# Supporting Information

# Total Synthesis of (+)-cystothiazole A

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General experimental procedures. Characterization data for new compounds. $^{1}$H and $^{13}$C NMR spectra. and HPLC for isomere or enantioenriched compound.

**General:** All non-aqueous reactions were run under an inert atmosphere (nitrogen or argon) with rigid exclusion of moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds.[1] All glassware was stored in the oven and/or was flame-dried prior to use under an inert atmosphere. Anhydrous solvents were obtained either by filtration through drying columns (THF, ether, $CH_2Cl_2$, DMF, hexane) on a GlassContour system (Irvine, CA), by distillation over calcium hydride ($Et_3N$, pyridine, diisopropylamine, HMPA). Ethyl acetate and acetone was using as HPLC grade without further purification. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel (Merck 60 $F_{254}$). Visualization of the developed chromatogram was performed by UV absorbance, aqueous cerium molybdate, ethanolic phosphomolybdic acid, iodine, or aqueous potassium permanganate. Flash column chromatography was performed using 230-400 mesh silica (EM Science or Silicycle) of the indicated solvent system according to standard technique.[2] Preparative HPLC with an LCMS detector (LC = Liquid Handler from Gilson, MS = MSQ Surveyor from Thermo Finigan) using an Alltech type of column Prevail C 18 5m was use for the isolation of cystothiazole A. Melting points were obtained on a Buchi melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin Elmer Spectrum One FTIR and are reported in reciprocal centimeters ($cm^{-1}$). Nuclear magnetic resonance spectra ($^1H$, $^{13}C$, DEPT 135) were recorded either on a Bruker AV 300, AMX 300, AV 400, ARX 400. Chemical shifts for $^1H$ NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, d 7.27 ppm or benzene, d 7.16 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sept = septuplet, m = multiplet and br = broad), coupling constant in Hz, integration, and assignment. Chemical shifts for $^{13}C$ NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform (77.00 ppm) or deuterobenzene (128 ppm) as the internal standard. All spectra were obtained with complete proton decoupling. When ambiguous, proton and carbon assignments were established using COSY, HMQC and DEPT experiments. Optical rotations were determined with a Perkin-Elmer 341 polarimeter at 589 or 546 nm. Data are reported as follows: $[a]_D^{temp}$, concentration (*c* in g/100 mL), and solvent. High resolution mass spectra were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal. Low resolution mass spectra were performed on an Agilent 1100 Series LC system equipped with a diode array UV detector; or on an Agilent 1100 Series LC system equipped with an electrospray or APCI mass detector with

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[1] Shriver, D. F.; Drezdzon, M. A. *The manipulation of air-sensitive compounds*; 2nd Edition ed.; Wiley: New York, 1986.

[2] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

simultaneous diode array UV detection. Combustion analyses were performed by the Laboratoire d'analyse élémentaire de l'Université de Montréal.

**Reagents:** Unless otherwise stated, commercial reagents were used without purification. Coumpond (+)-**2**[3], **7**[4], (-)-**10**[5], **1 9**[4] were compared to authentic samples.

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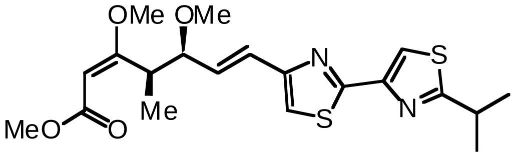
[3] Backhaus, D. *Tetrahedron Lett*. **2000**, *41*, 2087.

[4] Williams, D. R.; Samarjit, S.; Clark, M. P. *J. Org. Chem*. **2001**, *66*, 8463.

[5] Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc*. **1994**, *116*, 4077.

## Experimental Section



(+)-*E*-**1**

### **Cystothiazole A** ((+)-*E*-**1**)

The phosphonium solution **3** (1.73 mL) which was prepared as described above was diluted with DMF (3.3 mL) followed by the addition of aldehyde (+)-**2** (12 mg, 0.055 mmol) and the resulting mixture was cooled down to -20 °C. DBU (17 mL, 0.110 mmol) was then added and the reaction was warm up to 0 °C and stirred over a 24 h period. The reaction was concentrated under vacuum and the residu was filtered through a plug of silica gel and eluting with 30 % EtOAc/hexanes and concentrated the volatil under reduced pressure. The filterate was concentrated under reduced pressure. The yellow oil was quickly purified to afford cystothiazole A as a mixture: (+)-*E*-**1**/(+)-*Z*-**1** 6.9:1 (72%). Its olefin isomer was distinguished by $^1$H NMR signal d 5.07 (s, 1H, C*H*=C(OMe)), 3.68 (s, 6H). Further purification was achieved by preparative HPLC to afford pure cystothiazole A (+)-*E*-**1** and NMR spectra were identical with those reported.[6] R$_f$ 0.27 (20% EtOAc /hexanes); $[a]_D^{20}$ 104° (*c* 0.21, CHCl$_3$), lit.[6] $[a]^{20}_D$ 109° (*c* 0.24, CHCl$_3$), $^1$H NMR (300 MHz, CDCl$_3$) d 7.88 (s, 1H, C*H*S), 7.10 (s, 1H, C*H*S), 6.58 (d, *J* = 15.7 Hz, 1H, CH(OMe)CH=C*H*), 6.40 (dd, *J* = 15.7 Hz, 1H, CH(OMe)C*H*=CH), 4.96 (s, 1H, C*H*=C(OMe)), 4.17 (dq, *J* = 7.2, 7.2 Hz, 1H, C*H*OMe), 3.81 (dd, *J* = 7.2, 7.2 Hz, 1H, C*H*CH$_3$), 3.66 (s, 3H, COC*H*$_3$), 3.60 (s, 3H, OC*H*$_3$), 3.37 (sept, *J* = 7.1 Hz, 1H, C*H*(CH$_3$)$_2$), 3.33 (s, 3H, OC*H*$_3$), 1.43 (d, *J* = 6.9 Hz, 6H, CH(C*H*$_3$)$_2$), 1.21 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) d 178.7, 176.7, 167.7, 162.7, 154.2, 148.4, 131.9, 125.3, 115.2, 114.9, 91.1, 84.4, 57.0, 55.5, 50.8, 39.8, 33.3, 23.1, 14.1; IR (film) n 2928, 1708, 1623, 1145, 1094 cm$^{-1}$; HRMS (FAB) calcd for $C_{20}H_{26}N_2O_4S_2$ [M+H]: 423.1420, Found : 423.1419.

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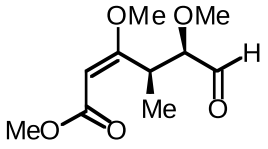
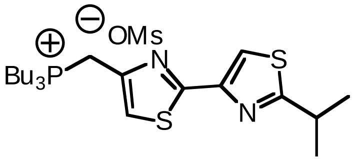
[6] Sakagami, Y.; Ojika, M.; Suzuki, Y.; Tsukamoto, A.; Fudou, R.; Yoshimura, T. *J. Antibio.* **1998**, *51*, 275.



**2**

### Methyl (4*E*)-5-deoxy-2,3,4-tri-*O*-methyl-L-*treo*-hex-4-enuronate (2).

To a solution of the alcohol **15** (48,9 mg, 0.22 mmol) in $CH_2Cl_2$ (3 mL) was added in one portion the Dess-Martin reagent (104 mg, 0.25 mmol) and the resulting mixture was stirred for 1 h period at room temperature. The reaction was then quenched by addition of an aqueous saturated solution of $Na_2S_2O_3$ (5 mL). After 5 min of mixing, the resulting biphasique solution was diluted with ether (10 mL) and aqueous layer was discarded. Ether layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, concentrated to afford (+)-**2** (48.0 mg, 99%) as colorless oil. $R_f$ 0.57 (40% EtOAc/hexanes); $[a]_D^{20}$ +105.0° (*c* 0.46, $CHCl_3$), lit.[7] $[a]_D^{20}$ +104,7° (*c* 0.55, $CHCl_3$), $^1H$ NMR was identical with previously reported see reference 7. $^1H$ NMR (300 MHz, $CDCl_3$) d 9.10 (d, *J* = 2.5 Hz, 1H, C*H*O), 4.49 (dt, *J* = 7.1, 7.1 Hz, 1H, C*H*$OCH_3$), 3.69 (s, 3H, OC$H_3$), 3.64 (s, 3H, OC$H_3$), 3.57 (dd, *J* = 6.9, 2.4 Hz, 1H, C*H*$CH_3$), 3.43 (s, 3H, OC$H_3$), 1.20 (d, *J* = 7.1 Hz, 3H, CHC$H_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$) d 202.1, 174.3, 167.5, 91.8, 87.3, 58.5, 55.6, 50.9, 36.4, 13.8.



**3**

### tributyl[(2'-isopropyl-2,4'-bi-1,3-thiazol-4-yl)methyl]!phosphonium mesylate (3).

To a solution of the alcohol **20** (40 mg, 0.17 mmol) in $CH_2Cl_2$ (3 mL) was added triethylamine (35.0 mL, 0.25 mmol), the resulting mixture was cooled down to 0 °C and the methanesulfonyl chloride (15.5 mL, 0.2 mmol) was added dropwise. After 1 h of mixing, the reaction was quenched by adding an aqueous solution of 10% HCl (5 mL) and diluted with ether (15 mL). The aqueous phase was then discarded, and the organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (10 mL), dried over anhydrous $MgSO_4$, filtered and

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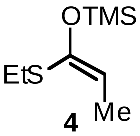
[7] Backhaus, D. *Tetrahedron Lett.* **2000**, *41*, 2087.

concentrated under reduced pressure. The resulting white solid was dissolved in DMF (5 mL), tributylphosphine (166 mL, 0.66 mmol) was added and the reaction was stirred over a 12 h period at room temperature. The resulting solution was warm up to 40 °C for 30 min and cooled to room temperature. The resulting phosphonium **3** solution was then use without further purification for the Wittig olefination step.

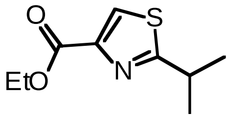


**4**

*Z* : *E* = 91:9

### {[(1*Z*)-1-(Ethylthio)prop-1-enyl]oxy}(trimethyl)silane (4).

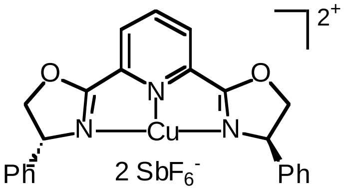
To a solution of diispropylamine (5.28 mL, 51 mmol) in anhydrous THF (80 mL) to -20 °C was added a solution of butyllithium (1.59 M in THF), stirred for 15 min, and cooled to -78 °C. A solution of the thioester **8** (6 g, 51 mmol) in THF (20 mL) was cannulated slowly into the yellow solution and stirred for an additional 15 min. Chlorotrimethylsilane (6.44 mL, 51 mmol) was added, and the solution was stirred for an additional 1 h at -78 °C. The solution was warmed to room temperature over a 1 h period before being diluted with pentane (150 mL) and washed with phosphate buffer pH 7 (100 mL). The organic layer was dried over $Na_2SO_4$ anh., concentrated, and distilled under vacuum to furnish the (Z) silylketene thioacetal **4** (66 °C, 5 mm Hg, 8.6 g, 89 %, 91:1 (*Z*/*E*)). $^1$H NMR (300 MHz, $CDCl_3$) d 5.05 (q, *J* = 6.8 Hz, 1H, $CHCH_3$), 2.65 (q, *J* = 7.4 Hz, 2H, $CH_2S$), 1.59 (d, *J* = 6.8 Hz, 3H, $CHCH_3$), 1.24 (t, *J* = 7.4 Hz, 3H, $CH_3CH_2S$), 0.26 (s, 9H, $Si(CH_3)_3$). Its olefin isomer was distinguished by $^1$H NMR 1.68 (d, *J* = 6.8 Hz, 3H).



**7**

### Ethyl 2-isopropyl-1,3-thiazole-4-carboxylate (7).

To a solution of thiazoline **17** (4.86 g, 24.1 mmol) in $CH_2Cl_2$ (90 mL) at 0 °C was added DBU (7.23 mL, 48.3 mmol) and the resulting mixture was stirred for 10 min. The bromotrichloromethane (2.38 mL, 24.1 mmol) was added dropwise and the reaction was then warm up to room temperature. After 1 h, the reaction was quenched with a satureted aqueous solution of $NaHCO_3$ and transfert in a seperatory funnel and the aqueous phase was discarded. The organic phase was then dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by column chromatography on silica gel (20% EtOAc/hexanes) to afford thiazole **7** (4.8 g, 99%) as a colorless oil. $R_f$ 0.3 (20% EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) d 7.96 (s, 1H, C*H*S), 4.31 (q, *J* = 7.2 Hz, 2H, $CH_2CH_3$), 3.33 (sept, *J* = 6.8 Hz, 1H, $CH(CH_3)_2$), 1.32 (d, *J* = 6.8 Hz, 6H, $(CH_3)_2$), 1.30 (t, *J* = 7.2 Hz, 3H, $CH_2CH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) d 178.8, 161.4, 146.4, 126.2, 61.1, 33. 4, 23.1, 14.2; IR (film) n 2983, 1736, 1372, 1253, 1043 cm$^{-1}$; HRMS (MAB) calcd for $C_9H_{13}NO_2S$ $[M]^+$:199.0679, Found : 199.0669.



**9**

### [Cu((*R*, *R*)-phenyl-bis(oxazolinyle)pyridine)]$(SbF_6)_2$ (9).

The Evans procedure[8] was employed for the synthesis of this catalyst. To a solution of (*R*, *R*)-bis(phenyloxazolinyl)pyridine (138 mg, 0.375 mmol) in $CH_2Cl_2$ anh. (9 mL) was added $CuCl_2$ (51 mg, 0.375 mmol) solid and the resulting suspension was stirred over a 1 h period. To the resulting fluorescent green

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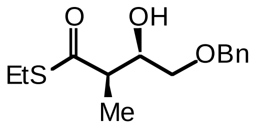
[8] Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669.

suspension was added $AgSbF_6$ (258 mg, 0.750 mmol) solid and stirred for an additional 3 h in the absence of light and filtered through an oven-dried glass pipet tightly packed with cotton to remove the white AgCl precipitate, yielding active catalyst $[Cu((R, R)\text{-Ph-pybox})](SbF_6)_2$ **9** as a clear blue solution (0.042 M in $CH_2Cl_2$).

