First Total Synthesis of Mosin B

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Supporting Information

All melting points are uncorrected. Optical rotations were measured using a JASCO DIP-360 digital polarimeter. ^{1}H NMR spectra were recorded in $CDCl_3$ solution with a JEOL JNM-GX500 spectrometer (500 MHz). ^{13}C NMR spectra were recorded in $CDCl_3$ solution with a JEOL JNM-AL300 spectrometer (75 MHz) and a JEOL JNM-EX270 spectrometer (67.8 MHz). All signals are expressed as ppm downfield from tetramethylsilane used as an internal standard (δ value). IR absorption spectra (FT: diffuse reflectance spectroscopy) were recorded with KBr powder, and only noteworthy absorptions (cm^{-1}) are listed. Mass spectra were taken with a JEOL JMS-D300 or a JEOL JMS-600 mass spectrometer. High resolution mass spectra were obtained with a JEOL JMS-D300 or a JEOL JMS-600 mass spectrometer. FAB mass spectra were obtained with a JEOL-JMS-700 mass spectrometer. Column chromatography was carried out using Merck silica gel 60 (70-230 mesh). All air or moisture-sensitive reactions were carried out in flame-dried glassware under an atmosphere of Ar or N_2. All solvents were dried and distilled according to standard procedures. All organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated with a rotary evaporator under reduced pressure.

(2*E*,6*R*,7*S*)-6,7-*O*-Isopropylidene-2-nonadecene-1,6,7-triol (7). $LiAlH_4$ (22.0 mg, 0.579 mmol) was added to a solution of **17** (102 mg, 0.289 mmol) in Et_2O (2.89 mL) with stirring at rt. The whole was refluxed for 3 h. Saturated Rochelle salt was added to the mixture. After stirred for 10 min, the mixture was extracted with EtOAc, and the combined organic layers were washed with water and brine prior drying and solvent evaporation. The residue was chromatogaraphed on silica gel with hexane–EtOAc (3:1) to give **7** (92.4 mg, 90%) as a colorless oil. $[\alpha]^{28}_{D}$ +4.3 (*c* 1.02, $CHCl_3$). ^{1}H NMR δ: 0.88 (t, 3H, *J* = 6.7 Hz), 1.26–1.63 (m, 24H), 1.34 (s, 3H), 1.43 (s, 3H), 2.06–2.13 (m, 1H), 2.45–2.32 (m, 1H), 4.01–4.06 (m, 2H), 4.09–4.11 (m, 2H), 5.66–5.76 (m, 2H). ^{13}C NMR δ: (67.8 MHz) 14.1, 22.6, 26.0, 26.2, 28.6, 28.7, 29.3 (2C), 29.5, 29.6, 29.6 (3C), 29.6, 29.7, 31.9, 63.5, 77.3, 78.0, 107.4, 129.5, 132.2.

IR 3396. MS (FAB) *m/z*: 355 $(M+H)^+$. Anal. Calcd for $C_{22}H_{42}O_3$: C, 74.52; H, 11.94. Found: C, 74.46; H, 11.85.

(2*R*,3*R*,6*R*,7*S*)-1,2:3,6-Diepoxy-7-hydroxynonadecane (18). $I(coll)_2ClO_4$ (552 mg, 1.18 mmol) was added to a solution of **7** (348 mg, 0.981 mmol) in MeCN–water (100:1, 9.8 mL) with stirring at rt. After 5 min, water was added to the mixture, and the mixture was extracted with EtOAc. The combined organic layers were washed with water and brine prior to drying and solvent evaporation. K_2CO_3 (814 mg, 5.89 mmol) was added to a solution of the residue in MeOH (9.8 mL) with stirring at rt. After 30 min, water was added to the mixture, and the mixture was extracted with $CHCl_3$. The combined organic layers were washed with saturated NH_4Cl, water, and brine prior to drying and solvent evaporation. The residue was chromatogaraphed on silica gel with hexane–EtOAc (3:1) to give **18** (244 mg, 80% in 2 steps) as a colorless crystals. Mp: 52.0–52.5 °C (hexane). $[\alpha]^{28}_D$ +1.5 (*c* 1.04, $CHCl_3$). ^{1}H NMR δ: 0.88 (t, 3H, *J* = 7.0 Hz), 1.25–1.51 (m, 22H), 1.83–1.94 (m, 3H), 2.01 (br s, 1H), 2.05–2.16 (m, 1H), 2.70 (dd, 1H, *J* = 5.2, 2.7 Hz), 2.79 (t, 1H, *J* = 4.5 Hz), 2.98 (dt, 1H, *J* = 4.5, 2.7 Hz), 3.82 (dt, 1H, *J* = 6.1, 3.1 Hz), 3.87 (dd, 1H, *J* = 12.2, 6.7 Hz), 3.94 (ddd, 1H, *J* = 8.9, 5.8, 3.1 Hz). ^{13}C NMR δ: (67.8 MHz) 14.1, 22.6, 24.6, 25.9, 29.0, 29.3, 29.5, 29.6, 29.6 (2C), 29.6 (2C), 31.9, 32.5, 44.2, 54.2, 71.5, 79.2, 83.0. IR 3421. MS (FAB) *m/z*: 319 $(M+Li)^+$. Anal. Calcd for $C_{19}H_{36}O_3$: C, 73.03; H, 11.61. Found: C, 72.86; H, 11.22.

