

Supporting Information

Formal [5 + 2] Cycloaddition of Vinylethylene Carbonates with Oxazol-5-(4*H*)-ones for Synthesis of 3,4-Dihydrooxepin-2(7*H*)-ones

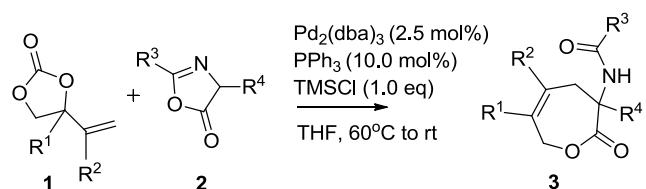
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1. General Information

Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on 400 MHz instrument (400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR) and calibrated using tetramethylsilane (TMS) as internal reference. High resolution mass spectra (HRMS) were recorded under electrospray ionization (ESI) conditions. The melting point of compounds was determined by a melting point instrument. Flash column chromatography was performed on silica gel (0.035-0.070 mm) using compressed air. Thin layer chromatography (TLC) was carried out on 0.25 mm SDS silica gel coated glass plates (60F254). Eluted plates were visualized using a 254 nm UV lamp. Unless otherwise indicated, all reagents were commercially available and used without further purification. All solvents were distilled from the appropriate drying agents immediately before using. Substituted vinylethylene carbonates **1a-1j** were synthesized according to the reported procedures.¹ Oxazol-5-(4*H*)-ones **2a-2j** were prepared according to literature procedures.²

2. General Procedure for [5 + 2] Cycloaddition

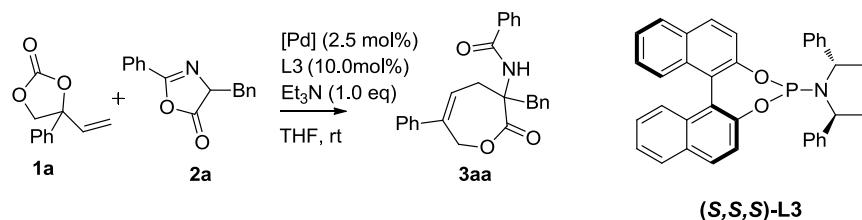


A mixture of vinylethylene carbonates **1** (1.0 equiv, 0.1 mmol), oxazol-5-(4*H*)-ones **2** (1.0 equiv, 0.1 mmol), $\text{Pd}_2(\text{dba})_3$ (2.5 mol%), PPh_3 (10.0 mol%) in THF (1.0 mL) was stirred at 60°C for 5 minutes. After that, TMSCl (1.0 equiv, 0.1 mmol) was added at rt, and the resulted reaction mixture continued to be stirred until the reaction was completed as indicated by TLC plate. The reaction mixture was concentrated under reduced pressure and the resulted crude products were purified by flash column chromatography on silica gel (petroleum ether / ethyl acetate/ CH_2Cl_2 = 10:1:10) to afford products **3** (67-99% yields).

3. General Procedure for Asymmetric Catalytic [5 + 2] Cycloaddition

A mixture of vinylethylene carbonate **1a** (1.0 equiv, 0.1 mmol), oxazol-5-(4*H*)-one **2a** (1.0 equiv, 0.1 mmol), Pd precatalyst (2.5 mol%), chiral ligand (10.0 mol%) and Et_3N (1.0 equiv, 0.1 mmol) was stirred in THF (1.0 mL) at rt until the reaction was completed indicated by TLC plate. The reaction mixture was concentrated under reduced pressure and the resulted crude product was purified by flash column chromatography on silica gel (petroleum ether / ethyl acetate/ CH_2Cl_2 = 10:1:10) to afford product **3aa**.

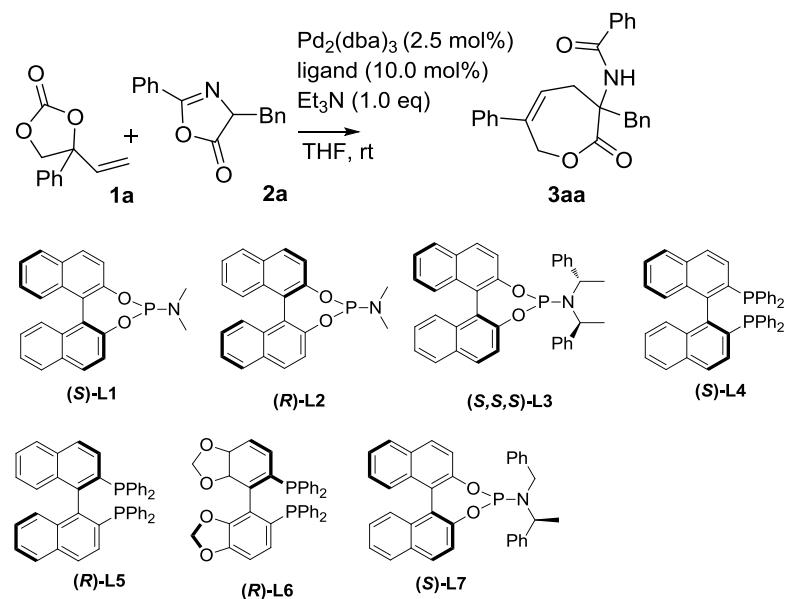
Table S1 Screening of Pd precatalysts^a



Entry	[Pd]	Time (h)	Yield ^b (%)	ee ^c
1	Pd(PPh ₃) ₄	2	21	5
2	Pd(OAc) ₂	2	25	19
3	Pd ₂ (dba) ₃	2	55	39
4	Pd(PPh ₃) ₂ Cl ₂	2	17	0
5	[Pd ₂ (dba) ₃] CHCl ₃	2	38	6

^a Reactions were carried out with **1a** (0.1 mmol), **2a** (0.1 mmol), [Pd] (2.5 mol%), **L3** (10.0 mol%), Et₃N (0.1 mmol) in THF (1.0 mL) at rt. ^b Isolated yield. ^c Determined by chiral HPLC analysis.

Table S2 Screening of chiral ligands^a

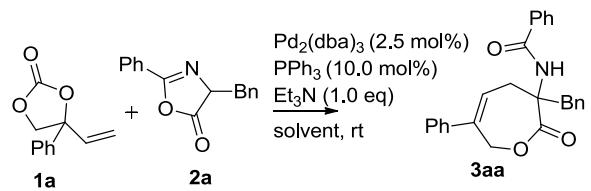


Entry	Ligand	Time (h)	Yield ^b (%)	ee ^c
1	L1	2	7	6
2	L2	2	25	9
3	L3	2	55	39
4	L4	2	43	9
5	L5	2	38	8
6	L6	2	5	13
7	L7	2	62	38

^a Reactions were carried out with **1a** (0.1 mmol), **2a** (0.1 mmol), Pd₂(dba)₃ (2.5 mol%), chiral ligand (10.0 mol%), Et₃N (0.1 mmol) in THF (1.0 mL) at rt. ^b Isolated chemical yield. ^c Determined by chiral HPLC analysis.

4. Screening of Solvents

A mixture of vinyl ethylene carbonate **1a** (1.0 equiv, 0.1 mmol), oxazol-5(4H)-one **2a** (1.0 equiv, 0.1 mmol), Pd₂(dba)₃ (2.5 mol%), PPh₃ (10.0 mol%) and Et₃N (1.0 equiv, 0.1 mmol) in the specified solvent (1.0 mL) was stirred at rt until the reaction was completed indicated by TLC plate. The reaction mixture was concentrated under reduced pressure and the resulted crude products were purified by flash column chromatography on silica gel (petroleum ether / ethyl acetate/CH₂Cl₂ = 10:1:10) to afford product **3aa**.

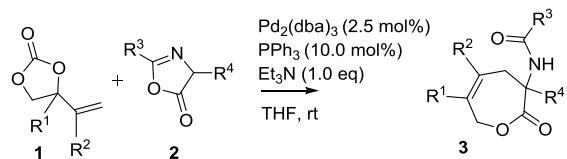
Table S3 Screening of Solvents^a

Entry	Solvent	Time (h)	Yield ^b (%)
1	DCM	4	trace
2	THF	4	75
3	Toluene	4	42
4	EtOH	4	trace
5	1,2-DCE	4	trace
6	CHCl ₃	4	trace

^a Reactions were carried out with **1a** (0.1 mmol), **2a** (0.1 mmol), Pd₂(dba)₃ (2.5 mol%), PPh₃ (10.0 mol%), Et₃N (0.1 mmol) in the specified solvent (1.0 mL) at rt. ^b Isolated yield.

5. Extension of Reaction Scope in the Presence of Et₃N

A mixture of vinylethylene carbonates **1** (1.0 equiv, 0.1 mmol), oxazol-5-(4*H*)-ones **2** (1.0 equiv, 0.1 mmol), Pd₂(dba)₃ (2.5 mol%), PPh₃ (10.0 mol%) and Et₃N (1.0 equiv, 0.1 mmol) in THF (1.0 mL) was stirred at room temperature. The reaction mixture was concentrated under reduced pressure and the crude products were purified by flash column chromatography on silica gel (petroleum ether / ethyl acetate/CH₂Cl₂ = 10:1:10) to afford products **3**.

Table S4 Extension of reaction scope^a

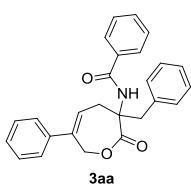
Entry	1 (R ¹ , R ²)	2 (R ³ , R ⁴)	3	Time (h)	Yield ^b (%)
1	1a (Ph, H)	2a (Ph, Bn)	3aa	3	75
2	1a (Ph, H)	2b (4-MeC ₆ H ₄ , Bn)	3ab	3	39
3	1a (Ph, H)	2c (4-BrC ₆ H ₄ , Bn)	3ac	3	51
4	1a (Ph, H)	2d (4-ClC ₆ H ₄ , Bn)	3ad	3	23
5	1a (Ph, H)	2f (3,4-di-ClC ₆ H ₃ , Bn)	3af	3	40
6	1a (Ph, H)	2g (Ph, Ph)	3ag	6	nr ^c
7	1a (Ph, H)	2h (Ph, H)	3ah	6	nr ^c
8	1b (4-BrC ₆ H ₄ , H)	2a (Ph, Bn)	3ba	3	15
9	1c (4-ClC ₆ H ₄ , H)	2a (Ph, Bn)	3ca	3	30
10	1d (4-FC ₆ H ₄ , H)	2a (Ph, Bn)	3da	3	43
11	1e (4-MeC ₆ H ₄ , H)	2a (Ph, Bn)	3ea	3	55

12	1f (4-OMeC ₆ H ₄ , H)	2a (Ph, Bn)	3fa	3	42
13	1g (3-ClC ₆ H ₄ , H)	2a (Ph, Bn)	3ga	3	32
14	1h (2-ClC ₆ H ₄ , H)	2a (Ph, Bn)	3ha	6	nr ^c
15	1i (Ph, Me)	2a (Ph, Bn)	3ia	6	nr ^c
16	1e (4-MeC ₆ H ₄ , H)	2b (4-MeC ₆ H ₄ , Bn)	3eb	3	31
17	1f (4-OMeC ₆ H ₄ , H)	2b (4-MeC ₆ H ₄ , Bn)	3fb	3	45

^aThe reaction mixture of **1** (0.1 mmol), **2** (0.1mmol), Pd₂(dba)₃ (2.5 mol%), PPh₃ (10.0 mol%) and Et₃N (0.1 mmol) was stirred at rt. in THF (1.0 mL). ^b Isolated yield. ^c No reaction.

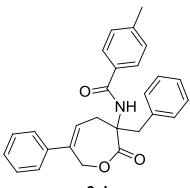
6. Characterization

N-(3-benzyl-2-oxo-6-phenyl-2,3,4,7-tetrahydroxepin-3-yl)benzamide (3aa): White solid, yield:



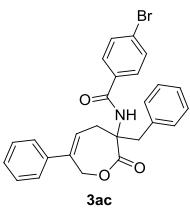
31.8 mg, 80%; M.P. = 172.8-173.9 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.74 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 6.8 Hz, 1H), 7.46-7.43 (m, 2H), 7.35-7.28 (m, 8H), 7.21 (d, *J* = 7.2 Hz, 2H), 6.71 (s, 1H), 6.08-6.06 (m, 1H), 5.47 (d, *J* = 15.6 Hz, 1H), 5.02 (d, *J* = 15.6 Hz, 1H), 3.67 (d, *J* = 14.0 Hz, 1H), 3.44 (d, *J* = 14.0 Hz, 1H), 3.13 (dd, *J* = 17.6, 5.6 Hz, 1H), 2.90 (d, *J* = 17.6 Hz, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 172.5, 167.0, 140.1, 139.6, 135.3, 133.3, 132.2, 130.8, 128.8, 128.7, 128.6, 128.1, 127.4, 127.0, 126.0, 125.9, 69.0, 63.2, 41.2, 33.5 ppm; HRMS (ESI) calculated for C₂₆H₂₄NO₃[M + H]⁺: 398.1751, found 398.1750.

N-(3-benzyl-2-oxo-6-phenyl-2,3,4,7-tetrahydroxepin-3-yl)-4-methylbenzamide (3ab): White solid, yield:



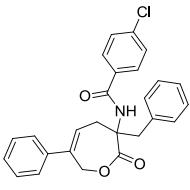
27.5 mg, 67%; M.P. = 163.5-163.9 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.65 (d, *J* = 8.0 Hz, 2H), 7.35-7.30 (m, 6H), 7.28-7.18 (m, 6H), 6.71 (s, 1H), 6.03 (d, *J* = 4.4 Hz, 1H), 5.45 (d, *J* = 15.6 Hz, 1H), 4.95 (d, *J* = 15.2 Hz, 1H), 3.69 (d, *J* = 14.0 Hz, 1H), 3.37 (d, *J* = 14.0 Hz, 1H), 3.08 (dd, *J* = 17.6, 5.6 Hz, 1H), 2.85 (d, *J* = 18.0 Hz, 1H), 2.41 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 172.3, 167.0, 142.8, 139.8, 139.7, 135.5, 130.9, 130.4, 129.5, 128.7, 128.6, 128.0, 127.3, 127.1, 126.1, 125.8, 68.9, 62.7, 41.3, 33.7, 21.5 ppm; HRMS (ESI) calculated for C₂₇H₂₆NO₃[M + H]⁺: 412.1907, found 412.1911.

N-(3-benzyl-2-oxo-6-phenyl-2,3,4,7-tetrahydroxepin-3-yl)-4-bromobenzamide (3ac): White solid, yield:



36.5 mg, 77%; M.P. = 157.0-157.5 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.58 (s, 4H), 7.37-7.28 (m, 8H), 7.18 (d, *J* = 6.4 Hz, 2H), 6.72 (s, 1H), 6.10 (t, *J* = 5.2 Hz, 1H), 5.43 (d, *J* = 15.2 Hz, 1H), 5.05 (d, *J* = 15.2 Hz, 1H), 3.62 (d, *J* = 14.0 Hz, 1H), 3.45 (d, *J* = 14.0 Hz, 1H), 3.16 (dd, *J* = 17.6, 5.6 Hz, 1H), 2.92 (dd, *J* = 17.2, 4.4 Hz, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 172.5, 166.0, 140.1, 139.4, 135.2, 132.2, 132.1, 130.6, 128.8, 128.7, 128.6, 128.1, 127.5, 127.0, 126.1, 126.0, 69.0, 63.7, 41.1, 33.4 ppm; HRMS (ESI) calculated for C₂₆H₂₃BrNO₃ [M + H]⁺: 476.0856, found 476.0856.

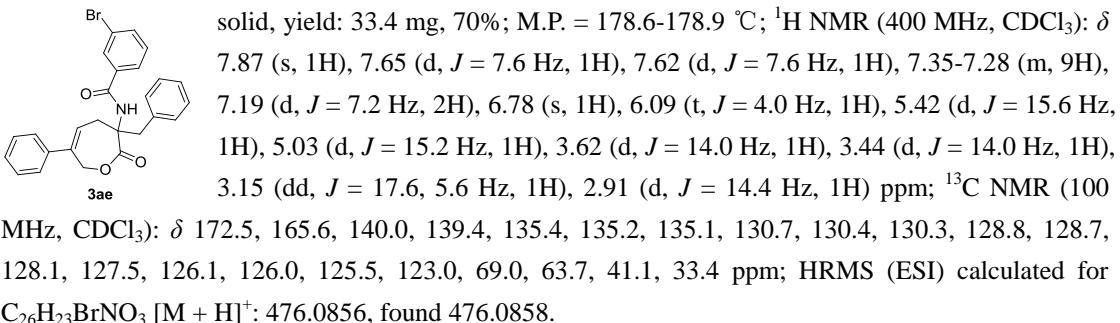
N-(3-benzyl-2-oxo-6-phenyl-2,3,4,7-tetrahydroxepin-3-yl)-4-chlorobenzamide (3ad): White solid, yield:



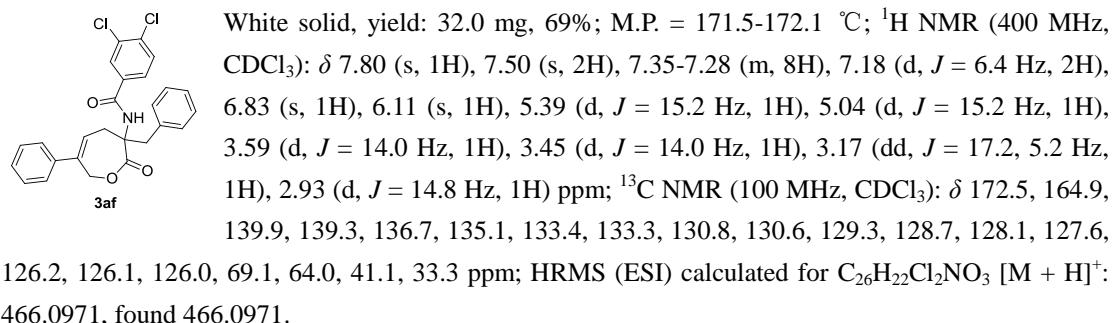
38.8 mg, 90%; M.P. = 104.8-105.6 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.36-7.28 (m, 8H), 7.19 (d, *J* = 7.2 Hz, 2H), 6.72 (s, 1H), 6.10 (t, *J* = 5.2 Hz, 1H), 5.43 (d, *J* = 15.2 Hz, 1H), 5.05 (d, *J* = 15.6 Hz, 1H), 3.62 (d, *J* = 14.0 Hz, 1H), 3.46 (d, *J* = 14.4 Hz, 1H), 3.16 (dd, *J* = 17.6, 6.0 Hz, 1H), 2.92 (dd, *J* = 17.2, 4.0 Hz, 1H) ppm; ¹³C NMR (100 MHz,

CDCl_3): δ 172.6, 165.9, 140.2, 139.4, 138.5, 135.2, 131.8, 130.6, 129.1, 128.7, 128.6, 128.5, 128.1, 127.5, 126.1, 126.0, 69.0, 63.7, 41.1, 33.4 ppm; HRMS (ESI) calculated for $\text{C}_{26}\text{H}_{23}\text{ClNO}_3$ [M + H]⁺: 432.1361, found 432.1358.

