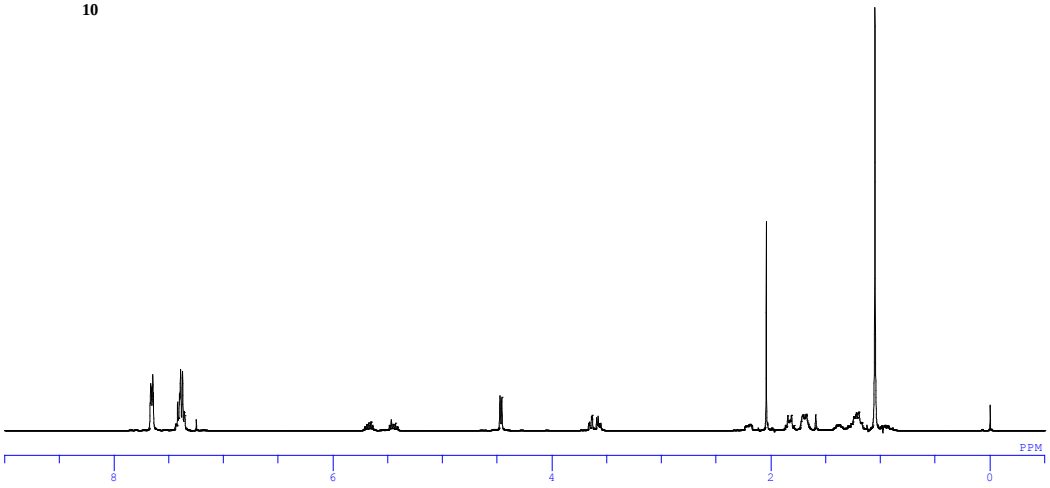

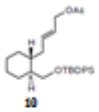

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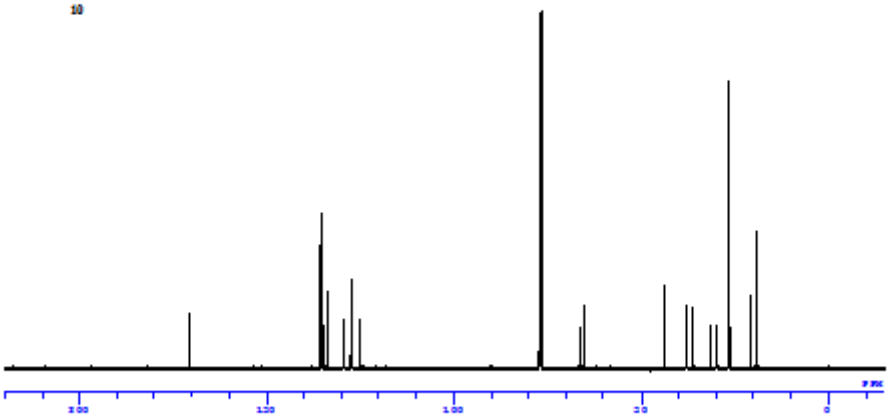

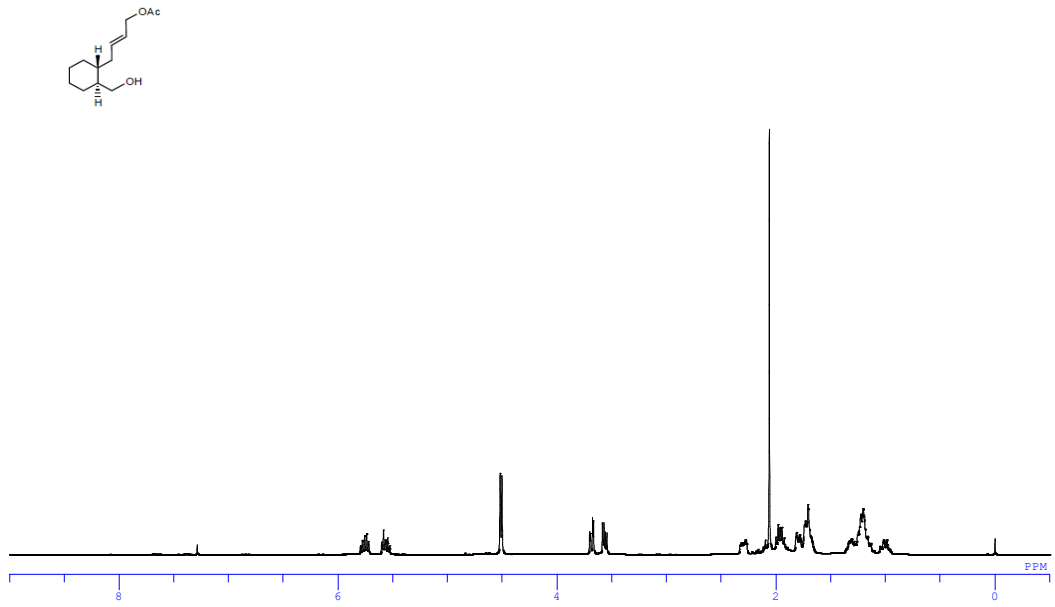
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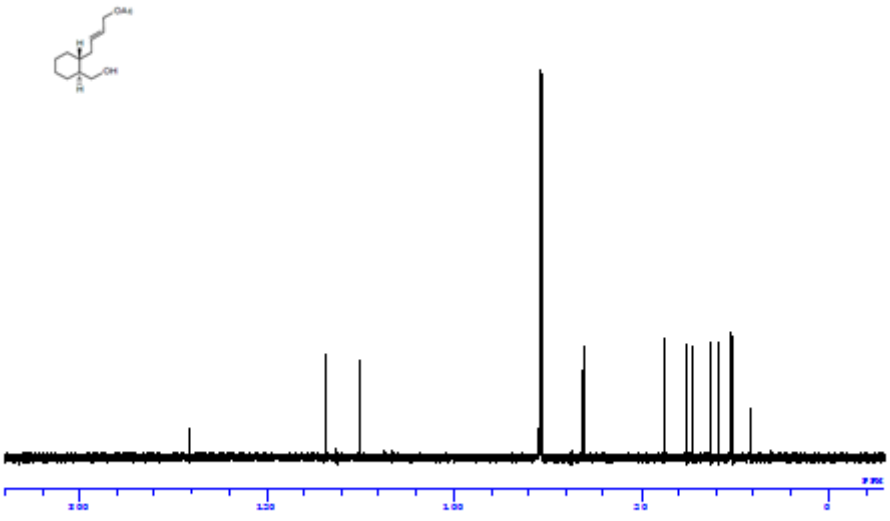

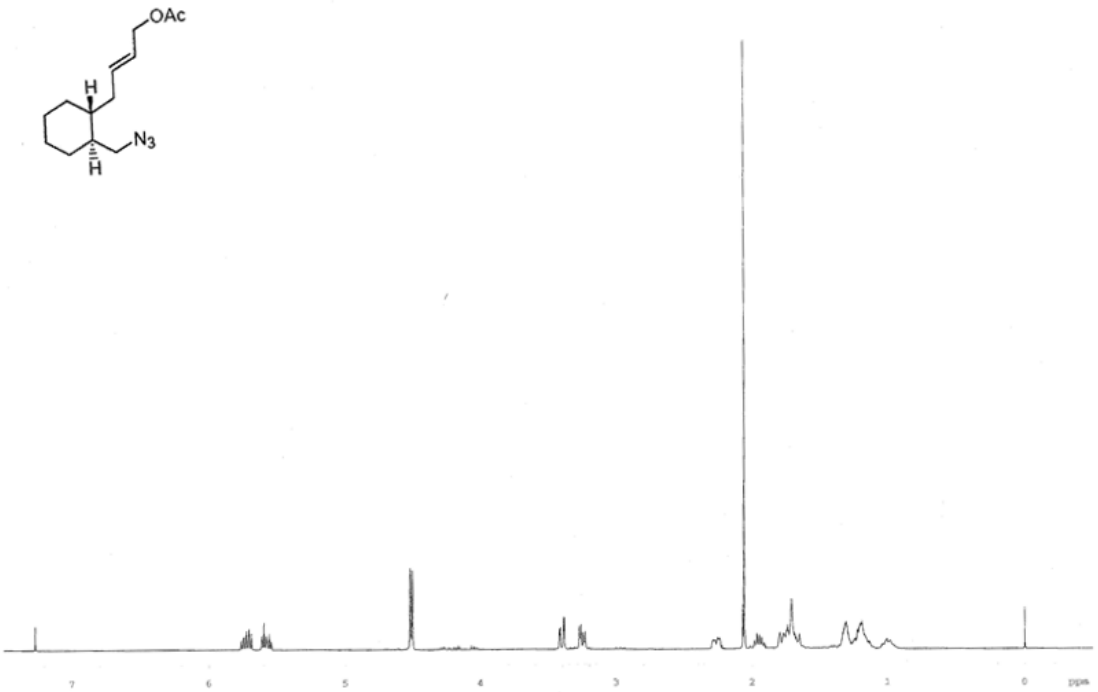
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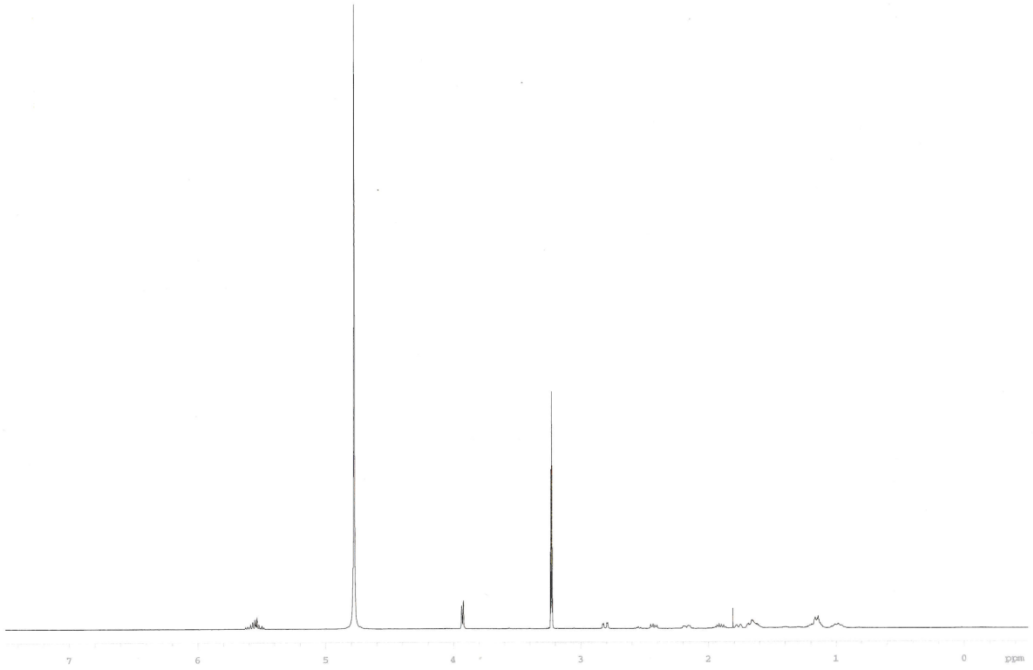
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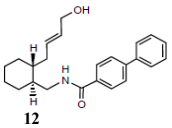

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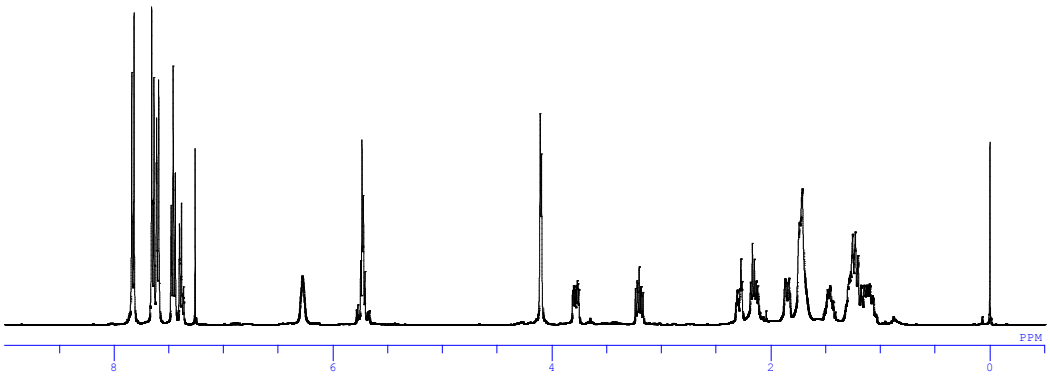

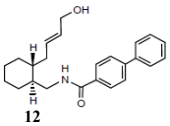

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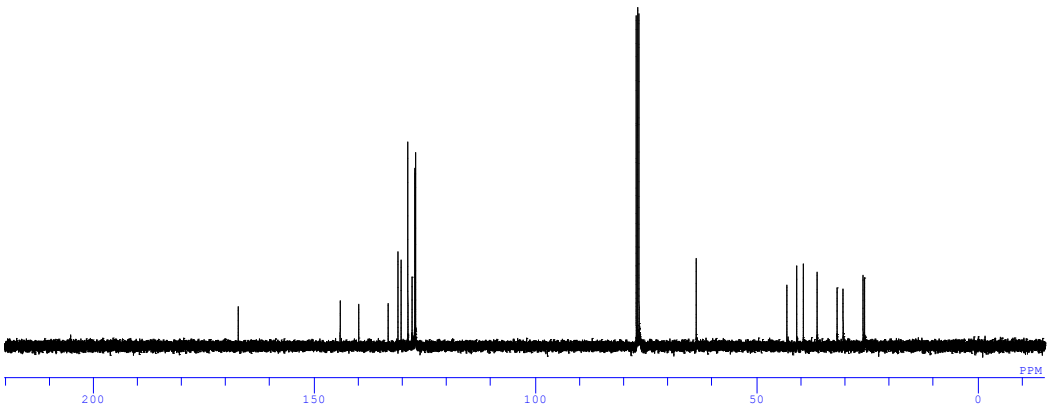

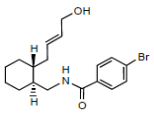

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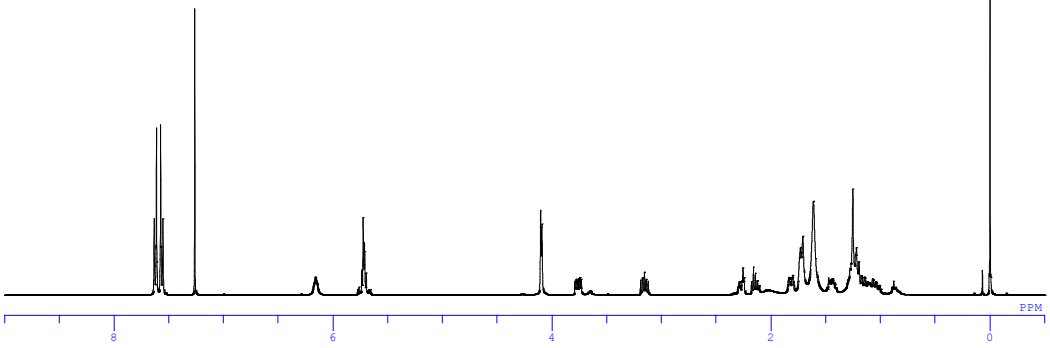

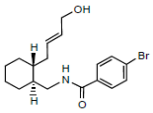

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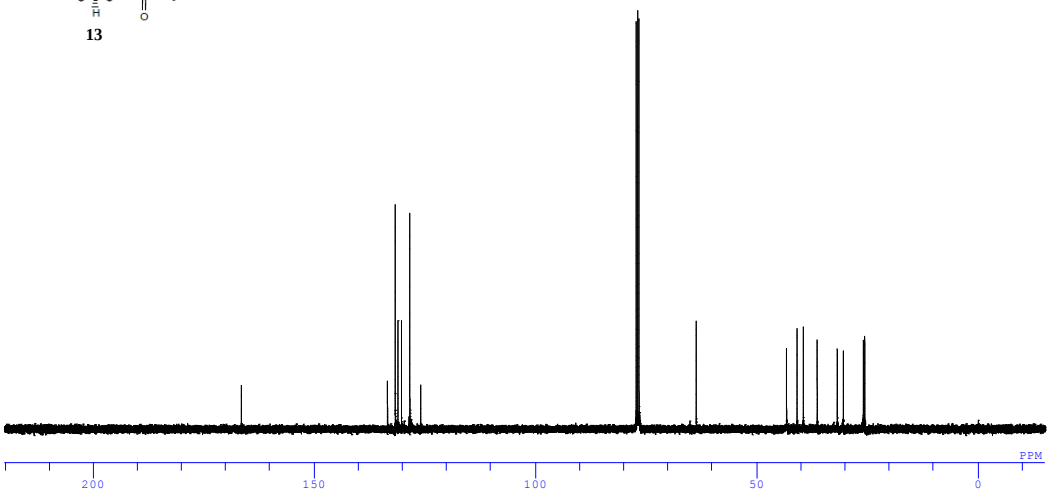

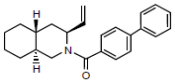

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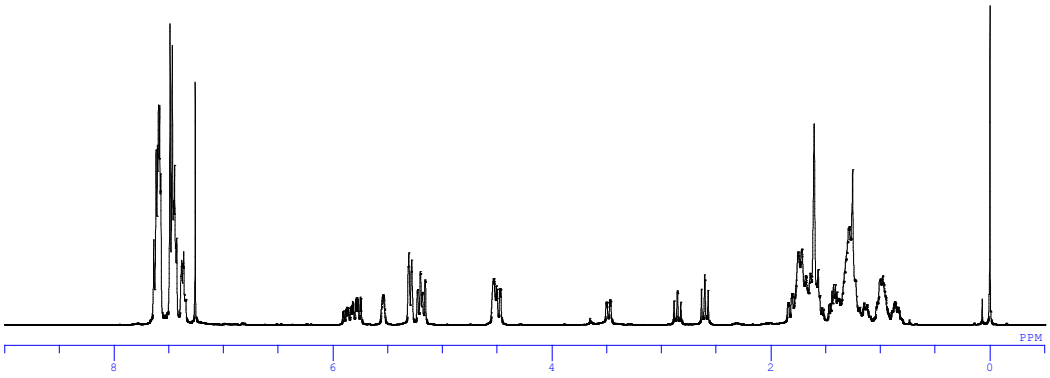

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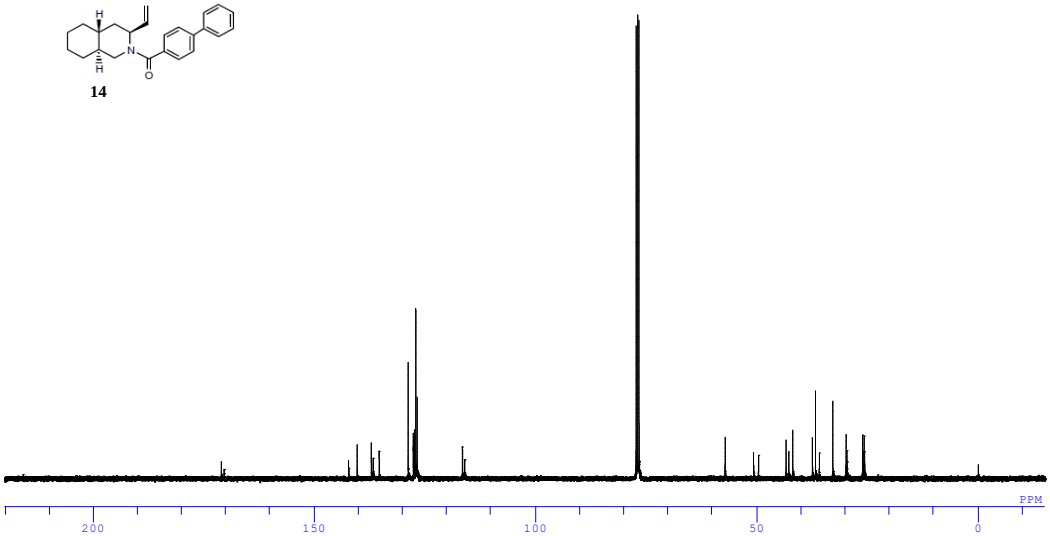

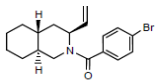

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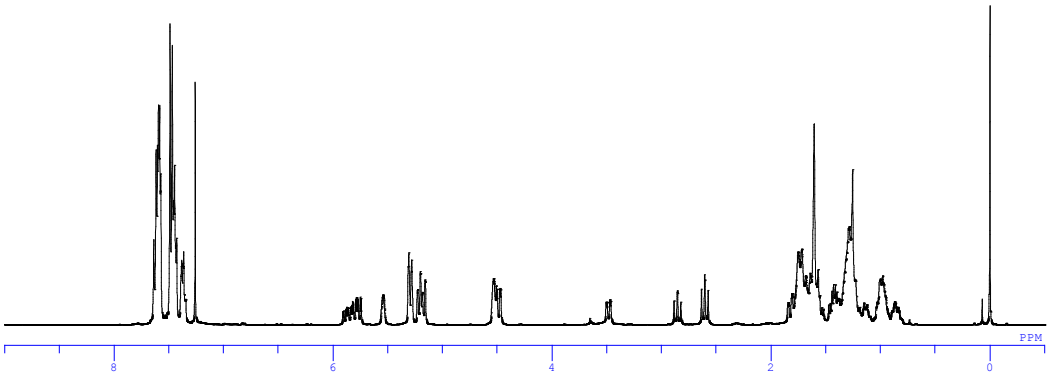

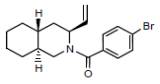

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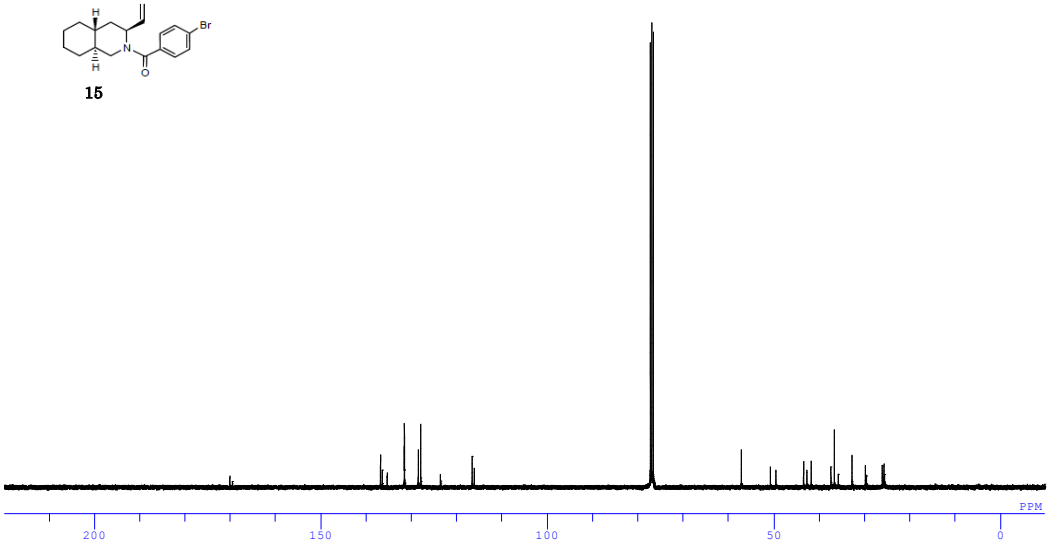

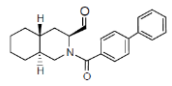

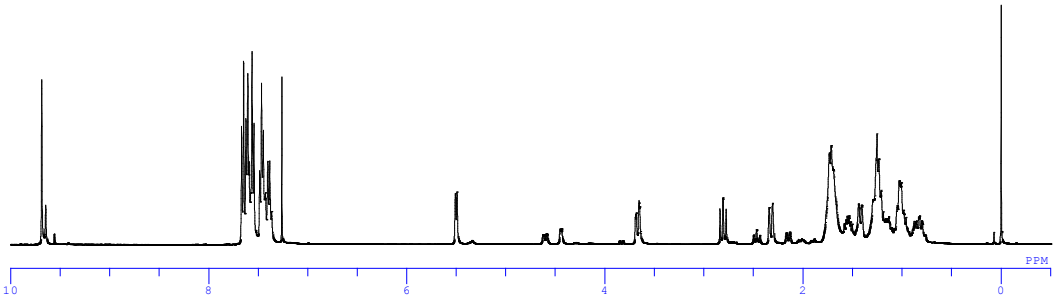

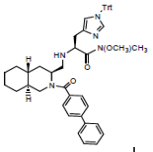

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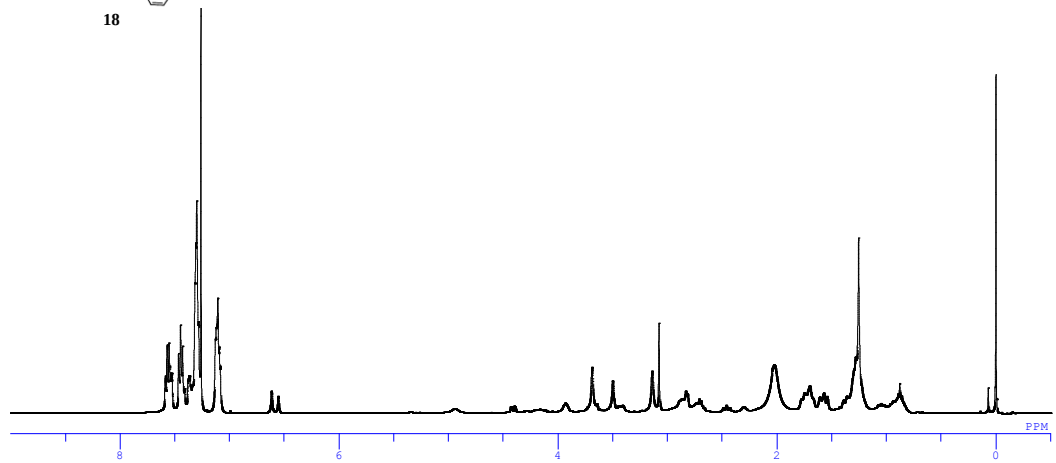

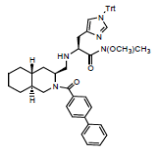

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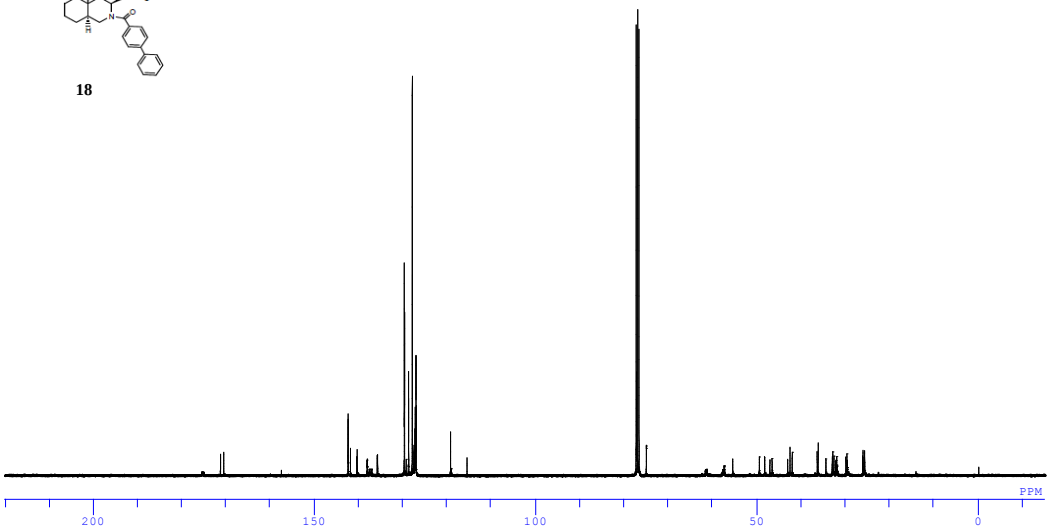

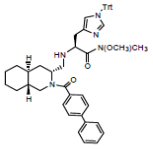

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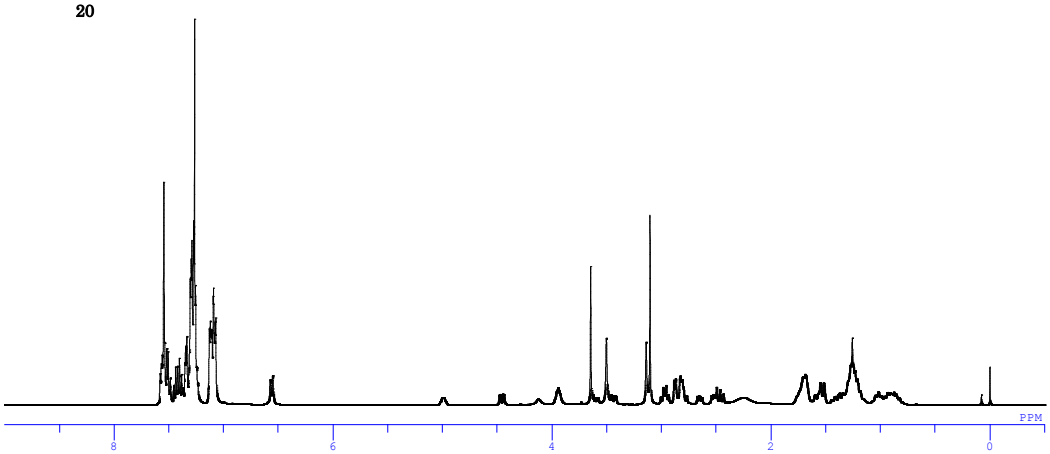

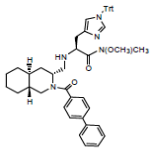

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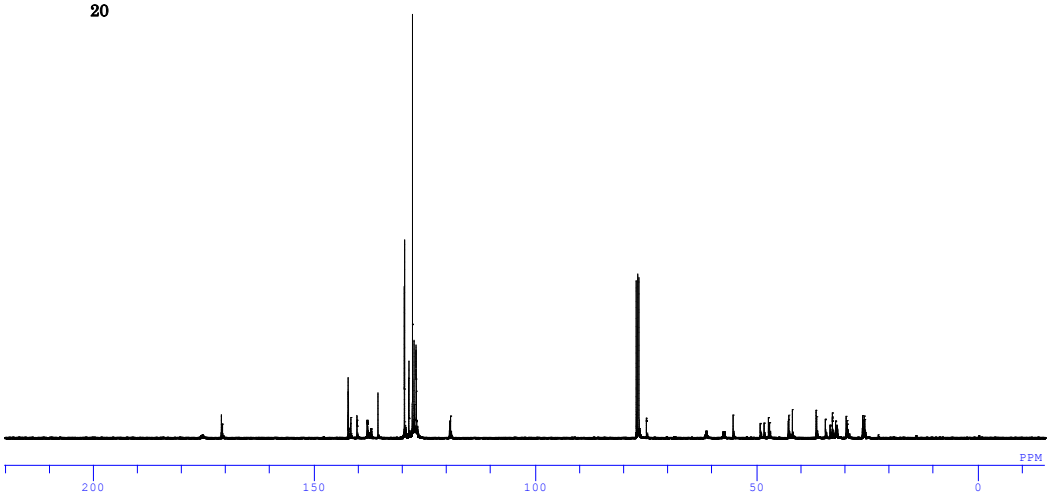

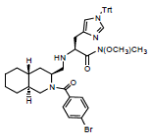

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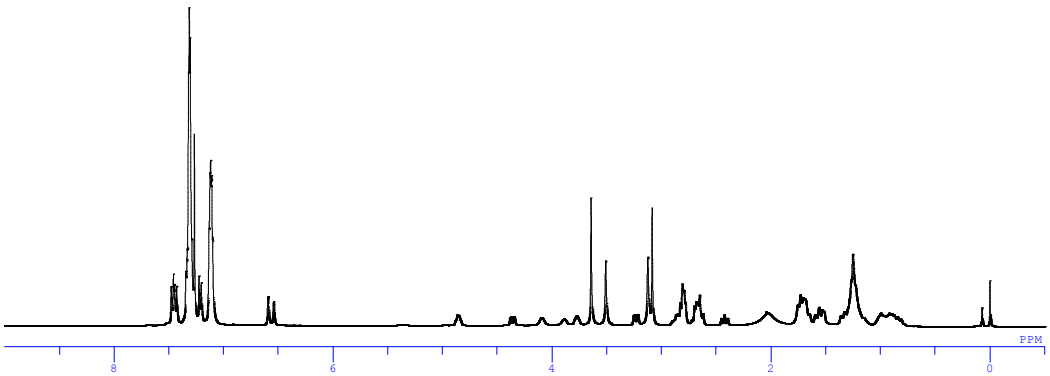

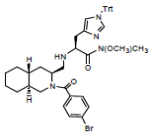

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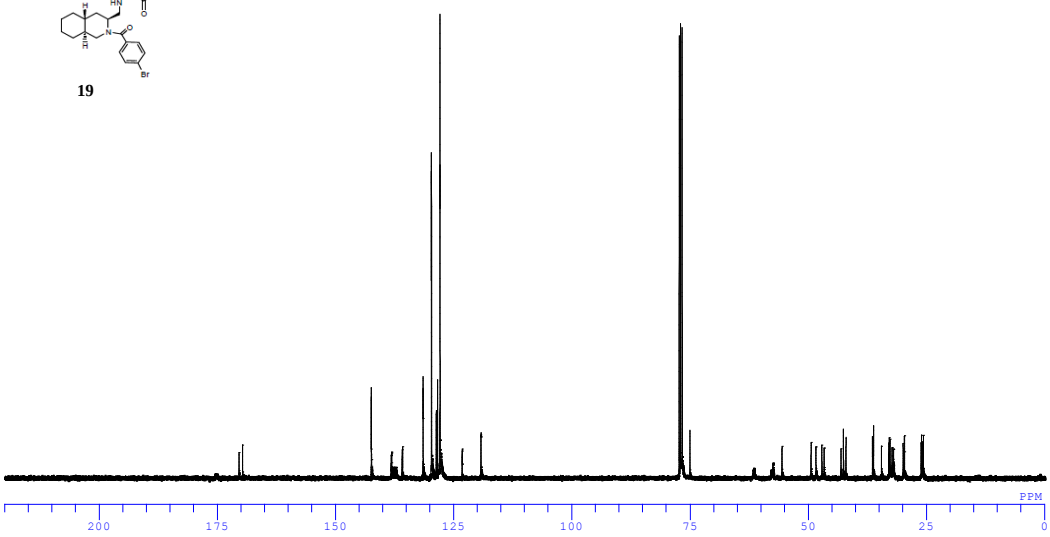

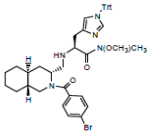

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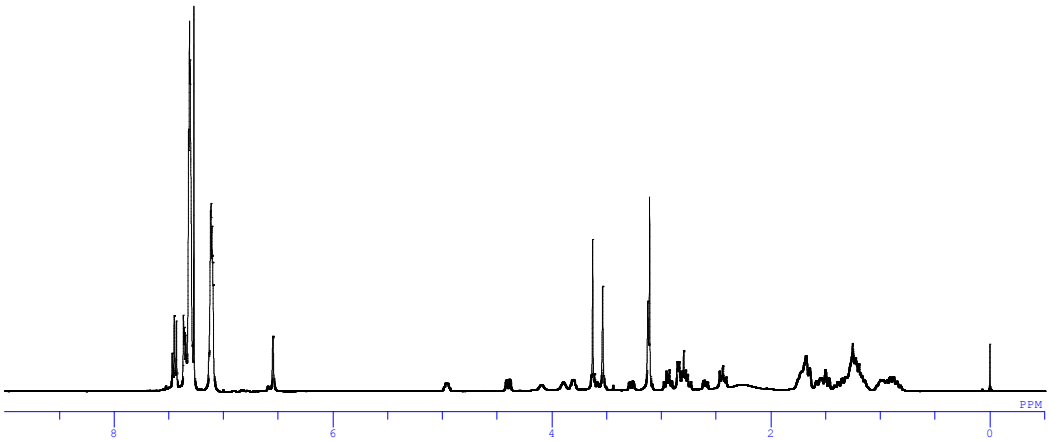

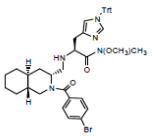

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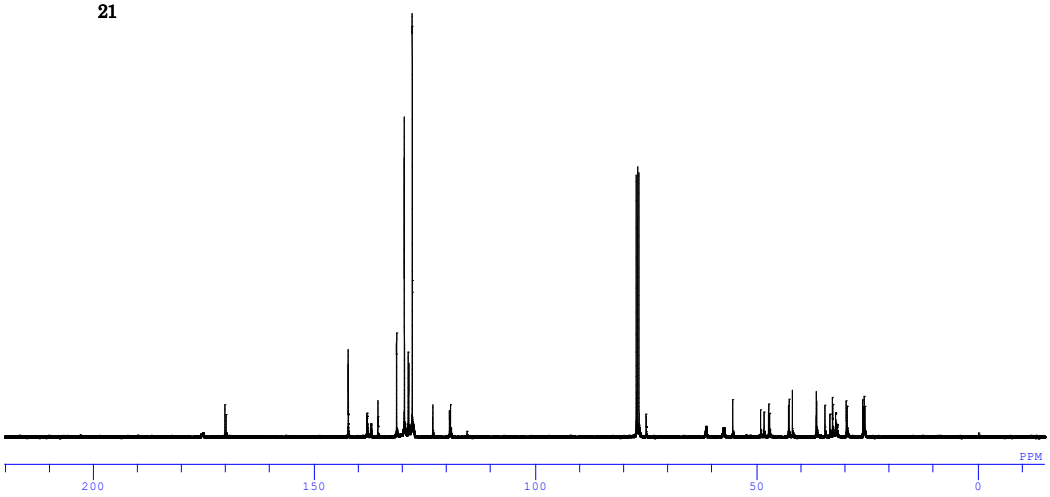

