Unprecedented Photochemical Induced Cascading Rearrangement of the 3-Azabicyclo[3.3.1]nonane skeleton

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Experimental

^{1}H and ^{13}C n.m.r spectra were recorded on a Bruker AV400 (400.13MHz; 100.62MHz) or a Bruker AC200 (200.13MHz; 50.32MHz) in deuteriochloroform ($CDCl_3$). Coupling constants are given in Hz and chemical shifts are expressed as □ values in ppm. High and low resolution EI mass spectral data were obtained on a KRATOS MS 25 RFA. Microanalyses were performed by the University of Queensland Microanalytical Service. Column chromatography was undertaken on silica gel (Flash Silica gel 230–400 mesh), with distilled solvents. Anhydrous solvents were prepared according to Perin and Armarego, 'Purification of laboratory solvents', 3rd Ed. Melting points were determined on a Fischer Johns Melting Point apparatus and are uncorrected. Methylmagnesium bromide and *n*-BuLi was purchased from the Aldrich Chem. Co.

Ethyl 5-bromo-3-methyl-9-[2-oxo-2-(2-hydroxy-3-methoxy)-*E*-ethylidene]-3-azabicyclo[3.3.1]nonanecarboxylate

Ethyl 5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-isopropoxy)phenylethynyl]-3-azabicyclo[3.3.1]nonanecarboxylate[11] **6** (0.205 g, 0.041 mmol) was rapidly dissolved in trifluoroacetic acid (3 mL) at room temperature. The solution was cooled in an ice-bath and trimethylsilyltrifluorosulfonate (0.23 mL, 1.29 mmol) added rapidly. After addition the flask was taken out of the bath and stirred at room temperature for 1 h. The reaction mixture was then transferred, *via* Pasture pipette, to a separatory funnel containing a saturated solution of sodium hydrogen carbonate (50 mL) and extracted with dichloromethane (3 x 10 mL). The residue was dried under vacuum, redissolved in anhydrous THF (3 mL) and sodium hydride added until effervesence ceased. The mixture was quenched with saturated ammonium chloride solution and extracted with dichloromethane (3 x 10 mL). Column chromatography (ethyl acetate / dichloromethane, 5:95) afforded the title compound as a bright yellow viscous oil (0.13 g, 70%).

^{1}H NMR (400MHz, $CDCl_3$) □ 0.83 (t, J 7.1, 3H), 1.56-1.65 (m, 1H), 2.20 (s, 3H), 2.21-2.28 (m, 2H), 2.40-2.51 (m, 1H), 2.63 (d, J 11.1, 1H), 2.69-2.76 (m, 1H), 2.85 (dd, J 10.6, 2.4, 1H), 2.93-

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3.07 (m, 2H), 3.50 (dd, J 10.6, 1.3, 1H), 3.66-3.85 (m, 2H), 3.89 (s, 3H), 6.87 (t, J 8.1, 1H), 7.03-7.07 (m, 1H), 7.38 (s, 1H), 7.42 (dd, J 8.1, 1.4, 1H), 12.26 (s, OH).

^{13}C NMR (100MHz, $CDCl_3$) 13.3, 23.6, 36.3, 44.6, 47.3, 52.4, 56.2, 60.9, 64.1, 71.1, 71.5, 117.1, 118.4, 120.1, 122.6, 123.0, 148.7, 152.7, 153.0, 172.3, 199.5.

Mass spectrum m/z (EI) 453 ($M^{+\bullet}$, 4%), 451 ($M^{+\bullet}$, 5%), 408 (2), 406 (2), 372 (80), 326 (20), 302 (20), 300 (21), 298 (14), 286 (6), 283 (6), 279 (15), 256 (8), 222 (17), 220 (30), 206 (19), 167 (39), 151 (98), 149 (100), 129 (11), 113 (18).

Anal. Calcd. for $C_{21}H_{26}BrNO_5$: $M^{+\bullet}$ 451.0995. Found: 451.0989.