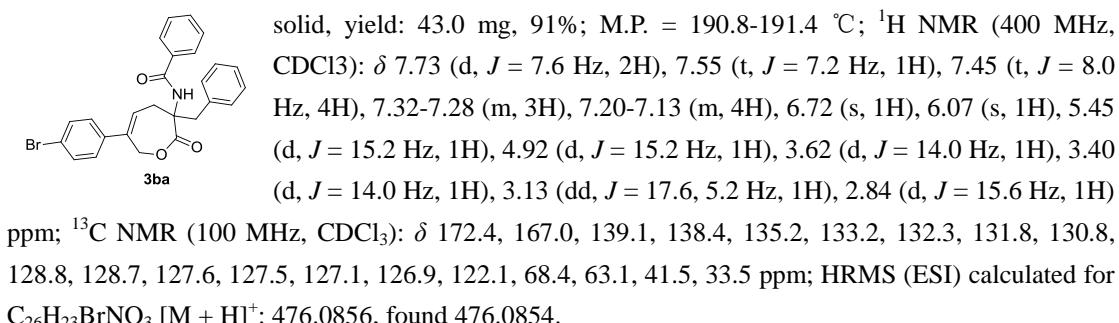
N-(3-benzyl-2-oxo-6-phenyl-2,3,4,7-tetrahydroxepin-3-yl)-3-bromobenzamide (3ae): White



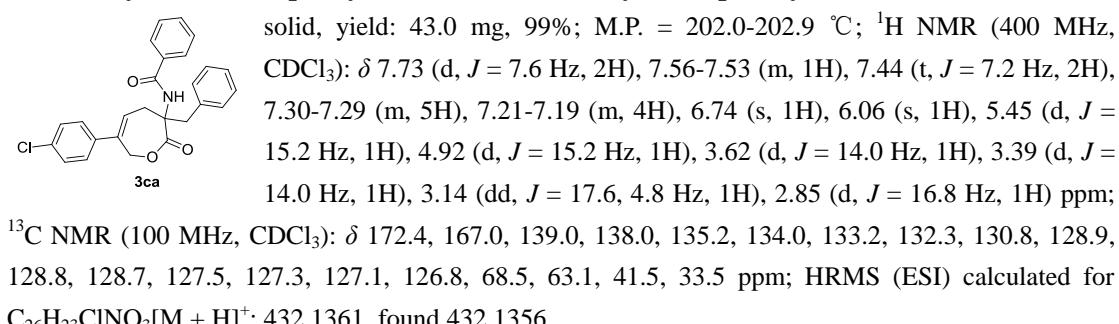
N-(3-benzyl-2-oxo-6-phenyl-2,3,4,7-tetrahydroxepin-3-yl)-3,4-dichlorobenzamide (3af):



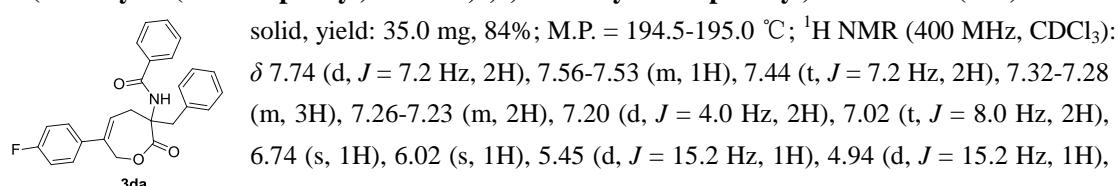
N-(3-benzyl-6-(4-bromophenyl)-2-oxo-2,3,4,7-tetrahydroxepin-3-yl)benzamide (3ba): White



N-(3-benzyl-6-(4-chlorophenyl)-2-oxo-2,3,4,7-tetrahydroxepin-3-yl)benzamide (3ca): White



N-(3-benzyl-6-(4-fluorophenyl)-2-oxo-2,3,4,7-tetrahydroxepin-3-yl)benzamide (3da): White



3.63 (d, $J = 14.0$ Hz, 1H), 3.41 (d, $J = 14.0$ Hz, 1H), 3.13 (dd, $J = 17.2, 4.4$ Hz, 1H), 2.86 (d, $J = 16.8$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 172.4, 167.0, 162.5 (d, $J = 246.3$ Hz), 139.1, 135.7 (d, $J = 3.4$ Hz), 135.3, 133.2, 132.2, 130.8, 128.8, 128.7, 127.8 (d, $J = 8.0$ Hz), 127.4, 127.1, 126.2, 115.6 (d, $J = 21.5$ Hz), 68.8, 63.1, 41.4, 33.5 ppm; HRMS (ESI) calculated for $\text{C}_{26}\text{H}_{23}\text{FNO}_3$ [$\text{M} + \text{H}]^+$: 416.1656, found 416.1657.

N-(3-benzyl-2-oxo-6-(p-tolyl)-2,3,4,7-tetrahydrooxepin-3-yl)benzamide (3ea): White solid, yield: 28.0 mg, 68%; M.P. = 193.3-194.1 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.74 (d, $J = 7.6$ Hz, 2H), 7.54 (t, $J = 7.2$ Hz, 1H), 7.44 (t, $J = 7.2$ Hz, 2H), 7.33-7.28 (m, 3H), 7.21-7.14 (m, 6H), 6.72 (s, 1H), 6.04 (s, 1H), 5.44 (d, $J = 15.2$ Hz, 1H), 5.00 (d, $J = 15.2$ Hz, 1H), 3.67 (d, $J = 14.0$ Hz, 1H), 3.42 (d, $J = 14.0$ Hz, 1H), 3.11 (dd, $J = 17.6, 5.2$ Hz, 1H), 2.88 (d, $J = 16.4$ Hz, 1H), 2.35 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 172.5, 167.0, 139.8, 138.0, 136.7, 135.4, 133.3, 132.2, 130.8, 129.4, 128.8, 128.6, 127.4, 127.1, 125.9, 125.0, 69.0, 63.1, 41.2, 33.5, 21.1 ppm; HRMS (ESI) calculated for $\text{C}_{27}\text{H}_{26}\text{NO}_3$ [$\text{M} + \text{H}]^+$: 412.1907, found 412.1901.

N-(3-benzyl-6-(4-methoxyphenyl)-2-oxo-2,3,4,7-tetrahydrooxepin-3-yl)benzamide (3fa): White solid, yield: 35.0 mg, 82%; M.P. = 199.2-200.3 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.73 (d, $J = 7.6$ Hz, 2H), 7.54 (t, $J = 7.2$ Hz, 1H), 7.44 (t, $J = 7.2$ Hz, 2H), 7.32-7.28 (m, 3H), 7.23-7.19 (m, 4H), 6.87 (d, $J = 8.4$ Hz, 2H), 6.73 (s, 1H), 5.99 (s, 1H), 5.43 (d, $J = 15.2$ Hz, 1H), 4.98 (d, $J = 15.2$ Hz, 1H), 3.80 (s, 3H), 3.66 (d, $J = 14.0$ Hz, 1H), 3.41 (d, $J = 14.0$ Hz, 1H), 3.10 (dd, $J = 17.6, 5.6$ Hz, 1H), 2.86 (d, $J = 15.6$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 172.5, 167.0, 159.6, 139.5, 135.4, 133.3, 132.2, 132.0, 130.8, 128.8, 128.6, 127.4, 127.2, 127.1, 124.4, 114.1, 69.0, 63.1, 55.3, 41.2, 33.5 ppm; HRMS (ESI) calculated for $\text{C}_{27}\text{H}_{26}\text{NO}_4$ [$\text{M} + \text{H}]^+$: 428.1856, found 428.1850.

N-(3-benzyl-6-(3-chlorophenyl)-2-oxo-2,3,4,7-tetrahydrooxepin-3-yl)benzamide (3ga): White solid, yield: 36.0 mg, 84%; M.P. = 202.0-202.1 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.73 (d, $J = 7.6$ Hz, 2H), 7.55 (t, $J = 7.2$ Hz, 1H), 7.47-7.43 (m, 2H), 7.33-7.28 (m, 4H), 7.27-7.16 (m, 5H), 6.71 (s, 1H), 6.10 (s, 1H), 5.46 (d, $J = 14.8$ Hz, 1H), 4.95 (d, $J = 15.2$ Hz, 1H), 3.62 (d, $J = 13.6$ Hz, 1H), 3.43 (d, $J = 13.6$ Hz, 1H), 3.17 (dd, $J = 17.2, 5.2$ Hz, 1H), 2.87 (d, $J = 14.0$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 172.4, 167.0, 141.3, 139.1, 135.1, 134.7, 133.2, 132.3, 130.8, 129.9, 128.8, 128.7, 128.1, 127.6, 127.5, 127.1, 126.3, 124.1, 68.4, 63.3, 41.6, 33.5 ppm; HRMS (ESI) calculated for $\text{C}_{26}\text{H}_{23}\text{ClNO}_3$ [$\text{M} + \text{H}]^+$: 432.1361, found 432.1356.

N-(3-benzyl-6-(4-fluorophenyl)-2-oxo-2,3,4,7-tetrahydrooxepin-3-yl)-4-methylbenzamide (3db): White solid, yield: 30.0 mg, 70%; M.P. = 196.8-197.4 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.63 (d, $J = 7.6$ Hz, 2H), 7.32-7.28 (m, 3H), 7.26-7.18 (m, 6H), 7.02 (t, $J = 8.4$ Hz, 2H), 6.60 (s, 1H), 6.01 (t, $J = 4.0$ Hz, 1H), 5.44 (d, $J = 15.2$ Hz, 1H), 4.95 (d, $J = 15.2$ Hz, 1H), 3.64 (d, $J = 14.0$ Hz, 1H), 3.42 (d, $J = 14.0$ Hz, 1H), 3.11 (dd, $J = 17.6, 6.0$ Hz, 1H), 2.88-2.84 (m, 1H), 2.41 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 172.4, 166.9, 162.5 (d, $J = 246.2$ Hz), 142.8, 139.2, 135.7 (d, $J = 3.2$ Hz), 135.3, 130.8, 130.4, 129.5, 128.6, 127.7 (d, $J = 8.0$ Hz), 127.4, 127.1, 126.1, 115.6 (d, $J = 21.5$ Hz), 68.8, 63.0, 41.4, 33.5, 21.5 ppm; HRMS (ESI) calculated for $\text{C}_{27}\text{H}_{25}\text{FNO}_3$ [$\text{M} + \text{H}]^+$: 430.1813, found 430.1806.

N-(3-benzyl-6-(4-fluorophenyl)-2-oxo-2,3,4,7-tetrahydroxepin-3-yl)-4-bromobenzamide

(3dc): White solid, yield: 47.0 mg, 95%; M.P. = 199.1-199.5 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.58 (s, 4H), 7.32-7.29 (m, 3H), 7.28-7.17 (m, 4H), 7.03 (t, J = 8.4 Hz, 2H), 6.73 (s, 1H), 6.05 (t, J = 5.2 Hz, 1H), 5.41 (d, J = 15.2 Hz, 1H), 4.99 (d, J = 14.8 Hz, 1H), 3.58 (d, J = 14.0 Hz, 1H), 3.45 (d, J = 14.0 Hz, 1H), 3.17 (dd, J = 17.2, 5.6 Hz, 1H), 2.89 (dd, J = 17.2, 4.4 Hz, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 172.5, 166.0, 162.6 (d, J = 246.5 Hz), 139.3, 135.5 (d, J = 3.2 Hz), 135.1, 132.2, 132.1, 130.6, 128.7, 128.6, 127.7 (d, J = 8.1 Hz), 127.5, 127.0, 126.3, 115.6 (d, J = 21.4 Hz), 68.9, 63.7, 41.3, 33.3 ppm; HRMS (ESI) calculated for C₂₆H₂₂BrFNO₃ [M + H]⁺: 494.0762, found 494.0766.

N-(3-benzyl-6-(4-fluorophenyl)-2-oxo-2,3,4,7-tetrahydroxepin-3-yl)-4-chlorobenzamide

(3dd): White solid, yield: 38.0 mg, 85%; M.P. = 199.8-200.4 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.66 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.34-7.29 (m, 3H), 7.28-7.17 (m, 4H), 7.04 (t, J = 8.4 Hz, 2H), 6.71 (s, 1H), 6.05 (t, J = 5.2 Hz, 1H), 5.42 (d, J = 15.2 Hz, 1H), 5.00 (d, J = 15.2 Hz, 1H), 3.59 (d, J = 14.0 Hz, 1H), 3.45 (d, J = 14.0 Hz, 1H), 3.17 (dd, J = 17.6, 6.0 Hz, 1H), 2.89 (dd, J = 17.6, 5.2 Hz, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 172.6, 165.9, 162.6 (d, J = 246.5 Hz), 139.4, 138.6, 135.4 (d, J = 3.2 Hz), 135.1, 131.8, 130.6, 129.1, 128.7, 128.4, 127.7 (d, J = 8.1 Hz), 127.5, 126.3, 115.7 (d, J = 21.4 Hz), 68.9, 63.8, 41.3, 33.3 ppm; HRMS (ESI) calculated for C₂₆H₂₂ClFNO₃ [M + H]⁺: 450.1267, found 450.1270.

N-(3-benzyl-6-(4-fluorophenyl)-2-oxo-2,3,4,7-tetrahydroxepin-3-yl)-3-bromobenzamide

(3de): White solid, yield: 38.0 mg, 77%; M.P. = 181.6-182.4 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.86 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.34-7.29 (m, 4H), 7.27-7.23 (m, 2H), 7.18 (d, J = 7.2 Hz, 2H), 7.03 (t, J = 8.4 Hz, 2H), 6.77 (s, 1H), 6.05 (t, J = 5.2 Hz, 1H), 5.40 (d, J = 15.2 Hz, 1H), 4.97 (d, J = 15.2 Hz, 1H), 3.59 (d, J = 14.0 Hz, 1H), 3.44 (d, J = 14.0 Hz, 1H), 3.16 (dd, J = 17.6, 6.0 Hz, 1H), 2.89 (dd, J = 17.2, 4.4 Hz, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 172.5, 165.6, 162.6 (d, J = 246.3 Hz), 139.2, 135.5 (d, J = 3.3 Hz), 135.4, 135.1, 135.0, 130.6, 130.4, 130.3, 128.7, 127.7 (d, J = 8.0 Hz), 127.5, 126.3, 125.5, 123.0, 115.6 (d, J = 21.4 Hz), 68.9, 63.8, 41.3, 33.4 ppm; HRMS (ESI) calculated for C₂₆H₂₂BrFNO₃ [M + H]⁺: 494.0762, found 494.0766.

N-(3-benzyl-2-oxo-6-(p-tolyl)-2,3,4,7-tetrahydroxepin-3-yl)-4-methylbenzamide (3eb): White

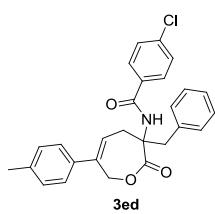
solid, yield: 30.0 mg, 71%; M.P. = 187.3-187.9 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.64 (d, J = 8.0 Hz, 2H), 7.32-7.28 (m, 3H), 7.24 (d, J = 7.6 Hz, 2H), 7.20-7.14 (m, 6H), 6.63 (s, 1H), 6.01 (s, 1H), 5.43 (d, J = 15.2 Hz, 1H), 4.98 (d, J = 15.6 Hz, 1H), 3.69 (d, J = 14.0 Hz, 1H), 3.38 (d, J = 14.0 Hz, 1H), 3.06 (dd, J = 17.6, 5.2 Hz, 1H), 2.85 (d, J = 16.4 Hz, 1H), 2.41 (s, 3H), 2.35 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 172.4, 166.9, 142.8, 139.6, 138.0, 136.8, 135.5, 130.9, 130.4, 129.5, 129.4, 128.6, 127.3, 127.1, 125.9, 124.9, 69.0, 62.8, 41.2, 33.6, 21.5, 21.1 ppm; HRMS (ESI) calculated for C₂₈H₂₈NO₃ [M + H]⁺: 426.2064, found 426.2056.

N-(3-benzyl-2-oxo-6-(p-tolyl)-2,3,4,7-tetrahydroxepin-3-yl)-4-bromobenzamide (3ec): White

solid, yield: 46.0 mg, 94%; M.P. = 209.0-209.9 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.57 (s, 4H), 7.32-7.28 (m, 3H), 7.18-7.14 (m, 6H), 6.74 (s, 1H), 6.06 (t, J = 5.2 Hz, 1H), 5.40 (d, J = 15.2 Hz, 1H), 5.02 (d, J = 15.2 Hz, 1H), 3.62 (d, J = 14.0 Hz, 1H), 3.43 (d, J = 14.0 Hz, 1H), 3.13 (dd, J = 17.6, 5.6 Hz, 1H),

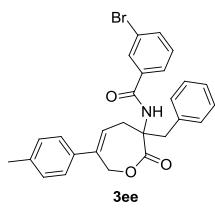
2.92-2.88 (m, 1H), 2.35 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 172.6, 166.0, 139.9, 138.1, 136.5, 135.2, 132.3, 132.0, 130.7, 129.4, 128.7, 128.6, 127.5, 127.0, 125.9, 125.2, 69.1, 63.6, 41.0, 33.3, 21.1 ppm; HRMS (ESI) calculated for $\text{C}_{27}\text{H}_{25}\text{BrNO}_3$ [M + H] $^+$: 490.1012, found 490.1010.

N-(3-benzyl-2-oxo-6-(p-tolyl)-2,3,4,7-tetrahydroxepin-3-yl)-4-chlorobenzamide (3ed): White



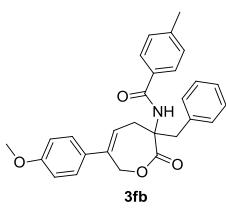
solid, yield: 35.0 mg, 79%; M.P. = 204.7-205.0 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.66 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.33-7.28 (m, 3H), 7.18-7.15 (m, 6H), 6.72 (s, 1H), 6.06 (t, J = 5.2 Hz, 1H), 5.40 (d, J = 15.2 Hz, 1H), 5.03 (d, J = 15.2 Hz, 1H), 3.62 (d, J = 14.0 Hz, 1H), 3.43 (d, J = 14.0 Hz, 1H), 3.13 (dd, J = 17.6, 6.0 Hz, 1H), 2.90 (dd, J = 17.2, 4.0 Hz, 1H), 2.36 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 172.6, 165.9, 139.9, 138.5, 138.1, 136.5, 135.2, 131.8, 130.7, 129.4, 129.1, 128.7, 128.5, 127.5, 125.9, 125.2, 69.1, 63.6, 41.0, 33.3, 21.1 ppm; HRMS (ESI) calculated for $\text{C}_{27}\text{H}_{25}\text{ClNO}_3$ [M + H] $^+$: 446.1517, found 446.1509.

N-(3-benzyl-2-oxo-6-(p-tolyl)-2,3,4,7-tetrahydroxepin-3-yl)-3-bromobenzamide (3ee): White



solid, yield: 37.5 mg, 77%; M.P. = 190.0-190.3 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.87 (s, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.34-7.28 (m, 4H), 7.20-7.15 (m, 6H), 6.74 (s, 1H), 6.07 (t, J = 5.2 Hz, 1H), 5.39 (d, J = 15.2 Hz, 1H), 5.04 (d, J = 15.2 Hz, 1H), 3.62 (d, J = 14.4 Hz, 1H), 3.45 (d, J = 14.0 Hz, 1H), 3.14 (dd, J = 17.6, 6.0 Hz, 1H), 2.92 (dd, J = 17.6, 4.8 Hz, 1H), 2.36 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 172.5, 165.5, 139.9, 138.1, 136.5, 135.5, 135.2, 135.1, 130.7, 130.4, 130.3, 129.4, 128.7, 127.5, 125.9, 125.5, 125.2, 123.0, 69.1, 63.8, 41.0, 33.3, 21.1 ppm; HRMS (ESI) calculated for $\text{C}_{27}\text{H}_{25}\text{BrNO}_3$ [M + H] $^+$: 490.1012, found 490.1012.

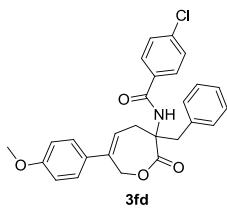
N-(3-benzyl-6-(4-methoxyphenyl)-2-oxo-2,3,4,7-tetrahydroxepin-3-yl)-4-methylbenzamide (3fb):



White solid, yield: 31.0 mg, 70%; M.P. = 184.6-185.5 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.63 (d, J = 7.6 Hz, 2H), 7.32-7.28 (m, 3H), 7.25-7.18 (m, 6H), 6.87 (d, J = 8.4 Hz, 2H), 6.63 (s, 1H), 5.96 (s, 1H), 5.42 (d, J = 15.2 Hz, 1H), 4.97 (d, J = 15.6 Hz, 1H), 3.81 (s, 3H), 3.67 (d, J = 14.0 Hz, 1H), 3.39 (d, J = 14.0 Hz, 1H), 3.06 (dd, J = 17.6, 5.2 Hz, 1H), 2.84 (d, J = 17.2 Hz, 1H), 2.41 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 172.5, 166.9, 159.5, 142.8, 139.4, 135.5, 132.1, 130.9, 130.4, 129.5, 128.6, 127.3, 127.2, 127.1, 124.2, 114.1, 69.0, 62.8, 55.3, 41.2, 33.5, 21.5 ppm; HRMS (ESI) calculated for $\text{C}_{28}\text{H}_{28}\text{NO}_4$ [M + H] $^+$: 442.2013, found 442.2001.

N-(3-benzyl-6-(4-methoxyphenyl)-2-oxo-2,3,4,7-tetrahydroxepin-3-yl)-4-bromobenzamide (3fc): White solid, yield: 49.6 mg, 98%; M.P. = 139.0-139.4 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.57 (s, 4H), 7.32-7.28 (m, 3H), 7.23-7.17 (m, 4H), 6.87 (d, J = 8.4 Hz, 2H), 6.74 (s, 1H), 6.00 (t, J = 5.2 Hz, 1H), 5.39 (d, J = 15.2 Hz, 1H), 5.01 (d, J = 15.6 Hz, 1H), 3.81 (s, 3H), 3.60 (d, J = 14.0 Hz, 1H), 3.42 (d, J = 14.0 Hz, 1H), 3.13 (dd, J = 17.6, 5.6 Hz, 1H), 2.87 (dd, J = 17.2, 4.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 172.6, 166.0, 159.6, 139.5, 135.0, 132.2, 132.0, 131.8, 130.7, 128.7, 128.6, 127.5, 127.2, 127.0, 124.4, 114.1, 69.0, 63.5, 55.4, 41.1, 33.3 ppm; HRMS (ESI) calculated for $\text{C}_{27}\text{H}_{25}\text{BrNO}_4$ [M + H] $^+$: 506.0961, found 506.0965.