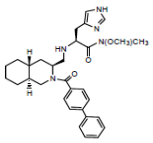

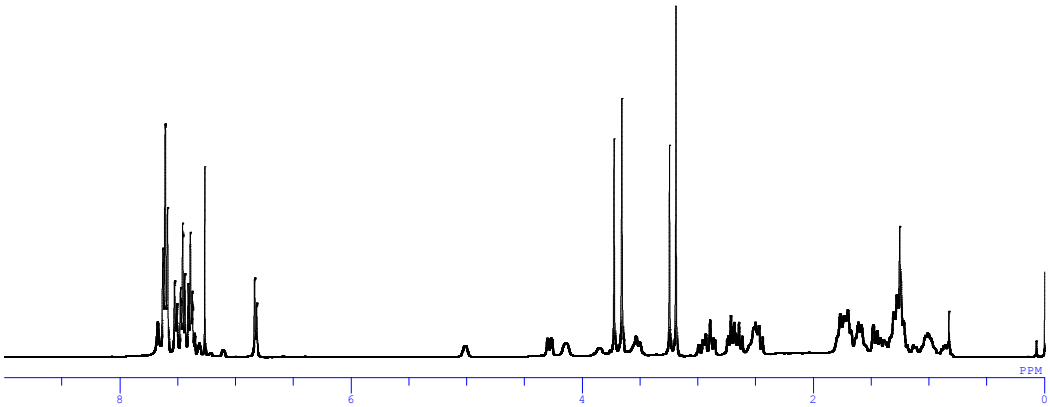

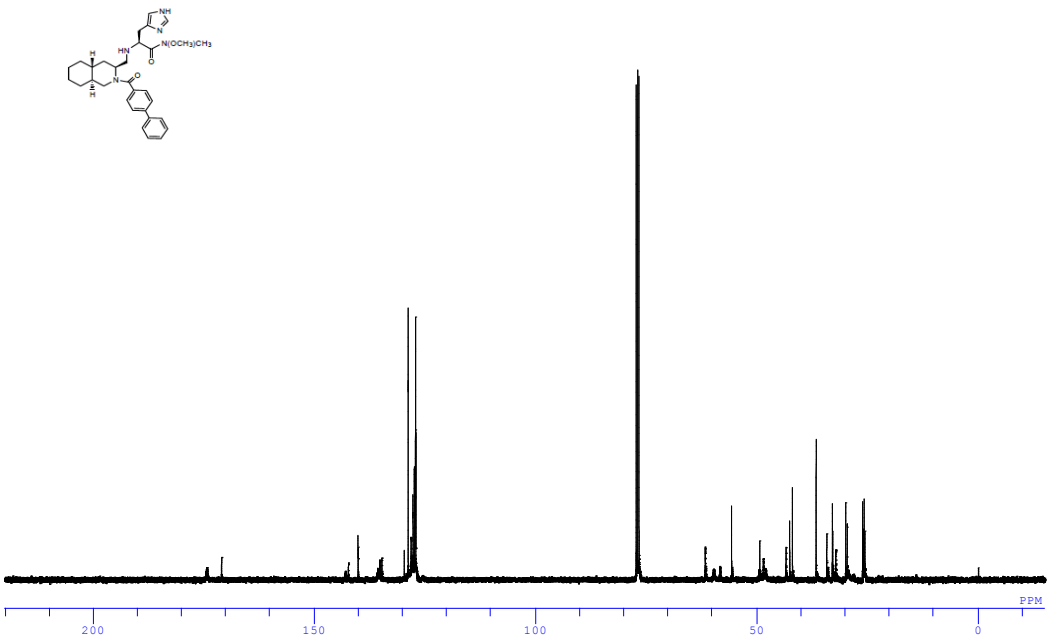
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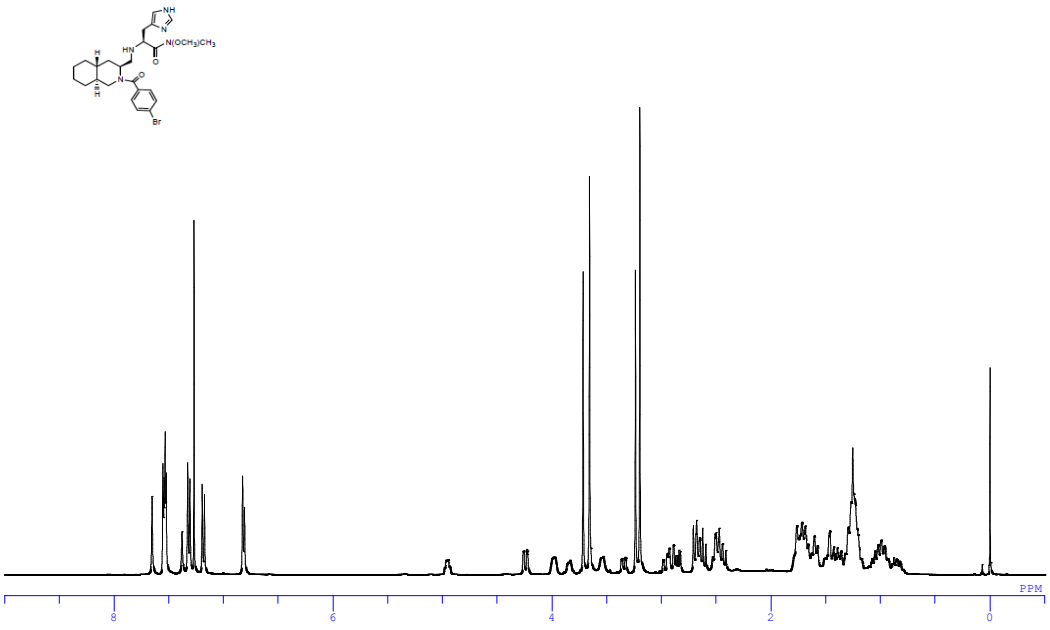
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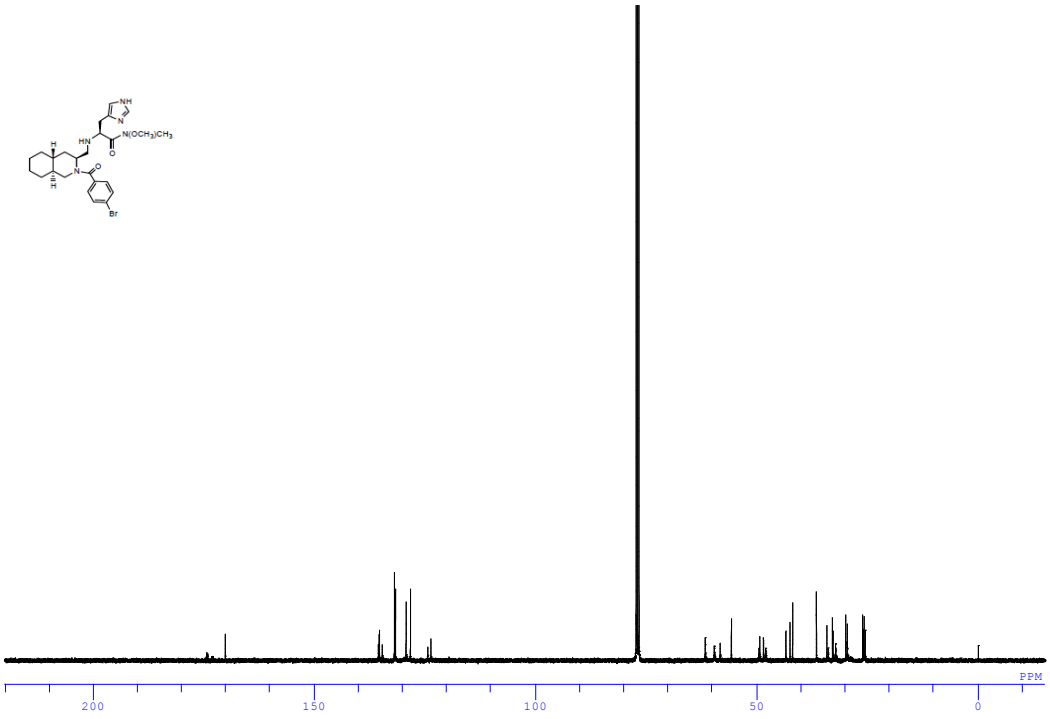
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Br
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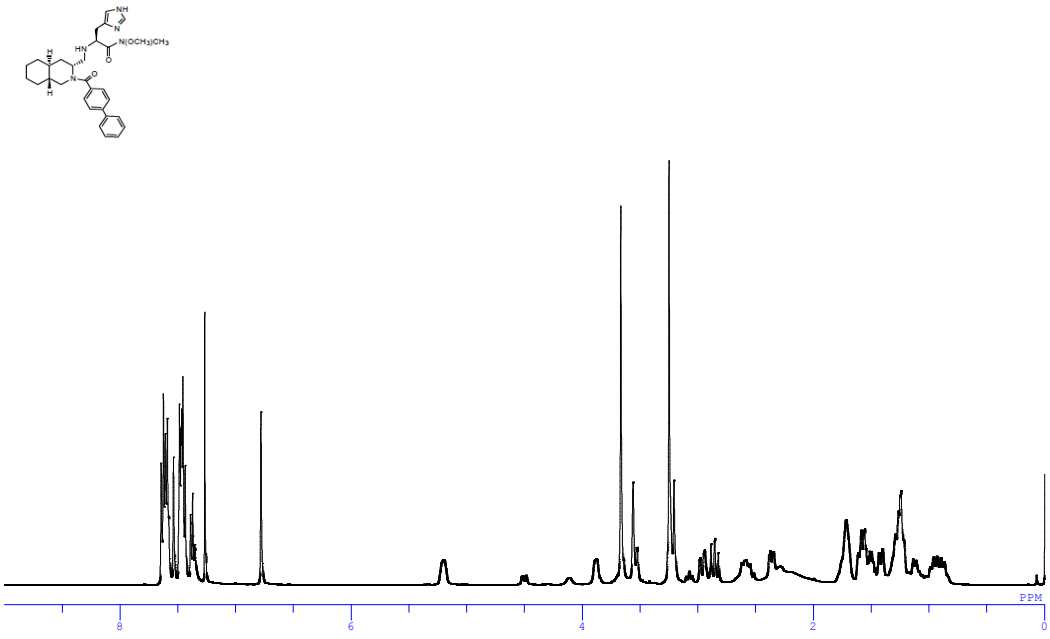
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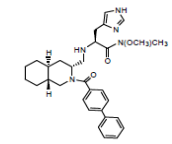
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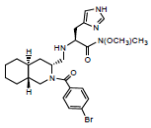
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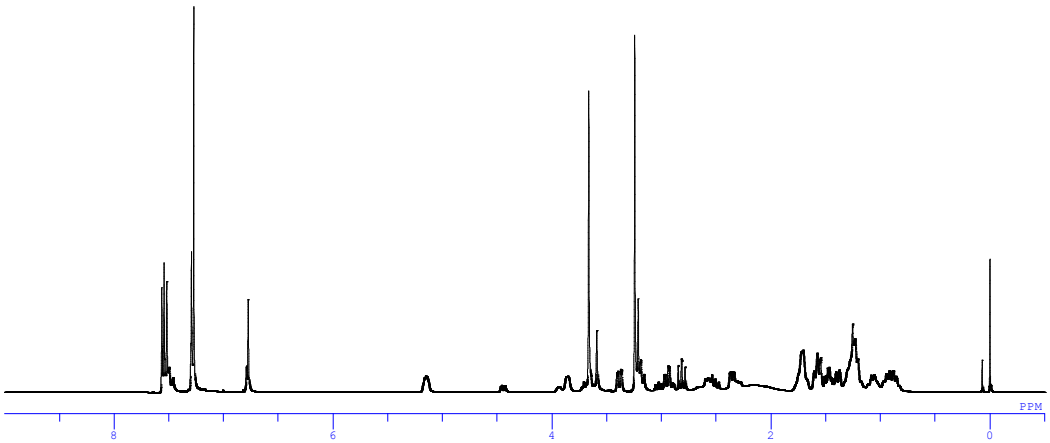
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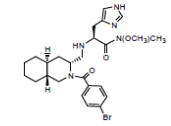

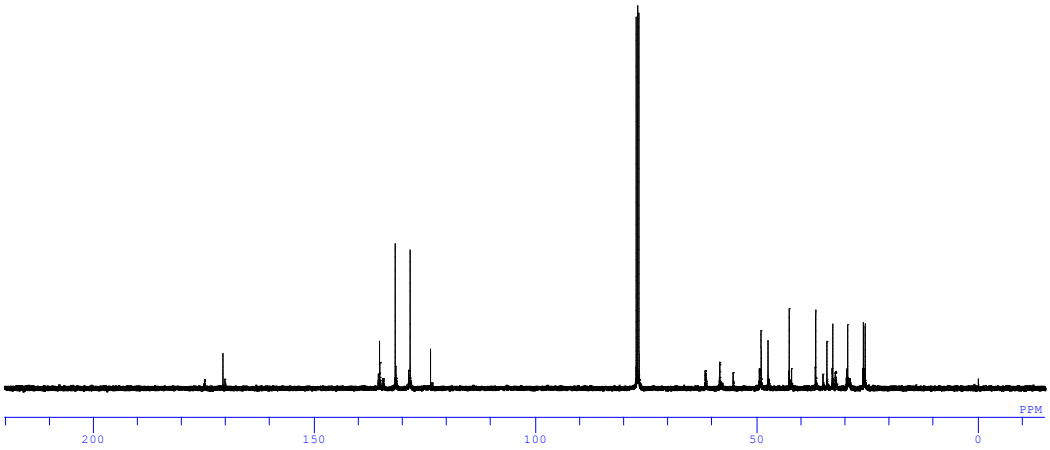

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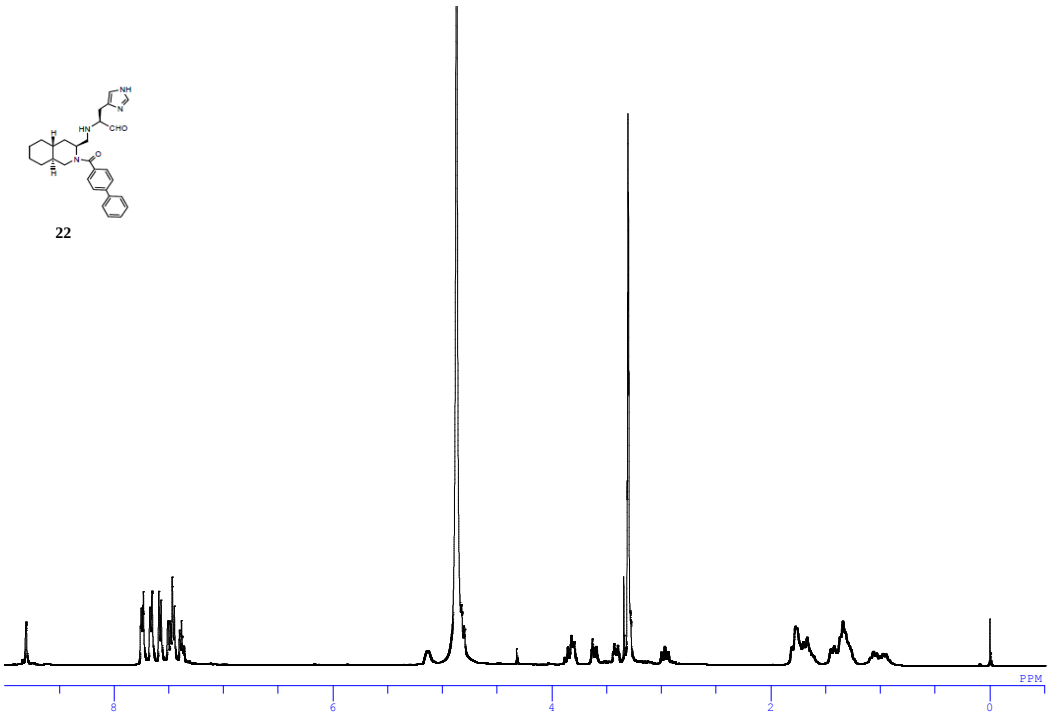

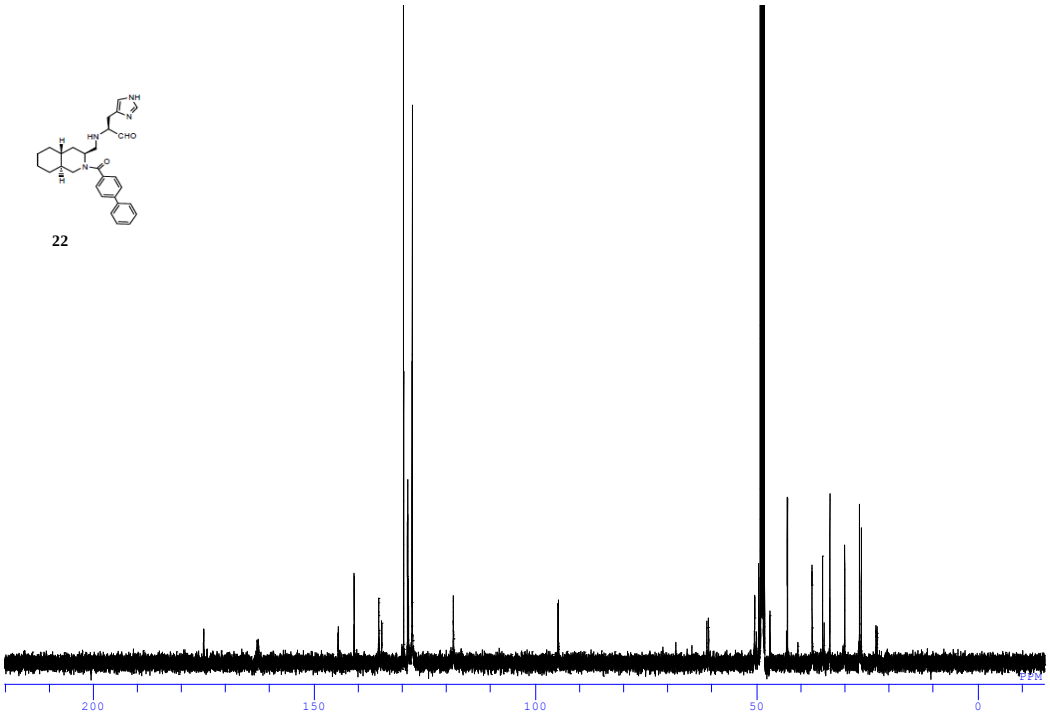

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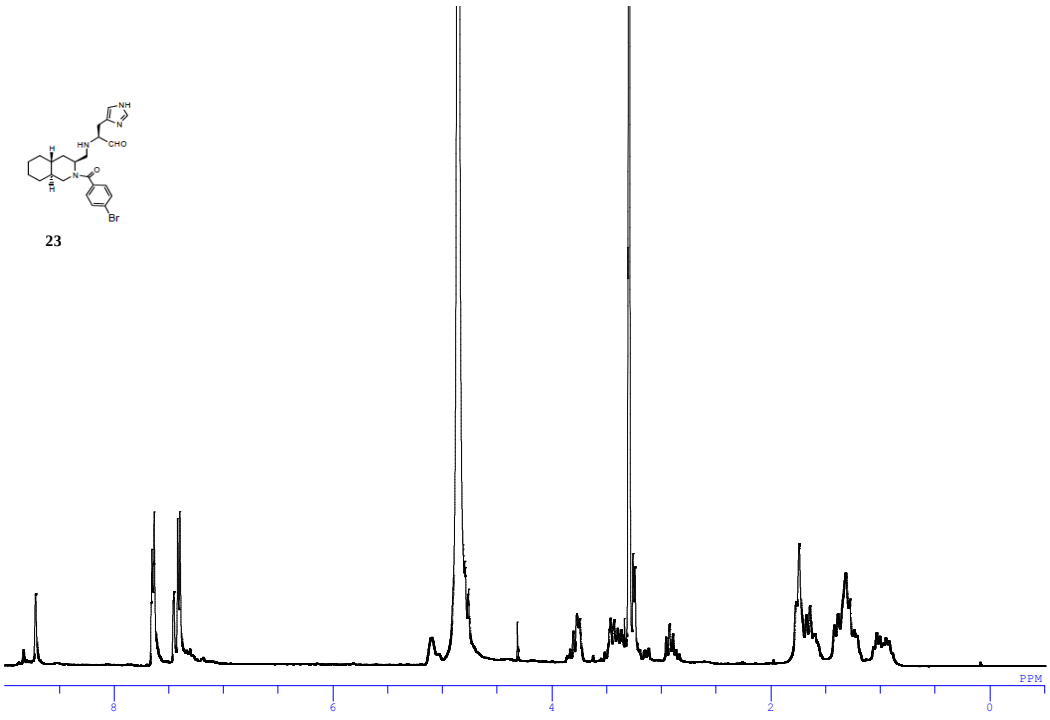

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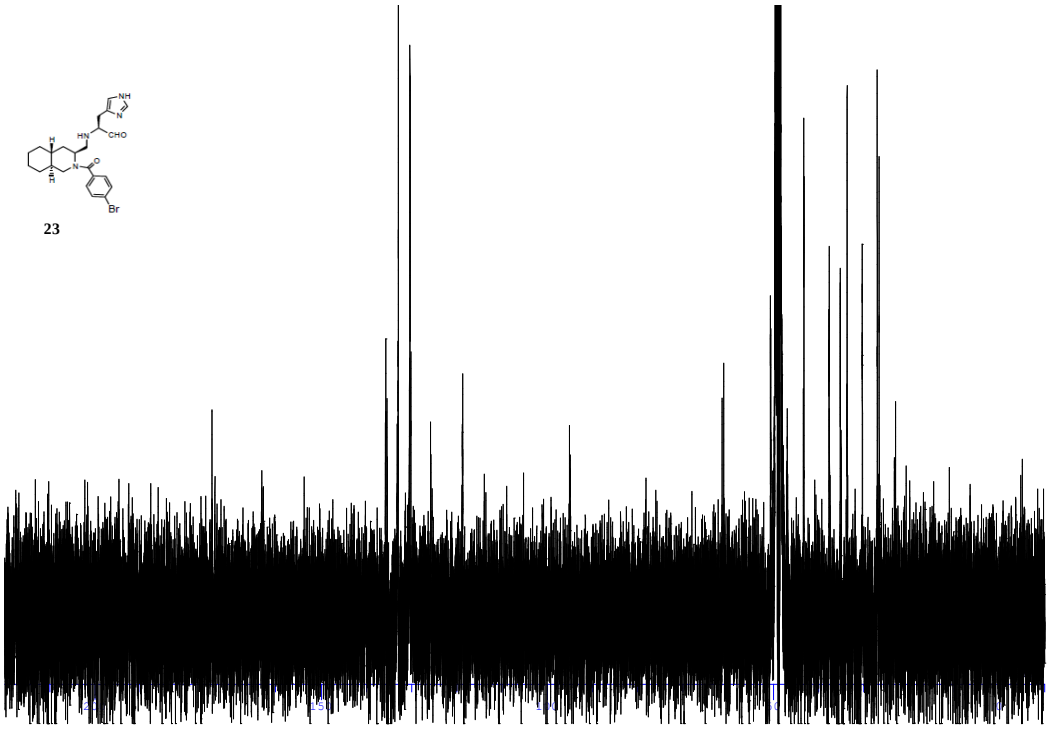

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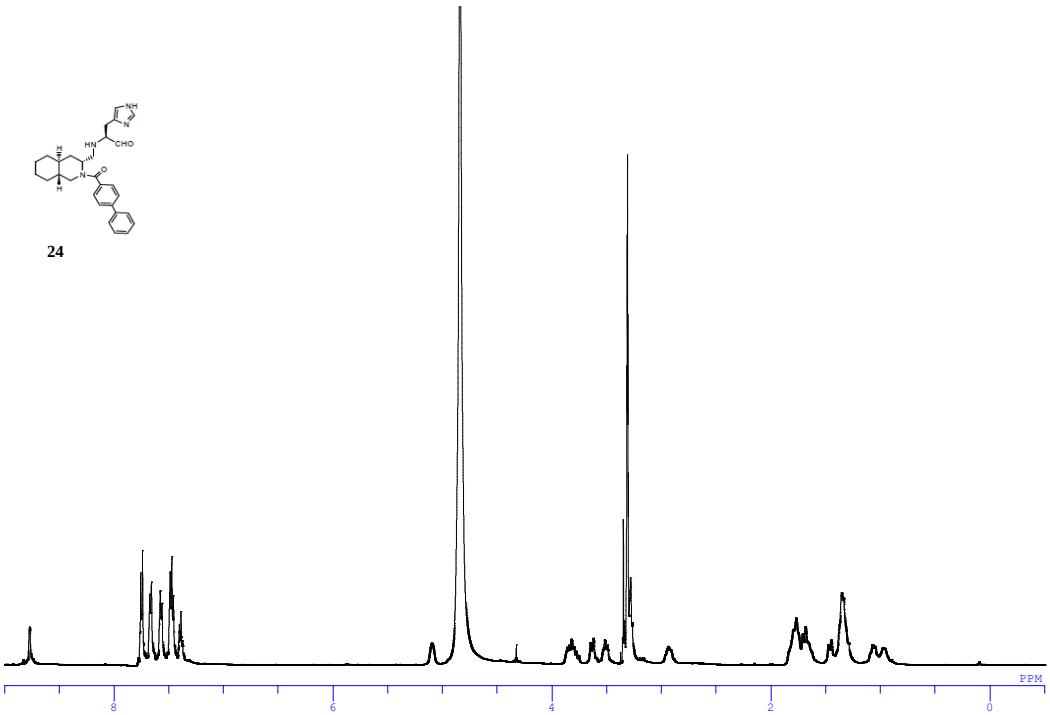

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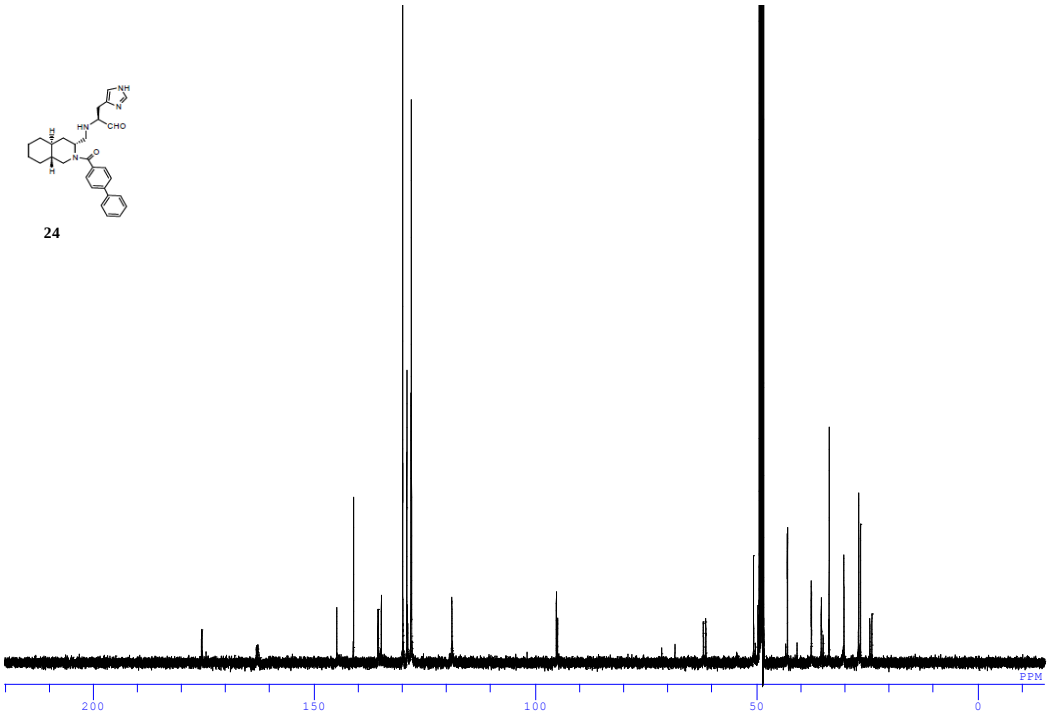

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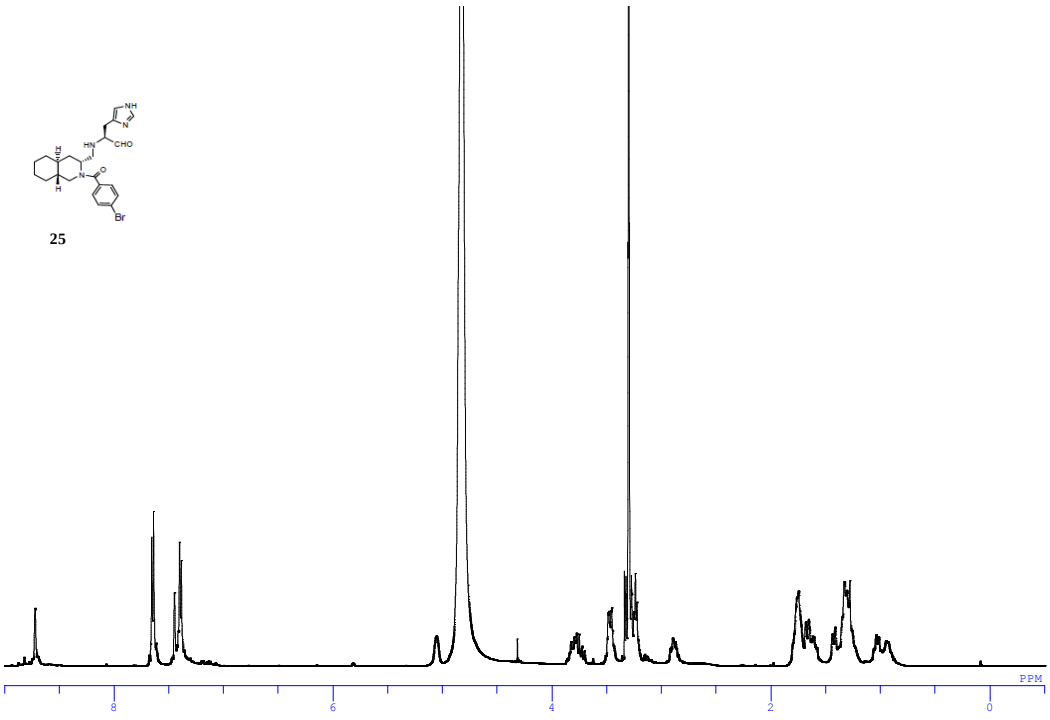

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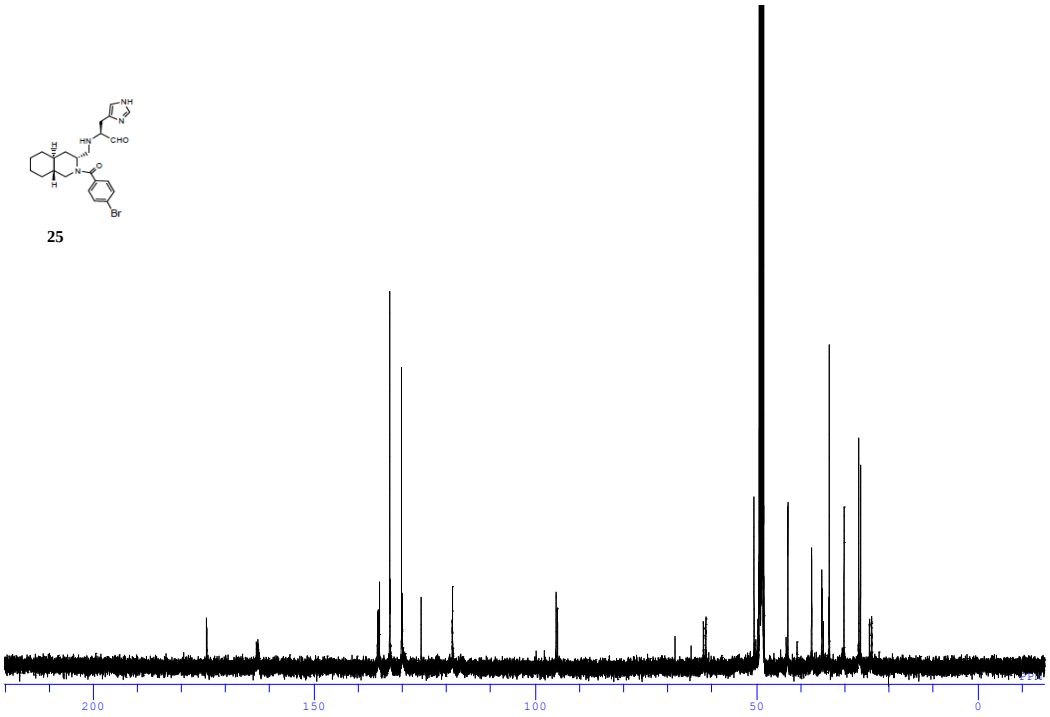
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100
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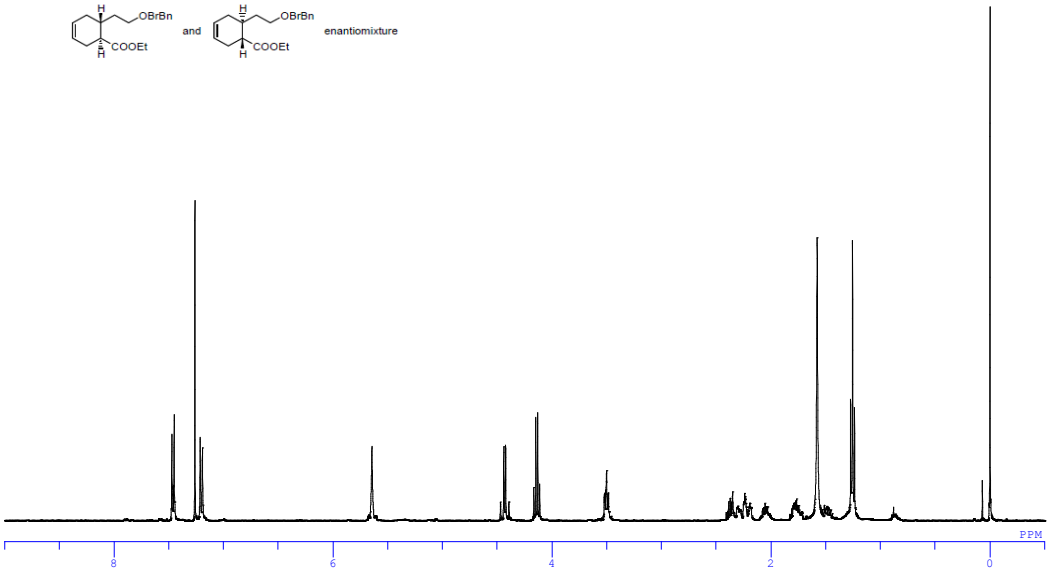
0
PPM

OBrBn
COOEt
and
OBrBn
COOEt
enantiomixture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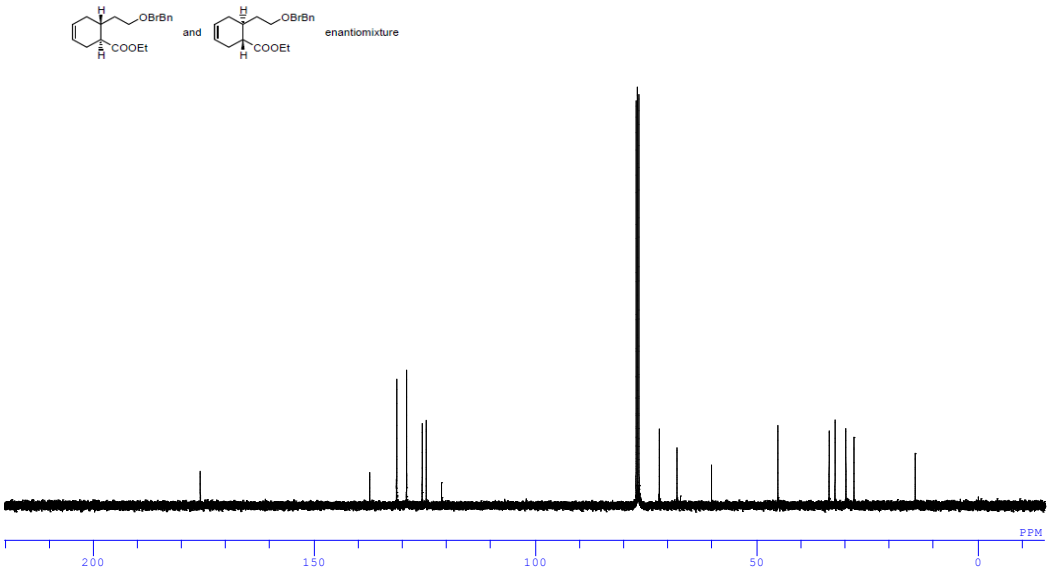
PPM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COOEt
and
OBrBn
COOEt
enantiomixture
PPM
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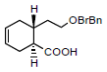
150
100
50
0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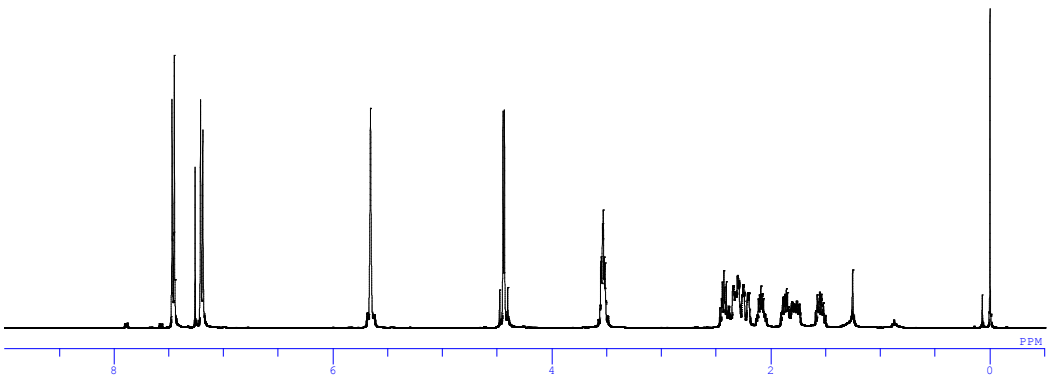
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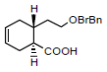