(8*R*,9*R*,12*R*,13*S*)-9,12-Epoxy-8,13-dihydroxy-1-pentacosene (19). 6-Bromo-1-hexene (0.090 mL, 0.672 mmol) was added to a mixture of Mg (17.2 mg, 0.706 mmol) in THF (0.34 mL) with stirring at rt. After 1.5 h, THF (0.34 mL) was added to the mixture. The mixture was cooled at –30 ºC, and CuBr (9.6 mg, 0.0672 mmol) was added to the mixture. After 5 min, **18** (10.5 mg, 0.0336 mmol) in THF (0.34 mL) was added to the mixture, and the whole was stirred at 0 ºC for 1 h. The reaction was quenched with saturated NH_4Cl, and the solvent was concentrated under the reduced pressure. The residue was extracted with EtOAc, and the combined organic layers were washed with water and brine prior to drying and solvent evaporation. The residue was chromatogaraphed on silica gel with hexane–EtOAc (2:1) to give **19** (11.8 mg, 89%) as a colorless crystals. Mp: 55.0–56.0 °C (hexane). $[\alpha]^{28}_D$ +14.0 (*c* 1.03, $CHCl_3$). ^{1}H NMR δ: 0.88 (t, 3H, *J* = 6.7 Hz), 1.26–1.43 (m, 28H), 1.50–1.53 (m, 2H), 1.62–1.67 (m, 1H), 1.82–1.94 (m, 2H), 1.97–2.01 (m, 1H), 2.03–2.07 (m, 3H), 2.37 (br s, 1H), 3.38–3.39 (m, 1H), 3.79–3.89 (m, 3H), 4.93 (dd, 1H, *J* = 10.4, 1.8 Hz), 4.99 (dq, 1H, *J* = 17.1, 1.8 Hz), 5.81 (ddt, 1H, *J* = 17.1, 10.4, 6.7 Hz). ^{13}C NMR δ: (67.8 MHz) 14.1, 22.6, 25.2, 25.4, 26.0, 28.6, 28.8, 29.1, 29.3, 29.5, 29.6, 29.6 (2C), 29.6, 29.7, 31.9, 32.5, 33.0, 33.7, 71.4, 74.3,

82.3, 83.3, 114.2, 139.0. IR 3425. MS (FAB) *m/z*: 397 $(M+H)^+$. Anal. Calcd for $C_{25}H_{48}O_3$: C, 75.70; H, 12.20. Found: C, 75.62; H, 11.95.

(5*S*,*EZ*)-3-[(2*R*)-2-(*tert*-Butyldimethylsilyl)oxy-6-iodo-5-hexenyl]-5-methyl-2,5-dihydro-furan-2-one (26). A solution of *m*-CPBA (10.5 mg, 0.061 mmol) in CH_2Cl_2 (0.6 mL) was added to a solution of **25** (27.7 mg, 0.051 mmol) in CH_2Cl_2 (0.6 mL) with stirring at 0 ºC. After 20 min, the mixture was partitioned between Et_2O and saturated. The organic layer was separated, and washed with saturated $NaHCO_3$ and brine prior to drying and solvent evaporation. The residue was dissolved in toluene (1.8 mL), and the mixture was stirred at 130 ºC for 20 min. The solvent was concentrated in *vacuo*. The crude was chromatographed on silica gel with hexane–EtOAc (20:1) to give **26** (9:1 *E*/*Z*-mixture, 18.8 mg, 85% in 2 steps) as a colorless oil. $[\alpha]^{25}_D$ +15.1 (*c* 1.33, $CHCl_3$). ^{1}H NMR δ: 0.04 (s, 2.7H), 0.05 (s, 0.3H), 0.06 (s, 2.7H), 0.09 (s, 0.3H), 0.88 (s, 8H), 0.89 (s, 1H), 1.42 (d, 3H, *J* = 6.7 Hz), 1.53 (dt, 2H, *J* = 7.9, 6.1 Hz), 2.05–2.28 (m, 2H), 2.40 (dd, 0.9H, *J* = 14.6, 5.5 Hz), 2.41 (dd, 0.1H, *J* = 14.6, 5.5 Hz), 2.46 (dd, 0.9H, *J* = 14.6, 5.5 Hz), 2.50 (dd, 0.1H, *J* = 14.6, 6.1 Hz), 3.97 (quintet, 0.9H, *J* = 5.8 Hz), 4.02 (quintet, 0.1H, *J* = 5.8 Hz), 5.02 (dq, 1H, *J* = 6.7, 1.2 Hz), 6.02 (dt, 0.9H, *J* = 14.0, 1.5 Hz), 6.16–6.21 (m, 0.2H), 6.49 (dt, 0.9H, *J* = 14.0, 7.3 Hz), 7.12 (d, 0.9H, *J* = 1.2 Hz), 7.15 (d, 0.1H, *J* = 1.2 Hz). ^{13}C NMR (75 MHz) δ: –4.6, –4.5, 17.9, 18.9, 25.8 (3C), 30.5 (0.1C), 31.7 (0.9C), 32.6, 34.7 (0.1C), 35.2 (0.9C), 69.2 (0.9C), 69.4 (0.1C), 74.9 (0.9C), 77.5, 82.8 (0.1C), 130.3 (0.9C), 130.4 (0.1C), 140.6 (0.1C), 145.8 (0.9C), 151.8, 173.8. IR 1755. MS (EI) *m/z* (%): 436 (M^+, 2.3), 379 (100). HRMS (EI) Calcd for $C_{17}H_{29}IO_3Si$: 436.0931. Found: 436.0928.

