An Efficient Entry into Medium Ring Keto-Lactones. The Ruthenium Tetraoxide-Promoted Oxidative Cleavage of β-Hydroxyethers

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Supporting Information

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General Methods. Ruthenium trichloride hydrate ($RuCl_3.nH_2O$) was purchased from Aldrich and used as received. Calculations were based on n = 1. The other reagents and solvents were also purchased from standard chemical suppliers and were purified by usual methods. The filtration on silica pad was performed using silica gel Acros (80-230 Mesh). TLC analyses were performed with silica gel plates Merck, using vanilline or *p*-anisaldehyde solution for visualization.

1. RuO_4-Promoted Oxidative Cleavage of Hexahydro-benzofuran-3a-ols 1a-d. General Procedure. To 7 mL of a 3:2:2 mixture of H_2O:CCl_4:CH_3CN, respectively, was added 1 mmol of the hexahydro-benzofuran-3a-ols **1a-d**. To this solution were added 4.1 mmol of $NaIO_4$ and 2.4 mol% of $RuCl_3.nH_2O$. The reactional mixture was magnetically stirred at room temperature for 1h 15 min. Then, water was added and the aqueous phase was extracted with CH_2Cl_2 (three times). The combined organic phases were washed with brine (twice) and concentrated by removing part of the solvent under reduced pressure. The resulting residue was then filtered through a small silica gel pad (*ca.* 10cm), washing with CH_2Cl_2. The filtrate was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to afford **3a-d** in the yields shown in Scheme 1 and Table 1, with more than 99% chromatographic purity.

1.1. *trans*-4,8-Dimethyl-oxonane-2,7-dione (3a): colorless oil; IR (film) 1739 and 1719 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (d, J = 6.7 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H), 1.48-1.55 (m, 1H), 1.96-2.16 (m, 3H), 2.21 (ddd, J = 4.6, 7.0 and 15.4 Hz, 1H), 2.47 (ddd, J = 0.8, 3.7 and 14.1 Hz, 1H), 2.64 (ddd, J = 3.7, 10.8 and 15.4 Hz, 1H), 3.19-3.26 (m, 1H), 3.82 (dd, J = 8.8 and 10.6 Hz, 1H), 4.91 (dd, J = 7.2 and 10.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.2, 22.6, 30.1, 31.8, 41.1, 42.5, 43.6, 67.0, 173.9, 213.0; MS *m/z* 184 (0.2, M^+); HRMS calcd for $C_{10}H_{16}O_3$ 184.1099, found 184.1090.

1.2. 4-Methyl-oxonane-2,7-dione (3b): colorless oil; IR (film) 1738 and 1712 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (d, *J* = 6.5 Hz, 3H), 1.51-1.63 (m, 1H), 1.89-2.12 (m, 3H), 2.25 (ddd, *J* = 4.3, 6.6 and 14.9 Hz, 1H), 2.45-2.50 (m, 1H), 2.59 (ddd, *J* = 3.7, 11.2 and 14.9 Hz, 1H), 2.69 (dt, *J* = 6.7 and 13.4 Hz, 1H), 2.87 (dt, *J* = 6.7 and 13.4 Hz, 1H), 4.39 (dt, *J* = 6.7 and 10.9 Hz, 1H), 4.75 (dt, *J* = 6.7 and 10.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 32.0, 32.4, 41.5, 41.7, 42.9, 60.7, 174.2, 211.1; MS *m/z* 170 (4.8, M^+); HRMS calcd for $C_9H_{14}O_3$ 170.0943, found 170.0947.

1.3. 4-*tert*-Butyl-oxonane-2,7-dione (3c): colorless oil; IR (film) 1738 and 1709 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.55-1.61 (m, 2H), 1.94-2.08 (m, 2H), 2.26-2.36 (m, 2H), 2.51-2.57 (m, 2H), 3.10 (ddd, *J* = 6.2, 10.3 and 13.2 Hz, 1H), 4.36 (dt, *J* = 5.1 and 10.5 Hz, 1H), 4.72 (ddd, *J* = 3.2, 6.3 and 10.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.8, 27.2, 34.0, 37.4, 39.4, 46.5, 46.9, 61.9, 175.1, 211.4; MS *m/z* 212 (2.4, M^+); HRMS calcd for $C_{12}H_{20}O_3$ 212.1412, found 212.1416.

1.4. *trans*-4-*tert*-Butyl-8-methyl-oxonane-2,7-dione (3d): white solid; IR (KBr) 1726 and 1717 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 9H), 0.99 (d, *J* = 6.7 Hz, 3H), 1.54-1.64 (m, 2H), 1.91-2.08 (m, 2H), 2.20-2.30 (m, 1H), 2.51-2.59 (m, 2H), 3.27-3.39 (m, 1H), 3.86 (t, *J* = 10.2 Hz, 1H), 4.70 (dd, *J* = 6.0 and 10.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.0, 24.6, 27.2, 33.9, 37.3, 41.5, 45.7, 46.4, 67.8, 174.9, 214.4; MS *m/z* 226 (1.3, M^+); Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.06; H, 9.72.

2. Reaction of Hexahydro-benzofuran-3-ol 4a with Ruthenium Tetraoxide. To a solution of **4a** (0.227 g, 1.34 mmol) in 10,5 mL of a mixture of H_2O:CCl_4:CH_3CN (3:2:2) was added $NaIO_4$ (1.17 g, 5.49 mmol) and $RuCl_3.nH_2O$ (0.014 g, 5.0 mol%). The reactional mixture was magnetically stirred at room temperature for 30 min. Then, water was added and the aqueous phase was extracted with CH_2Cl_2 (three times). The combined organic phases were washed with brine (twice) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (gradient elution 0-20% AcOEt in hexanes) affording **5** (0.101 g, 0.656 mmol, 48%) as a colorless oil. **2-Acetyl-5-methyl-cyclohexanone 5**:[1] IR (film) 1715 and

1611 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (d, *J* = 6.5 Hz, 3H), 1.18-1.32 (m, 1H), 1.70-1.85 (m, 2H), 1.94-2.03 (m, 1H), 2.13 (s, 3H), 2.30-2.43 (m, 3H), 15.9 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 23.8, 25.1, 28.0, 30.9, 39.2, 106.5, 181.6, 199.0; MS *m/z* 154 (59, M^+). Dione **5** exists predominantly in the enol form.[2]