Ethyl 5-bromo-3-methyl-9-[2-oxo-2-(2-isopropoxy-3-methoxy)-*E*-ethylidene]-3-azabicyclo[3.3.1]nonanecarboxylate 7

Ethyl 5-bromo-3-methyl-9-[2-oxo-2-(2-hydroxy-3-methoxy)-*E*-ethylidene]-3-azabicyclo[3.3.1]nonanecarboxylate (0.156 g, 0.345 mmol) was dissolved in *N,N*-dimethylformamide (1.5 mL) followed by addition of 2-bromopropane (0.97 mL, 10.3 mmol) and potassium carbonate (0.095 g, 0.69 mmol). The mixture was then stirred at room temperature for 16 h. Excess 2-bromopropane and *N,N*-dimethylformamide were removed under high vacuum and the residue suspended in dichloromethane (5 mL) and passed through celite. Column chromatography (diethyl ether/light petroleum, ~1:4) of the residue on silica gel afforded the title compound (0.159 g, 93%) as a pale yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) 1.22-1.30 (m, 9H), 1.54-1.63 (m, 1H), 1.96-2.05 (m, 1H), 2.17 (s, 3H), 2.36-2.49 (m, 2H), 2.51-2.60 (m, 1H), 2.79 (dd, J 10.7, 2.4, 1H), 2.87 (dd, J 11.1, 2.4, 1H), 2.89-3.03 (m, 1H), 2.97 (dd, J 11.1, 1.3, 1H), 3.28 (dd, J 10.7, 1.3, 1H), 3.82 (s, 3H), 4.13-4.25 (m, 2H), 4.59 (sept, J 6.2, 1H), 6.99-7.07 (m, 2H), 7.42 (AB, 1H).

^{13}C NMR (100MHz, $CDCl_3$) 14.1, 22.3, 22.4, 23.6, 35.9, 44.8, 46.2, 54.9, 56.1, 61.2, 63.1, 65.4, 71.3, 76.1, 116.1, 122.8, 123.7, 125.7, 134.3, 142.4, 147.0, 153.5, 172.7, 195.3.

Mass spectrum m/z (EI) 494 ($M^{+\bullet}$, 0.5%), 492 ($M^{+\bullet}$, 0.5%), 414 (77), 368 (7), 354 (7), 340 (2), 326 (9), 315 (1), 302 (11), 300 (12), 283 (2), 256 (2), 220 (27), 208 (5), 206 (8), 193 (49), 174 (2), 151 (100), 148 (6), 146 (5), 134 (6), 120 (4).

Anal. Calcd. for $C_{24}H_{32}BrNO_5$: $M^{+\bullet}$ 414.2280 (-HBr). Found: 414.2277.

Photolysis of ethyl 5-bromo-3-methyl-9-[2-oxo-2-(2-isopropoxy-3-methoxy)-*E*-ethylidene]-3-azabicyclo[3.3.1]nonanecarboxylate 7

Ethyl 5-bromo-3-methyl-9-[2-oxo-2-(2-isopropoxy-3-methoxy)-*E*-ethylidene]-3-azabicyclo[3.3.1]nonanecarboxylate **7** (0.171 g, 0.346 mmol) was dissolved in oxygen free *N,N*-

dimethylformamide (150 mL) and irradiated through pyrex in a 1 litre Hanovia photochemical reactor using a 4W arc lamp for 10 days. The solvent was then removed under high vacuum using an in-line trap and the residue subjected to column chromatography (diethyl ether / light petroleum, 3:7 to 6:4), which afforded tricycle **8** (0.030 g, 18%) in fraction one and a mixture of *E* and *Z* enones (1:1) (0.088 g, 51%) in fraction two.

Ethyl 3a-bromo-2-methyl-1,3,3a,4,5,6,7,7a-octahydro-9-(2-isopropoxy-3-methoxyphenyl)-isoindolo[1,7a-b]furan-7-carboxylate **8**.

