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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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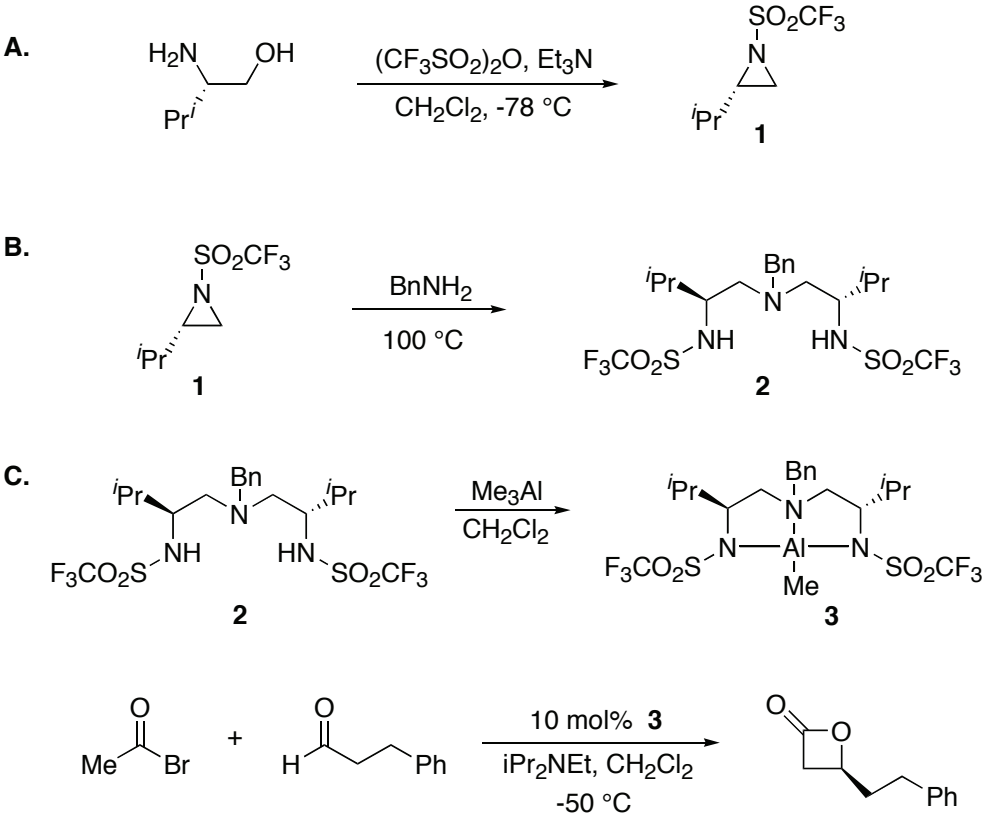
Organic Syntheses, Vol. 82, p. 170-178 (2005); Coll. Vol. 11, p. 506-513 (2009).

CATALYTIC ASYMMETRIC ACYL HALIDE-ALDEHYDE CYCLOCONDENSATION REACTION

[(4*S*)-4-(2-Phenylethyl)-2-oxetanone]



Submitted by Scott G. Nelson and Paul M. Mills.[1]
Checked by Takashi Ohshima and Masakatsu Shibasaki.

1. Procedure

Caution! Dialkylzinc compounds, especially in undiluted form, are pyrophoric and must not be allowed to come into contact with air or moisture. These compounds should only be handled by individuals trained in their proper and safe use. [Note added January 2011].

A. (S)-N-Trifluoromethylsulfonyl-2-isopropylaziridine. An oven-dried, 500 mL, round-bottomed flask is equipped with Teflon-coated magnetic stirring bar and sealed with a rubber septum containing a needle

adapter to a N_2 source. The flask is charged with (*S*)-valinol (8.30 g, 80.5 mmol) (Note 1), triethylamine (26.3 mL, 189 mmol) (Note 2) and dichloromethane (135 mL) (Note 3). The flask is placed in a –78 °C dry ice-acetone bath (Note 4) and, to the well-stirred solution, is added of trifluoromethanesulfonic anhydride (31.8 mL, 189 mmol) (Note 5) via syringe over 20 min (Note 6). The resulting reaction mixture is held at –78 ˚C for 5 h. The reaction mixture is transferred to a 500 mL separatory funnel containing 200 mL of 0.1 N HCl and the mixture is thoroughly shaken and the layers are separated. The organic portion is washed successively with one portion of 0.1 M HCl (200 mL), two portions of saturated aqueous $NaHCO_3$ (200 mL each) and one portion of brine (200 mL). The organic portion is dried over anhydrous magnesium sulfate (Note 7), filtered and concentrated under reduced pressure on a rotary evaporator (Note 8) to afford 16.8-16.9 g (96-97%) of (*S*)-*N*-trifluoromethylsulfonyl-2 -isopropylaziridine (**1**) as a pale yellow oil (Note 9). The (*S*)-*N*-trifluoromethylsulfonyl-2-isopropylaziridine is used in the next transformation without further purification.