3. Reaction of Hexahydro-benzofuran-3-ol 4b with Ruthenium Tetraoxide. To a solution of **4b** (1.03 g, 6.06 mmol) in 42 mL of a mixture of H_2O:CCl_4:CH_3CN (3:2:2) was added $NaIO_4$ (5.17 g, 24.2 mmol) and $RuCl_3.nH_2O$ (0.063 g, 5.0 mol%). The reactional mixture was magnetically stirred at room temperature for 4 hours. Then, water was added and the aqueous phase was extracted with CH_2Cl_2 (three times). The combined organic phases were washed with brine (twice) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (gradient elution 0-50% AcOEt in hexanes) affording the dione **5** (0.371 g, 2.41 mmol, 40%) as a colorless oil, the ceto-formate **6** (0.129 g, 0.701 mmol, 12%) as a colorless viscous oil, and the α-hydroxy-lactone **7** (0.162 g, 0.880 mmol, 15%), as a white solid. **Formic acid 2-acetyl-5-methyl-cyclohexyl ester 6:** IR (film) 1722 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (d , *J* = 6.6 Hz, 3H), 0.93-1.07 (m, 2H), 1.37 (dq, *J* = 3.6 and 13.2 Hz, 1H), 1.55-1.61 (m, 1H), 1,73-1.78 (m, 1H), 1.97 (qd, *J* = 3,6 and 13.2 Hz, 1H), 2.11-2.16 (m, 1H), 2,18 (s, 3H), 2.63 (ddd, *J* = 3.8, 10.6 and 12.7 Hz, 1H), 5.10 (dt, *J* = 4.5 and 10.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 27.8, 29.3, 30.8, 33.3, 39.3, 55.1, 73.1, 160.3, 209,5; MS *m/z* 185 (11, M^++1); Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.20; H, 8.70. **3-Hydroxy-3,6-dimethyl-hexahydro-benzofuran-2-one 7:** IR (KBr) 3471, 1764 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 0.99-1.13 (m, 1H), 1.03 (d, *J* = 6.6 Hz, 3H), 1.20-1.37 (m, 2H), 1.31 (s, 3H), 1.55-1.65 (m, 1H), 1.81-2.01 (m, 3H), 2.22-2.29 (m, 1H), 2.97 (br s, H-OH), 3.81 (dt, *J* = 3.9 and 11.0 Hz, 1H); ^{13}C NMR(125 MHz, $CDCl_3$) δ 18.1, 22.0, 22.5, 31.3, 33.8, 38.7, 53.6, 74.8, 79.9, 180.5; MS *m/z* 140 (8.7, M^+); Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.95; H, 8.35.

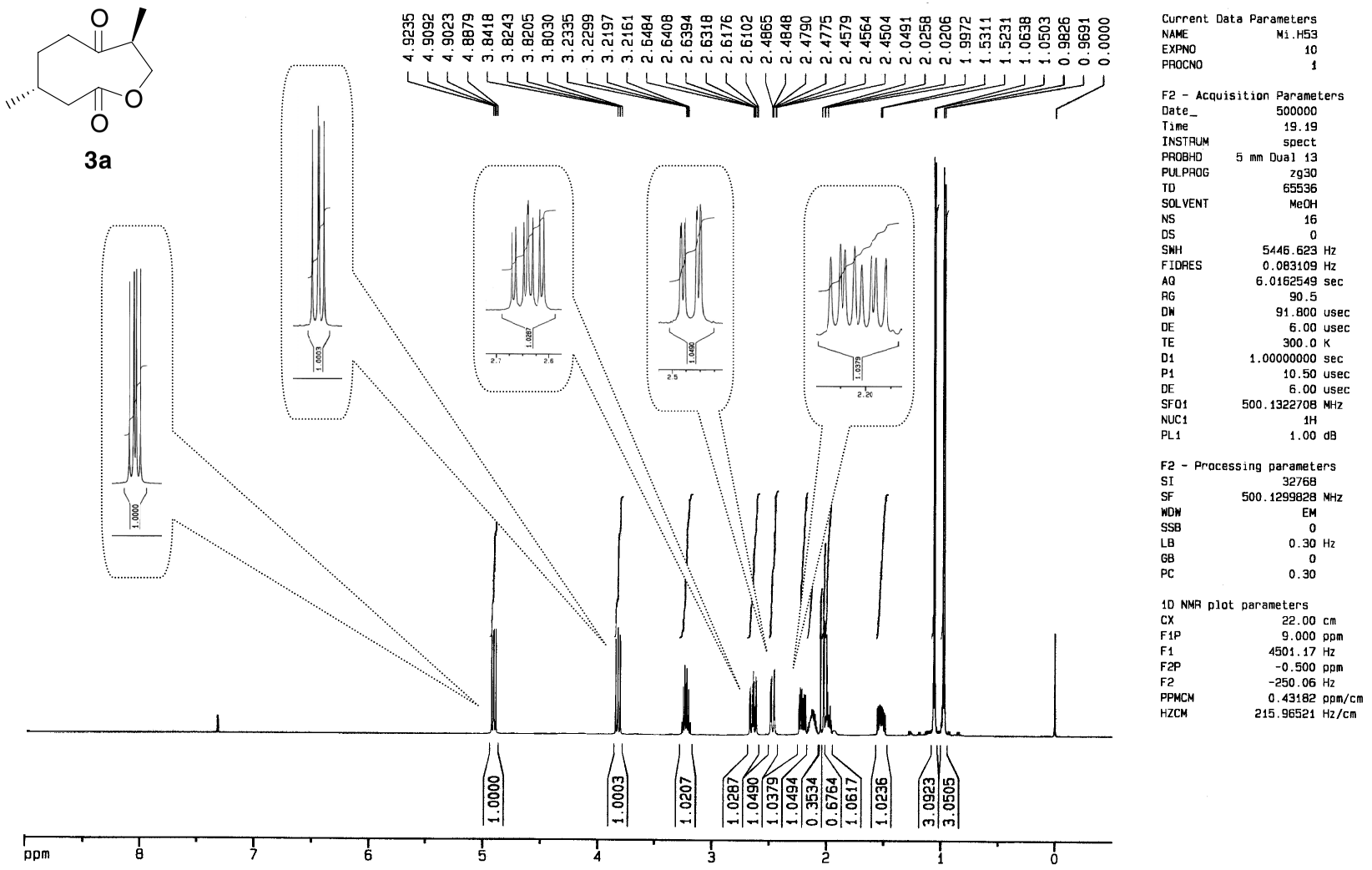

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Figure S1. ^{1}H NMR spectrum of **3a** ($CDCl_3$, 500 MHz, TMS, δ)