^{1}H NMR (400MHz, $CDCl_3$) δ 1.00 (t, J 7.1, 3H), 1.23 (d, J 6.2, 3H), 1.29 (d, J 6.2, 3H), 1.54-1.82 (m, 3H), 1.84-1.91 (m, 1H), 2.19-2.26 (m, 1H), 2.34-2.44 (m, 1H), 2.51 (s, 3H), 2.83-2.92 (m, 2H), 3.35 (d, J 8.0, 1H), 3.81 (s, 3H), 3.84-4.00 (m, 2H), 4.67 (sept, J 6.2, 1H), 5.63 (s, 1H), 5.67 (s, 1H), 6.80-6.84 (m, 1H), 6.96 (t, J 16, 1H), 7.22-7.27 (m, 1H).

^{13}C NMR (100MHz, $CDCl_3$) δ 13.9, 21.3, 22.2, 22.5, 26.3, 34.3, 40.0, 45.9, 55.9, 60.4, 65.18, 65.25, 69.5, 74.2, 94.4, 107.4, 112.7, 119.6, 122.9, 125.2, 144.7, 152.95, 153.04, 173.8.

Mass spectrum m/z (EI) 494 ($M^{+\bullet}$, 0.5%), 492 ($M^{+\bullet}$, 0.5%), 414 (100), 368 (29), 326 (6), 298 (5), 282 (2), 270 (2), 256 (2), 220 (63), 208 (10), 193 (87), 175 (2), 151 (89), 148 (6), 146 (8), 134 (22), 120 (8).

Anal. Calcd. for $C_{24}H_{32}BrNO_5$: $M^{+\bullet}$ 414.2280 (-HBr). Found: 414.2279.

Diethyl 3-(4-methoxyphenylmethyl)-9-[2-oxo-2-(3,4-dimethoxy)ethylidene]-3-azabicyclo[3.3.1]nonane-1,5-dicarboxylate 9

To diethyl 3-methyl-9-*exo*-hydroxy-9-[2-(3,4-dimethoxy)phenylethynyl]-3-azabicyclo[3.3.1]nonane-1,5-dicarboxylate [7(*exo*):3(*endo*)] (0.430 g, 0.76 mmol) at room temperature was added a mixture of trifluoroacetic acid (0.5 mL) and borontrifluoride diethyl etherate (0.3 mL, 2.36 mmol). After stirring at room temperature for 1 h the reaction mixture was then transferred, *via* Pasture pipette, to a separatory funnel containing a saturated solution of sodium hydrogen carbonate (50 mL) and extracted with dichloromethane (3 x 10 mL). The residue was subjected to column chromatography (diethyl ether / dichloromethane / light petroleum, gradient) afforded the title compound **9** (0.381 g, 89%) (fraction 1) and the corresponding α-hydroxyketone (0.009 g, 2%) (fraction 2).

Diethyl 3-(4-methoxyphenylmethyl)-9-[2-oxo-2-(3,4-dimethoxy)ethylidene]-3-azabicyclo[3.3.1]nonane-1,5-dicarboxylate **9**, m.p. 168-170 °C.

^{1}H NMR (400MHz, $CDCl_3$) δ 0.74 (t, J 7.2, 3H), 1.29 (t, J 7.1, 3H), 1.60-1.71 (m, 1H), 1.99-2.08 (m, 1H), 2.13-2.22 (m, 1H), 2.24-2.42 (m, 2H), 2.66 (dd, J 11.1, 1.6, 1H), 2.82 (dd, J 11.1, 1.6, 1H), 2.90-3.07 (m, 3H), 3.41 (AB, 2H), 3.57-3.74 (m, 2H), 3.79 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 4.14-

4.26 (m, 2H), 6.24 (s, 1H), 6.82-6.87 (m, 3H), 7.19-7.22 (m, 2H), 7.46 (d, J 1.9, 1H), 7.54 (dd, J 8.3, 1.9, 1H).

^{13}C NMR (100MHz, $CDCl_3$) 13.3, 14.3, 20.9, 36.6, 36.9, 49.9, 53.2, 55.22, 55.97, 55.05, 60.3, 61.0, 61.9, 62.0, 62.5, 109.9, 110.2, 113.8, 119.7, 123.9, 129.8, 130.3, 130.6, 149.1, 152.4, 153.3, 158.7, 173.0, 173.7, 191.5.

