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Highly efficient dual catalysis approach for C-glycosylation: addition of (o-azaaryl)carboxaldehyde to glycals

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General information

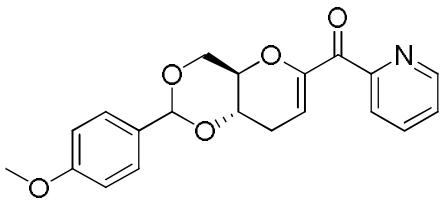
General: All the reactions were carried out in a flame or oven dried glassware with freshly distilled dry solvents under anhydrous conditions unless otherwise indicated. Organic solutions were concentrated under reduced pressure by rotary evaporation with a water bath (temperature below 40 °C). Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60–F254) using UV light at 254 nm as a visualizing agent and a $KMnO_4$ solution as stain. Product purification by flash column chromatography was accomplished using silica gel 60 (0.010–0.063 nm). Technical grade solvents were used for chromatography and were distilled prior to use. Optical rotations were measured in $CHCl_3$ or MeOH on a Schmidt + Haensdch polarimeter with a 1 cm cell (*c* given in g/100 mL). IR spectra were recorded using FTIR Restige-21 (Shimadzu). NMR spectra were recorded at room temperature on 400 MHz Bruker AVIII 400. The residual solvent signals were taken as the reference (7.26 ppm for 1H NMR spectra and 77.0 ppm for ^{13}C NMR spectra in $CDCl_3$). Sometimes the TMS signal at 0.0 ppm was used an internal standard for ^{1}H NMR spectra. Chemical shift (δ) is reported in ppm, coupling constants (J) are given in Hz. The following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet or unresolved. HR-MS (ESI) spectra were recorded on a Waters Q-Tof premierTM mass spectrometer.

Material: All the palladium catalysts and phosphine ligands were purchased from commercial suppliers without any further purification. All the anhydrous solvent was purchase from commercial suppliers for direct use. The glycal starting materials (**1a**, **1b**, **1c**, **1d**) was synthesized by their respective reported methods.[1] Heterocyclic

aldehyde **2a**, **2b**, **2c**, **2d**, **2f**, **2h**, **2i**, **2j** and **2k** was purchased from commercial suppliers for direct use. Aldehyde **2e** and **2g** was synthesized by the reported synthetic methods.[2]

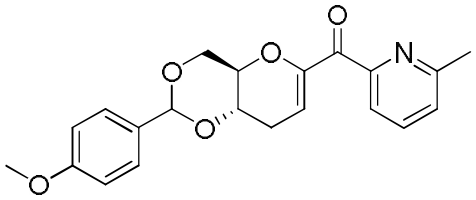
Experimental procedure and data

General procedure of Pd-NHC dual catalysis of *C*-glycosylation of glycals and 2-pyridine carboxaldehyde: synthesis of ((4aR,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)(pyridin-2-yl)methanone (3a): To a round bottom flask containing the solution of **1a** (67 mg, 0.2 mmol), $Pd_2(dba)_3$ (9mg, 0.01mmol), 1,1'Bis(di-*tert*-butylphosphino)ferrocene (14 mg, 0.03 mmol) in toluene (2.0 mL), 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.06 mL, 0.4 mmol) was added dropwise. The mixture was stirred at room temperature for 5 minutes. Then 2-pyridinecarboxaldehyde **2a** (28 µL, 0.3 mmol) was added in a period of 10 minutes. The resulting solution was then heated to 80 °C for 3.5 hours. The mixture was then diluted with ethyl acetate (10 mL), filtered, washed with water (10 mL) and brine (10 mL). The organic layer was evaporated and the residue was purified by flash column chromatography (EtOAc/Hexane = 1/2) to afford the product as yellow solid. (63mg, 90%)

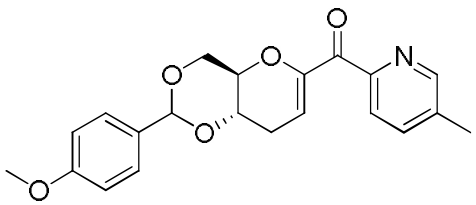


((4aR,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)(pyridin-2-yl)methanone (3a): This compound was prepared following the general procedure by the eluent EtOAc/Hexane = 1/2 as a yellow solid. (63 mg, 90%) mp 171–173 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.51–2.59 (qd, J = 2.9, 9.6 Hz, 1H), 2.64–2.71 (dt, J = 5.8, 18.7 Hz, 1H), 3.80 (s, 3H), 3.92–3.97 (m, 2H), 3.99–4.04 (m, 1H), 4.53–4.61 (m, 1H), 5.61 (s, 1H), 6.52–6.54 (dd, J = 2.9, 5.6 Hz, 1H), 6.89–6.91

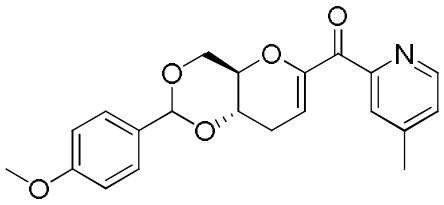
(d, *J* = 8.7 Hz, 2H), 7.42–7.47 (m, 3H), 7.82–7.88 (m, 2H), 8.65–8.66 (d, *J* = 4.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 27.9, 55.3, 68.8, 70.4, 73.8, 101.7, 113.8, 117.9, 124.5, 126.2, 127.5, 129.7, 137.1, 148.3, 149.5, 154.7, 160.2, 186.9 $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 53.5 (*c* 2.20, $CHCl_3$); HRMS (ESI) calcd for $C_{20}H_{20}NO_5$ $[M+H]^+$: 354.1341, found 354.1336.



((4aR,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)(6-methylpyridin-2-yl)methanone (3b): This compound was prepared following the general procedure by the eluent EtOAc/Hexane = 1/2 as a brown solid. (61 mg, 83%) mp 182–184 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.50–2.58 (qd, *J* = 2.9, 9.5 Hz, 1H), 2.62 (s, 3H), 2.64–2.70 (m, 1H), 3.80 (s, 3H), 3.92–3.95 (m, 2H), 3.97–4.02 (m, 1H), 4.56–4.59 (m, 1H), 5.61 (s, 1H), 6.54–6.56 (dd, *J* = 2.9, 5.6 Hz, 1H), 6.88–6.91 (d, *J* = 8.7 Hz, 2H), 7.28–7.30 (d, *J* = 7.6 Hz, 1H), 7.43–7.45 (d, *J* = 8.7 Hz, 2H), 7.68–7.72 (t, *J* = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 24.5, 28.0, 55.3, 68.9, 70.3, 73.8, 101.7, 113.7, 118.0, 121.5, 125.8, 127.5, 129.7, 137.1, 149.5, 154.3, 157.5, 160.2, 187.1 $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 53.7 (*c* 2.60, $CHCl_3$); HRMS (ESI) calcd for $C_{21}H_{22}NO_5$ $[M+H]^+$: 368.1498, found 368.1498

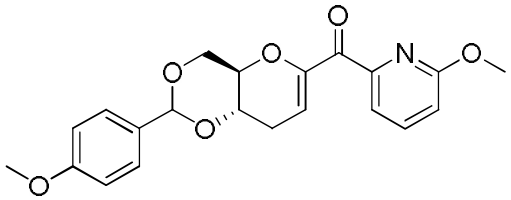


((4aR,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)(5-methylpyridin-2-yl)methanone (3c): This compound was prepared following the general procedure by the eluent EtOAc/Hexane = 1/2 as a yellow solid. (57 mg, 78%) mp 160–163 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.41 (s, 3H), 2.51–2.58 (qd, J = 2.9, 9.6 Hz, 1H), 2.63–2.71 (dt, J = 5.9, 18.7 Hz, 1H), 3.80 (s, 3H), 3.92–3.94 (m, 2H), 3.98–4.04 (m, 1H), 4.55–4.58 (m, 1H), 5.61 (s, 1H), 6.53–6.55 (dd, J = 2.9, 5.7 Hz, 1H), 6.88–6.91 (m, 2H), 7.42–7.45 (m, 2H), 7.61–7.64 (m, 1H), 7.79–7.81 (d, J = 8.0 Hz, 1H), 8.47–8.47 (dd, J = 0.6, 1.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 18.6, 27.9, 55.3, 68.9, 70.4, 73.8, 101.7, 113.7, 117.3, 124.3, 127.5, 129.7, 136.6, 137.4, 148.8, 149.6, 152.1, 160.2, 186.8 $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 58.1 (c 2.00, $CHCl_3$); HRMS (ESI) calcd for $C_{21}H_{22}NO_5$ $[M+H]^+$: 368.1498, found 368.1501.

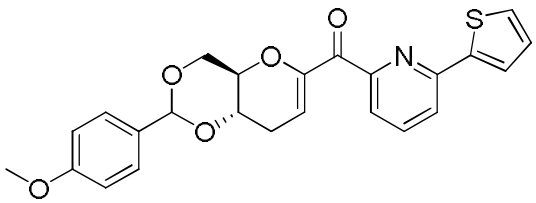


((4aR,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)(4-methylpyridin-2-yl)methanone (3d): This compound was prepared following the general procedure by the eluent EtOAc/Hexane = 1/2 as a yellow solid. (60 mg, 82%) mp 150–152 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.42 (s, 3H), 2.51–2.59 (qd, J = 2.9, 9.6 Hz, 1H), 2.63–2.71 (dt, J = 5.8, 18.7 Hz, 1H), 3.80 (s, 3H), 3.89–3.96 (m, 2H), 3.98–4.04 (m, 1H), 4.54–4.59 (m, 1H), 5.61 (s, 1H), 6.51–6.53 (dd, J = 3.0, 5.6 Hz, 1H), 6.88–6.91 (m, 2H), 7.25–7.25 (d, J = 0.8 Hz, 2H), 7.42–7.45 (m, 1H), 7.68 (s, 1H), 8.49–8.50 (d, J = 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 21.1, 27.9, 55.3, 68.8, 70.4, 73.8, 101.7, 113.7, 117.8, 125.3, 127.0, 127.5, 129.7, 148.1, 148.6, 149.5,

154.6, 160.2, 187.3 $[\alpha]_D^{20}$ = 58.3 (*c* 2.10, $CHCl_3$); HRMS (ESI) calcd for $C_{21}H_{22}NO_5$ $[M+H]^+$: 368.1498, found 368.1497.

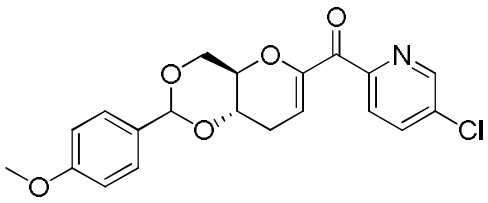


((4aR,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)(6-methoxypyridin-2-yl)methanone (3e): This compound was prepared following the general procedure by the eluent EtOAc/Hexane = 1/2 as a pale yellow solid. (55 mg, 71%) mp 143–145 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.50–2.57 (qd, *J* = 2.9, 9.6 Hz, 1H), 2.62–2.70 (dt, *J* = 5.9, 18.6 Hz, 1H), 3.81 (s, 3H), 3.91–3.95 (m, 2H), 3.97 (s, 3H), 4.00–4.04 (m, 1H), 4.56–4.59 (m, 1H), 5.62 (s, 1H), 6.61–6.63 (dd, *J* = 2.9, 5.6 Hz, 1H), 6.89–6.92 (d, *J* = 8.8 Hz, 2H), 7.43–7.45 (d, *J* = 8.7 Hz, 2H), 7.47–7.49 (d, *J* =7.4 Hz, 1H), 7.67–7.71 (dd, *J* = 7.4, 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 27.9, 53.6, 55.3, 68.9, 70.4, 73.9, 77.2, 101.7, 113.8, 114.2, 116.1, 117.7, 127.5, 129.8, 139.1, 149.8, 151.9, 160.3, 162.8, 186.5 $[\alpha]_D^{20}$ = 28.8 (*c* 1.50, $CHCl_3$); HRMS (ESI) calcd for $C_{21}H_{22}NO_6$ $[M+H]^+$: 384.1447, found 384.1441.

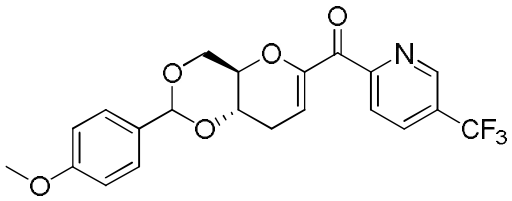


((4aR,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)(6-(thiophen-2-yl)pyridin-2-yl)methanone (3f): This compound was prepared following the general procedure by the eluent EtOAc/Hexane = 1/2 as a bright yellow

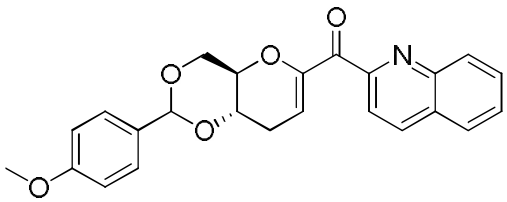
solid. (74 mg, 85%) mp 171–172 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.54–2.61 (qd, J = 2.9, 9.6 Hz, 1H), 2.66–2.73 (dt, J = 5.9, 18.7 Hz, 1H), 3.81 (s, 3H), 3.95–3.97 (m, 2H), 3.99–4.05 (m, 1H), 4.56–4.63 (m, 1H), 5.63 (s, 1H), 5.91–5.93 (dd, J = 3.0, 5.6 Hz, 1H), 6.71–6.73 (dd, J = 2.9, 5.6 Hz, 1H), 6.90–6.92 (d, J = 8.7, 2H), 7.42–7.44 (m, 3H), 7.68–7.69 (dd, J = 1.0, 5.0 Hz, 1H), 7.75–7.77 (d, J = 7.4 Hz, 1H), 7.82–7.86 (m, 1H), 7.94–7.94 (d, J = 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 28.0, 55.3, 68.9, 70.4, 73.9, 101.7, 113.8, 117.5, 122.3, 122.4, 124.3, 126.2, 126.7, 127.5, 129.8, 137.7, 141.5, 149.6, 152.2, 154.4, 160.3, 186.8 $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 44.0 (c 2.50, $CHCl_3$); HRMS (ESI) calcd for $C_{24}H_{22}NO_5S$ $[M+H]^+$: 436.1219, found 436.1216



(5-chloropyridin-2-yl)((4aR,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydro-pyrano[3,2-d][1,3]dioxin-6-yl)methanone (3g): This compound was prepared following the general procedure by the eluent EtOAc/Hexane = 1/2 to as a white solid. (25 mg, 32%) mp 200–201 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.41 (s, 3H), 2.52–2.59 (qd, J = 2.9, 9.6 Hz, 1H), 2.65–2.73 (dt, J = 5.9, 18.7 Hz, 1H), 3.81 (s, 3H), 3.92–3.95 (m, 2H), 3.98–4.02 (m, 1H), 4.55–4.58 (m, 1H), 5.62 (s, 1H), 6.55–6.57 (dd, J = 2.9, 5.6 Hz, 1H), 6.92–6.92 (d, J = 2.9 Hz, 2H), 7.43–7.45 (d, J = 8.7, Hz, 2H), 7.80–7.83 (dd, J = 2.3, 8.4 Hz, 1H), 7.86–7.89 (d, J = 8.4 Hz, 1H), 8.60–8.61 (d, J = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 27.9, 55.3, 68.8, 70.5, 73.7, 101.7, 113.8, 117.7, 125.5, 127.5, 129.7, 135.2, 136.9, 147.3, 149.3, 152.4, 160.3, 186.8 $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 16.1 (c 0.90, $CHCl_3$); HRMS (ESI) calcd for $C_{20}H_{19}NO_5Cl$ $[M+H]^+$: 388.0952, found 388.0955.

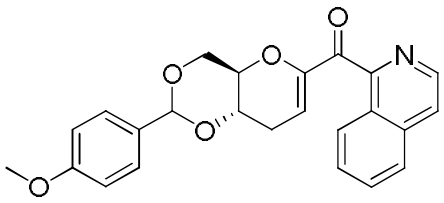


((4aR,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)(5-(trifluoromethyl)pyridin-2-yl)methanone (3h): This compound was prepared following the general procedure by the eluent EtOAc/Hexane = 1/2 as a white solid. (38 mg, 45%) mp 195–197 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.52–2.60 (qd, J = 2.9, 9.6 Hz, 1H), 2.66–2.74 (dt, J = 5.8, 18.9 Hz, 1H), 3.81 (s, 3H), 3.90–3.96 (m, 2H), 3.97–4.05 (m, 1H), 4.56–4.61 (m, 1H), 5.62 (s, 1H), 6.53–6.56 (dd, J = 3.0, 5.7 Hz, 1H), 6.89–6.92 (dd, J = 2.0, 6.8 Hz, 2H), 7.45–7.45 (d, J = 1.8, Hz, 2H), 7.98–8.00 (d, J = 8.2 Hz, 1H), 8.08–8.11 (dd, J = 1.8, 8.2 Hz, 1H), 8.91–8.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 28.0, 55.3, 68.8, 70.6, 73.6, 101.8, 113.8, 118.4, 124.2, 127.5, 129.6, 134.4, 134.4, 145.3, 145.3, 149.3, 160.3, 185.6 $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 28.8 (c 1.10, $CHCl_3$); HRMS (ESI) calcd for $C_{21}H_{22}NO_6$ $[M+H]^+$: 384.1447, found 384.1441.

