ELECTRONIC SUPPLEMENTARY INFORMATION (ESI)

Total Synthesis of (-)-Flustramines A, B and (-)-Flustramides A, B via Domino Olefination/Isomerization/Claisen Rearrangement Sequence

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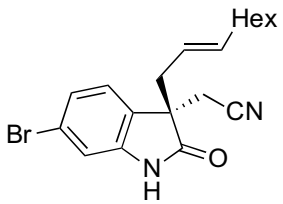
General

All melting points are uncorrected, and were measured on a Yanagimoto micromelting point apparatus. Optical rotations were obtained on a JASCO DIP-140 digital polarimeter. Optical purities were determined on a HPLC (JASCO UV-975) instrument equipped with AD (Daicel Chemical Ind., Ltd., Chiralpak®), OD (Daicel Chemical Ind., Ltd., Chiralcel®). IR spectra were recorded on a Shimadzu FTIR-8100 or Shimadzu FTIR-8400s spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were measured on a JEOL JNM-EX 270 (270 MHz), JEOL JNM-AL 300 (300 MHz) or JEOL JNM-GSX 400 (400 MHz) spectrometer with tetramethylsilane as an internal standard. *J*-Values are given in Hz. Mass spectra were recorded on a JEOL JMS-DX 302 or JEOL JMS 700 instrument with a direct inlet system operating at 70 eV. Elemental analyses were obtained using a Perkin-Elmer Model 240B elemental analyzer. Column chromatography was carried out on silica gel (Kanto Chemical Co. Inc., 230-400 mesh and Merck, 230-400 mesh).

Experimental Ditails

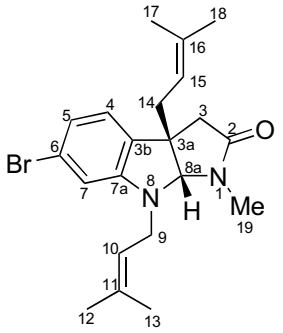
2-{(*S*)-6-Bromo-3-[(*E*)-non-2-enyl]-2-oxoindolin-3-yl}acetonitrile [(+)-10]



A solution of phosphonate **8** (3.20 cm^3, 20.0 mmol) and *t*-BuOK (2.00 g, 18.2 mmol) in DMF (30 cm^3) was stirred at room temperature for 1 h. After cooling the mixture to -78 °C, a solution of indolin-3-one **7** (2.40 g, 6.08 mmol) in DMF (15 cm^3) was added dropwise to the mixture. The mixture was warmed slowly to room temperature and stirred at the same temperature for 2.5 h. The resulting mixture was neutralized with 10% aqueous HCl, and extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give a residue, which was chromatographed by silica gel column with AcOEt-hexane (1:4) as eluent to afford (+)-**10** (1.60 g, 70%) as a viscous oil. $[\alpha]_D^{25}$ +24.3 (*c* 1.17, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$: 3432, 3198, 3027, 3013,

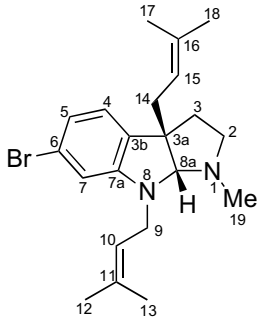
2255, 1720, 1613; δ_H (300 MHz, $CDCl_3$): 0.87 (3H, t, *J* 7.0, $(CH_2)_4CH_3$), 1.07-1.33 (8H, m, $CH_2(CH_2)_4CH_3$), 1.88 (2H, m, $CHCH_2(CH_2)_4$), 2.56 (1H, dd, *J* 13.8 and 7.9, C*H*HCH=CH$(CH_2)_5$), 2.63 (1H, dd, *J* 13.8 and 7.9, CH*H*CH=CH$(CH_2)_5$), 2.65 (1H, d, *J* 16.7, C*H*HCN), 2.84 (1H, d, *J* 16.7, CH*H*CN), 5.08 (1H, dt, *J* 15.1 and 7.9, CH_2CH=CH$(CH_2)_5$), 5.50 (1H, dt, *J* 15.1 and 6.8, CH_2CH=C*H*$(CH_2)_5$), 7.10 (1H, s, Ar-H), 7.26 (2H, s, Ar-H), 8.08 (1H, brs, NH); δ_C (100 MHz, $CDCl_3$): 14.2, 22.7, 24.7, 28.7, 29.2, 31.7, 32.5, 39.3, 49.5, 113.6, 116.0, 120.9, 122.6, 125.1, 125.9, 128.3, 137.4, 141.5, 178.3; *m/z* (EI): 376 (M+2, 5%), 374 (M^+, 5), 252 (96), 250 (100), 225 (27), 223 (28), 208 (8), 206 (7), 170 (8), 83 (19), 69 (29), 55 (14); HRMS (EI): Found, 374.0989 ($C_{19}H_{23}BrN_2O$ requires 374.0994). The ratio (99:1) of enantiomers was determined by HPLC [OD, *i*-PrOH-hexane (1:15)].

(3a*S*,8a*S*)-6-Bromo-1-methyl-3a,8-bis-(3-methylbut-2-enyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-2(1*H*)-one [(-)-4] : flustramide B



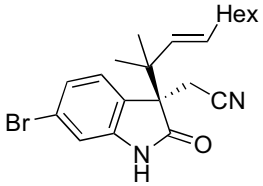
Under nitrogen, alane-*N*,*N*-dimethylethylamine complex (0.5 M in toluene, 715 mm^3, 0.36 mmol) was added to a solution of amide (-)-**15** (30.0 mg, 0.071 mmol) in THF (3 cm^3) at -15 °C. The reaction mixture was stirred at the same temperature for 5 min, and treated with THF-H_2O (1:1, 6 cm^3). The resulted mixture was filtered through Celite, and then the filtrate was evaporated *in vacuo*. The residue was basified with saturated aqueous $NaHCO_3$, and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with AcOEt-hexane (1:1) as an eluent to give flustramide B [(-)-**4**] (27.3 mg, 95%) as a colorless oil. $[\alpha]_D^{18}$ -116.1 (*c* 1.72, $CHCl_3$), $[\alpha]_D^{18}$ -104.2 (*c* 1.75, EtOH), [lit.[4b] $[\alpha]_D^{20}$ -180.0 (*c* 0.47, EtOH)]; $\nu_{max}(CHCl_3)/cm^{-1}$: 3019, 2974, 2928, 2856, 1682, 1595, 1489; δ_H (300 MHz, $CDCl_3$): 1.56 (3H, s, C(17)Me), 1.70 (3H, s, C(18)Me), 1.74 (3H, s, C(12)Me), 1.75 (3H, s, C(13)Me), 2.31 (1H, dd, *J* 14.8 and 7.4, C(14)H), 2.38 (1H, dd, *J* 14.8 and 7.4, C(14)H), 2.64 (2H, s, C(3)H), 2.87 (3H, s, C(19)Me), 3.88 (1H, dd, *J* 15.6 and 6.6, C(9)H), 3.96 (1H, dd, *J* 15.6 and 6.6, C(9)H), 4.72 (1H, s, C(8a)H), 4.96 (1H, t, *J* 7.3, C(15)H), 5.19 (1H, t, *J* 6.6, C(10)H), 6.60 (1H, s, ArH), 6.84 (2H, s, ArH); δ_C (100 MHz, $CDCl_3$): 18.1(2C), 25.7, 25.9, 27.9, 37.4, 41.7, 46.5, 49.5, 87.4, 111.6, 118.2, 120.1, 121.5, 122.2, 124.3, 134.3, 135.97, 136.01, 150.5, 172.8; *m/z* (EI): 404 (M+2, 95%), 402 (M^+, 93), 335 (31), 333 (28), 267 (100), 265 (100), 210 (30), 208 (31), 69 (72); HRMS (EI): Found, 402.1309 ($C_{21}H_{27}BrN_2O$ requires 402.1307).

(3a*S*,8a*R*)-6-Bromo-1-methyl-3a,8-bis(3-methylbut-2-enyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole [(-)-2] : flustramine B



A solution of (-)-**4** (20.0 mg, 0.049 mmol) and alane-*N*,*N*-dimethylethylamine complex (0.5 M in toluene, 149 mm^3, 0.0743 mmol) in THF (3.5 cm^3) was stirred at room temperature under nitrogen for 5 min. After treated with THF-H_2O (1:1, 10 cm^3), the resulting mixture was filtered through Celite, and then the filtrate was concentrated under reduced pressure. The residue was basified with saturated aqueous $NaHCO_3$, and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to give a residue, which was chromatographed by silica gel column with AcOEt-hexane (3:2) as an eluent to give flustramine B [(-)-**2**] (18.7 mg, 97%) as a colorless oil. $[\alpha]_D$ -105.9 (*c* 0.77, $CHCl_3$), $[\alpha]_D$ -103.5 (*c* 0.75, EtOH); [lit. $[\alpha]_D^{20}$ -511 (*c* 0.0039, EtOH)[2b], $[\alpha]_D$ -93.5 (*c* 1.5, EtOH)[14]]; $\nu_{max}(CHCl_3)/cm^{-1}$: 2963, 2930, 2857, 1595, 1485; δ_H (300 MHz, $CDCl_3$): 1.56 (3H, s, C(17)Me), 1.65 (3H, s, C(18)Me), 1.71 (3H, s, C(12)Me), 1.72 (3H, s, C(13)Me), 1.86 (1H, ddd, *J* 11.9, 5.7 and 3.5, C(3)H), 2.03 (1H, ddd, *J* 11.9, 9.3 and 6.8, C(3)H), 2.38 (2H, d, *J* 7.5 Hz, C(14)H), 2.47 (3H, s, C(19)Me), 2.56 (1H, td, *J* 9.3 and 5.7, C(2)H), 2.67 (1H, ddd, *J* 9.3, 6.8 and 3.5, C(2)H), 3.79 (1H, dd, *J* 16.1 and 7.1, C(9)H), 3.87 (1H, dd, *J* 16.1 and 5.8, C(9)H), 4.28 (1H, s, C(8a)H), 4.93 (1H, t, *J* 7.5, C(15)H), 5.13 (1H, t, *J* 5.8, C(10)H), 6.49 (1H, d, *J* 1.7, C(7)H), 6.72 (1H, dd, *J* 7.8 and 1.7, C(5)H), 6.79 (1H, d, *J* 7.8, C(4)H); δ_C (100 MHz, $CDCl_3$): 18.2, 18.3, 25.8, 26.0, 29.8, 38.2, 38.4, 39.0, 46.3, 52.8, 56.8, 91.6, 109.9, 119.8, 120.2, 120.5, 121.2, 123.8, 133.7, 134.6, 152.9; *m/z* (EI): 390 (M+2, 43%), 388 (M^+, 43), 321 (96), 319 (100), 290 (28), 288 (28), 278 (31), 276 (32), 253 (33), 251 (39), 210 (18), 172 (12), 171 (13), 69 (30); HRMS (EI): Found, 388.1520 ($C_{21}H_{29}BrN_2$ requires 388.1514).