Mass spectrum m/z (EI) 565 ($M^{+\bullet}$, 13%), 536 (2), 520 (3), 492 (10), 474 (2), 444 (4), 429 (2), 416 (2), 400 (16), 385 (2), 370 (3), 354 (4), 343 (2), 330 (1), 312 (3), 297 (1), 278 (1), 263 (2), 206 (1), 191 (1), 180 (2), 165 (26), 121 (100).

Anal. Calcd. for $C_{32}H_{39}NO_8$: C, 67.95; H, 6.95; N, 2.48; $M^{+\bullet}$ 565.2676. Found: C, 68.05; H, 7.07; N, 2.34; 565.2676

Diethyl 2-(4-methoxyphenylmethyl)-1,3,3a,4,5,6,7,7a-octahydro-9-(3,4-dimethoxyphenyl)-isoindolo[1,7a-b]furan-3a,7-dicarboxylate 10

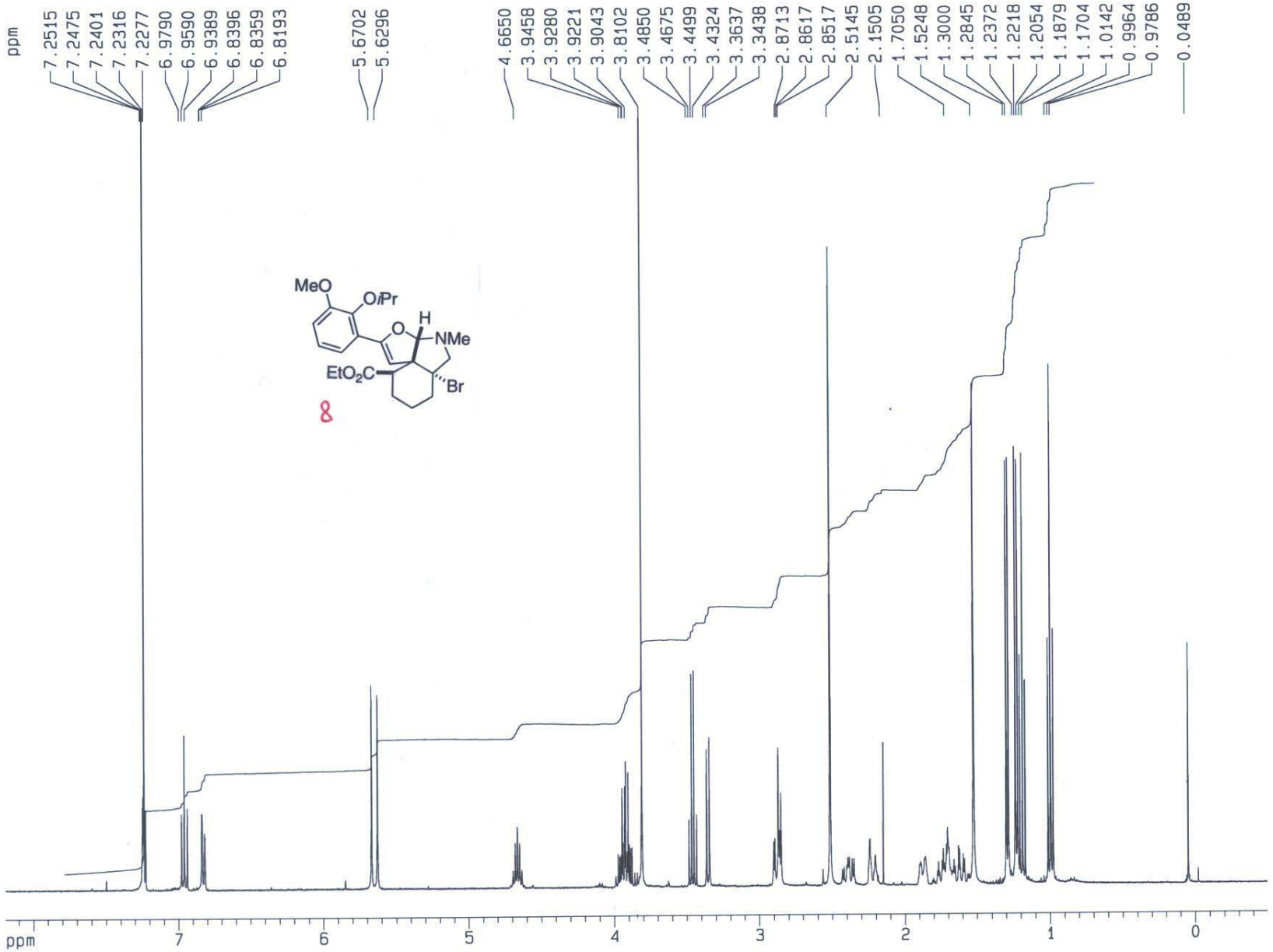
Diethyl 3-methyl-9-[2-oxo-2-(3,4-dimethoxy)ethylidene]-3-azabicyclo[3.3.1]nonane-1,5-dicarboxylate **9** (0.100 g, 0.177 mmol) was dissolved in oxygen free *N,N*-dimethylformamide (10 mL) under argon in a 10 mm n.m.r tube (PP-528) and irradiated for 1 h with a Hanovia high pressure mercury-xeon vapour lamp (1000W). [Note: the light was passed through a water filter (30 cm long) at ~5 °C and the sample placed 10 cm from the end of the cooling tube.] The solvent was then removed under high vacuum using an in-line trap and the residue subjected to column chromatography (diethyl ether / dichloromethane / light petroleum, gradient), which afforded tricycle **10** (0.076 g, 76%) and recovered starting material **9** (0.012 g, 12%) in that order. Yield based on recovered starting material 86%, m.p. 109-111 °C (partial), 115-116 °C.