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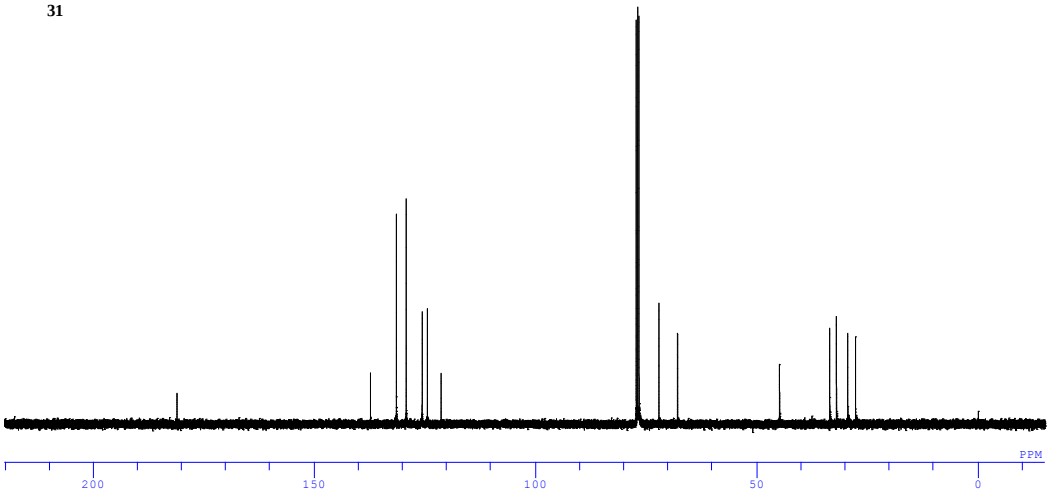

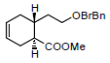

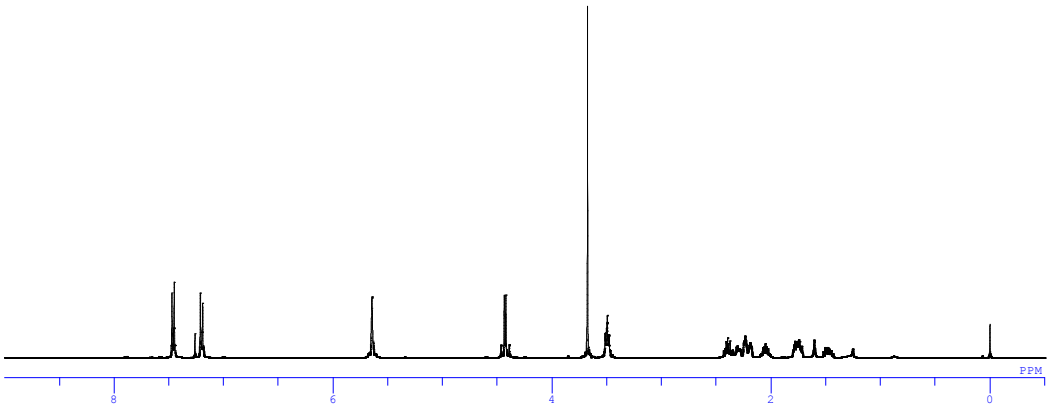

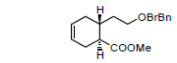
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COOMe
H


PPM
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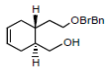
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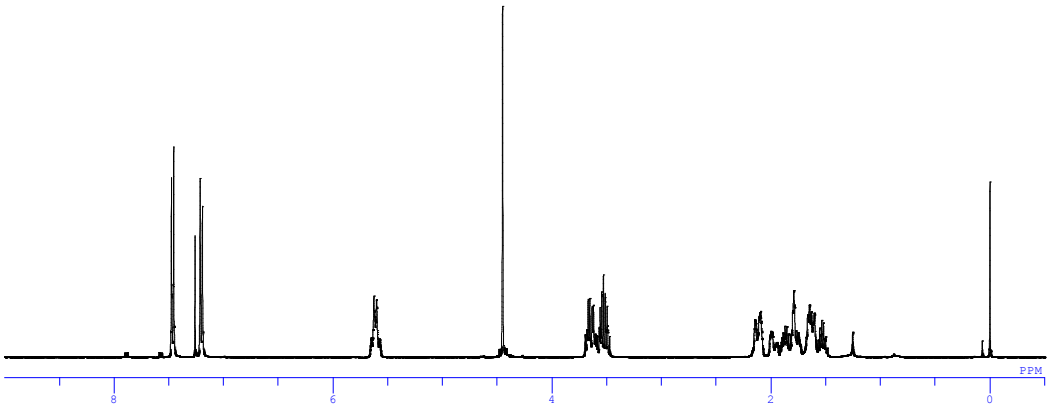
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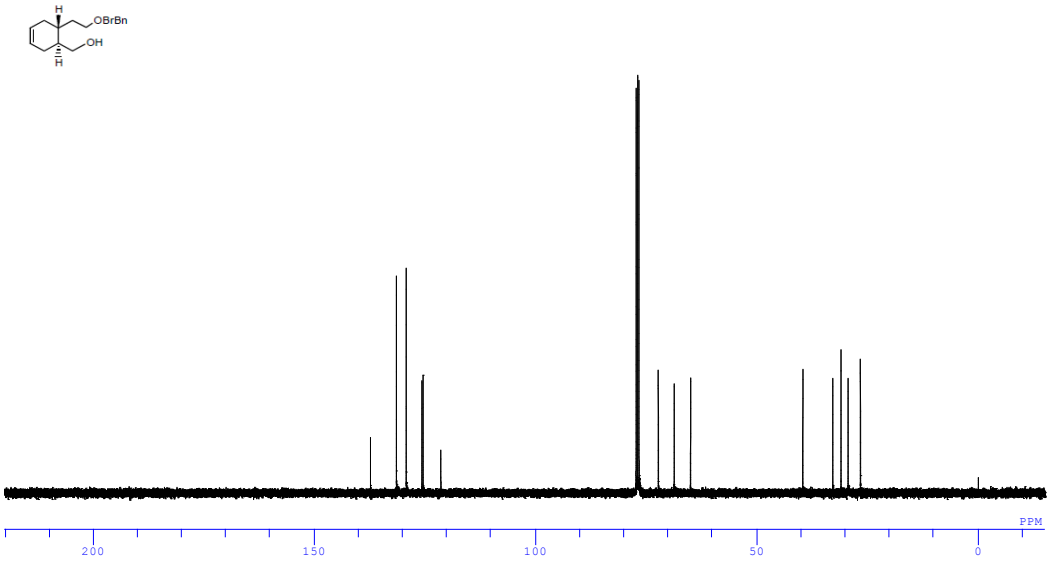
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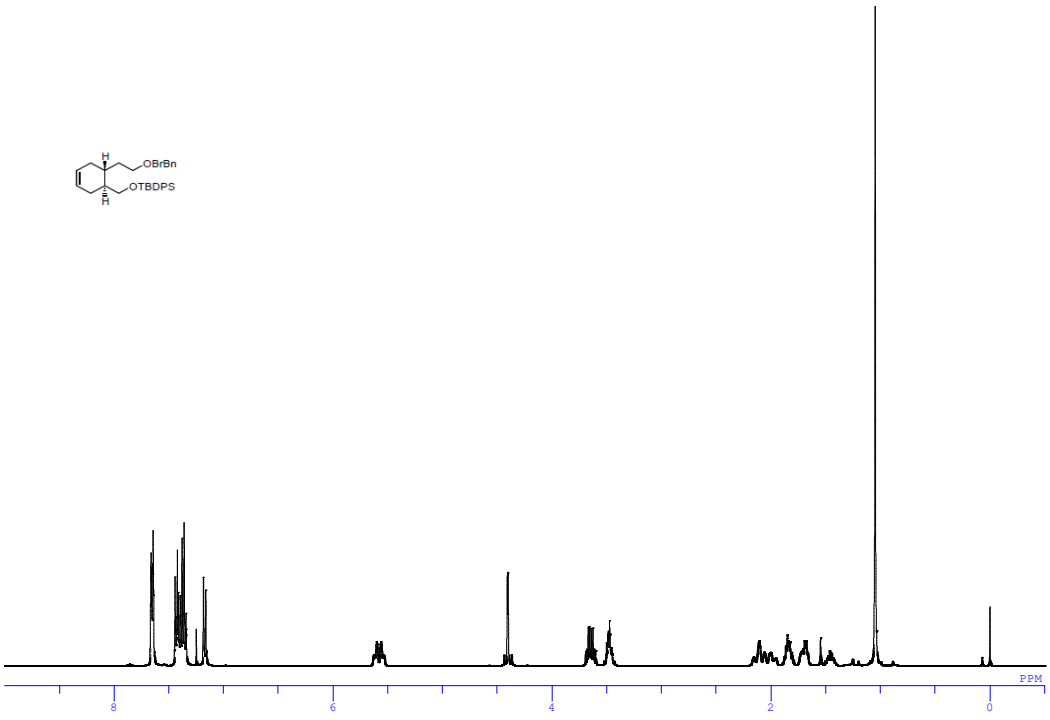
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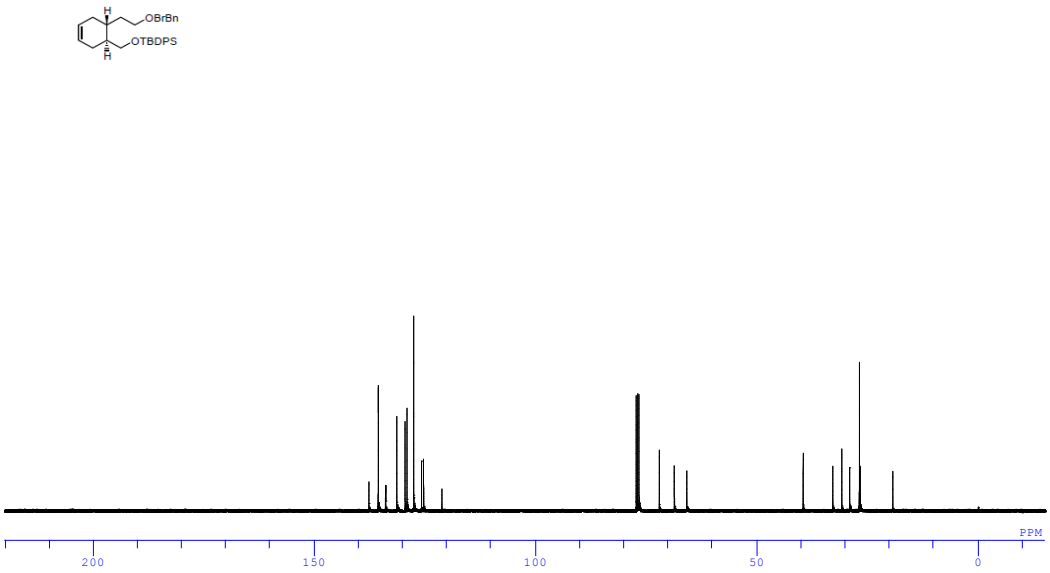
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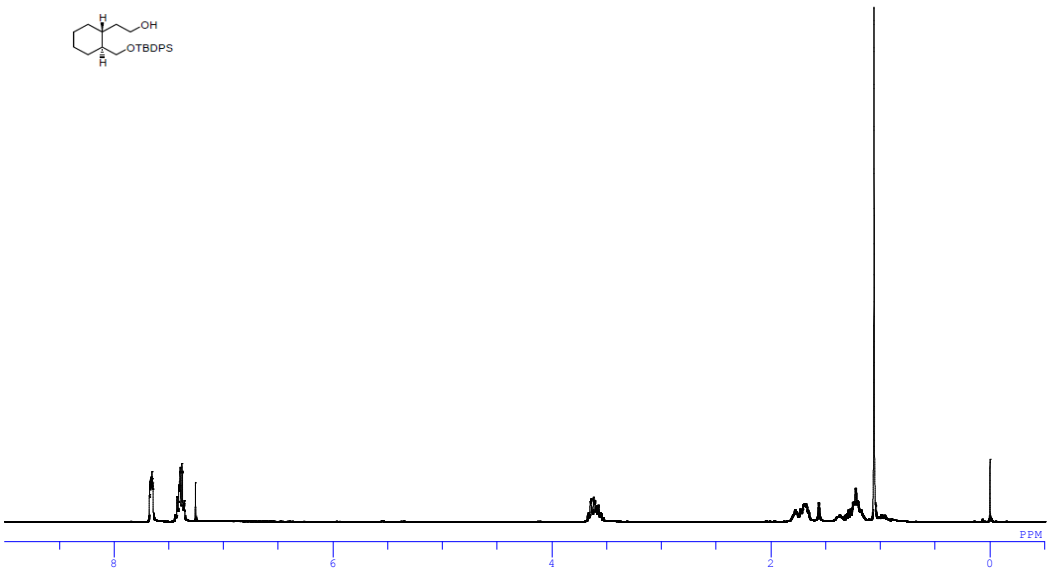
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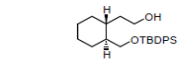

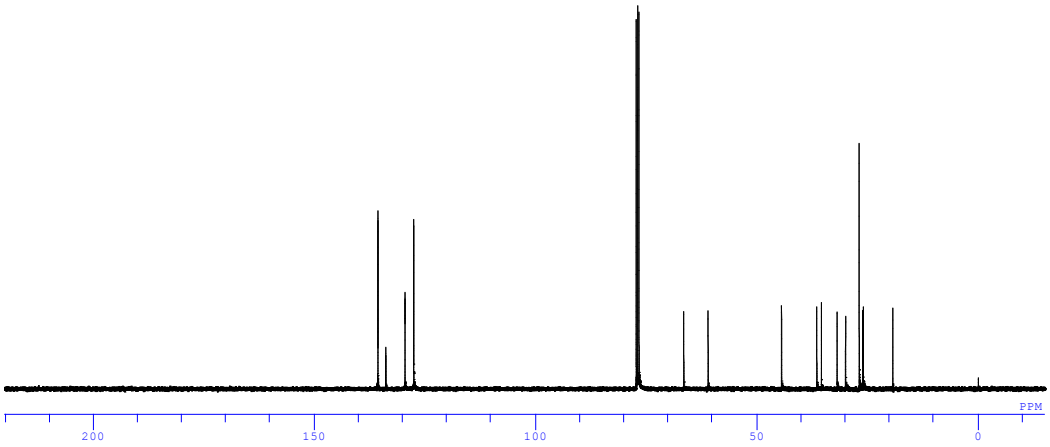

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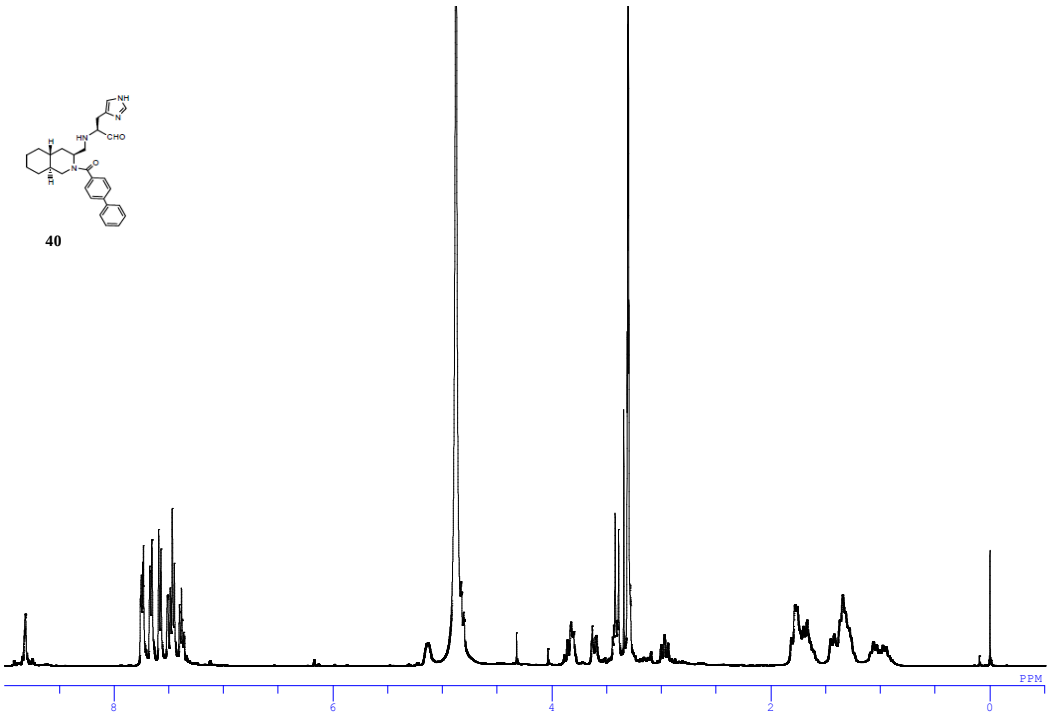

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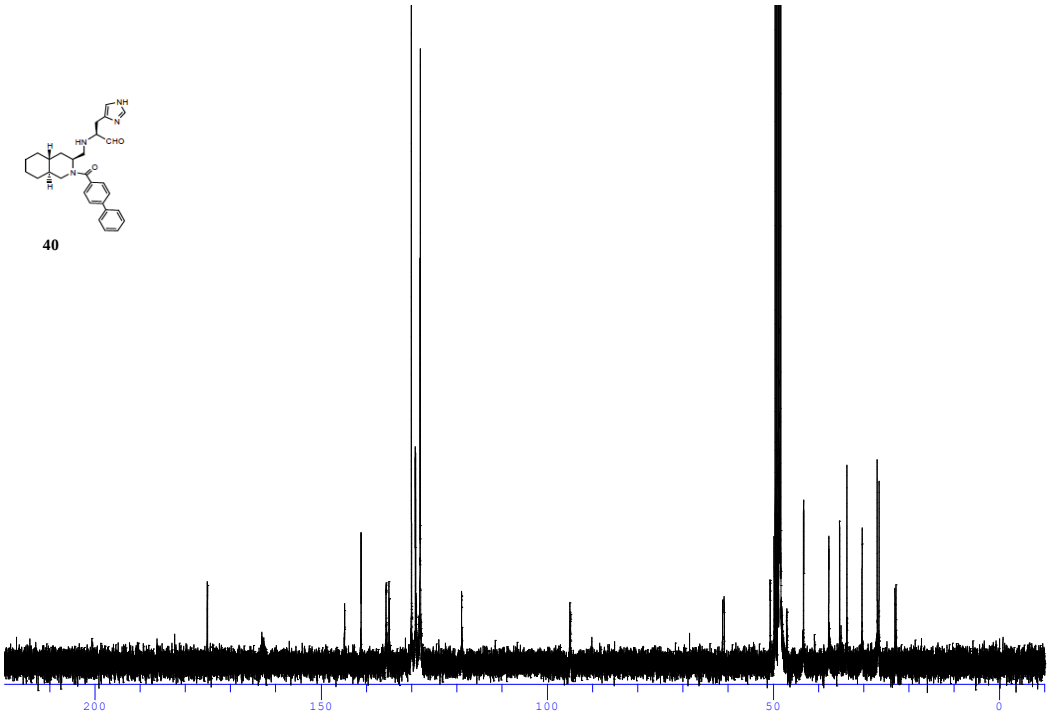

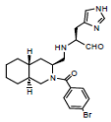

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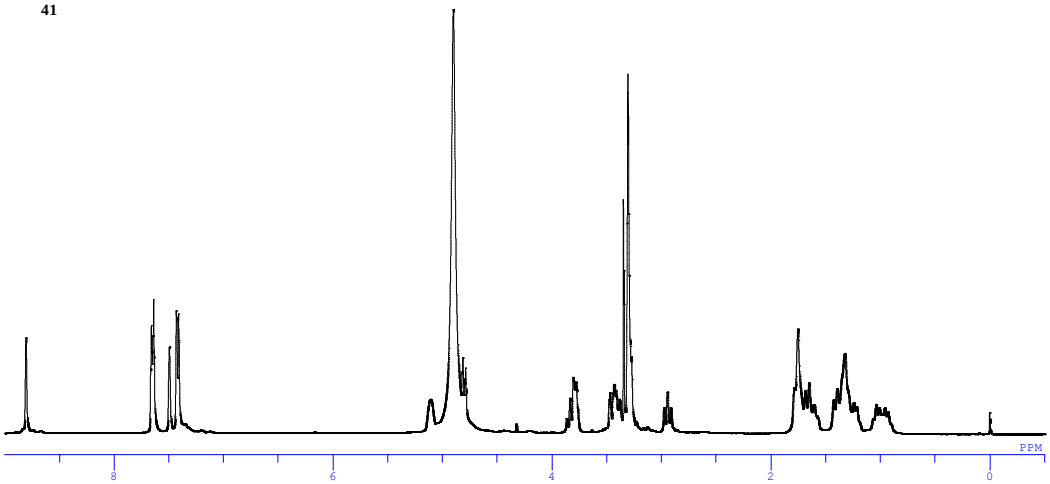

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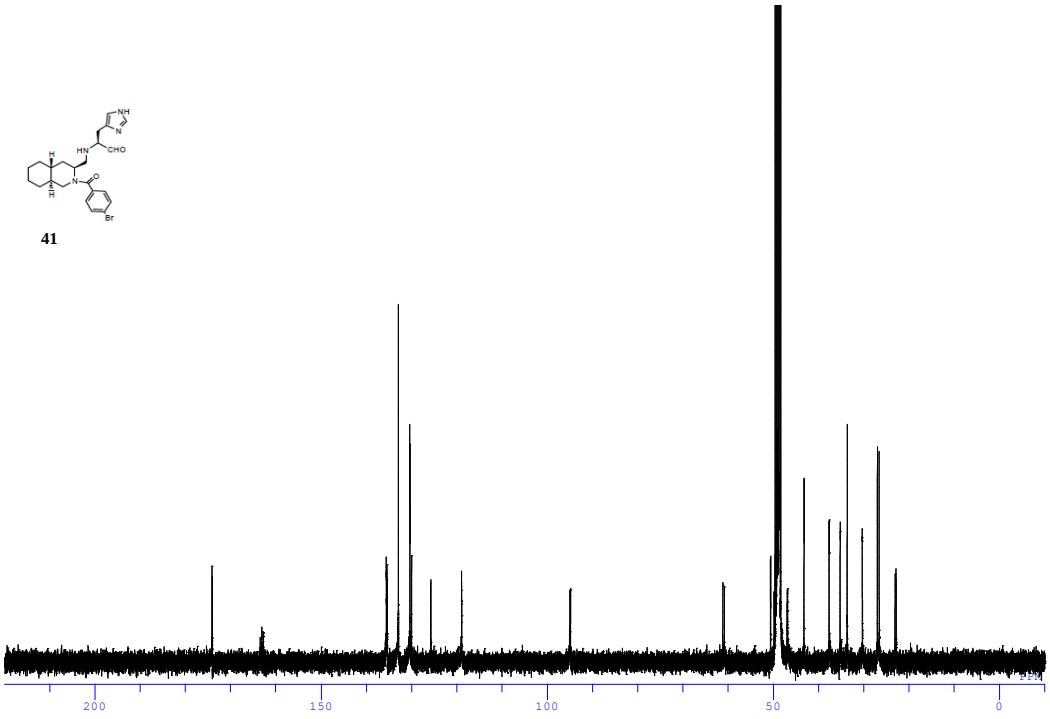

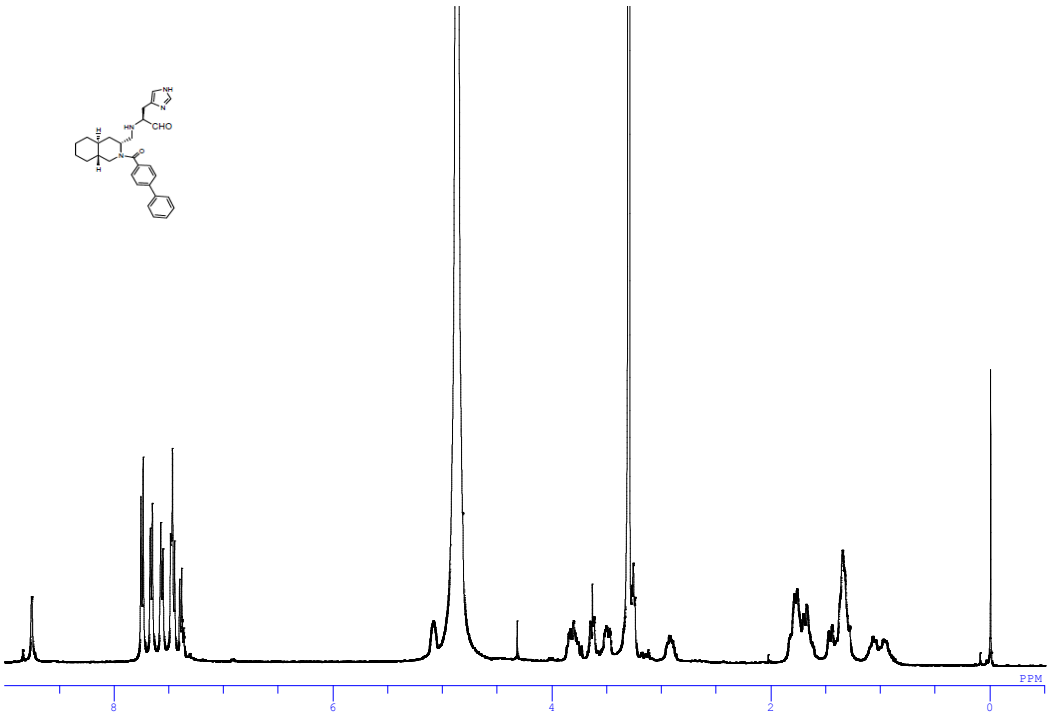

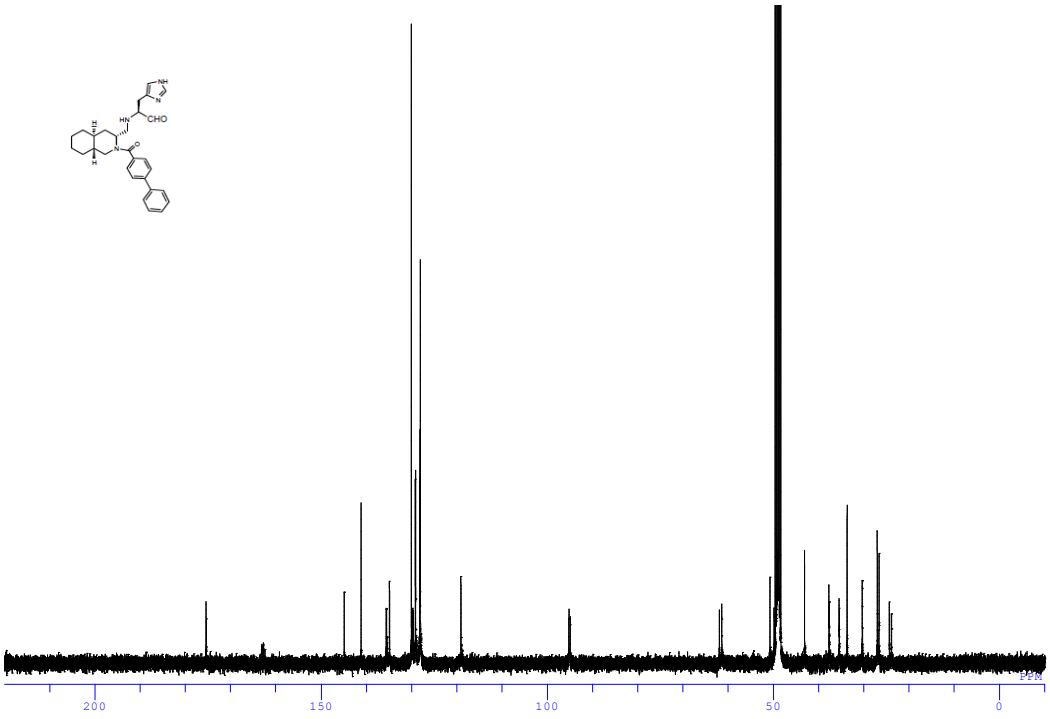
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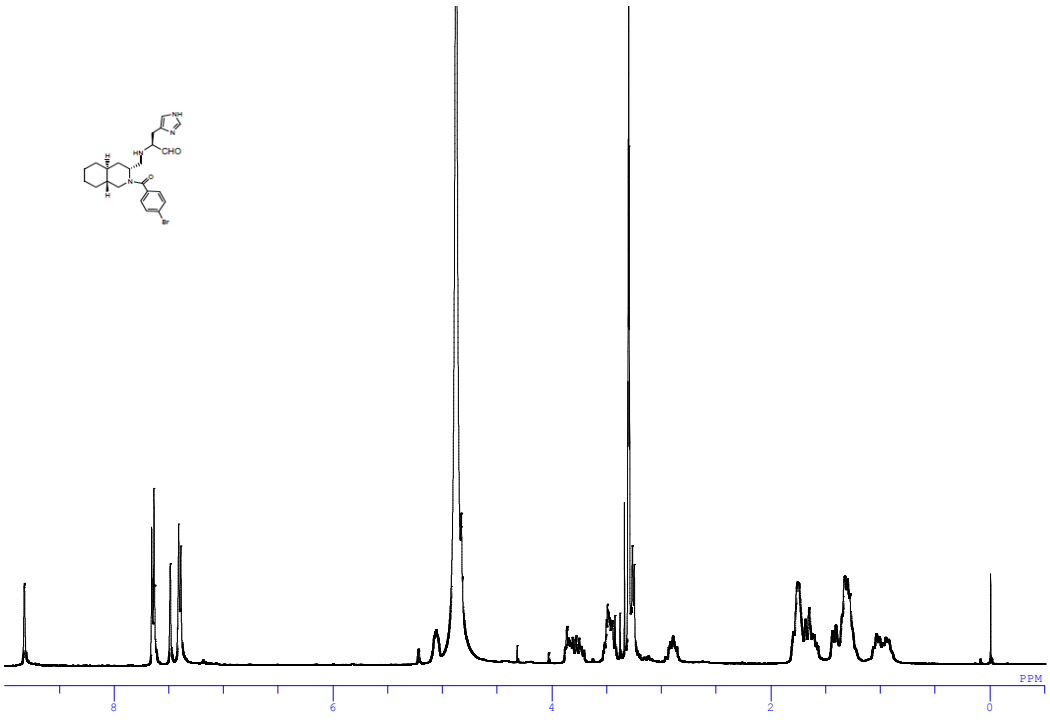
CHO
Br
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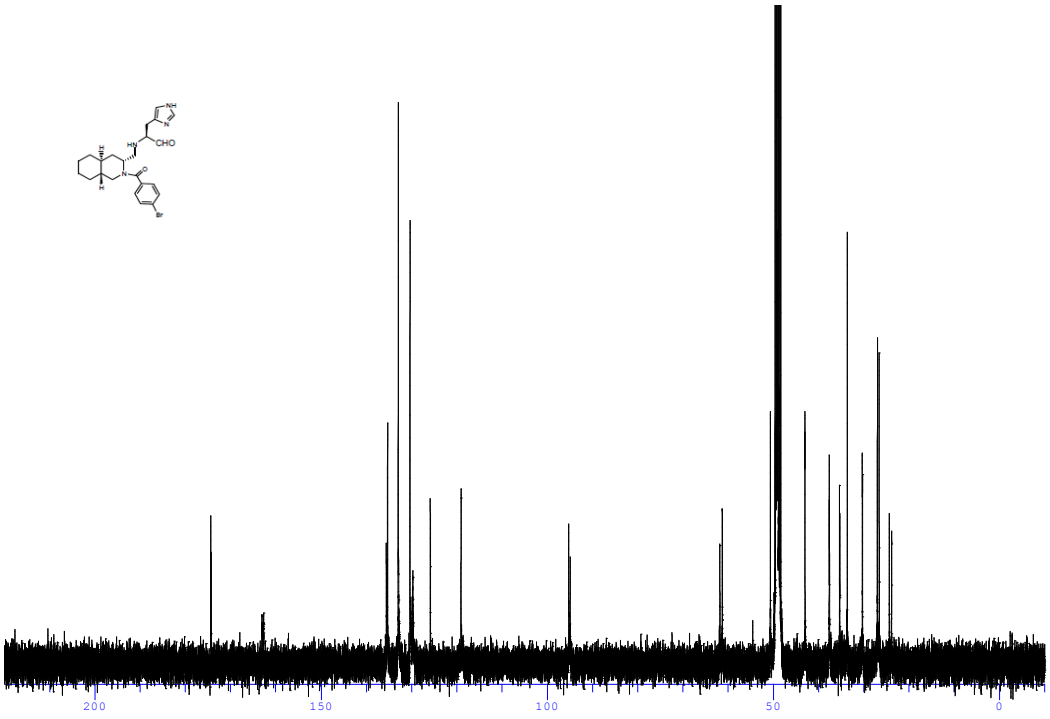
PPM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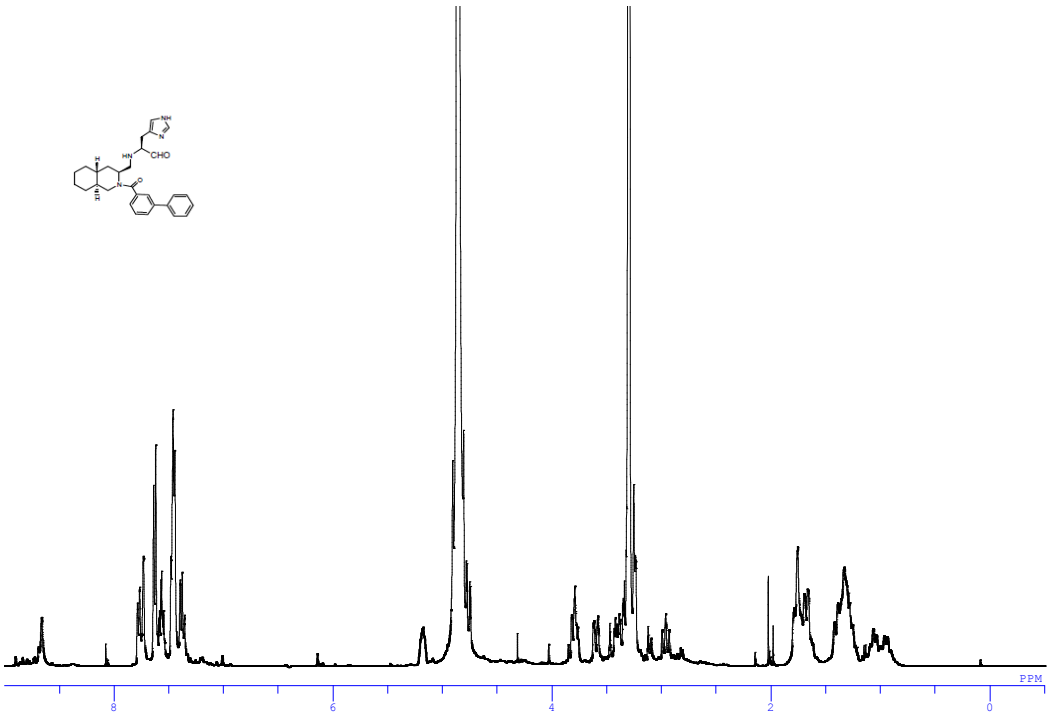
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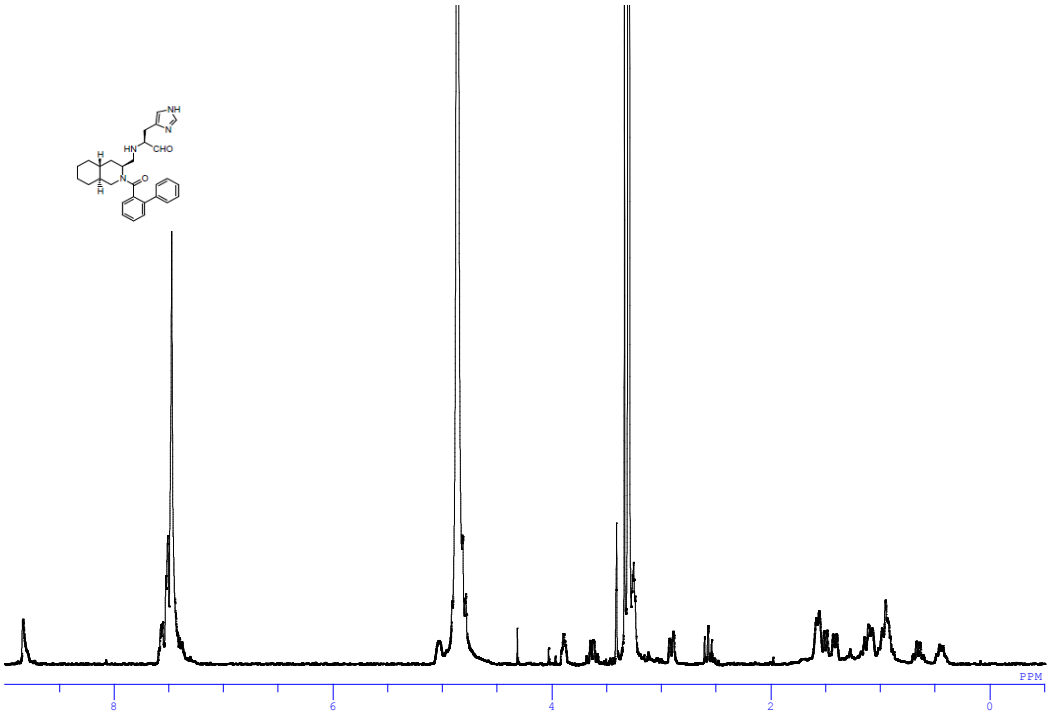
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CHO
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PPM
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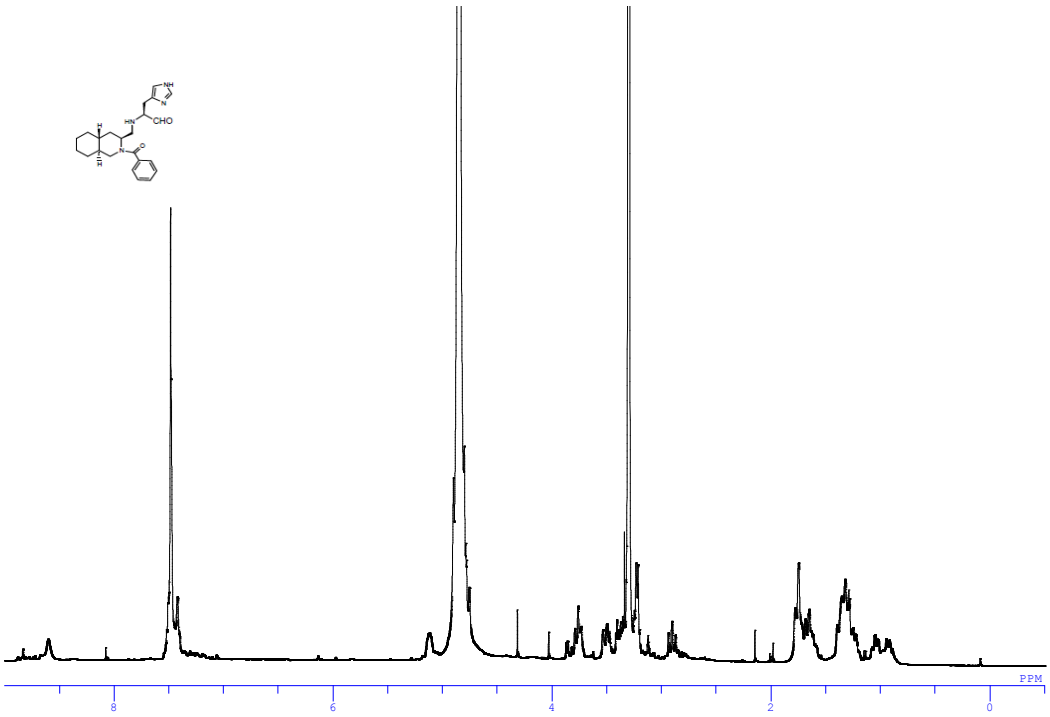
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HN
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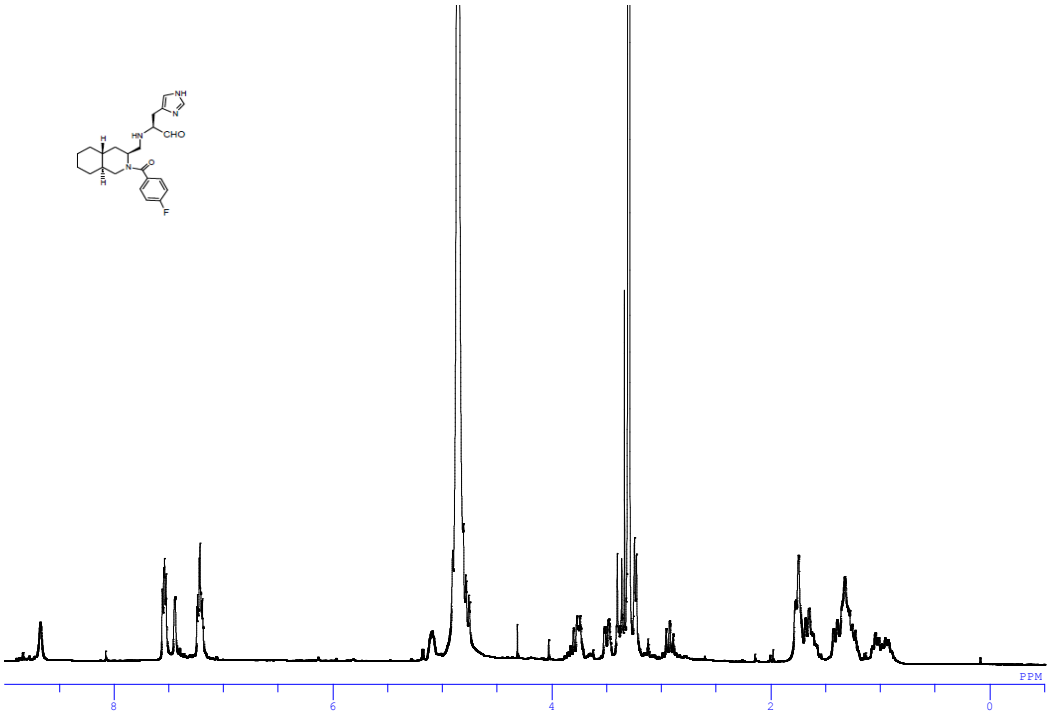
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PPM
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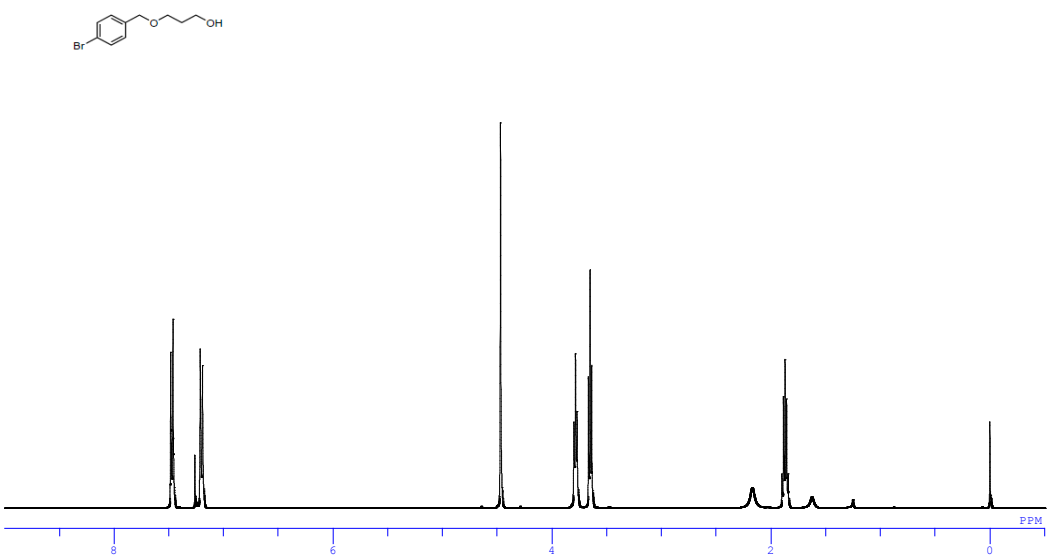
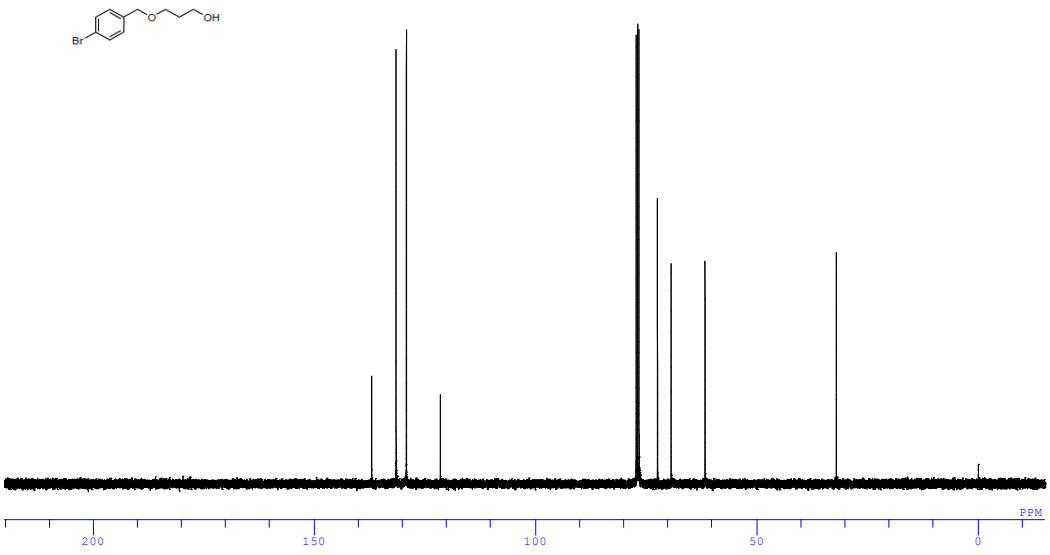
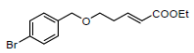
(b) Compounds included in the supporting information



