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JO961872F

Efficient Synthesis of Enantiopure Indolizidinone Amino Acids, Rigid Dipeptide Mimetics

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Supplementary Material

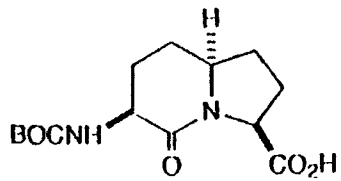
Reference numbers refer to references in the manuscript.

(2*S*)-γ-Methyl L-Glutamate was prepared from (2*S*)-glutamic acid (36.8 g, 0.26 mol) according to the literature procedure,[23c] which gave 21.6 g (54%): R_f = 0.2 in eluant A; mp 185 °C, lit.[23c] mp 182 °C; $[\alpha]^{20}_D$ 13.4° (*c* 1, H_2O); ^1H NMR (D_2O) δ 2.15-2.3 (m, 2 H), 2.6-2.65 (dt, 2 H, *J* = 7.6, 4.1), 3.7 (s, 3 H), 3.8 (t, 1H, *J* = 6.4); ^{13}C NMR δ 26.2, 30.4, 53.1, 54.7, 174.6, 176.0; MS calcd for $C_6H_{11}NO_4$ (MH^+) 162.17, found 161.1. **(2*R*)-γ-Methyl D-Glutamate** was prepared from (2*R*)-glutamic acid (18.4 g, 0.13 mol) in the same manner which gave 15 g (54%): $[\alpha]^{20}_D$ –28.5° (*c* 2, HCl 6N).

(2*S*)-Dimethyl L-Glutamate Hydrochloride was prepared in 98% yield from L-glutamate (14.71 g, 0.10 mmol) according to the literature procedure for the synthesis of dimethyl aspartate,[23a] which gave 21.17 g: R_f = 0.59 in eluant A; mp 89 °C; $[\alpha]^{20}_D$ 27° (*c* 5, H_2O); ^1H NMR δ 2.24-2.29 (m, 2 H), 2.45-2.62 (m, 2 H), 3.52 (s, 3 H), 3.70 (s, 3 H), 4.21 (s br, 1 H); ^{13}C NMR δ 24.9, 29.4, 51.5, 52.2, 53.0, 169.4, 172.5; HRMS calcd for $C_7H_{14}NO_4$ (MH^+) 176.0916, found 176.0923.

(2*S*)-γ-Methyl L-*N*-(PhF)Glutamate was synthesized from γ-methyl L-glutamate (8.06 g, 50 mmol) by the literature method,[19d] which gave 10.41 g (85%); R_f = 0.65 in eluant B; mp 144 °C, lit.[19d] mp 142-143°C; $[\alpha]^{20}_D$ –77° (*c* 0.7, $CHCl_3$); HRMS calcd for $C_{25}H_{23}NO_4$ (MH^+) 402.1705, found 402.1699. **(2*R*)-γ-methyl D-*N*-(PhF)glutamate** was synthesized from γ-methyl D-glutamate via the same method: $[\alpha]^{20}_D$ 72° (*c* 0.7, $CHCl_3$).

(2*S*)-Dimethyl L-*N*-(PhF)Glutamate ((2*S*)-2b) was prepared from (2*S*)-dimethyl L-glutamate hydrochloride (10.65 g, 50.3 mmol) according to the literature procedure for dimethyl *N*-(PhF)aspartate,[23a] which gave 18.9 g (90%) of (2*S*)-**2b**: R_f = 0.55 in eluant C; mp 62 °C; $[\alpha]^{20}_D$ –293.3° (*c* 1.12, $CHCl_3$); ^1H NMR δ 1.72-1.89 (m, 2 H), 2.39-2.57 (m, 2 H), 2.68 (m, 1 H), 3.04 (s br, 1 H), 3.29 (s, 3H), 3.66 (s, 3H), 7.1-7.7 (m, 13 H); ^{13}C NMR δ 29.6, 30.1, 51.2, 51.3, 54.6, 72.6, 173.3, 176.1; HRMS calcd for $C_{26}H_{26}NO_4$ (MH^+) 416.1878, found 416.1862.



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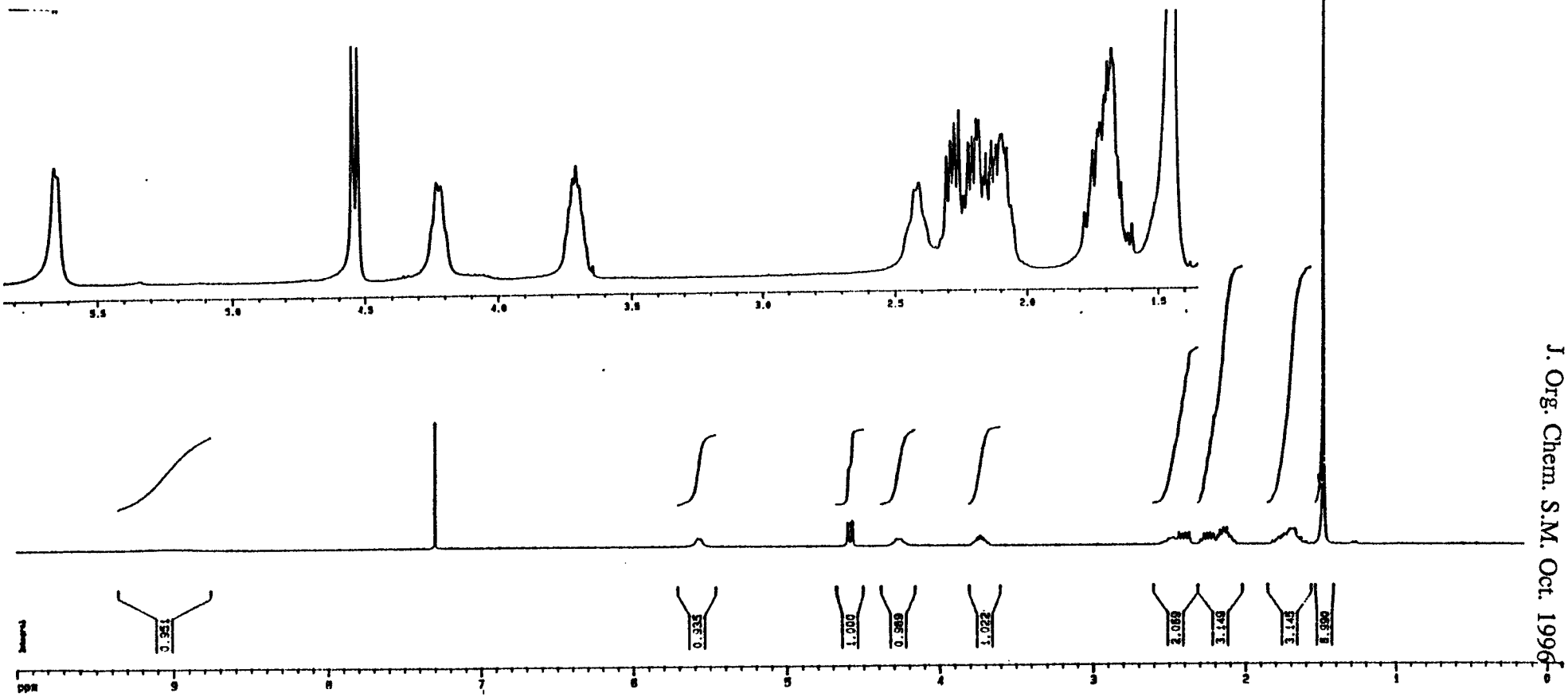

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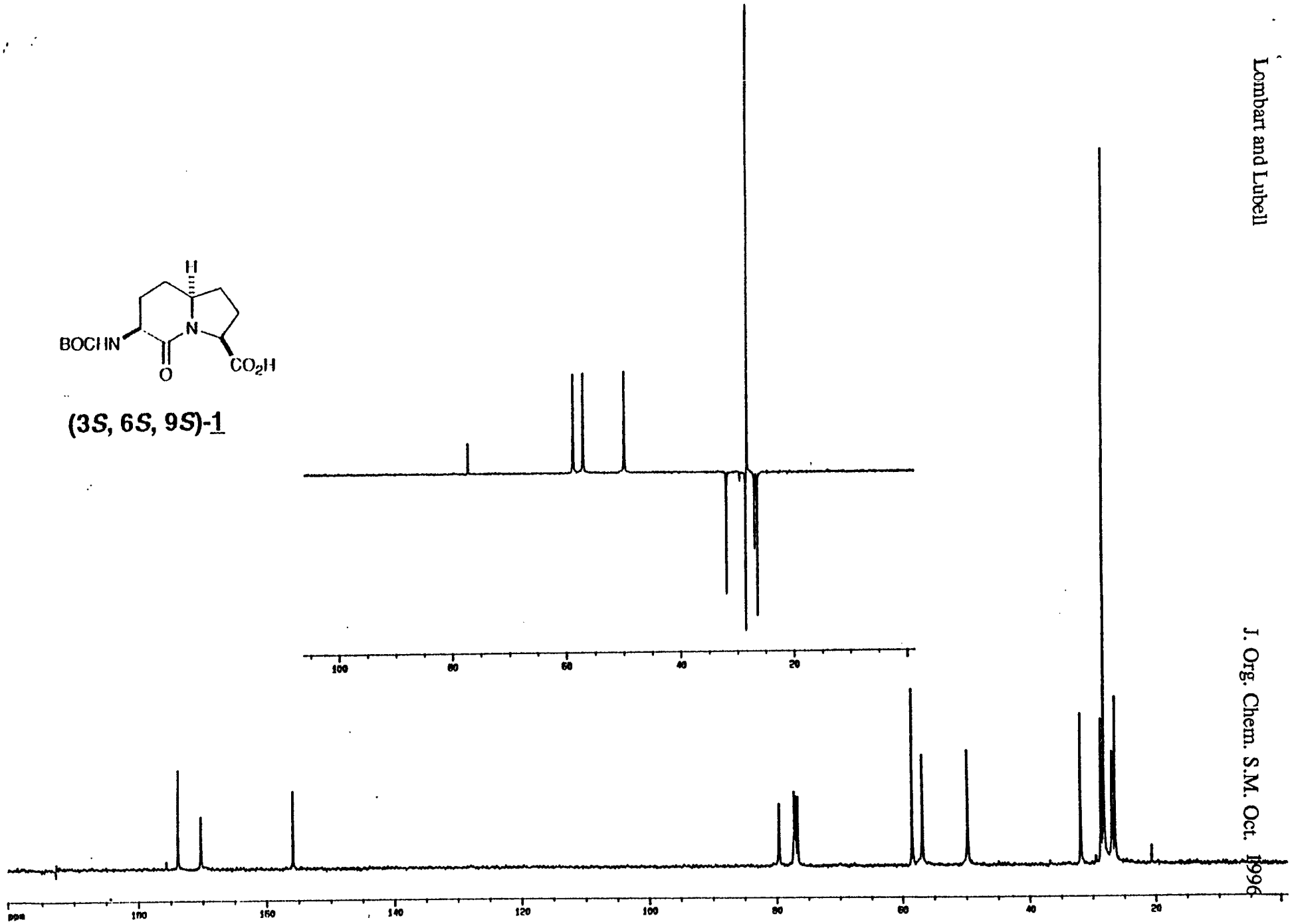

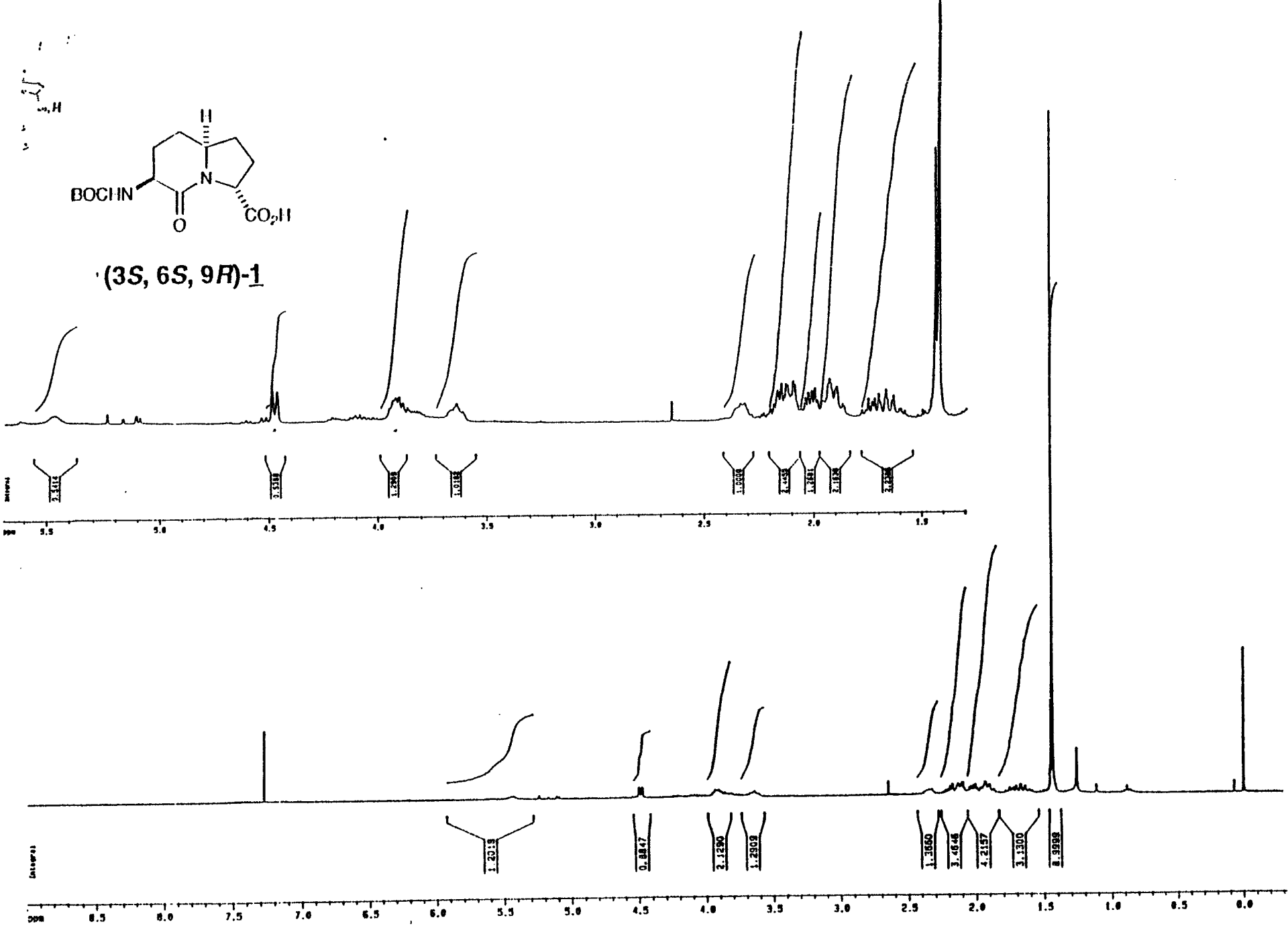

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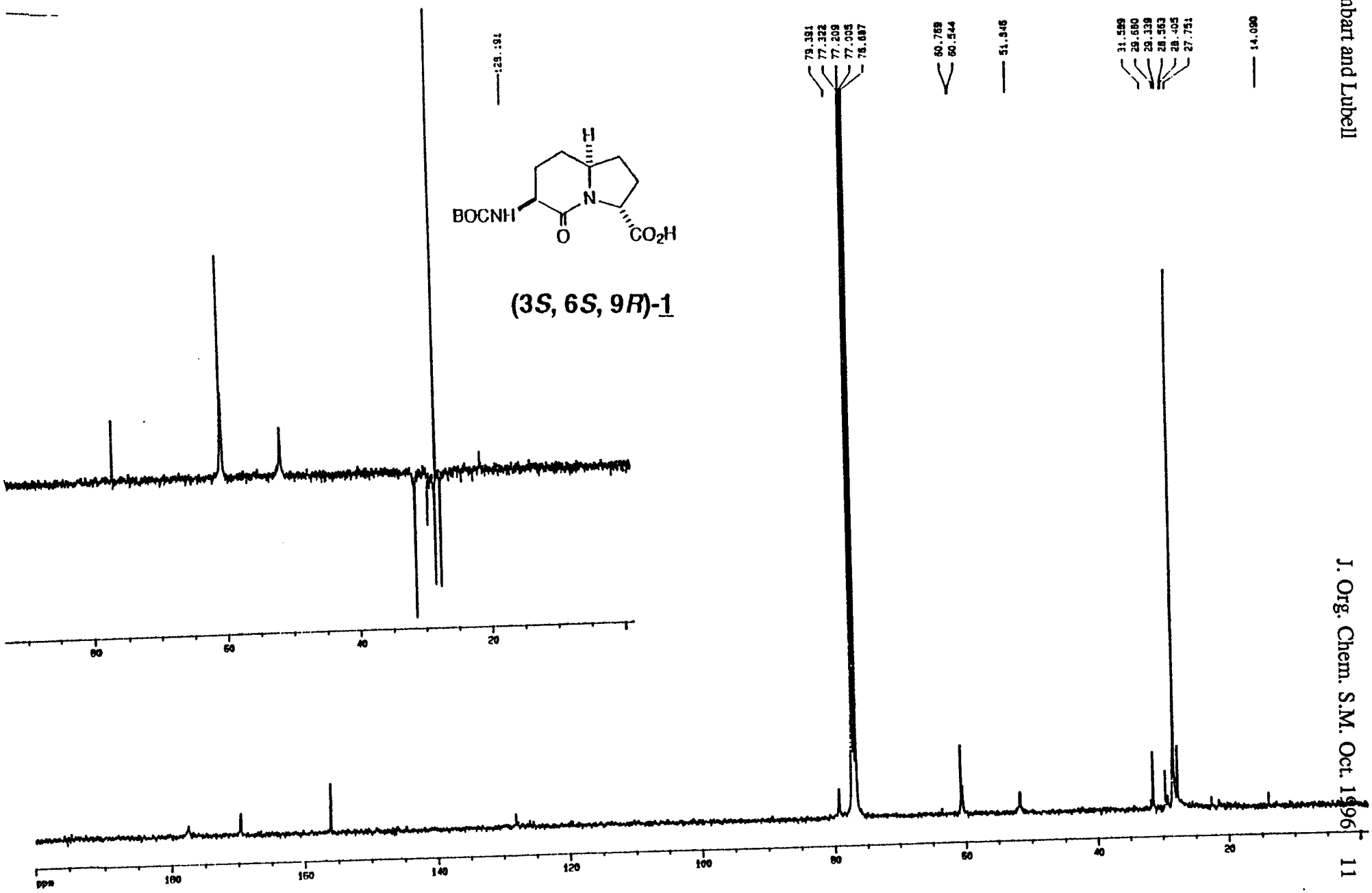