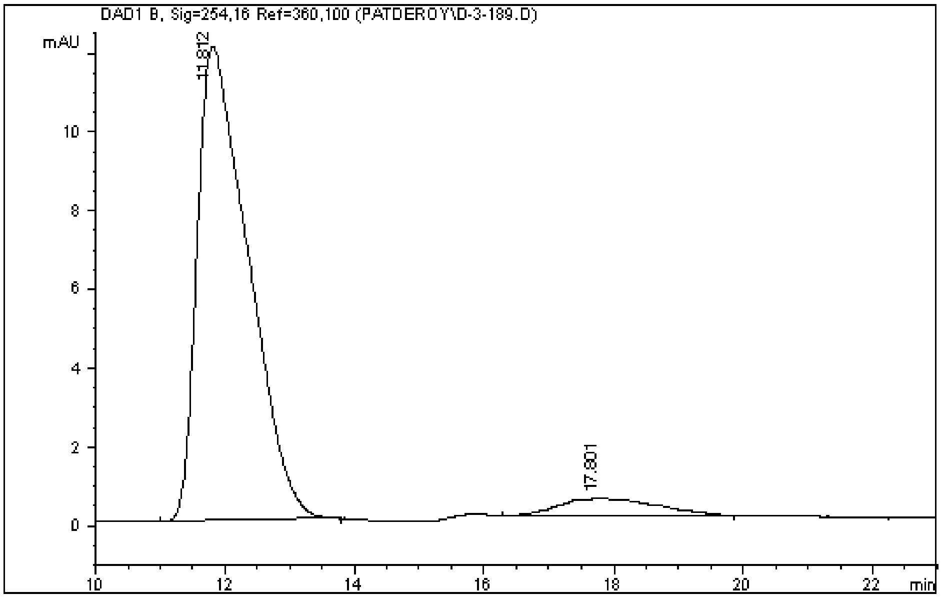


**10**

### *S*-Ethyl (2*R*,3*S*)-4-(benzyloxy)-3-hydroxy-2-methoxybutanethioate (10).

To a -78 °C solution of $[Cu((R, R)\text{-Ph-pybox})](SbF_6)_2$ **9** (which was prepared as described above) in $CH_2Cl_2$ anh. (10 mL) was added commercialy available benzyloxyacetaldehyde **5** (563 mg, 3.75 mmol), followed by a silylketene acetal **4** (855 mg, 4.50 mmol). The resulting solution was stirred at -78 °C for 12 h. The reaction mixture was then filtered through a plug of silica gel and eluted with $Et_2O$. Concentration of the ether solution gave a clear oil, which was dissolved in THF (30 mL) and 1 N HCl ( 6 mL). After standing at room temperature for 15 min, this solution was poured into a seperatory funnel and diluted with ether (150!ml), and water (50 mL). After mixing, the aqueous layer was discarded, and the ether layer was washed with saturated aqueous $NaHCO_3$ and brine. The resulting organic phase was dried over anhydrous $MgSO_4$, filtered, concentrated and purified by column chromatography on silica gel (15-20% EtOAc/hexanes) to afforded (-)-**10** (935.7 mg, 93%, 97.5 : 2.5 syn:anti by NMR $^1H$, as colorless oil). Product ratios were also determined by HPLC with Chiralcel OD column (96:4 hexanes/2-propanol): *syn*-(2*R*,3*S*) $t_r$ = 11.7 min; *syn*-(2*S*,3*R*) $t_r$ = 13.93 min; *anti*-(2*S*,3*S*) $t_r$ = 15.8 min; *anti*-(2*R*,3*R*) $t_r$ = 17.9 min; 94:6 syn:anti; >98% syn *ee*. NMR spectra was identical with those reported.[5] $R_f$ 0.33 (20 % EtOAc/hexanes); $[a]_D^{20}$ -42.4 ° (*c* 0.55, $CH_2Cl_2$), lit.[8] $[a]_D^{20}$ +41.1° (*c* 3.6, $CH_2Cl_2$) for the other enantiomer, $^1H$!NMR (400 MHz, $CDCl_3$) d 7.28-7.29 (m, 5H, 5 $CH_{Aro}$), 4.56 (d, *J* = 12.0 Hz, 1H, $CH_aPh$), 4.53 (d, *J* = 11.9 Hz, 1H, $CH_bPh$), 4.04 (dt, *J* = 4.4, 5.9 Hz, 1H, CHOH), 3.47 (m, 2H, $CH_2OBn$), 2.85 (q, *J* = 7.2 Hz, 2H, $CH_2S$), 2.81 (m, 1H, $CH(CH_3)COS$), 2.61 (br, 1H, CHOH), 1.25 (d, J = 7.2 Hz, 3H, $CHCH_3$), 1.23 (t, *J* = 7.2 Hz, 3H, $CH_3CH_2S$); $^{13}C$ NMR (100 MHz, $CDCl_3$) d 202.8, 137.7, 128.4 (2), 127.8 (2), 73.4, 71.5, 71.1, 50.7, 23.2, 14.6, 13.1; IR (film) n 3442, 2968, 2930, 2870, 1678, 1453, 1096, 1061, 956, 736, 697 $cm^{-1}$; HRMS (MAB) calcd for $C_{14}H_{20}O_3S$ $[M]^+$: 268.1133, Found : 268.1135.

Evans aldol



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|   1|    11.812|MM      |  0.913|    659.026|  93.617|                |
|   2|    17.801|MM      |  1.737|     44.936|   6.383|                |
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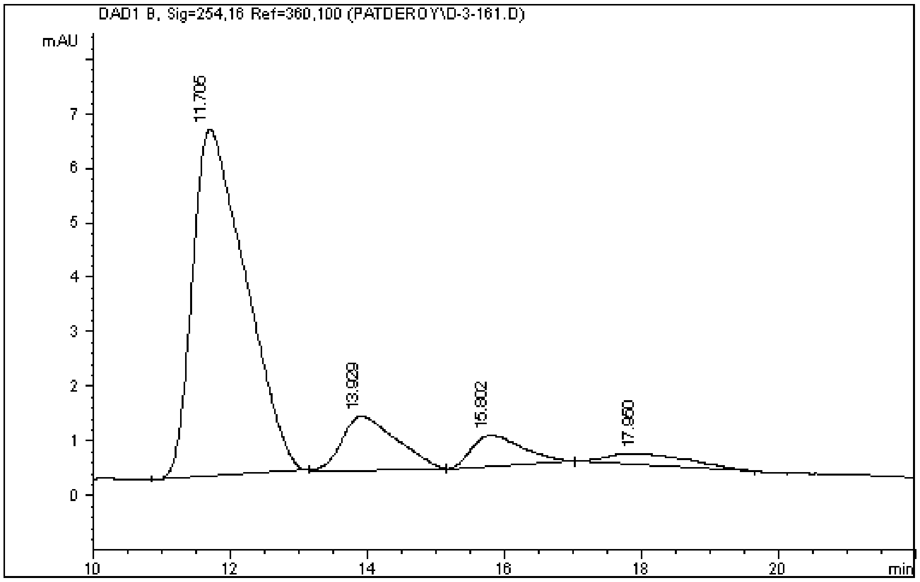
Aldol Mixture



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|   1|    11.705|MM      |  0.899|    343.599|  77.325|                |
|   2|    13.929|MM      |  0.923|     54.667|  12.303|                |
|   3|    15.802|MM      |  0.837|     28.687|   6.456|                |
|   4|    17.950|MM      |  1.440|     17.402|   3.916|                |
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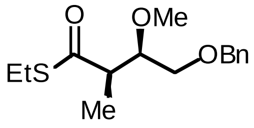
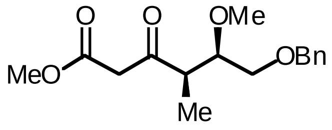


**11**

**_S_-Ethyl (2_R_,3_S_)-4-(benzyloxy)-2,3-dimethoxybutanethioate (11).**

To a solution of alcohol **10** (890.9 mg, 3.32 mmol) in $CH_2Cl_2$ (33 mL) at 0!°C was added proton-Sponge (2.5 g, 13.3 mmol) and stirred until everything come soluble (approximetly 5 min). Tetramethyloxonium tetrafluoroborate (1.96 g, 13.3 mmol) was then added and the resulting mixture was stirred for a 20 h period. The reaction mixture was then filtered through a plug of silica gel and eluted with 20 % EtOAc/hexanes. Concentration under reduced pressure gave a yellow oil, which was purified by column chromatography on silica gel (5% EtOAc/hexanes) to afforded **11** (892.5 mg, 95%) as a colorless oil. $R_f$ 0.40 (15% EtOAc/hexanes); $[a]_D^{20}$ -7.9° (*c* 0.355, $CHCl_3$), $^1$H NMR (300 MHz, $CDCl_3$) d 7.31-7.25 (m, 5H, 5 C$H_{Aro}$), 4.56 (d, *J* = 12.0 Hz, 1H, C$H_a$Ph), 4.51 (d, *J* = 12.0 Hz, 1H, C$H_b$Ph), 3.66 (q, *J* = 6.2 Hz, 1H, C*H*O$CH_3$), 3.57-3.48 (m, 2H, C$H_2$OBn), 3.44 (s, 3H, CHOC$H_3$), 2.98 (t, *J* = 6.5 Hz, 1H, C*H*($CH_3$)COS), 2.86 (q, *J* = 7.4 Hz, 2H), 1.23 (t, *J* = 7.4 Hz, 3H, C$H_3$$CH_2$S), 1.22 (d, *J* = 7 Hz, 3H, CHC$H_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) d 201.9, 138.1, 128.3 (2), 127.62 (2), 127.56, 81.0, 73.3, 69.8, 58.79, 58.77, 50.1, 23.2, 14.6, 13.0; IR (film) n 2972, 2873, 2930, 1679, 1454, 1099, 958 cm$^{-1}$; HRMS (MAB) calcd for $C_{15}H_{22}O_3S$ $[M]^+$: 282.1290, Found : 282. 1290.

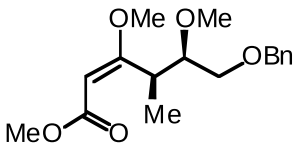


**13**

**Methyl 6-_O_-benzyl-2-deoxy-4,5-di-_O_-methyl-L-_treo_-hex-3-ulosonate (13).**

To a solution of thioester **11** (209 mg, 0.74 mmol) in acetone (7 mL) was added 10% Pd/C (20 mg) and this mixture was cooled down to 0 °C, followed by quick addition of trimethylsilane (591 mL, 3.70 mmol) and the reaction was stirred for 10 min. The reaction mixture was then filtered through Celite and concentrated under reduced pressure. The corresponding aldehyde was then diluted in $CH_2Cl_2$

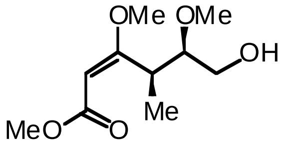
(2 mL) and added to a suspension of anhydrous $SnCl_2$ in $CH_2Cl_2$ (3 mL) charge with methyldiazoacetate **12** (220 mL). The resulting mixture was stirred vigourously over a 3 h period and then filtered through a plug of silica gel and eluting with 40 % EtOAc/hexanes and concentrated the volatil under reduced pressure. The residual yellow oil was purified by column chromatography on silica gel (10% EtOAc /hexanes) to afford b-ketoester (-)-**13** (185 mg, 85%) as a colorless oil. Ratio of 10.5:1 between b-ketoester **13** and enol form. $R_f$ 0.18 (15% EtOAc/hexanes); $[a]_D^{20}$ -16.0° (*c* 0.45, $CHCl_3$), $^1H$ NMR (300 MHz, $C_6D_6$) d 7.28-7.05 (m, 5H, $CH_{Aro}$), 4.25 (d, *J* = 12.0 Hz, 1H, $CH_aPh$), 4.19 (d, *J* = 12.0 Hz, 1H, $CH_bPh$), 3.46 (m, 1H, CHOCH3), 3.35-3.18 (m, 4H, 2 $CH_2$), 3.30 (s, 3H, $CH_3CO$), 3.11 (s, 3H, $OCH_3$, 2.78 (dq, *J* = 7.0, 5.7 Hz, 1H, $CH(CH_3)CO$), 1.04 (d, *J* = 7.0 Hz, 3H, $CHCH_3$); Enol form distinguished by $^1H$ NMR d5.2 (s, 1H), 1.16 (d, *J* = 6.95 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) d 204.4, 168.1, 139.1, 129.0 (2), 128.23 (2), 128.17, 81.6, 73.8, 70.2, 58.5, 51.9, 40.1, 48.7, 12.4; IR (film) n 2937, 1748, 1713, 1454, 1319, 1254, 1095, 1033, 738, 699 $cm^{-1}$; HRMS (MAB) calcd for $C_{16}H_{22}O_5$ $[M]^+$ 294.1469, Found : 294.1467.



**14**

### Methyl (2*E*)-6-*O*-benzyl-2-deoxy-3,4,5-tri-*O*-methyl-L-*treo*-hex-2-enoate (14).

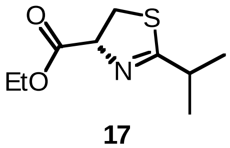
A solution of b-ketoester **13** (126.8 mg, 0.43 mmol) in HMPA (1 mL) was added dropwise to a suspension of 60% suspension of NaH in oil (38.0 mg, 0.94 mmol) in HMPA (1.1 mL) at 10 °C and the resulting mixture was stirred until the evolution of gaz was over. After 10 min of stirring, dimethylsulfate (89.7 mL, 0.94 mmol) was added and the solution was warmed to room temperature and stirred for an additional 15 minutes. The reaction was then quenched with water (10 mL) and diluted with ether. After mixing, the aqueous layer was discarded, and the ether layer dried over anhydrous $MgSO_4$, filtered, concentrated and purified by column chromatography on silica gel (10% EtOAc/hexanes) to afforded (+)-**14** (935.7 mg, 83%, 110.1 mg, ratio *E*/*Z* = 19:1) as colorless oil. $R_f$ 0.28 (15% EtOAc/hexanes); $[a]_D^{20}$ +64.0 ° (*c* 0.22, $CHCl_3$),!$^1H$ NMR (400 MHz, $CDCl_3$) d 7.36-7.30 (m, 5H, $CH_{Aro}$), 4.96 (s, 1H, $CHCO_2Me$), 4.55 (d, *J* = 12.0 Hz, 1H, $CH_aPh$), 4.49 (d, *J* = 12.0 Hz, 1H, $CH_bPh$), 4.12 (quint, *J* = 7.05 Hz, 1H, $CHOCH_3$), 3.66 (s, 3H, $CO_2CH_3$), 3.56 (s, 3H, $CHC(OCH_3)CH$), 3.54-3.38 (m, 3H, C*H*$_2$OBn et C*H*CH$_3$), 3.48 (s, 3H, C*H*OCH$_3$), 1.16 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$); Its isomer was distinguished by $^1$H NMR signal d 5.09 (s, 1H), 1.38 (d, *J* = 5.7 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) d 176.6, 167.5, 138.4, 128.1(2), 127.4 (2), 127.3, 90.8, 82.3, 73.1, 71.6, 58.6, 55.3, 50.7, 36.54, 14.4; IR (film) n 2937, 1709, 1620, 1454, 1138, 1097, 1043 cm$^{-1}$; HRMS (MAB) calcd for $C_{17}H_{24}O_5$ [M]$^+$ 308.1624, Found : 308.1631.



**15**

**Methyl (2*E*)-2-deoxy-3,4,5-tri-*O*-methyl-L-*treo*-hex-2-enoate (15).**

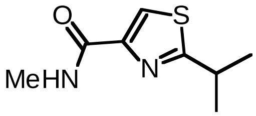
To a solution of benzylether **14** (100 mg, 0.32 mmol) in EtOAc (2 mL) was charged with 20% Pd(OH)$_2$ wet (10 mg) and stirred under a hydrogene atmosphere for 10 min period. The reaction was then filtered through Celite and concentrated under reduced pressure. The residual clear oil was then purified by column chromatography on silica gel (40% EtOAc/hexanes) to afforded (+)-**15** (70.5 mg, 99%) as a colorless oil. R$_f$ 0.18 (40% EtOAc/hexanes); [a]$_D^{20}$ +90.3° (c 0.18, CHCl$_3$), $^1$H NMR (300 MHz, CDCl$_3$) d 5.04 (s, 1H, C*H*CO$_2$Me), 4.10 (dq, *J* = 8.8, 6.9 Hz, 1H, C*H*OCH$_3$), 3.68 (s, 3H, CO$_2$C*H*$_3$), 3.62 (s, 3H, CHC(OC*H*$_3$)CH), 3.44 (s, 3H, CHOC*H*$_3$), 3.32-3.22 (m, 2H, C*H*$_2$OH), 1.16 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) d 176.4, 168.5, 91.3, 83.5, 61.2, 57.9, 55.5, 51.1, 35.9, 14.4; IR (film) n 3418, 2940, 1708, 1618, 1438, 1382, 1266, 1194, 1136, 1087, 1042 cm$^{-1}$; LRMS (APCI, pos) calcd for $C_{10}H_{18}O_5$ [M]$^+$: 218.11, Found : 219.1.



**17**

**ethyl (4*R*)-2-isopropyl-4,5-dihydro-1,3-thiazole-4-carboxylate (17).**

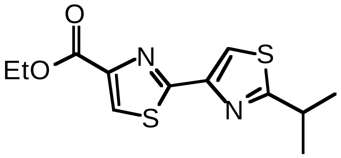
To a solution of amide **16** (3 g, 29.6 mmol) in CH$_2$Cl$_2$ (148 mL) was added pyridine (7.2 mL, 89.0 mmol) and the mixture was cooled down to -40 °C. Trifluoromethansulfonic anhydride (Tf$_2$O) (4.98 mL, 29.6 mmol) was added and the resulting yellow mixture was warm up to room temperature and stirred for a 2 h period. The resulting clear yellow solution was cooled down to -30 °C and *L*-cystein hydrochloride (5.0 g, 26.9 mmol) was added follow by of pyridine (7.2 mL, 89.0 mmol). The reaction was stirred for 15 min, warm up to room temperature and stirred for an additional 1 h. The reaction was then filtered through a plug of silica gel and eluting with 25 % EtOAc/hexanes and concentrated the volatil under reduced pressure. The residual yellow oil was then purified by column chromatography on silica gel (20% EtOAc /hexanes) to afford thiazoline **17** (4.869 g, 90%) as a colorless oil. $R_f$ 0.36 (20% EtOAc/benzene); $[a]_D^{20}$ 94° (*c* 0.81, $CHCl_3$), $^1$H NMR (300 MHz, $CDCl_3$) d 5.04 (dd, *J* = 9.6, 8.6 Hz, 1H, C*H*N), 4.24 (q, J = 7.2 Hz, 2H, $CH_2CH_3$), 3.50 (dd, J = 11.2, 8.6 Hz, 1H, $CH_aS$), 3.46 (dd, *J* = 11.2, 8.9 Hz, 1H, $CH_bS$), 2.89 (qq, J = 7.2, 6.8 Hz, 1H, $CH(CH_3)_2$)), 1.31 (t, *J* = 7.2 Hz, 3H, $CH_2CH_3$), 1.24 (d, *J* = 7.2 Hz, 3H, $CH_3$), 1.23 (d, J = 6.8 Hz, 3H, $CH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) d 180.6, 171.0, 77.8, 61.6, 34.9, 34.1, 21.2, 21.1, 14.1; IR (film) n 2969, 2935, 1736, 1616, 1465, 1180, 1032 $cm^{-1}$.



