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# SUPPORTING INFORMATION – PART I EXPERIMENTAL DETAILS

**Palladium-Catalyzed Stereoselective Domino Arylation-Acylation: An Entry to Chiral Tetrahydrofluorenone Scaffolds**

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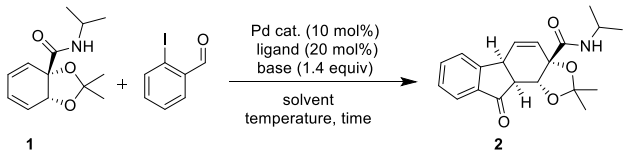
# REACTION OPTIMIZATION

**Table S1. Optimization of Reaction Conditions.**



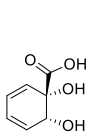

1 2

| Entry | ArI | Solvent | Catalyst | Ligand | Base | T | time | **2** | Conversion |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 eq | DMF | $Pd(OAc)_2$ | $P((4\text{-}CF_3)C_6H_4)_3$ | AgOAc | 70 | 24 | 55% | 94% |
| 2 | 2 eq | Dioxane | $Pd(OAc)_2$ | $P((4\text{-}CF_3)C_6H_4)_3$ | AgOAc | 70 | 24 | 61% | 100% |
| 3 | 2 eq | DCE | $Pd(OAc)_2$ | $P((4\text{-}CF_3)C_6H_4)_3$ | AgOAc | 70 | 24 | 62% | 100% |
| **4** | **2 eq** | **MeCN** | **$Pd(OAc)_2$** | **$P((4\text{-}CF_3)C_6H_4)_3$** | **AgOAc** | **70** | **24** | **66%** | **100%** |
| 5 | 2 eq | EtOH | $Pd(OAc)_2$ | $P((4\text{-}CF_3)C_6H_4)_3$ | AgOAc | 70 | 24 | 5% | 85% |
| 6 | 2 eq | THF | $Pd(OAc)_2$ | $P((4\text{-}CF_3)C_6H_4)_3$ | AgOAc | 70 | 24 | 11% | 96% |
| 7 | 2 eq | MeCN | $Pd(OAc)_2$ | $PPh_3$ | AgOAc | 70 | 16 | 6% | 9% |
| 8 | 2 eq | MeCN | $Pd(OAc)_2$ | $P(4\text{-}F\text{-}C_6H_4)_3$ | AgOAc | 70 | 16 | 5% | 10% |
| 9 | 2 eq | MeCN | $Pd(OAc)_2$ | Tri(2-furyl)phosphine | AgOAc | 70 | 16 | 41% | 92% |
| 10 | 2 eq | MeCN | $Pd(OAc)_2$ | Tri-o-tolylphosphine | AgOAc | 70 | 16 | 2% | 4% |
| 11 | 2 eq | MeCN | $Pd(OAc)_2$ | DPPF | AgOAc | 70 | 16 | 46% | 94% |
| 12 | 2 eq | MeCN | $Pd(OAc)_2$ | $P(OPh)_3$ | AgOAc | 70 | 16 | 32% | 54% |
| 13 | 2 eq | MeCN | $Pd(OAc)_2$ | - | AgOAc | 70 | 16 | 47% | 93% |
| 14 | 2 eq | MeCN | - | $P((4\text{-}CF_3)C_6H_4)_3$ | AgOAc | 70 | 16 | - | 0% |
| 15 | 2 eq | MeCN | $Pd(dba)_2$ | $P((4\text{-}CF_3)C_6H_4)_3$ | AgOAc | 70 | 16 | - | 0% |
| 16 | 2 eq | MeCN | $Pd(OAc)_2$ | $P((4\text{-}CF_3)C_6H_4)_3$ | NaOAc | 70 | 16 | - | 0% |
| 17 | 2 eq | MeCN | $Pd(TFA)_2$ | $P((4\text{-}CF_3)C_6H_4)_3$ | AgTFA | 70 | 16 | 17% | 81% |
| 18 | 2 eq | MeCN | $Pd(OAc)_2$ | $P((4\text{-}CF_3)C_6H_4)_3$ | $Ag_2CO_3$ | 70 | 16 | 2% | 12% |
| 19 | 2 eq | MeCN | $Pd(OAc)_2$ | $P((4\text{-}CF_3)C_6H_4)_3$ | $Ag_2O$ | 70 | 16 | 1% | 16% |
| 20 | 2 eq | MeCN | $Pd(OAc)_2$ | $P((4\text{-}CF_3)C_6H_4)_3$ | AgOAc (1.2 equiv) | 70 | 16 | 53% | 79% |
| 21 | 2 eq | MeCN | $Pd(OAc)_2$ (20%) | $P((4\text{-}CF_3)C_6H_4)_3$ (40%) | AgOAc | 70 | 16 | 58% | 100% |
| 22 | 2 eq | MeCN | $Pd(OAc)_2$ (5%) | $P((4\text{-}CF_3)C_6H_4)_3$ (10%) | AgOAc | 70 | 16 | 10% | 13% |
| 23 | 1.5 eq | MeCN | $Pd(OAc)_2$ | $P((4\text{-}CF_3)C_6H_4)_3$ | AgOAc | 70 | 16 | 64% | 97% |
| 24 | 1.2 eq | MeCN | $Pd(OAc)_2$ | $P((4\text{-}CF_3)C_6H_4)_3$ | AgOAc | 70 | 16 | 24% | 48% |
| 25 | 3 eq | MeCN | $Pd(OAc)_2$ | $P((4\text{-}CF_3)C_6H_4)_3$ | AgOAc | 70 | 16 | 63% | 99% |
| 26 | 2 eq | MeCN | $Pd(OAc)_2$ | $P((4\text{-}CF_3)C_6H_4)_3$ | AgOAc | 70 | 12 | 49% | 73% |
| 27 | 2 eq | MeCN | $Pd(OAc)_2$ | $P((4\text{-}CF_3)C_6H_4)_3$ | AgOAc | 80 | 16 | 62% | 100% |
| 28 | 2 eq | MeCN | $Pd(OAc)_2$ | $P((4\text{-}CF_3)C_6H_4)_3$ | AgOAc | 60 | 16 | 43% | 58% |

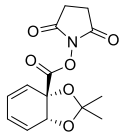
[a] NMR yield using p-xylene as internal standard.

# EXPERIMENTAL PROCEDURES

**General Considerations.** Diene **1**,[1] Weinreb amide **6**,[1] alcohol **7**,[2] carboxylic acid **8**,[1] methyl ester **9**,[1] carboxylic acid **23**,[1] activated ester **24**,[1] 2-iodobenzaldehyde,[3] 3-iodo-1H-indole-2-carbaldehyde[4] and 3-iodothiophene-2-carbaldehyde[5] were synthesized according to literature procedures. All other solvents and reagents were purchased from commercial suppliers and used without purification or drying, unless otherwise stated. Structural assignments were made with additional information from gradient correlation spectroscopy(gCOSY), gradient heteronuclear single-quantum coherence(gHSQC), and gradient heteronuclear multiple-bond correlation(gHMBC) experiments.



**23**



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**Analytical Methods.** Column chromatography was performed on a Biotage Isolera Spektra One with Biotage SNAP KP-sil (silica gel) or KP-C18-HS (C18, reverse phase) columns. NMR spectra, $^{1}$H NMR and $^{13}$C NMR, were recorded on an Agilent 400 MHz (101 MHz for$^{13}$C NMR). The chemical shifts for $^{1}$H and $^{13}$C NMR spectra are reported in parts per million (ppm) using the residual solvent peak for reference. The following abbreviations are used for reporting NMR peaks: singlet (s), doublet (d), triplet (t), quartet (q), heptet (hept), multiplet (m), and apparent (app). All coupling constants (*J*) are reported in hertz (Hz). ATR-FTIR spectra were recorded on a PerkinElmer Spectrum Frontier infrared spectrometer with a pike-GladiATR module and reported in wavenumber ($cm^{-1}$). Melting points were recorded on a Büchi Melting Point B-545. High-resolution mass spectrometry (HRMS) was performed on an Agilent 1290 infinity LC system equipped with an autosampler tandem to an Agilent 6520 Accurate Mass Q-TOF LC/MS.

**General procedure for palladium-catalyzed tandem arylation-cyclization reactions.** To a Radleys Carousel reduced volume reaction tube equipped with stirrer bar was added the relevant diene starting material **1** or **3**-**9** (0.1 mmol), aryl iodide (0.2 mmol), AgOAc (23.4 mg, 0.14 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), tris(4-(trifluoromethyl)phenyl)phosphine (9.3 mg, 0.02 mmol) and solvent (0.5 mL). The vessel was then placed under an argon atmosphere, sealed and placed in a Radleys Carousel 12 Plus Reaction Station™ with reflux jacket where it was stirred at ambient temperature for 1 hour, after which it was heated at 80 or 100 °C for 16 hours. The solvent was removed under a stream of nitrogen and the reaction mixture was purified directly by flash column chromatography affording cyclized products **2** and **10**-**20**.

**2-Iodo-4-methoxybenzaldehyde.** A solution of 3-iodoanisole (500 µL, 4.2 mmol) in 15 mL dichloromethane in a microwave reaction vial equipped with a stirrer bar was cooled in an ice bath. $SnCl_4$ (1000 µL, 8.5 mmol) was added dropwise over two minutes, followed by dropwise addition of α,α−dichloromethyl methyl ether (420 µL, 1.1 mmol) over two minutes. The ice bath was removed and the reaction was stirred at room temperature for 1 hour. The reaction mixture was then poured in a mixture of 5 M HCl (10 mL) and crushed ice (10 g), followed by extraction with dichloromethane (2*10 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/EtOAc 96:4) followed by recrystallization from methanol yielded 2-iodo-4-methoxybenzaldehyde as a crystalline solid (221 mg, 20%). Analysis data are in accordance with published data for this compound.[6]

**(3a*S*,5a*S*,10a*S*,10b*R*)-*N*-Isopropyl-2,2-dimethyl-10-oxo-5a,10,10a,10b-tetrahydro-3aH-fluoreno[1,2-d][1,3]dioxole-3a-carboxamide (2).** Synthesized according to the general procedure using diene **1** (23.7 mg, 0.1 mmol), 2-iodobenzaldehyde (46.4 mg, 0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), tris(4-(trifluoromethyl)phenyl)phosphine (9.3 mg, 0.02 mmol) at 80 °C using 0.5 mL acetonitrile as solvent. The reaction mixture was purified by flash chromatography (petroleum ether/EtOAc 80:20) affording **2** as a viscous pale yellow oil (20.9 mg, 61%). This product was also synthesized on a 1 mmol scale, yielding 198 mg of 2 (58%); $[\alpha]_D^{20}$ = −38 (c = 0.3, EtOH); $\nu_{MAX}$ (neat) 1772, 1663 $cm^{-1}$; $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 7.85 (d, *J* = 7.6 Hz, 1H), 7.63 – 7.58 (m, 1H), 7.58 – 7.54 (m, 1H), 7.44 – 7.34 (m, 1H), 6.49 (d, *J* = 8.5 Hz, 1H), 6.16 (dd, *J* = 10.2, 4.1 Hz, 1H), 5.41 (ddd, *J* = 10.2, 2.2, 1.5 Hz, 1H), 4.88 (dd, *J* = 1.8, 1.5 Hz, 1H), 4.09 (ddd, *J* = 7.3, 4.1, 2.2 Hz, 1H), 3.94 (dhept, *J* = 8.5, 6.6 Hz, 1H), 3.31 (dd, *J* = 7.3, 1.8 Hz, 1H), 1.51 (s, 3H), 1.47 (s, 3H), 1.13 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.6 Hz, 3H); $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 202.3, 168.8, 155.1, 135.5, 135.0, 129.6, 128.1, 125.8, 124.9, 124.7, 109.5, 79.0, 76.0, 46.9, 41.0, 36.7, 28.0, 26.4, 23.0, 22.7; HRMS (ESI+) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{23}NO_4Na$ 364.1525; Found 364.1524.

**(3a*S*,7a*R*)-*N*,2,2-Trimethylbenzo[d][1,3]dioxole-3a(7aH)-carboxamide (3).** Activated ester **24** (335 mg, 1.1 mmol) and methylamine hydrochloride (116 mg, 1.7 mmol) were dissolved in 6 mL tetrahydrofuran in a microwave reaction vial. The vial was capped and *N*,*N*-diisopropylethylamine (390 µL, 2.3 mmol) was added. The solution was stirred at room temperature for 90 minutes, after which it was diluted with water (20 mL) and extracted with dichloromethane (4*15 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/EtOAc 71:29) afforded **3** as a crystalline solid (147 mg, 62%); mp 42-44 °C; $[\alpha]_D^{20}$ = −273 (c = 1.1, EtOH); $\nu_{MAX}$ (neat) 1654 $cm^{-1}$; $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 6.74 (s, 1H), 6.15 – 6.08 (m, 2H), 6.02 – 5.95 (m, 1H), 5.67 – 5.62 (m, 1H), 4.86 (dd, *J* = 4.1, 0.7 Hz, 1H), 2.85 (d, *J* = 5.0 Hz, 3H), 1.45 (s, 3H), 1.40 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 173.1, 125.7, 125.0, 124.5, 124.2, 107.3, 80.5, 73.6, 27.1, 26.2, 25.9; HRMS (ESI+) m/z: $[M+Na]^+$ Calcd for $C_{11}H_{15}NO_3Na$ 232.0950; Found 232.0956.

**(3a*S*,7a*R*)-*N*,*N*,2,2-Tetramethylbenzo[d][1,3]dioxole-3a(7aH)-carboxamide (4).** Activated ester **24** (293 mg, 1.0 mmol) and dimethylamine hydrochloride (122 mg, 1.5 mmol) were dissolved in 5 mL acetonitrile in a microwave reaction vial. The vial was capped and *N*,*N*-diisopropylethylamine (360 µL, 2.1 mmol) was added. The solution was stirred at room temperature for 5 hours,

after which it was diluted with water (20 mL) and extracted with dichloromethane (4*15 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash chromatography (dichloromethane/2-propanol 98:2) afforded **4** as an off-white crystalline solid (57.5 mg, 26%); mp 55-57 °C; $[\alpha]_D^{20}$ = −424 (c = 0.5, EtOH); $\nu_{MAX}$ (neat) 1626 $cm^{-1}$; $^1H$ NMR (400 MHz, Chloroform-*d*) δ 6.12 – 6.06 (m, 3H), 5.85 – 5.80 (m, 1H), 5.33 (d, *J* = 3.2 Hz, 1H), 3.27 (s, 3H), 2.96 (s, 3H), 1.41 (s, 3H), 1.36 (s, 3H); $^{13}C$ NMR (101 MHz, Chloroform-*d*) δ 171.2, 126.7, 125.0, 124.4, 123.4, 105.7, 80.8, 73.7, 37.8, 37.2, 27.1, 25.2; HRMS (ESI+) m/z: $[M+Na]^+$ Calcd for $C_{12}H_{17}NO_3Na$ 246.1106; Found 246.1106.

**(3a*S*,7a*R*)-2,2-Dimethyl-*N*-phenylbenzo[d][1,3]dioxole-3a(7aH)-carboxamide (5).** Carboxylic acid **23** (312 mg, 2.0 mmol) was dissolved in acetone (1.5 mL) and 2,2-dimethoxypropane (1.8 mL) in a microwave reaction vial. *p*-Toluenesulfonic acid monohydrate (5 mg, 0.03 mmol) was added, the vial was capped and allowed to react at room temperature for 2 hours. The solution was then diluted with brine and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude acetal-protected MAO-product **8** was then redissolved in *N*,*N*-dimethylformamide (4 mL) in a microwave reaction vial. *N*,*N*-Diisopropylethylamine (700 µL, 4 mmol), HATU (836 mg, 2.1 mmol) and aniline (200 µL, 2.2 mmol) were added and the vial was stirred in a heating block at 50 °C for 16 hours. The solvent was removed under reduced pressure and the crude reaction mixture was dissolved in dichloromethane (10 mL), washed with 5% aqueous LiCl solution (10 mL), and the aqueous phase was then extracted with an additional 10 mL dichloromethane. The combined organic extracts were dried over $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/EtOAc 90:10) afforded **5** as an off-white crystalline solid (483 mg, 89%); mp 125-127 °C; $[\alpha]_D^{20}$ = −358 (c = 1.0, EtOH); $\nu_{MAX}$ (neat) 1672 $cm^{-1}$; $^1H$ NMR (400 MHz, Chloroform-*d*) δ 8.54 (s, 1H), 7.60 – 7.55 (m, 2H), 7.38 – 7.32 (m, 2H), 7.17 – 7.12 (m, 1H), 6.23 – 6.14 (m, 2H), 6.07 – 6.02 (m, 1H), 5.79 – 5.74 (m, 1H), 5.00 (dd, *J* = 4.1, 0.9 Hz, 1H), 1.54 (s, 3H), 1.48 (s, 3H); $^{13}C$ NMR (101 MHz, Chloroform-*d*) δ 170.6, 137.2, 129.3, 125.1 (two overlapping carbons), 125.0, 124.8, 124.2, 119.6, 1076, 80.6, 73.9, 27.1, 25.8; HRMS (ESI+) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{17}NO_3Na$ 294.1106; Found 294.1106.

**(3a*S*,5a*S*,10a*S*,10b*R*)-8-Methoxy-*N*,2,2-trimethyl-10-oxo-5a,10,10a,10b-tetrahydro-3aH-fluoreno[1,2-d][1,3]dioxole-3a-carboxamide (10).** Synthesized according to the general procedure using diene **3** (20.9 mg, 0.1 mmol), 2-iodo-5-methoxybenzaldehyde (52.4 mg, 0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01mmol), tris(4-(trifluoromethyl)phenyl)phosphine (9.3 mg, 0.02 mmol) at 80 °C using 0.5 mL acetonitrile as solvent. The reaction mixture was purified by flash chromatography (petroleum ether/EtOAc 48:52) affording **10** as a pale yellow viscous oil (21.1 mg, 61%); $[\alpha]_D^{20}$ = −47 (c = 1.1, EtOH); $\nu_{MAX}$ (neat) 1716, 1664 $cm^{-1}$; $^1H$ NMR (400 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 8.4 Hz, 1H), 7.30 (d, *J* = 2.6 Hz, 1H), 7.19 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.70 – 6.63 (m, 1H), 6.13 (dd, *J* = 10.2, 4.1 Hz, 1H), 5.37 (ddd, *J* = 10.2, 2.5, 1.5 Hz, 1H), 4.88 (dd, *J* = 1.7, 1.5 Hz, 1H), 4.01 (ddd, *J* = 7.1, 4.1, 2.5 Hz, 1H), 3.83 (s, 3H), 3.34 (dd, *J* = 7.1, 1.7 Hz, 1H), 2.73 (d, *J* = 5.0 Hz, 3H), 1.50 (s, 3H), 1.46 (s, 3H); $^{13}C$ NMR (101 MHz, Chloroform-*d*) δ 202.4, 170.4, 159.9, 148.0, 136.7, 129.8, 126.4, 124.6, 124.4, 109.6, 105.9, 79.2, 75.9, 55.7, 47.5, 36.0, 28.1, 26.6, 26.1; HRMS (ESI+) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{21}NO_5Na$ 366.1317; Found 366.1317.

**(3a*S*,5a*S*,10a*S*,10b*R*)-8-Methoxy-*N*,*N*,2,2-tetramethyl-10-oxo-5a,10,10a,10b-tetrahydro-3aH-fluoreno[1,2-d][1,3]dioxole-3a-carboxamide (11).** Synthesized according to the general procedure using diene **4** (22.3 mg, 0.1 mmol), 2-iodo-5-methoxybenzaldehyde (52.4 mg, 0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01mmol), tris(4-(trifluoromethyl)phenyl)phosphine (9.3 mg, 0.02 mmol) at 80 °C using 0.5 mL acetonitrile as solvent. The reaction mixture was purified by flash chromatography (petroleum ether/EtOAc 74:26) affording **11** as a pale yellow solid, partially crystallizing over time (14.6 mg, 41%); $[\alpha]_D^{20}$ = −115 (c = 1.0, EtOH); $\nu_{MAX}$ (neat) 1715, 1662 $cm^{-1}$; $^1H$ NMR (400 MHz, Chloroform-*d*) δ 7.39 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 2.6 Hz, 1H), 7.16 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.14 (dd, *J* = 10.3, 4.6 Hz, 1H), 5.63 (ddd, *J* = 10.3, 2.1, 1.5 Hz, 1H), 5.11 (dd, *J* = 1.5, 1.3 Hz, 1H), 4.00 (ddd, *J* = 7.4, 4.6, 2.1 Hz, 1H), 3.83 (s, 3H), 3.32 (dd, *J* = 7.4, 1.3 Hz, 1H), 3.15 (s, 3H), 2.75 (s, 3H), 1.45 – 1.43 (m, 6H); $^{13}C$ NMR (101 MHz, Chloroform-*d*) δ 202.7, 169.2, 159.7, 147.6, 137.3, 129.6, 126.2, 124.7, 124.2, 108.9, 105.9, 80.2, 77.1, 55.7, 47.5, 37.7, 36.8, 36.0, 28.5, 26.8; HRMS (ESI+) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{23}NO_5Na$ 380.1474; Found 380.1475.

