

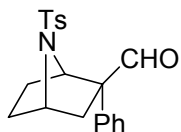
**Aza-Prins-Pinacol Approach to
7-Azabicyclo[2.2.1]heptanes and Ring Expansion to
[3.2.1]-Tropanes**

Supporting Information

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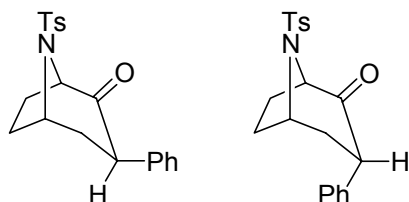
(±)-(1*R**,2*R**,4*S**) -2-Phenyl-7-(toluene-4-sulfonyl)-7-aza-bicyclo[2.2.1]heptane-2-carbaldehyde
7a



Magnesium turnings (0.97 g, 40.0 mmol) were immersed with diethyl ether (20 ml) in a reaction vessel equipped with reflux condenser. A solution of α -bromo-styrene (1.30 ml, 10.0 mmol) in diethyl ether (3.7 ml) was added causing exothermic formation of the Grignard reagent. Separately, a solution of the aldehyde **5a** (1.73 g, 6.11 mmol) in diethyl ether (30 ml) was cooled to -30 °C. The Grignard reagent solution (18.3 ml, assumed concentration 0.40 M, 7.34 mmol) was added *via* syringe, causing rapid precipitation. The reaction was allowed to warm to ambient temperature for 10 min before being quenched by addition of saturated aqueous NH_4Cl solution (50 ml). The mixture was extracted into diethyl ether (2 x 70 ml), the combined organics washed with brine and then dried over Na_2SO_4 . Flash Column Chromatography (eluant 3 : 2 petroleum : diethyl ether) isolated the *rearrangement precursor* **6a** as a mixture of diastereoisomers (1.41 g, 59 %) as a white foam; ν_{max} / cm^{-1} 3479, 2987, 2950, 1598; m/z (CI) 405 [$\text{M}(\text{NH}_4)^+$, 10%], 356 [(MH^+) -MeOH, 100%]; Found: $\text{M}(\text{NH}_4)^+$, 405.1838. $\text{C}_{21}\text{H}_{29}\text{N}_2\text{O}_4\text{S}$ requires: 405.1848.

To a 0 °C solution of rearrangement precursor **6a** (50 mg, 0.13 mmol) in dichloromethane (1 ml) was added SnCl_4 solution (0.13 ml, 1.0 M in heptanes, 0.13 mmol). The whole was stirred at 0 °C for 8 min before being quenched by addition of saturated aqueous NaHCO_3 (5 ml). The mixture was extracted into dichloromethane (2 x 10 ml), dried over Na_2SO_4 , filtered and solvent removed *in vacuo* to give *aldehyde* **7a** (44 mg, 96 %) as a colourless oil; ν_{max} / cm^{-1} (film) 3061, 2985, 2961, 2881, 1727, 1598; δ_{H} (250 MHz, CDCl_3) 9.24 (1H, s, -CHO), 7.78 (2H, d, $J_{8.2}$, - SO_2 -C-CH), 7.41-7.27 (5H, m, Ar-H), 7.15-7.09 (2H, m, Ar-H), 4.82 (1H, d, $J_{4.0}$, N-CH-C-CHO), 4.34-4.28 (1H, m, N-CH-CH₂-C-CHO), 2.92 (1H, ddd, $J_{12.2}$, 5.2, 1.8, *exo* -CHH-C-CHO), 2.43 (3H, s, Ar-CH₃), 2.11-1.93 (2H, m, -CHH-CHH- both *exo*), 1.75 (1H, d, $J_{12.2}$, *endo* -CHH-C-CHO), 1.68-1.55 (1H, m, *endo* CHH-CH(N)-C-CHO), 1.51-1.37 (1H, m, *endo* CHH-CH(N)-CH₂-); δ_{C} (125 MHz, CDCl_3) 197.0 (CH), 143.8 (C), 137.2 (C), 134.9 (C), 129.6 (CH), 129.2 (CH), 128.6 (CH), 127.9 (CH), 127.7 (CH), 65.5 (C), 62.9 (CH), 59.6 (CH), 37.0 (CH₂), 30.9 (CH₂), 23.9 (CH₂), 21.6 (CH₃); m/z (CI) 356 (MH^+ , 60 %); Found: MH^+ , 356.1315. $\text{C}_{20}\text{H}_{22}\text{NO}_3\text{S}$ requires: 356.1320.

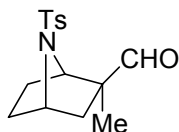
(\pm)-(1*R**, 3*R**, 5*S**)-3-Phenyl-8-(toluene-4-sulfonyl)-8-aza-bicyclo[3.2.1]octan-2-one **8a**
and (\pm)-(1*R**, 3*S**, 5*S**)-3-Phenyl-8-(toluene-4-sulfonyl)-8-aza-bicyclo[3.2.1]octan-2-one **9a**



To a 0 °C solution of rearrangement precursor **6a** (113 mg, 0.29 mmol) in dichloromethane (2.3 ml) was added SnCl₄ solution (0.58 ml, 1.0 M in heptanes, 0.58 mmol). The mixture was allowed to warm to ambient temperature and stirred for 16 h. The reaction was quenched by addition of saturated aqueous NaHCO₃ (10 ml). The mixture was extracted into chloroform (2 x 20 ml) and combined organics dried over Na₂SO₄. Flash Column Chromatography (eluant 1 : 1 petroleum : diethyl ether) isolated the isomeric *tropanes* **8a** (62 mg, 60 %, white crystals) and **9a** (16 mg, 16 %, white gum) as pure compounds; Data for **8a**: m.p. 181-183 °C; ν_{\max} / cm⁻¹ (film) 3030, 2961, 2883, 1726, 1595; δ_{H} (250 MHz, CDCl₃) 7.81 (2H, d, *J*8.1, SO₂-C-CH), 7.34 (2H, d, *J*8.1, Ar-H), 7.31-7.24 (3H, m, Ar-H), 6.99-6.94 (2H, m, Ar-H), 4.63-4.56 [1H, m, N-CH-(CH₂)₂], 4.41-4.36 (1H, m, N-CH-C=O), 3.59 (1H, dd, *J*11.6, 7.6, Ph-CH-C=O), 2.47 (3H, s, Ar-CH₃), 2.42-2.13 (2H, m, CH₂-CH-Ph), 2.10-1.87 (4H, m, CH₂-CH₂); δ_{C} (125 MHz, CDCl₃) 202.2 (C), 144.2 (C), 137.5 (C), 136.7 (C), 129.9 (CH), 129.0 (CH), 128.6 (CH), 127.7 (CH), 127.3 (CH), 66.1 (CH), 57.1 (CH), 49.3 (CH), 41.6 (CH₂), 28.2 (CH₂), 27.6 (CH₂), 21.6 (CH₃); *m/z* (CI) 373 [M(NH₄)⁺, 100%]; Found: MH⁺, 356.1318. C₂₀H₂₂NO₃S requires: 356.1320;

Data for **9a**: ν_{\max} / cm⁻¹ (film) 2957, 2929, 2873, 1730, 1597; δ_{H} (250 MHz, CDCl₃) 7.79 (2H, d, *J*8.5, SO₂-C-CH), 7.38-7.23 (5H, m, Ar-H), 7.06-7.00 (2H, m, Ar-H), 4.66-4.48 (2H, m, CH-N-CH), 3.92 (1H, t, *J*11.3, Ph-CH-C=O), 3.01-2.86 (1H, m, CHH-CH-Ph), 2.46-2.37 (1H, m, CHH-CH-Ph), 1.87-1.38 (4H, m, CH₂-CH₂); δ_{C} (125 MHz, CDCl₃) 208.8 (C), 144.2 (C), 137.2 (C), 136.9 (C), 130.0 (CH), 128.9 (CH), 128.6 (CH), 127.3 (CH), 125.7 (CH), 66.1 (CH), 55.3 (CH), 49.7 (CH), 36.9 (CH₂), 31.7 (CH₂), 28.3 (CH₂), 21.6 (CH₃); *m/z* (CI) 373 [M(NH₄)⁺, 100%]; Found: M(NH₄)⁺, 373.1582. C₂₀H₂₅N₂O₃S requires: 373.1586.

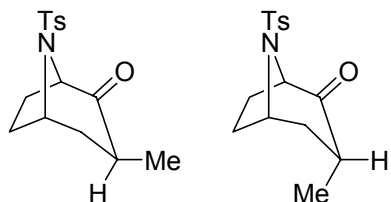
(±)-(1*R**, 2*R**, 4*S**)-2-Methyl-7-(toluene-4-sulfonyl)-7-aza-bicyclo[2.2.1]heptane-2-carbaldehyde
7b



Magnesium turnings (0.58 g, 24.0 mmol) were immersed with diethyl ether (20.5 ml) in a reaction vessel equipped with reflux condenser. A crystal of iodine was added and the mixture stirred until the iodine colour disappeared. An initial quantity of neat 2-bromopropene (0.20 ml) was added, initiating Grignard reagent formation. Further 2-bromopropene (0.33 ml) was added, maintaining reflux. Separately, a solution of the aldehyde **5a** (0.42 g, 1.48 mmol) in diethyl ether (10 ml) was cooled to -30 °C. The Grignard reagent solution (6.14 ml, assumed concentration 0.29 M, 1.78 mmol) was added *via* syringe, causing rapid precipitation. The reaction was allowed to warm to ambient temperature for 10 min before being quenched by addition of saturated aqueous NH₄Cl solution (20 ml). The mixture was extracted into diethyl ether (2 x 20 ml), the combined organics washed with brine and then dried over Na₂SO₄. Flash Column Chromatography (eluant 3 : 2 petroleum : diethyl ether) isolated the *rearrangement precursor* **6b** as a mixture of diastereoisomers (0.19 g, 40 %) as a colourless oil; ν_{\max} / cm⁻¹ (film) 3492, 2979, 2951, 1651, 1598; m/z (CI) 343 [M(NH₄)⁺, 15%], 294 [(MH)⁺-MeOH, 100%]; Found: M(NH₄)⁺, 343.1687. C₁₆H₂₇N₂O₄S requires: 343.1692.

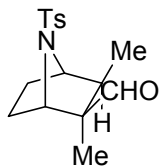
To a 0 °C solution of rearrangement precursor **6b** (26 mg, 0.08 mmol) in dichloromethane (1 ml) was added SnCl₄ solution (80 µl, 1.0 M in heptanes, 0.08 mmol). The whole was stirred at 0 °C for 8 min before being quenched by addition of saturated aqueous NaHCO₃ (5 ml). The mixture was extracted into dichloromethane (2 x 10 ml), dried over Na₂SO₄, filtered and solvent removed *in vacuo* to give aldehyde **7b** (19 mg, 81 %) as a colourless oil; ν_{\max} / cm⁻¹ (film) 2964, 2926, 1726, 1598; δ_{H} (250 MHz, CDCl₃) 9.40 (1H, s, -CHO), 7.74 (2H, d, *J*8.2, SO₂-C-CH), 7.28 (2H, d, *J*8.2, Ar-H), 4.21-4.16 (2H, m, CH-N-CH), 2.42 (3H, s, Ar-CH₃), 2.37 (1H, ddd, *J*12.3, 5.5, 2.4, *exo* CHH-C(Me)-C=O), 2.05-1.42 (4H, m, CH₂-CH₂), 1.08 (3H, s, CH₃-C-C=O), 1.04 (1H, d, *J*12.3, *endo* CHH-C(Me)-C=O); δ_{C} (100 MHz, CDCl₃) 202.6 (CH), 143.8 (C), 137.1 (C), 129.6 (CH), 127.6 (CH), 63.8 (CH), 60.1 (CH), 54.1 (C), 40.0 (CH₂), 30.3 (CH₂), 23.7 (CH₂), 21.6 (CH₃), 16.8 (CH₃); m/z (CI) 311 [M(NH₄)⁺, 100%]; Found: M(NH₄)⁺, 311.1435. C₁₅H₂₃N₂O₃S requires: 311.1429.

(\pm)-(1*R**, 3*S**, 5*S**)-3-Methyl-8-(toluene-4-sulfonyl)-8-aza-bicyclo[3.2.1]octan-2-one **8b**
and (\pm)-(1*R**, 3*R**, 5*S**)-3-Methyl-8-(toluene-4-sulfonyl)-8-aza-bicyclo[3.2.1]octan-2-one **9b**



To a 0 °C solution of rearrangement precursor **6b** (40 mg, 0.12 mmol) in dichloromethane (1 ml) was added SnCl₄ solution (0.24 ml, 1.0 M in heptanes, 0.24 mmol). The mixture was allowed to warm to ambient temperature and stirred for 16 h. The reaction was quenched by addition of saturated aqueous NaHCO₃ (10 ml). The mixture was extracted into chloroform (2 x 15 ml) and combined organics dried over Na₂SO₄. Flash Column Chromatography (eluant 1 : 1 petroleum : diethyl ether) isolated the isomeric *tropanes* **8b** (13 mg, 37 %, white gum) and **9b** (6 mg, 17 %, colourless oil) as pure compounds; Data for **8b**: ν_{\max} / cm⁻¹ (film) 2961, 2924, 1724, 1595; δ_{H} (250 MHz, CDCl₃) 7.74 (2H, d, *J*8.2, SO₂-C-CH), 7.30 (2H, d, *J*8.2, Ar-H), 4.48-4.40 [1H, m, N-CH-(CH₂)₂], 4.29-4.23 (1H, m, N-CH-C=O), 2.51-2.34 (1H, m, CH-Me), 2.43 (3H, s, Ar-CH₃), 2.03-1.66 (6H, m, C-CH₂-C), 0.97 (3H, d, *J*6.7, CH-CH₃); δ_{C} (100 MHz, CDCl₃) 204.8 (C), 144.0 (C), 136.5 (C), 129.8 (CH), 127.6 (CH), 65.7 (CH), 57.1 (CH), 40.8 (CH), 36.6 (CH₂), 27.8 (CH₂), 27.6 (CH₂), 21.6 (CH₃), 14.1 (CH₃); *m/z* (CI) 311 [M(NH₄)⁺, 100%]; Found: M(NH₄)⁺, 311.1426. C₁₅H₂₃N₂O₃S requires: 311.1429; Data for **9b**: ν_{\max} / cm⁻¹ (film) 2969, 2934, 2874, 1726, 1597; δ_{H} (250 MHz, CDCl₃) 7.74 (2H, d, *J*8.1, SO₂-C-CH), 7.30 (2H, d, *J*8.1, Ar-H), 4.51-4.42 [1H, m, N-CH-(CH₂)₂], 4.38-4.32 (1H, m, N-CH-C=O), 2.80-2.62 (1H, m, CH-CH₃), 2.43 (3H, s, Ar-CH₃), 1.83-0.86 (6H, m, C-CH₂-C), 1.04 (3H, d, *J*6.4, CH-CH₃); δ_{C} (125 MHz, CDCl₃) 211.6 (C), 144.0 (C), 137.0 (C), 129.9 (CH), 127.3 (CH), 65.8 (CH), 55.1 (CH), 37.4 (CH), 36.3 (CH₂), 31.5 (CH₂), 28.5 (CH₂), 21.5 (CH₃), 14.6 (CH₃); *m/z* (CI) 311 [M(NH₄)⁺, 100%]; Found: 294.1158. C₁₅H₂₀NO₃S requires: 294.1164.

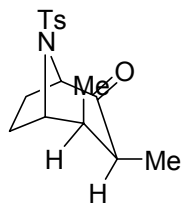
(±)-(1*R**, 2*S**, 3*R**, 4*S**)-(*trans*-2,3-Dimethyl)-7-(toluene-4-sulfonyl)-7-aza-bicyclo[2.2.1]heptane-2-carbaldehyde **7c**



A solution of (*Z*)-2-bromo-but-2-ene (0.16 ml, 1.55 mmol) in diethyl ether (10 ml) was cooled to -78 °C. ^tBuLi (1.82 ml, 1.7 M in pentane, 3.10 mmol) was added and the mixture stirred at -78 °C for 1 h. Solid MgBr₂·OEt₂ (364 mg, 1.41 mmol) was introduced and the temperature raised to 0 °C for 30 min. Separately, the aldehyde **5a** (367 mg, 1.30 mmol) was dissolved in diethyl ether (7 ml) and the whole cooled to 0 °C. The entire organometallic solution (at 0 °C) was transferred into this *via* canula with stirring. Stirred a further 5 min at ambient temperature before quenching with saturated aqueous NH₄Cl (20 ml). The mixture was extracted into diethyl ether (2 x 20 ml) and combined organics dried over Na₂SO₄. Flash Column Chromatography (eluant 3 : 2 petroleum : diethyl ether, gradient rising to 1 : 1) isolated the desired *rearrangement precursor* **6c** as a mixture of diastereoisomers (177 mg, 40 %) as a colourless oil; ν_{\max} / cm⁻¹ (film) 3488, 2978, 2946, 1598; *m/z* (CI) 357 [M(NH₄)⁺, 5%], 308 [(MH⁺)-MeOH, 90%]; Found: 357.1840 [M(NH₄)⁺]. C₁₇H₂₉N₂O₄S requires: 357.1848.