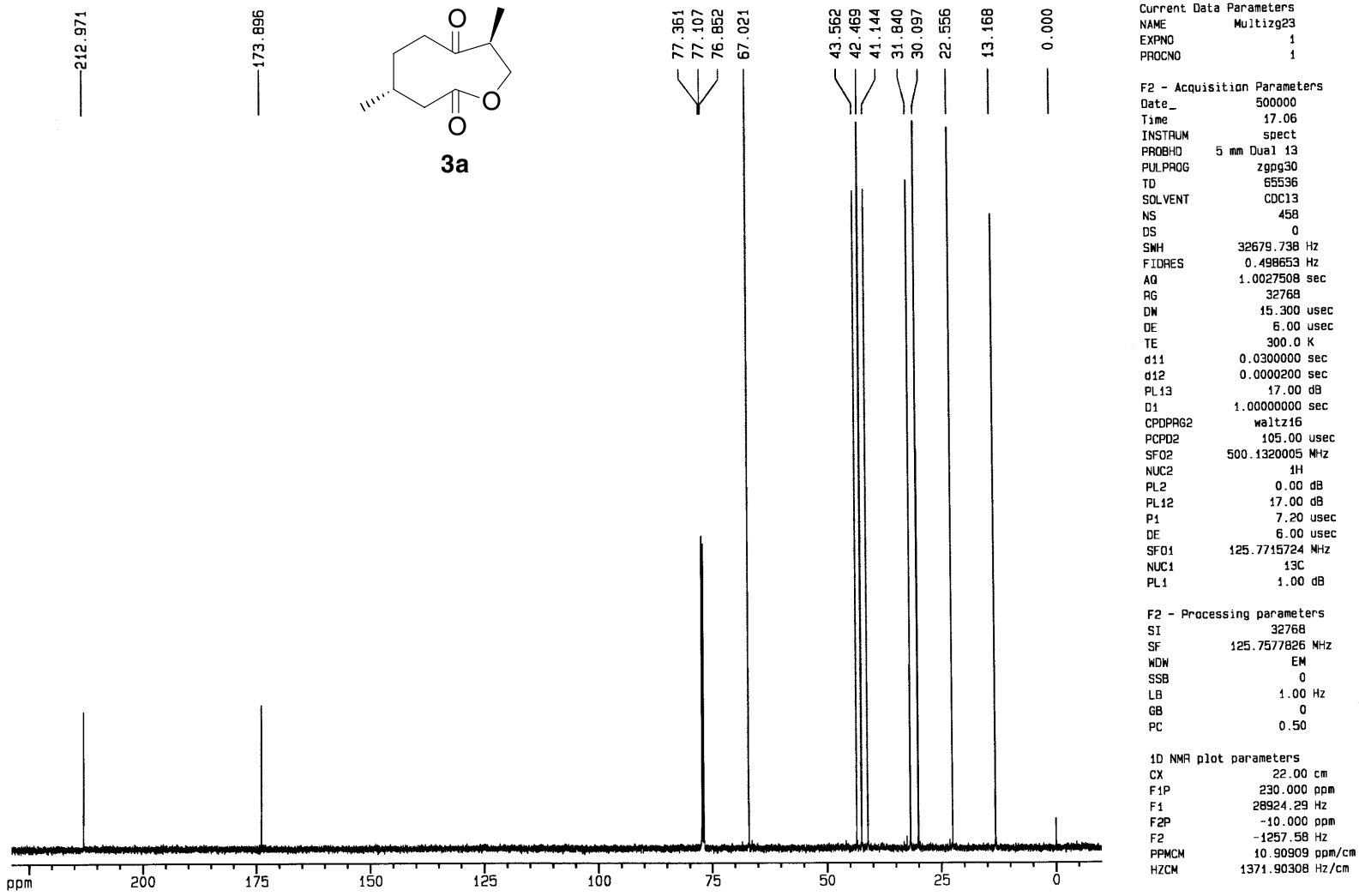

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Figure S2. ^{13}C NMR spectrum of **3a** ($CDCl_3$, 125 MHz, TMS, δ)