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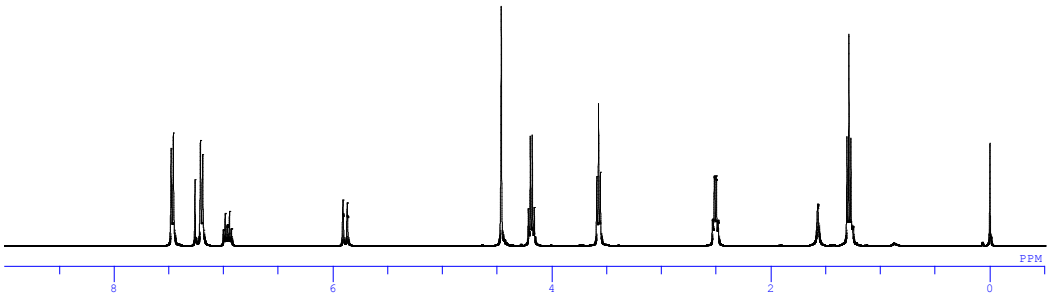
Br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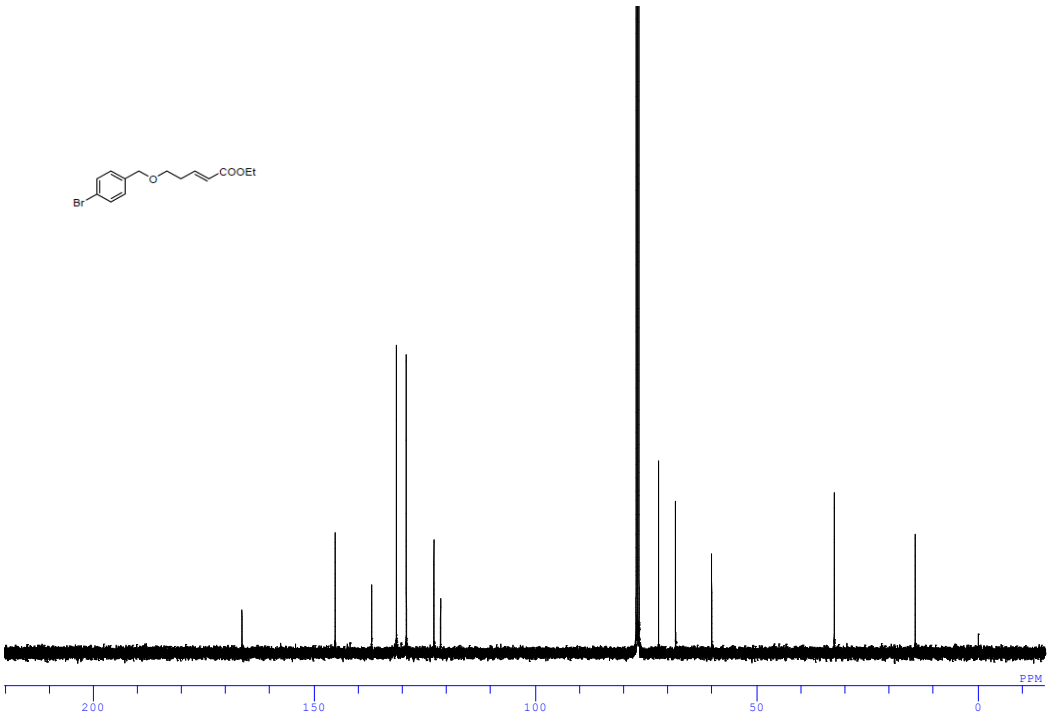
COOEt
Br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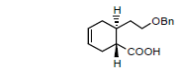
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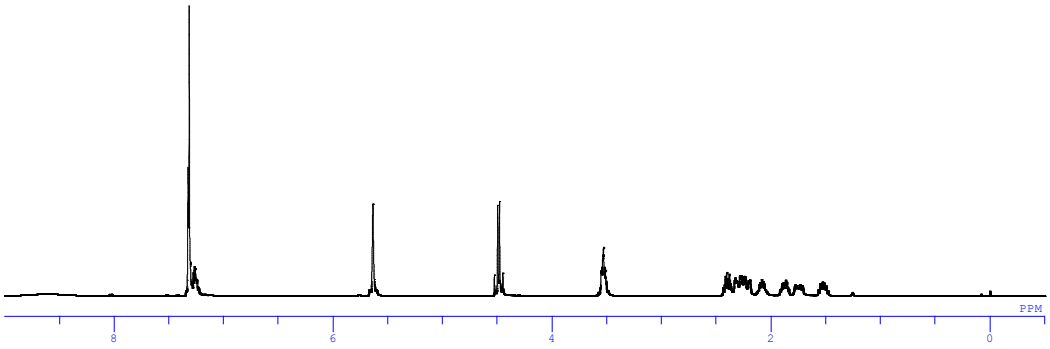
COOH
H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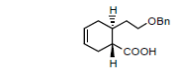
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OBn
COOH
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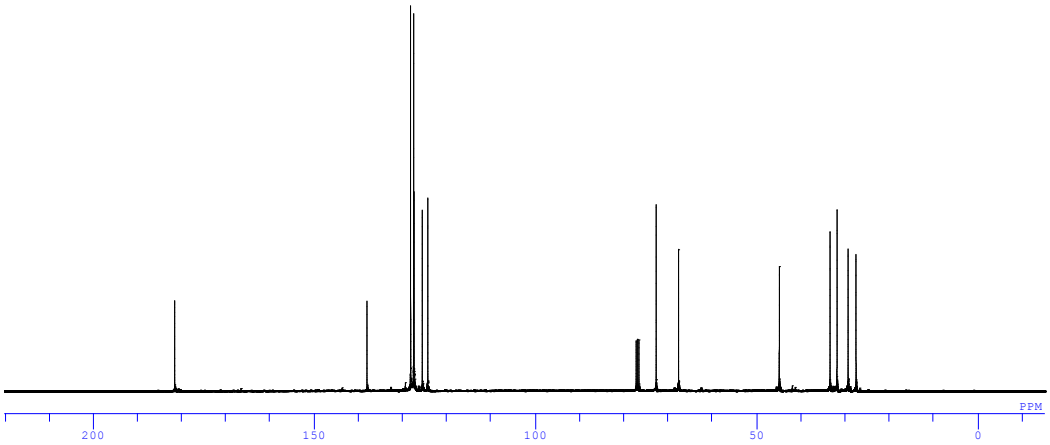
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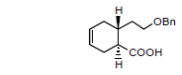
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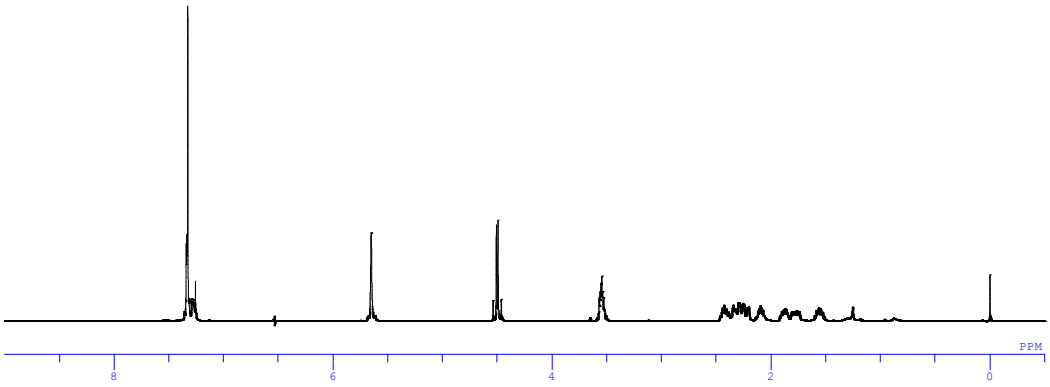
OBn
COOH
H


PPM
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4
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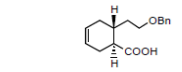
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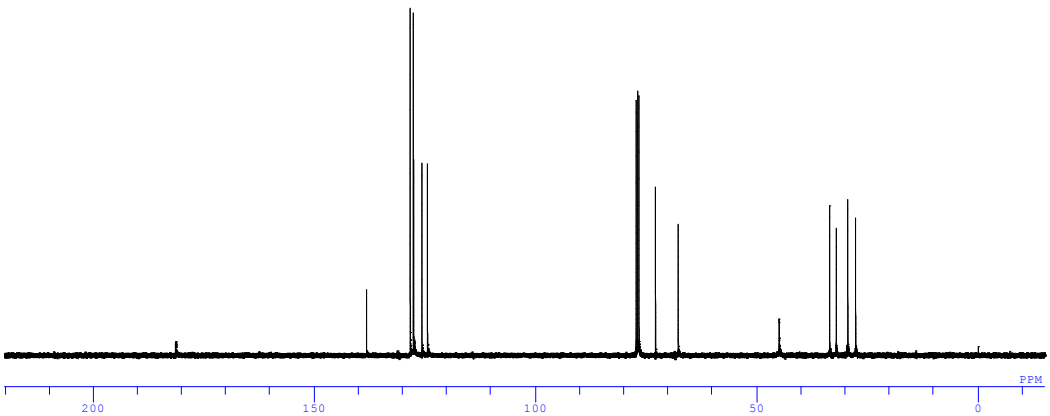
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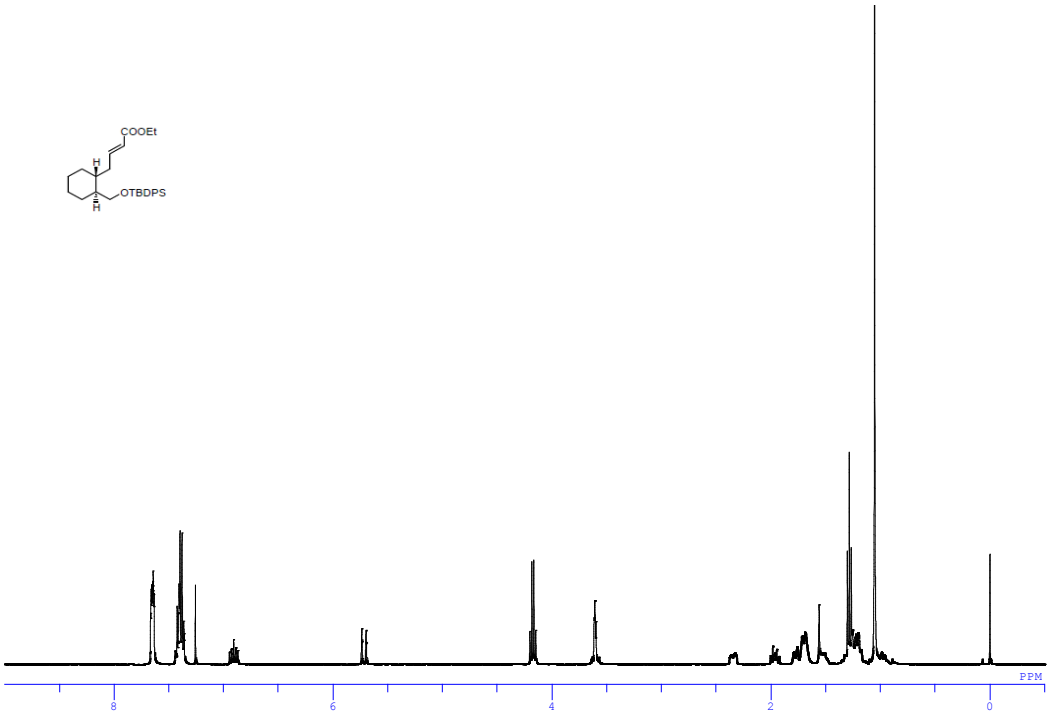
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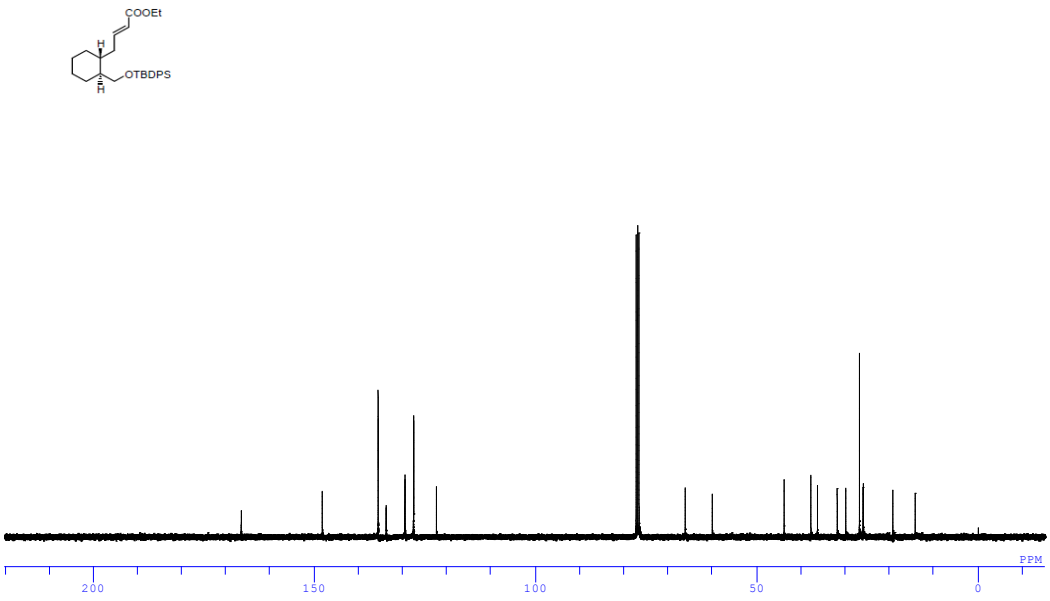
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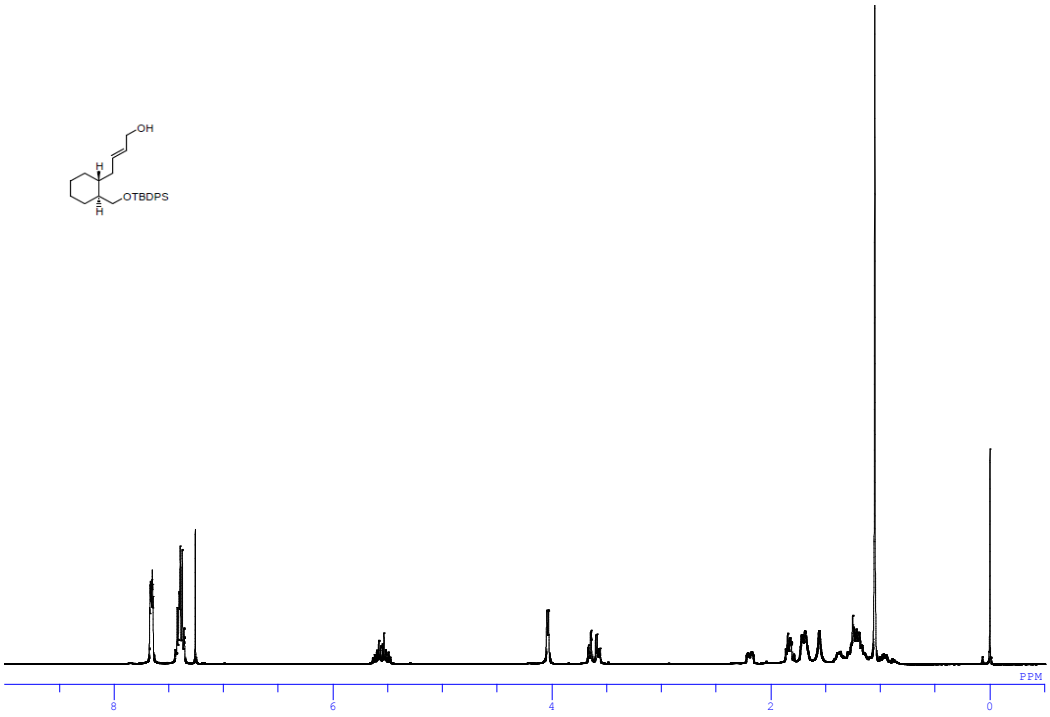
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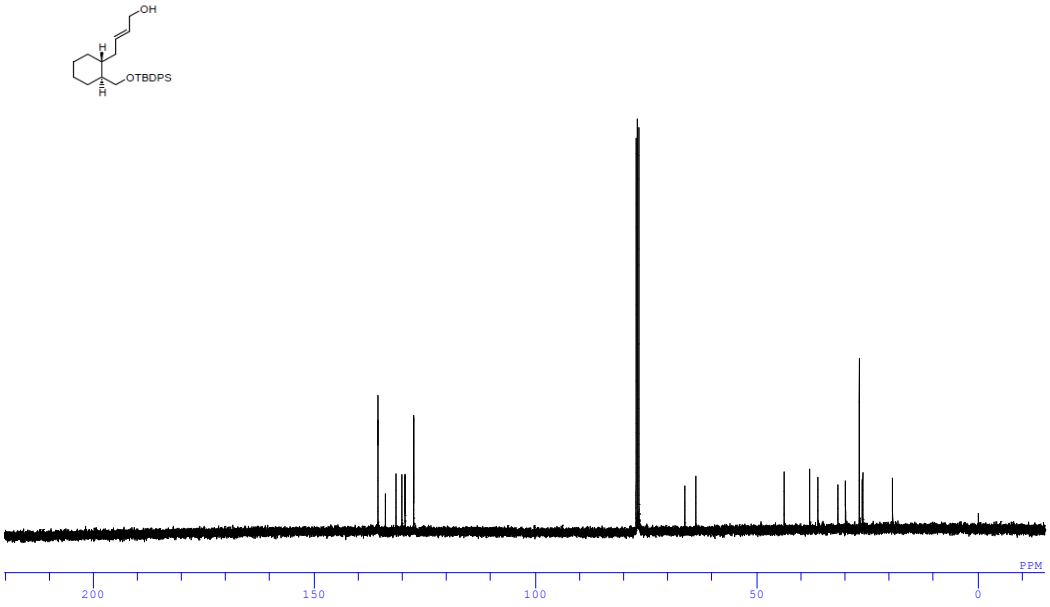
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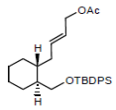

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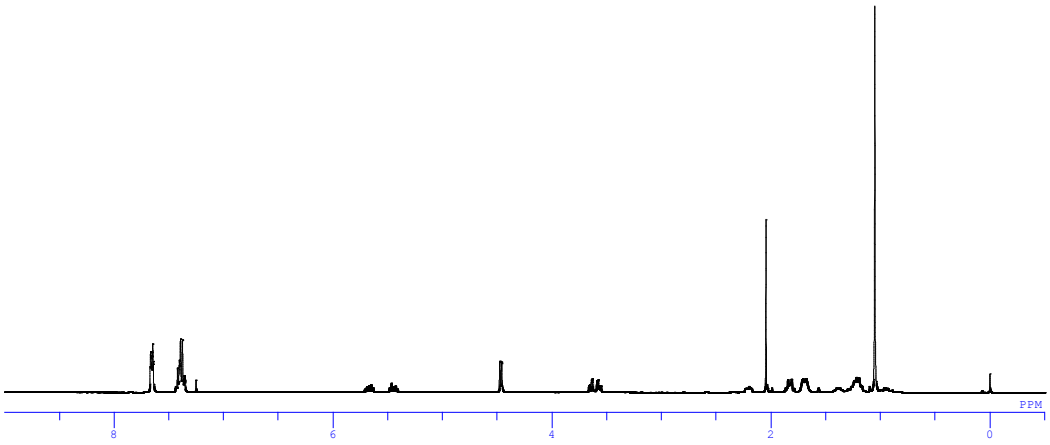

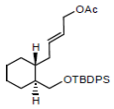

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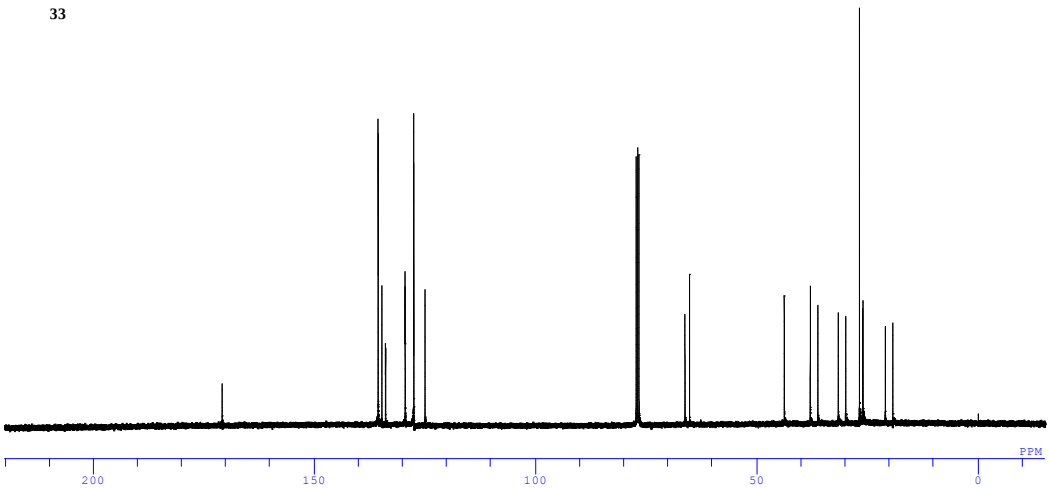

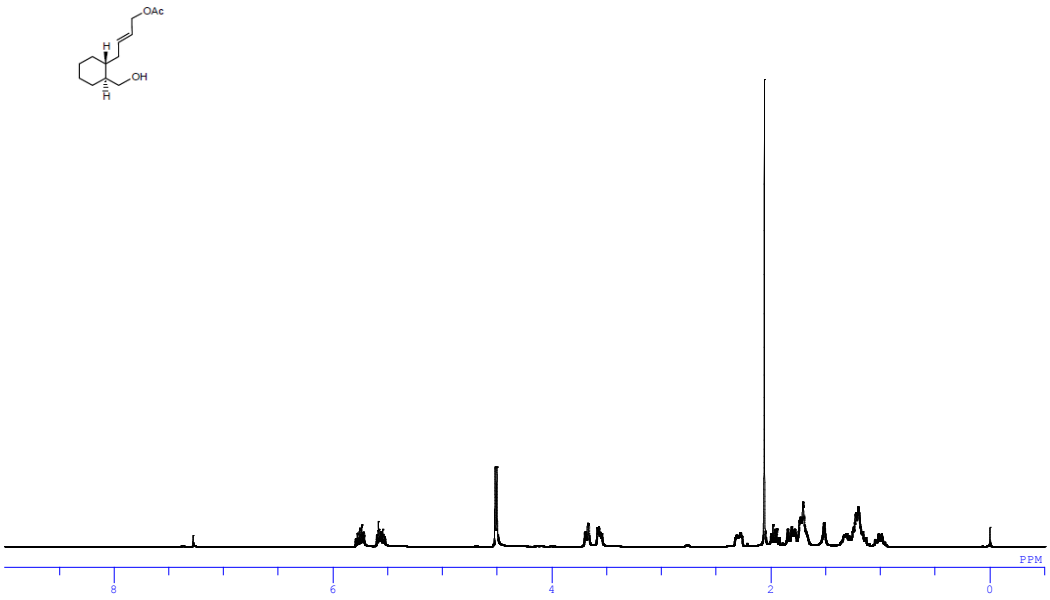
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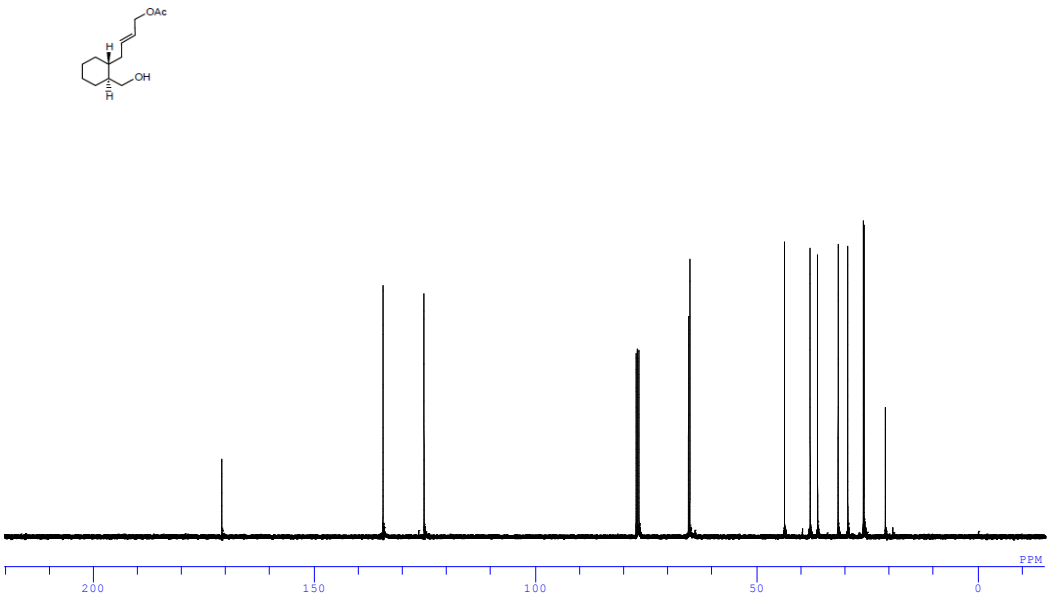
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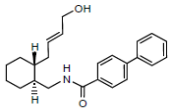

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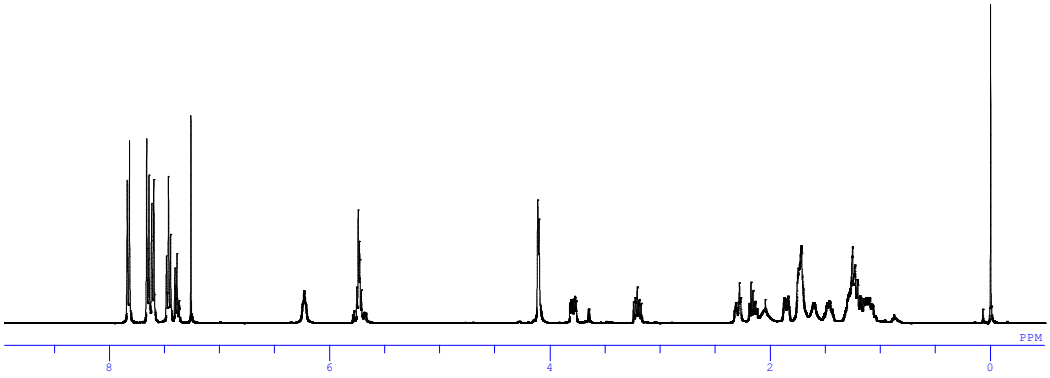

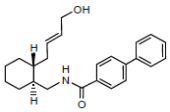

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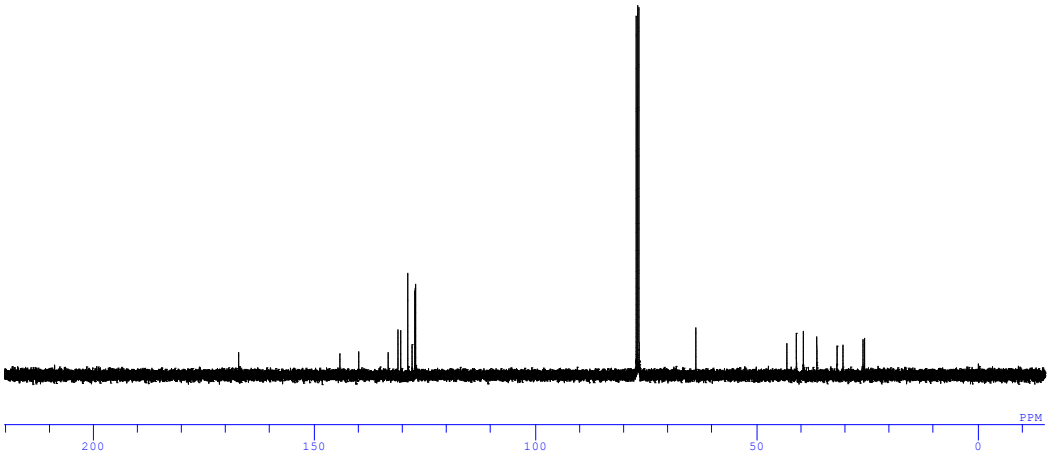

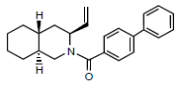

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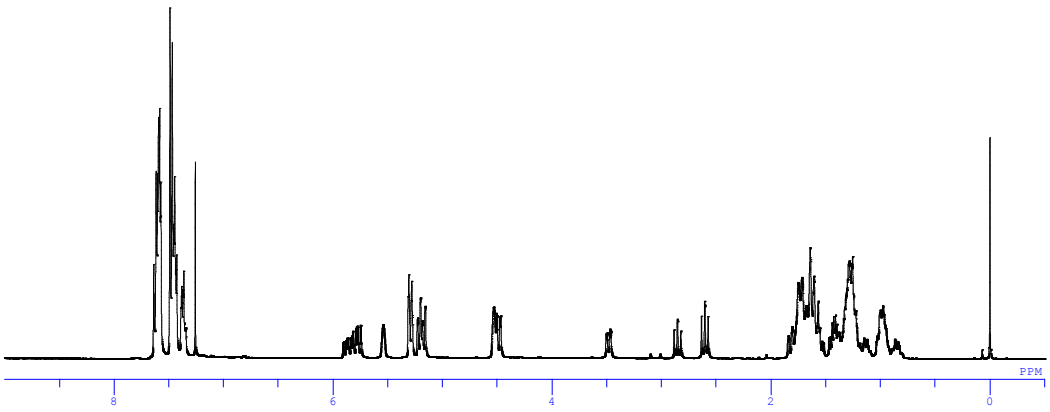

