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SUPPORTING INFORMATION

Title: Model Studies Towards Stephaoxocanes: Construction of the 2-Oxa-4-azaphenalene Core of Stephaoxocanidine and Eletefine

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Synthesis and spectral data for compounds **6 - 9**, **12**, **15**, **18** and **20**.

2-Bromo-5-methoxy-benzaldehyde (6): A solution of bromine (5.68 mL, 110.29 mmol) in glacial acetic acid (10 mL) was added dropwise to a magnetically stirred solution of 3-methoxybenzaldehyde (5500 mg, 36.77 mmol) in glacial acetic acid (30 mL) kept in an cold water bath (4-6ºC). After stirring overnight at room temperature, the solution was poured over cold water containing crushed ice (approximately 250 mL). The solid thus produced was filtered and the residue was repeatedly washed with cold water, filtered and dried under reduced pressure. The combined filtrates were extracted with CH_2Cl_2 (3 x 40 mL) and the extract was successively washed with 10% $NaHSO_3$ until disappearance of the reddish color, and with brine (2 x 10 mL); then it was dried over Na_2SO_4 concentrated under reduced pressure, chromatographed and combined with the filtered solids, furnishing aldehyde **6** (7376 mg, 34.31 mmol, 93%), as a white solid m.p. 74.5-76°C (Lit.[22] 74-76°C); IR (KBr, ν)= 2960, 2840, 1690, 1674, 1600, 1570, 1474, 1304, 1284, 1244, 1198, 1170, 934, 866 and 820 cm^{-1}; ^1H NMR= 3.85 (s, 3 H, OC*H*$_3$), 7.04 (dd, J_1= 3.2, J_2= 8.8, 1 H, H-4), 7.42 (d, J= 3,2, 1 H, H-6), 7.53 (d, J= 8.8, 1 H, H-3) and 10.32 (s, 1 H, C*H*O); ^{13}C NMR (δ)= 55.53 (OCH_3), 112.52 (C-6), 117.74 (C-2), 122.85 (C-4), 133.75 (C-1), 134.35 (C-3), 159.05 (C-5) and 191.49 (CHO).

(1*S, 2*S**)-1-(2-Bromo-5-methoxy-phenyl)-propane-1,2-diol (8):** A mixture of NaH (≈ 55% dispersion in mineral oil, 706 mg, ≈ 14.69 mmol) and dry DMSO (2.08 mL, 29.40 mmol) was stirred at 60ºC during 1 h under an argon atmosphere; after cooling to room temperature, anhydrous THF (42 mL) was added, followed by oven-dried ethyltriphenylphosphonium iodide (4859 mg, 11.63 mmol) and the resulting mixture was heated 30 min at 60°C, when a solution of aldehyde **6** (2000 mg, 9.30 mmol), in THF (15 mL) was introduced and the reaction was again warmed at 60°C during 1 h. Then, the reaction was submitted to the standard work-up procedure, washing the combined organic phases with 10% $NaHSO_3$ (10 mL). This furnished an oil containing a mixture of isomeric olefins **7** (*E*/*Z*≈ 0.7), which was dissolved in dry toluene (30 mL) and successively treated with a solution of thiophenol in toluene (0.597 M, 2.40 mL, 1.43 mmol), and AIBN (125 mg, 0.764 mmol). After heating at 80ºC during 3 h, the solvent was evaporated under reduced pressure and the resulting residue was chromatographed, furnishing ***E*-7** (1897 mg, 8.36 mmol, 90%), as a colorless oil. IR (ν)= 2959, 2933, 2852, 1590, 1566, 1473, 1464, 1453, 1439, 1432, 1416, 1289, 1263, 1236, 1167, 1129, 1053, 1017, 962,

802 and 741 cm^{-1}; ^1H NMR (δ)= 1.92 (dd, J_1= 1.7, J_2= 6.6, 3 H, CH_3), 3.80 (s, 3 H, OCH_3), 6.18 (dq, J_1= 6.6, J_2= 15.6, 1 H, =C*H*-CH_3), 6.65 (dd, J_1= 3.1, J_2= 8.8, 1 H, H-5'), 6.69 (dq, J_1= 1.7, J_2= 15.6, 1 H, Ar-C*H*=), 7.00 (d, J= 3.1, 1 H, H-3') and 7.40 (d, J= 8.8, 1 H, H-6'); ^{13}C NMR (δ)= 18.47 (*C*H_3), 55.28 (O*C*H_3), 111.79 (C-3'), 113.62 (C-1'), 114.16 (C-5'), 128.82 (=*C*H-CH_3), 129.81 (Ar-*C*H=), 133.14 (C-6'), 138.26 (C-2') and 158.76 (C-4'). Without further treatment, olefin ***E*-7** (1897 mg, 8.36 mmol) was dissolved in a cold mixture of H_2O (10 mL) and acetone (20 mL); NMO (1338 mg, 11.44 mmol) was added, followed by an OsO_4 solution in *tert*-butanol (10 mg/mL, 3.8 mL, 0.15 mmol) and the reaction was stirred for 15 h at room temperature. Then, 10% $NaHSO_3$ (5 mL) and Celite were incorporated and after stirring for 30 min, the suspension was filtered and the residue washed with EtOAc (10 mL). Most of the acetone was removed under reduced pressure and the organic products were submitted to the standard work-up procedure, yielding diol **8** (1860 mg, 7.13 mmol, 85%), as an oil. IR (ν)= 3390, 2974, 2934, 2836, 1598, 1572, 1464, 1416, 1404, 1368, 1286, 1238, 1190, 1166, 1138, 1120, 1048, 1014, 916, 856, 824, 806, 758, 734, 710, 640 and 624 cm^{-1}; ^1H NMR (δ)= 1.22 (d, J= 6.4, 3 H, CH_3), 2.36 (bd, J= 3.9, 1 H, CH_3-CHO*H*), 2.87 (bd, J= 4.7, 1 H, Ar-CHO*H*), 3.80 (s, 3 H, OCH_3), 3.95 (ddq, J_1= 3.9, J_2= 5.5, J_3= 6.4, 1 H, CH_3-C*H*OH), 4.88 (dd, J_1= 4.7, J_2= 5.5, 1 H, Ar-C*H*OH), 6.72 (dd, J_1= 3.1, J_2= 8.8, 1 H, H-4'), 7.04 (d, J= 3.1, 1 H, H-6') and 7.42 (d, J= 8.8, 1 H, H-3'); ^{13}C NMR (δ)= 18.72 (*C*H_3), 55.33 (O*C*H_3), 71.4 (*C*H-CH_3), 76.3 (Ar-*C*H), 112.91 (C-2'), 113.64 (C-4'), 115.05 (C-6'), 133.15 (C-3'), 141.45 (C-1') and 158.95 (C-5'); HRMS: M^+= 260.00490; $C_{10}H_{13}BrO_3$ requires M^+= 260.00481.