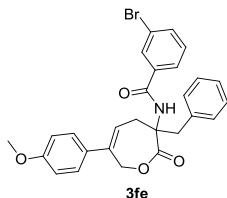
N-(3-benzyl-6-(4-methoxyphenyl)-2-oxo-2,3,4,7-tetrahydroxepin-3-yl)-4-chlorobenzamide (3fd): White solid, yield: 46.0 mg, 99%; M.P. = 157.2-157.7 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.65 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.34-7.28 (m, 3H), 7.23-7.17 (m, 4H), 6.87 (d, J = 8.8 Hz, 2H), 6.75 (s, 1H), 6.00 (t, J = 4.8 Hz, 1H), 5.39 (d, J = 15.2 Hz, 1H), 5.00 (d, J = 15.2 Hz, 1H), 3.81 (s,



3H), 3.61 (d, $J = 14.0$ Hz, 1H), 3.42 (d, $J = 14.0$ Hz, 1H), 3.12 (dd, $J = 17.2, 5.6$ Hz, 1H), 2.87 (dd, $J = 17.2, 4.4$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 172.6, 165.9, 159.6, 139.5, 138.5, 135.3, 131.8, 131.7, 130.7, 129.1, 128.7, 128.5, 127.5, 127.2, 124.4, 114.1, 69.0, 63.5, 55.3, 41.1, 33.3 ppm; HRMS (ESI) calculated for $\text{C}_{27}\text{H}_{25}\text{ClNO}_4$ [$\text{M} + \text{H}]^+$: 462.1467, found 462.1456.

N-(3-benzyl-6-(4-methoxyphenyl)-2-oxo-2,3,4,7-tetrahydroxepin-3-yl)-3-bromobenzamide

(3fe): White solid, yield: 49.0 mg, 97%; M.P. = 160.6-161.1 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.86 (s,



1H), 7.65 (d, $J = 8.0$ Hz, 1H), 7.60 (d, $J = 7.6$ Hz, 1H), 7.35-7.29 (m, 4H), 7.25-7.18 (m, 4H), 6.88 (d, $J = 8.8$ Hz, 2H), 6.72 (s, 1H), 6.02 (t, $J = 5.2$ Hz, 1H), 5.39 (d, $J = 15.2$ Hz, 1H), 5.03 (d, $J = 15.2$ Hz, 1H), 3.82 (s, 3H), 3.61 (d, $J = 14.0$ Hz, 1H), 3.46 (d, $J = 14.0$ Hz, 1H), 3.14 (dd, $J = 17.2, 6.0$ Hz, 1H), 2.90 (dd, $J = 17.6, 4.4$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 172.6, 165.5, 159.6, 139.6, 135.5, 135.2, 135.1, 131.8, 130.6, 130.4, 130.3, 128.7,

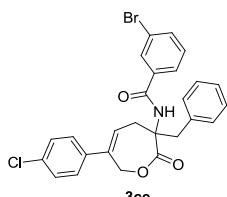
127.5, 127.2, 125.5, 124.5, 123.0, 114.1, 69.1, 63.8, 55.3, 41.1, 33.3 ppm; HRMS (ESI) calculated for $\text{C}_{27}\text{H}_{25}\text{BrNO}_4$ [$\text{M} + \text{H}]^+$: 506.0961, found 506.0953.

N-(3-benzyl-6-(4-bromophenyl)-2-oxo-2,3,4,7-tetrahydroxepin-3-yl)-3-bromobenzamide

(3be): White solid, yield: 44.0 mg, 79%; M.P. = 200.5-201.4 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.86 (s, 1H), 7.66 (d, $J = 6.4$ Hz, 1H), 7.61 (d, $J = 6.0$ Hz, 1H), 7.47 (d, $J = 6.8$ Hz, 2H), 7.31 (s, 4H), 7.16 (d, $J = 8.4$ Hz, 4H), 6.73 (s, 1H), 6.11 (s, 1H), 5.40 (d, $J = 14.8$ Hz, 1H), 4.98 (d, $J = 15.2$ Hz, 1H), 3.57 (d, $J = 13.2$ Hz, 1H), 3.46 (d, $J = 13.6$ Hz, 1H), 3.18 (d, $J = 14.0$ Hz, 1H), 2.90 (d, $J = 15.6$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 172.5, 165.6, 139.2, 138.2, 135.4, 135.1, 135.0, 131.9, 130.6, 130.3, 128.8, 127.6, 127.5, 127.1, 125.5, 123.0, 122.2, 68.6, 63.9, 41.4, 33.4 ppm; HRMS (ESI) calculated for $\text{C}_{26}\text{H}_{22}\text{Br}_2\text{NO}_3$ [$\text{M} + \text{H}]^+$: 553.9961, found 553.9961.

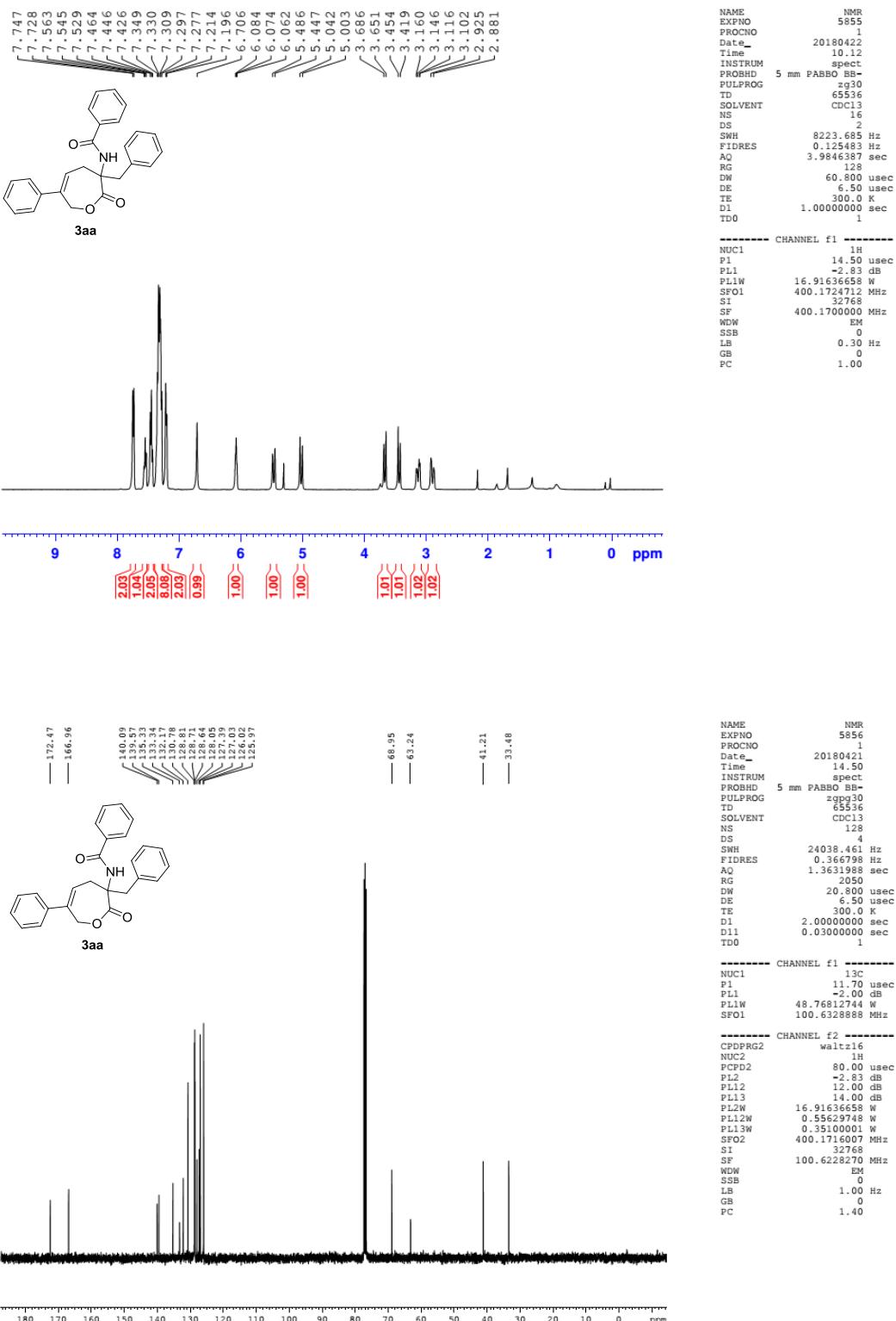
N-(3-benzyl-6-(4-chlorophenyl)-2-oxo-2,3,4,7-tetrahydroxepin-3-yl)-3-bromobenzamide

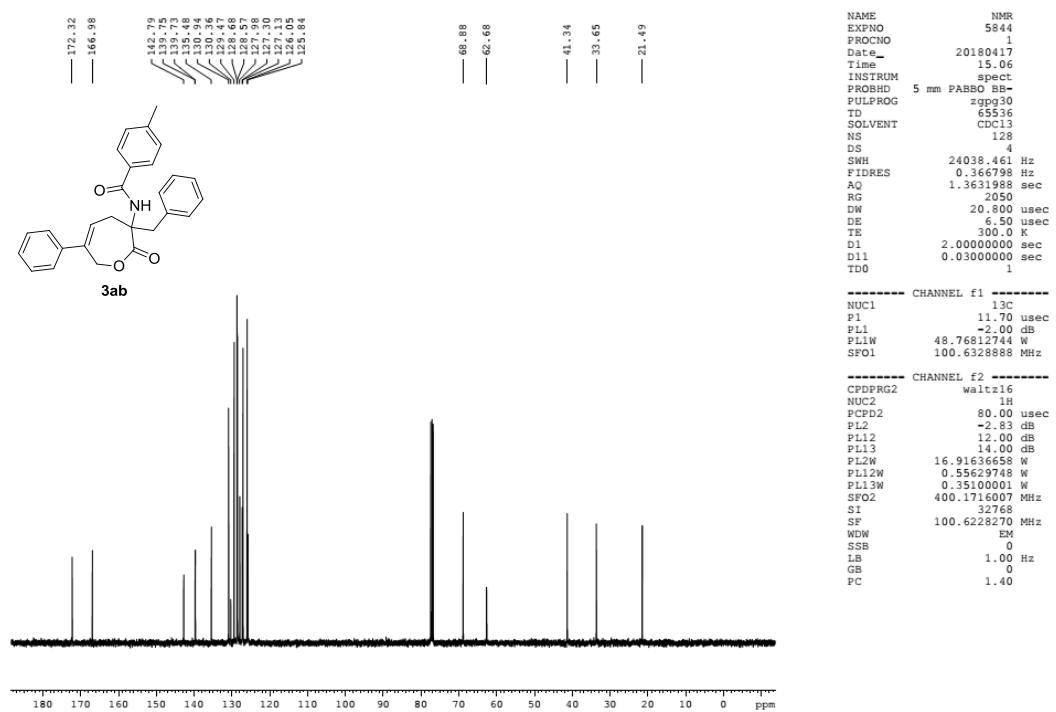
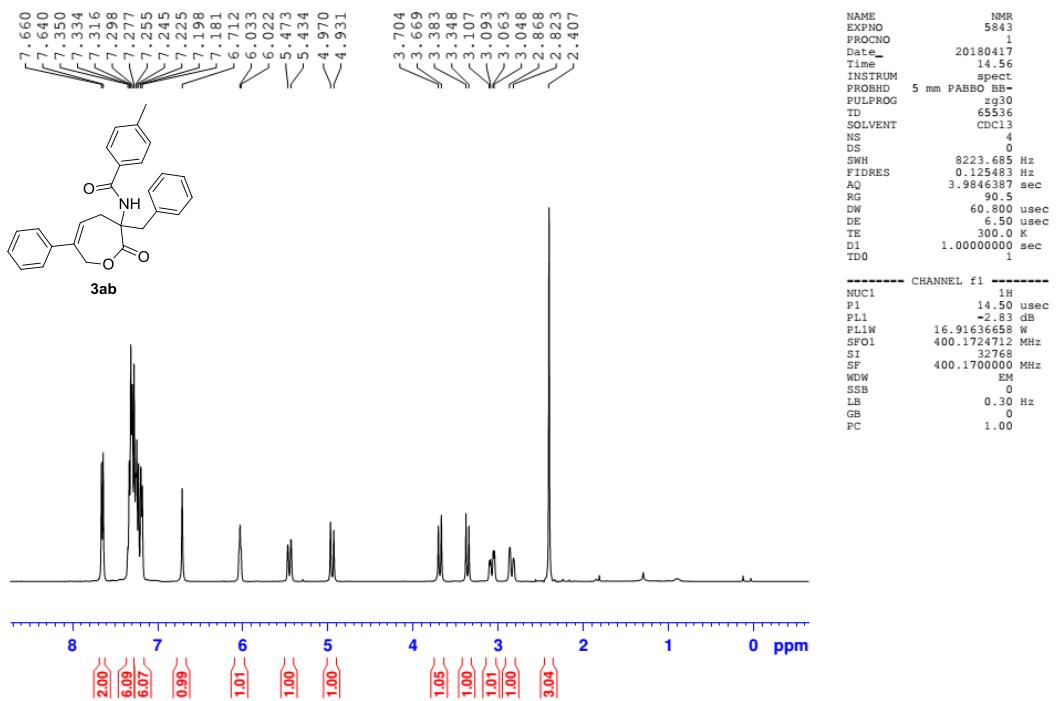
(3ce): White solid, yield: 38.0 mg, 75%; M.P. = 206.2-206.5 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.86

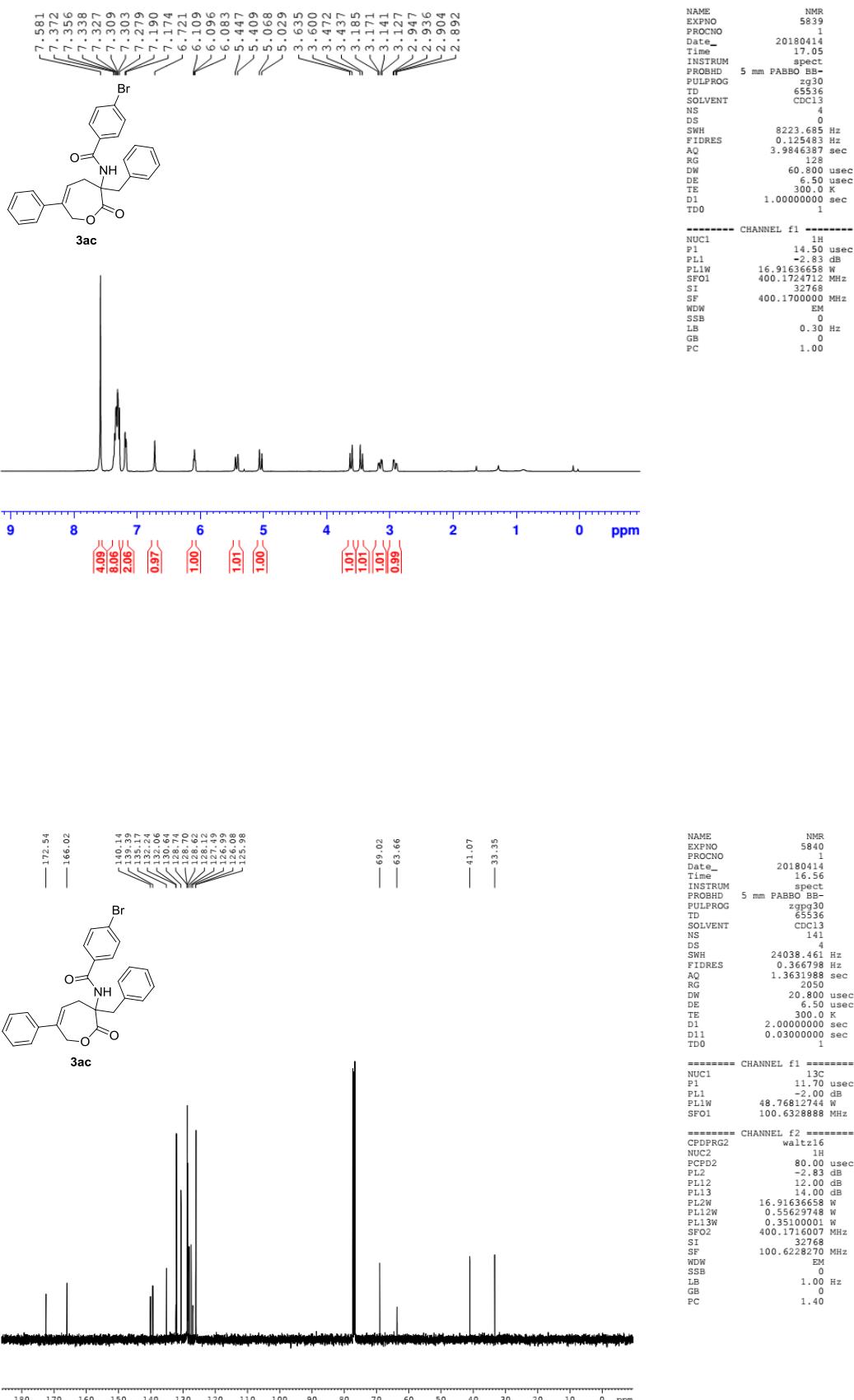


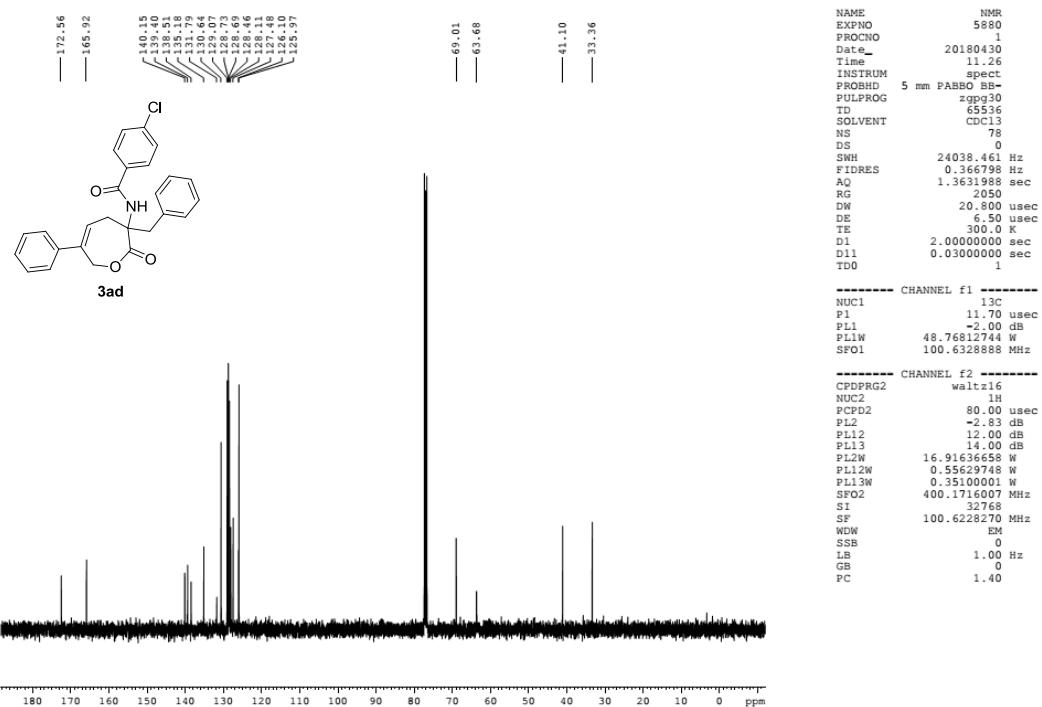
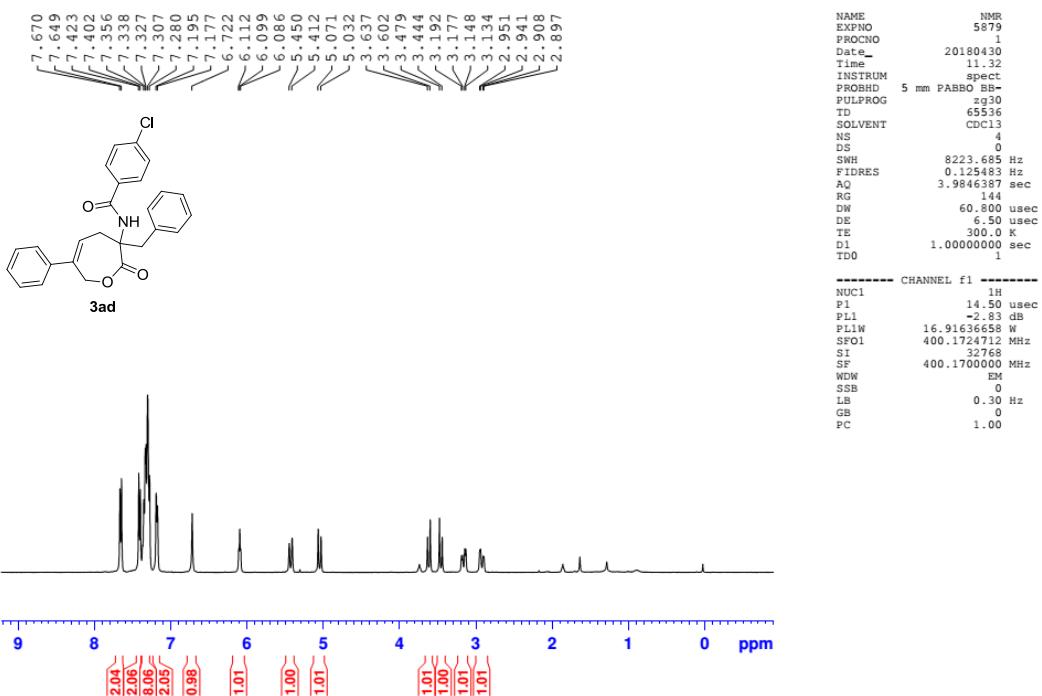
(s, 1H), 7.66 (d, $J = 7.6$ Hz, 1H), 7.61 (d, $J = 7.6$ Hz, 1H), 7.33-7.28 (m, 6H), 7.23-7.18 (m, 4H), 6.73 (s, 1H), 6.10 (t, $J = 4.8$ Hz, 1H), 5.41 (d, $J = 15.2$ Hz, 1H), 4.99 (d, $J = 15.2$ Hz, 1H), 3.58 (d, $J = 14.0$ Hz, 1H), 3.46 (d, $J = 14.0$ Hz, 1H), 3.19 (dd, $J = 17.2, 6.0$ Hz, 1H), 2.91 (dd, $J = 16.8, 4.4$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 172.5, 165.6, 139.2, 137.7, 135.4, 135.1, 135.0, 134.1, 130.6, 130.3, 128.9, 128.8, 127.6, 127.2, 127.0, 125.5, 123.0, 68.7, 64.0, 41.4, 33.3 ppm; HRMS (ESI) calculated for $\text{C}_{26}\text{H}_{22}\text{BrClNO}_3$ [$\text{M} + \text{H}]^+$: 510.0466, found 510.0458.