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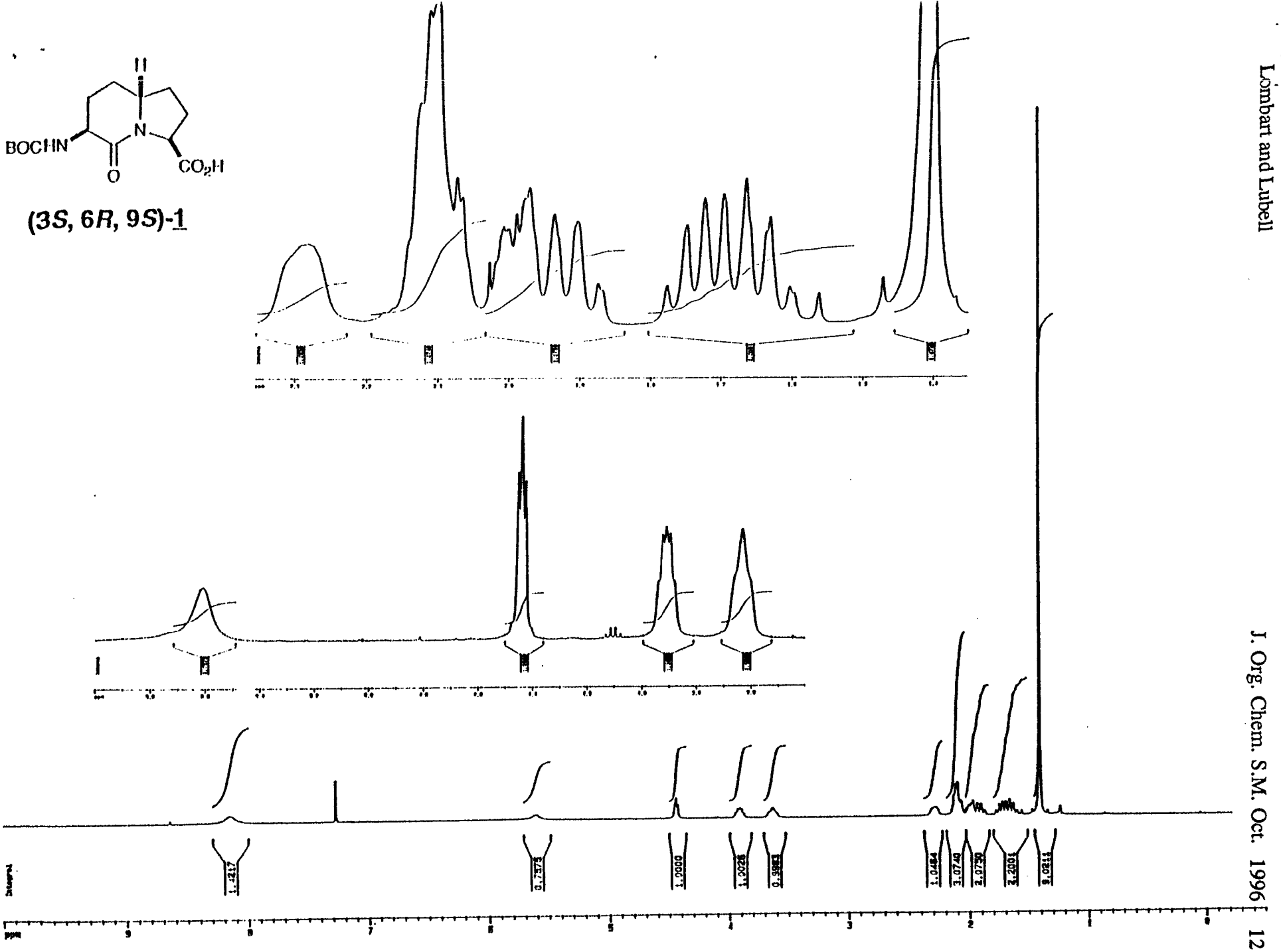

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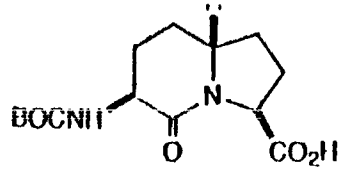

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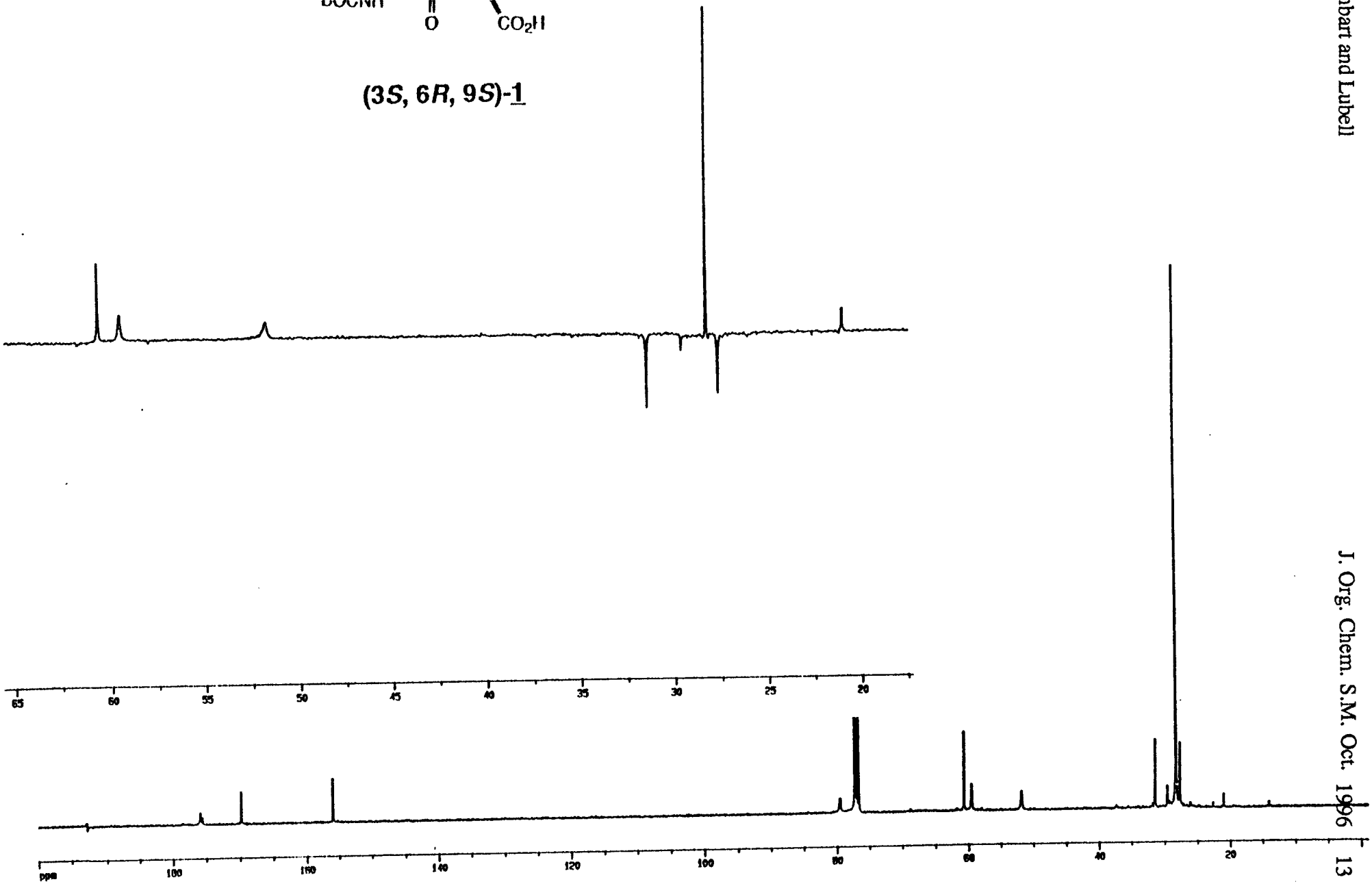

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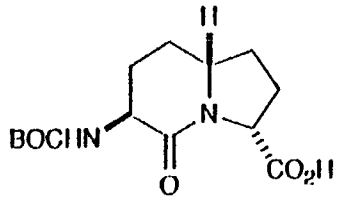

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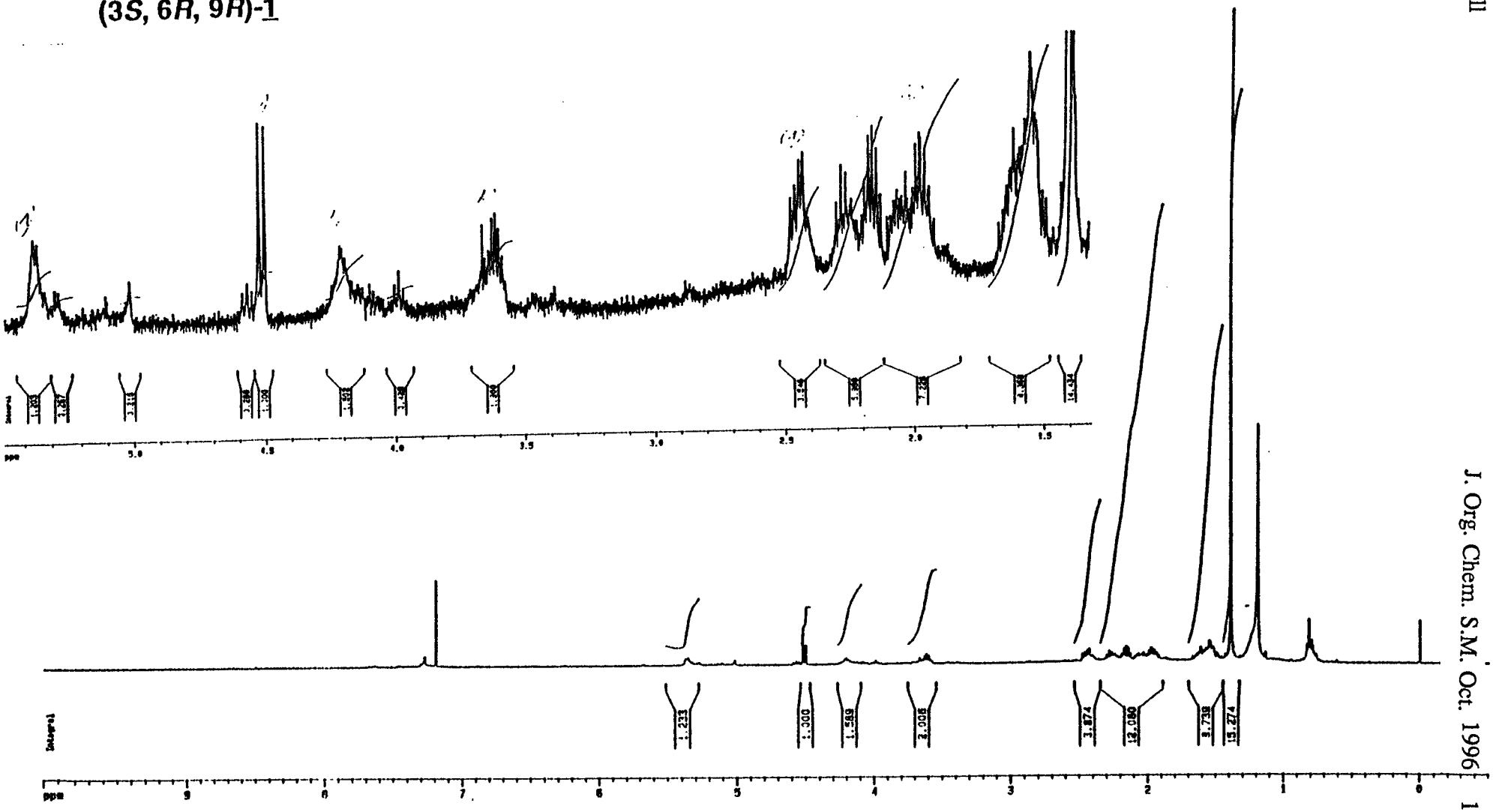

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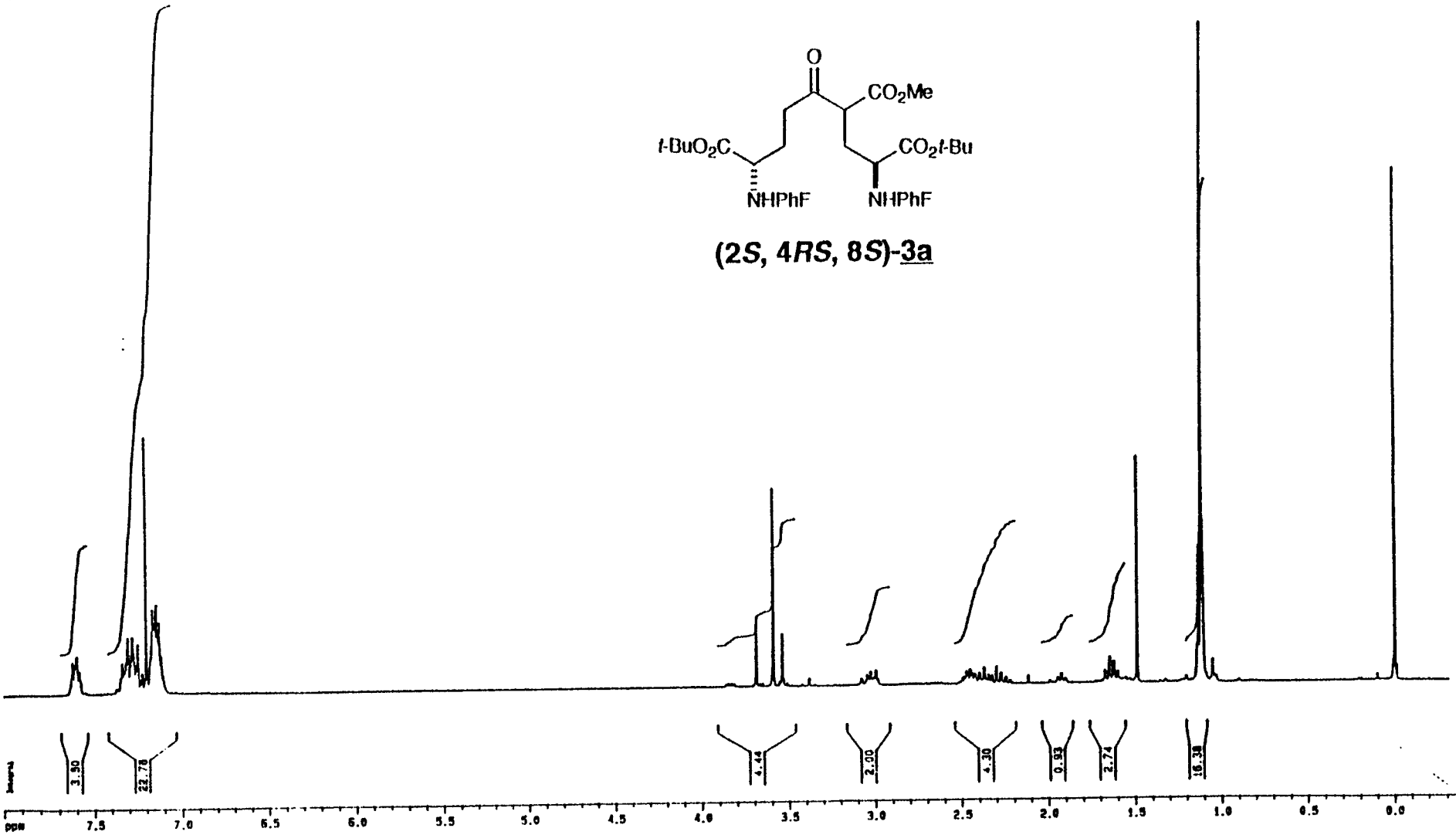
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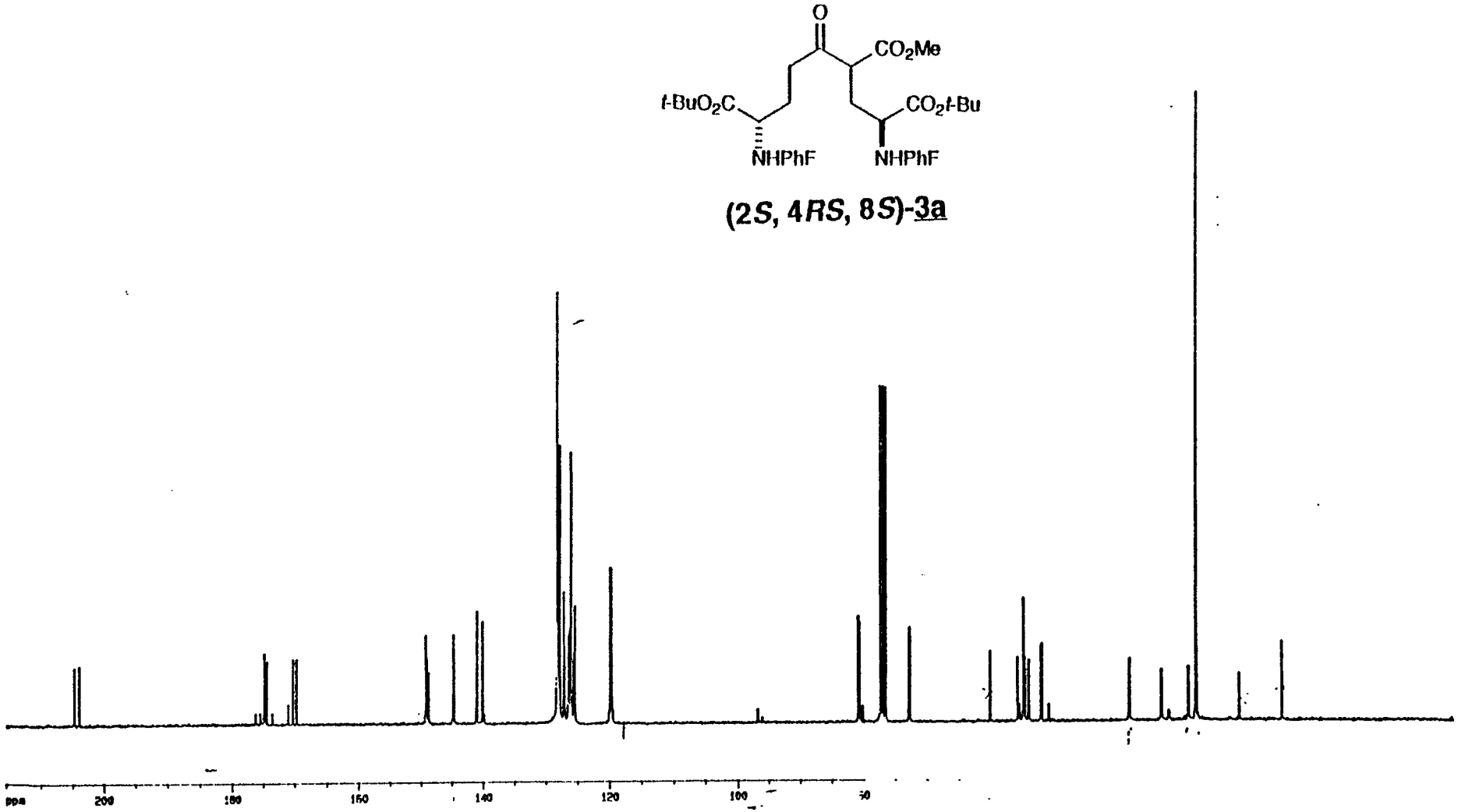
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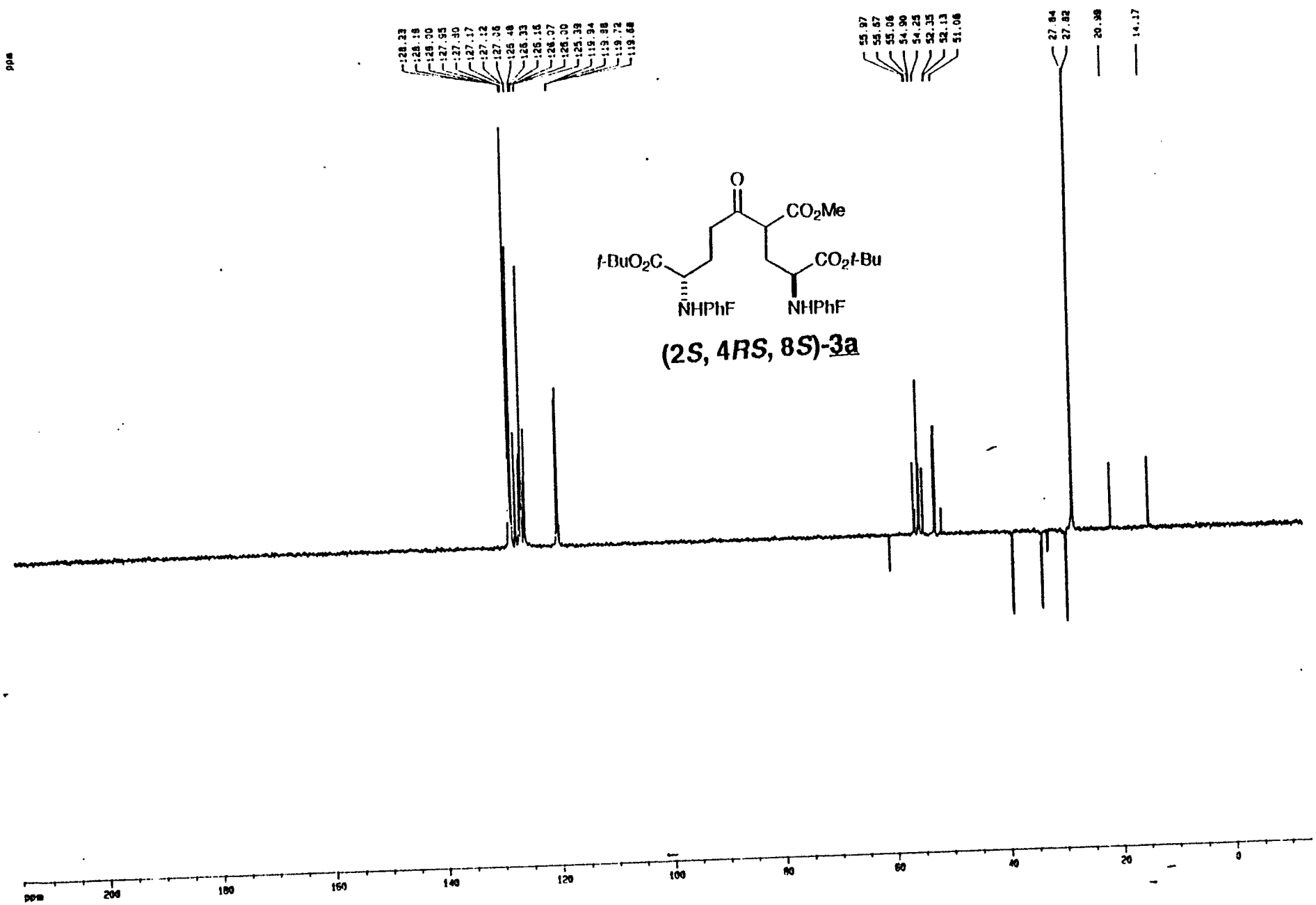
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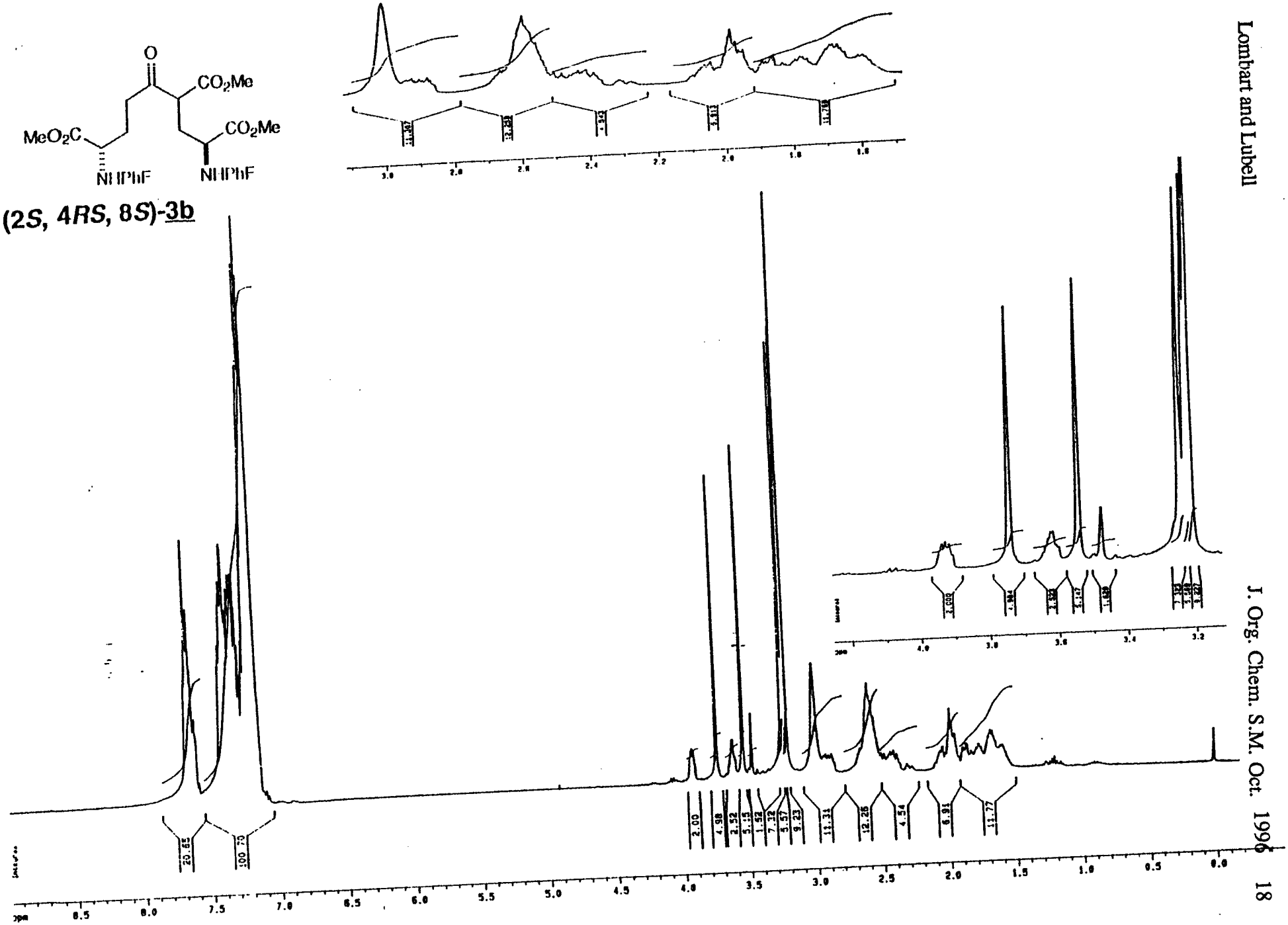

