



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

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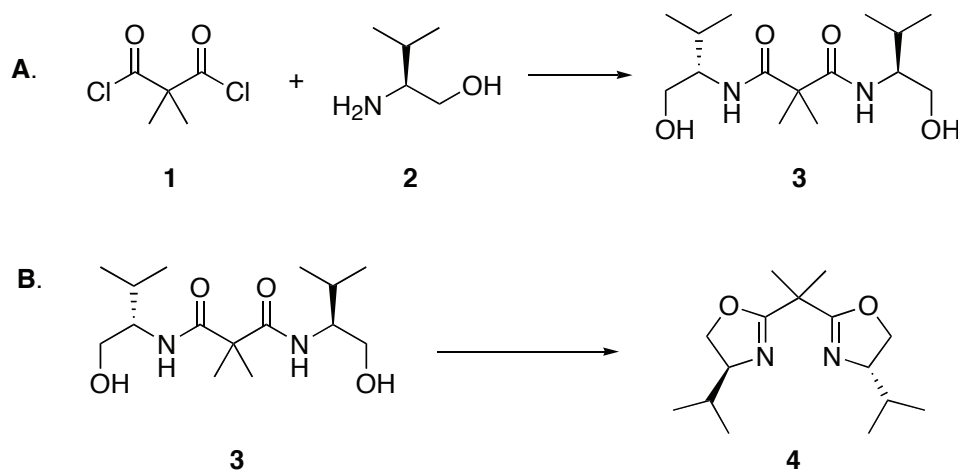
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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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**SYNTHESIS OF (-)-(S,S)- BIS(4-ISOPROPYLOXAZOLINE)  
(4S, 4S')-2,2'-(Propane-2,2-diyl)bis(4-isopropyl-4,5-dihydrooxazole)**



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Checked by Peter Wipf and Nilukshi Jayasuriya.<sup>4</sup>

## 1. Procedure

*A. (-)-(S,S)-N,N'-Bis(1-hydroxymethyl-2-methylpropyl)-2,2-dimethylpropanediamide (3):* An oven-dried 250 mL, 3-necked round-bottom flask equipped with a stirring bar and two 50 mL pressure-equalizing addition funnels connected to a mineral oil bubbler is purged with nitrogen and charged with (L)-valinol (**2**, 5.13 g, 0.050 mol, Note 1). The flask is immersed in an ice bath at 0 °C and triethylamine (17.4 mL, 0.124 mol, Note 2) is added dropwise via the first addition funnel. 2,2-Dimethylpropanedioyl dichloride (3.3 mL, 0.25 mol, Note 3) in dry dichloromethane (25 mL, Note 4) is then added dropwise over 25 minutes via the second addition funnel. The internal temperature increases from 0 °C to 10 °C during the addition. Subsequently, the ice bath is removed and the reaction mixture is allowed to warm to room temperature. Stirring is continued for 45 min, resulting in a colorless precipitate that is dissolved by addition of dry dichloromethane (120 mL). After addition of aqueous HCl (1 N, 30 mL), the aqueous layer is separated and extracted with dichloromethane (3 x 15 mL). The combined organic layers are washed with saturated NaHCO<sub>3</sub> solution (30 mL) and

brine (30 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to afford crude **3** as a pale yellow solid. Recrystallization of the crude product from ethyl acetate (40 mL) yields **3** (4.30 g, 14.2 mmol, 57%) as white crystals. The mother liquor is concentrated and the residue recrystallized from ethyl acetate (10 mL) to yield a second crop of **3** (1.60 g, 5.27 mmol, 21%); the process is repeated to yield a third crop of **3** (0.440 g, 1.45 mmol, 6%, total yield: 6.40 g, 21.1 mmol, 84%, Note 5).

B. *(-)-(S,S)-Bis(4-isopropylloxazoline) (4)*: An oven-dried 500 mL, 2-necked round-bottom flask equipped with a stirring bar and a 50 mL, pressure-equalizing addition funnel connected to a mineral oil bubbler is purged with nitrogen and charged with *(-)-(S,S)-N,N'*-bis-(1-hydroxymethyl-2-methylpropyl)-2,2-dimethylmalonamide (**3**, 5.5 g, 18.4 mmol), 4-dimethylaminopyridine (0.204 g, 1.67 mmol, Note 6) and dry dichloromethane (130 mL, Note 4). The flask is immersed in a water bath at room temperature and triethylamine (10.25 mL, 73.4 mmol, Note 2) is added slowly via syringe. Subsequently, tosyl chloride (7.10 g, 37 mmol, 2.0 equiv., Note 7), dissolved in dry dichloromethane (15 mL), is added dropwise over 30 minutes via the addition funnel. After completion of the addition, the funnel is rinsed with dry dichloromethane (2.5 mL) and the reaction mixture is stirred for an additional 27 h at room temperature (Note 8). The reaction mixture is treated with saturated NH<sub>4</sub>Cl solution (70 mL) followed by water (40 mL). The aqueous layer is separated and extracted with dichloromethane (3 x 55 mL), and the combined organic layers are dried over MgSO<sub>4</sub>. The organic solution is filtered and concentrated under vacuum. The oily residue is treated with hot pentane (40 mL, Note 9), stirred for 5 min and the supernatant liquid is decanted. This procedure is repeated three times and the collected pentane layers are combined and concentrated under vacuum to yield **4** (4.05 g, 15.2 mmol, 83%, Note 10) as a colorless oil.

## 2. Notes

1. (L)-Valinol was prepared from (L)-valine in 81% yield in an analogous way to the reduction of (*S*)-*tert*-leucine to (*S*)-*tert*-leucinol according to Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541, or purchased from Aldrich Chemical Company, Inc.

2. Triethylamine was obtained from Alfa Aesar and was distilled prior to use from calcium hydride under nitrogen.

3. 2,2-Dimethylpropanedioyl dichloride was purchased from Aldrich Chemical Company, Inc. or synthesized from 2,2-dimethylmalonic acid in 90% yield according to Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541.