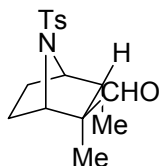
To a 0 °C solution of rearrangement precursor **6c** (55 mg, 0.16 mmol) in dichloromethane (1 ml) was added SnCl₄ solution (0.16 ml, 1.0 M in heptanes, 0.16 mmol). The whole was stirred at 0 °C for 8 min before being quenched by addition of saturated aqueous NaHCO₃ (5 ml). The mixture was extracted into dichloromethane (2 x 10 ml) and combined organics dried over Na₂SO₄. Flash Column Chromatography (eluant 2 : 1 petroleum : diethyl ether) afforded the *aldehyde* **7c** (31 mg, 62 %) as white crystals, m.p. 129-130 °C (dec); ν_{\max} / cm⁻¹ (film) 2965, 2927, 2877, 1721; δ_{H} (250 MHz, CDCl₃) 9.47 (1H, s, -CHO), 7.83-7.77 (2H, m, SO₂-C-CH), 7.33-7.28 (2H, m, Ar-H), 4.11 (1H, d, *J*4.3, N-CH-C-CHO), 3.81 (1H, d, *J*3.7, N-CH-CH-CH₃), 2.43 (3H, s, Ar-CH₃), 2.09-1.78 (3H, m, CH₂-CHH), 1.62-1.48 (1H, m, CH₂-CHH), 1.55 (1H, q, *J*7.3, CH-CH₃), 1.03 (3H, s, CH₃-C-CHO), 0.88 (3H, d, *J*7.3, CH-CH₃); δ_{C} (125 MHz, CDCl₃) 204.5 (CH), 143.8 (C), 137.3 (C), 129.7 (CH), 127.5 (CH), 66.0 (CH), 64.8 (CH), 56.2 (C), 51.5 (CH), 30.0 (CH₂), 23.7 (CH₂), 21.6 (CH₃), 17.0 (CH₃), 16.0 (CH₃); *m/z* (CI) 308 (MH⁺, 100%); Found: 308.1330. C₁₆H₂₂NO₃S requires: 308.1320.

(±)-(1*R**, 3*S**, 4*R**, 5*S**)-3,4-Dimethyl-8-(toluene-4-sulfonyl)-8-aza-bicyclo[3.2.1]octan-2-one **8c**



To a 0 °C solution of rearrangement precursor **6c** (49 mg, 0.14 mmol) in dichloromethane (1 ml) was added SnCl₄ solution (0.28 ml, 1.0 M in heptanes, 0.28 mmol). The mixture was allowed to warm to ambient temperature and stirred for 16 h. The reaction was quenched by addition of saturated aqueous NaHCO₃ (10 ml). The mixture was extracted into chloroform (2 x 15 ml) and combined organics dried over Na₂SO₄. Flash Column Chromatography (eluant 3 : 2 petroleum : diethyl ether) isolated the product *tropane* **8c** (21 mg, 49 %) as a colourless oil; ν_{max} / cm⁻¹ (film) 2965, 2933, 2875, 1726; δ_{H} (250 MHz, CDCl₃) 7.78-7.72 (2H, m, SO₂-C-CH), 7.30 (2H, d, *J*7.9, Ar-H), 4.40-4.34 (1H, m, Me-CH-CH-N), 4.03 (1H, d, *J*7.6, N-CH-C=O), 2.43 (3H, s, Ar-CH₃), 2.20 (1H, dq, *J*6.8, 6.8, Me-CH-C=O), 1.87-1.57 (3H, m, CH₂-CHH), 1.37-1.26 (1H, m, CH₂-CHH), 1.24 (3H, d, *J*6.1, CH₃-CH-CH-N), 1.22-1.10 (1H, m, Me-CH-CH-N), 1.03 (3H, d, *J*6.8, CH₃-CH-C=O); δ_{C} (125 MHz, CDCl₃) 211.8 (C), 144.0 (C), 136.9 (C), 129.9 (CH), 127.4 (CH), 65.9 (CH), 62.7 (CH), 45.9 (CH), 43.3 (CH), 30.4 (CH₂), 29.0 (CH₂), 21.6 (CH₃), 21.1 (CH₃), 13.0 (CH₃); *m/z* (CI) 325 [M(NH₄)⁺, 100%], 308 (MH⁺, 35%); Found: (MH⁺) 308.1323. C₁₆H₂₂NO₃S requires: 308.1320.

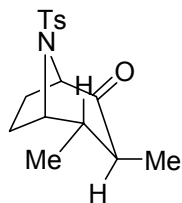
(\pm)-(1*R**, 2*S**, 3*S**, 4*S**)-(*cis*-2,3-Dimethyl)-7-(toluene-4-sulfonyl)-7-aza-bicyclo[2.2.1]heptane-2-carbaldehyde **7d**



A solution of (*E*)-2-bromo-but-2-ene (0.16 ml, 1.55 mmol) in diethyl ether (10 ml) was cooled to -78 °C. ^tBuLi (1.82 ml, 1.7 M in pentane, 3.10 mmol) was added and the mixture stirred at -78 °C for 1 h. Solid MgBr₂.OEt₂ (364 mg, 1.41 mmol) was introduced and the temperature raised to 0 °C for 30 min. Separately, the aldehyde **5a** (351 mg, 1.24 mmol) was dissolved in diethyl ether (7 ml) and the whole cooled to 0 °C. The entire organometallic solution (at 0 °C) was transferred into this *via* canula with stirring. Stirred a further 5 min at ambient temperature before quenching with saturated aqueous NH₄Cl (20 ml). The mixture was extracted into diethyl ether (2 x 20 ml) and combined organics dried over Na₂SO₄. Flash Column Chromatography (eluant 3 : 2 petroleum : diethyl ether) isolated the desired *rearrangement precursor* **6d** as a mixture of diastereoisomers (252 mg, 60 %) as a colourless oil; ν_{\max} / cm⁻¹ (film) 3497, 2980, 2937, 2865, 2835, 1598; m/z (CI) 357 [M(NH₄)⁺, 10%], 308 [(MH⁺)-MeOH, 100%]; Found: 357.1846 [M(NH₄)⁺]. C₁₇H₂₉N₂O₄S requires: 357.1848.

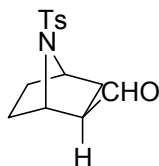
To a 0 °C solution of rearrangement precursor **6d** (72 mg, 0.21 mmol) in dichloromethane (1.5 ml) was added SnCl₄ solution (0.21 ml, 1.0 M in heptanes, 0.21 mmol). The whole was stirred at 0 °C for 8 min before being quenched by addition of saturated aqueous NaHCO₃ (7 ml). The mixture was extracted into dichloromethane (2 x 15 ml) and combined organics dried over Na₂SO₄. Flash Column Chromatography (eluant 3 : 2 petroleum : diethyl ether) afforded the *aldehyde* **7d** (40 mg, 61 %) as white crystals, m.p. 126-128 °C; ν_{\max} / cm⁻¹ (film) 2971, 2929, 2882, 1721, 1597; δ_{H} (250 MHz, CDCl₃) 9.38 (1H, s, -CHO), 7.78-7.72 (2H, m, SO₂-C-CH), 7.28 (2H, d, *J*7.9, Ar-H), 4.14 (1H, d, *J*4.6, N-CH-C-CHO), 4.09-4.04 (1H, m, N-CH-CH-CH₃), 2.48 (1H, qd, *J*7.5, 4.6, CH-CH₃), 2.42 (3H, s, Ar-CH₃), 1.97-1.71 (4H, m, CH₂-CH₂), 0.90 (3H, s, CH₃-C-CHO), 0.86 (3H, d, *J*7.5, CH-CH₃); δ_{C} (125 MHz, CDCl₃) 202.7 (CH), 143.7 (C), 137.4 (C), 129.6 (CH), 127.5 (CH), 65.0 (CH), 64.3 (CH), 54.5 (C), 38.1 (CH), 23.7 (CH₂), 22.8 (CH₂), 21.5 (CH₃), 11.6 (CH₃), 10.7 (CH₃); m/z (CI) 308 (MH⁺, 100%); Found: (MH⁺) 308.1332. C₁₆H₂₂NO₃S requires: 308.1320.

(±)-(1*R**, 3*S**, 4*S**, 5*S**)-3,4-Dimethyl-8-(toluene-4-sulfonyl)-8-aza-bicyclo[3.2.1]octan-2-one **8d**



To a 0 °C solution of rearrangement precursor **6d** (63 mg, 0.19 mmol) in dichloromethane (1.2 ml) was added SnCl₄ solution (0.37 ml, 1.0 M in heptanes, 0.37 mmol). The mixture was allowed to warm to ambient temperature and stirred for 16 h. The reaction was quenched by addition of saturated aqueous NaHCO₃ (10 ml). The mixture was extracted into chloroform (2 x 15 ml) and combined organics dried over Na₂SO₄. Flash Column Chromatography (eluant 3 : 2 petroleum : diethyl ether) isolated the product *tropane* **8d** (24 mg, 42 %) as a white solid, m.p. 107-110 °C; ν_{\max} / cm⁻¹ (film) 2971, 2933, 2882, 1724, 1597; δ_{H} (250 MHz, CDCl₃) 7.76-7.70 (2H, m, SO₂-C-CH), 7.29 (2H, d, *J*8.2, Ar-H), 4.26 (1H, d, *J*7.0, N-CH-C=O), 4.17 (1H, dd, *J*7.3, 3.7, Me-CH-CH-N), 2.43 (3H, s, Ar-CH₃), 2.05-1.56 (6H, m, CH₂-CH₂, Me-CH-CH-Me), 1.00 (3H, d, *J*6.4, CH₃-CH-CH-N), 1.00 (3H, d, *J*6.4, CH₃-CH-C=O); δ_{C} (100 MHz, CDCl₃) 204.2 (CH), 144.0 (C), 136.7 (C), 129.8 (CH), 127.5 (CH), 65.3 (CH), 62.1 (CH), 44.0 (CH), 43.9 (CH), 27.7 (CH₂), 22.4 (CH₂), 21.6 (CH₃), 16.2 (CH₃), 11.5 (CH₃); *m/z* (CI) 325 [M(NH₄)⁺, 100%], 308 (MH⁺, 35%); Found: (MH⁺) 308.1320. C₁₆H₂₂NO₃S requires: 308.1320.

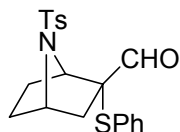
(±)-(1R*, 2S*, 4S*)-7-(Toluene-4-sulfonyl)-7-aza-bicyclo[2.2.1]heptane-2-carbaldehyde **7e**



To a solution of the aldehyde **5a** (380 mg, 1.34 mmol) in diethyl ether (10 ml) at -30 °C was added vinyl magnesium bromide solution (1.61 ml, 1.0 M, 1.61 mmol). The reaction was allowed to warm to ambient temperature for 10 min before being quenched by addition of saturated aqueous NH₄Cl solution (20 ml). The mixture was extracted into diethyl ether (2 x 30 ml), the combined organics washed with brine and then dried over Na₂SO₄. Flash Column Chromatography (eluant 3 : 2 petroleum : diethyl ether, gradient rising to 1 : 1) isolated the *rearrangement precursor* **6e** as a mixture of diastereoisomers (236 mg, 56 %) as a colourless oil; ν_{\max} / cm⁻¹ (film) 3541, 3069, 2986, 2955, 2835, 1598, 1557; m/z (CI) 329 [M(NH₄)⁺, 20%], 280 [(MH⁺)-MeOH, 100%]; Found: 329.1544 [M(NH₄)⁺]. C₁₅H₂₅N₂O₄S requires: 329.1535.

To a 0 °C solution of rearrangement precursor **6e** (34 mg, 0.11 mmol) in dichloromethane (1 ml) was added SnCl₄ solution (0.11 ml, 1.0 M in heptanes, 0.11 mmol). The mixture was allowed to warm to ambient temperature and stirred for 14.5 h, before being quenched by addition of saturated aqueous NaHCO₃ (5 ml). The mixture was extracted into dichloromethane (2 x 10 ml) and combined organics dried over Na₂SO₄. Flash Column Chromatography (eluant 2 : 3 petroleum : diethyl ether, gradient rising to 1 : 2) afforded the *aldehyde* **7e** (10 mg, 32 %) as a white gum; ν_{\max} / cm⁻¹ (film) 2956, 2925, 2881, 1722, 1598; δ_{H} (250 MHz, CDCl₃) 9.49 (1H, d, *J*1.8, -CHO), 7.78-7.72 (2H, m, SO₂-C-CH), 7.31-7.26 (2H, m, Ar-H), 4.44 (1H, d, *J*4.0, N-CH-CH-CHO), 4.29 [1H, t, *J*4.9, N-CH-(CH₂)₂], 2.48-2.41 (1H, m, CH-CHO), 2.42 (3H, s, Ar-CH₃), 2.27-2.16 (1H, m, *exo* -CHH-C-CHO), 2.03-1.95 (2H, m, -CHH-CHH- both *exo*), 1.70-1.50 (3H, m, -CHH-CHH- and -CHH-C-CHO, all *endo*); δ_{C} (100 MHz, CDCl₃) 200.7 (CH), 143.9 (C), 137.1 (C), 129.6 (CH), 127.6 (CH), 60.0 (CH), 58.9 (CH), 54.5 (CH), 32.1 (CH₂), 29.9 (CH₂), 29.1 (CH₂), 21.6 (CH₃); m/z (CI) 280 (MH⁺, 100%); Found: 280.0999. C₁₄H₁₈NO₃S requires: 280.1007.

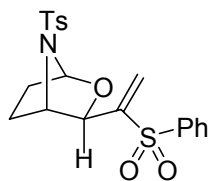
(±)-(1*R**, 2*R**, 4*S**)-2-Phenylsulfanyl-7-(toluene-4-sulfonyl)-7-aza-bicyclo[2.2.1]heptane-2-carbaldehyde **7f**



A solution of TMEDA (0.24 ml, 1.57 mmol) in tetrahydrofuran (6 ml) was cooled to -78 °C and ⁿBuLi (0.63 ml, 2.5 M, 1.57 mmol) added. A solution of phenylthioethylene (214 mg, 1.57 mmol) in tetrahydrofuran (4.5 ml) was added over 10 min. The mixture was stirred a further 30 min at -78 °C. Solid MgBr₂·OEt₂ (405 mg, 1.57 mmol) was added and the reaction warmed to 0 °C, causing dissolution of the solid. Separately, the aldehyde **5a** (365 mg, 1.29 mmol) was dissolved in tetrahydrofuran (6 ml) and the solution cooled to -30 °C. The entire organometallic solution was transferred into this *via* canula and the resulting mixture warmed to ambient temperature over 15 min. The reaction was quenched by addition of saturated aqueous NH₄Cl (30 ml) and extracted into diethyl ether (2 x 30 ml). The combined organics were dried over Na₂SO₄ and Flash Column Chromatography (eluant 3 : 2 petroleum : diethyl ether) isolated *sulfide 6f*, a mixture of diastereoisomers (205 mg, 38 %), as a colourless oil; *m/z* (CI) 437 [M(NH₄)⁺, 85%]; Found: 437.1576. C₂₁H₂₉N₂O₄S₂ requires: 437.1569.

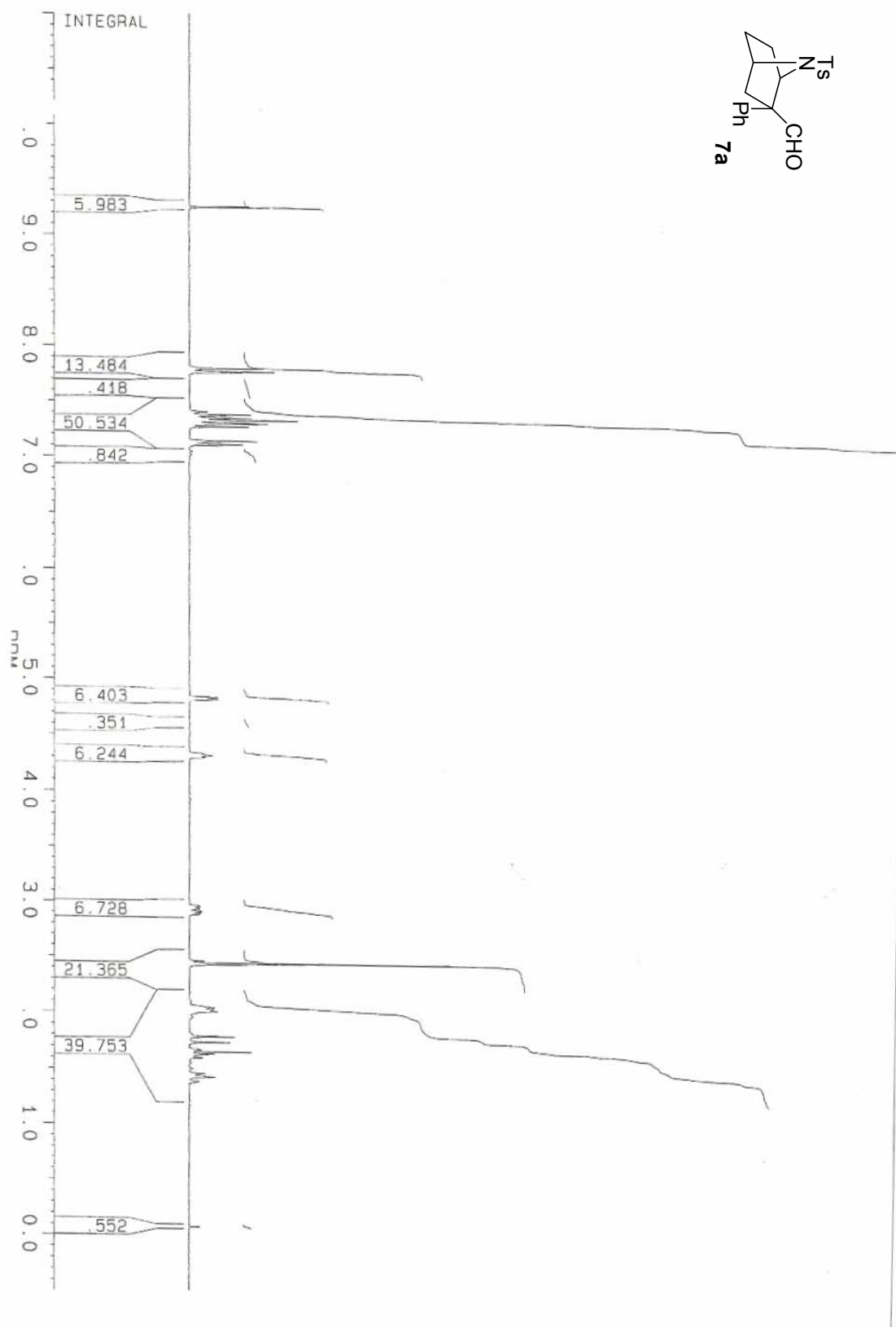
To a 0 °C solution of sulfide **6f** (38 mg, 0.091 mmol) in dichloromethane (1 ml) was added SnCl₄ solution (91 µl, 1.0 M in heptanes, 0.091 mmol). The whole was stirred at 0 °C for 1 min before being quenched by addition of saturated aqueous NaHCO₃ (5 ml). The mixture was extracted into dichloromethane (2 x 10 ml), dried over Na₂SO₄, filtered and solvent removed *in vacuo* to afford a crude residue. Flash Column Chromatography (eluant 1 : 1 petroleum : diethyl ether) isolated the *aldehyde 7f* (4 mg, 11 %) as a colourless oil; *v*_{max} / cm⁻¹ (film) 3062, 2960, 1721, 1597; δ_H (250 MHz, CDCl₃) 9.10 (1H, s, -CHO), 7.67 (2H, d, *J*8.2, SO₂-C-CH), 7.39-7.21 (7H, m, Ar-H), 4.41-4.36 (1H, m, N-CH-C-CHO), 4.27-4.21 [1H, m, N-CH(CH₂)₂], 2.69-2.55 (1H, m, *endo* -CHH-CH₂-), 2.54-2.40 (1H, m, *exo* -CHH-C-CHO), 2.40 (3H, s, Ar-CH₃), 2.19-2.00 (2H, m, -CHH-CHH- both *exo*), 1.74-1.61 (1H, m, *endo* -CHH-CH₂-), 1.24 (1H, d, *J*12.8, *endo* -CHH-C-CHO); δ_C (125 MHz, CDCl₃) 192.0 (CH), 143.8 (C), 137.2 (C), 136.6 (C), 134.9 (CH), 129.5 (CH), 129.3 (CH), 129.3 (CH), 127.5 (CH), 64.8 (C), 62.3 (CH), 59.6 (CH), 38.7 (CH₂), 30.6 (CH₂), 24.2 (CH₂), 21.5 (CH₃); *m/z* (CI) 388 (MH⁺, 100%); Found: 388.1031. C₂₀H₂₂NO₃S₂ requires: 388.1041.