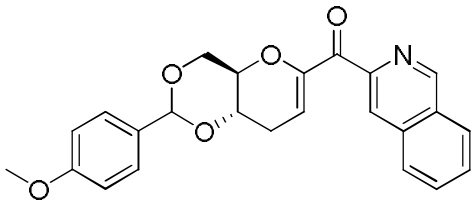


((4aR,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)(quinolin-2-yl)methanone (3i): This compound was prepared following the general procedure by the eluent EtOAc/Hexane = 1/2 as a brown solid. (59 mg, 73%) mp 162–164 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.55–2.63 (qd, J = 2.9, 9.6 Hz, 1H),

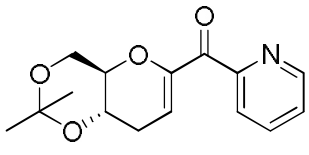
2.64–2.71 (dt, *J* = 5.9, 18.6 Hz, 1H), 3.81 (s, 3H), 3.95–4.07 (m, 3H), 4.58–4.64 (m, 1H), 5.64 (s, 1H), 6.76–6.78 (dd, *J* = 2.9, 5.6 Hz, 1H), 6.89–6.93 (m, 2H), 7.44–7.47 (m, 2H), 7.63–7.67 (ddd, *J* = 1.1, 7.0, 8.1 Hz, 1H), 7.78–7.82 (ddd, *J* = 1.4, 6.9, 8.4 Hz, 1H), 7.87–7.89 (d, *J* = 8.2 Hz, 1H), 7.92–7.95 (d, *J* = 8.5 Hz, 1H), 8.18–8.20 (d, *J* = 8.6 Hz, 1H), 8.28–8.30 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 28.1, 55.3, 68.9, 70.5, 73.8, 101.8, 113.8, 118.6, 120.7, 127.5, 127.7, 128.4, 128.9, 129.8, 130.3, 137.1, 146.6, 149.5, 154.3, 160.3, 187.1 $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 49.2 (*c* 1.60, $CHCl_3$); HRMS (ESI) calcd for $C_{24}H_{22}NO_5$ $[M+H]^+$: 404.1498, found 404.1493



isoquinolin-1-yl((4aR,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)methanone (3j): This compound was prepared following the general procedure by the eluent EtOAc/Hexane = 1/2 as a yellow solid. (56 mg, 70%) mp 197–200 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.46–2.33 (qd, *J* = 2.9, 9.4 Hz, 1H), 2.57–2.65 (dt, *J* = 5.8, 18.8 Hz, 1H), 3.80 (s, 3H), 3.94–4.05 (m, 3H), 4.58–4.65 (m, 1H), 5.62 (s, 1H), 5.91– 5.93 (dd, *J* = 3.0, 5.6 Hz, 1H), 6.88–6.92 (m, 2H), 7.43–7.45 (d, *J* = 8.7 Hz, 2H), 7.62–7.66 (ddd, *J* = 1.2, 5.9, 8.2 Hz, 1H), 7.72–7.78 (m, 2H), 7.88–7.90 (d, *J* = 8.2 Hz, 1H), 8.10–8.12 (d, *J* = 8.4 Hz, 1H), 8.54–8.56 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 28.0, 55.3, 68.8, 70.6, 73.7, 101.8, 113.8, 118.3, 122.7, 125.9, 126.2, 127.1, 127.5, 128.4, 129.7, 130.8, 136.6, 141.0, 150.6, 155.6, 160.3, 188.7 $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 35.9 (*c* 1.20, $CHCl_3$); HRMS (ESI) calcd for $C_{24}H_{22}NO_5$ $[M+H]^+$: 404.1498, found 404.1491

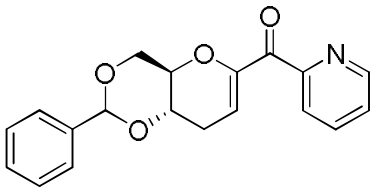


isoquinolin-3-yl((4aR,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)methanone (3k): This compound was prepared following the general procedure by the eluent EtOAc/Hexane = 1/2 as a yellow solid. (55 mg, 68%) mp 171–172 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.55–2.62 (qd, J = 2.9, 9.6 Hz, 1H), 2.66–2.74 (dt, J = 5.8, 18.6 Hz, 1H), 3.81 (s, 3H), 3.94–3.99 (m, 2H), 4.01–4.08 (m, 1H), 4.56–4.63 (m, 1H), 5.63 (s, 1H), 6.58–6.60 (dd, J = 2.9, 5.6 Hz, 1H), 6.90–6.92 (dd, J =2.0, 6.8, 2H), 7.44–7.46 (dd, J = 1.9, 6.8, 2H), 7.72–7.81 (m, 2H), 7.96–7.98 (d, J = 8.0 Hz, 1H), 8.05–8.07 (d, J = 8.0 Hz, 1H), 8.35 (s, 1H), 9.27 (s, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 28.0, 55.3, 68.9, 70.5, 73.9, 101.7, 113.8, 117.0, 123.2, 127.5, 127.6, 128.1, 129.5, 129.7, 131.2, 135.6, 148.4, 150.0, 160.2, 187.2, 126.7, 127.5, 129.8, 137.7, 141.5, 149.6, 152.2, 154.4, 160.3, 186.8 $[\alpha]_D^{20}$ = 53.4 (c 2.00, $CHCl_3$); HRMS (ESI) calcd for $C_{24}H_{22}NO_5$ $[M+H]^+$: 404.1498, found 404.1500

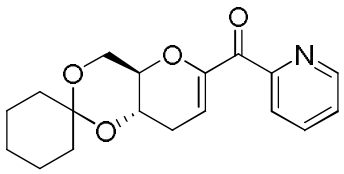


((4aR,8aS)-2,2-dimethyl-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)(pyridin-2-yl)methanone (3l): This compound was prepared following the general procedure by the eluent EtOAc/Hexane = 1/5 as a white solid. (45 mg, 82%) mp 84–

86 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44 （s, 3H), 1.55 (s, 3H), 2.35–2.43 (qd, J = 2.9, 9.8 Hz, 1H), 2.48–2.56 (dt, J = 5.8, 18.5 Hz, 1H), 3.74–3.80 (m, 1H), 3.95–4.00 (t, J = 10.8 Hz, 1H), 4.02–4.09 (m, 1H), 4.15–4.19 (dd, J = 5.5, 11.0 Hz, 1H), 6.46–6.48 (q, J = 2.9 Hz, 1H), 7.42–7.46 (ddd, J = 2.0, 4.8, 6.9 Hz, 1H), 7.81–7.87 (m, 2H), 8.63–8.65 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 19.0, 28.4, 29.1, 62.1, 66.3, 71.5, 99.7, 118.0, 124.5, 126.1, 137.1, 148.3, 149.5, 154.7, 187.0 $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 62.8 (c 1.50, $CHCl_3$); HRMS (ESI) calcd for $C_{15}H_{18}NO_4$ $[M+H]^+$: 276.1236, found 276.1233



((4aR,8aS)-2-phenyl-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)(pyridin-2-yl)methanone (3m): This compound was prepared following the general procedure by the eluent EtOAc/Hexane = 1/3 as a white solid. (56 mg, 87%) mp 140–141 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.53–2.61 (qd, J = 2.9, 12.6 Hz, 1H), 2.62–2.70 (dt, J = 5.9, 18.6 Hz, 1H), 3.92–3.99 (m, 2H), 3.99–4.07 (m, 1H), 4.57–4.62 (m, 1H), 5.66 (s, 1H), 6.54–6.56 (dd, J = 2.9, 5.7 Hz, 1H), 7.35–7.41 (m, 3H), 7.43–7.47 (m, 1H), 7.50–7.53 (m, 2H), 7.82–7.89 (m, 2H), 8.64–8.67 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 27.9, 68.9, 70.4, 73.9, 77.2, 101.8, 117.8, 124.5, 126.2 ， 128.4, 129.2, 148.3, 149.5, 154.7, 186.9 $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 90.9 (c 1.10, $CHCl_3$); HRMS (ESI) calcd for $C_{21}H_{22}NO_6$ $[M+H]^+$: 324.1236, found 324.1227.



pyridin-2-yl((4a'R,8a'S)-4',4a',8',8a'-tetrahydrospiro[cyclohexane-1,2'-pyrano-[3,2-d][1,3]dioxine]-6'-yl)methanone (3n): This compound was prepared following the general procedure by the eluent EtOAc/Hexane = 1/4 as a brown oil. (45 mg, 72%) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41–1.53 (m, 4H), 1.58–1.67 (m, 4H), 1.90–1.93 (m, 1H), 2.04–2.08 (m, 1H), 2.36–2.44 (qd, J = 2.8, 9.7 Hz, 1H), 2.49–2.56 (dt, J = 5.9, 18.4 Hz, 1H), 3.75–3.82 (m, 1H), 3.95–4.00 (m, 1H), 4.06–4.10 (m, 1H), 4.12–4.18 (m, 1H), 6.45–6.48 (dd, J = 2.8, 5.7 Hz, 1H), 7.43–7.46 (m, 1H), 7.81–7.87 (m, 2H), 8.64–8.66 (d, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 22.5, 22.7, 25.6, 27.8, 28.5, 38.0, 61.4, 65.4, 71.8, 99.8, 118.1, 124.5, 126.1, 137.0, 148.3, 149.5, 154.8, 187.1 $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 21.1 (c 1.10, $CHCl_3$); HRMS (ESI) calcd for $C_{18}H_{22}NO_4$ $[M+H]^+$: 316.1549, found 316.1551.

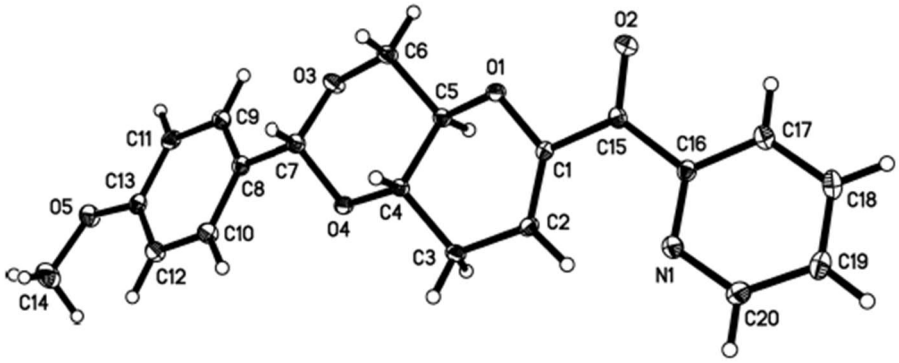
References

1. (a) Barrows, R. S.; Lindwall, H. G. *J. Am. Chem. Soc.* **1942**, *64*, 2430. (b) Jones, S. W.; Palmer, C. F.; Paul, J. M.; Tiffin, P. D. *Tetrahedron Lett.* **1999**, *40*, 1211.

2. (a) Ma, J.; Ng, S.; Zeng, J.; Chen, P.; Than, A.; Zhang, J.; Zhao, Y. *Chem. Eur. J*. **2010**, *16*, 4533. (b) Doetz, K. H.; Otto, F.; Nieger, M. *J. Organomet. Chem.* **2001**, *621*, 77.