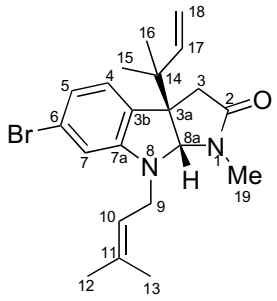
2-{(*R*)-6-Bromo-3-[(*E*)-2-methyldec-3-en-2-yl]-2-oxoindolin-3-yl}acetonitrile [(-)-19]



A solution of phosphonate **8** (1.52 cm^3, 9.37 mmol) and *t*-BuOK (956 mg, 8.52 mmol) in dry DMF (20 cm^3) was stirred at room temperature for 1.5 h. After cooling the mixture to -78 °C, a solution of indolin-3-one **18** (1.20 g, 2.84 mmol) in dry DMF (8.4 cm^3) was added dropwise to the mixture. The mixture was warmed slowly to room temperature and stirred at the same temperature for 2.5 h. The resulting mixture was neutralized with 10% HCl, and extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure

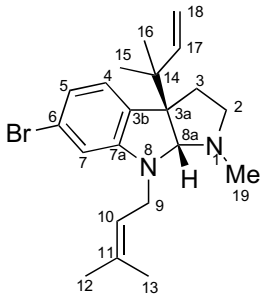
to obtain a residue, which was chromatographed on silica gel column with AcOEt-hexane (1:7) as an eluent to afford (-)-**19** (1.60 g, 70%) as pale yellow crystals. Mp 100-105°C (AcOEt-hexane); $[\alpha]_D^{25}$ -90.6 (*c* 1.32, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$: 3429, 2959, 2928, 2855, 2253, 1730, 1612, 1481; δ_H (300 MHz, $CDCl_3$): 0.89 (3H, t, *J* 7.0, $(CH_2)_5CH_3$), 1.01 (3H, s, -C*Me*(Me)-), 1.16 (3H, s, -CMe(*Me*)-), 1.28-1.43 (8H, m, $CH_2(CH_2)_4CH_3$), 2.06 (2H, td, *J* 6.8 and 6.4, $CHCH_2(CH_2)_4$), 2.82 (1H, d, *J* 16.5, C*H*HCN), 2.98 (1H, d, *J* 16.5, CH*H*CN), 5.46 (1H, dt, *J* 15.6 and 6.4, CH=C*H*CH_2), 5.55 (1H, d, *J* 15.6, C*H*=$CHCH_2$), 7.07 (1H, d, *J* 1.8, Ar7-H), 7.09 (1H, d, *J* 8.1, Ar4-H), 7.20 (1H, dd, *J* 8.1 and 1.8, Ar5-H) 7.68 (1H, brs, NH); δ_C (100 MHz, $CDCl_3$): 14.2, 21.6, 22.4, 22.8, 22.9, 29.0, 29.5, 31.8, 32.9, 41.1, 55.6, 113.1, 116.4, 122.7, 125.1, 126.9, 127.3, 131.8, 132.8, 142.3, 177.4; *m/z* (FAB): 405 (M+2, 21%), 403 (M^+, 18), 325 (20), 250 (5), 252 (6), 185 (72), 153 (100), 93 (96), 69 (40), HRMS (FAB): 403.1391 ($C_{21}H_{28}BrN_2O$ (M +1) requires 403.1385); Anal. Calcd for $C_{21}H_{27}BrN_2O$: C, 62.53; H, 6.75; N, 6.95; Found: C, 62.64; H, 6.78; N, 7.06. The ratio (98:2) of enantiomers was determined by HPLC [OD, *i*-PrOH-hexane (1:7)].

(3a*R*,8a*S*)-6-Bromo-1-methyl-8-(3-methylbut-2-enyl)-3a-(2-methylbut-3-en-2-yl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2(1*H*)-one [(-)-3] : flustramide A

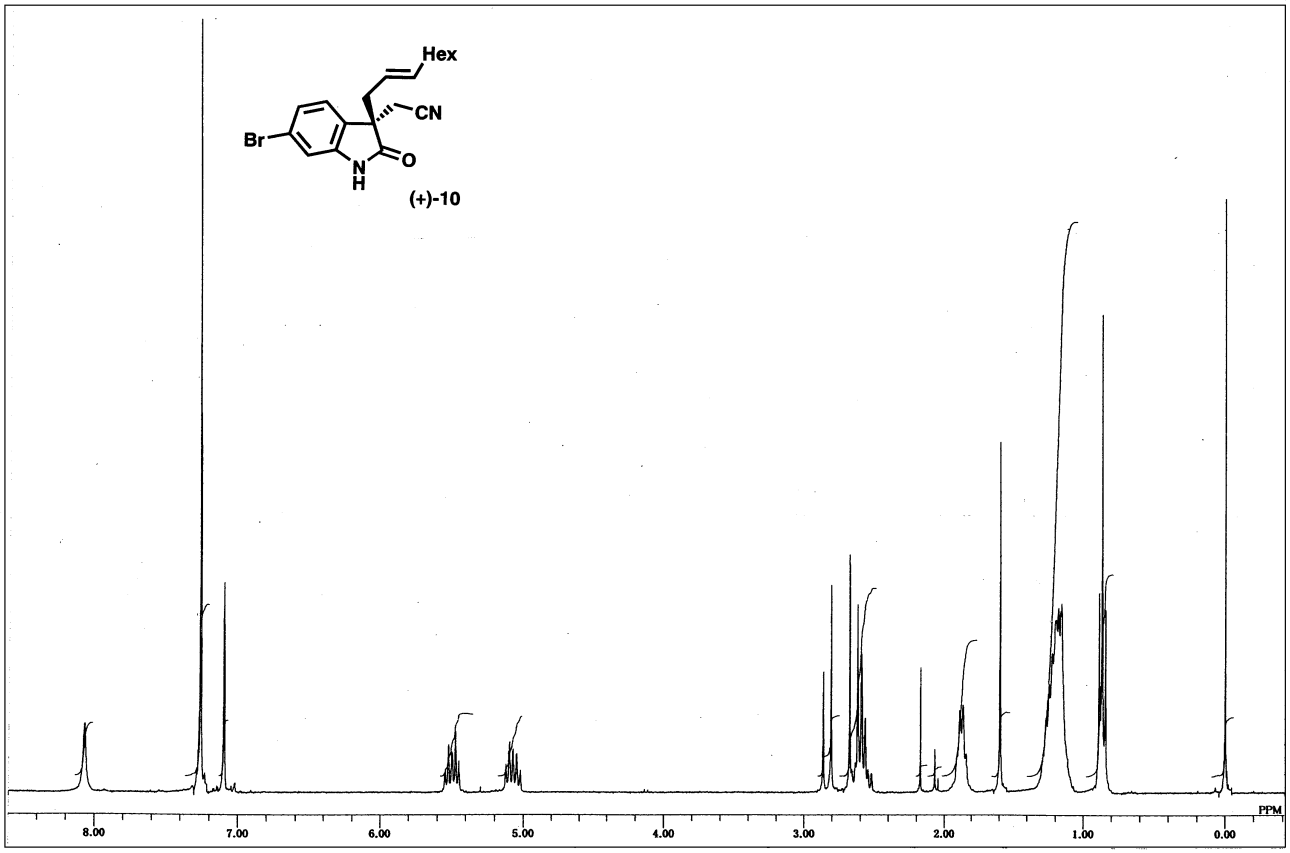


Alane-*N*,*N*-dimethylethylamine complex (0.5 M in toluene, 1.19 cm^3, 0.60 mmol) was added to a solution of amide (-)-**24** (50.0 mg, 0.12 mmol) in THF (5 cm^3) at -15 °C under nitrogen. After stirring for 5 min at the same temperature, the reaction mixture was treated with THF-H_2O (1:1, 10 cm^3). The resulting mixture was filtered through Celite, and then the filtrate was evaporated *in vacuo*. The residue was basified with saturated aqueous $NaHCO_3$, and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with AcOEt-hexane (1:1) as an eluent to give flustramide A [(-)-**3**] (44.3 mg, 92%) as a colorless oil. $[\alpha]_D^{18}$ -75.3 (*c* 1.19, $CHCl_3$), $[\alpha]_D^{18}$ -73.2 (*c* 1.09, EtOH); $\nu_{max}(CHCl_3)/cm^{-1}$: 3007, 2972, 2934, 1681, 1593, 1490; δ_H (300 MHz, $CDCl_3$): 0.94 (3H, s, C(15)Me), 1.03 (3H, s, C(16)Me), 1.75 (3H, s, C(12)Me), 1.77 (3H, s, C(13)Me), 2.54 (1H, d, *J* 17.4, C(3)H) 2.84 (1H, d, *J* 17.4, C(3)H), 2.85 (3H, s, C(3)H) 3.93 (2H, d, *J* 6.6, C(9)H), 4.83 (1H, s, C(8a)H), 5.05 (1H, dd, *J* 17.4 and 1.1, C(18)H), 5.17 (1H, dd, *J* 10.8 and 1.1, C(18)H), 5.26 (1H, t, *J* 6.6, C(10)H), 5.78 (1H, dd, *J* 17.4 and 10.8, C(17)H), 6.56 (1H, d, *J* 1.7, C(7)H), 6.81 (1H, dd, *J* 7.9 and 1.7, C(5)H), 6.92 (1H, dd, *J* 7.9, C(4)H); δ_C (67.8 MHz, $CDCl_3$): 18.1, 21.8, 22.6, 25.7, 28.0, 39.4, 41.2, 46.3, 55.4, 86.0, 111.0, 114.6, 120.4, 120.8, 122.6, 126.2, 131.8, 135.7, 143.3, 151.1, 172.6; *m/z* (EI): 404 (M+2, 37%), 402 (M^+, 37), 335 (44), 333 (45), 267 (95), 295 (97), 210 (20), 208 (20), 69 (100), 41 (18); HRMS (EI): Found, 402.1301 ($C_{21}H_{27}BrN_2O$ requires 402.1307).