(2*S, 4*S**, 5*S**)-4-(2-Bromo-5-methoxyphenyl)-2,5-dimethyl-[1,3]dioxolane (9a) and (2*R**, 4*S**, 5*S**)-4-(2-bromo-5-methoxyphenyl)-2,5-dimethyl-[1,3]dioxolane (9b):** Under a dry argon atmosphere, acetaldehyde dimethyl acetal (1.2 mL, 8.2 mmol) and (+)-10-camphorsulfonic acid (50 mg) were successively added to a solution of diol **8** (1070 mg, 4.10 mmol) in dry CH_2Cl_2 (55 mL). After stirring 4 h at 35ºC, the reaction was treated with saturated $NaHCO_3$ (15 mL) and submitted to the standard work-up procedure, affording an inseparable mixture (**9a**:**9b** ≈ 2.7 by NMR integration of the signal of the acetalic proton) of dioxolanes **9a** and **9b** (1050 mg, 3.7 mmol, 90%), as a colorless oil. IR (ν)= 2988, 2936, 1594, 1572, 1462, 1446, 1414, 1388, 1366, 1288, 1272, 1236, 1164, 1140, 1116, 1096, 1072, 1052, 1026, 1010 and 872 cm^{-1}. **Acetal 9a:** ^1H NMR (δ)= 1.48 (d, J= 6.1, 3 H, CH_3-5), 1.49 (d, J= 4.8, 3 H, CH_3-

2), 3.81 (s, 3 H, OCH_3), 3.91 (dq, J_1= 6.1, J_2= 7.5, 1 H, H-5), 4.96 (d, J= 7.5, 1 H, H-4), 5.51 (q, J= 4.8, 1 H, H-2), 6.73 (dd, J_1= 3.1, J_2= 8.8, 1 H, H-4'), 7.03 (d, J= 3.1, 1 H, H-6') and 7.42 (d, J= 8.8, 1 H, H-3'); ^{13}C NMR (δ)= 17.46 (*C*H_3-5), 20.79 (*C*H_3-2), 55.39 (O*C*H_3), 81.76 (C-5), 82.27 (C-4), 102.26 (C-2), 112.62 (C-2'), 113.50 (C-4'), 115.10 (C-6'), 133.44 (C-3'), 139.51 (C-1') and 159.15 (C-5'). HRMS: M^+= 286.02090; $C_{12}H_{15}BrO_3$ requires M^+= 286.02046. **Acetal 9b:** ^{1}H NMR (δ)= 1.46 (d, J= 6.3, 3 H, CH_3-5), 1.55 (d, J= 4.8, 3 H, CH_3-2), 3.81 (s, 3 H, OCH_3), 4.04 (dq, J_1= 5.2, J_2= 6.3, 1 H, H-5), 5.00 (d, J= 5.2, 1 H, H-4), 5.42 (q, J= 4.8, 1 H, H-2), 6.72 (dd, J_1= 3.2, J_2= 8.8, 1 H, H-4'), 7.13 (d, J= 3.2, 1 H, H-6') and 7.41 (d, J= 8.8, 1 H, H-3'); ^{13}C NMR (δ)= 18.07 (*C*H_3-5), 20.05 (*C*H_3-2), 55.22 (O*C*H_3), 79.88 (C-5), 83.04 (C-4), 100.57 (C-2), 112.20 (C-2'), 113.21 (C-4'), 115.01 (C-6'), 133.05 (C-3'), 139.85 (C-1') and 159.09 (C-5').

(1*S, 3*S**)-5-Bromo-8-methoxy-1,3-dimethyl-isochroman-4-one (12):** IR (ν)= 2978, 2938, 2838, 1708, 1580, 1570, 1460, 1436, 1260, 1230, 1200, 1114, 1098, 1064, 990 and 826 cm^{-1}; ^{1}H NMR (δ)= 1.47 (d, J= 6.3, 3 H, CH_3-3), 1.56 (d, J= 6.6, 3 H, CH_3-1), 3.87 (s, 3 H, OCH_3), 4.58 (q, J= 6.3, 1 H, H-3), 5.32 (q, J= 6.6, 1 H, H-1), 6.99 (d, J= 8.8, 1 H, H-7) and 7.54 (d, J= 8.7, 1 H, H-6); ^{13}C NMR (δ)= 17.16 (*C*H_3-3),* 17.49 (*C*H_3-1),* 55.72 (O*C*H_3), 66.80 (C-1), 70.74 (C-3), 111.12 (C-7), 115.43 (C-5), 133.92.27 (C-8a), 134.23 (C-6), 137.78 (C-4a), 153.47 (C-8) and 195.05 (C-4).

(1*S, 3*S**)-8-Methoxy-1,3-dimethyl-isochroman-4-one (15):** IR (ν)= 2978, 2930, 1688, 1578, 1466, 1438, 1400, 1356, 1323, 1280, 1256, 1192, 1154, 1124, 1098, 991, 942, 850, 818, 722, 647 and 616 cm^{-1}; ^{1}H NMR (δ)= 1.44 (d, J= 6.3, 3 H, CH_3-3), 1.59 (d, J= 6.6, 3 H, CH_3-1), 3.89 (s, 3 H, OCH_3), 4.61 (q, J= 6.3, 1 H, H-3), 5.35 (q, J= 6.6, 1 H, H-1), 7.09 (d, J= 8.1, 1 H, H-7), 7.21 (d, J= 7.7, 1 H, H-5) and 7.34 (dd, J_1= 7.7, J_2= 8.1, 1 H, H-6); ^{13}C NMR (δ)= 17.15 (*C*H_3-3),* 17.56 (*C*H_3-1),* 55.42 (O*C*H_3), 66.63 (C-1), 71.24 (C-3), 109.57 (C-7), 121.50 (C-5), 130.91 (C-8a), 131.08 (C-6), 138.38 (C-4a), 153.91 (C-8) and 195.16 (C-4).

8-Methoxy-1,3-dimethyl-1*H*-isochromene (18): IR (ν)= 2924, 2852, 1652, 1602, 1578, 1474, 1438, 1380, 1264, 1154, 1112, 1086, 1062, 1026 and 802 cm^{-1}; ^{1}H NMR (δ)= 1.37 (d, J= 6.4, 3 H, CH_3-1), 1.89 (d, J= 0.8, 3 H, CH_3-3), 3.80 (s, 3 H, OCH_3), 5.51 (d, J= 0.8, 1 H, H-4), 5.65 (q, J= 6.4, 1 H, H-1), 6.53 (d, J= 7.9, 1 H, H-7), 6.65 (d, J= 7.9, 1 H, H-5) and 7.11 (dd, J_1= 7.9, J_2= 7.9, 1 H, H-6);

^{13}C NMR (δ)= 19.19 (*C*H$_3$-3),* 20.10 (*C*H$_3$-1),* 55.12 (O*C*H$_3$), 69.38 (C-1), 99.18 (C-4), 107.82 (C-7), 115.40 (C-5), 119.18 (C-8a), 127.99 (C-6), 131.32 (C-4a), 151.83 (C-3) and 153.98 (C-8).

(1*S, 3*S**, 4*S**)-*N*-(8-Methoxy-1,3-dimethyl-isochroman-4-yl)-4-methyl-*N*-(2-oxo-ethyl)-benzene sulfonamide (20):** IR (ν)= 2983, 2936, 2840, 1729, 1653, 1589, 1472, 1456, 1440, 1370, 1335, 1303, 1262, 1170, 1156, 1104, 1086, 1064, 1034, 975, 936, 820, 732, 714 and 662 cm^{-1}; ^{1}H NMR (δ)= 1.22 (d, *J*= 6.5, 3 H, C*H*$_3$-3), 1.43 (d, *J*= 6.6, 3 H, C*H*$_3$-1), 2.47 (s, 3 H, Ar-*CH*$_3$), 3.42 (dd, *J*$_1$= 2.2, *J*$_2$= 18.8, 1 H, C*H*$_2$CH), 3.80 (s, 3 H, OC*H*$_3$-8), 3.84 (dd, *J*$_1$= 2.2, *J*$_2$= 18.8, 1 H, C*H*$_2$CH), 4.17 (dq, *J*$_1$= 2.8, *J*$_2$= 6.5, 1 H, H-3), 4.83 (d, *J*= 2.6, 1 H, H-4), 4.96 (q, *J*= 6.6, 1 H, H-1), 6.51 (d, *J*= 7.7, 1 H, H-7), 6.73 (d, *J*= 7.7, 1 H, H-5), 7.06 (dd, *J*$_1$= 7.7, *J*$_2$= 7.7, 1 H, H-6), 7.36 (d, *J*= 8.0, 2 H, H-3' and H-5'), 7.77 (d, *J*= 8.0, 2 H, H-2' and H-6') and 9.23 (t, *J*= 2.2, 1 H, CHO); ^{13}C NMR (δ)= 17.69 (*C*H$_3$-1), 18.16 (*C*H$_3$-3), 21.45 (Ar-*C*H$_3$), 54.42 (*C*H$_2$CH), 55.06 (C-4), 55.83 (O*C*H$_3$-8), 66.60 (C-1), 68.24 (C-3), 109.83 (C-7), 121.16 (C-5), 127.30 (C-6), 127.90 (C-3' and C-5'), 129.27 (C-2' and C-6'), 129.76 (C-8a), 131.76 (C-1'), 137.22 (C-4a), 143.86 (C-4'), 154.94 (C-8) and 199.70 (CHO).