(5*S*)-3-[(2*R*,7*RS*,13*R*,*E*)-2,13-Bis-(*tert*-butyldimethylsilyl)oxy-13-[(2*R*,5*R*)-5-[(1*S*)-1-(*tert*-butyldimethylsilyl)oxytridesyl]tetrahydrofuran-2-yl]-7-hydroxytridec-5-enyl]-5-methyl-2,5-dihydrofuran-2-one (22). $NaIO_4$ (187 mg, 0.876 mmol) was added to a solution of diol (274 mg, 0.416 mmol) in CH_2Cl_2–acetone–H_2O (10:6:1, 8.5 mL) with stirring at 0 ºC. After the whole was stirred at rt for 12 h, Et_2O was added to the mixture. The organic layer was separated and dried. After filtration, the solvent was evaporated. The residue was chromatographed on silica gel with hexane-EtOAc (3:1) to give **21** (195.8 mg, 75%) as a colorless oil. The aldehyde was unstable and used in the next step.

$CrCl_2$ (291 mg, 2.37 mmol) and $NiCl_2$ (1.5 mg, 0.012 mmol) was added to a mixture of **21** (149 mg, 0.237 mmol) and **26** (207 mg, 0.447 mmol) in DMF–Me_2S (1:1, 3.6 mL) with stirring at rt. After 20 h, EtOAc and saturated NH_4Cl was added to the reaction mixture. The whole was stirred for 10 min. The mixture was extracted with EtOAc, and the combined

extracts were washed with water and brine prior to drying and solvent evaporation. The crude was chromatographed on silica gel with hexane–EtOAc (5:1) to give **22** (1:1 diastereomeric mixture, 158 mg, 71%) as a colorless oil. $[\alpha]^{19}_{D}$ +16.9 (*c* 0.93, $CHCl_3$). ^{1}H NMR δ: 0.02 (s, 3H), 0.03 (s, 3H), 0.035 (s, 3H), 0.039 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.88 (br s, 30H), 1.25-1.31 (m, 32H), 1.41 (d, 3H, *J* = 6.7 Hz), 1.49-1.58 (m, 2H), 1.62 (dt, 1H, *J* = 11.6, 8.5 Hz), 1.77-1.84 (m, 2H), 1.86 (dt, 1H, *J* = 6.7, 4.3 Hz), 2.02-2.17 (m, 2H), 2.43-2.45 (m, 2H), 3.50-3.53 (m, 1H), 3.70 (dt, 1H, *J* = 6.1, 4.3 Hz), 3.81 (dt, 1H, *J* = 7.3, 4.3 Hz), 3.87 (dt, 1H, *J* = 8.5, 6.1 Hz), 3.98 (ddt, 1H, *J* = 11.6, 8.5, 3.1 Hz), 4.02 (q, 1H, *J* = 6.7 Hz), 5.01 (dq, 1H, *J* = 6.7, 1.2 Hz), 5.47 (dd, 1H, *J* = 15.3, 7.0 Hz), 5.60 (dt, 1H, *J* = 15.9, 6.7 Hz), 7.12 (d, 0.5H, *J* = 1.2 Hz), 7.13 (0.5H, *J* = 1.2 Hz). ^{13}C NMR (75 MHz) δ: –4.6, –4.5, –4.4 (2C), –4.24, –4.19, 14.1, 18.0, 18.2, 18.2, 18.9 (0.5C), 19.0 (0.5C), 22.7, 25.2, 25.5, 25.6, 25.7 (0.5C), 25.8 (0.5C), 26.0 (9C), 26.7, 27.7, 27.9, 29.3, 29.6, 29.6 (2C), 29.7 (2C), 29.9, 31.9, 32.6 (0.5C), 32.7 (0.5C), 32.9, 34.7, 36.2, 37.3, 69.5 (0.5C), 69.6 (0.5C), 73.0 (0.5C), 73.0 (0.5C), 73.7, 75.1, 77.5, 81.9, 82.0, 130.6 (0.5C), 130.7 (0.5C), 131.1 (0.5C), 131.2 (0.5C), 133.5 (0.5C), 133.6 (0.5C), 151.7, 174.0. IR 3502, 1759. MS (FAB) *m/z*: 960 $(M+Na)^+$. HRMS (FAB) Calcd for $C_{53}H_{104}O_7Si_3+Na^+$: 959.6987. Found: 959.6962.