**18**

**2-isopropyl-*N*-methyl-1,3-thiazole-4-carboxamide (18).**

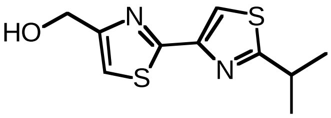
Thiazolester **7** (4.8 g, 24.1 mmol) was diluted in $MeNH_2$ 2.5M in MeOH (50 mL) and stirred for a 12 h period time and concentrated under reduced pressure. The crude yellow oil was purified by column chromatography on silica gel; (35-50% EtOAc/hexanes) to afforded amide **18** (4.1g, 92%) as a pale yellow oil. $R_f$ 0.26 (35% EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) d 7.95 (s, 1H, C*H*S), 7.34 (br, 1H, N*H*Me), 3.27 (sept, *J* = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.00 (d, *J* = 4.1 Hz, 3H, $NHCH_3$), 1.40 (d, *J* = 6.9 Hz, 6H, $(CH_3)_2$); $^{13}$C NMR (75 MHz, $CDCl_3$) d 177.8, 161.9, 149.3, 121.6, 33.1, 25.9, 22.9; IR (film) n 3333,2965, 2932, 1649, 1545, 1493, 1408, 1248 $cm^{-1}$; HRMS (MAB) calcd for $C_8H_{12}N_2OS$ $[M]^+$: 184.0670, Found: 184.0677.



**19**

### Ethyl (4*R*)-2'-isopropyl-2,4'-bi-1,3-thiazole-4-carboxylate (19).

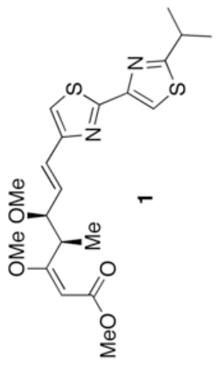
To a solution of amide **18** (1.922 g, 10 mmol) in $CH_2Cl_2$ (50 mL) was added pyridine (4.22 mL, 52.2 mmol) and this resulting mixture was cooled down to -40 °C. $Tf_2O$ (1.76 mL, 10 mmol) was then added dropwise and the reaction was stirred for 1 h. The resulting yellow solution was then warm up to room temperature and stirred for a 15 h period. The reaction was cooled down to -40 °C and *L*-cystein hydrochloride (2.32 g, 12 mmol) was added follow by the addition of pyridine (4.22 mL, 52.2 mmol). The resulting mixture was warm up to -10 °C for 1 h period and filtered through a plug of silica gel and eluting with 30 % EtOAc/hexanes and concentrated the volatil under reduced pressure. The residual yellow oil (2.23 g) was diluted in $CH_2Cl_2$ (50 mL) and cooled down to 0 °C. DBU (2.38 mL, 15.7 mmol) was added and the resulting mixture was stirred for 10 min. Bromotrichloromethane (0.77 mL, 7.84 mmol) was then added and the reaction was warm up to room temperature. After 15 min of mixing, filtered through a plug of silica gel eluting with 20 % EtOAc/hexanes and concentrated the volatil under reduced pressure. The yellow crude was purified by column chromatography on silica gel (10-20% EtOAc/hexanes) to afford bisthiazole **19** (2.04 g, 69%) as a white solid. m.p. 68-70 °C; $R_f$ 0.63 (30% EtOAc/hexanes); $^1H$ NMR (300 MHz, $CDCl_3$) d 8.16 (s, 1H, C*H*S), 8.02 (s, 1H, C*H*S), 4.44 (q, *J* = 7.1 Hz, 2H, $CH_2CH_3$), 3.36 (sept, *J* = 6.9 Hz, 1H, $CH(CH_3)_2$), 1.44 (d, *J* = 6.9 Hz, 6H, $(CH_3)_2$), 1.41 (t, *J* = 7.1 Hz, 3H, $CH_3$), ; $^{13}C$ NMR (75 MHz, $CDCl_3$) d 178.6, 163.7, 161.4, 147.7, 147.6, 127.5, 116, 9, 61.4, 33.2, 23.0, 14.3; IR (film) n 3129, 2959, 1732, 1535, 1474, 1196, 1181, 1089, 1032, 747 $cm^{-1}$; HRMS (MAB) calcd for $C_{12}H_{14}N_2O_2S_2$ $[M]^+$: 282.0503, Found : 282.0501. ; Anal. calcd for $C_{12}H_{14}N_2O_2S_2$: C, 51.04; H, 5.00; N, 9,92; S, 22.71; Found: C, 51.10; H, 5.01; N, 9.92; S, 23.09.



**20**

**(2'-Isopropyl-2,4'-bi-1,3-thiazol-4-yl)methanol (20).**

To a solution of the ester **19** (50.0 mg, 0.177 mmol ) in THF (2 mL) at -20 °C was added in one portion LiAlH$_4$ (6.72 mg, 0.177 mmol) solide and stirred the resulting grey suspension for 5 min. The reaction was then warm up at room temperature and stirred for an additional 10 min. The reaction was quenched by slow addition of Na$_2$SO$_4$•10H$_2$O solid until no evolution of gaz occur and then filtered through Celite. The resulting filtrate was concentrated under reduced pressure and the residu was purified by column chromatography on silica gel (40-50% EtOAc/hexanes) to afford alcohol **20** (39.5 mg, 93%) as a white solid. m.p 55-56 °C; R$_f$ 0.20 (40% EtOAc/hexanes); $^1$H NMR (300 MHz, CDCl$_3$) d 7.84 (s, 1H, C*H*S), 7.18 (s, 1H, C*H*S), 4.80 (s, 2H, C*H*$_2$OH), 3.93 (br, 1H, O*H*), 3.35 (sept, *J* = 6.9 Hz, 1H, C*H*(CH$_3$)$_2$), 1.41 (d, *J* = 6.9 Hz, 6H, (CH$_3$)$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$) d 178.7, 163.7, 157.2, 148.2, 115.3, 115.0, 60.6, 33.3, 23.1; IR (film) n 3232, 3129, 3093, 2962, 1732, 1535, 1446, 1312, 1192, 1067, 1032, 806, 784, 738! cm$^{\text{!-1}}$; HRMS (MAB) calcd C$_{10}$H$_{12}$N$_2$OS$_2$ [M]$^+$: 240.0391, found : 240.0393.



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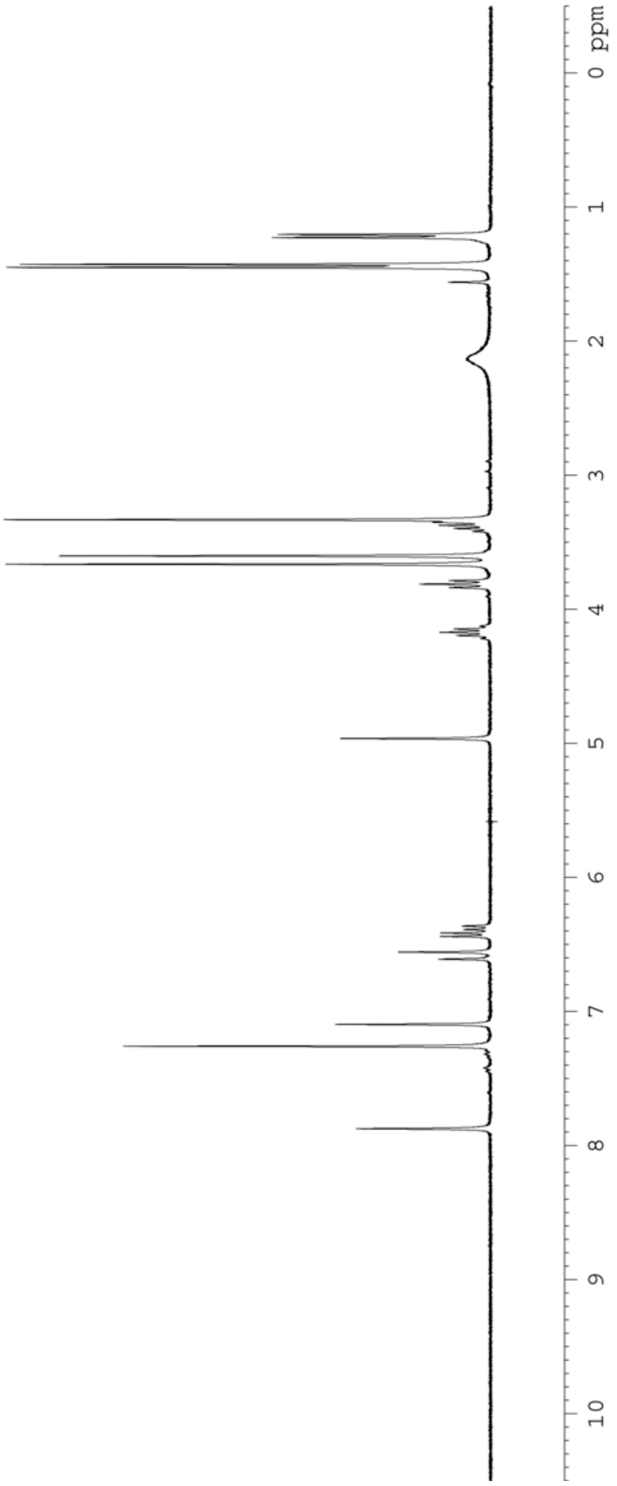

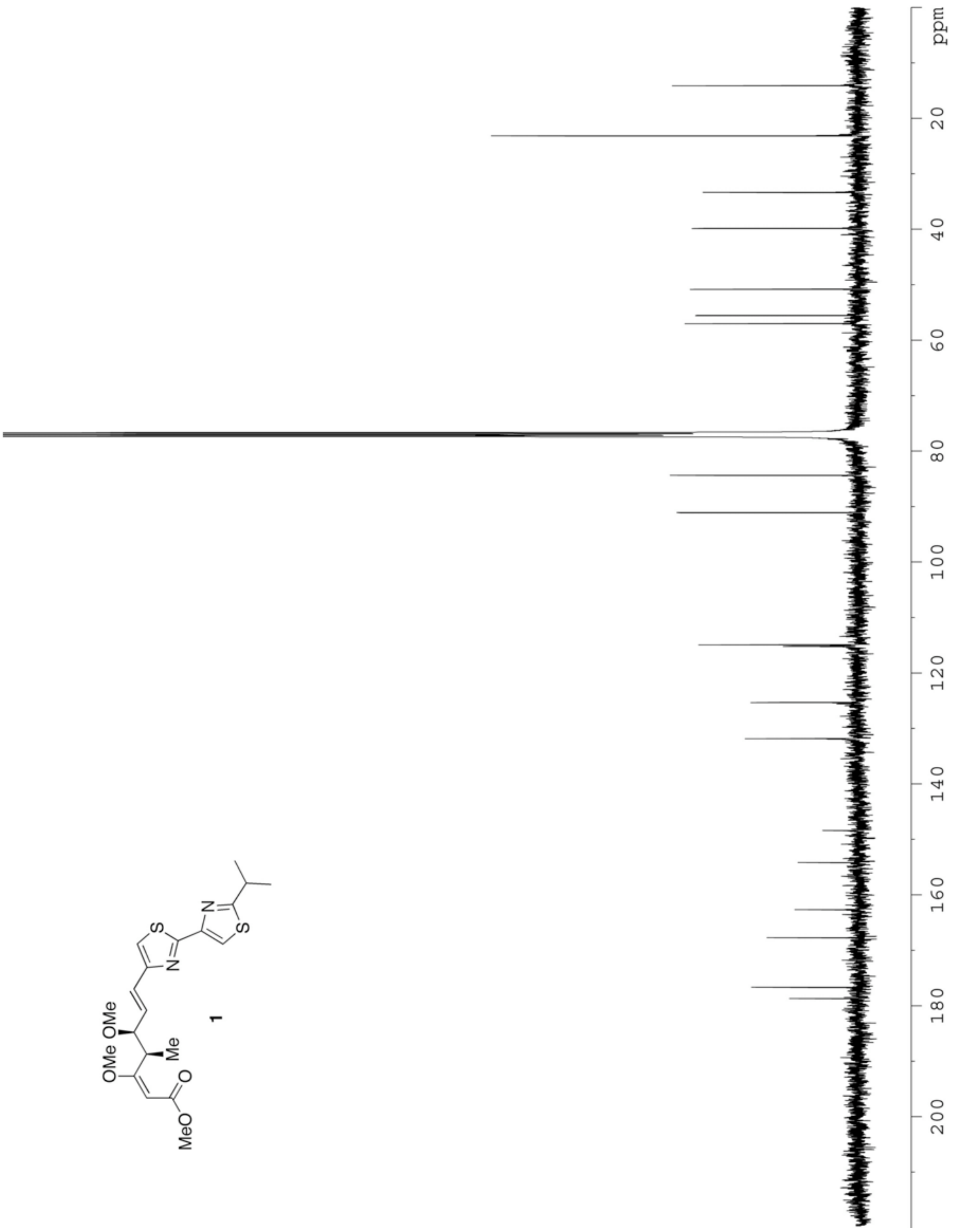
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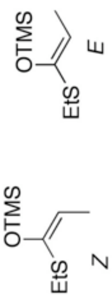

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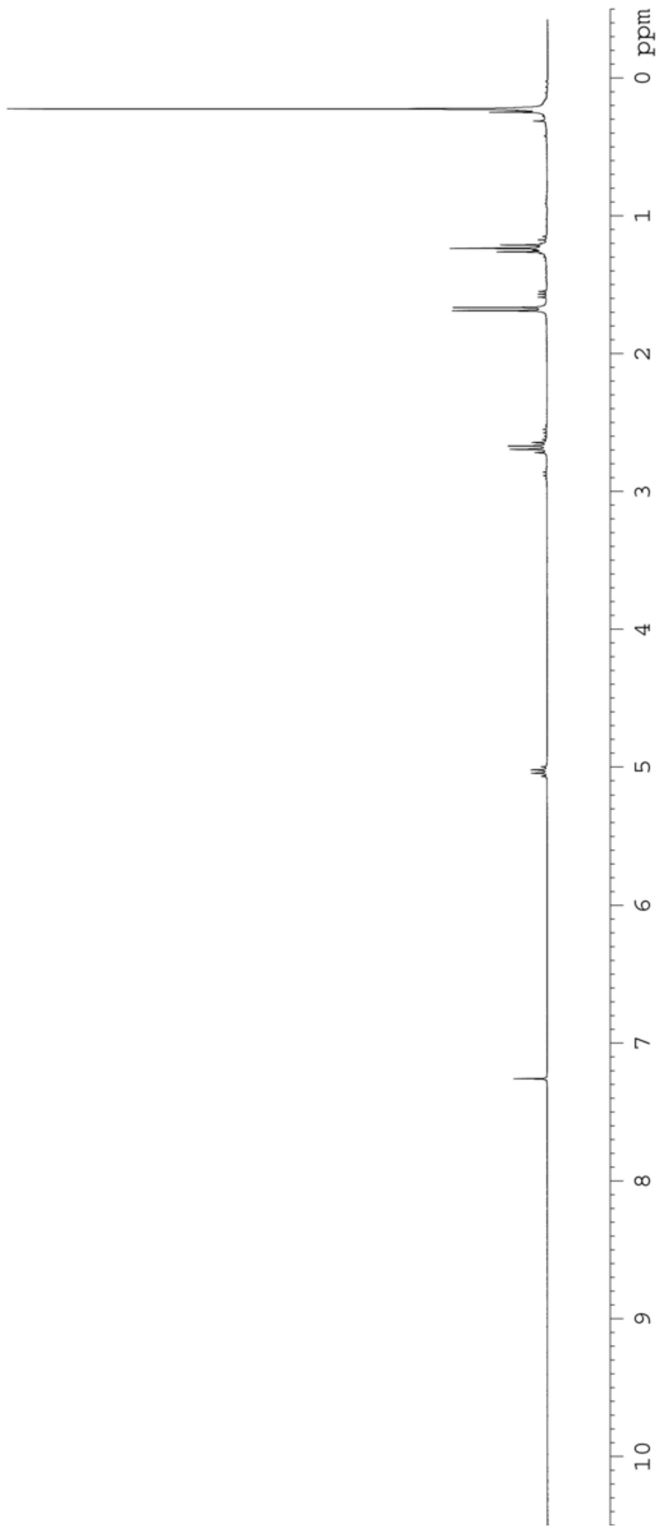