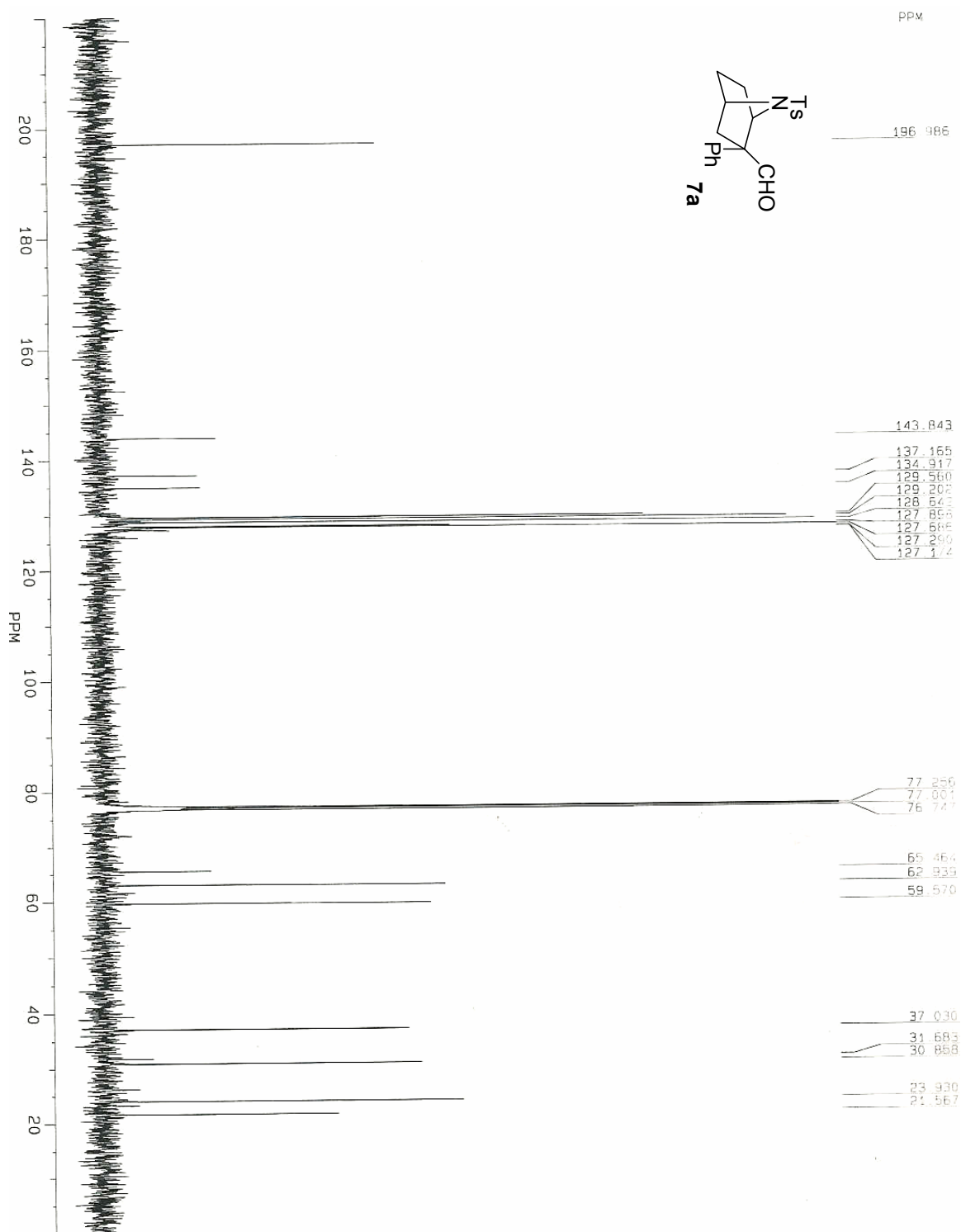
(±)-(1*R**, 3*S**, 4*R**)-3-(1-Benzenesulfonyl-vinyl)-7-(toluene-4-sulfonyl)-2-oxa-7-aza-bicyclo[2.2.1]heptane **10**

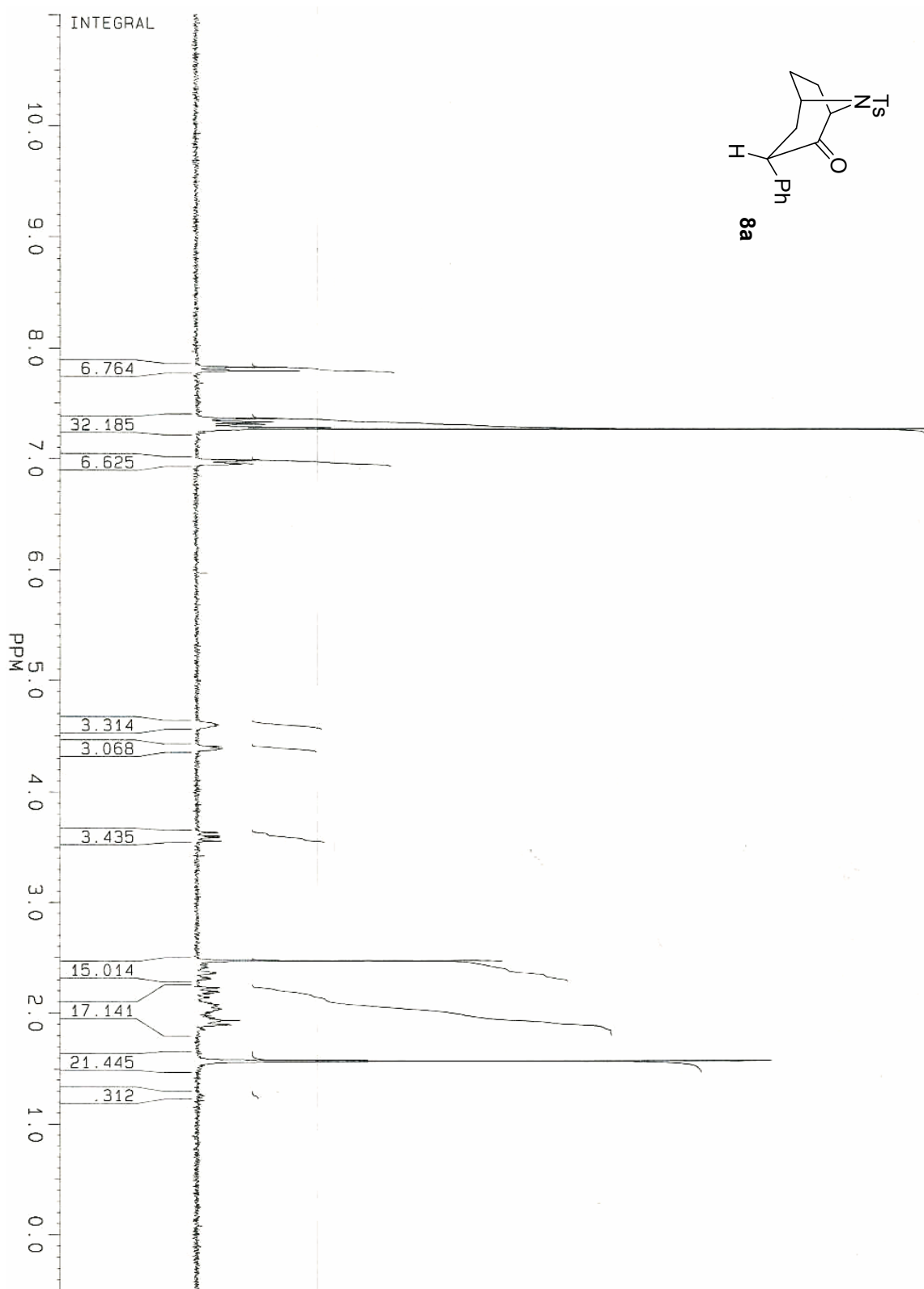


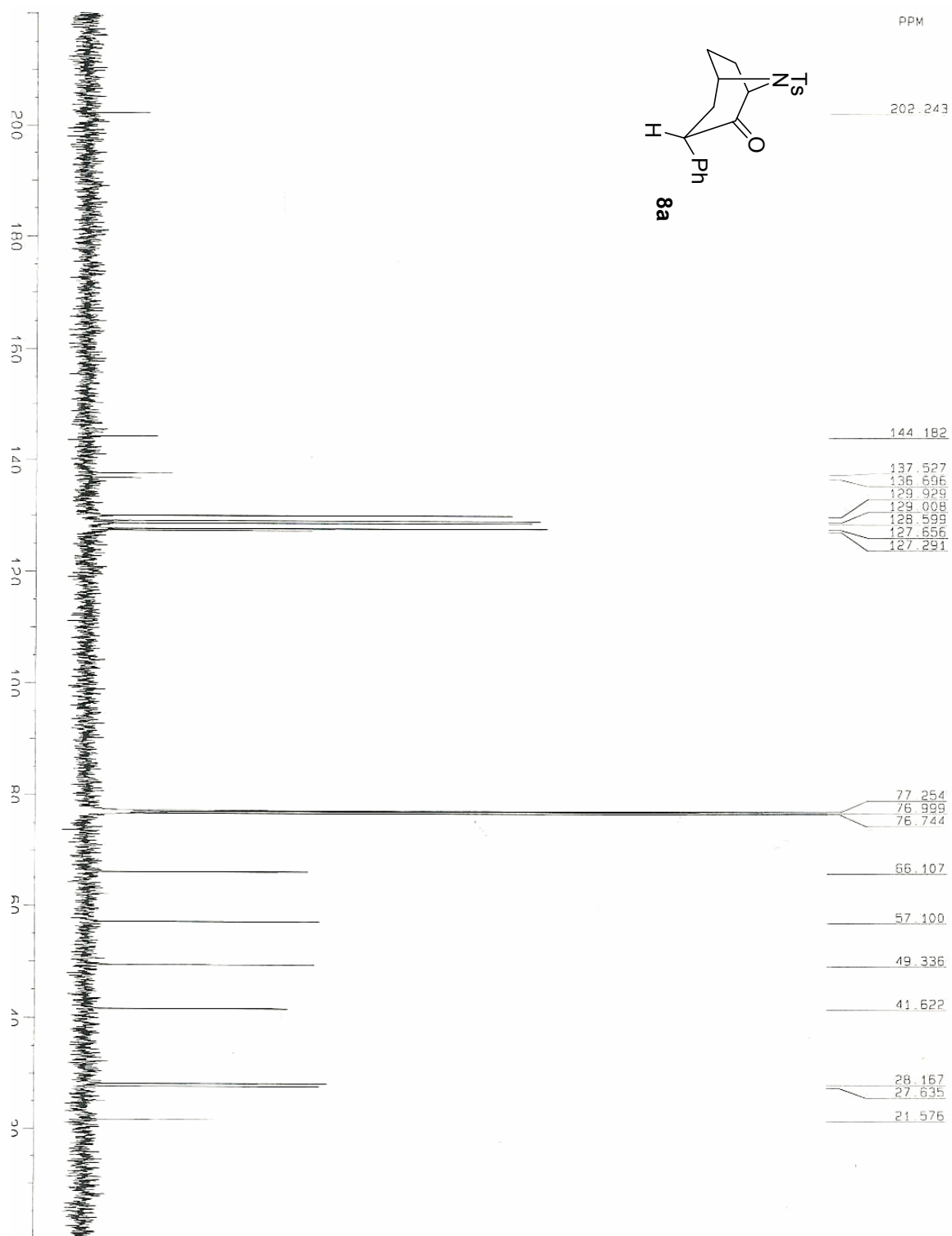
To a solution of sulfide **6f** (71 mg, 0.17 mmol) in dichloromethane (5 ml) was added NaHCO₃ (36 mg, 0.43 mmol) and the mixture cooled to -78 °C. *m*-chloroperbenzoic acid solution (0.38 M in dichloromethane as determined by iodometric titration, 0.89 ml, 0.34 mmol) was added and the whole stirred at -78 °C for 2 h. The reaction was warmed to ambient temperature and stirred for 17 h before being quenched by addition of saturated aqueous NaHCO₃ (20 ml). Extraction into chloroform (2 x 20 ml), drying over Na₂SO₄ and removal of solvent *in vacuo* gave a crude residue which was purified by Flash Column Chromatography (eluant 2 : 3 petroleum : diethyl ether) to afford the desired sulfone **6h** (50 mg, 65 %) as a mixture of diastereoisomers; *m/z* (CI) 469 [M(NH₄)⁺, 5%], 420 [(MH⁺)-MeOH, 50%]; Found [M(NH₄)⁺]: 469.1447. C₂₁H₂₉N₂O₆S₂ requires: 469.1467.

