

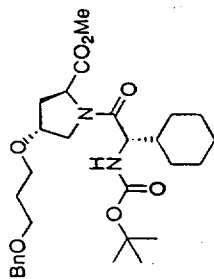
## Novel Dipeptide Macrocycles from 4-oxo, -thio, and -amino Substituted Proline Derivatives

Ashok Arasappan,\* Kevin X. Chen, Tejal N. Parekh,<sup>†</sup> F. George Njoroge, and Viyyoor Girijavallabhan

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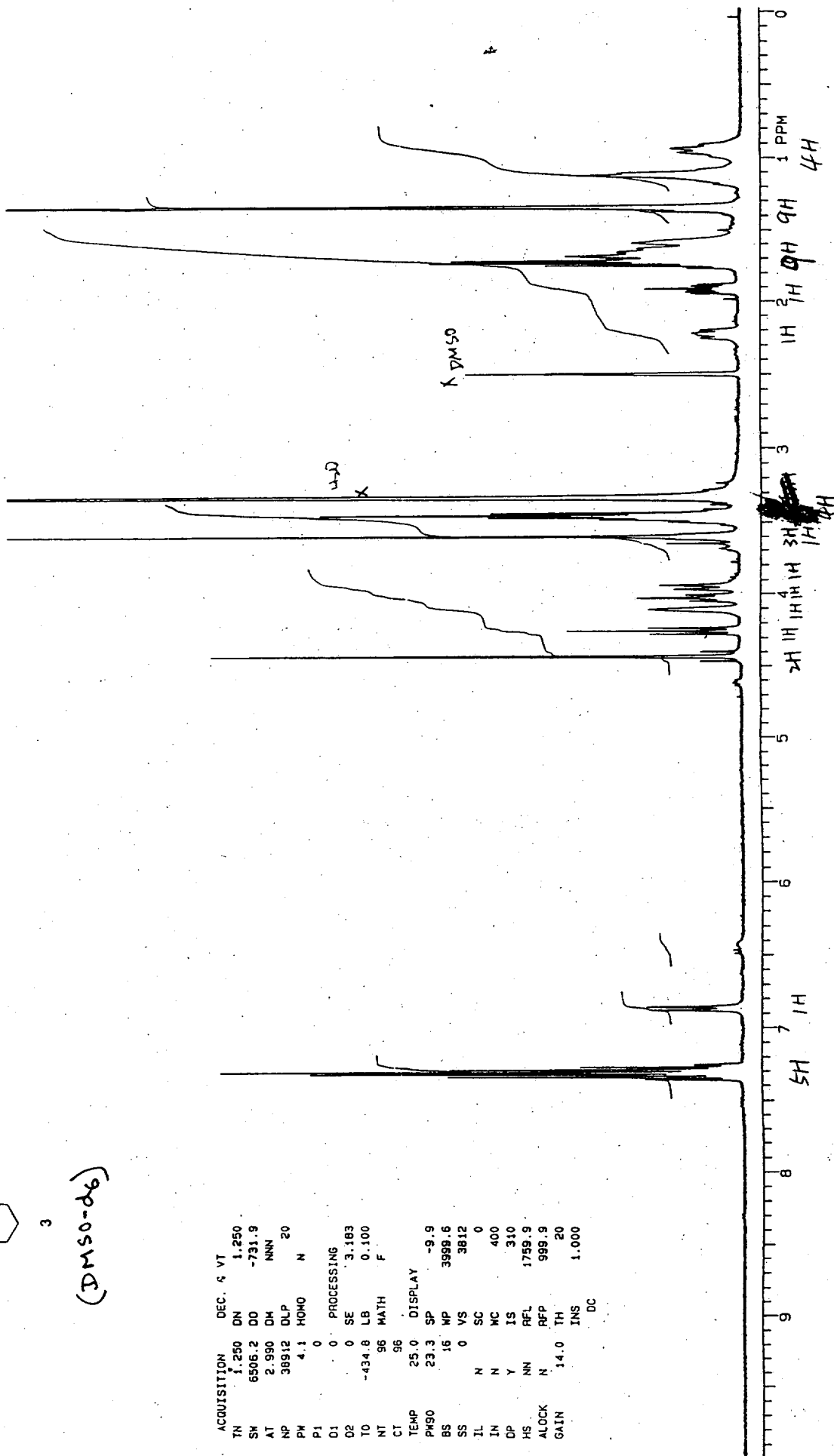
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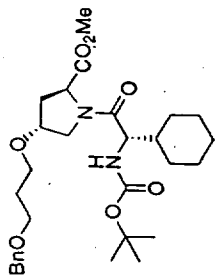
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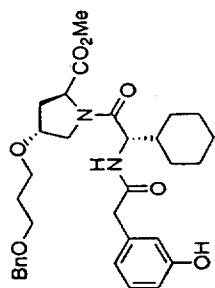
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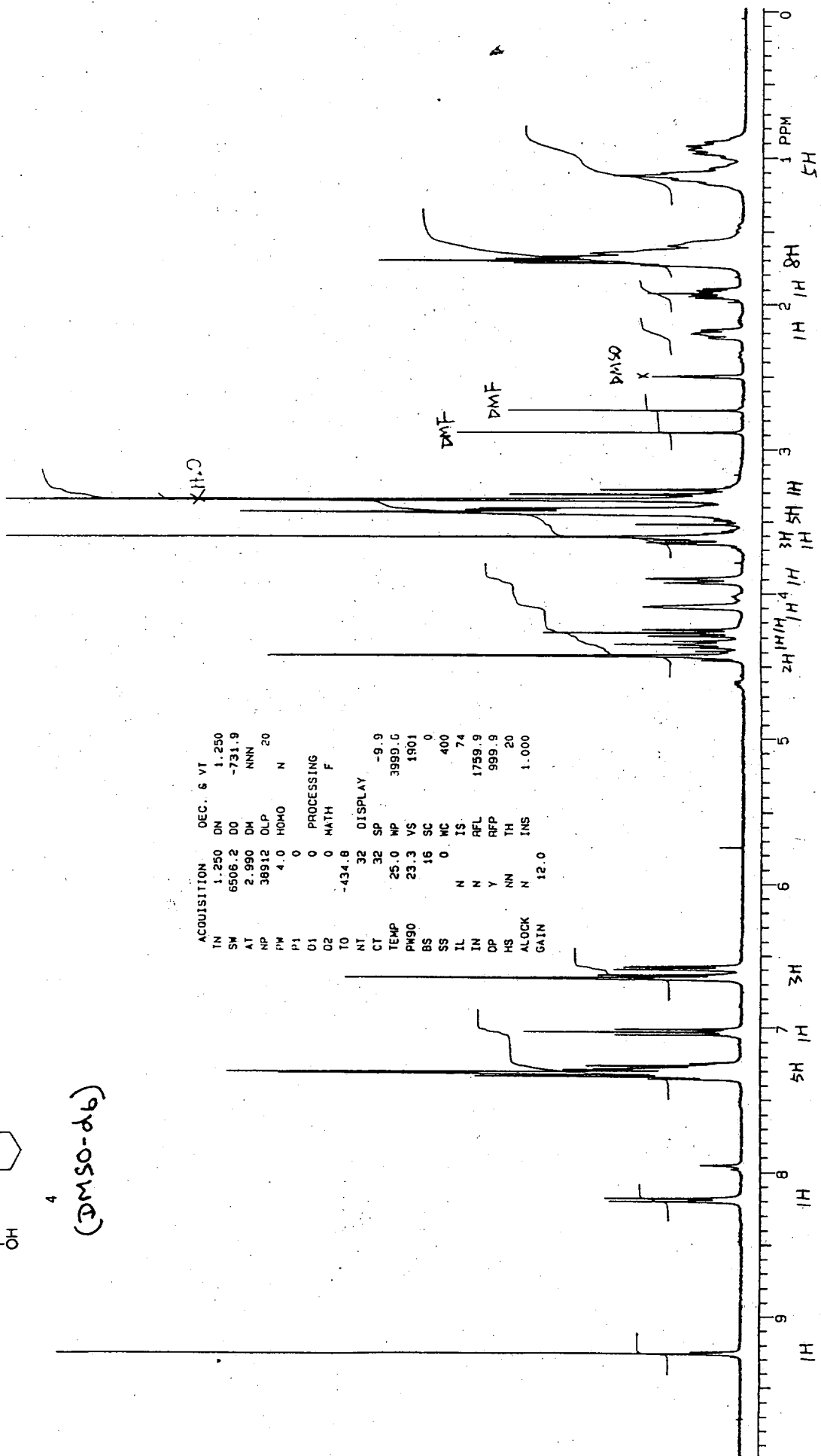