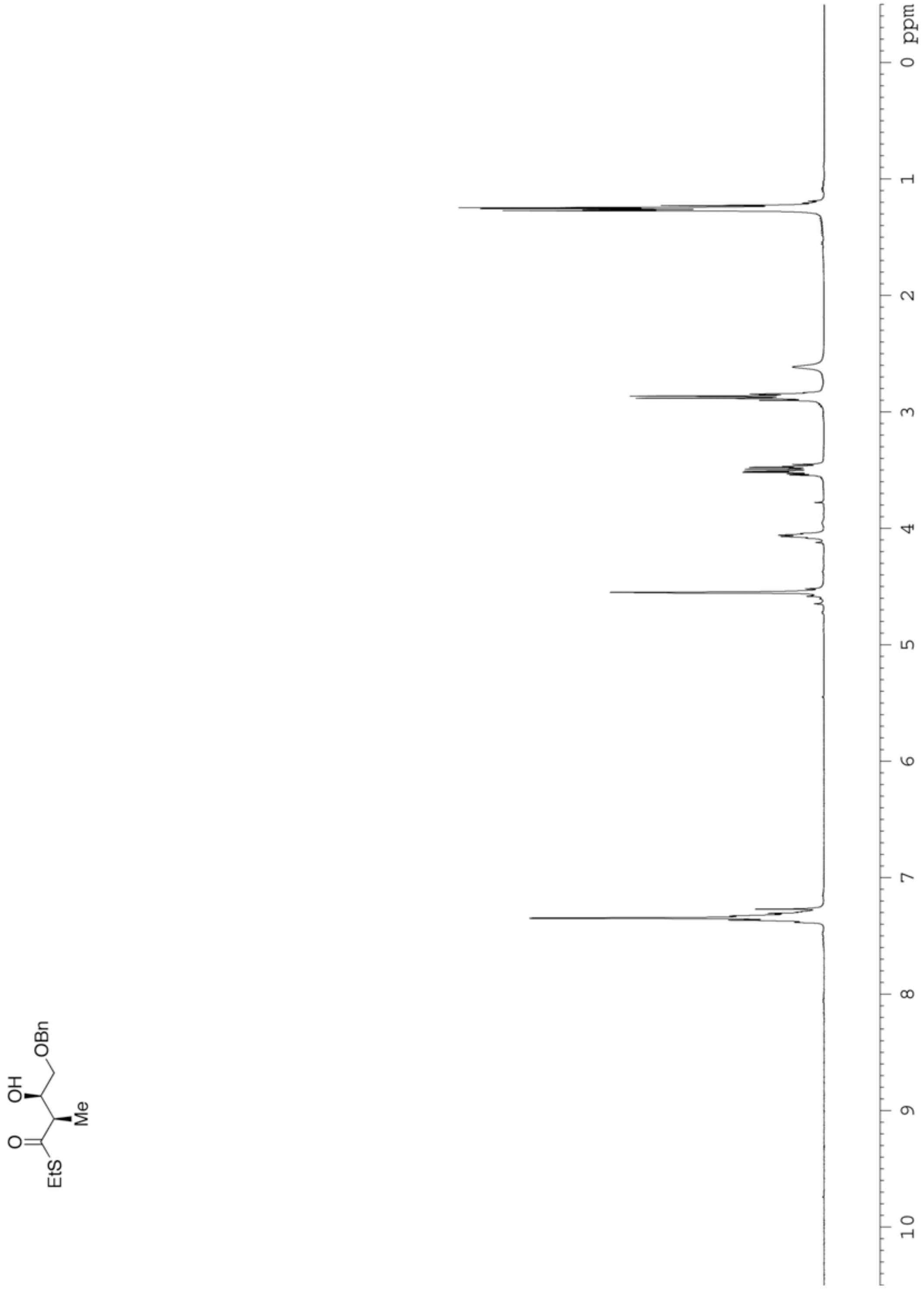
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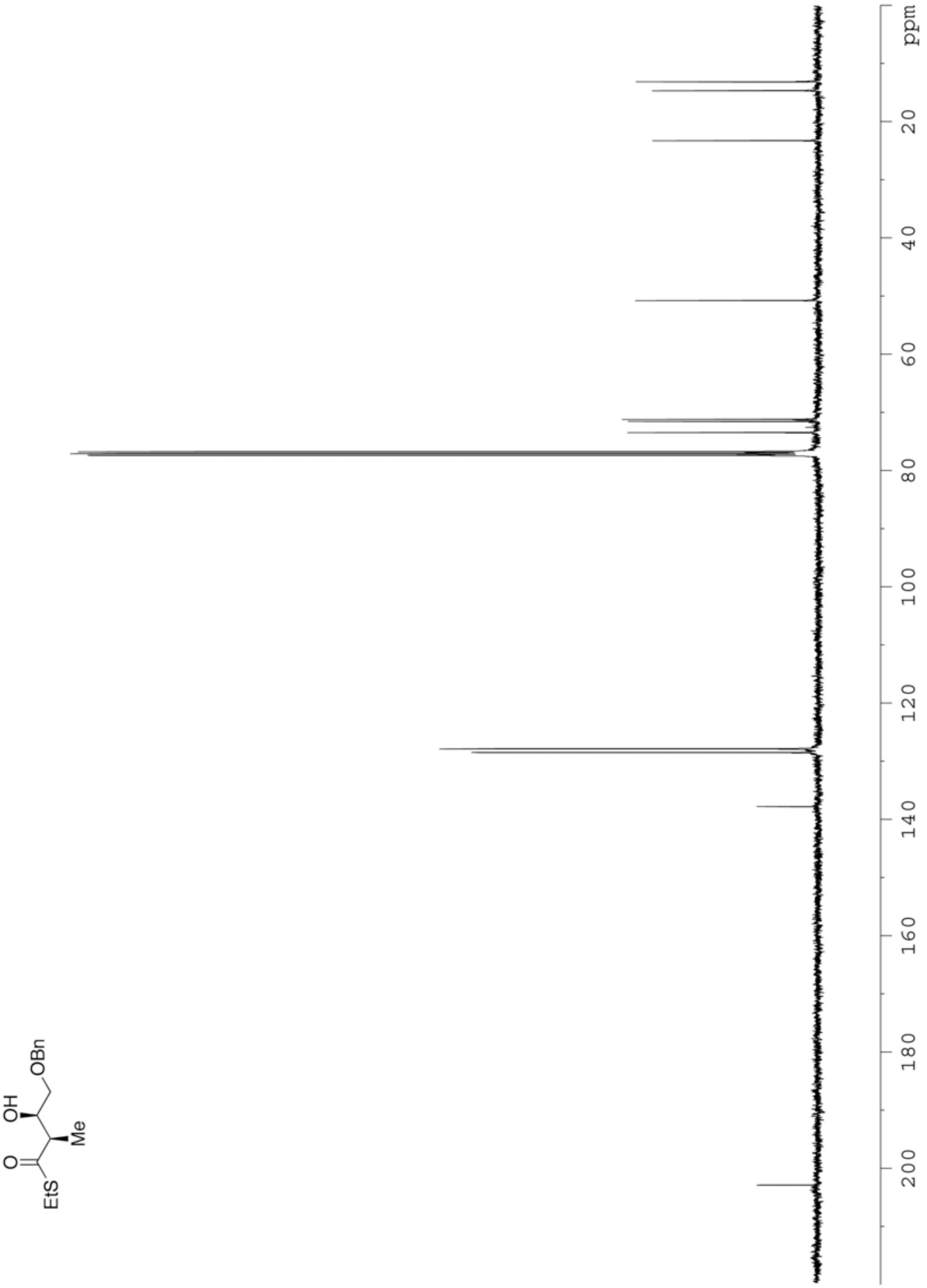
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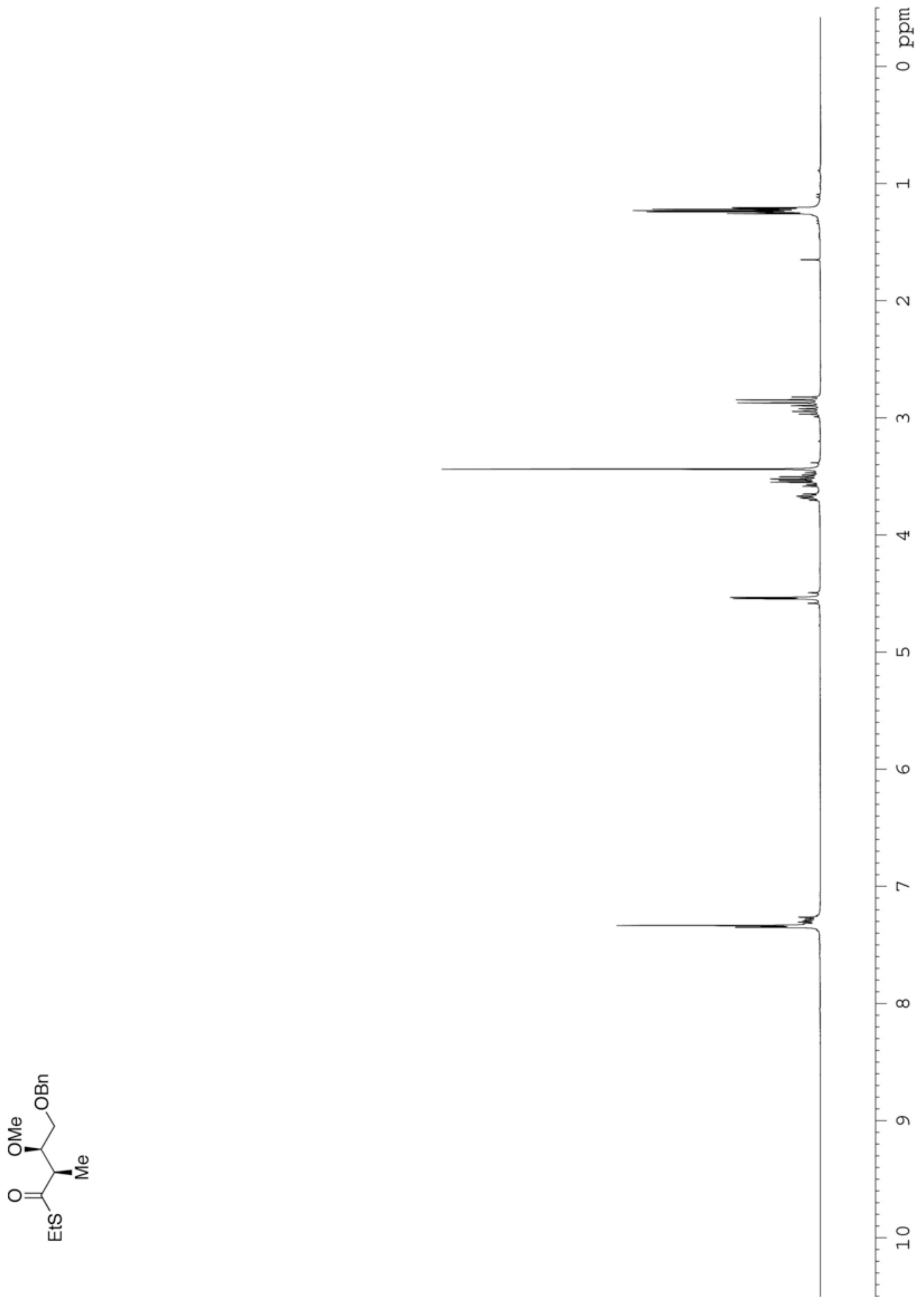
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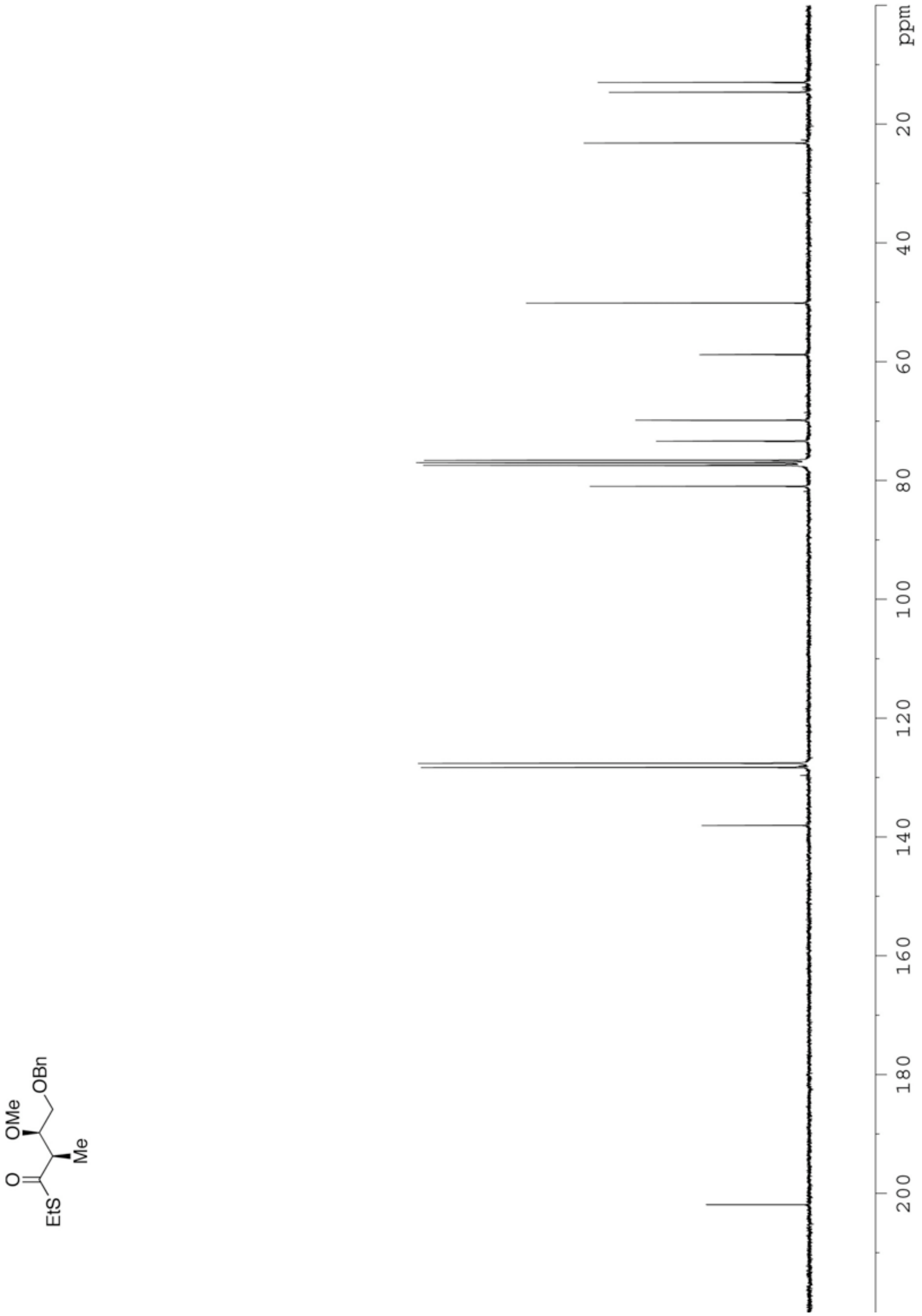
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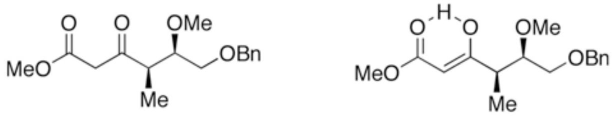