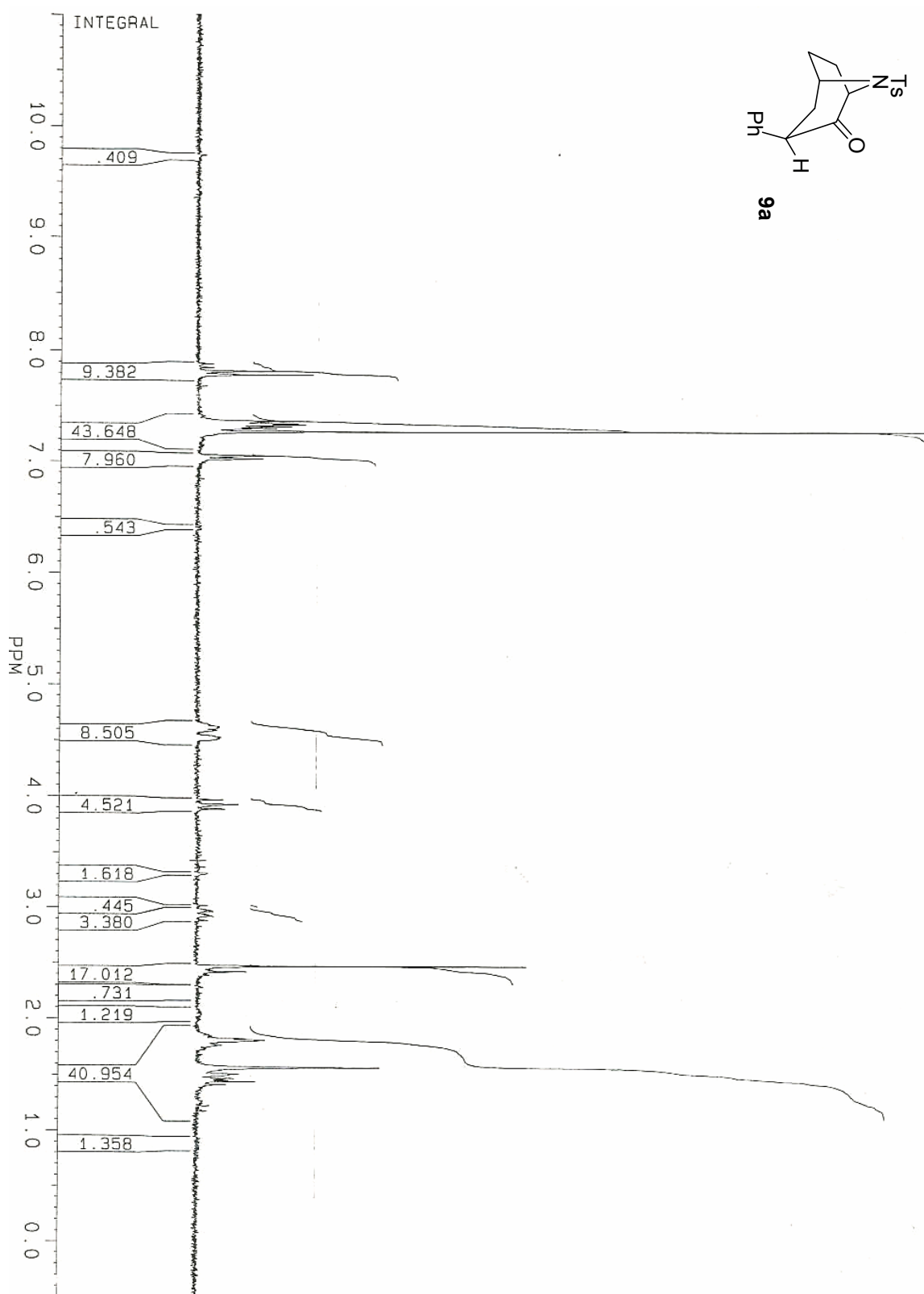
To a 0 °C solution of sulfone **6h** (23 mg, 0.051 mmol) in dichloromethane (1 ml) was added SnCl₄ solution (51 µl, 1.0 M in heptanes, 0.051 mmol). The whole was stirred at 0 °C for 8 min before being quenched by addition of saturated aqueous NaHCO₃ (5 ml). The mixture was extracted into dichloromethane (2 x 10 ml), dried over Na₂SO₄, filtered and solvent removed *in vacuo* to afford a crude residue. Flash Column Chromatography (eluant 2 : 3 petroleum : diethyl ether) isolated the *bicycle* **10** (14 mg, 66 %) as an amorphous powder; ν_{\max} / cm⁻¹ (film) 3060, 2953, 1761, 1598; δ_{H} (250 MHz, CDCl₃) 8.25-8.17 (2H, m, Ar-**H**), 7.71-7.64 (3H, m, Ar-**H**), 7.57 (2H, d, *J*8.2, SO₂-C-**CH**), 7.23 (2H, d, *J*8.2, Ar-**H**), 6.53 (1H, s, C=**CHH**), 6.05 (1H, s, C=**CHH**), 5.18 (1H, s, O-**CH**-C=C), 4.57 (1H, d, *J*4.6, N-**CH**-O), 4.40-4.31 (1H, m, **CH**-CH-C=C), 2.38 (3H, s, Ar-**CH**₃), 2.23-2.09 [1H, m, *endo* **CHH**-CH(N)-CH], 1.51-1.41 [1H, m, *endo* **CHH**-CH(N)-O], 1.27-1.16 [1H, m, *exo* **CHH**-CH(N)-CH], 0.83-0.67 [1H, m, *exo* **CHH**-CH(N)-O]; δ_{C} (125 MHz, CDCl₃) 150.6 (C), 143.2 (C), 138.3 (C), 135.8 (C), 133.5 (CH), 129.7 (CH), 129.6 (CH), 129.1 (CH), 127.5 (CH), 126.2 (CH₂), 90.4 (CH), 73.1 (CH), 62.8 (CH), 32.5 (CH₂), 21.5 (CH₃), 20.9 (CH₂); *m/z* (CI) 437 [M(NH₄)⁺, 50%]; Found (MH⁺): 420.0927. C₂₀H₂₂NO₅S₂ requires: 420.0939.

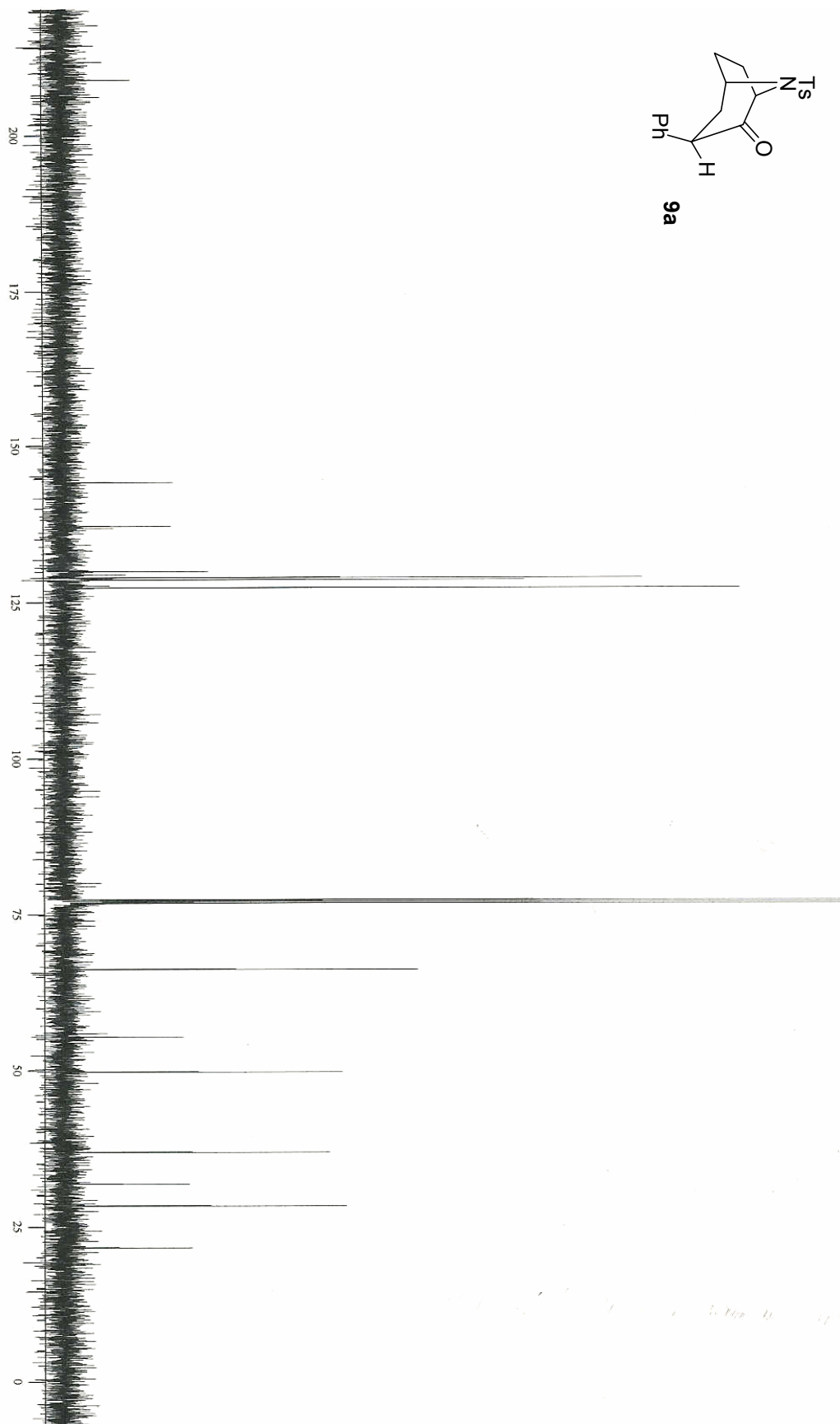


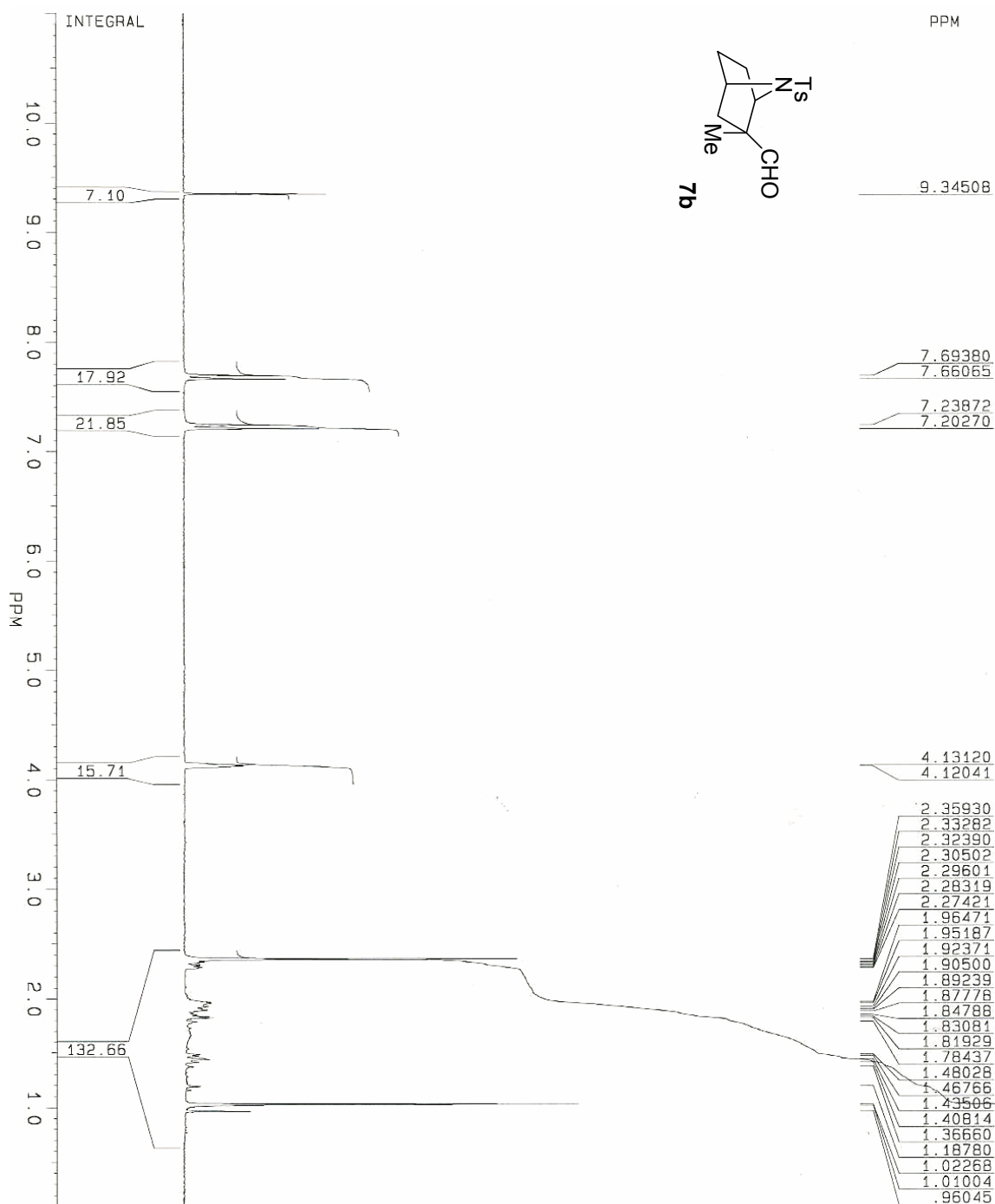


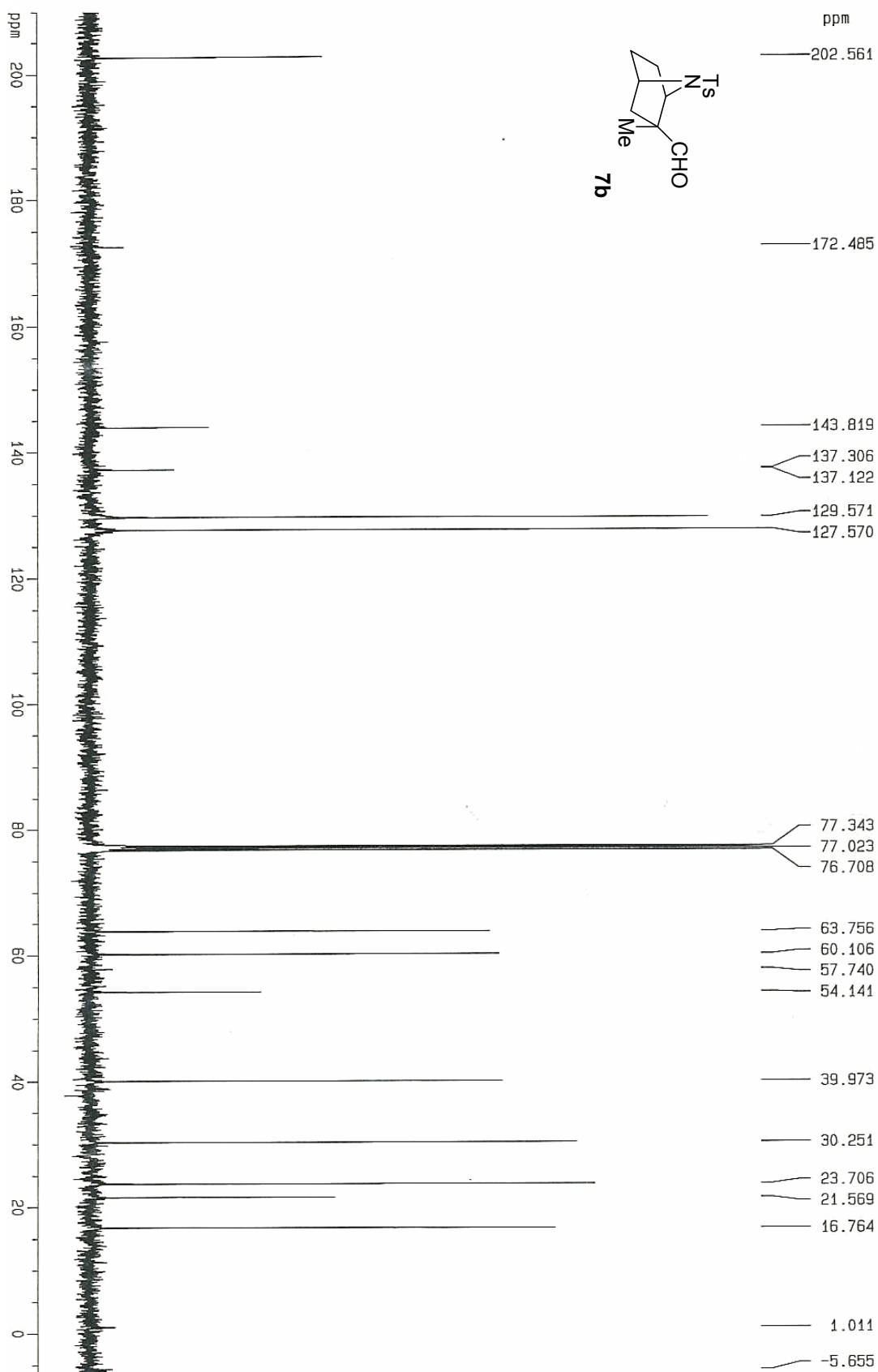


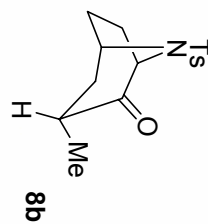
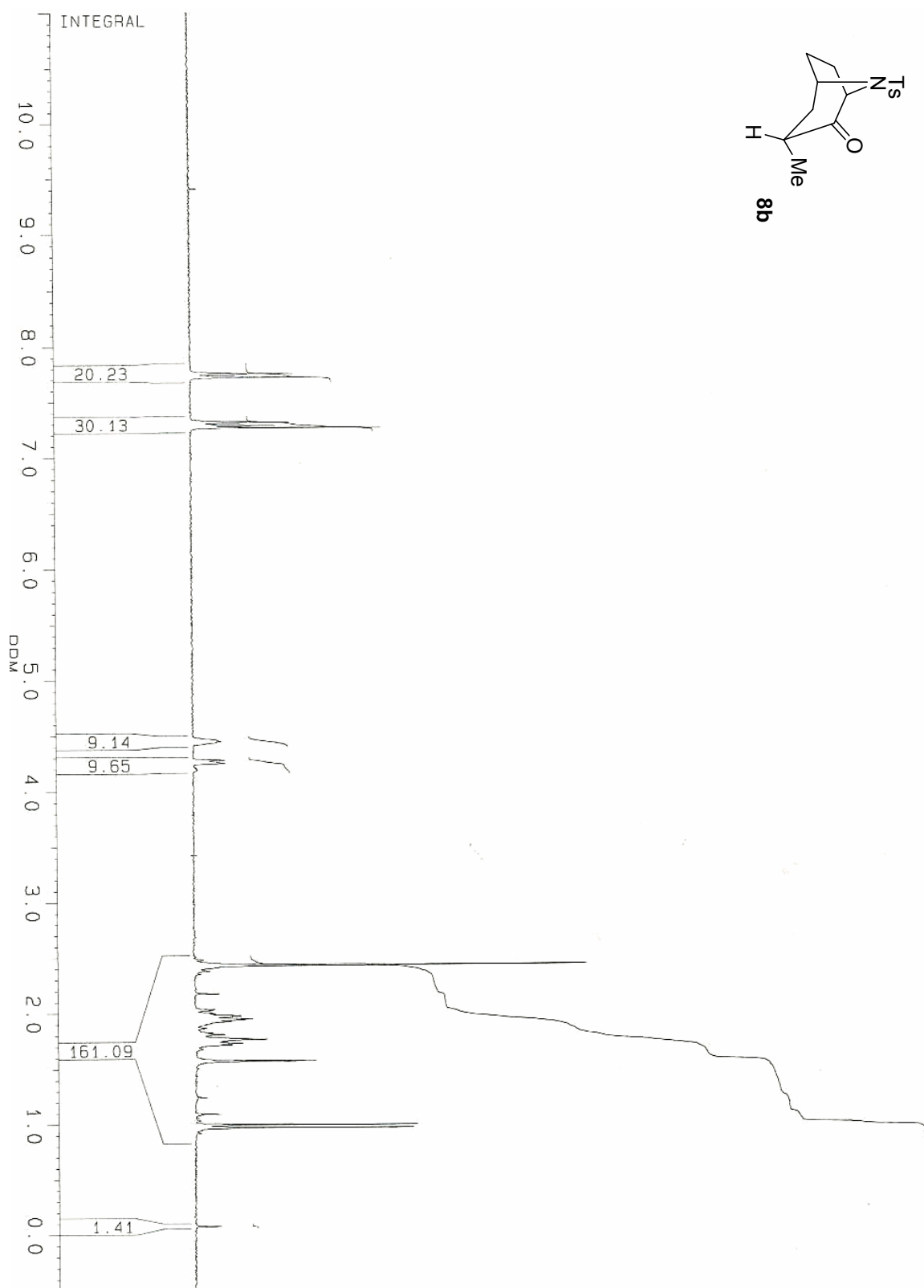