4. Dichloromethane was purified by filtration through activated alumina.

5. Physical properties and spectral data for **3** are as follows:  $R_f$  0.25 (EtOAc:MeOH, 95:5);  $[\alpha]_D^{24}$   $-6.0$  (c 0.50, CH<sub>2</sub>Cl<sub>2</sub>); mp 98–99 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ : 0.92 (d,  $J = 6.8$  Hz, 6 H), 0.96 (d,  $J = 6.8$  Hz, 6 H), 1.50 (s, 6 H), 1.82 (oct,  $J = 6.8$  Hz, 2 H), 2.66 (bs, 2 H), 3.52 (m, 2 H), 3.69–3.86 (m, 4 H), 6.41 (d,  $J = 8.6$  Hz, 2 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ : 18.8, 19.6, 23.7, 29.1, 50.2, 57.1, 63.5, 174.5; IR (KBr) cm<sup>-1</sup> 3349, 3380, 2962, 2886, 1658, 1530, 1049, 1033; MS (ES)  $m/z$  (%) 405.2 (20), 325.2 ([M+Na]<sup>+</sup>, 100), 285.2 (10); HRMS (ES) calcd. for C<sub>15</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>Na 325.2103, found 325.2084; Anal. calcd. for C<sub>15</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>: C, 59.57; H, 10.00; N, 9.26. found: C, 59.01; H, 10.12; N, 9.11.

6. 4-Dimethylaminopyridine was obtained from the Aldrich Chemical Company, Inc and used as received.

7. Tosyl chloride was obtained from the Aldrich Chemical Company, Inc and used as received.

8. After the reaction mixture was stirred for 27 h, the submitters noticed crystalline solid precipitate. The solid precipitate was dissolved by adding dichloromethane (50 mL) prior to workup. The checkers, however, did not observe any precipitate.

9. In some experiments, a cloudy precipitate was formed, which was then dissolved in dichloromethane (2.5 mL per mmol of **3**) prior to workup.

10. An analytically pure sample for characterization purposes was obtained by Kugelrohr distillation (95–100 °C, 0.5 mmHg) of the crude material. Physical properties and spectral data for **4** are as follows  $R_f$  0.25 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 19:1);  $[\alpha]_D^{24}$   $-107.5$  (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ : 0.85 (d,  $J = 6.8$  Hz, 6 H), 0.91 (d,  $J = 6.8$  Hz, 6 H), 1.51 (s, 6 H), 1.88–1.73 (m, 2 H), 4.06–3.93 (m, 4 H), 4.26–4.15 (m, 2 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ : 17.3, 18.5, 24.4, 32.2, 38.5, 69.9, 71.5, 168.7; IR (film) cm<sup>-1</sup> 3308, 2960, 2874, 1746, 1525, 1353, 1303, 1037, 1017, 895, 815, 714; MS (EI)  $m/z$  (%) 266 (M<sup>+</sup>, 15), 265 (30), 223 (100), 195 (30), 155 (65), 137 (97),

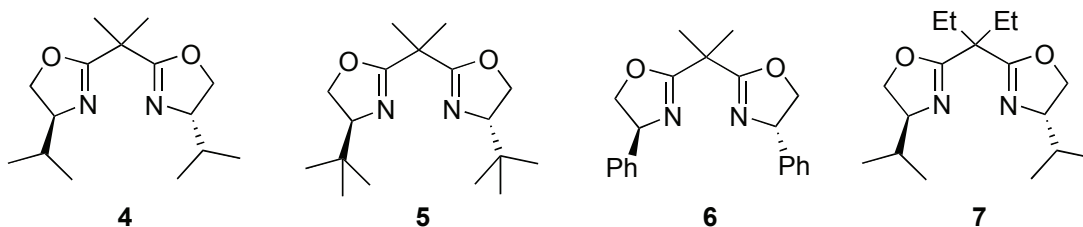
110 (50); HRMS (EI) calcd for  $C_{15}H_{26}N_2O_2$  266.1994, found 266.1987; Anal. calcd for  $C_{15}H_{26}N_2O_2$ : C, 67.63; H, 9.84; N, 10.52. found C, 66.65; H, 9.81; N, 10.08.

### Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

### 3. Discussion

Since the discovery of oxazolines as ligands for catalysis,<sup>5</sup> bis(oxazolines)<sup>6</sup> have proved to be privileged structures because they promote a great number of metal-catalyzed transformations with unprecedented selectivity. Most commonly, bis(oxazolines) can be obtained from amino alcohols, either by a two-step condensation/cyclization sequence with acid chlorides as described here, or by condensation with dinitriles in the presence of a metal salt such as zinc(II) chloride<sup>7</sup>, trifluoromethanesulfonic acid<sup>8</sup> or stepwise formation of the corresponding imidates<sup>9</sup> followed by cyclization. While the commercially available *tert*-butyl-substituted bis(oxazoline) **5**<sup>10,11</sup> often gives rise to the highest selectivities, a number of applications<sup>12</sup> have been developed in which the bis(4-isopropoxyloxazoline) **4** or the phenyl-substituted bis(oxazoline) **6** will give similar or even better results. Moreover, for the synthesis of **5** the unnatural and therefore expensive amino acid *tert*-leucine is required. Consequently, bis(4-isopropoxyloxazoline) **4**, available as either enantiomer from inexpensive (*S*)- or (*R*)-valine, is an attractive alternative for large scale applications if equally good enantioselectivity can be achieved.



The procedure described here for bis(4-isopropylloxazoline) **4** closely resembles the previously reported protocols for the bis(4-ethylloxazoline) **7**<sup>13</sup> and the bis(4-*tert*-butylloxazoline) ligand **5**.<sup>10</sup> The main differences can be found in the workup conditions, which accommodate the quite different solubility and crystallization properties of intermediates and final ligands.

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## Appendix

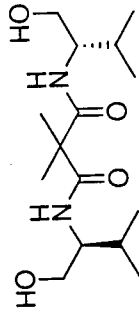
### Chemical Abstracts Nomenclature (Registry Number)