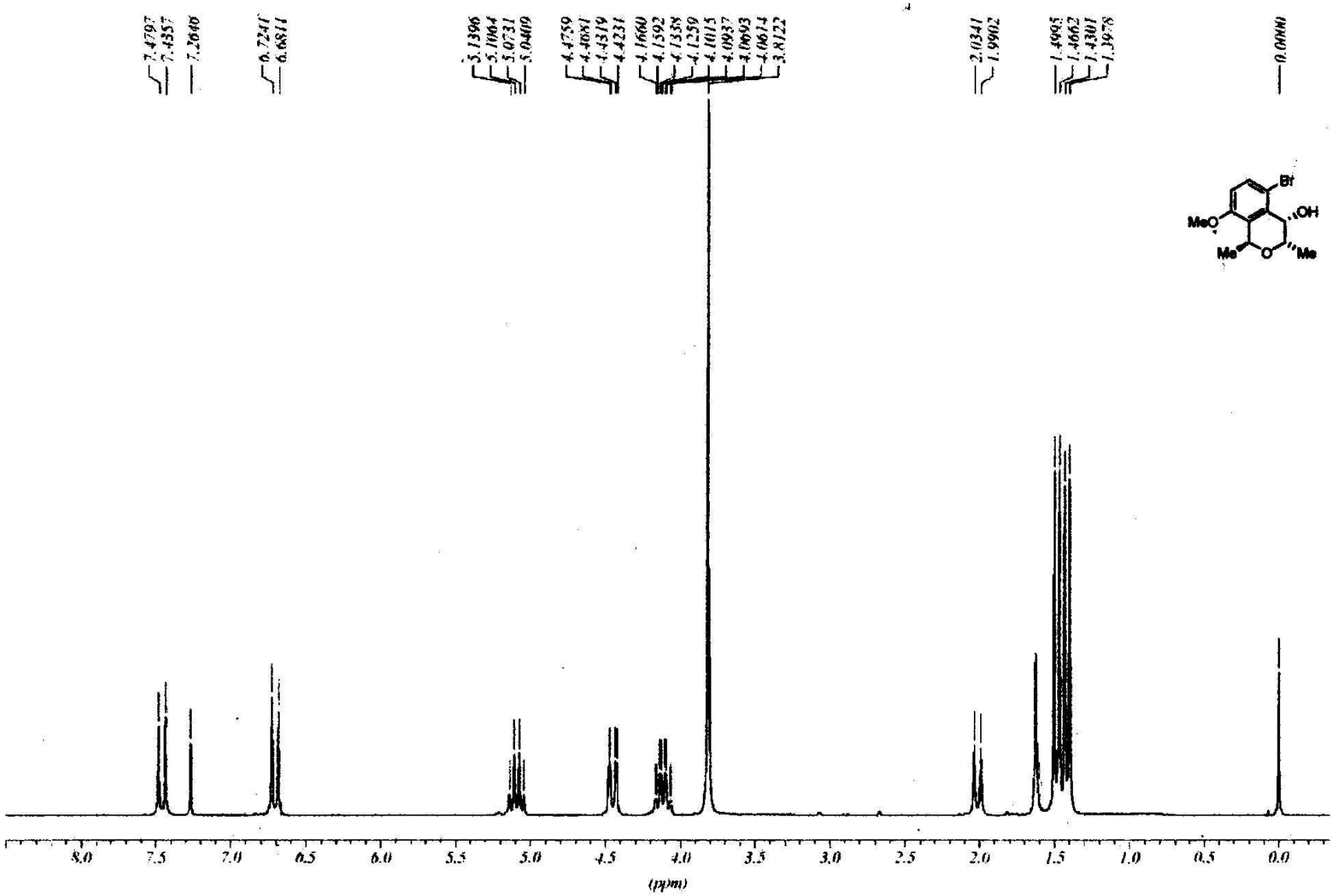

Figure 1. ^{1}H NMR spectrum of isochroman-4-ol **10**

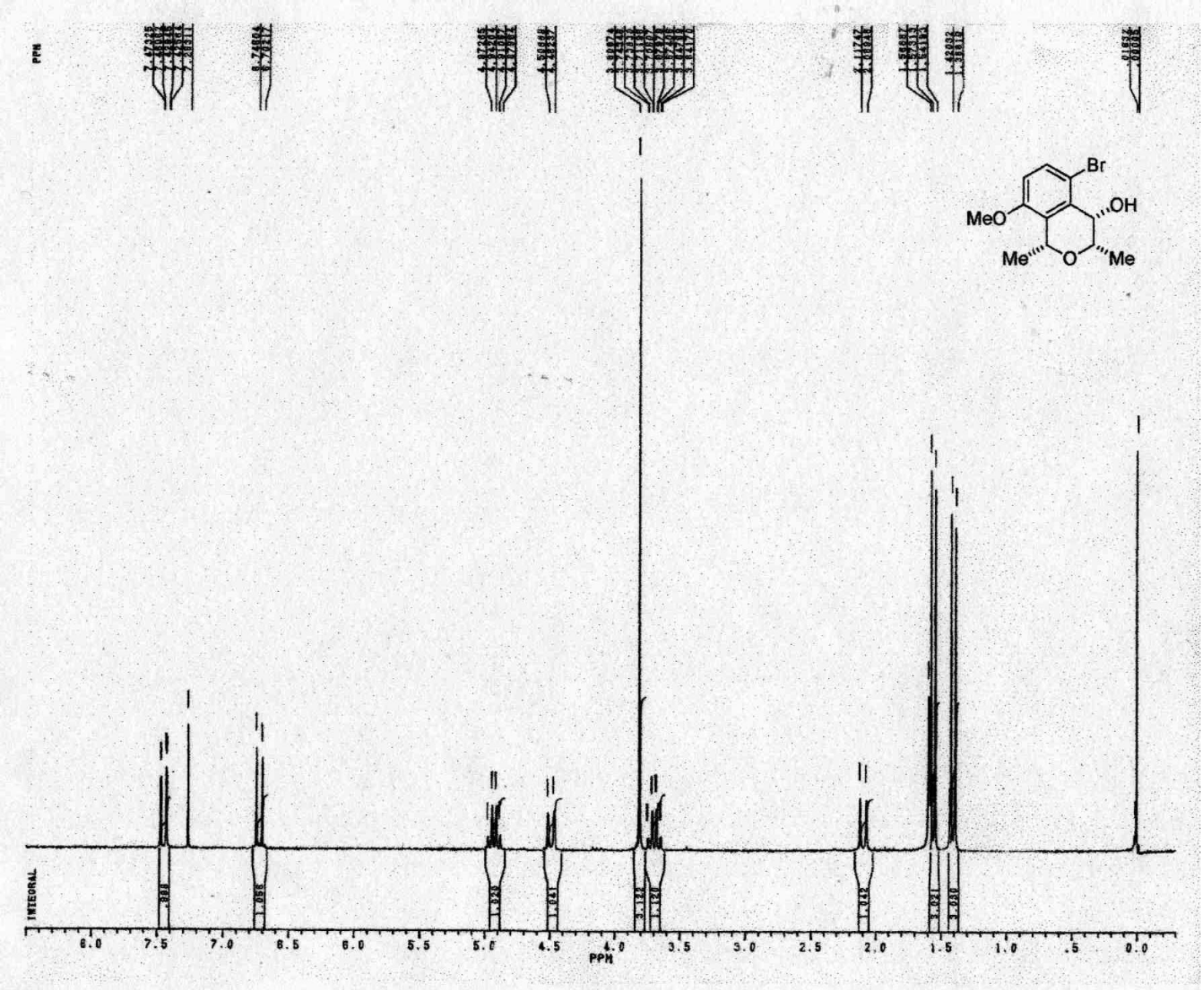

Figure 2. ^{1}H NMR spectrum of all-*cis* isochroman-4-ol **11**