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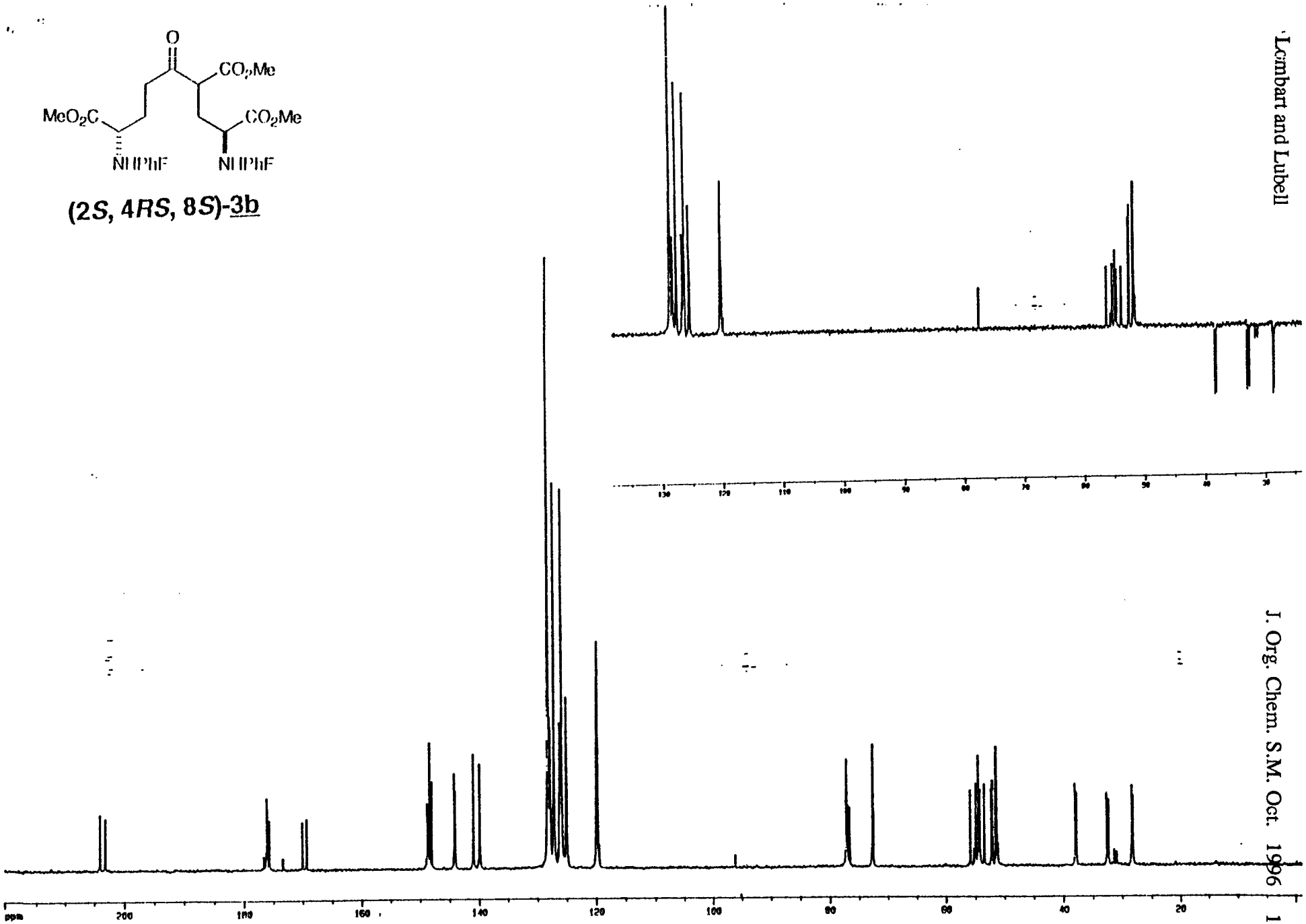

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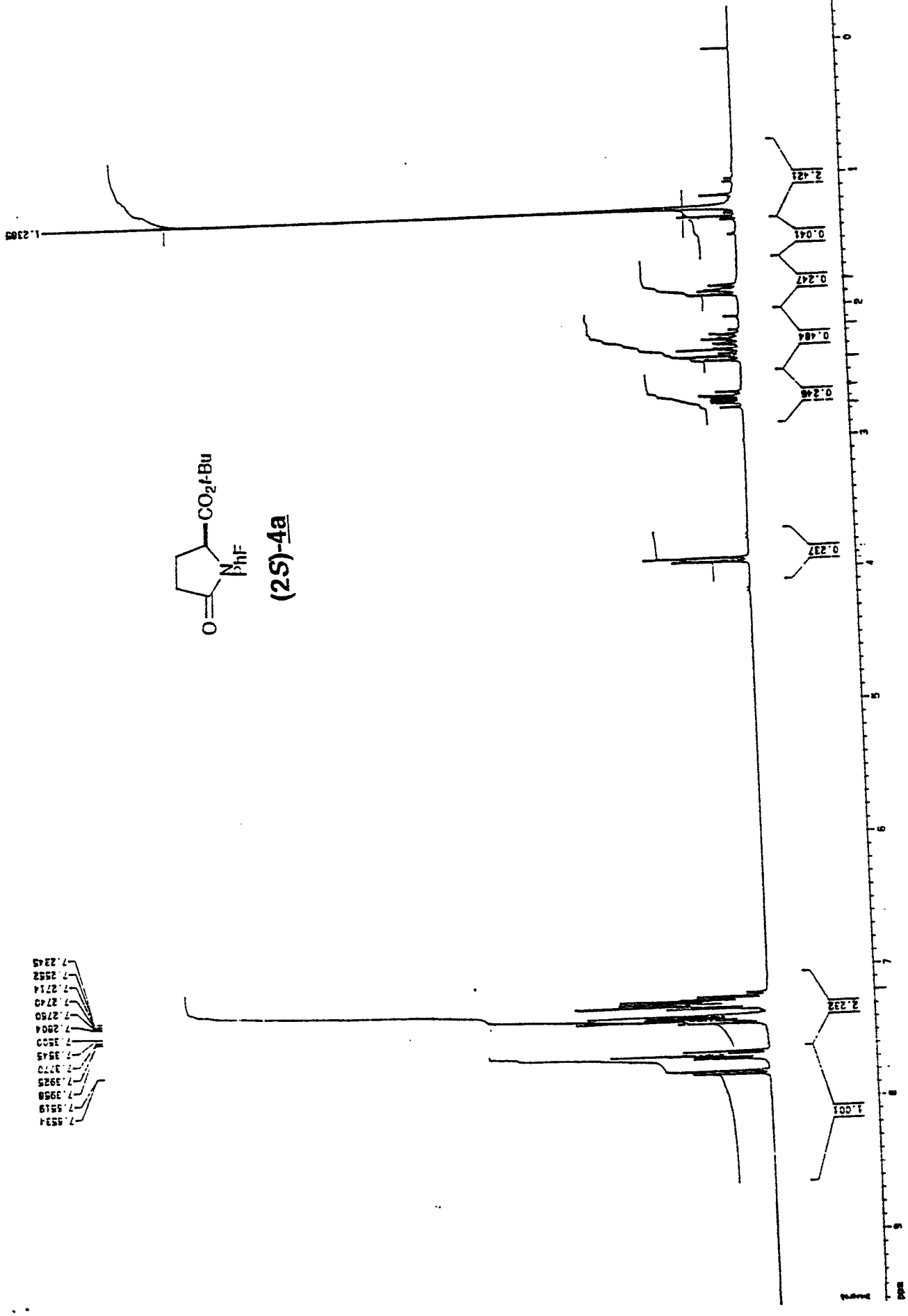

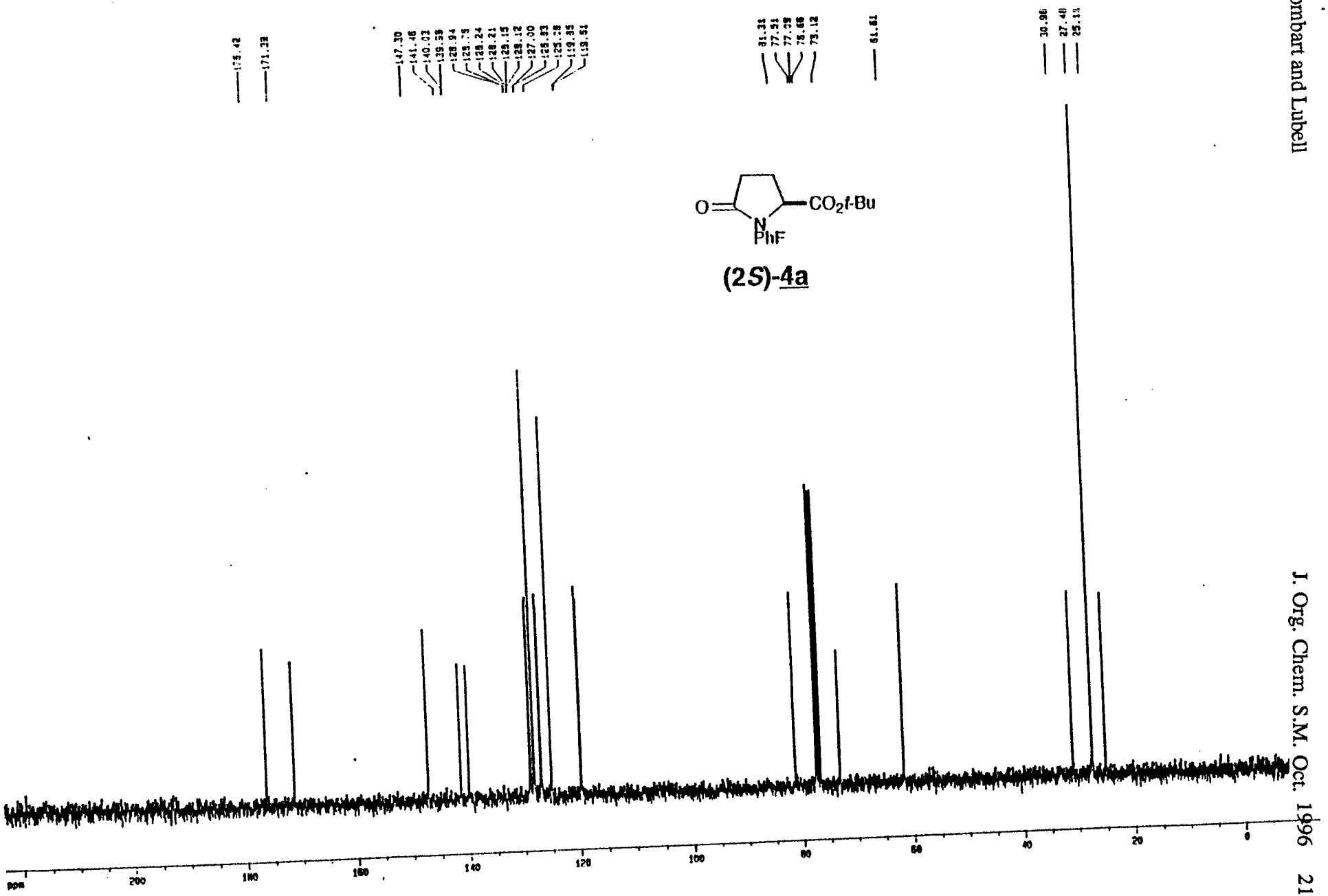

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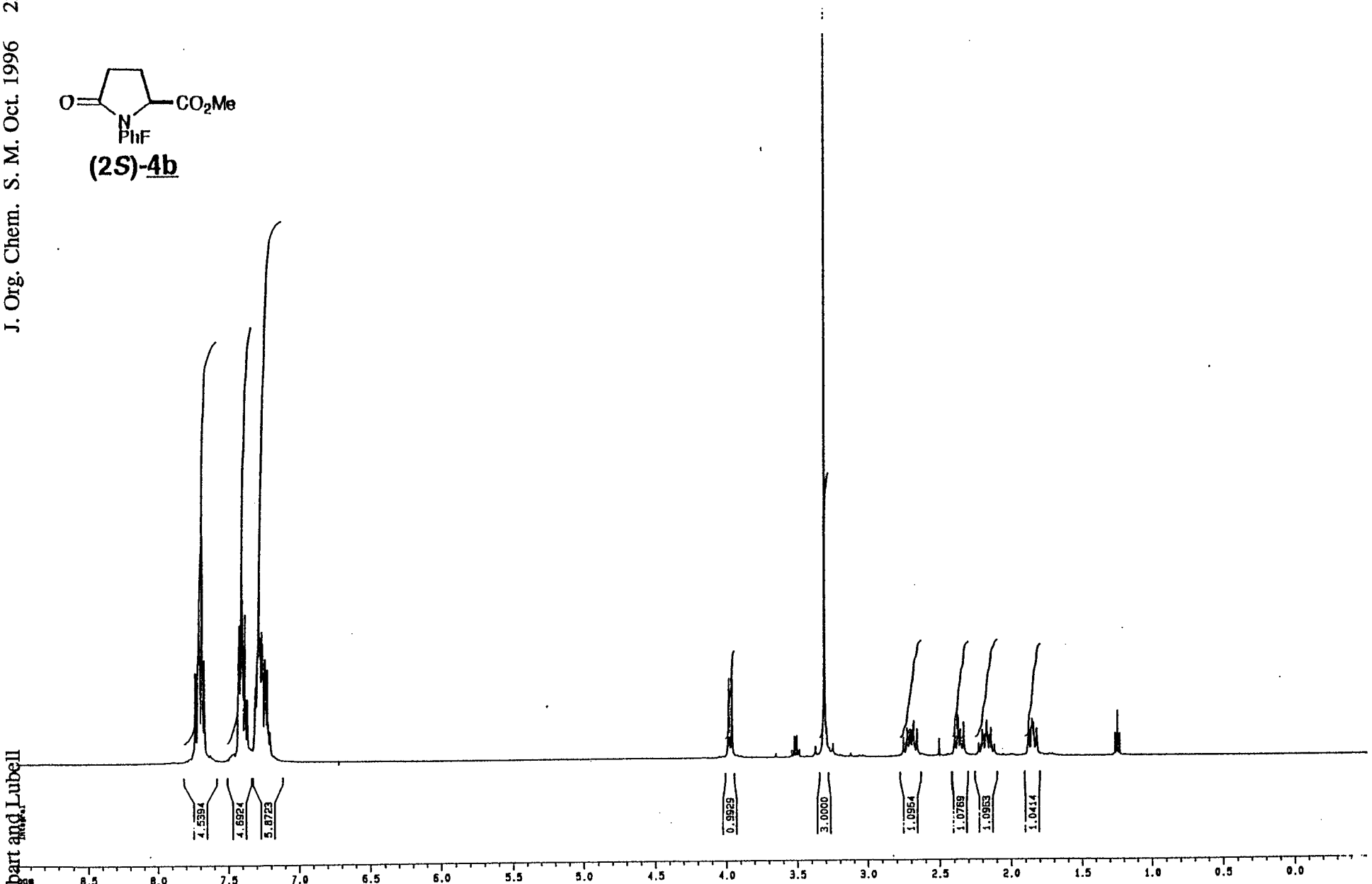
(2*S*)-4b