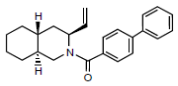

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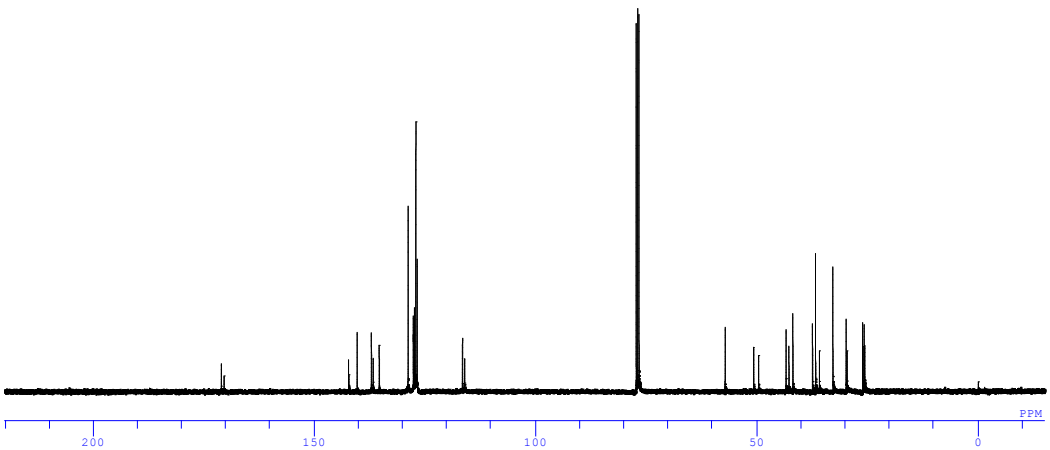

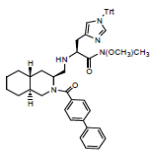

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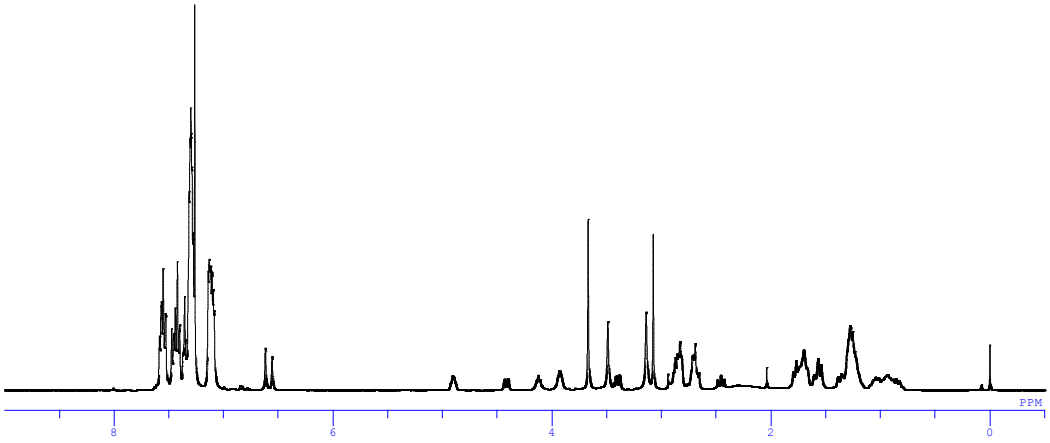

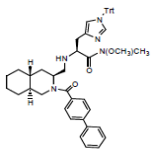

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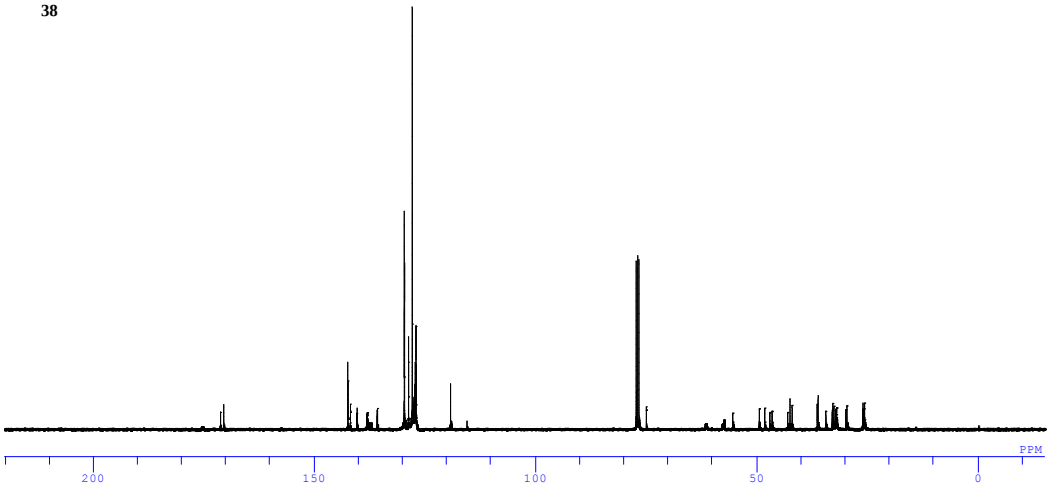

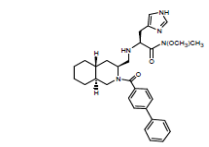

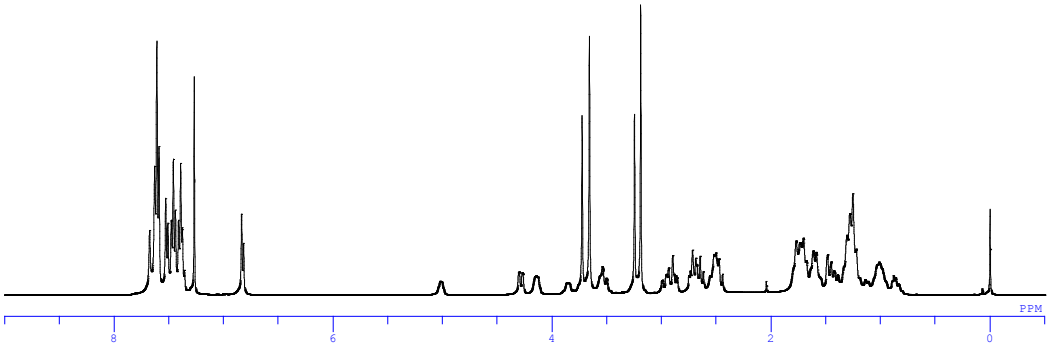
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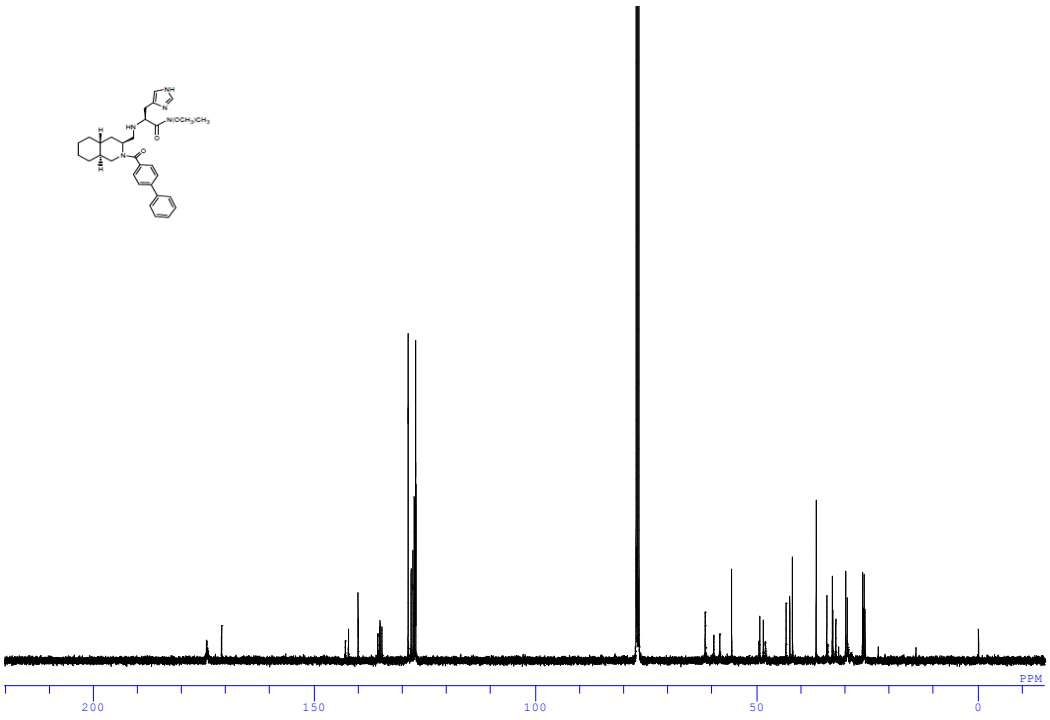
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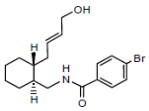

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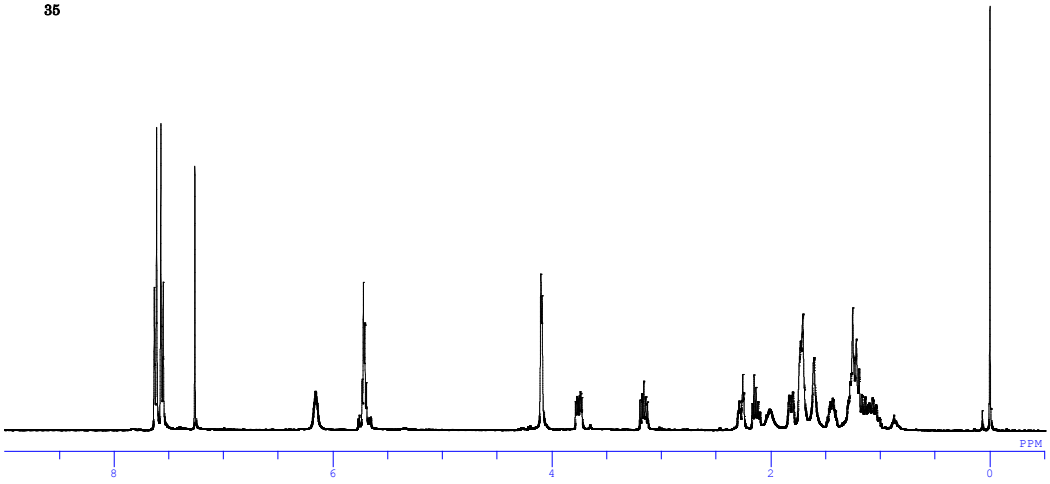

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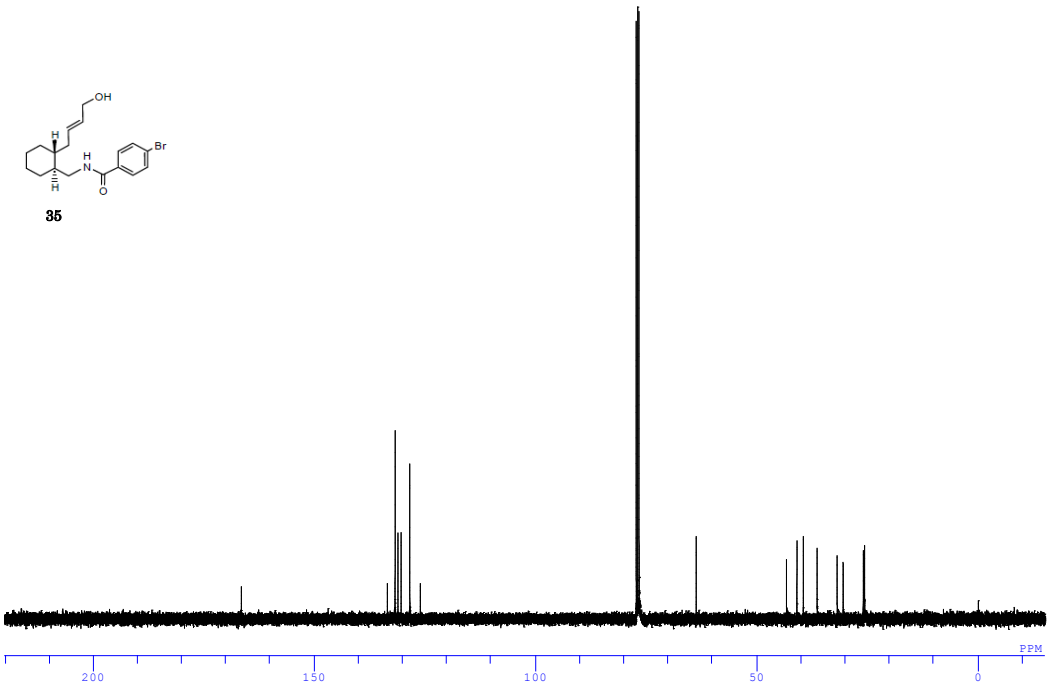

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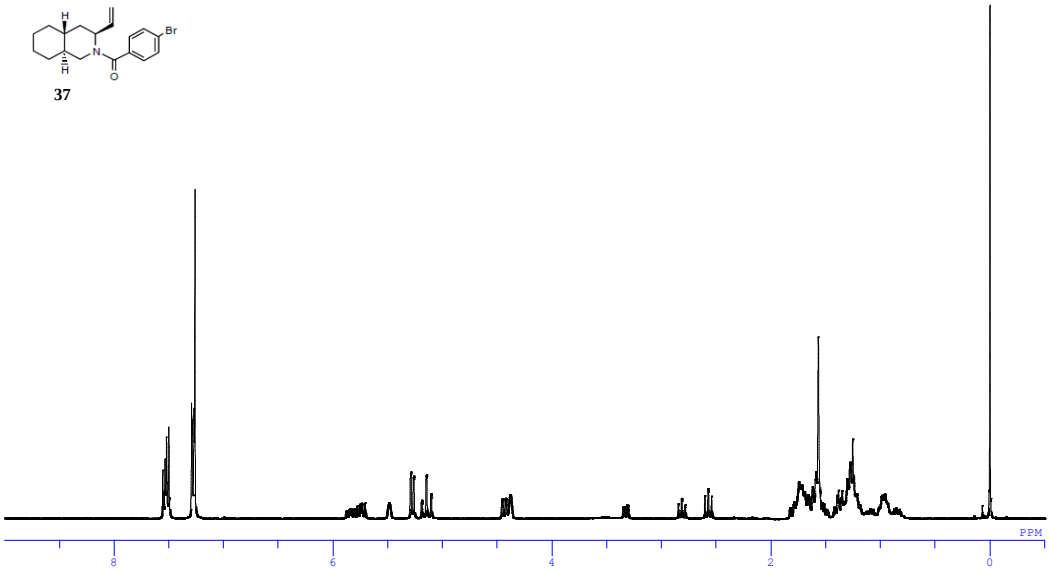

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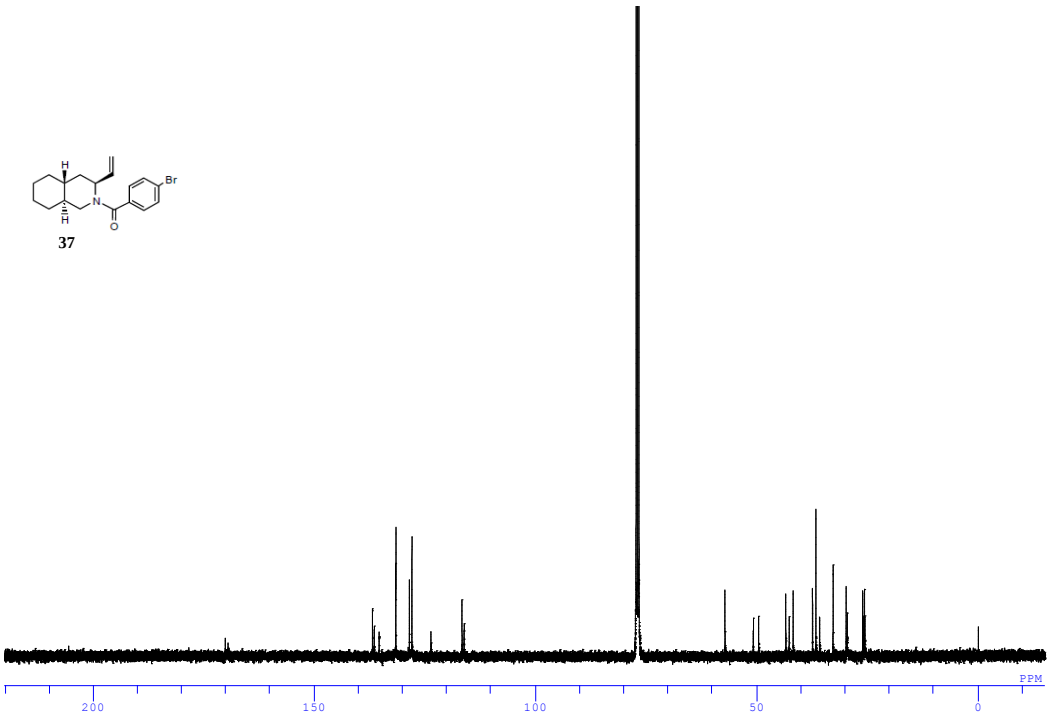

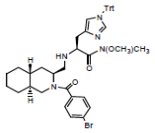

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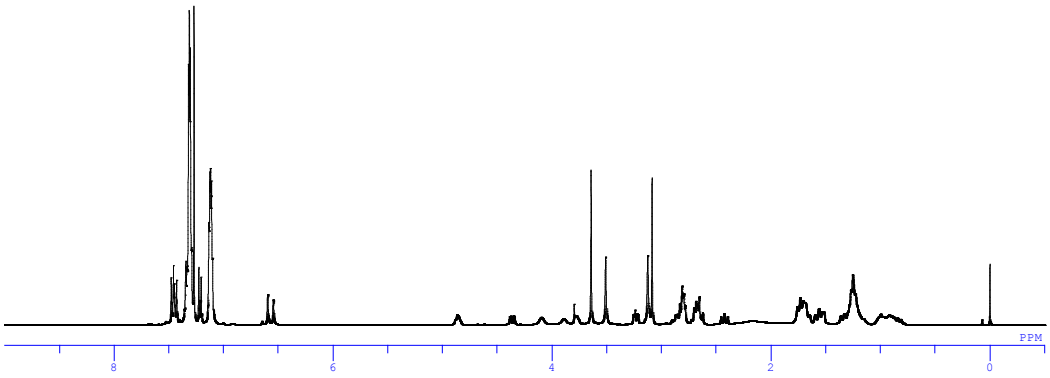

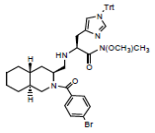

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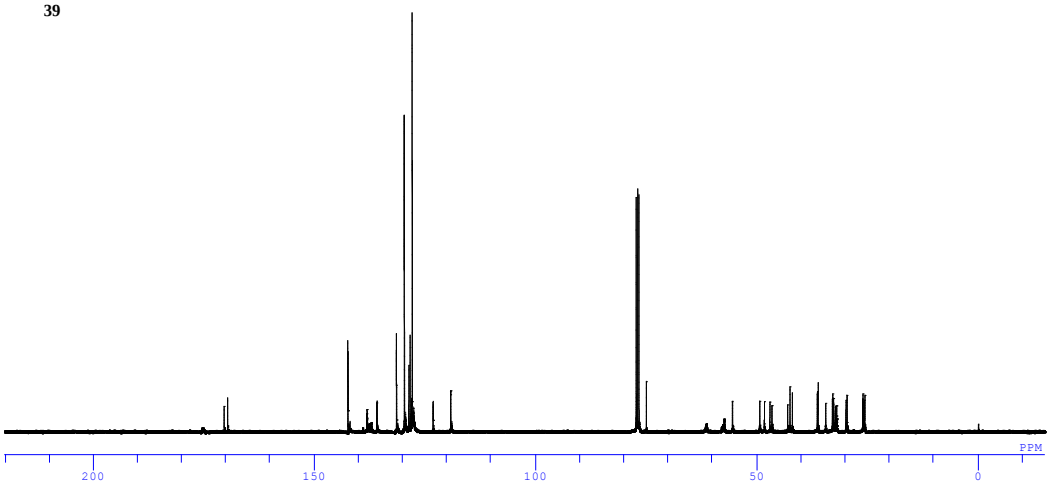