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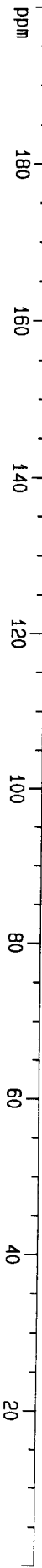
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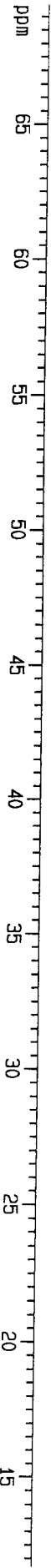
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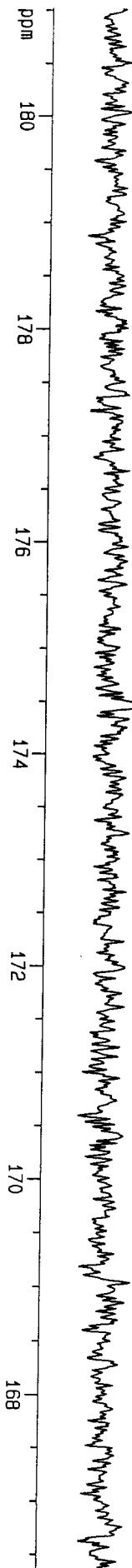
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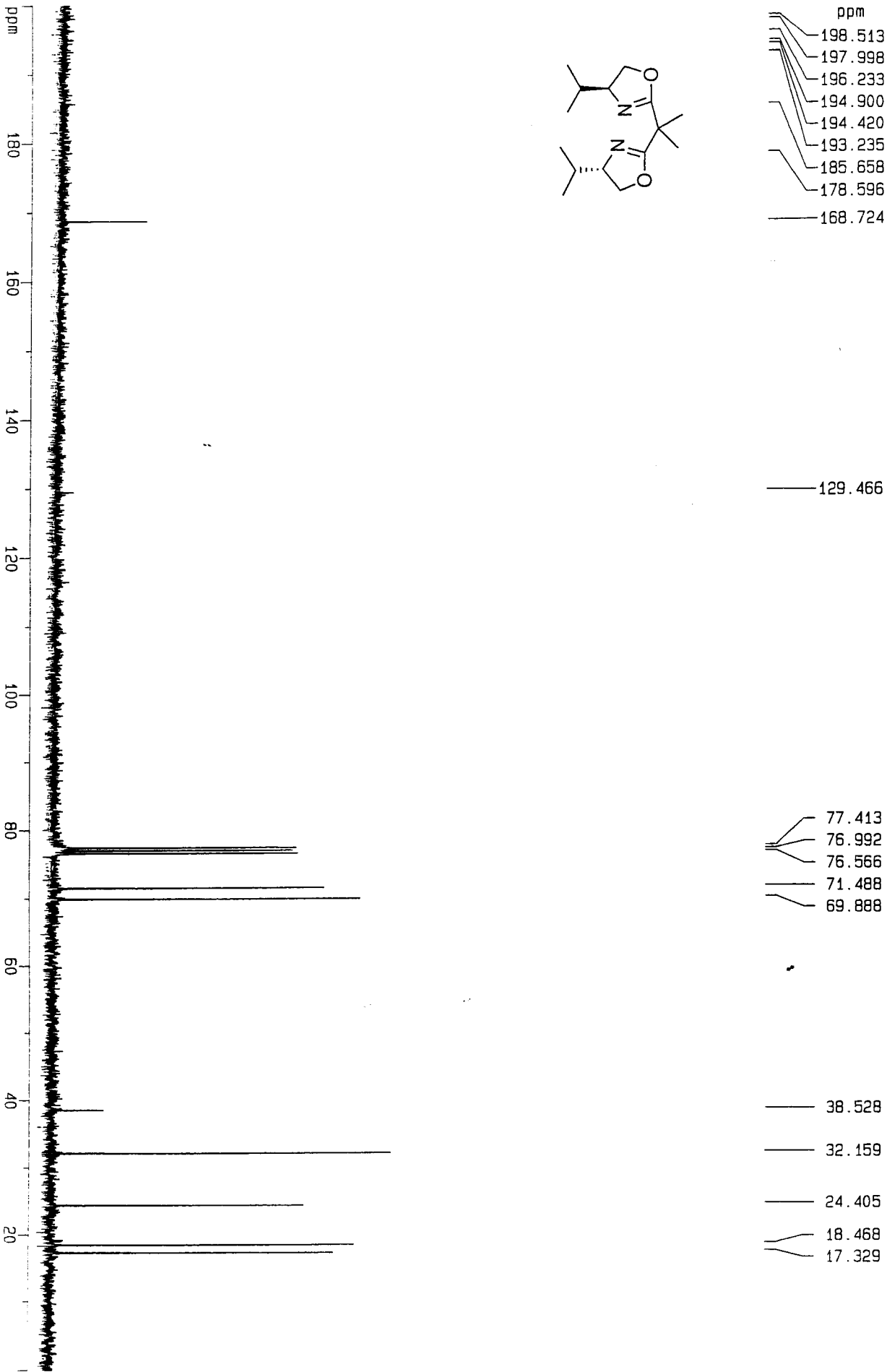


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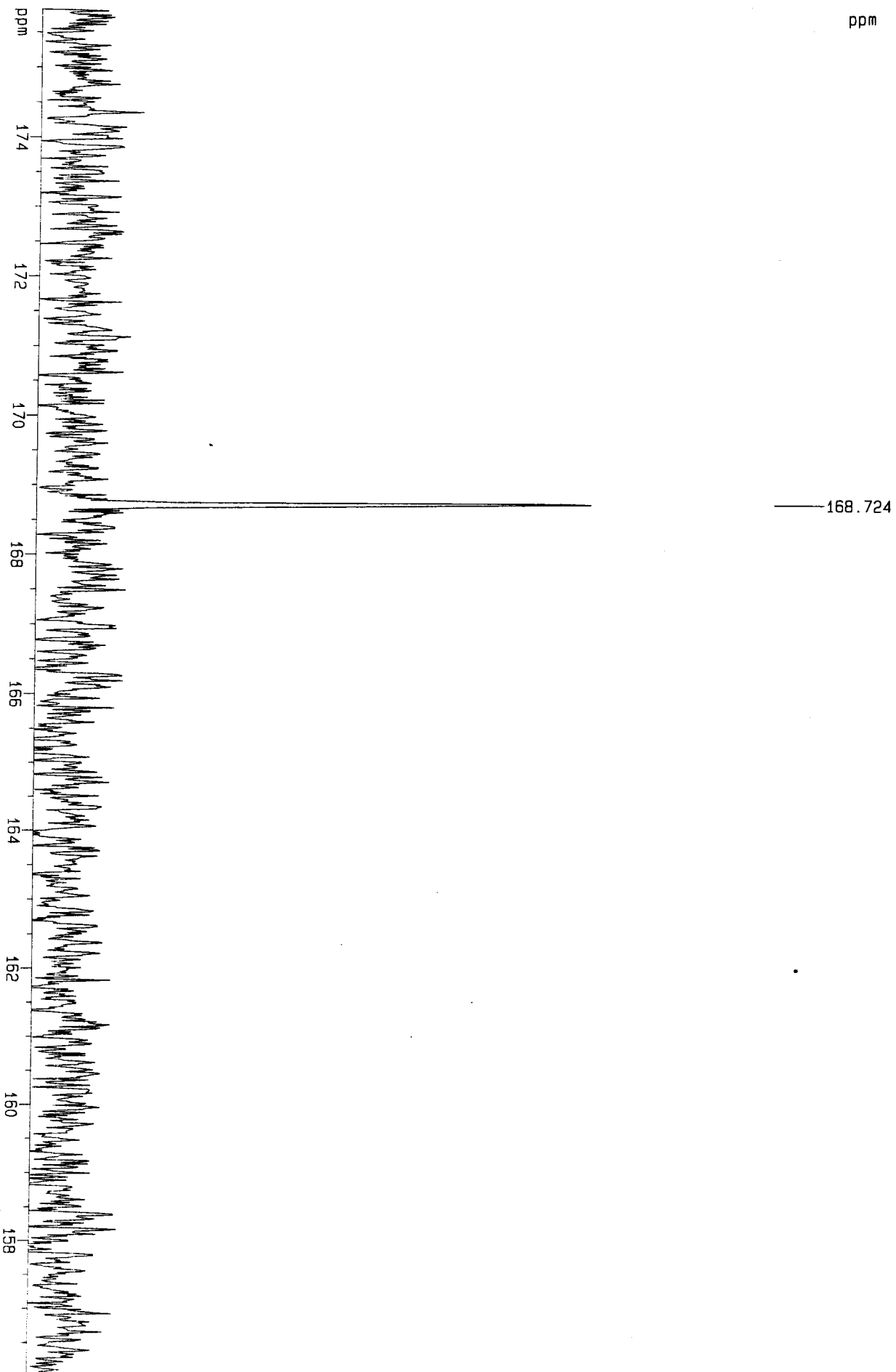