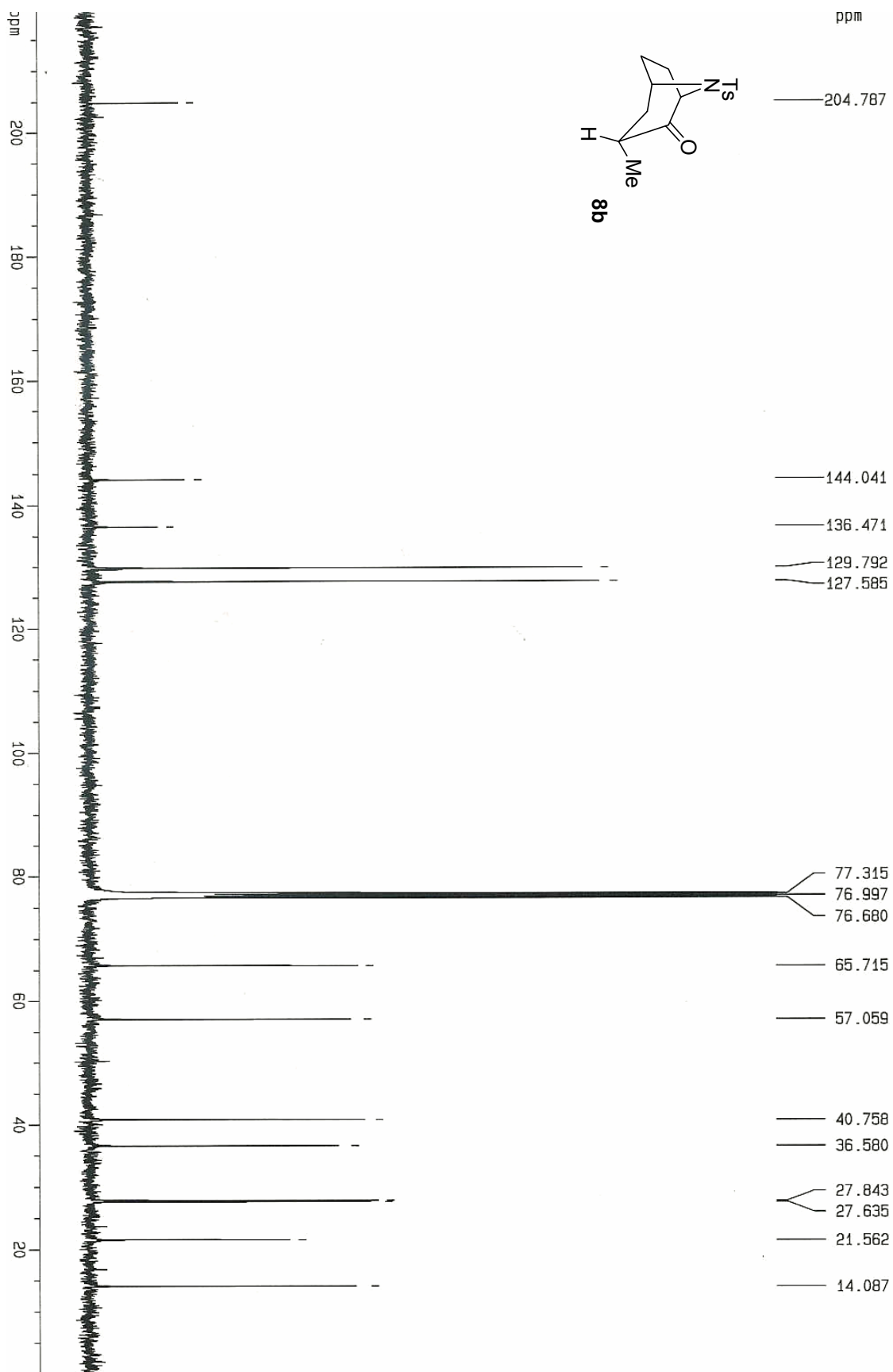


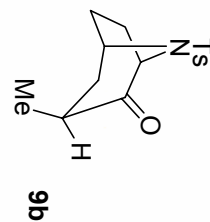
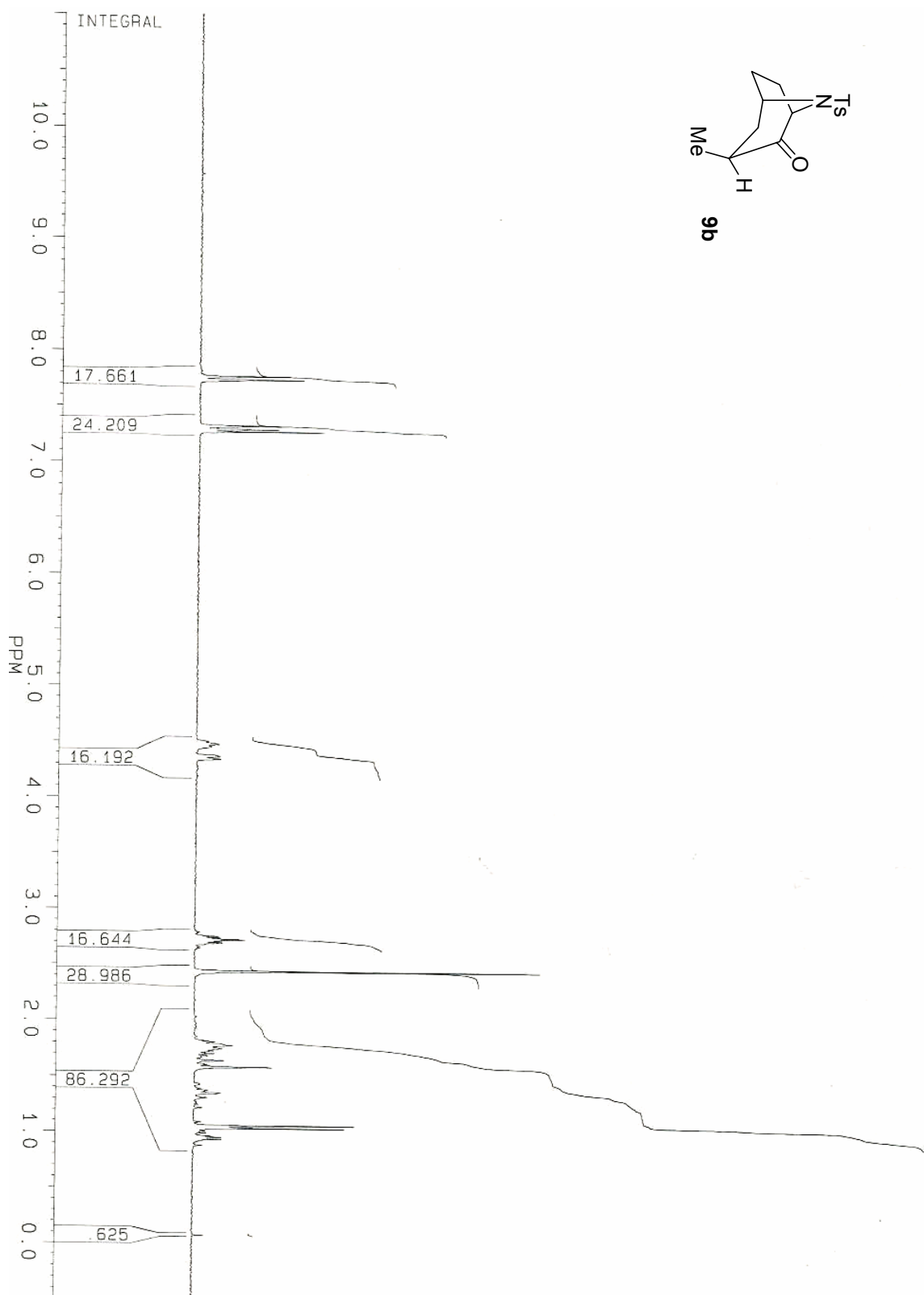