**(3a*S*,5a*S*,10a*S*,10b*R*)-8-Methoxy-2,2-dimethyl-10-oxo-*N*-phenyl-5a,10,10a,10b-tetrahydro-3aH-fluoreno[1,2-d][1,3]dioxole-3a-carboxamide (12).** Synthesized according to the general procedure using diene **5** (27.1 mg, 0.1 mmol), 2-iodo-5-methoxybenzaldehyde (52.4 mg, 0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01mmol), tris(4-(trifluoromethyl)phenyl)phosphine (9.3 mg, 0.02 mmol) at 100 °C using 0.5 mL 1,4-dioxane as solvent. The reaction mixture was purified by reversed phase flash chromatography (water/methanol 35:65) affording **12** as a pale yellow amorphous solid (13.1 mg, 32%); $[\alpha]_D^{20}$ = −40 (c = 0.7, EtOH); $\nu_{MAX}$ (neat) 1715, 1686 $cm^{-1}$; $^1H$ NMR (400 MHz, Chloroform-*d*) δ 8.47 (s, 1H), 7.51 – 7.41 (m, 3H), 7.31 (d, *J* = 2.6 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.26 – 7.24 (m, 1H), 7.22 (dd, *J* = 8.4, 2.6 Hz, 1H), 7.07 (t, *J*= 7.4 Hz, 1H), 6.19 (dd, *J* = 10.2, 4.1 Hz, 1H), 5.47 (ddd, *J* = 10.2, 2.2, 1.4 Hz, 1H), 5.03 (dd, *J* = 1.7, 1.4 Hz, 1H), 4.05 (ddd, *J* = 7.1, 4.1, 2.2 Hz, 1H), 3.85 (s, 3H), 3.38 (dd, *J* = 7.1, 1.7 Hz, 1H), 1.59 (s, 3H), 1.53 (s, 3H); $^{13}C$ NMR (101 MHz, Chloroform-*d*) δ 202.1, 167.8, 160.0, 148.0, 137.1, 136.7, 130.5, 129.1, 126.5, 124.7 (two overlapping carbons), 123.9, 119.9, 110.0, 106.0, 79.3, 75.9, 55.8, 47.6, 36.0, 28.1, 26.6; HRMS (ESI+) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{23}NO_5Na$ 428.1474; Found 428.1473.

**(3a*S*,5a*S*,10a*S*,10b*R*)-*N*-Isopropyl-8-methoxy-2,2-dimethyl-10-oxo-5a,10,10a,10b-tetrahydro-3aH-fluoreno[1,2-d][1,3]dioxole-3a-carboxamide (13).** Synthesized according to the general procedure using diene **1** (23.7 mg, 0.1 mmol), 2-iodo-5-methoxybenzaldehyde (52.4 mg, 0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), tris(4-(trifluoromethyl)phenyl)phosphine (9.3 mg, 0.02 mmol) at 80 °C using 0.5 mL acetonitrile as solvent. The reaction mixture was purified by flash chromatography (petroleum ether/EtOAc 80:20) affording **13** as a viscous pale yellow oil (27.4 mg, 74%); $[\alpha]_D^{20}$ = -44 (c = 1.2, EtOH); $\nu_{MAX}$ (neat) 1717, 1671 $cm^{-1}$; $^1H$ NMR (400 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 8.4 Hz, 1H), 7.28 (d, *J* = 2.5 Hz, 1H), 7.18 (ddd, *J* = 8.4, 2.5, 0.9 Hz, 1H), 6.49 (d, *J* = 8.6 Hz, 1H), 6.12 (ddd, *J* = 10.2, 4.0, 1.1 Hz, 1H), 5.36 (ddd, *J* = 10.2, 2.1, 1.5 Hz, 1H), 4.86 (dd, *J* = 1.8, 1.5 Hz, 1H), 3.99 (ddd, *J* = 7.1, 4.0, 2.1 Hz, 1H), 3.94 (dhept, *J* = 8.6, 6.6 Hz, 1H), 3.81 (d, *J* = 0.9 Hz, 3H), 3.32 (ddd, *J* = 7.1, 1.8, 1.1 Hz, 1H), 1.50 (s, 3H), 1.46 (s, 3H), 1.12 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H); $^{13}C$ NMR (101 MHz, Chloroform-*d*) δ 202.2, 168.8, 159.9, 148.0, 136.7,

129.8, 126.4, 124.5, 124.2, 109.5, 105.9, 79.0, 76.9, 55.7, 47.5, 41.0, 36.0, 28.0, 26.4, 22.9, 22.7; HRMS (ESI+) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{25}NO_5Na$ 394.1630; Found 394.1628.

**(3a*S*,5a*S*,10a*S*,10b*R*)-*N*,8-Dimethoxy-*N*,2,2-trimethyl-10-oxo-5a,10,10a,10b-tetrahydro-3aH-fluoreno[1,2-d][1,3]dioxole-3a-carboxamide (14).** Synthesized according to the general procedure using diene **6** (23.9 mg, 0.1 mmol), 2-iodo-5-methoxybenzaldehyde (52.4 mg, 0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01mmol), tris(4-(trifluoromethyl)phenyl)phosphine (9.3 mg, 0.02 mmol) at 80 °C using 0.5 mL acetonitrile as solvent. The reaction mixture was purified by flash chromatography (petroleum ether/EtOAc 72:28) affording **14** as a pale yellow amorphous solid (16.1 mg, 43%); $[\alpha]_D^{20} = -110$ (c = 0.7, EtOH); $\nu_{MAX}$ (neat) 1713, 1684 $cm^{-1}$; $^1H$ NMR (400 MHz, Chloroform-*d*) δ 7.42 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 2.6 Hz, 1H), 7.18 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.10 (dd, *J* = 10.3, 4.3 Hz, 1H), 5.73 (ddd, *J* = 10.3, 2.2, 1.7 Hz, 1H), 5.15 (dd, *J* = 1.7, 1.5 Hz, 1H), 4.01 (ddd, *J* = 7.3, 4.3, 2.2 Hz, 1H), 3.83 (s, 3H), 3.51 (s, 3H), 3.35 (dd, *J* = 7.3, 1.5 Hz, 1H), 3.05 (s, 3H), 1.47 (s, 3H), 1.47 (s, 3H); $^{13}C$ NMR (101 MHz, Chloroform-*d*) δ 202.5, 159.8, 147.8, 137.1, 129.1, 126.3, 124.5, 124.4, 109.0, 105.8, 79.7, 76.1, 61.4, 55.7, 47.7, 36.0, 33.7, 28.5, 26.6, amide C=O too weak to be detected by $^{13}C$ NMR but is detected by IR; HRMS (ESI+) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{23}NO_6Na$ 396.1423; Found 396.1426.

**(3a*R*,5a*S*,10a*S*,10b*R*)-3a-(Hydroxymethyl)-8-methoxy-2,2-dimethyl-3a,5a,10a,10b-tetrahydro-10H-fluoreno[1,2-d][1,3]dioxol-10-one (15).** Synthesized according to the general procedure using alcohol **7** (18.2 mg, 0.1 mmol), 2-iodo-5-methoxybenzaldehyde (52.4 mg, 0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01mmol), tris(4-(trifluoromethyl)phenyl)phosphine (9.3 mg, 0.02 mmol) at 100 °C using 0.5 mL *N*,*N*-dimethylformamide as solvent. The reaction mixture was purified by flash chromatography (petroleum ether/EtOAc 77:23) affording **15** as a pale yellow amorphous sticky solid (4.5 mg, 14%); $[\alpha]_D^{20} = 39$ (c = 0.3, EtOH); $\nu_{MAX}$ (neat) 3482 (broad), 1702 $cm^{-1}$; $^1H$ NMR (400 MHz, Chloroform-*d*) δ 7.46 (d, *J* = 8.3 Hz, 1H), 7.23 (dd, *J* = 8.3, 2.6 Hz, 1H), 7.20 (d, *J* = 2.6 Hz, 1H), 5.96 (dd, *J* = 10.3, 3.7 Hz, 1H), 5.39 (ddd, *J* = 10.3, 2.8, 1.4 Hz, 1H), 4.96 (dd, *J* = 2.6, 1.4 Hz, 1H), 4.02 (ddd, *J* = 7.2, 3,7, 2.8 Hz, 1H), 3.83 (s, 3H), 3.46 (d, *J* = 12.0 Hz, 1H) 3.46 (dd, *J* = 7.2, 2.6 Hz, 1H), 3.20 (d, *J* = 12.0 Hz, 1H), 1.47 (s, 3H), 1.45 (s, 3H), signal for -O*H* not seen; $^{13}C$ NMR (101 MHz, Chloroform-*d*) δ 203.8, 160.0, 149.0, 136.7, 130.2, 126.6, 126.1, 124.8, 108.4, 105.8, 78.6, 73.6, 64.4, 55.8, 48.9, 36.9, 28.2, 27.2; HRMS (ESI+) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{20}O_5Na$ 339.1208; Found 339.1211.

**(3a*S*,5a*S*,10a*S*,10b*R*)-*N*-isopropyl-7-methoxy-2,2-dimethyl-10-oxo-5a,10,10a,10b-tetrahydro-3aH-fluoreno[1,2-d][1,3]dioxole-3a-carboxamide (16).** Synthesized according to the general procedure using diene **1** (23.7 mg, 0.1 mmol), 2-iodo-4-methoxybenzaldehyde (52.4 mg, 0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01mmol), tris(4-(trifluoromethyl)phenyl)phosphine (9.3 mg, 0.02 mmol) at 100 °C using 0.5 mL 1,4-dioxane as solvent. The reaction mixture was purified by flash chromatography (petroleum ether/EtOAc 72:28) affording **16** as a viscous pale yellow oil (21.5 mg, 58%); $[\alpha]_D^{20} = 6$ (c = 1.0, EtOH); $\nu_{MAX}$ (neat) 1708, 1672 $cm^{-1}$; $^1H$ NMR (400 MHz, Chloroform-*d*) δ 7.79 (d, *J* = 8.5 Hz, 1H), 6.98 (d, *J* = 2.2 Hz, 1H), 6.91 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.47 (d, *J* = 8.4 Hz, 1H), 6.15 (dd, *J* = 10.2, 4.2 Hz, 1H), 5.42 (ddd, *J* = 10.2, 2.2, 1.6 Hz, 1H), 4.86 (app t, *J* = 1.6 Hz, 1H), 4.01 (ddd, *J* = 7.3, 4.2, 2.2 Hz, 1H), 3.95 (dhept, *J* = 8.4, 6.6 Hz, 1H), 3.88 (s, 3H), 3.30 (dd, *J* = 7.3, 1.6 Hz, 1H), 1.51 (s, 3H), 1.47 (s, 3H), 1.12 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H); $^{13}C$ NMR (101 MHz, Chloroform-*d*) δ 200.3, 168.5, 165.4, 157.7, 129.2, 128.6, 126.4, 124.7, 115.5, 109.28, 109.27, 78.9, 75.9, 55.7, 46.9, 40.9, 36.5, 27.9, 26.2, 22.8, 22.6.; HRMS (ESI+) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{25}NO_5Na$ 394.1630; Found 394.1630.

**(3a*S*,5a*S*,10a*S*,10b*R*)-6-Fluoro-*N*-isopropyl-2,2-dimethyl-10-oxo-5a,10,10a,10b-tetrahydro-3aH-fluoreno[1,2-d][1,3]dioxole-3a-carboxamide (17).** Synthesized according to the general procedure using diene **1** (23.7 mg, 0.1 mmol), 3-fluoro-2-iodobenzaldehyde (50.0 mg, 0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01mmol), tris(4-(trifluoromethyl)phenyl)phosphine (9.3 mg, 0.02 mmol) at 100 °C using 0.5 mL 1,4-dioxane as solvent. The reaction mixture was purified by flash chromatography (petroleum ether/EtOAc 75:25) affording **17** as a pale yellow solid, partially crystallizing over time (23.2 mg, 65%); $[\alpha]_D^{20} = -28$ (c = 1.2, EtOH); $\nu_{MAX}$ (neat) 1720, 1681 $cm^{-1}$; $^1H$ NMR (400 MHz, Chloroform-*d*) δ 7.57 (ddd, *J* = 8.2, 7.6, 4.9 Hz, 1H), 7.33 (dd, *J* = 7.6, 0.7 Hz, 1H), 6.99 (ddd, *J* = 9.0, 8.2, 0.7 Hz, 1H), 6.48 (d, *J* = 8.5 Hz, 1H), 6.11 (dd, *J* = 10.2, 4.2 Hz, 1H), 5.43 (ddd, *J* = 10.2, 2.2, 1.5 Hz, 1H), 4.83 (dd, *J* = 1.7, 1.5 Hz, 1H), 4.08 (ddd, *J* = 7.5, 4.2, 2.2 Hz, 1H), 3.94 (dhept, *J* = 8.5, 6.6 Hz, 1H), 3.32 (dd, *J* = 7.5, 1.7 Hz, 1H), 1.51 (s, 3H), 1.46 (s, 3H), 1.13 (d, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H); $^{13}C$ NMR (101 MHz, Chloroform-*d*) δ 198.4, 168.6, 159.3 (d, *J* = 265.1 Hz), 157.2 (d, *J* = 2.3 Hz), 136.9 (d, *J* = 8.2 Hz), 128.8, 125.2, 123.5 (d, *J* = 13.2 Hz), 121.6 (d, *J* = 4.2 Hz), 115.1 (d, *J* = 19.4 Hz), 109.6, 78.9, 75.9, 47.2, 41.1, 36.7, 28.0, 26.4, 22.9, 22.7; HRMS (ESI+) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{22}FNO_4Na$ 382.1431; Found 382.1431.

**(3a*S*,5a*S*,10a*S*,10b*R*)-8-Bromo-*N*-isopropyl-2,2-dimethyl-10-oxo-5a,10,10a,10b-tetrahydro-3aH-fluoreno[1,2-d][1,3]dioxole-3a-carboxamide (18).** Synthesized according to the general procedure using diene **1** (23.7 mg, 0.1 mmol), 2-iodo-5-bromobenzaldehyde (62.2 mg, 0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01mmol), tris(4-(trifluoromethyl)phenyl)phosphine (9.3 mg, 0.02 mmol) at 100 °C using 0.5 mL 1,4-dioxane as solvent. The reaction mixture was purified by reversed phase flash chromatography (water/methanol 38:62) affording **18** as a pale yellow amorphous solid 20.5 mg, 49%); $[\alpha]_D^{20} = -14$ (c = 0.9, EtOH); $\nu_{MAX}$ (neat) 1720, 1664 $cm^{-1}$; $^1H$ NMR (400 MHz, Chloroform-*d*) δ 7.97 (d, *J* = 1.9 Hz, 1H), 7.70 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 6.49 (d, *J* = 8.5 Hz, 1H), 6.11 (dd, *J* = 10.2, 4.2 Hz, 1H), 5.42 (ddd, *J* = 10.2, 2.2, 1.5 Hz, 1H), 4.84 (dd, *J* = 1.7, 1.5 Hz, 1H), 4.04 (ddd, *J* = 7.3, 4.2, 2.2 Hz, 1H), 3.93 (dhept, *J* = 8.5, 6.6 Hz, 1H), 3.33 (dd, *J* = 7.3, 1.7 Hz, 1H), 1.51 (s, 3H), 1.46 (s, 3H), 1.13 (d, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H); $^{13}C$ NMR (101 MHz, Chloroform-*d*) δ 200.9, 168.7, 153.7, 137.8, 137.3, 128.9, 127.8, 127.3, 125.2, 122.4, 109.7, 78.9, 75.9, 47.1, 41.1, 36.4, 28.0, 26.4, 23.0, 22.7; HRMS (ESI+) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{22}BrNO_4Na$ 442.0630; Found 442.0609.

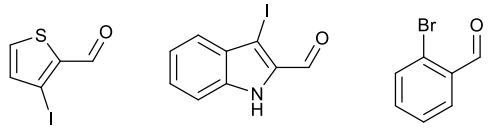
**(3a*S*,5a*S*,10a*S*,10b*R*)-*N*-Isopropyl-2,2-dimethyl-10-oxo-7-(trifluoromethyl)-5a,10,10a,10b-tetrahydro-3aH-fluoreno[1,2-d][1,3]dioxole-3a-carboxamide (19).** Synthesized according to the general procedure using diene **1** (23.7 mg, 0.1 mmol), 2-iodo-4-trifluoromethylbenzaldehyde (60.0 mg, 0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01mmol), tris(4-(trifluoromethyl)phenyl)phosphine (9.3 mg, 0.02 mmol) at 100 °C using 0.5 mL 1,4-dioxane as solvent. The reaction mixture was purified by flash chromatography (petroleum ether/EtOAc 88:12) affording **19** as a pale yellow amorphous solid (26.1 mg, 64%); $[\alpha]_D^{20} = -21$ (c = 0.9, EtOH); $\nu_{MAX}$ (neat) 1728,

1673 $cm^{-1}$; $^1H$ NMR (400 MHz, Chloroform-*d*) δ 7.96 (d, *J* = 8.0 Hz, 1H), 7.83 (dq, *J* = 1.5, 0.8 Hz, 1H), 7.66 (ddq, *J* = 8.0, 1.5, 0.7 Hz, 1H), 6.51 (d, *J* = 8.5 Hz, 1H), 6.17 (dd, *J* = 10.2, 4.2 Hz, 1H), 5.46 (ddd, *J* = 10.2, 2.2, 1.5 Hz, 1H), 4.86 (dd, *J* = 1.7, 1.5 Hz, 1H), 4.15 (ddd, *J* = 7.4, 4.2, 2.2 Hz, 1H), 3.92 (dhept, *J* = 8.5, 6.6 Hz, 1H), 3.37 (dd, *J* = 7.4, 1.7 Hz, 1H), 1.52 (s, 3H), 1.48 (s, 3H), 1.13 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.6 Hz, 3H); $^{13}C$ NMR (101 MHz, Chloroform-*d*) δ 201.4, 168.7, 155.2, 138.2, 136.3 (q, *J* = 32.2 Hz), 128.5, 125.6, 125.4, 125.3 (q, *J* = 3.6 Hz), 123.7 (q, *J* = 3.9 Hz), 123.1 (q, *J* = 273.7 Hz), 109.8, 78.9, 75.9, 47.0, 41.1, 36.7, 28.0, 26.4, 23.0, 22.7; HRMS (ESI+) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{22}F_3NO_4Na$ 432.1399; Found 432.1396.

**(3a*S*,5a*S*,10a*S*,10b*R*)-*N*-Isopropyl-2,2,7,8-tetramethyl-10-oxo-5a,10,10a,10b-tetrahydro-3aH-fluoreno[1,2-d][1,3]dioxole-3a-carboxamide (20).** Synthesized according to the general procedure using diene **1** (23.7 mg, 0.1 mmol), 2-iodo-4,5-dimethylbenzaldehyde (52.0 mg, 0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01mmol), tris(4-(trifluoromethyl)phenyl)phosphine (9.3 mg, 0.02 mmol) at 80 °C using 0.5 mL acetonitrile as solvent. The reaction mixture was purified by reversed phase flash chromatography (water/methanol 40:60) affording **20** as a sticky amorphous solid (19.2 mg, 55%); $[\alpha]_D^{20} = -4$ (c = 0.9, EtOH); $\nu_{MAX}$ (neat) 1714, 1672 $cm^{-1}$; $^1H$ NMR (400 MHz, Chloroform-*d*) δ 7.62 (s, 1H), 7.32 (s, 1H), 6.47 (d, *J* = 8.5 Hz, 1H), 6.15 (dd, *J* = 10.2, 4.1 Hz, 1H), 5.37 (ddd, *J* = 10.2, 2.2, 1.5 Hz, 1H), 4.86 (dd, *J* = 1.7, 1.5 Hz, 1H), 4.00 (ddd, *J* = 7.2, 4.1, 2.2 Hz, 1H), 3.93 (dhept, *J* = 8.5, 6.6 Hz, 1H), 3.28 (dd, *J* = 7.2, 1.7 Hz, 1H), 2.33 (s, 3H), 2.27 (s, 3H), 1.50 (s, 3H), 1.47 (s, 3H), 1.12 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H); $^{13}C$ NMR (101 MHz, Chloroform-*d*) δ 202.1, 168.7, 153.3, 145.3, 137.0, 133.6, 129.8, 126.5, 125.2, 124.4, 109.4, 79.1, 76.2, 47.0, 41.0, 36.3, 28.1, 26.4, 23.0, 22.8, 21.0, 19.9; HRMS (ESI+) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{27}NO_4Na$ 392.1838; Found 392.1840.

**(1*R*,2*S*,4a*S*,9a*S*)-1,2-Dihydroxy-*N*-isopropyl-9-oxo-2,4a,9,9a-tetrahydro-1H-fluorene-2-carboxamide (21).** To a methanol (4 mL) solution of cyclization product **2** (51.0 mg) in a microwave reaction vial equipped with a stirrer bar, 2 mL of 2.5 M aqueous HCl was added. The vial was capped and heated in a heating block at 40 °C for 16 h. The crude reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (6*10 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/EtOAc 40:60) afforded diol **21** (27.5 mg, 61%) as a white crystalline solid; mp 193-196 °C; $[\alpha]_D^{20} = 95$ (c = 1.0, EtOH); $\nu_{MAX}$ (neat) 3370 (broad), 1702, 1660 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 7.75 – 7.67 (m, 2H), 7.65 (d, *J* = 7.7 Hz, 1H), 7.48 – 7.43 (m, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 6.33 (dd, *J* = 9.9, 3.8 Hz, 1H), 5.61 (dd, *J* = 9.9, 2.6 Hz, 1H), 5.53 (s, 1H), 4.90 (d, *J* = 7.6 Hz, 1H), 4.09 (ddd, *J* = 6.8, 3.8, 2.6 Hz, 1H), 3.79 (dhept, *J* = 8.3, 6.5 Hz, 1H), 3.68 (dd, *J* = 9.7, 7.6 Hz, 1H), 2.96 (dd, *J* = 9.7, 6.8 Hz, 1H), 1.04 (d, *J* = 6.5 Hz, 3H), 1.04 (d, *J* = 6.5 Hz, 3H) ; $^{13}C$ NMR (101 MHz, DMSO-$d_6$) δ 204.4, 172.3, 154.1, 135.4, 134.6, 129.0, 128.9, 127.7, 125.5, 123.2, 73.8, 69.8, 50.1, 40.4, 39.7, 22.3, 22.3; HRMS (ESI+) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{19}NO_4Na$ 324.1212; Found 324.1211.