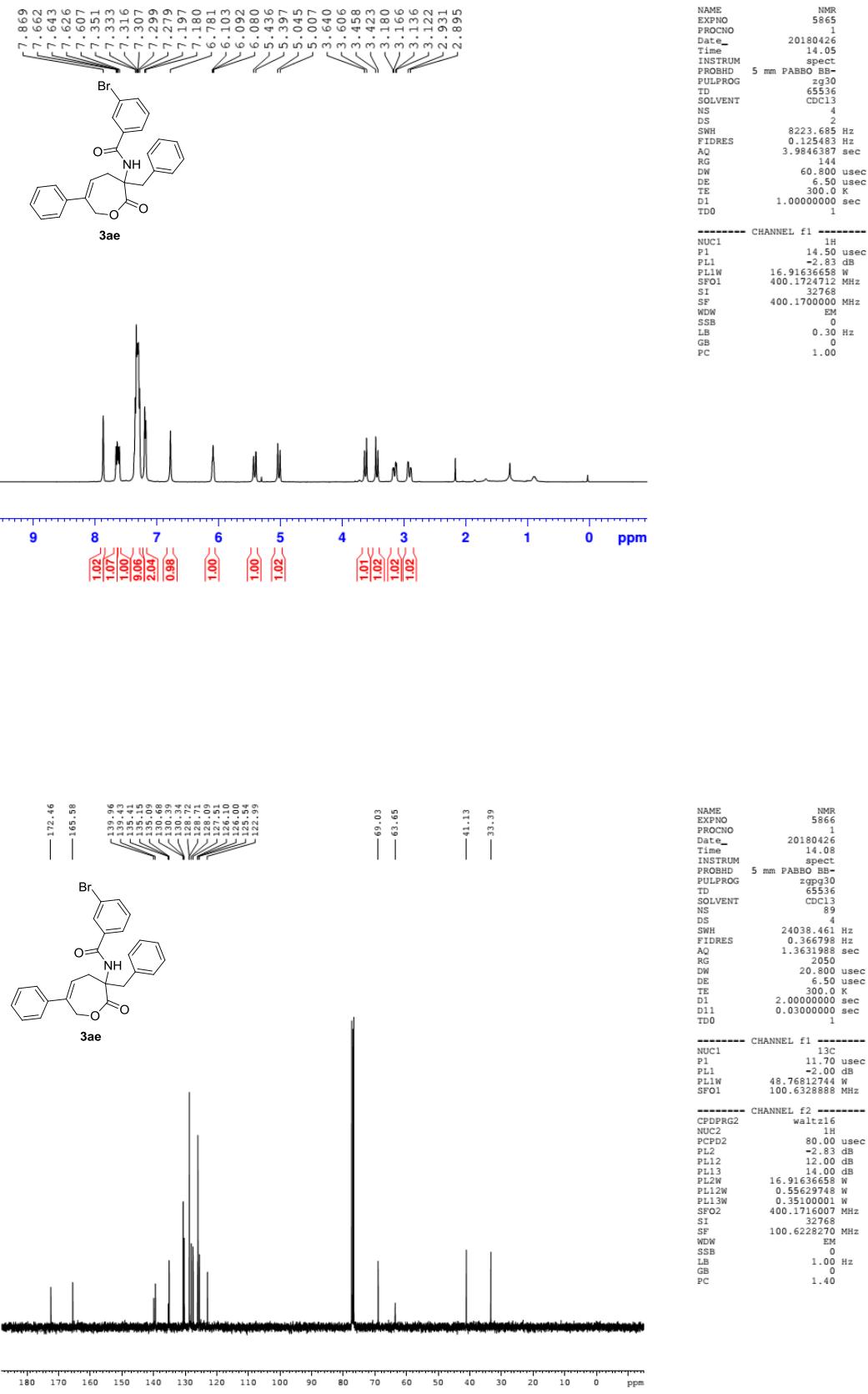
7. ^1H and ^{13}C NMR spectra

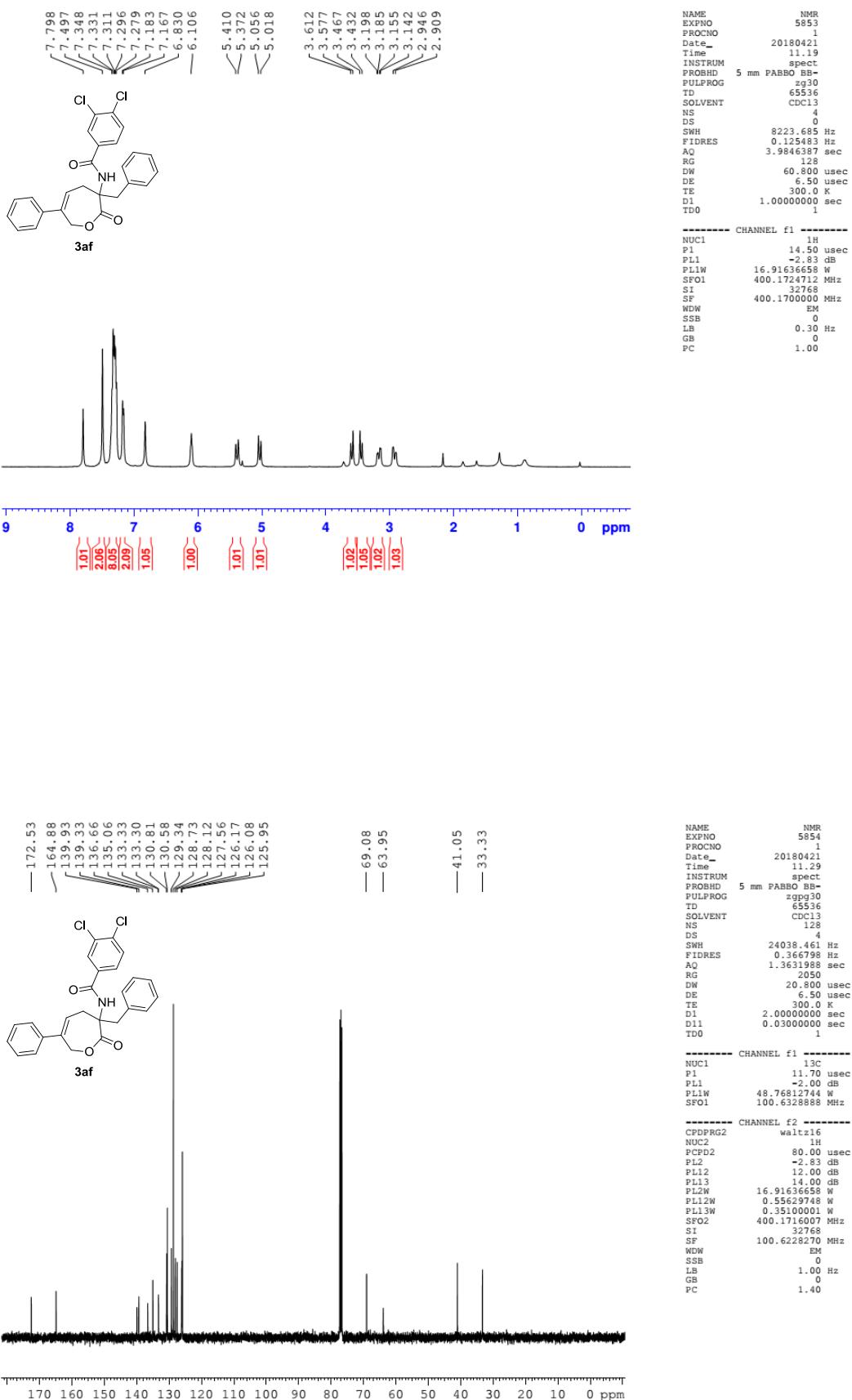


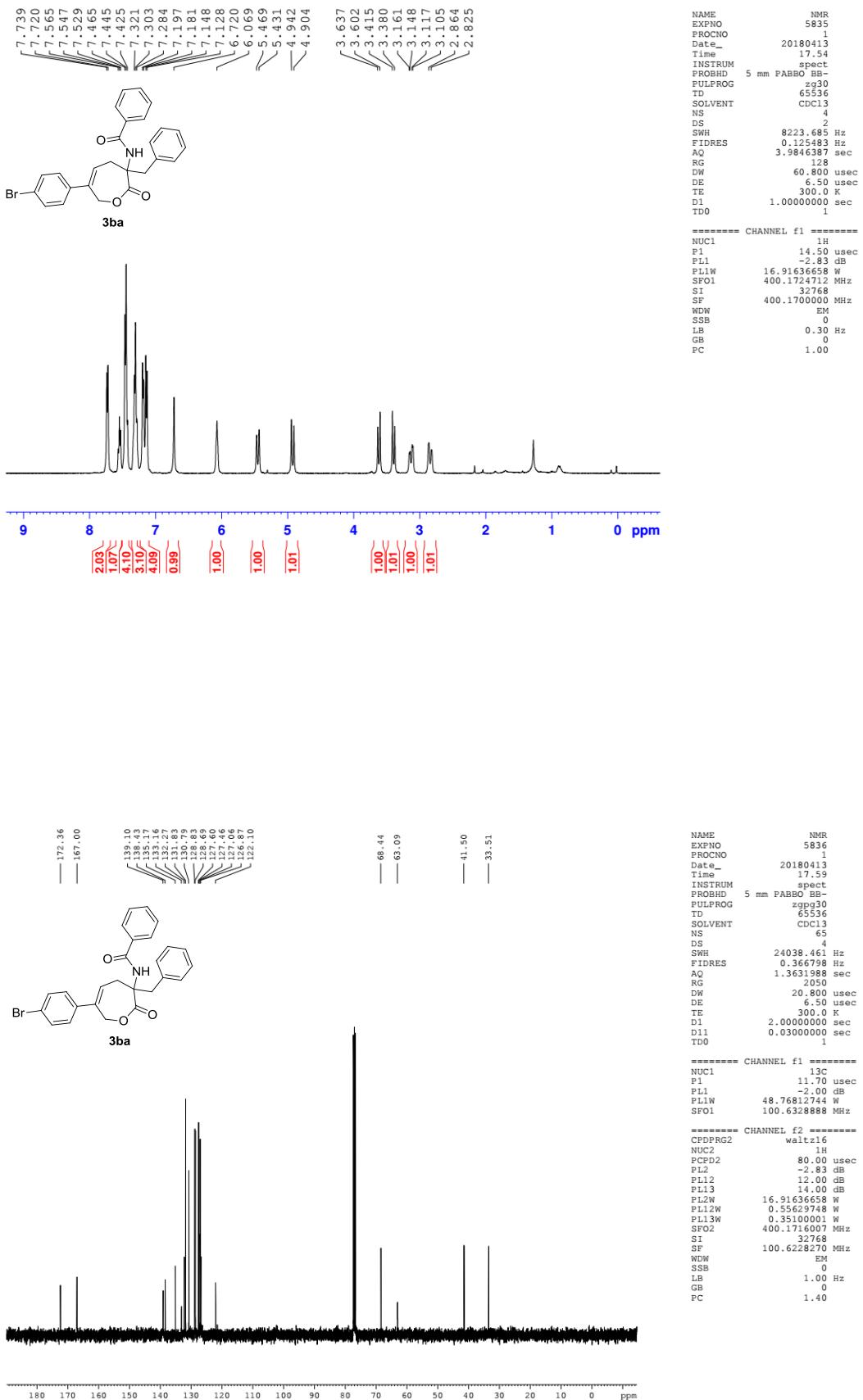


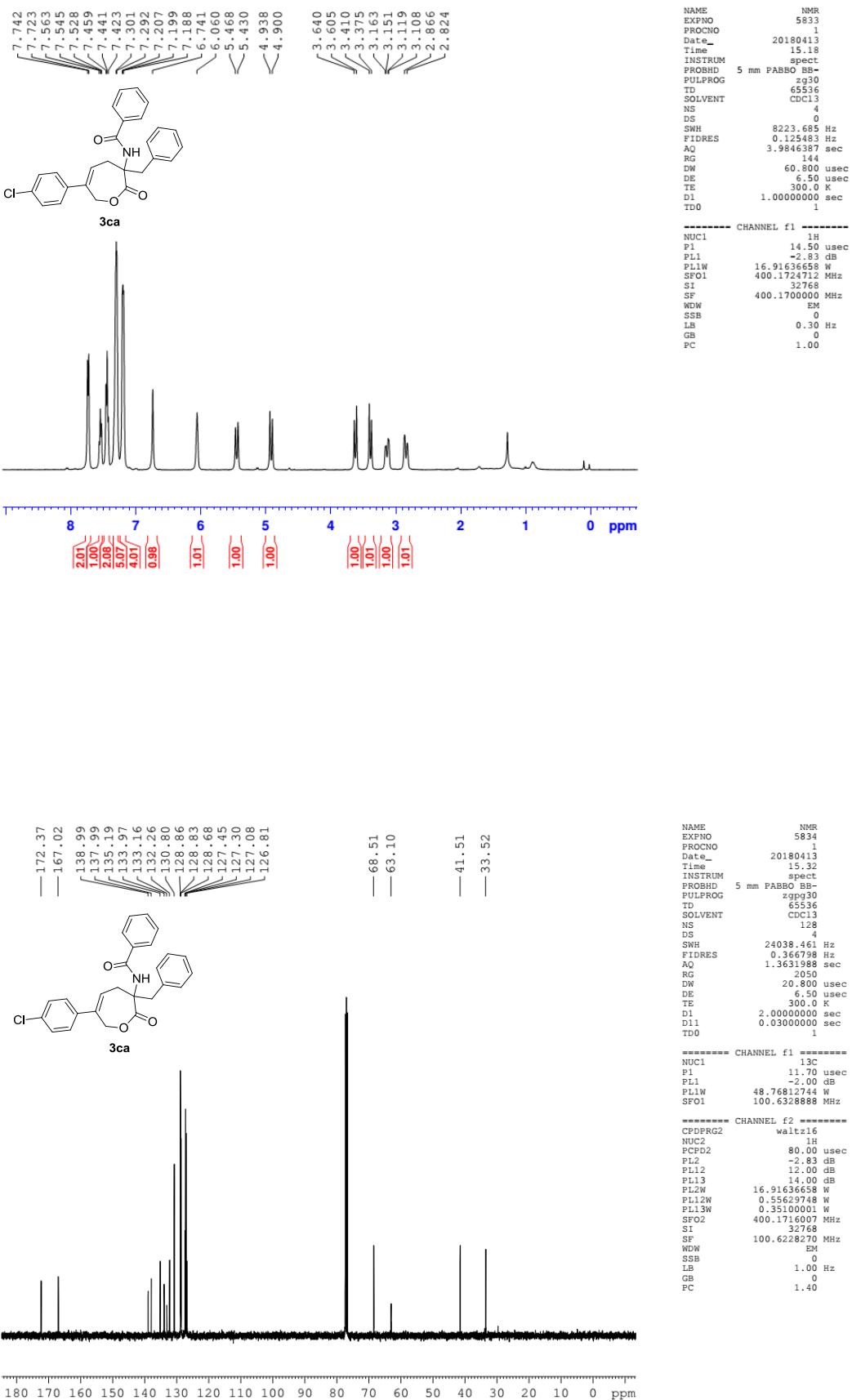


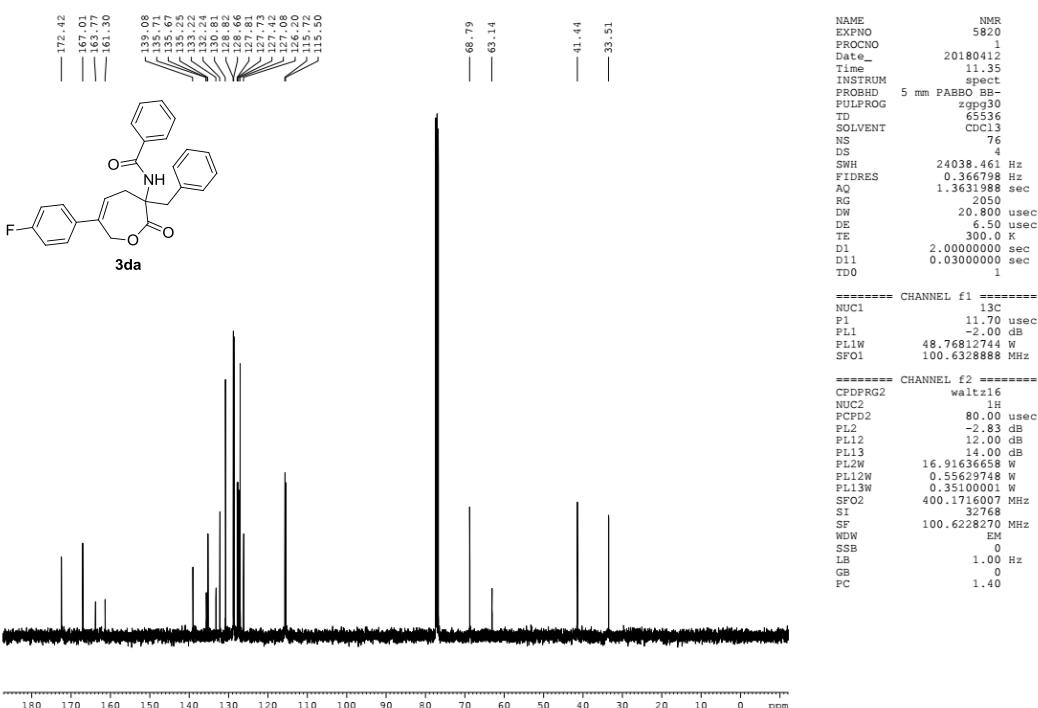
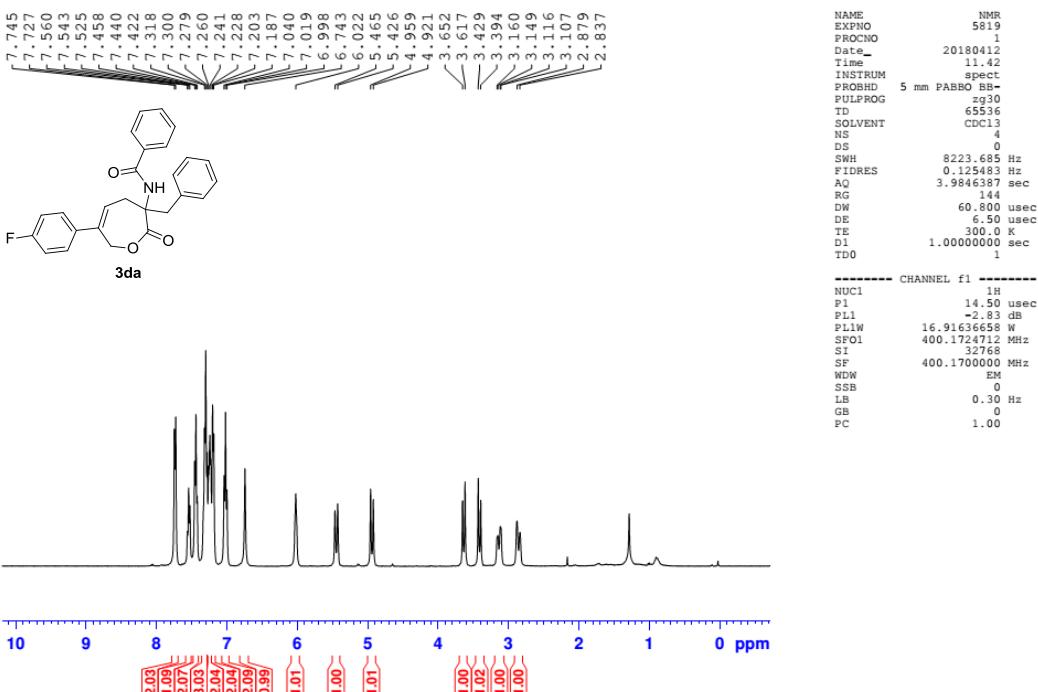