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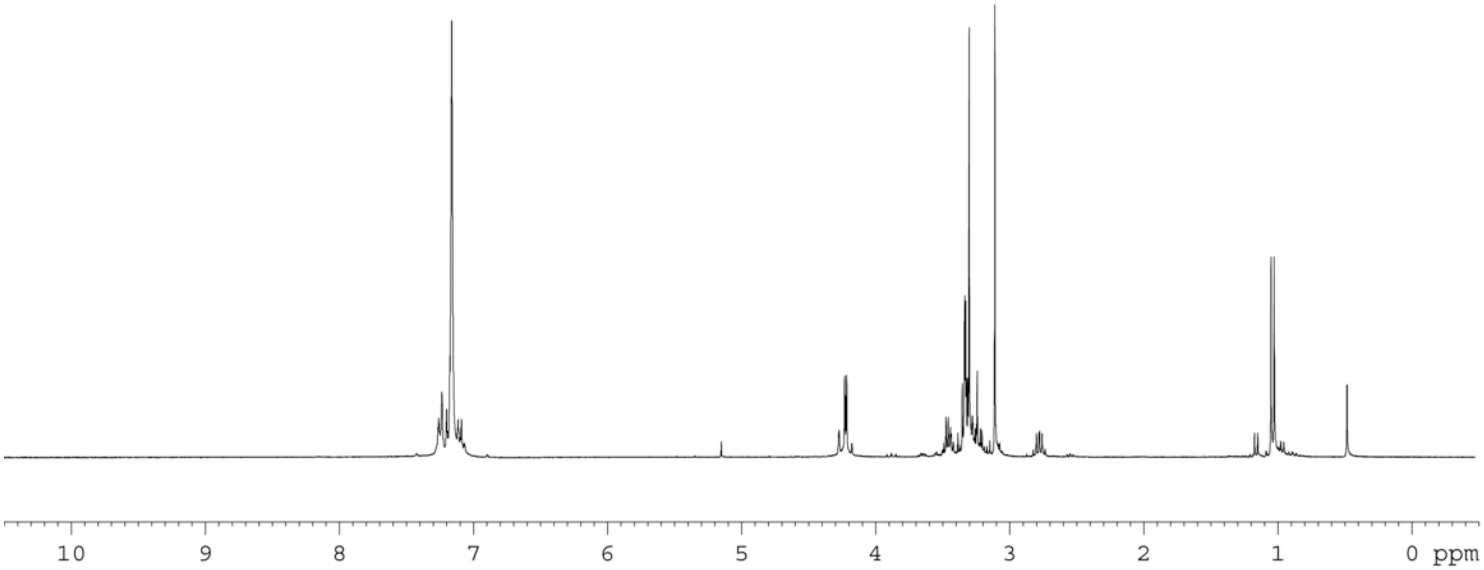

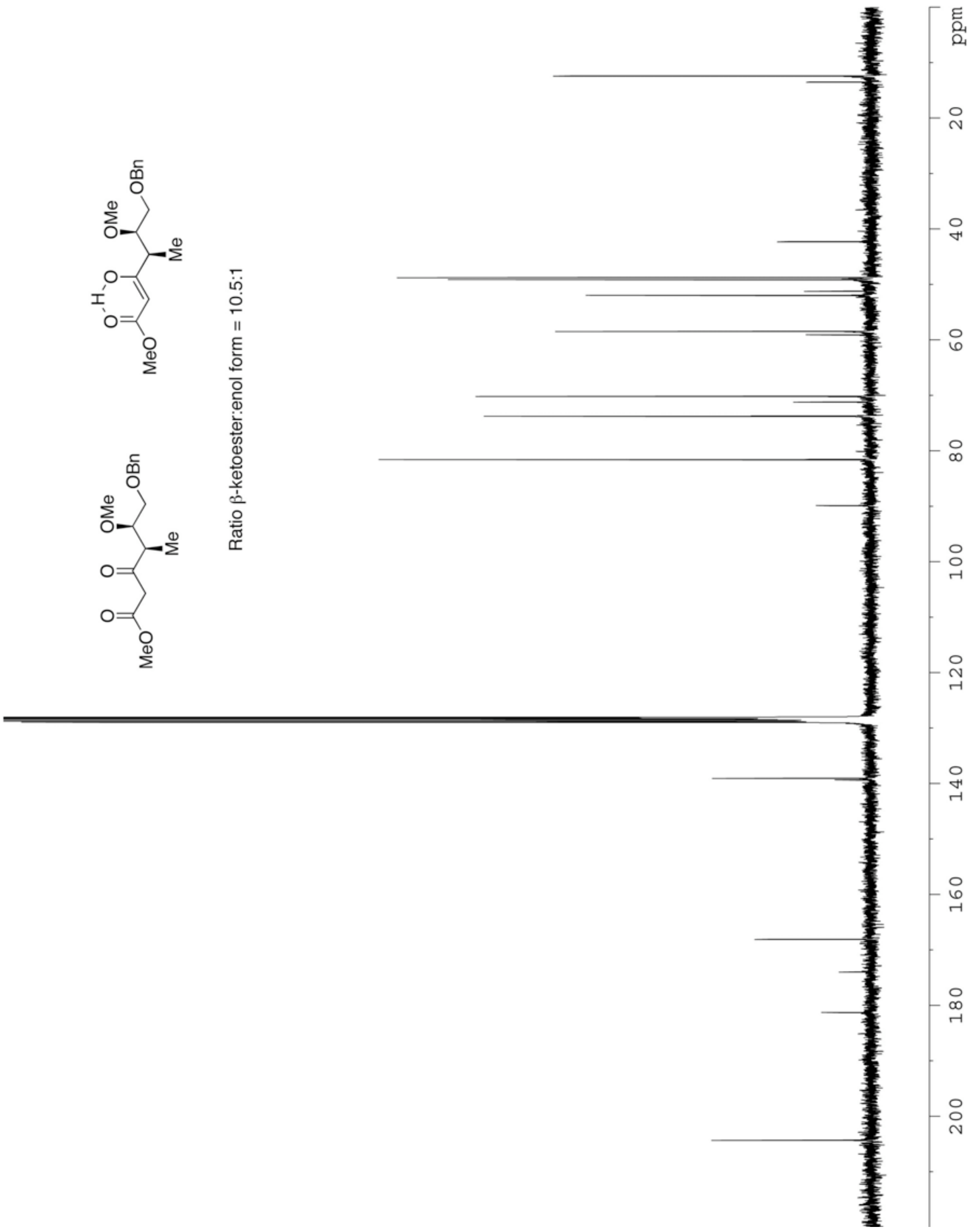

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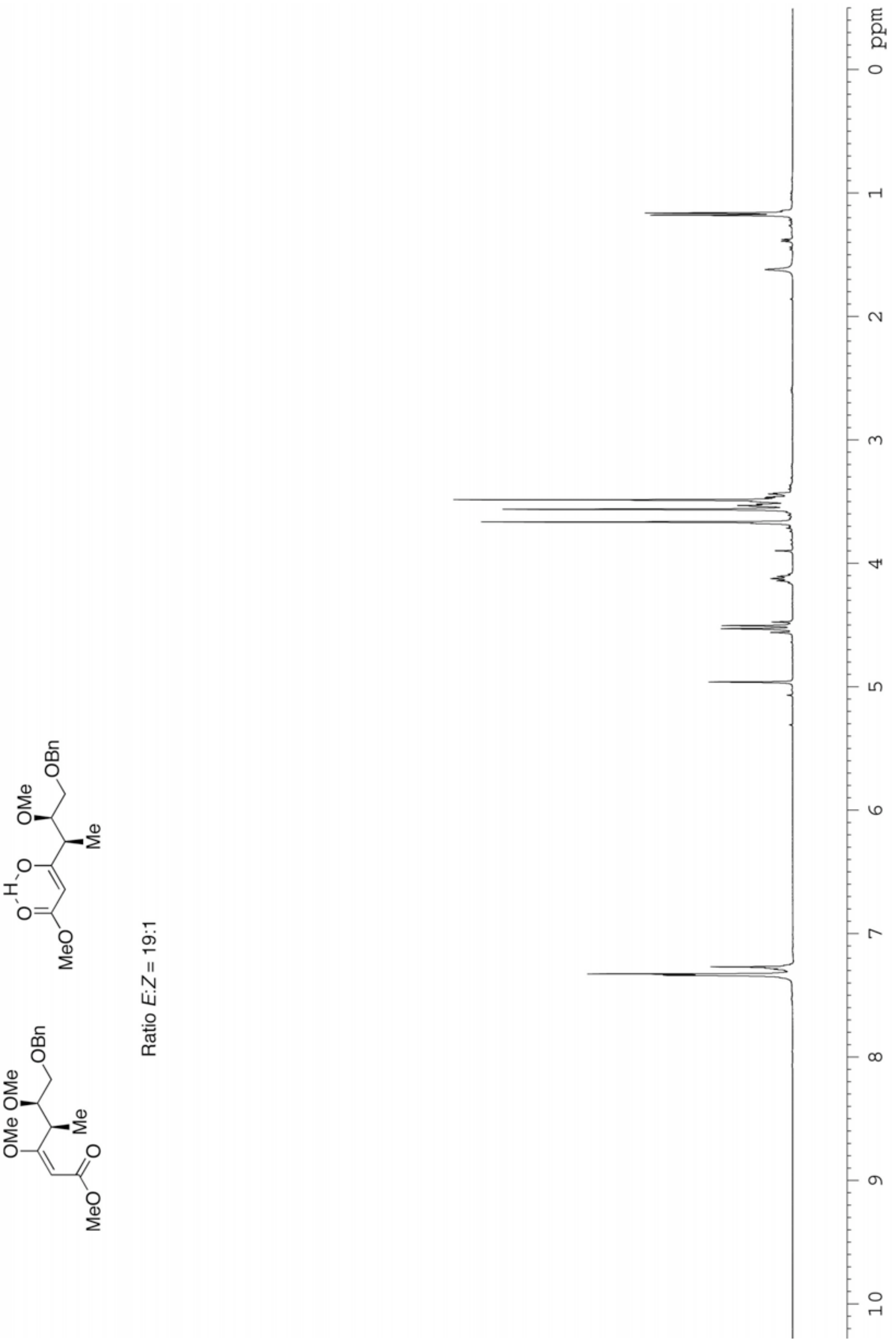