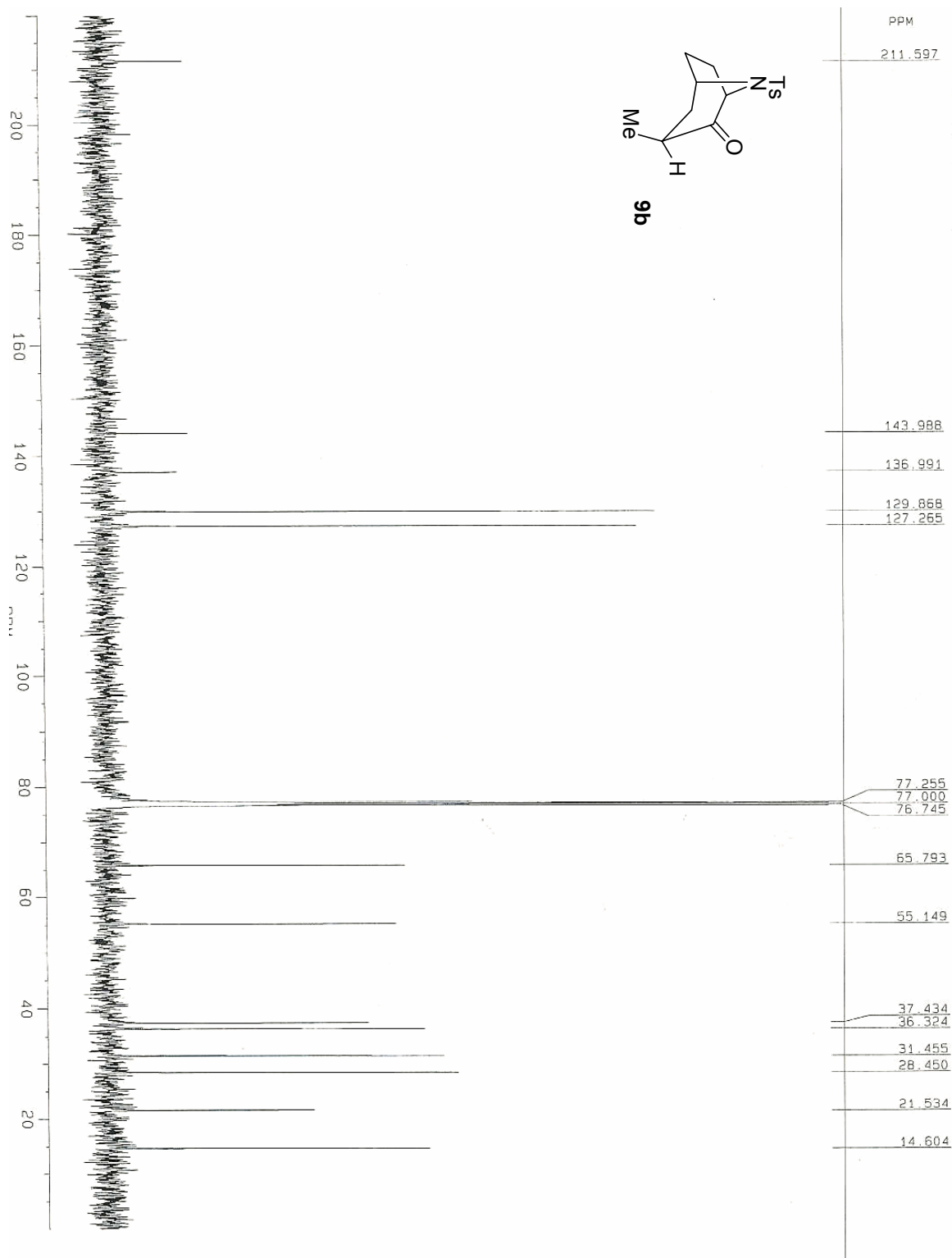


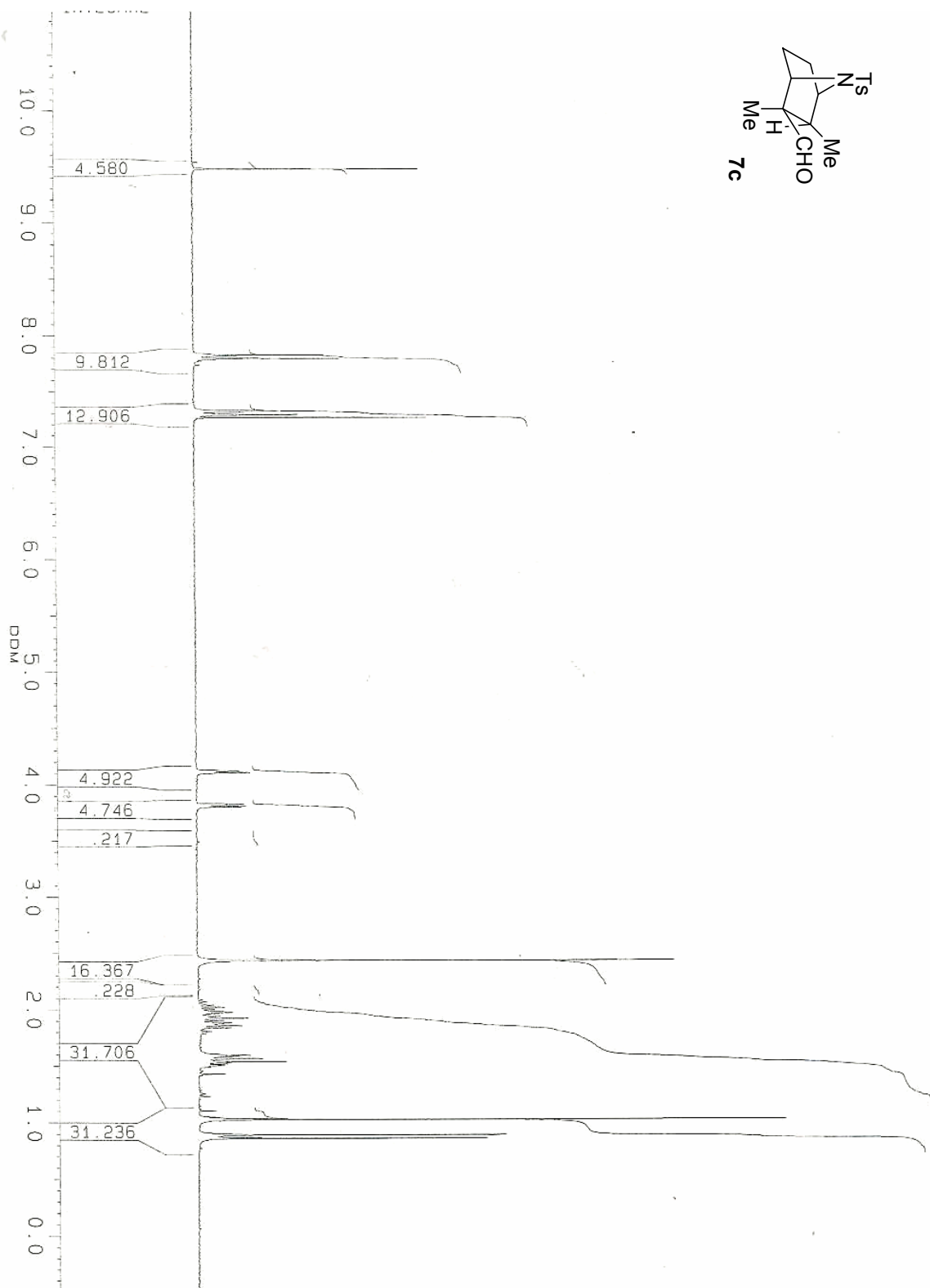


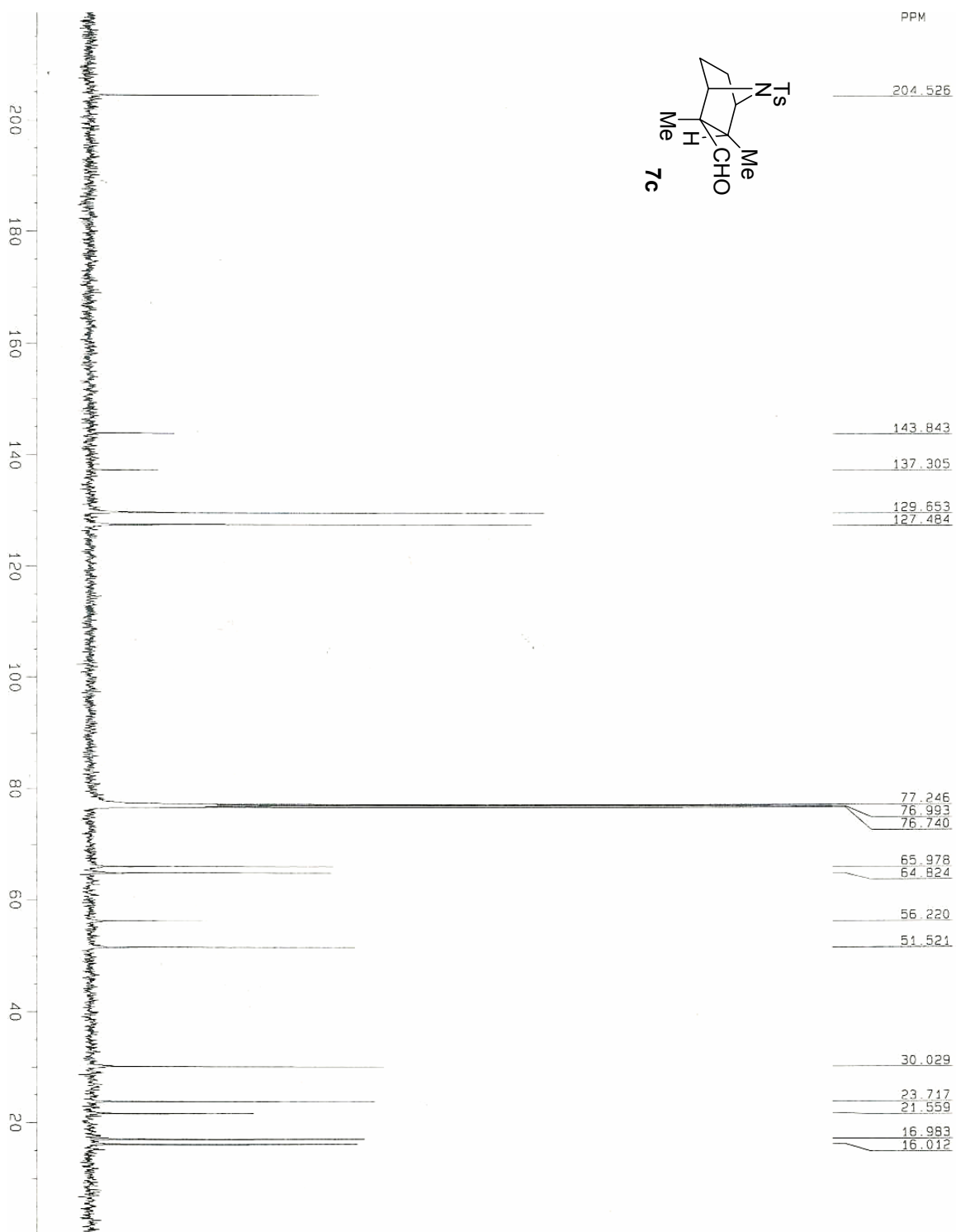


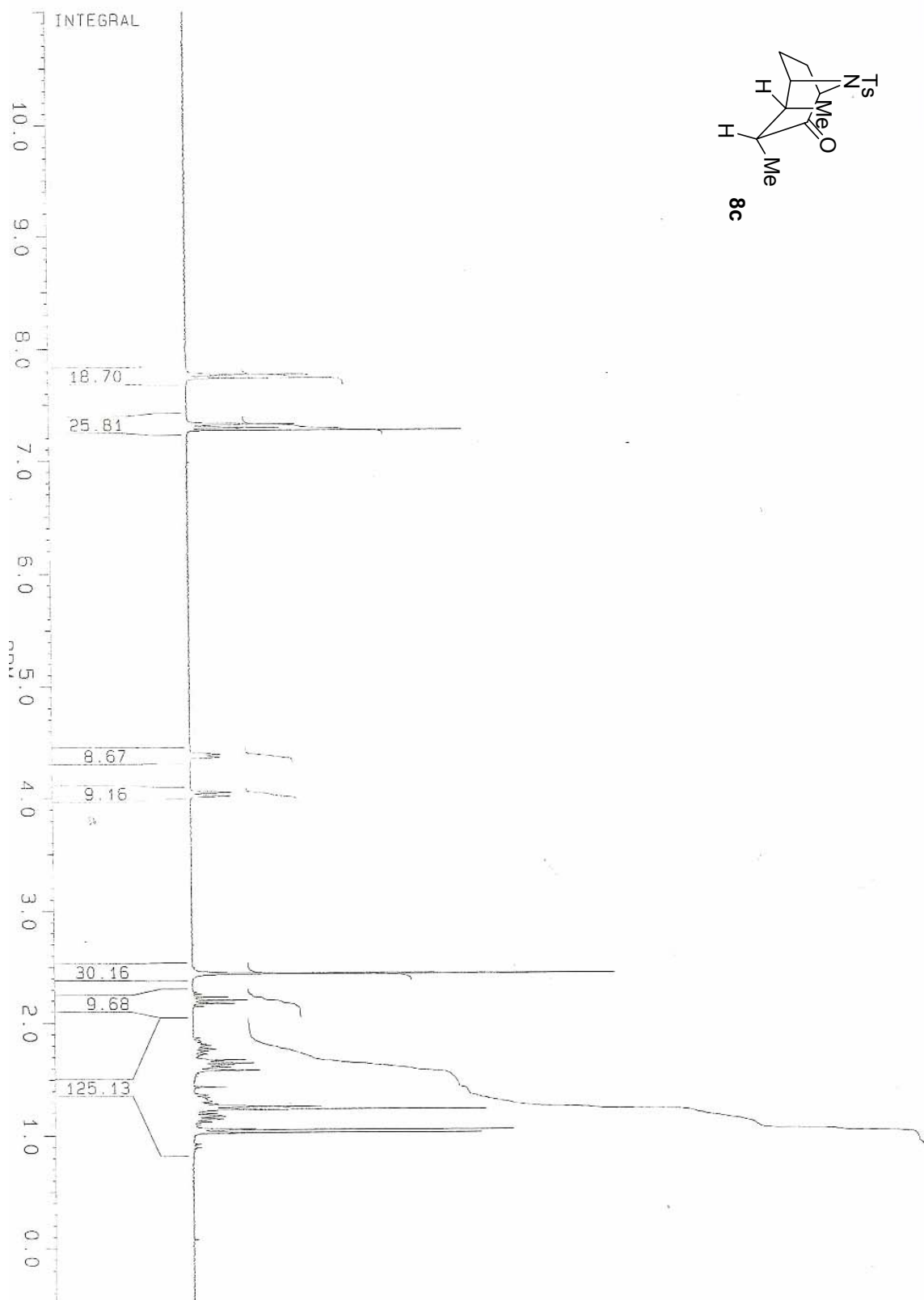


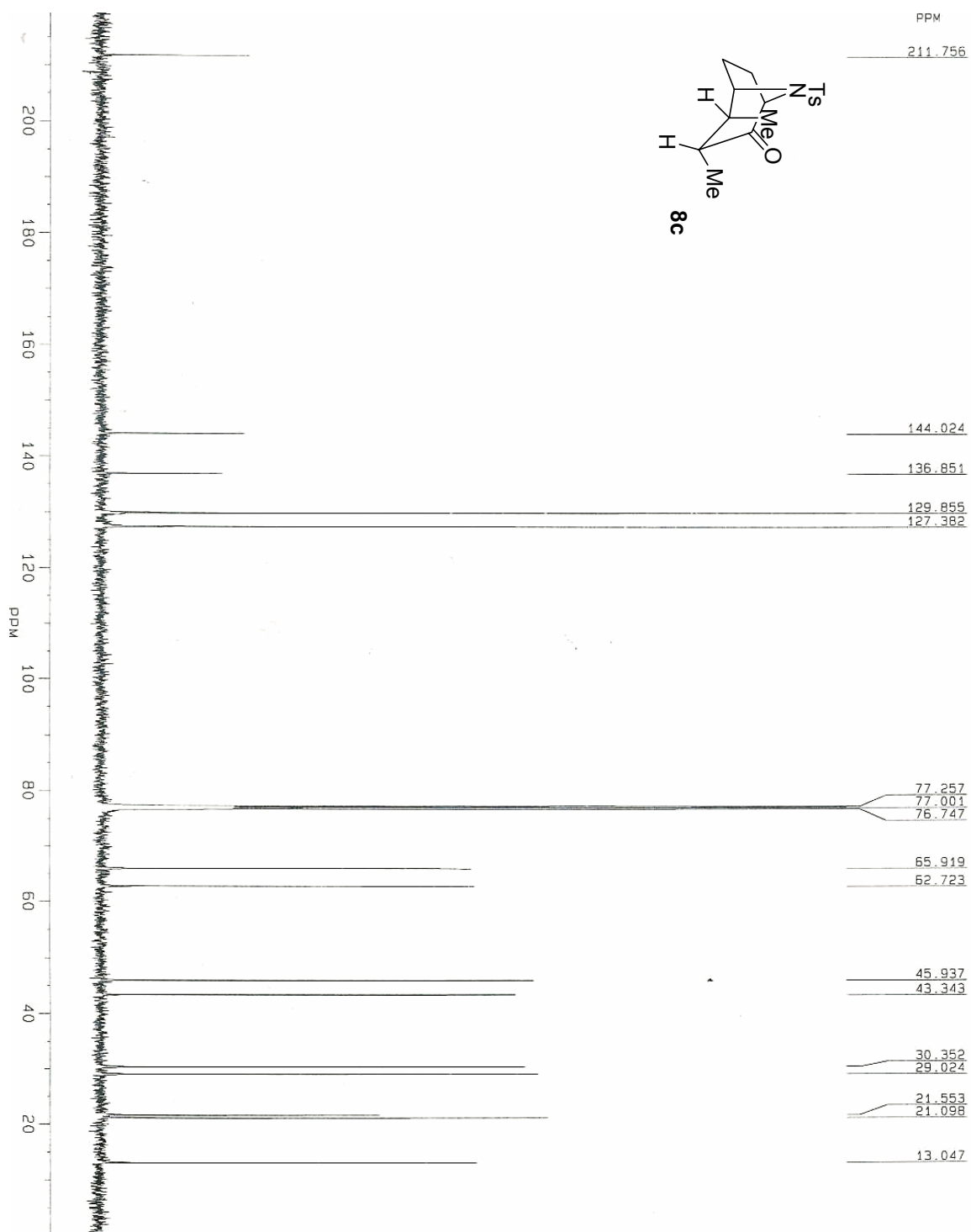