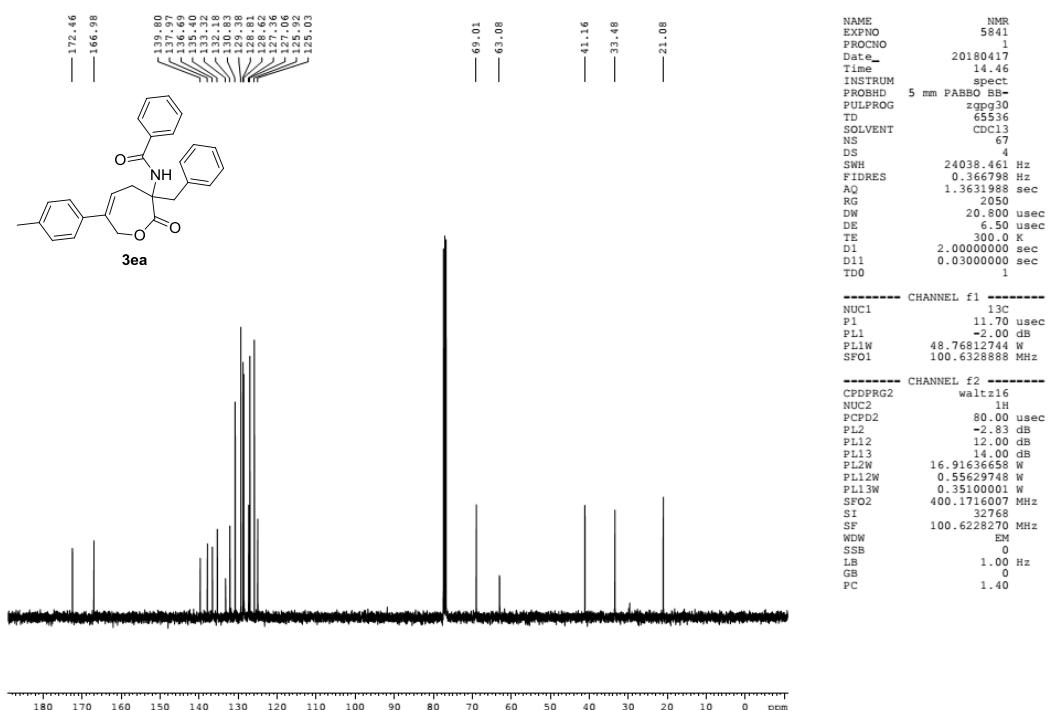
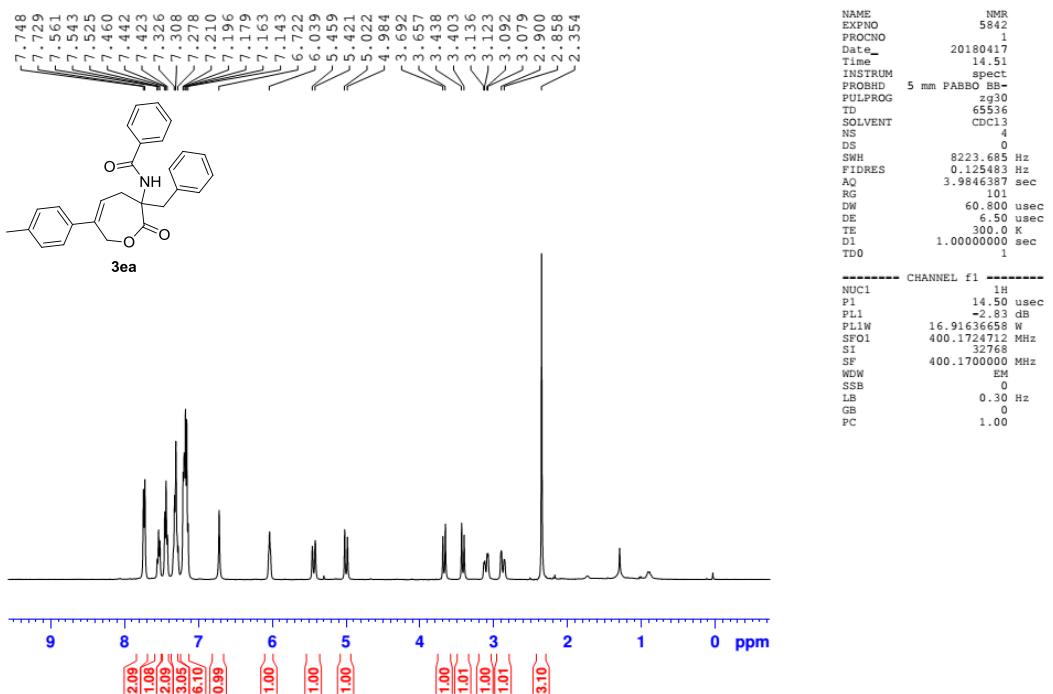


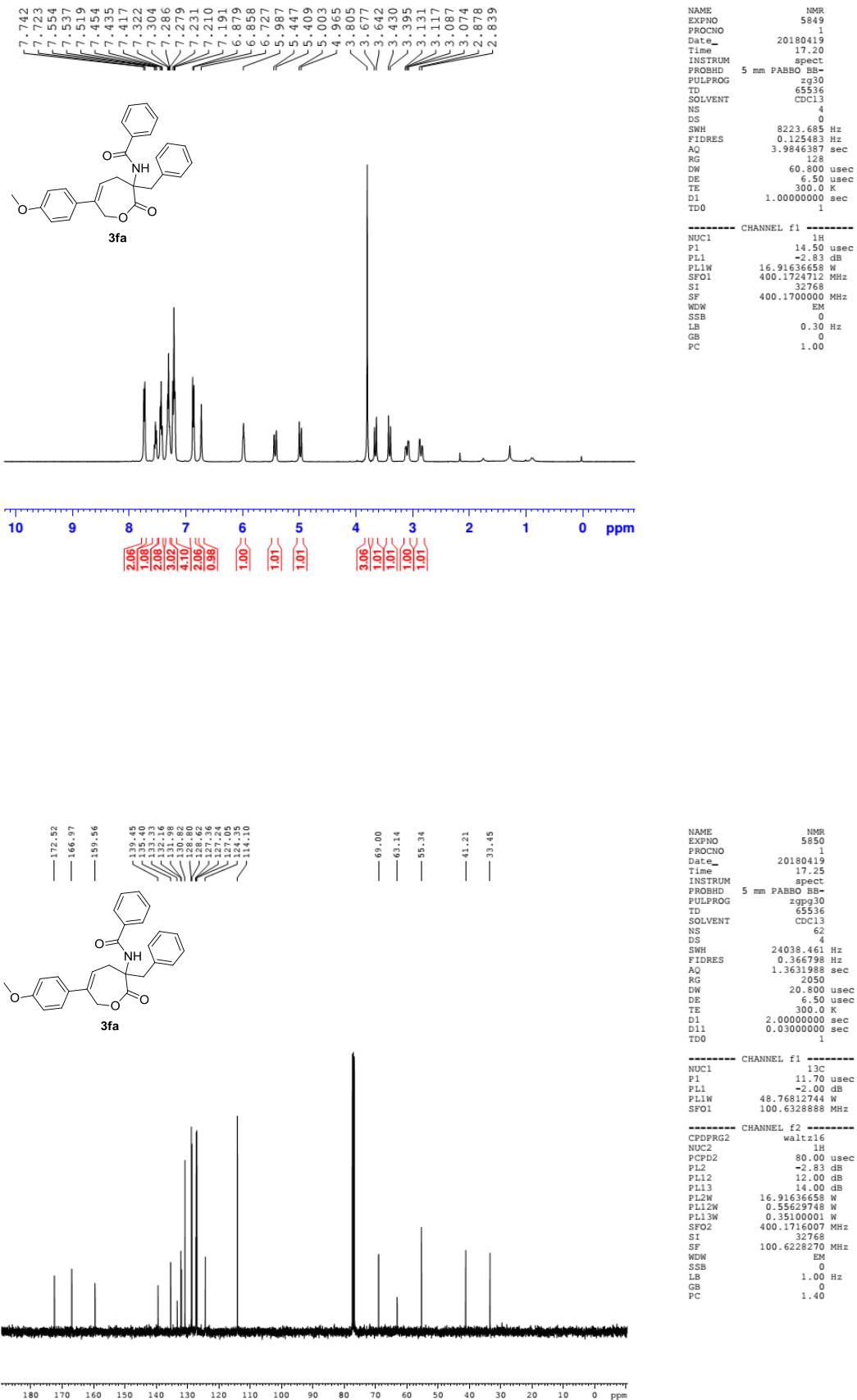


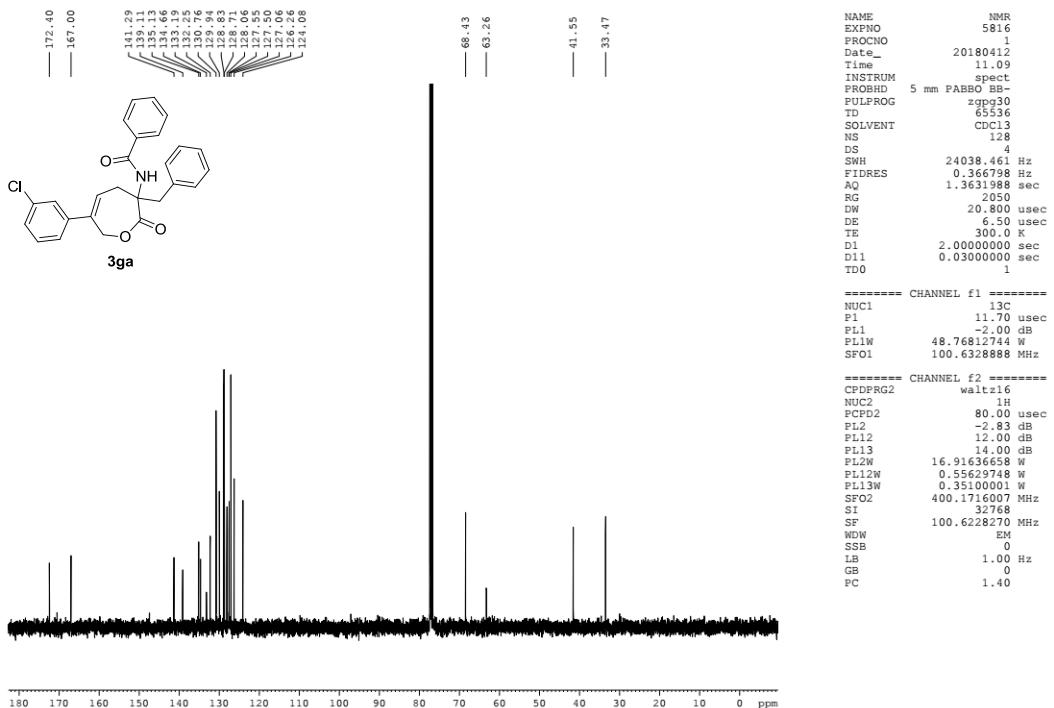
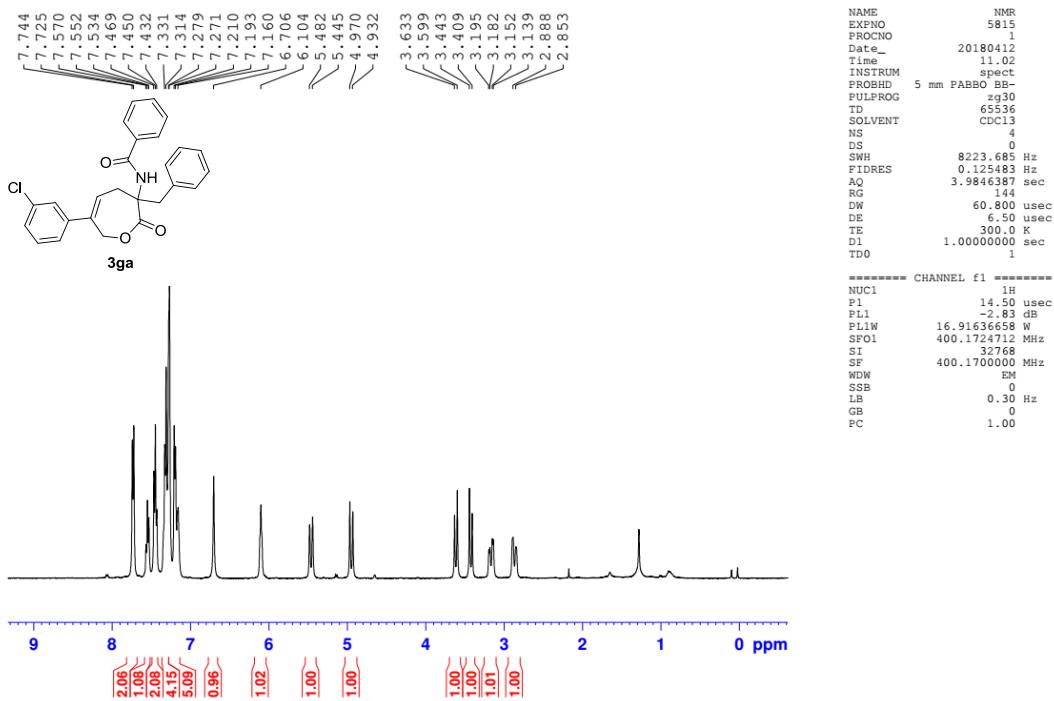


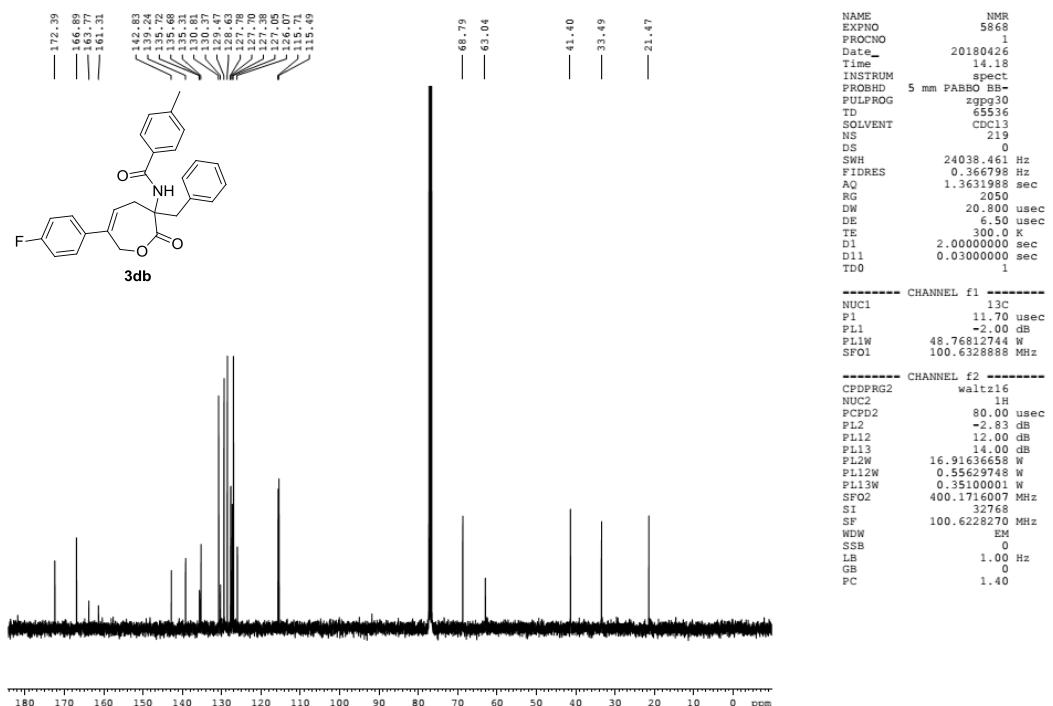
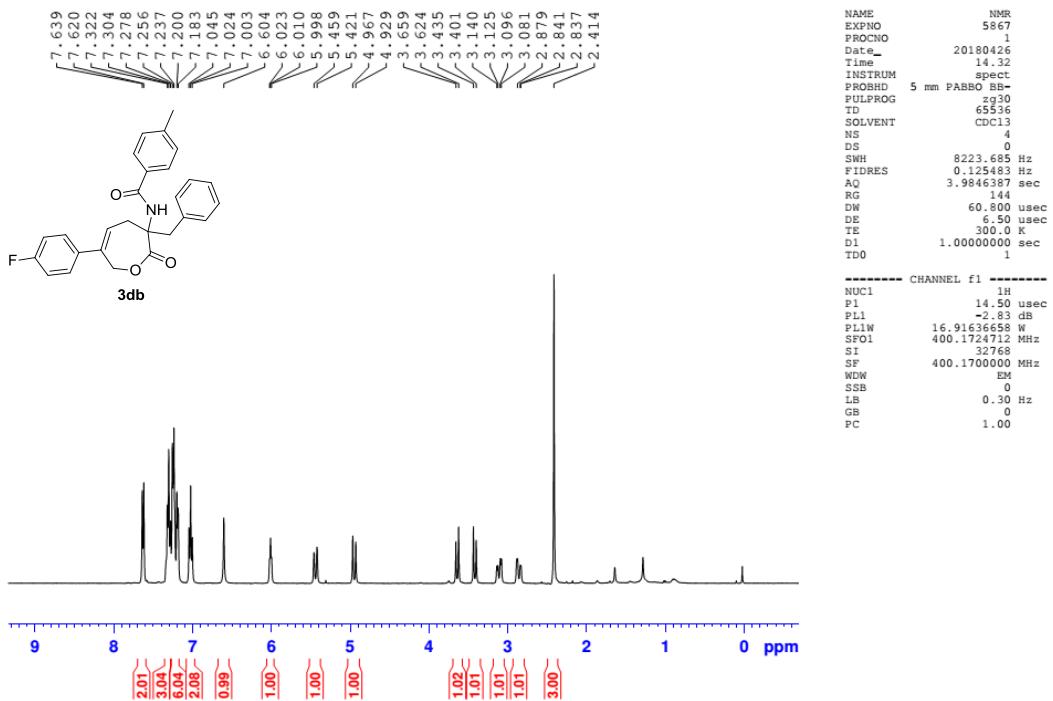