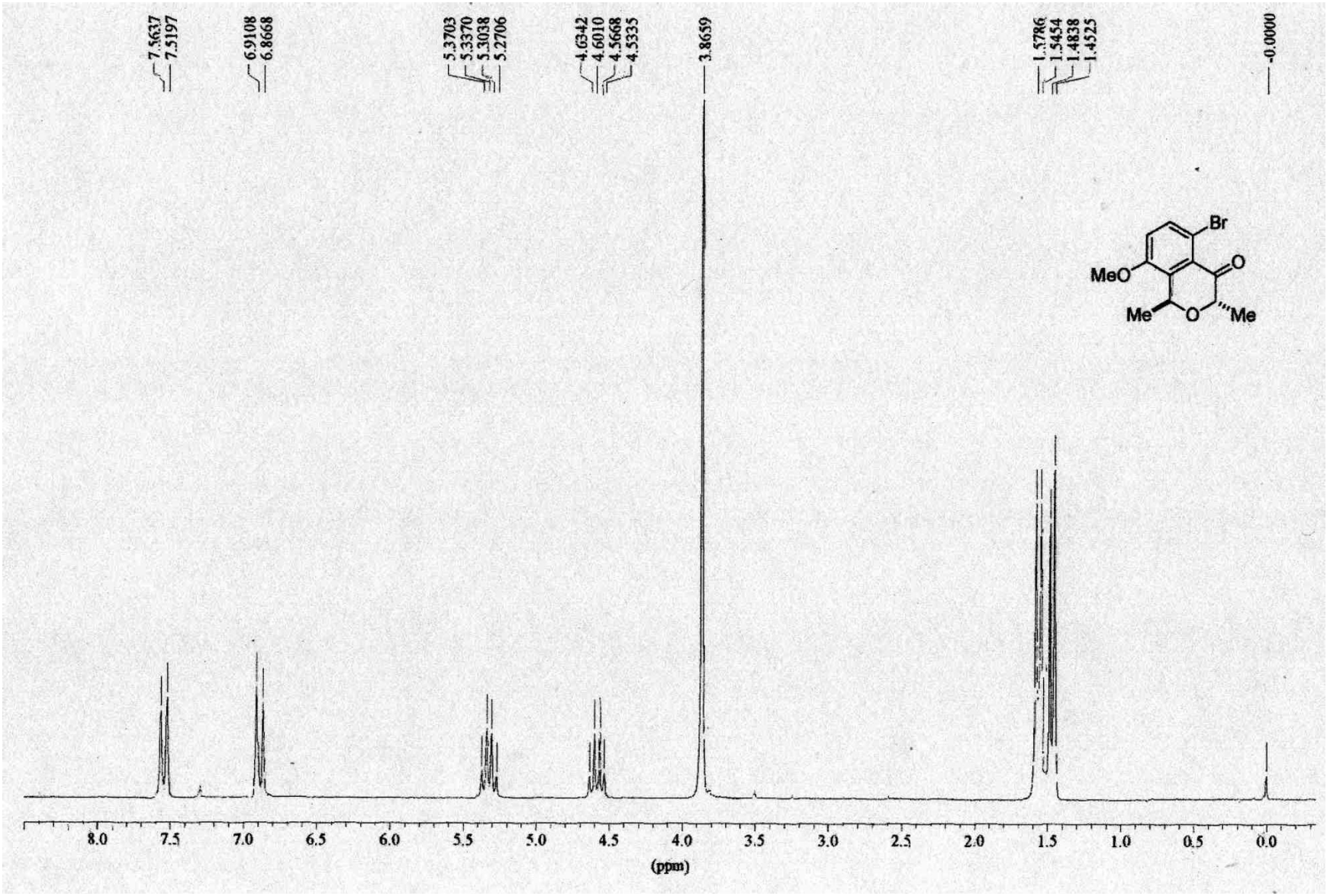

Figure 3. ^{1}H NMR spectrum of ketone **12**

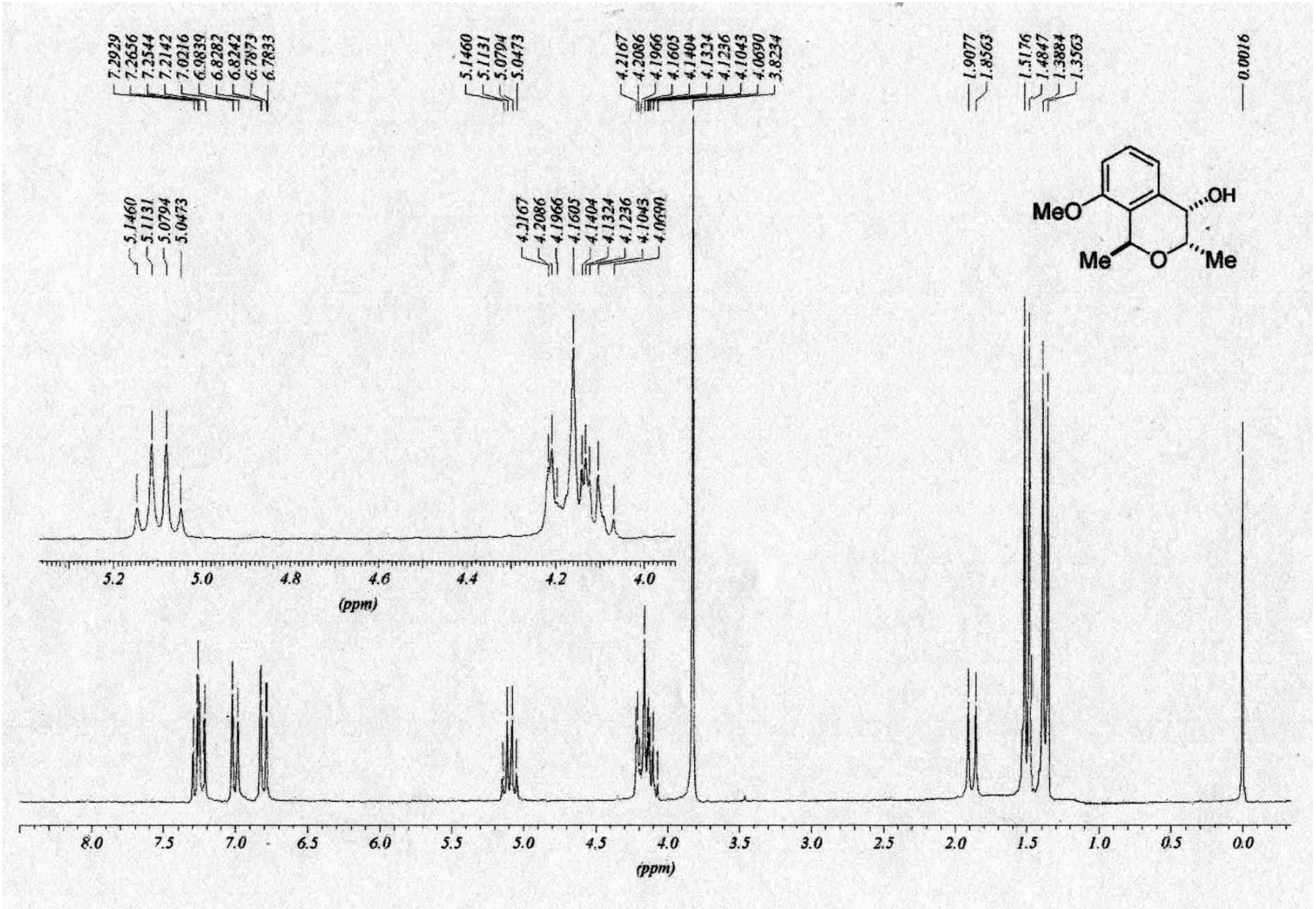

Figure 4. ^{1}H NMR spectrum of debrominated isochroman-4-ol **14**