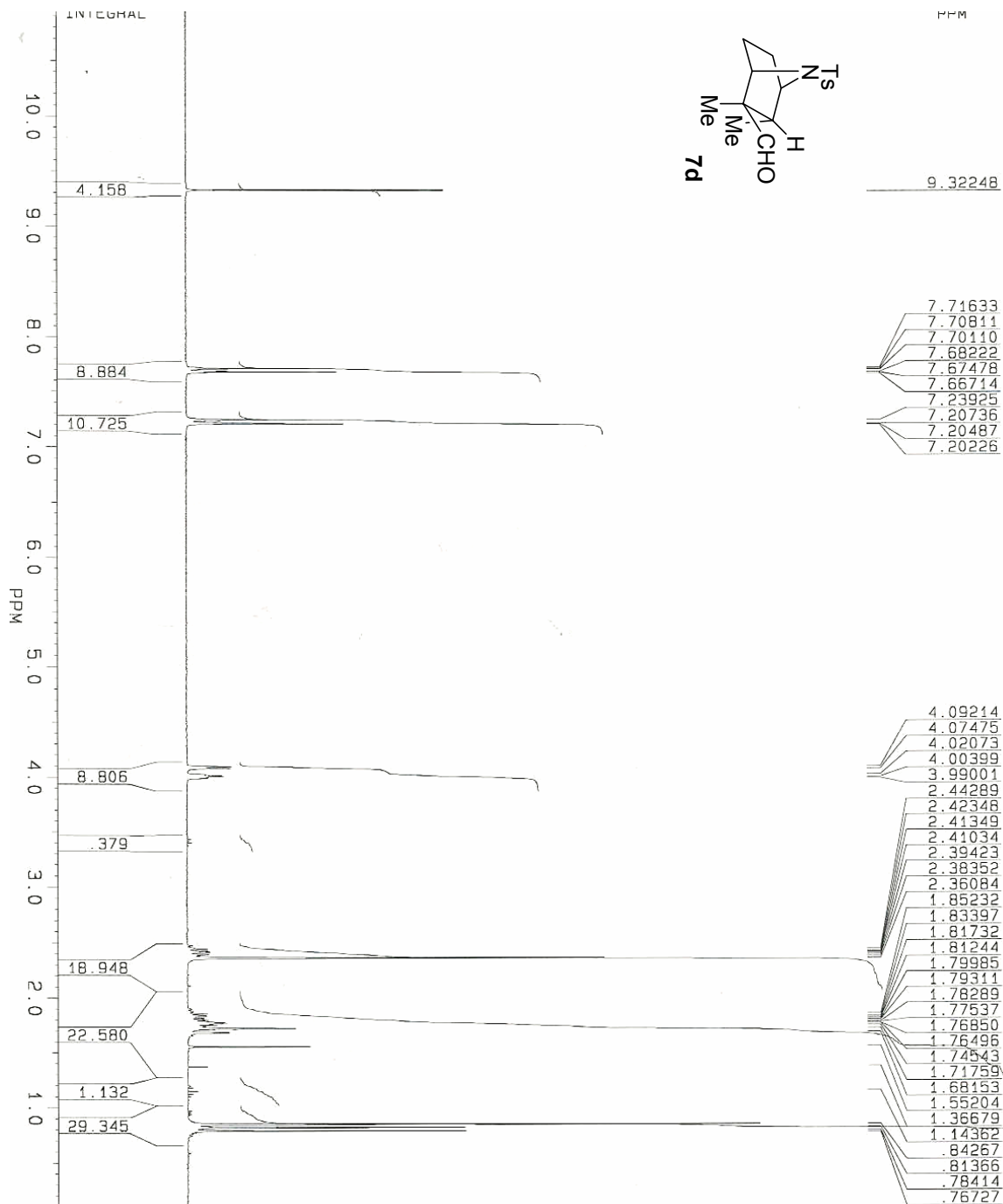


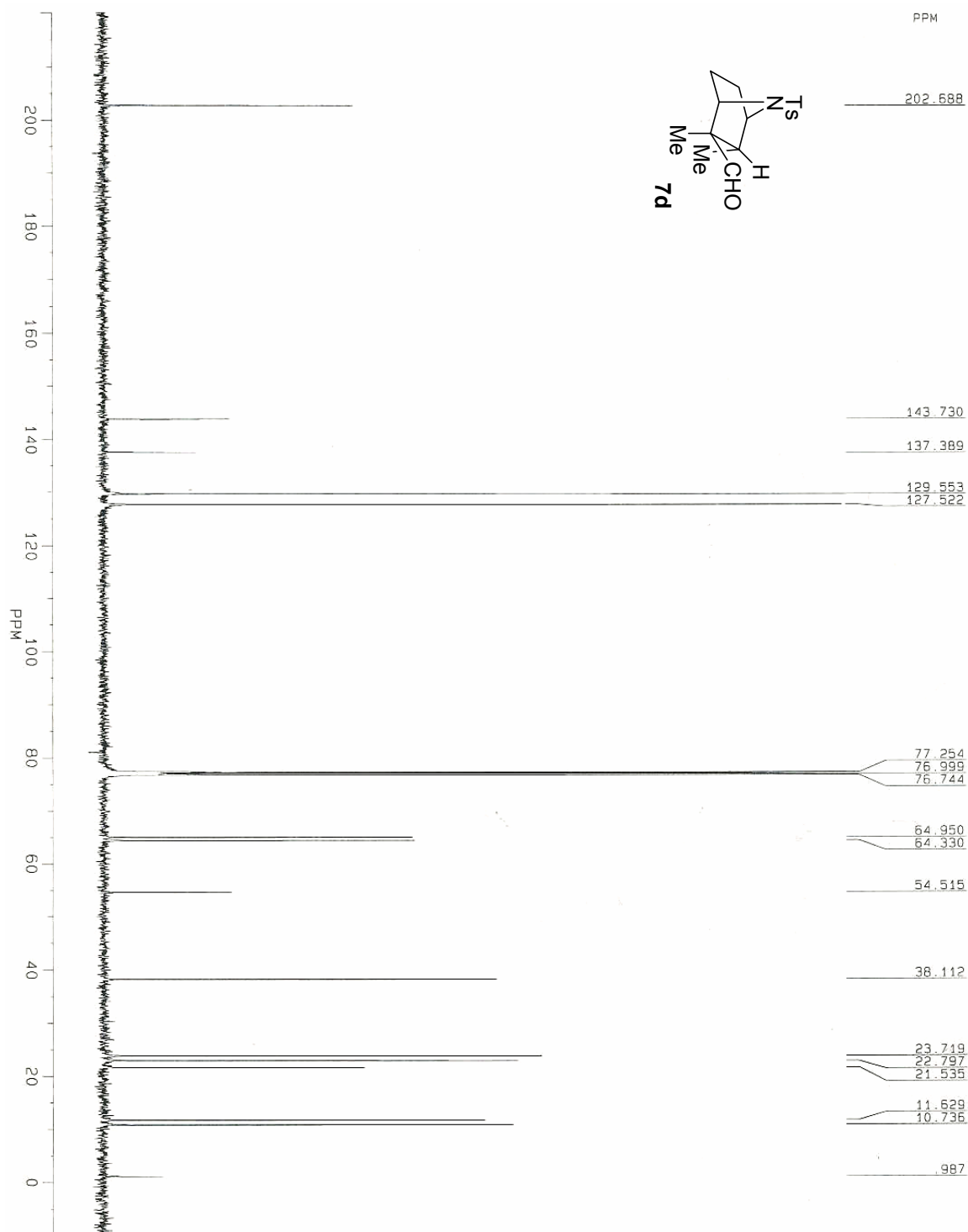


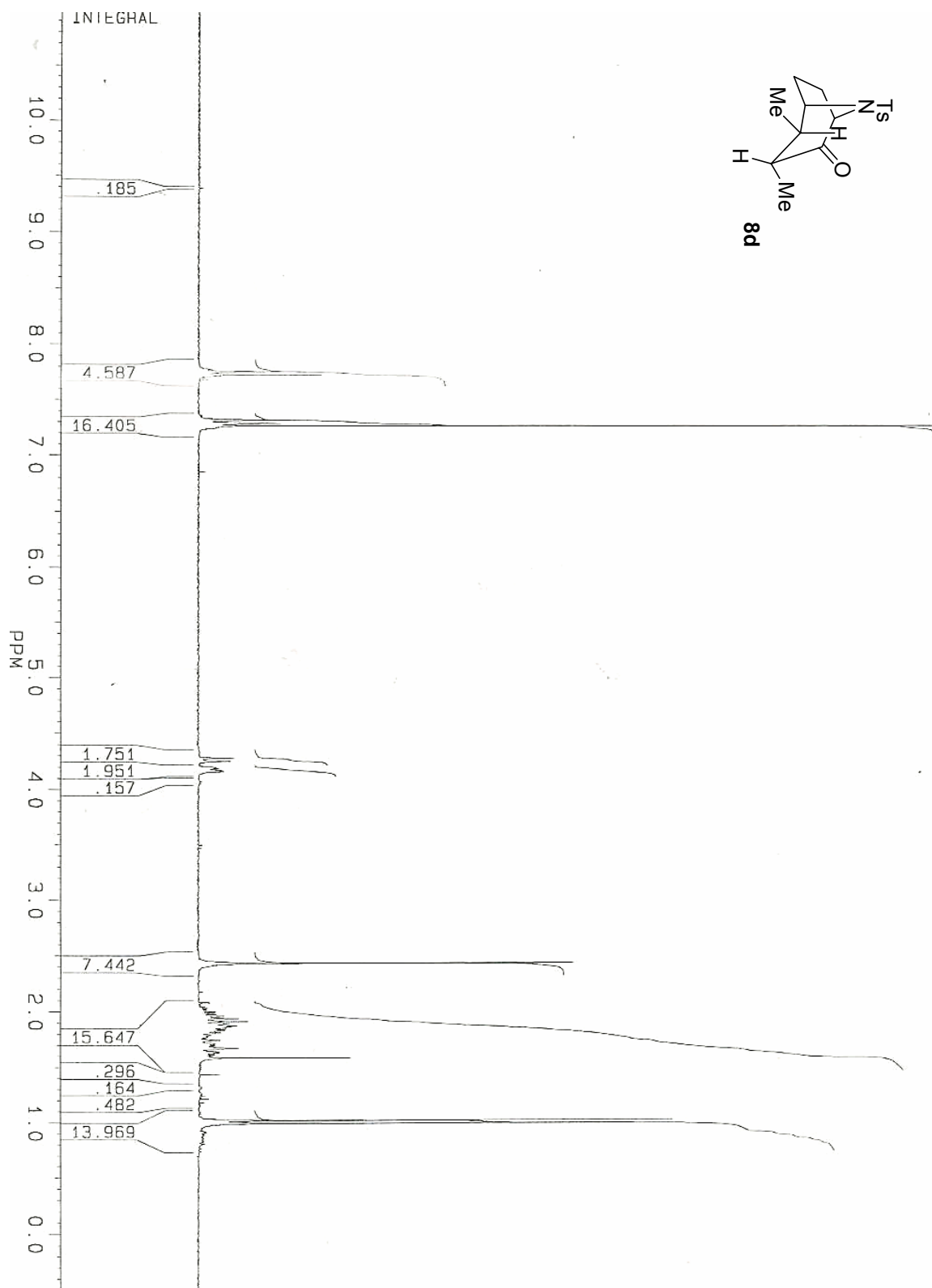


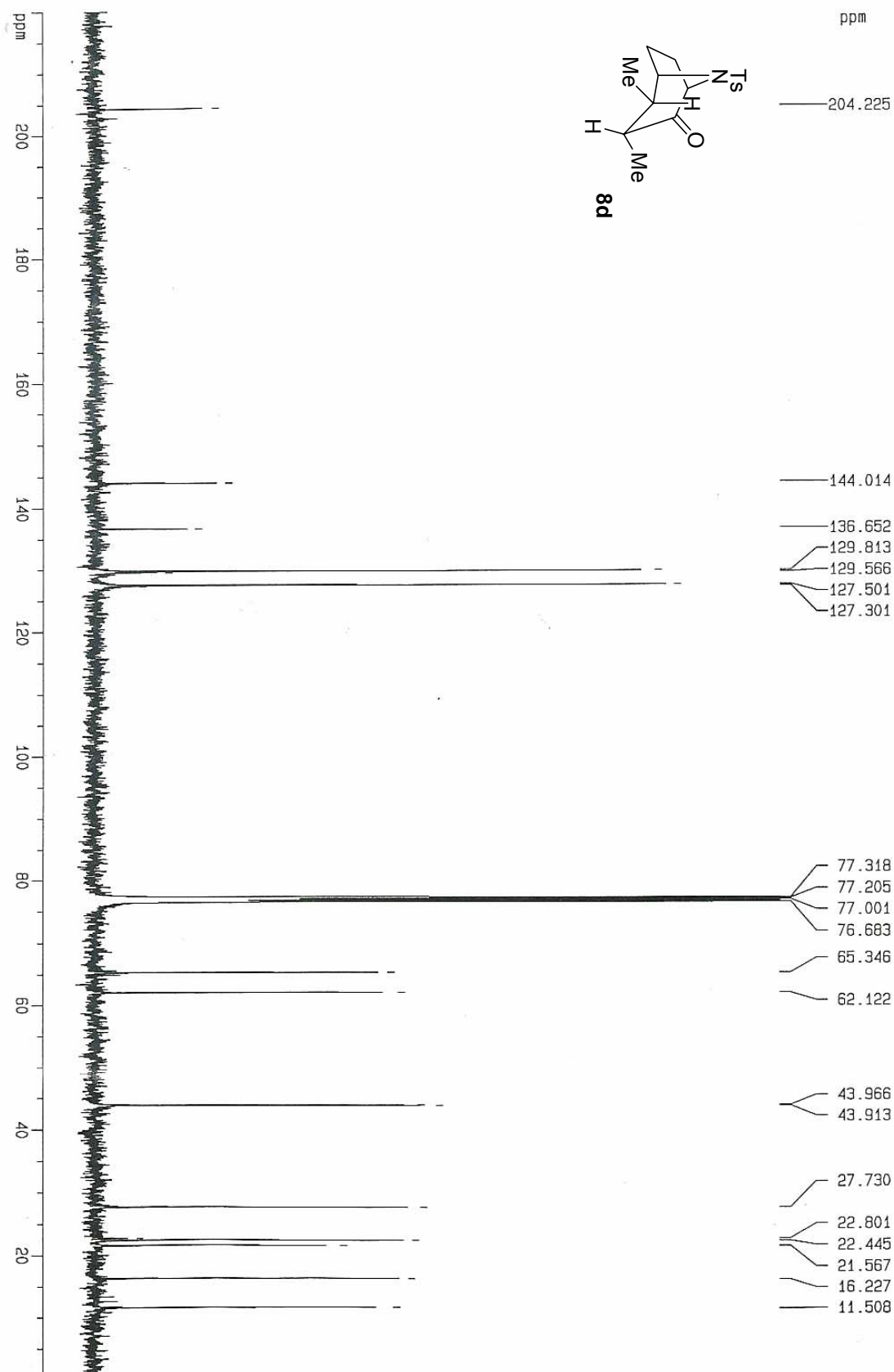


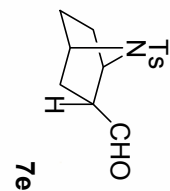
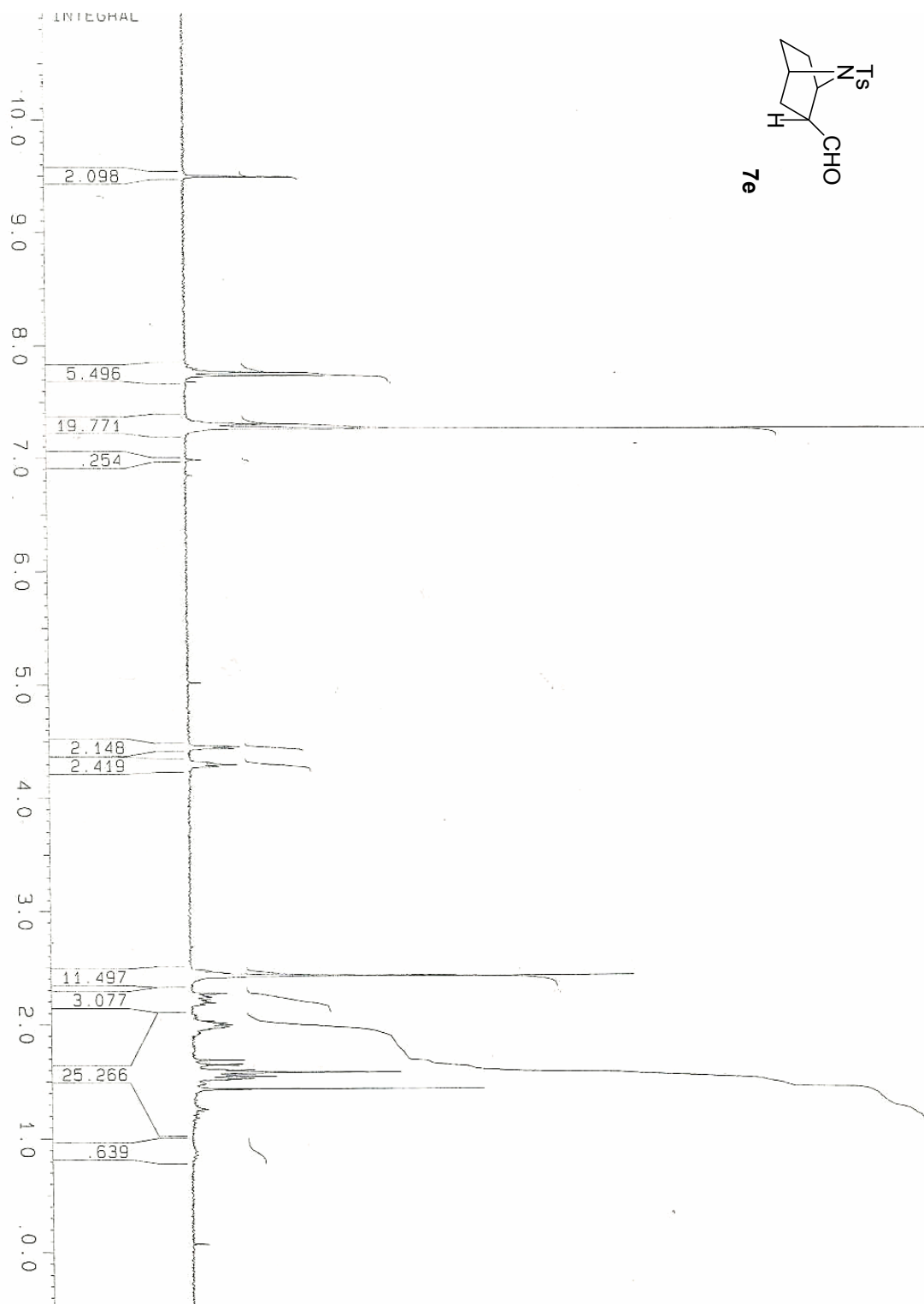