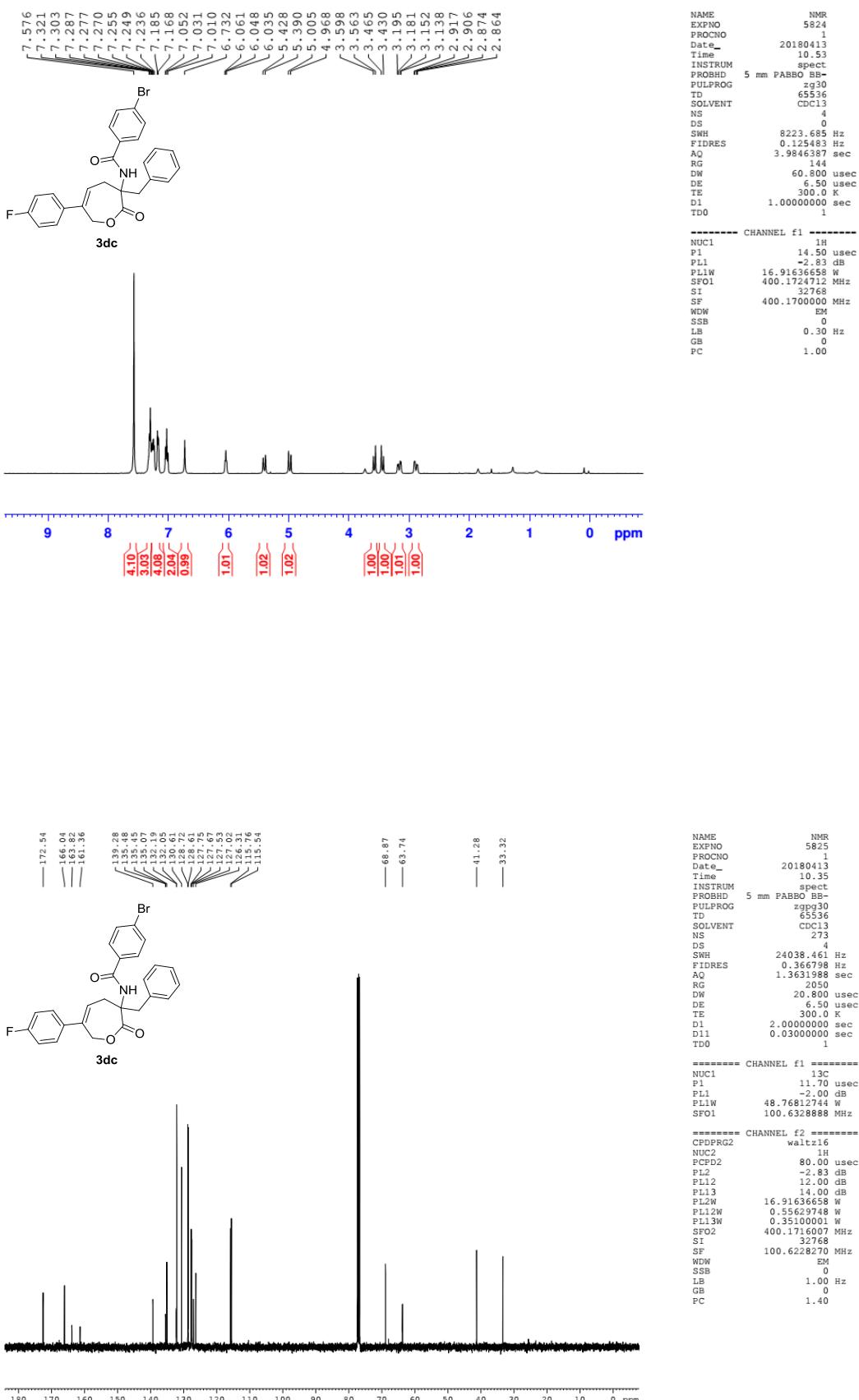


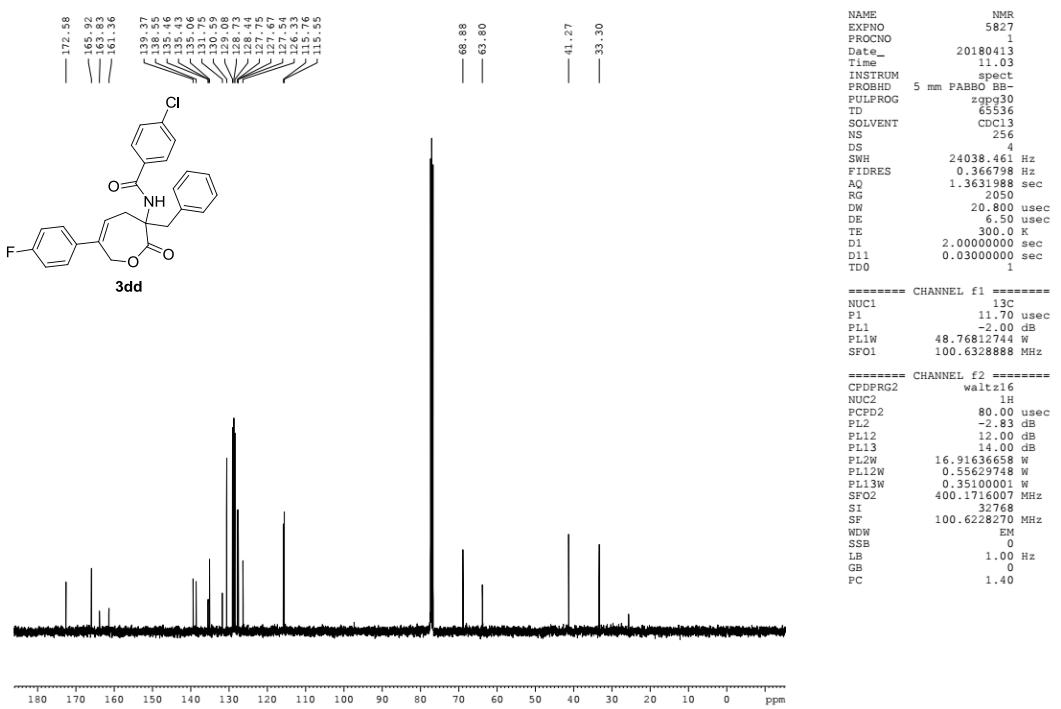
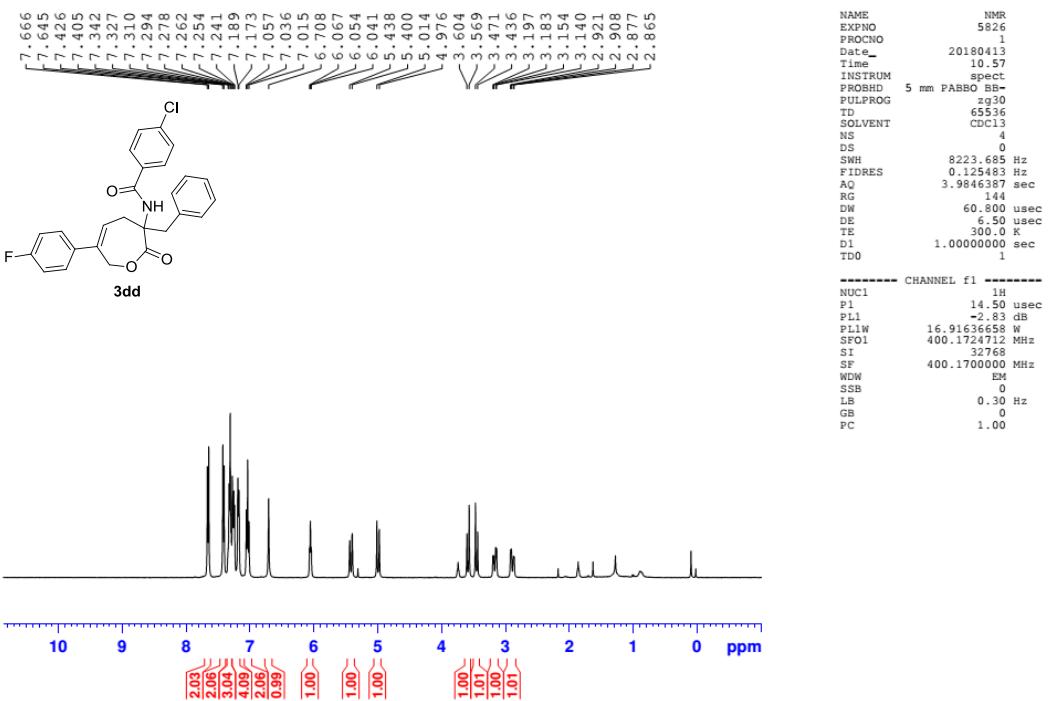


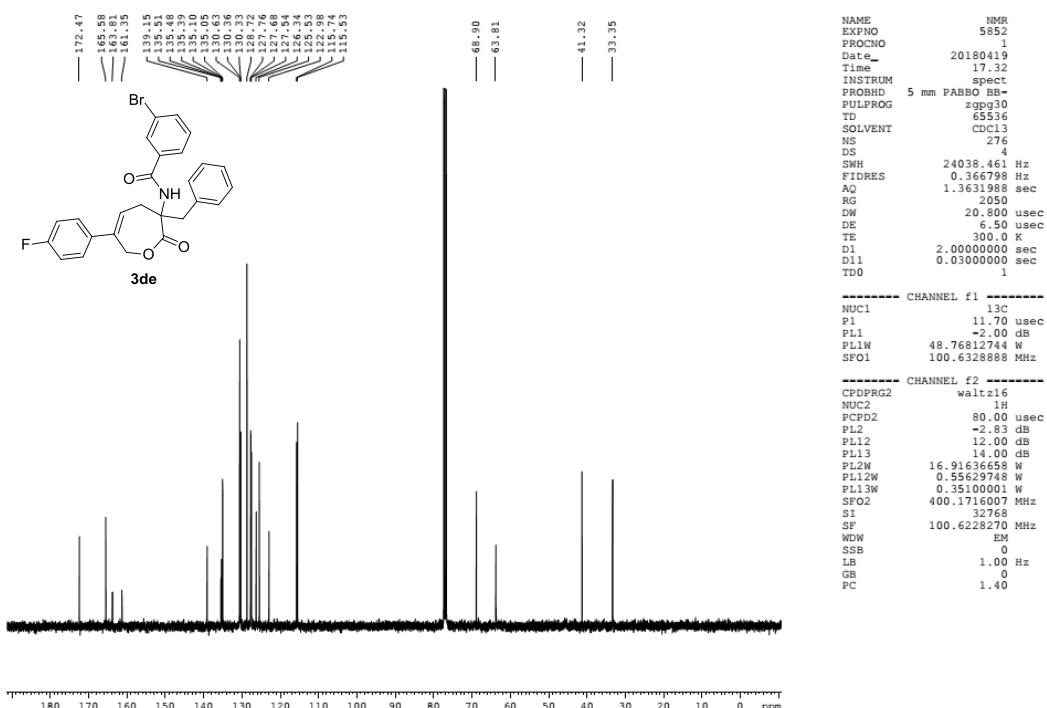
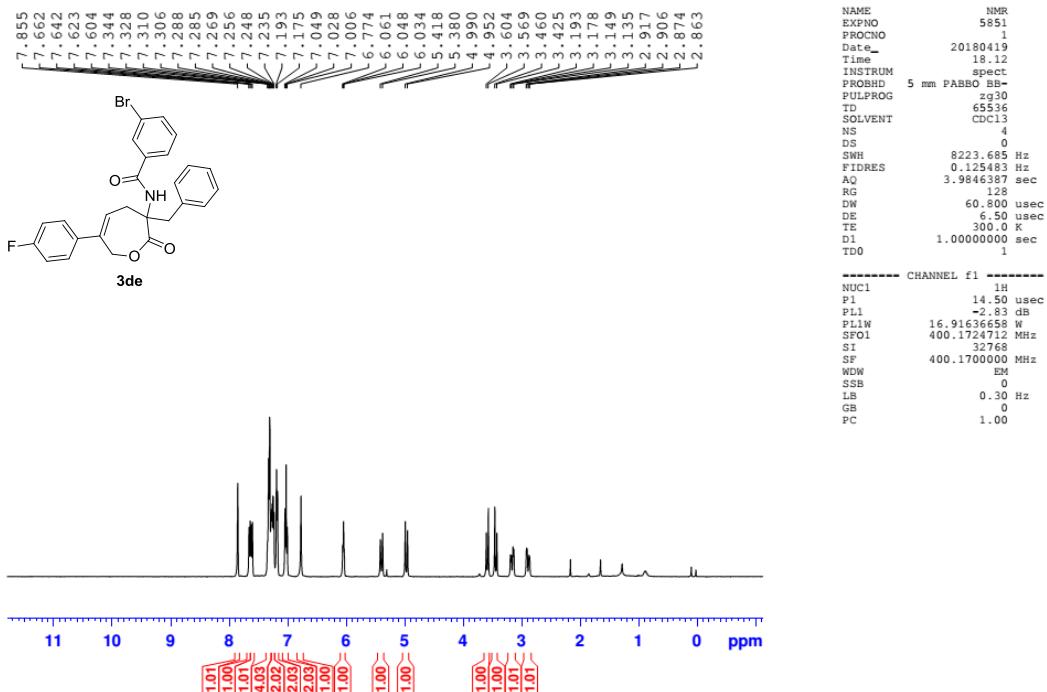


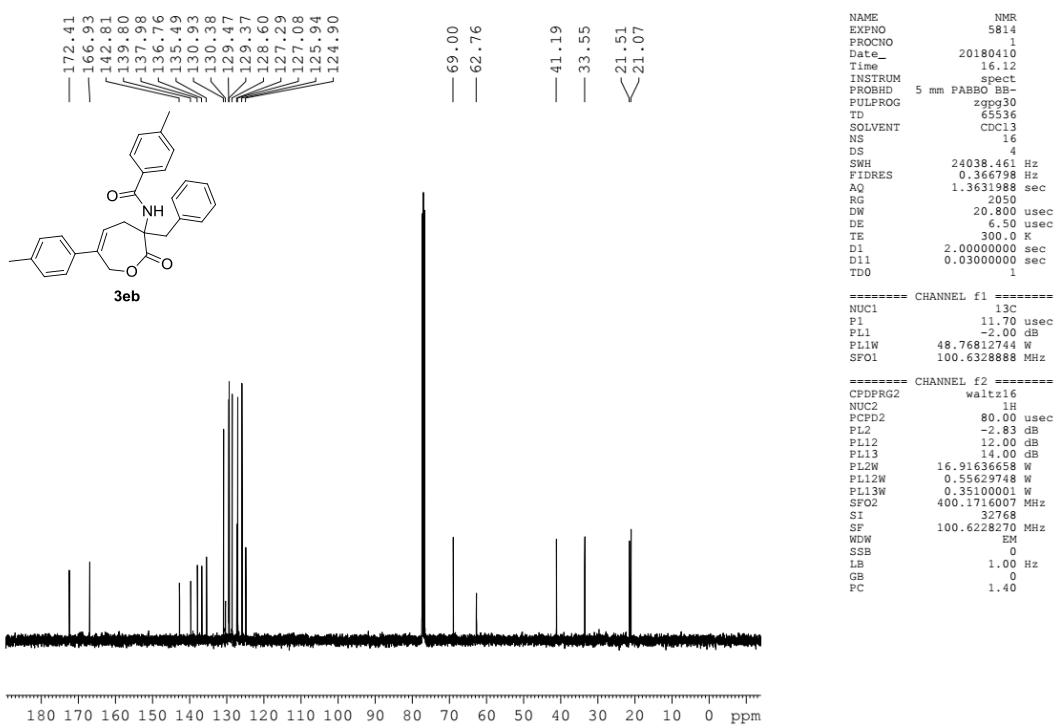
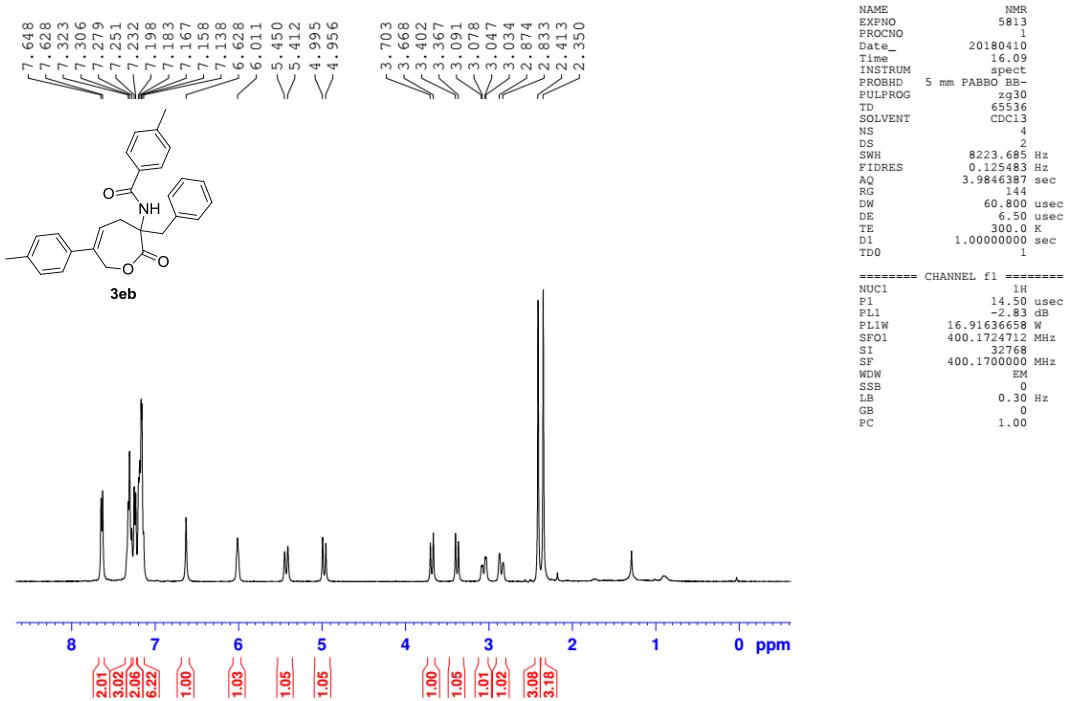