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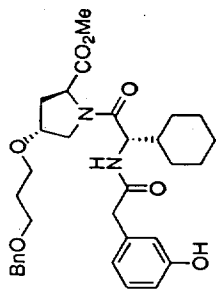


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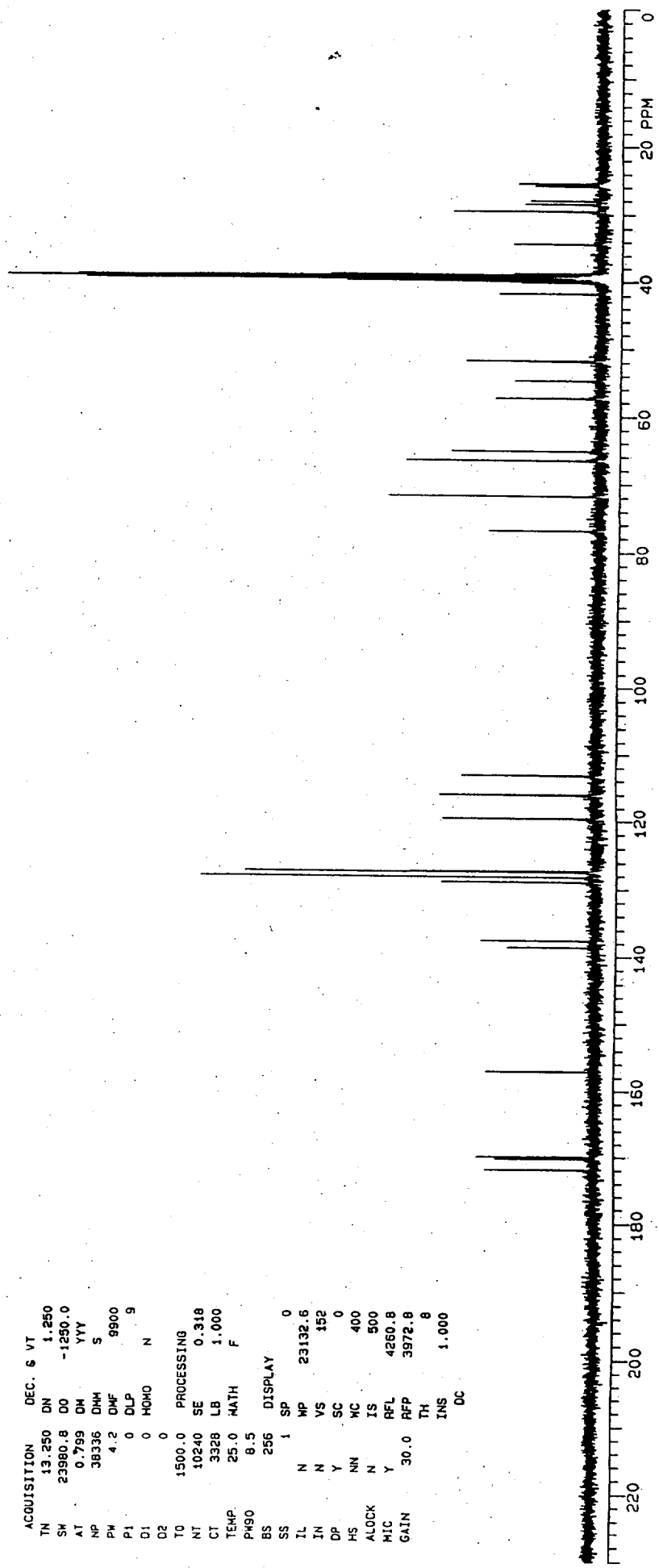


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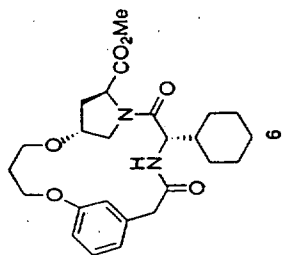