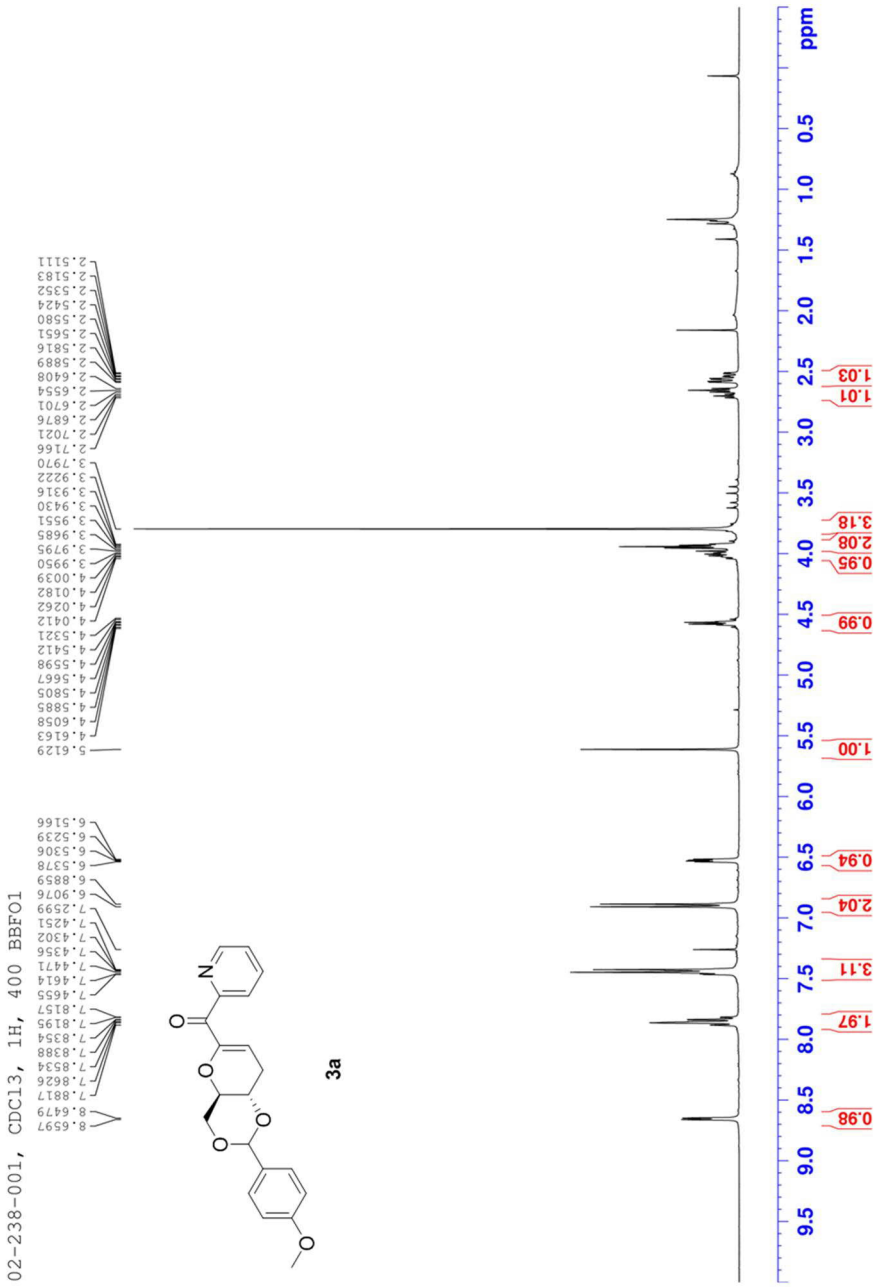
Crystal Data

Crystal Image of Compound **3a**



Basic Crystal Data of Compound 3a

Chemical formula	$C_{20}H_{19}NO_5$	
Formula weight	353.36	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal size	0.400 x 0.410 x 0.420 mm	
Crystal habit	colorless block	
Crystal system	monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 7.3058(7) Å	α = 90°
	b = 6.2839(6) Å	β = 97.945(2)°
	c = 18.0298(16) Å	γ = 90°
Volume	819.78(13) $Å^3$	
Z	2	
Density (calculated)	1.432 g/cm^3	
Absorption coefficient	0.103 mm^{-1}	
F(000)	372	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7.8157
7.4655
7.4614
7.4471
7.4356
7.4302
7.4251
7.2599
6.9076
6.8859
6.5378
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6.5166
5.6129
4.6163
4.6058
4.5885
4.5805
4.5667
4.5598
4.5412
4.5321
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4.0182
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3.9795
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3.9430
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3a
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1.00
0.99
0.95
2.08
3.18
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1.03
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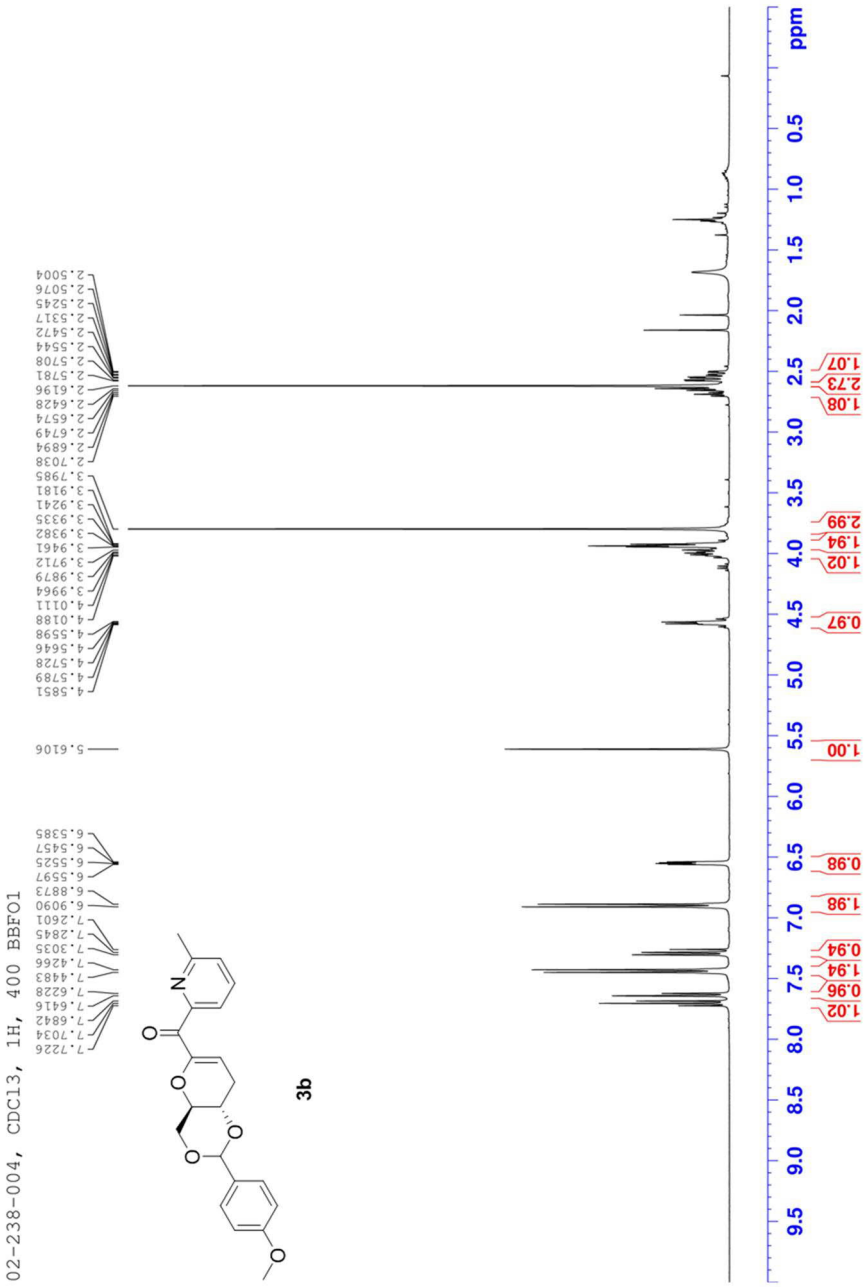
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7.2845
7.2601
6.9090
6.8873
6.5597
6.5525
6.5457
6.5385
5.6106
4.5851
4.5789
4.5728
4.5646
4.5598