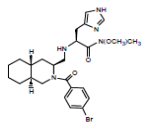

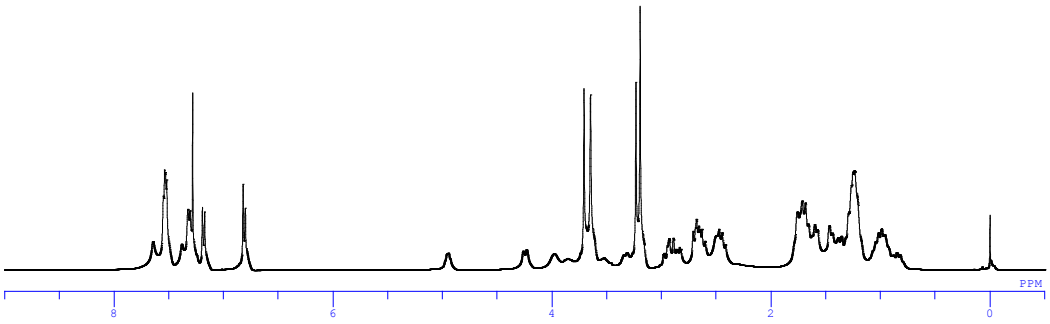
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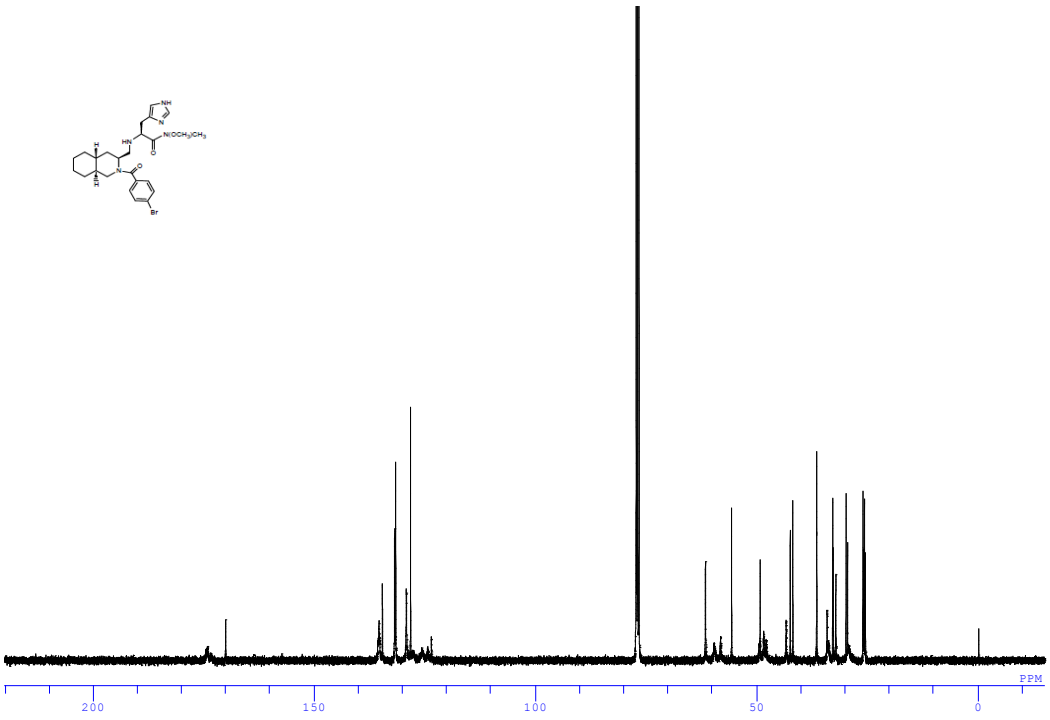
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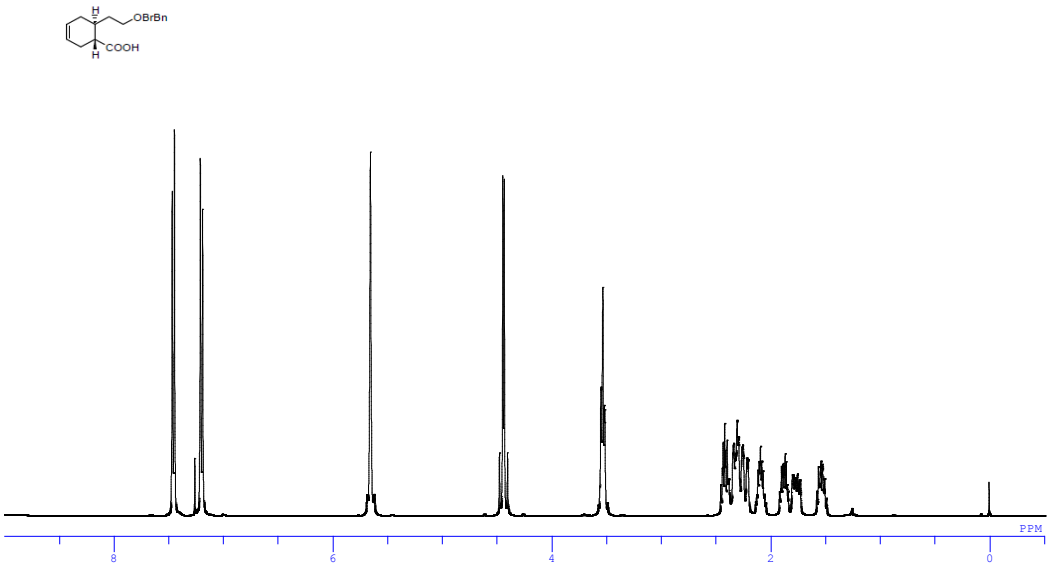
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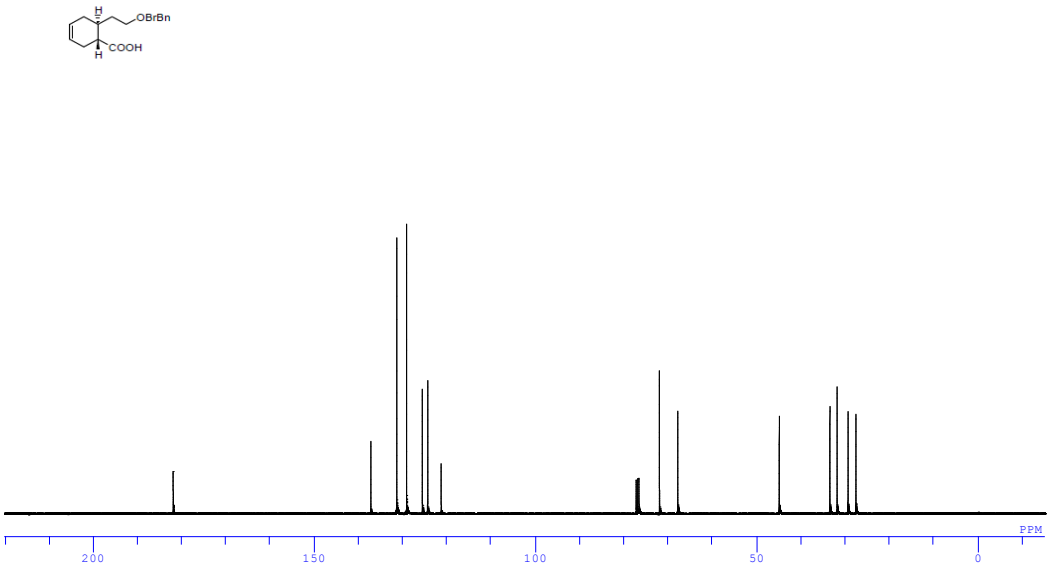
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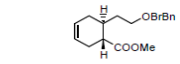
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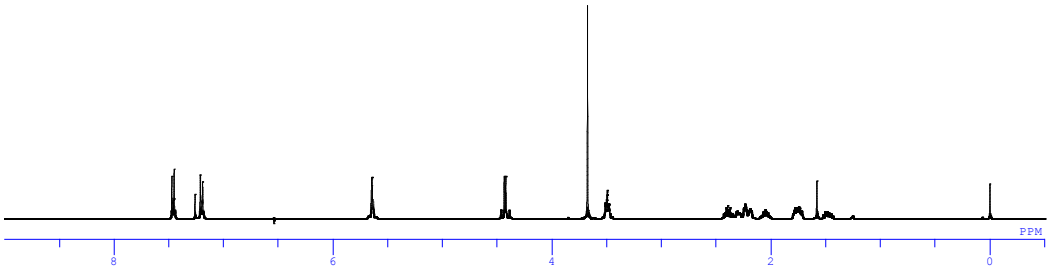
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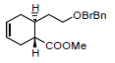
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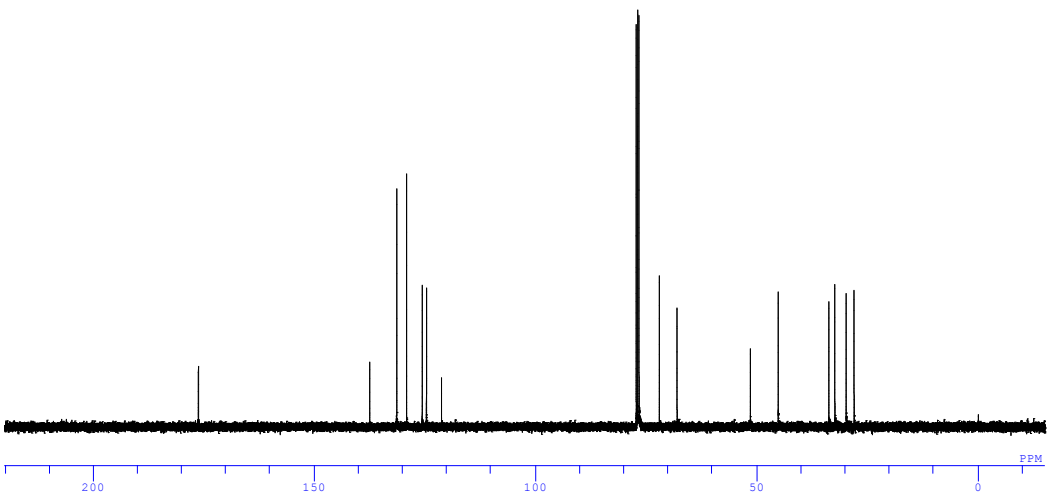
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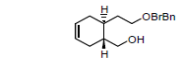
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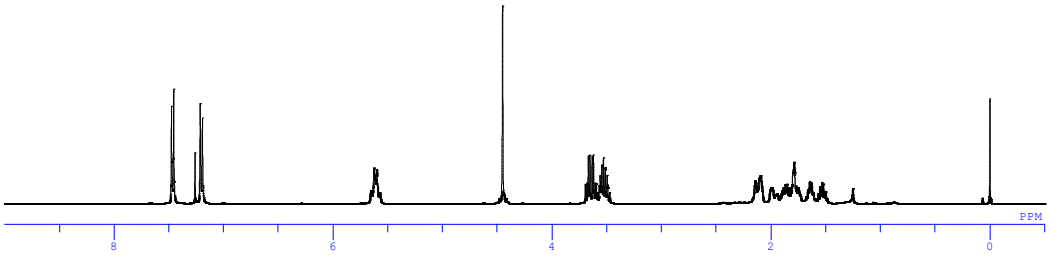
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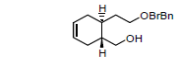
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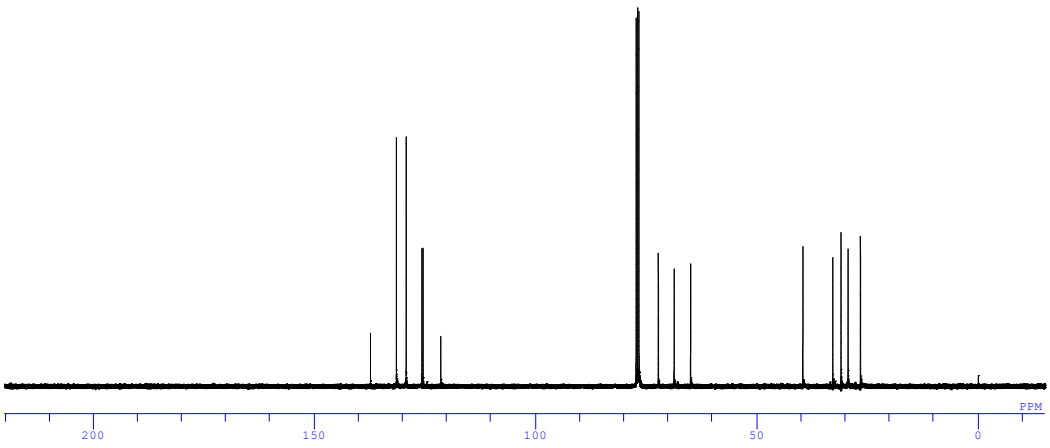
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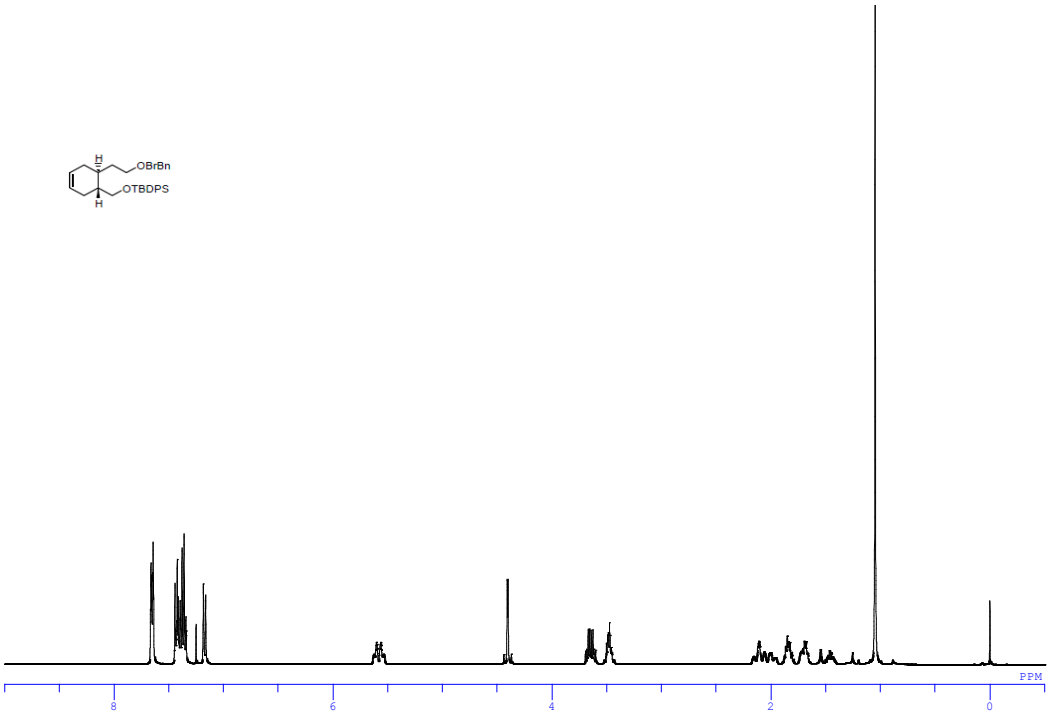
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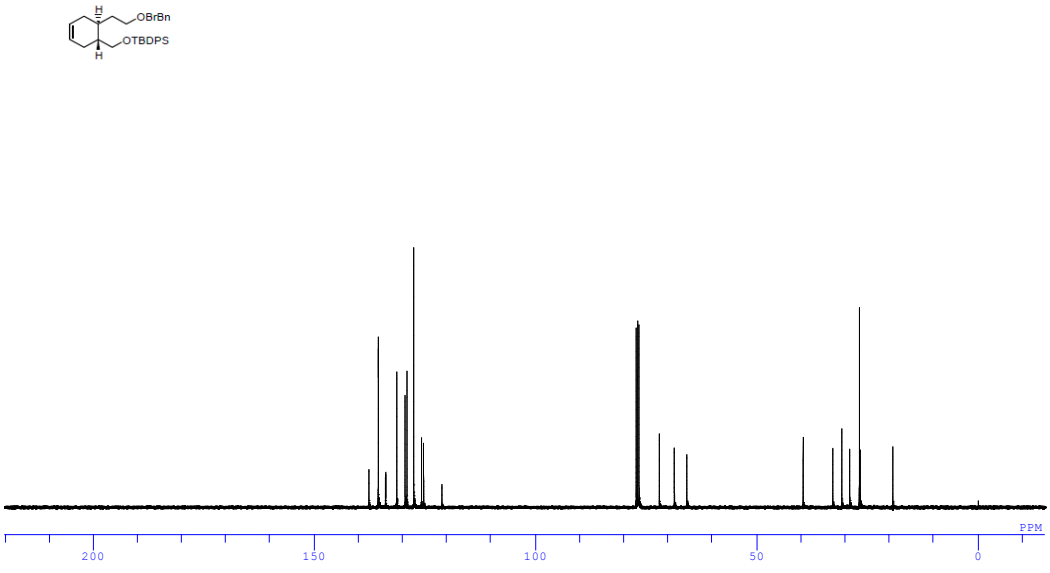
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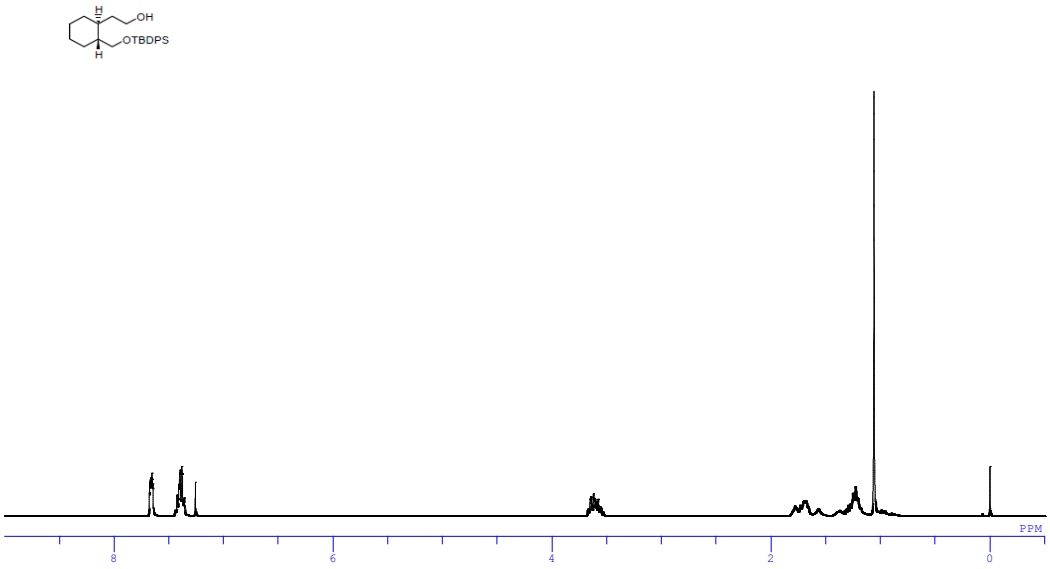
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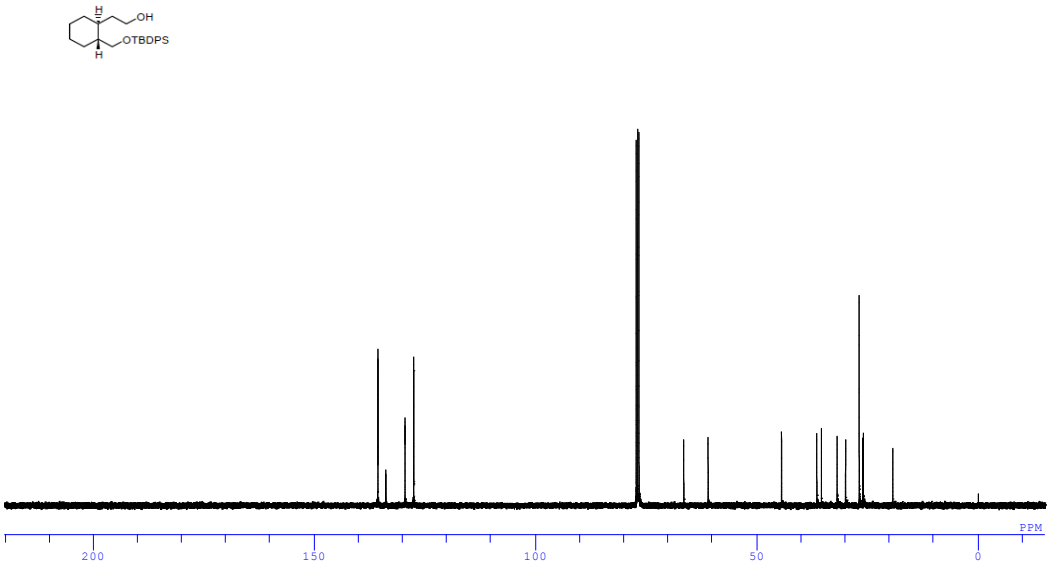
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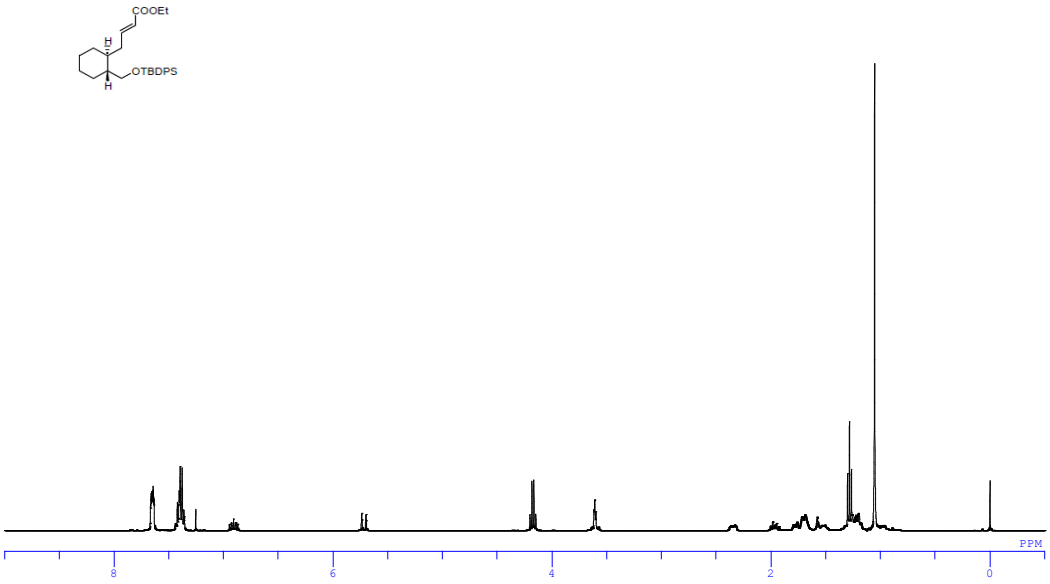
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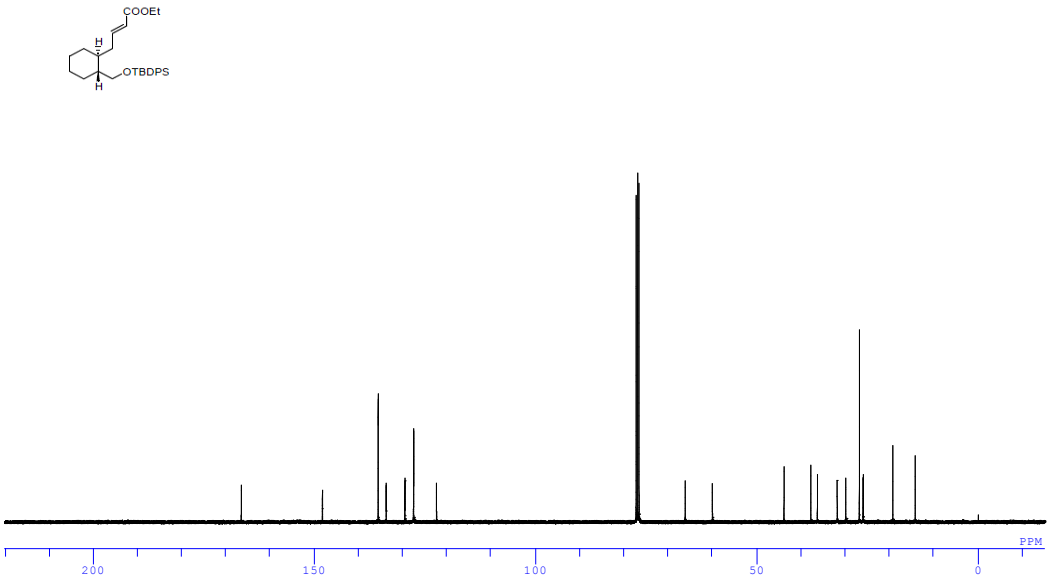
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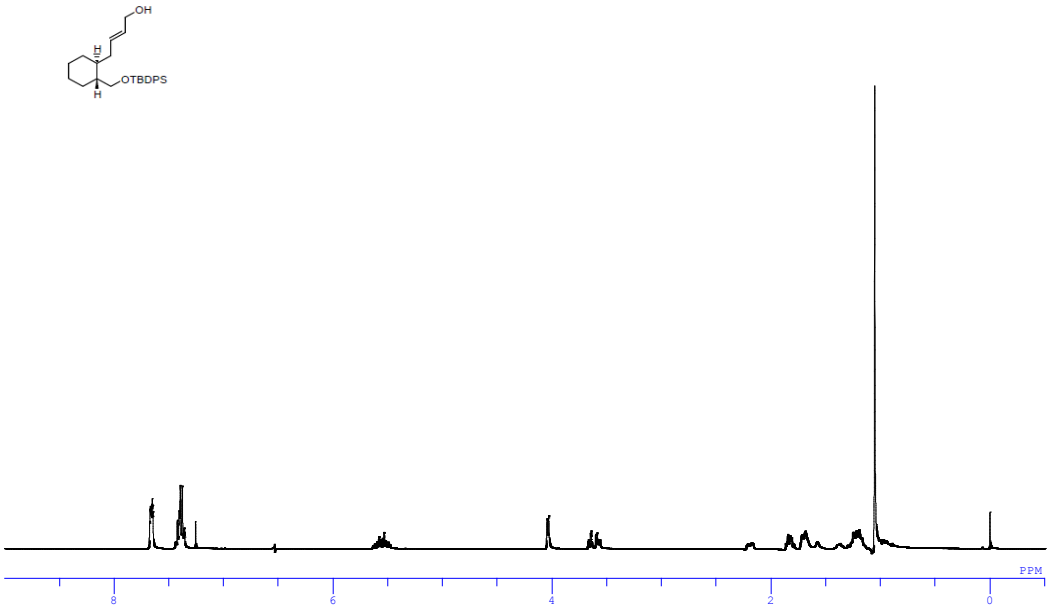
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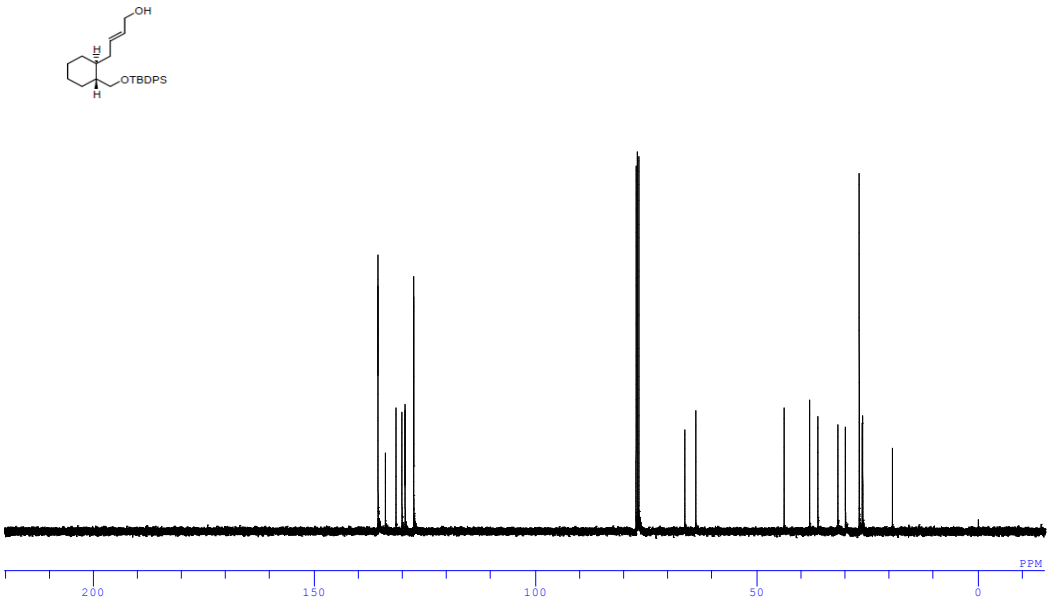
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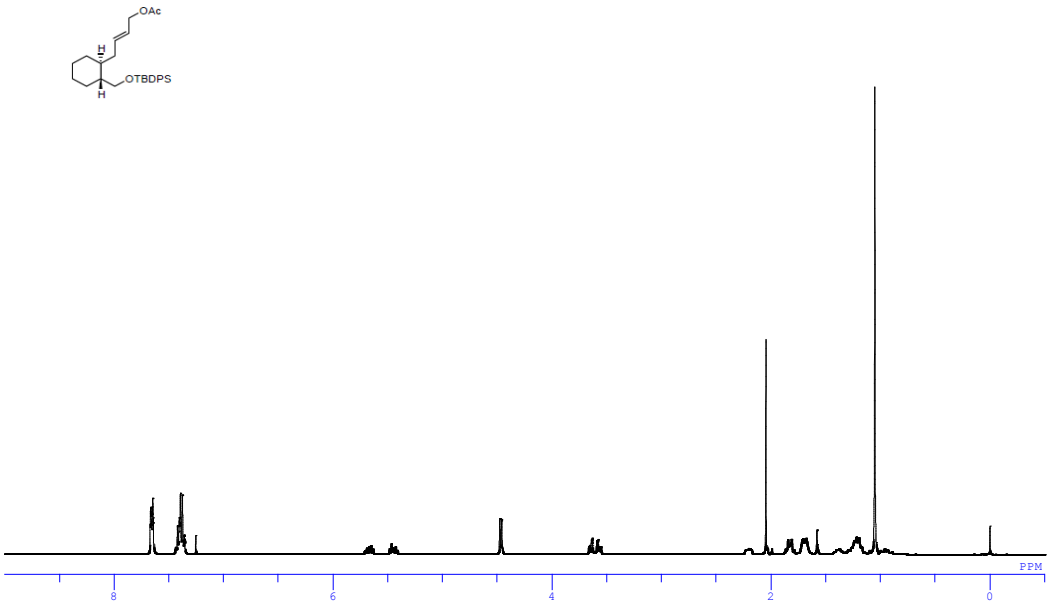
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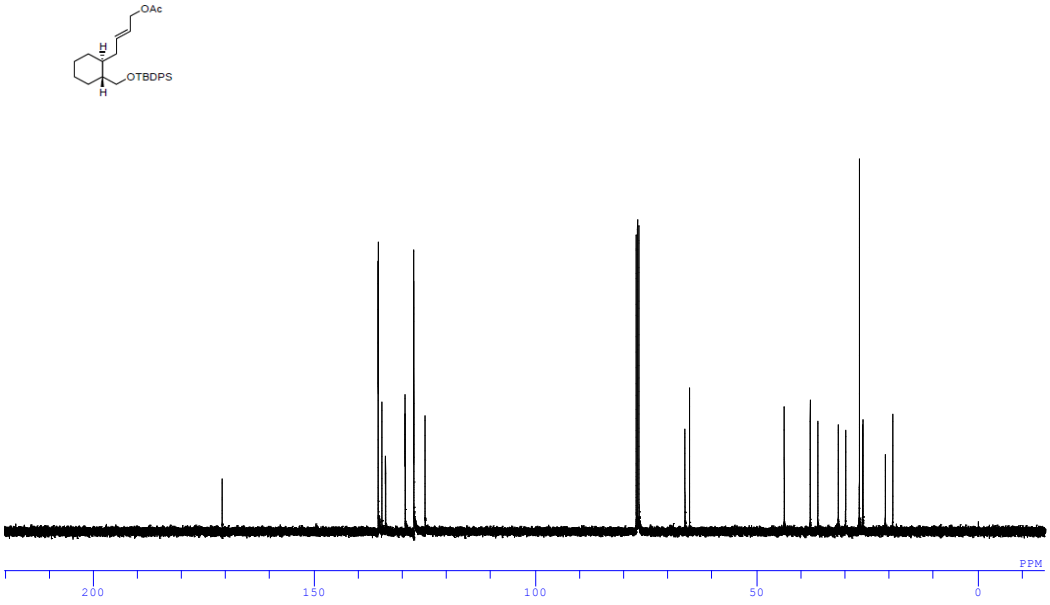
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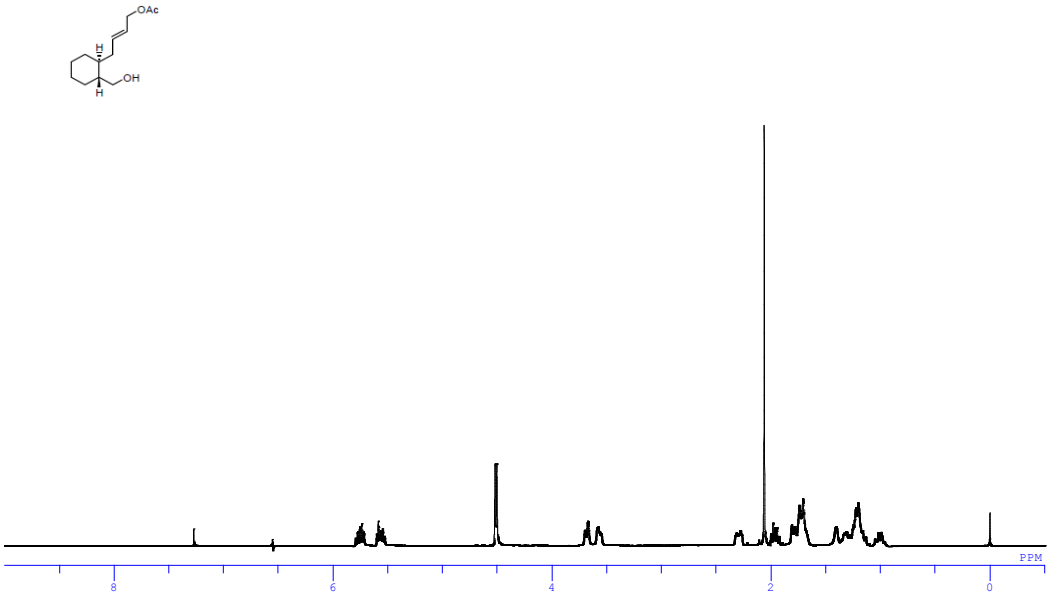
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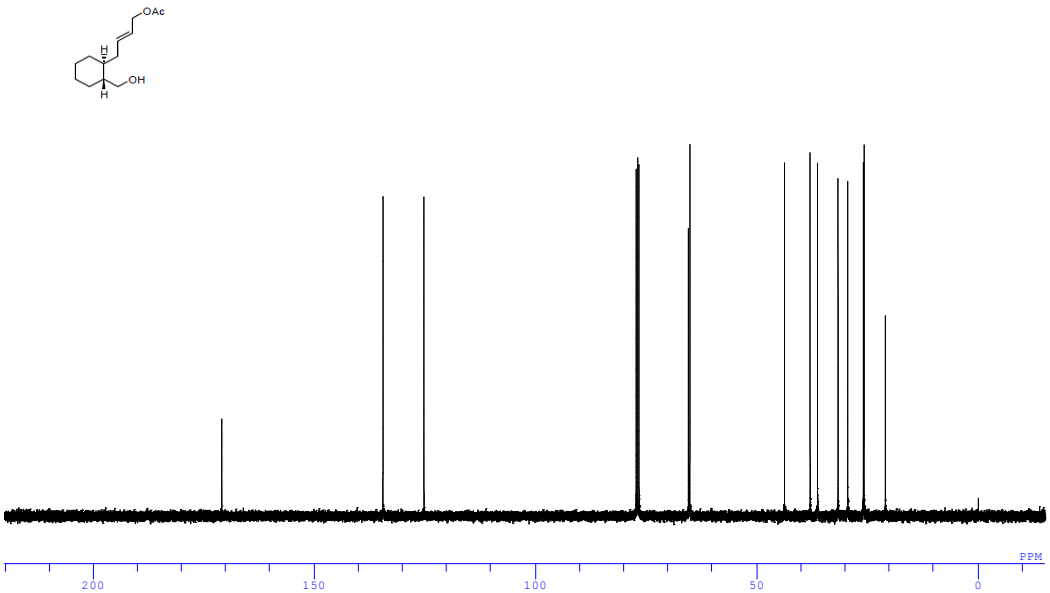
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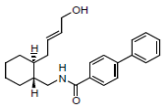
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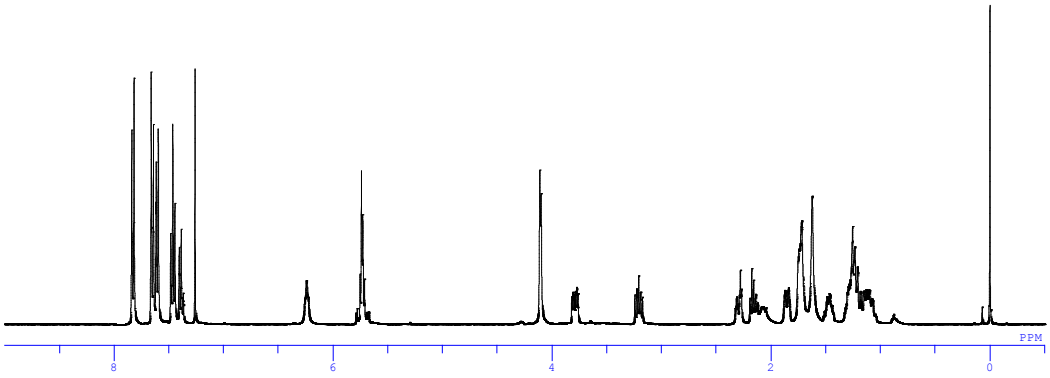
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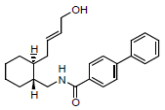
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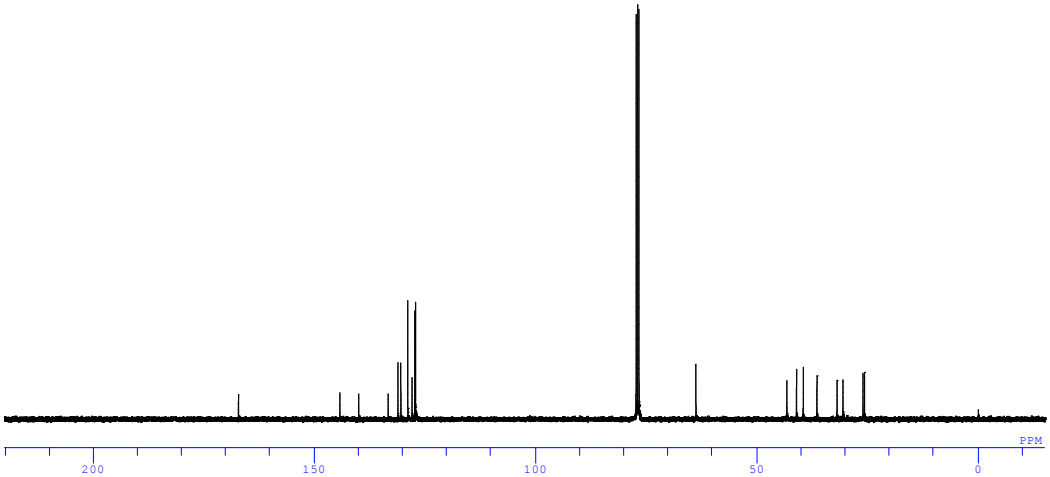
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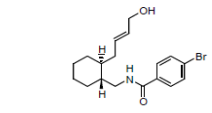
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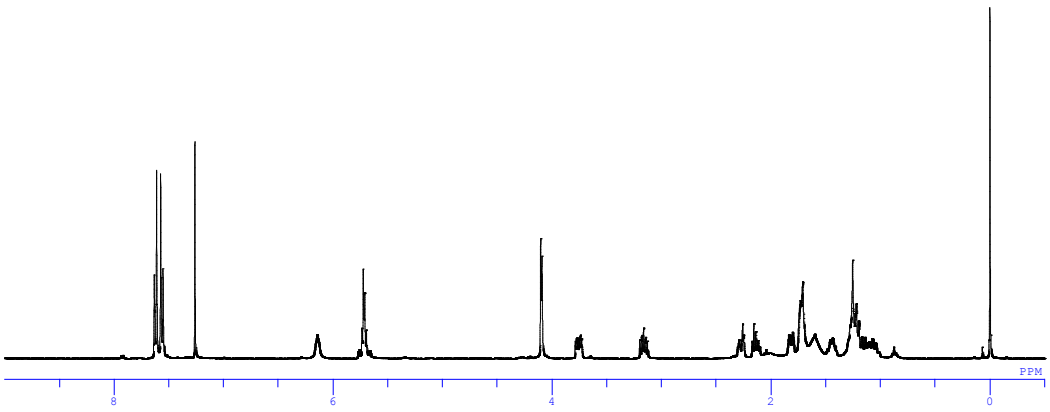
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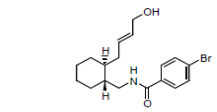
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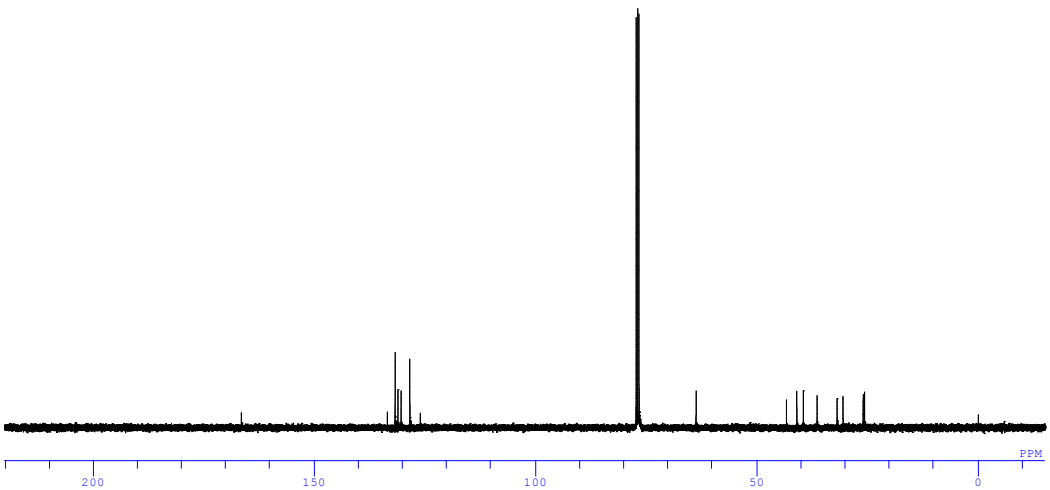
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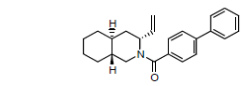