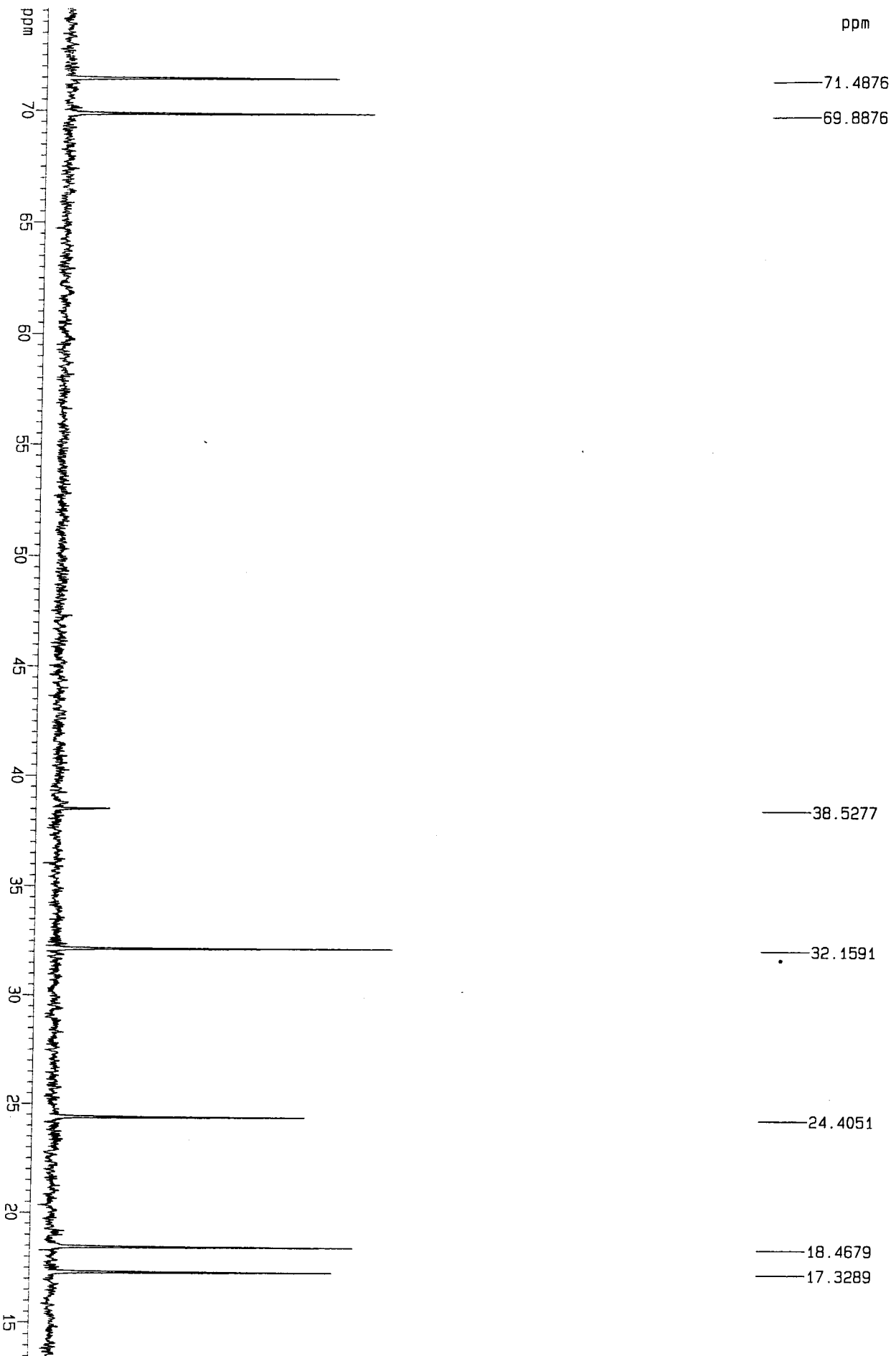
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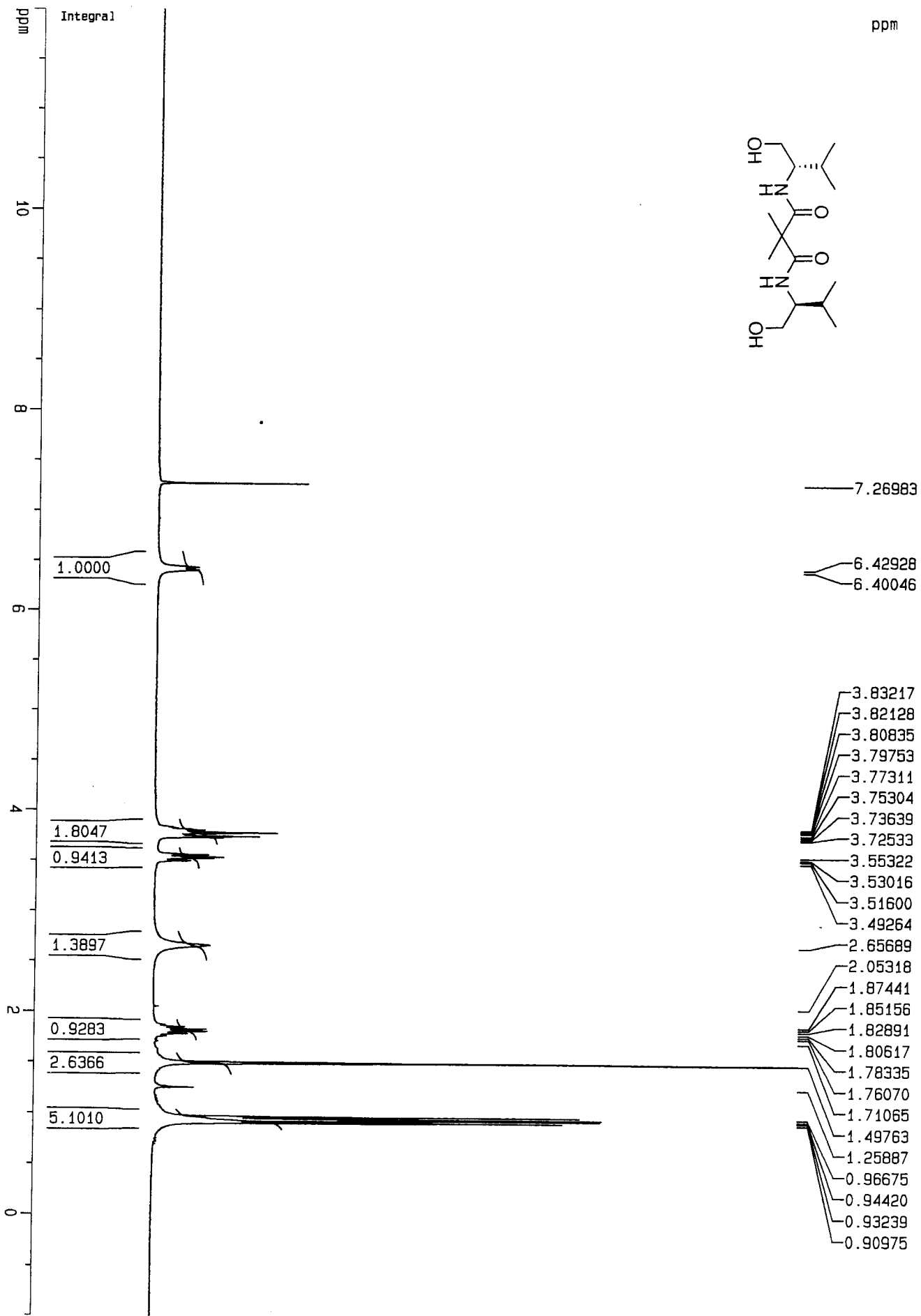
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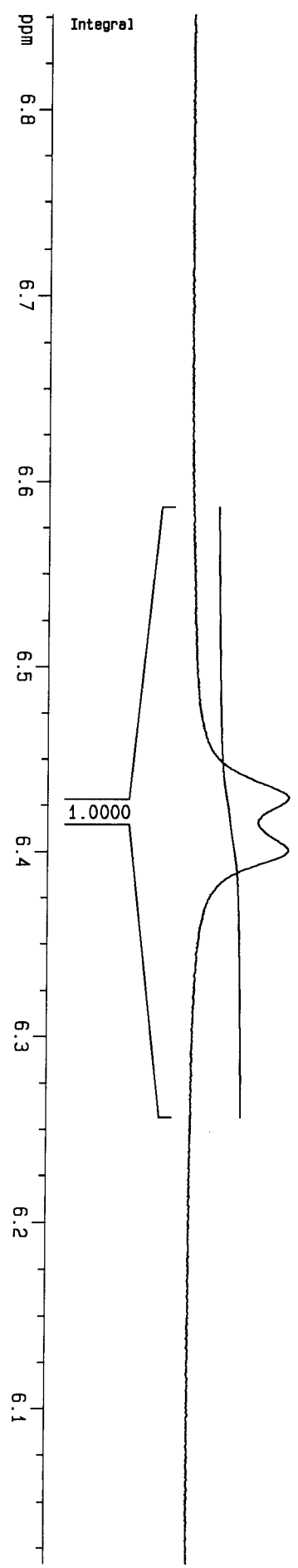