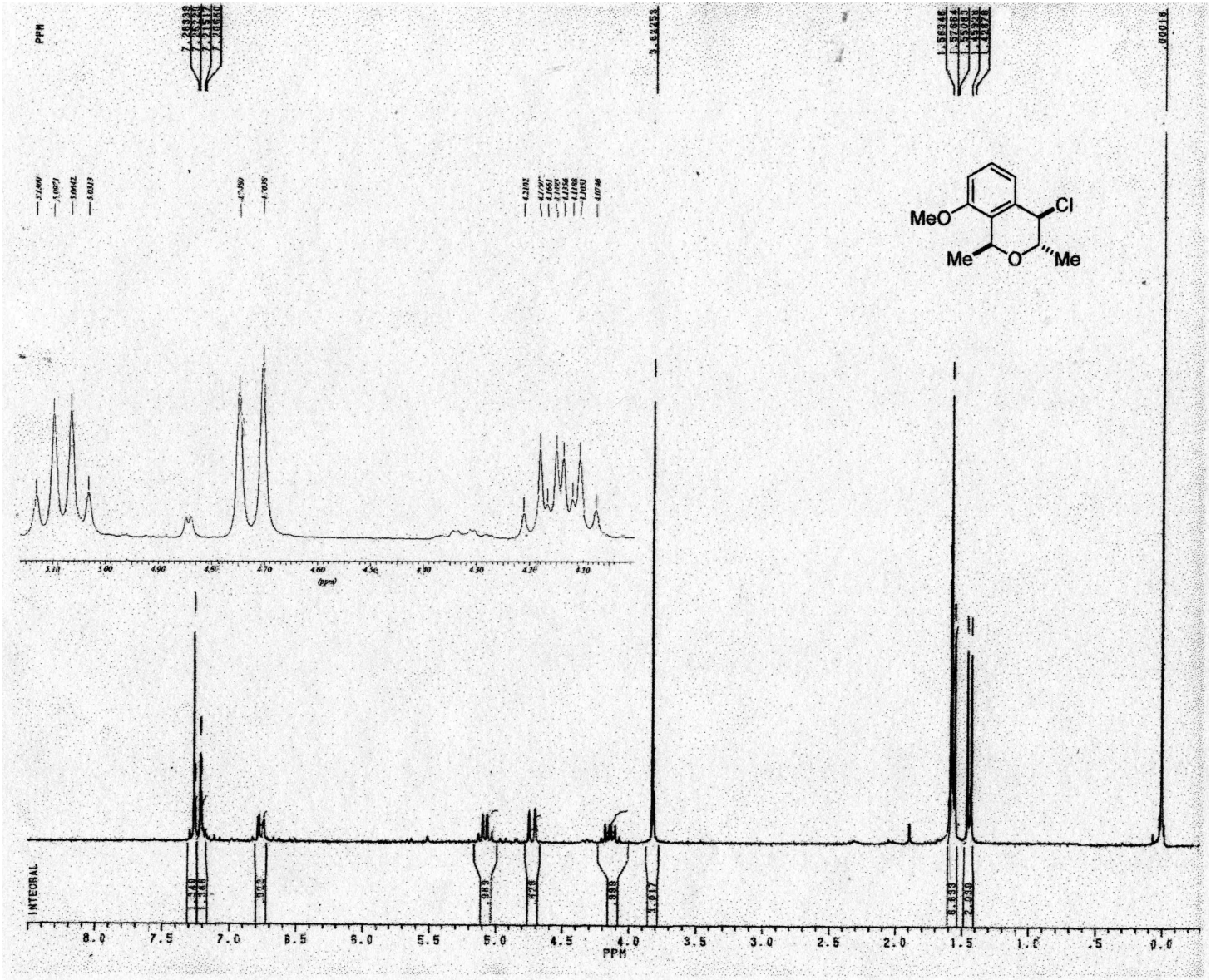

Figure 5. ^{1}H NMR spectrum of chloride **17**

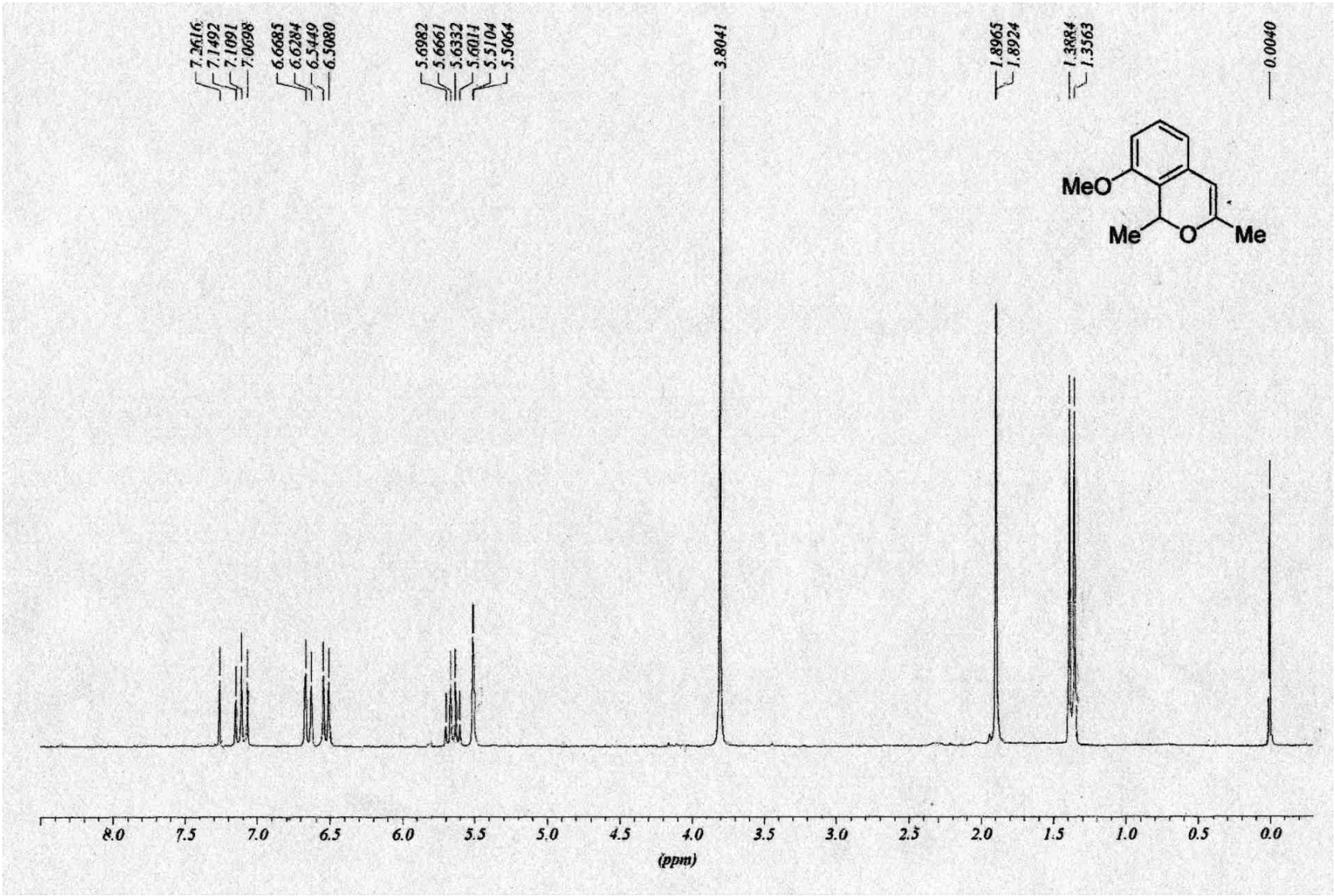

Figure 6. ^{1}H NMR spectrum of isochromene **18**