4.0188
4.0111
3.9964
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3.9712
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3.9382
3.9335
3.9241
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3.7985
2.7038
2.6894
2.6749
2.6574
2.6428
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2.5781
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2.5544
2.5472
2.5317
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2.5076
2.5004
3b
ppm
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8.5
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7.5
7.0
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6.0
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5.0
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4.0
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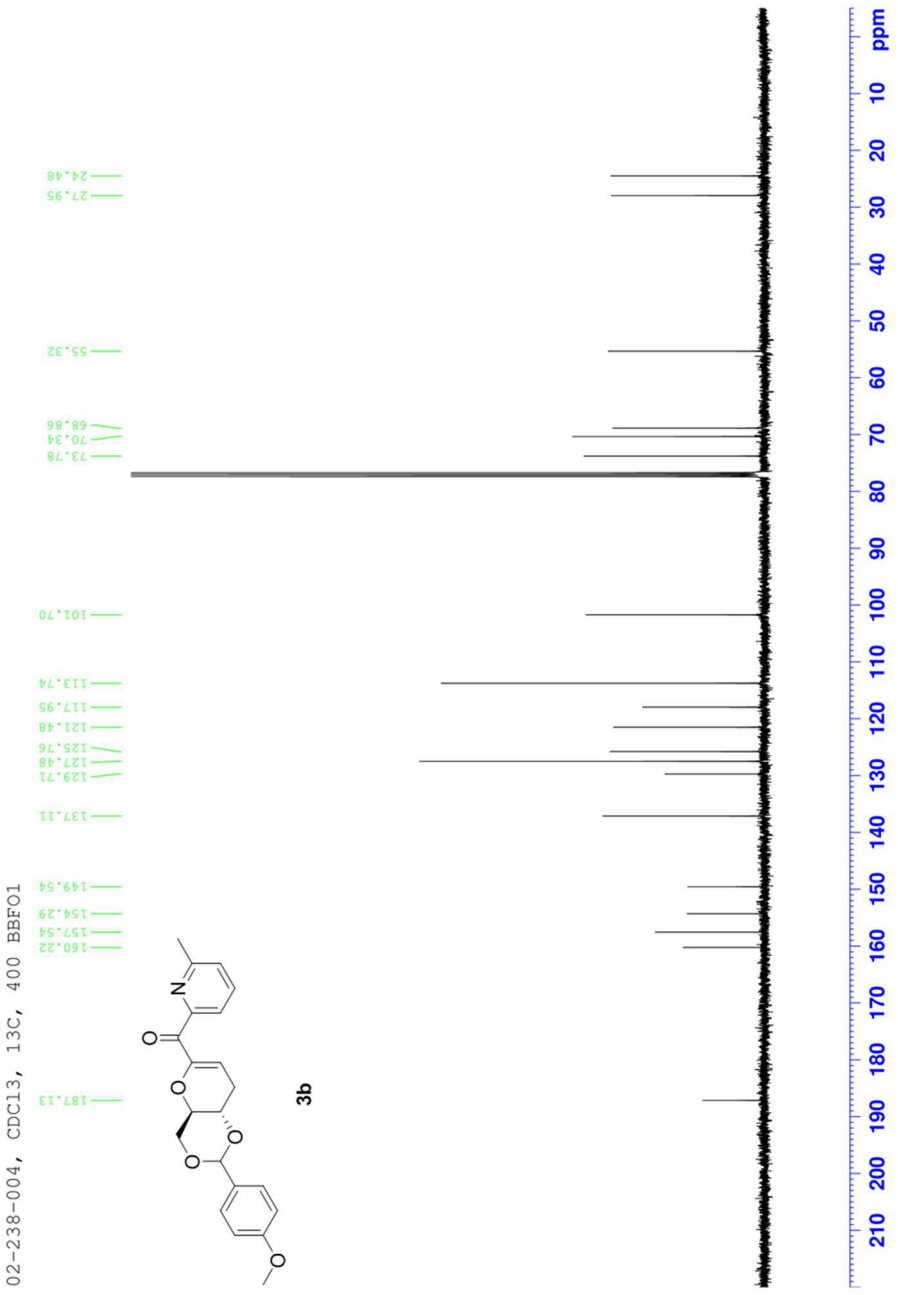
1.07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157.54
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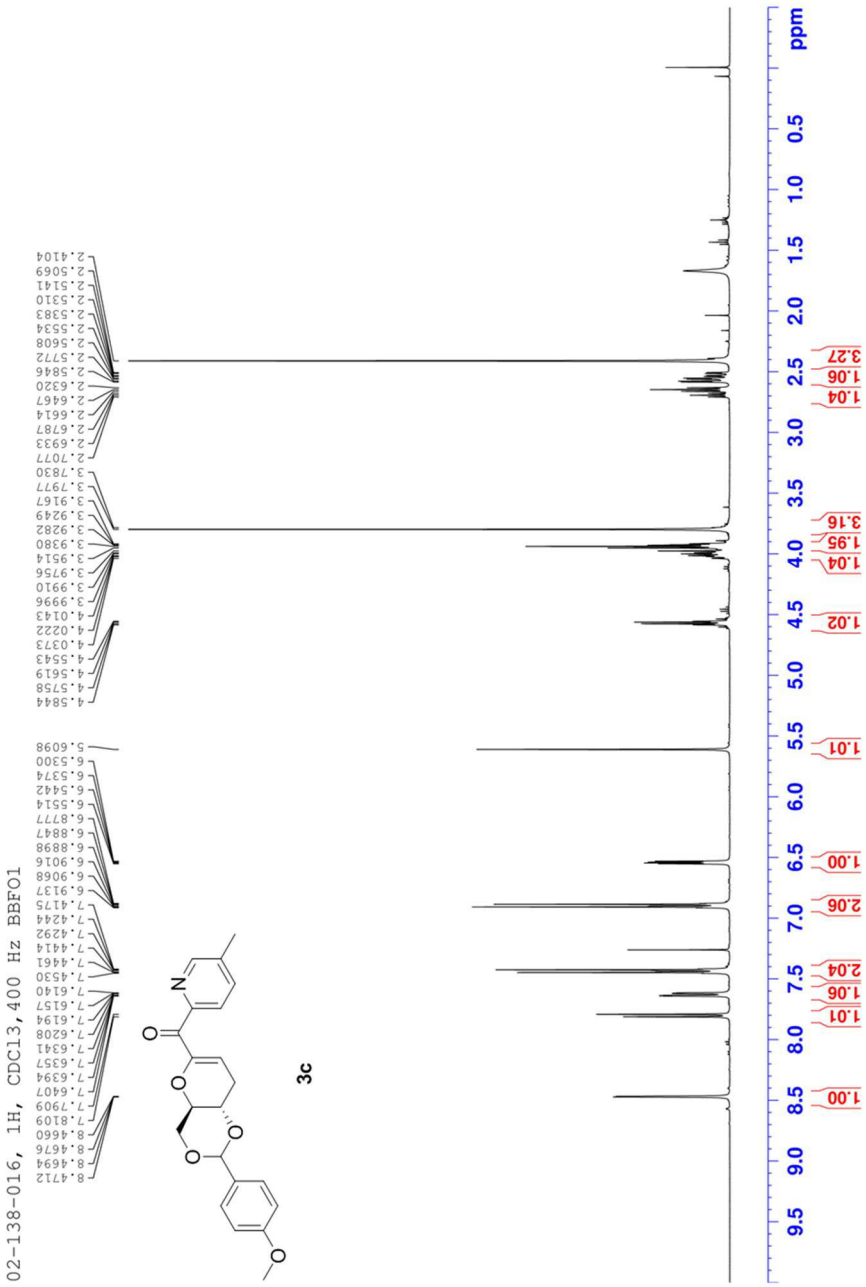
187.13
3b
ppm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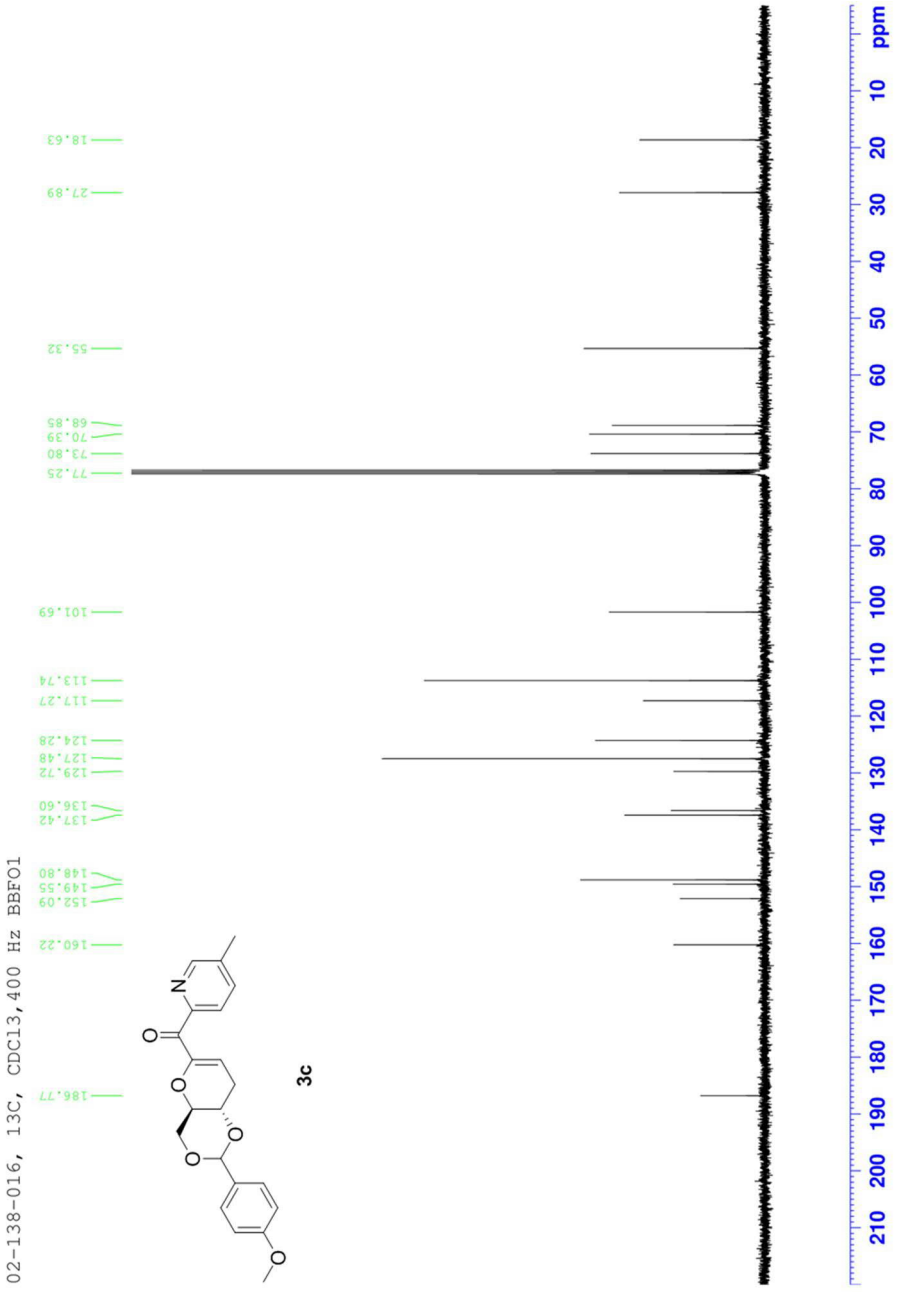
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55.32
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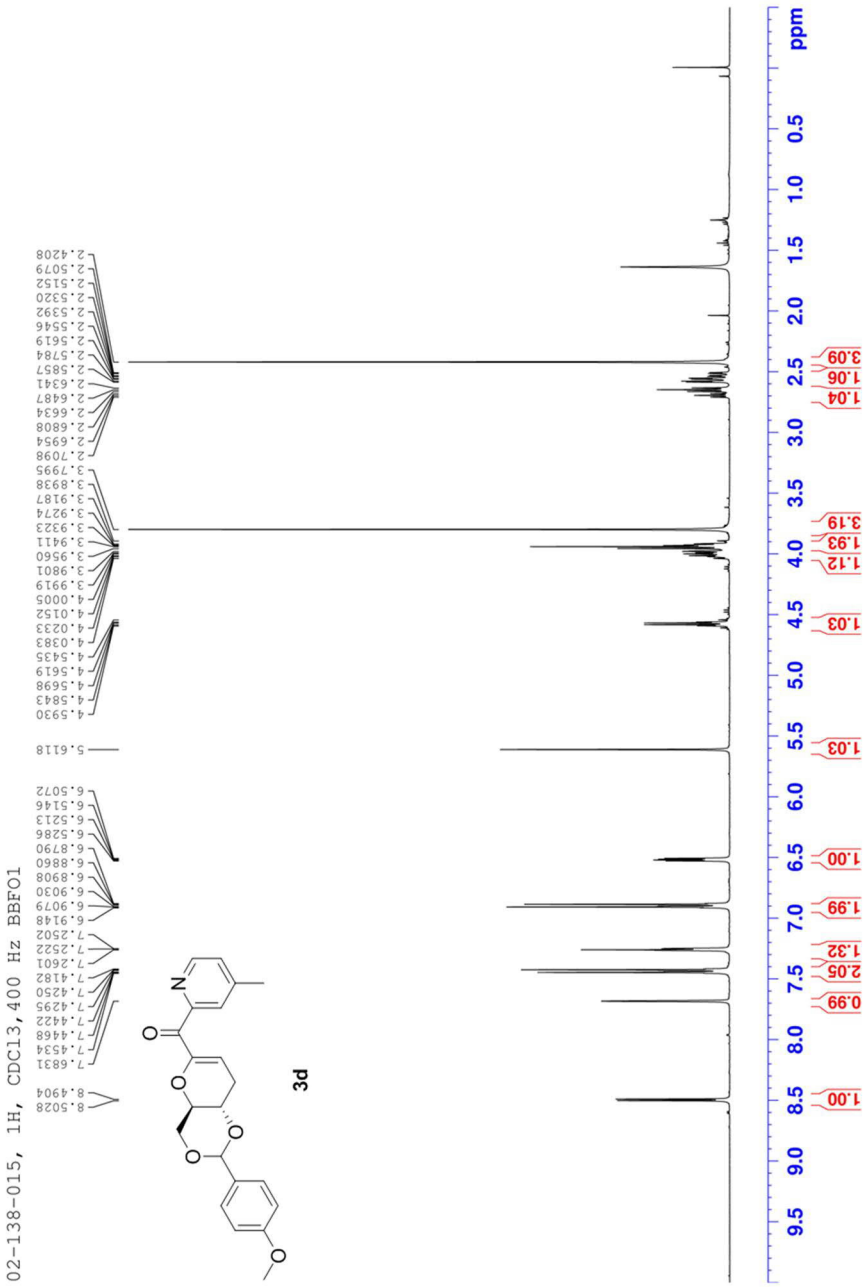
18.63
3c
ppm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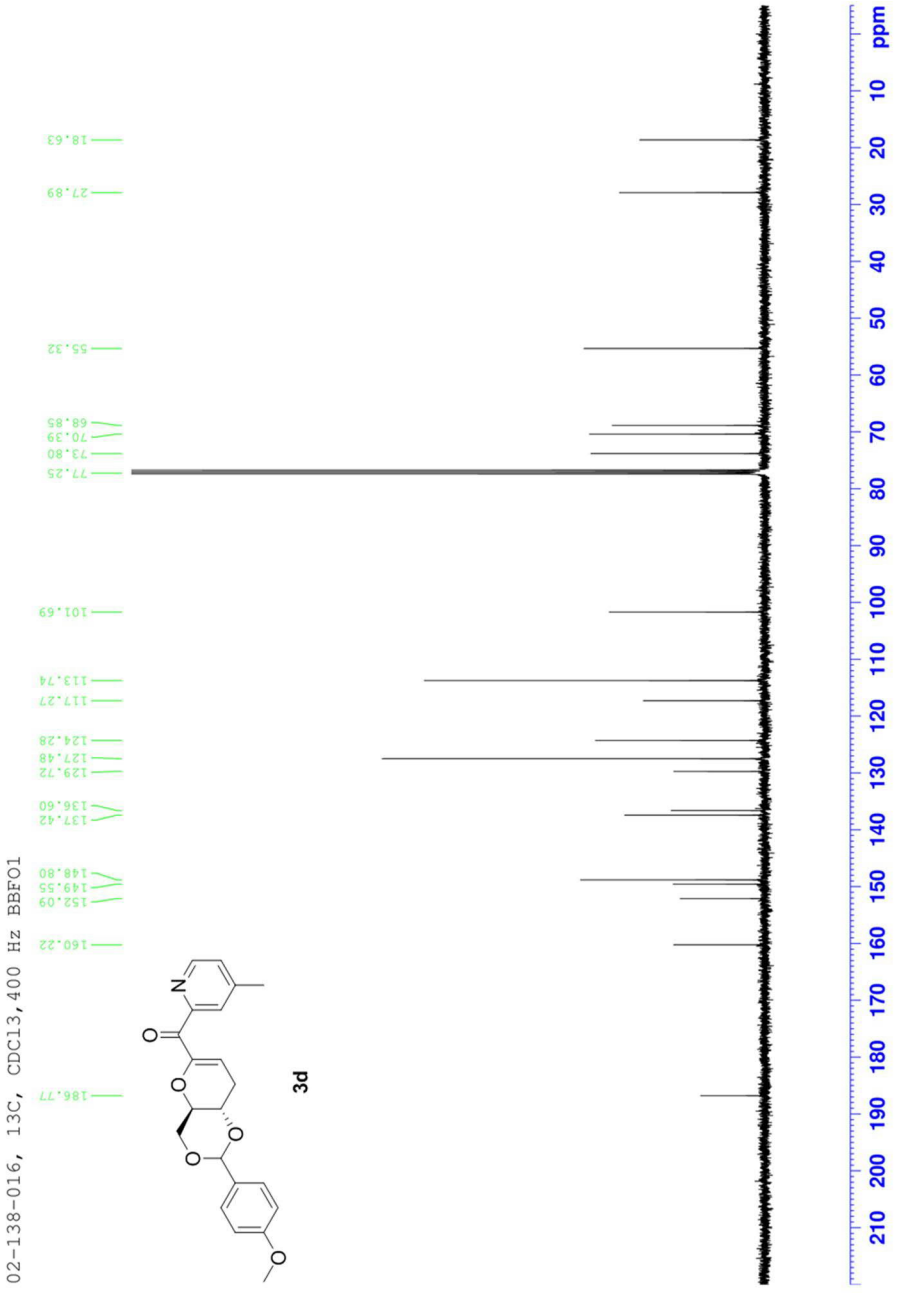
ppm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148.80