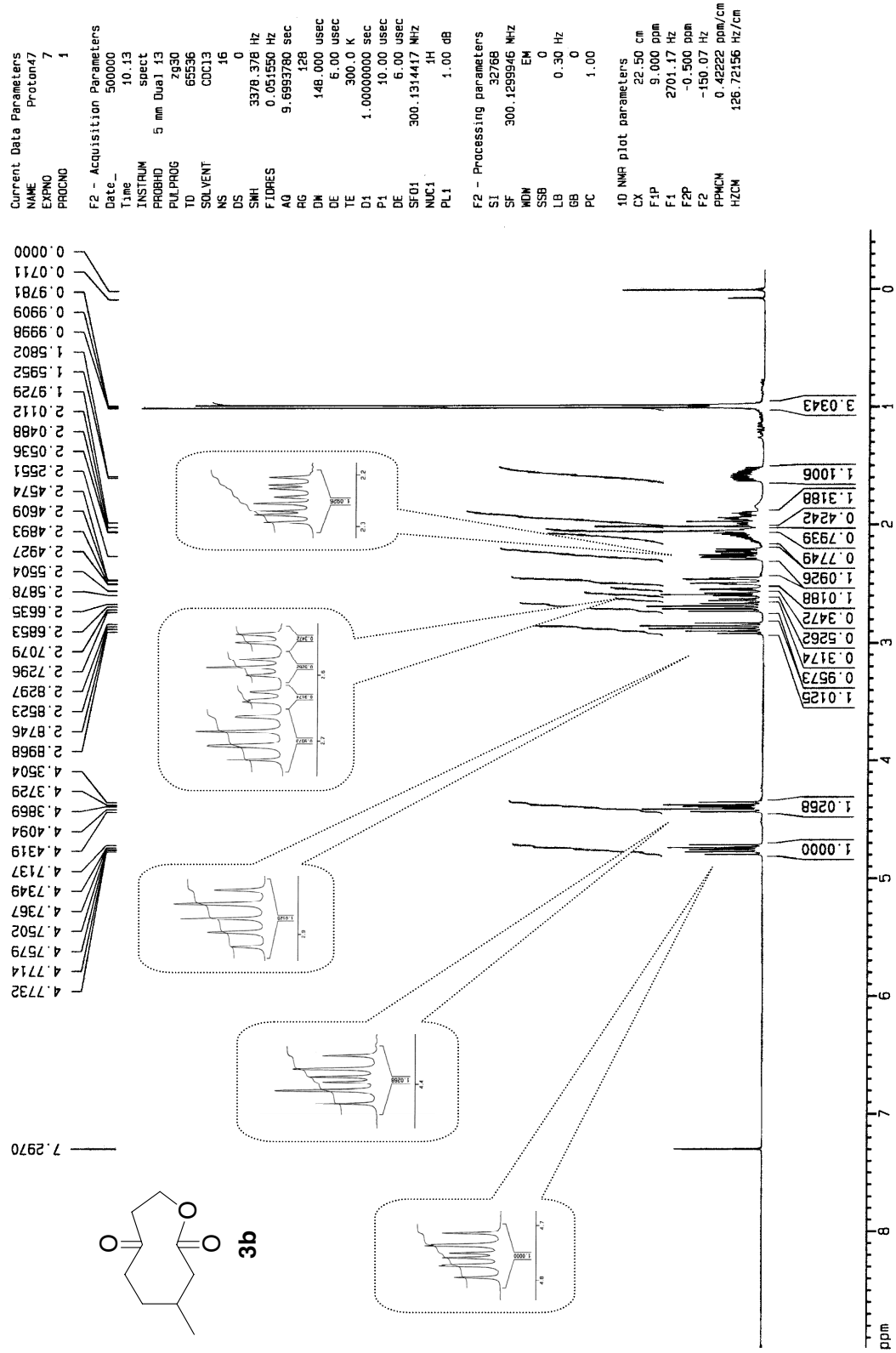


Figure S3. ^{1}H NMR spectrum of **3b** ($CDCl_3$, 300 MHz, TMS, δ)