^{1}H NMR (400MHz, $CDCl_3$) 0.99 (t, J 7.1, 3H), 1.23 (t, J 7.1, 3H), 1.55-1.73 (m, 3H), 1.78-1.91 (m, 2H), 2.01-2.11 (m, 1H), 2.52 (d, J 8.7, 1H), 3.10 (d, J 8.7, 1H), 3.14-3.20 (m, 1H), 3.72 (d, J 13.6, 1H), 3.78 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 3.88-4.03 (m, 2H), 4.09-4.17 (m, 2H), 4.16 (d, J 13.6, 1H), 4.90 (s, 1H), 5.90 (s, 1H), 6.78-6.88 (m, 3H), 7.03 (d, J 2.0, 1H), 7.14 (dd, J 2.0, J 8.3, 1H), 7.23-7.28 (m, 2H).

^{13}C NMR (100MHz, $CDCl_3$) 14.1, 14.2, 21.4, 25.6, 33.1, 46.8, 51.2, 54.4, 55.2, 55.90, 55.93, 56.3, 60.1, 60.3, 60.8, 96.7, 97.9, 108.6, 110.7, 113.7, 118.4, 123.4, 129.6, 131.1, 148.6, 149.5, 157.1, 158.6, 173.9, 174.5.

Mass spectrum m/z (EI) 565 ($M^{+\bullet}$, 13%), 520 (11), 492 (10), 474 (5), 444 (4), 424 (2), 416 (3), 400 (16), 165 (26), 121 (100).

Anal. Calcd. for $C_{32}H_{39}NO_8$: C, 67.95; H, 6.95; N, 2.48; $M^{+\bullet}$ 565.2676. Found: C, 67.79; H, 6.90; N, 2.41; 565.2674.