(5*S*)-3-[(2*R*,13*R*)-2,13-Dihydroxy-13-[(2*R*,5*R*)-5-[(1*S*)-1-hydroxytridesyl]tetrahydrofuran-2-yl]-7-oxotridecyl]-5-methyl-2,5-dihydrofuran-2-one (1a). Four drops of 48% HF (aq.) was added to a solution of tri-TBS ether (84.9 mg, 0.091 mmol) in THF–CH_3CN (1.5:1, 1.5 mL) with stirring at rt. After stirred at rt for 2.5 h, brine and CH_2Cl_2 was added to the reaction mixture, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine prior to drying and solvent evaporation. The crude was chromatographed on silica gel with EtOAc to give **1a** (39.0 mg, 72%) as a white waxy solid.

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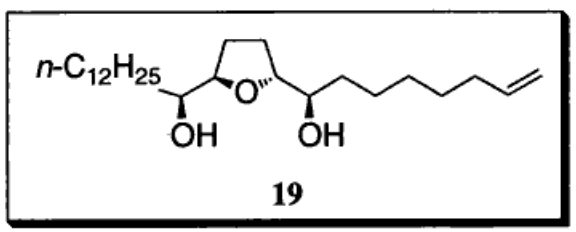

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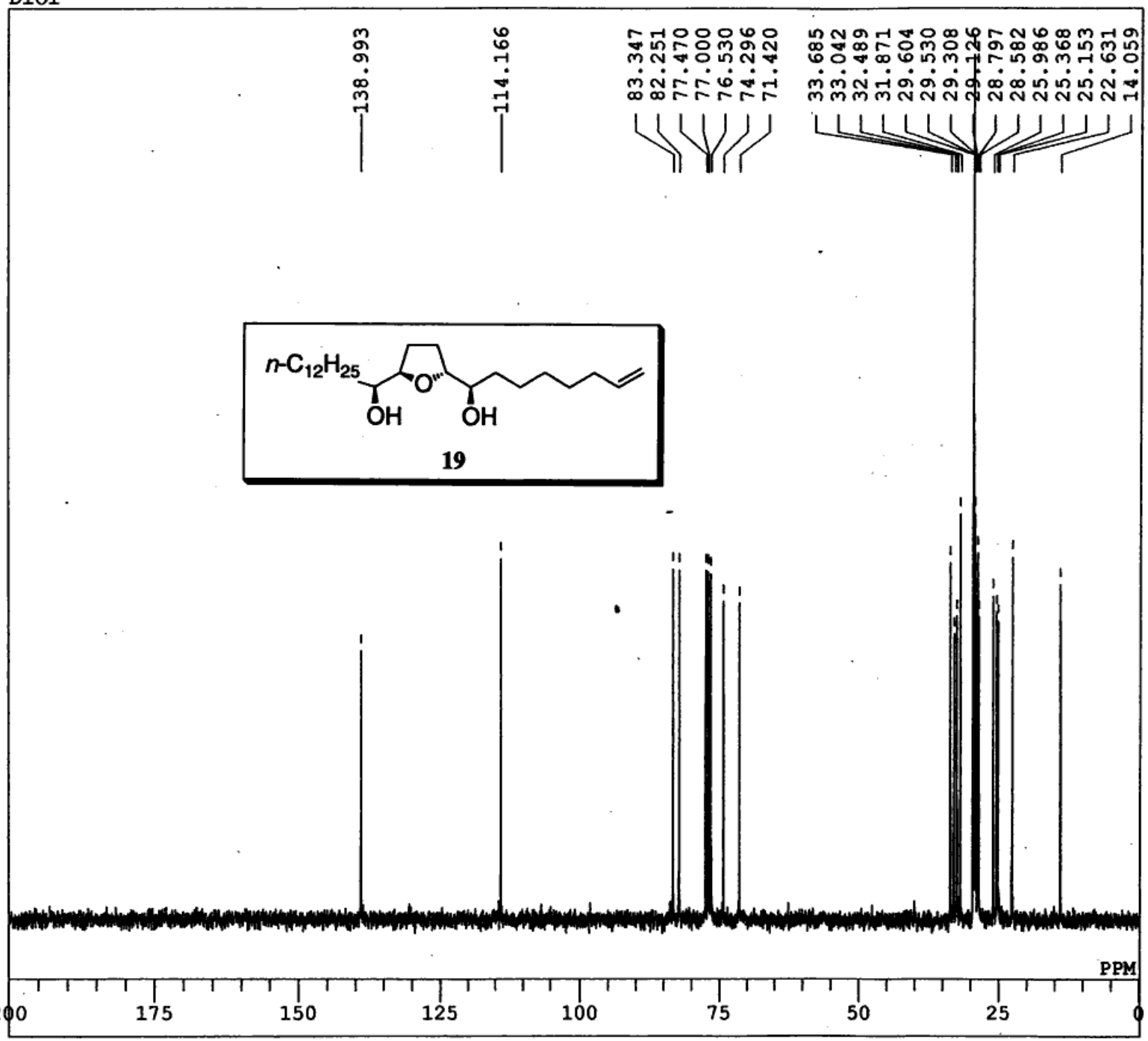