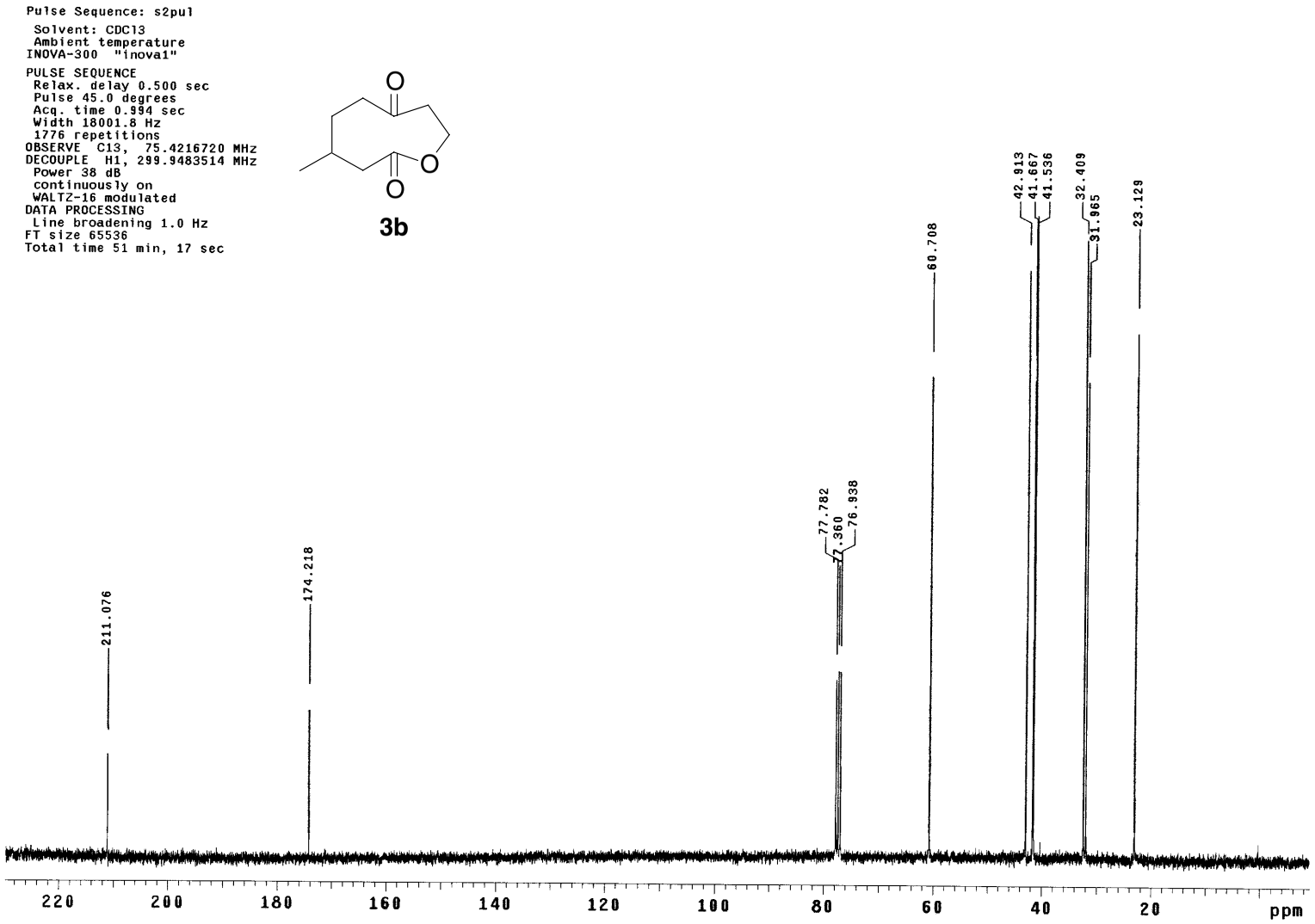
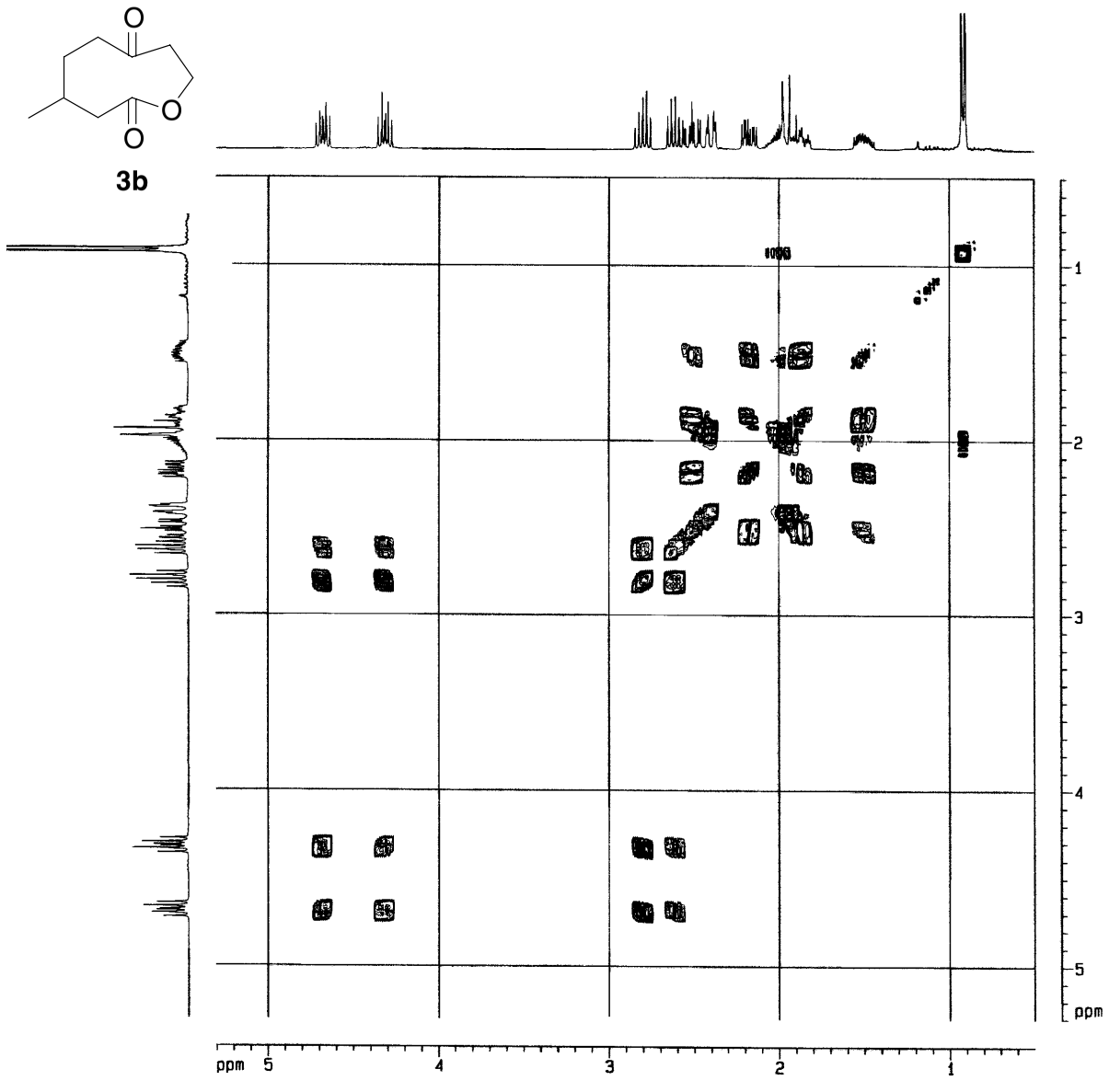


Figure S4. ^{13}C NMR spectrum of **3b** ($CDCl_3$, 75 MHz, TMS, δ)



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2D NMR plot parameters

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F1HI	148.49 Hz
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F2HZCM	96.09125 Hz/cm
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Figure S5. COSY spectrum of **3b** ($CDCl_3$, 300 MHz, TMS, δ)