**Aryl iodides that did not afford the desired product:**



## NMR SPECTRA

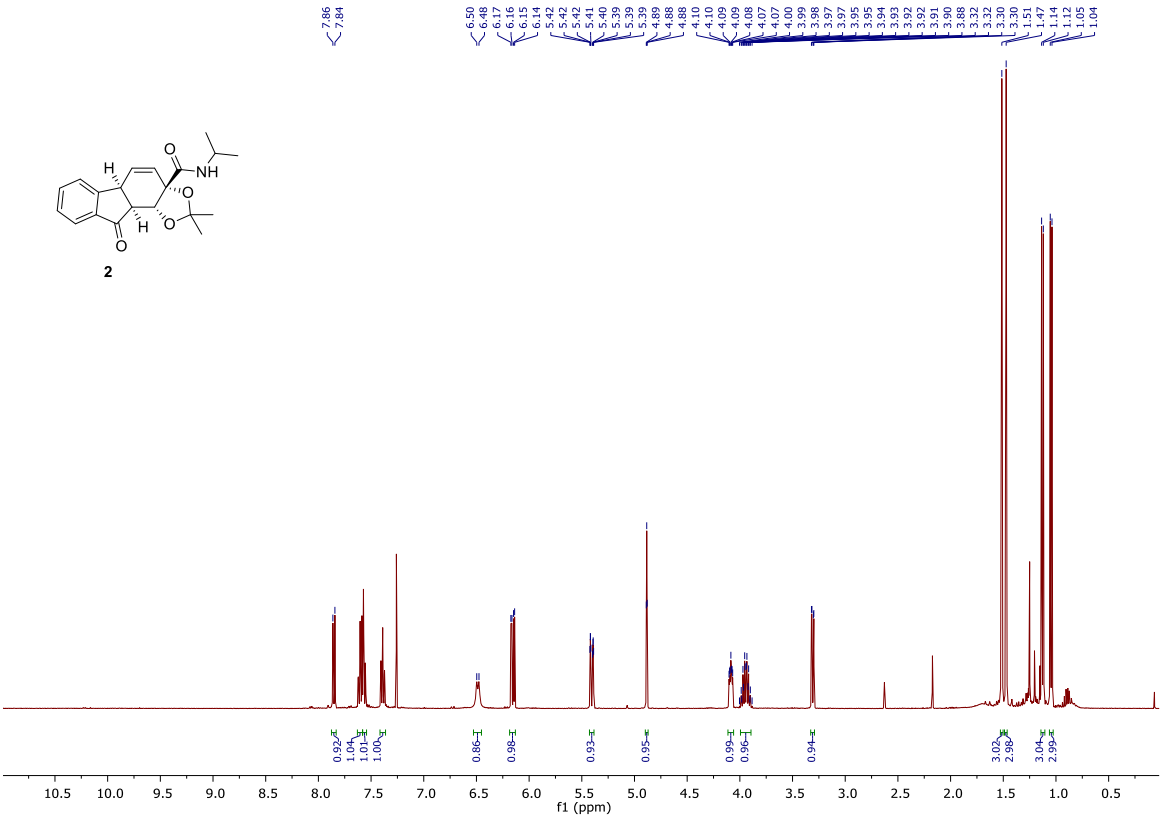



**Figure S1.** $^{1}$H NMR (400 MHz) spectrum of **2** in $CDCl_3$.

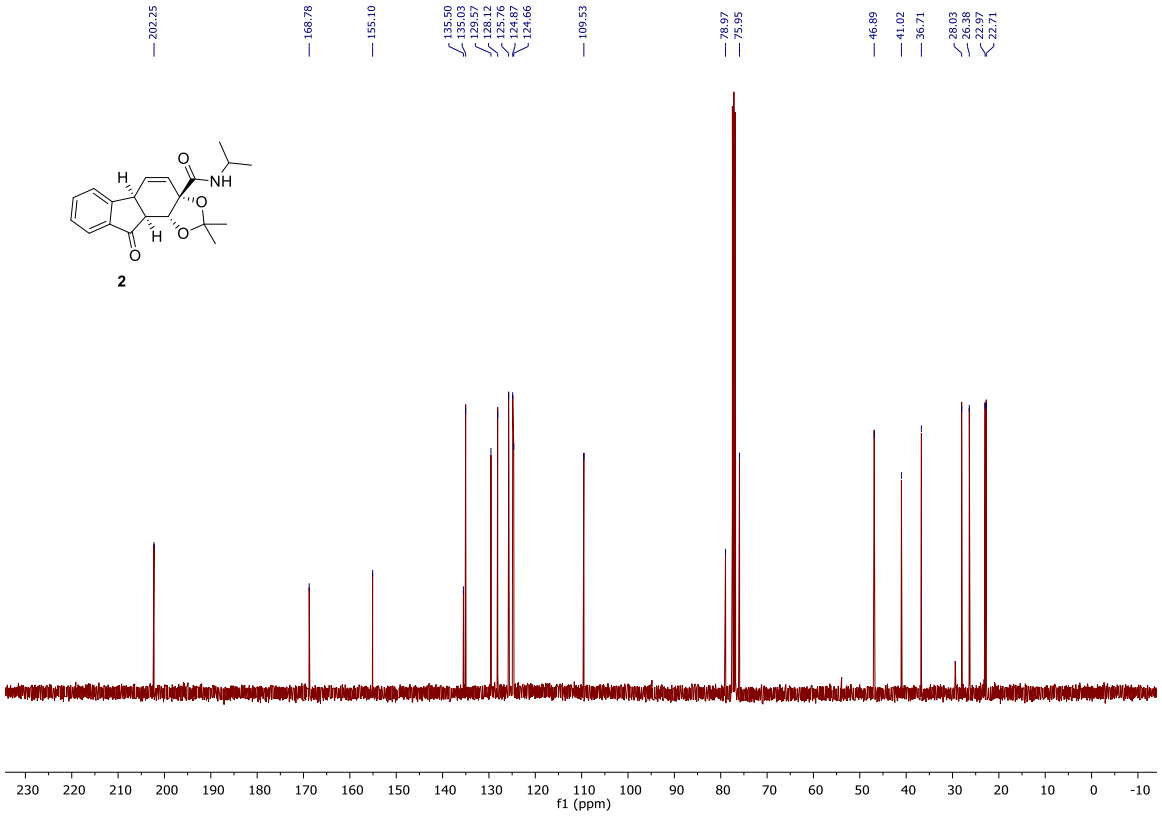



**Figure S2.** $^{13}$C NMR (101 MHz) spectrum of **2** in $CDCl_3$.

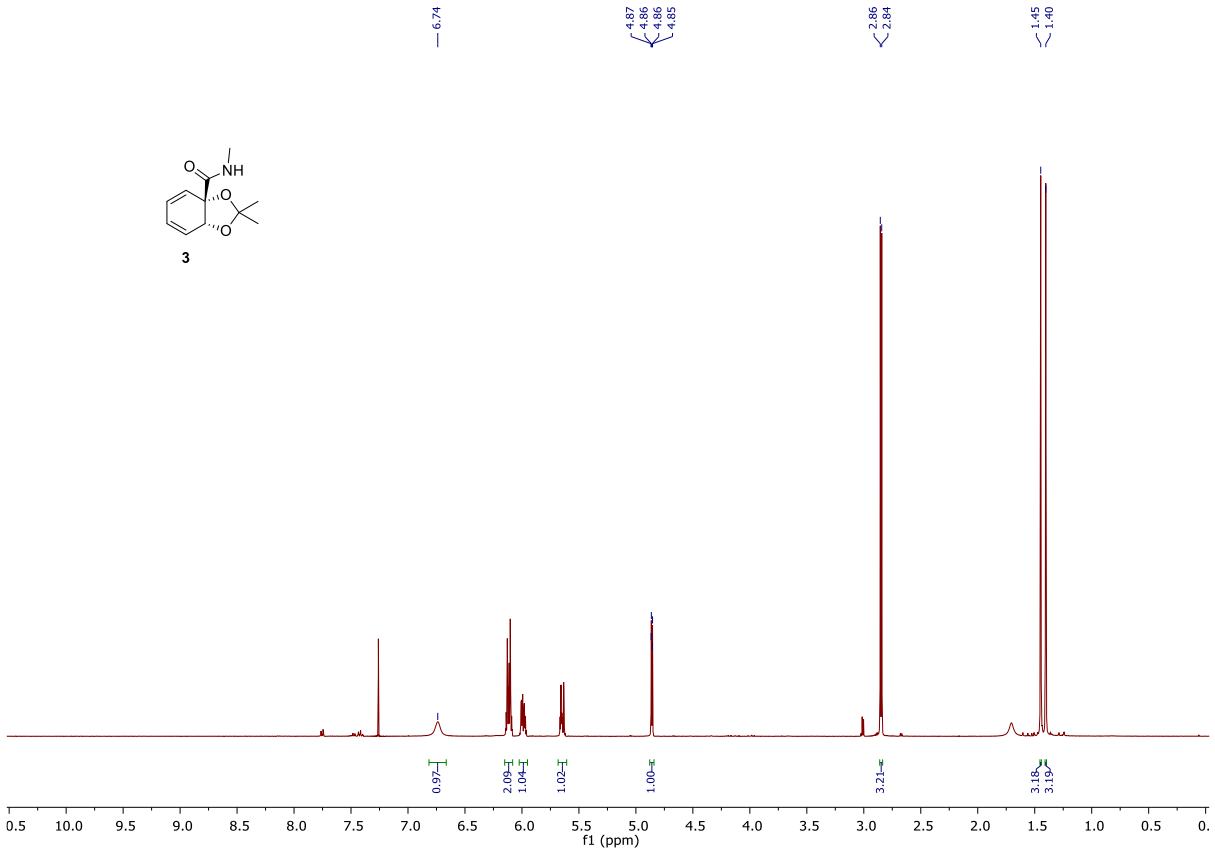



**Figure S3.** $^{1}$H NMR (400 MHz) spectrum of **3** in $CDCl_3$.

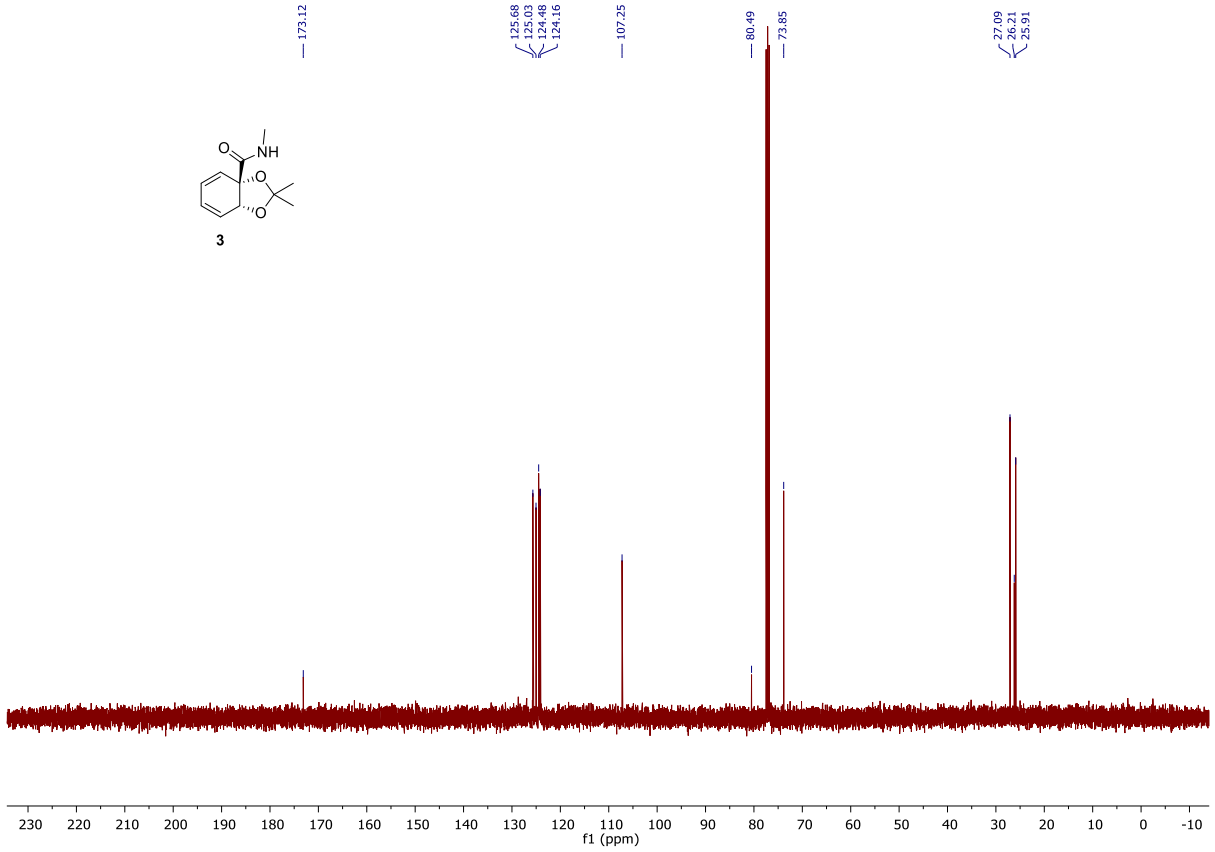



**Figure S4.** $^{13}$C NMR (101 MHz) spectrum of **3** in $CDCl_3$.

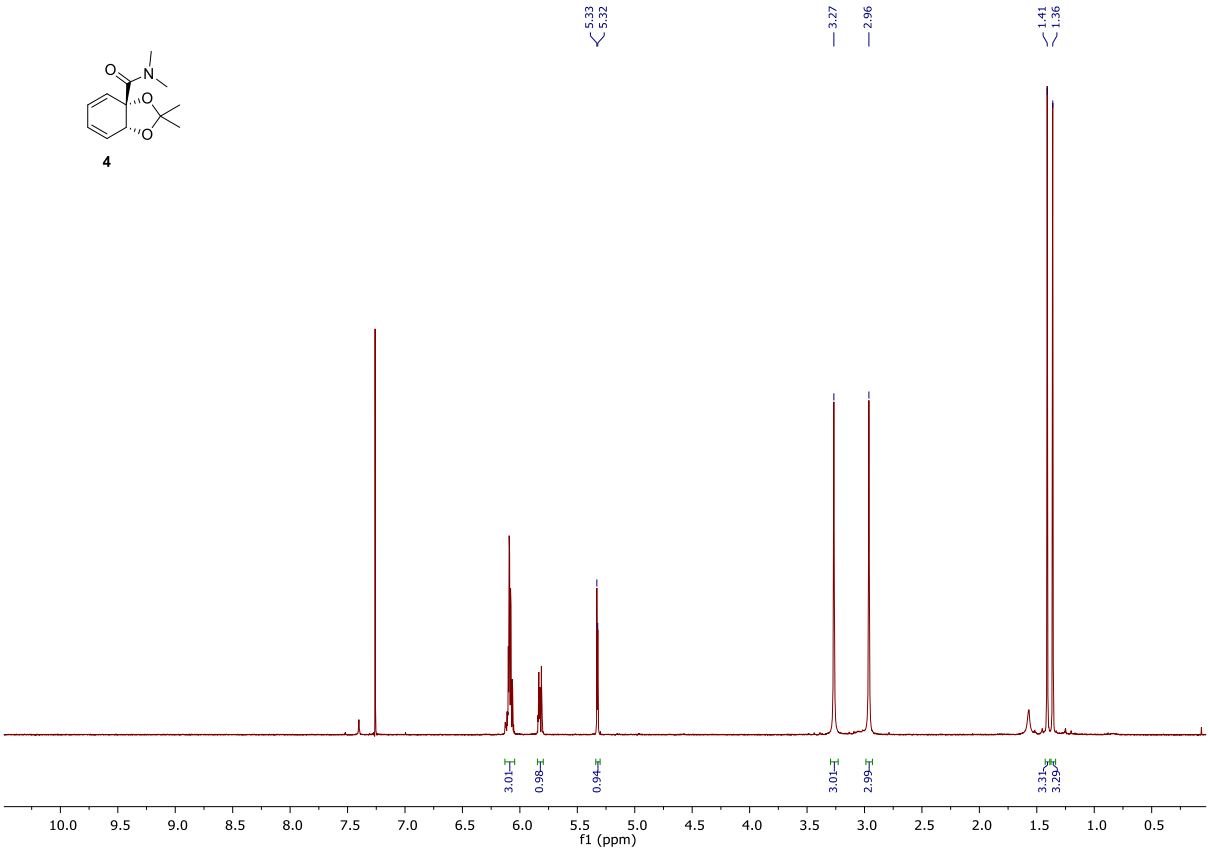



**Figure S5.** $^{1}$H NMR (400 MHz) spectrum of **4** in $CDCl_3$.

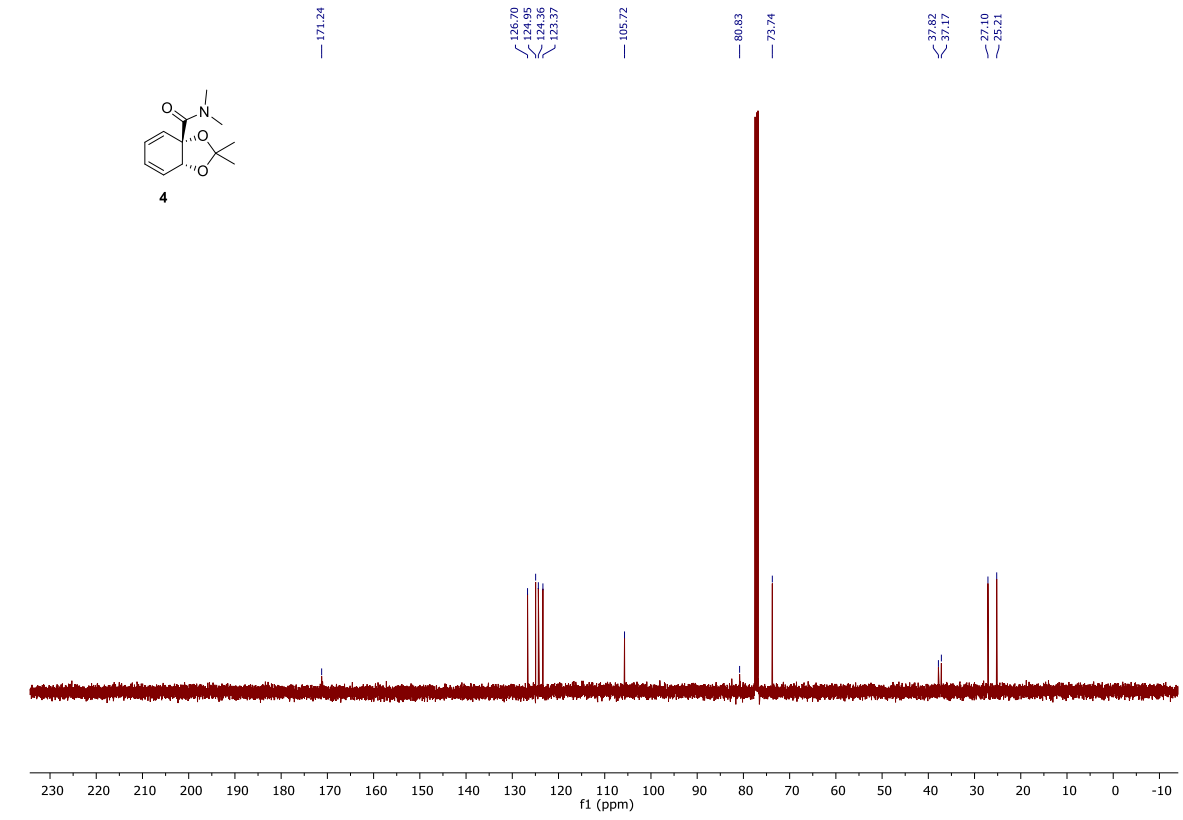



**Figure S6.** $^{13}$C NMR (101 MHz) spectrum of **4** in $CDCl_3$.

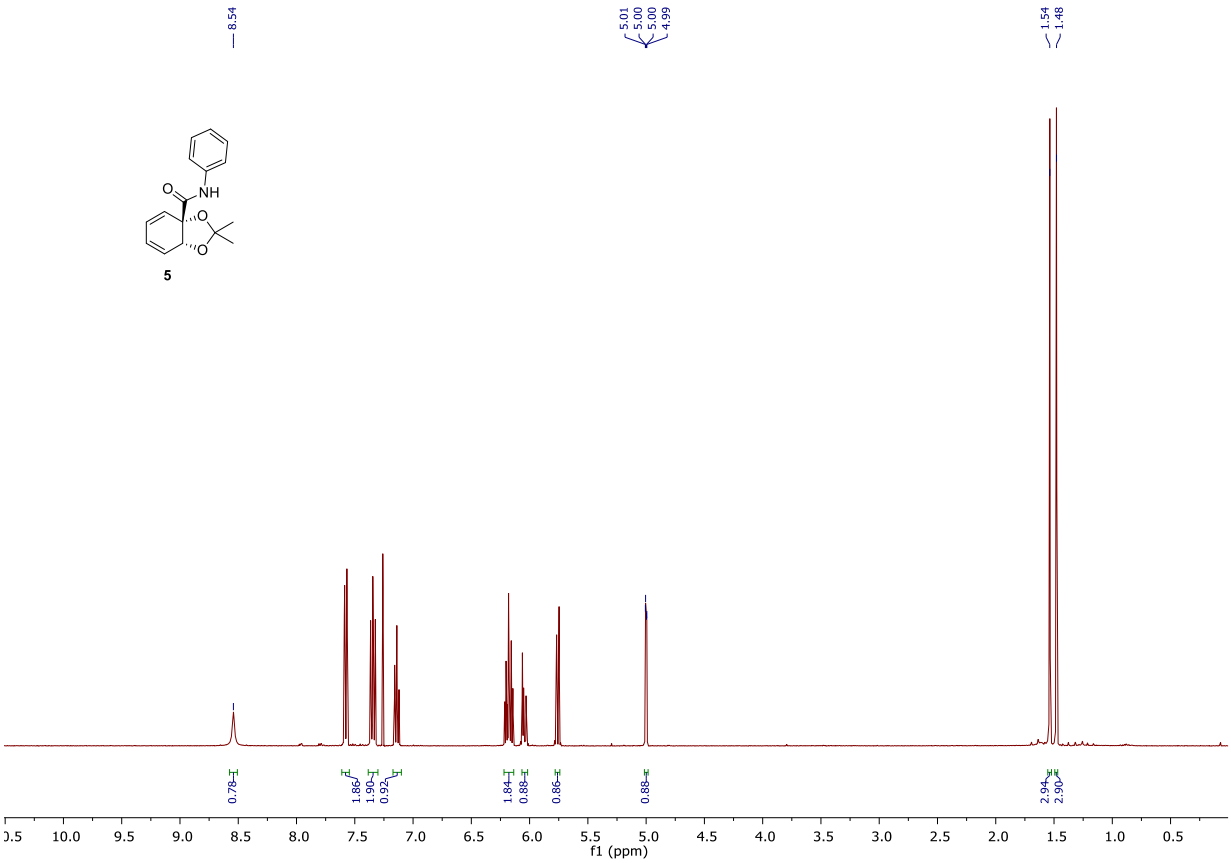



**Figure S7.** $^{1}$H NMR (400 MHz) spectrum of **5** in $CDCl_3$.

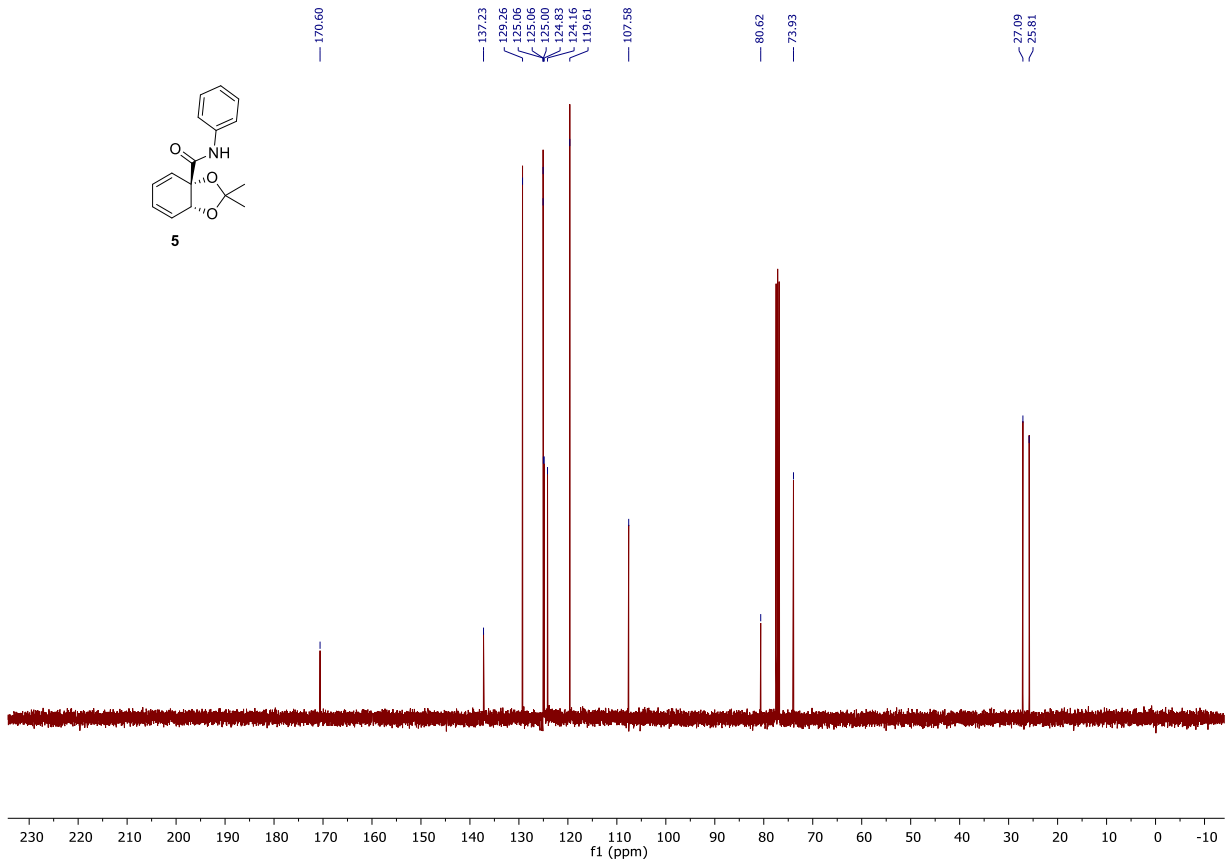