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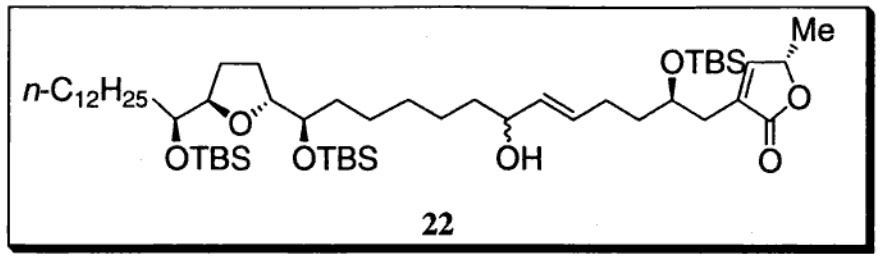

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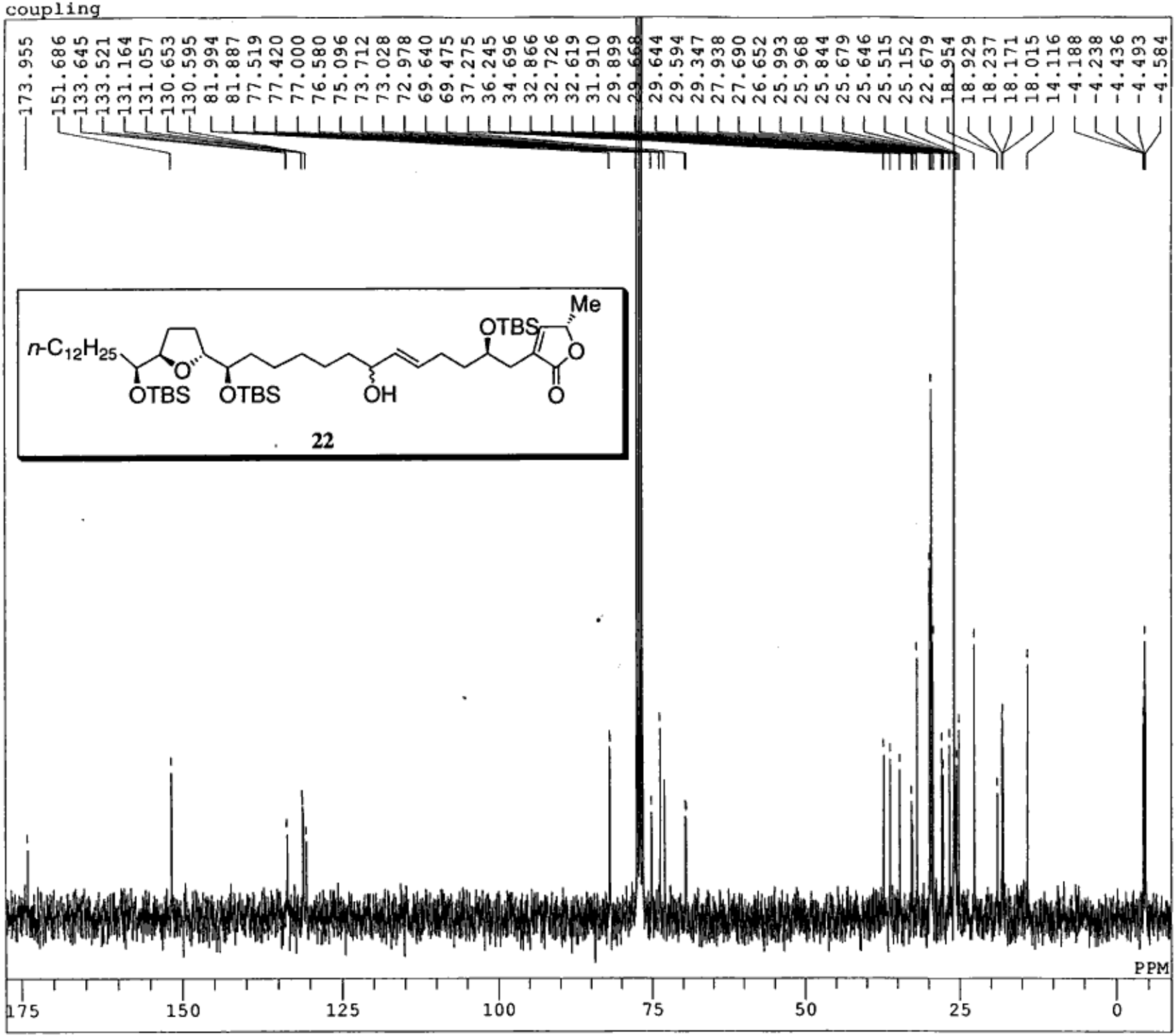