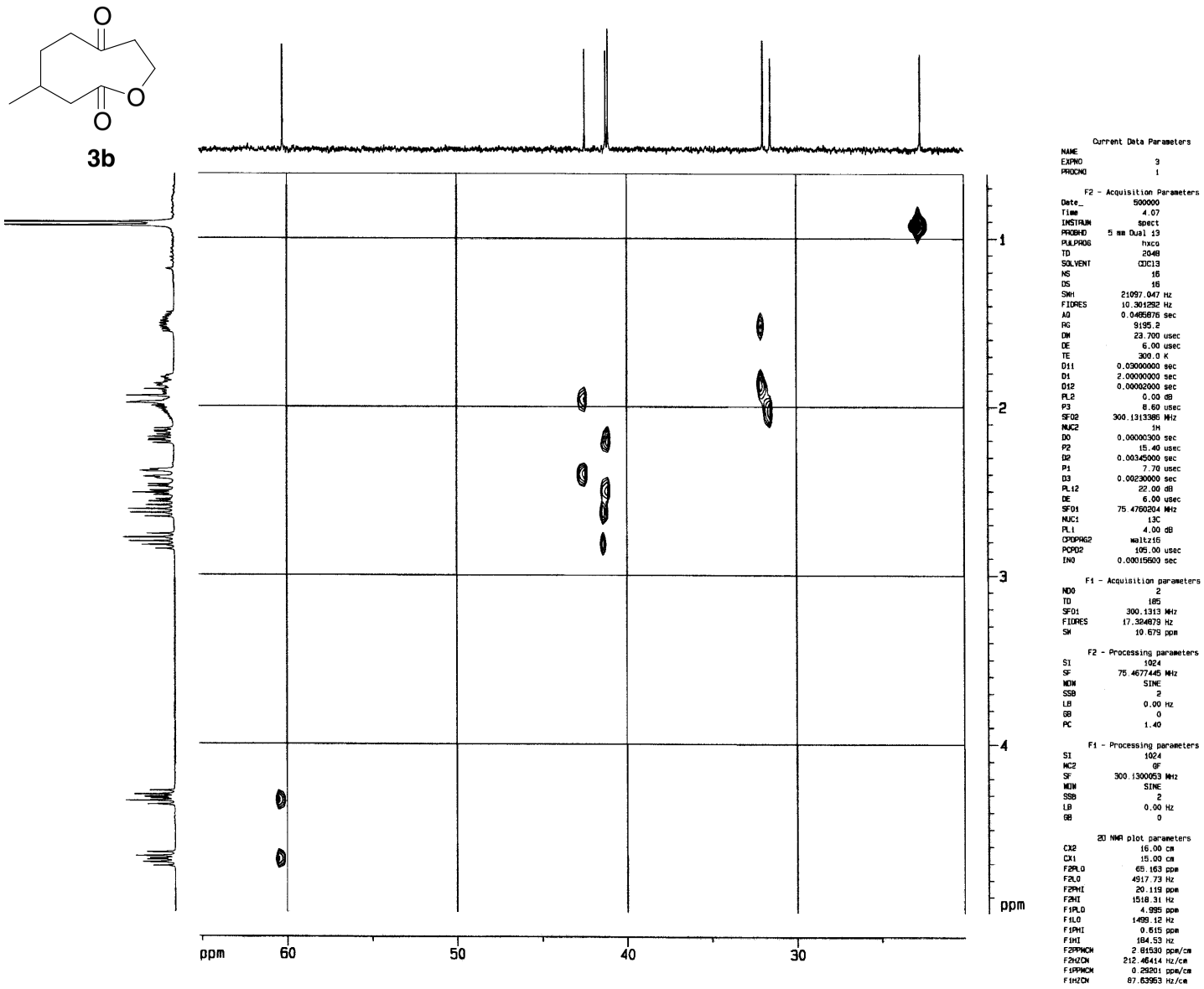

Figure S6. HETCOR spectrum of **3b** ($CDCl_3$, 300 MHz, TMS, δ)

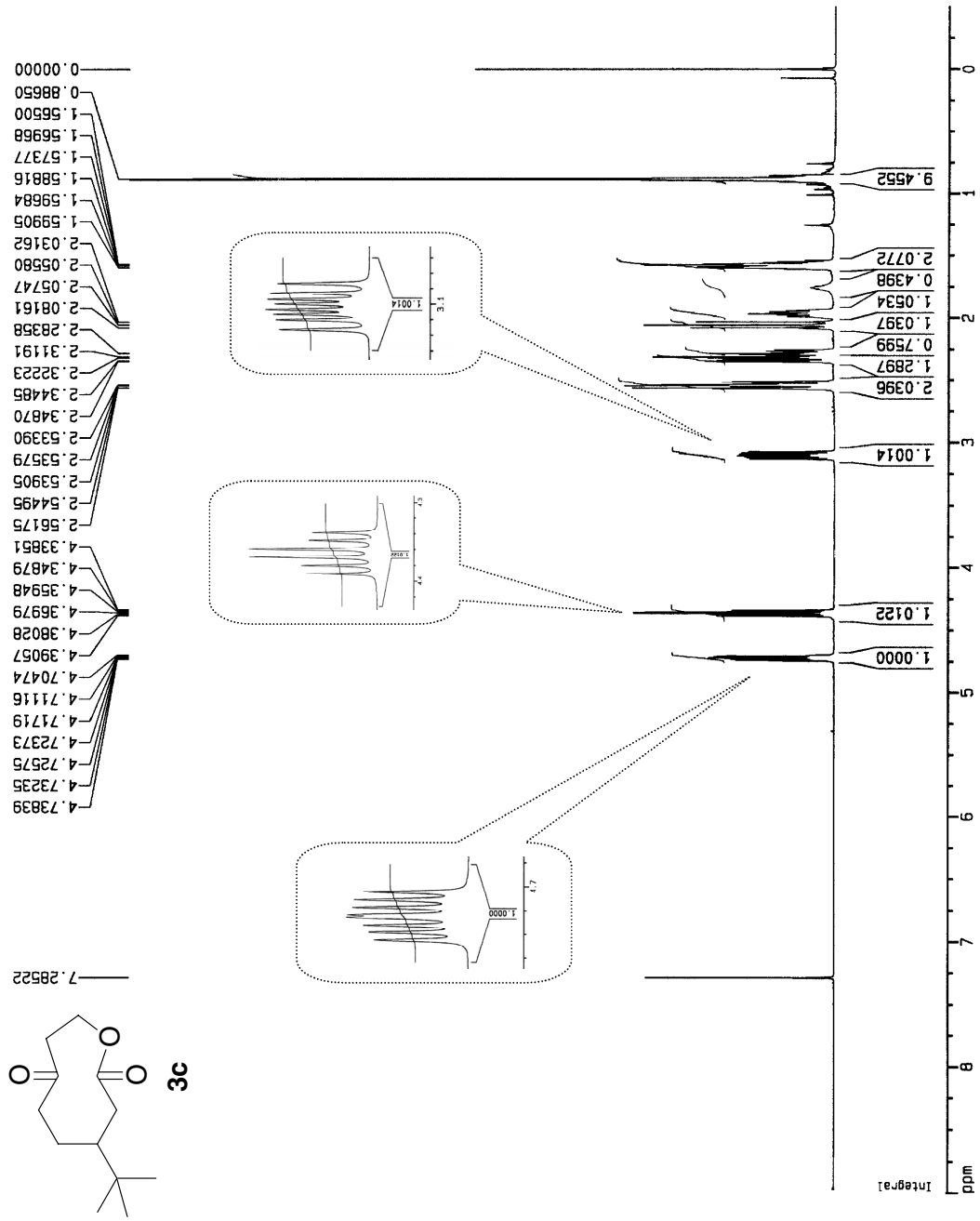

Figure S7. ^{1}H NMR spectrum of **3c** ($CDCl_3$, 500 MHz, TMS, δ)