**Figure S8.** $^{13}$C NMR (101 MHz) spectrum of **5** in $CDCl_3$.

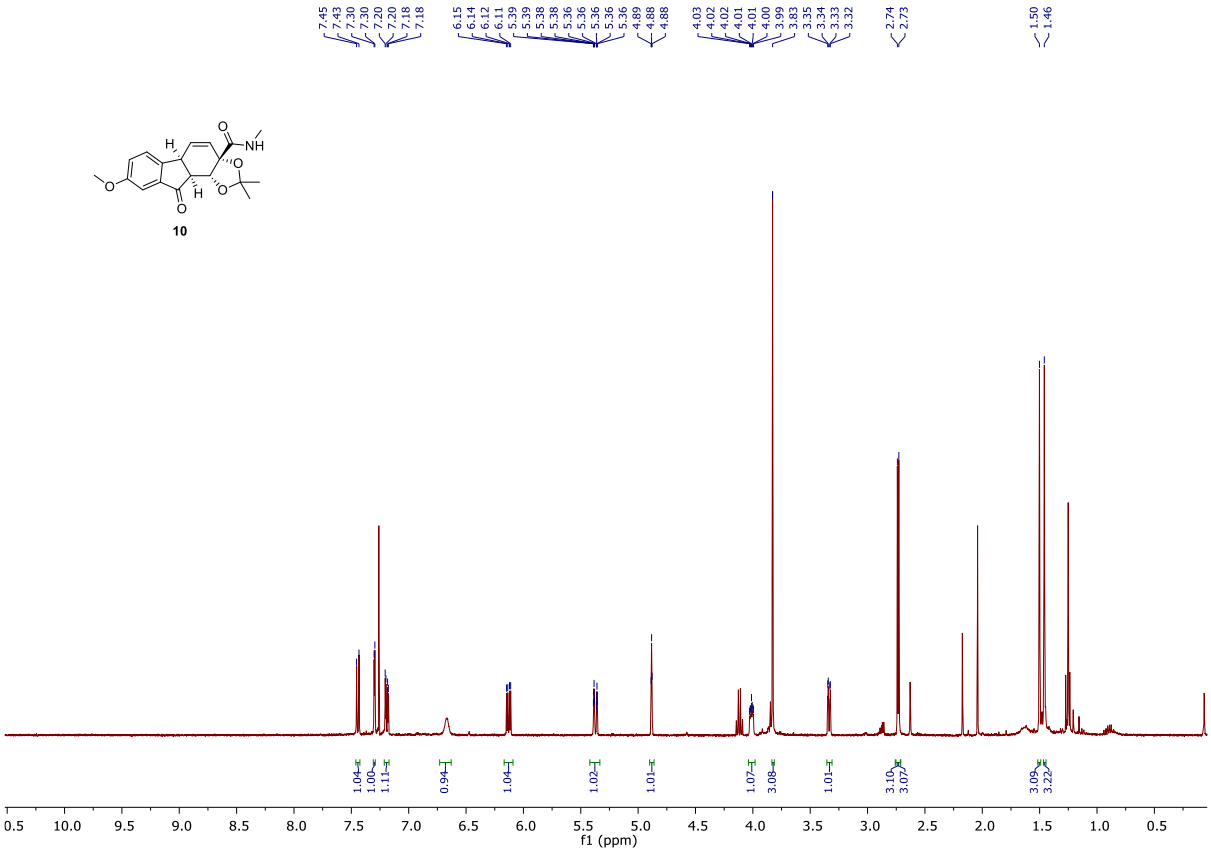



**Figure S9.** $^{1}$H NMR (400 MHz) spectrum of **10** in $CDCl_3$.

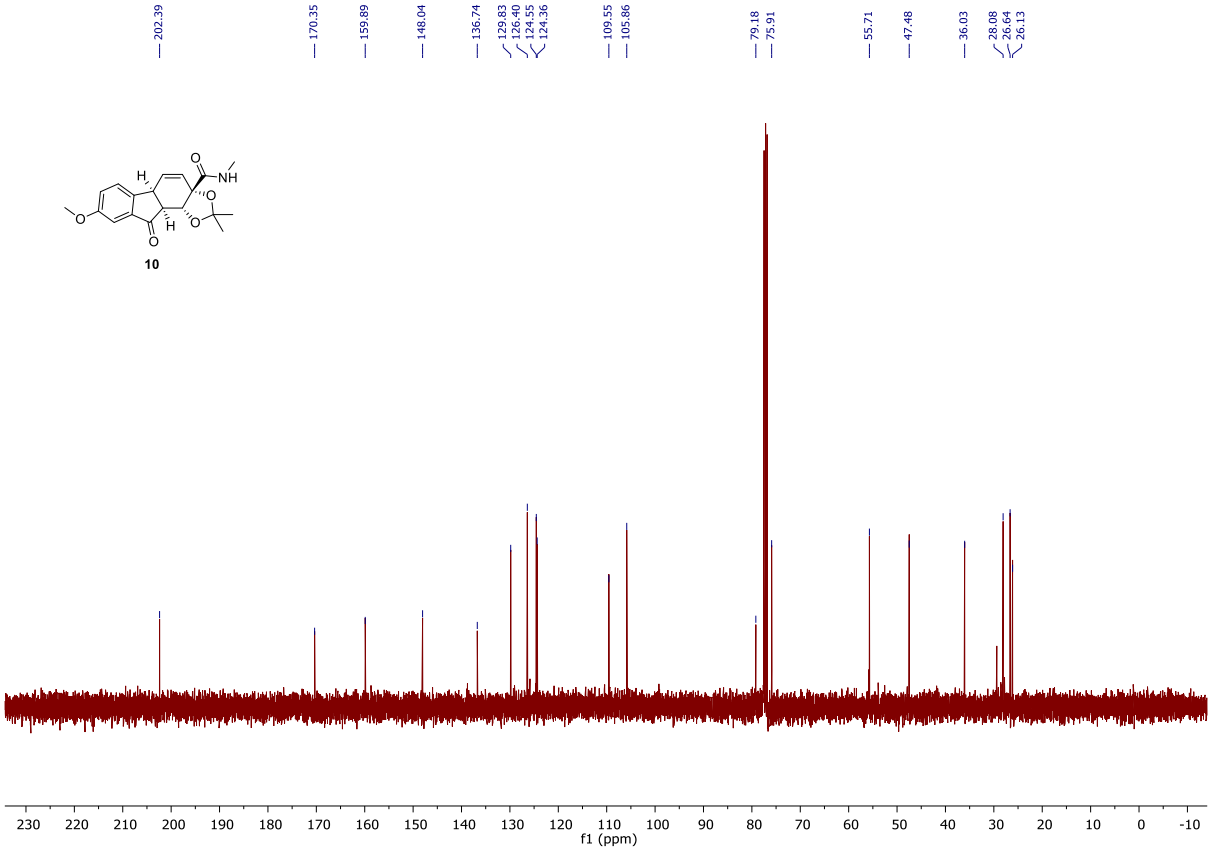



**Figure S10.** $^{13}$C NMR (101 MHz) spectrum of **10** in $CDCl_3$.

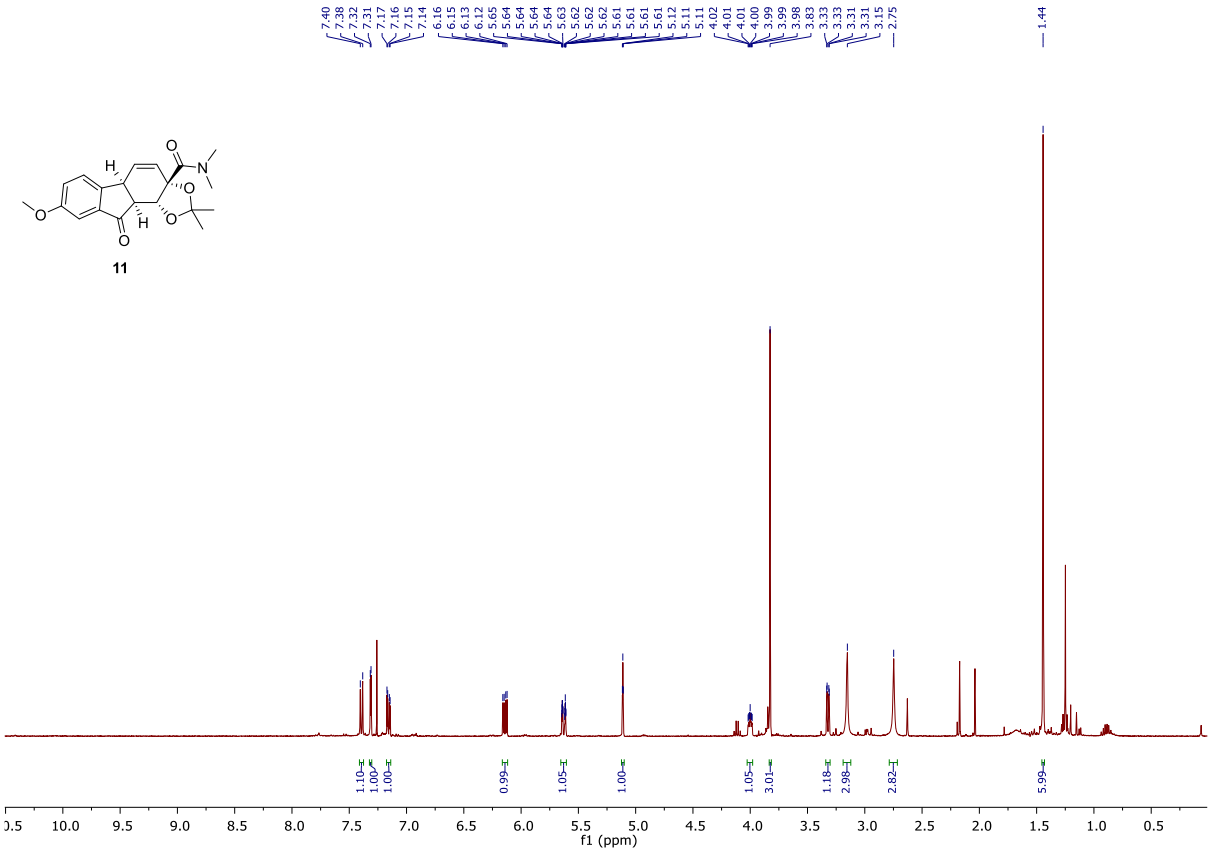



**Figure S11.** $^{1}$H NMR (400 MHz) spectrum of **11** in $CDCl_3$.

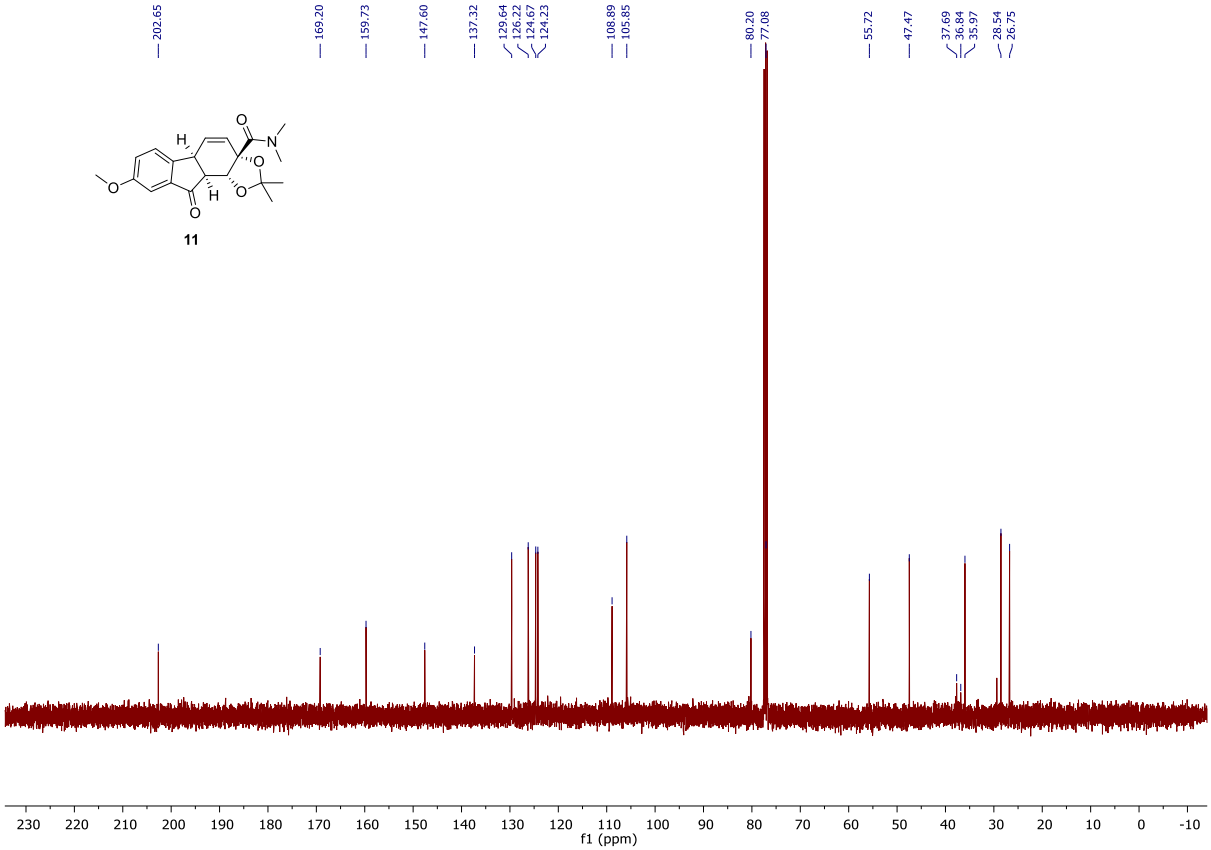



**Figure S12.** $^{13}$C NMR (101 MHz) spectrum of **11** in $CDCl_3$.

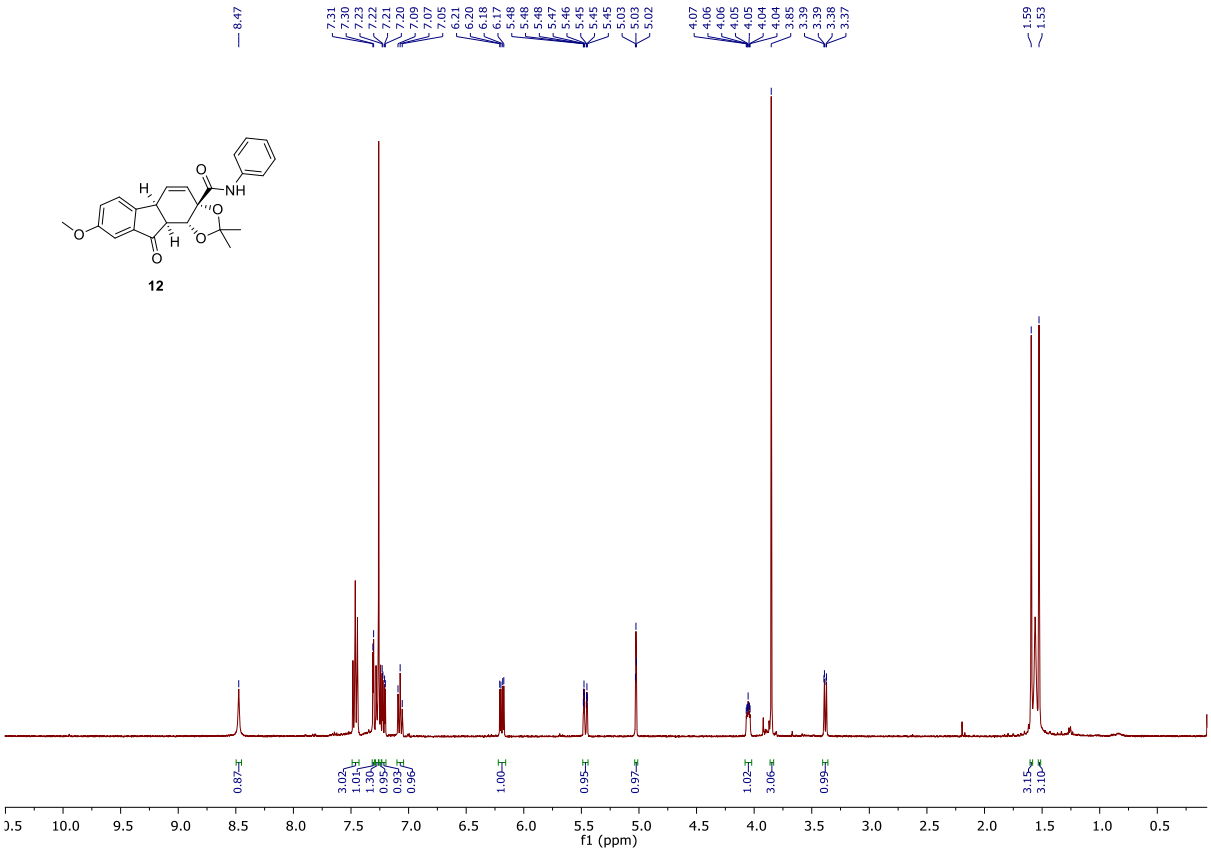



**Figure S13.** $^{1}$H NMR (400 MHz) spectrum of **12** in $CDCl_3$.

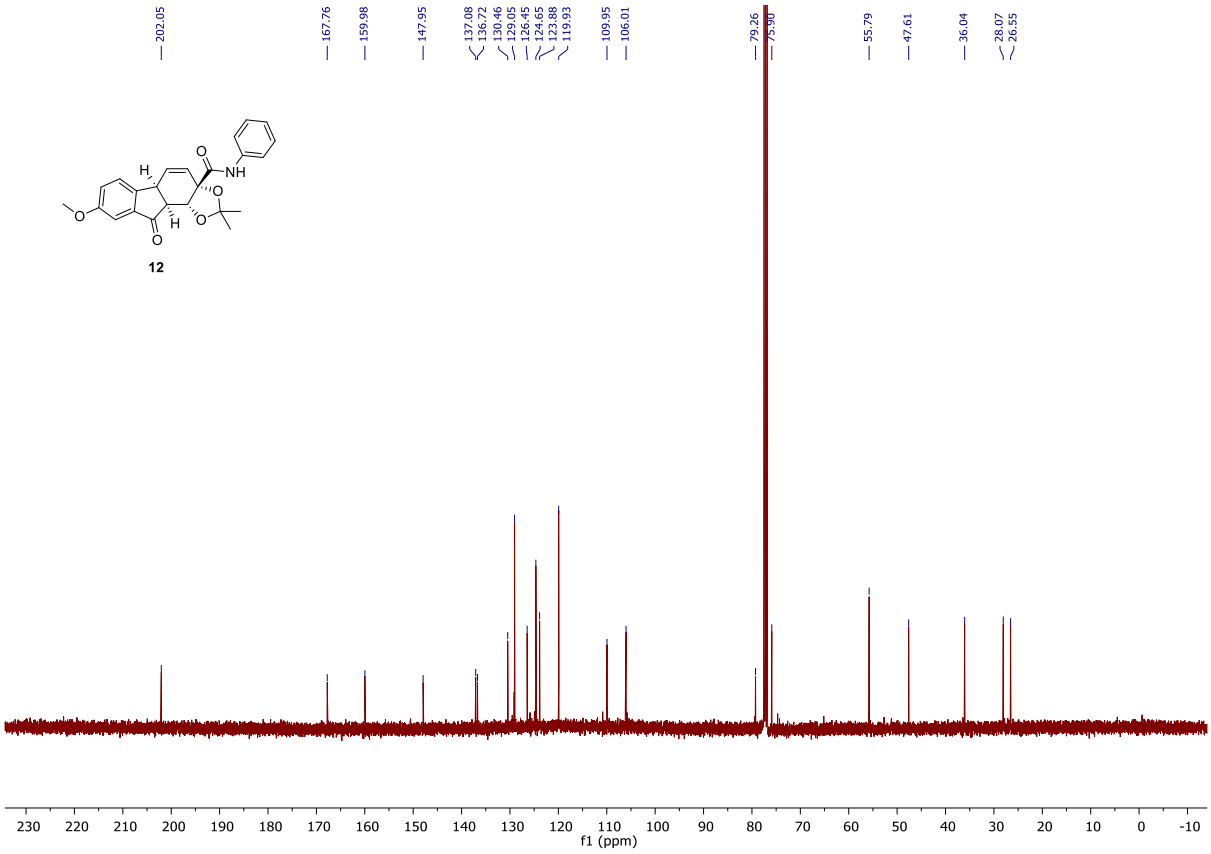



**Figure S14.** $^{13}$C NMR (101 MHz) spectrum of **12** in $CDCl_3$.

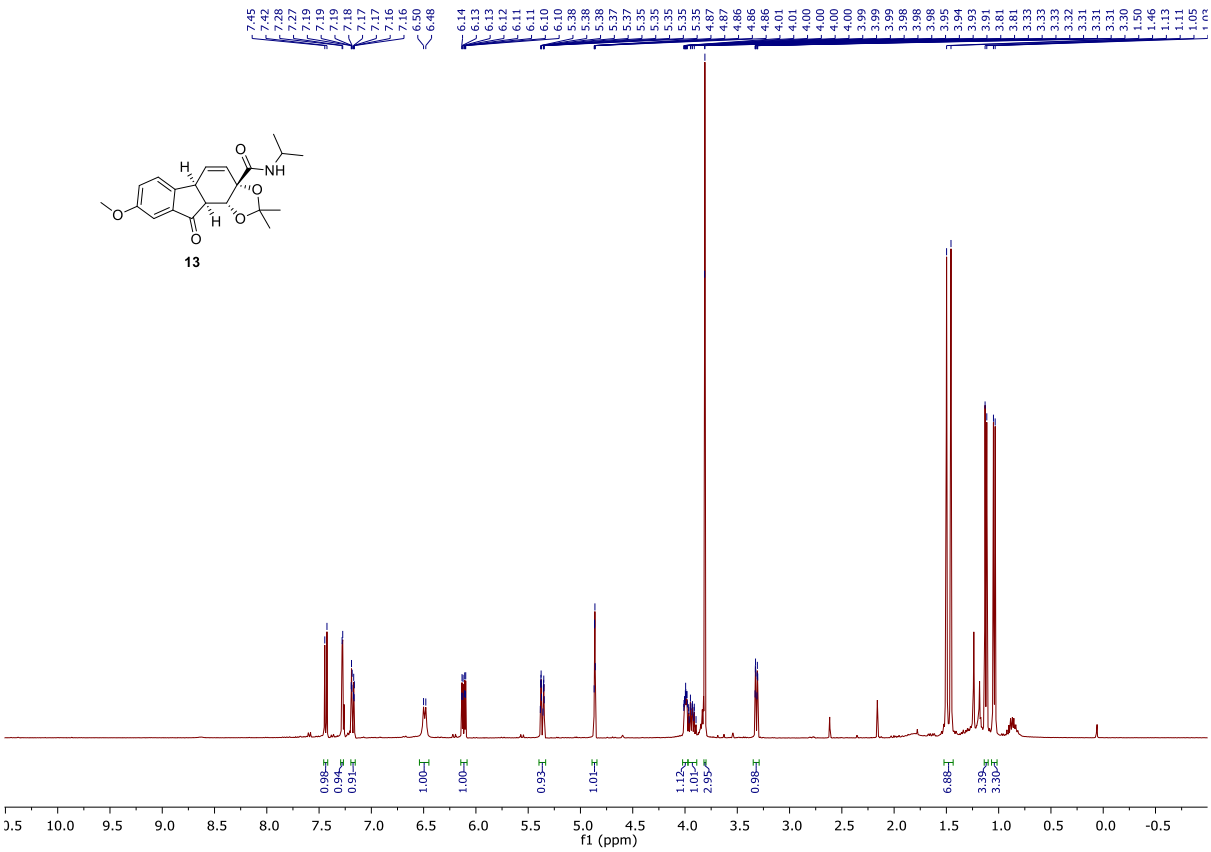



**Figure S15.** $^{1}$H NMR (400 MHz) spectrum of **13** in $CDCl_3$.

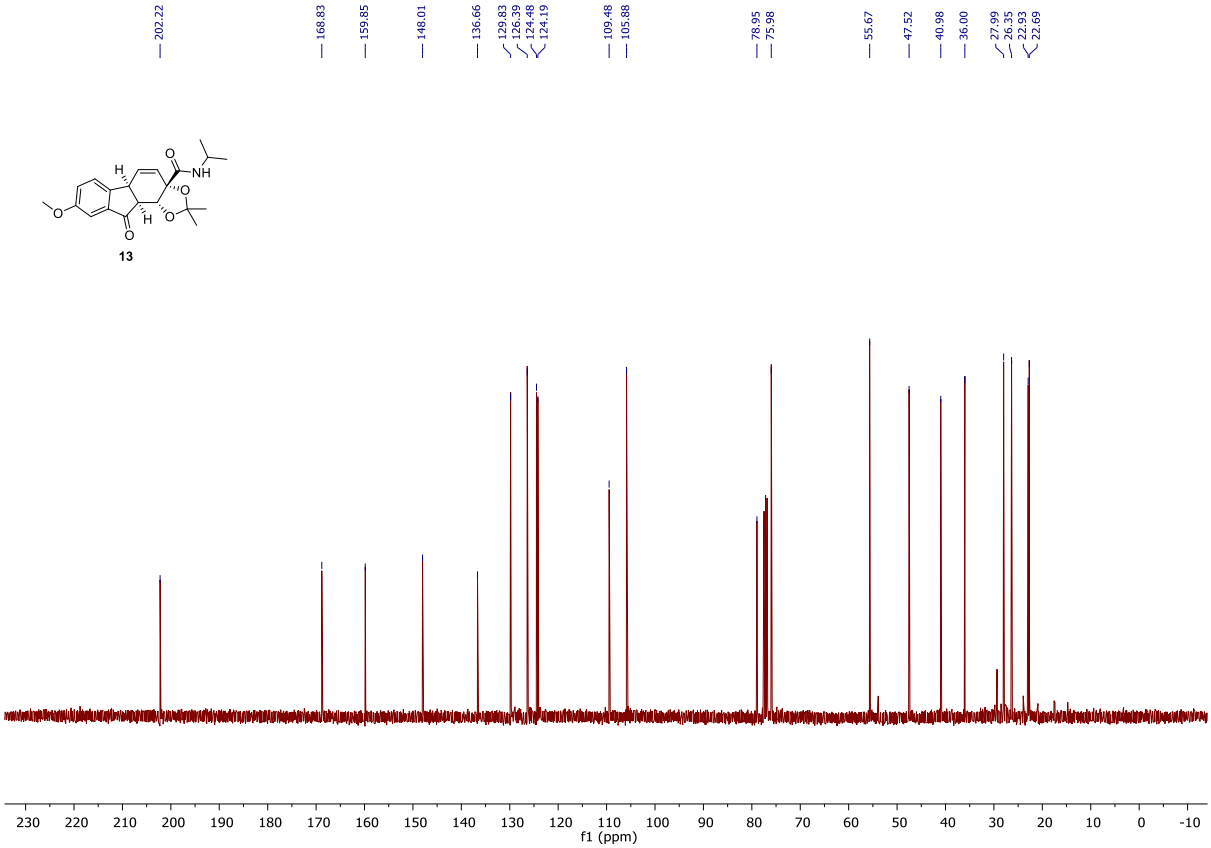