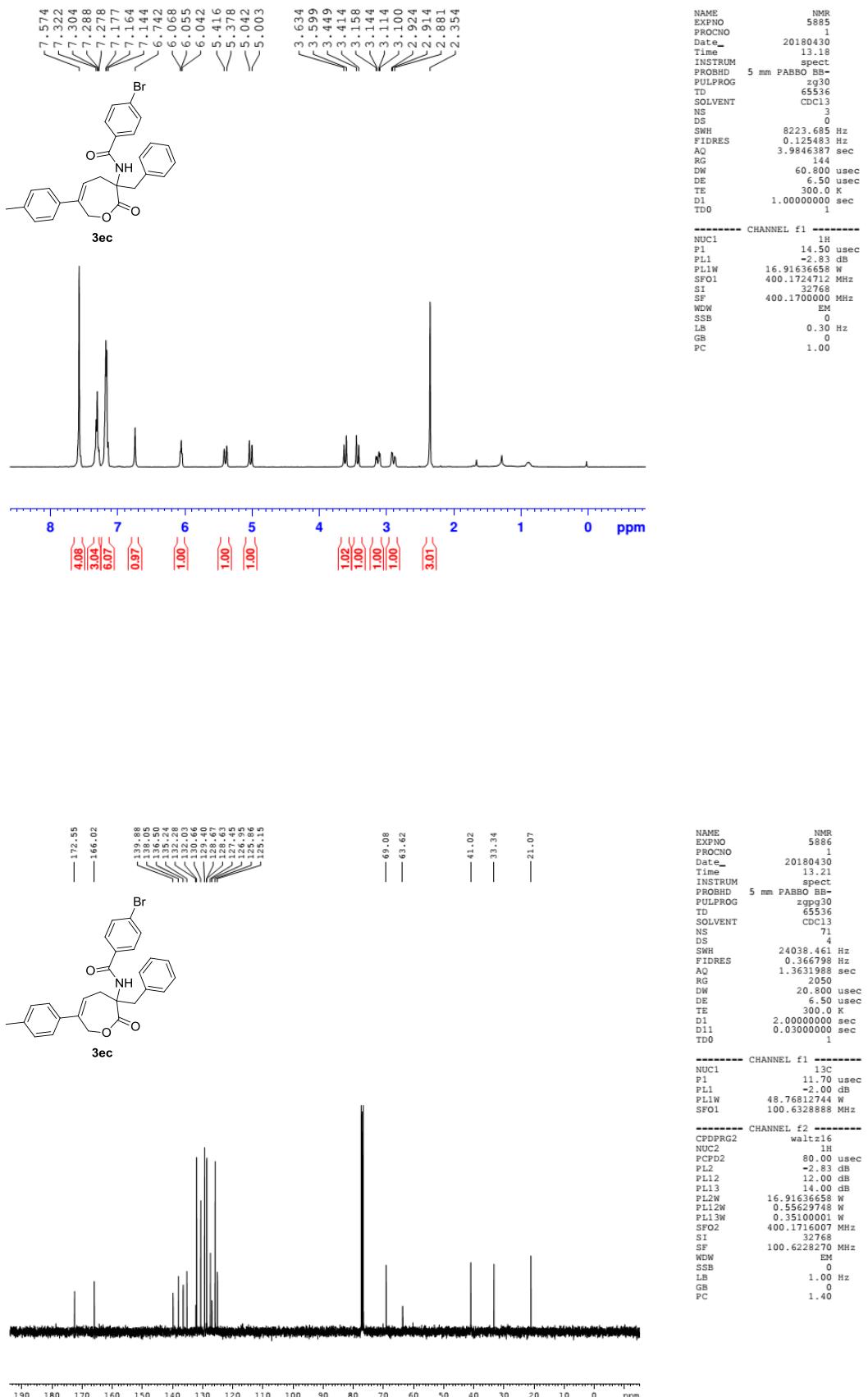


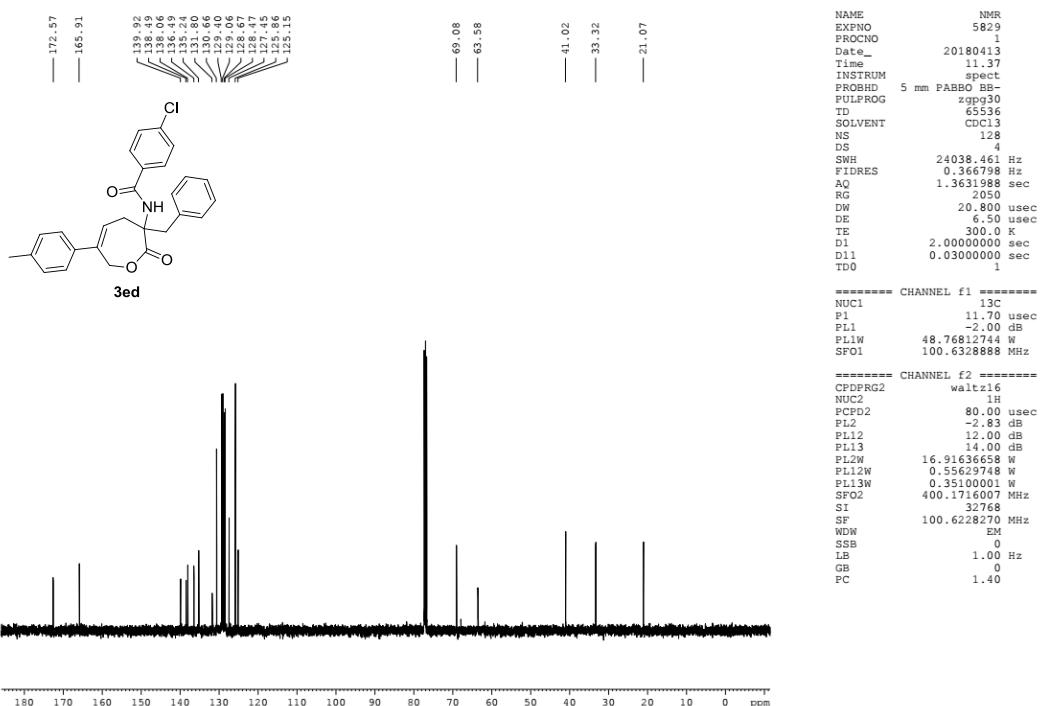
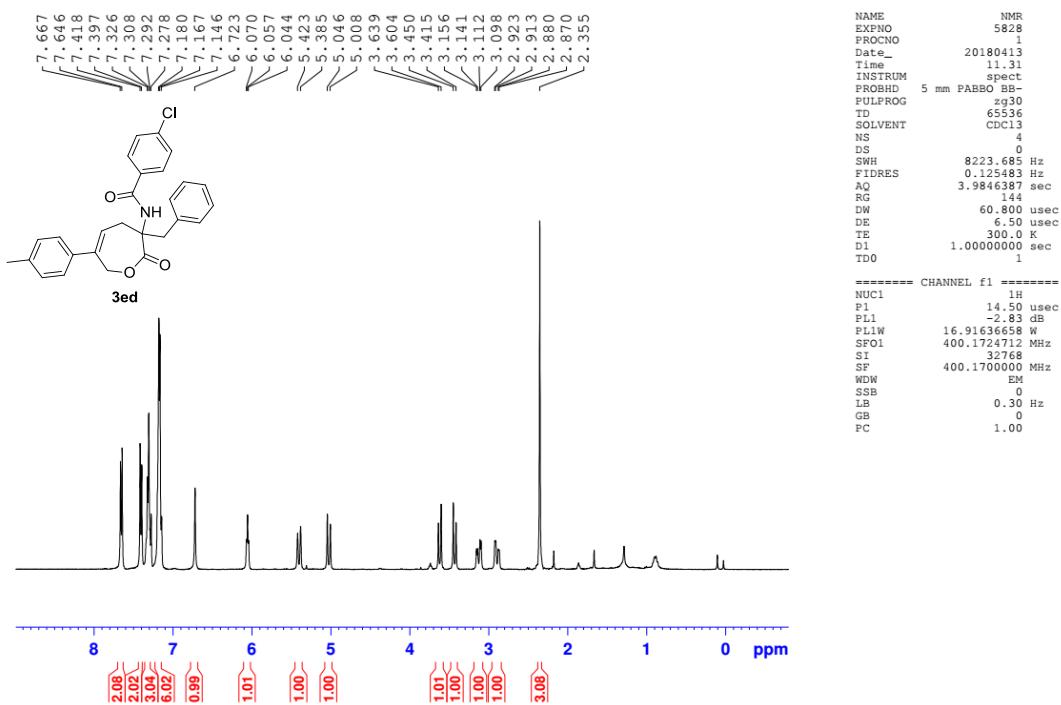


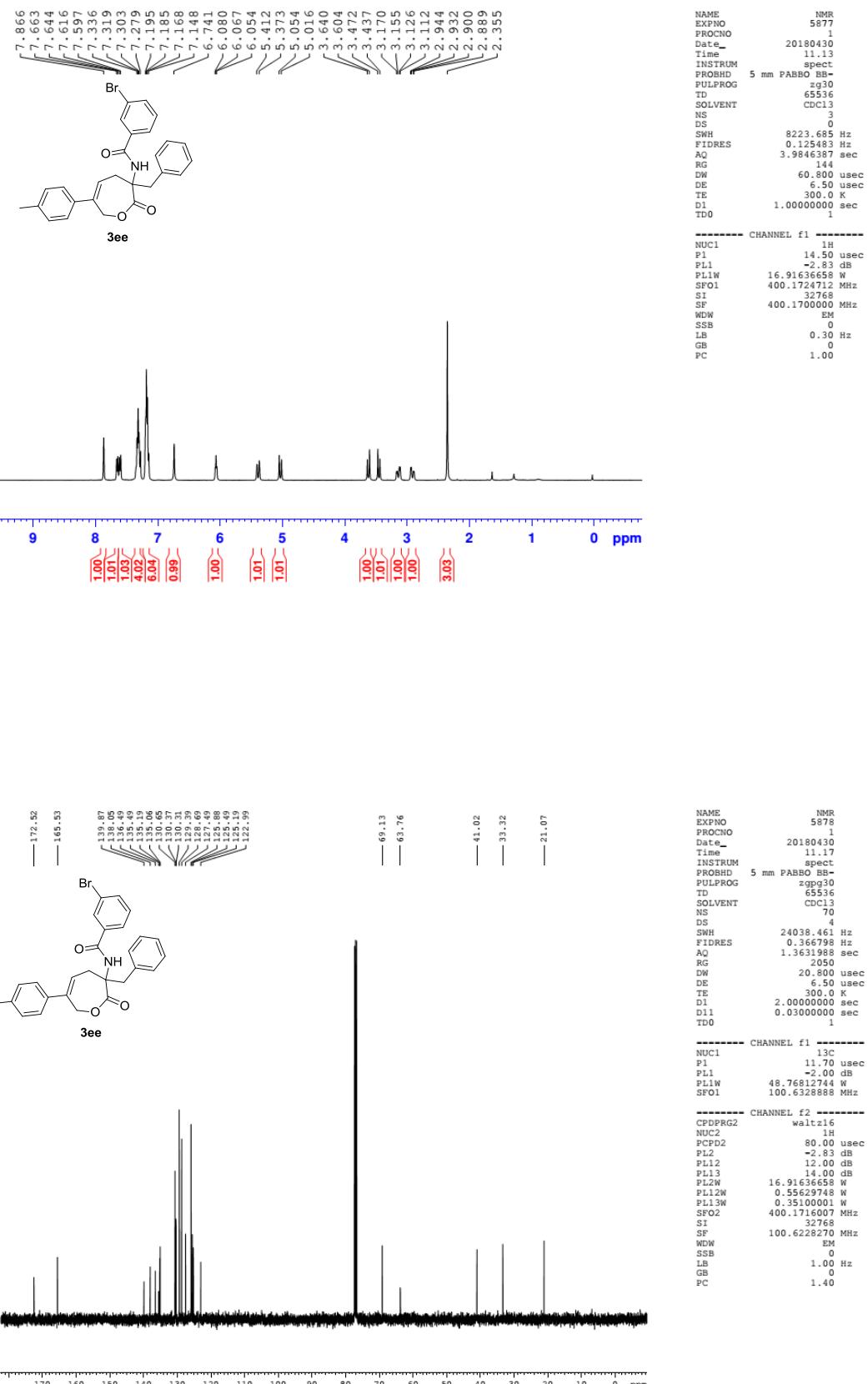


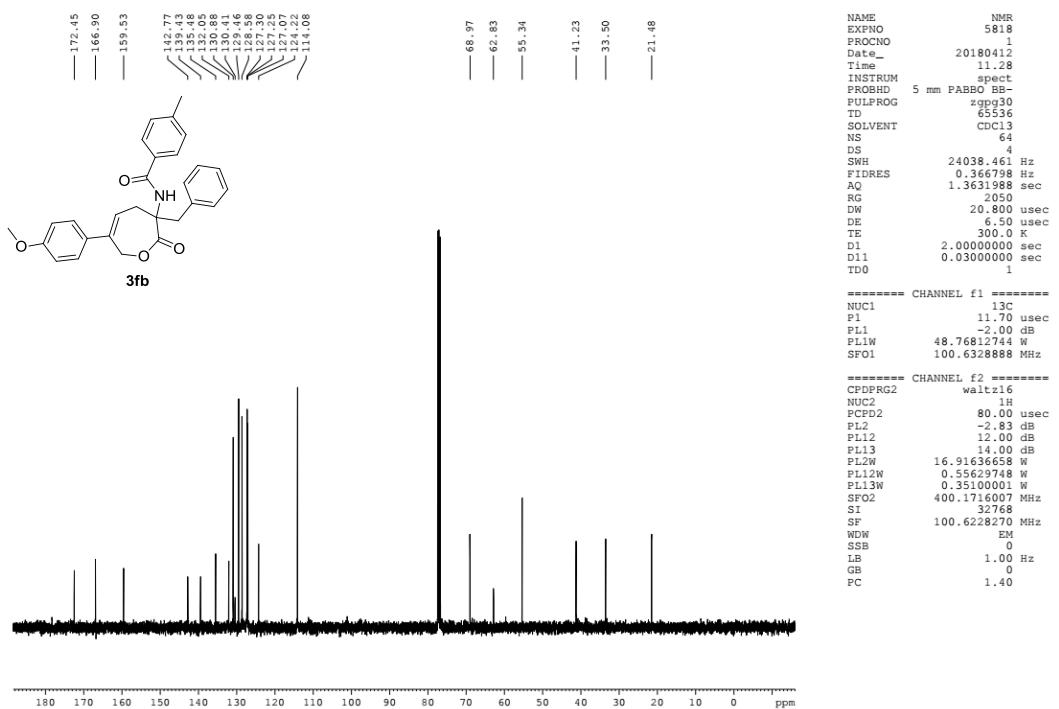
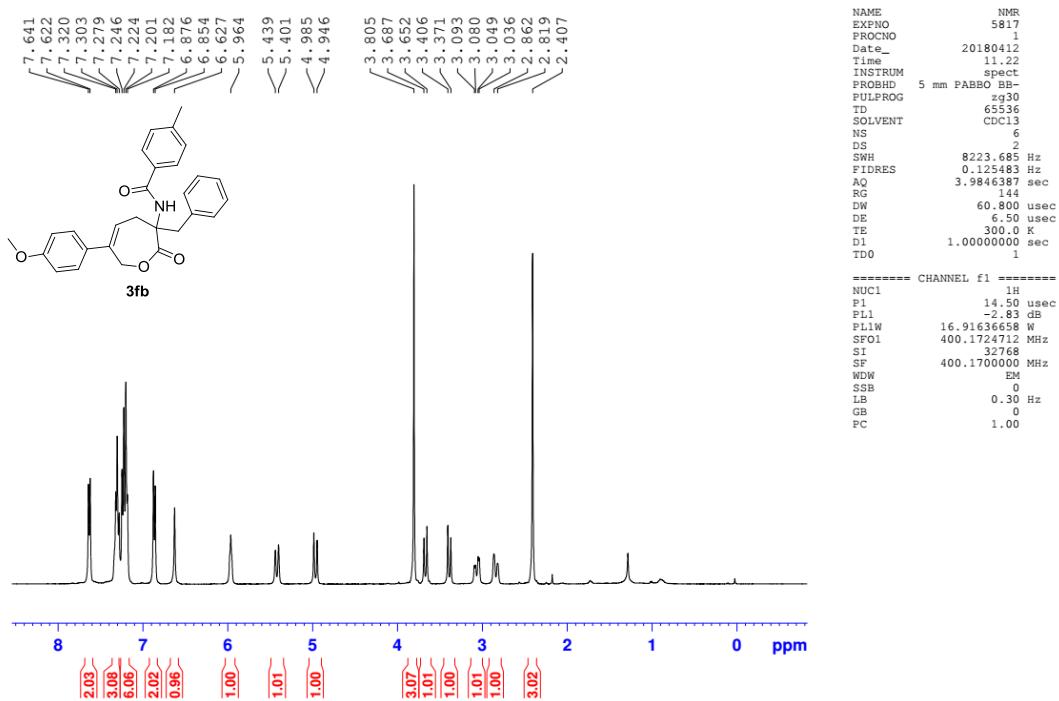


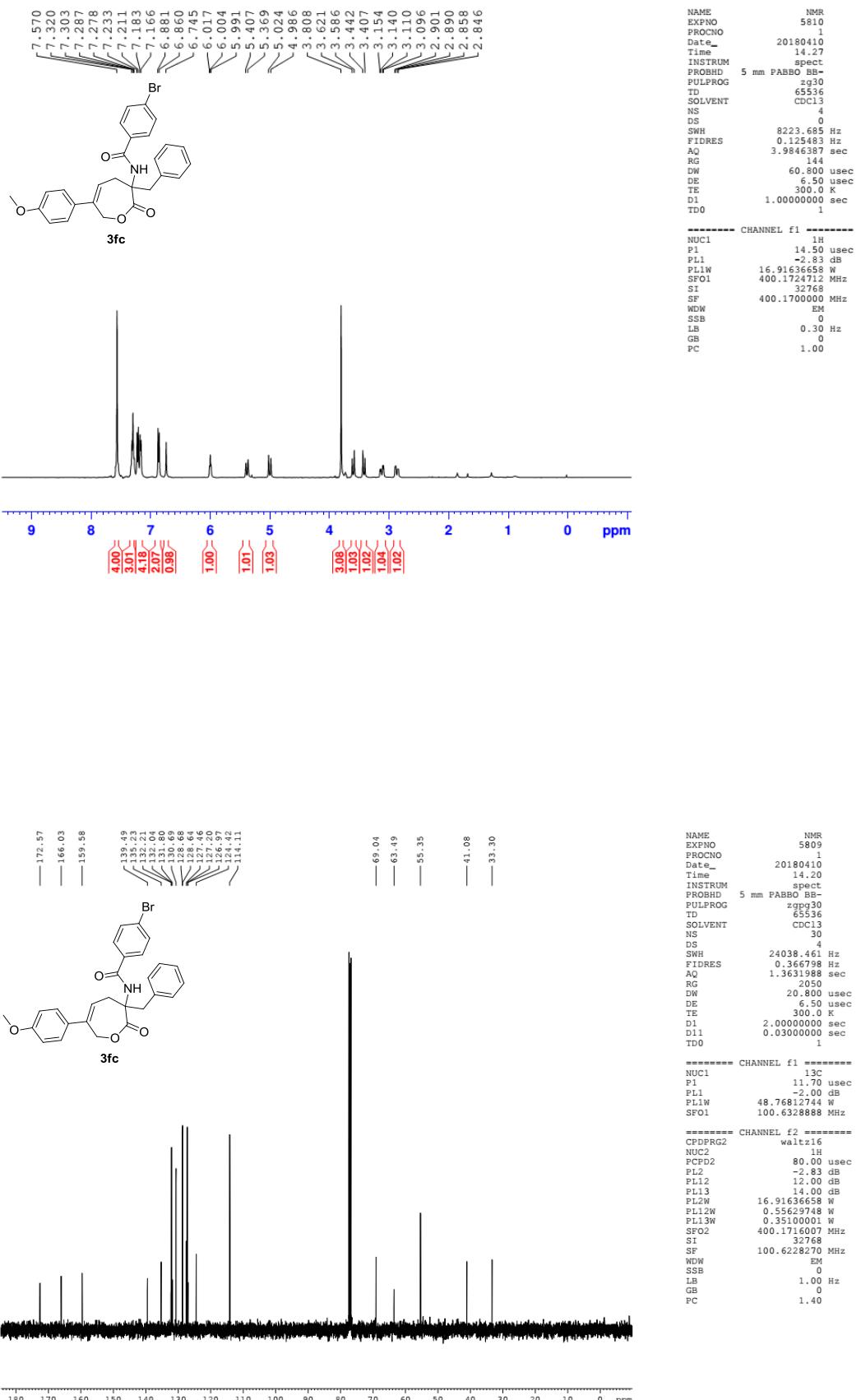


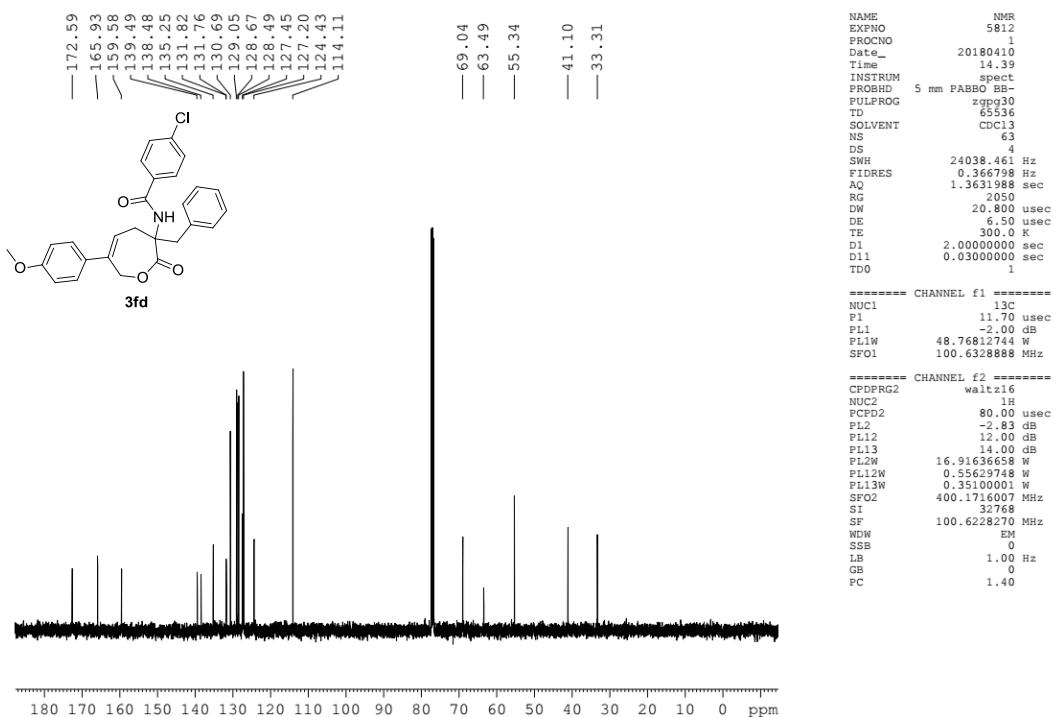
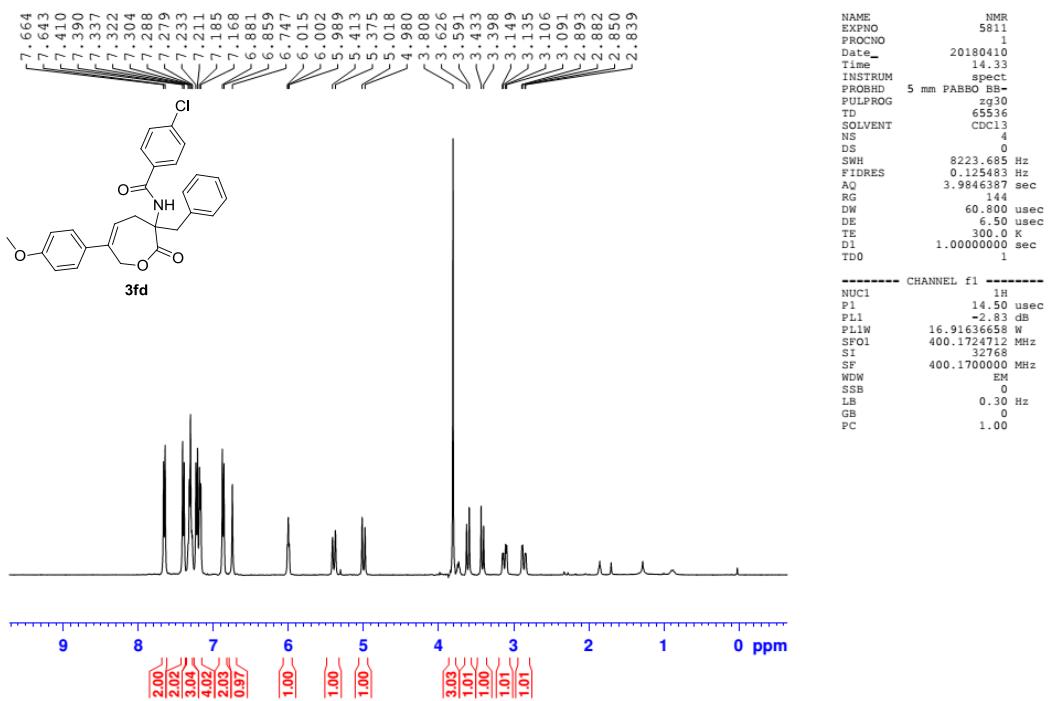