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136.60
129.72
127.48
124.28
117.27
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101.69
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73.80
70.39
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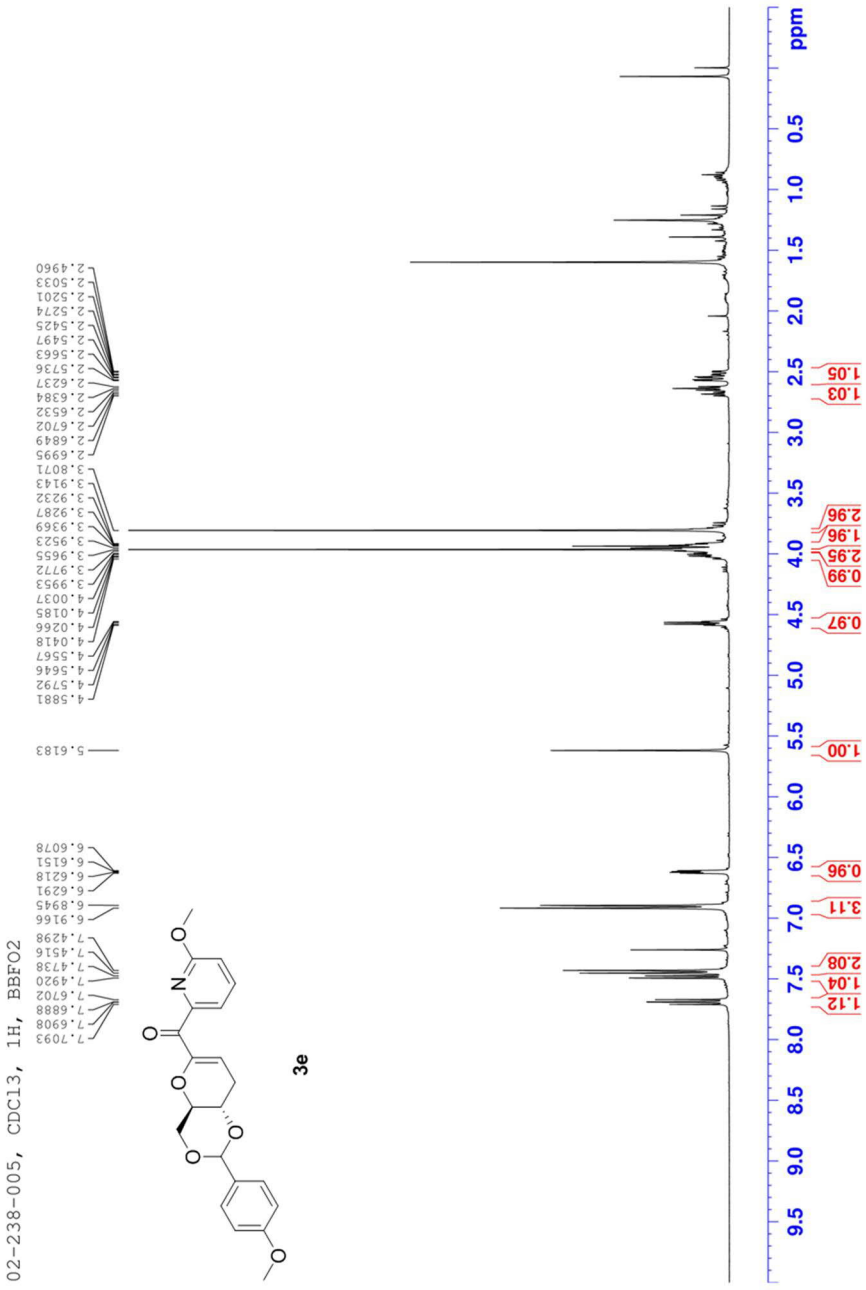
55.32
27.89
18.63
3d
ppm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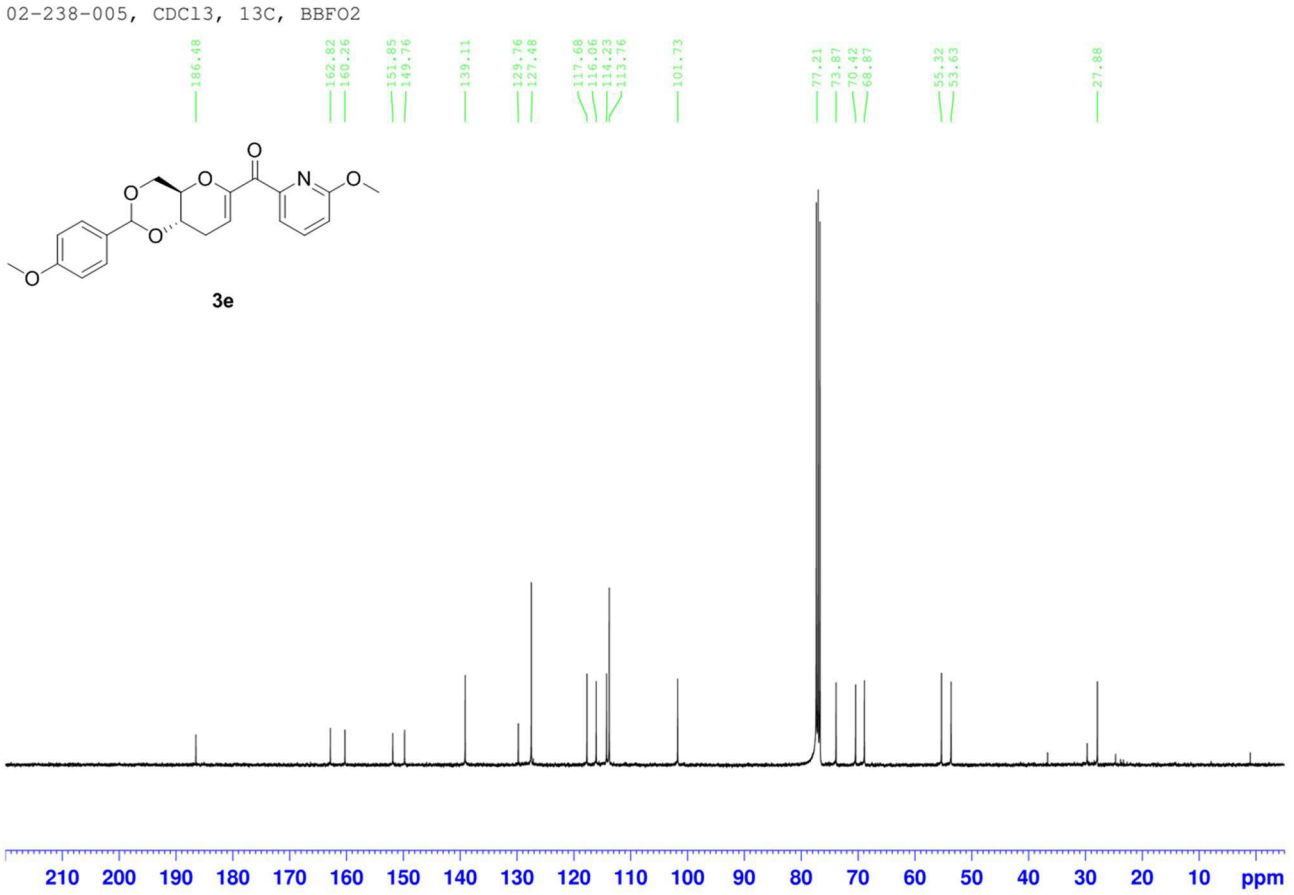
ppm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117.68
116.06
114.23
113.76
101.73
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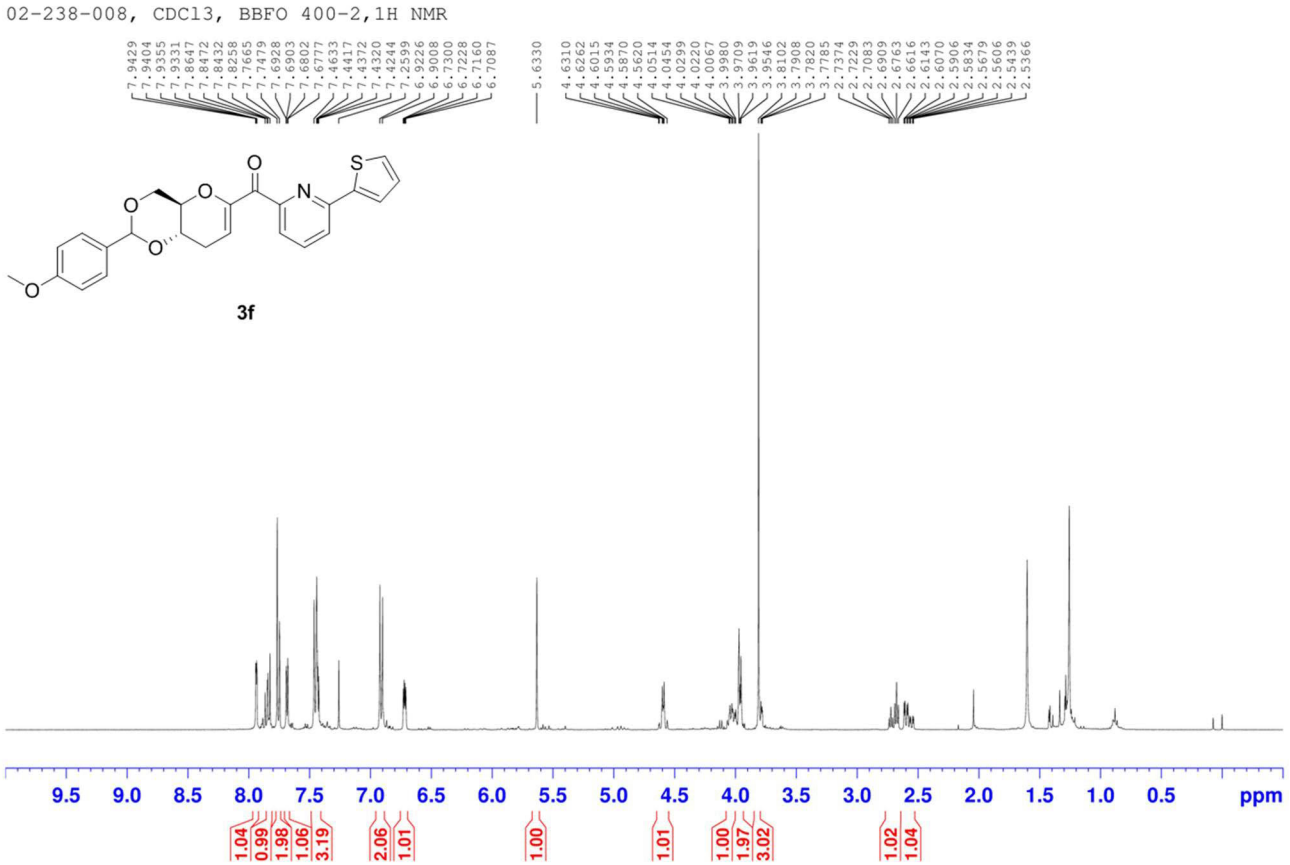
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7.6903
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O
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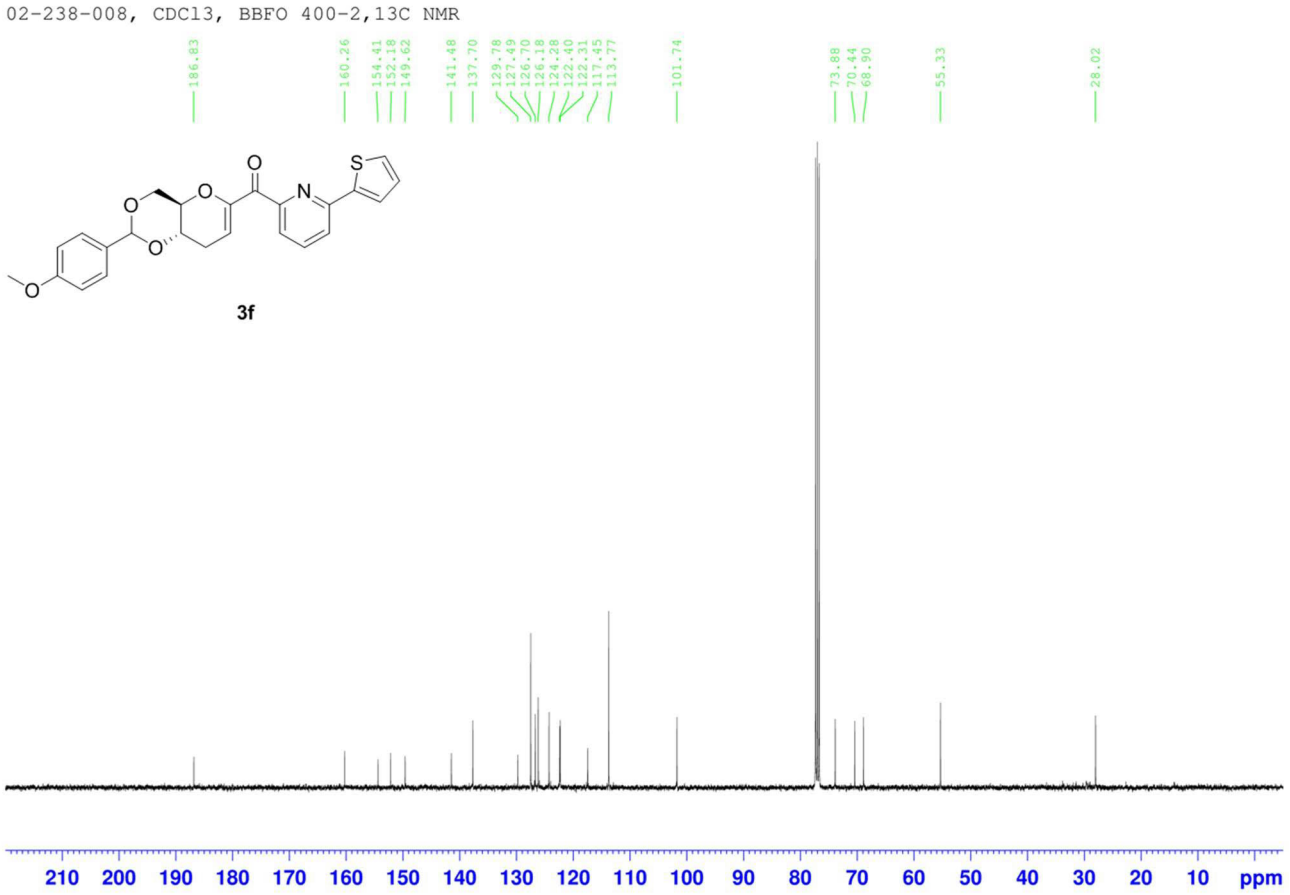
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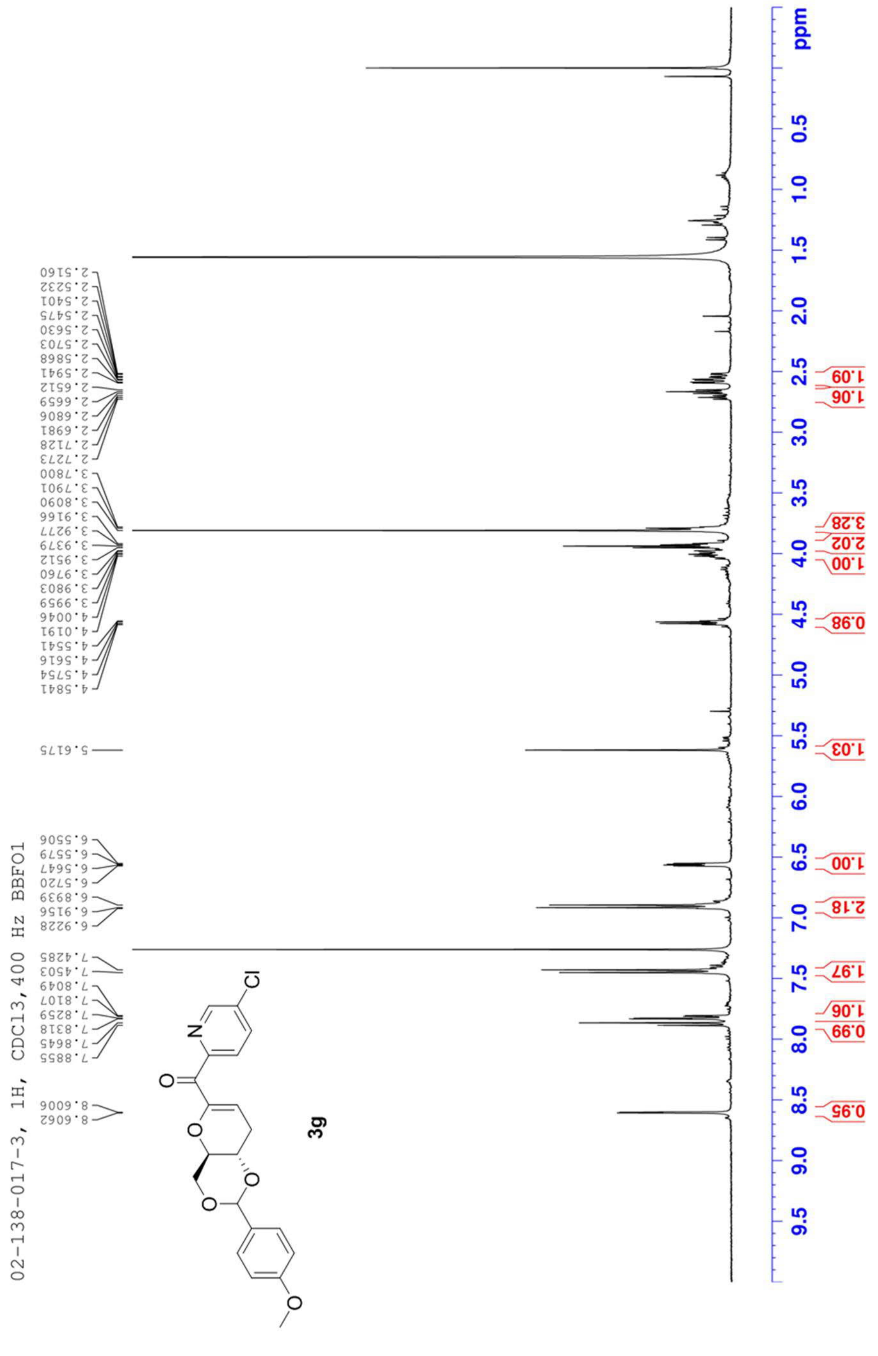
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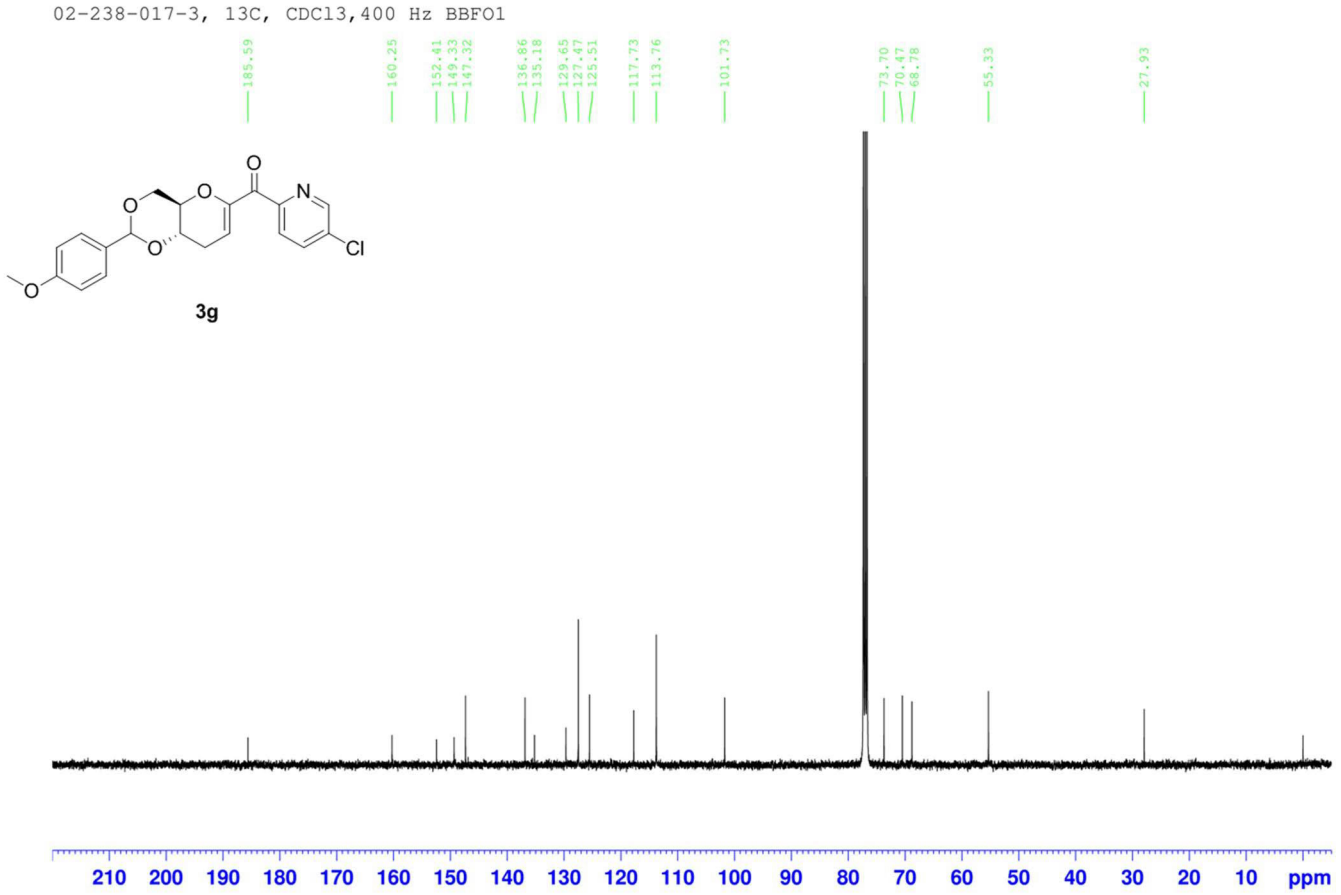
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68.78
55.33
27.93
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O
O
O
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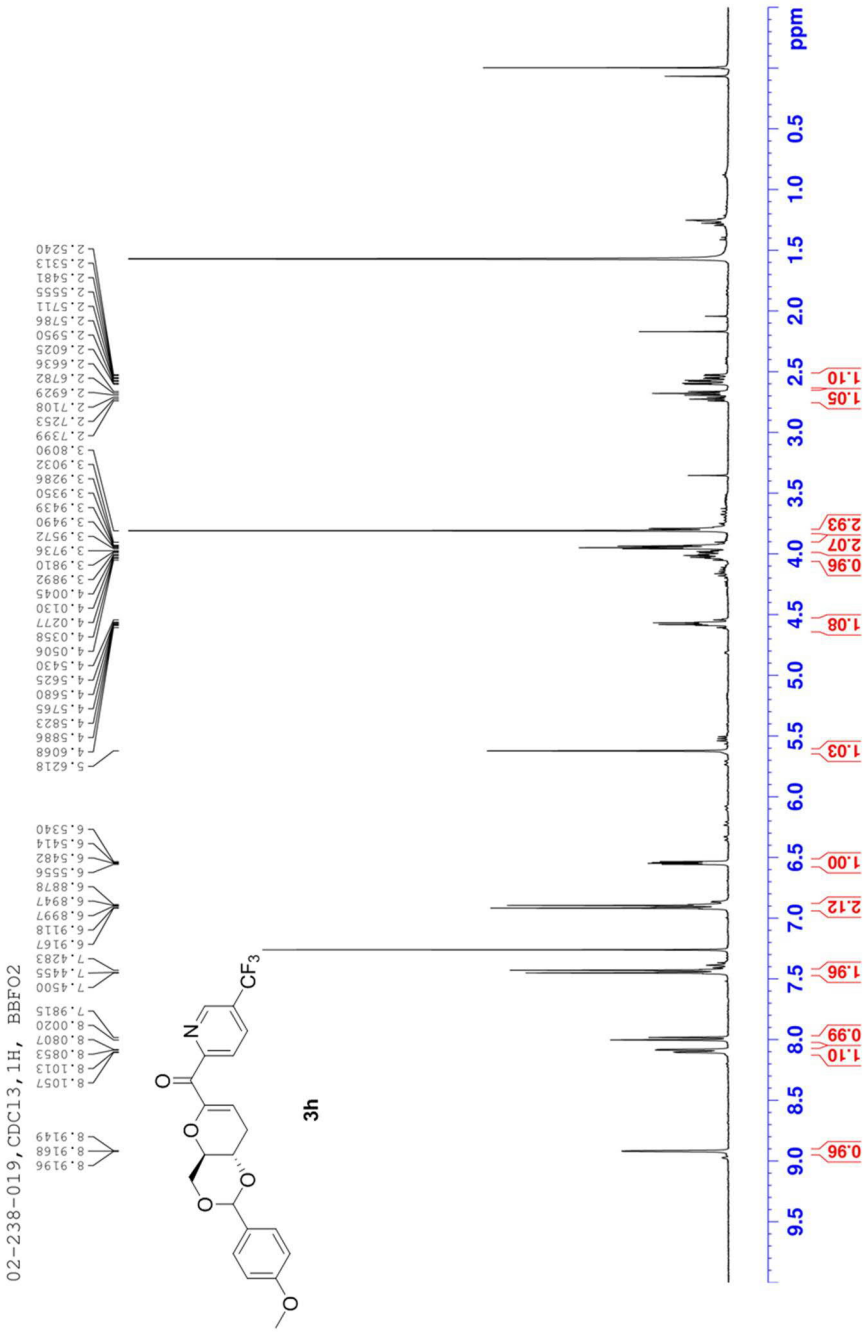
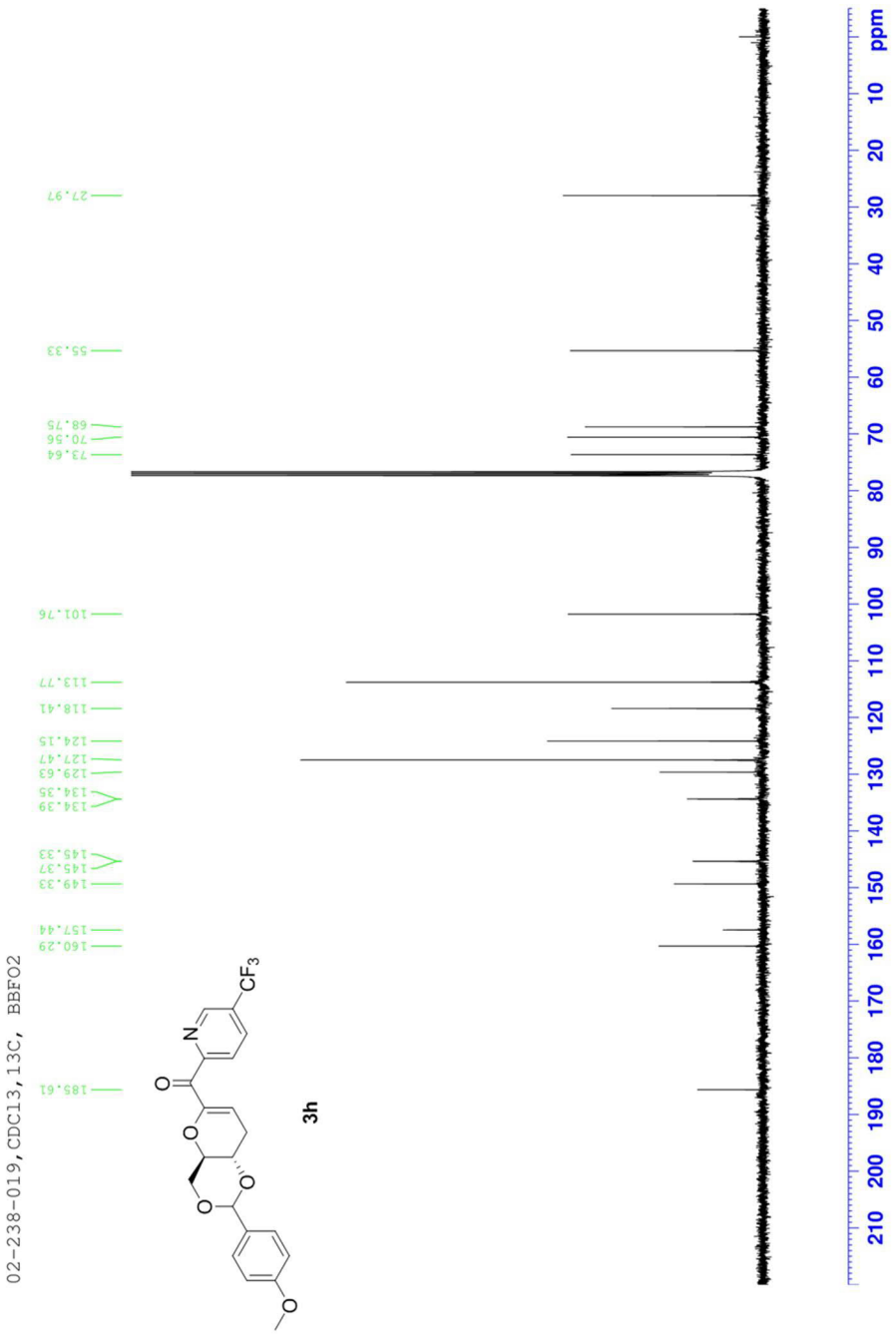
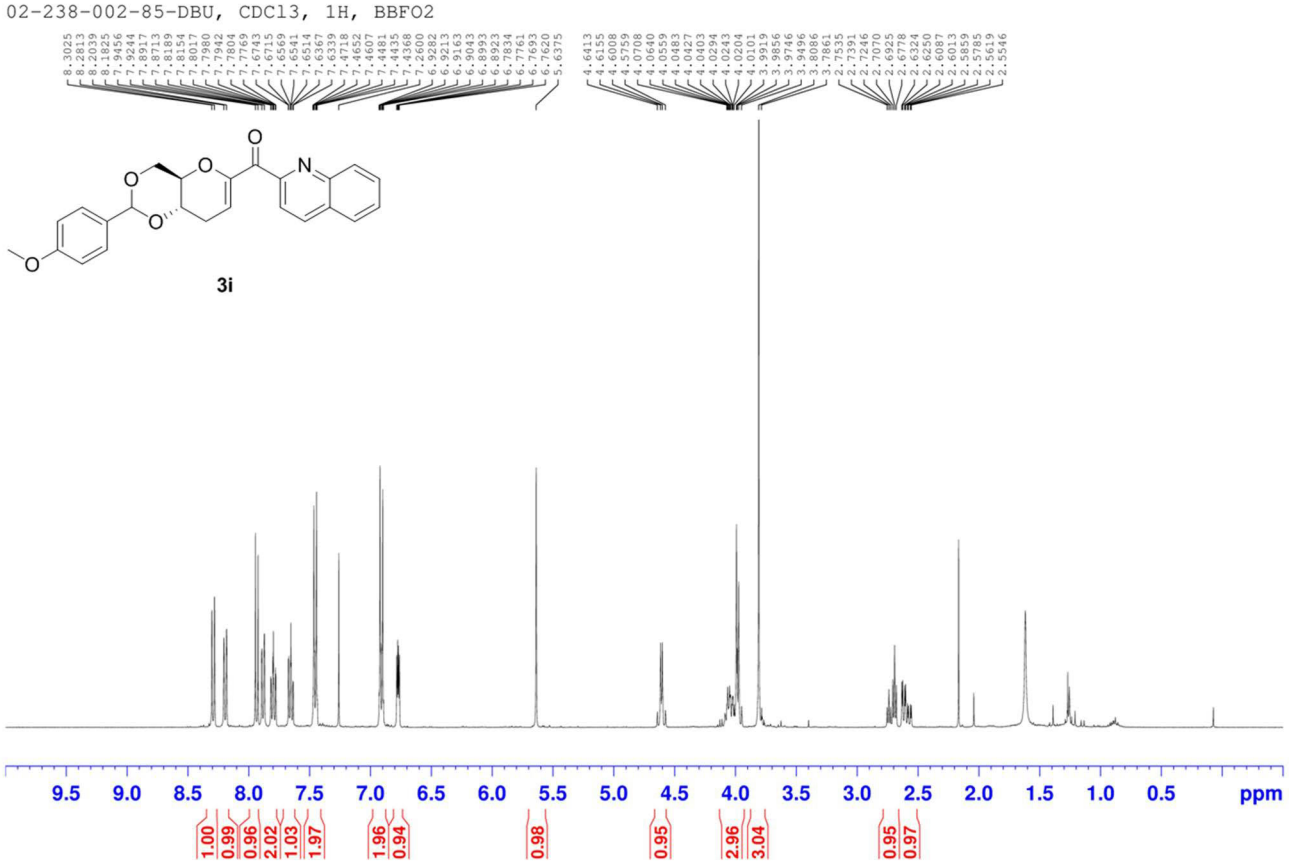
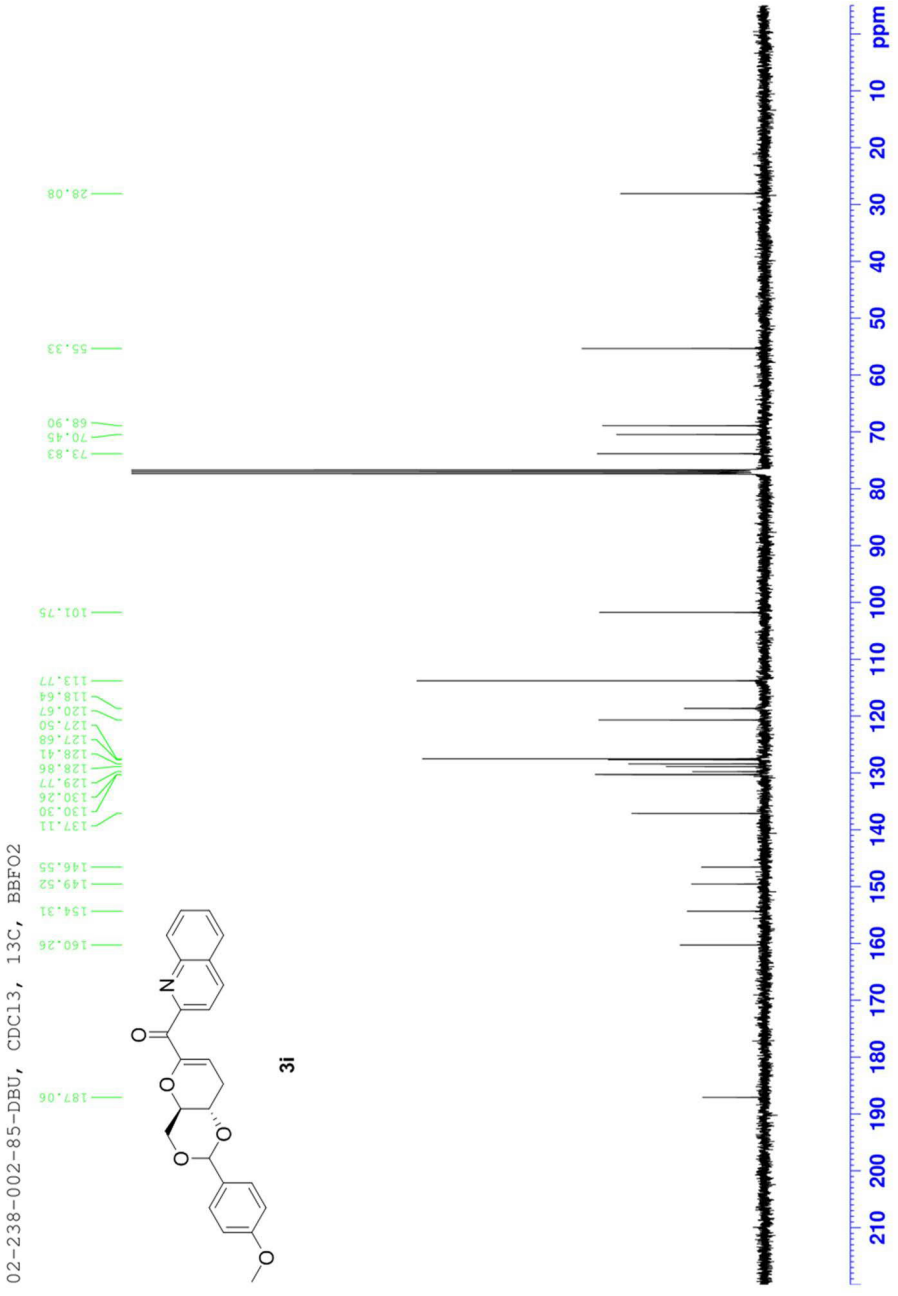
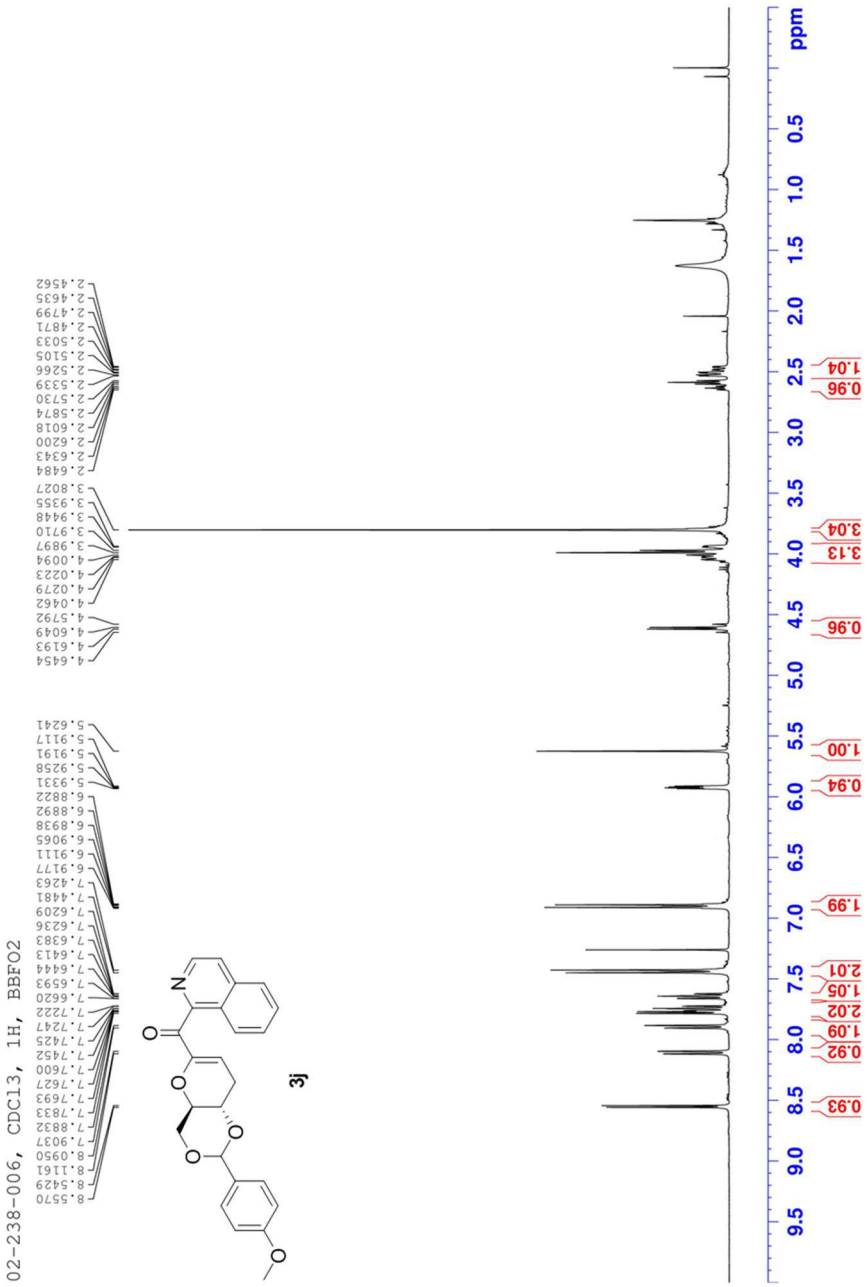
O
3g
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