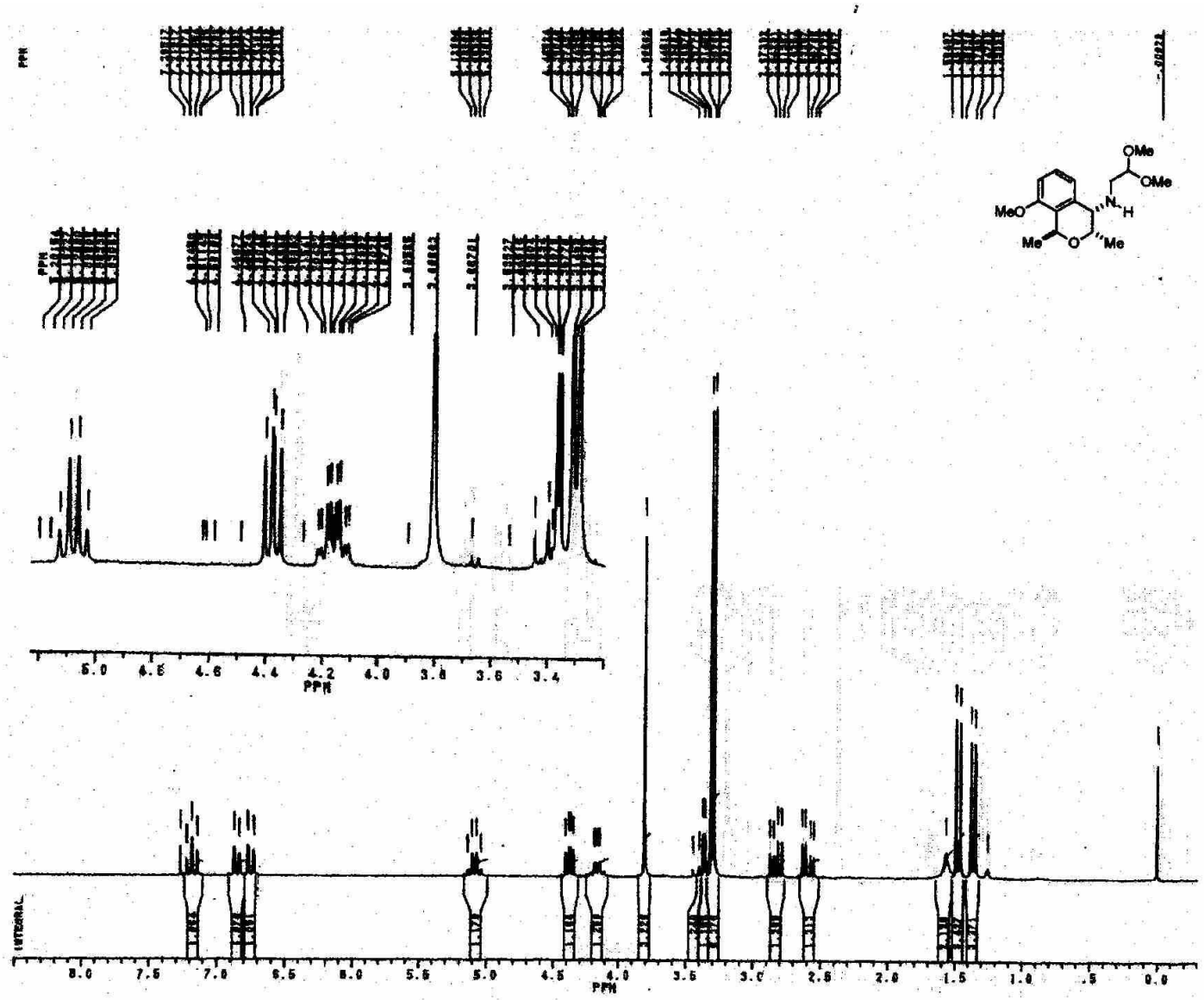

Figure 7. ^{1}H NMR of aminoacetal **16**

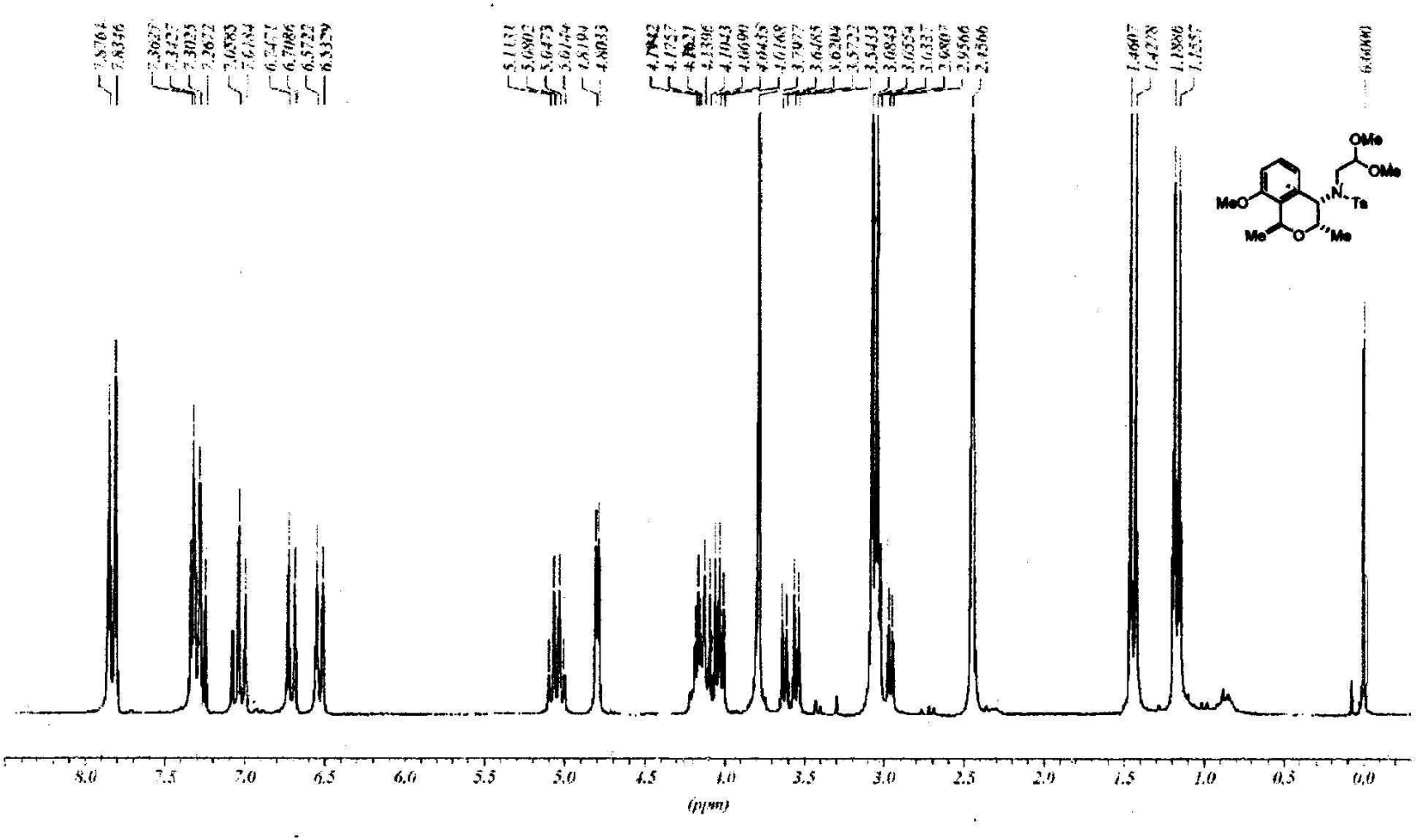

Figure 8. ^{1}H NMR spectrum of sulfonamidoacetal **19**