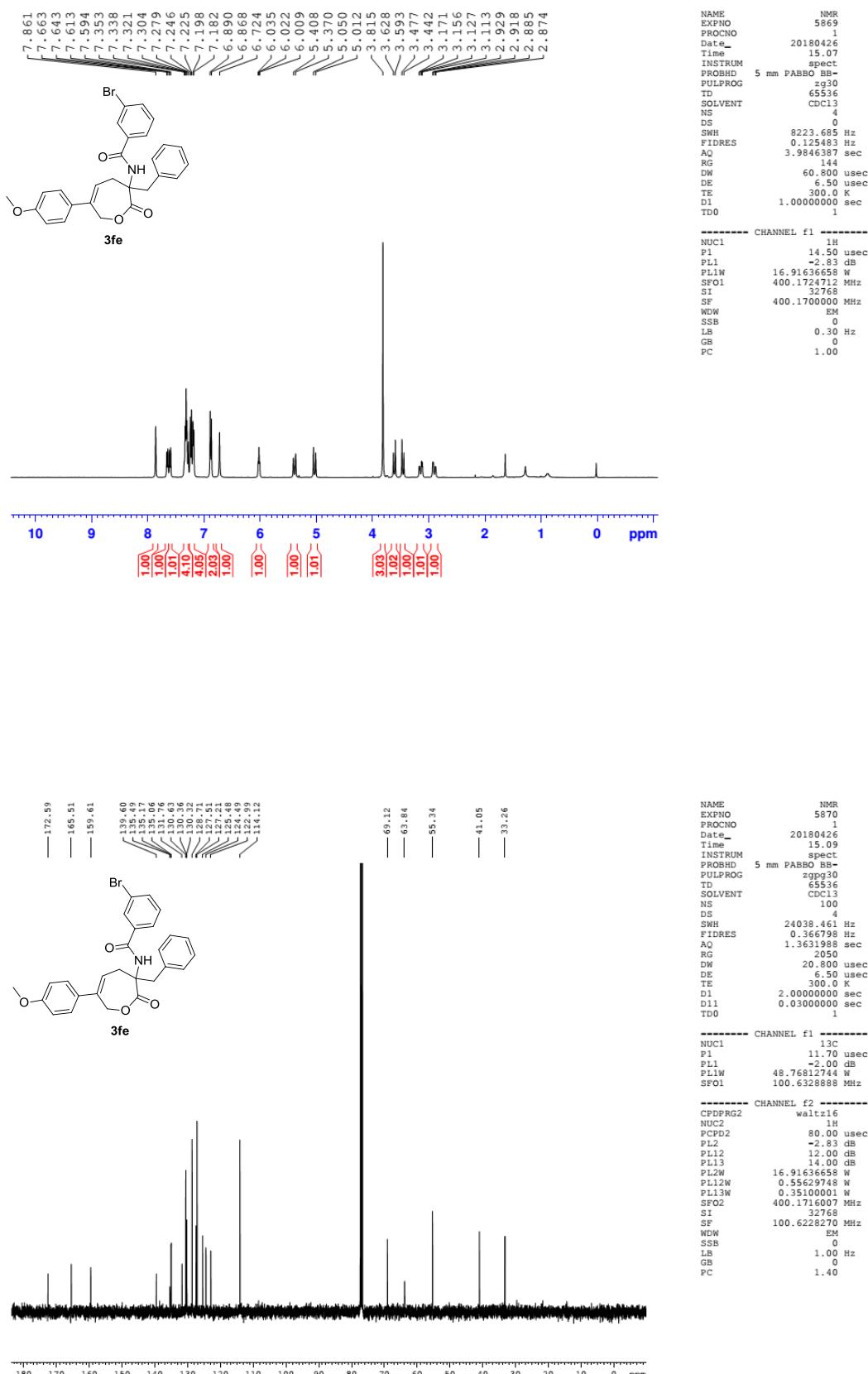


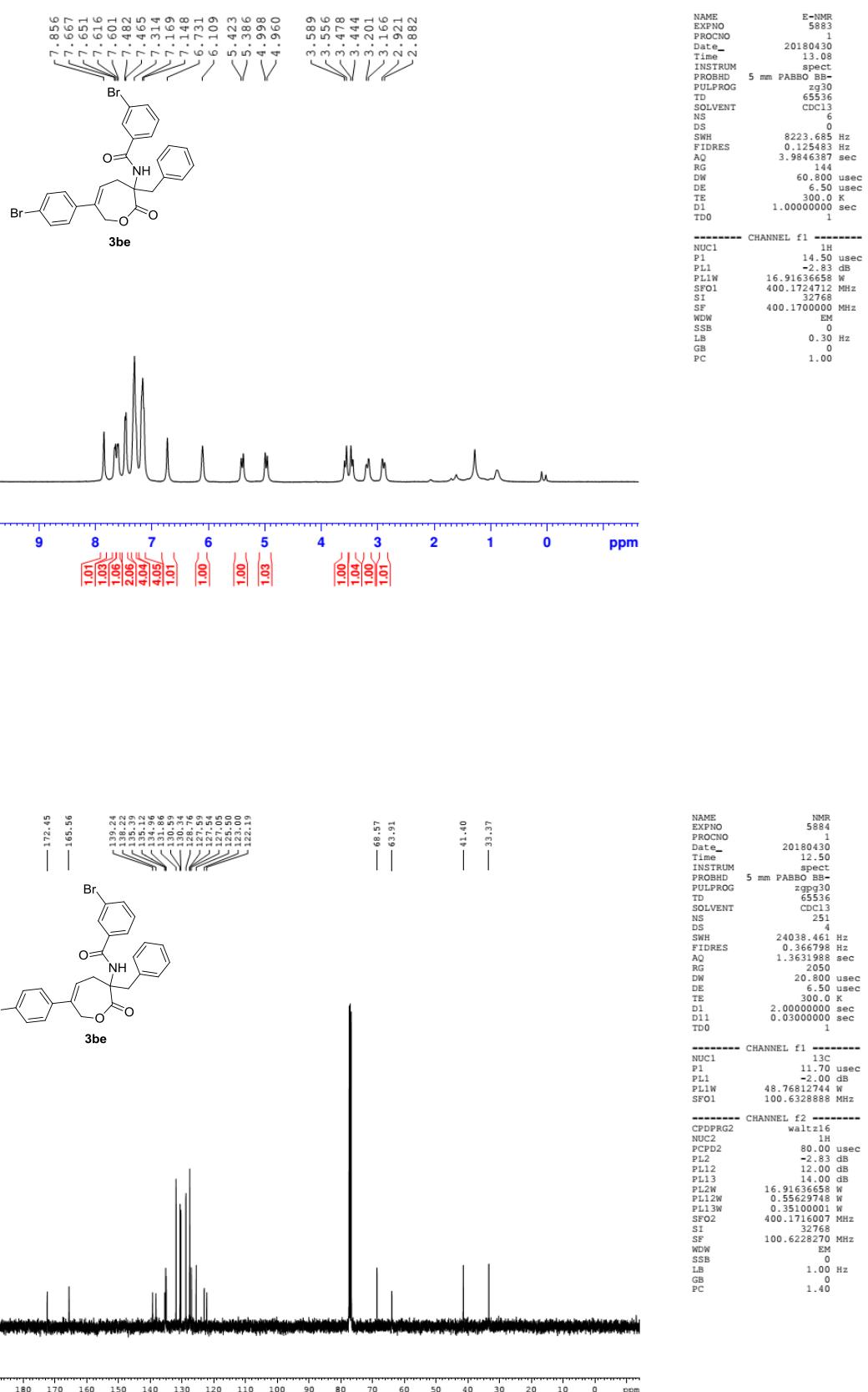


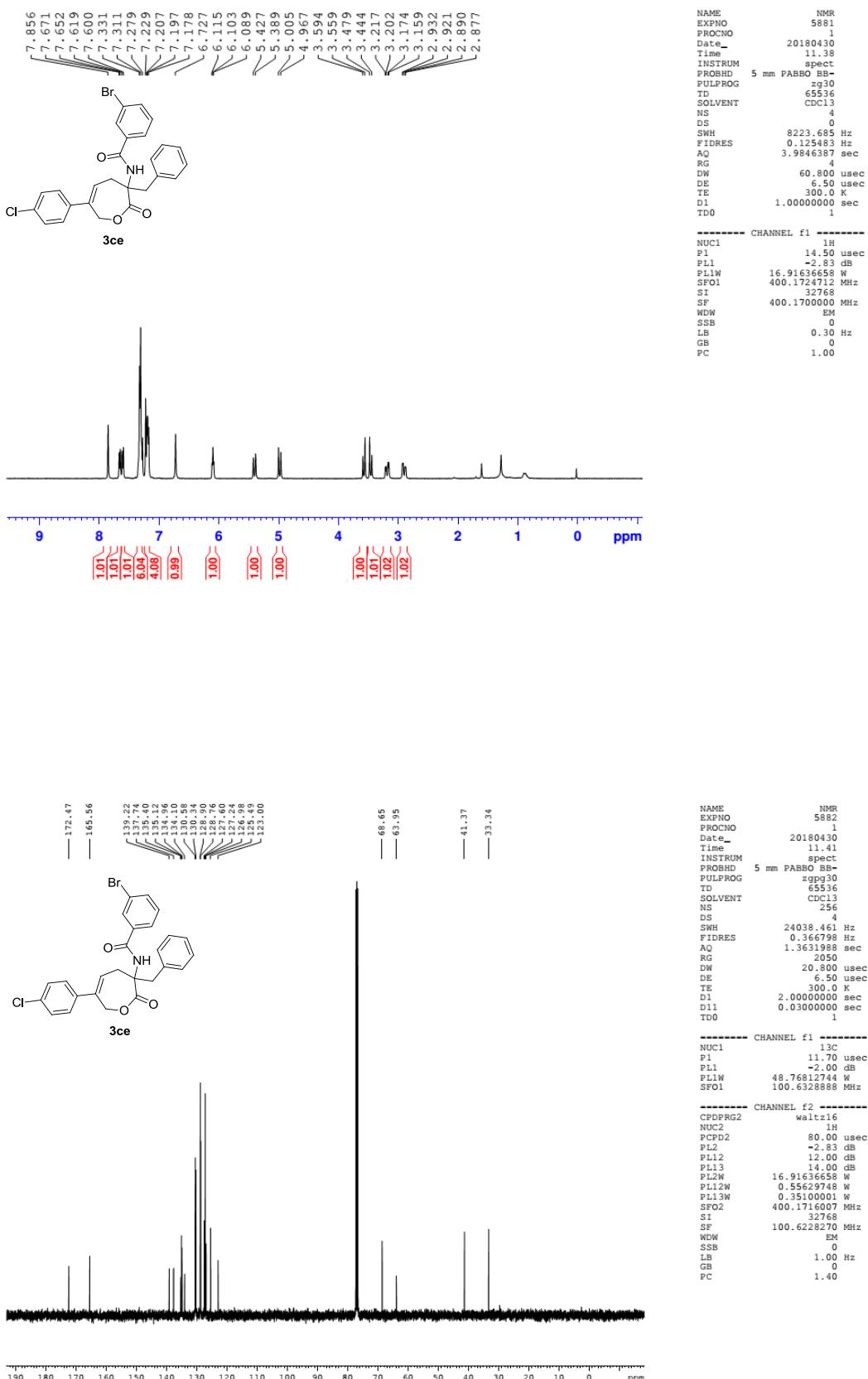




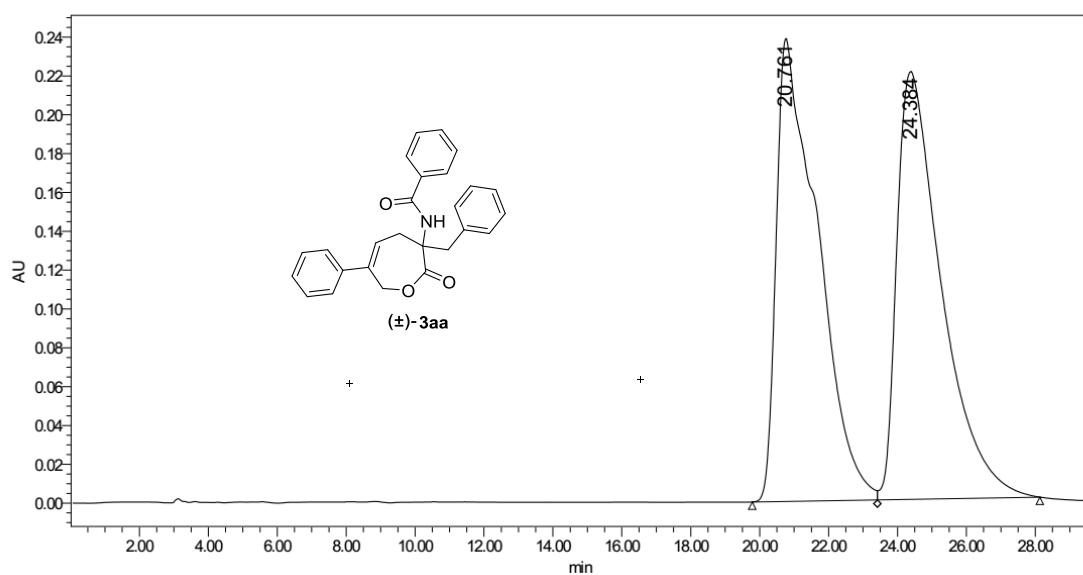






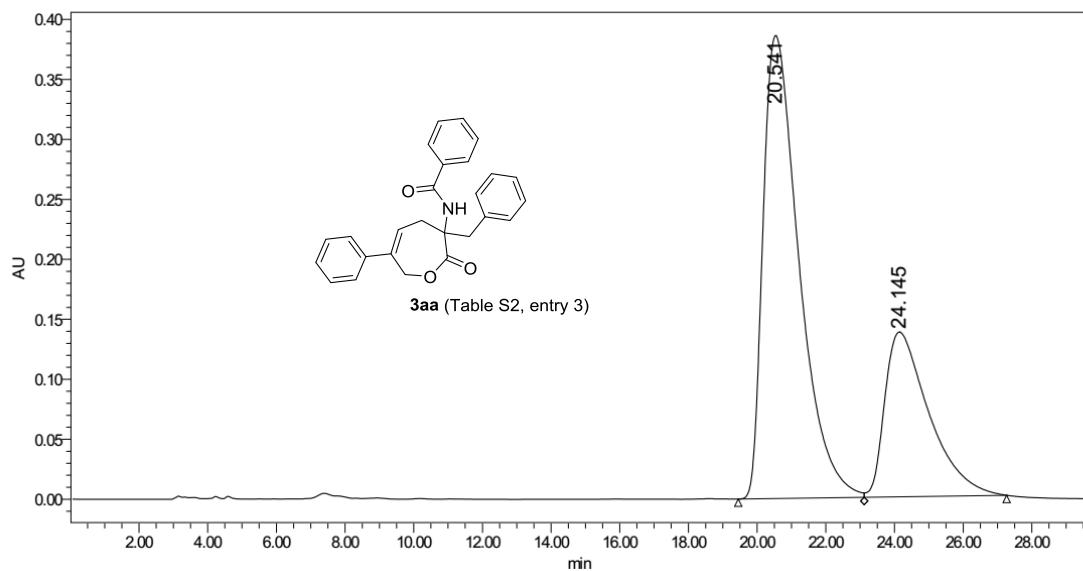


8. Copy of HPLC Spectra of Compound 3aa



<Column Performance Report>

entry	R.T	Area	% Area	Height
1	20.761	19839980	50.09	238276
2	24.384	19766027	49.91	220134



<Column Performance Report>

entry	R.T	Area	% Area	Height
1	20.541	28042686	69.56	385964
2	24.145	12274457	30.44	137383

9. X-Ray Crystal Data of Compound 3ad

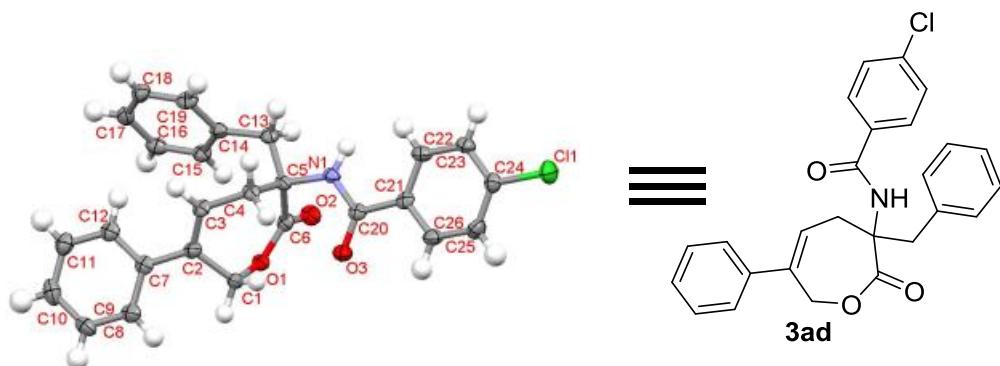


Figure S1 X-ray single crystal structure of **3ad** (with thermal ellipsoids shown at the 50% probability level)

Identification code	3ad					
Empirical formula	C ₂₆ H ₂₂ ClNO ₃					
Formula weight	431.89					
Temperature	133.15 K					
Crystal system, space group	Triclinic, P-1					
Unit cell dimensions	a = 9.588(4) Å	alpha = 88.60(2) deg.	b = 14.091(7) Å	beta = 78.027(16) deg.	c = 15.915(7) Å	gamma = 88.20(3) deg.
Volume	2102.0(16) Å ³					
Z, Calculated density	4, 1.365 g/cm ³					
Absorption coefficient	0.211 mm ⁻¹					
F(000)	904.0					
Crystal size	0.2 × 0.18 × 0.14 mm ³					
Radiation	MoKα ($\lambda = 0.71073$)					
Theta range for data collection	6.028 to 50.038 deg.					
Index ranges	-11 ≤ h ≤ 11, -16 ≤ k ≤ 16, -18 ≤ l ≤ 18					

Reflections collected / uniqueIndependent reflections	20434 / 7111 [R _{int} = 0.0834, R _{sigma} = 0.0770]
Data / restraints / parameters	7111 / 2 / 567
Goodness-of-fit on F ²	1.112
Final R indices [I>2sigma(I)]	R ₁ = 0.0868, wR ₂ = 0.2250
R indices (all data)	R ₁ = 0.1070, wR ₂ = 0.2348
Largest diff. peak and hole	0.70/-0.33 e.Å ⁻³

10. References

- 1 (a) A. Khan, R. Zheng, Y. Kan, J. Ye, J. Xing and Y. J. Zhang, *Angew. Chem. Int. Ed.*, 2014, **53**, 6439; (b) L. Yang, A. Khan, R. Zheng, L. Y. Jin and Y. J. Zhang, *Org. lett.*, 2015, **17**, 6230.
- 2 (a) J. Marco-Martinez, S. Reboreda, M. Izquierdo, V. Marcos, J. L. Lopez, S. Filippone and N. Martin, *J. Am. Chem. Soc.*, 2014, **136**, 2897; (b) S. Dong, X. Liu, Y. Zhu, P. He, L. Lin and X. Feng, *J. Am. Chem. Soc.*, 2013, **135**, 10026; (c) W. R. C., S. Alexander, N. Dominik, S. S. r. M. M., H. Christine, B. Jonathan and S. P. R., *Angew. Chem. Int. Ed.*, 2016, **55**, 2719.