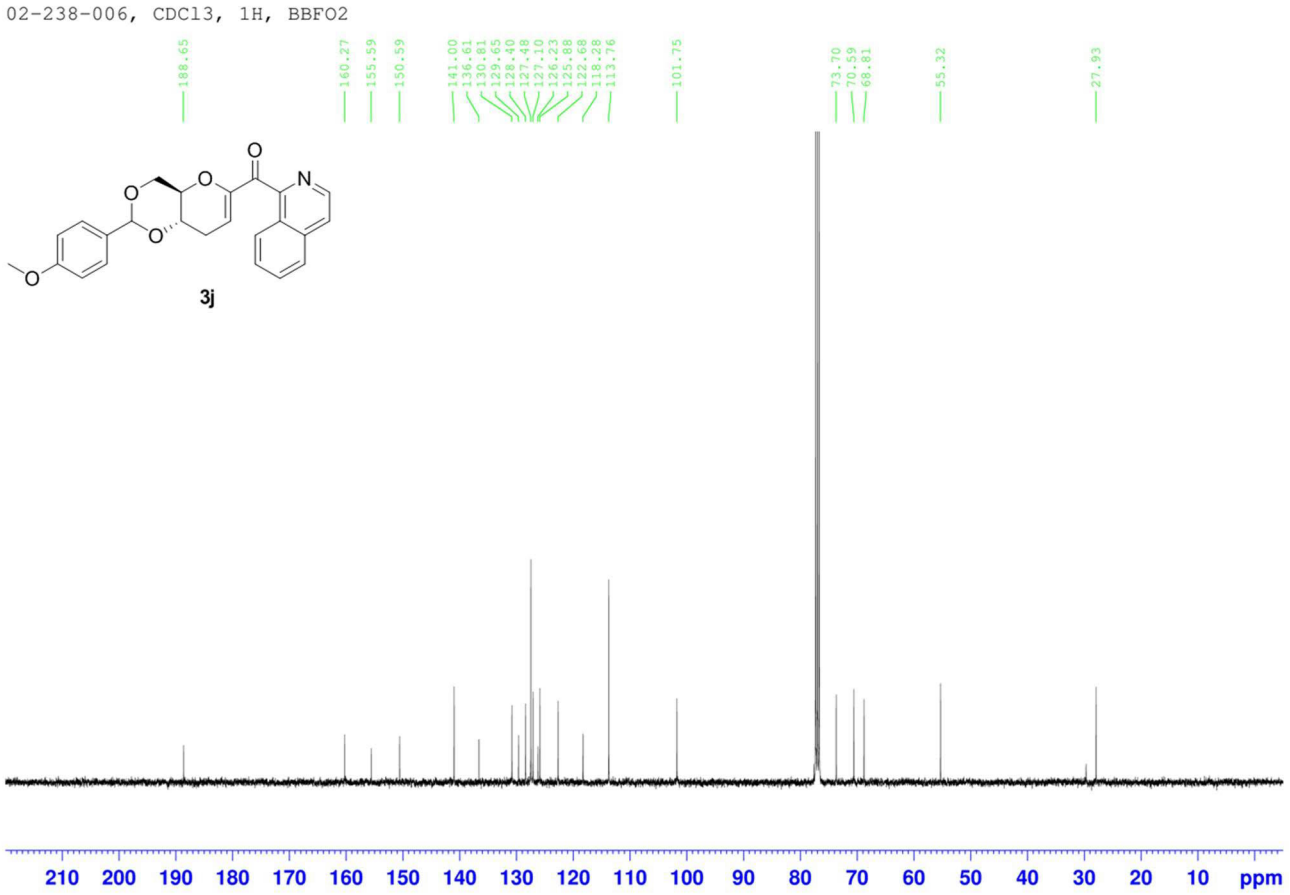

02-238-019,CDCl3,1H, BBFO2
8.9196
8.9168
8.9149
8.1057
8.1013
8.0853
8.0807
8.0020
7.9815
7.4500
7.4455
7.4283
6.9167
6.9118
6.8997
6.8947
6.8878
6.5556
6.5482
6.5414
6.5340
5.6218
4.6068
4.5886
4.5823
4.5765
4.5680
4.5625
4.5430
4.0506
4.0358
4.0277
4.0130
4.0045
3.9892
3.9810
3.9736
3.9572
3.9490
3.9439
3.9350
3.9286
3.9032
3.8090
2.7399
2.7253
2.7108
2.6929
2.6782
2.6636
2.6025
2.5950
2.5786
2.5711
2.5555
2.5481
2.5313
2.5240
3h
ppm
1.10
1.05
2.93
2.07
0.96
1.08
1.03
1.00
2.12
1.96
0.99
1.10
0.96