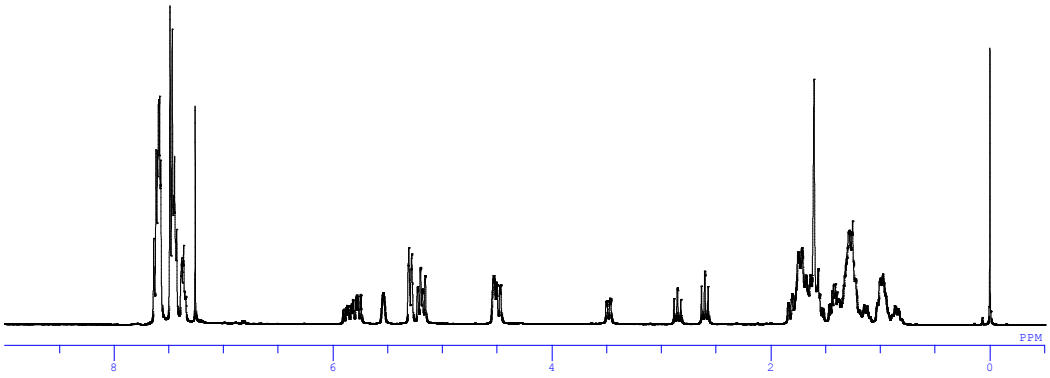
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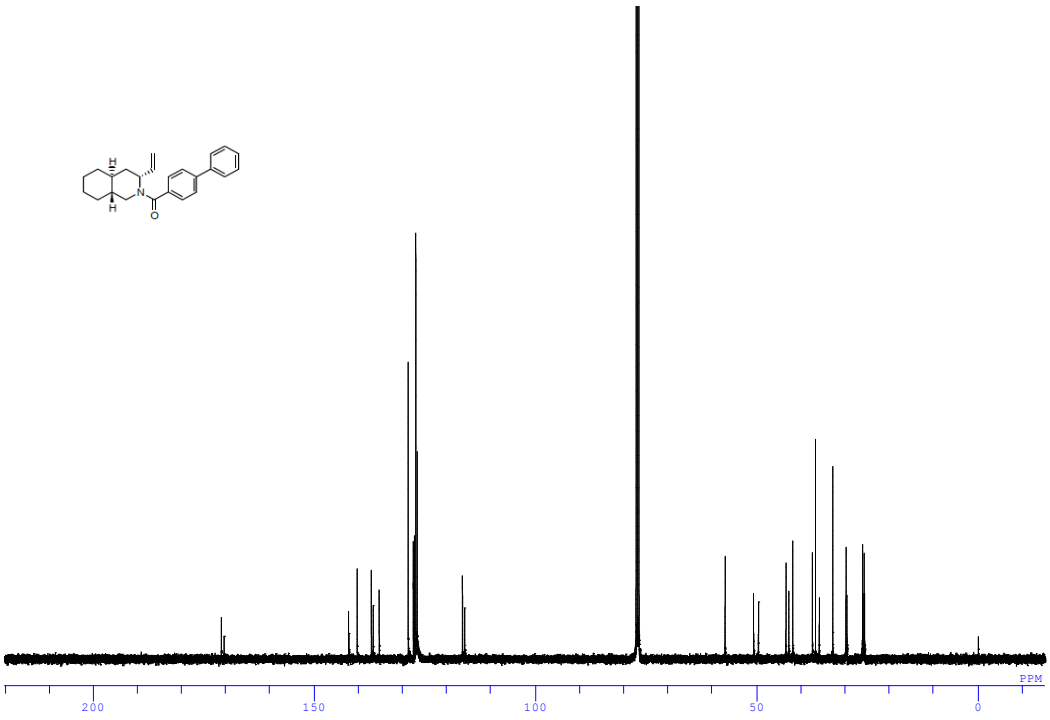
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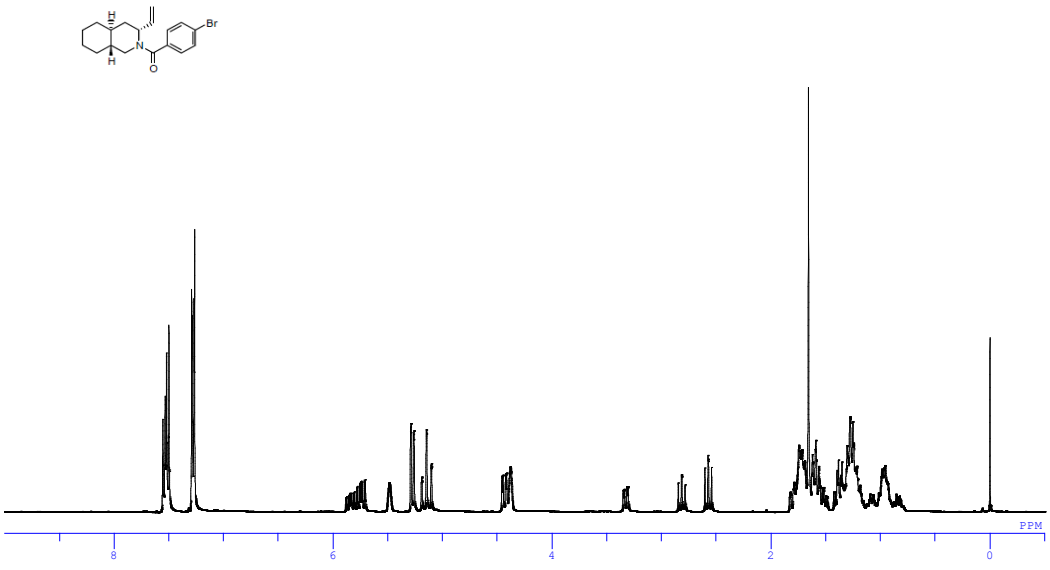
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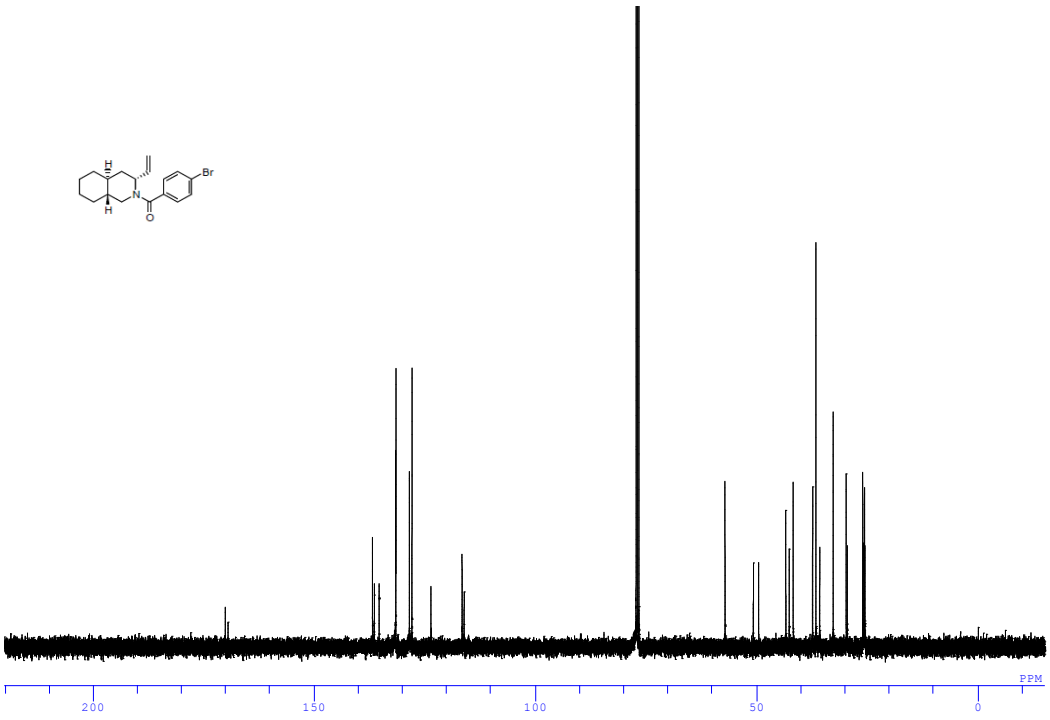
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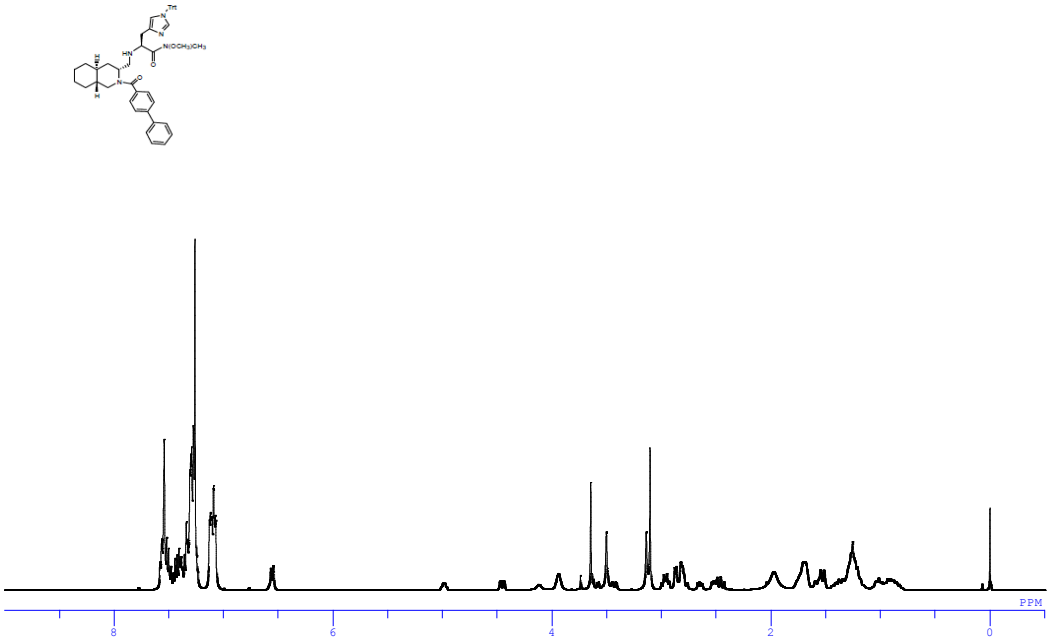
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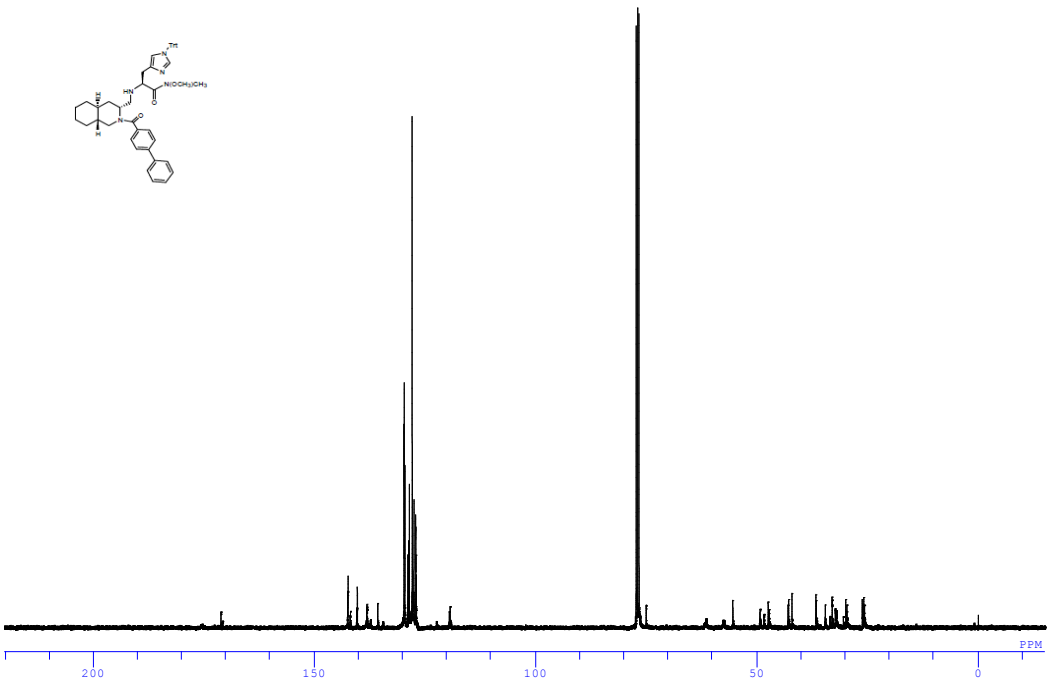
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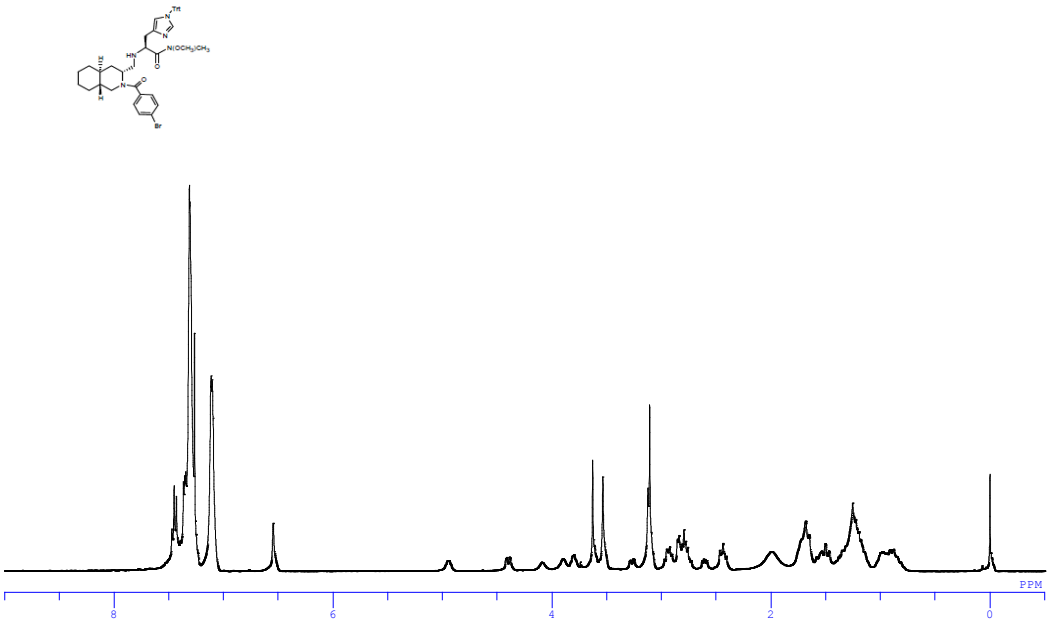
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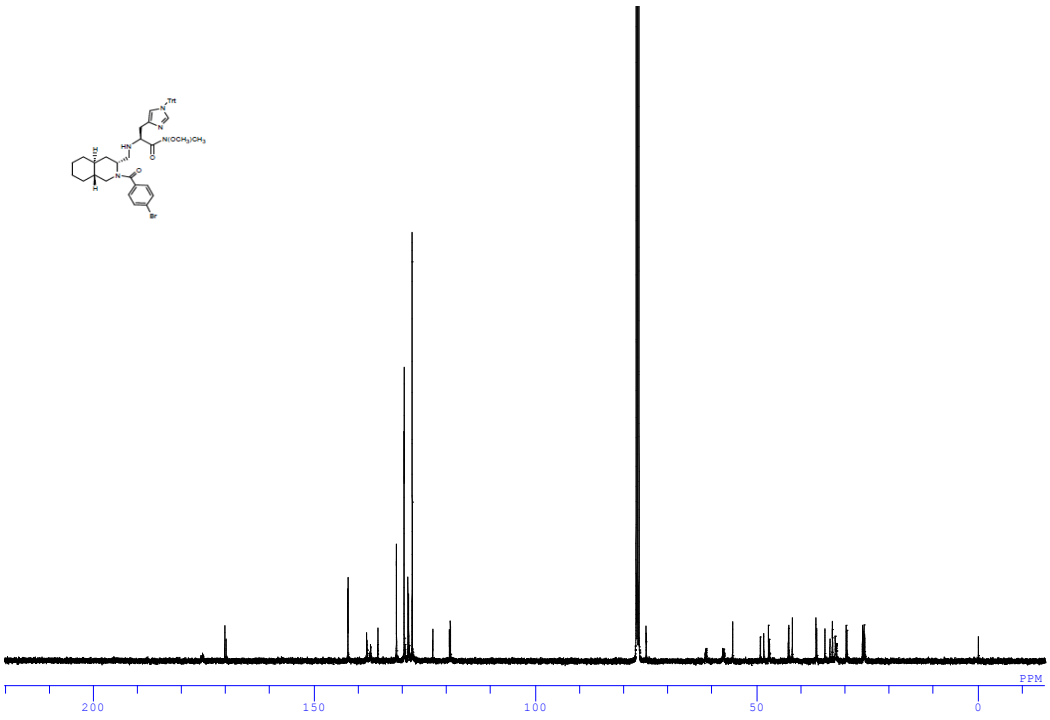
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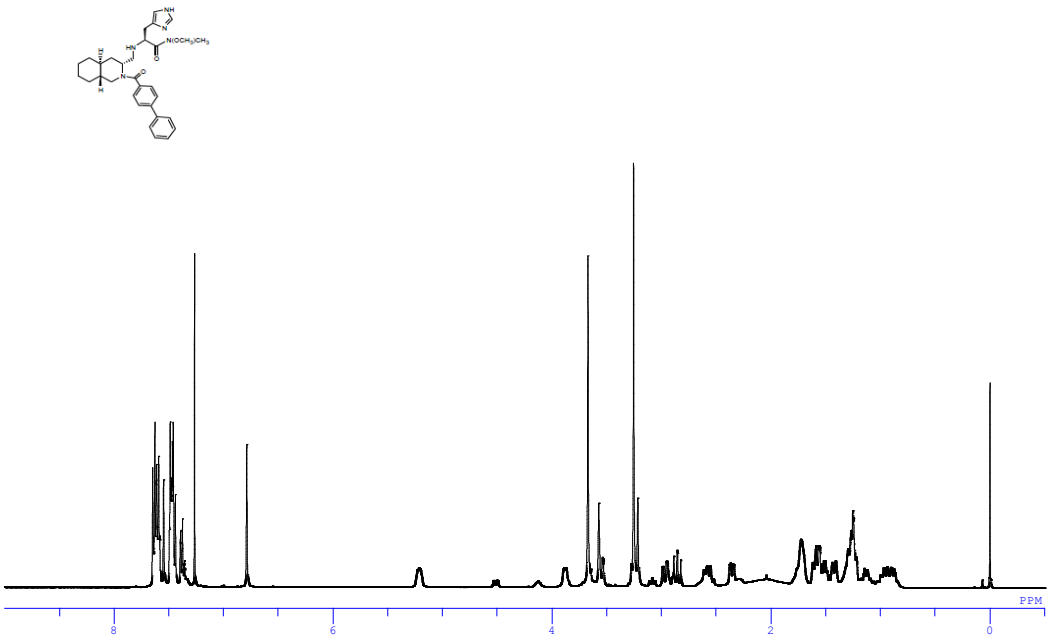
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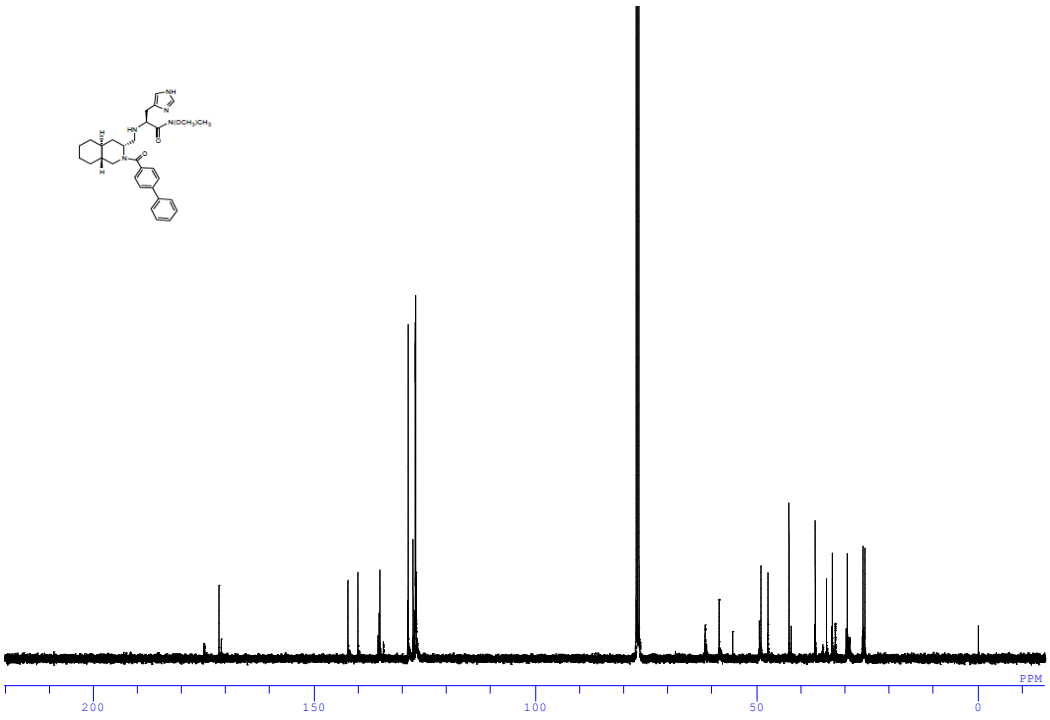
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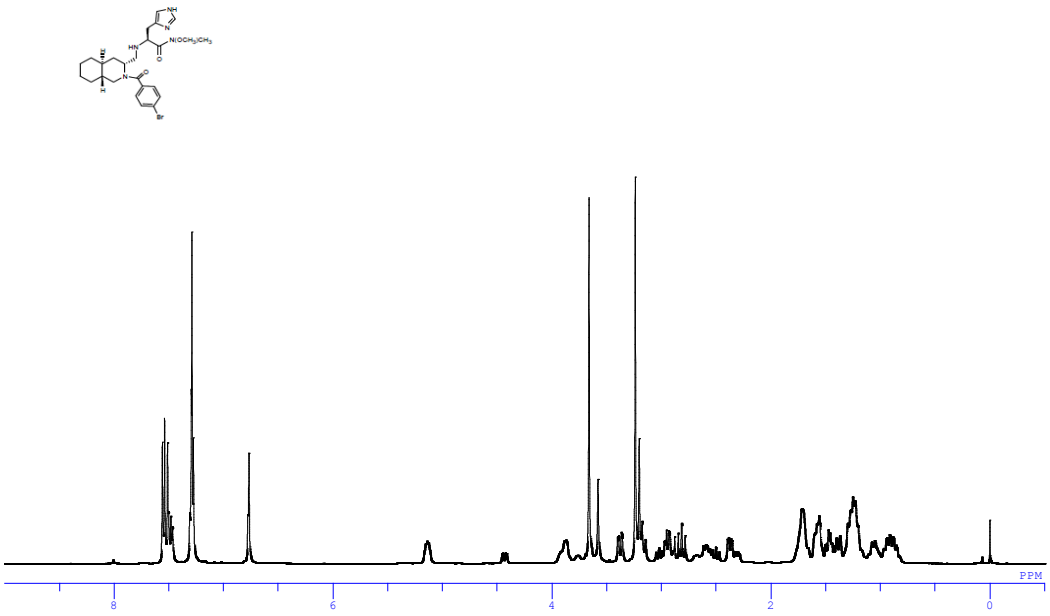
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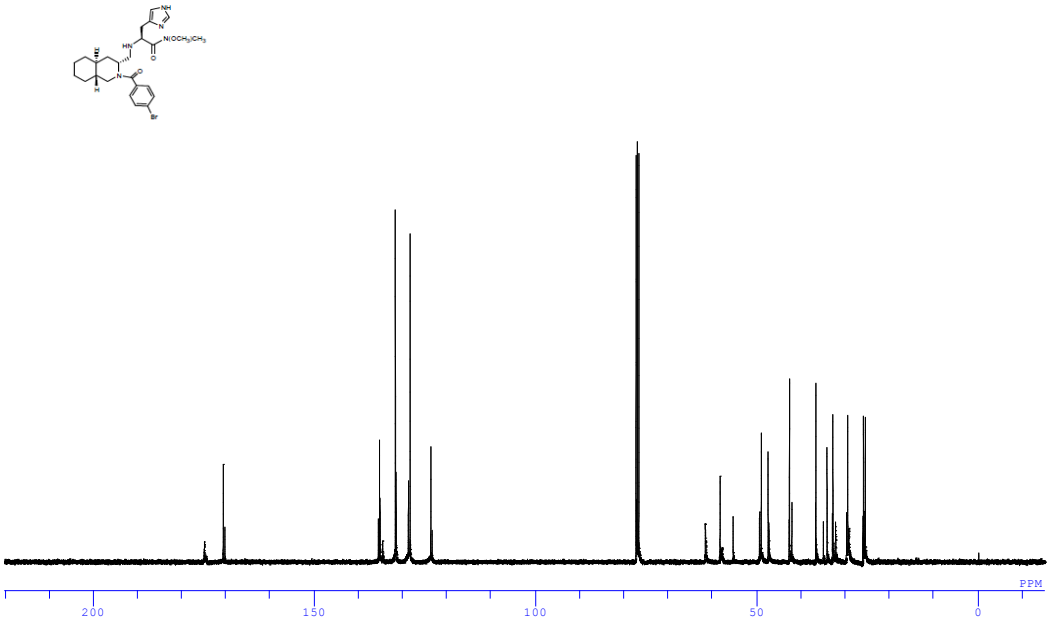
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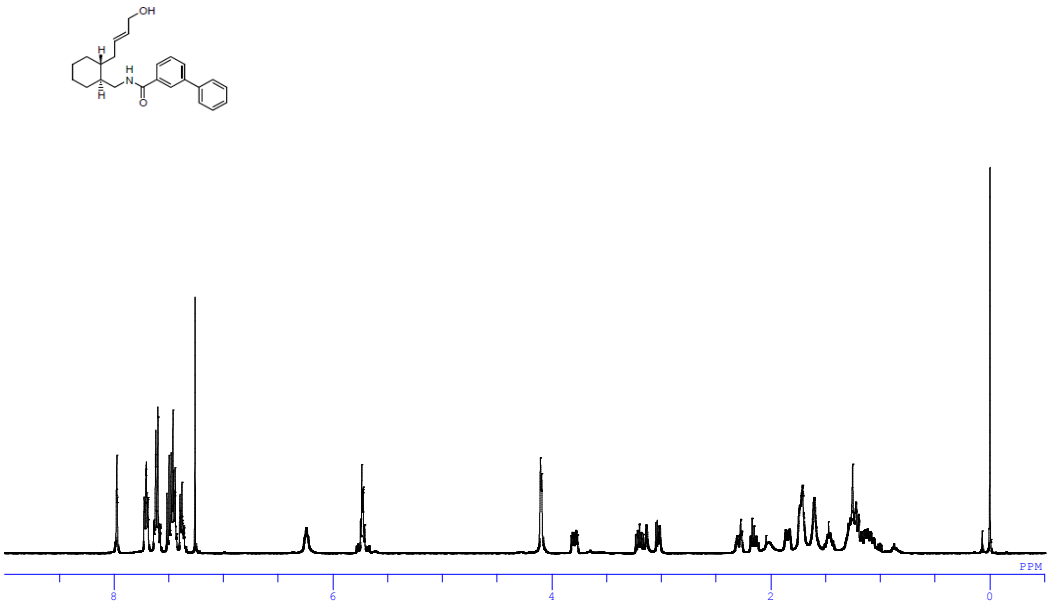
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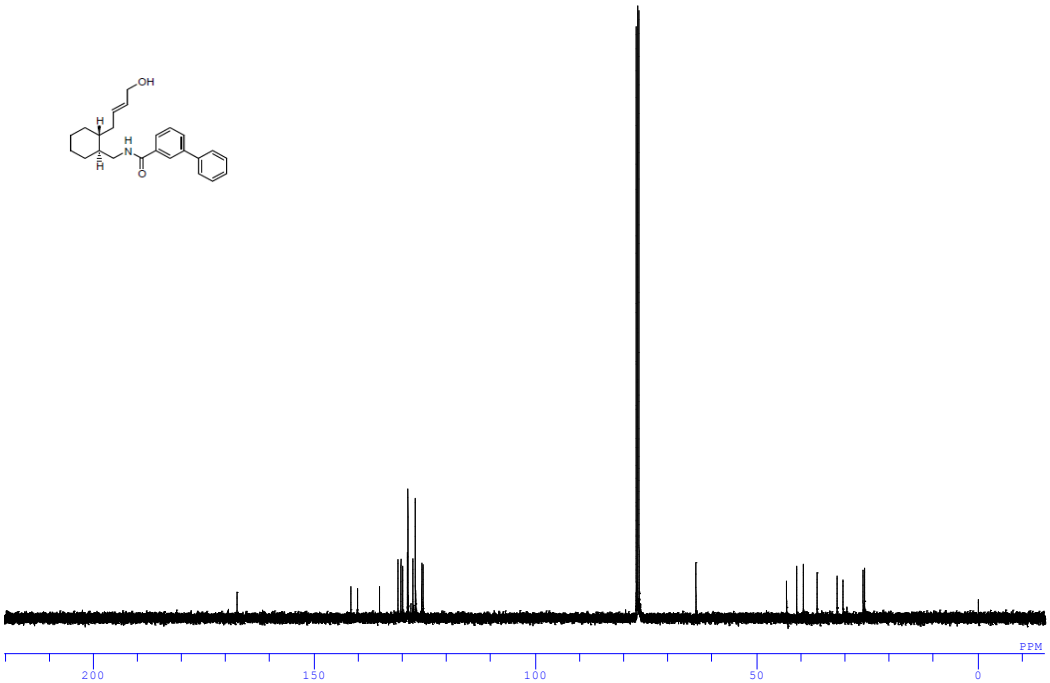
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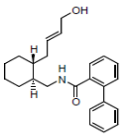
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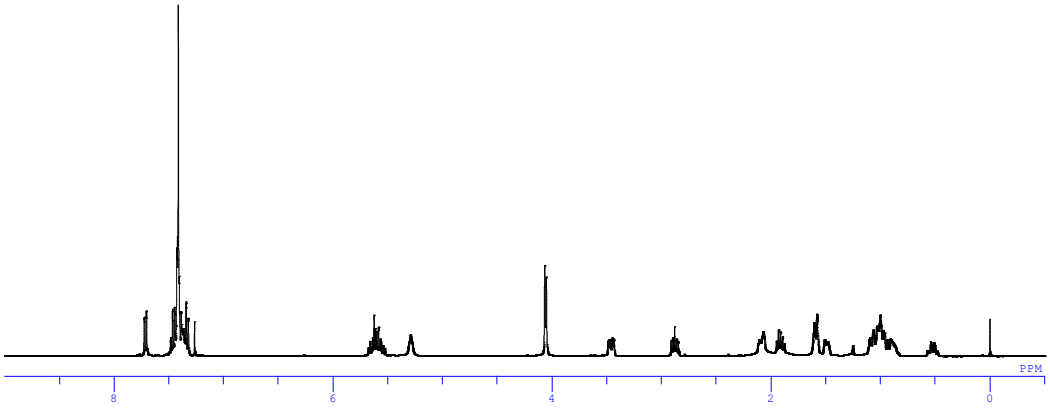
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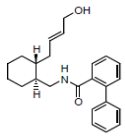
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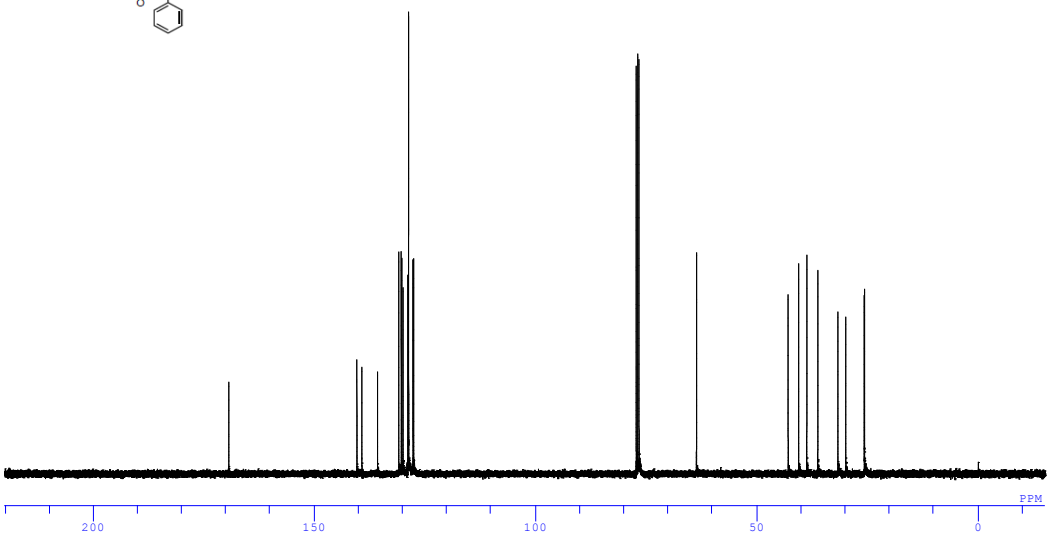
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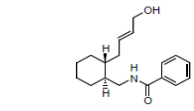
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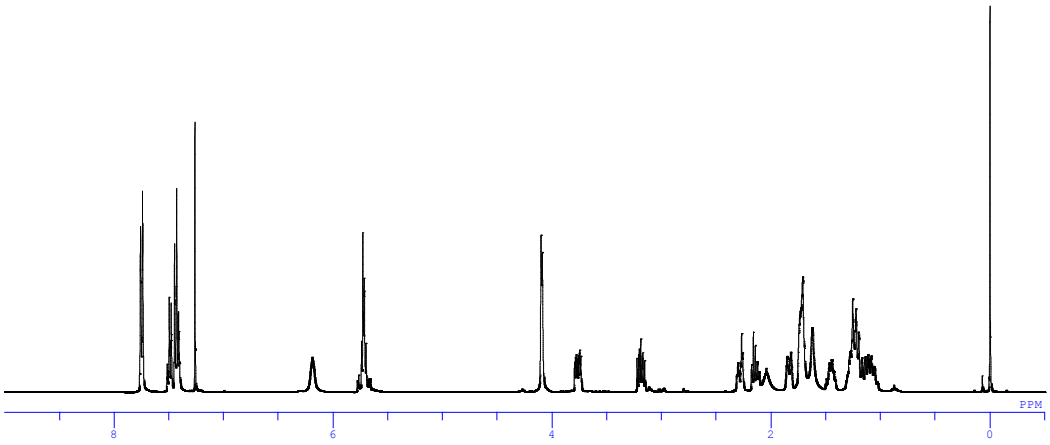
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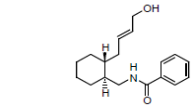
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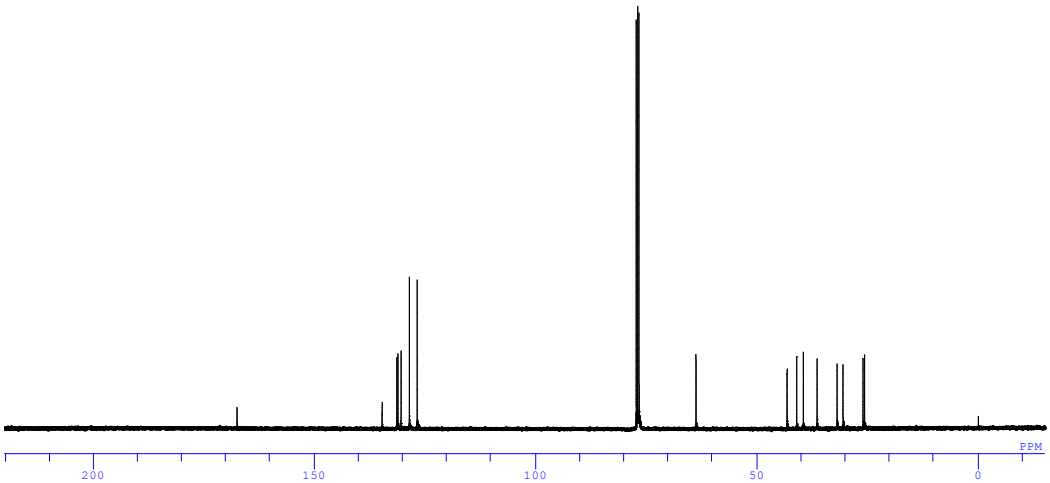
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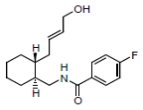
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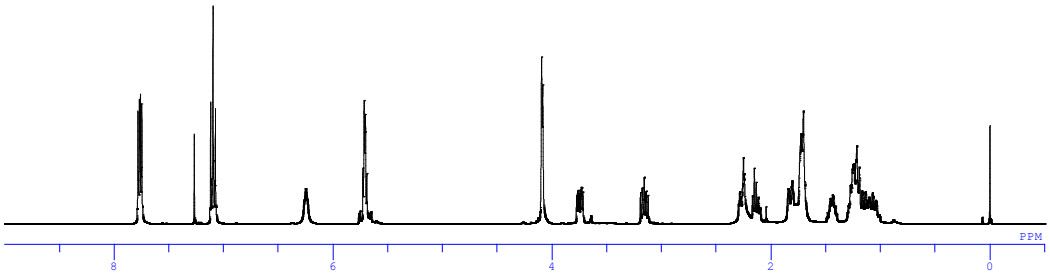
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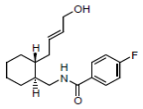
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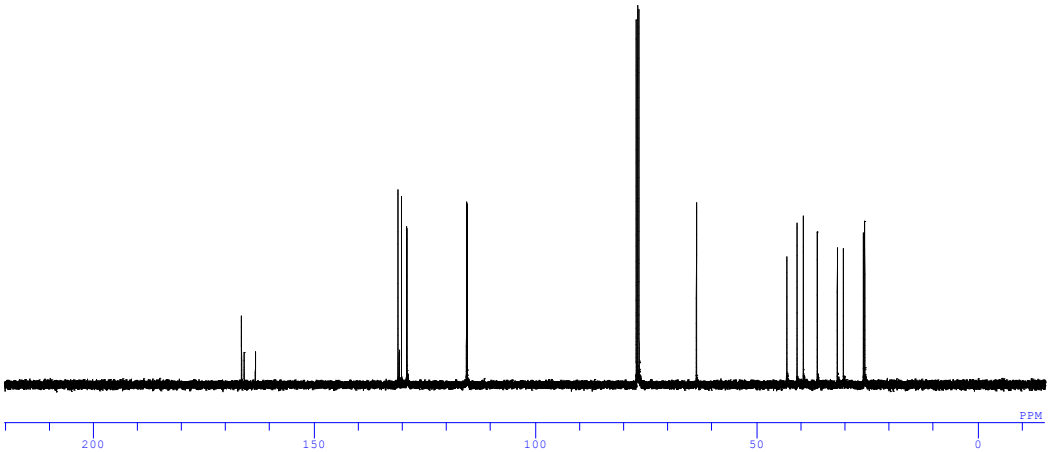
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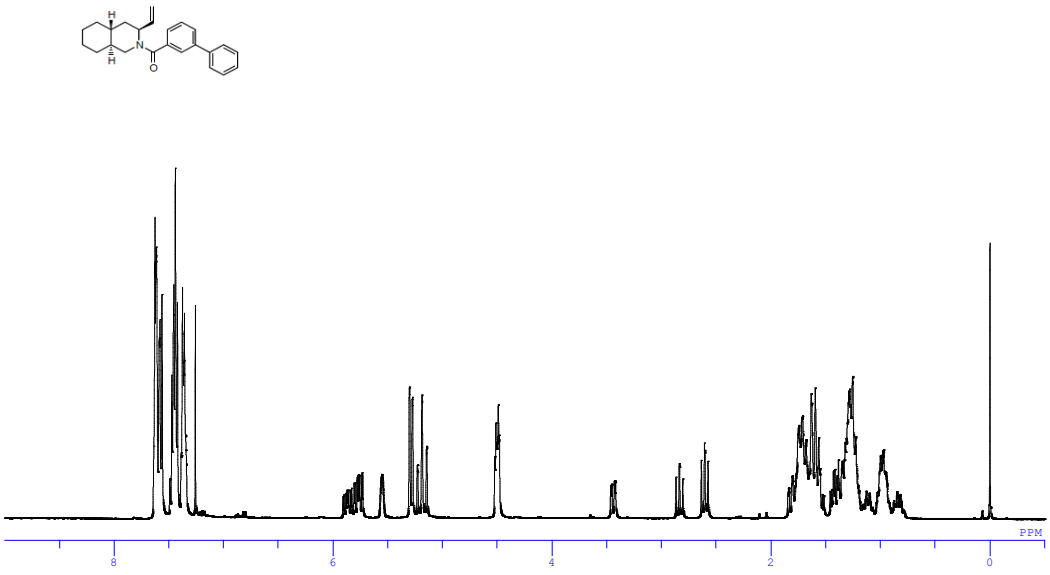
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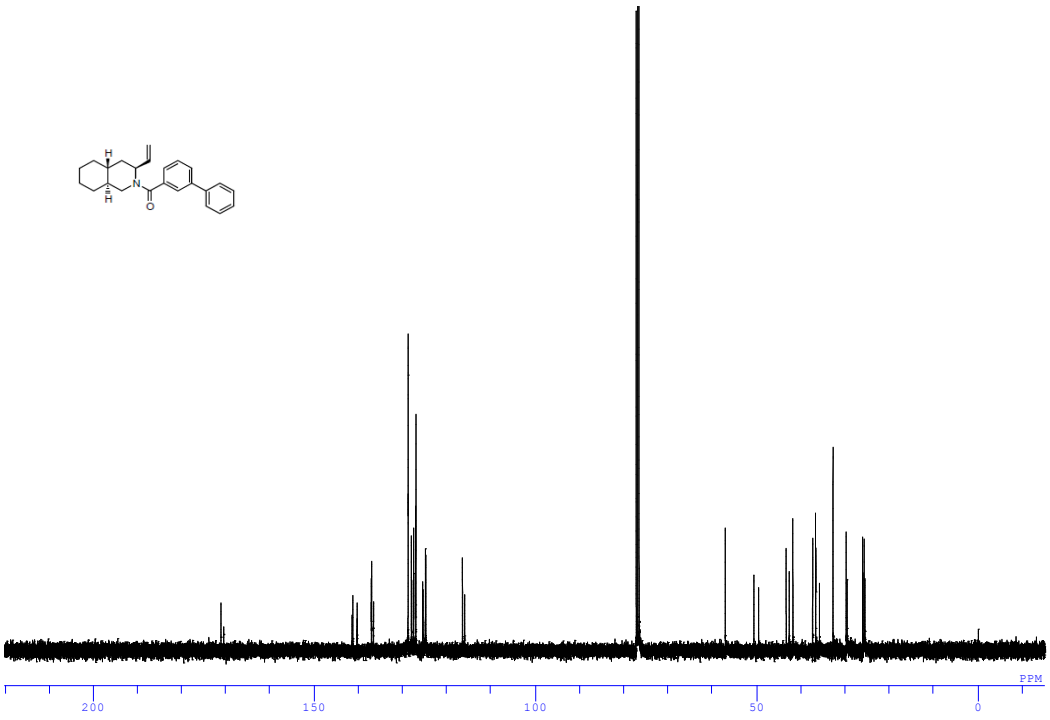
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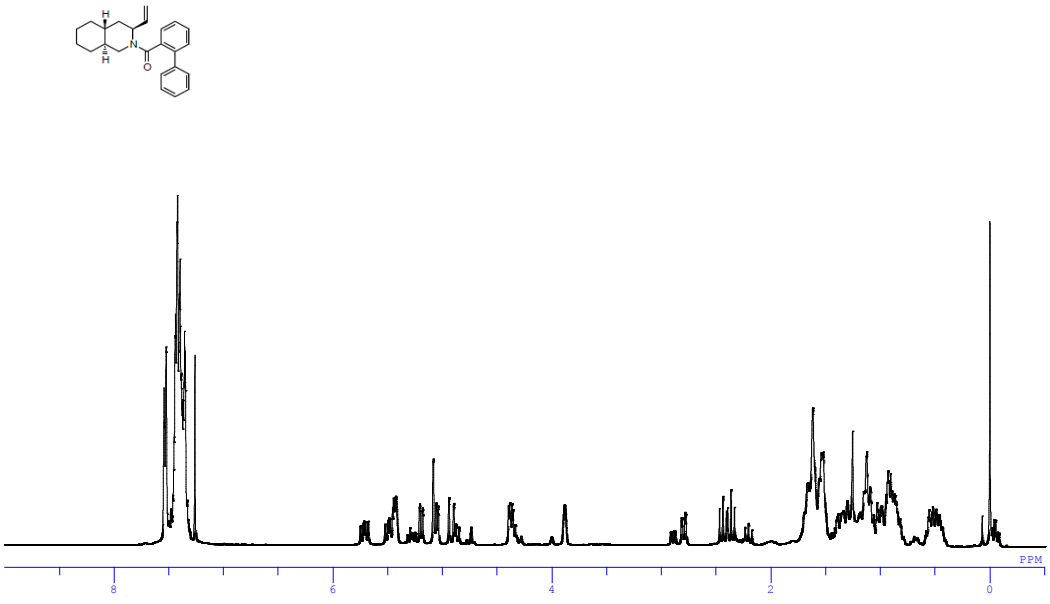
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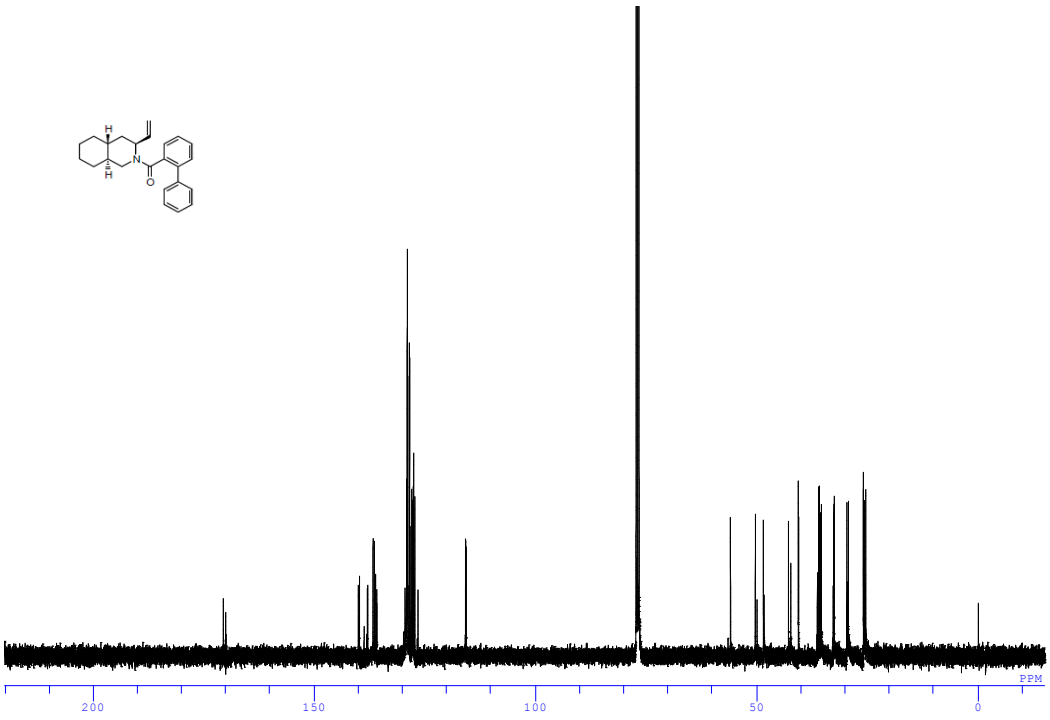
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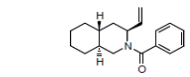

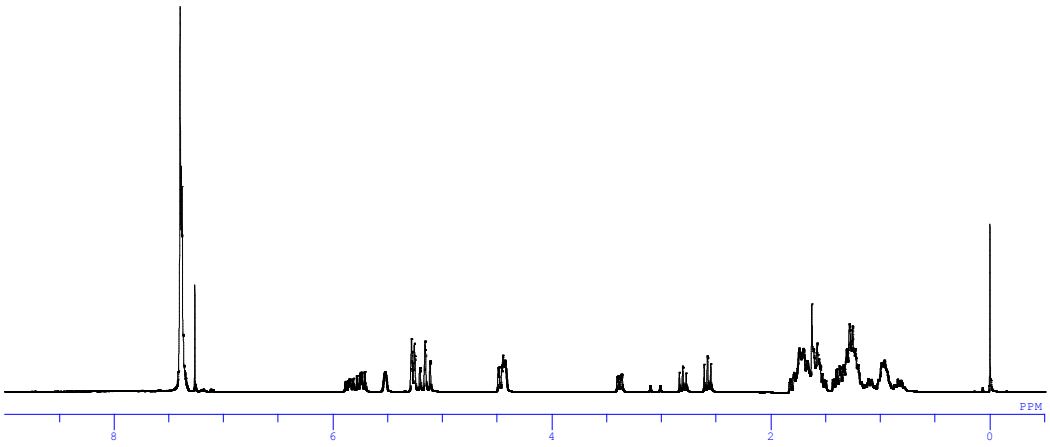
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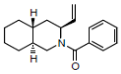