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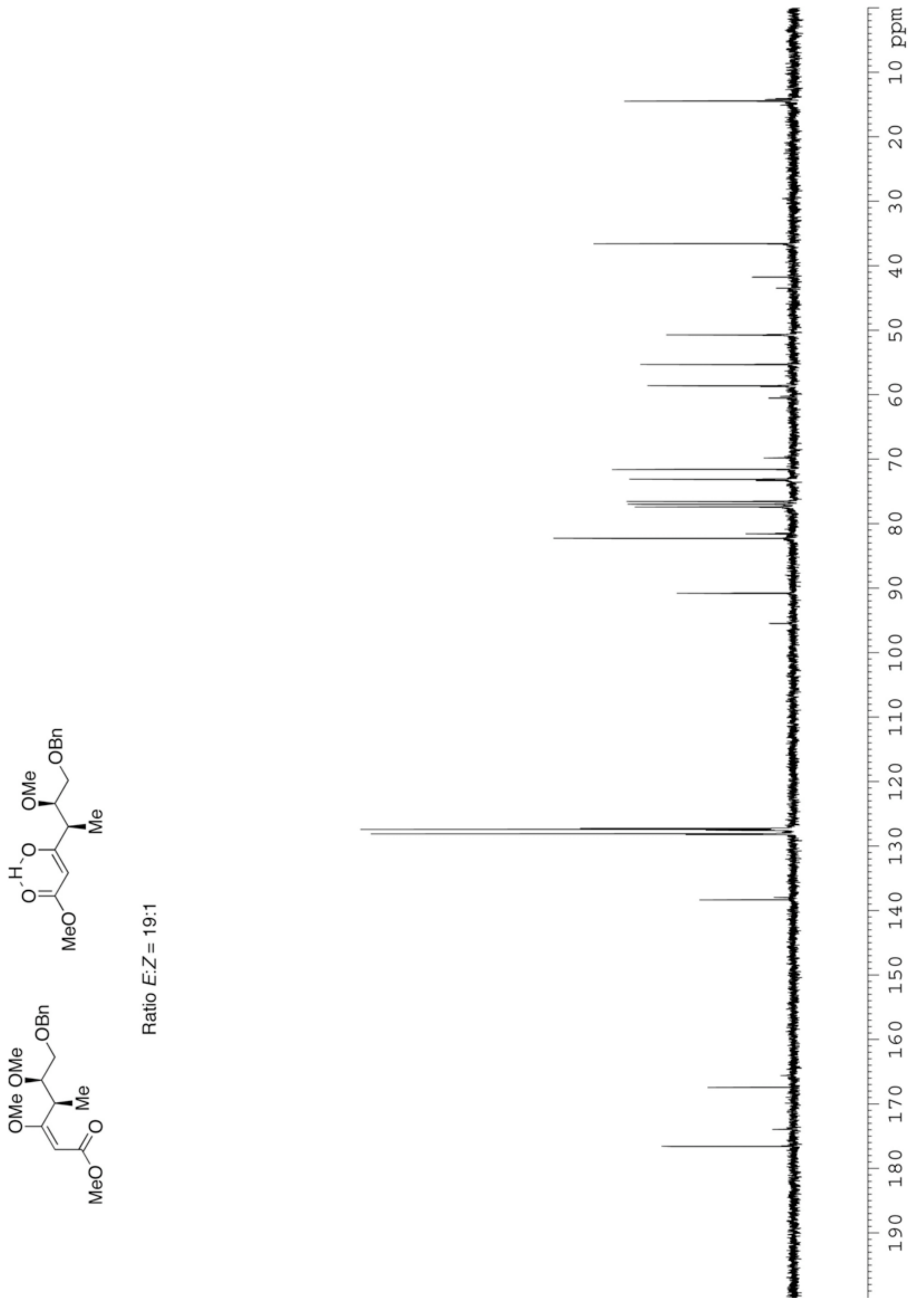
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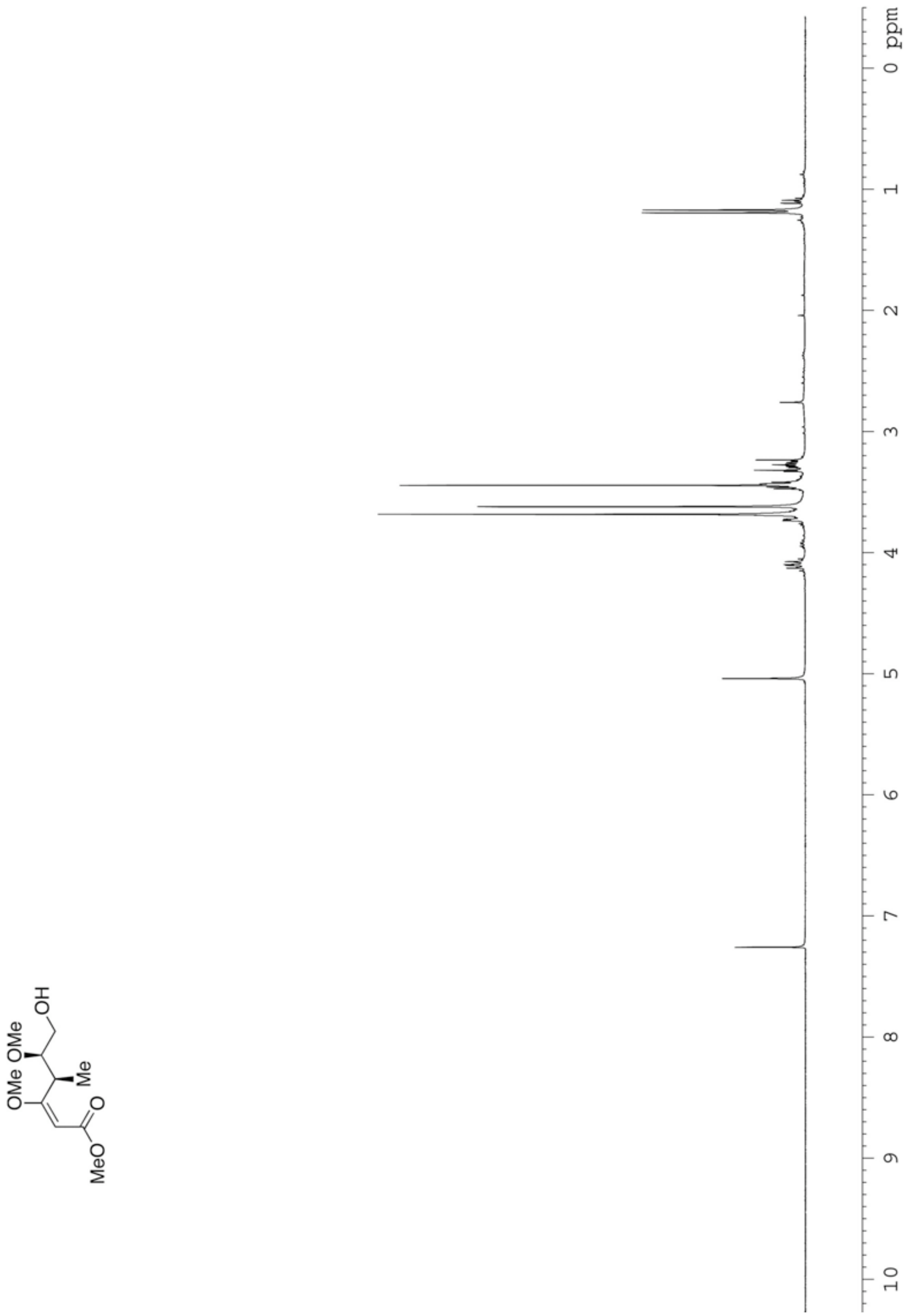
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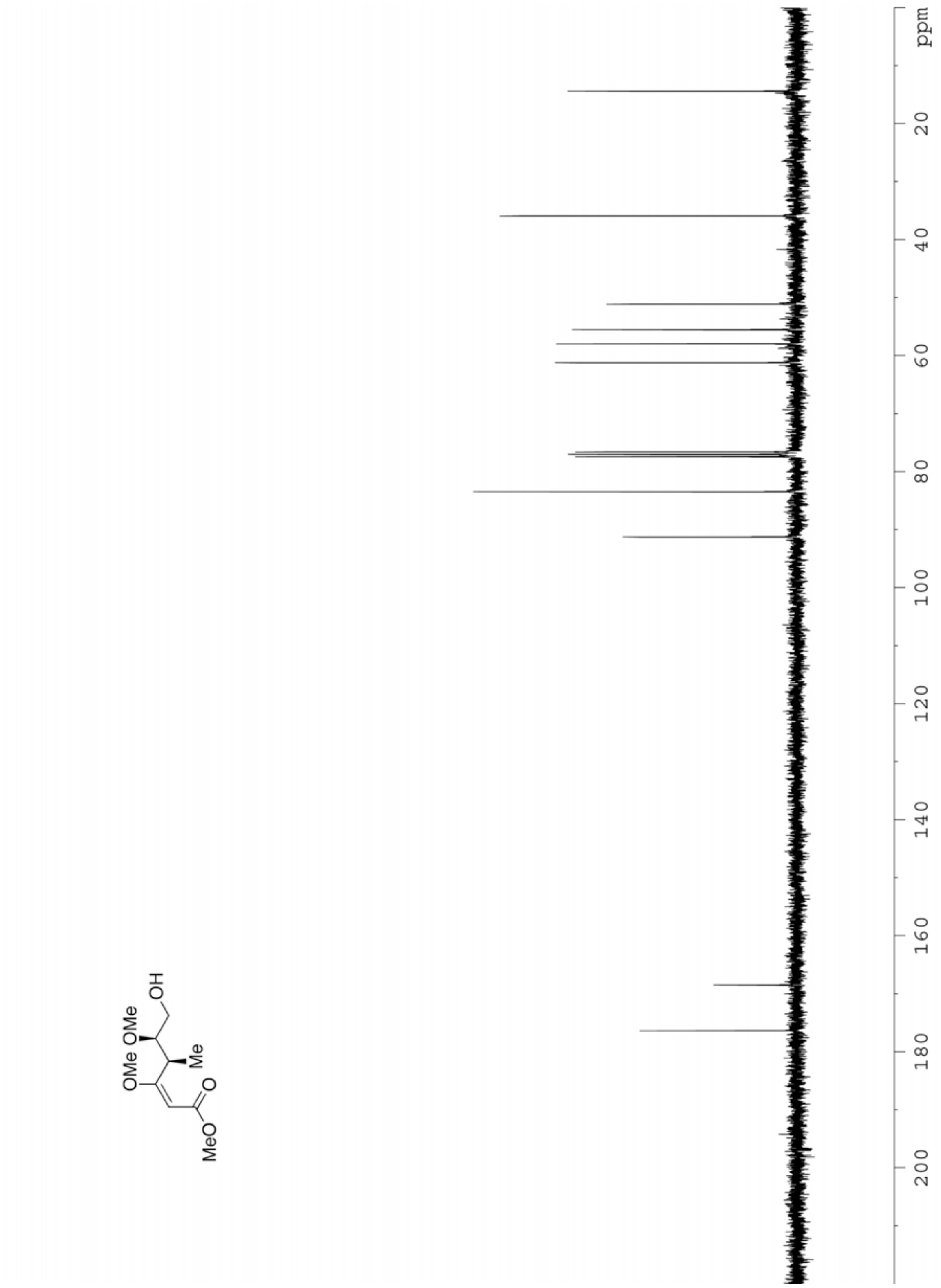
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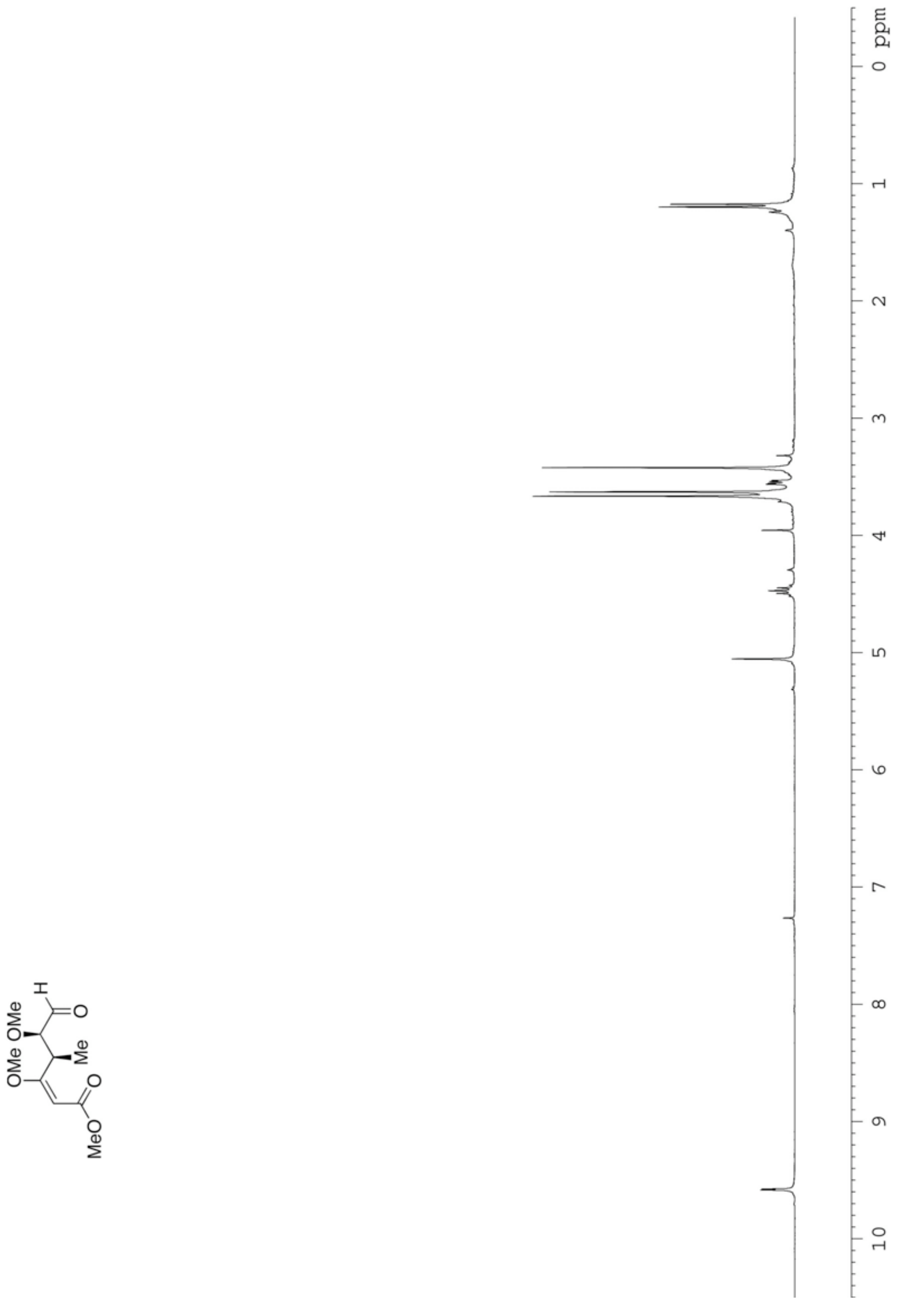
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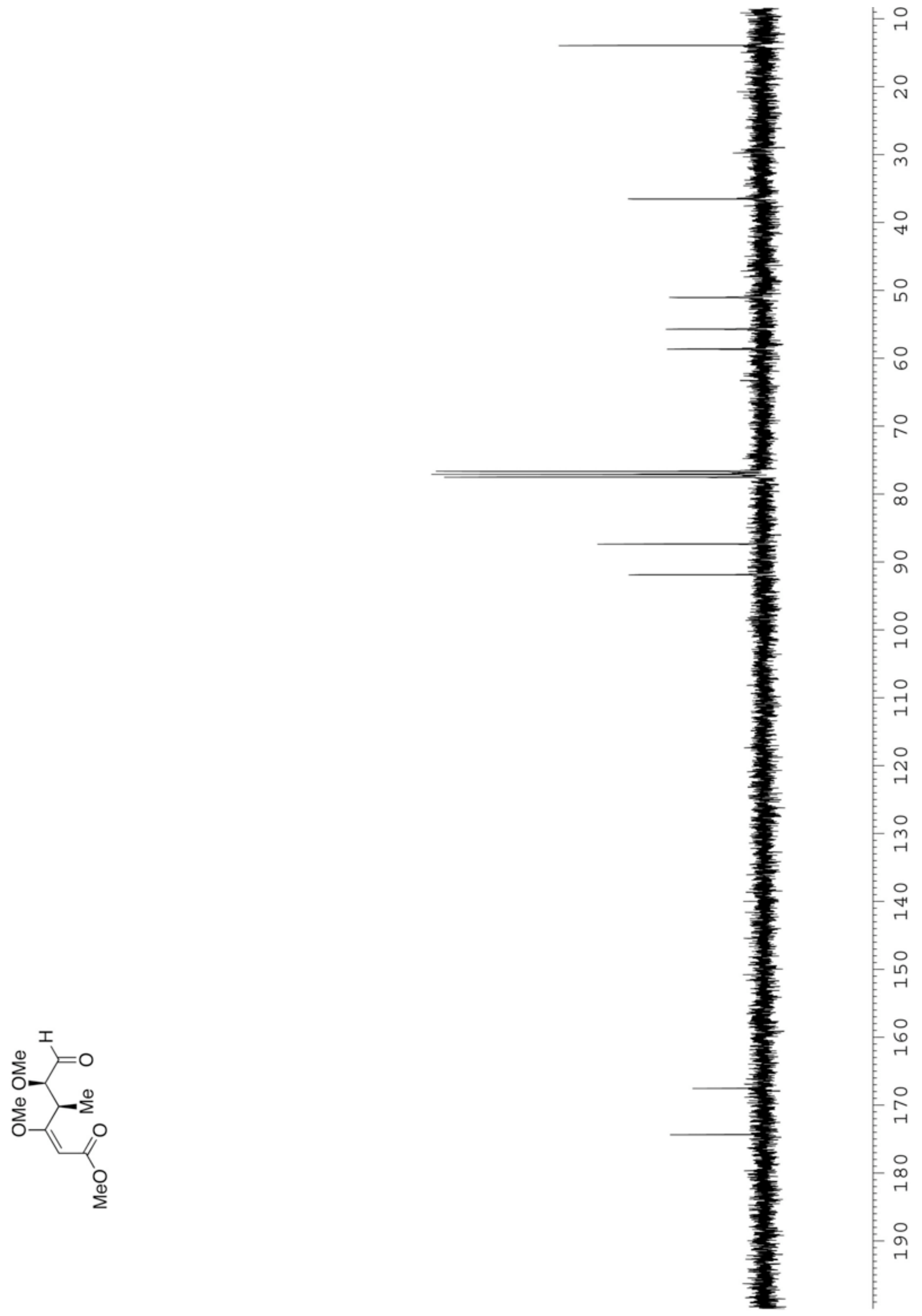
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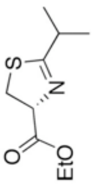