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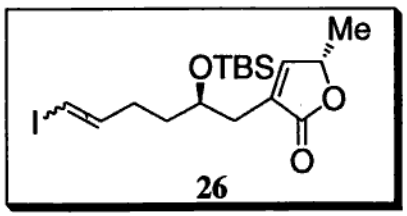

26

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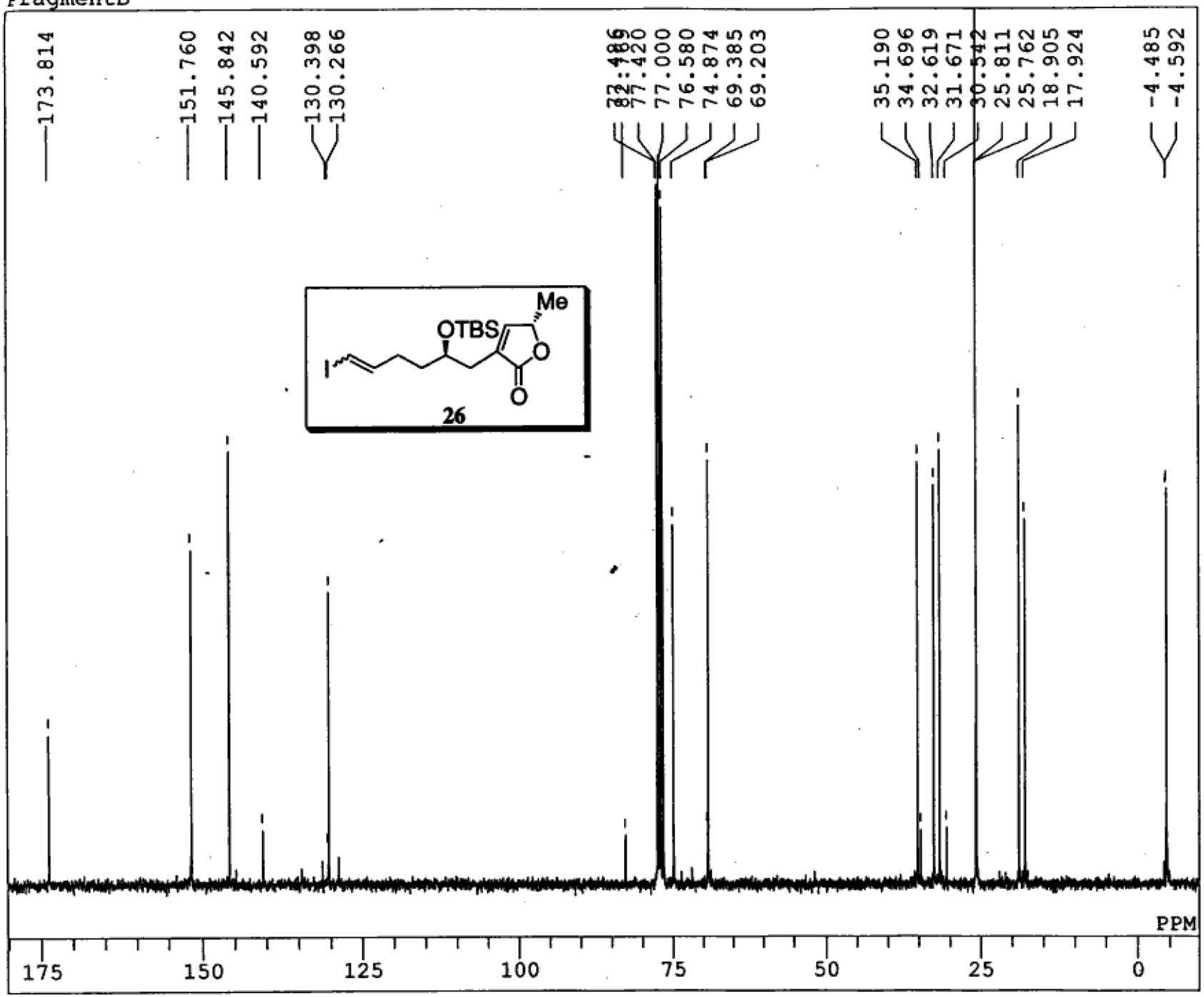

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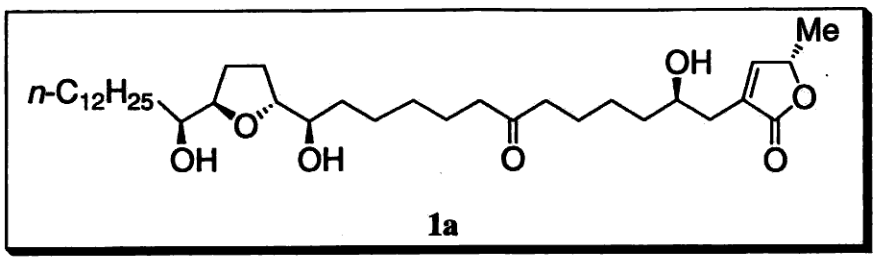