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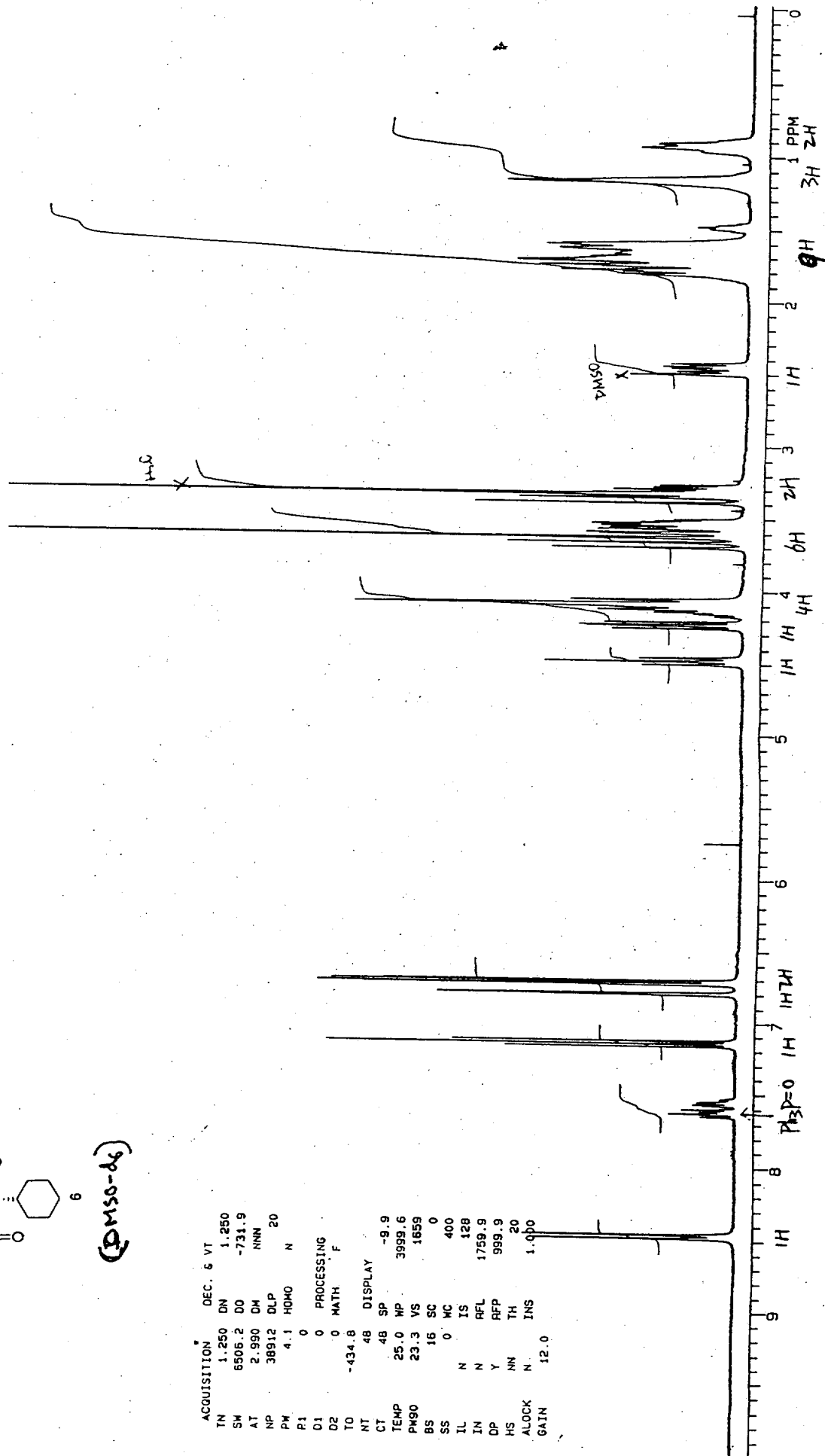
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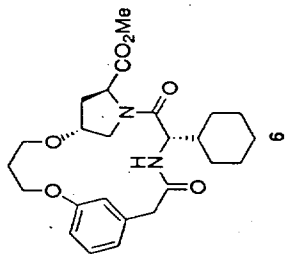


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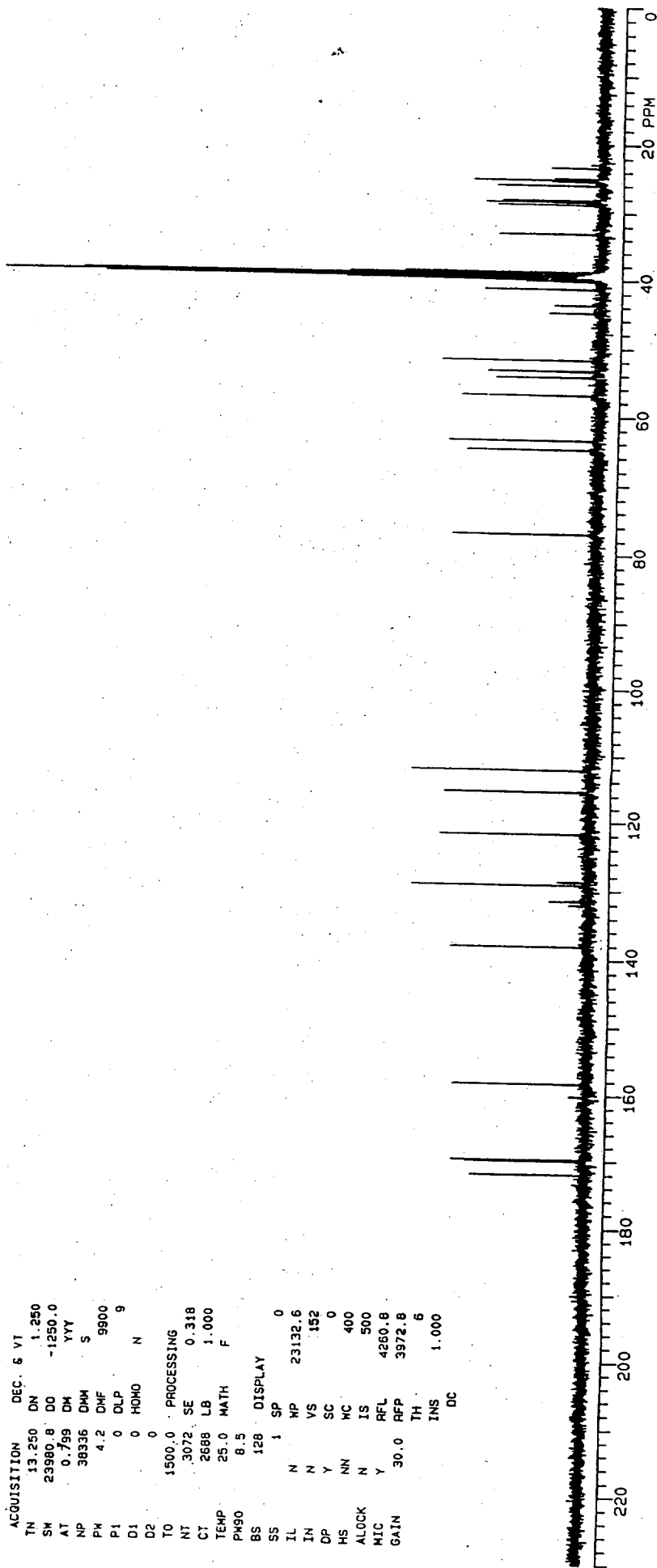
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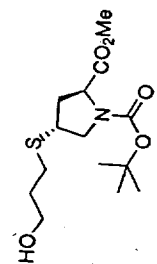