**Figure S16.** $^{13}$C NMR (101 MHz) spectrum of **13** in $CDCl_3$.

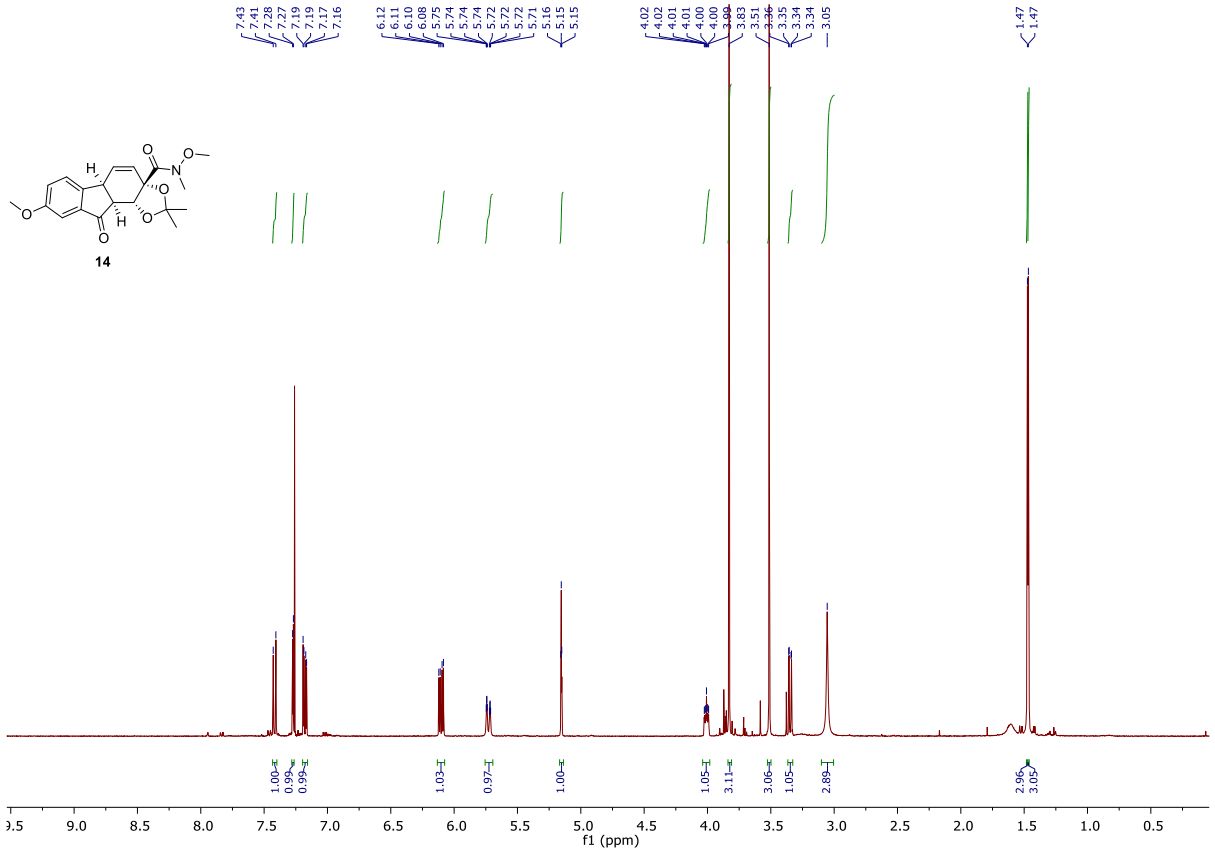



**Figure S17.** $^{1}$H NMR (400 MHz) spectrum of **14** in $CDCl_3$.

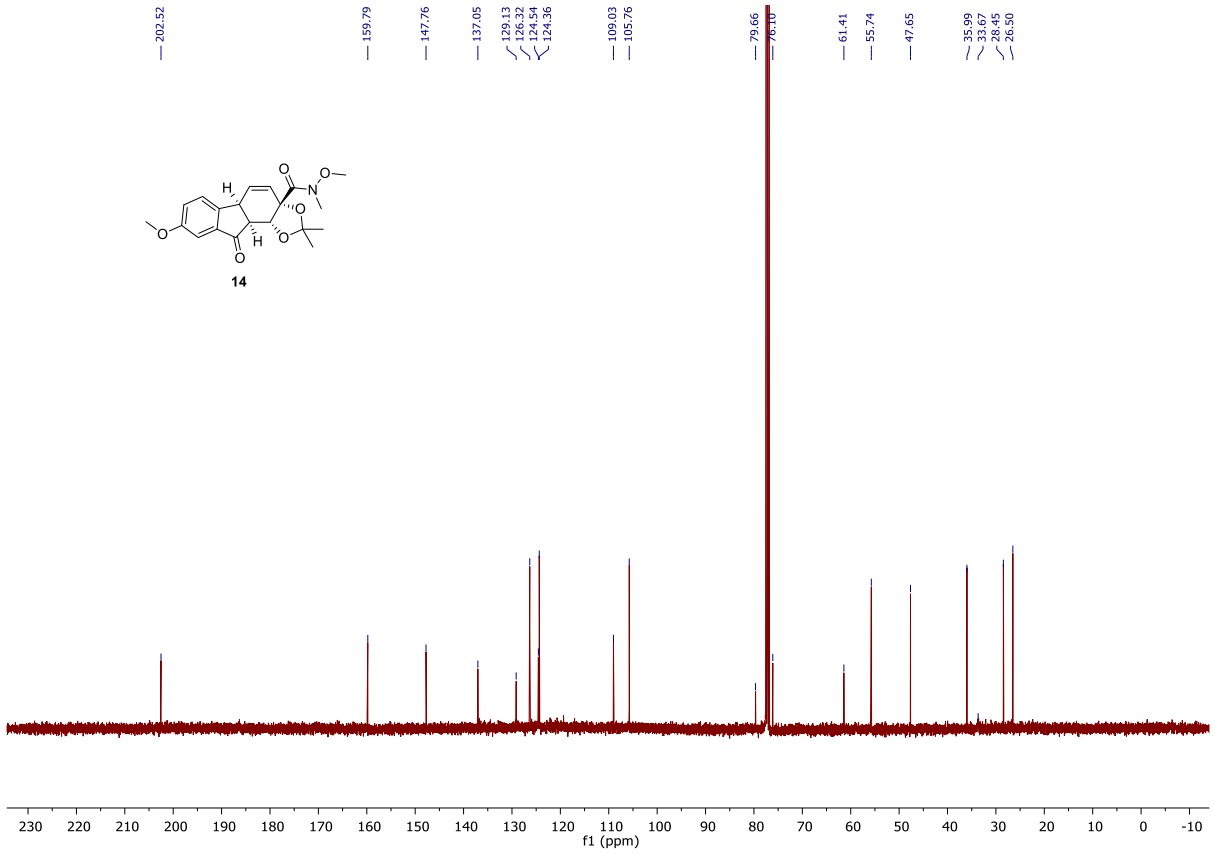



**Figure S18.** $^{13}$C NMR (101 MHz) spectrum of **14** in $CDCl_3$.

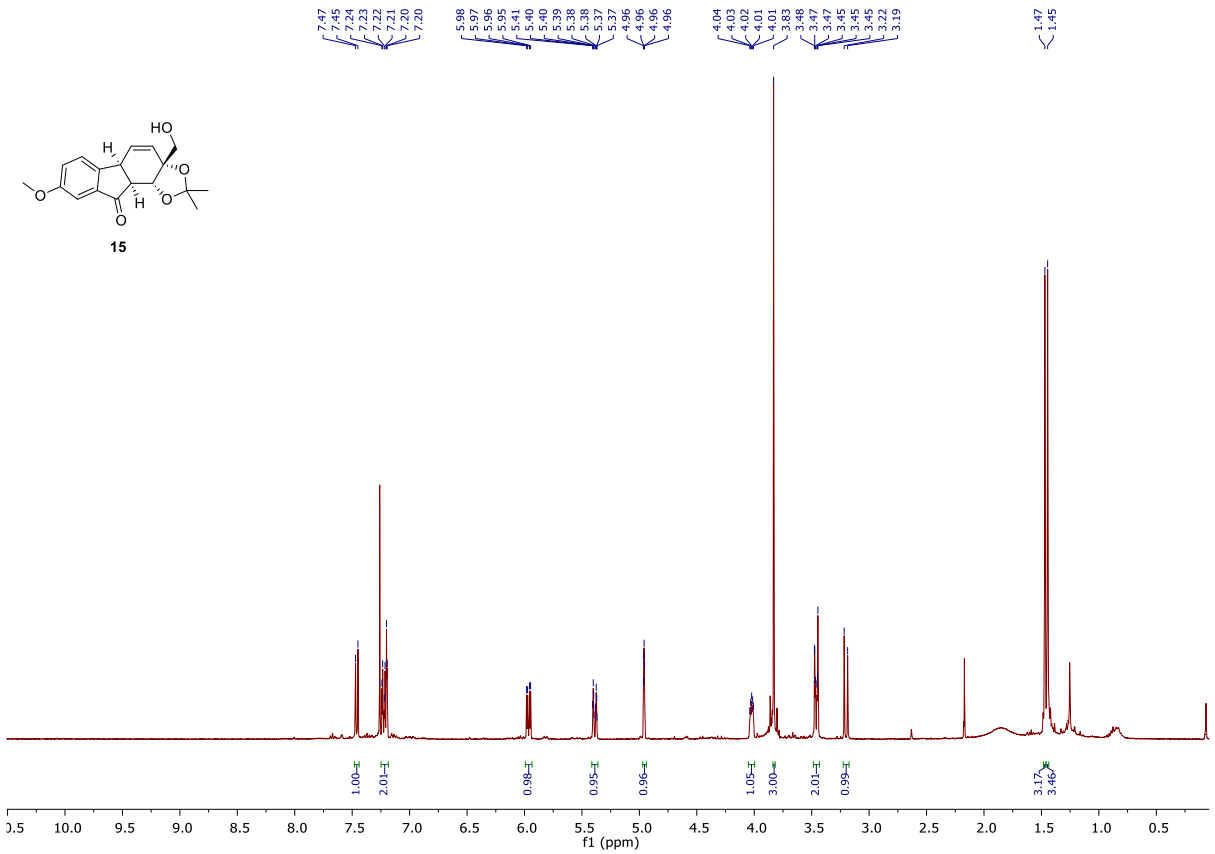



**Figure S19.** $^{1}$H NMR (400 MHz) spectrum of **15** in $CDCl_3$.

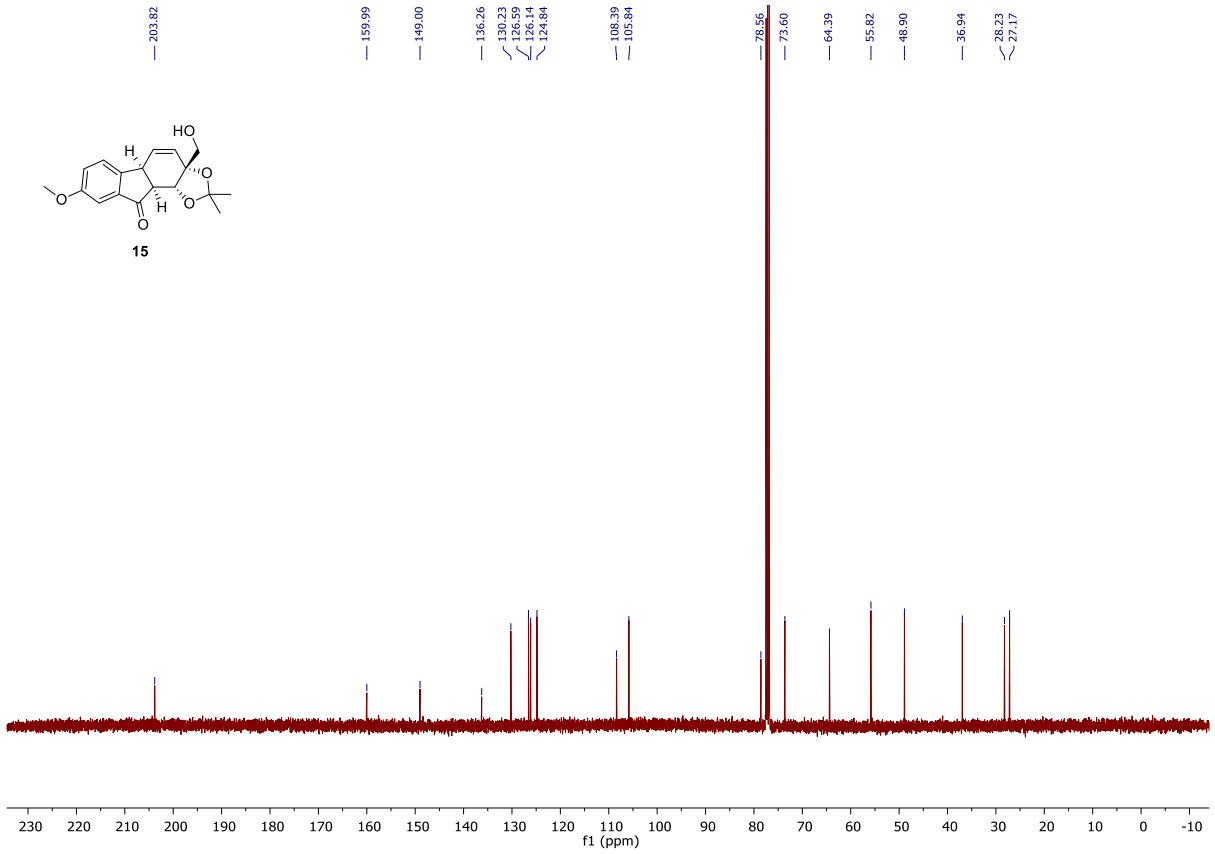



**Figure S20.** $^{13}$C NMR (101 MHz) spectrum of **15** in $CDCl_3$.

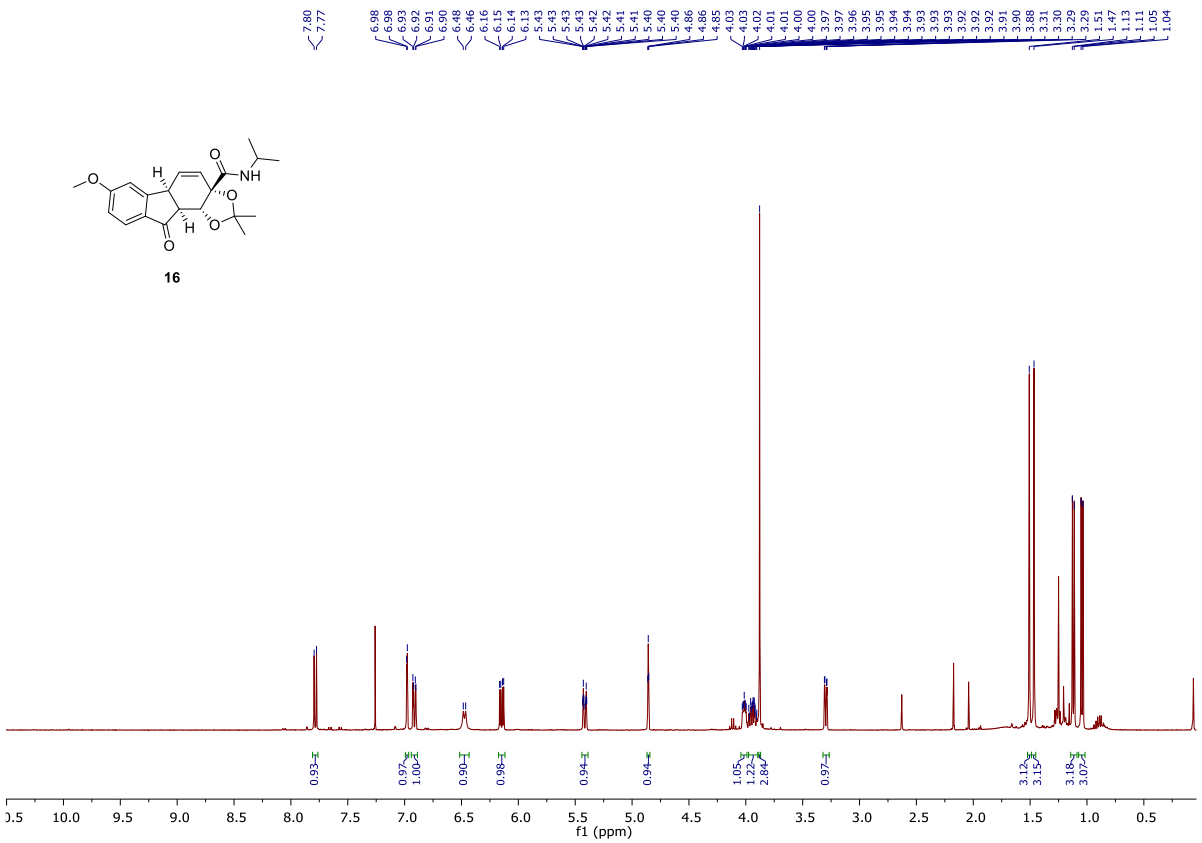



**Figure S21.** $^{1}$H NMR (400 MHz) spectrum of **16** in $CDCl_3$.

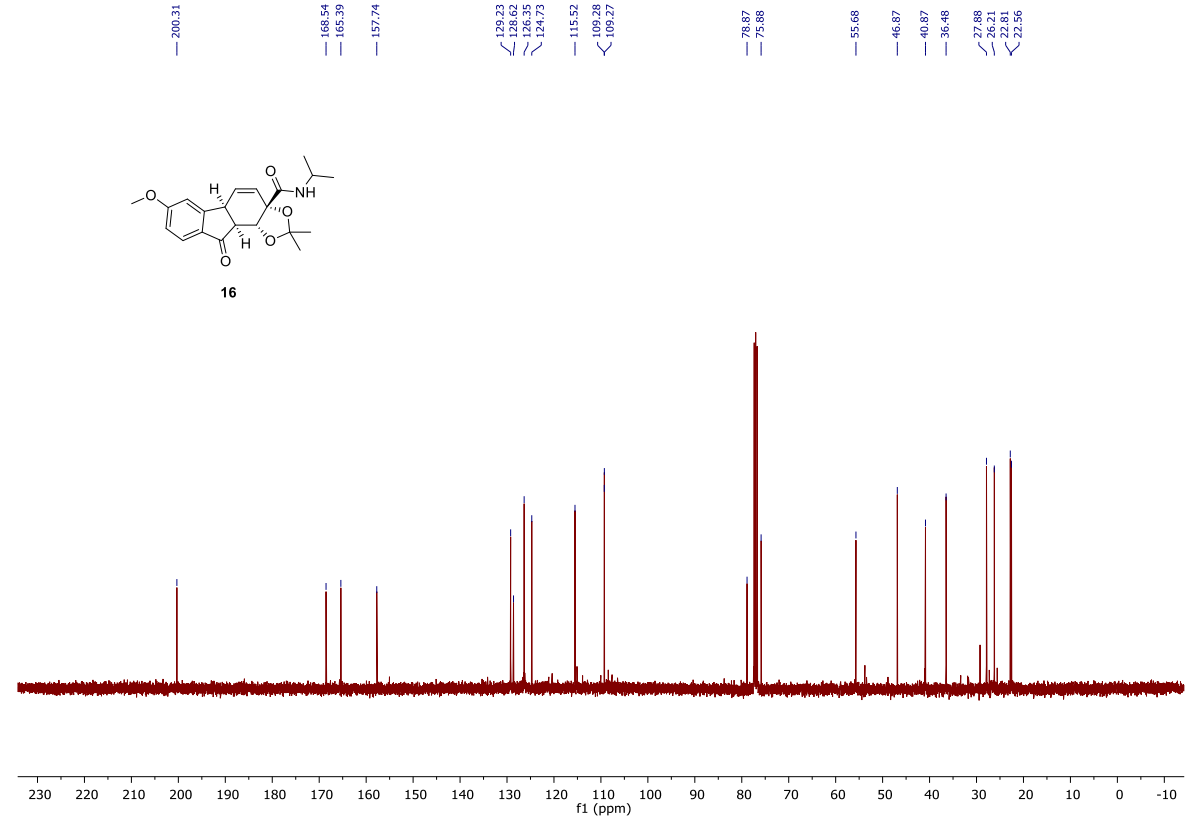



**Figure S22.** $^{13}$C NMR (101 MHz) spectrum of **16** in $CDCl_3$.

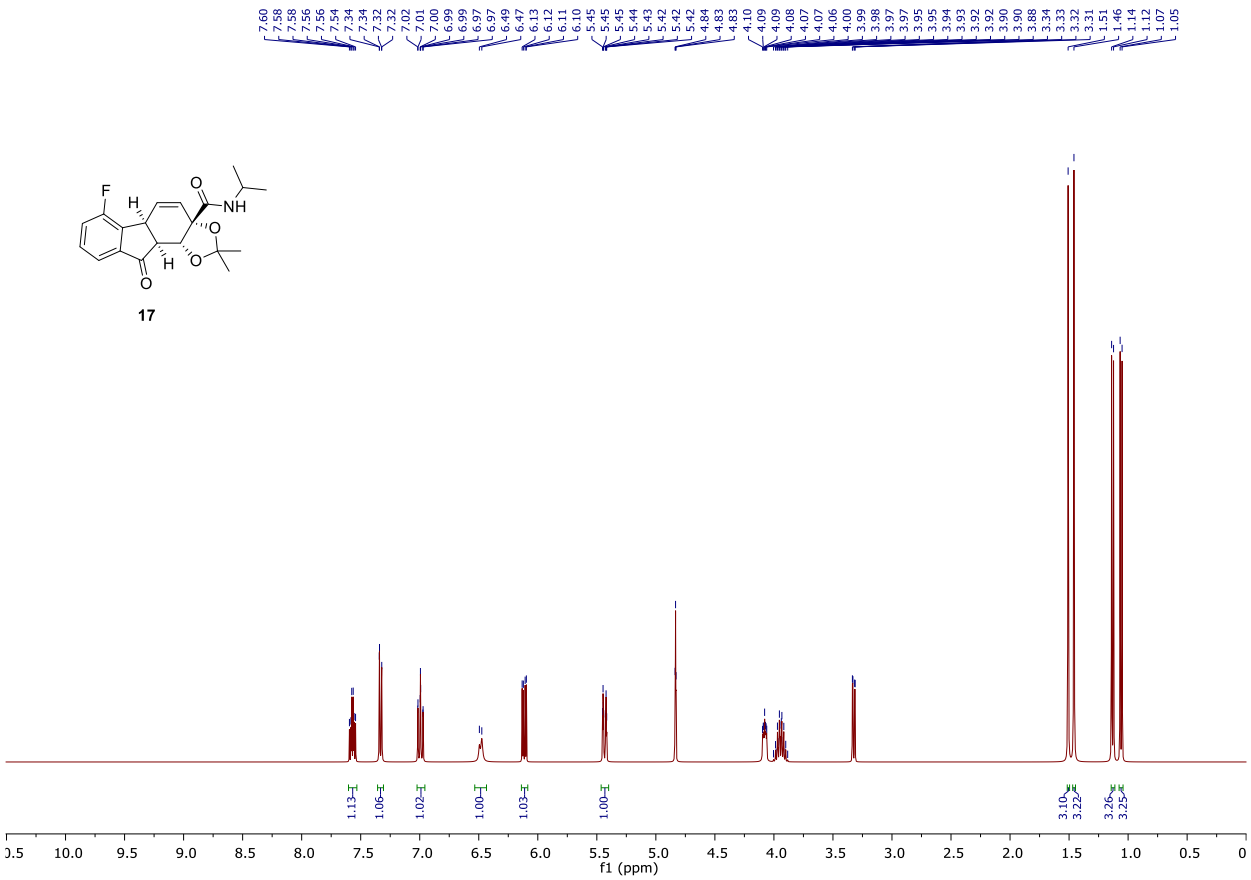



**Figure S23.** $^{1}$H NMR (400 MHz) spectrum of **17** in $CDCl_3$.

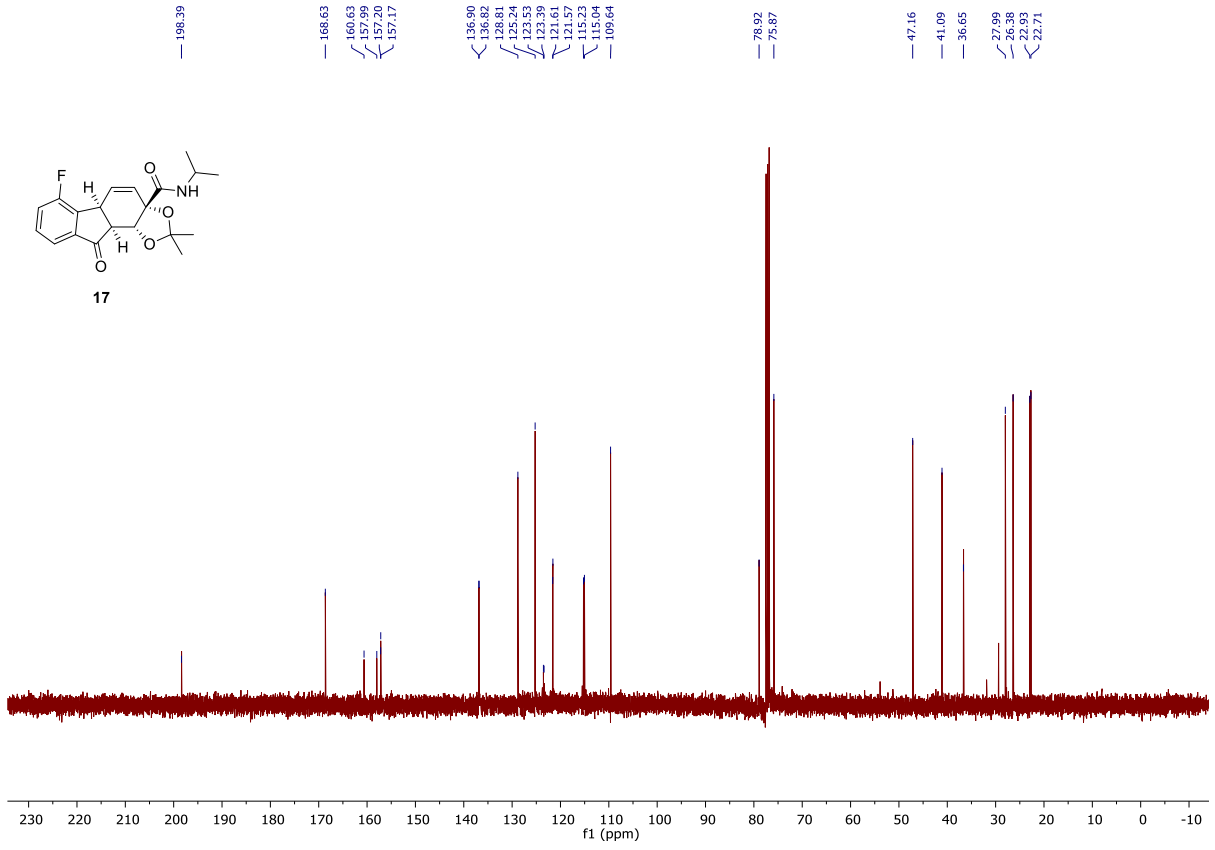