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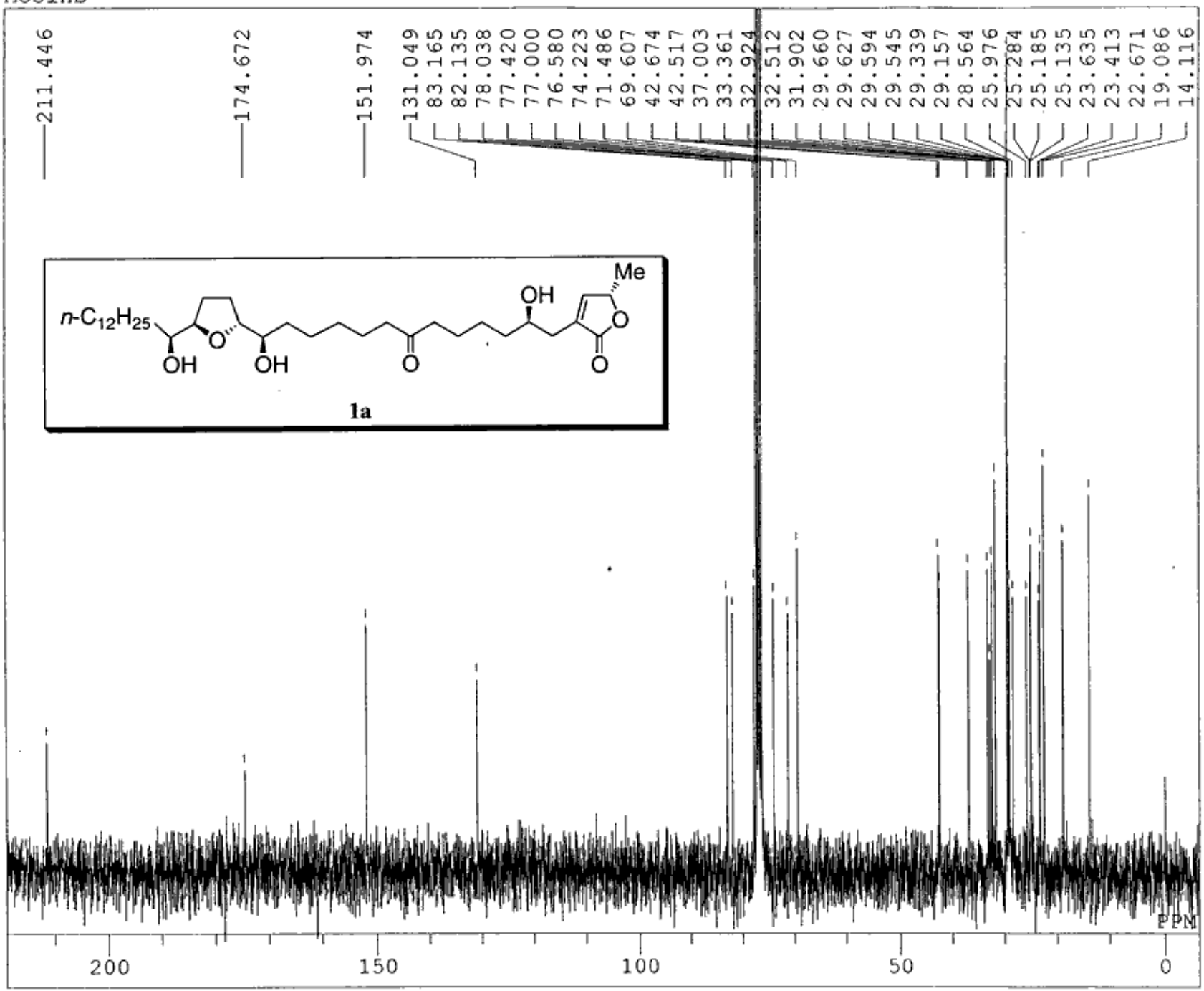
MosinB



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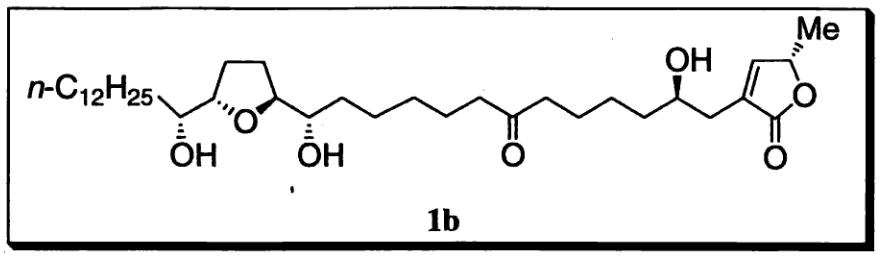
1H Line