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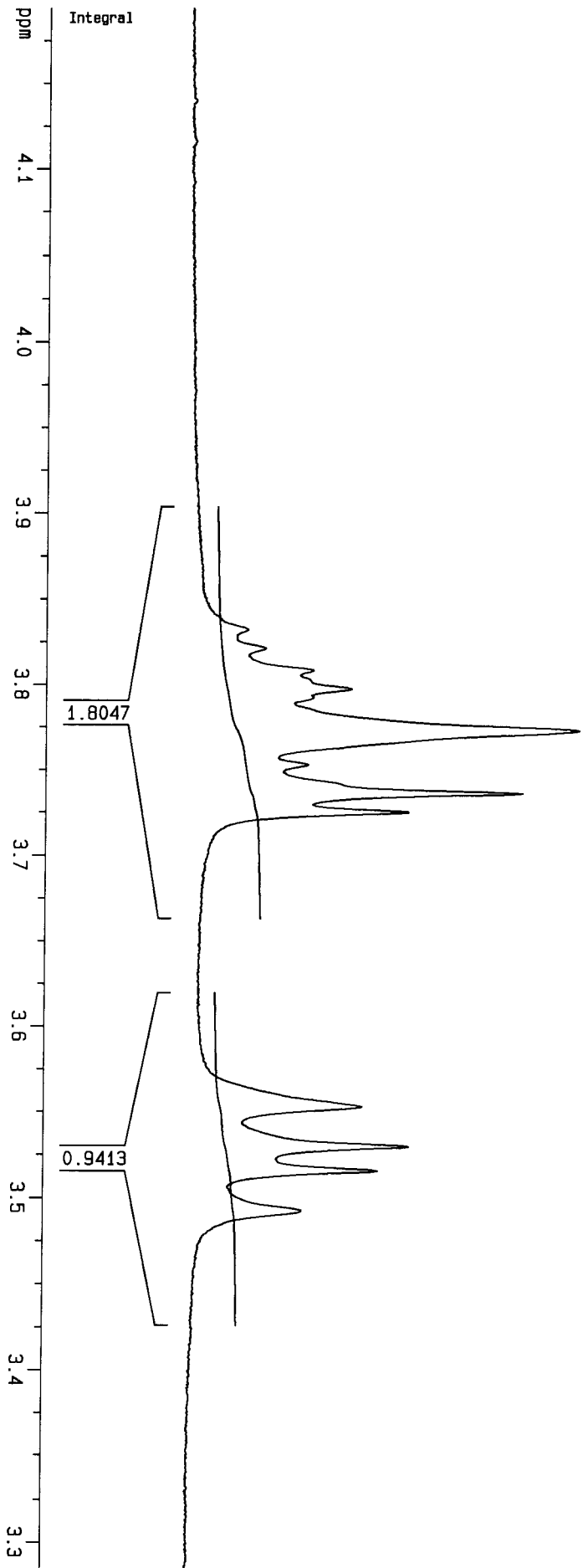