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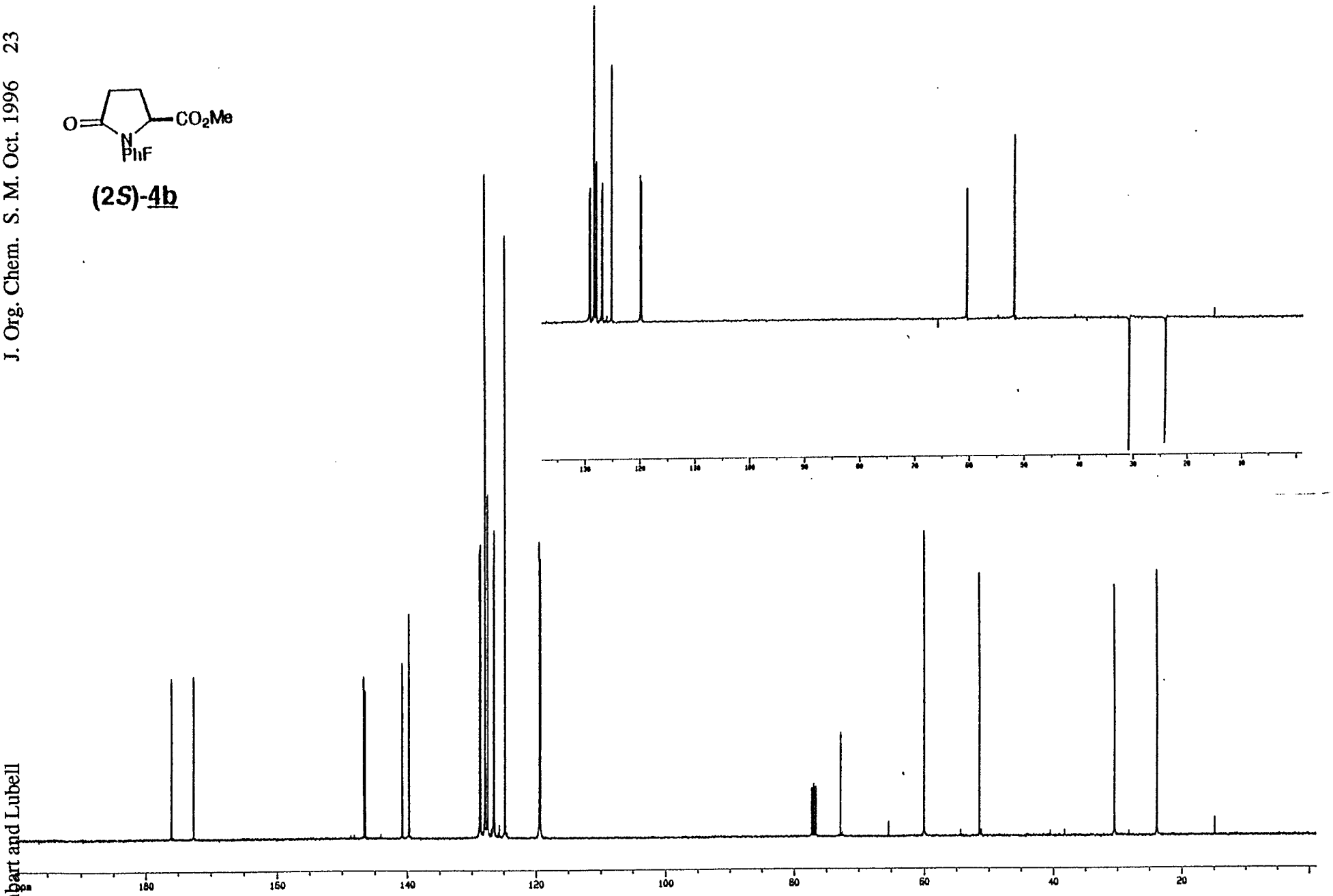

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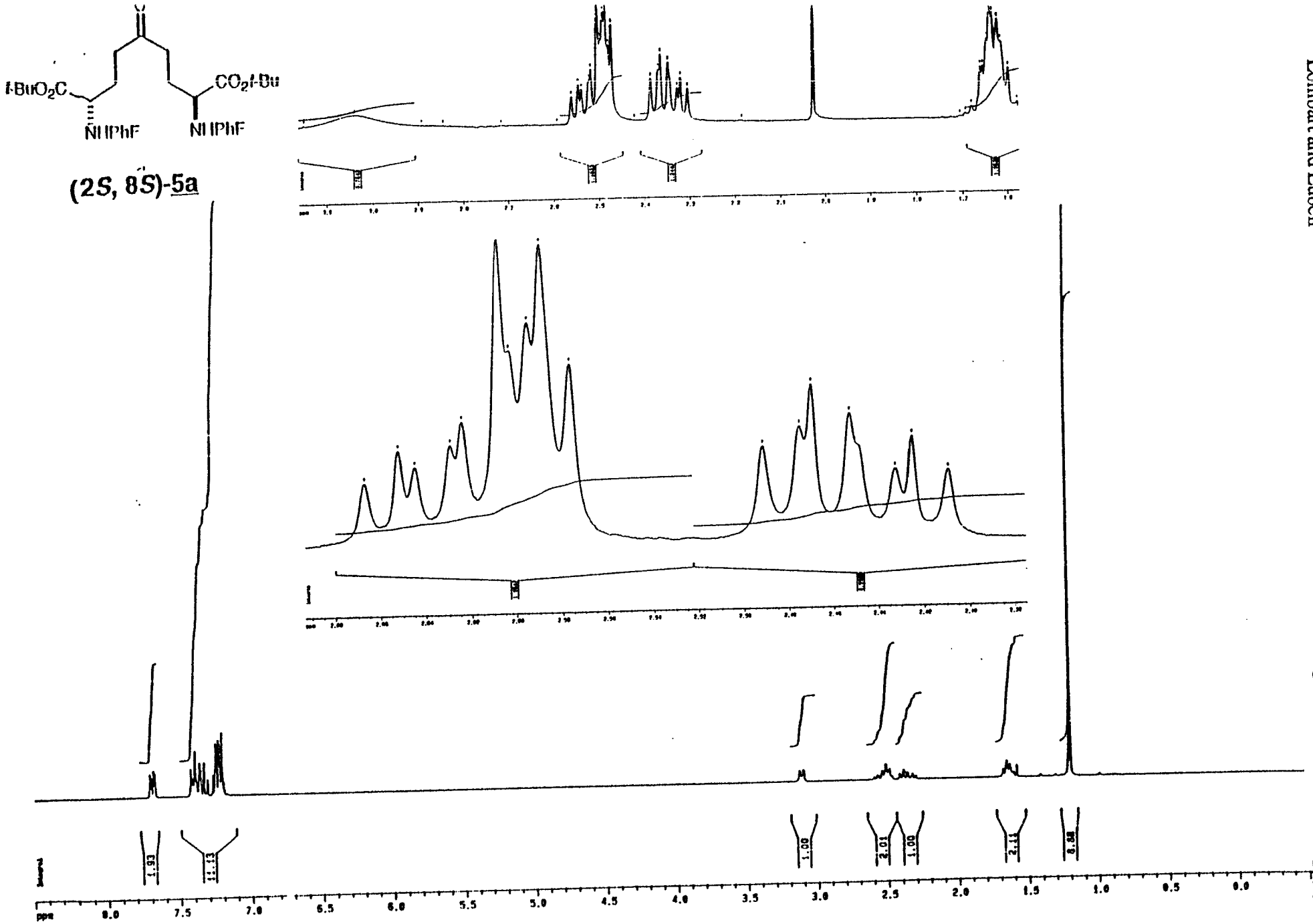

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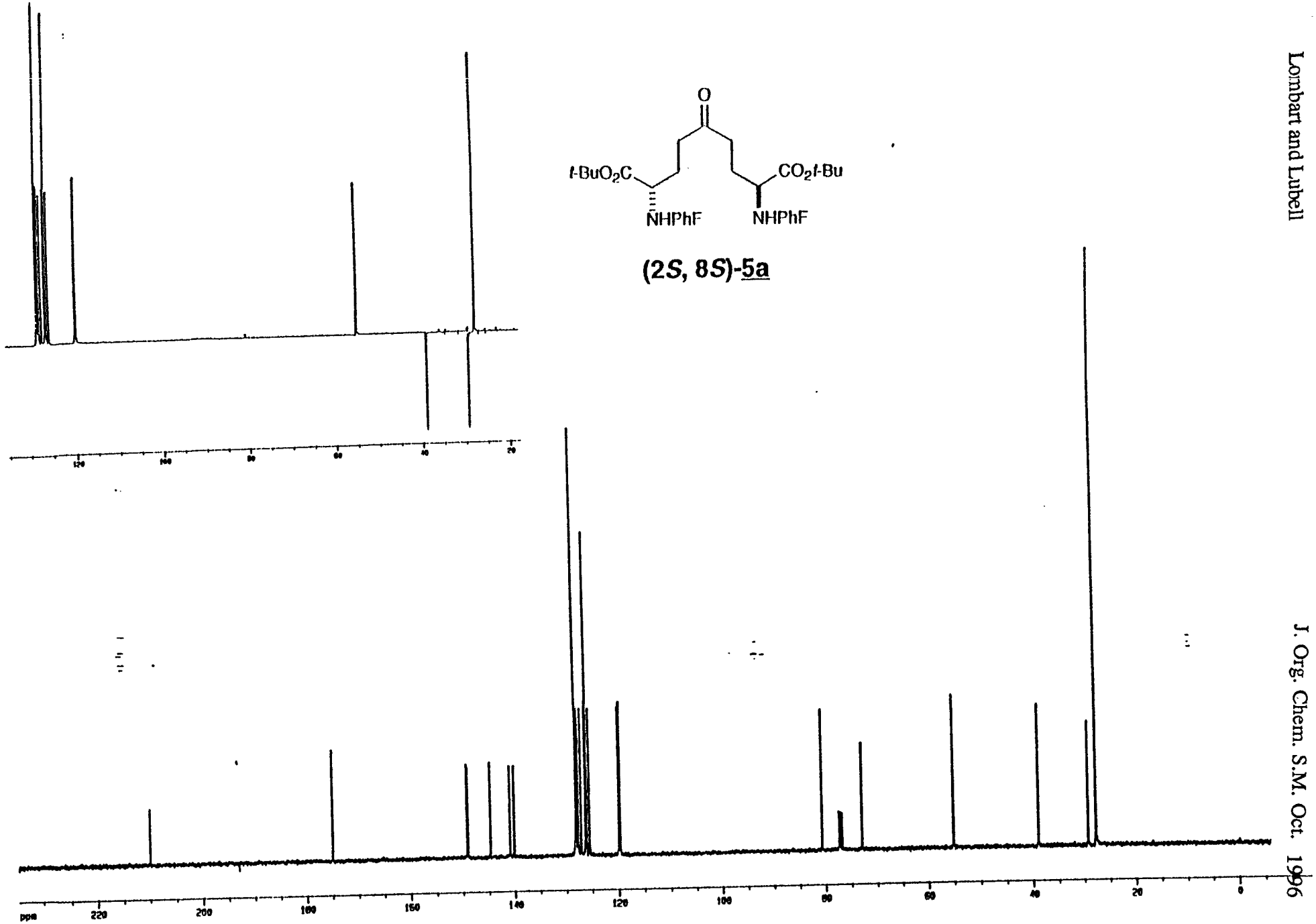

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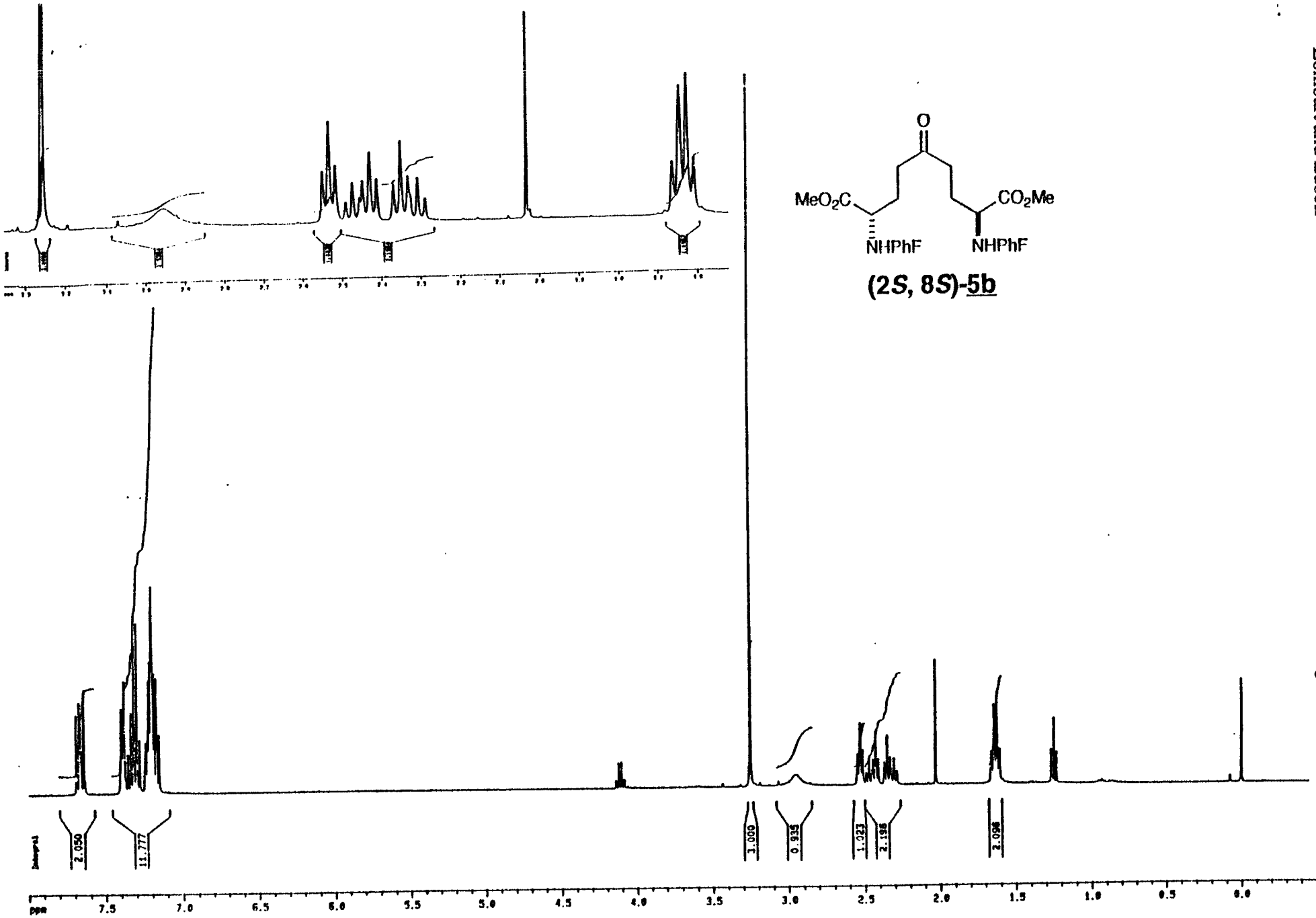

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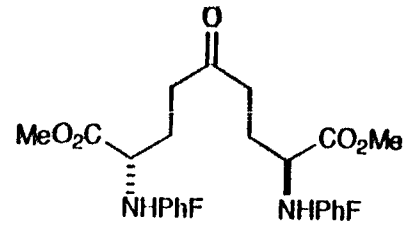

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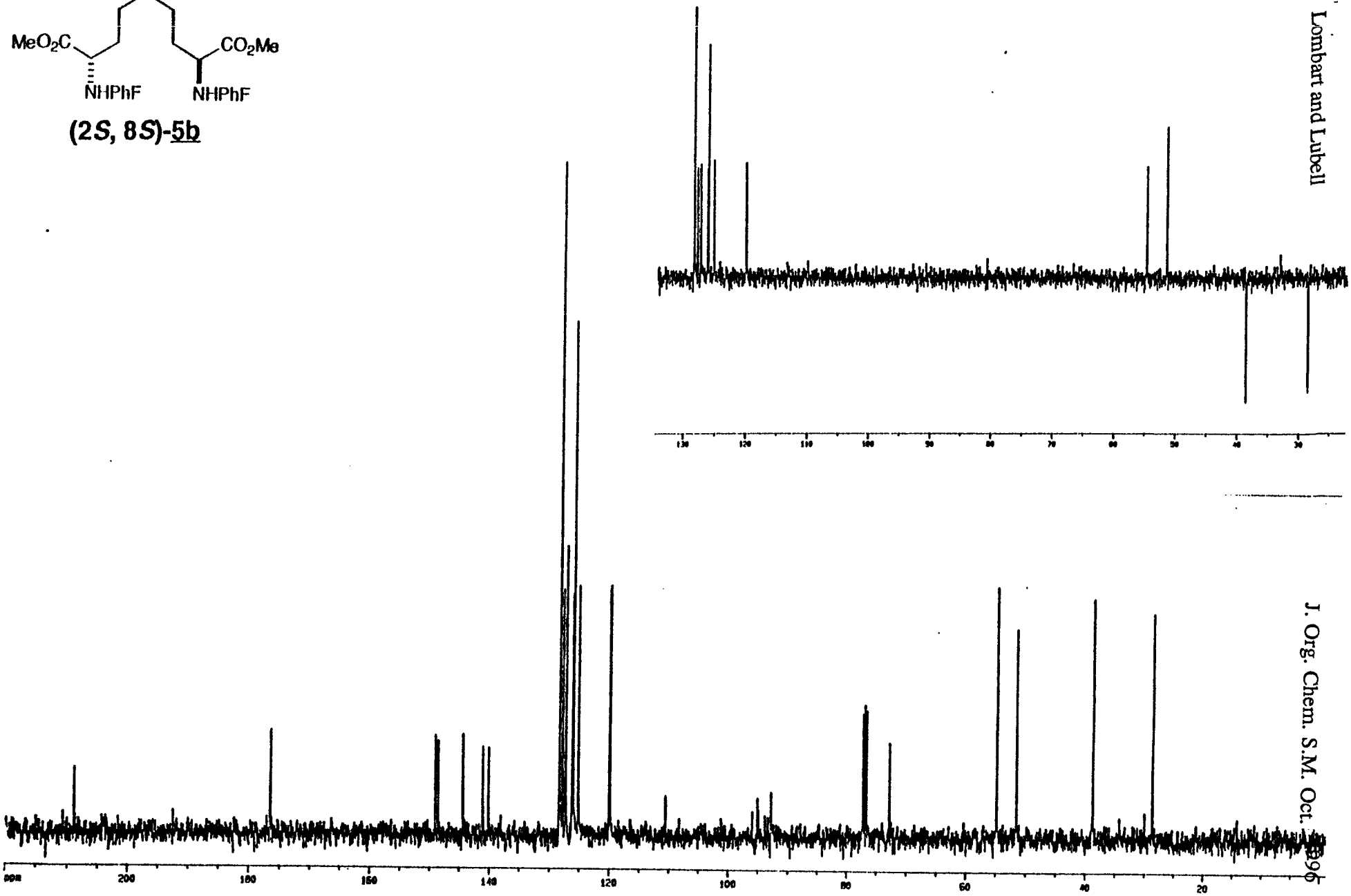