1b

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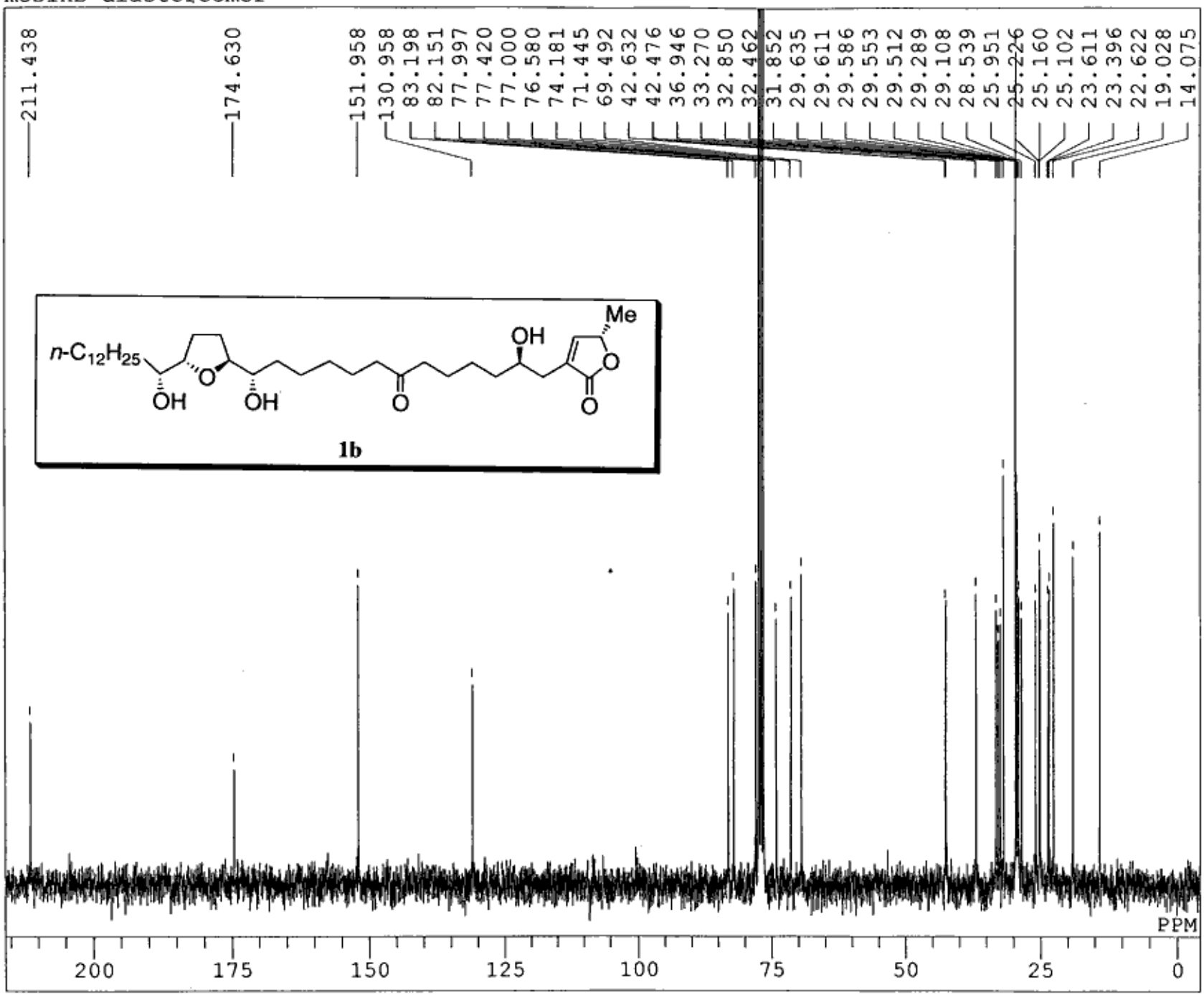
PW1	:	2.63 usec
OBNUC	:	1H
OBFRQ	:	500.00 MHz
OBSET	:	162167.63 Hz
RGAIN	:	17
SCANS	:	16 times
SLVNT	:	CDCL3
SPINNING	:	12 Hz
TEMP	:	23.3 C

mosinB diastereomer



DFILE	F:\467 MOSIN B DIA
COMNT	mosinB diastereome
DATIM	Wed Sep 06 16:18:4
OBNUC	13C
EXMOD	BCM
OBFRQ	75.45 MHz
OBSET	124.00 KHz
OBFIN	1840.0 Hz
POINT	32768
FREQU	20408.1 Hz
SCANS	600
ACQTM	1.606 sec
PD	1.394 sec
PW1	4.0 us
IRNUC	1H
CTEMP	20.5 c
SLVNT	CDCL3
EXREF	77.00 ppm
BF	1.20 Hz
RGAIN	24