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F2 - Processing parameters

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1D NMR plot parameters

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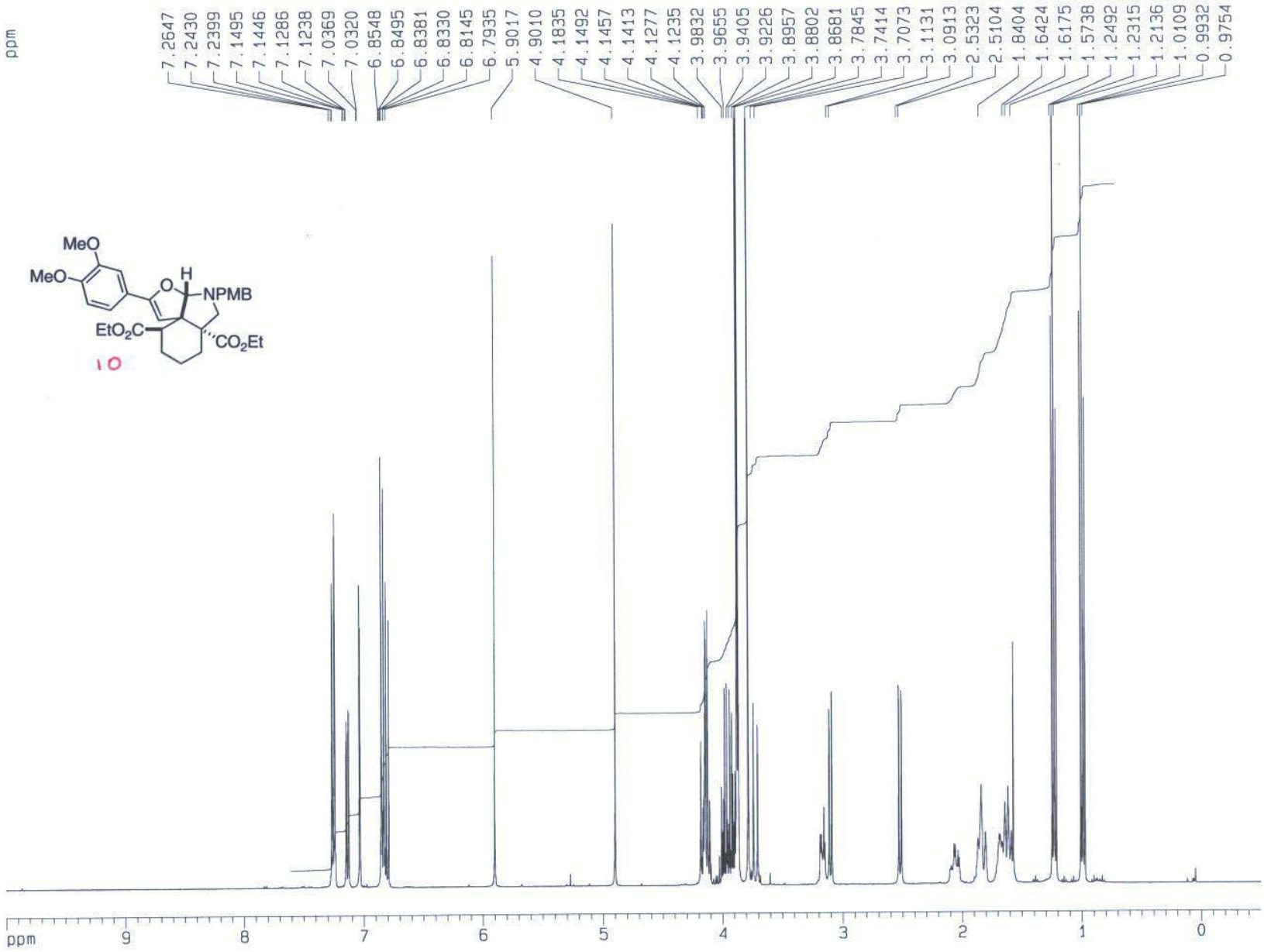

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TE	305.0 K
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======== CHANNEL f1 ========

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F2 - Processing parameters

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GB	0
PC	1.00

1D NMR plot parameters

CX	22.00 cm
CY	45.72 cm
F1P	10.000 ppm
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F2	-200.06 Hz
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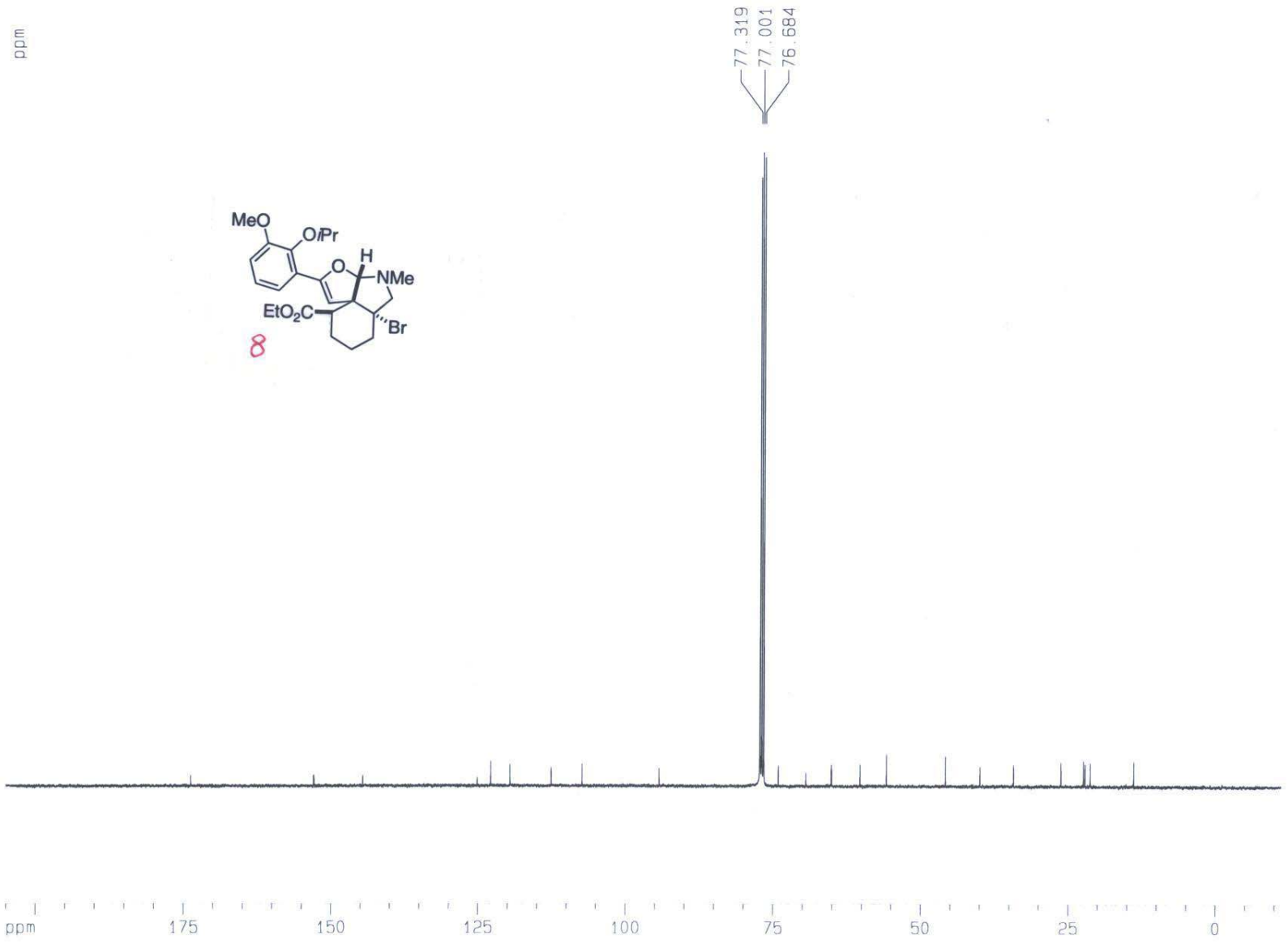