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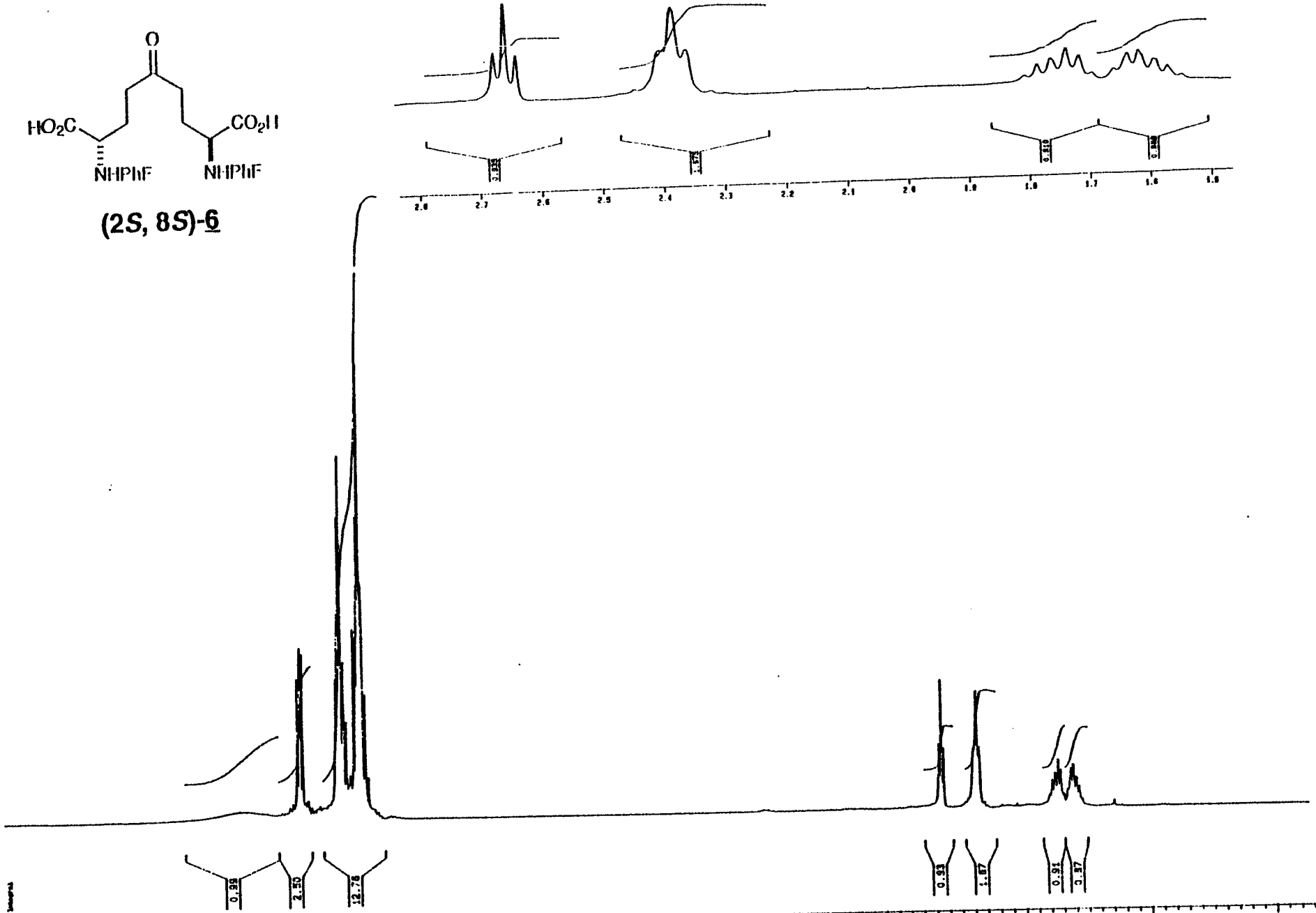

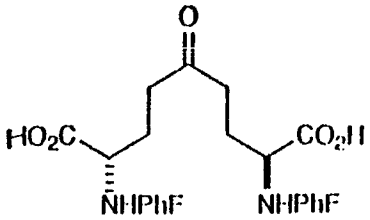

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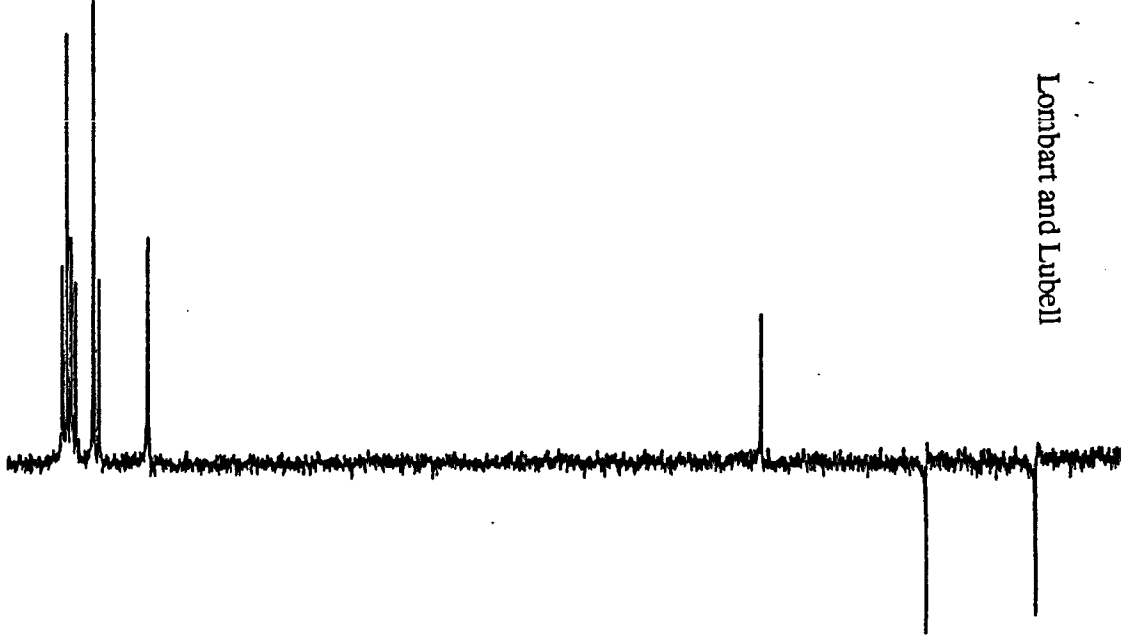

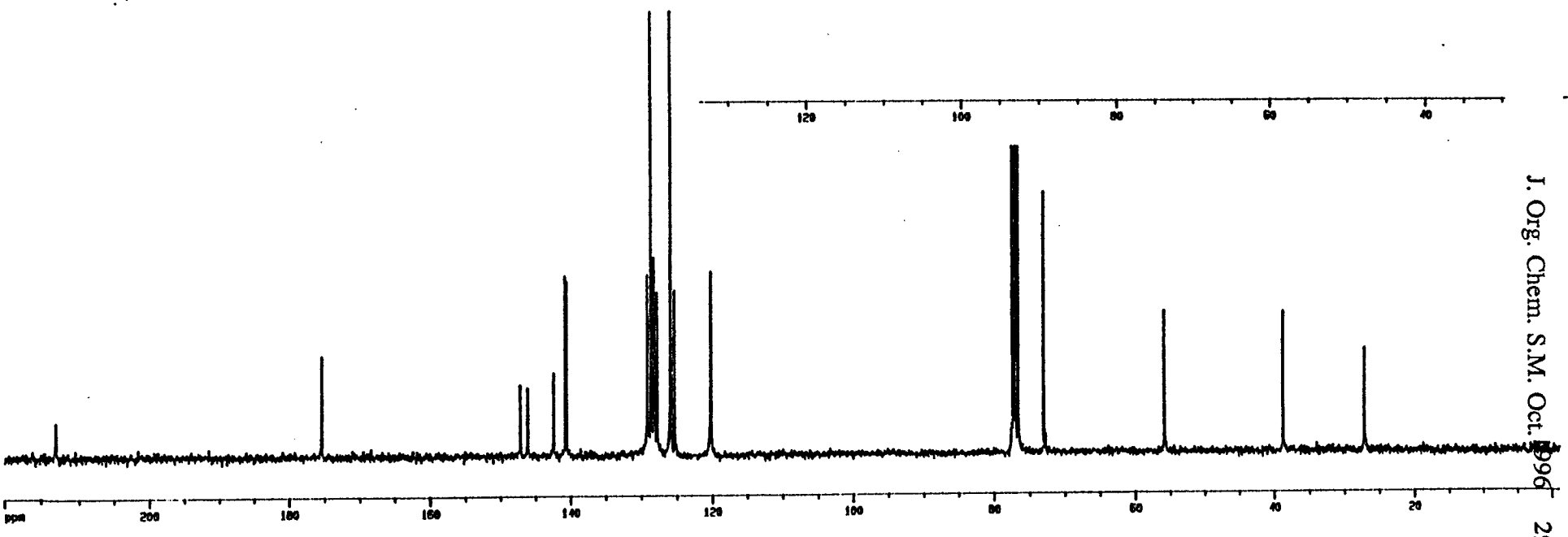

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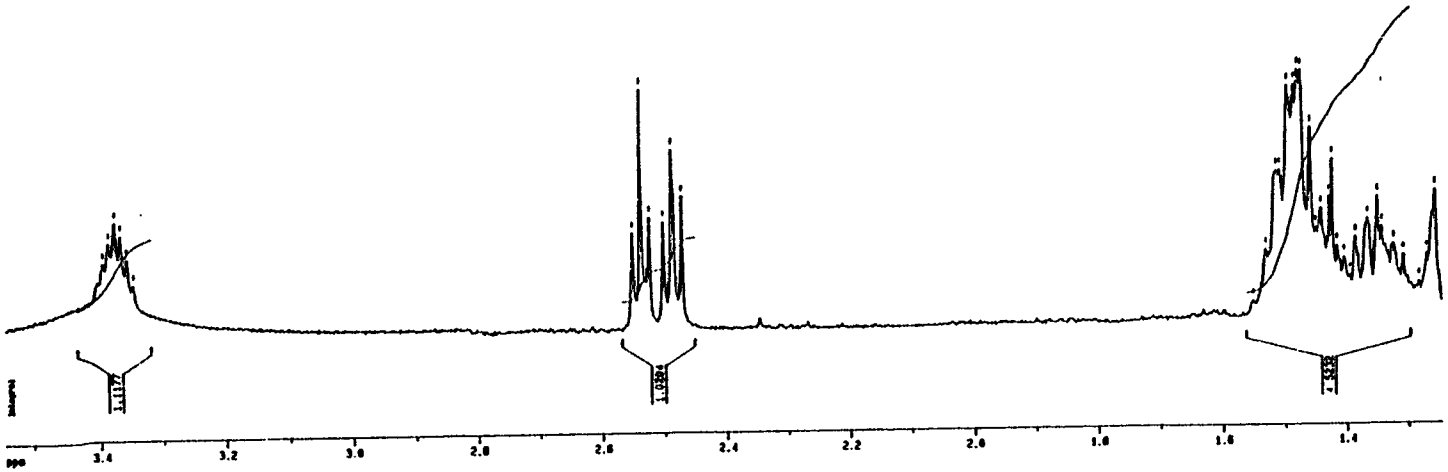

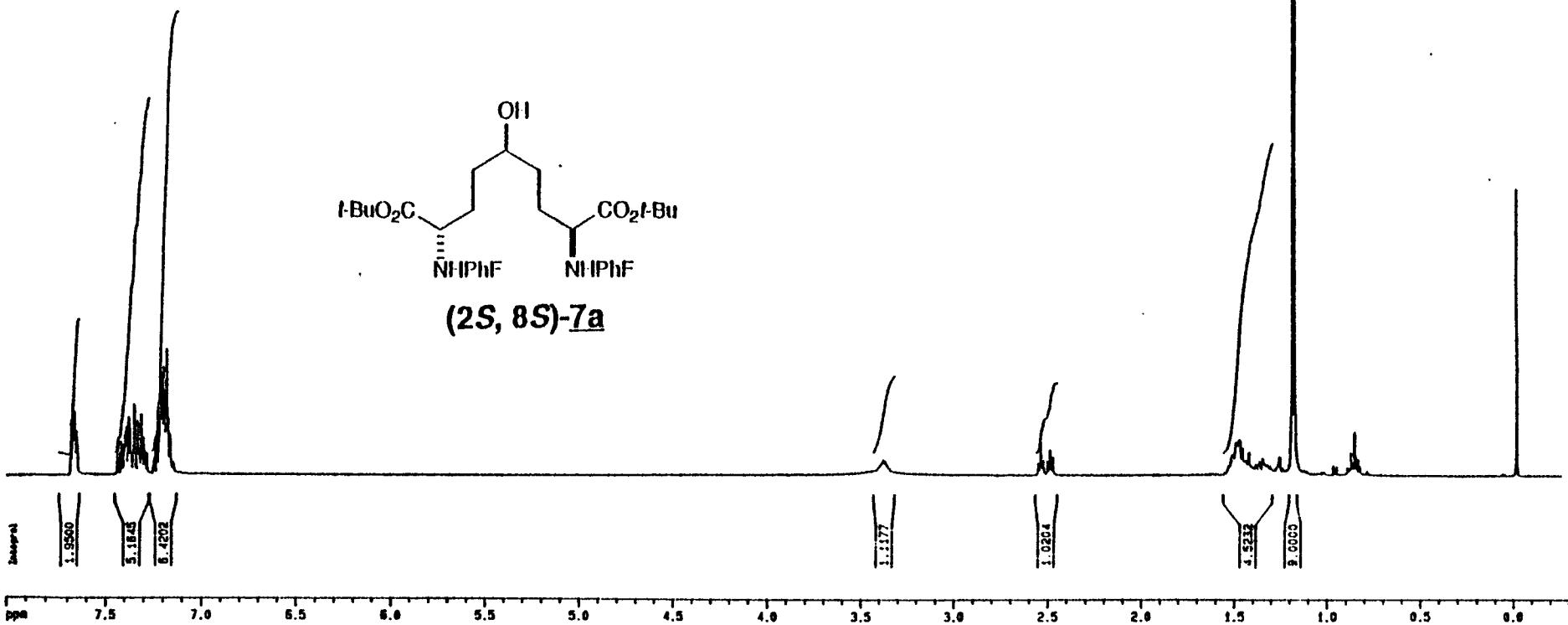

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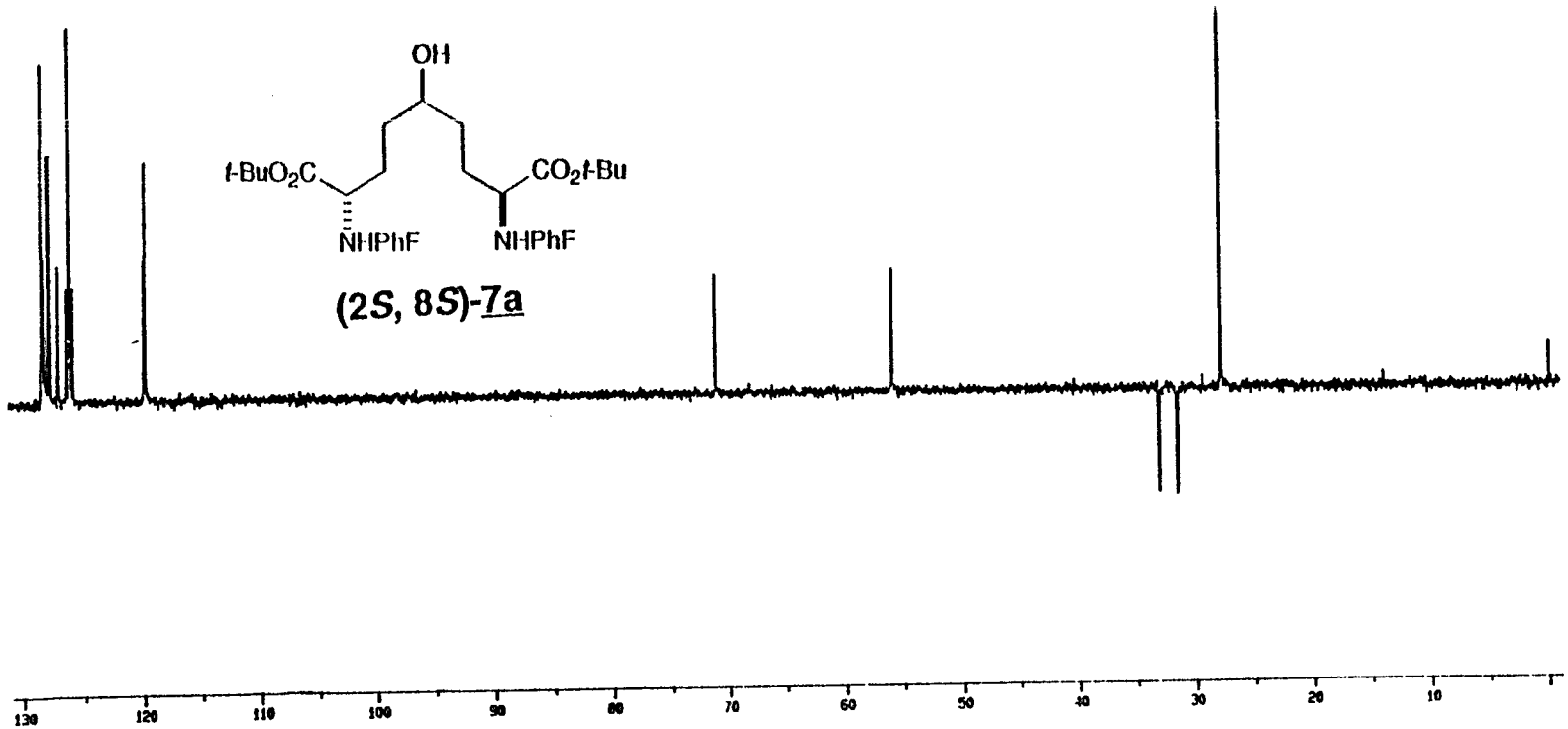