(3a*R*,8a*R*)-6-Bromo-1-methyl-8-(3-methylbut-2-enyl)-3a-(2-methylbut-3-en-2-yl)-1,2,3,3a,8,8a-hexahydro pyrrolo[2,3-*b*]indole [(-)-1]: flustramine A



Under nitrogen, alane-*N*,*N*-dimethylethylamine complex (0.5 M in toluene, 260 mm^3, 0.13 mmol) was added to a solution of (-)-**3** (35.0 mg, 0.087 mmol) in THF (7 cm^3) at room temperature. The reaction mixture was stirred at the same temperature for 5 min, treated with THF-H_2O (1:1, 10 cm^3), and filtered through Celite. The filtrate was evaporated to give a residue, which was basified with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with AcOEt-hexane (3:2) as an eluent to give flustramine A (-)-**1** (30.3 mg, 90%) as a colorless oil. $[\alpha]_D^{18}$ -136.9 (*c* 0.75, $CHCl_3$), $[\alpha]_D^{18}$ -139.4 (*c* 0.73, EtOH); [lit.[3] $[\alpha]_D^{22}$ -40.0 (*c* 0.1, EtOH)]; $\nu_{max}(CHCl_3)/cm^{-1}$: 2963, 2930, 2857, 1595, 1485; δ_H (300 MHz, $CDCl_3$): 0.95 (3H, s, C(15)Me), 1.00 (3H, s, C(16)Me), 1.72 (3H, s, C(12)Me), 1.73 (1H, ddd, *J* 11.8, 5.3 and 2.6 Hz, C(3)H), 1.75 (3H, s, C(13)Me), 2.23 (1H, ddd, *J* 11.8, 9.7 and 6.8, C(3)H), 2.42 (3H, s, C(19)Me), 2.43 (1H, ddd, *J* 9.9, 9.7 and 5.3, C(2)H), 2.65 (1H, ddd, *J* 9.9, 6.8 and 2.6, C(2)H), 3.82 (1H, dd, *J* 16.7 and 6.3, C(9)H), 3.84 (1H, dd, *J* 16.7 and 5.8, C(9)H), 4.34 (1H, s, C(8a)H), 4.98 (1H, d, *J* 17.4, C(18)H), 5.06 (1H, d, *J* 10.8, C(18)H), 5.22 (1H, dd, 6.3 and 5.8, C(10)H), 5.94 (1H, dd, *J* 17.4 and 10.8, C(17)H), 6.47 (1H, d, *J* 1.5, C(7)H), 6.68 (1H, dd, *J* 7.8 and 1.5, C(5)H), 6.90 (1H, d, *J* 7.8, C(4)-H); δ_C (67.8 MHz, $CDCl_3$): 18.1, 22.5, 23.5, 25.6, 34.5, 37.8, 41.3, 45.9, 53.1, 63.4, 89.3, 109.3, 113.0, 119.1, 120.9, 121.7, 125.8, 132.5, 134.6, 144.9, 