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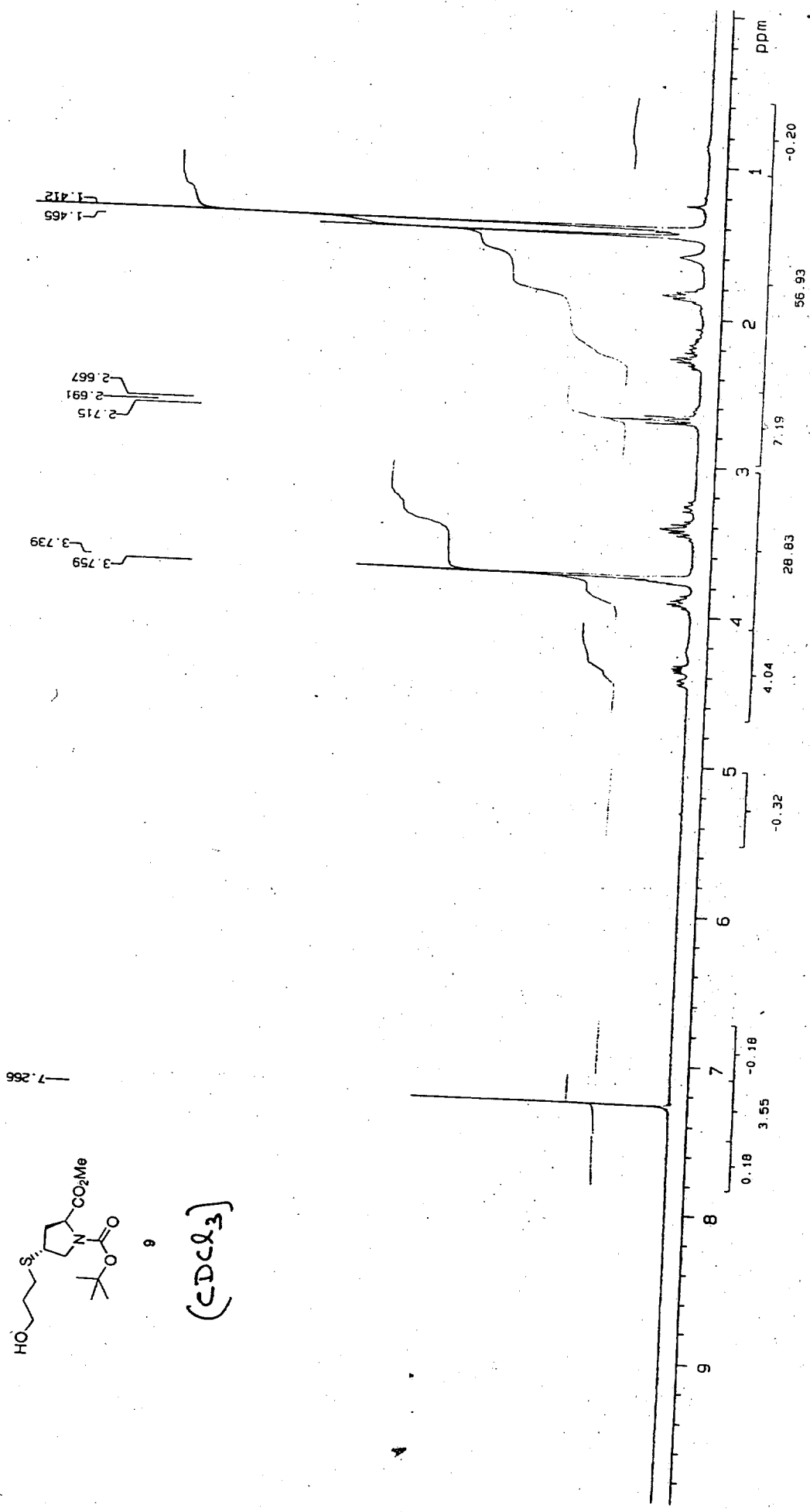
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5