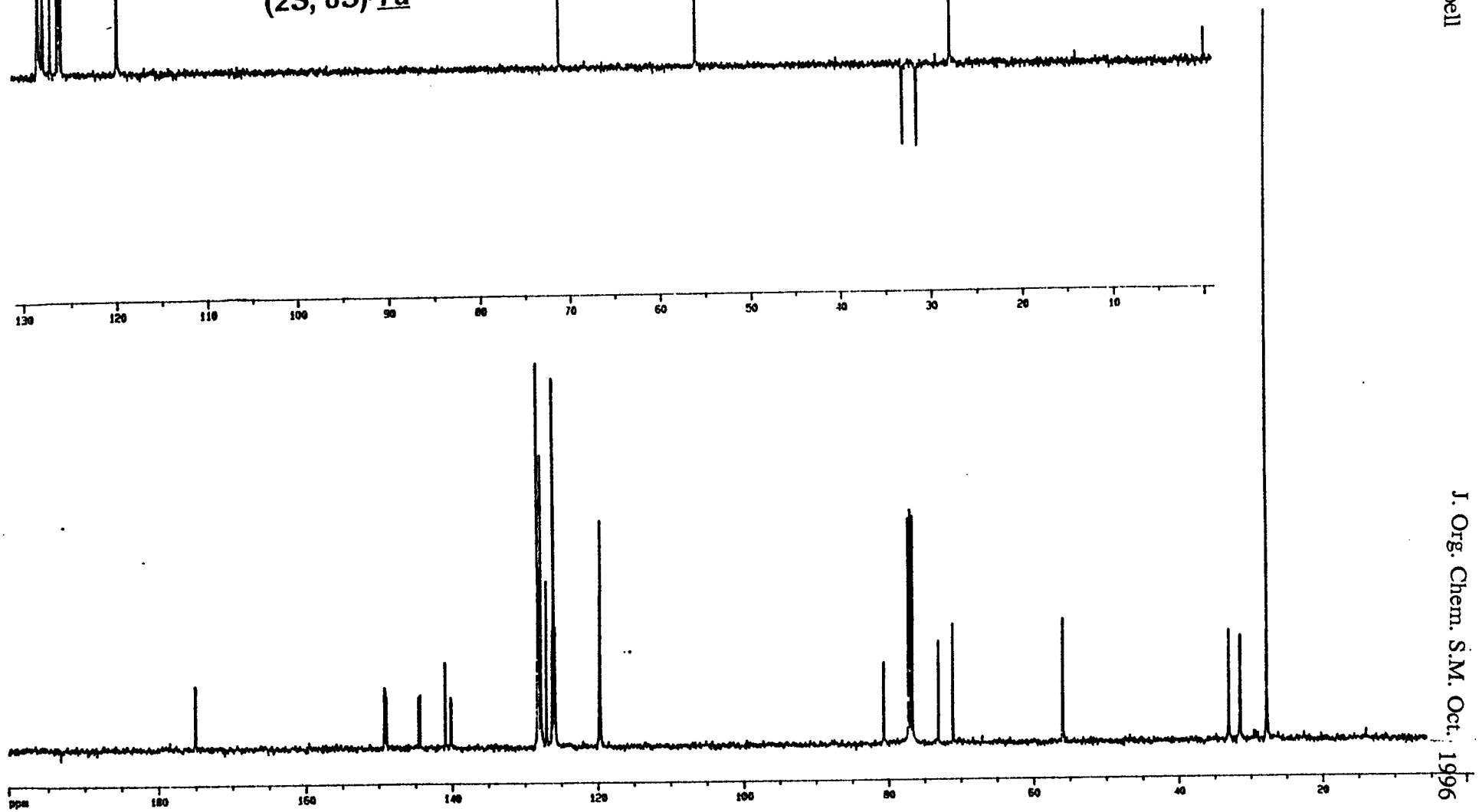

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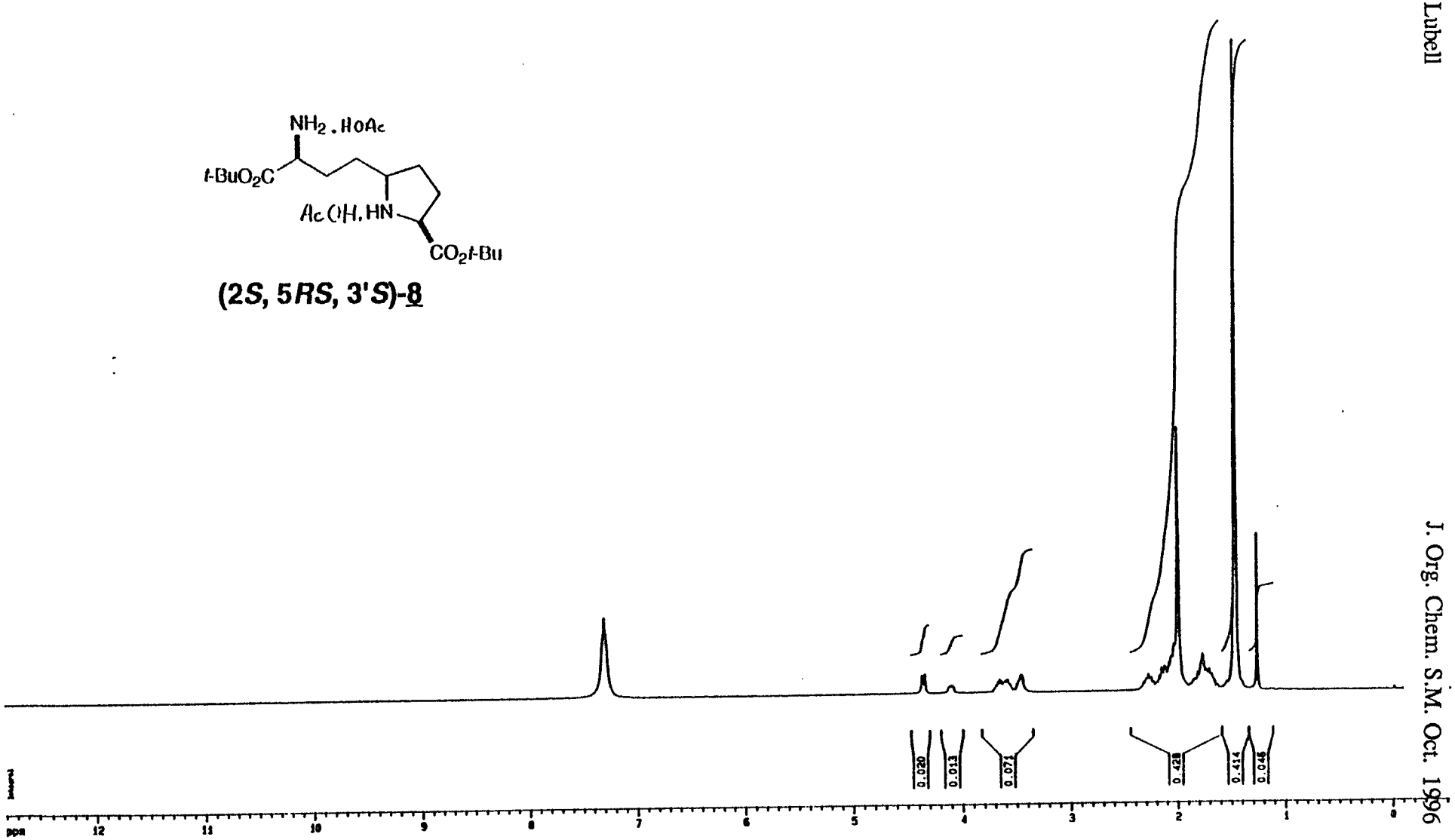
(2*S*, 5*RS*, 3'*S*)-8



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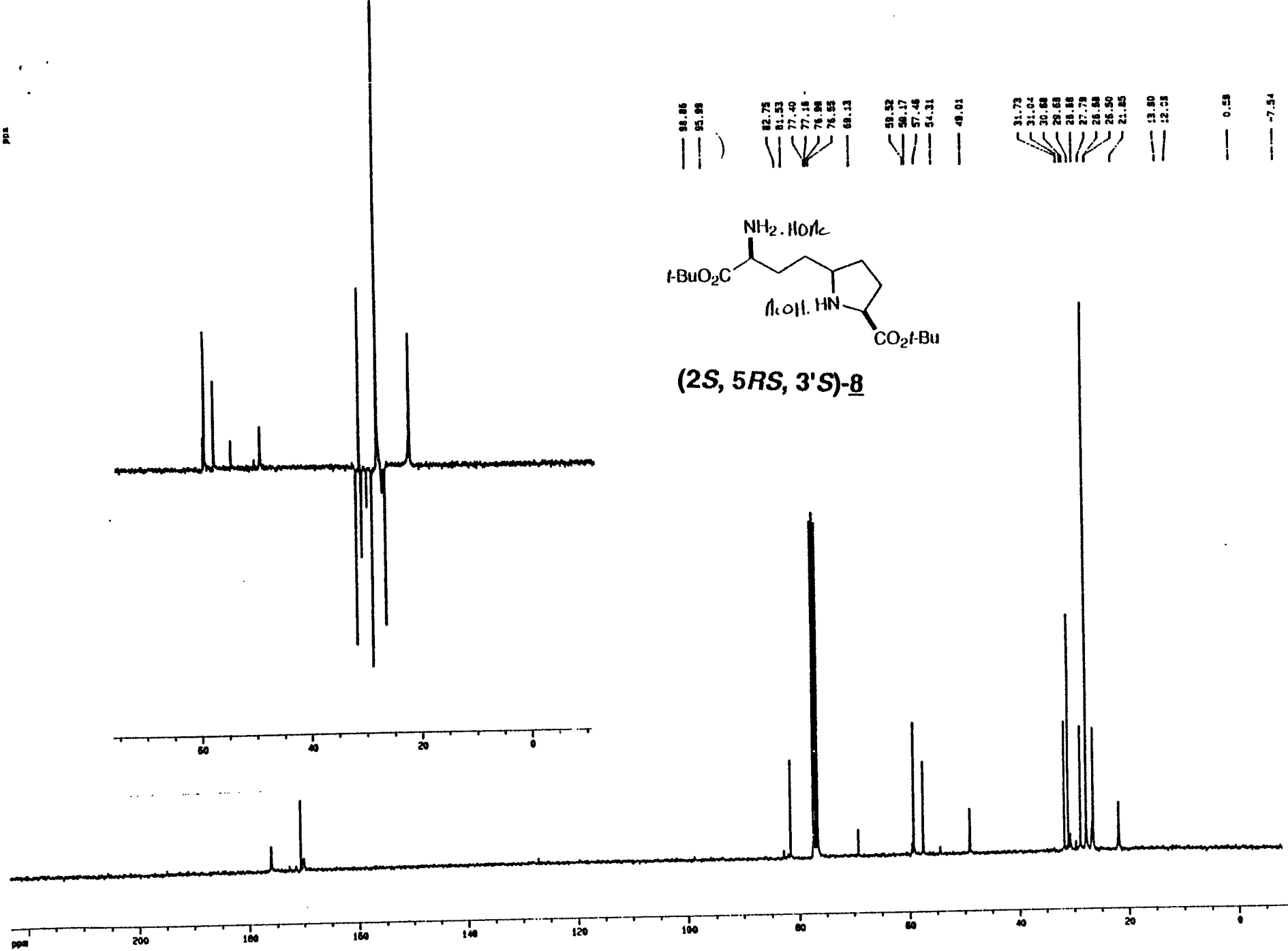

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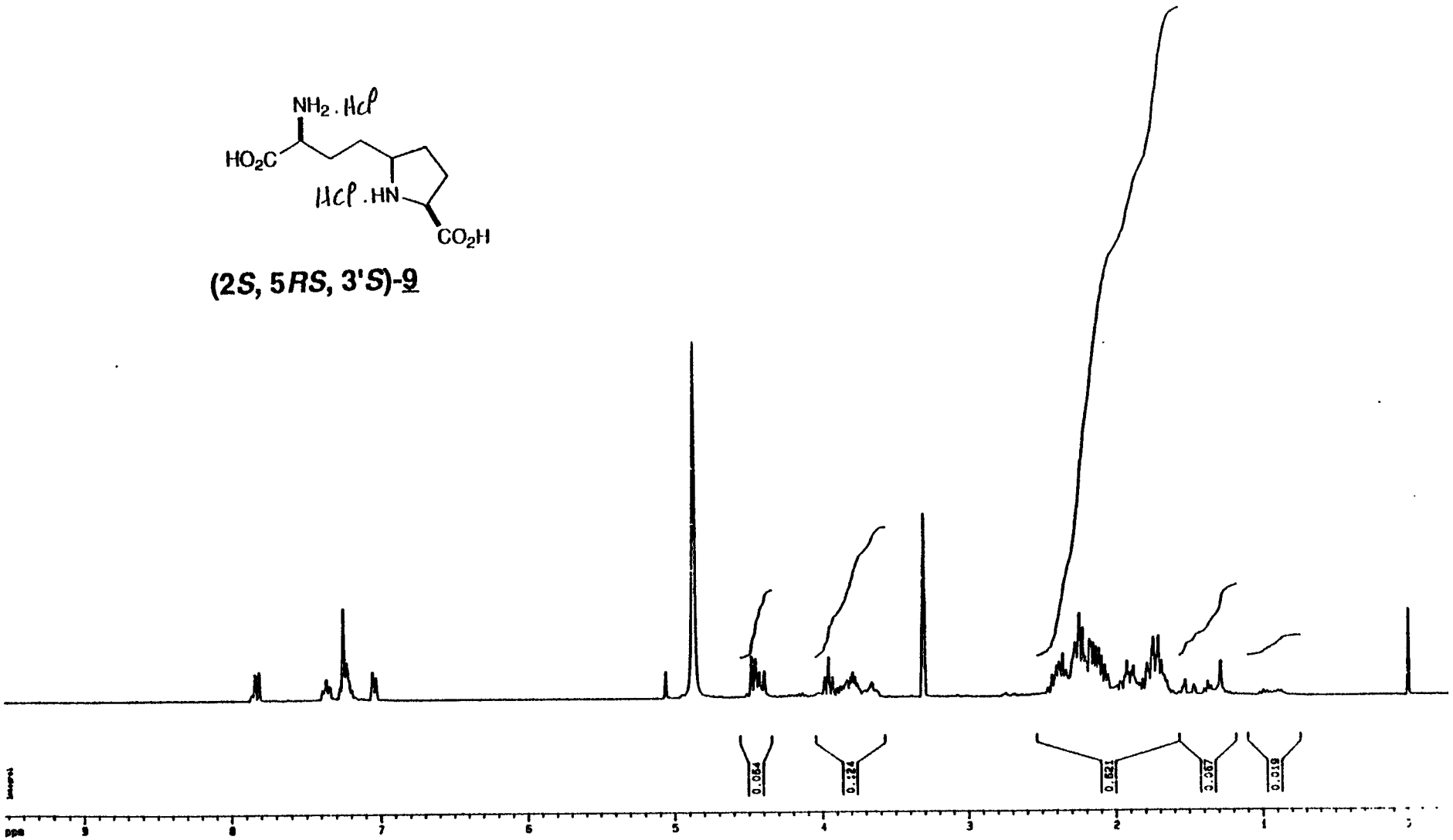
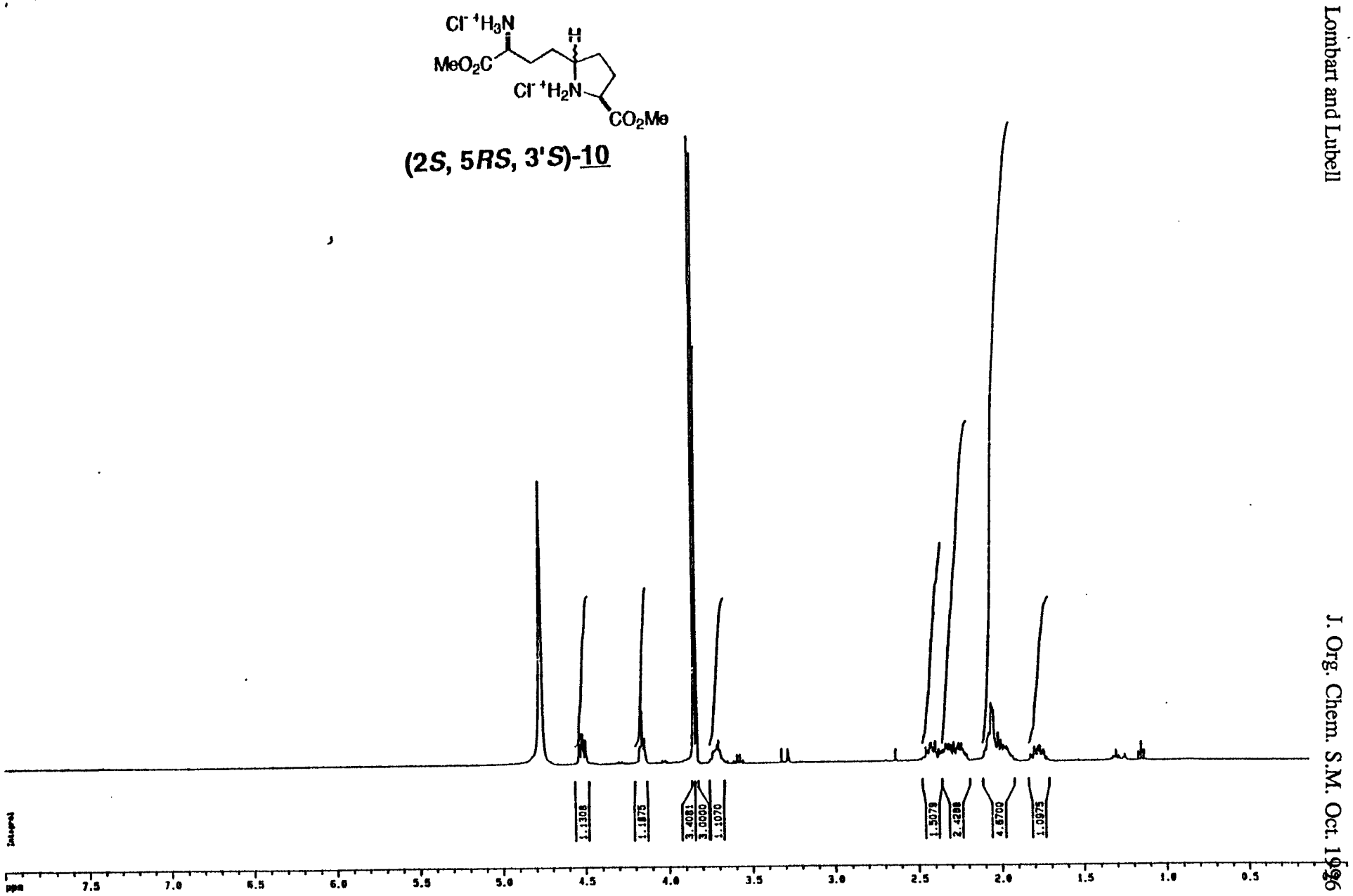
(2*S*, 5*RS*, 3'*S*)-9





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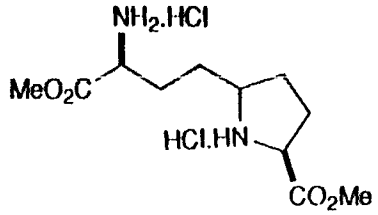

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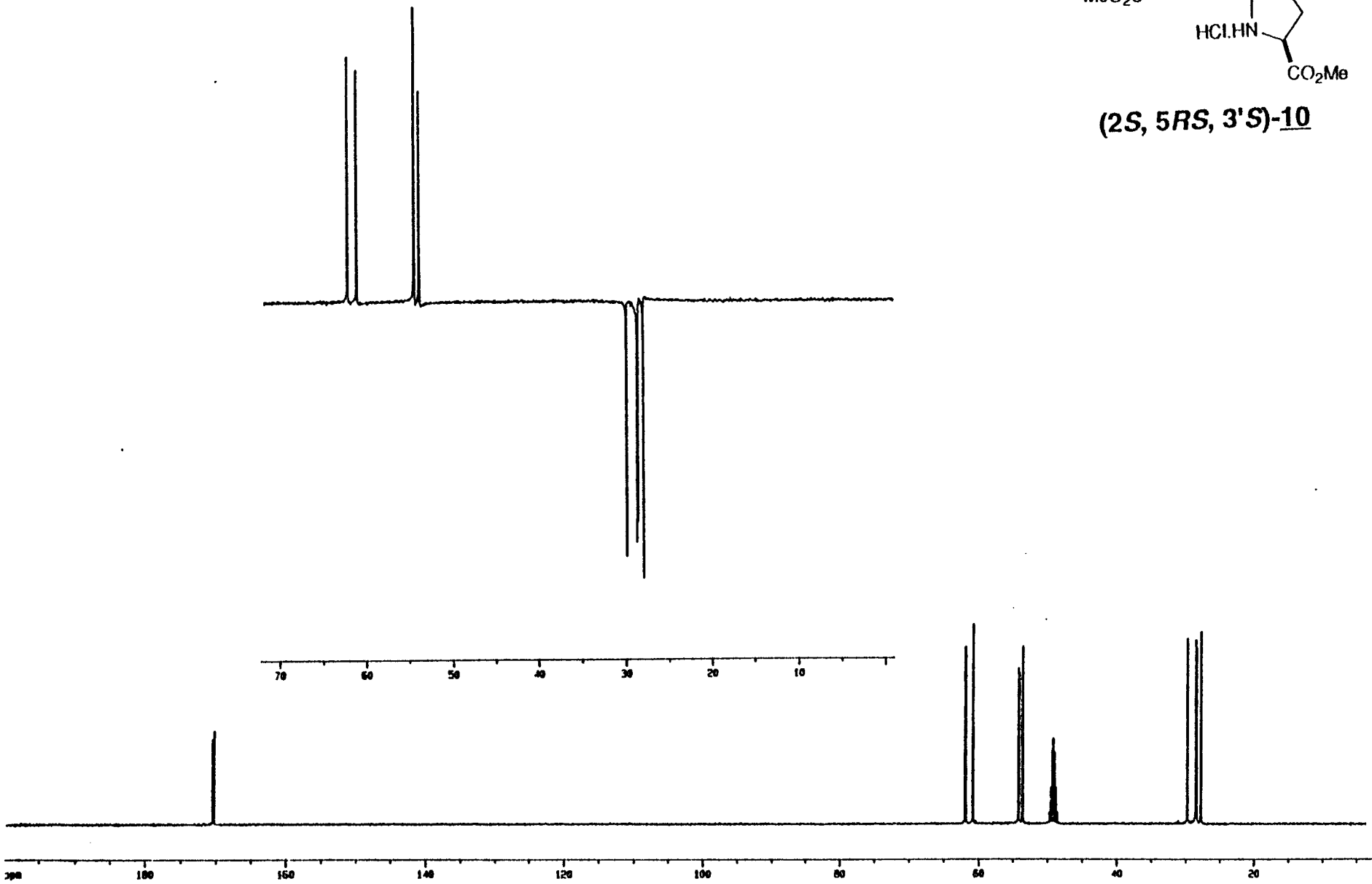