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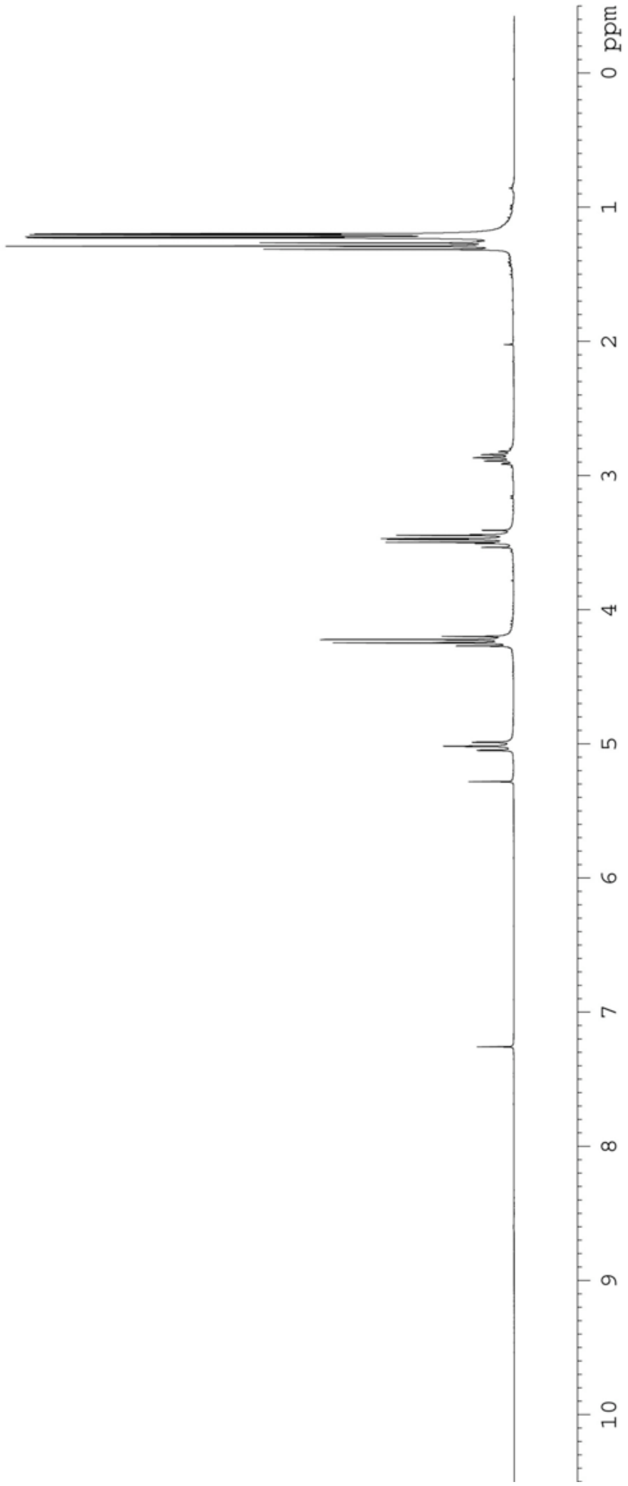
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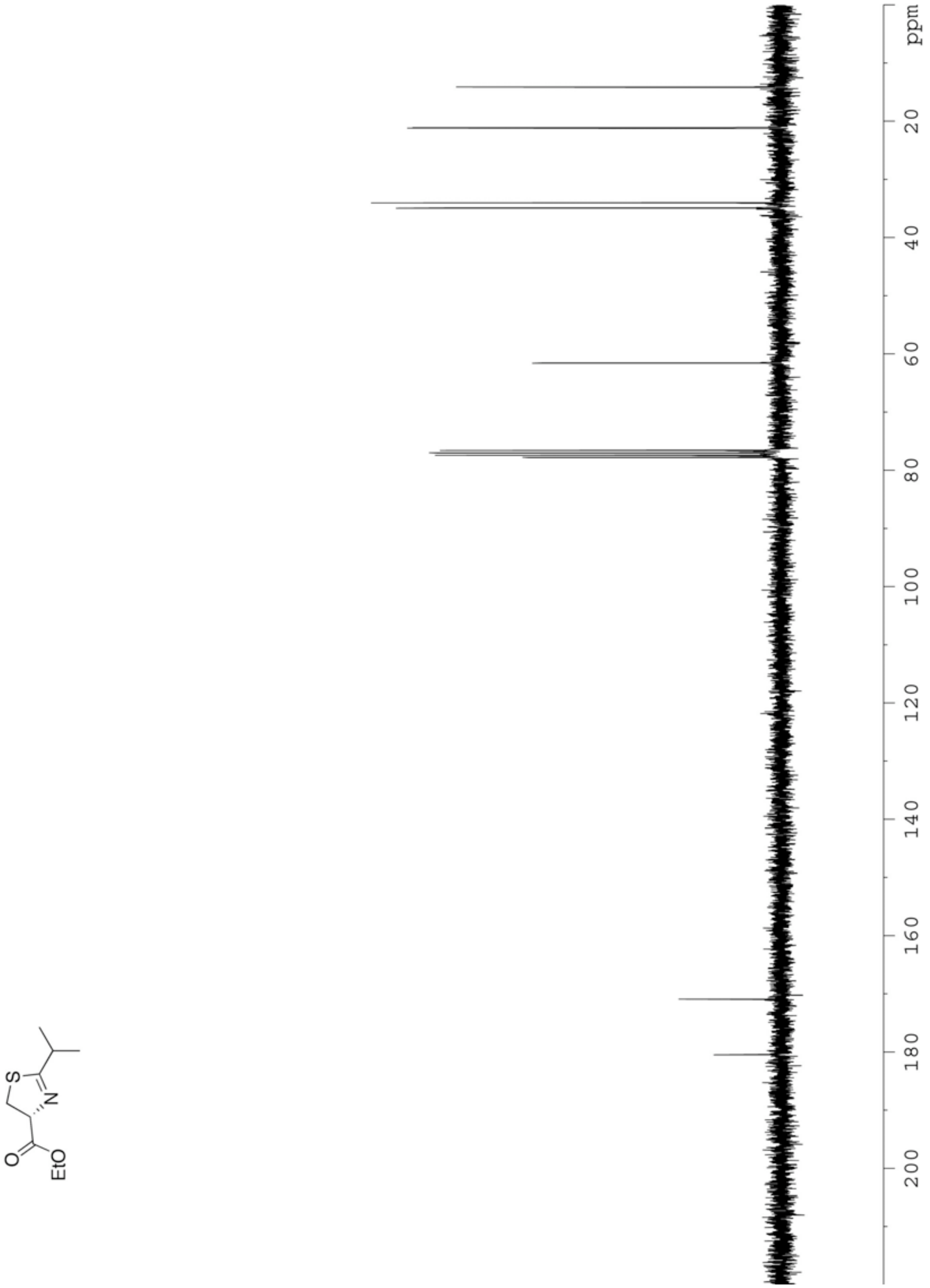
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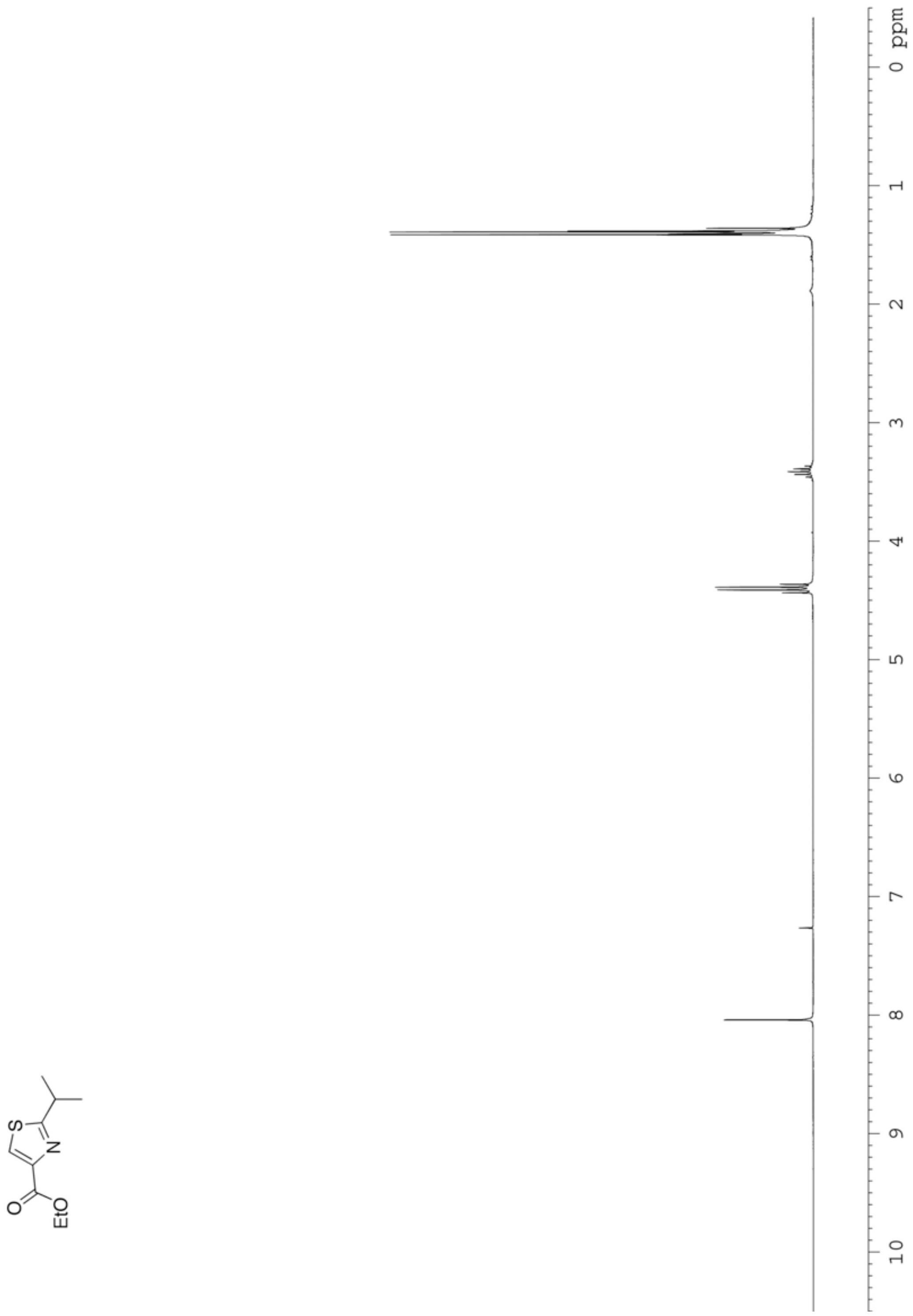
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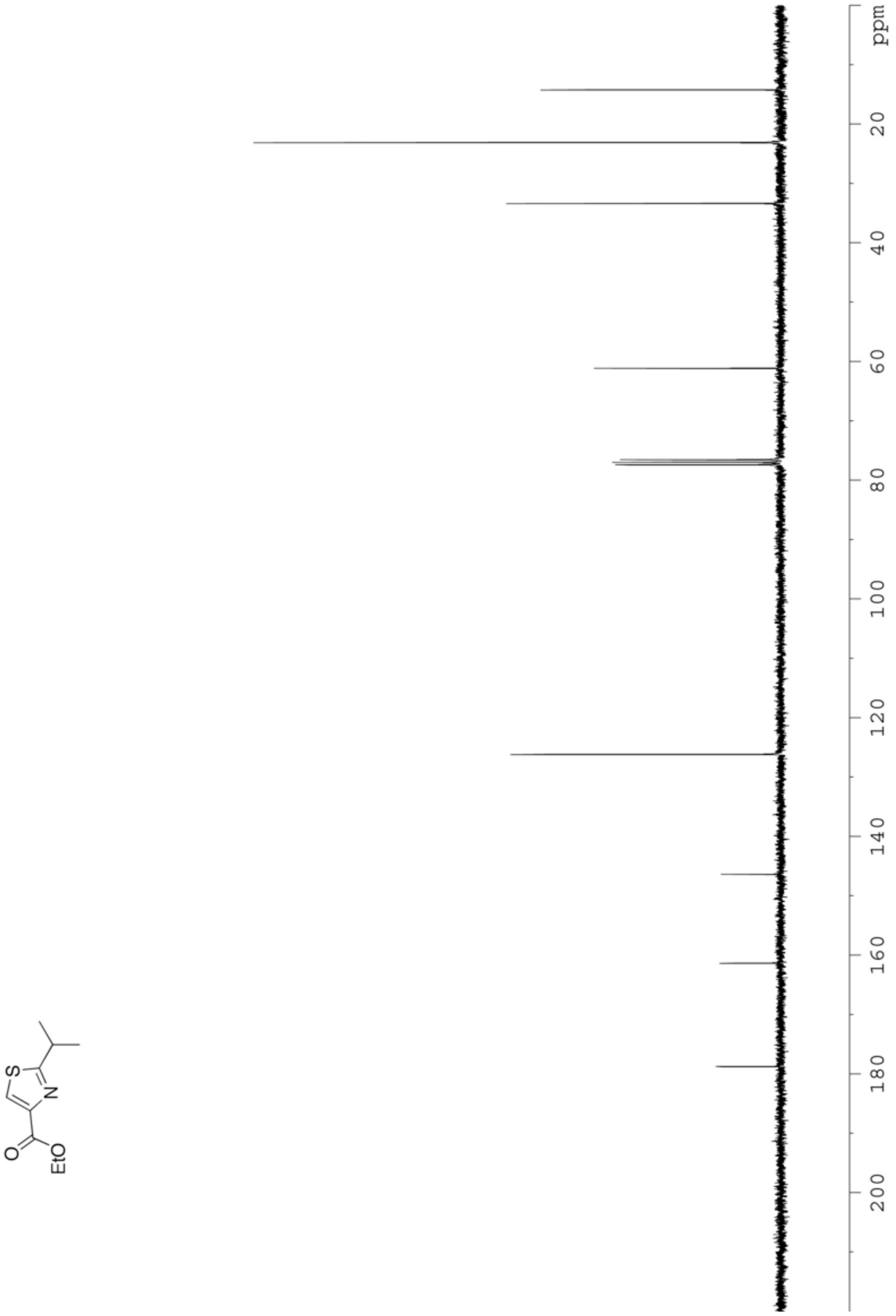
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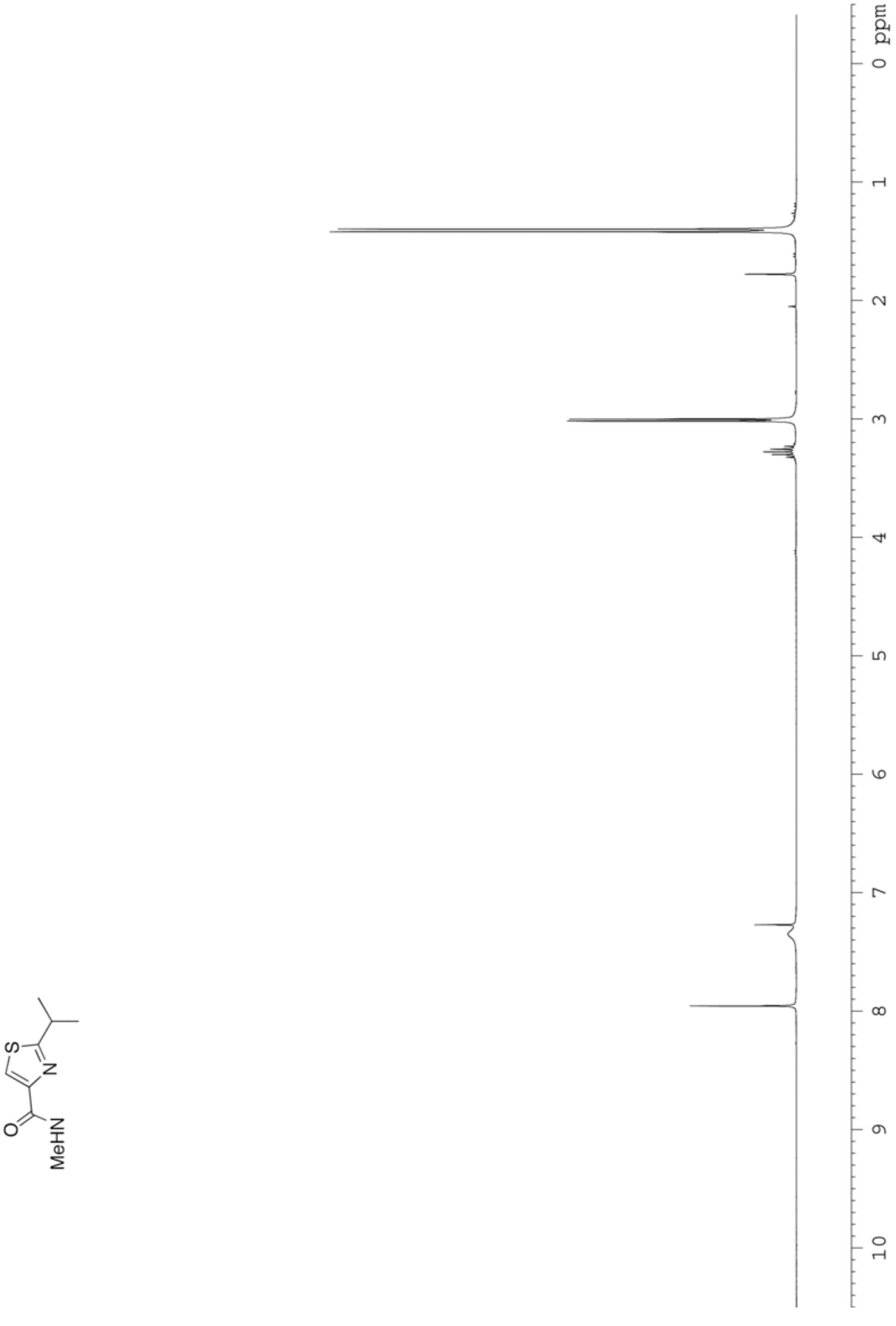
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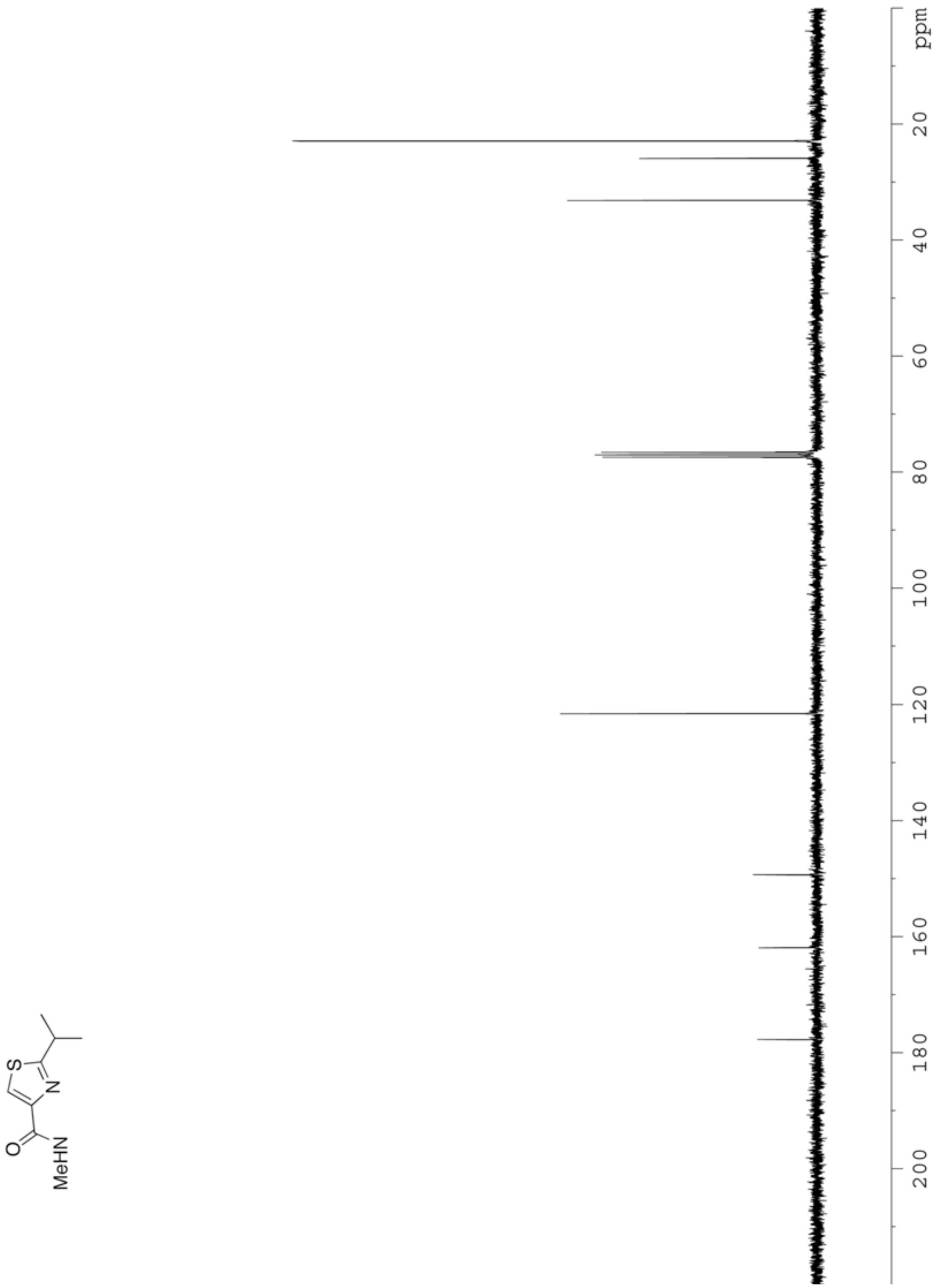
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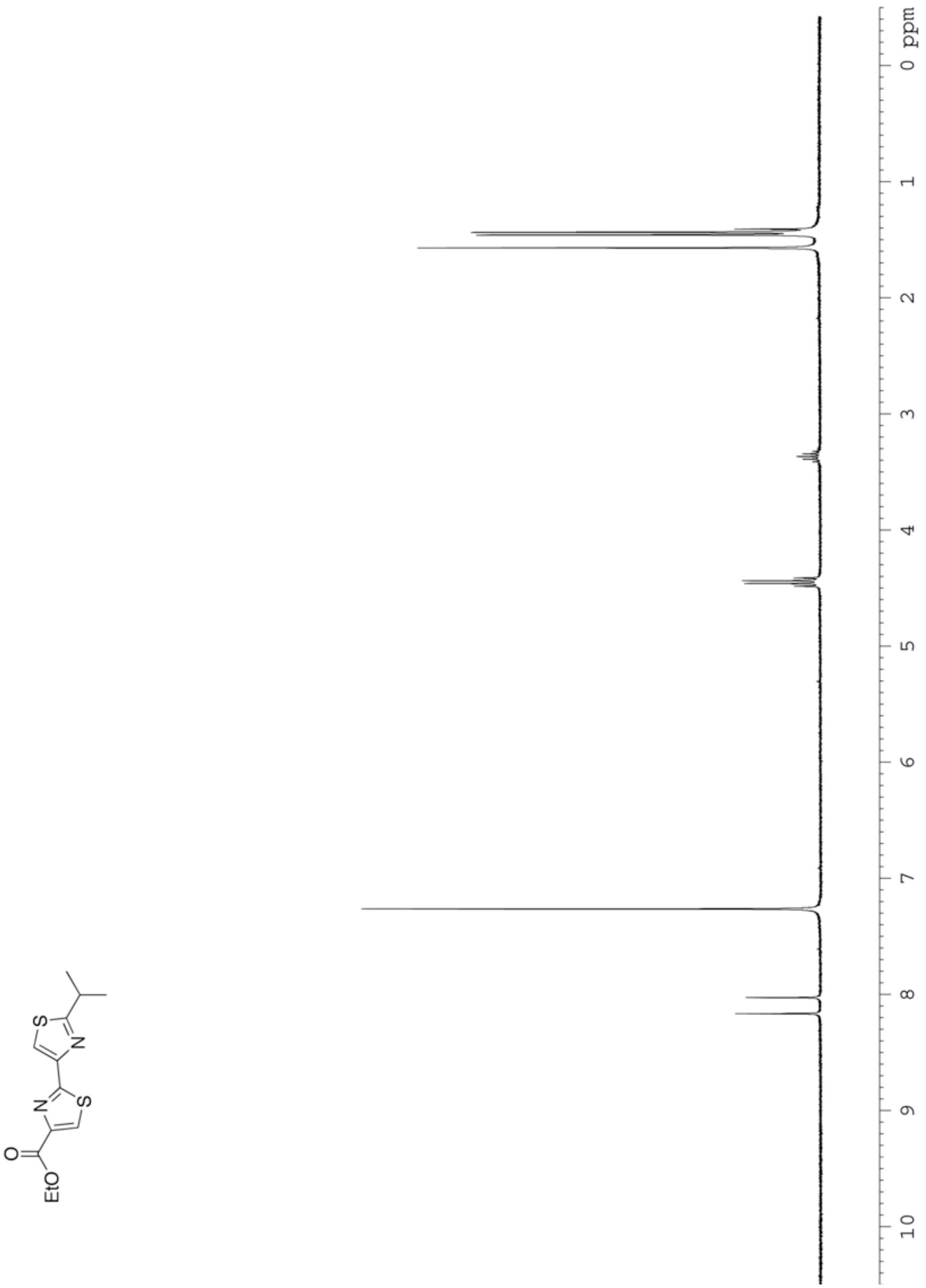