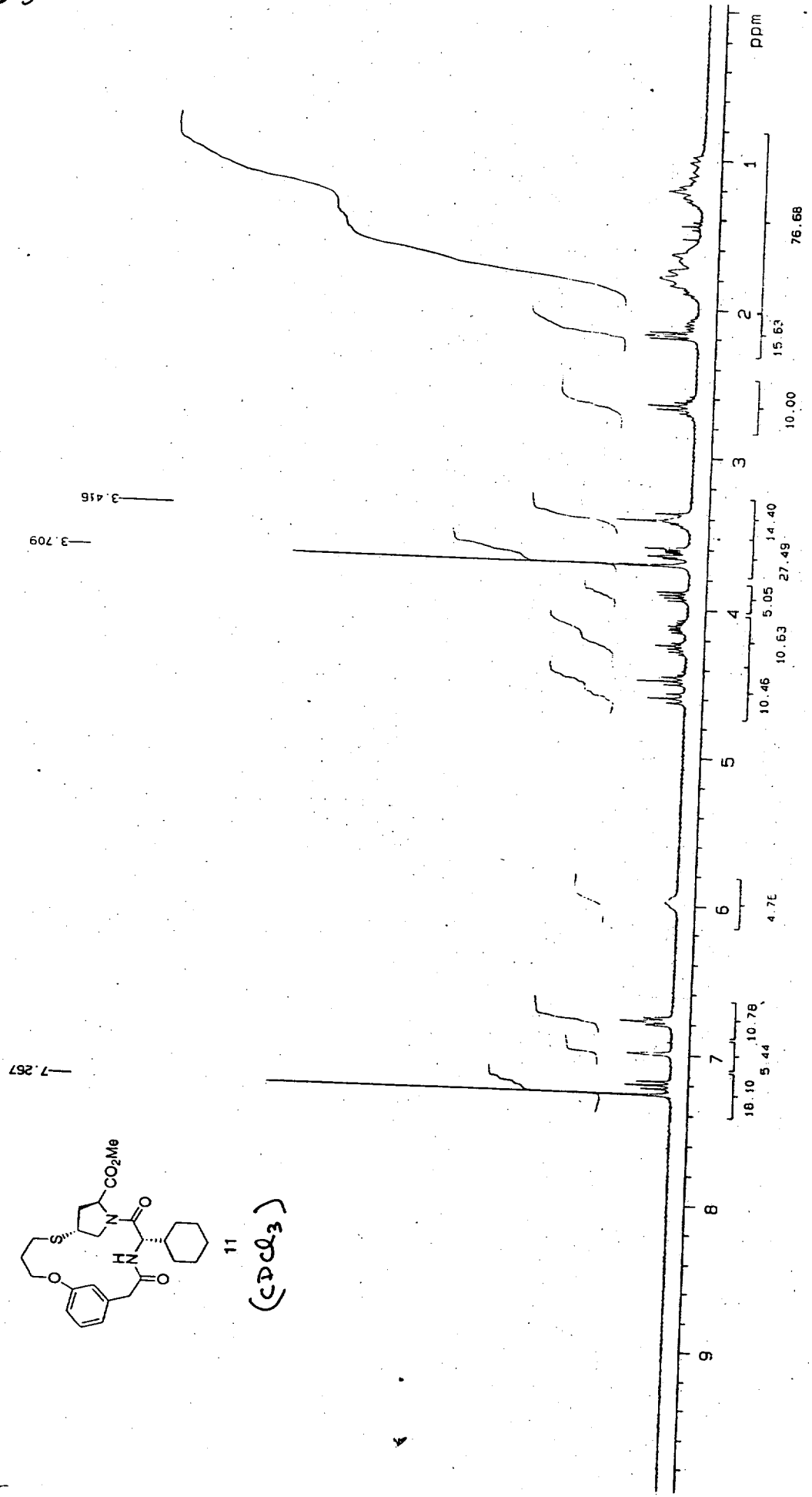
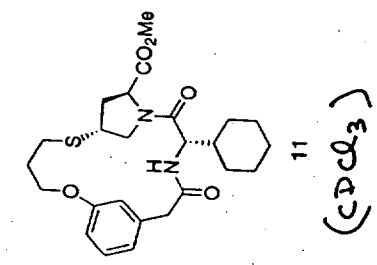
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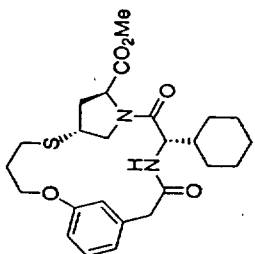
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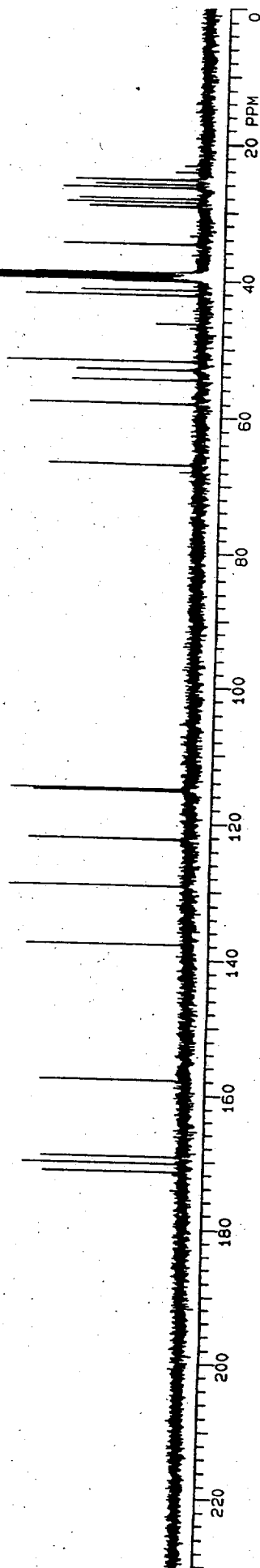
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06	12994.7	129.202	50.086
07	12256.5	122.260	44.189
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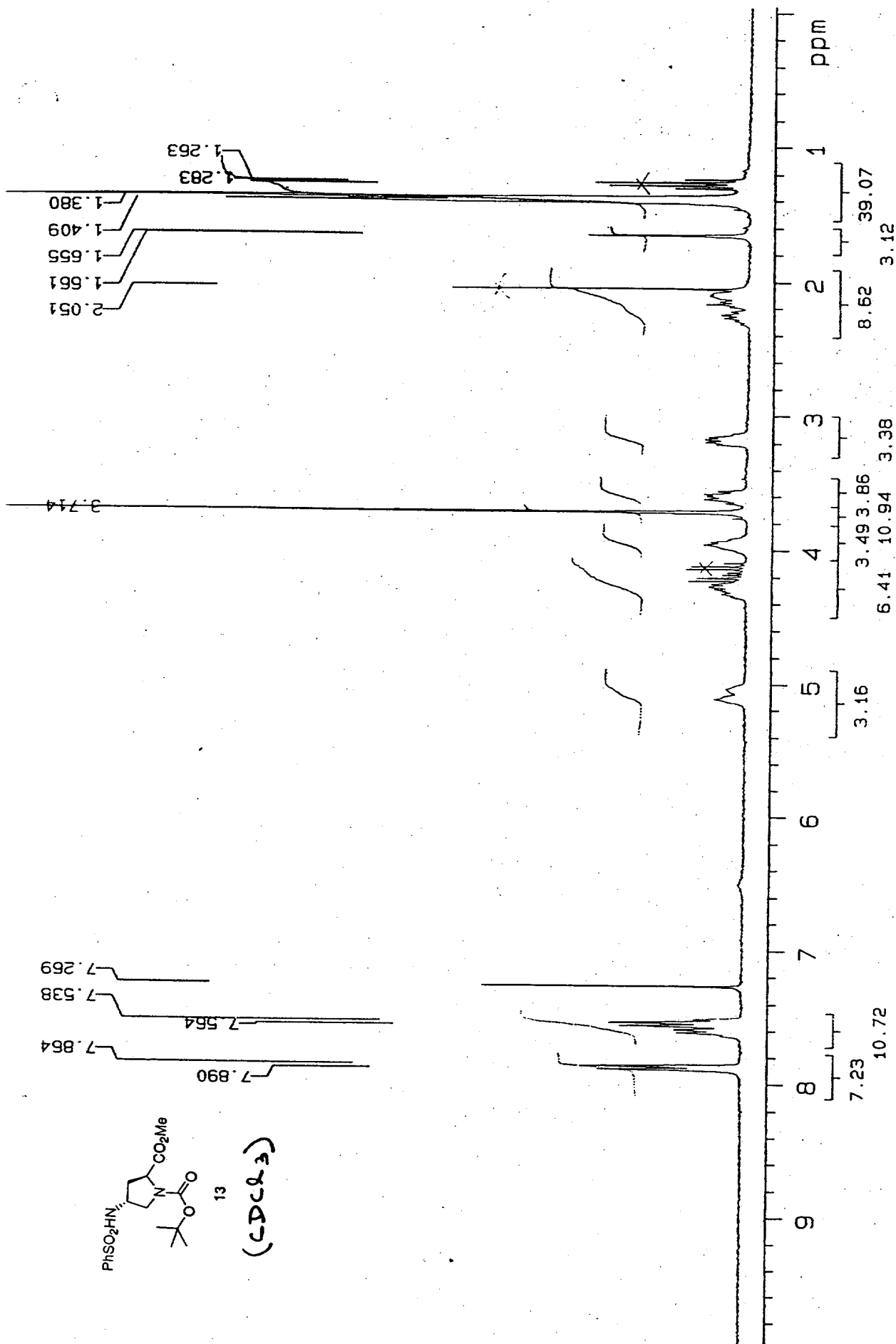


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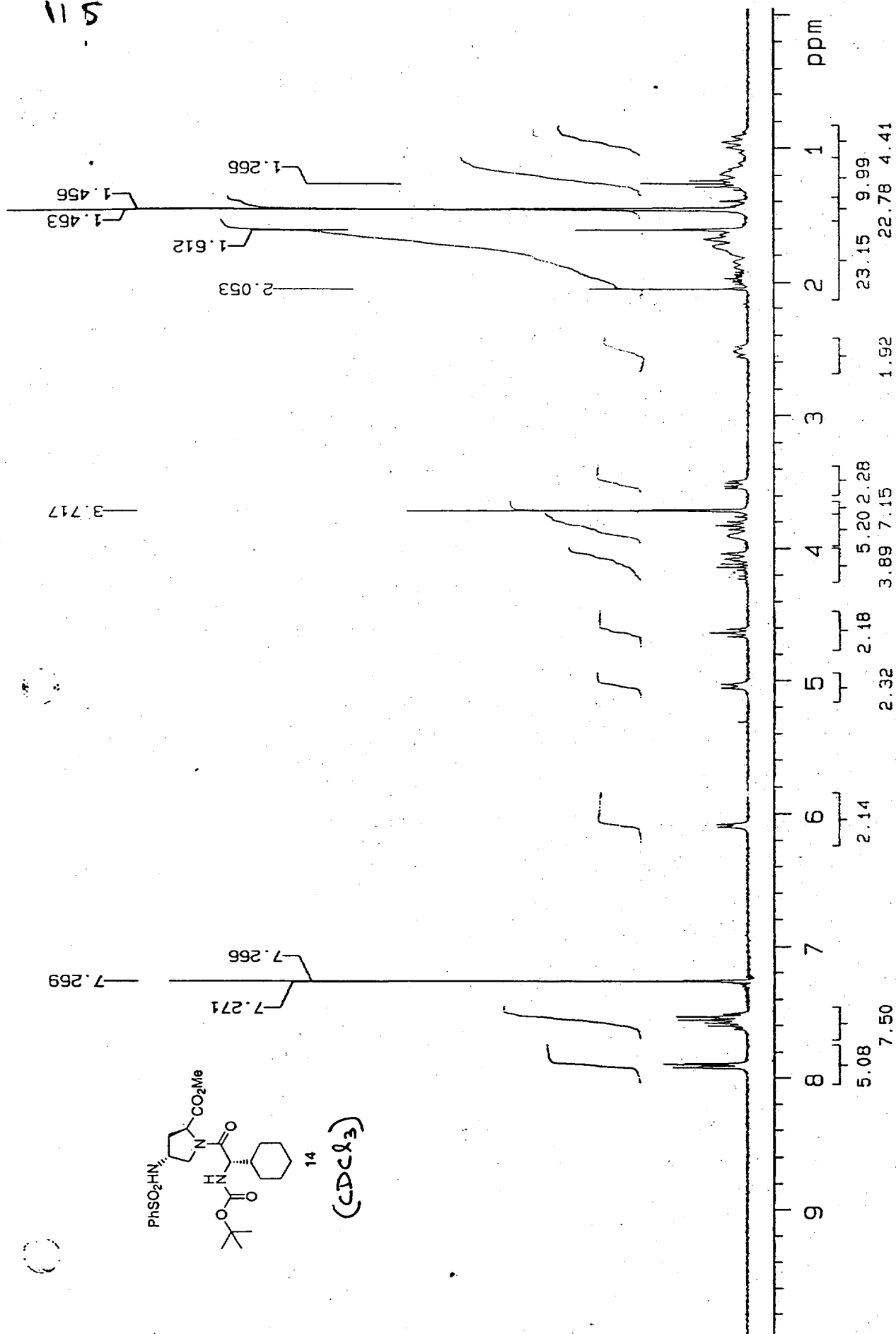
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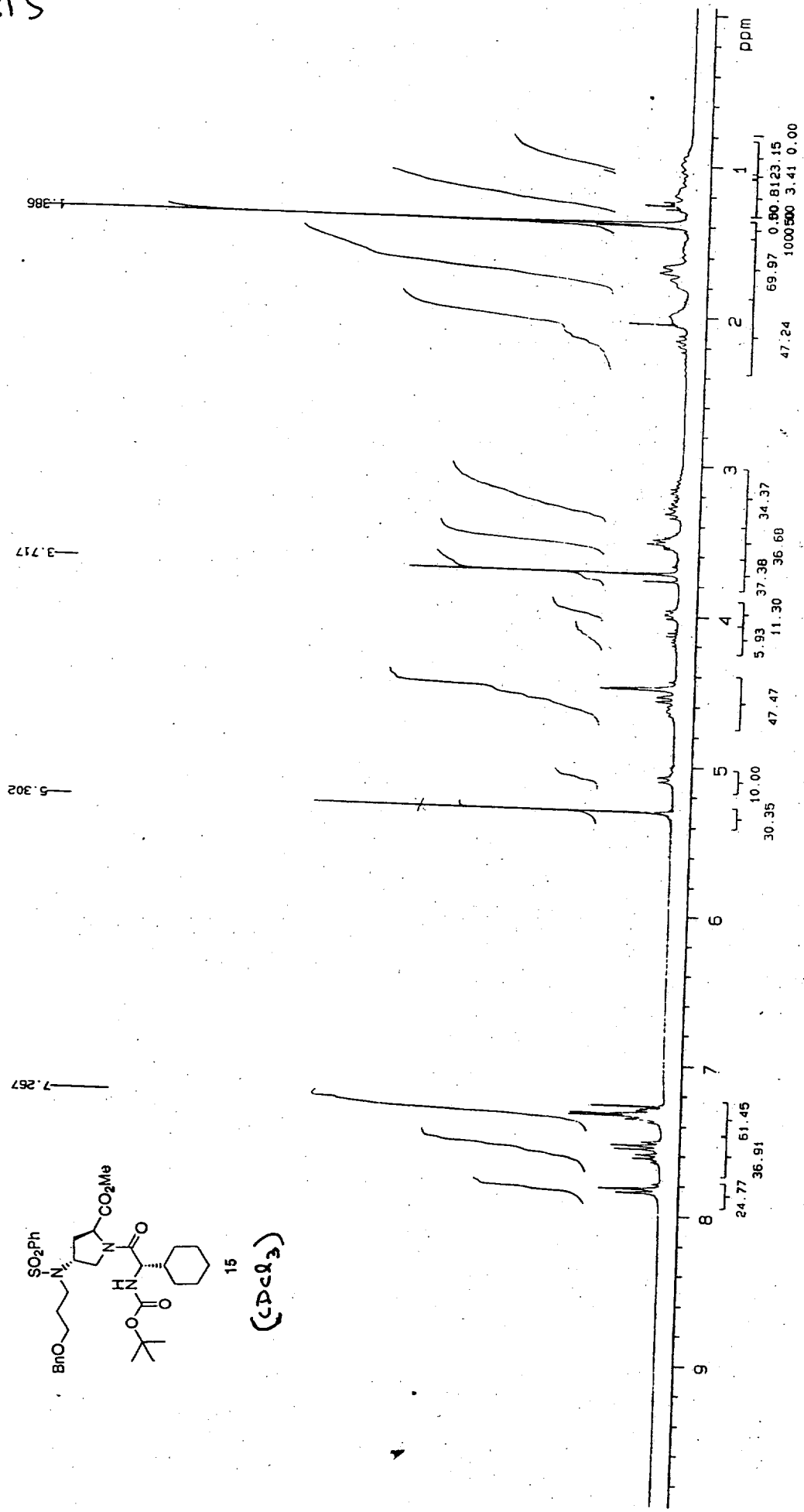
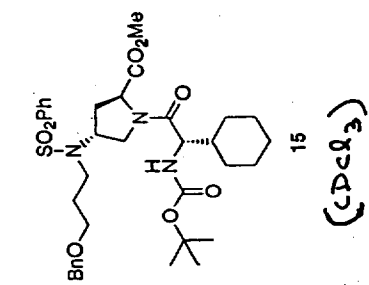