B. (2S,6S)-4-Benzyl-1,7-bis(trifluoromethylsulfonyl)-2,6-diisopropyl-1,4,7-triazaheptane. A flame-dried, 250 mL round-bottomed flask containing a Teflon-coated magnetic stirring bar is charged with (*S*)-*N*-trifluoromethylsulfonyl-2-isopropylaziridine (**1**) (16.9 g, 77.8 mmol). Benzylamine (4.03 mL, 37.0 mmol) (Note 10) is added resulting in a mild exotherm (Note 11). Once the exotherm subsided (approx. 10 min), the reaction flask is placed in a 100 ˚C oil bath and held at this temperature for 12 h. The crude product mixture is separated by flash chromatography on silica gel (approx. 300 g) (Note 12) using 10% ethyl acetate in hexane as the eluent (Note 13) to give 20.4 - 21.4 g of pale yellow sticky solid, which included 18.1-18.5 g of **2** (90-92% yield based on ^{1}H NMR analysis), ethyl acetate, and trace amount of yellow material (Note 14). This sticky solid is further purified by trituration with hexane (20 mL, vigorous stirring) and after filtration 15.6-16.0 g (78-80%) of the triamide **2** is obtained as a white powder (Note 15).

C. Acyl halide-aldehyde cyclocondensation: (4S)-4-(2- Phenethyl)-

oxetan-2-one. An oven-dried, 500 mL, three neck round-bottomed flask is equipped with a Teflon-coated magnetic stirring bar and a 125 mL addition funnel and is sealed with rubber septa containing a needle adapter to a N_2 source and a Teflon-coated thermocouple probe attached to a digital thermometer. The flask is charged with triamine **2** (4.00 g, 7.40 mmol) and dichloromethane (150 mL), whereupon a 2 M hexanes solution of trimethylaluminum (3.70 mL) (Note 16) is added at ambient temperature (23 ˚C) (CAUTION: Methane gas evolution). The resulting solution is stirred at 23 ˚C for 2 h before being cooled to –50 °C (Note 17). Once the reaction mixture has reached –50 ˚C, diisopropylethylamine (22.0 mL, 126 mmol) (Note 18) and acetyl bromide (10.4 mL, 141 mmol) (Note 19) are added consecutively via syringe at a rate that maintains the internal reaction temperature ≤ –42 °C. The addition funnel is charged with hydrocinnamaldehyde (9.75 mL, 74.0 mmol) and CH_2Cl_2 (10 mL) and this solution is added dropwise to the reaction mixture at a rate that maintains the internal temperature at ≤ –46 ˚C (Note 20). Once addition is complete, the reaction mixture is stirred at –50 ˚C for 16 h. The reaction mixture is diluted with 350 mL CH_2Cl_2 then transferred to a 2 L separatory funnel containing 800 mL of 0.1 M HCl and the mixture is thoroughly shaken and the layers are separated. The organic portion is washed consecutively with two portions of 0.1 M HCl (800 mL each), three portions of saturated aqueous $NaHCO_3$ (800 mL each) and two portions of brine (800 mL each). After each washing, the separated aqueous payer is extracted with one portion of diethyl ether (400 mL) using the same portion of ether for each extraction; the ethereal extract is reserved until washing of the CH_2Cl_2 layer is complete. The CH_2Cl_2 solution and the ether extract are combined, dried over anhydrous sodium sulfate (Note 21), filtered and concentrated under reduced pressure on a rotary evaporator. The crude product mixture is distilled under reduced pressure (100 ˚C at 5 Pa using turbo-molecular pump) (Note 22) yielding 10.4 g (80%) of (4*S*)-4-(2-phenethyl)oxetan-2-one (Notes 23 and 24).

2. Notes

1. The submitters prepared (*S*)-valinol according to an *Organic Syntheses* procedure employing 200 g (1.71 mol) of (*S*)-valine, 100 g (2.64 mol) of lithium aluminum hydride and 6 L of THF; the THF is used directly from a freshly opened bottle and is not distilled. The crude product mixture was purified by vacuum distillation (80 ˚C at 7 mm Hg) to afford 118 g (67%) of (*S*)-valinol. See: Dickman, D. A.; Meyers, A. I. *Org. Synth., Coll. Vol. VII* **1990**, 530. The checker used commercially available (*S*)-valinol, which was purchased from Aldrich Chemical Company, after distillation (70 ˚C at 1.3 kPa).