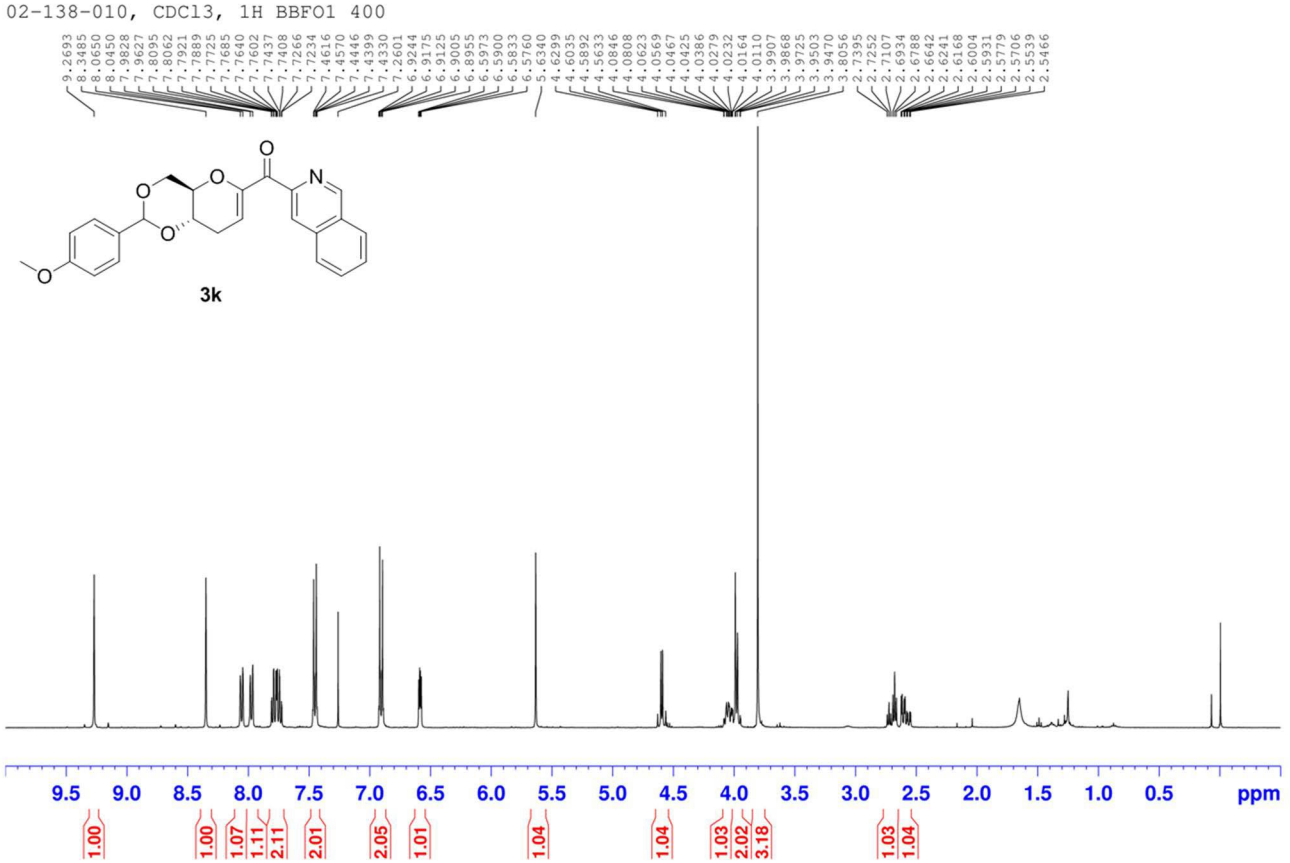

02-238-019,CDCl3,13C, BBFO2
185.61
160.29
157.44
149.33
145.37
145.33
134.39
134.35
129.63
127.47
124.15
118.41
113.77
101.76
73.64
70.56
68.75
55.33
27.97
3h
ppm

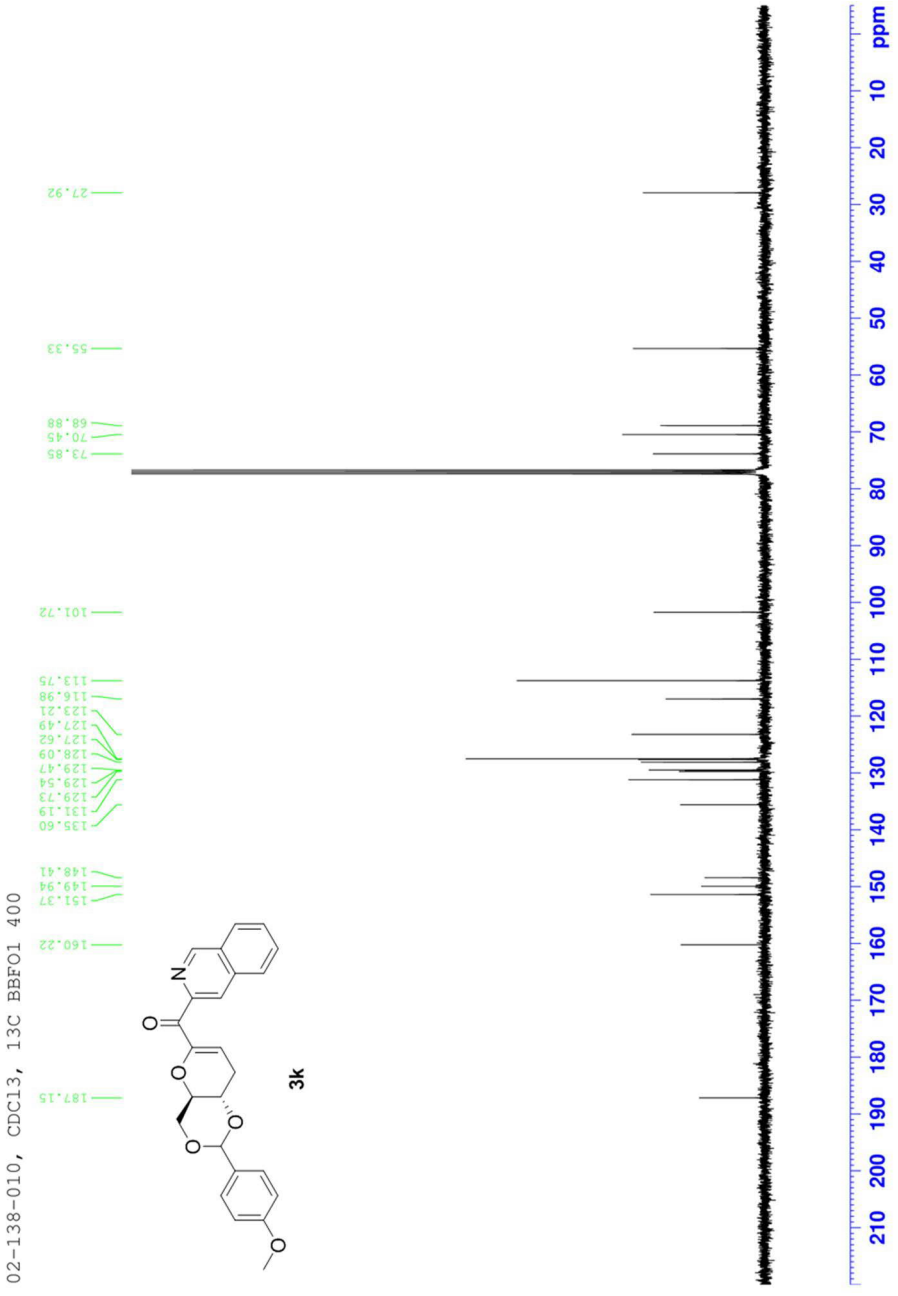

02-238-002-85-DBU, CDCl3, 1H, BBFO2
3i
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00 0.99 0.96 2.02 1.03 1.97 1.96 0.94 0.98 0.95 2.96 3.04 0.95 0.97

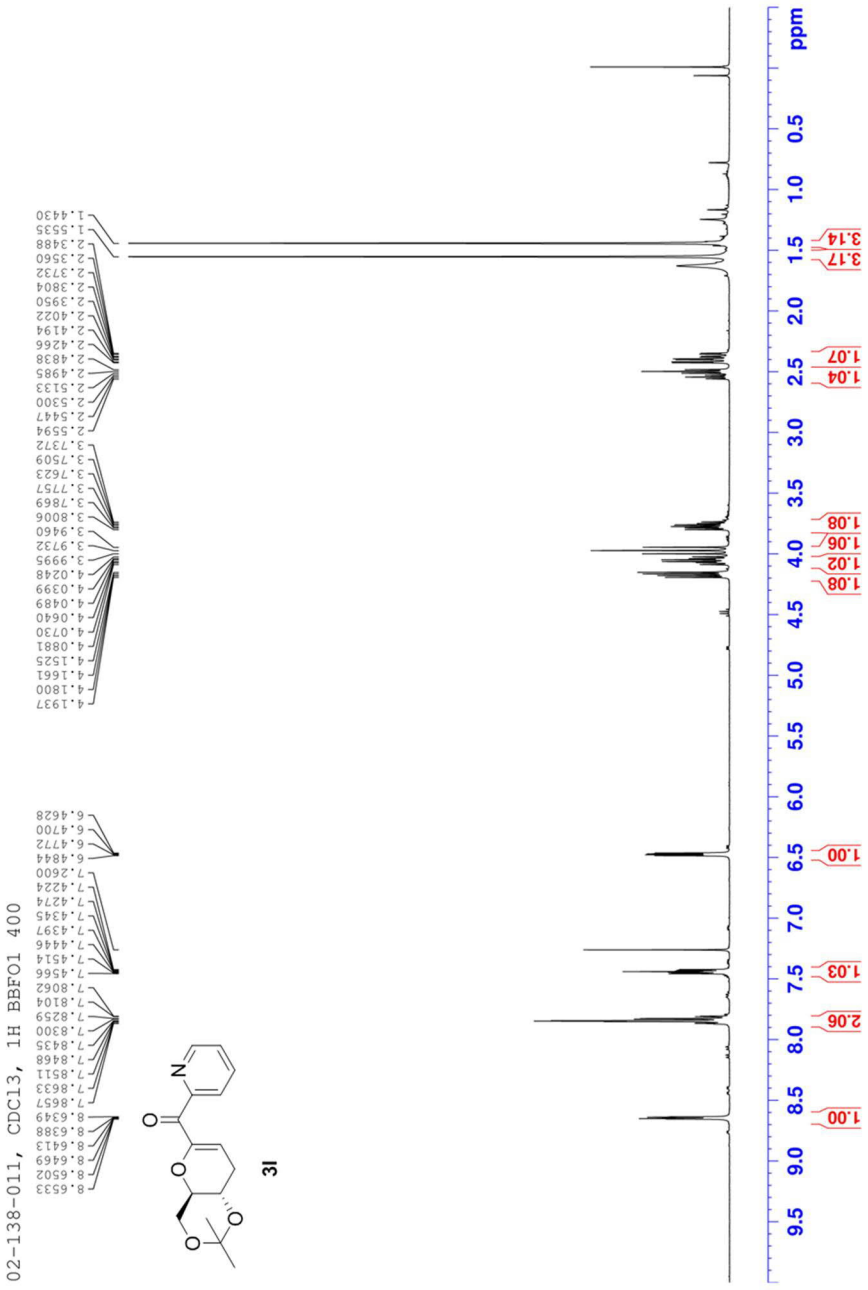

02-238-002-85-DBU, CDCl3, 13C, BBFO2
187.06
160.26
154.31
149.52
146.55
137.11
130.30
130.26
129.77
128.86
128.41
127.68
127.50
120.67
118.64
113.77
101.75
73.83
70.45
68.90
55.33
28.08
3i
O
N
O
O
O
O
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

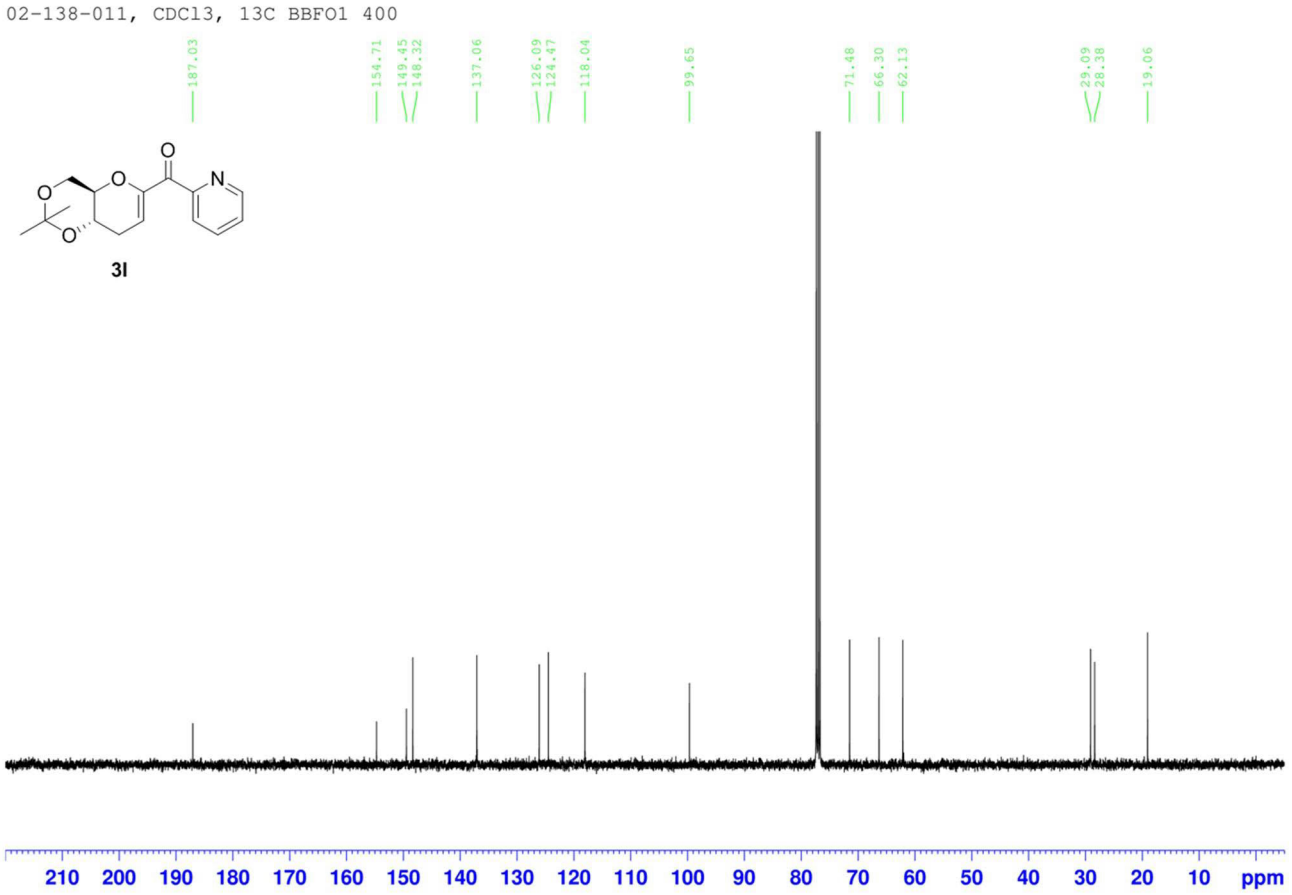

02-238-006, CDC13, 1H, BBFO2
8.5570
8.5429
8.1161
8.0950
7.9037
7.8832
7.7833
7.7693
7.7627
7.7600
7.7452
7.7425
7.7247
7.7222
7.6620
7.6593
7.6444
7.6413
7.6383
7.6236
7.6209
7.4481
7.4263
6.9177
6.9111
6.9065
6.8938
6.8892
6.8822
5.9331
5.9258
5.9191
5.9117
5.6241
4.6554
4.6193
4.6049
4.5792
4.0462
4.0279
4.0223
4.0094
3.9897
3.9710
3.9448
3.9355
3.8027
2.6484
2.6343
2.6200
2.6018
2.5874
2.5730
2.5339
2.5266
2.5105
2.5033
2.4871
2.4799
2.4635
2.4562
3j
0.93
0.92
1.09
2.02
1.05
2.01
1.99
0.94
1.00
0.96
3.04
3.13
0.96
1.04
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