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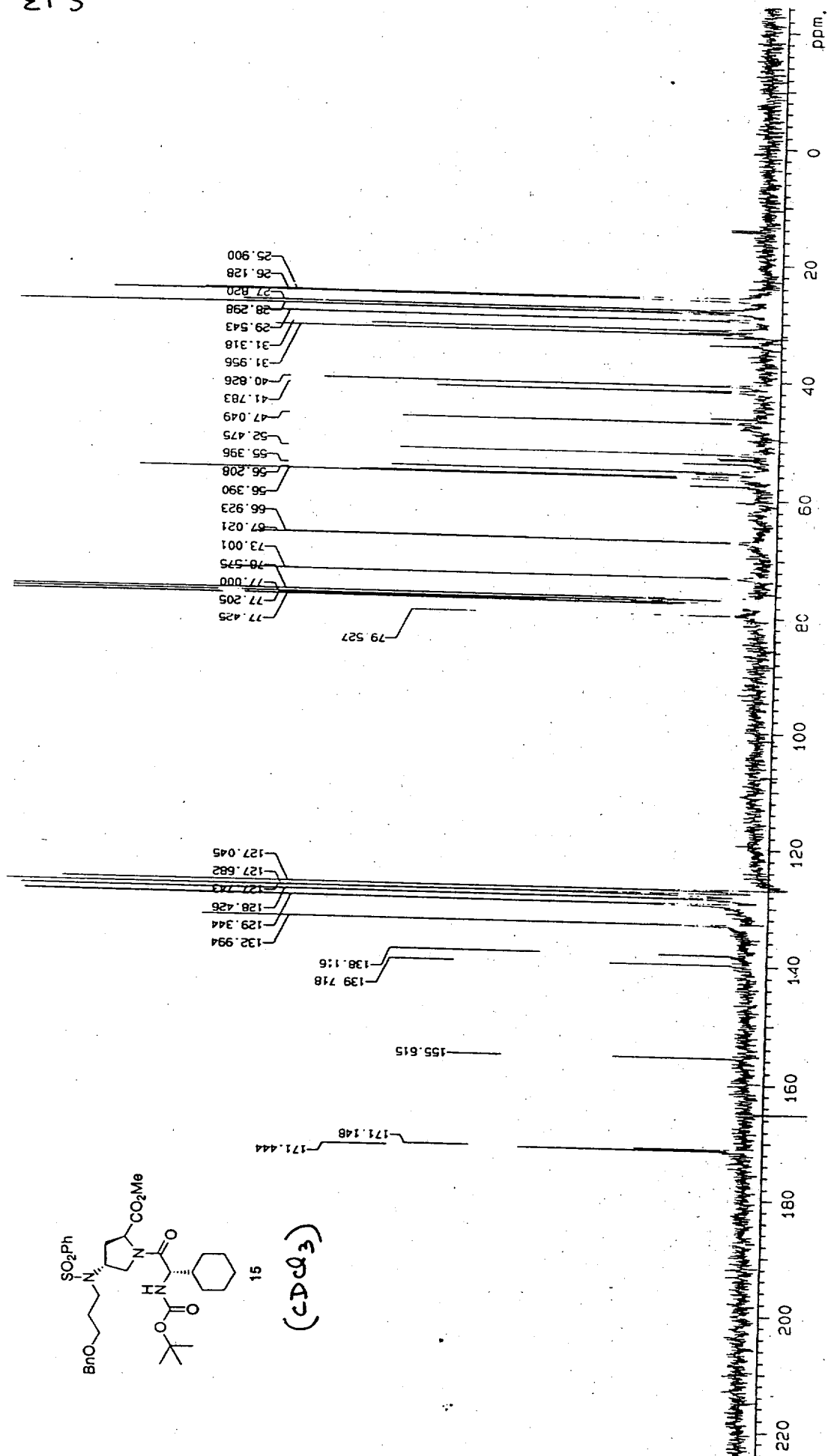
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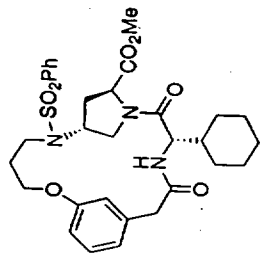
S12