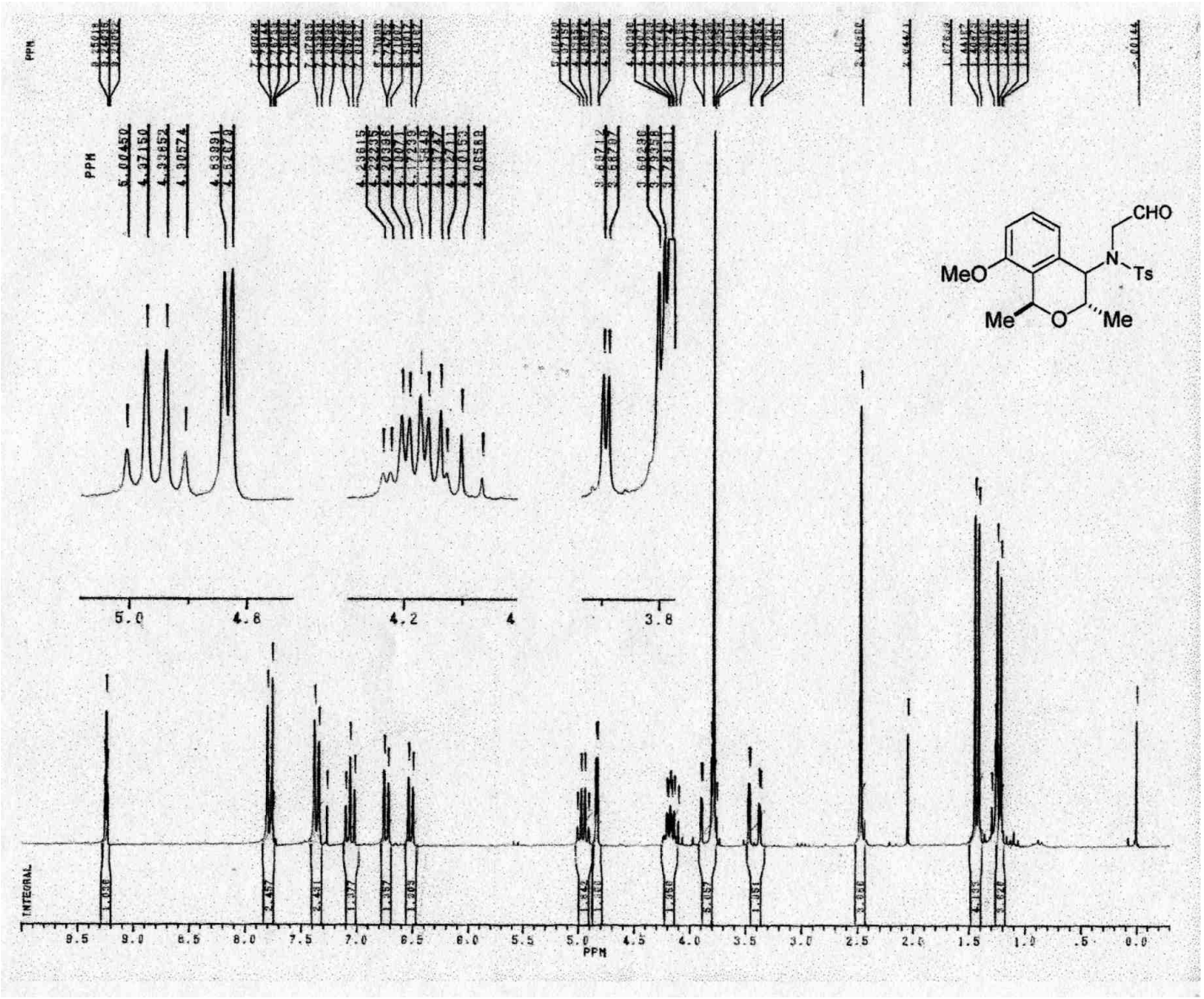

Figure 9. ^{1}H NMR spectrum of aldehyde **20**

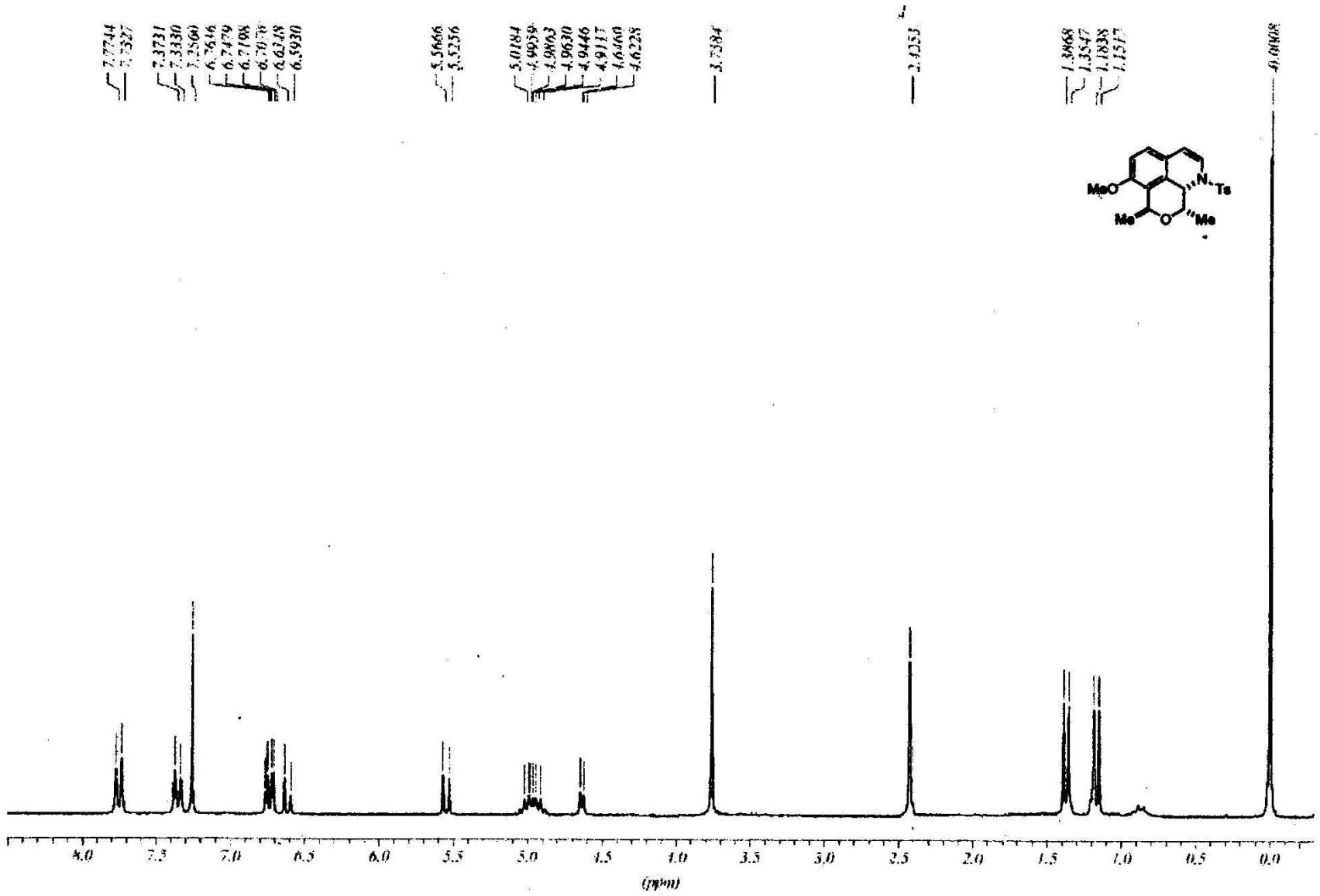

Figure 10. ^{1}H NMR of oxazaphenalene **21**