153.6; *m/z* (EI): 390 (M+2, 43%), 388 (M^+, 43), 321 (96), 319 (100), 290 (28), 288 (28), 278 (31), 276 (32), 253 (33), 251 (39), 210 (18), 172 (12), 171 (13), 69 (30); HRMS (EI): Found, 388.1518 ($C_{21}H_{29}BrN_2$ requires 388.1514).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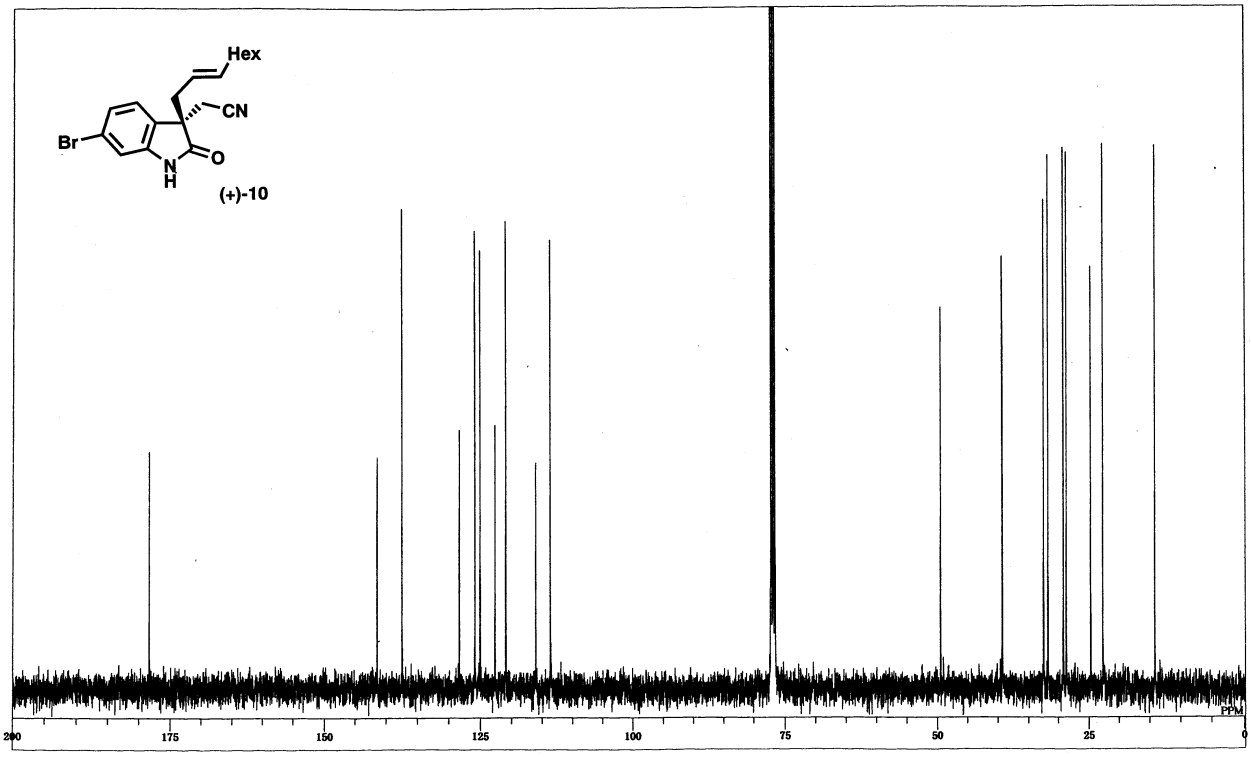
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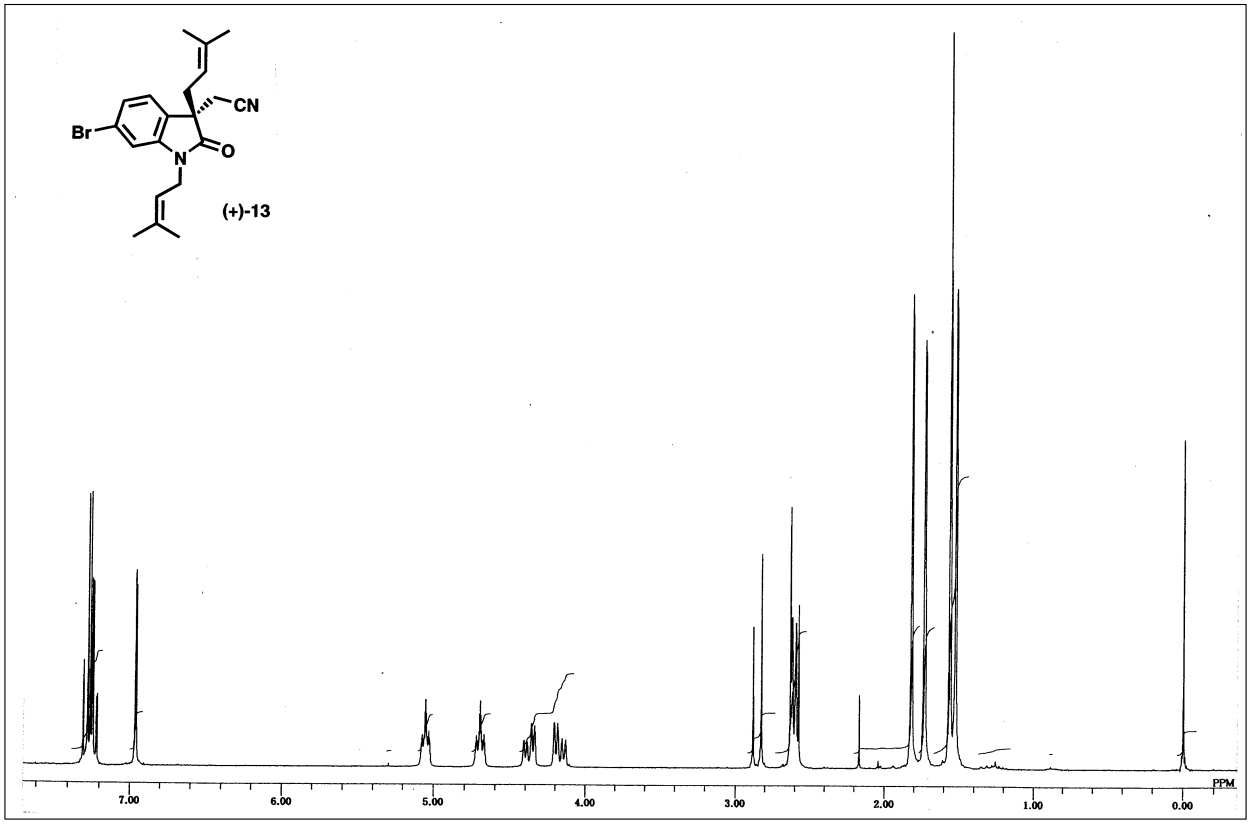
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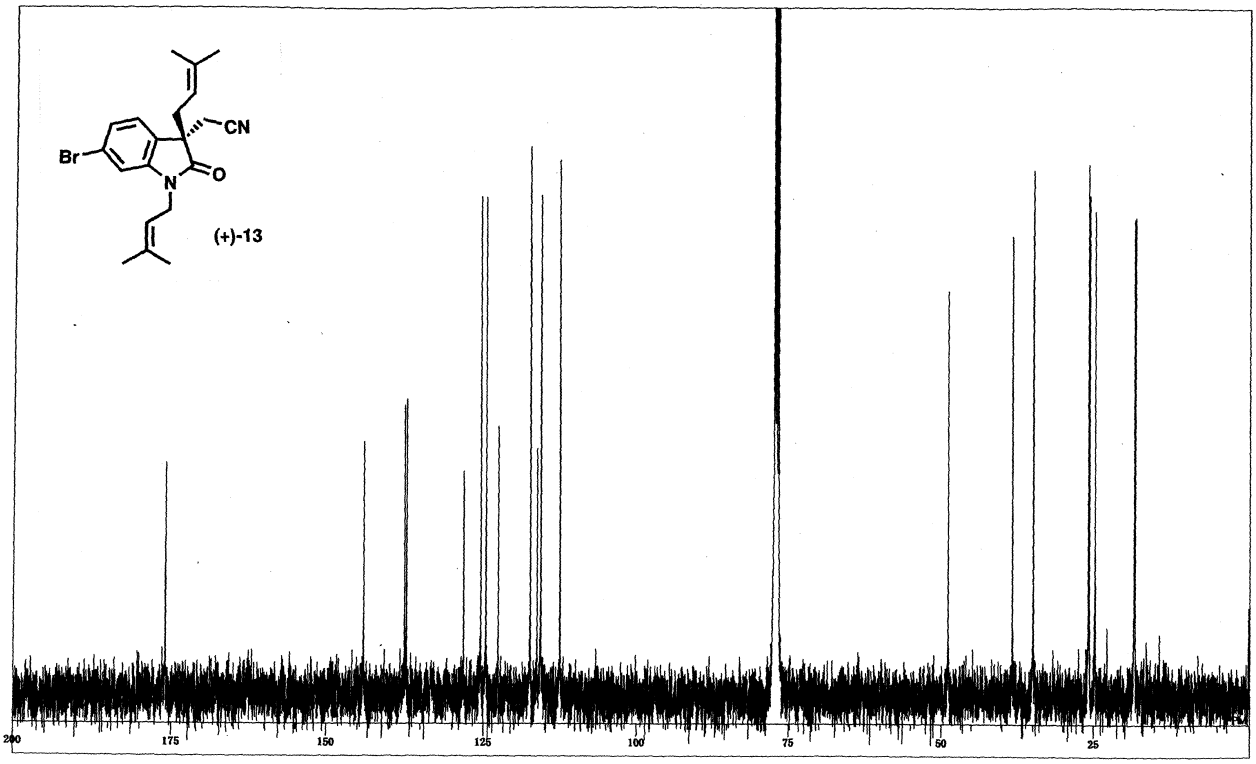
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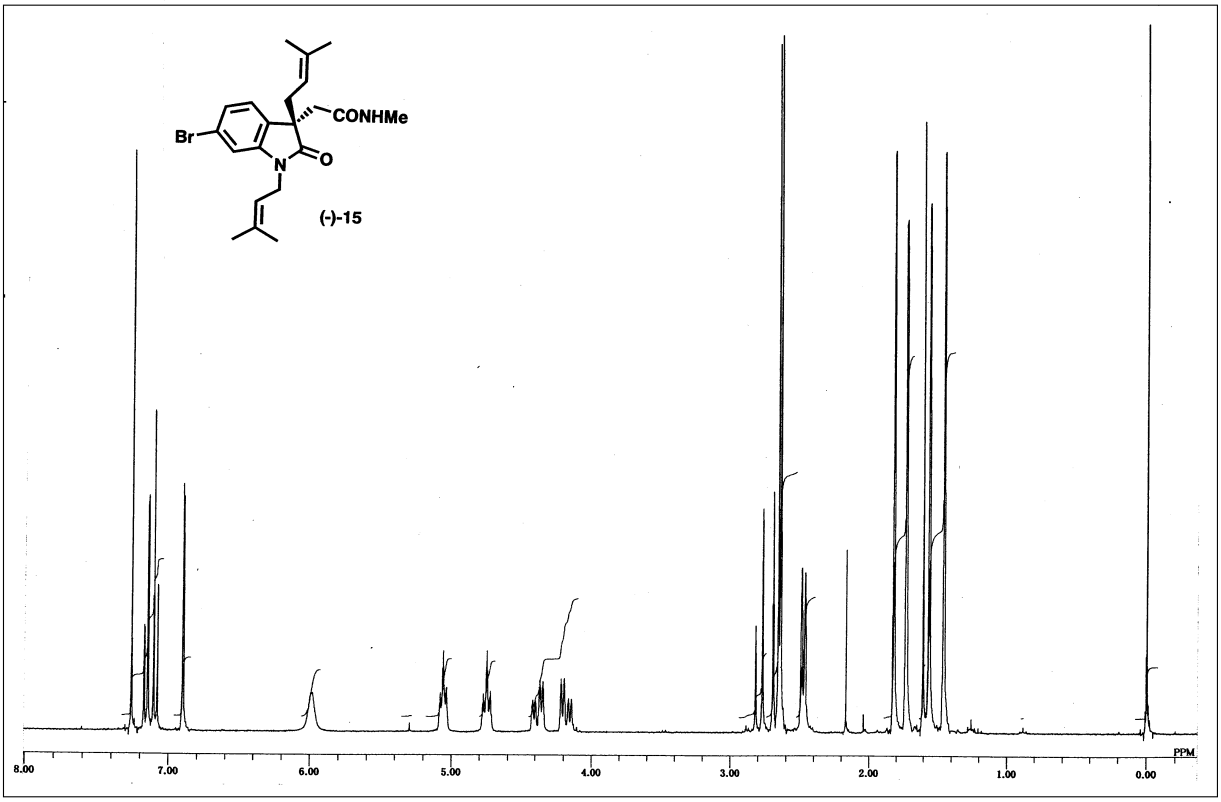
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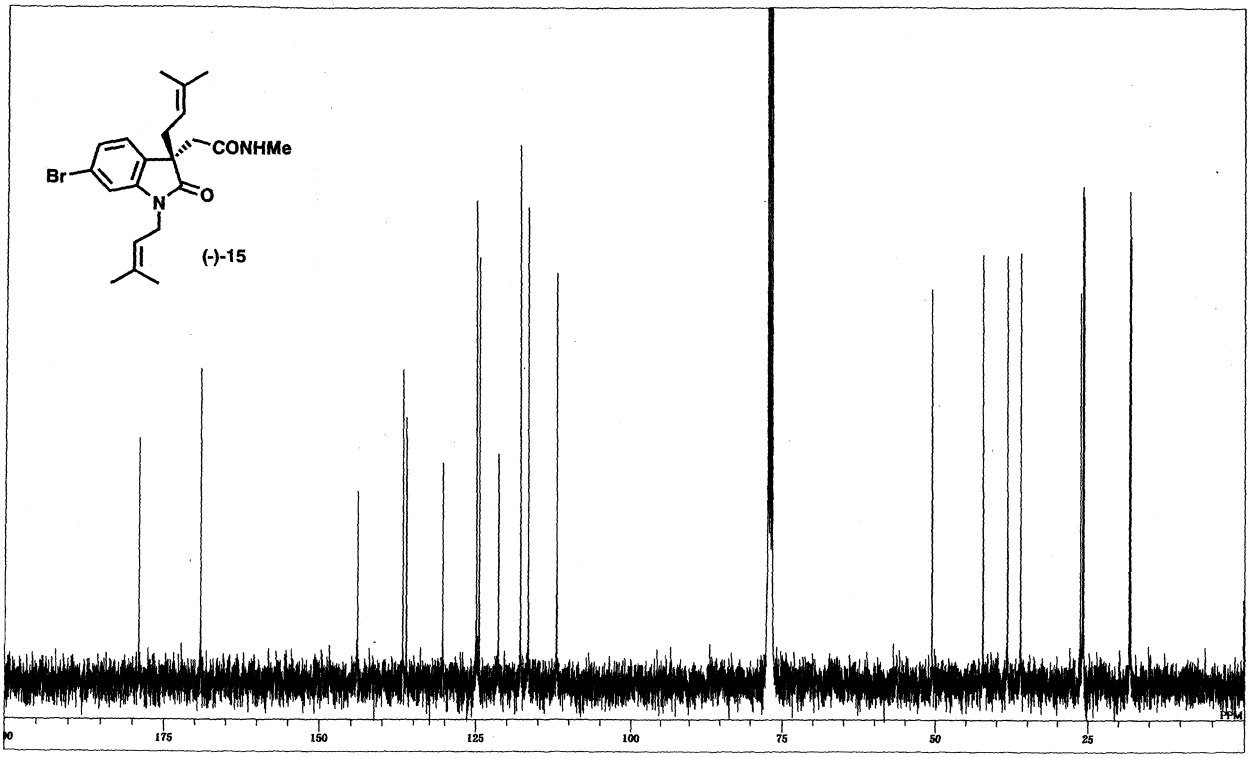
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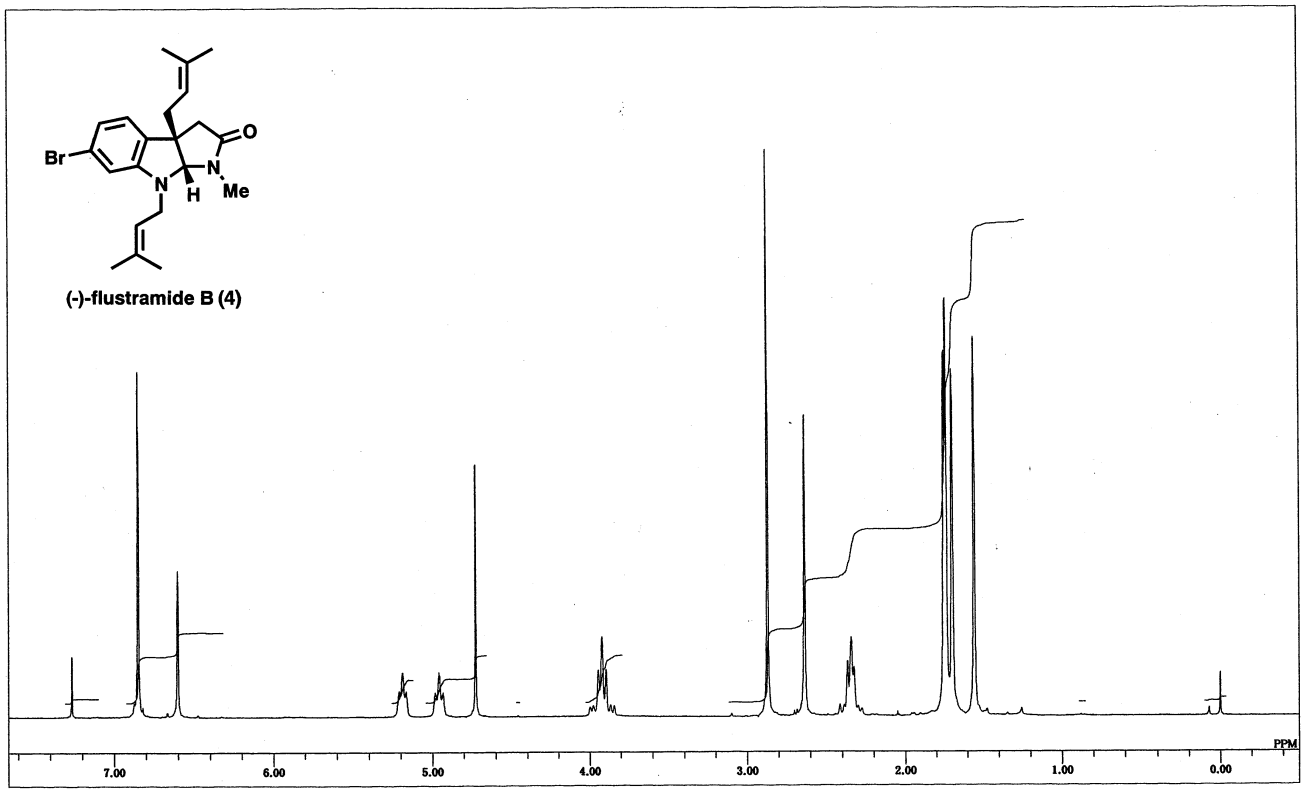
Br
O
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H
N
Me
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PPM
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6.00
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4.00
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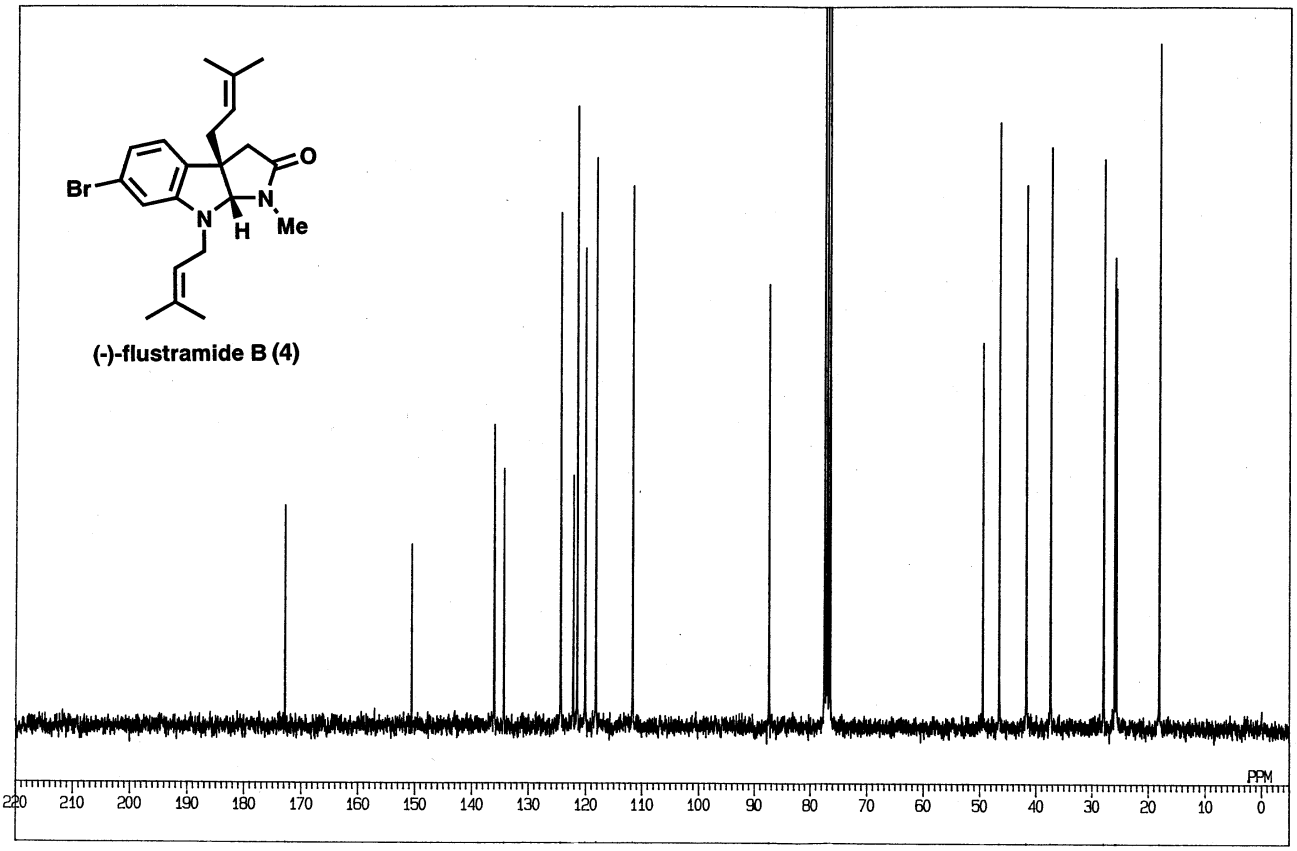
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O
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H
N
Me
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PPM
220
210
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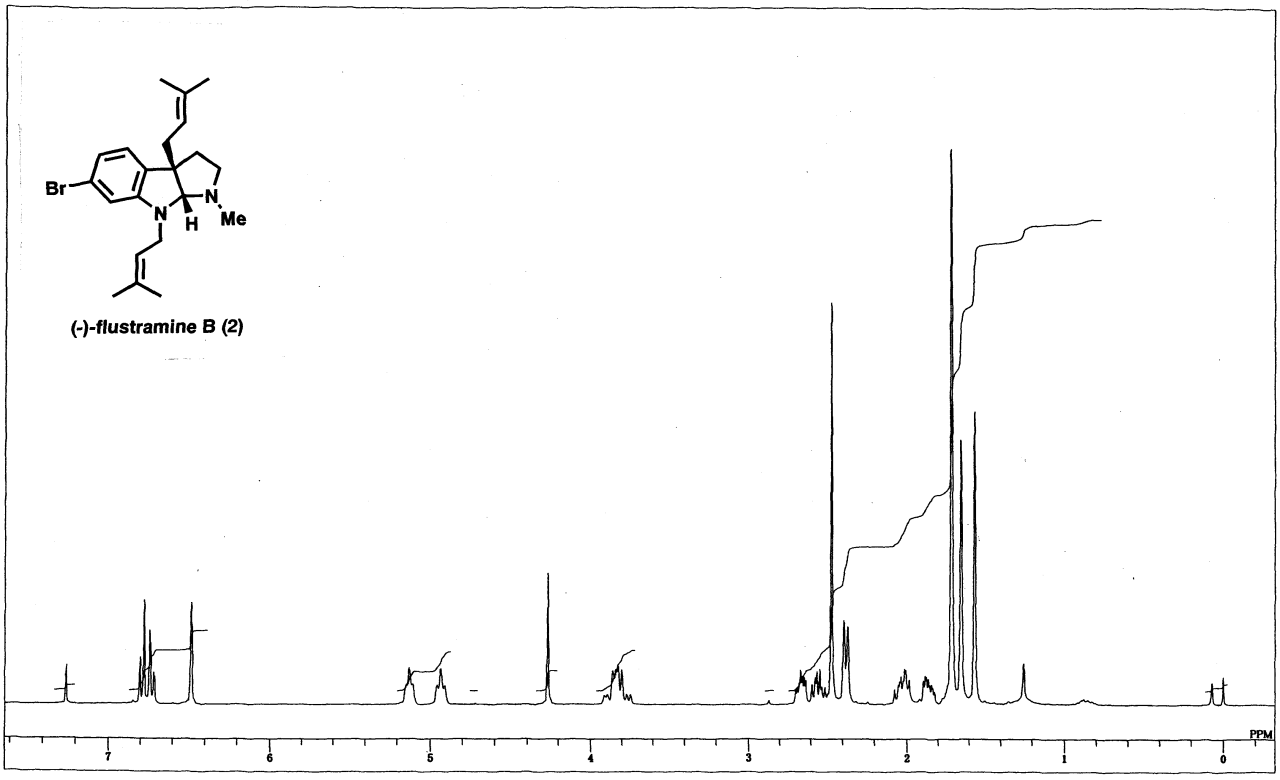
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N
Me
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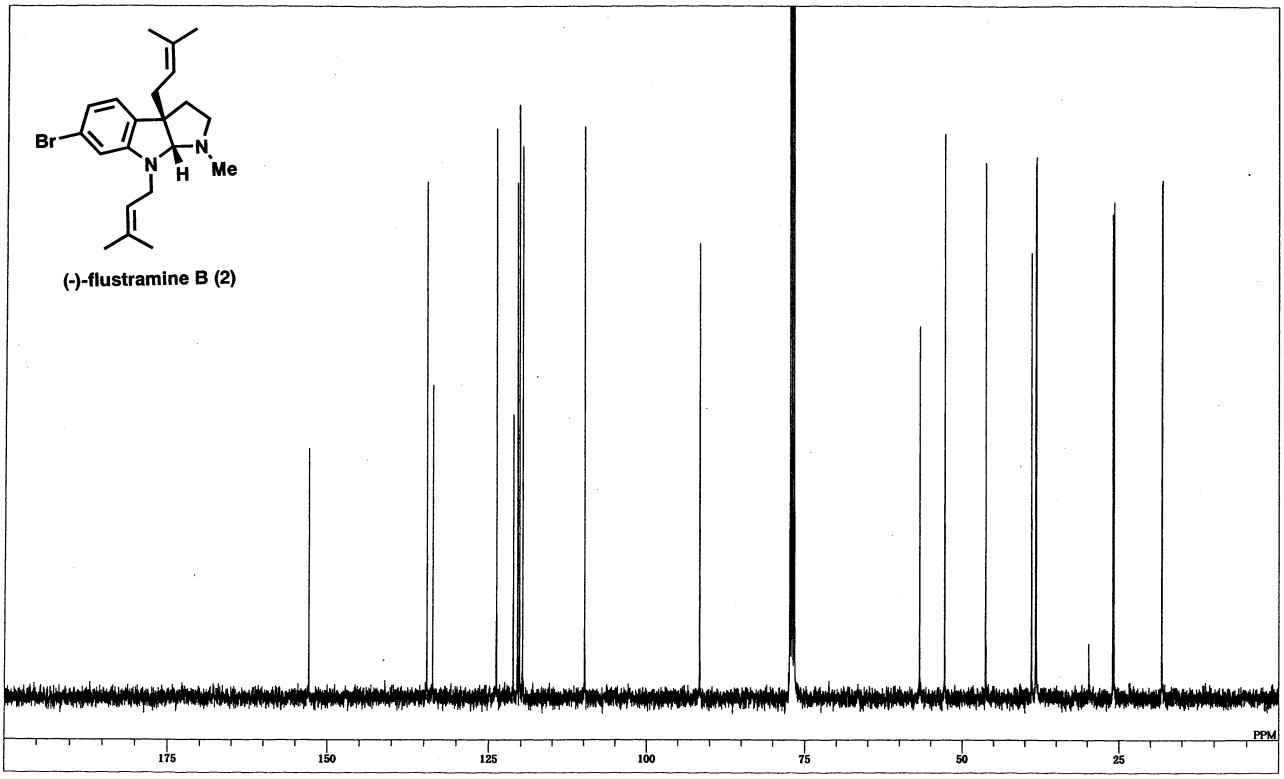
4
3
2
1
0
PPM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H
N
Me
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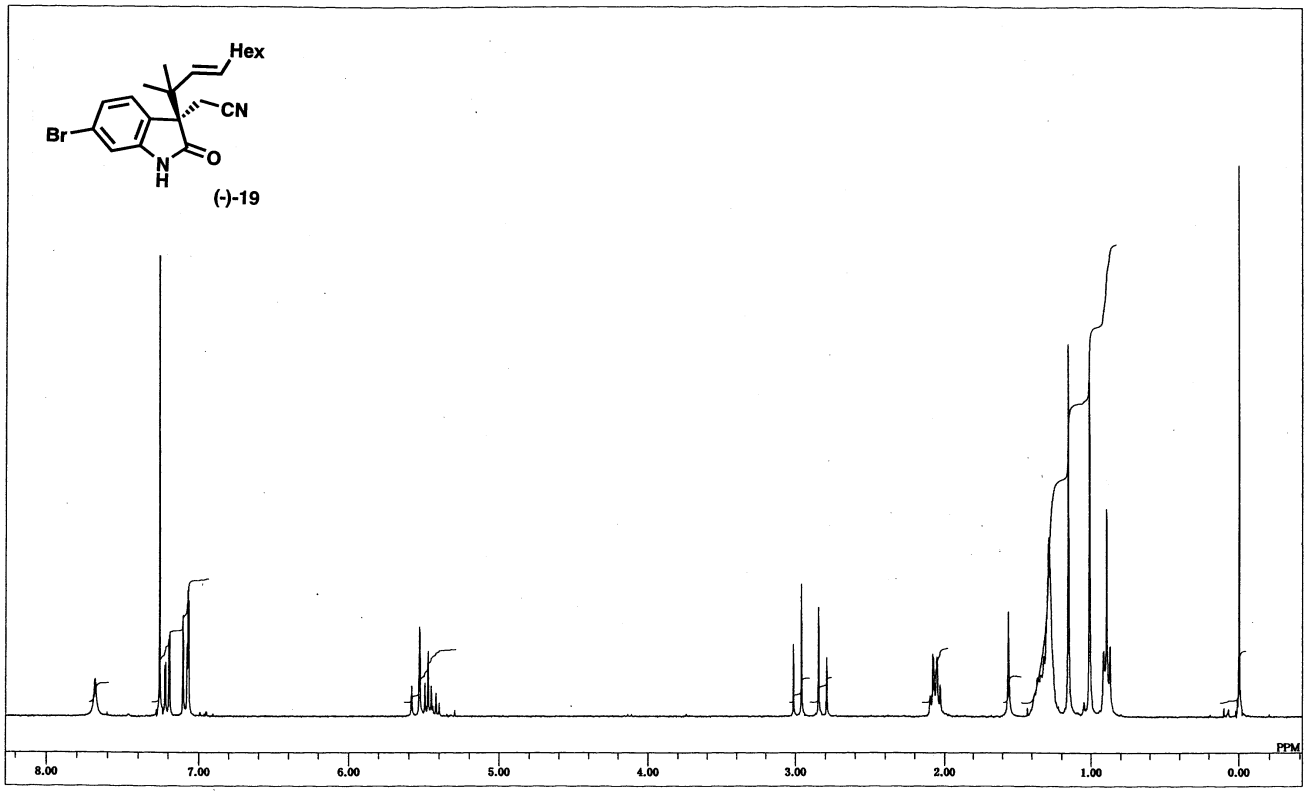
175