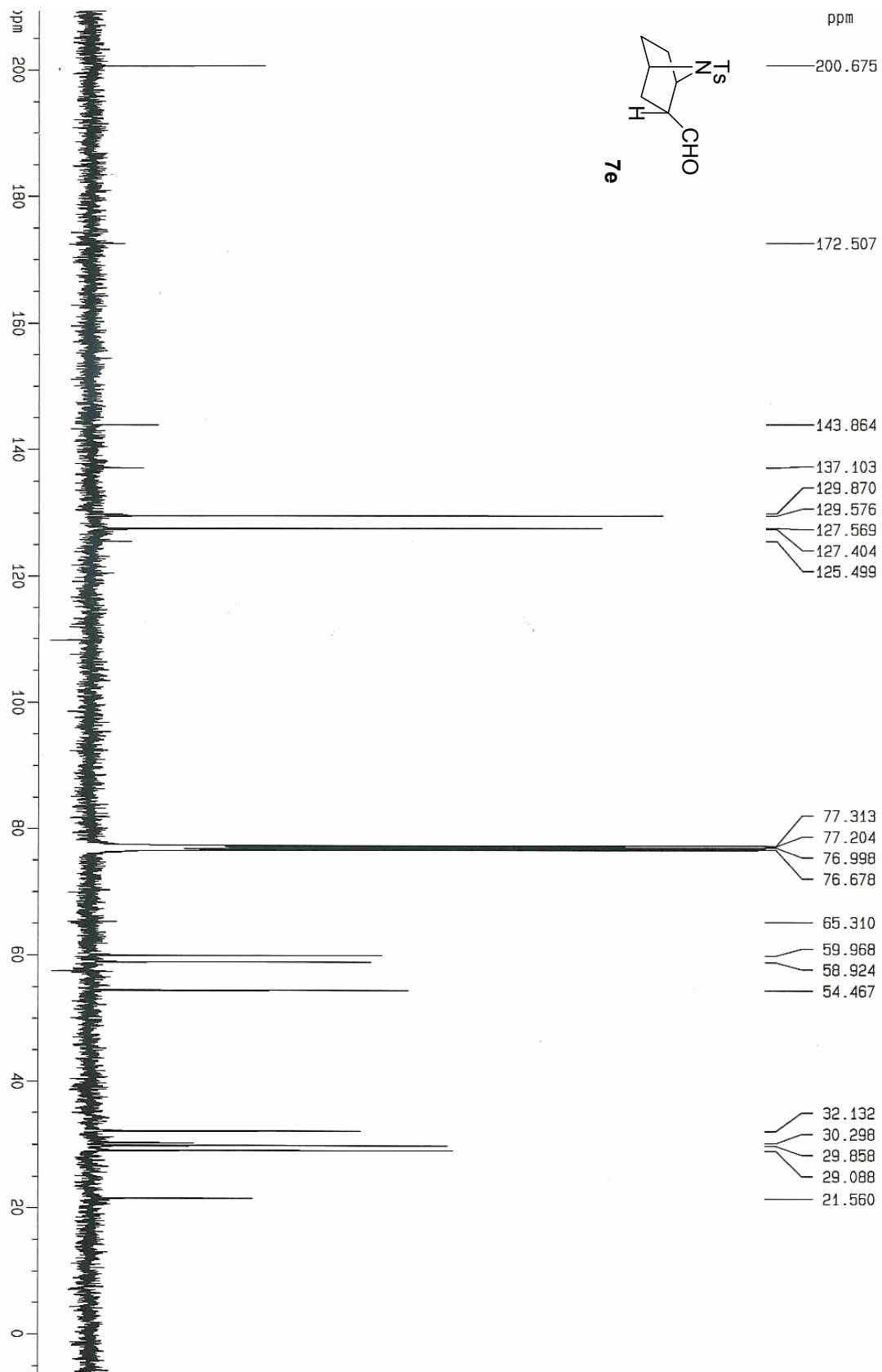


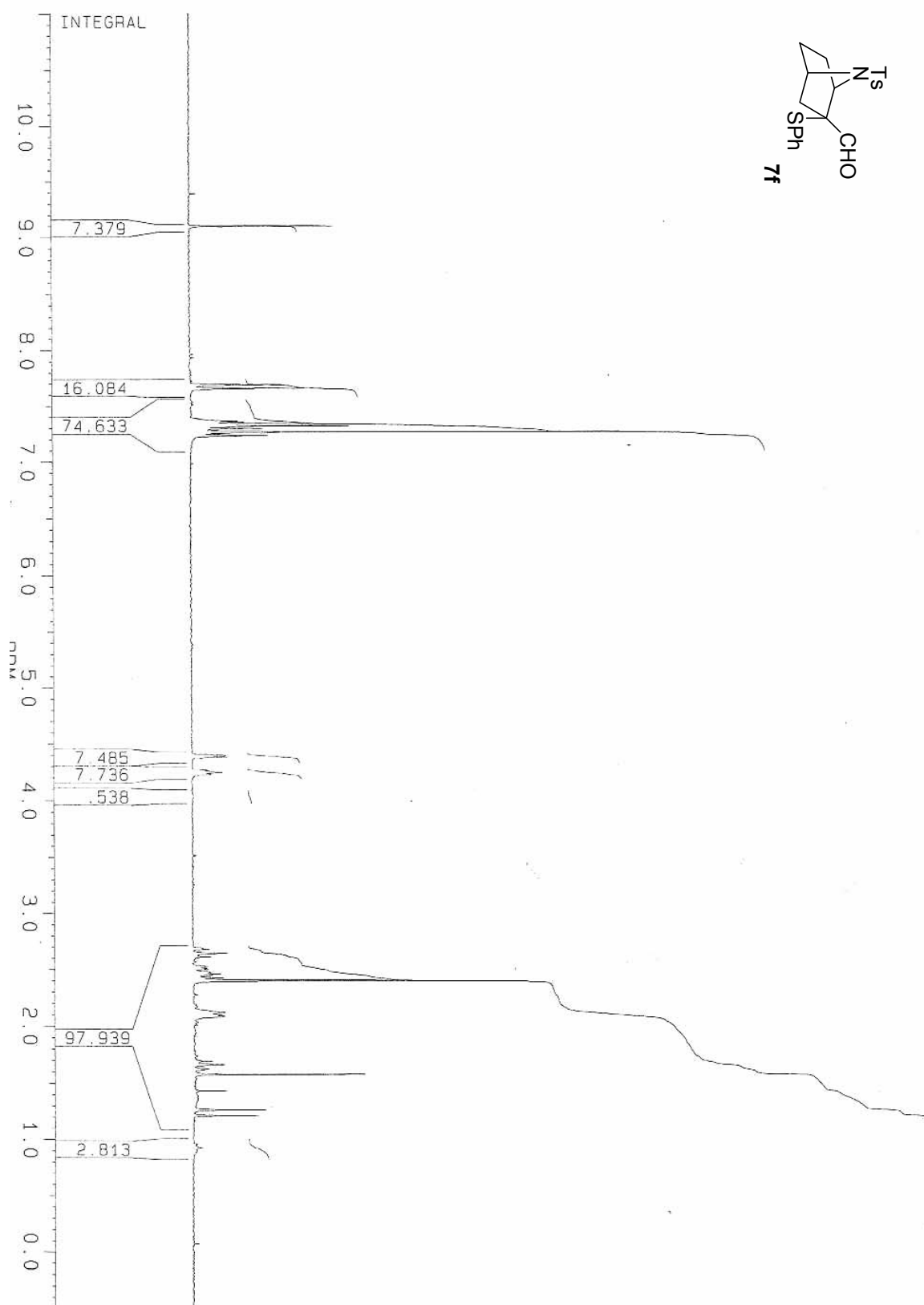


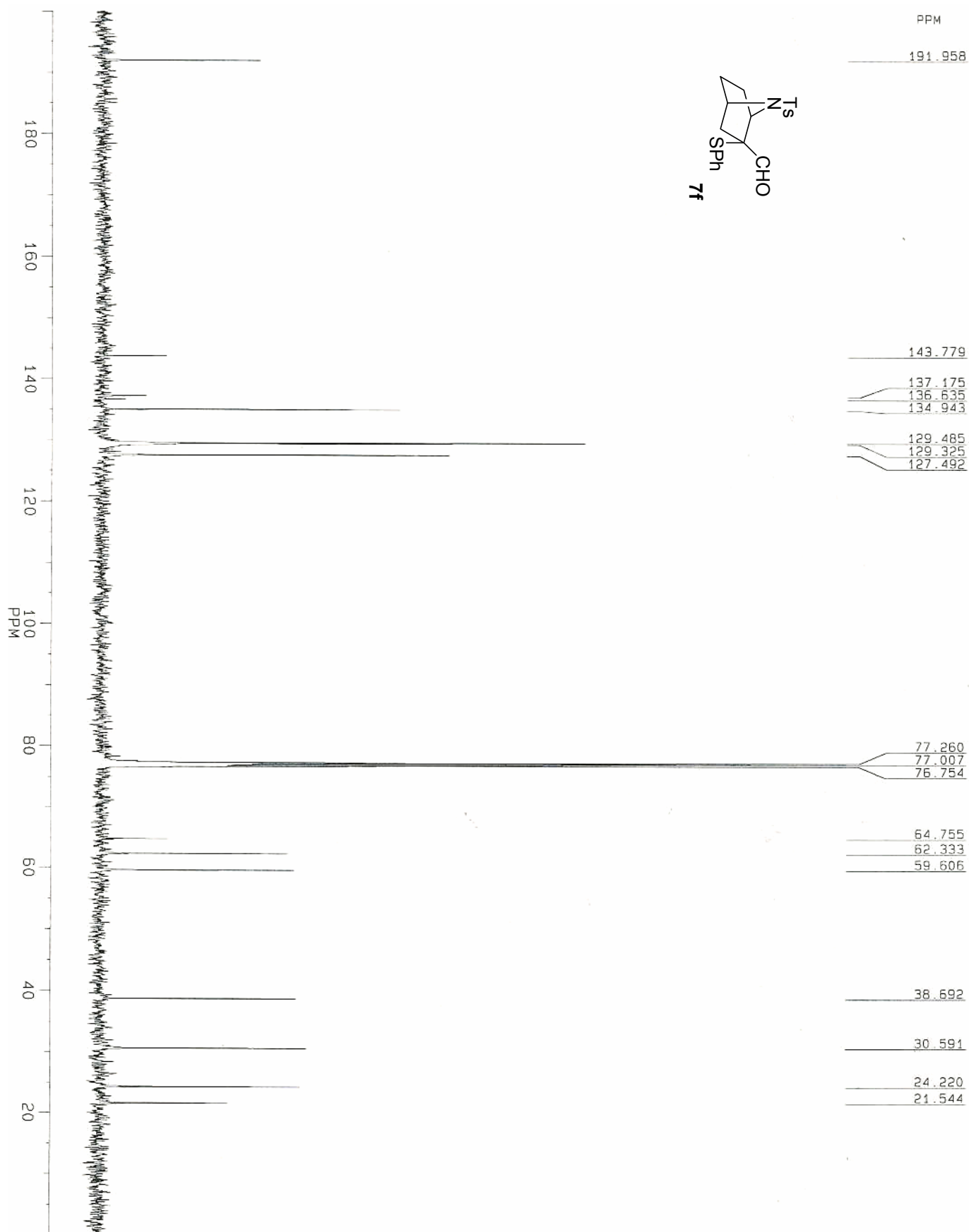


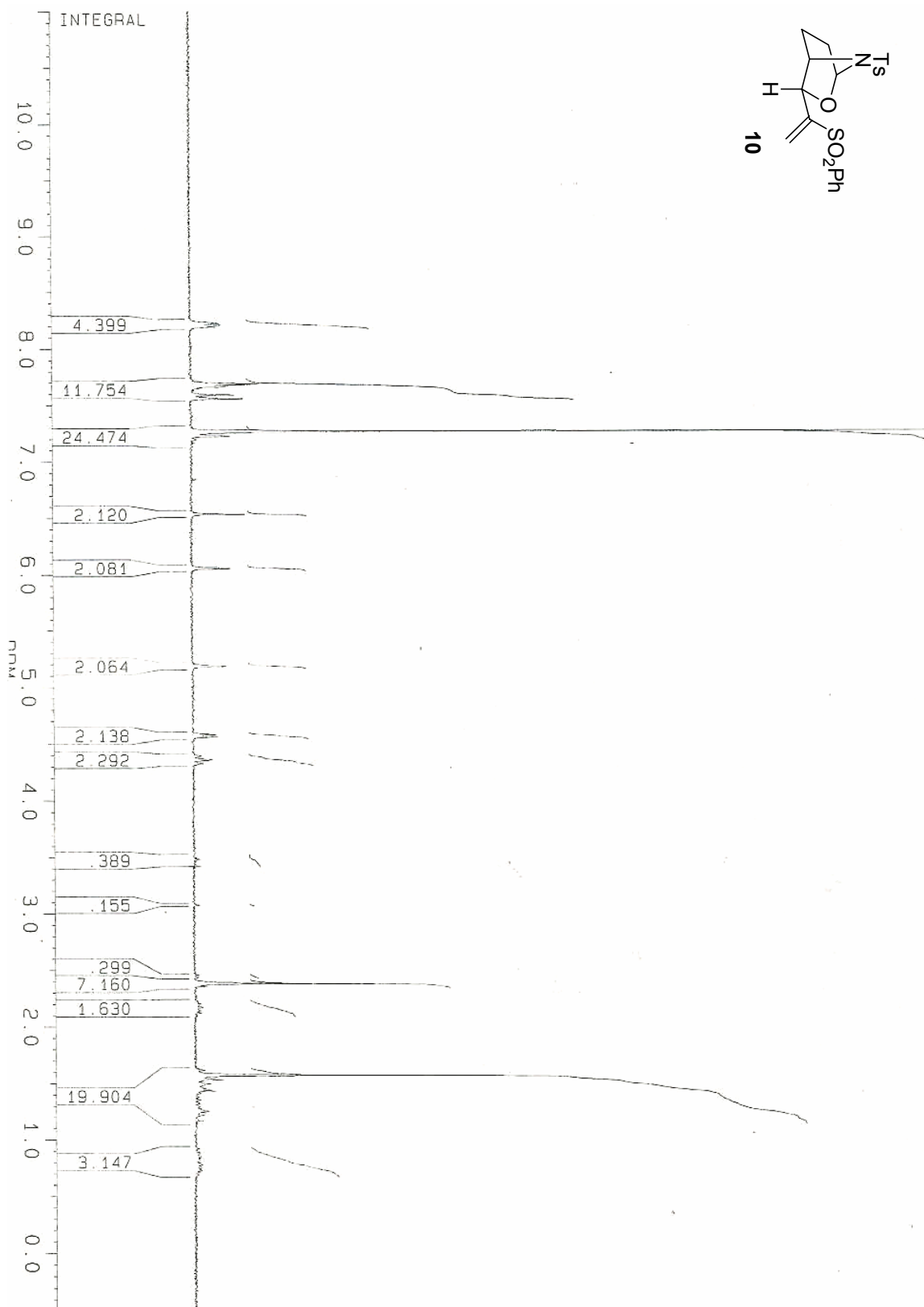


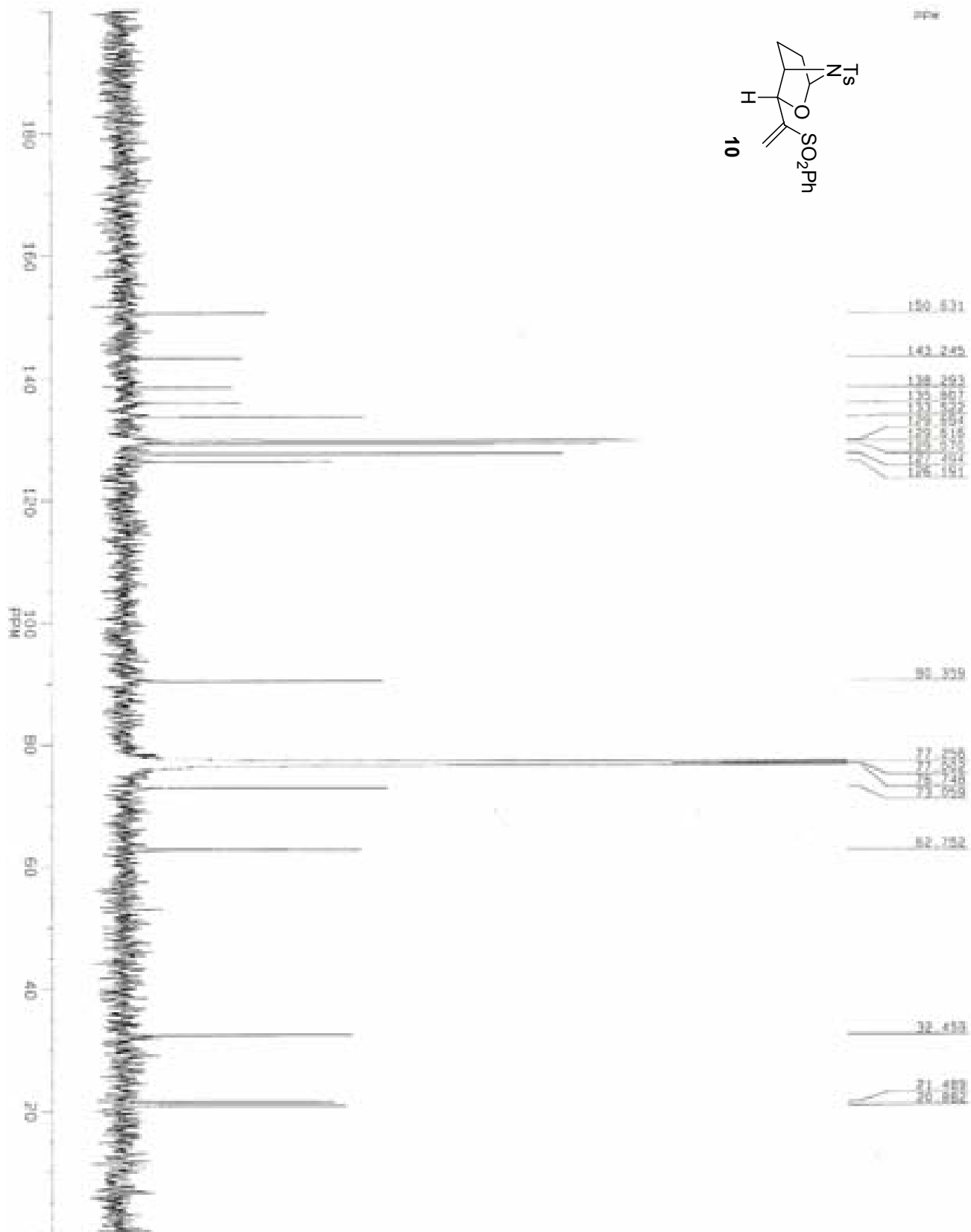
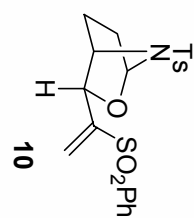












Assignment of Stereochemical Configuration

7-azabicyclo[2.2.1]heptanes

The relative stereochemical configuration of products **7a** and **7b** was established on the basis of nOe studies (Figure 1).

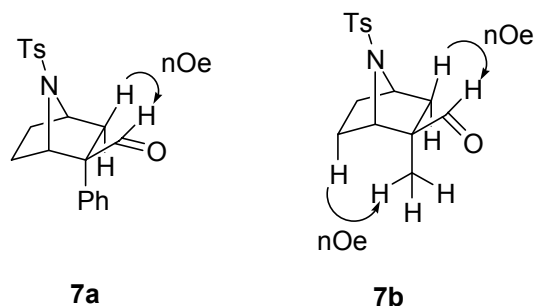


Figure 1

Much stereochemical information can be obtained from the observed magnitude of coupling constants around the [2.2.1] ring system (Figure 2).

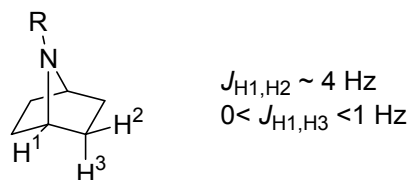


Figure 2

3J Coupling between bridgehead proton H^1 and pseudo-equatorial H^2 is readily observable. However, the dihedral angle between H^1 and pseudo-axial H^3 is close to 90° and consequently 3J coupling is frequently negligible. This is the case for Epibatidine itself,¹ and this effect has been observed with analogues, including one study where such findings were rationalised using *in-silico* molecular modelling.²

All compounds **7** have proton nmr spectra consistent with this model. Compounds **7c** and **7e** (Figure 3) give doublet signals for the emboldened protons, whilst in compound **7d**, an isomer of **7c**, the proton indicated gives a strongly triplet-like multiplet. The relative configuration of **7e**, and of the $-(CHMe)-$ methine centres in **7c** and **7d**, are principally assigned on this basis.

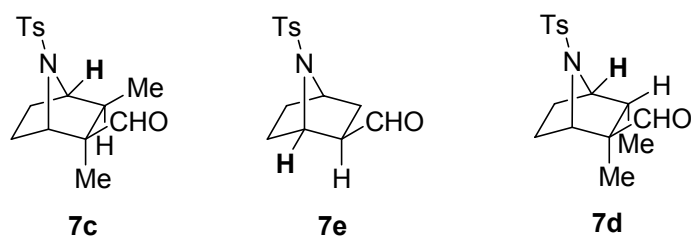


Figure 3

Furthermore, nOe experiments (Figure 4) on **7c** and **7d** showed interactions establishing the *exo* orientation of their aldehyde groups.

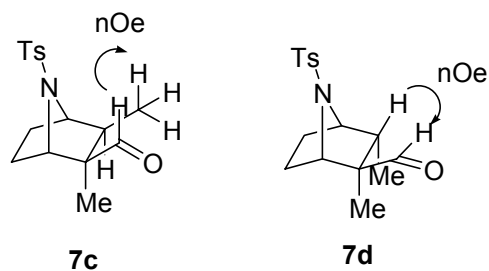


Figure 4

[3.2.1] Tropanes

The relative configuration of major products **8a** and **8b** was established on the basis of nOe studies (Figure 5).

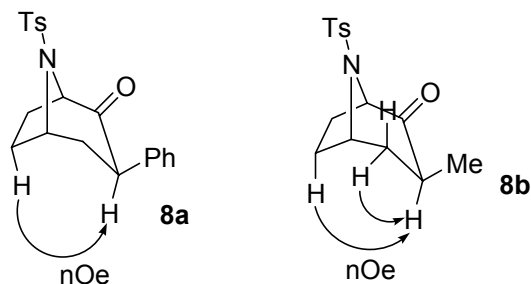


Figure 5

As is normally the case,³ an equatorial proton at position C-3 in compounds **9** gives a proton nmr signal at markedly lower field than an axial proton in isomeric tropanes **8**

(Table 1). In this regard, the spectrum of trace product **9c** is useful in assigning C-3 configuration to **8c** (Figure 6).

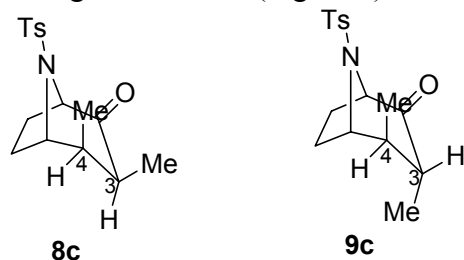


Figure 6

Table 1

C-3 methine proton chemical shift δ (ppm)			
8a	3.59	9a	3.92
8b	2.51-2.34 (m)	9b	2.80-2.62 (m)
8c	2.20	9c	2.58

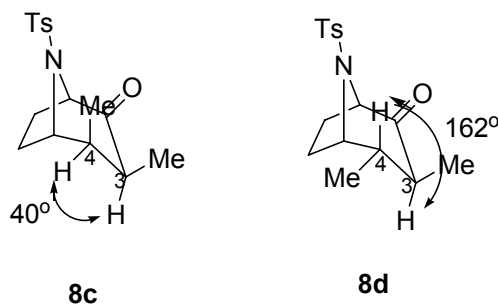


Figure 7. Predicted dihedral angles

Dihedral angles between the C-3 and C-4 methine hydrogens of **8c** and **8d** were predicted using *in-silico* molecular modelling (Spartan® software, Figure 7). The predicted angle for **8c** is 40°, which is consistent with the observed 3J coupling of 6.8 Hz. The magnitude of this coupling constant between C-3 and C-4 hydrogens was similar for **9c** (7.0 Hz). However, the dihedral angle for **8d** is predicted to be 162°. Karplus curve analysis, assuming a typical 3J coupling of 12Hz for antiperiplanar (180°) alignment in a rigid cyclohexane, gives a predicted value of $J \approx 10 - 11$ Hz. Selective decoupling of the two ring system methyl groups of **8d** in its 500 MHz proton nmr spectrum permitted an experimental measurement of $J = 10.8$ Hz. This is only consistent with a *pseudo*-transdiaxial coupling.

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