02-238-006, CDCl3, 1H, BBFO2
188.65
160.27
155.59
150.59
141.00
136.61
130.81
129.65
128.40
127.48
127.10
126.23
125.88
122.68
118.28
113.76
101.75
73.70
70.59
68.81
55.32
27.93
O
O
O
O
N
O
3j
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

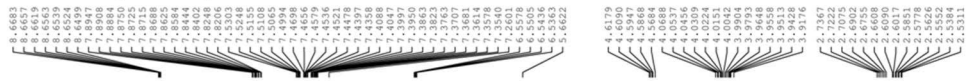

02-138-010, CDCl3, 1H BBFO1 400
9.2693
8.3485
8.0650
8.0450
7.9828
7.9627
7.8095
7.8062
7.7921
7.7889
7.7725
7.7685
7.7640
7.7602
7.7437
7.7408
7.7266
7.7234
7.4616
7.4570
7.4446
7.4399
7.4330
7.2601
6.9244
6.9175
6.9125
6.9005
6.8955
6.5973
6.5900
6.5833
6.5760
5.6340
4.6299
4.6035
4.5892
4.5633
4.0846
4.0808
4.0623
4.0569
4.0467
4.0425
4.0386
4.0279
4.0232
4.0164
4.0110
3.9907
3.9868
3.9725
3.9503
3.9470
3.8056
2.7395
2.7252
2.7107
2.6934
2.6788
2.6642
2.6241
2.6168
2.6004
2.5931
2.5779
2.5706
2.5539
2.5466
O
O
O
O
N
O
3k
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.00
1.07
1.11
2.11
2.01
2.05
1.01
1.04
1.04
1.03
2.02
3.18
1.03
1.04

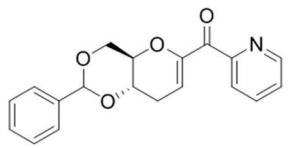

02-138-010, CDC13, 13C BBFO1 400
187.15
160.22
151.37
149.94
148.41
135.60
131.19
129.73
129.54
129.47
128.09
127.62
127.49
123.21
116.98
113.75
101.72
73.85
70.45
68.88
55.33
27.92
3k
O
N
O
O
O
O
O
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210


02-138-011, CDC13, 1H BBFO1 400
8.6533
8.6502
8.6469
8.6413
8.6388
8.6349
7.8657
7.8633
7.8511
7.8468
7.8435
7.8300
7.8259
7.8104
7.8062
7.4566
7.4514
7.4446
7.4397
7.4345
7.4274
7.4224
7.2600
6.4844
6.4772
6.4700
6.4628
4.1937
4.1800
4.1661
4.1525
4.0881
4.0730
4.0640
4.0489
4.0399
4.0248
3.9995
3.9732
3.9460
3.8006
3.7869
3.7757
3.7623
3.7509
3.7372
2.5594
2.5447
2.5300
2.5133
2.4985
2.4838
2.4266
2.4194
2.4022
2.3950
2.3804
2.3732
2.3560
2.3488
1.5535
1.4430
3.14
3.17
1.07
1.04
1.08
1.06
1.02
1.08
1.00
1.03
2.06
1.00
ppm
3l

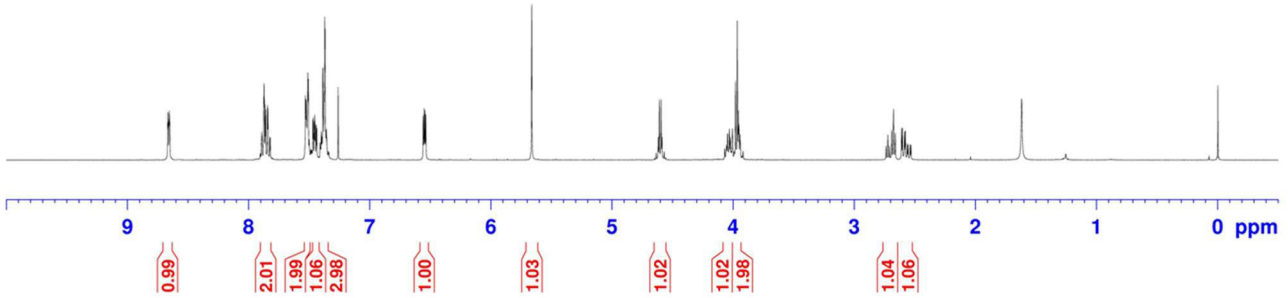

02-138-011, CDCl3, 13C BBFO1 400
187.03
154.71
149.45
148.32
137.06
126.09
124.47
118.04
99.65
71.48
66.30
62.13
29.09
28.38
19.06
3l
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

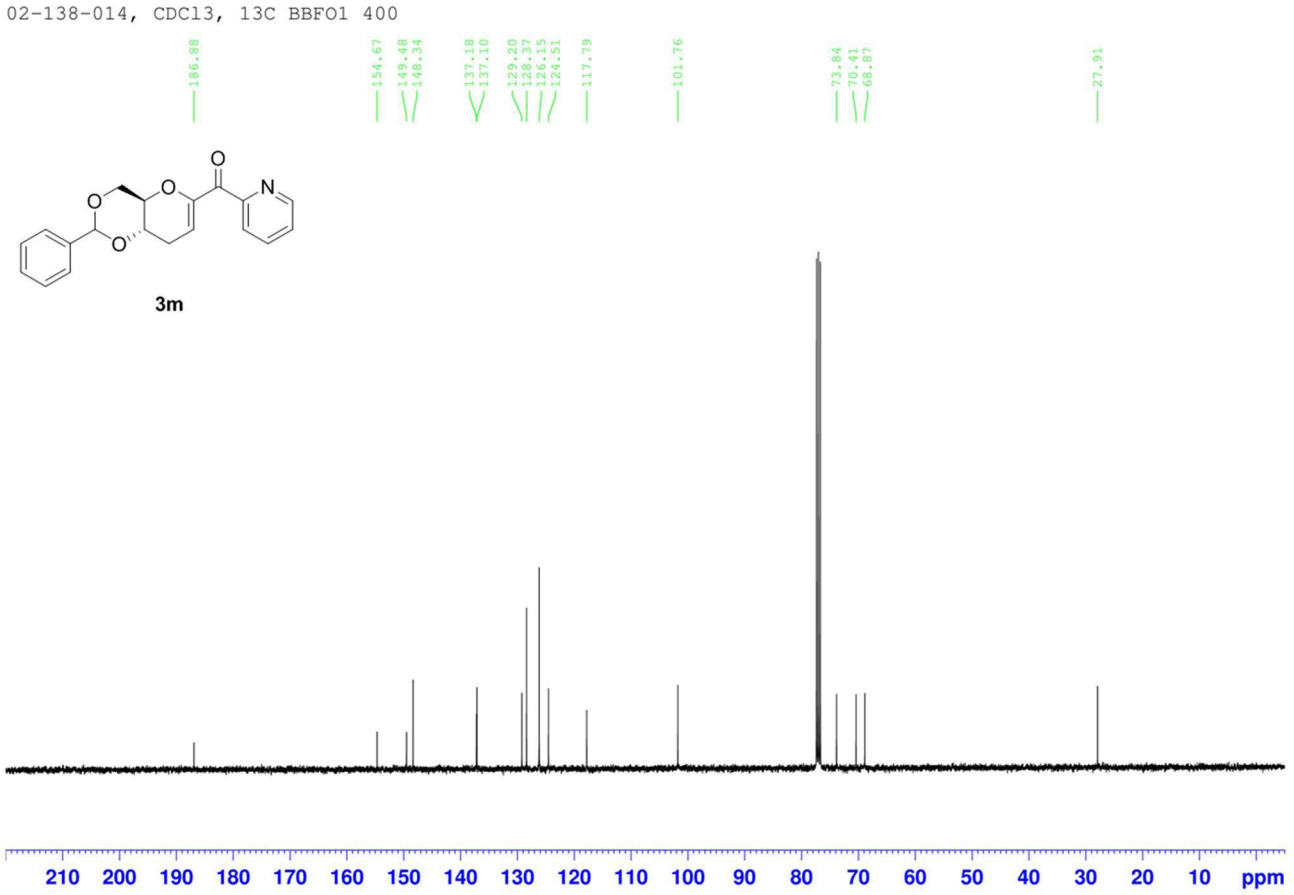
02-138-014, CDCl3, 1H BBFO1 400

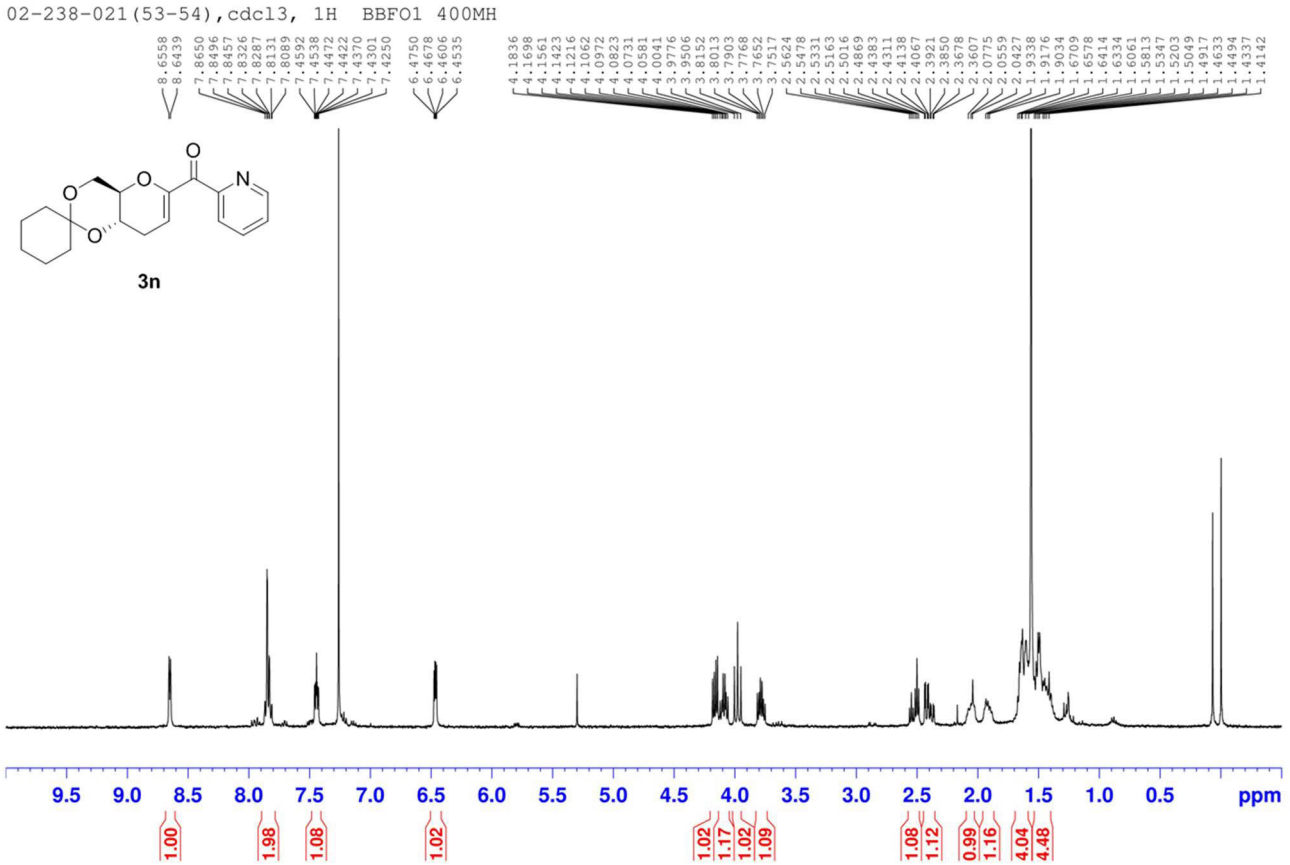


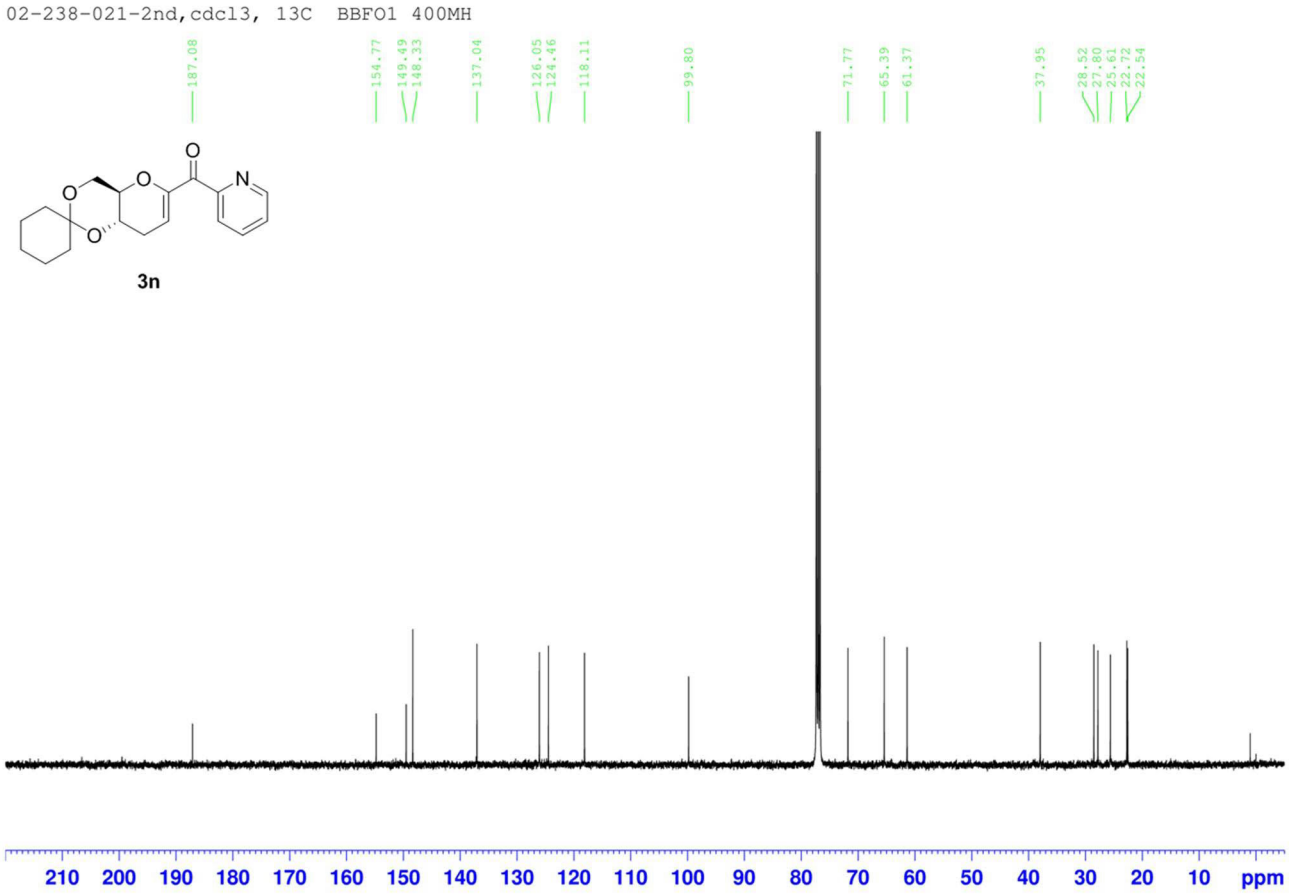


3m




02-138-014, CDCl3, 13C BBFO1 400
186.88
154.67
149.48
148.34
137.18
137.10
129.20
128.37
126.15
124.51
117.79
101.76
73.84
70.41
68.87
27.91
O
O
O
O
N
3m
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


02-238-021(53-54),cdcl3, 1H BBFO1 400MH
3n
ppm


02-238-021-2nd,cdcl3, 13C BBFO1 400MH
187.08
154.77
149.49
148.33
137.04
126.05
124.46
118.11
99.80
71.77
65.39
61.37
37.95
28.52
27.80
25.61
22.72
22.54
O
O
O
O
N
3n
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm