Studies towards the total synthesis of Cytotoxic Sponge Alkaloid Pyrinodemin A

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Supporting Information

General Procedures

Proton magnetic resonance spectra were recorded on Varian Gemini 200 (200MHz), Brüker AC200 (200MHz), Brüker DPX400 (400MHz), Brüker AM500 (500MHz), and Brüker AMX500 (500MHz), spectrometers at ambient temperature. Proton spectra assignments are supported by ^{1}H-^{1}H COSY where necessary. Chemical shifts (δ_H) are reported in parts per million (ppm) and are referenced to the residual solvent peak. Coupling constants (*J*) are recorded to the nearest 0.5 Hz.

Carbon magnetic resonance spectra were recorded on Varian Gemini 200 (50.3MHz), Brüker AC200 (50.3MHz), Brüker DPX400 (100.6MHz), Brüker AM500 (125.8MHz), and Brüker AMX500 (125.8MHz), spectrometers at ambient temperature. Chemical shifts (δ_C) are reported in parts per million (ppm) and are referenced to the residual solvent peak. Carbon spectra assignments are supported by DEPT analysis and ^{13}C-^{1}H correlations where necessary.

For consistency when assigning NMR spectra, the following numbering system has been used for pyridine:

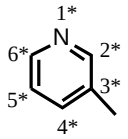


Figure 1. Numbering of 3-methylpyridine

Low-resolution mass spectra were recorded using a TRIO-1 GCMS spectrometer, a Micromass Platform (APCI) spectrometer, Micromass Autospec spectrometer (CI^+) and a micromass ZAB spectrometer (CI^+, EI). Only molecular ions (M^+), fragments from molecular ions and other major peaks are reported. High-resolution mass spectra were recorded by Mr. R. G. Procter on a Micromass Autospec spectrometer and are accurate to ±10ppm.

Microanalyses were carried out on an Elementar Vario EL at the Inorganic Chemistry Laboratory and by Elemental Microanalysis Limited, and are quoted to the nearest 0.1% for all elements except hydrogen which is quoted to the nearest 0.05%.

Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 Fourier Transform spectrometer as a thin film between NaCl plates. Absorption maxima (ν_{max}) of the major peaks are reported in wavenumbers (cm^{-1}).

The melting point of IBX was measured using a Cambridge Instruments Gallen^{TM} III hot stage melting point apparatus and is uncorrected.

Thin layer chromatography (TLC) was performed using Merck aluminium foil backed plates pre-coated with silica gel 60 F_{254} (1.05554). Visualisation was by the quenching of UV fluorescence (λ_{max} = 254nm), staining with 10% w/v ammonium molybdate in 1M sulphuric acid or 20% w/v phosphomolybdic acid in ethanol, followed by heating. Retention factors (R_f) are reported to 2 decimal places.

Column chromatography was performed using ICN silica 32-63, 60Å. Kügelrohr distillations were performed using a Büchi Glass Oven B-580 distillation apparatus at the temperature and pressure specified.

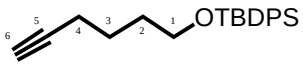
Anhydrous diethyl ether, and THF were obtained by distillation from sodium/benzophenone ketyl under nitrogen, anhydrous DCM was distilled from calcium hydride under nitrogen. PE 30-40 refers to the fraction of light petroleum ether boiling between 30 and 40 °C, PE 40-60 refers to the fraction of light petroleum ether boiling between 40 and 60°C, and were distilled before use. All water used was distilled, except where otherwise indicated. Solvents were evaporated on a Büchi R110 Rotavaporator.

Diisopropylamine, 3-methylpyridine, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), and benzene were distilled from calcium hydride under argon or under reduced pressure and stored over 4Å molecular sieves under argon until used. Dimethyl sulphoxide was dried over 4Å molecular sieves. Imidazole was dried under vacuum before use.

Commercial solutions of ^{n}BuLi were titrated against 1,3-diphenylacetone-*p*-toluenesulphonylhydrazone in THF prior to use[1]. All other reagents were purified in accordance with the instructions in D Perrin and W Armarego, "Purification of Laboratory Chemicals" Pergamon Press, third edition, 1988, or used as obtained from commercial sources.

Experimental Procedures

Preparation of 1-tert-*butyldiphenylsilyloxy-hex-5-yne* **6**



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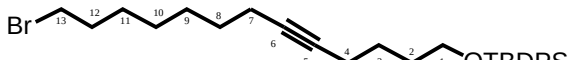
To a stirred solution of 5-hexyn-1-ol (**5**, 1.07g, 10.9mmol) and dried imidazole (1.84g, 27.1mmol) in anhydrous THF (20ml) at 0°C under argon was added *tert*-butyldiphenylchlorosilane (3.2ml, 12.4mmol) dropwise. After the addition was complete, the mixture was stirred at room temperature for 2 hours. The reaction was quenched with $NH_4Cl_{(aq)}$ (sat., 50ml), and extracted with a 1:1 mixture of Et_2O and PE 30-40 (3 × 50ml). The organic phases were washed with $NaCl_{(aq)}$ (sat., 25ml) and dried over $MgSO_4$. Removal of solvent *in vacuo* afforded the crude product which was purified by flash chromatography (25% benzene, 75% PE 30-40) to yield 1-*tert*-butyldiphenylsilyloxy-hex-5-yne **6** (3.54g, 10.5,mmol, 96%) as a colourless oil; R_f = 0.33 (25% benzene, 75% PE 30-40); ν_{max}/cm^{-1} (thin film) 3308 (m), 3071 (m), 3050 (m), 2932 (s), 2857 (s), 2120 (w), 1590 (w), 1472 (m), 1428 (s), 1390 (m), 1362 (m), 1112 (s), 824 (s), 741 (s), 702 (s), 614 (s); microanalysis found C, 78.3; H, 8.55 $C_{22}H_{28}OSi$ requires C, 78.5; H, 8.39; δ_H (200MHz, $CDCl_3$) 1.18 (9H, s, $C(C\underline{H}_3)_3$), 1.70-1.90 (4H, m, H-2, H-3), 2.05 (1H, t, *J* 3.0Hz H-6), 2.25-2.40 (2H, m, H-4), 3.80 (2H, t, *J* 6Hz, H-1), 7.40-7.60 (6H, m, Ph-H) 7.75-7.85 (4H, m, Ph-H); δC (50.3 MHz, $CDCl_3$) 18.7 (1C, C-4), 19.7 (1C, $\underline{C}(CH_3)_3$), 25.5 (1C, C-3), 27.4 (3C, $C(\underline{C}H_3)_3$), 32.1 (1C, C-2), 63.8 (1C, C-1), 68.8 (1C, C-6), 85.0 (1C, C-5), 128.1 (4CH, Ph), 130.1 (2CH, Ph), 134.5 (2C, Ar<u>C</u>-Si), 136.1 (4CH, Ph).

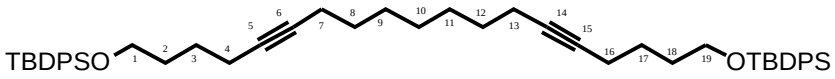
*Preparation of 13-bromo-1-*tert*-butyldiphenylsilyloxy-tridec-5-yne* **7**



7

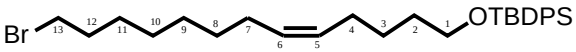
To a stirred solution of 1-*tert*-butyldiphenylsilyloxy-hex-5-yne **6** (11.5g, 34.3mmol) in anhydrous THF (80ml) under argon at -16°C was added ^{n}BuLi (2.22M in hexanes, 15.5ml, 34.4mmol). After stirring at -16°C for 30 minutes, the yellow solution formed was added dropwise *via* cannula to a mixture of 1,7-dibromoheptane (23.5ml, 138mmol) and DMPU (20ml) under argon at -16°C, followed by anhydrous THF (2 × 40ml) rinse. The mixture was stirred for 2.5 hours from -16°C to room temperature. The mixture was quenched with H_2O (300ml) and $NH_4Cl_{(aq)}$ (sat., 50ml), then extracted into EtOAc (3 × 200ml). The organic phases were washed with half-saturated brine (50ml H_2O, 50ml sat. $NaCl_{(aq)}$) and dried over $MgSO_4$. Removal of solvent *in vacuo* afforded the crude product which was purified by flash chromatography (15% DCM, 85% PE 30-40) to yield 13-bromo-1-*tert*-butyldiphenylsilyloxy-tridec-5-yne **7** (12.0g, 23.3mmol, 68%) as a colourless oil; Rf = 0.12 (15% DCM, 85% PE 30-40); νmax/cm^{-1} (thin film) 3071 (m), 2932 (s), 2857 (s), 1590 (w), 1472 (m), 1428 (s), 1390 (m), 1361 (m), 1111 (s); m/z Probe CI^{+} (NH3) 514.9 (MH^{+} 81Br, 11%), 513 (MH^{+} ^{79}Br, 10%), 456.9 ([MH - ^{t}BuH]$^{+}$, 7%), 377.0 (16%), 337.0 (41%), 268.9 (100%), 215.9 (23%), 198.9 (29%); HRMS found MH^{+} = 513.2185, $C_{29}H_{42}OSiBr$ requires 513.2188; microanalysis found C, 67.8; H, 8.06. $C_{29}H_{41}OSiBr$ requires C, 67.8; H, 8.05; δH (200MHz, CDCl3) 1.15 (9H, s, C(CH3)3), 1.30-1.65 (8H, m, H-8 to H-11), 1.65-1.85 (4H, m, H-2, H-3), 1.85-2.05 (2H, m, H-12), 2.17-2.31 (4H, m, H-4, H-7), 3.47 (2H, t, J 7.0Hz, H-13), 3.78 (2H, t, J 6.0Hz, H-1), 7.40-7.58 (6H, m, Ph-H), 7.70-7.85 (4H, m, Ph-H); δC (50.3 MHz, CDCl3) 19.0, 19.2 (2CH2, C-4, C-7), 19.7 (1C, C(CH3)3), 26.0 (1C, C-3), 27.4 (3C, C(CH3)3), 28.5, 28.8, 29.1, 29.5 (4CH2, C-8 to C-11), 32.2 (1C, C-2), 33.2, 34.4 (2CH2, C-12, C-13), 64.0 (1C, C-1), 80.6, 80.7 (2CH, C-5, C-6), 128.0 (4CH, Ph), 130.0 (2CH, Ph), 134.5 (2C, ArC-Si), 136.0 (4CH, Ph).

Also isolated was 1,19-di-*tert*-butyldiphenylsilyloxynondec-5,14-diyne



(0.924g, 1.22mmol, 3.5% yield) as a colourless oil; R_f = 0.07; ν_{max}/cm^{-1} (thin film) 3071(m), 2932 (s), 1472 (s), 1428 (s), 1390 (m), 1112 (s), 1008 (m), 823 (s), 703 (s), 614 (s); m/z Probe CI^+ (NH_3) 769.1 (MH^+, 95%), 711.1 ($[MH - {}^tBuH]^+$, 100%); δ_H (200MHz, $CDCl_3$) 1.10 (18H, s, C(C<u>H</u>$_3$)$_3$), 1.30-1.80 (18H, m, H-2, H-3, H-8 to H-12, H-17, H-18), 2.10-2.30 (8H, m, H-4, H-7, H-13, H-16), 3.75 (4H, t, *J* 6.0Hz, H-1, H-19), 7.40-7.55 (12H, m, Ph-<u>H</u>), 7.70-7.80 (8H, m, Ph-<u>H</u>); δ_C (50.3 MHz, $CDCl_3$) 19.0, 19.2 (4C, C-4, C-7, C13, C-16), 19.7 (1C, <u>C</u>(CH_3)$_3$), 26.1 (2C, C-3, C-17), 27.4 (3C, C(<u>C</u>H_3)$_3$), 29.2, 29.6 (5CH_2, C-8 to C-12), 32.2 (2C, C-2, C-18), 64.0 (2C, C-1, C-19), 80.6, 80.7 (4CH, C-5, C-6, C-14, C-15), 128.1 (8CH, Ph), 130.0 (4CH, Ph), 134.5 (4C, Ar<u>C</u>-Si), 136.0 (8CH, Ph).

Preparation of Z-*13-bromo-1*-tert- *butyldiphenylsilyloxy-tridec-5-ene* **8**

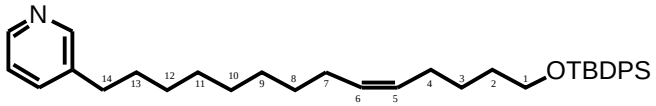


8

To a solution of 13-bromo-1-*tert*-butyldiphenylsilyloxy-tridec-5-yne **7** (13.0g, 25.4mmol) and anhydrous benzene (120ml) were added Lindlar's catalyst (3.91g) and quinoline (0.36ml) under argon. The mixture was stirred under hydrogen gas (1atm, balloon) for 2 hours. The mixture was then filtered through cellulose and washed with benzene (300ml). The organic phase was washed with $KHSO_{4(aq)}$ (1%, 90ml), neutralised with $NaHCO_{3(aq)}$ (sat., 100ml), then with $NaCl_{(aq)}$ (sat., 200ml) and dried over $MgSO_4$. Removal of solvent *in vacuo* afforded the crude product which was purified by flash chromatography (15% benzene, 85% cyclohexane) to yield *Z*-13-bromo-1-*tert*-butyldiphenylsilyloxy-tridec-5-ene **8** (12.3g, 23.9mmol, 94%) as a colourless oil; R_f = 0.36 (15% benzene, 85% cyclohexane); ν_{max}/cm^{-1} (thin film) 3056 (m), 3001 (m), 2931

(s), 2857 (s), 1590 (w), 1472 (m), 1428 (s), 1389 (m), 1112 (s), 824 (m), 702 (s), 614 (m); m/z Probe CI^+ (NH_3) 517.0 (MH^+ ^{81}Br, 52%), 515 (46%), 437.1 (46%), 435.0 (45%), 396.1 (15%), 379.0 (28%), 269.0 (39%), 256.0 (26%), 215.9 (32%), 196.0 (100%), 179.0 (37%), 123.2 (34%), 107.9 (39%), 95.5 (47%); HRMS found 515.2355, $C_{29}H_{44}OSiBr$ requires 515.2345; microanalysis found C, 67.3; H, 8.34. $C_{29}H_{43}OSiBr$ requires C, 67.6; H, 8.35; δ_H (200MHz, $CDCl_3$) 1.15 (9H, s, $C(C\underline{H}_3)_3$), 1.32-1.60 (10H, m, H-3 and H-8 to H-11), 1.60-1.80 (2H, m, H-2), 1.93 (2H, quin, *J* 7.0Hz, H-12), 2.05-2.20 (4H, m, H-4, H-7), 3.49 (2H, t, *J* 7.0Hz, H-13), 3.76 (2H, t, *J* 6.0Hz, H-1), 5.35-5.55 (2H, m, H-5, H-6), 7.40-7.60 (6H, m, Ph-H), 7.70-7.85 (4H, m, Ph-H); δ_C (50.3 MHz, $CDCl_3$) 19.7 (1C, $\underline{C}(CH_3)_3$), 26.4 (1C, C-3), 27.4 (3C, $C(\underline{C}H_3)_3$), 27.6, 28.6, 29.1, 29.5, 30.1 ($5CH_2$, C-4, and C-7 to C-11), 32.7 (1C, C-2), 33.3, 34.5 ($2CH_2$, C-12, C-13), 64.3 (1C, C-1), 128.1 (4CH, Ph), 130.0 (2CH, Ph), 130.3, 130.4 (2CH, C-5, C-6), 134.6 (2C, Ar$\underline{C}$-Si), 136.0 (4CH, Ph).

Preparation of Z*-1-*tert*-butyldiphenylsilyloxy-14-(pyridin-3-yl)-tetradec-5-ene* **9**

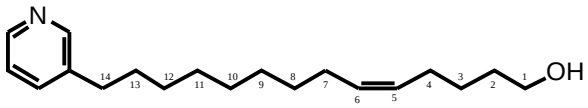


9

To a stirred solution of diisopropylamine (1.10ml 7.84mmol) in anhydrous THF (20ml) under argon was added ^{n}BuLi (2.25M in hexanes, 3.5ml, 7.87mmol) keeping the solution at a constant 0°C by internal monitoring. The pale yellow solution was stirred at 0°C for 30 minutes and subsequent addition of DMPU (1.0ml 8.26mmol) turned the solution bright yellow. After 15 minutes stirring, 3-methylpyridine (0.76ml 7.79mmol) was added over 10 minutes. After a further 30 minutes stirring at 0°C, the blood red solution was cooled to -78°C and turned orange. To this was added a -78°C solution of *Z*-13-bromo-1-*tert*-butyldiphenylsilyloxy-tridec-5-ene **8** (1.33g 2.59mmol) in anhydrous THF (20ml) by cannula under argon over a period of 10 minutes, followed by anhydrous THF (2 x 10ml) rinse. The reaction was stirred for 20 hours from -78°C to room temperature. The reaction was quenched with $NH_4Cl_{(aq)}$ (sat., 50ml) and H_2O

(50ml) and extracted with EtOAc (3 × 100ml). The organic phases were washed with $NaCl_{(aq)}$ (sat., 60ml) and dried over $MgSO_4$. Removal of solvent *in vacuo* afforded the crude product which was purified by flash chromatography (25% EtOAc, 75% benzene) to yield *Z*-1-*tert*-butyldiphenylsilyloxy-14-(pyridin-3-yl)-tetradec-5-ene **9** (0.861g, 1.63mmol, 63%) as a pale yellow oil; R_f = 0.27 (25% EtOAc, 75% benzene); ν_{max}/cm^{-1} (thin film) 3056 (m), 3001 (m), 2928 (s), 2857 (s), 1590 (w), 1574 (m), 1572, (s), 1428 (s), 1389 (m), 1186 (m), 1111 (s), 824 (s), 703 (s), 666 (s); m/z Probe CI^+ (NH_3) 528.4 (MH^+, 100%), 470.3 ([MH - $^tBuH]^+$, 62%), 450.3 ([MH - PhH]$^+$, 3%); HRMS found 528.3666 $C_{25}H_{50}NOSi$ requires 528.3662; microanalysis found C, 79.5; H, 9.37; N, 2.7. $C_{25}H_{49}NOSi$ requires C, 79.6; H, 9.36; N, 2.7; δ_H (200MHz, $CDCl_3$) 1.13 (9H, s, C(C<u>H</u>$_3$)$_3$), 1.30-1.58 (12H, m, H-3 and H-8 to H-12), 1.58-1.80 (4H, m, H-2, H-13), 2.00-2.20 (4H, m, H-4, H-7), 2.67 (2H, t, *J* 7.5Hz, H-14), 3.75 (2H, t, *J* 6.5Hz, H-1), 5.30-5.52 (2H, m, H-5, H-6), 7.20-7.30 (1H, m, Py H-5*) 7.40-7.60 (7H, m, 1H Py H-4*, 6H Ph-<u>H</u>), 7.70-7.80 (4H, m, Ph-<u>H</u>), 8.45–8.55 (2H, m, Py H-2*, H-6*); δ_C (50.3 MHz, CDCl3) 19.7 (1C, <u>C</u>(CH$_3$)$_3$), 26.4 (1CH_2, C-3), 27.3 (3C, C(<u>C</u>H$_3$)$_3$), 27.7, 29.6, 29.7, 29.9, 30.2, 31.6, 32.7, 33.5 (10CH_2, C-2, C-4, C-7 to C-14), 64.3 (1C, C-1), 123.7 (1C, Py C-5*), 128.0 (4C, Ph), 129.9 (2CH, Ph), 130.2, 130.5 (2CH, C-5, C-6), 134.6 (2C, Ar<u>C</u>-Si), 136.0 (4CH, Ph) 136.2 (1C, Py C-4*), 138.4 (1C, Py C-3*), 147.6, 150.5 (2C, Py C-2*, C-6*).

Preparation of Z*-14-(pyridin-3-yl)-tetradec-5-en-1-ol* **10**

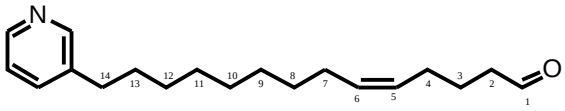


10

To a stirred solution of *Z*-1-*tert*-butyldiphenylsilyloxy-14-(pyridin-3-yl)-tetradec-5-ene **9** (7.43g, 14.1mmol) in methanol (150ml) was added ammonium fluoride (7.30g, 197mmol). The mixture was kept at 67°C for 3 hours under argon. The reaction was quenched with $NaHCO_{3(aq)}$ (sat., 150ml) and H_2O (150ml) and extracted with EtOAc (3 × 200ml). The organic phases were washed with $NaCl_{(aq)}$ (sat., 100ml) and dried over

$MgSO_4$. Removal of solvent *in vacuo* afforded the crude product which was purified by flash chromatography (20% EtOAc, 40% Et_3N, 40% PE 30-40) to yield *Z*-14-(pyridin-3-yl)-tetradec-5-en-1-ol **10** (3.03g, 10.5mmol, 97%) as a pale yellow oil; R_f = 0.31 (20% EtOAc, 40% Et_3N, 40% PE 30-40); ν_{max}/cm^{-1} (thin film) 3332 (br, m), 3001 (m), 2927 (s), 2871 (s), 1663 (w), 1590 (w), 1465 (m), 1424 (m), 1186 (w), 1067 (m) 731 (m); m/z Probe CI^+ (NH_3) 290.3 (MH^+, 100%), 259.2 ([MH - $CH_2OH]^+$), 4%), 244.2 ([MH - $CH_3CH_2OH]^+$, 9%), 230.2 ([MH - $CH_3CH_2CH_2OH]^+$, 5%); HRMS found MH^+ = 290.2490, $C_{19}H_{32}NO$ requires 290.2484); δ_H (200MHz, $CDCl_3$) 1.20-1.55 (12H, m, H-3 and H-8 to H-12), 1.55-1.75 (4H, m, H-2, H-13), 1.90-2.20 (4H, m, H-4, H-7), 2.62 (2H, t, *J* 7.5Hz, H-14), 3.66 (2H, t, *J* 6.5Hz, H-1), 5.27-5.55 (2H, m, H-5, H-6), 7.15-7.30 (1H, m, Py H-5*) 7.45-7.60 (1H, m, Py H-4*), 8.35 –8.50 (2H, br, s, Py H-2*, H-6*); δ_C (50.3 MHz, $CDCl_3$) 26.4 (1C, C-3), 27.4, 27.6, 29.5, 29.6, 29.8, 30.1, 31.5, 32.9, 33.4 (10CH_2, C-2, C-4, C-7 to C-14), 62.8 (1C, C-1), 123.7 (1C, Py C-5*), 129.9, 130.6 (2CH, C-5, C-6) 136.4 (1C, Py C-4*), 138.5 (1C, Py C-3*), 147.3, 150.1 (2C, Py C-2*, C-6*).

Preparation of Z*-14-(pyridin-3-yl)-tetradec-5-en-1-al* **3**

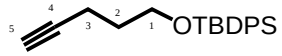


3

To a stirred solution of IBX (0.565g, 2.02mmol) in DMSO (7ml) under argon was added a solution of *Z*-14-(pyridin-3-yl)-tetradec-5-en-1-ol **10** (0.389g, 1.34mmol) in anhydrous THF (1ml) by cannula under argon followed by anhydrous THF (4 × 1ml) rinse. The reaction mixture was stirred for 3.5 hours after which time it was diluted by H_2O (100ml), filtered through a sintered glass funnel, and extracted with EtOAc (4 × 30ml). The organic phases were washed with $NaCl_{(aq)}$ (sat., 30ml) and dried over Na_2SO_4. Filtration and removal of solvent *in vacuo* afforded the crude product which was purified by flash chromatography (40% PE 40-60, 60% EtOAc) to yield Z-14-(pyridin-3-yl)-tetradec-5-en-1-al **3** (0.357g, 1.24mmol, 92%) as a pale yellow oil;

R_f = 0.29 (40% PE 30-40, 60% EtOAc); ν_{max}/cm^{-1} (thin film) 3005 (m), 2927 (s), 2855 (s), 2718 (m), 1725 (s), 1654 (w), 1575 (m), 1478 (m), 1422 (s), 1188 (w), 1027 (m), 784 (m), 715 (s); m/z APCI 288.3 (MH^+, 100%); HRMS found MH^+ = 288.2322, $C_{19}H_{30}NO$ requires 288.2327; δ_H (200MHz, $CDCl_3$) 1.32 (10H, br, s, H-8 to H-12), 1.55-1.80 (4H, m, H-3, H-13), 1.95-2.20 (4H, m, H-4, H-7), 2.46 (2H, dt, J_1 7.5Hz, J_2 2.0Hz, H-2), 2.63 (2H, t, J 7.5Hz, H-14), 5.25-5.50 (2H, m, H-5, H-6), 7.22 (1H, dd, J_1 8.0Hz, J_2 5.0Hz, Py H-5*) 7.51 (1H, br, d, J 7.5Hz, Py H-4*), 8.40 –8.50 (2H, m, Py, H-2*, H-6*), 9.80 (0.5H, t, J 2.0Hz, H-1); δ_C (50.3 MHz, $CDCl_3$) 22.5 (1C, C-3), 26.9, 27.6, 29.5, 29.7, 29.8, 30.0, 31.5, 33.4, (9CH_2, C-4 and C-7 to C-14), 43.7 (1C, C-2), 123.6 (1C, Py C-5*), 128.7, 131.7 (2CH, C-5, C-6) 136.2 (1C, Py C-4*), 138.4 (1C, Py C-3*), 147.6, 150.4 (2C, Py C-2*, C-6*), 203.0 (1C, C-1).

Preparation of 1-tert-*butyldiphenylsilyloxy-pent-4-yne* **12**

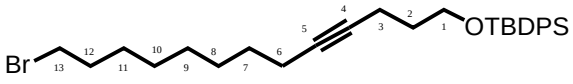


12

To a stirred solution of 4-pentyn-1-ol (**11**, 1.63g, 19.3mmol) and dried imidazole (2.91g, 42.7mmol) in anhydrous THF at 0°C (30ml) under argon was added *tert*-butyldiphenylchlorosilane (5.40ml, 20.9mmol) dropwise. The mixture was stirred at room temperature for 2 hours, then was quenched with $NH_4Cl_{(aq)}$ (sat., 90ml), and extracted with a 1:1 mixture of Et_2O and PE 30-40 (3 × 90ml). The organic phases were washed with $NaCl_{(aq)}$ (sat., 90ml) and dried over $MgSO_4$. Removal of solvent *in vacuo* afforded the crude product which was purified by flash chromatography (25% benzene, 75% PE 30-40) to yield 1-*tert*-butyldiphenylsilyloxy-pent-4-yne **12** (5.79g, 17.94,mmol, 93%) as a colourless oil; R_f = 0.41 (25% benzene, 75% PE 30-40); ν_{max}/cm^{-1} (thin film) 3307 (m), 3072 (m), 2932 (s), 2858 (s), 1473 (m), 1428 (s), 1390 (m), 1362 (w), 1190 (w), 1111 (s); m/z Probe CI^+ (NH_3) 340 ($[MNH_4]^+$, 4%), 323 (MH^+, 100%), 282 (12%), 265 ($[MH - {}^tBuH]^+$, 7%), 256 (10%); HRMS found MH^+ = 323.1823, $C_{21}H_{27}OSi$ requires 323.1831; δ_H (200MHz, $CDCl_3$) 1.20 (9H, s, $C(C\underline{H}_3)_3$), 1.80 (2H, quin, J 6.0Hz, H-2), 2.05 (1H, t, J 2.5Hz, H-6), 2.50 (2H,

td, J_1 7.0Hz, J_2 2.5Hz, H-3), 3.90 (2H, t, *J* 6.0Hz, H-1), 7.40-7.55 (6H, m, Ph-H) 7.70-7.80 (4H, m, Ph-H); δ_C (50.3 MHz, $CDCl_3$) 15.5 (1C, C-3), 19.8 (1C, $\underline{C}(CH_3)_3$), 27.4 (3C, $C(\underline{C}H_3)_3$), 32.0 (1C, C-2), 62.8 (1C, C-1), 68.9 (1C, C-5), 84.7 (1C, C-4), 128.2 (4CH, Ph), 130.1 (2CH, Ph), 134.3 (2C, Ar<u>C</u>-Si), 136.1 (4CH, Ph).

*Preparation of 13-bromo-1-*tert*-butyldiphenylsilyloxy-tridec-4-yne* **13**

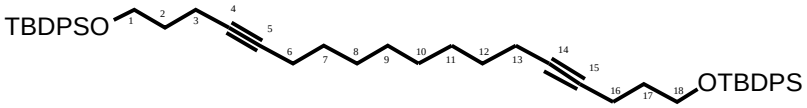


13

To a stirred solution of 1-*tert*-butyldiphenylsilyloxy-pent-4-yne **12** (5.77g, 17.9mmol) in anhydrous THF (40ml) under argon at -16°C was added ^{n}BuLi (2.22M in hexanes, 8.10ml, 18.0mmol). After stirring at -16°C for 30 minutes, the yellow solution formed was added dropwise *via* cannula to a mixture of 1,8-dibromooctane (13.2ml, 71.6mmol) and DMPU (10ml) under argon at -16°C, followed by anhydrous THF (2 × 20ml) rinse. The solution was stirred for 2 hours from -16°C to room temperature. The mixture was quenched with H_2O (300ml) and $NH_4Cl_{(aq)}$ (sat., 50ml), then extracted into EtOAc (3 × 150ml). The organic phases were washed with half-saturated brine (45ml H_2O, 45ml sat. $NaCl_{(aq)}$) and dried over $MgSO_4$. Removal of solvent *in vacuo* afforded the crude product which was purified by flash chromatography (15% DCM, 85% PE 30-40) to yield 13-bromo-1-*tert*-butyldiphenylsilyloxy-tridec-4-yne **13** (7.12g, 13.9mmol, 77%) as a colourless oil; R_f = 0.13 (15% DCM, 85% PE 30-40); ν_{max}/cm^{-1} (thin film) 3309 (w), 3071 (m), 2930 (s), 2857 (s), 1472 (m), 1428 (s), 1390 (w), 1361 (w), 1260 (w), 1189 (w), 1111 (s); m/z Probe CI^+ (NH_3) 515.2 (MH^+ ^{81}Br, 9%), 513.2 (MH^+ ^{79}Br, 9%), 340.2 (6%), 323.2 (100%), 282.2 (12%), 265.2 (6%), 256.2 (11%); HRMS found MH^+ = 513.2186, $C_{29}H_{42}OSiBr$ requires 513.2188; microanalysis found C, 67.7; H, 8.08. $C_{29}H_{41}OSiBr$ requires C, 67.8; H, 8.09; δ_H (200MHz, $CDCl_3$) 1.15 (9H, s, $C(C\underline{H}_3)_3$), 1.30-1.60 (10H, m, H-7 to H-11), 1.75-2.05 (4H, m, H-2, H-12), 2.15-2.25 (2H, m, H-6), 2.35-2.45 (2H, m, H-3), 3.50 (2H, t, *J* 7.0Hz H-13), 3.85 (2H, t, *J* 6.0Hz, H-1), 7.40-7.55 (6H, m, Ph-H), 7.70-7.80 (4H, m, Ph-H); δ_C (50.3 MHz,

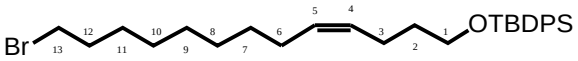
$CDCl_3$) 15.8, (1C, C-3), 19.2 (1C, C-6), 19.7 (1C, $\underline{C}(CH_3)_3$), 27.3 (3C, $C(\underline{C}H_3)_3$), 28.6, 29.1, 29.2 29.4, 29.5 (5C, C-7 to C-11), 32.5 (1C, C-2), 33.3 (1C, C-12), 34.5 (1C, C-13), 63.0 (1C, C-1), 80.2, 80.8 (2C, C-4, C-5), 128.1 (4CH, Ph), 130.0 (2CH, Ph), 134.5 (2C, Ar$\underline{C}$-Si), 136.0 (4CH, Ph).

Also isolated was 1,18-di-*tert*-butyldiphenylsilyloxyoctadec-4,14-diyne



(0.599g, 0.78mmol, 4.4% yield) as a colourless oil; R_f = 0.08; δ_H (200MHz, $CDCl_3$) 1.10 (18H, s, $C(C\underline{H}_3)_3$), 1.30-1.60 (12H, m, H-7 to H-12), 1.80 (4H, quin, *J* 7.0Hz, H-3, H-17), 2.10-2.25 (4H, m, H-6, H-13), 2.30-2.45 (4H, m, H-3, H-16), 3.80 (4H, t, *J* 6.0Hz, H-1, H-18), 7.40-7.55 (12H, m, Ph-$\underline{H}$), 7.70-7.80 (8H, m, Ph-$\underline{H}$); δ_C (50.3 MHz, $CDCl_3$) 15.8, (2C, C-3, C-16), 19.2 (2C, C-6, C-13), 19.7 (1C, $\underline{C}(CH_3)_3$), 27.3 (3C, $C(\underline{C}H_3)_3$), 29.4, 29.6 ($6CH_2$, C-7 to C-12), 32.5 (2C, C-2, C-17), 63.0 (2C, C-1, C-18), 80.1, 80.9 (4C, C-4, C-5, C-14, C-15), 128.1 (8CH, Ph), 130.0 (4CH, Ph), 134.4 (4C, Ar$\underline{C}$-Si), 136.0 (8CH, Ph).

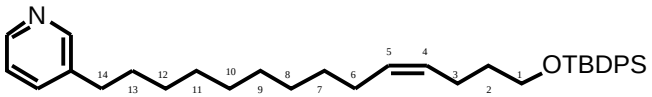
Preparation of Z*-13-bromo-1-*tert*- butyldiphenylsilyloxy-tridec-4-ene* **14**



14

To a solution of 13-bromo-1-*tert*-butyldiphenylsilyloxy-tridec-4-yne **13** (1.01g, 1.97mmol) and anhydrous benzene (20ml) were added Lindlar's catalyst (0.304g) and quinoline (30μl) under argon. The mixture was stirred under hydrogen gas (1atm, balloon) for 2 hours. The mixture was filtered through cellulose and washed with benzene (180ml). The organic phase was washed with $KHSO_4$ (1%, 50ml), neutralised with $NaHCO_{3(aq)}$ (sat., 50ml), then with $NaCl_{(aq)}$ (sat., 100ml) and dried over $MgSO_4$. Removal of solvent *in vacuo* afforded the crude product which was purified by flash chromatography (15% benzene, 85% cyclohexane) to yield *Z*-13-bromo-1-*tert*-butyldiphenylsilyloxy-tridec-4-ene **14** (0.983g, 1.91mmol, 97%) as a colourless oil; R_f = 0.26 (15% benzene, 85% cyclohexane); ν_{max}/cm^{-1} (thin film) 3071 (m), 3001 (m), 2930 (s), 2856 (s), 1590 (w), 1475 (m), 1428 (s), 1390 (w), 1361 (w), 1261 (w), 1189 (w), 1112 (s); m/z Probe CI^+ (NH_3) 534.4 ($[MNH_4]^{+\ 81}Br$, 6%) 517.4 ($MH^{+\ 81}Br$, 100%), 515 ($MH^{+\ 79}Br$, 99%), 437.5 ($[MH - Br]^+$, 4%), 325.3 (4%), 256.3 (5%), 196.2 (13%), 179.3 (15%), 137.2 (5%), 123.2 (7%), 95.2 (8%); HRMS found MH^+ 515.2349, $C_{29}H_{44}OSiBr$ requires 515.2345; microanalysis found C, 67.7; H, 8.30. $C_{29}H_{43}OSiBr$ requires C, 67.6; H, 8.35; δ_H (200MHz, $CDCl_3$) 1.15 (9H, s, $C(C\underline{H}_3)_3$), 1.30-1.60 (10H, m, H-7 to H-11), 1.70 (2H, quin, *J* 6.0Hz H-2), 1.95 (2H, quin, *J* 7.0Hz H-12), 2.05-2.30 (4H, m, H-3, H-6), 3.50 (2H, t, *J* 7.0Hz, H-13), 3.76 (2H, t, *J* 6.5Hz, H-1), 5.35-5.55 (2H, m, H-4, H-5), 7.40-7.60 (6H, m, Ph-H), 7.70-7.85 (4H, m, Ph-H); δ_C (50.3 MHz, $CDCl_3$) 19.7 (1C, $\underline{C}(CH_3)_3$), 24.0 ($1CH_2$), 27.4 (3C, $C(\underline{C}H_3)_3$), 27.7, 28.7, 29.2, 29.7, 29.8, 30.2, ($6CH_2$, C-6 to C-11), 33.2, 33.3, 34.5 (3C, C-2, C-12, C-13), 63.9 (1C, C-1), 128.1 (4CH, Ph), 129.7 (1CH, C=C), 130.0 (2CH, Ph), 130.8 (1CH, C=C), 134.6 (2C, Ar$\underline{C}$-Si), 136.1 (4CH, Ph).

Preparation of Z-*1*-tert-*butyldiphenylsilyloxy-14-(pyridin-3-yl)-tetradec-4-ene* **15**

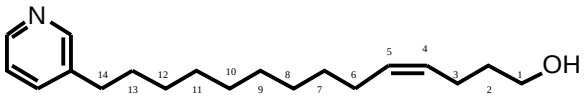


15

To a stirred solution of diisopropylamine (8ml, 57mmol) in anhydrous THF (40ml) under argon was added ^{n}BuLi (2.22M in hexanes, 25.8ml, 57.3mmol) keeping the solution at a constant 0°C by internal monitoring. The pale yellow solution was stirred at 0°C for 30 minutes and subsequent addition of DMPU (6.90ml 56.9mmol) turned the solution bright yellow. After 15 minutes stirring, 3-methylpyridine (5.60ml 57.4 mmol) was added over 10 minutes. After a further 30 minute stir at 0°C, the blood red solution was cooled to -78°C and turned orange. To this was added a -78°C solution of *Z*-13-bromo-1-*tert*-butyldiphenylsilyloxy-tridec-4-ene **14** (9.82g 19mmol) in anhydrous THF (40ml) by cannula under argon over a period of 10 minutes, followed by THF (2 × 20ml) rinse. The reaction was stirred for 20 hours from -78°C to room temperature. The reaction was quenched with $NH_4Cl_{(aq)}$ (sat., 100ml) and H_2O (100ml) and extracted with EtOAc (3 × 200ml). The organic phases were washed with $NaCl_{(aq)}$ (sat., 100ml) and dried over $MgSO_4$. Removal of solvent *in vacuo* afforded the crude product which was purified by flash chromatography (25% EtOAc, 75% benzene) to yield *Z*-1-*tert*-butyldiphenylsilyloxy-14-(pyridin-3-yl)-tetradec-4-ene **15** (5.91g, 11.2mmol, 59%) as a pale yellow oil; R_f = 0.25 (25% EtOAc, 75% benzene); ν_{max}/cm^{-1} (thin film) 3071 (w), 3000 (m), 2929 (s), 2856 (s), 1590 (w), 1574 (w), 1472 (m), 1428 (s), 1390 (w), 1361 (w), 1261 (w), 1189 (w), 1112 (s), 824 (m), 702 (s); m/z Probe CI^+ (NH_3) 528.3 (MH^+, 100%), 470.5 ([MH – ^{t}BuH]$^+$, 45%), 199.1 (5%), 94.0 (11%); HRMS found MH^+ = 528.3658, $C_{35}H_{50}NOSi$ requires 528.3662; δ_H (200MHz, $CDCl_3$) 1.14 (9H, s, C(C<u>H</u>$_3$)$_3$), 1.30-1.50 (12H, br, s, H-7 to H-12), 1.70 (4H, quin, *J* 7.0Hz, H-2, H-13), 2.02-2.30 (4H, m, H-3, H-6), 2.67, (2H, t, *J* 7.5Hz, H-14) 3.75 (2H, t, *J* 6.5Hz, H-1), 5.32-5.55 (2H, m, H-4, H-5), 7.20-7.32 (1H, m, Py H-5*) 7.40-7.60 (7H, m, 6H Ph-<u>H</u>, 1H Py H-4*), 7.70-7.80 (4H, m, Ph-<u>H</u>), 8.47-8.57 (2H, m, Py H-2*, H-6*); δ_C (50.3 MHz, $CDCl_3$) 19.7 (1C, <u>C</u>(CH$_3$)$_3$), 24.0 (1CH$_2$), 27.3 (3C, C(<u>C</u>H$_3$)$_3$), 27.7, 29.6,

29.8, 29.9, 30.0, 30.2, 31.6, 33.2, 33.5 ($10CH_2$), 63.9 (1C, C-1), 123.7 (1C, Py C-5*) 128.1 (4CH, Ph), 129.7 (1C, C=C), 130.0 (2CH, Ph), 130.9 (1C, C=C), 134.6 (2C, ArC-Si), 136.0 (4CH, Ph), 136.2 (1C, Py C-4*), 138.4 (1C, Py C-3*), 147.6, 150.4 (2C, Py C-2*, C-6*).

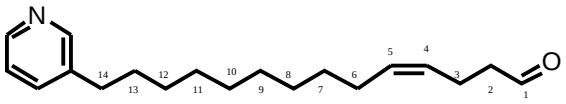
Preparation of Z*-14-(pyridin-3-yl)-tetradec-4-en-1-ol* **16**



16

To a stirred solution of *Z*-1-*tert*-butyldiphenylsilyloxy-14-(pyridin-3-yl)-tetradec-4-ene **15** (5.64g, 10.8mmol) in methanol (100ml) was added ammonium fluoride (5.59g, 151mmol). The mixture was kept at 75°C for 3.5 hours under argon. The reaction was quenched with $NaHCO_{3(aq)}$ (sat., 150ml) and H_2O (150ml) and extracted with EtOAc (3 × 200ml). The organic phases were washed with $NaCl_{(aq)}$ (sat., 100ml) and dried over $MgSO_4$. Removal of solvent *in vacuo* afforded the crude product which was purified by flash chromatography (20% EtOAc, 40% Et_3N, 40% PE 30-40) to yield *Z*-14-(pyridin-3-yl)-tetradec-4-en-1-ol **16** (3.03g, 10.5mmol, 97.0%) as a pale yellow oil; R_f = 0.29 (20% EtOAc, 40% Et_3N, 40% PE 30-40); ν_{max}/cm^{-1} (thin film) 3311 (br, m), 3000 (m), 2926 (s), 2860 (s), 1578 (w), 1465 (m), 1424 (s); m/z Probe CI^+ (NH_3) 290.3 (MH^+, 100%), 259.3 (5%), 244.3 (3%), 106.1 (5%); HRMS found MH^+ = 290.2484, $C_{19}H_{32}NO$ requires 290.2484; δ_H (200MHz, $CDCl_3$) 1.20-1.45 (12H, br, s, H-7 to H-12), 1.50-1.75 (4H, m, H-2, H-13), 1.95-2.20 (4H, m, H-3, H-6), 2.61, (2H, t, *J* 7.5Hz, H-14) 3.65 (2H, t, *J* 6.5Hz, H-1), 5.30-5.50 (2H, m, H-4, H-5), 7.20 (1H, dd, J_1 7.5Hz, J_2 5.0Hz Py H-5*) 7.50 (1H, br, d, *J* 8.0 Hz Py H-4*), 8.35-8.48 (2H, m, Py H-2*, H-6*); δ_C (50.3 MHz, $CDCl_3$) 24.1, 27.6, 29.5, 29.7, 29.8, 29.9, 30.1, 31.5, 33.2, 33.4 ($11CH_2$), 62.6 (1C, C-1), 123.8 (1C, Py C-5*), 129.5, 130.9 (2C, C-4, C-5), 136.5 (1C, Py C-4*), 138.5 (1C, Py C-3*), 147.3, 150.1 (2C, Py C-2*, C-6*).

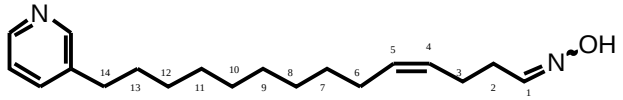
Preparation of Z*-14-(pyridin-3-yl)-tetradec-4-en-1-al* **17**



17

To a stirred solution of IBX (0.806g, 2.88mmol) in DMSO (8ml) under argon was added a solution of *Z*-14-(pyridin-3-yl)-tetradec-4-en-1-ol **16** (0.520g, 1.80mmol) in anhydrous THF (1ml) by cannula followed by anhydrous THF (4 × 1ml) rinse. The reaction mixture was stirred for 3.5 hours after which time it was diluted by H_2O (50ml), filtered through a sintered glass funnel, and extracted with EtOAc (3 × 20ml). The organic phases were washed with $NaCl_{(aq)}$ (sat., 20ml) and dried over Na_2SO_4. Removal of solvent *in vacuo* afforded the crude product which was purified by flash chromatography (40% PE 30-40, 60% EtOAc) to yield *Z*-14-(pyridin-3-yl)-tetradec-4-en-1-al **17** (0.475g, 1.65mmol, 92%) as a pale yellow oil; R_f = 0.36 (60% EtOAc, 40% PE 30-40); ν_{max}/cm^{-1} (thin film) 3428 (w), 3008 (m), 2926 (s), 2854 (s), 2719 (w), 1725 (s), 1575 (w), 1478 (m), 1465 (m), 1422 (s), 1189 (w) 1026 (w), 714 (s); m/z Probe APCI (NH_3) 288.3 (MH^+, 100%); HRMS found MH^+ = 288.2325, $C_{19}H_{30}NO$ requires 288.2327; δ_H (200MHz, $CDCl_3$) 1.30 (12H, br, s, H-7 to H-12), 1.50-1.70 (2H, m, H-13), 1.95-2.15 (2H, m, H-6), 2.30-2.45 (2H, m, H-3), 2.45-2.55 (2H, m, H-2) 2.60, (2H, t, *J* 7.5Hz, H-14), 5.25-5.52 (2H, m, H-4, H-5), 7.20 (1H, dd, *J* 5.0Hz, *J* 7.0Hz, Py H-5*), 7.50 (1H, br, d, *J* 7.5Hz, Py H-4*), 8.45 (2H, br, s, Py H-2*, H-6*), 9.78 (0.5H, t, *J* 1Hz, H-1); δ_C (50.3 MHz, $CDCl_3$) 20.5, 27.6, 29.5, 29.7, 29.8, 29.9, 29.9, 31.5, 33.4 ($10CH_2$), 44.2 (1C, C-2), 123.6 (1C, Py C-5*), 127.5, 132.0 (2CH, C-4, C-5), 136.1 (1C, Py C-4*), 138.3 (1C, Py C-3*), 147.6, 150.4 (2C, Py C-2*, C-6*), 202.6 (1C, C-1).

Preparation of Z*-14-(pyridin-3-yl)-tetradec-4-en-1-oxime* **18**

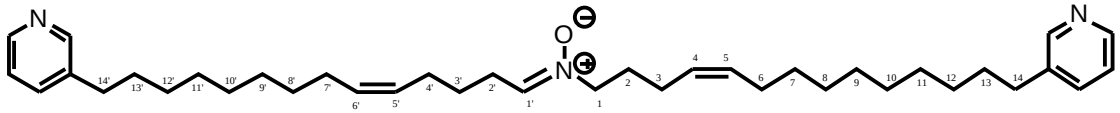


18

To a stirred solution of *Z*-14-(pyridin-3-yl)-tetradec-4-en-1-al **17** (0.220g. 0.767mmol) in anhydrous methanol (4ml) under argon were added sodium acetate (0.188g, 2.29mmol), then hydroxylamine hydrochloride (0.0529g, 0.7483mmol). The mixture was stirred for 4 hours at room temperature. The methanol was removed *in vacuo* and DCM (4ml) was added, with water (4ml) and $NaHCO_{3(s)}$ (0.228g, 2.71mmol, 3.5 equiv) to neutralise the acetic acid produced. The mixture was transferred to a separation funnel, diluted with H_2O (20ml) and extracted with EtOAc (3 × 30ml). The organic phases were washed with $NaHCO_{3(aq)}$ (sat., 20ml), H_2O (20ml), then with $NaCl_{(aq)}$ (sat., 20ml), and dried over Na_2SO_4. Removal of solvent *in vacuo* afforded the crude product which was purified by flash chromatography (flash silica, 40% PE 30-40, 60% EtOAc) to yield *Z*-14-(pyridin-3-yl)-tetradec-4-en-1-oxime **18** (0.215g, 7.11mmol, 93%) as a colourless oil; R_f = 0.29, 0.32 (*syn*/*anti* isomers, 40% PE 30-40, 60% EtOAc); ν_{max}/cm^{-1} (thin film) 3209 (br, m), 3081 (br, m), 3000 (m), 2926 (s), 2854 (s), 1640 (w), 1580 (m), 1453 (m), 1425 (m), 1326 (w), 1279 (w), 1190 (w), 1030 (w), 909 (w) 712 (m) ; m/z Probe APCI (NH_3) 303.3 (MH^+, 82%), 285.3 ($[MH - H_2O]^+$, 100%); HRMS found MH^+ = 303.2432, $C_{19}H_{31}N_2O$ requires 303.2436; The subscripts $_a$ and $_b$ differentiate between the *syn* and *anti* isomers, however they have not each been fully assigned. δ_H (200MHz, $CDCl_3$) 1.35 (12H, br, s, H-7 to H-12), 1.60-1.80 (2H, m, H-13), 2.00-2.20 (2H, m, H-6), 2.20-2.40 (3H, m, 2Hx0.5 H-2_a, 2H H-3), 2.40-2.60 (1H, m, 2Hx0.5 H-2_b) 2.68, (2H, t, *J* 7.5Hz, H-14), 5.30-5.60 (2H, m, H-4, H-5), 6.75-6.85 (0.5H, m, H-1_b), 7.25-7.35 (1H, m, Py H-5*) 7.49 (0.5H, m, H-1_a), 7.59 (1H, br, d, *J* 8.0Hz, Py H-4*), 8.40-8.50 (2H, m, Py H-2*, H-6*); δ_C (50.3 MHz, $CDCl_3$) 24.3, 25.0, 25.5, 27.7, 29.5, 29.5, 29.7, 29.8, 29.9, 30.0, 30.2, 31.5, 33.4 (11CH_2), 123.8, (1C, Py C-5*), 128.1, 128.4, 131.7 (2C, C-4, C-5), 136.7 (1C, Py

C-4*), 138.6 (1C, Py C-3*), 147.1, 149.9 (2C, Py C-2*, C-6*), 151.4 (1C, C-1 *anti* oxime), 152.0 (1C, C-1 *syn* oxime).

Preparation of nitrone **2**

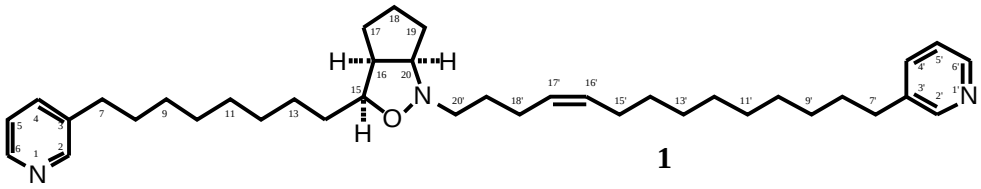


2

To a stirred solution of *Z*-14-(pyridin-3-yl)-tetradec-4-en-1-oxime **18** (0.169g, 0.559mmol) in methanol (45ml) at 0°C was added of methyl orange (indicator, 6mg) and conc. HCl (6 M) to turn the indicator red (approx. pH 3). Sodium cyanoborohydride (0.105g, 1.68mmol) in methanol (5ml) was added dropwise with concurrent addition of HCl to keep the mixture at pH 3. The mixture was stirred for 3 hours at 0°C. The mixture was basified (tested with pH paper) with 6N $NaOH_{(aq)}$,and worked up using solvents chilled to 0°C (to prevent decomposition of the hydroxylamine). The mixture was washed with $NaCl_{(aq)}$ (sat., 30ml) and extracted with chilled DCM (4 × 50ml). The organic phases were washed with H_2O (30ml) $NaCl_{(aq)}$ (sat., 20ml) and dried over Na_2SO_4. Removal of solvent *in vacuo* (no heating) to approximately 100ml DCM gave a solution of Z-14-(pyridin-3-yl)-tetradec-4-ene-1-hydroxylamine **4**. To the hydroxylamine solution, under argon, was added flame-dried Na_2SO_4 (8.61g, mass prior flame drying), and *Z*-14-(pyridin-3-yl)-tetradec-5-en-1-al **3** (0.175g, 0.609mmol) in anhydrous DCM (5ml + 4 × 5ml rinses) *via* cannula. The flask was stirred for 18 hours at room temperature. The crude reaction mixture was filtered, the solvent removed *in vacuo* and was purified by flash chromatography (30% Et_3N, 30% PE 30-40, 40% EtOAc) to yield nitrone **2** (0.286g, 0.498mmol, 89%) as a colourless oil; R_f = 0.10 (30% Et_3N, 30% PE 30-40, 40% EtOAc); ν_{max}/cm^{-1} (thin film) 3270 (br, m), 3003 (m), 2926 (s), 2853 (s), 1710 (m), 1670 (w), 1575 (m), 1478 (m), 1456 (m), 1422 (s), 1369 (w), 1277 (w), 1189 (w), 1128 (w), 1026 (m), 793 (w), 714 (s); m/z Probe APCI (NH_3) 596.6 (MNa^+, 30%) 574.6, (MH^+, 83%), 303.0 (50%), 288.3 (100%); HRMS found MH^+ = 574.4739, $C_{38}H_{60}N_3O$

requires 574.4736; δ_H (200MHz, $CDCl_3$) 1.20-1.45 (24H, br, s, H-7 to H-12, and H-8' to H-12'), 1.50-1.80 (6H, m, H-13, H-3', H-13'), 1.90-2.20 (10H, m, H-2, H-3, H-6, H-4', H-7'), 2.45-2.55 (2H, m, H-2'), 2.60 (4H, t, *J* 7.5Hz, H-14, H-14'), 3.80 (2H, m, H-1), 5.25-5.57 (4H, m, H-4, H-5, H-5', H-6'), 6.70 (1H, m, H-1'), 7.23 (2H, dd, J_1 7.5Hz, J_2 5.0Hz, Py H-5*), 7.52 (2H, br, d, *J* 7.5Hz, Py H-4*), 8.40-8.50 (4H, m, Py H-2*, H-6*); δ_C (50.3 MHz, $CDCl_3$) 24.3, 25.4, 26.1, 26.8, 27.5, 27.7, 28.5, 29.6, 29.7, 29.8, 29.9, 30.1, 31.5, ($18CH_2$), 33.4, 34.8 ($4CH_2$, C-13, C-14, C-13', C-14'), 65.0 (1C, C-1), 123.7 (2C, Py C-5*), 128.1, 128.8, 129.3, 130.8, 131.5, 132.0 (4C, C-4, C-5, C-5', C-6'), 136.4 (2C, Py C-4*), 138.5 (2C, Py C-3*), 140.0 (1C, C-1'), 147.4, 150.1 (4C, Py C-2*, C-6*).

Preparation of proposed structure for Pyrinodemin A **1**

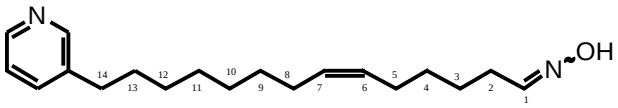


1

A solution of nitrone **2** (0.286g, 0.498mmol) in anhydrous benzene (250ml) was heated under reflux at 115°C for 24 hours under argon. The solvent was removed in vacuo, and the crude product was purified by flash chromatography (100% EtOAc) to yield compound **1** (0.118g, 0.206mmol, 41%) as a colourless oil; R_f = 0.13 (100% EtOAc); ν_{max}/cm^{-1} (thin film) 2927 (s), 2854 (s), 1574 (m), 1478 (m), 1464 (m), 1422 (m), 1026 (m); m/z Probe APCI (NH_3) 574 (MH^+, 100%), 286 (22%), 257 (20%), 220 (32%), 197 (27%); HRMS found 574.4735, $C_{38}H_{60}N_3O$ requires 574.4736; δ_H (200MHz, $CDCl_3$) 1.20-1.80 (36H, m, H-8 to H-14, H-17, H-18, H-19, H-8' to H-14', H-19'), 1.95-2.20 (4H, m, H-15', H-18'), 2.60 (4H, t, *J* 7.5Hz, H-7, H-7'), 2.60-2.70 (1H, m, H-20'), 2.75-2.95 (2H, m, H-16, H-20'†), 3.40-3.55 (1H, m, H-20), 4.00-4.12 (1H, m, H-15), 5.25-5.45 (2H, m, H-16', H-17'), 7.20 (2H, dd, J_1 5.0 Hz, J_2 7.5Hz, Py H-5*), 7.47 (2H, d, *J* 8.0Hz, Py H-4*), 8.44 (4H, br, s, Py H-2*, H-6*); δ_C (50.3MHz, $CDCl_3$) 25.3, 26.8, 26.9, 27.5, 27.7, 28.5, 29.2, 29.5, 29.7, 29.8, 29.9, 30.1, 31.5, 33.4 ($22CH_2$), 50.3 (1C, C-16), 56.9 (1C, C20'), 73.0 (1C, C-20), 78.1 (1C, C-15),

123.6 (2C, Py C-5*), 129.7, 130.8 (2CH, C-16', C-17'), 136.1 (2C, Py C-4*), 138.3 (2C, Py C-3*), 147.6, 150.4 (4C, Py C-2*, C-6*); δ_H (500MHz, $CDCl_3$) 1.20-1.35 (22H, m), 1.35-1.50 (4H, m), 1.50-1.70 (10H, m), 1.95-2.15 (4H, m, H-15', H-18'), 2.60 (4H, t, *J* 7.5Hz, H-7, H-7'), 2.52-2.65 (1H, m, H-20'), 2.76-2.88 (2H, m, H-16, H-20'†), 3.40-3.50 (1H, br, s, H-20), 4.00-4.10 (1H, m, H-15), 5.30-5.40 (2H, m, H-16', H-17'), 7.18 (2H, dd, J_1 5.0 Hz, J_2 7.5Hz, Py H-5*), 7.47 (2H, d, *J* 8.0Hz, Py H-4*), 8.34-8.50 (4H, br, s, Py H-2*, H-6*); δ_C (125.8MHz, $CDCl_3$) 24.8, 26.2, 26.4, 26.9, 27.1, 27.9, 28.7, 29.0, 29.2, 29.3, 29.4, 29.6, 31.0, 32.9 (CH_2), 49.8 (1C, C-16), 123.1 (2C, Py C-5*), 129.2, 130.3 (2CH, C-16', C-17'), 135.6 (2C, Py C-4*), 137.8 (2C, Py C-3*), 147.0, 149.8 (4C, Py C-2*, C-6*); δ_H (500MHz, CD_3OD) 1.27-1.37 (24H, H-8 to H-12, H-8' to H-14'), 1.33, 1.42 (2H, m, H-13), 1.46 (2H, m, H-18), 1.48 (1H, m, H-17), 1.50 (2H, m, H-14), 1.57 (2H, m, H-19'), 1.63 (1H, m, H-17), 1.65, 1.80 (2H, m, H-19), 2.03 (2H, m, H-15'), 2.10 (2H, m, H-18'), 2.65 (1H, m, H-20'), 2.65 (4H, t, *J* 7.5Hz, H-7, H-7'), 2.85-2.95 (2H, m, H-16, H-20'†), 3.50-3.60 (1H, m, H-20), 4.10-4.20 (1H, m, H-15), 5.40 (2H, m, H-17', H-16'), 7.30-7.40 (2H, m, Py-H), 7.65-7.75 (2H, d, *J* 8.0Hz, Py-H), 8.30-8.40 (4H, br, s, Py-H); δ_C (125.8 MHz, CD_3OD) 26.4, 27.8, 27.9, 28.7, 29.38, 30.8, 30.9, 31.0, 31.1, 31.2, 31.3, 31.4 ($18CH_2$), 32.8, 34.3 (4C, C-13, C-14, C13', C14'), 51.5 (1C, C-16), 58.1 (1C, C20'), 74.5 (1C, C-20), 79.6 (1C, C-15), 125.6 (2C, Py C-5*), 130.7, 131.9 (2CH, C-16', C-17'), 138.4 (2C, Py C-4*), 140.6 (2C, Py C-3*), 148.0, 150.5 (4C, Py C-2*, C-6*).

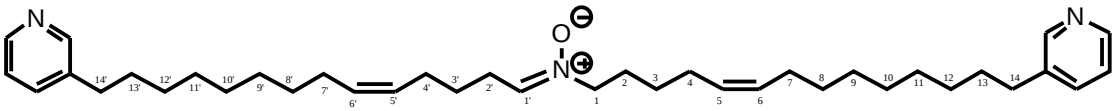
Preparation of Z*-14-(pyridin-3-yl)-tetradec-5-en-1-oxime***22**



22

To a stirred solution of *Z*-14-(pyridin-3-yl)-tetradec-5-en-1-al **3** (0.140g. 0.485mmol) in anhydrous methanol (4ml) under argon were added sodium acetate (0.120g, 1.404mmol), then hydroxylamine hydrochloride (0.102g, 1.46mmol). The mixture was stirred for 4 hours at room temperature. The methanol was removed *in vacuo* and DCM (4ml) was added, with water (4ml) and $NaHCO_{3(s)}$ (0.151g, 1.80mmol, 3.5 equiv) to neutralise the acetic acid produced. The mixture was transferred to a separation funnel, diluted with H_2O (20ml) and extracted with EtOAc (3 × 30ml). The organic phases were washed with $NaHCO_{3(aq)}$ (sat., 20ml), H_2O (20ml), then with $NaCl_{(aq)}$ (sat., 20ml), and dried over Na_2SO_4. Removal of solvent *in vacuo* afforded the crude product which was purified by flash chromatography (70% benzene, 30% EtOAc) to yield *Z*-14-(pyridin-3-yl)-tetradec-5-en-1-oxime **22** (0.124g, 0.410mmol, 84%) as a colourless oil; R_f = 0.14, 0.09 (*syn*/*anti* isomers, 70% benzene, 30% EtOAc); ν_{max}/cm^{-1} (thin film) 3204 (br, m), 3088 (br, m), 3014 (m), 2927 (s), 2855 (s), 1653 (w), 1580 (m), 1462 (m), 1425 (m), 1324 (br, w), 1190 (w), 1030 (w), 937 (br, w) 713 (m); m/z Probe APCI (NH_3) 303.3 (MH^+, 58%), 285.3 ($[MH - H_2O]^+$, 100%); HRMS found MH^+ = 303.2434, $C_{19}H_{31}N_2O$ requires 303.2436; The subscripts $_a$ and $_b$ differentiate between the *syn* and *anti* isomers, however they have not each been fully assigned. δ_H (200MHz, $CDCl_3$) 1.30 (10H, br, s, H-8 to H-12), 1.45-1.70 (4H, m, H-3, H-13), 1.90-2.15 (4H, m, H-4, H-7), 2.15-2.30 (1H, m, 2Hx0.5 H-2_a), 2.30-2.50 (1H, m, 2Hx0.5 H-2_b) 2.60, (2H, t, *J* 7.5Hz, H-14), 5.20-5.45 (2H, m, H-5, H-6), 6.70 (0.5H, t, *J* 5.5Hz, H-1_b), 7.15-7.20 (1H, m, Py H-5*) 7.40-7.55 (1.5H, m, 0.5H H-1_a, 1H Py H-4*), 8.35-8.45 (2H, m, Py H-2*, H-6*); δ_C (50.3 MHz, $CDCl_3$) 24.6, 26.2, 26.6, 26.8, 26.9, 27.2, 29.0, 29.2, 29.3, 29.6, 31.0, 32.9 (11CH_2), 123.4, (1C, Py C-5*), 128.7, 130.8 (2C, C-5, C-6), 136.2 (1C, Py C-4*), 138.2 (1C, Py C-3*), 146.7, 149.5 (2C, Py C-2*, C-6*), 151.4 (1C, C-1 *anti* oxime), 152.1 (1C, C-1 *syn* oxime).

Preparation of nitrone **20**

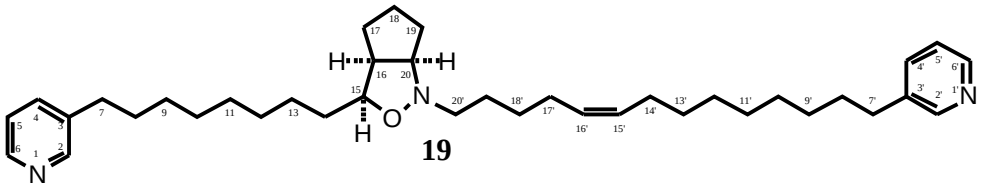


20

To a stirred solution of *Z*-14-(pyridin-3-yl)-tetradec-5-en-1-oxime **22** (0.119g, 0.394mmol) in methanol (10ml) at 0°C was added of methyl orange (indicator, 2mg) and conc. HCl (6 M) to turn the indicator red (approx. pH 3). Sodium cyanoborohydride (0.105g, 1.67mmol) in methanol (5ml) was added dropwise with concurrent addition of HCl to keep the mixture at pH 3. The mixture was stirred for 4 hours at 0°C. The mixture was basified (tested with pH paper) with 6N $NaOH_{(aq)}$, and worked up using solvents chilled to 0°C (to prevent decomposition of the hydroxylamine). The mixture was washed with $NaCl_{(aq)}$ (sat., 30ml) and extracted with chilled DCM (3 × 30ml). The organic phases were washed with H_2O (20ml) $NaCl_{(aq)}$ (sat., 30ml) and dried over Na_2SO_4. Removal of solvent *in vacuo* (no heating) to approximately 50ml DCM gave a solution of Z-14-(pyridin-3-yl)-tetradec-5-ene-1-hydroxylamine **21**. To the hydroxylamine solution, under argon, was added flame-dried Na_2SO_4 (5.20g, mass prior to flame drying), and *Z*-14-(pyridin-3-yl)-tetradec-5-en-1-al **3** (0.120g, 0.417mmol) in anhydrous DCM (5ml + 4 × 5ml rinses) *via* cannula. The flask was stirred for 18 hours at room temperature. The crude reaction mixture was filtered, solvent removed *in vacuo* and was purified by flash chromatography (50% EtOAc, 30% Et_3N, 20% PE 40-60) to yield nitrone **20** (0.162g, 0.282mmol, 71%) as a yellow oil; R_f = 0.29 (50% EtOAc, 30% Et_3N, 20% PE 40-60); ν_{max}/cm^{-1} (thin film) 3284 (br, m), 3003 (m), 2927 (s), 2854 (s), 1657 (m), 1576 (m), 1471 (m), 1422 (s), 861 (w), 756 (m), 714 (s); m/z Probe APCI (NH_3) 574.6 (MH^+, 100%), 288.2 (87%); HRMS found MH^+ = 574.4738, $C_{38}H_{60}N_3O$ requires 574.4736; δ_H (200MHz, $CDCl_3$) 1.25 (22H, br, s, H-3, H-8 to H-12, and H-8' to H-12'), 1.45-1.70 (6H, m, H-13, H-3', H-13'), 1.80-2.00 (2H, m, H-2), 1.85-2.15 (8H, m, H-4, H-7, H-4', H-7'), 2.40-2.55 (2H, m, H-2'), 2.55 (4H, t, *J* 7.5Hz, H-14, H-14'), 3.70 (2H, t, *J* 7.0Hz, H-1), 5.20-5.45 (4H, m, H-5, H-6, H-5', H-6'), 6.65 (1H, t, *J* 6.0Hz, H-1'), 7.15 (2H, dd, J_1 7.5Hz, J_2 5.0Hz, Py H-5*), 7.40 (2H, d, *J*

7.5Hz, Py H-4*), 8.40 (4H, m, Py H-2*, H-6*); δ_C (50.3 MHz, $CDCl_3$) 23.2, 25.6, 26.3, 26.5, 26.6, 27.0, 27.2, 27.5, 29.1, 29.2, 29.3, 29.4, 29.6, 31.1 ($18CH_2$), 32.9, 34.4 ($4CH_2$, C-13, C-14, C-13', C-14'), 65.3 (1C, C-1), 123.2 (2C, Py C-5*), 128.3, 128.7, 129.5, 130.0, 130.7, 131.0 (4C, C-4, C-5, C-5', C-6'), 135.8 (2C, Py C-4*), 137.9 (2C, Py C-3*), 139.1 (1C, C-1'), 147.0, 149.8 (4C, Py C-2*, C-6*).

Preparation of alternative structure for Pyrinodemin A **19**



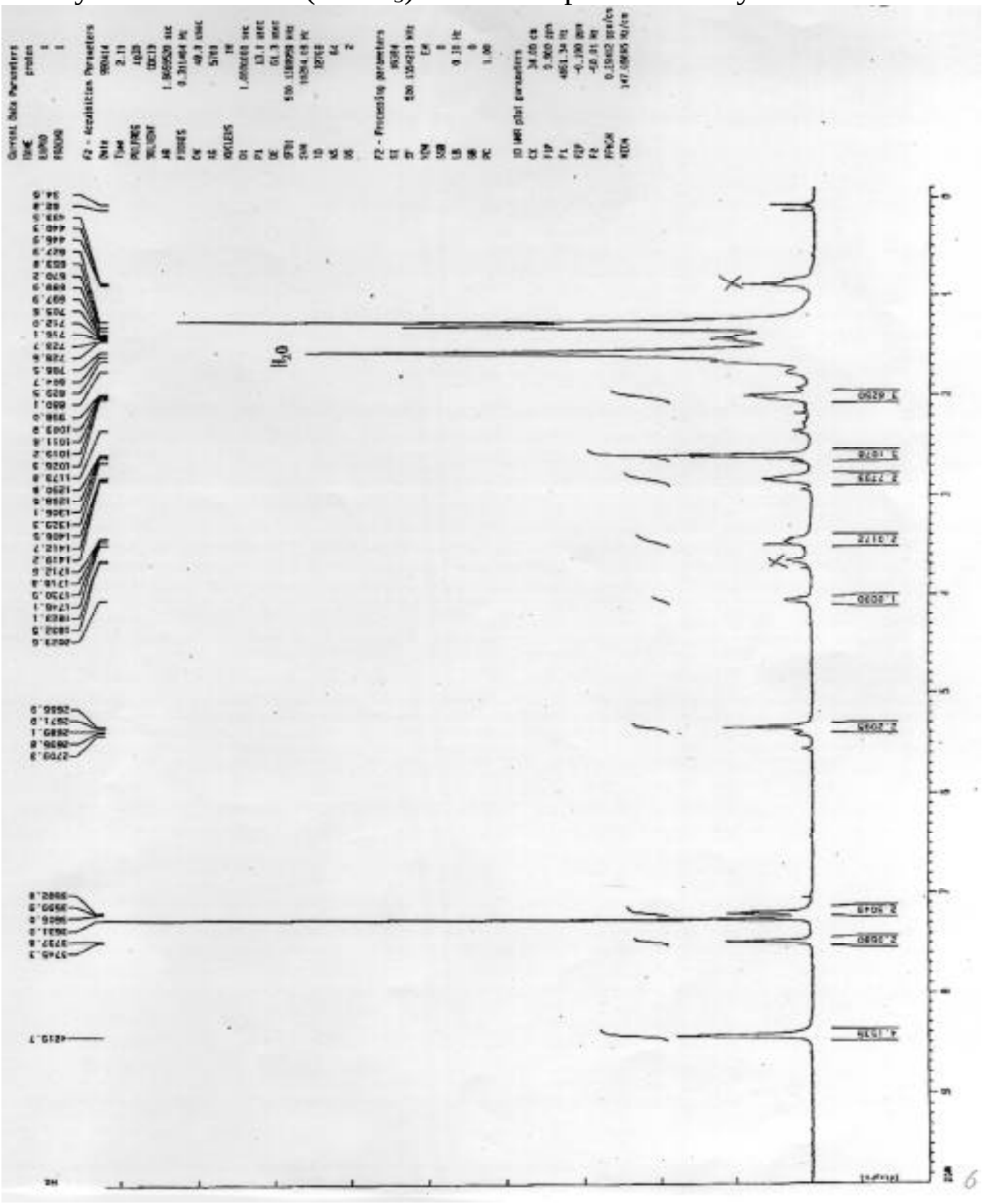
19

A solution of nitrone **20** (0.142g, 0.248mmol) in anhydrous benzene (100ml) was heated under reflux at 100°C for 18 hours under argon. The solvent was removed in vacuo, and the crude product was purified by flash chromatography (100% EtOAc) to yield compound **19** (0.089g, 0.155mmol, 63%) as a colourless oil; R_f = 0.32 (100% EtOAc); ν_{max}/cm^{-1} (thin film) 2928 (s), 2855 (s), 1575 (m), 1478 (m), 1465 (m), 1422 (m), 1337 (w), 1189 (w), 1026 (m), 793 (w), 714 (s); m/z Probe APCI (NH_3) 574.6 (MH^+, 100%), 355.4, 286.3, 220.2; EIMS (+ve ion) 572 (2%), 555 (3%), 365 (55%), 355 (10%), 327 (8%), 315 (4%), 301 (9%), 285 (49%), 270 (18%), 244 (43%), 231 (29%), 220 (38%), 204 (5%), 190 (21%), 176 (37%), 162 (16%), 148 (18%), 134 (13%), 120 (26%), 106 (100%), 93 (97%); HRMS found 574.4721, $C_{38}H_{60}N_3O$ requires 574.4736; δ_H (200MHz, $CDCl_3$) 1.15-1.80 (36H, m, H-8 to H-14, H-17, H-18, H-19, H-8' to H-13', H-18', H-19'), 1.85-2.10 (4H, m, H-14', H-17'), 2.40-2.60 (1H, m, H-20'), 2.55 (4H, t, *J* 7.5Hz, H-7, H-7'), 2.70-2.90 (2H, m, H-16, H-20'†), 3.35-3.50 (1H, m, H-20), 4.95-4.10 (1H, m, H-15), 5.20-5.40 (2H, m, H-15', H-16'), 7.15 (2H, dd, J_1 5.0 Hz, J_2 8.0Hz, Py H-5*), 7.45 (2H, d, *J* 8.0Hz, Py H-4*), 8.40 (4H, br, s, Py H-2*, H-6*); δ_C (50.3MHz, $CDCl_3$) 26.3, 26.4, 27.0, 27.1, 27.2, 27.5, 27.8, 28.7, 29.1, 29.2, 29.3, 29.4, 29.7, 31.1, 32.5, 33.0, 34.1, ($22CH_2$), 49.9 (1C, C-16), 56.9 (1C, C20'), 72.5 (1C, C-20), 77.7 (1C, C-15), 123.2 (2C, Py C-5*), 129.6, 130.0 (2CH, C-15', C-16'), 135.8 (2C, Py C-4*), 137.9 (2C, Py C-3*), 147.1, 149.9 (4C, Py C-

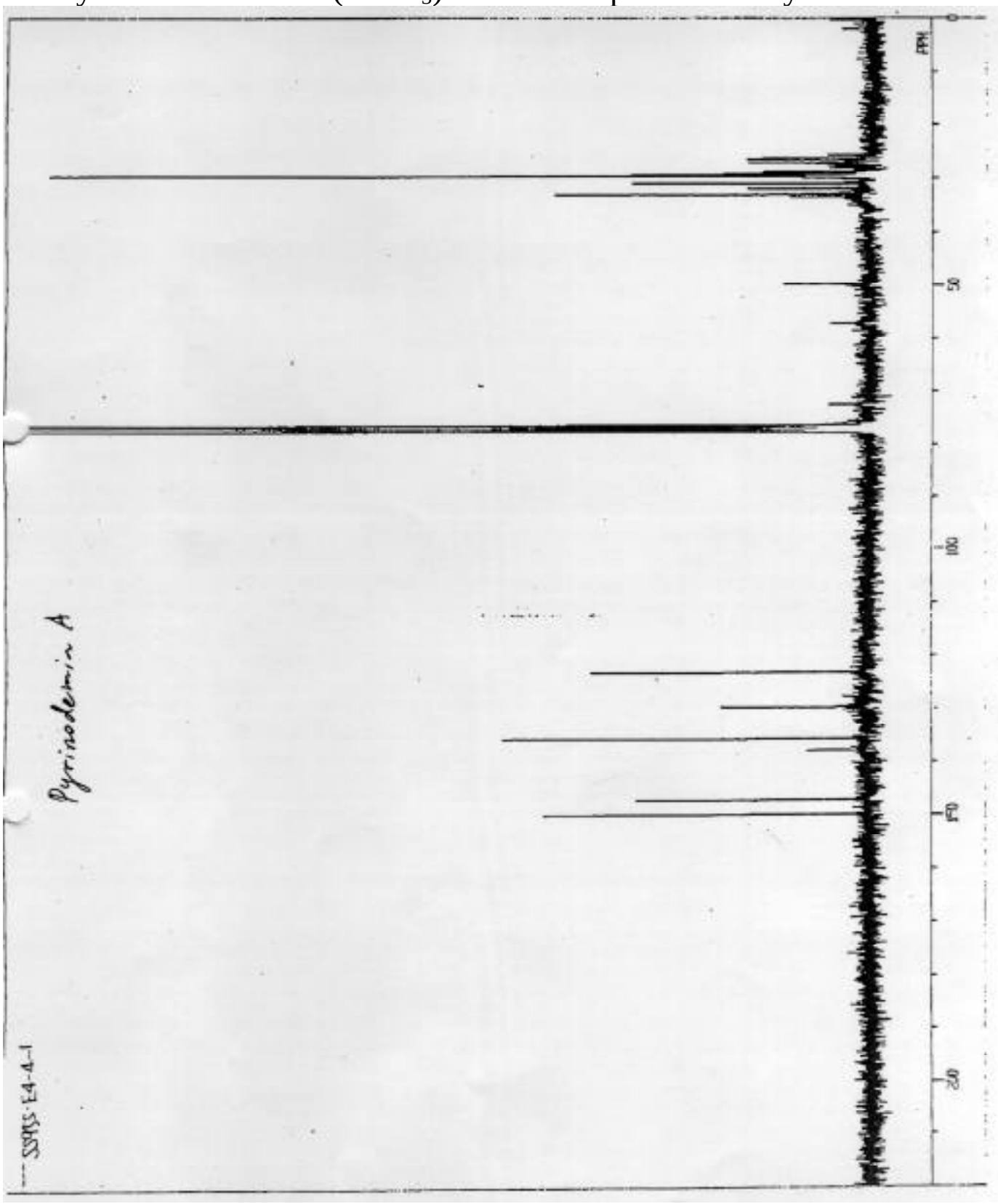
2*, C-6*); δ_H (500MHz, $CDCl_3$) 1.28-1.42 (18H, m, H-9 to H-12, and H-9' to H-13'), 1.34 (1H, m, H-13), 1.44 (2H, m, H-18'), 1.47 (1H, m, H-13†), 1.46 (1H, m, H-18), 1.49 (1H, m, H-17), 1.49 (1H, m, H-14), 1.59 (2H, m, H-19'), 1.59 (1H, m, H-14†), 1.64 (4H, m, H-8, H-8'), 1.69 (1H, m, H-17†), 1.70 (1H, m, H-18†), 1.72 (1H, m, H-19), 1.80 (1H, m, H-19†), 2.04 (2H, m, H-14'), 2.07 (2H, m, H-17'), 2.60-2.72 (1H, m, H-20'), 2.60 (4H, t, J 7.7Hz, H-7, H-7'), 2.78-2.89 (2H, m, H-16, H-20'†), 3.40-3.51 (1H, m, H-20), 4.00-4.08 (1H, m, H-15), 5.28-5.38 (2H, m, H-15', H-16'), 7.14-7.21 (2H, m, Py-H), 7.43-7.50 (2H, m, Py-H), 8.36-8.49 (4H, br, s, Py-H); δ_C (125.8 MHz, $CDCl_3$) 26.2, 26.3 (2C, C-17, C-18), 26.9 (1C, C-13), 27.0 (1C, C-17'), 27.1 (1C, C-14'), 27.4 (1C, C-18'), 27.7 (1C, C-19'), 28.6 (1C, C-14), 29.0, 29.1, 29.2, 29.3, 29.5, 29.6, (9C, C-9 to C-12 and C-9' to C-13'), 31.0 (2C, C-8, C-8'), 32.9 (2C, C-7, C-7'), 34.1, (1C, C-19), 49.8 (1C, C-16), 56.8 (1C, C20'), 72.5 (1C, C-20), 77.6 (1C, C-15), 123.1 (2C, Py C-5*), 129.5, 129.9 (2CH, C-15', C-16'), 135.7 (2C, Py C-4*), 137.9 (2C, Py C-3*), 147.0, 149.8 (4C, Py C-2*, C-6*).

[1] M. F. Lipton, C. M. Sorensen, A. C. Sadler, R. H. Shapiro, *J. Organomet. Chem.*, 1980, **186**, 155.

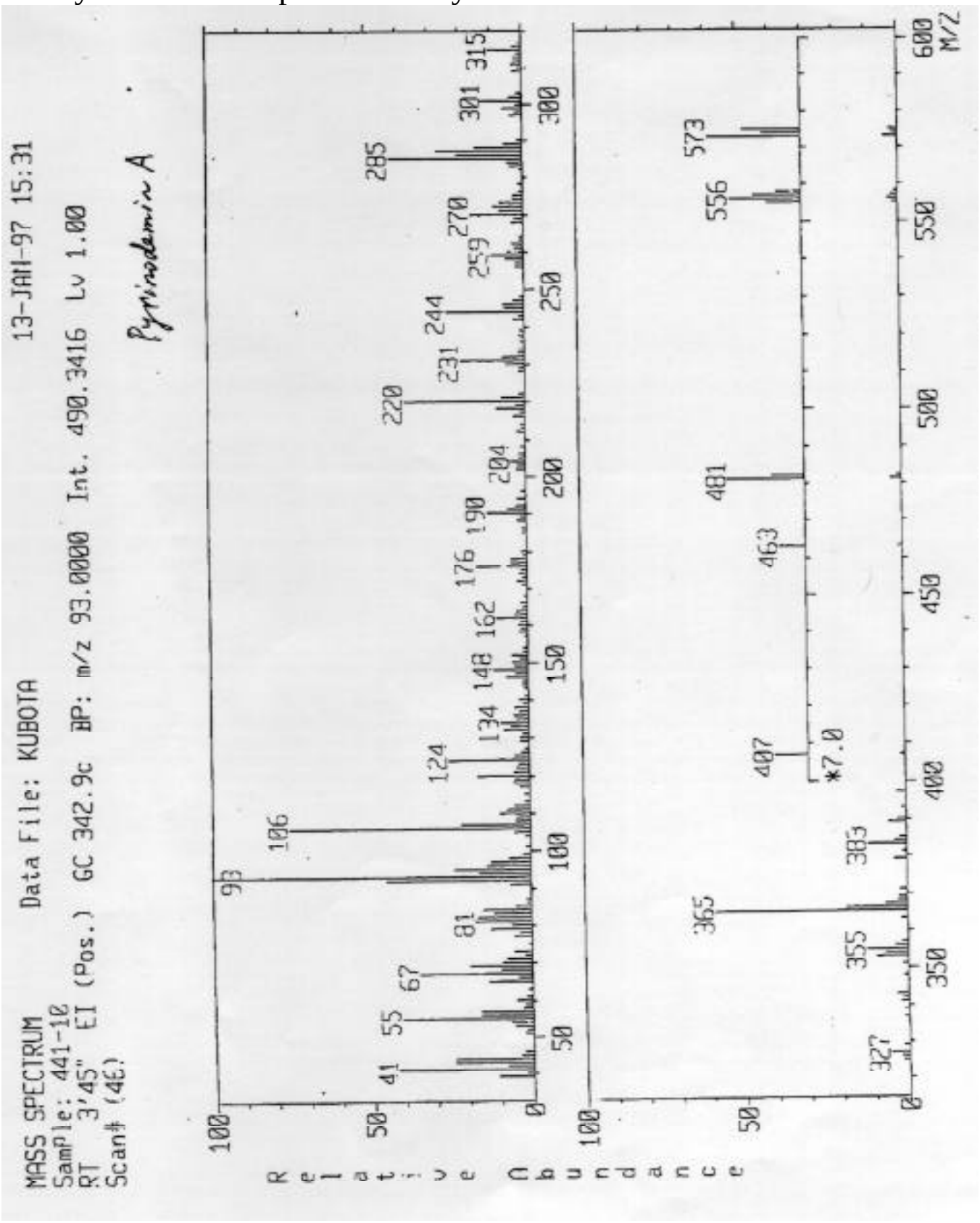
Kobayashi's 500MHz ($CDCl_3$) ^1H NMR spectrum of Pyrinodemin A



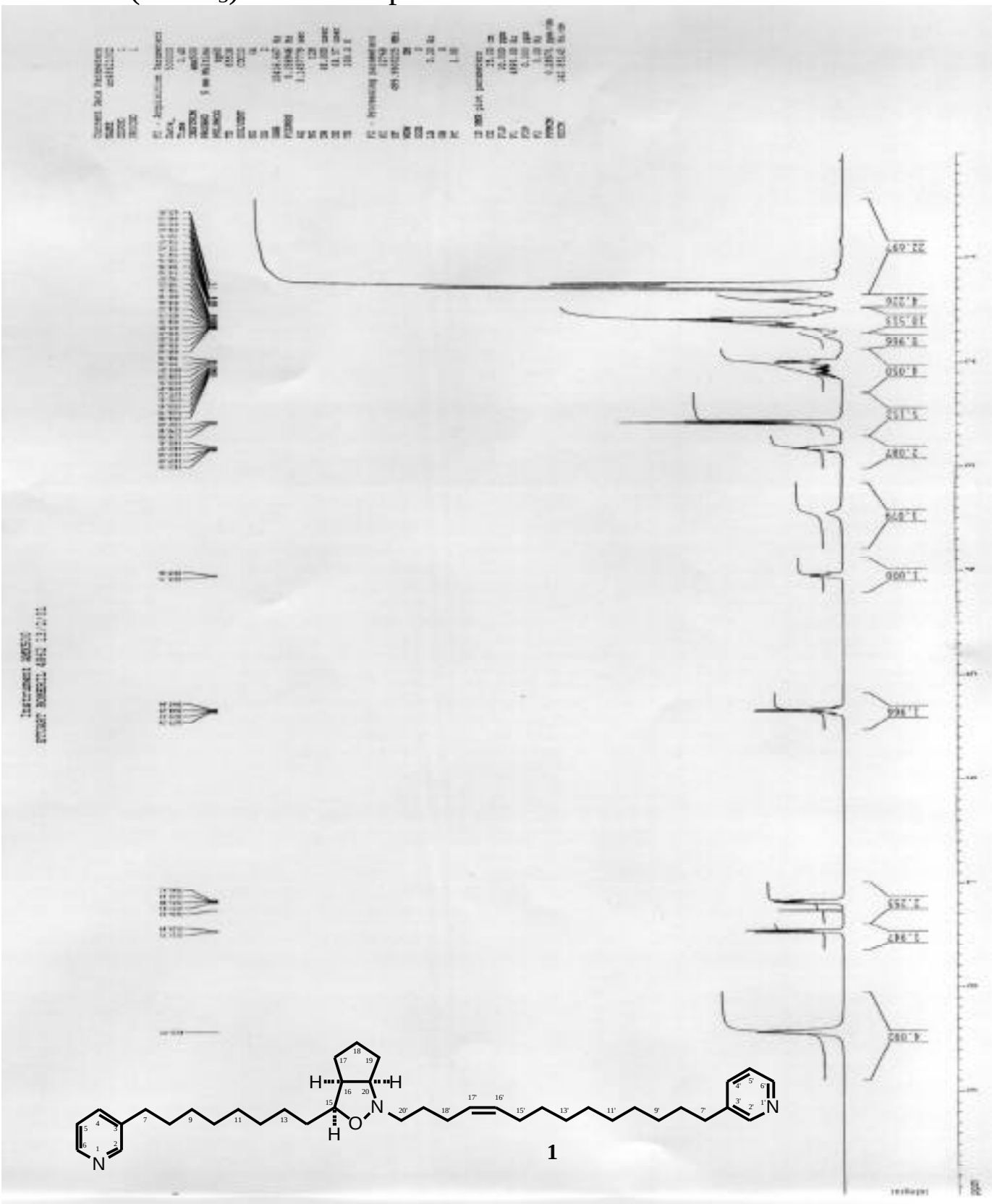
Kobayashi's 125.8MHz ($CDCl_3$) ^{13}C NMR spectrum of Pyrinodemin A



Kobayashi's EIMS spectrum of Pyrinodemin A



500MHz ($CDCl_3$) ^1H NMR spectrum of Structure **1**



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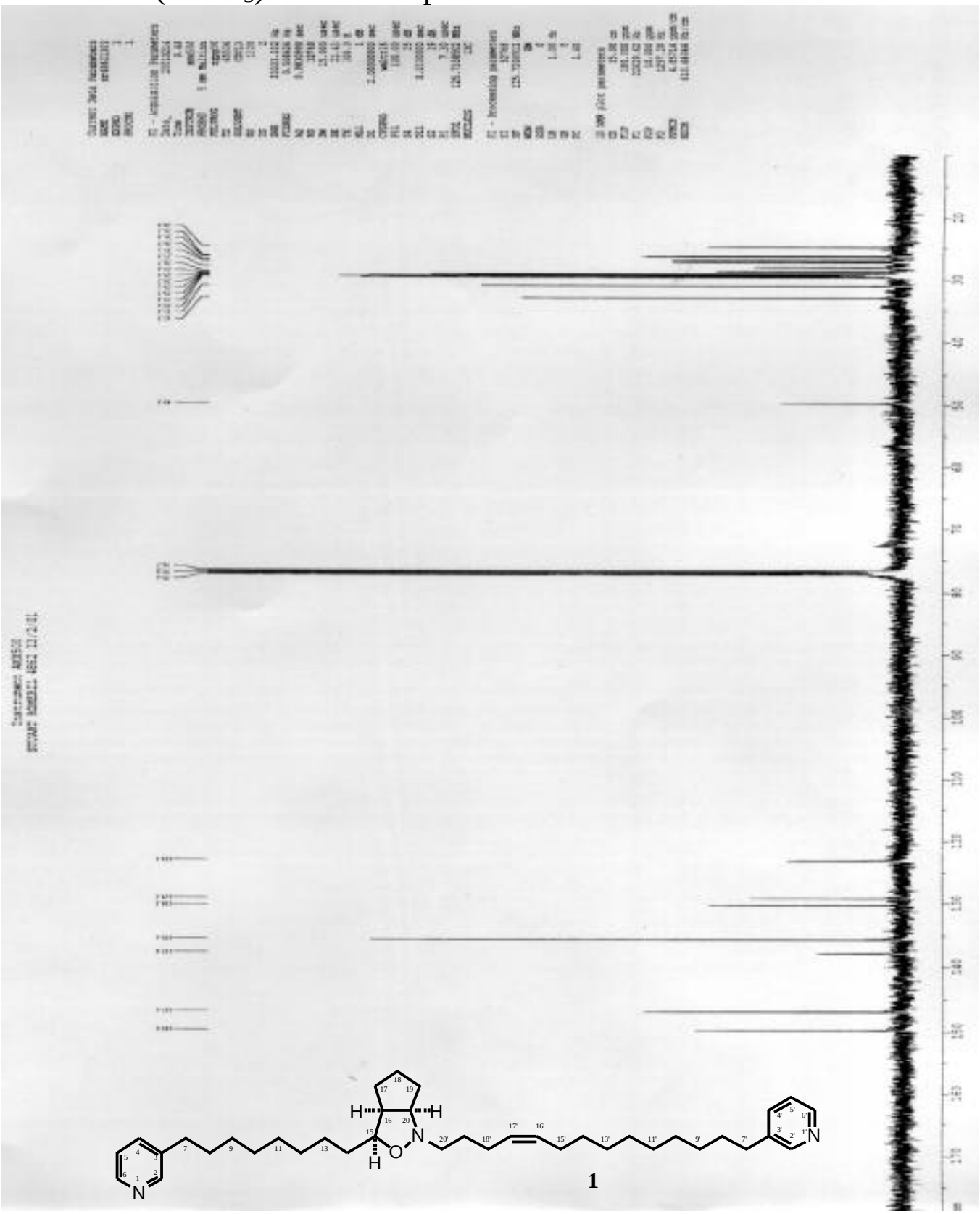
125.8MHz ($CDCl_3$) ^{13}C NMR spectrum of Structure **1**



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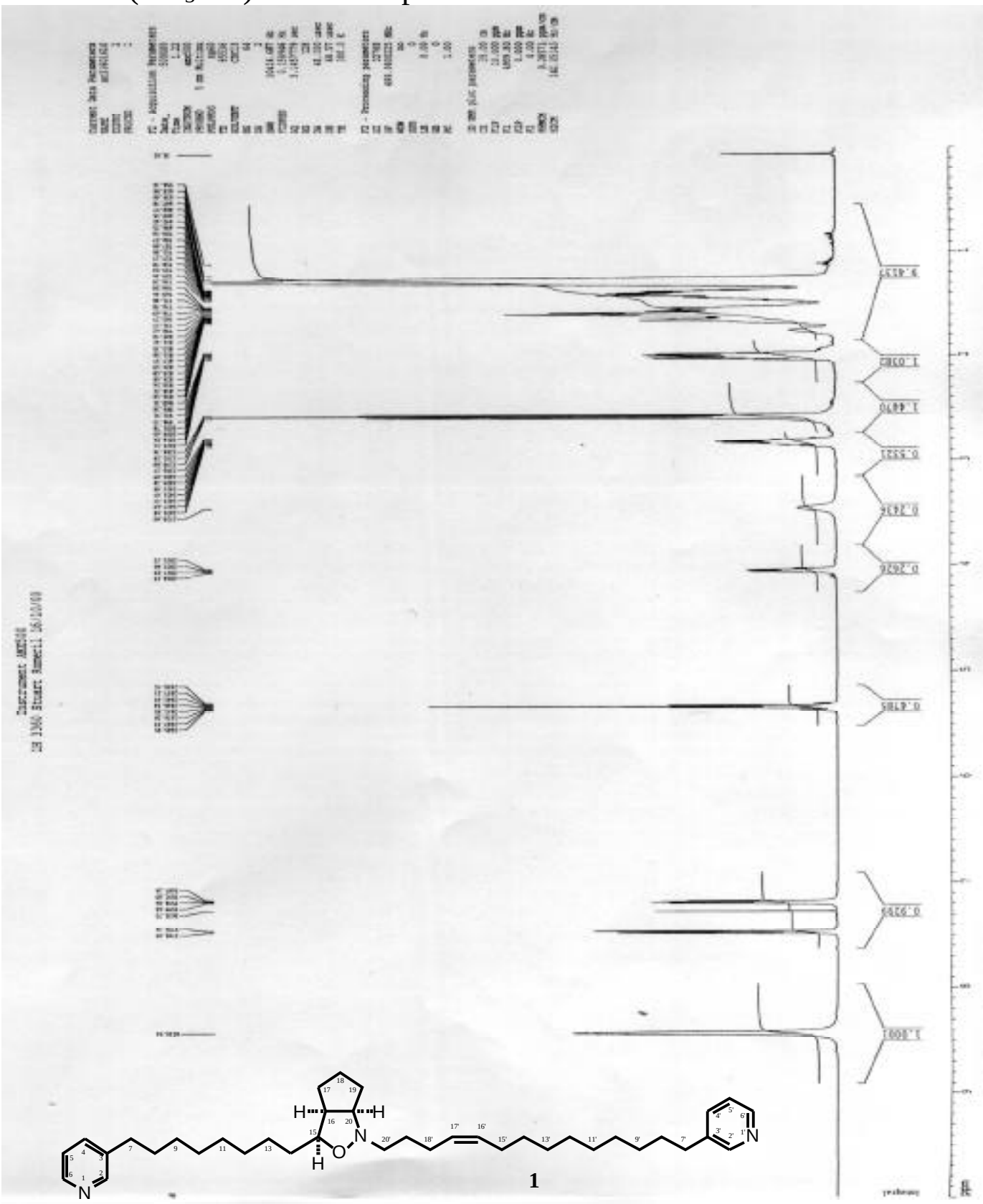
500MHz (CD_3OD) ^1H NMR spectrum of Structure **1**



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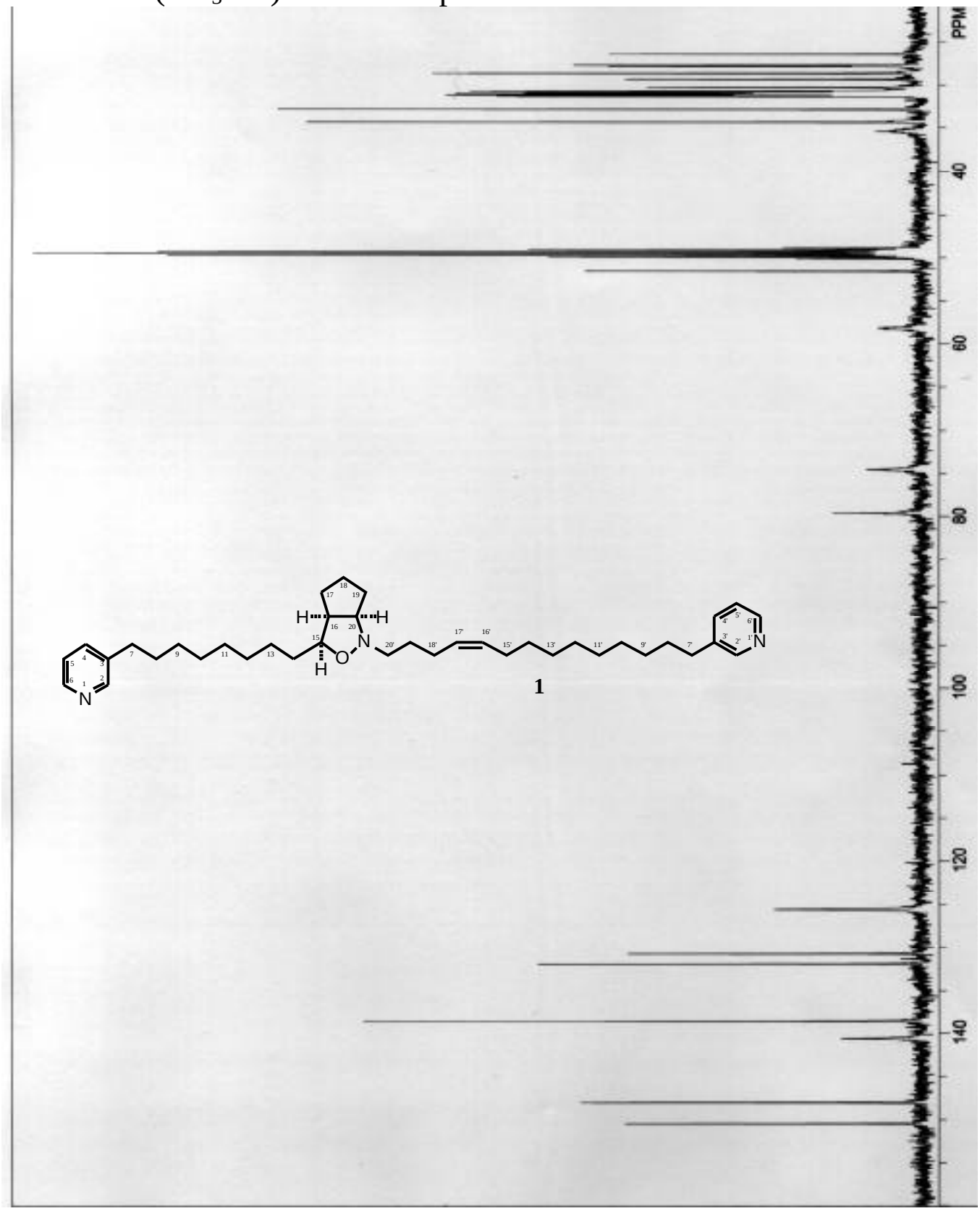
100.6MHz (CD_3OD) ^{13}C NMR spectrum of Structure **1**



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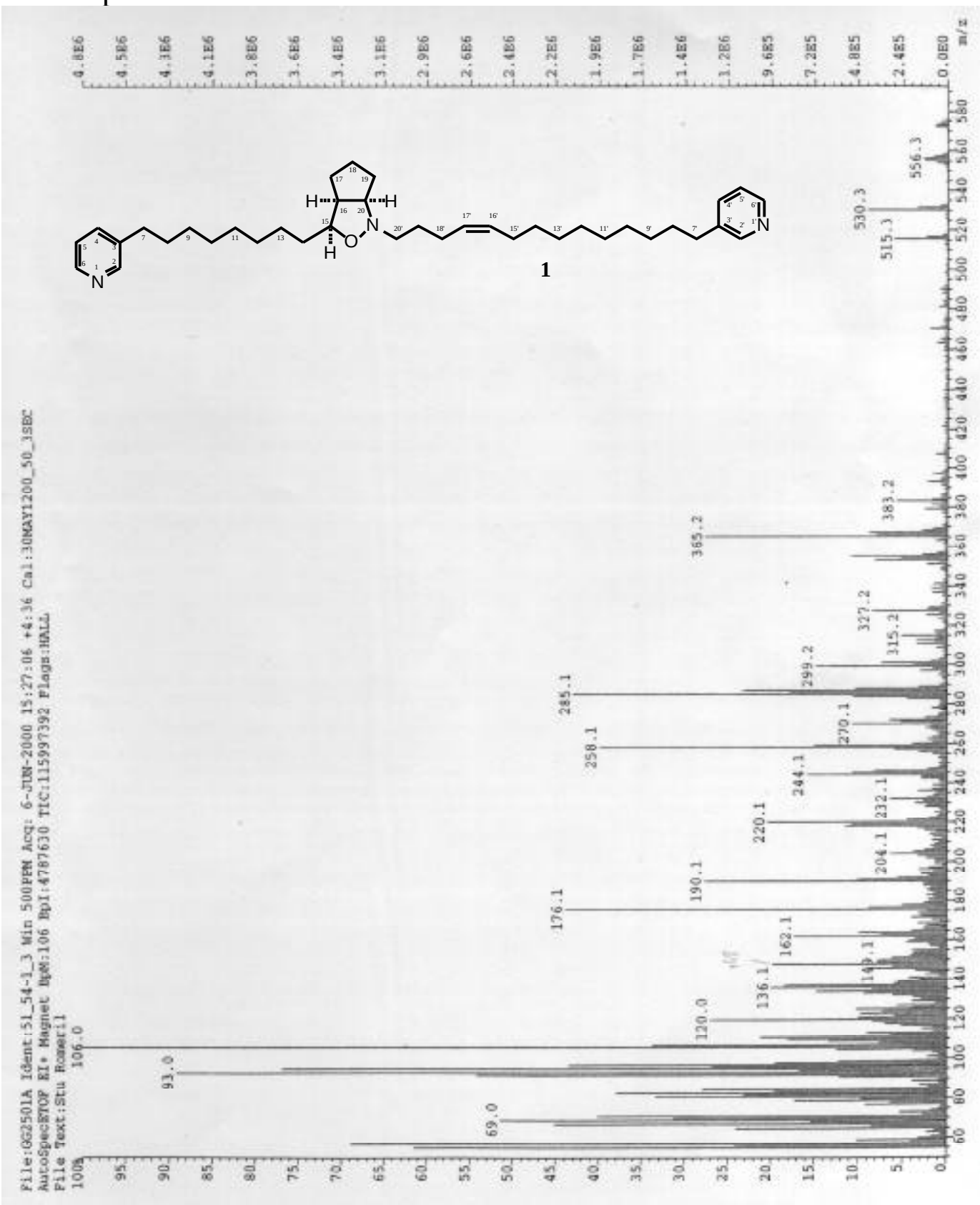
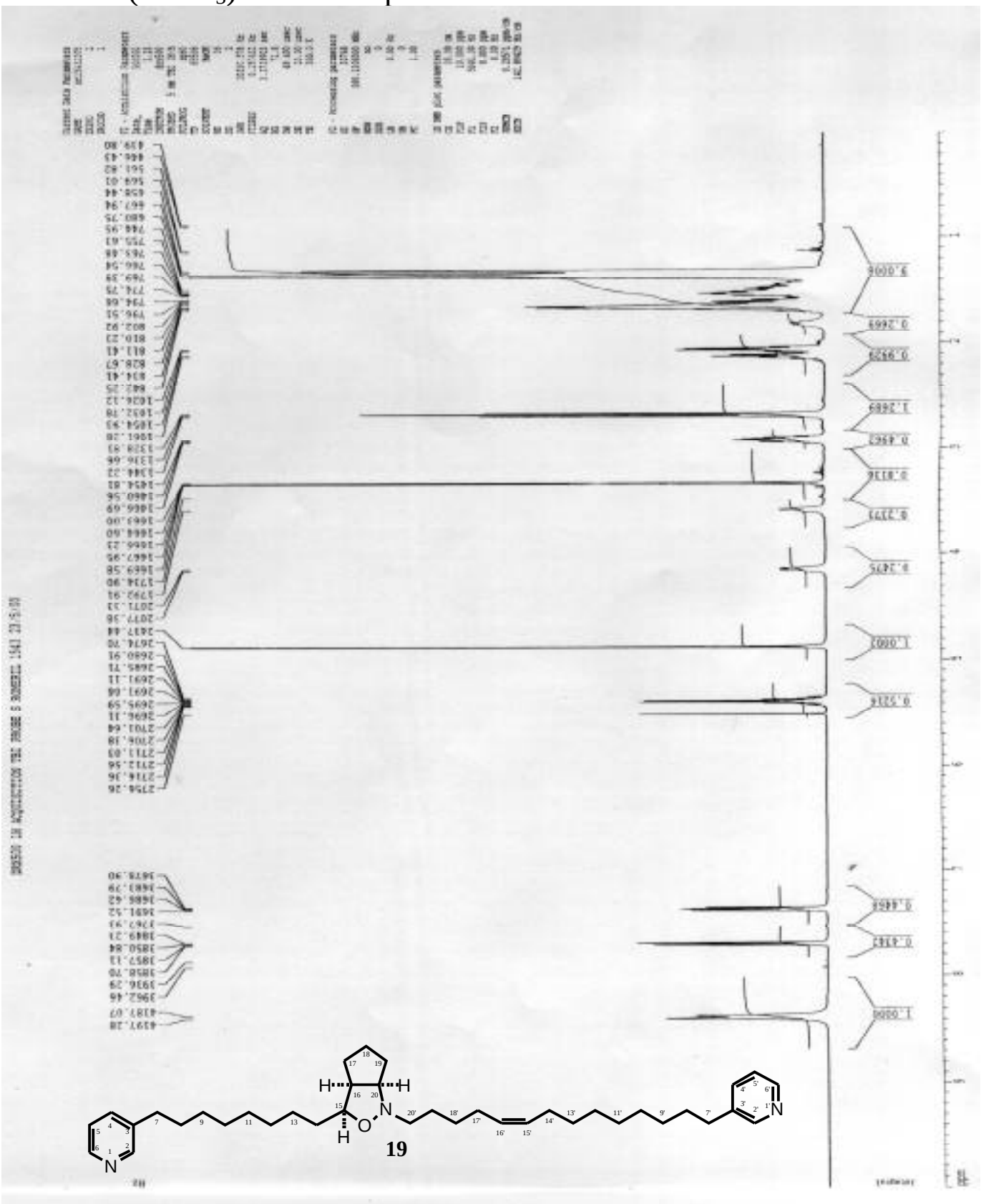
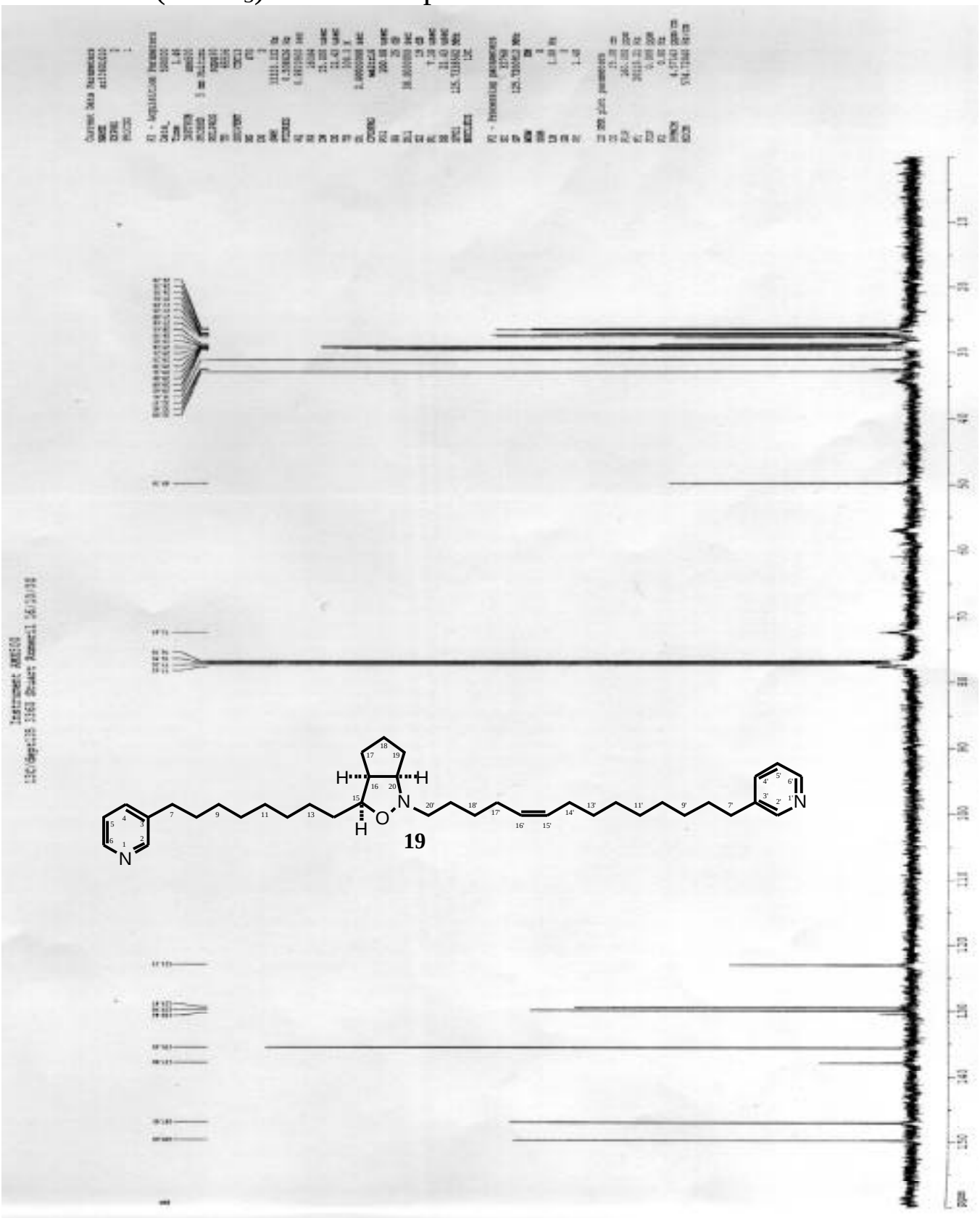
EIMS spectrum of Structure **1**



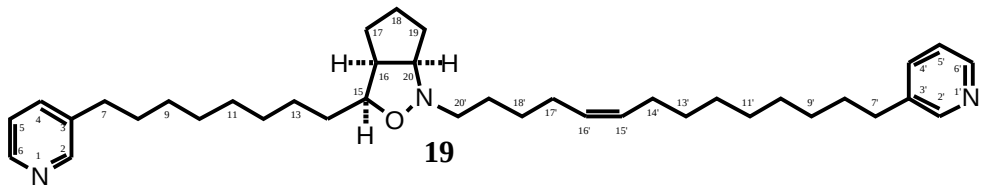
500MHz ($CDCl_3$) ^{1}H NMR spectrum of Structure **19**



125.8MHz ($CDCl_3$) ^{13}C NMR spectrum of Structure **19**



EIMS spectrum of Structure **19**



19