S13

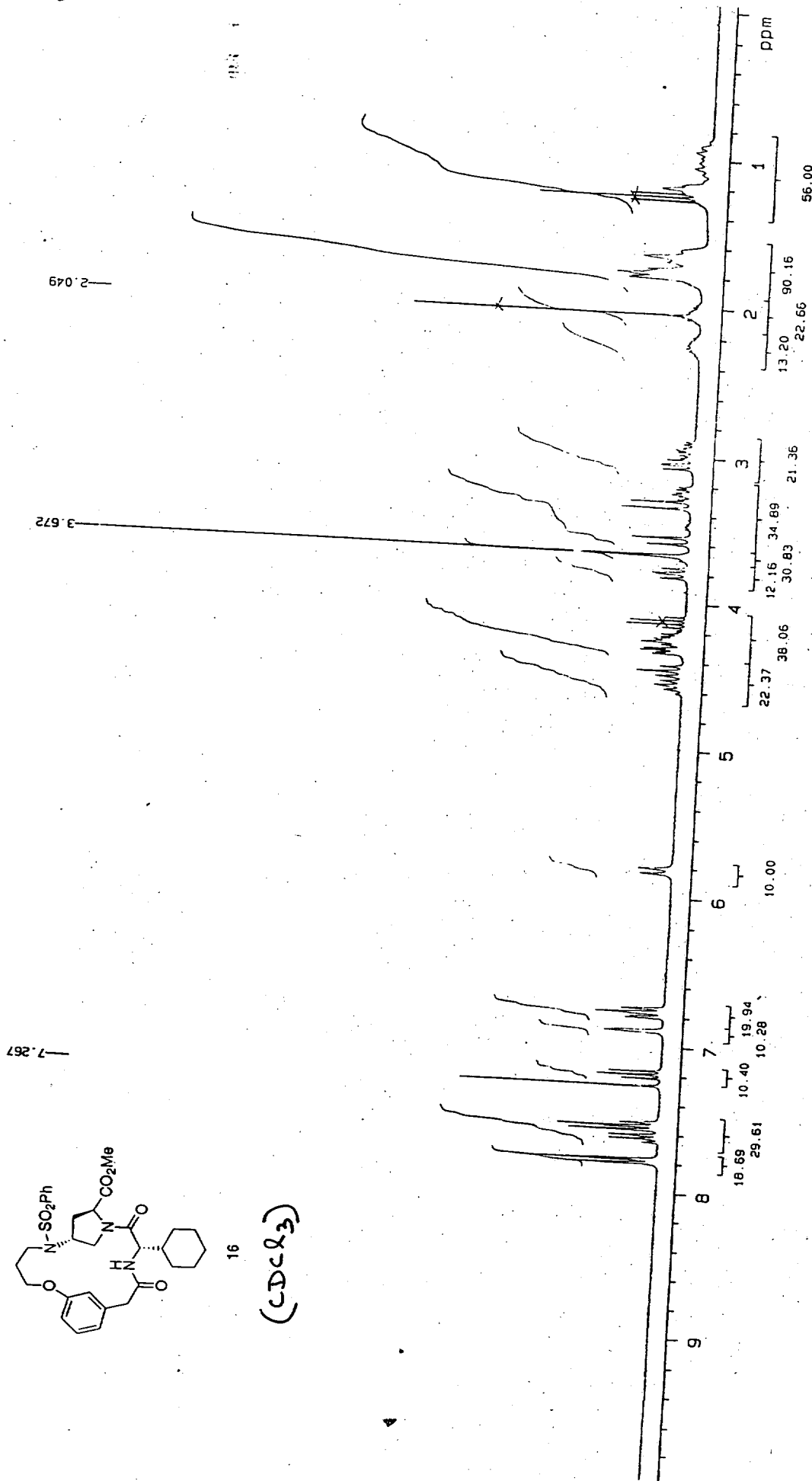


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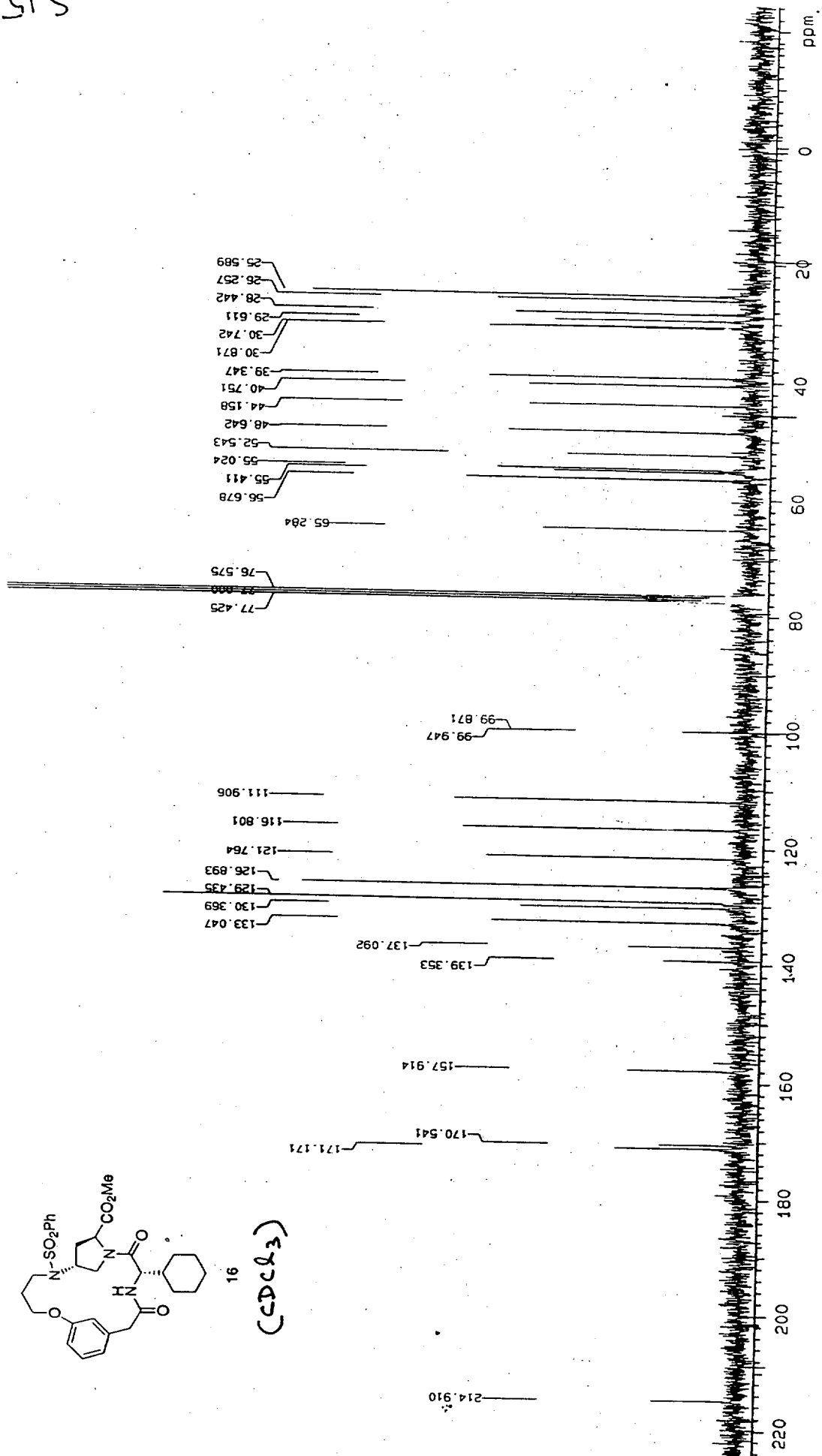


16

(CDCl<sub>3</sub>)



S 15





**4(S)-[[4-Bromophenyl)sulfonyl]oxy]-1,2(S)-pyrrolidinedicarboxylic Acid,**

**1-(1,1-Dimethylethyl) 2-Methyl Ester (8).** To a 0 °C solution of *cis*-4-hydroxyproline derivative **7** (10 g, 41 mmol) in dichloromethane (60 mL) was added triethylamine (28.68 mL, 204 mmol) slowly. 4-Bromobenzenesulfonyl chloride (20.91 g, 82 mmol) and DMAP (few crystals) were then added, and the temperature was maintained at 0 °C for 30 min. The reaction mixture was left standing in the refrigerator (~5 °C) overnight followed by slow warming to ambient temperature over 2 h. At this time, TLC analysis revealed complete consumption of the starting material. The reaction mixture was diluted with dichloromethane and washed with saturated sodium bicarbonate solution and 10% aqueous citric acid solution. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The crude mixture was purified by flash column chromatography using 100/0 to 95/5 dichloromethane/ethyl acetate to provide 18.4 g (97% yield) of the brosylate **8** as a white solid:  $[\alpha]_{\text{D}}^{20} = -23.07^{\circ}$  (c 1, CHCl<sub>3</sub>); <sup>1</sup>H NMR (mixture of rotamers, CDCl<sub>3</sub>) δ 1.41 and 1.45 (2s, 9H), 2.40–2.50 (m, 2H), 3.59–3.69 (m, 5H), 4.33–4.37 and 4.46 (2dd, 1H), 5.11 (m, 1H), 7.72–7.74 (m, 4H); <sup>13</sup>C NMR (mixture of rotamers, CDCl<sub>3</sub>) δ 28.18, 28.27, 36.01, 36.98, 51.59, 52.03, 52.20, 52.35, 56.95, 57.22, 57.28, 78.35, 79.53, 80.66, 129.10, 129.26, 132.66, 135.66, 135.81, 153.25, 153.64, 171.45, 171.78; HRMS (FAB) Calcd for C<sub>17</sub>H<sub>23</sub>NO<sub>7</sub>SBr 464.0379 (M<sub>+</sub>+H)<sup>+</sup>; found 464.0375.

**4(R)-[(Phenylsulfonyl)amino]-1,2(S)-pyrrolidinedicarboxylic Acid, 1-(1,1-Dimethylethyl)**

**2-Methyl Ester (13).** To a cold (0 °C) solution of **12** (5.4 g, 22.1 mmol) in dichloromethane (50 mL) were added triethylamine (6.8 mL, 48.6 mmol), DMAP (few crystals), and benzenesulfonyl chloride (3.29 g, 24.1 mmol). The reaction mixture was allowed to stand in the refrigerator (0–5 °C) overnight. The reaction mixture was washed with saturated NaHCO<sub>3</sub> and 10% citric acid solution. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was purified by flash chromatography using 95/5 dichloromethane/EtOAc to afford 5.0 g (59% yield) of **13**: <sup>1</sup>H NMR (mixture of rotamers, CDCl<sub>3</sub>) δ 1.38 and 1.41 (2s, 9H), 2.05–2.35 (m, 2H), 3.10–3.20 (m, 1H), 3.56–3.65 (m, 1H), 3.71 (s, 3H), 3.88–4.04 (m, 1H), 4.20–4.38 (m, 1H), 5.00–5.18 (m, 1H), 7.53–7.65 (m, 3H), 7.88 (app d, 2H); HRMS (FAB) calcd for C<sub>17</sub>H<sub>25</sub>N<sub>2</sub>O<sub>6</sub>S 385.1433 (M<sub>+</sub>+H)<sup>+</sup>; found 385.1428.