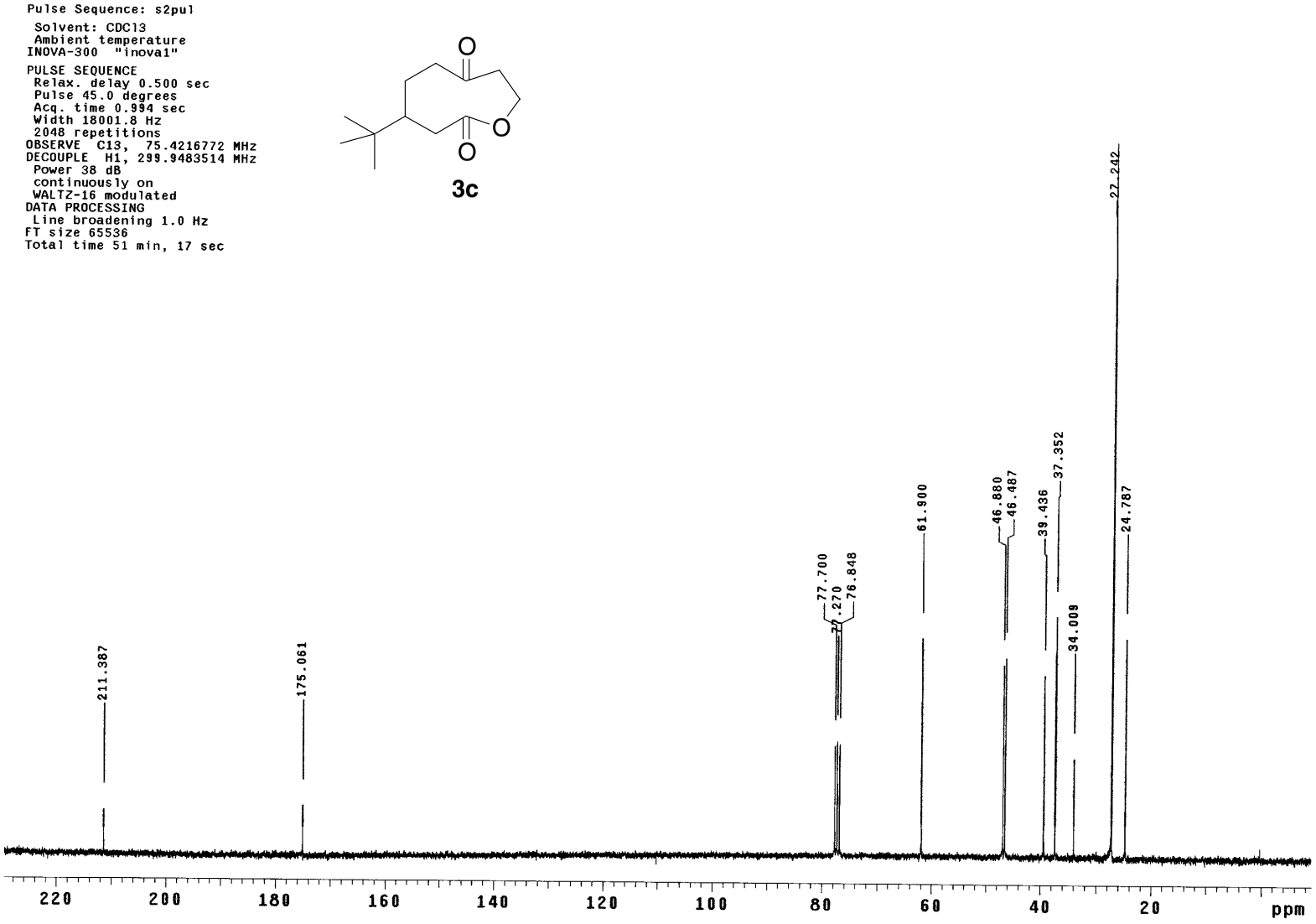

Figure S8. ^{13}C NMR spectrum of **3c** ($CDCl_3$, 75 MHz, TMS, δ)