150
125
100
75
50
25
PPM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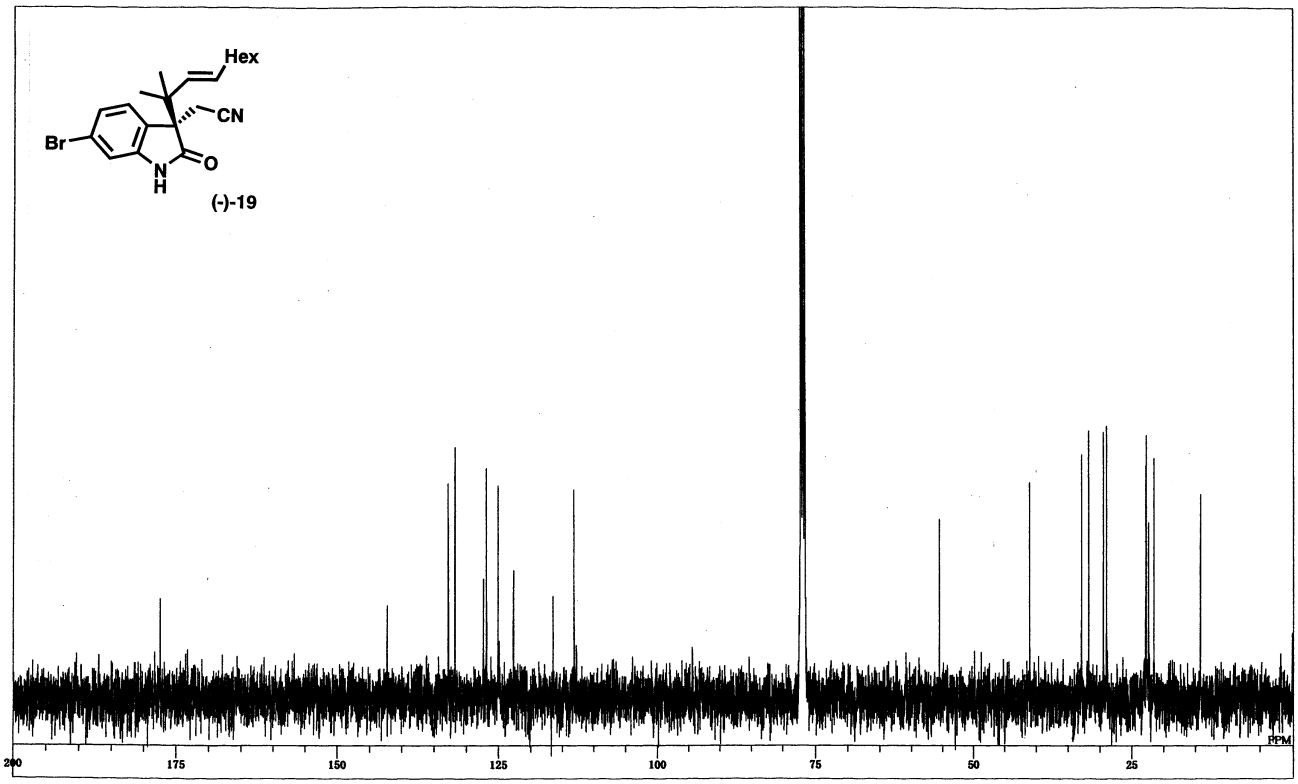
0.00
PPM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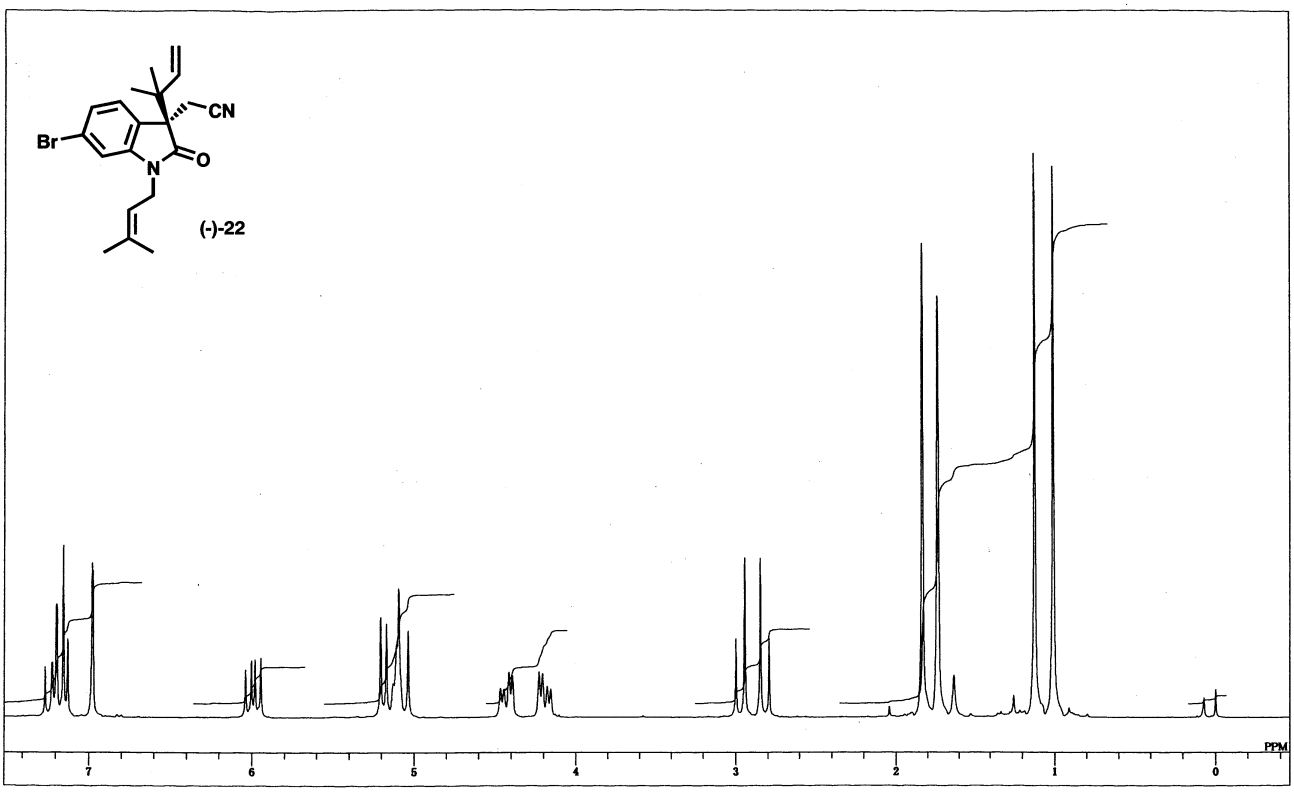
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PPM
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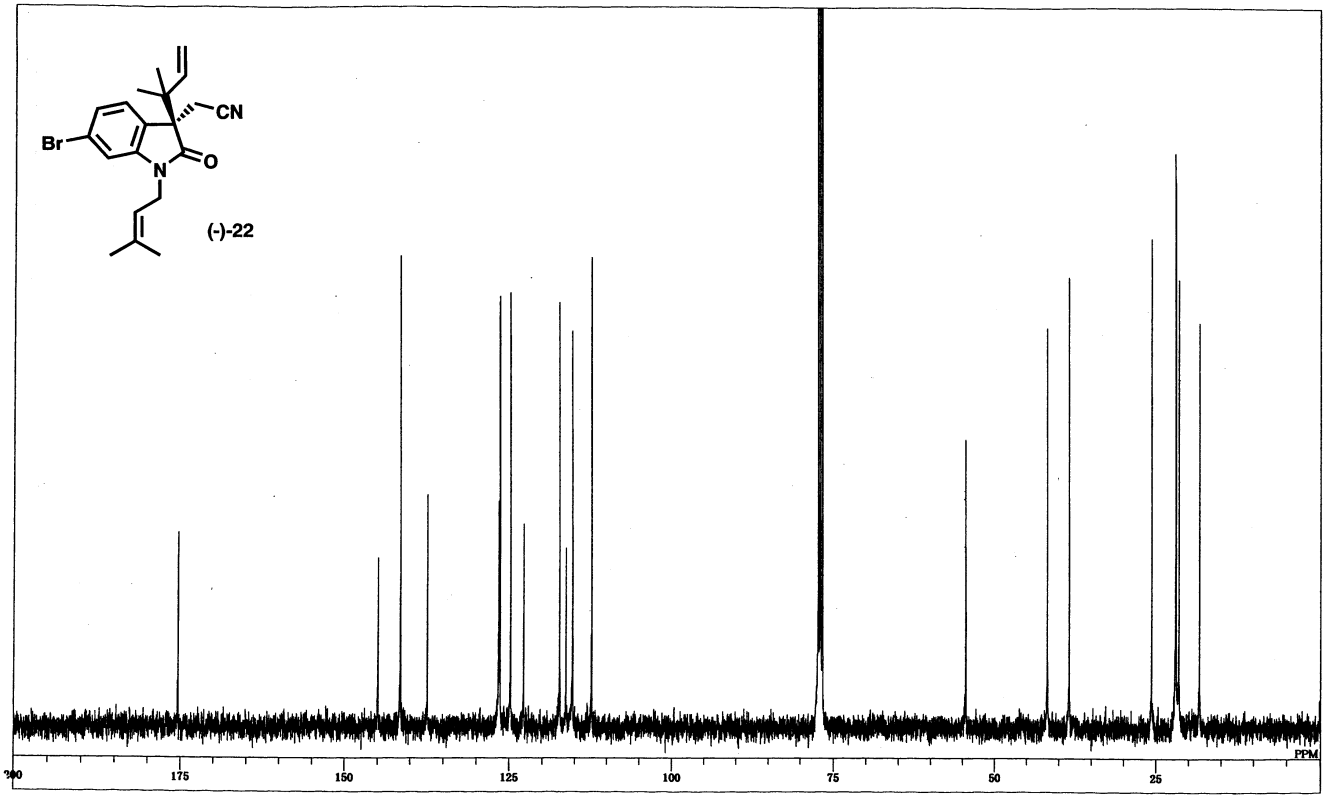
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PPM
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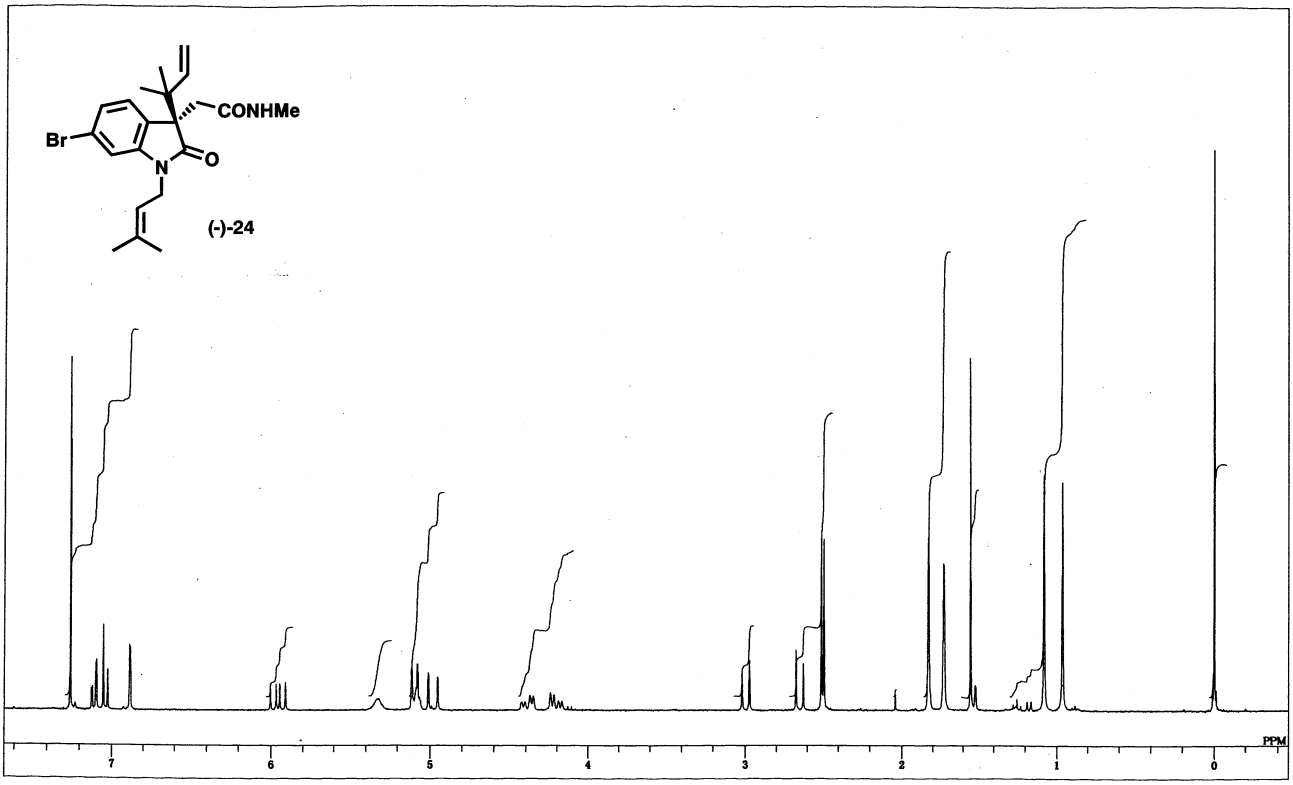
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(-)-24
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3
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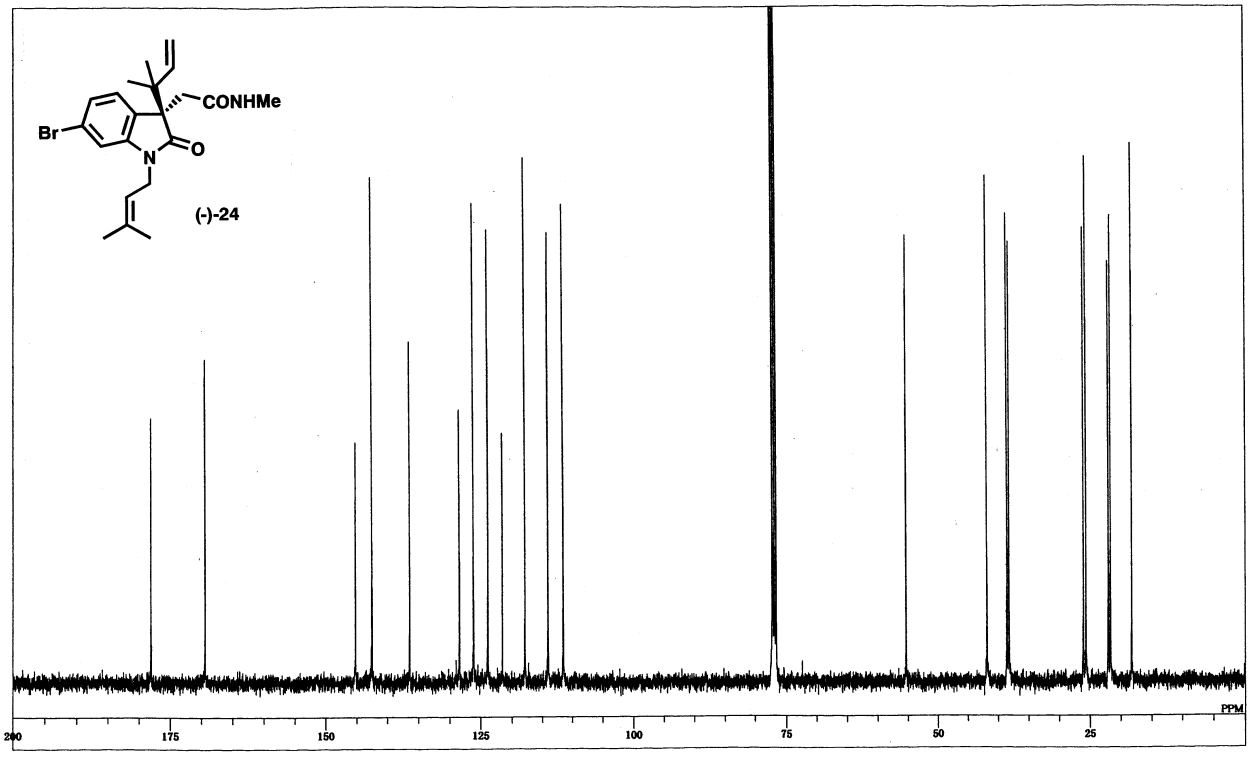
0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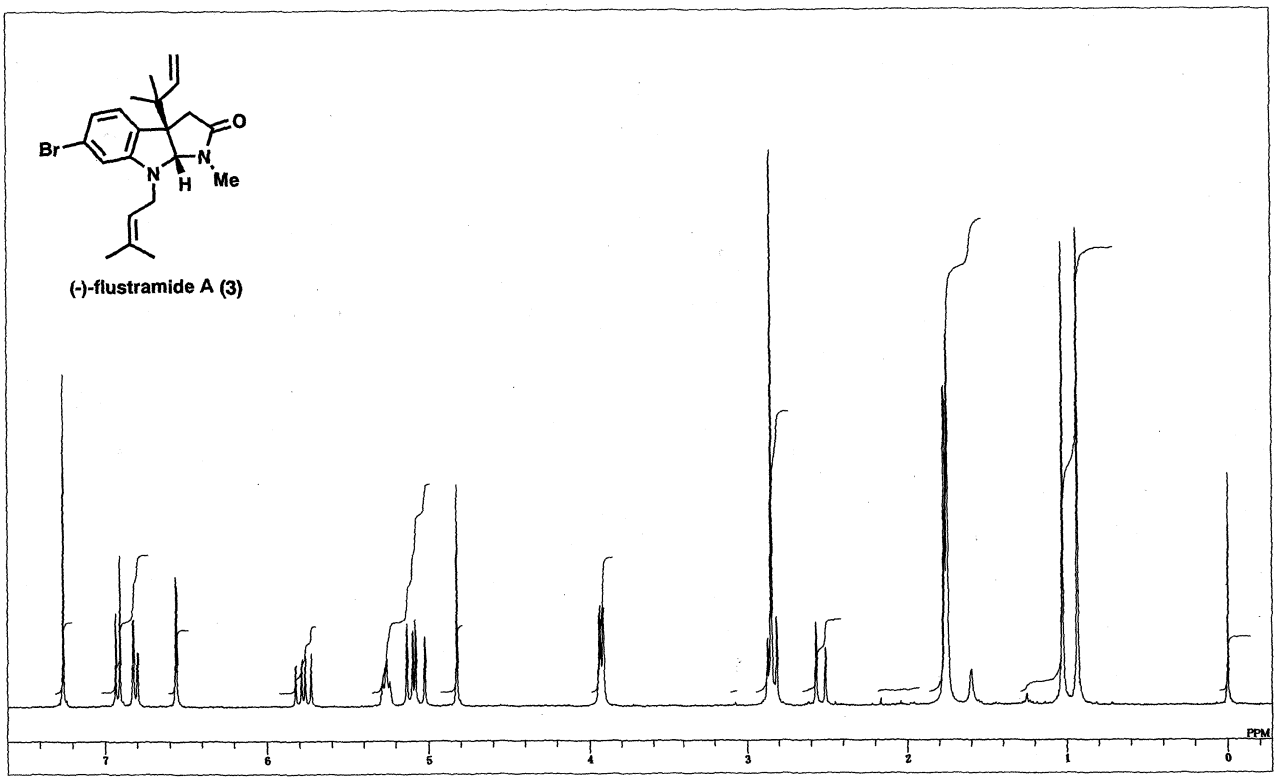
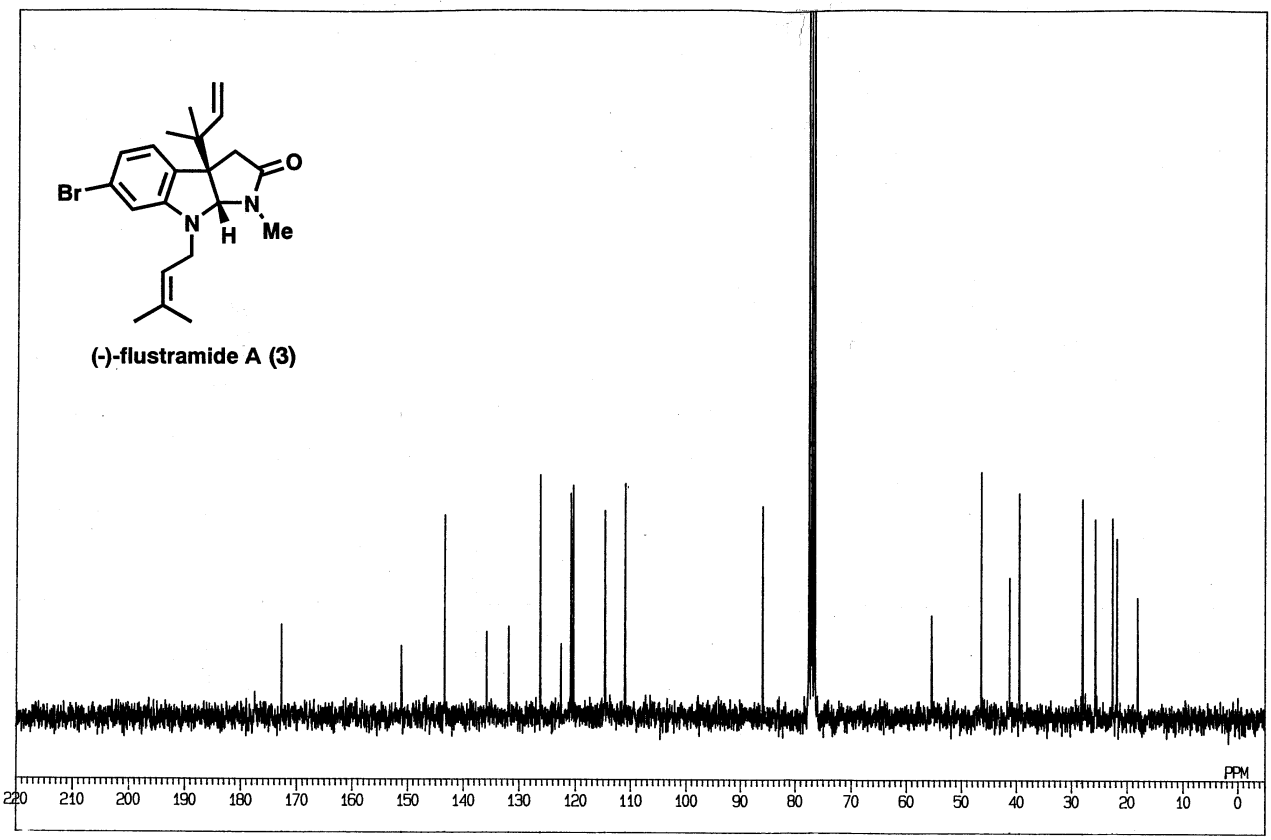

Br
O
N
Me
N
H
(-)-flustramide A (3)
PPM
7
6
5
4
3
2
1
0


Br
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N
Me
N
H
(-)-flustramide A (3)
PPM
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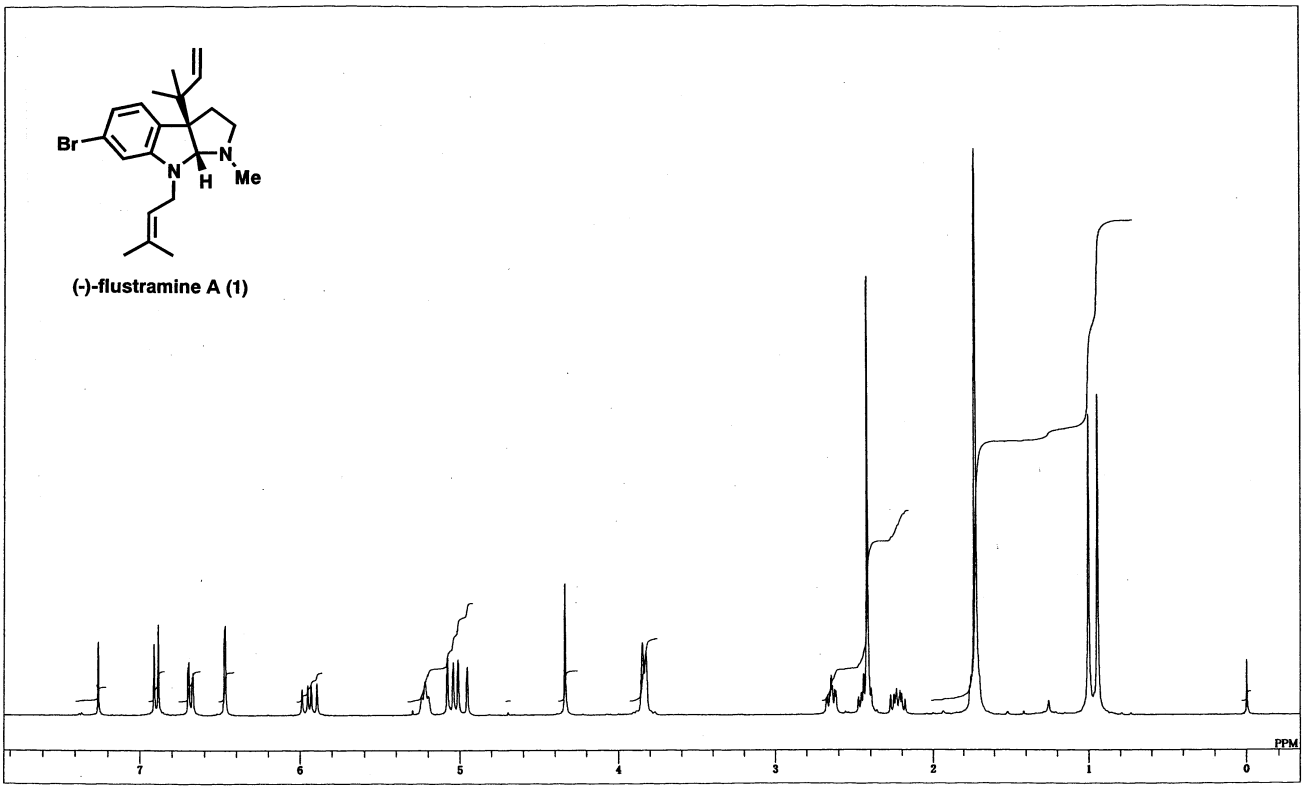
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N
Me
(-)-flustramine A (1)
PPM
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5
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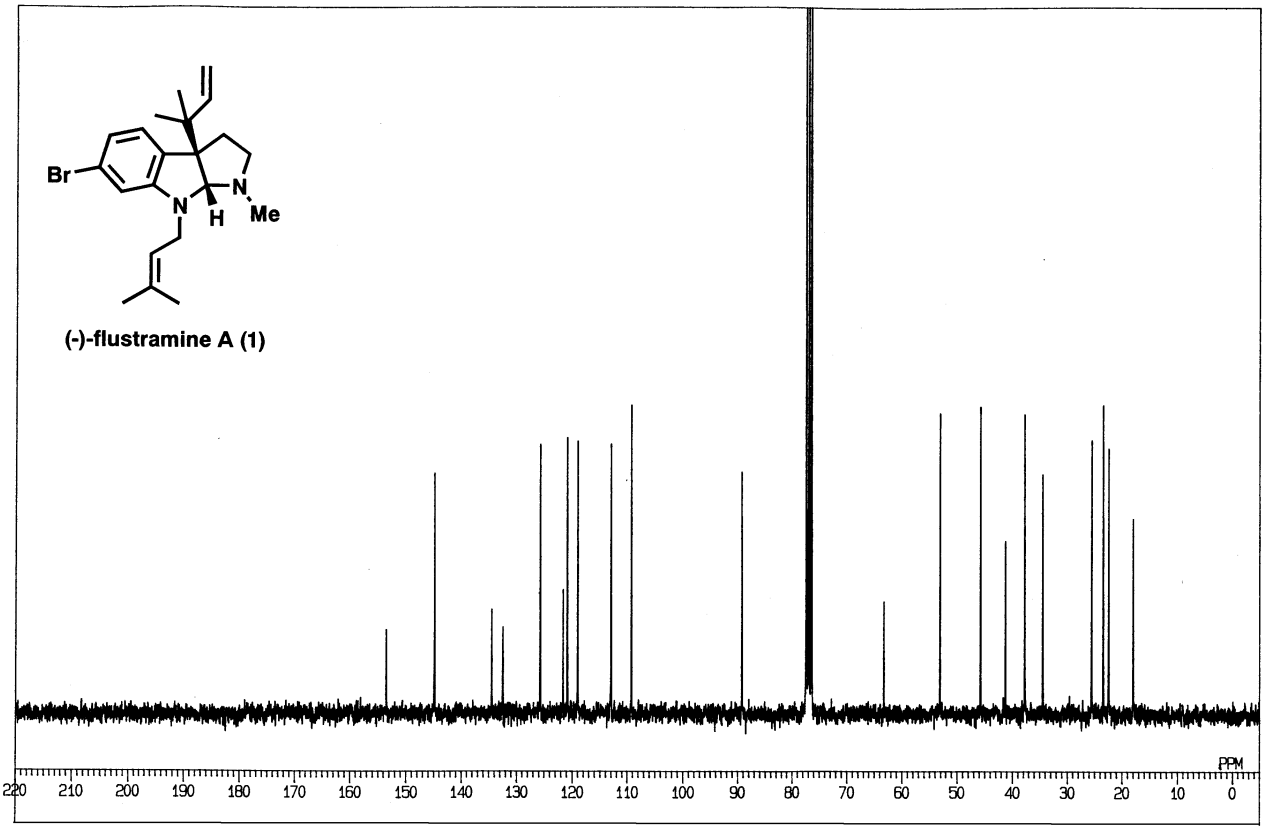
3
2
1
0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Me
(-)-flustramine A (1)
PPM
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0