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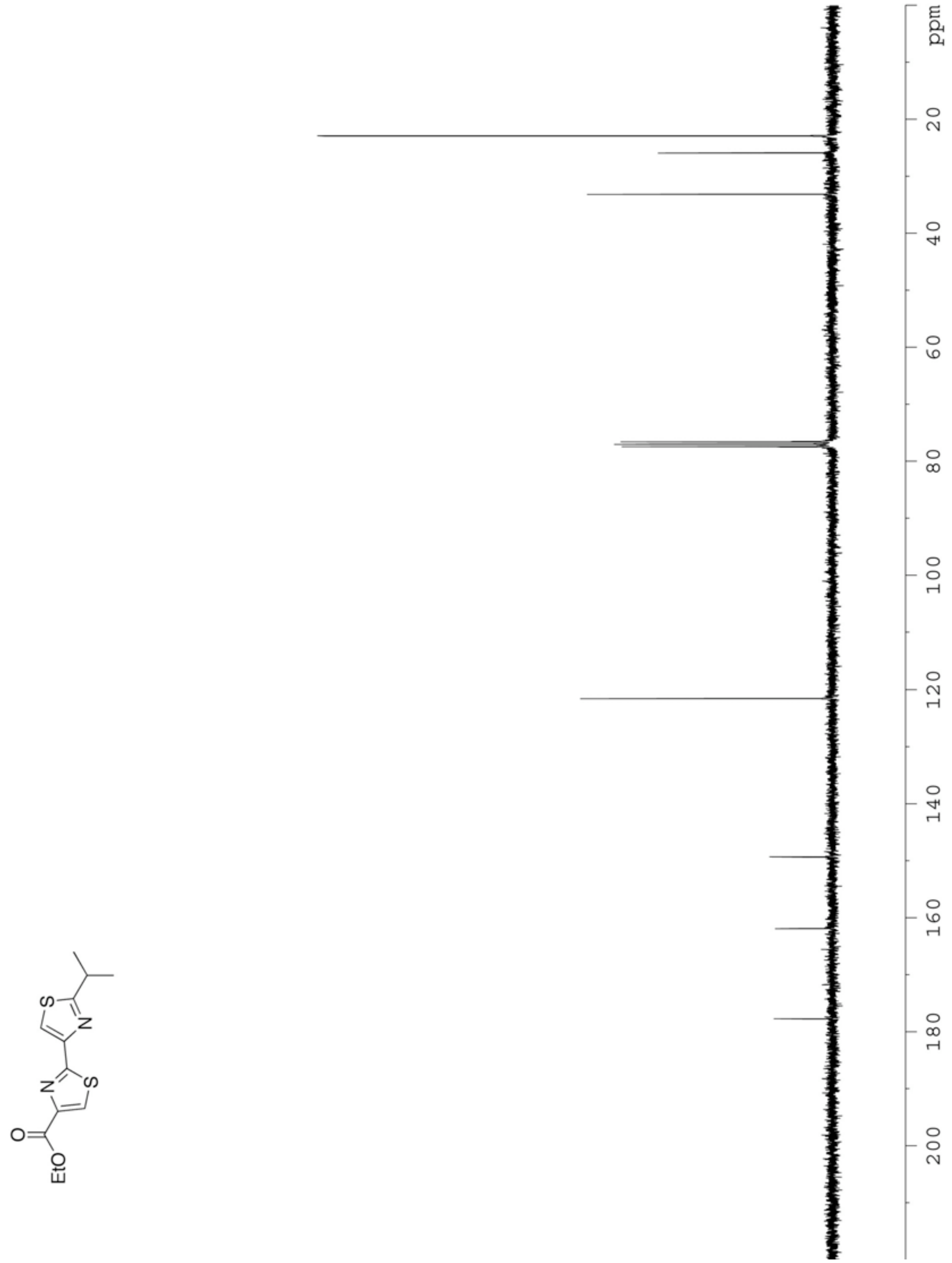
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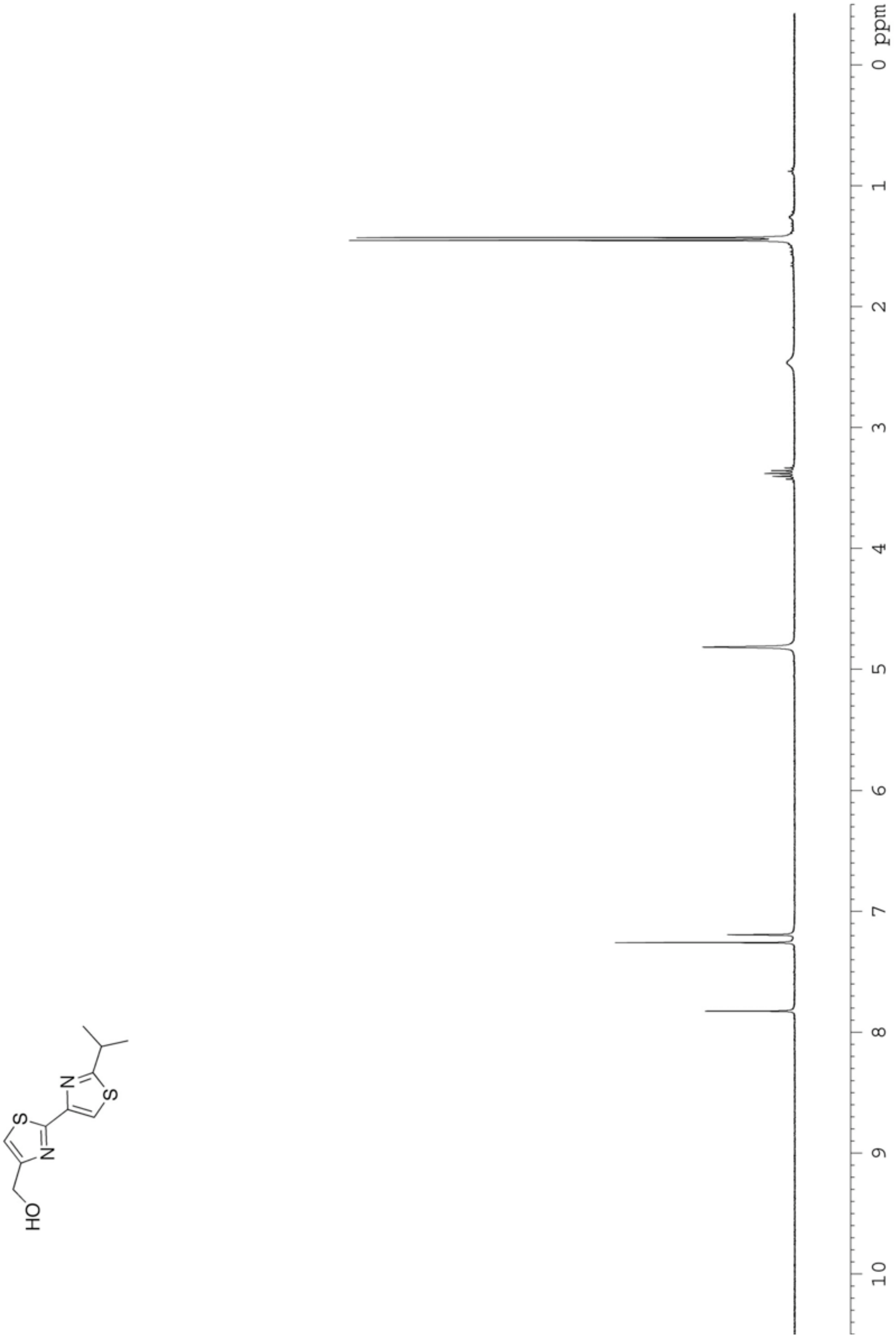
ppm
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2
3
4
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7
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S
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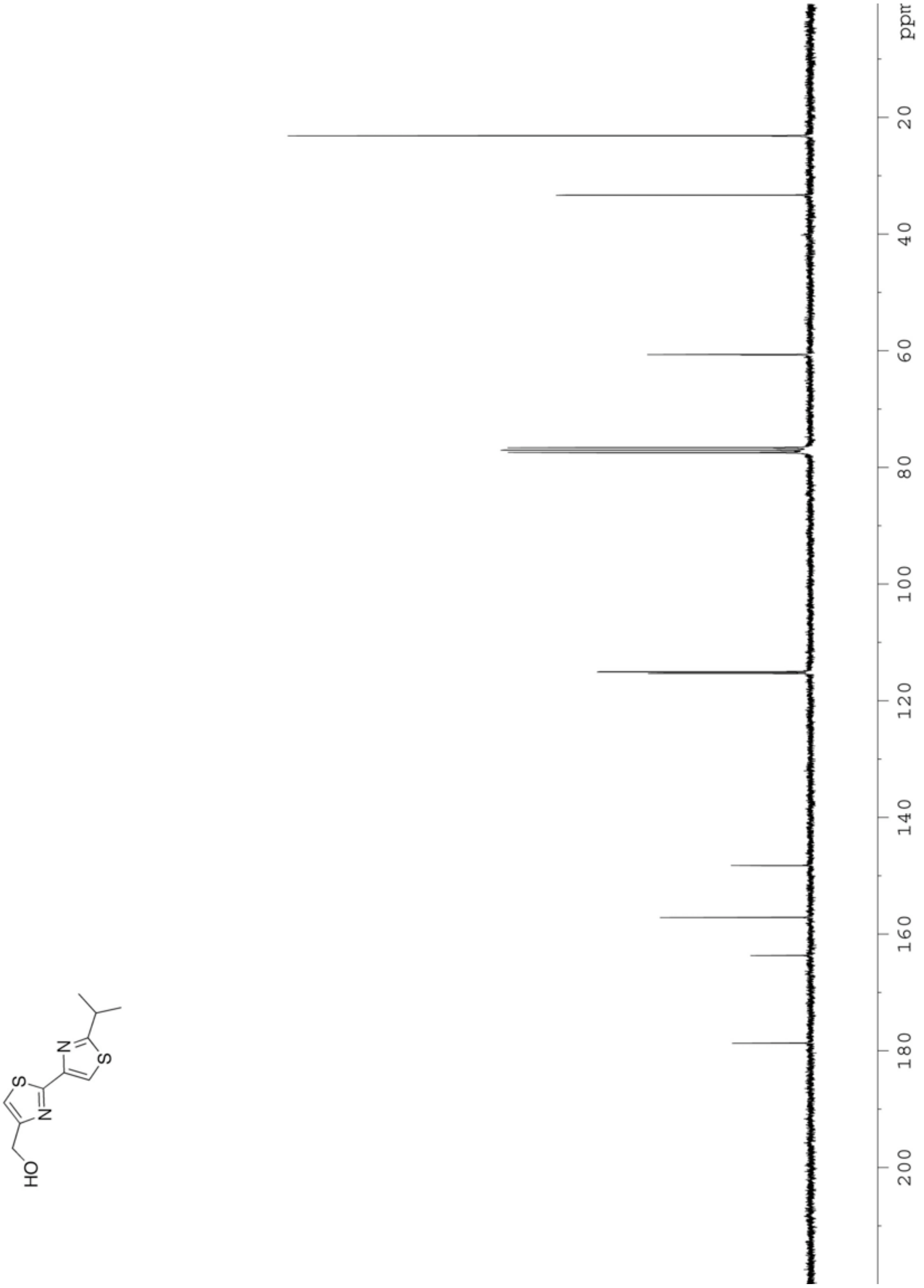
N
S


ppm
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60
80
100
120
140
160
180
200
HO
S
N
N
S