**Figure S24.** $^{13}$C NMR (101 MHz) spectrum of **17** in $CDCl_3$.

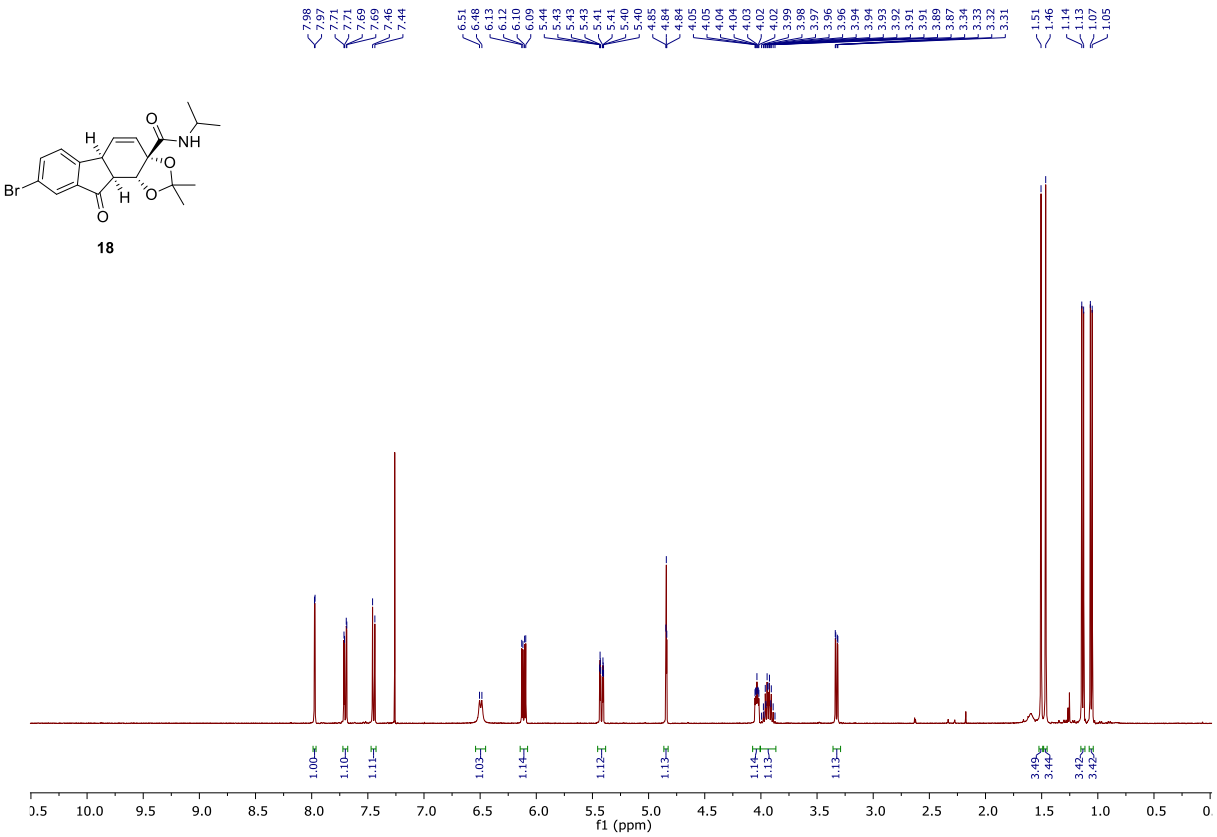



**Figure S25.** $^{1}$H NMR (400 MHz) spectrum of **18** in $CDCl_3$.

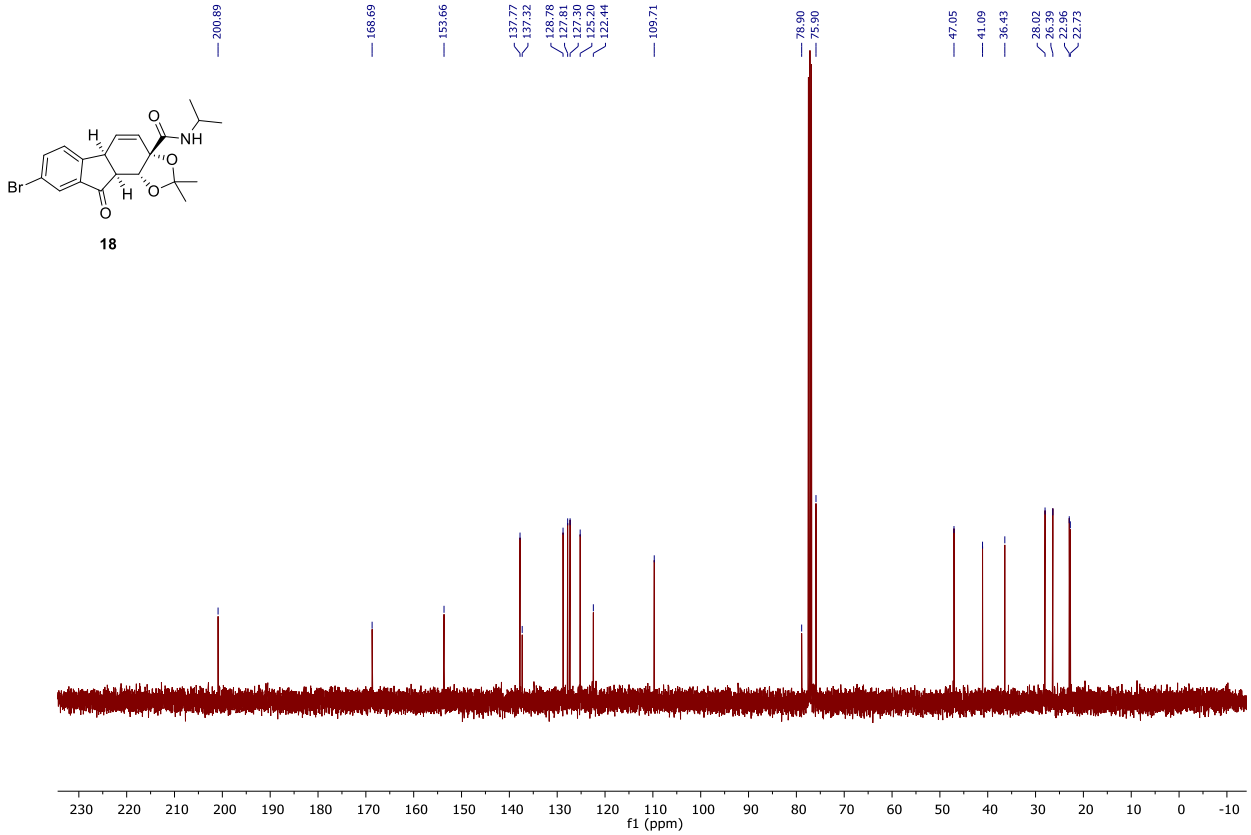



**Figure S26.** $^{13}$C NMR (101 MHz) spectrum of **18** in $CDCl_3$.

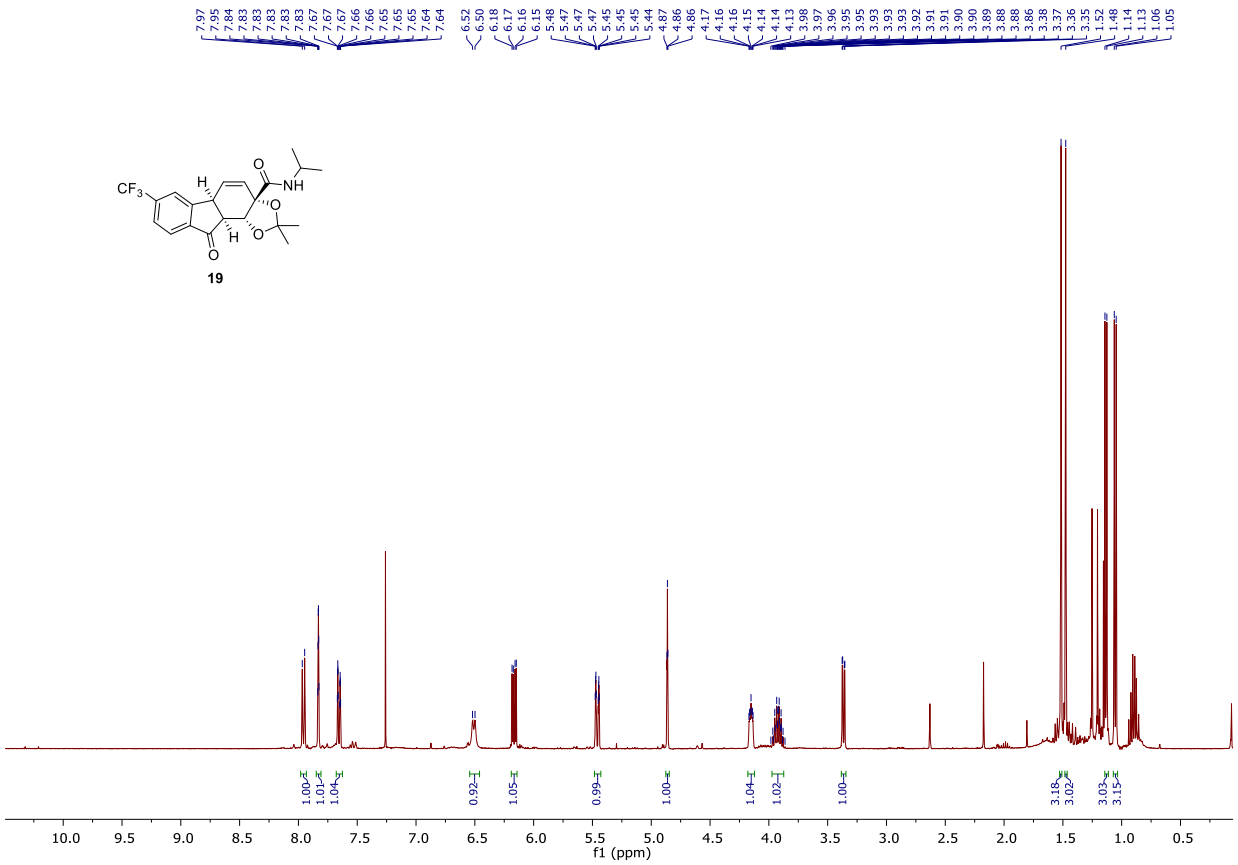



**Figure S27.** $^{1}$H NMR (400 MHz) spectrum of **19** in $CDCl_3$.

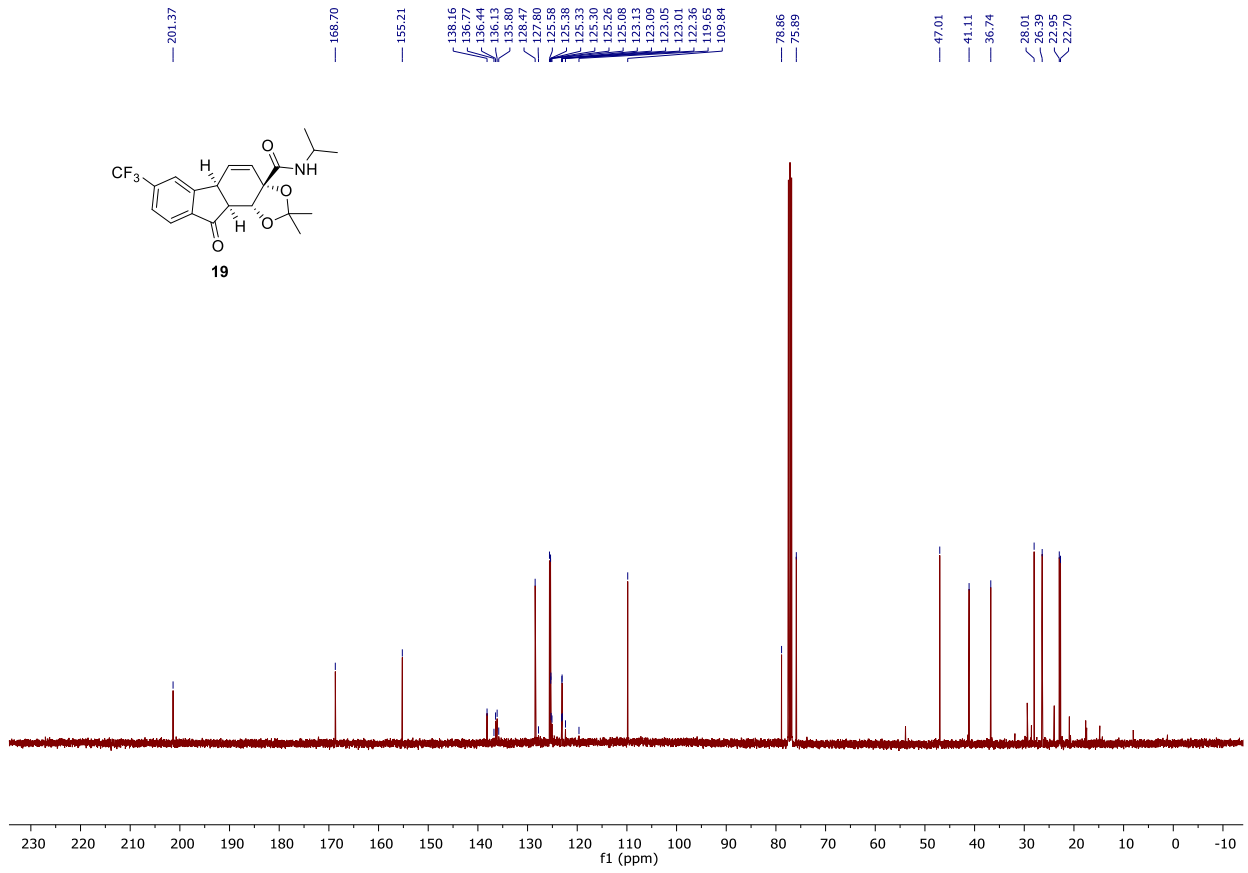



**Figure S28.** $^{13}$C NMR (101 MHz) spectrum of **19** in $CDCl_3$.

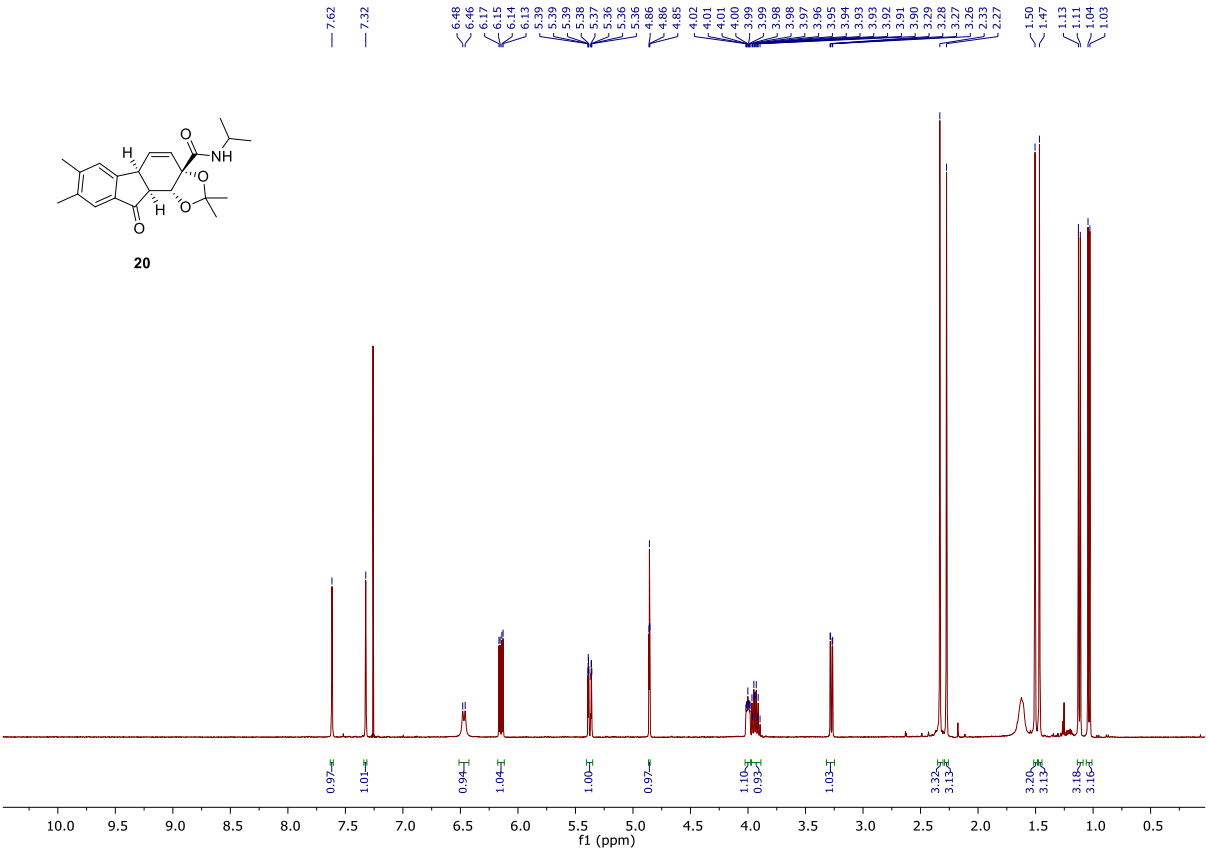



**Figure S29.** $^{1}$H NMR (400 MHz) spectrum of **20** in $CDCl_3$.

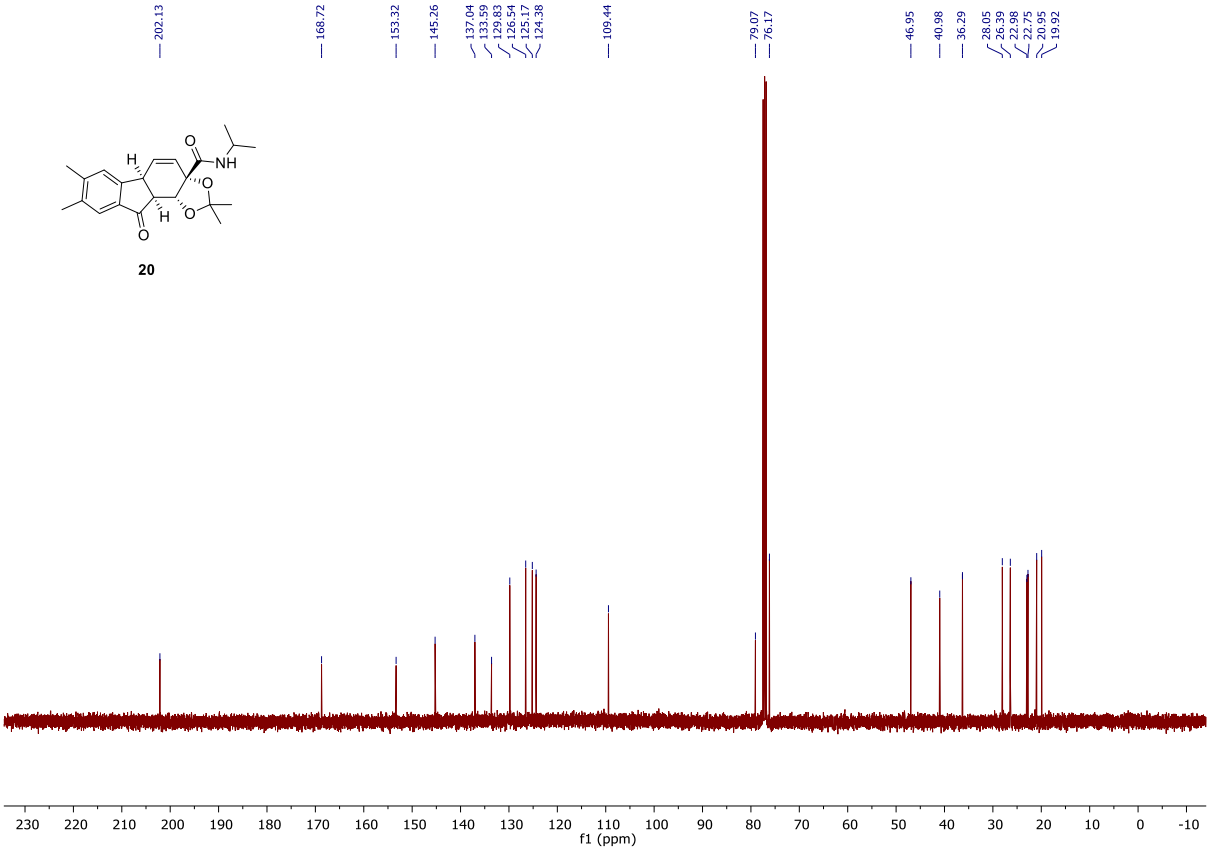



**Figure S30.** $^{13}$C NMR (101 MHz) spectrum of **20** in $CDCl_3$.

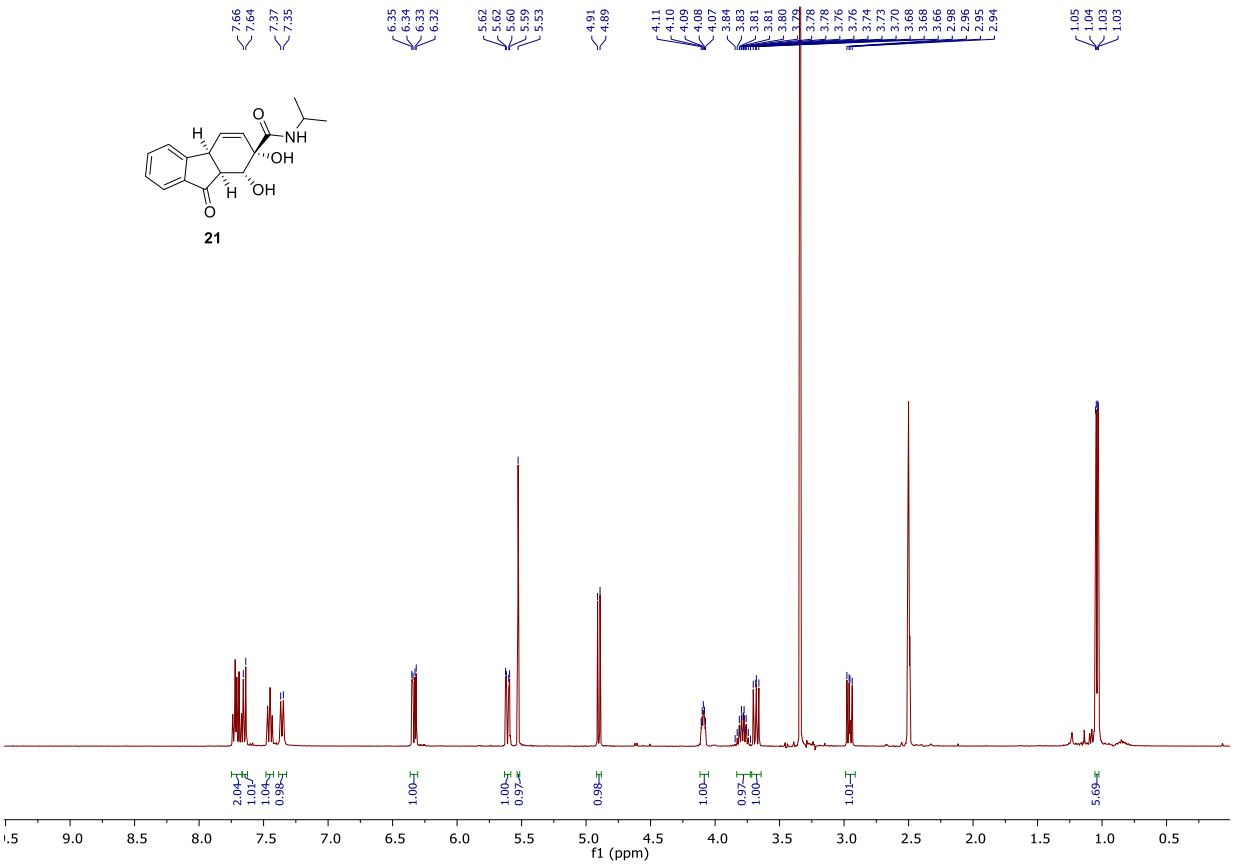