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SFO1	100.6225290 MHz

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F2 - Processing parameters

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1D NMR plot parameters

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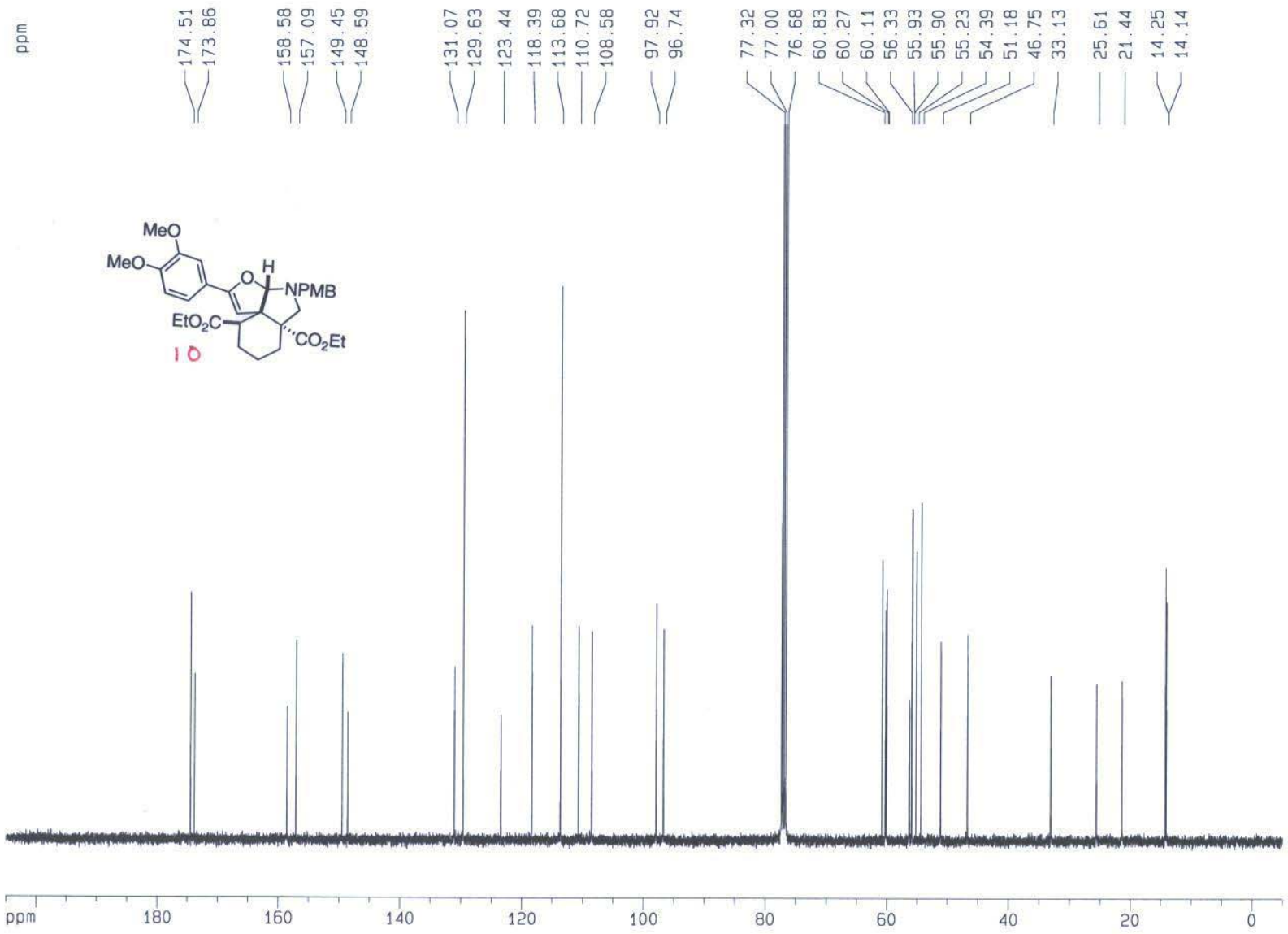

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======== CHANNEL f2 ========

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PL2	120.00 dB
PL12	19.60 dB
PL13	26.60 dB
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SSB	0
LB	0.50 Hz
GB	0
PC	1.00

1D NMR plot parameters

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CY	21.50 cm
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F1	20625.62 Hz
F2P	-5.000 ppm
F2	-503.07 Hz
PPMCM	9.76744 ppm/cm
HZCM	982.72943 Hz/cm