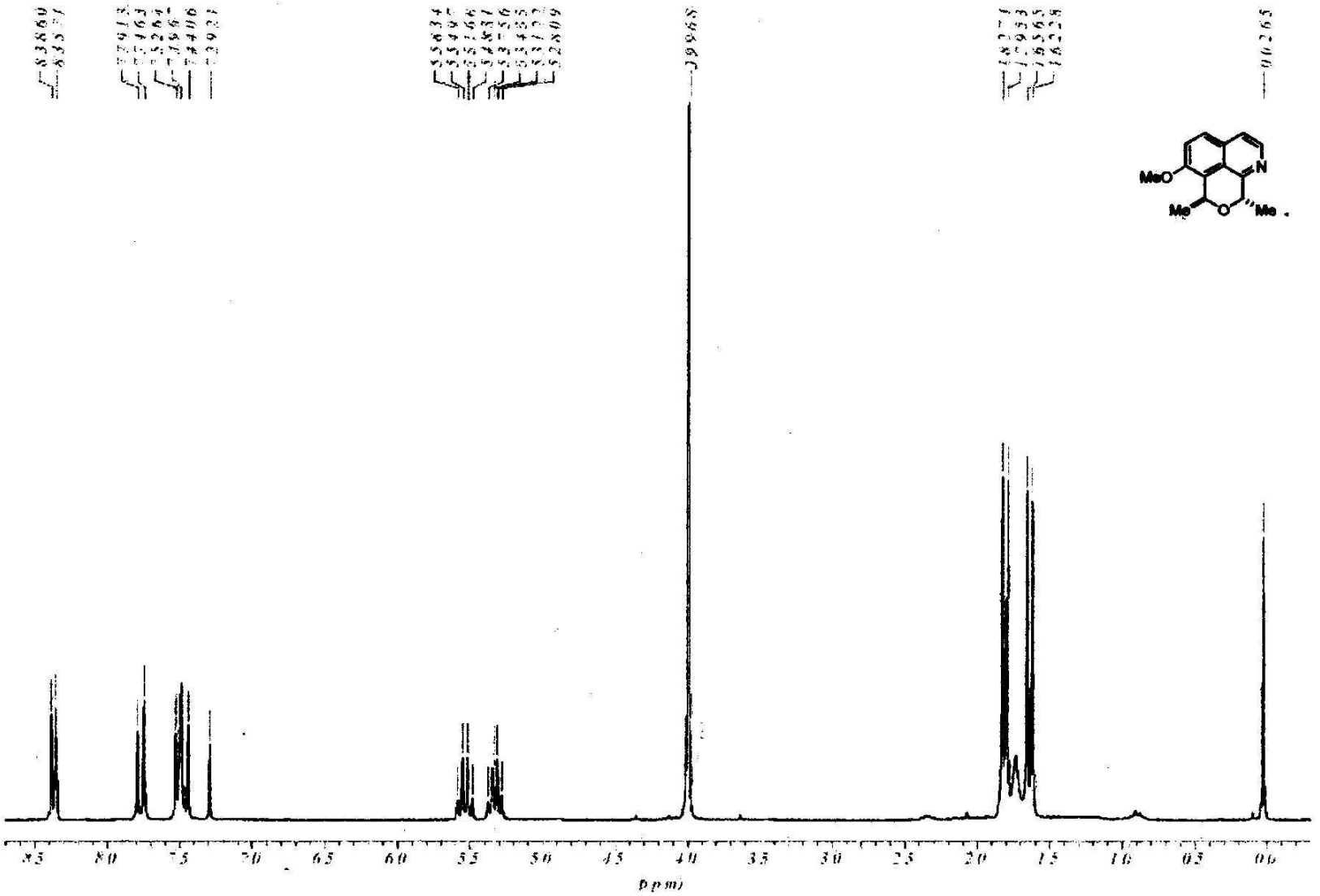

Figure 11. ^{1}H NMR spectrum of oxazaphenalene **4**

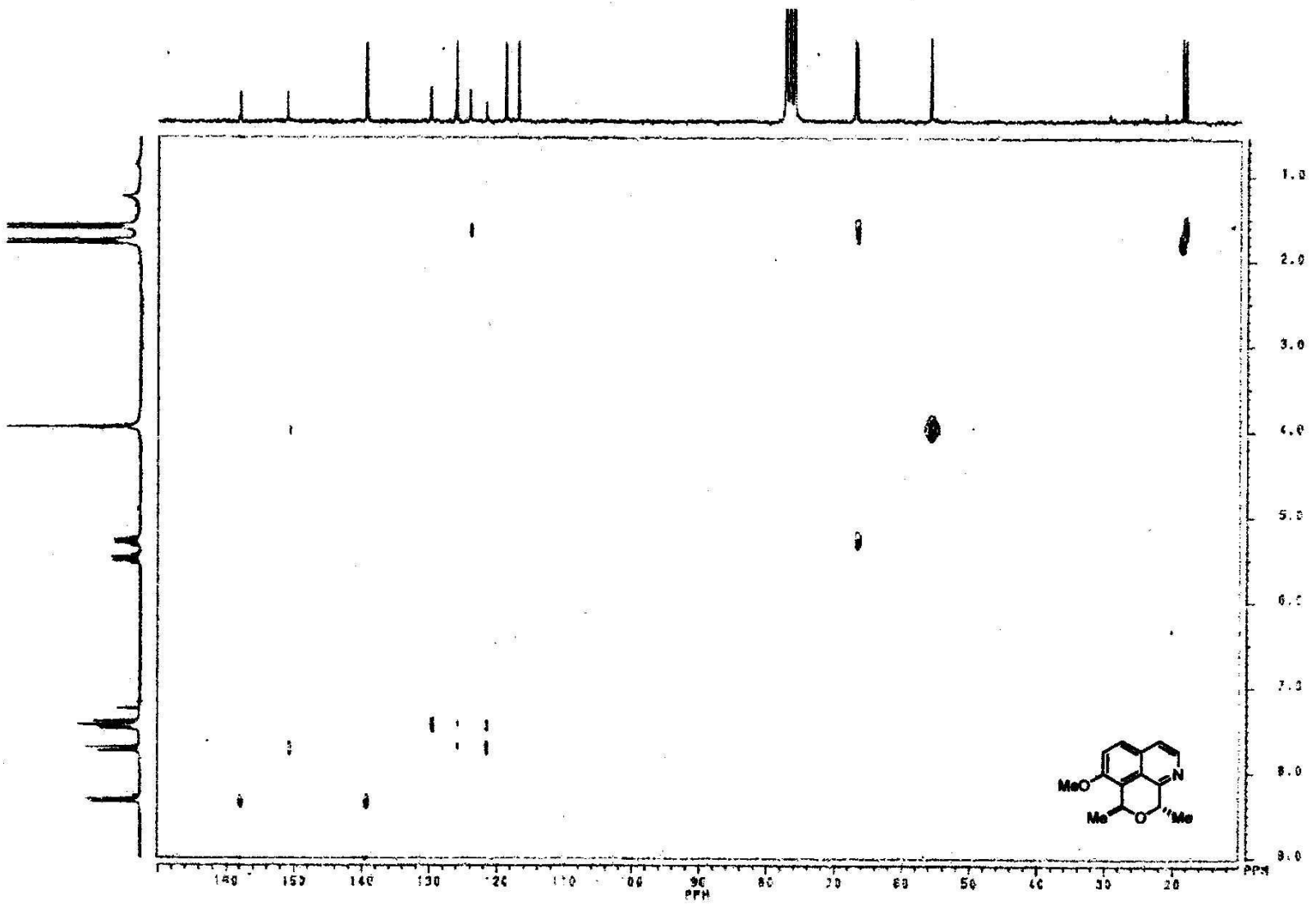

Figure 12. Heteronuclear C-H correlation NMR spectrum of oxazaphenalene **4**