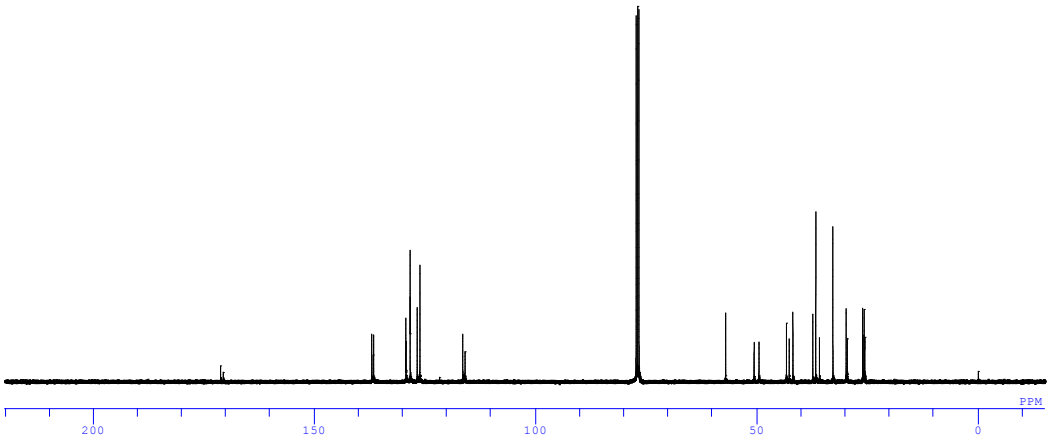
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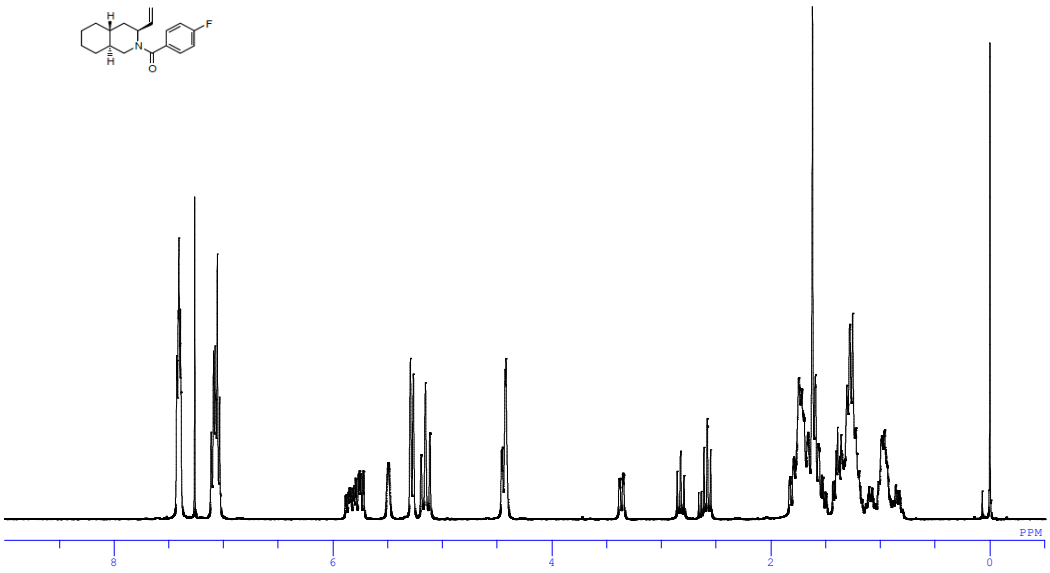
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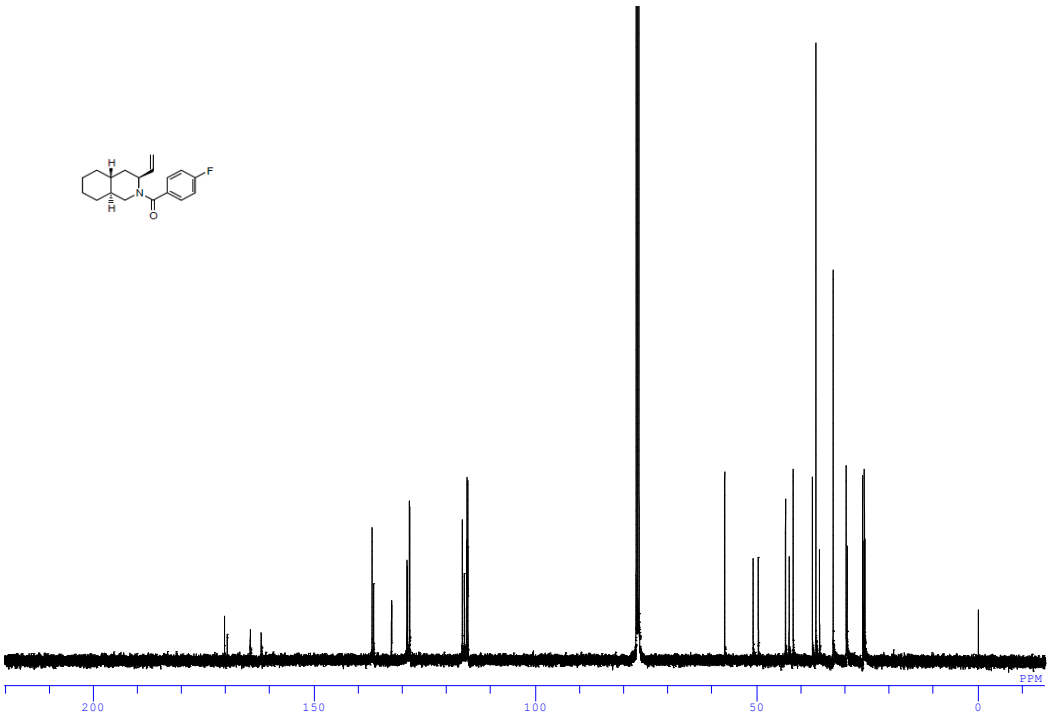
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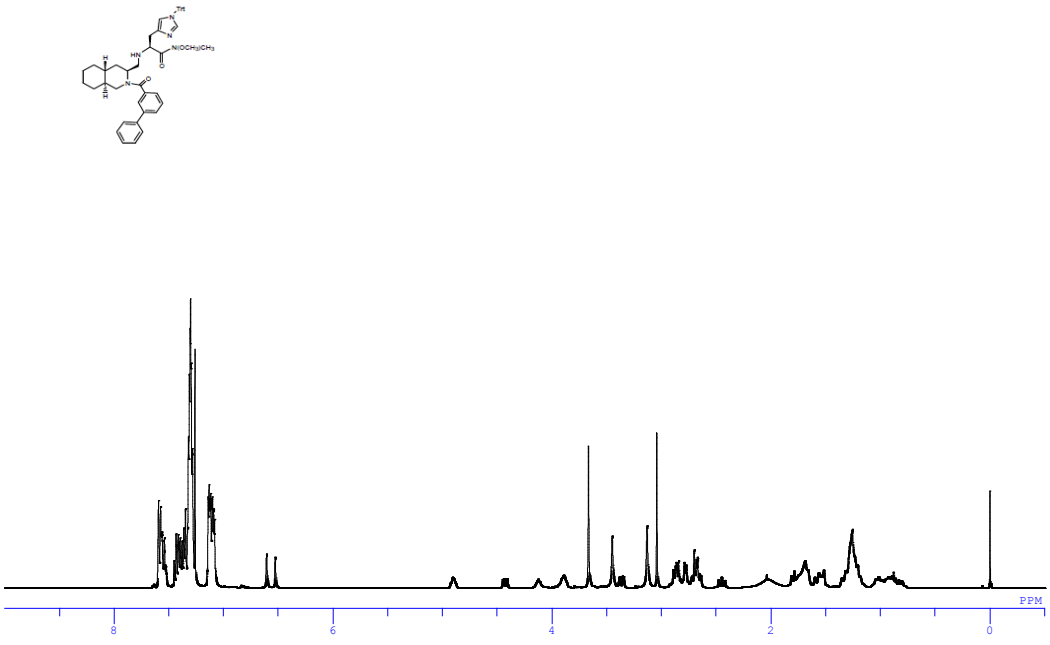
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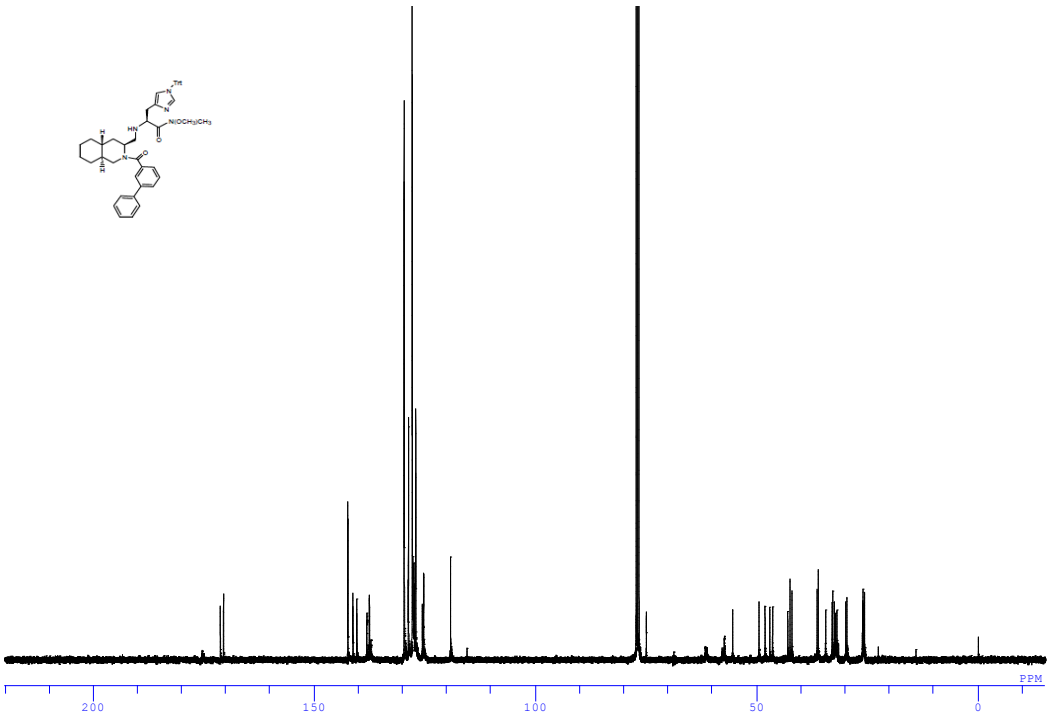
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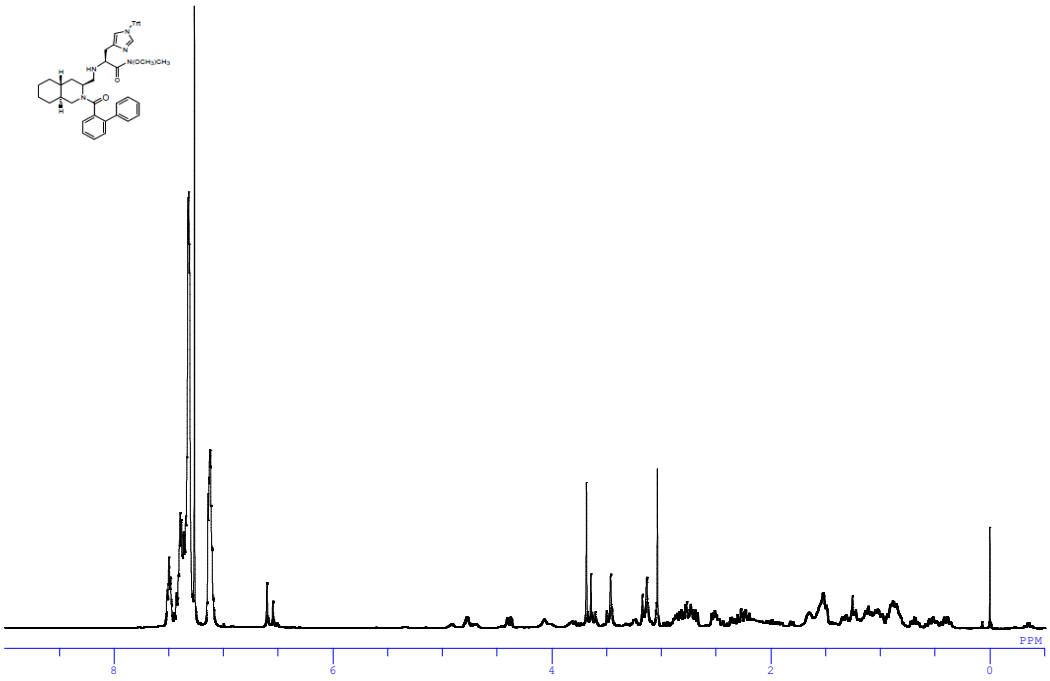
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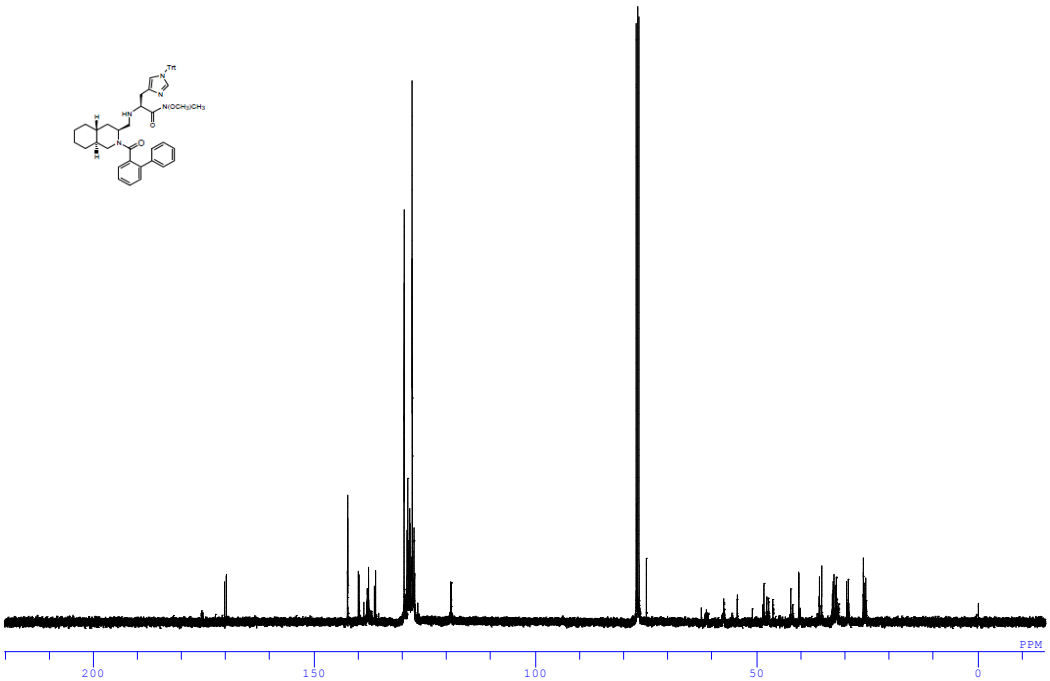
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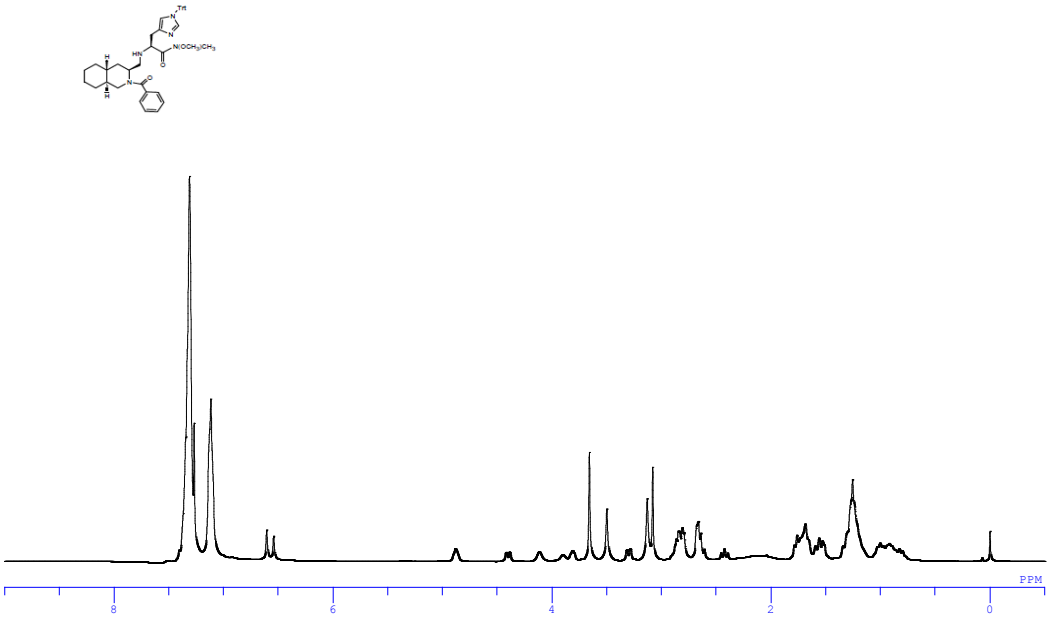
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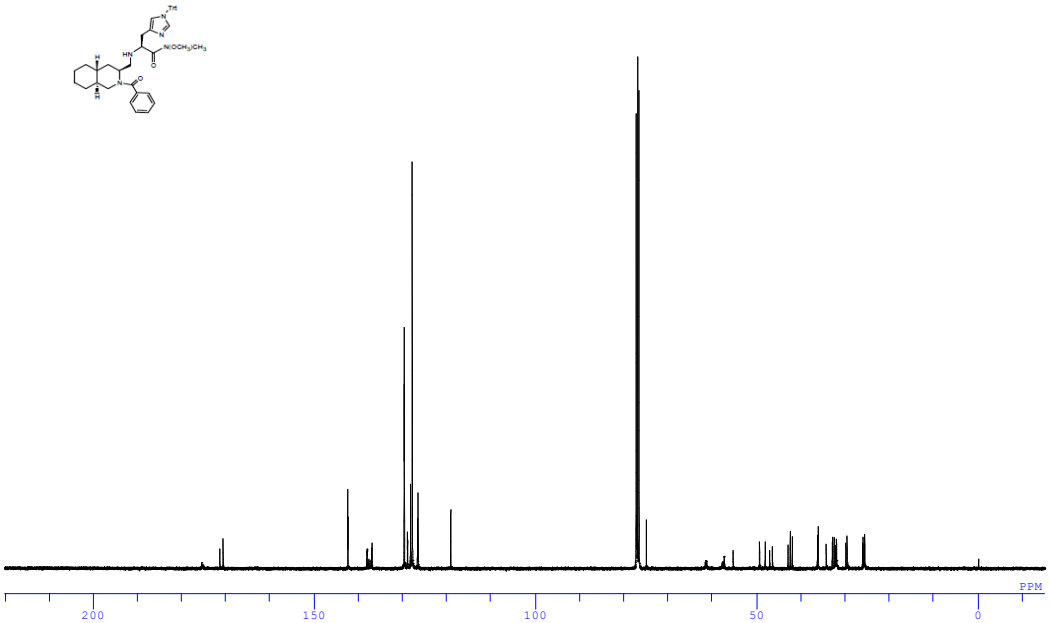
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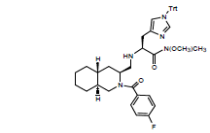

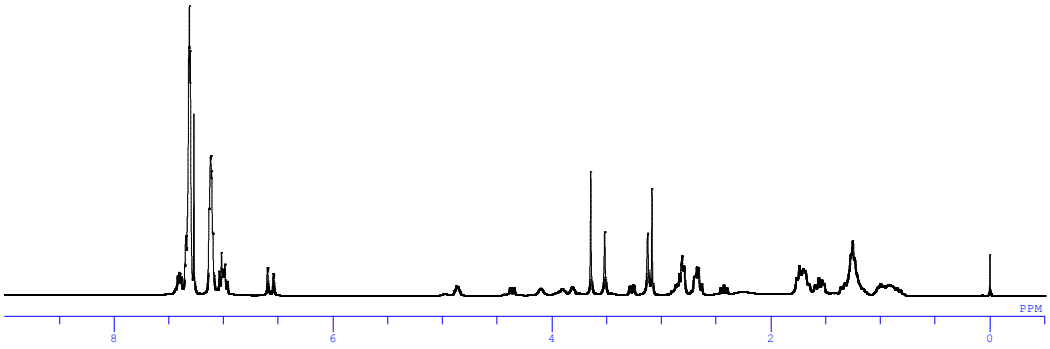
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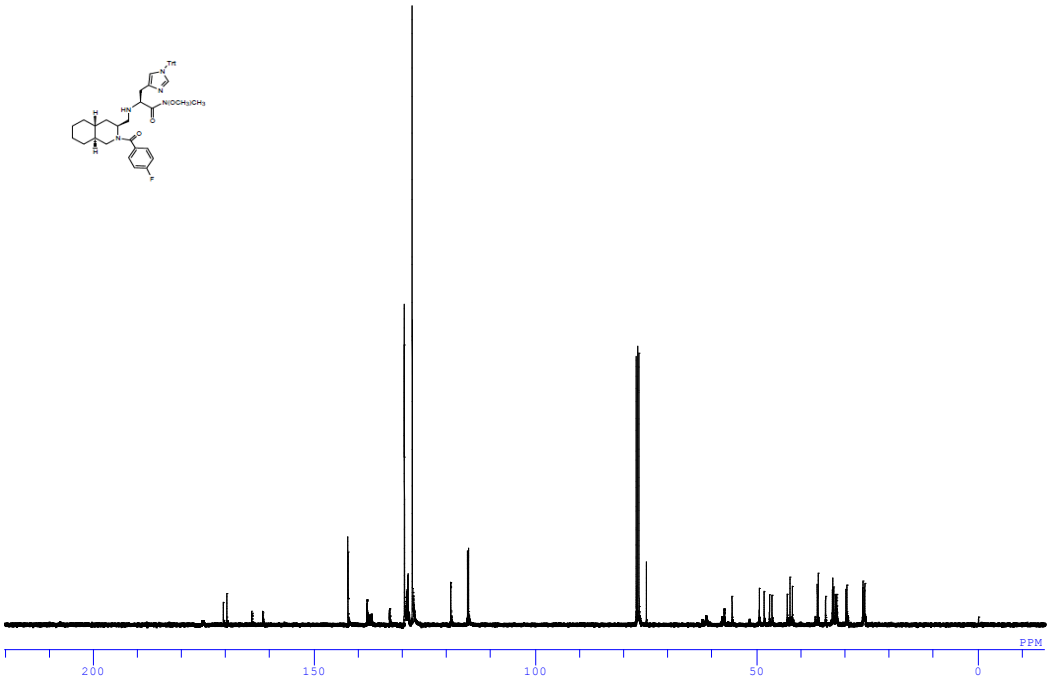
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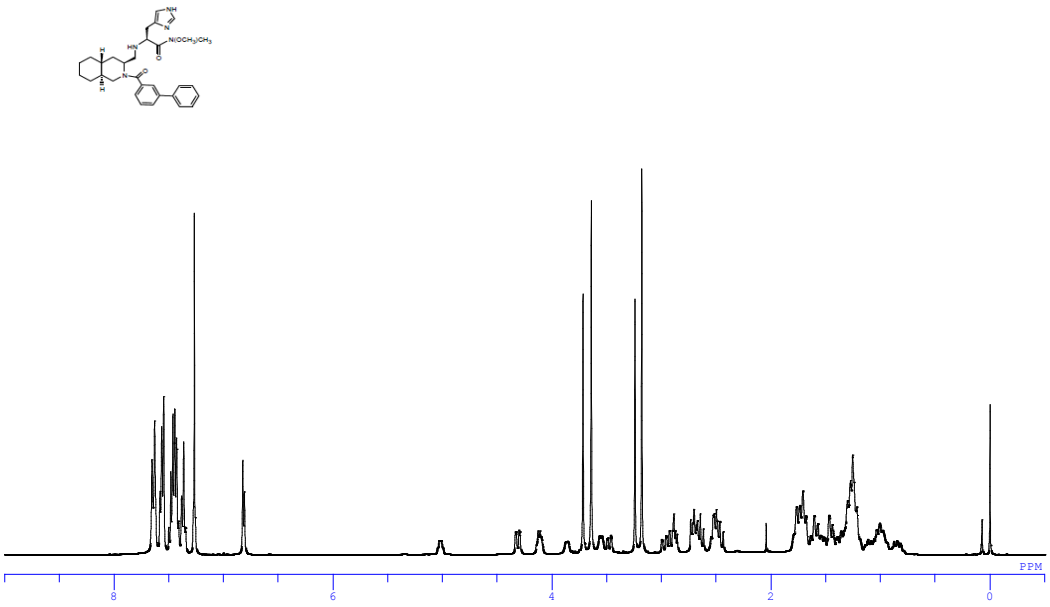
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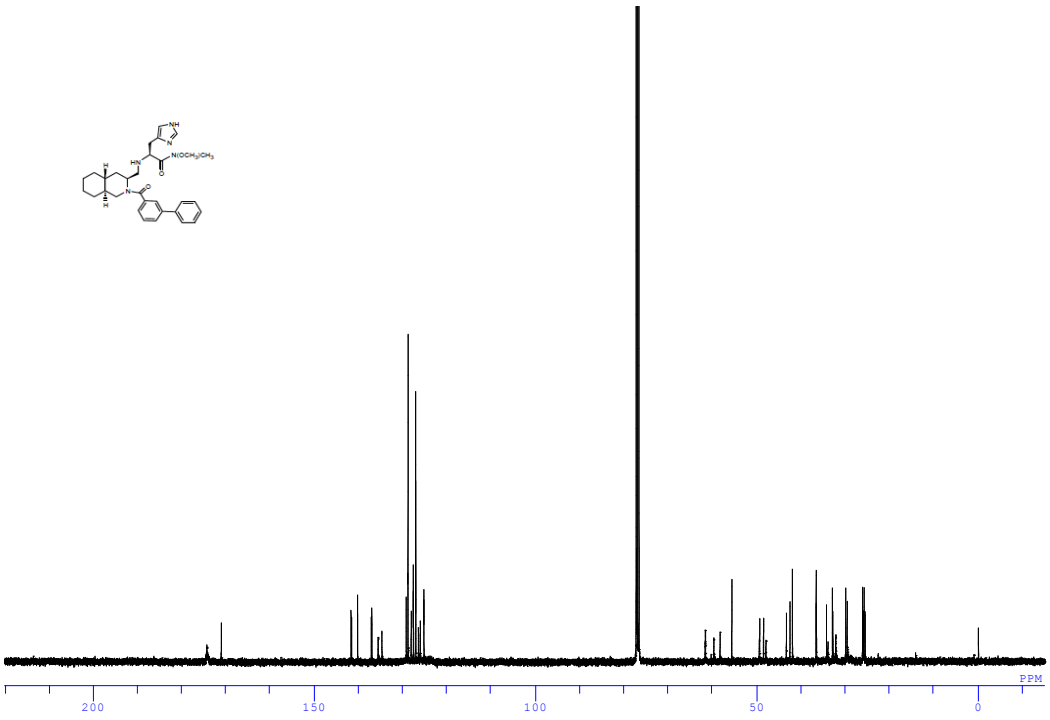
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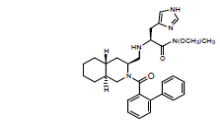

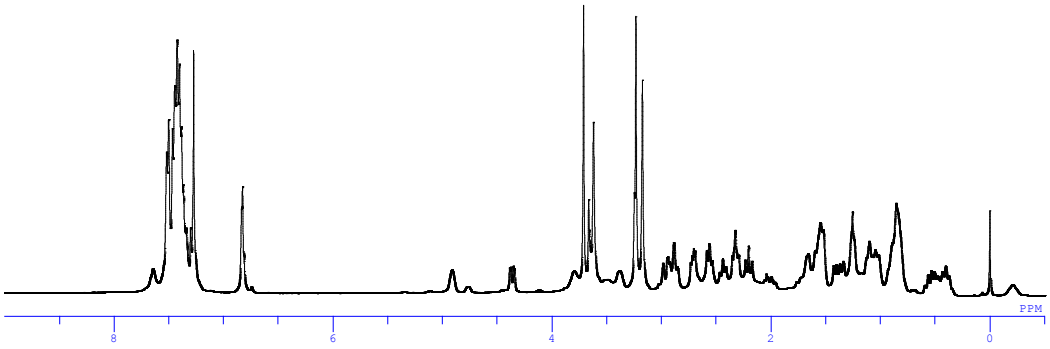
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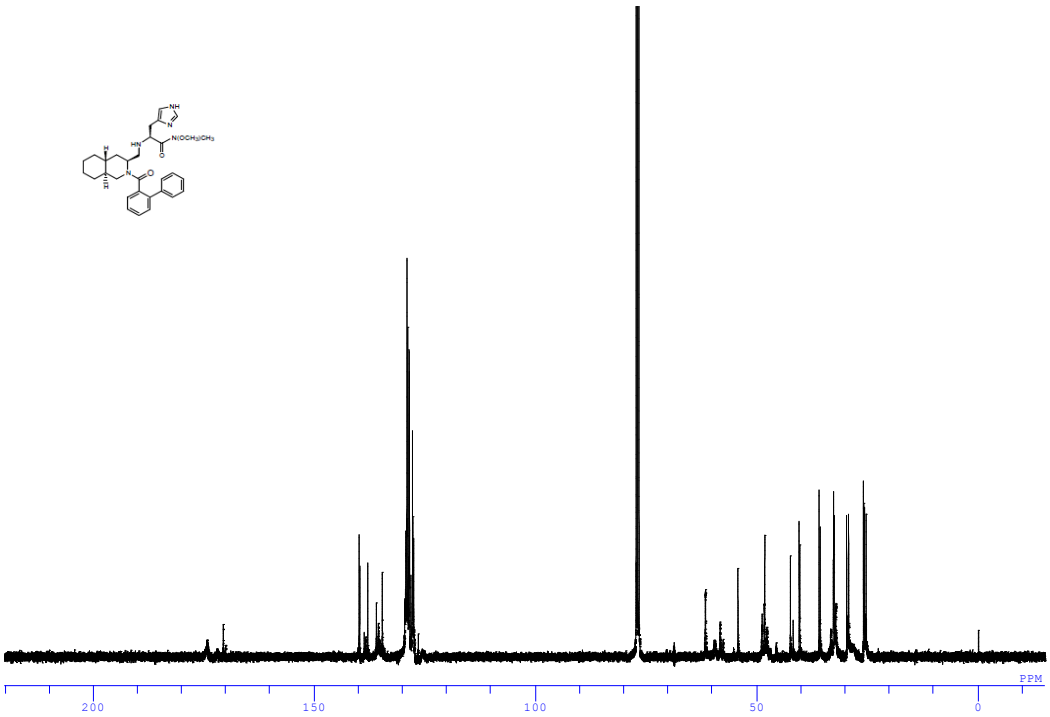
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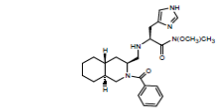

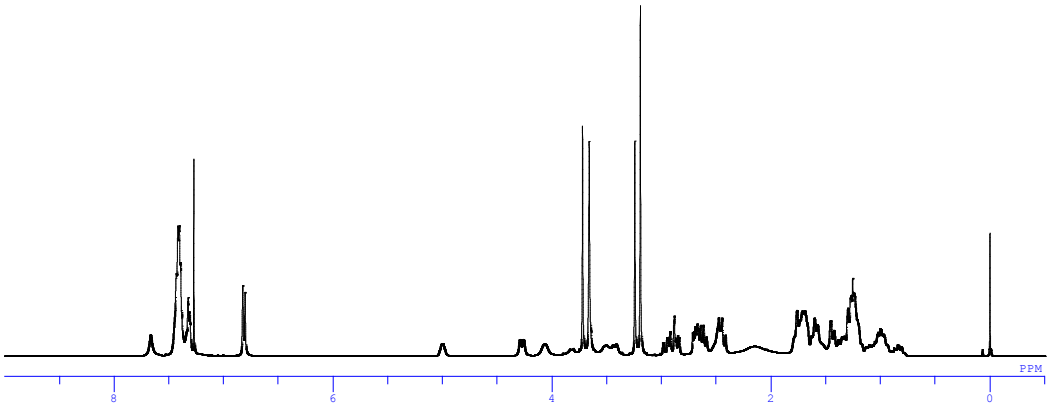
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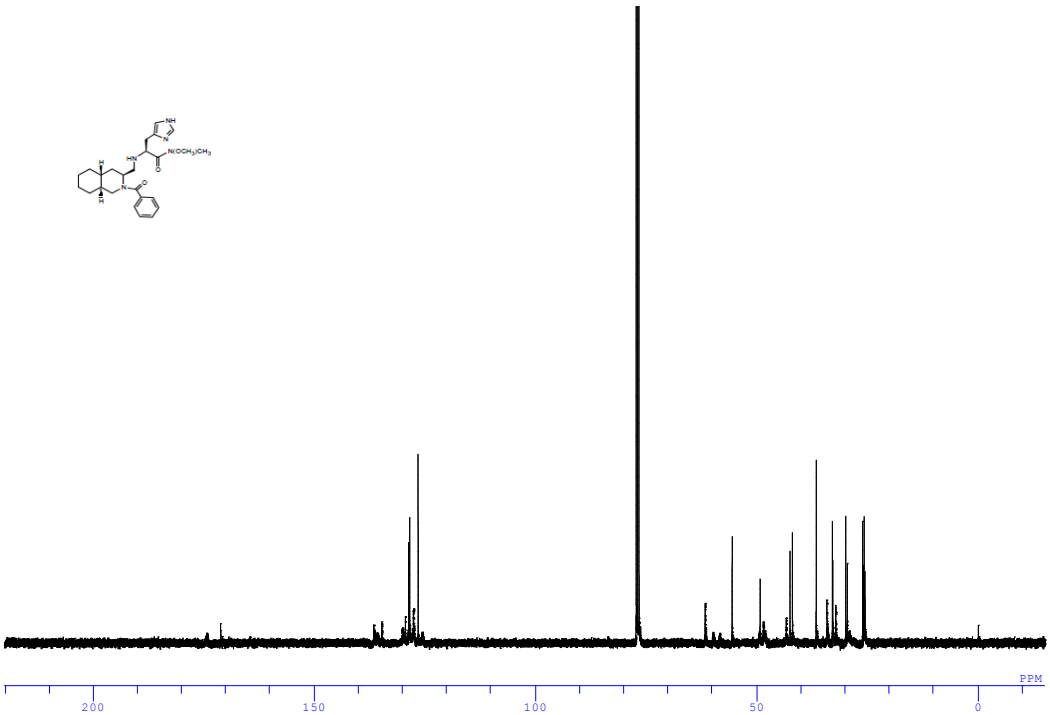
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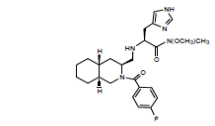

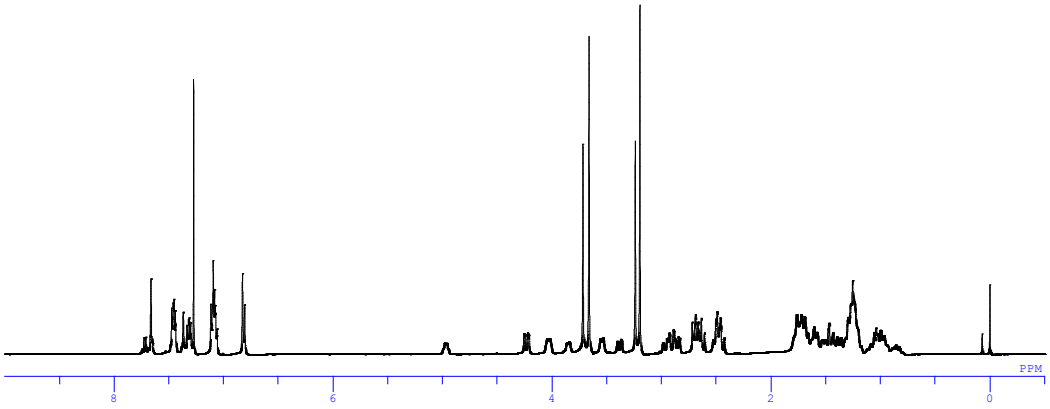
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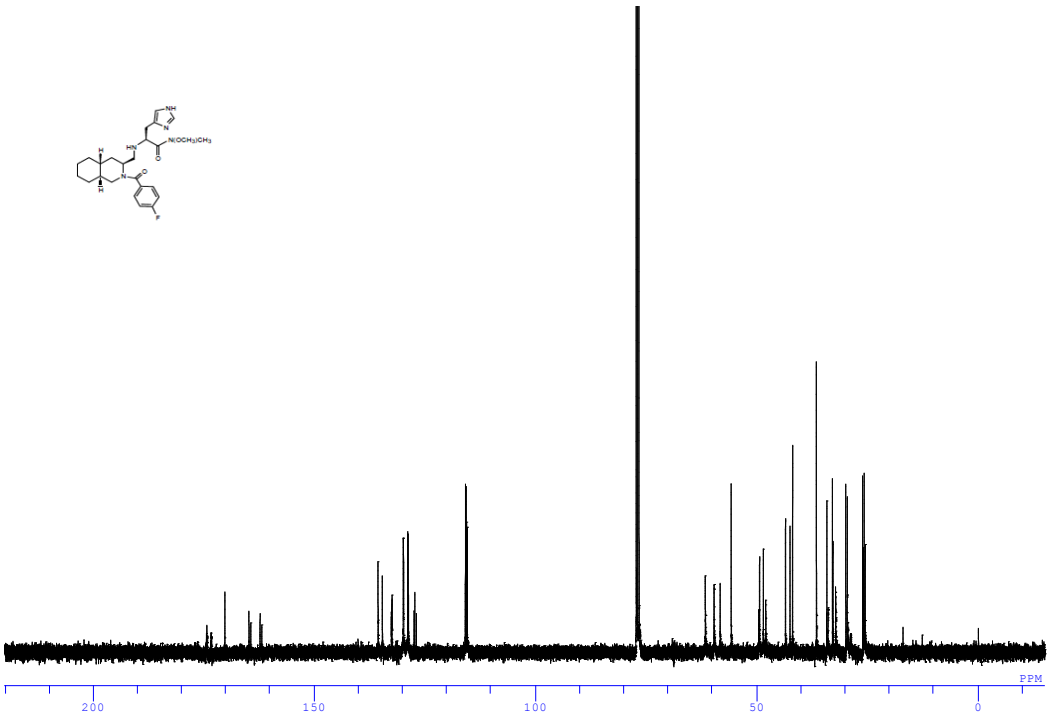
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