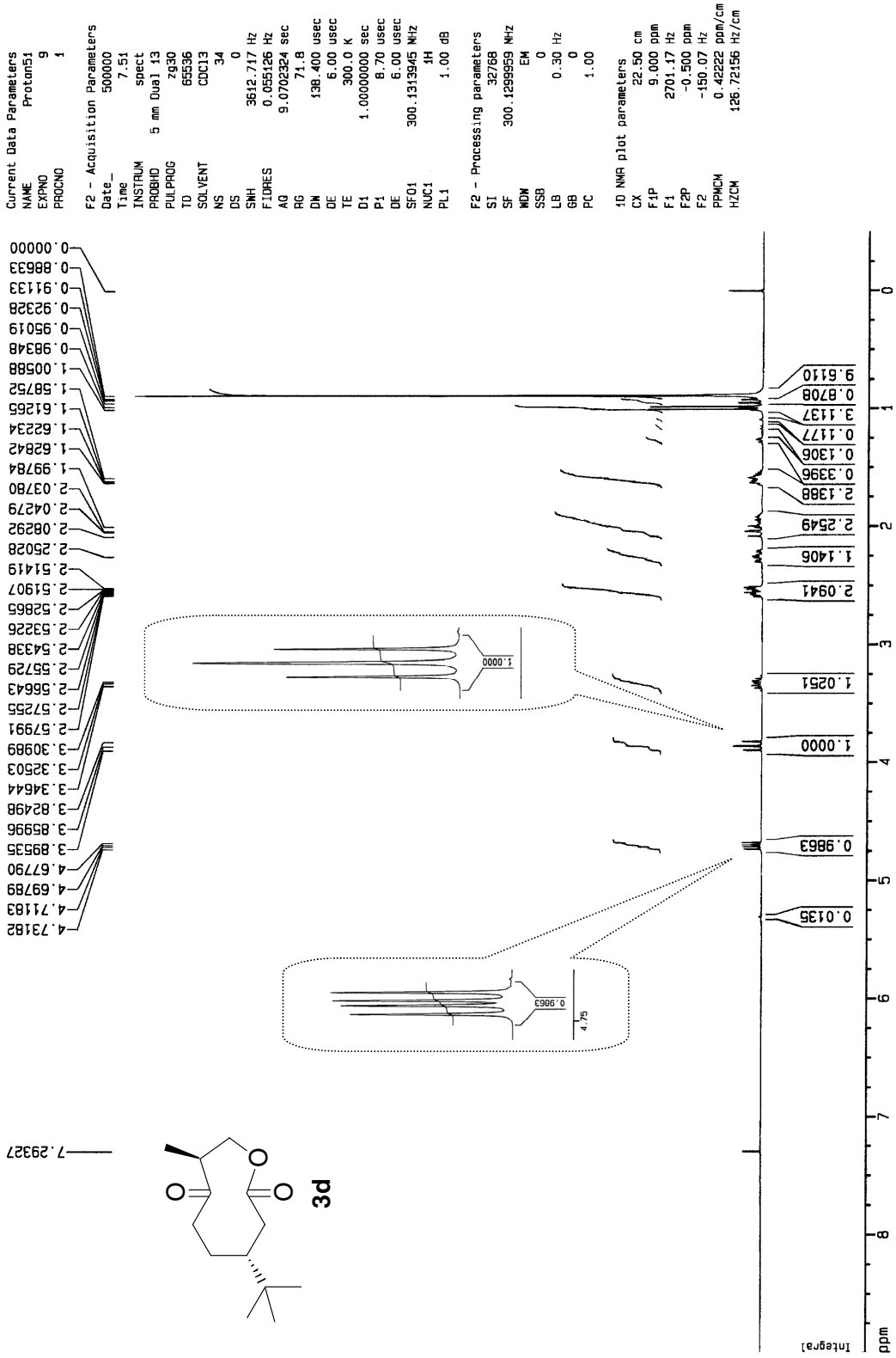

Figure S9. ^{1}H NMR spectrum of **3d** ($CDCl_3$, 300 MHz, TMS, δ)

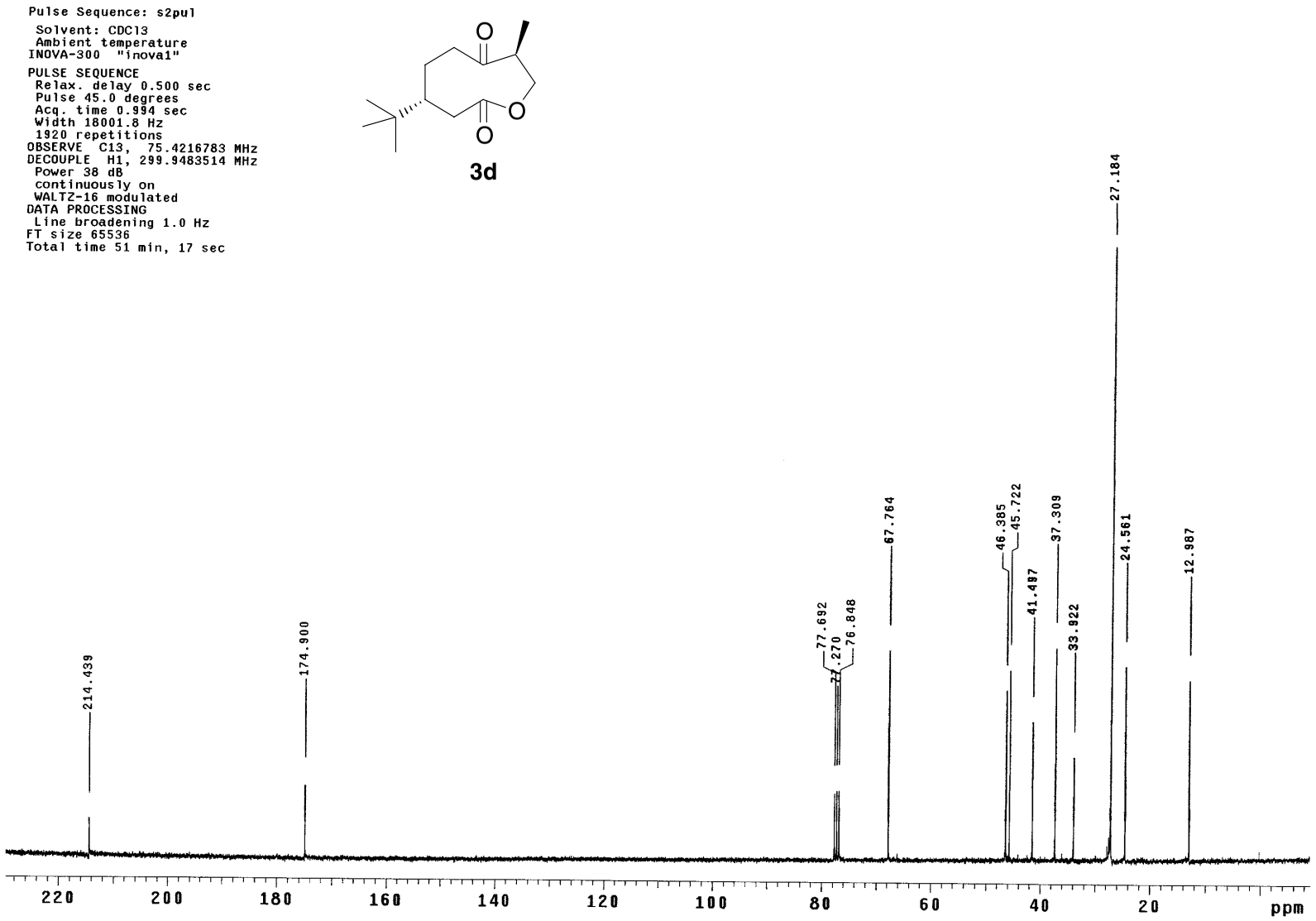

Figure S10. ^{13}C NMR spectrum of **3d** ($CDCl_3$, 75 MHz, TMS, δ)

References

1. Descotes, G.; Yvon, Q. *Bull. Soc. Chim. Fr.* **1968**, *8*, 3395.

2. Snider, B. B.; Shi, Z. *J. Am. Chem. Soc.* **1992**, *114*, 1790.