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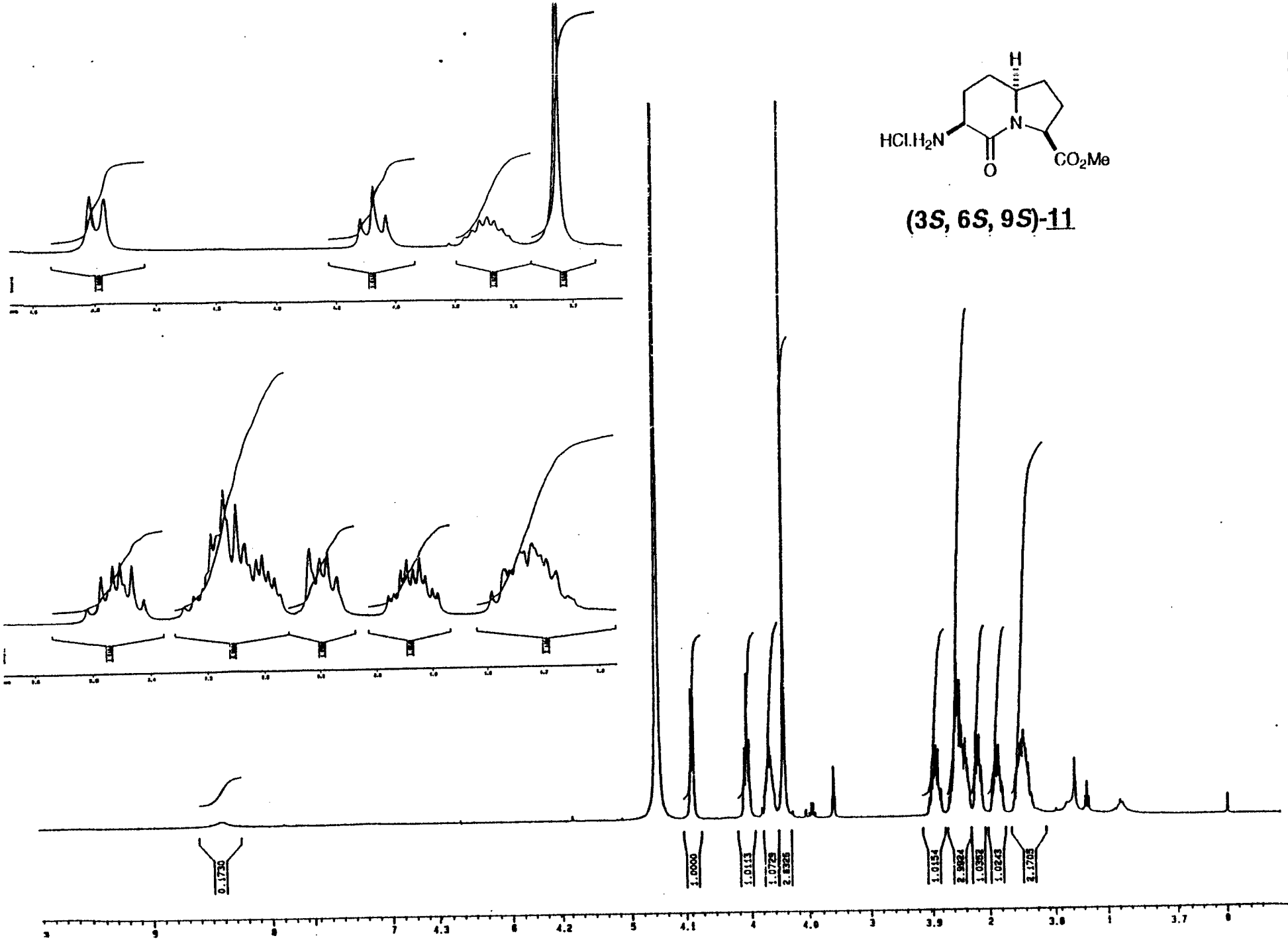

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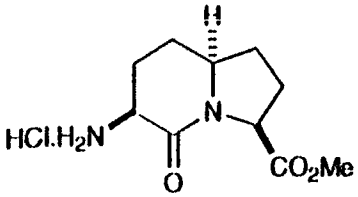

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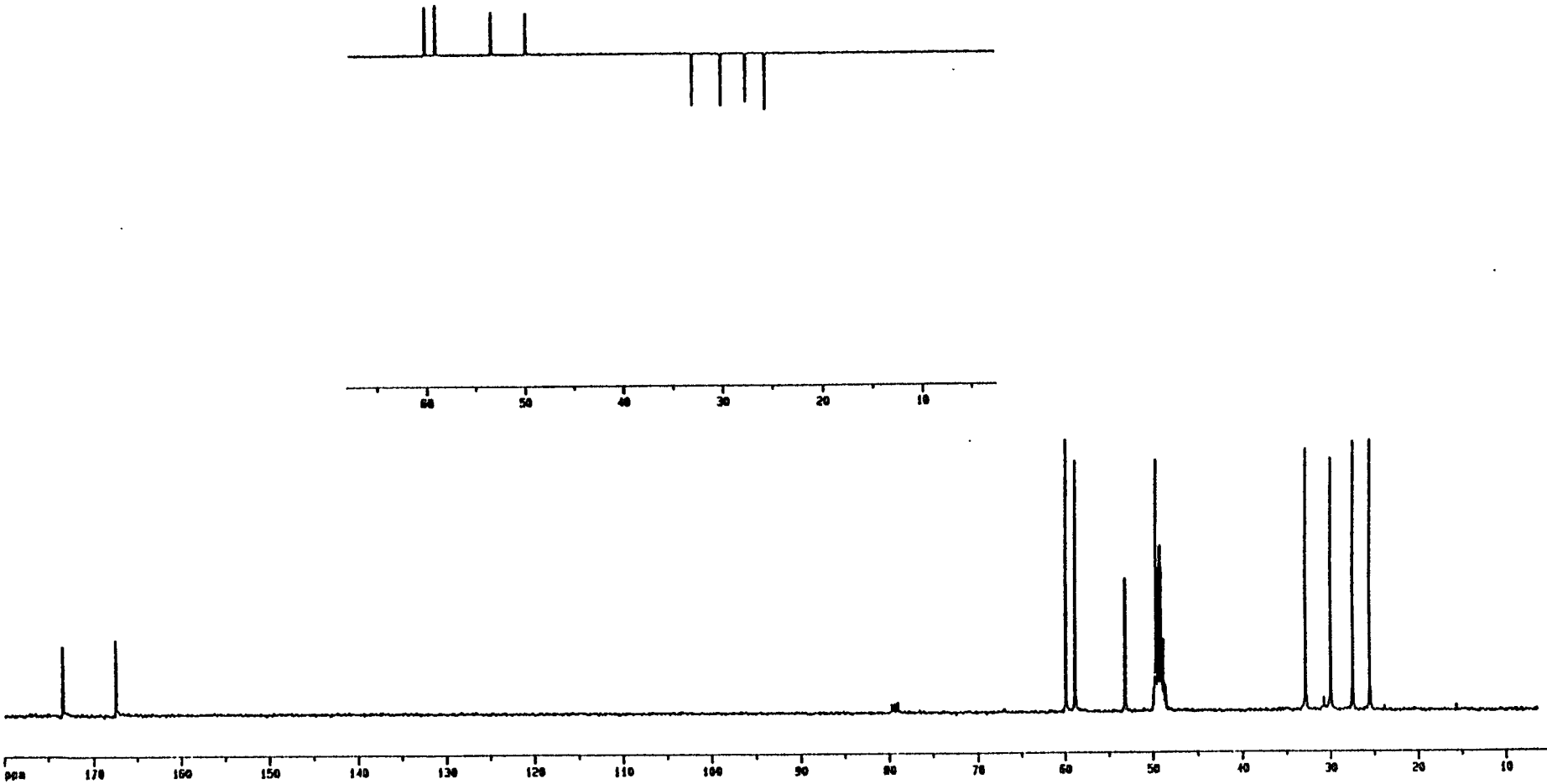

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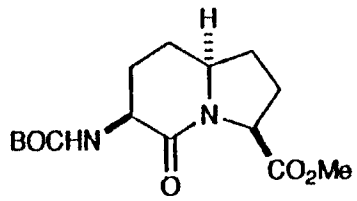

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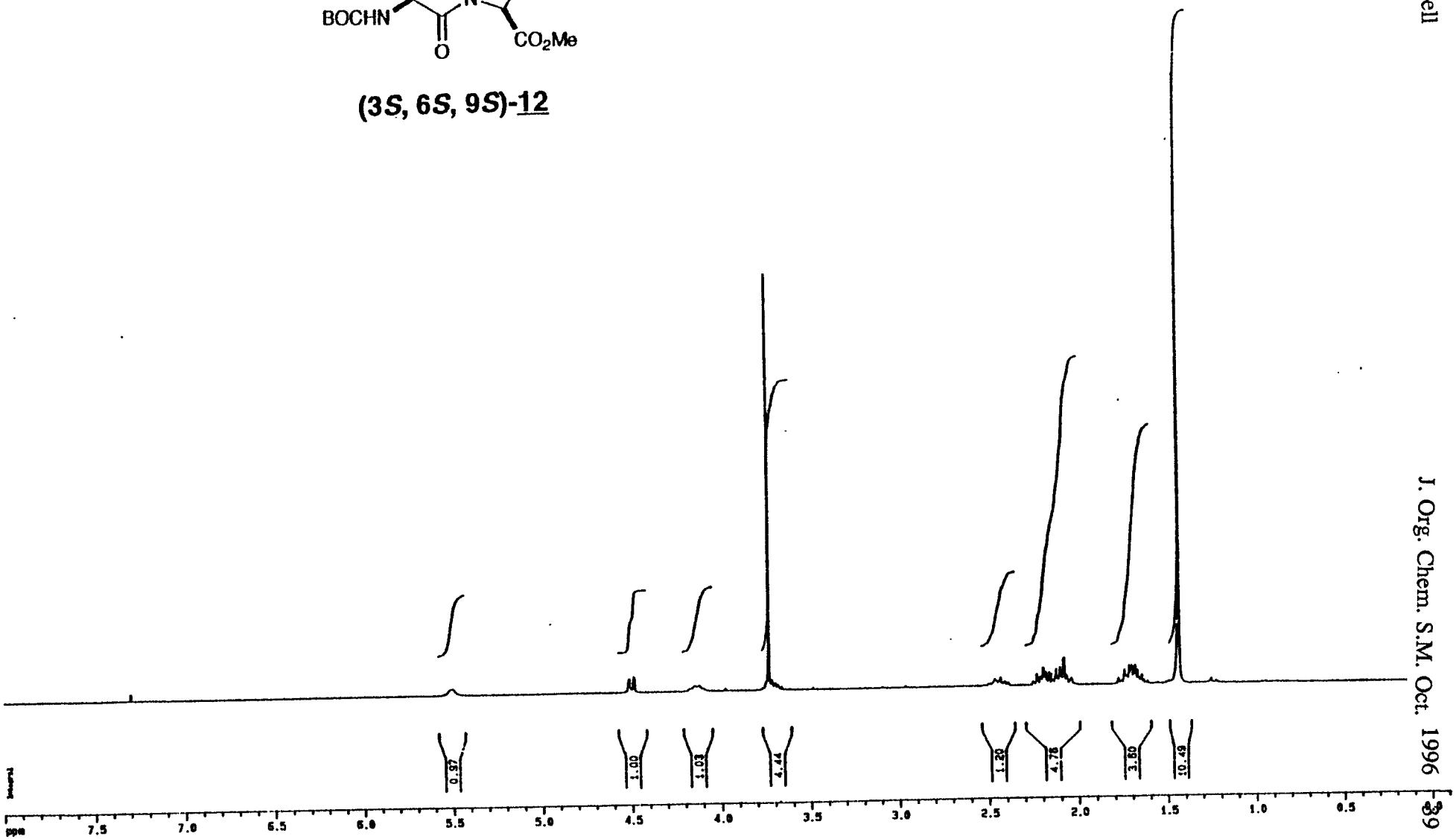

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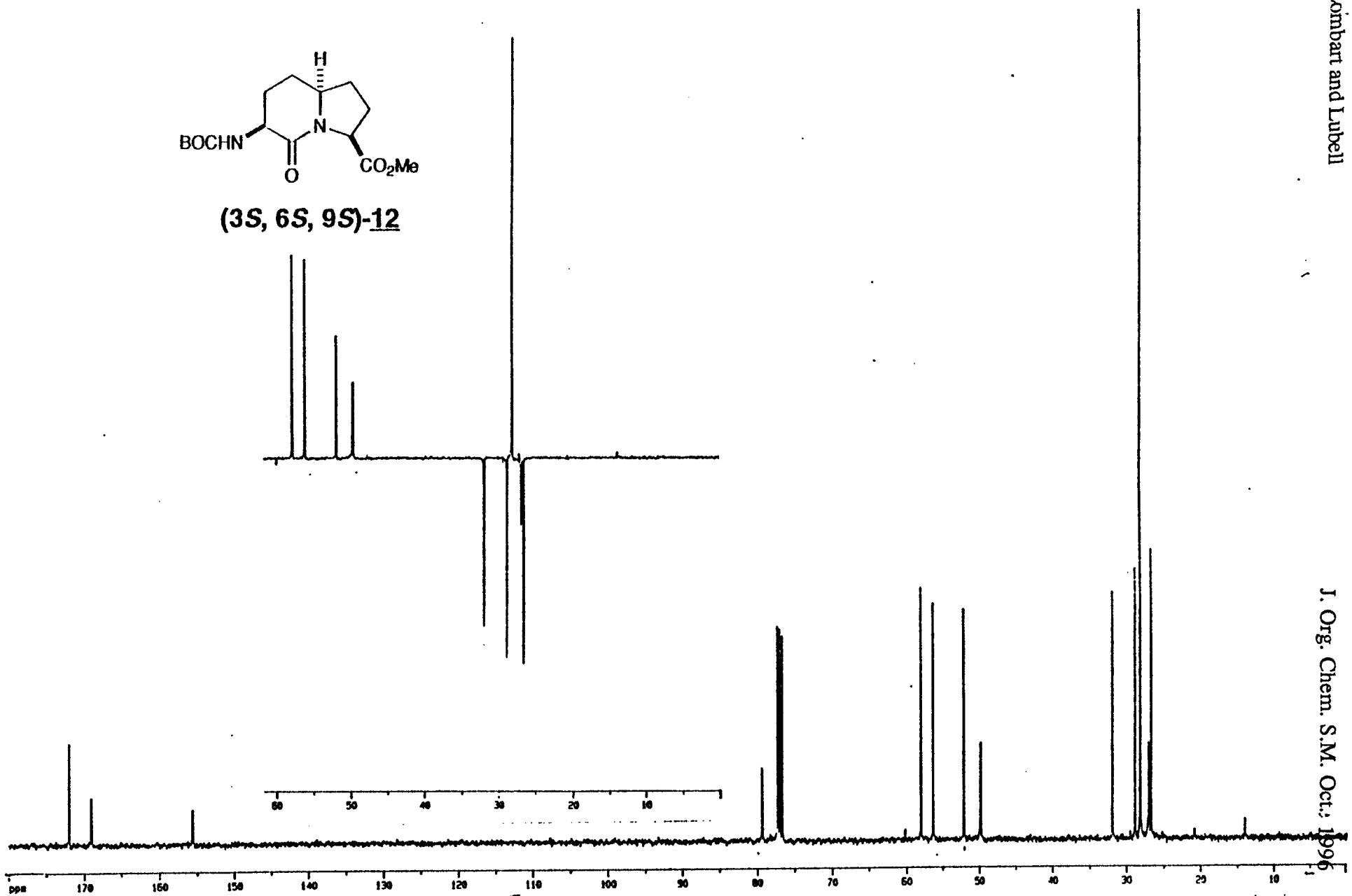
(3*S*, 6*S*, 9*S*)-12



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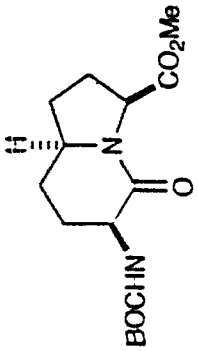

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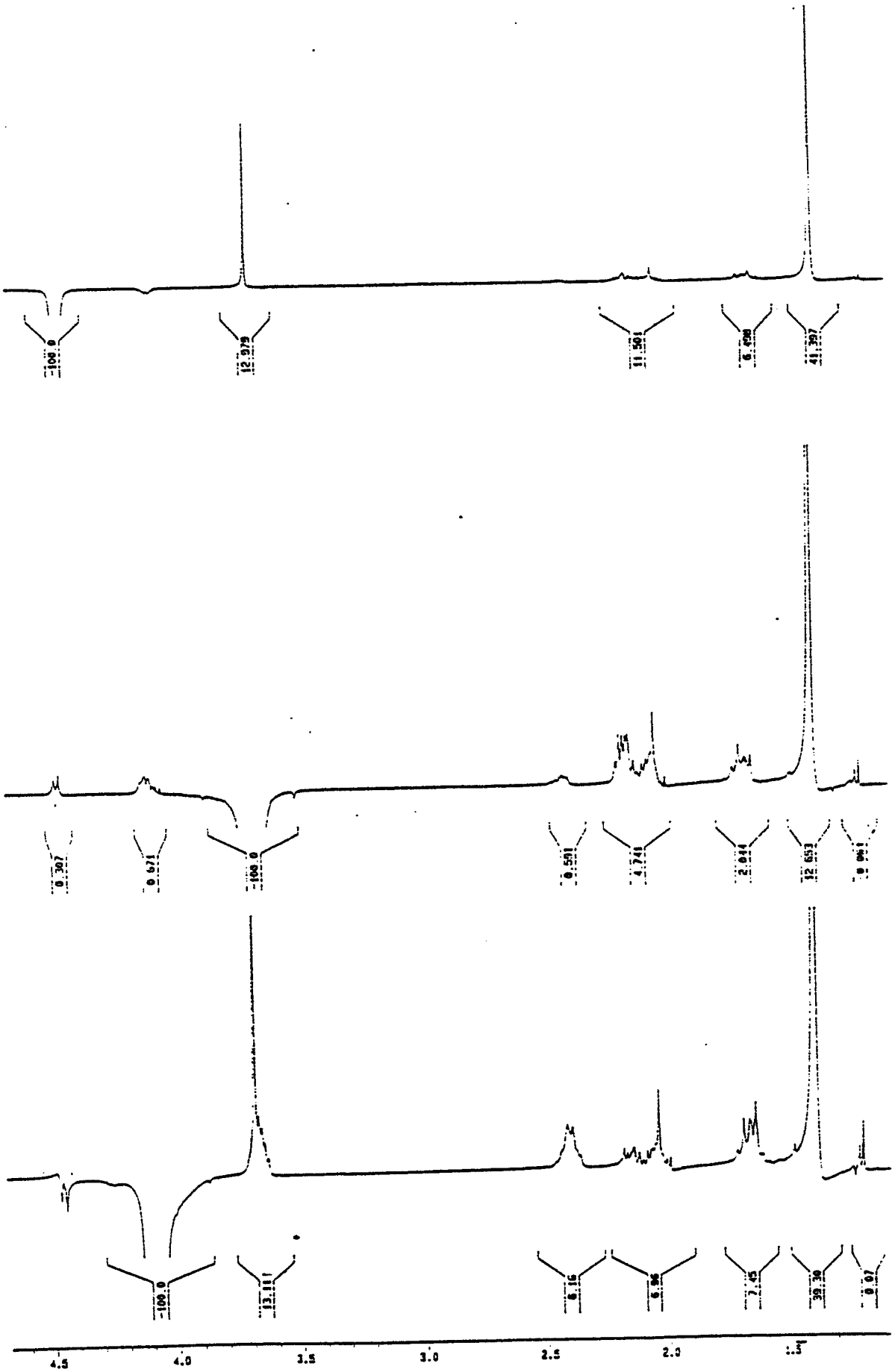

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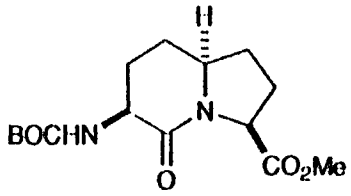

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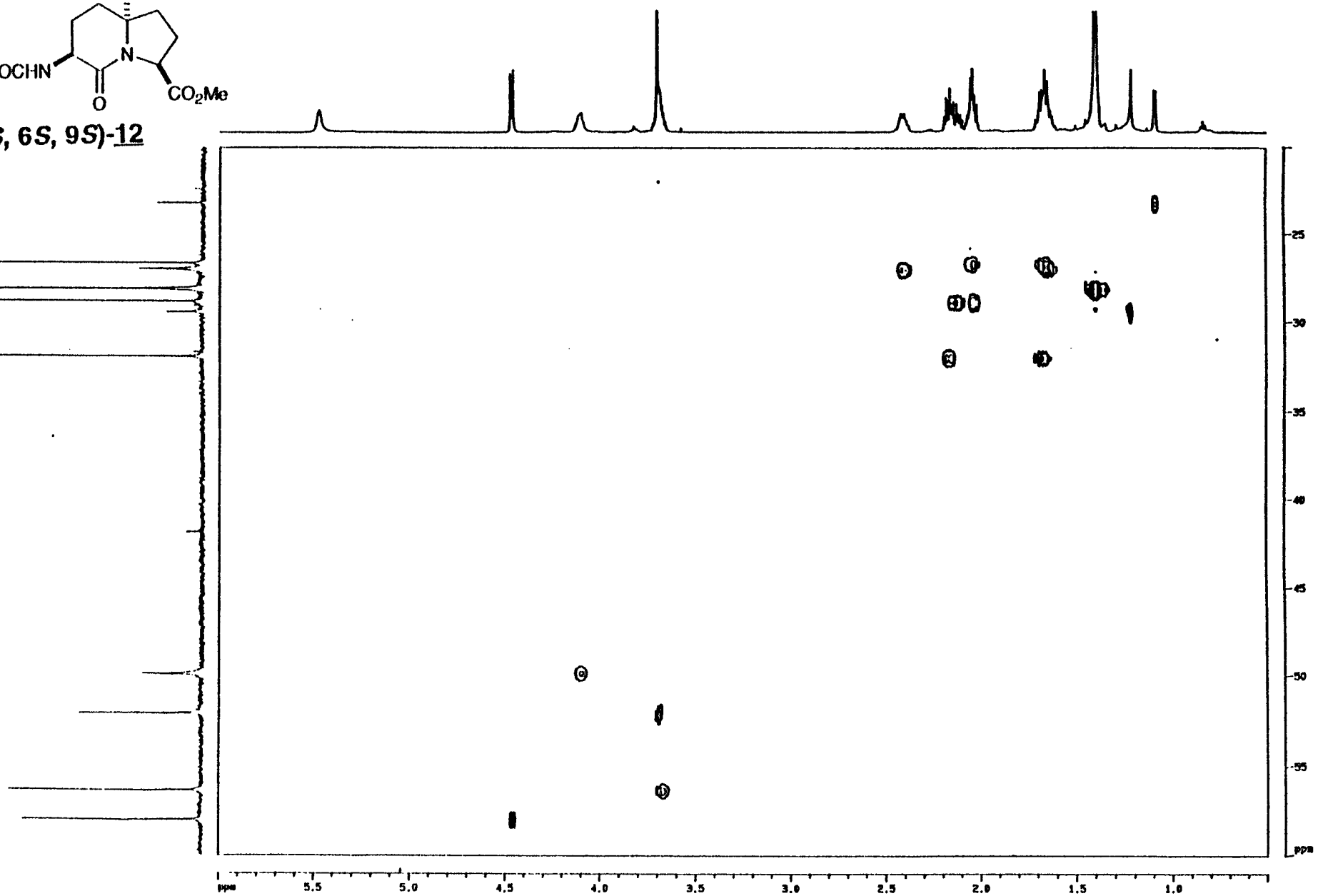