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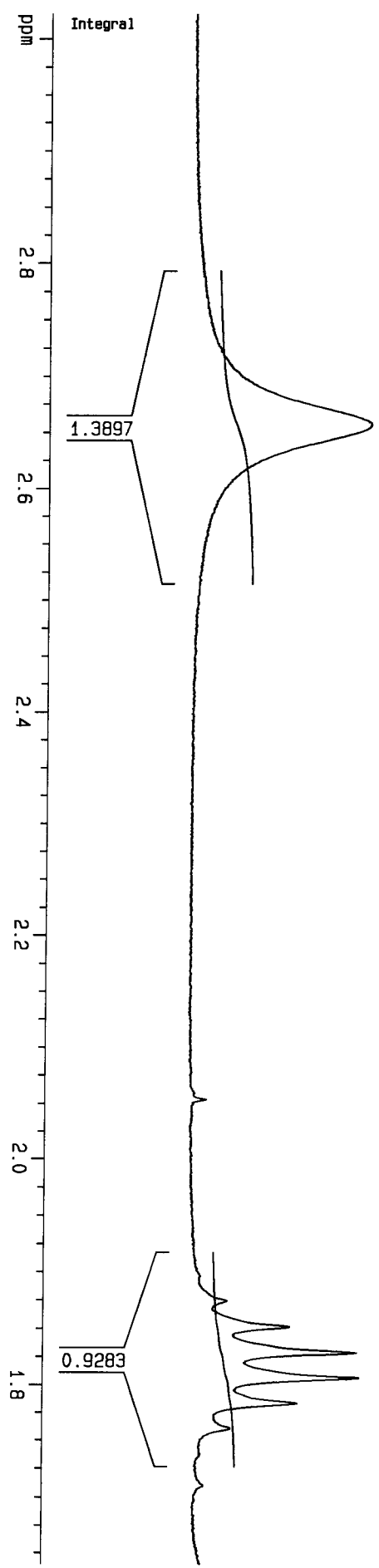
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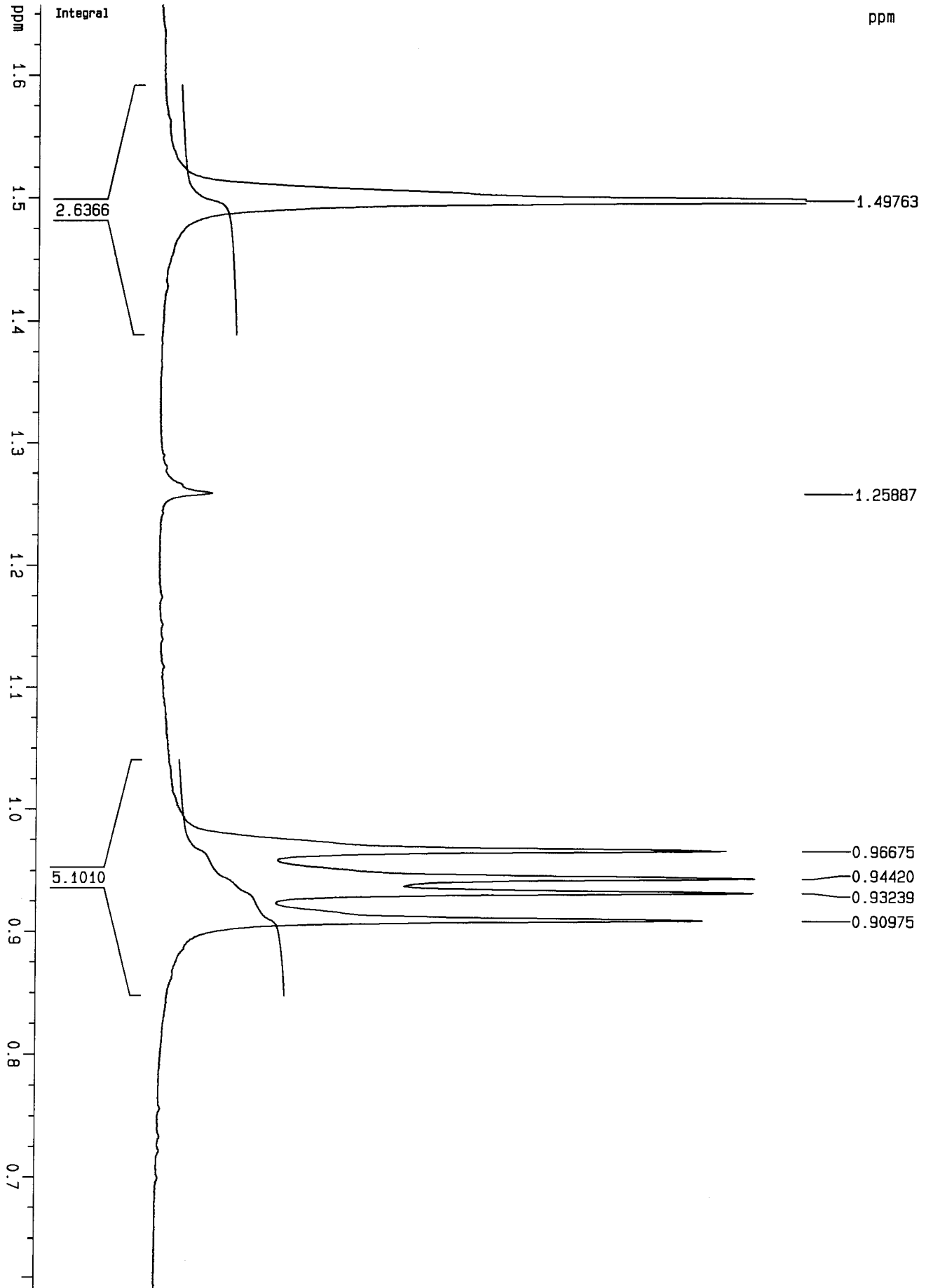