**Figure S31.** $^{1}$H NMR (400 MHz) spectrum of **21** in DMSO-$d_6$.

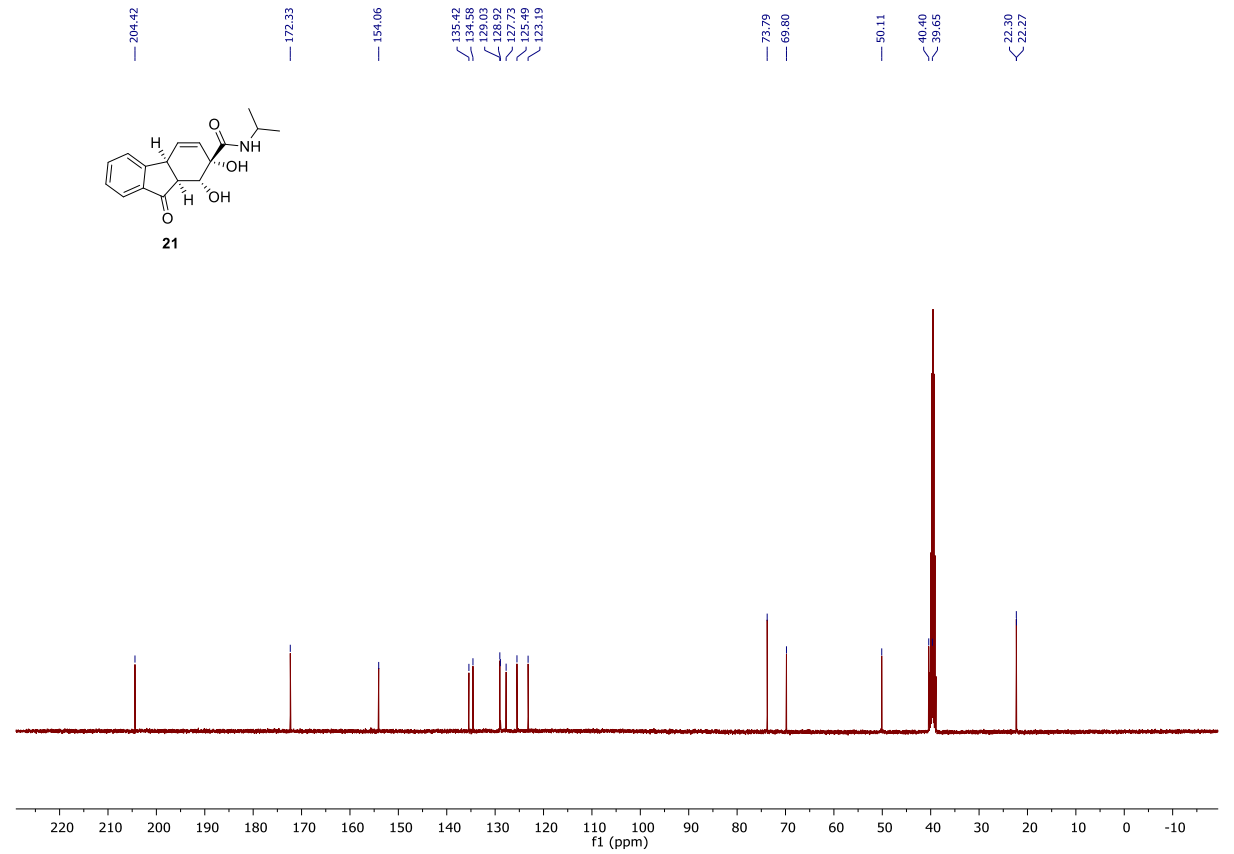



**Figure S32.** $^{13}$C NMR (101 MHz) spectrum of **21** in DMSO-$d_6$.

# CRYSTAL STRUCTURE DATA FOR COMPOUND 21

## X-ray Crystallography

Intensity data for compound **21** were collected at 150(2) K on a Rigaku SuperNova Dual EosS2 single crystal diffractometer using monochromated Cu-Kα radiation (λ = 1.54184 Å). Unit cell determination, data collection data reduction and absorption correction were performed using the CrysAlisPro software.[7] The structure was solved with SHELXT and refined by a full-matrix least-squares procedure based on F2 (SHELXL-2018/3).[8] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed onto calculated positions and refined using a riding model. OH-hydrogen atoms were located in the difference Fourier map and refined freely. Graphics were produced with ShelXle[9] and Ortep 3 for Windows[10].