Lombart and Lubell

Lombart 1

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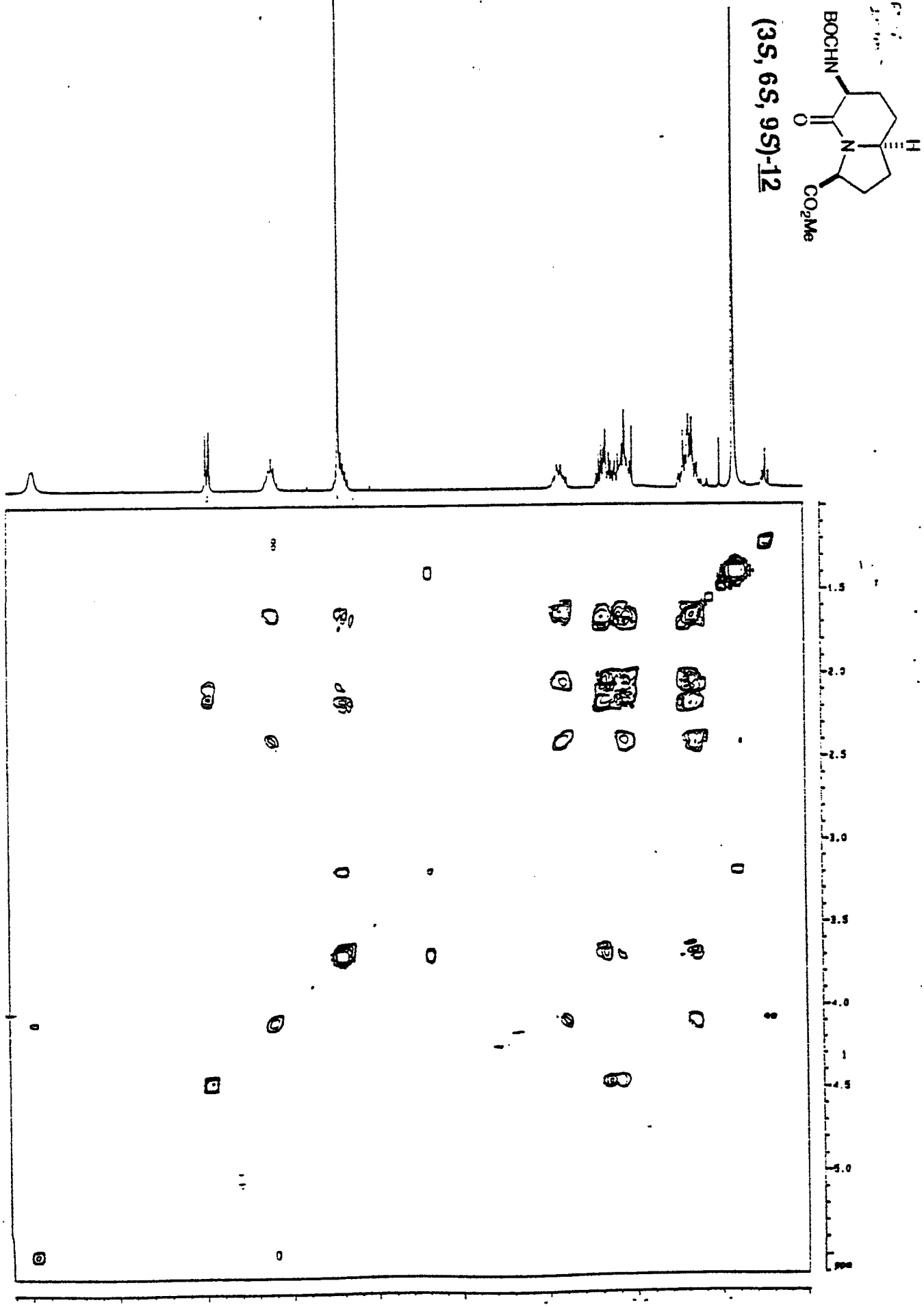

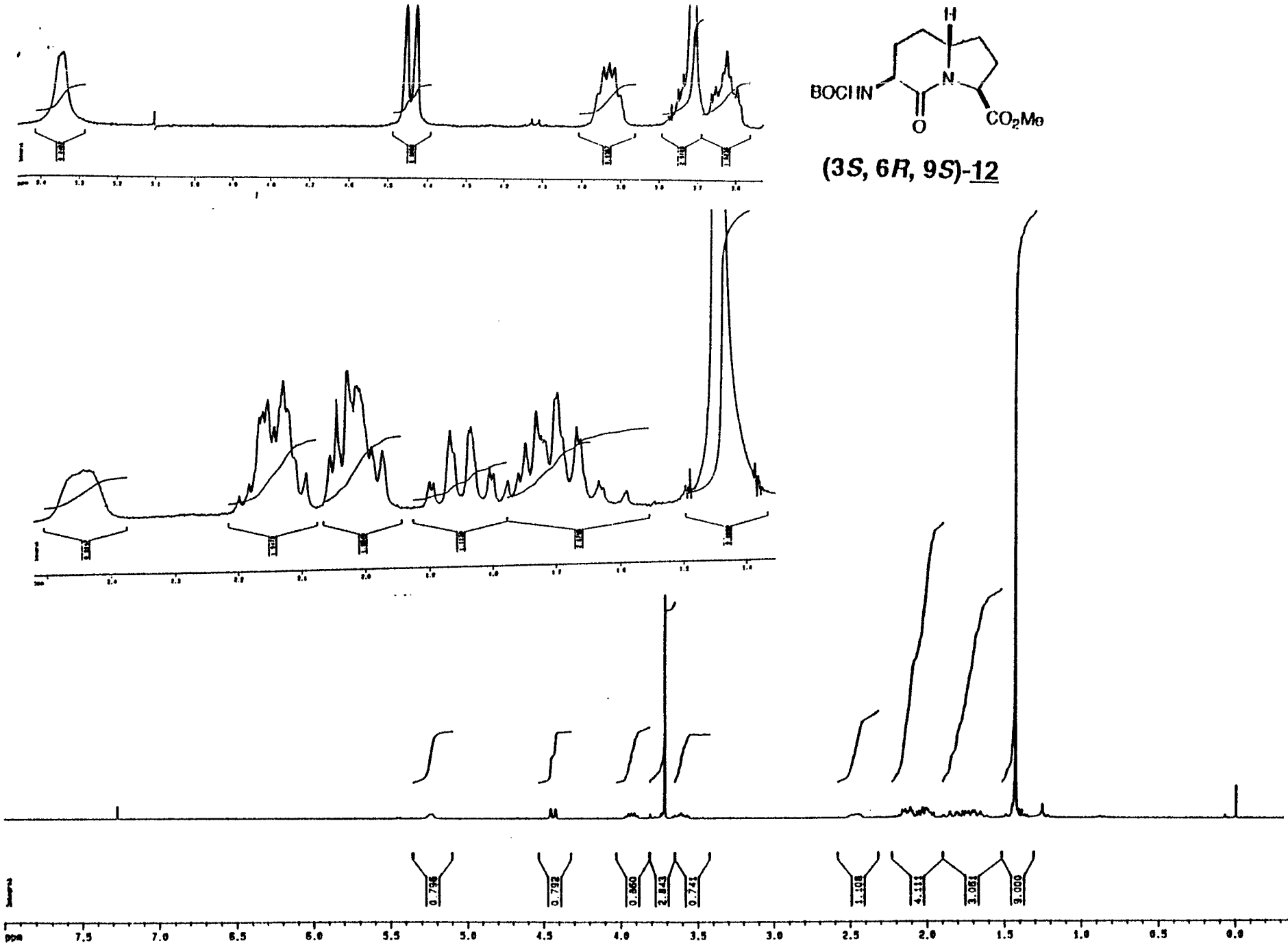

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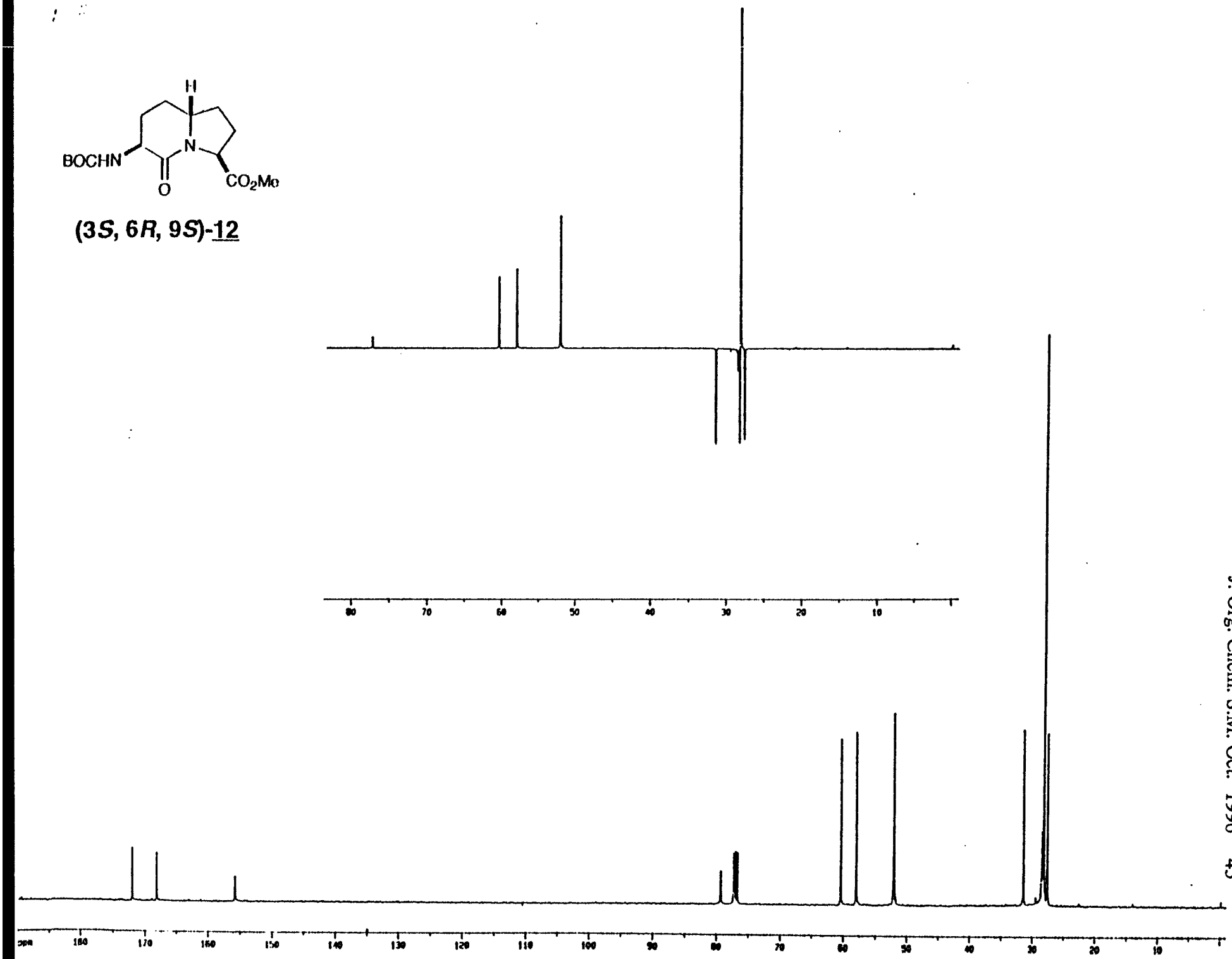
(3*S*, 6*R*, 9*S*)-12



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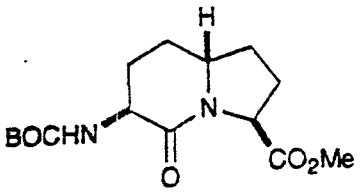
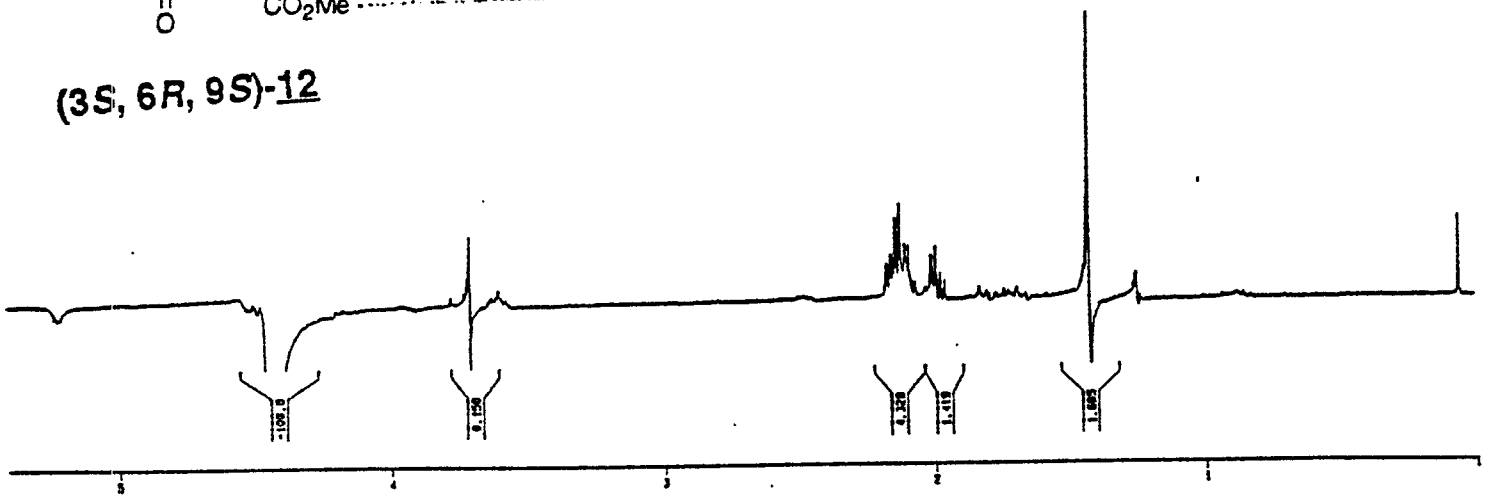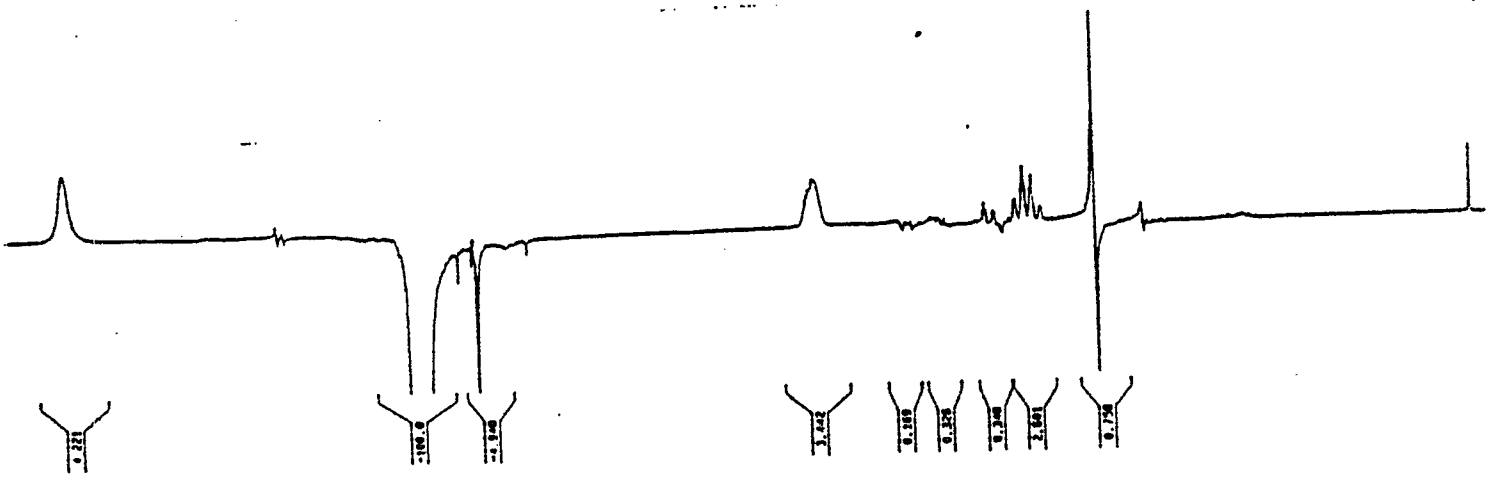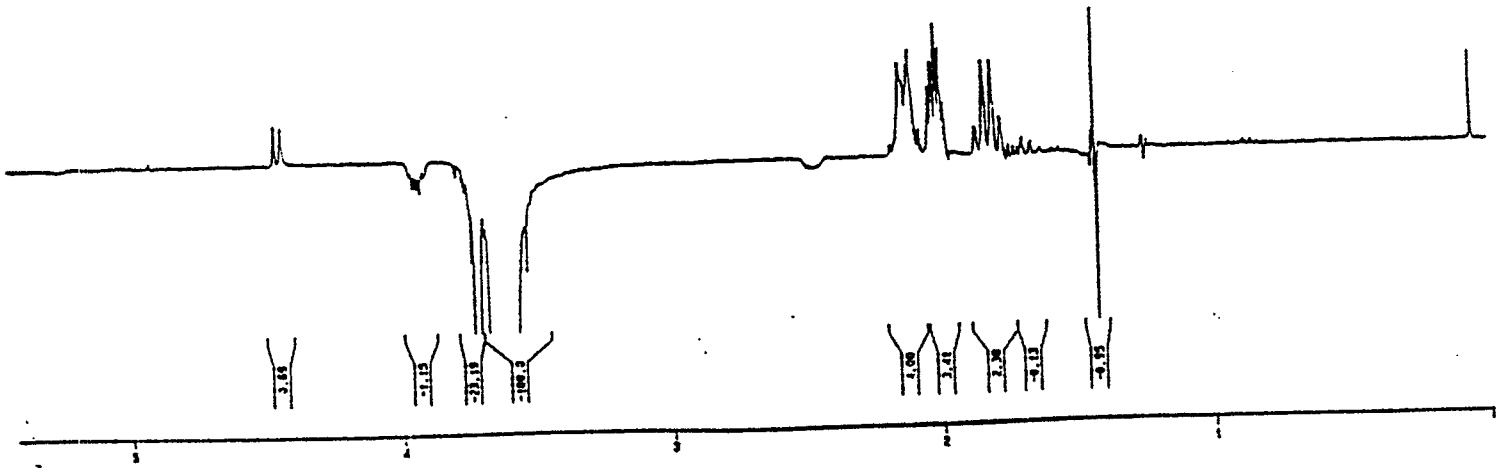
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