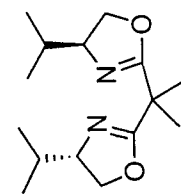
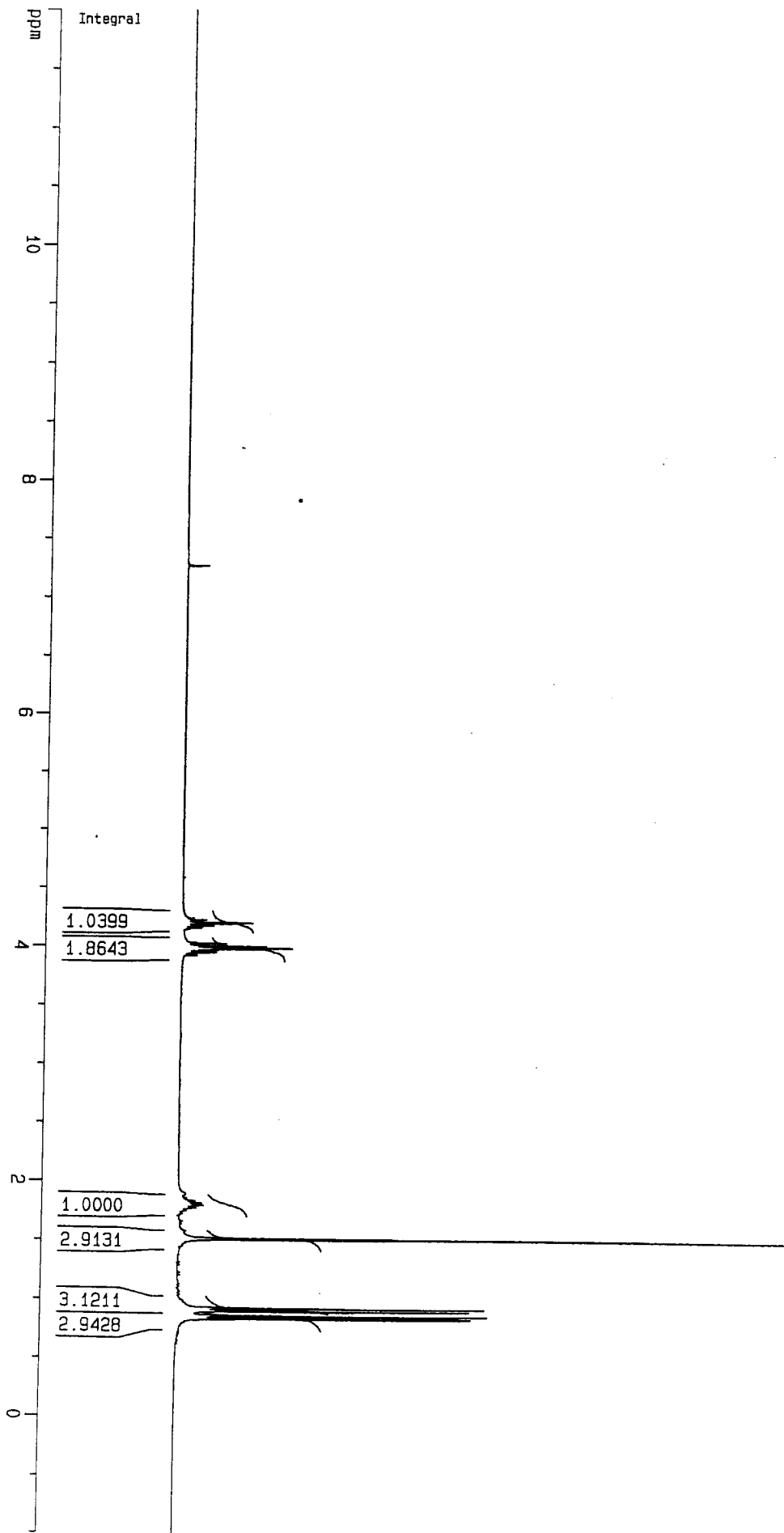
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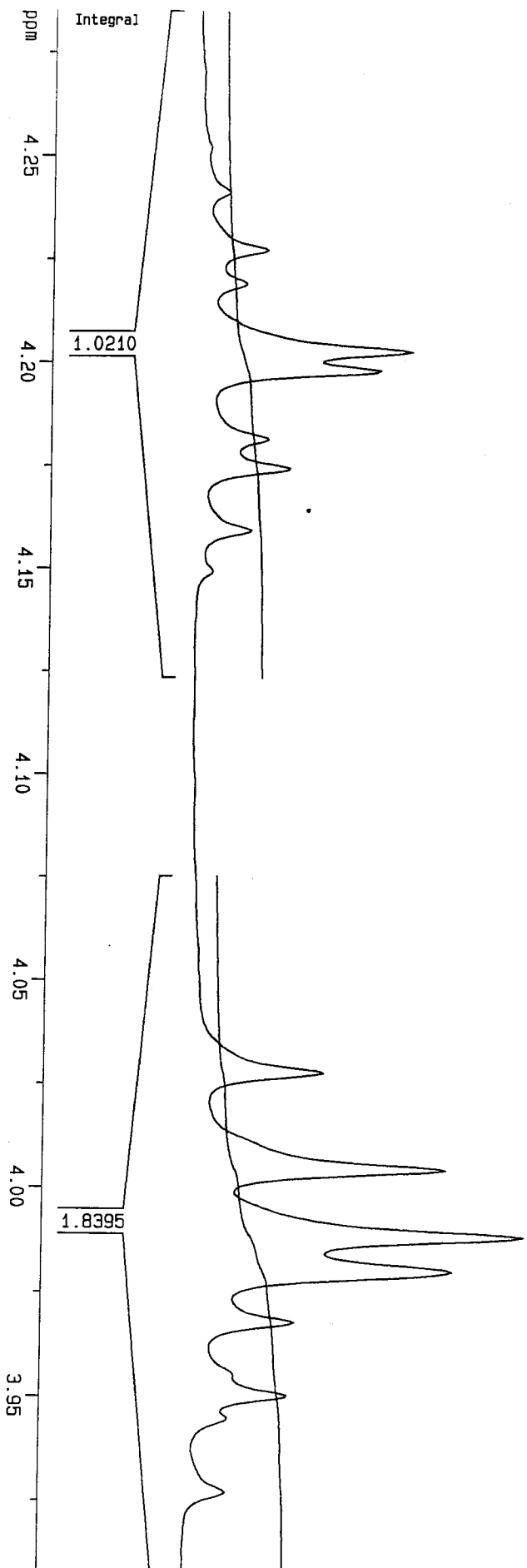
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