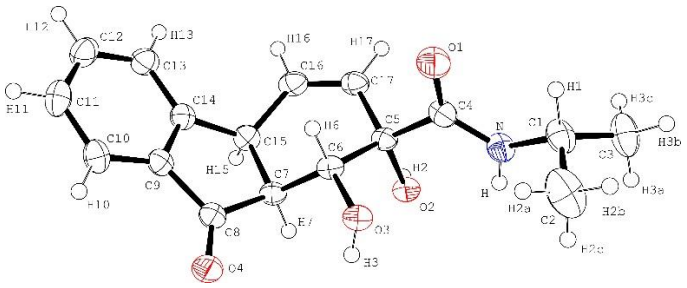



**Figure S33.** Solid state structure of **21**. Ellipsoids are represented at 50% probability. H atoms are shown as spheres of arbitrary radius. **CCDC 2043870**.

**Table S2.** Crystal data and structure refinement for **21**.

**CCDC 2043870**

| | |
|---|---|
| Identification code | s19sel15 |
| Empirical formula | C17 H19 N O4 |
| Formula weight | 301.33 |
| Temperature | 150.00(10) K |
| Wavelength | 1.54184 Å |
| Crystal system | Monoclinic |
| Space group | $P2_1$ |
| Unit cell dimensions | a = 11.0439(3) Å α= 90°. |
| | b = 5.6164(2) Å β= 97.184(2)°. |
| | c = 12.2401(3) Å γ = 90°. |
| Volume | 753.26(4) $Å^3$ |
| Z | 2 |
| Density (calculated) | 1.329 $Mg/m^3$ |
| Absorption coefficient | 0.778 $mm^{-1}$ |
| F(000) | 320 |
| Crystal size | 0.290 x 0.030 x 0.030 $mm^3$ |
| Theta range for data collection | 3.640 to 73.184°. |
| Index ranges | -13<=h<=13, -5<=k<=6, -15<=l<=15 |
| Reflections collected | 14636 |
| Independent reflections | 2749 [R(int) = 0.0415] |
| Completeness to theta = 67.684° | 100.0 % |
| Absorption correction | Gaussian |
| Max. and min. transmission | 1.000 and 0.722 |
| Refinement method | Full-matrix least-squares on F2 |
| Data / restraints / parameters | 2749 / 1 / 212 |
| Goodness-of-fit on F2 | 1.046 |
| Final R indices [I>2sigma(I)] | R1 = 0.0334, wR2 = 0.0835 |
| R indices (all data) | R1 = 0.0360, wR2 = 0.0851 |
| Absolute structure parameter | -0.06(15) |
| Extinction coefficient | n/a |
| Largest diff. peak and hole | 0.201 and -0.151 $e.Å^{-3}$ |

**Table S3.** Atomic coordinates (x104) and equivalent isotropic displacement parameters ($Å^2$x103) for **21**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| N | 1879(2) | 3967(4) | 7494(2) | 32(1) |
| O(1) | 3636(2) | 5358(5) | 6957(2) | 50(1) |
| O(2) | 1237(1) | 1837(3) | 5576(1) | 26(1) |
| O(3) | 1221(1) | 7027(3) | 5201(1) | 28(1) |
| O(4) | 784(2) | 8013(4) | 2705(1) | 39(1) |
| C(1) | 1988(2) | 5184(5) | 8557(2) | 38(1) |
| C(2) | 1138(4) | 7306(7) | 8503(3) | 63(1) |
| C(3) | 1734(3) | 3469(6) | 9453(2) | 50(1) |
| C(4) | 2666(2) | 4286(5) | 6771(2) | 31(1) |
| C(5) | 2320(2) | 3265(5) | 5616(2) | 26(1) |
| C(6) | 2081(2) | 5416(5) | 4834(2) | 25(1) |
| C(7) | 1713(2) | 4523(4) | 3659(2) | 26(1) |
| C(8) | 1611(2) | 6573(5) | 2843(2) | 28(1) |
| C(9) | 2706(2) | 6528(5) | 2261(2) | 28(1) |
| C(10) | 3073(2) | 8195(5) | 1527(2) | 34(1) |
| C(11) | 4189(2) | 7832(6) | 1141(2) | 40(1) |
| C(12) | 4882(2) | 5836(6) | 1468(2) | 40(1) |
| C(13) | 4491(2) | 4132(6) | 2156(2) | 35(1) |
| C(14) | 3376(2) | 4500(5) | 2558(2) | 28(1) |
| C(15) | 2728(2) | 2897(5) | 3299(2) | 29(1) |
| C(16) | 3548(2) | 1731(5) | 4219(2) | 32(1) |
| C(17) | 3372(2) | 1845(5) | 5265(2) | 31(1) |

**Table S4.** Bond lengths [Å] for **21**.

| | |
|---|---|
| N-C(4) | 1.328(3) |
| N-C(1) | 1.461(3) |
| N-H | 0.86(3) |
| O(1)-C(4) | 1.225(3) |
| O(2)-C(5) | 1.436(3) |
| O(2)-H(2) | 0.88(5) |
| O(3)-C(6) | 1.424(3) |
| O(3)-H(3) | 0.80(3) |
| O(4)-C(8) | 1.215(3) |
| C(1)-C(3) | 1.512(4) |
| C(1)-C(2) | 1.513(5) |
| C(1)-H(1) | 1.0000 |
| C(2)-H(2A) | 0.9800 |
| C(2)-H(2B) | 0.9800 |
| C(2)-H(2C) | 0.9800 |
| C(3)-H(3A) | 0.9800 |
| C(3)-H(3B) | 0.9800 |
| C(3)-H(3C) | 0.9800 |
| C(4)-C(5) | 1.529(3) |
| C(5)-C(17) | 1.515(3) |
| C(5)-C(6) | 1.543(3) |
| C(6)-C(7) | 1.530(3) |
| C(6)-H(6) | 1.0000 |
| C(7)-C(8) | 1.519(3) |
| C(7)-C(15) | 1.552(3) |
| C(7)-H(7) | 1.0000 |
| C(8)-C(9) | 1.479(3) |
| C(9)-C(14) | 1.382(4) |
| C(9)-C(10) | 1.393(3) |
| C(10)-C(11) | 1.388(3) |
| C(10)-H(10) | 0.9500 |
| C(11)-C(12) | 1.388(4) |
| C(11)-H(11) | 0.9500 |
| C(12)-C(13) | 1.380(4) |
| C(12)-H(12) | 0.9500 |
| C(13)-C(14) | 1.397(3) |

| | |
|---|---|
| C(13)-H(13) | 0.9500 |
| C(14)-C(15) | 1.520(3) |
| C(15)-C(16) | 1.504(3) |
| C(15)-H(15) | 1.0000 |
| C(16)-C(17) | 1.320(3) |
| C(16)-H(16) | 0.9500 |
| C(17)-H(17) | 0.9500 |

**Table S5.** Bond angles [°] for **21**.

| | |
|---|---|
| C(4)-N-C(1) | 122.9(2) |
| C(4)-N-H | 115.8(19) |
| C(1)-N-H | 119.8(19) |
| C(5)-O(2)-H(2) | 111(2) |
| C(6)-O(3)-H(3) | 108(3) |
| N-C(1)-C(3) | 110.3(2) |
| N-C(1)-C(2) | 110.4(2) |
| C(3)-C(1)-C(2) | 111.3(3) |
| N-C(1)-H(1) | 108.3 |
| C(3)-C(1)-H(1) | 108.3 |
| C(2)-C(1)-H(1) | 108.3 |
| C(1)-C(2)-H(2A) | 109.5 |
| C(1)-C(2)-H(2B) | 109.5 |
| H(2A)-C(2)-H(2B) | 109.5 |
| C(1)-C(2)-H(2C) | 109.5 |
| H(2A)-C(2)-H(2C) | 109.5 |
| H(2B)-C(2)-H(2C) | 109.5 |
| C(1)-C(3)-H(3A) | 109.5 |
| C(1)-C(3)-H(3B) | 109.5 |
| H(3A)-C(3)-H(3B) | 109.5 |
| C(1)-C(3)-H(3C) | 109.5 |
| H(3A)-C(3)-H(3C) | 109.5 |
| H(3B)-C(3)-H(3C) | 109.5 |
| O(1)-C(4)-N | 124.9(2) |
| O(1)-C(4)-C(5) | 117.9(2) |
| N-C(4)-C(5) | 117.16(19) |
| O(2)-C(5)-C(17) | 111.2(2) |
| O(2)-C(5)-C(4) | 110.62(17) |
| C(17)-C(5)-C(4) | 110.32(18) |
| O(2)-C(5)-C(6) | 109.81(17) |
| C(17)-C(5)-C(6) | 108.29(17) |
| C(4)-C(5)-C(6) | 106.4(2) |
| O(3)-C(6)-C(7) | 113.27(17) |
| O(3)-C(6)-C(5) | 111.80(17) |
| C(7)-C(6)-C(5) | 109.3(2) |
| O(3)-C(6)-H(6) | 107.4 |
| C(7)-C(6)-H(6) | 107.4 |

| | |
|---|---|
| C(5)-C(6)-H(6) | 107.4 |
| C(8)-C(7)-C(6) | 111.1(2) |
| C(8)-C(7)-C(15) | 104.89(17) |
| C(6)-C(7)-C(15) | 110.07(17) |
| C(8)-C(7)-H(7) | 110.2 |
| C(6)-C(7)-H(7) | 110.2 |
| C(15)-C(7)-H(7) | 110.2 |
| O(4)-C(8)-C(9) | 126.2(2) |
| O(4)-C(8)-C(7) | 126.0(2) |
| C(9)-C(8)-C(7) | 107.78(19) |
| C(14)-C(9)-C(10) | 122.3(2) |
| C(14)-C(9)-C(8) | 109.3(2) |
| C(10)-C(9)-C(8) | 128.4(2) |
| C(11)-C(10)-C(9) | 117.6(3) |
| C(11)-C(10)-H(10) | 121.2 |
| C(9)-C(10)-H(10) | 121.2 |
| C(12)-C(11)-C(10) | 120.1(3) |
| C(12)-C(11)-H(11) | 119.9 |
| C(10)-C(11)-H(11) | 119.9 |
| C(13)-C(12)-C(11) | 122.2(2) |
| C(13)-C(12)-H(12) | 118.9 |
| C(11)-C(12)-H(12) | 118.9 |
| C(12)-C(13)-C(14) | 118.0(3) |
| C(12)-C(13)-H(13) | 121.0 |
| C(14)-C(13)-H(13) | 121.0 |
| C(9)-C(14)-C(13) | 119.8(2) |
| C(9)-C(14)-C(15) | 111.61(19) |
| C(13)-C(14)-C(15) | 128.6(2) |
| C(16)-C(15)-C(14) | 114.87(19) |
| C(16)-C(15)-C(7) | 115.63(18) |
| C(14)-C(15)-C(7) | 103.4(2) |
| C(16)-C(15)-H(15) | 107.5 |
| C(14)-C(15)-H(15) | 107.5 |
| C(7)-C(15)-H(15) | 107.5 |
| C(17)-C(16)-C(15) | 123.9(2) |
| C(17)-C(16)-H(16) | 118.1 |
| C(15)-C(16)-H(16) | 118.1 |
| C(16)-C(17)-C(5) | 120.8(2) |
| C(16)-C(17)-H(17) | 119.6 |

| | |
|---|---|
| C(5)-C(17)-H(17) | 119.6 |

**Table S6.** Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **21**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| N | 34(1) | 31(1) | 30(1) | -3(1) | -1(1) | -11(1) |
| O(1) | 38(1) | 68(2) | 42(1) | -3(1) | -3(1) | -24(1) |
| O(2) | 25(1) | 19(1) | 34(1) | -2(1) | 3(1) | -3(1) |
| O(3) | 26(1) | 21(1) | 34(1) | -3(1) | 1(1) | 1(1) |
| O(4) | 35(1) | 38(1) | 45(1) | 13(1) | 7(1) | 14(1) |
| C(1) | 46(1) | 36(2) | 30(1) | -4(1) | -2(1) | -12(1) |
| C(2) | 100(3) | 38(2) | 49(2) | -11(2) | -5(2) | 5(2) |
| C(3) | 78(2) | 40(2) | 30(1) | -4(1) | 5(1) | -13(2) |
| C(4) | 31(1) | 27(1) | 32(1) | 6(1) | -2(1) | -6(1) |
| C(5) | 23(1) | 24(1) | 30(1) | 2(1) | 1(1) | -3(1) |
| C(6) | 23(1) | 21(1) | 32(1) | 0(1) | 3(1) | 0(1) |
| C(7) | 23(1) | 23(1) | 31(1) | -1(1) | 2(1) | 1(1) |
| C(8) | 28(1) | 27(1) | 28(1) | -1(1) | 1(1) | 2(1) |
| C(9) | 31(1) | 27(1) | 24(1) | -4(1) | 1(1) | 2(1) |
| C(10) | 47(1) | 28(1) | 26(1) | -2(1) | 5(1) | 1(1) |
| C(11) | 51(1) | 40(2) | 30(1) | -3(1) | 13(1) | -6(1) |
| C(12) | 34(1) | 55(2) | 32(1) | -7(1) | 10(1) | -1(1) |
| C(13) | 32(1) | 40(2) | 33(1) | -4(1) | 4(1) | 7(1) |
| C(14) | 30(1) | 28(1) | 24(1) | -5(1) | 2(1) | 0(1) |
| C(15) | 31(1) | 24(1) | 30(1) | -2(1) | 4(1) | 4(1) |
| C(16) | 28(1) | 25(1) | 45(1) | 6(1) | 6(1) | 7(1) |
| C(17) | 26(1) | 27(1) | 39(1) | 9(1) | 1(1) | 2(1) |

**Table S7.** Hydrogen coordinates (x104) and isotropic displacement parameters ($Å^2x10^3$) for **21**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H | 1210(30) | 3280(60) | 7250(20) | 38 |
| H(2) | 1400(30) | 340(80) | 5450(30) | 63(11) |
| H(3) | 560(30) | 6700(70) | 4890(30) | 51(9) |
| H(1) | 2845 | 5773 | 8730 | 45 |
| H(2A) | 1364 | 8442 | 7955 | 95 |
| H(2B) | 1204 | 8078 | 9226 | 95 |
| H(2C) | 296 | 6773 | 8293 | 95 |
| H(3A) | 884 | 2929 | 9316 | 74 |
| H(3B) | 1871 | 4272 | 10169 | 74 |
| H(3C) | 2281 | 2095 | 9456 | 74 |
| H(6) | 2870 | 6292 | 4842 | 30 |
| H(7) | 923 | 3636 | 3610 | 31 |
| H(10) | 2578 | 9532 | 1298 | 40 |
| H(11) | 4478 | 8952 | 653 | 48 |
| H(12) | 5652 | 5636 | 1209 | 48 |
| H(13) | 4965 | 2750 | 2351 | 42 |
| H(15) | 2318 | 1601 | 2829 | 34 |
| H(16) | 4233 | 861 | 4037 | 39 |
| H(17) | 3912 | 1028 | 5804 | 37 |

**Table S8.** Torsion angles [°] for **21**.

| | |
|---|---|
| C(4)-N-C(1)-C(3) | -137.2(3) |
| C(4)-N-C(1)-C(2) | 99.5(3) |
| C(1)-N-C(4)-O(1) | 9.9(4) |
| C(1)-N-C(4)-C(5) | -169.2(2) |
| O(1)-C(4)-C(5)-O(2) | 173.2(2) |
| N-C(4)-C(5)-O(2) | -7.7(3) |
| O(1)-C(4)-C(5)-C(17) | 49.8(3) |
| N-C(4)-C(5)-C(17) | -131.1(2) |
| O(1)-C(4)-C(5)-C(6) | -67.5(3) |
| N-C(4)-C(5)-C(6) | 111.6(2) |
| O(2)-C(5)-C(6)-O(3) | 66.7(2) |
| C(17)-C(5)-C(6)-O(3) | -171.70(18) |
| C(4)-C(5)-C(6)-O(3) | -53.1(2) |
| O(2)-C(5)-C(6)-C(7) | -59.6(2) |
| C(17)-C(5)-C(6)-C(7) | 62.0(2) |
| C(4)-C(5)-C(6)-C(7) | -179.35(16) |
| O(3)-C(6)-C(7)-C(8) | 61.1(2) |
| C(5)-C(6)-C(7)-C(8) | -173.51(16) |
| O(3)-C(6)-C(7)-C(15) | 176.79(19) |
| C(5)-C(6)-C(7)-C(15) | -57.8(2) |
| C(6)-C(7)-C(8)-O(4) | -75.2(3) |
| C(15)-C(7)-C(8)-O(4) | 165.9(2) |
| C(6)-C(7)-C(8)-C(9) | 103.8(2) |
| C(15)-C(7)-C(8)-C(9) | -15.1(2) |
| O(4)-C(8)-C(9)-C(14) | -174.1(2) |
| C(7)-C(8)-C(9)-C(14) | 6.9(2) |
| O(4)-C(8)-C(9)-C(10) | 6.3(4) |
| C(7)-C(8)-C(9)-C(10) | -172.7(2) |
| C(14)-C(9)-C(10)-C(11) | -3.7(3) |
| C(8)-C(9)-C(10)-C(11) | 175.8(2) |
| C(9)-C(10)-C(11)-C(12) | 1.5(4) |
| C(10)-C(11)-C(12)-C(13) | 1.4(4) |
| C(11)-C(12)-C(13)-C(14) | -2.2(4) |
| C(10)-C(9)-C(14)-C(13) | 3.0(3) |
| C(8)-C(9)-C(14)-C(13) | -176.6(2) |
| C(10)-C(9)-C(14)-C(15) | -175.7(2) |
| C(8)-C(9)-C(14)-C(15) | 4.7(2) |

| | |
|---|---|
| C(12)-C(13)-C(14)-C(9) | 0.0(3) |
| C(12)-C(13)-C(14)-C(15) | 178.5(2) |
| C(9)-C(14)-C(15)-C(16) | -140.8(2) |
| C(13)-C(14)-C(15)-C(16) | 40.7(3) |
| C(9)-C(14)-C(15)-C(7) | -13.9(2) |
| C(13)-C(14)-C(15)-C(7) | 167.5(2) |
| C(8)-C(7)-C(15)-C(16) | 143.4(2) |
| C(6)-C(7)-C(15)-C(16) | 23.9(3) |
| C(8)-C(7)-C(15)-C(14) | 17.0(2) |
| C(6)-C(7)-C(15)-C(14) | -102.5(2) |
| C(14)-C(15)-C(16)-C(17) | 127.0(3) |
| C(7)-C(15)-C(16)-C(17) | 6.6(4) |
| C(15)-C(16)-C(17)-C(5) | -1.9(4) |
| O(2)-C(5)-C(17)-C(16) | 88.4(3) |
| C(4)-C(5)-C(17)-C(16) | -148.5(2) |
| C(6)-C(5)-C(17)-C(16) | -32.4(3) |

**Table S9.** Hydrogen bonds for **21** [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| N-H...O(2) | 0.86(3) | 2.20(3) | 2.651(3) | 112(2) |
| N-H...O(4)#1 | 0.86(3) | 2.21(3) | 2.970(2) | 147(3) |
| O(2)-H(2)...O(3)#2 | 0.88(5) | 1.89(5) | 2.740(3) | 162(3) |
| O(3)-H(3)...O(2)#3 | 0.80(3) | 2.00(3) | 2.764(2) | 160(4) |

Symmetry transformations used to generate equivalent atoms:

#1 -x,y-1/2,-z+1 #2 x,y-1,z #3 -x,y+1/2,-z+1

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