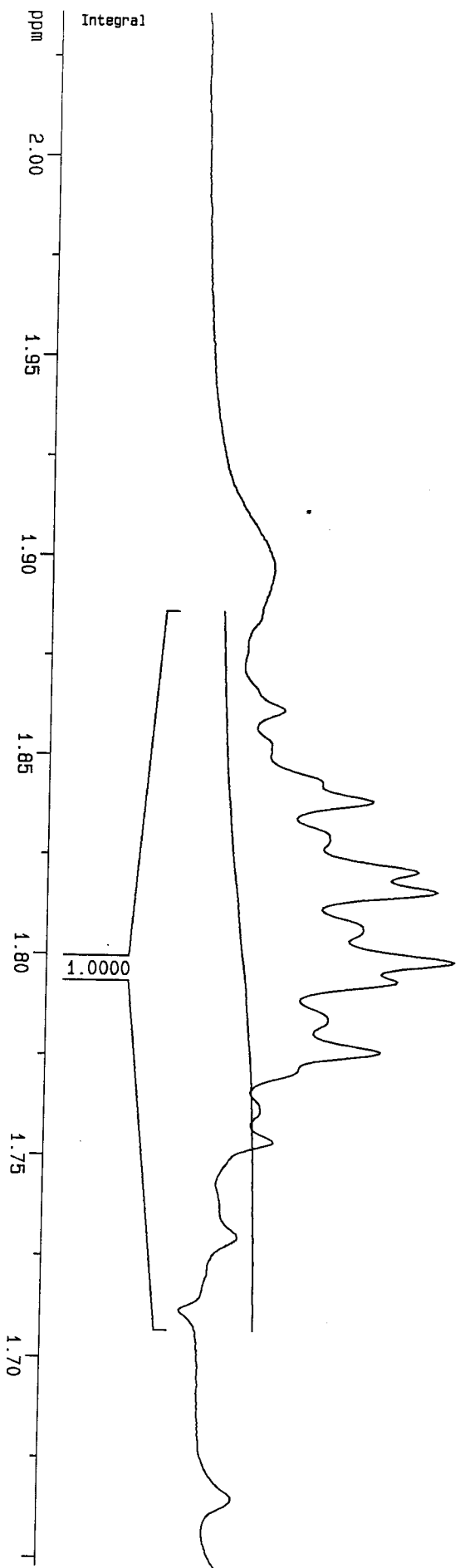
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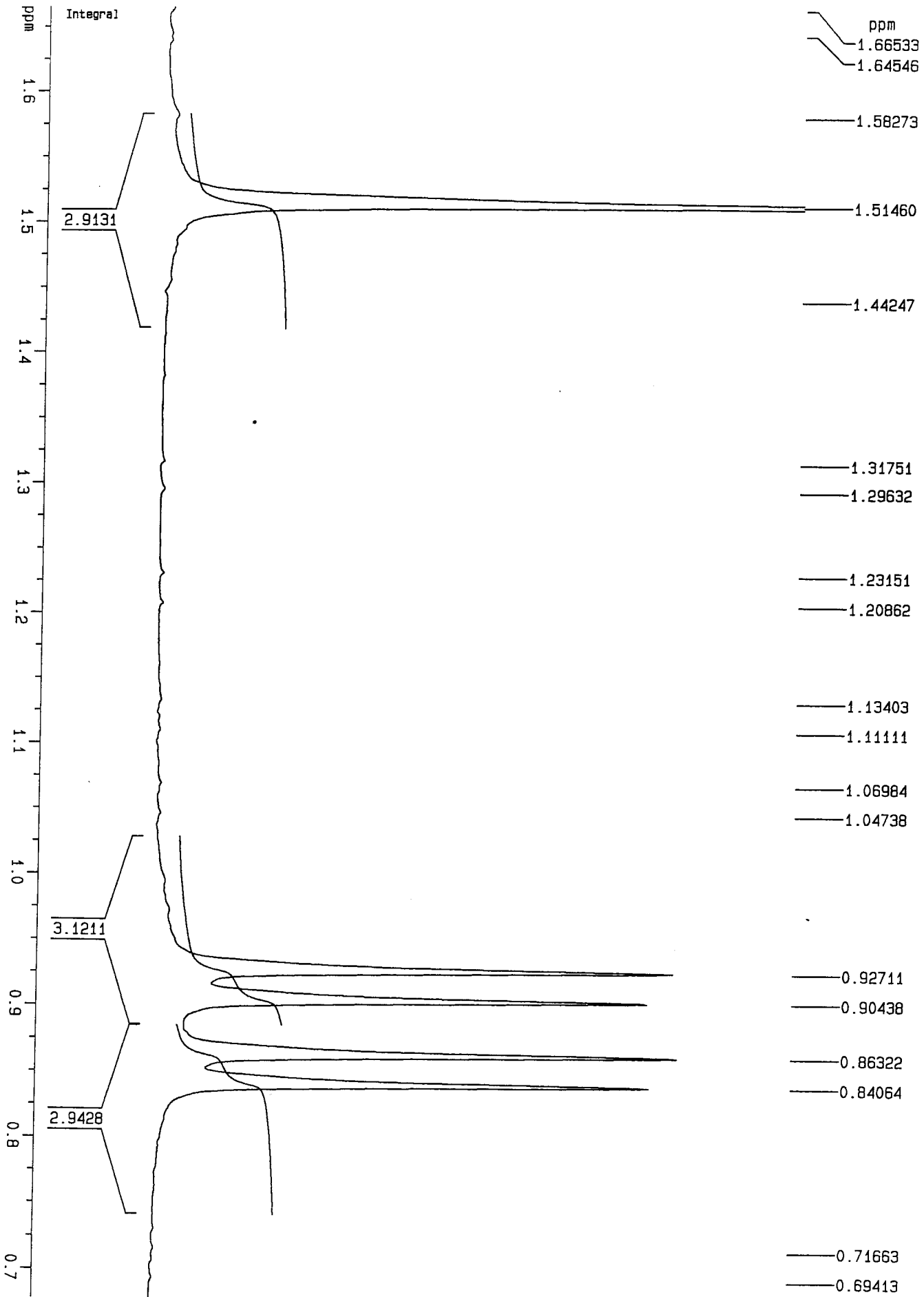
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