2. Triethylamine was purchased from Fisher Scientific Company and was freshly distilled over calcium hydride.

3. Methylene chloride was purchased from EM Science and was freshly distilled over calcium hydride.

4. Bath temperature was achieved using a dry ice-acetone slurry.

5. Trifluoromethanesulfonic anhydride was purchased from Aldrich Chemical Company and was used as received. The use of only 2 mol equivalent of trifluoromethanesulfonic anhydride (27.0 mL, 161 mmol) gave almost identical result.

6. Internal temperature was gradually increased to ca. –60 °C.

7. Anhydrous magnesium sulfate was purchased from EM Science.

8. The residue was concentrated using diaphragm pump (2 kPa). Concentration using oil-pump (0.5 kPa) caused loss of the product due to the low boiling point of the product.

9. Spectral data for the crude aziridine: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.90 (td, *J* = 7.0, 5.0 Hz, 1 H), 2.86 (d, *J* = 7.0 Hz, 1 H), 2.45 (d, *J* = 5.0 Hz, 1 H), 1.65 (octet, *J* = 7.0 Hz, 1 H), 1.05 (d, *J* = 7.0 Hz, 3 H), 1.03 (d, *J* = 7.0 Hz, 3 H).

10. Benzylamine was purchased from Aldrich Chemical Company and freshly distilled before use.

11. Internal temperature reached to 65 °C even when benzylamine was added very slowly (0.5 mL/min).

12. Silica gel was purchased from Merck (Silica gel 60, 230-400 mesh ASTM).

13. The submitters used 80% hexanes-20% ethyl acetate mixture as the eluent for flash chromatography on silica gel purchased from Bodman Industries (70-239 mesh). Using this eluent system, however, the checker obtained unsatisfactory separation.

14. The submitters used the pale yellow solid for the next reaction without further purification (90% yield). To maintain the purity of the triamide **2**, the checkers used the trituration technique.

15. The analytical data are as follows: mp 118-119 °C (lit. 112 ˚C); TLC R_f = 0.50 (hexane:EtOAc = 3:1) $[\alpha]_D$ –50° (*c* 1.6, MeOH); IR (NaCl) cm^{-1}: 3308, 2968, 2880, 2840, 1435, 1371, 1229, 1195, 1148, 1025; IR (KBr) cm^{-1}: 3262, 2969, 1449, 1379, 1231, 1195, 1151, 617; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.27 (m, 5 H), 5.40 (br s, 2 H), 3.94 (d, *J* = 13.5 Hz, 1 H), 3.61-3.56 (m, 2 H), 3.39 (d, *J* = 13.5 Hz, 1 H), 2.66 (dd, *J* = 13.5, 8.5 Hz, 2 H), 2.50 (dd, *J* = 13.5, 5.5 Hz, 2 H), 2.00-1.93 (m, 2 H), 0.87 (d, *J* = 7.0 Hz, 6 H), 0.84 (d, *J* = 6.9 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.0, 129.6, 128.6, 127.7, 119.3 (q, J_{CF} = 319 Hz), 58.60, 58.56, 55.4, 29.7, 18.1, 17.2; MS (EI, 70 eV): *m/z* 542 $(M+1)^+$, 540, 337, 91; HRMS *m/z* calcd for $C_{19}H_{29}F_6N_3O_4S_2$: 541.1504; found: 541.1516; Elemental Anal. calcd for $C_{19}H_{29}F_6N_3O_4S_2$: C, 42.14; H, 5.40; N, 7.76; found: C, 42.14; H, 5.40; N, 7.76.

16. Trimethylaluminum (2.0 M solution in hexanes) was purchased from Aldrich Chemical Company and was use as received.

17. Bath temperature was controlled using a circulating chiller equipped with a submersible cooling probe.

18. *N*,*N*-Diisopropylethylamine was purchased from Aldrich Chemical Company and was freshly distilled over calcium hydride.

19. Acetyl bromide was purchased from Aldrich Chemical Company and was freshly distilled over P_2O_5.

20. Hydrocinnamaldehyde was purchased from Aldrich Chemical Company and was freshly distilled over calcium hydride.

21. Anhydrous sodium sulfate was purchased from L. T. Baker.

22. The checkers experienced some decomposition of the β-lactone to 3-butenylbenzene during distillation, potentially caused by trace acidic impurities (c.f., *i*-Pr_2NEt•HBr) remaining in the crude product mixture). Alternatively, the crude product mixture can be purified by silica-gel column chromatography (10% EtOAc in hexane) to afford the product in 90% yield.

23. The analytical data are as follows: TLC R_f = 0.33 (hexane:EtOAc = 3:1) $[\alpha]_D$ –43.1° (*c* 1.12, CH_2Cl_2) –47.4° (*c* 1.6, $CHCl_3$, 92% ee); IR (NaCl): 3085, 2987, 1828, 1545, 1455, 1135, 700 cm^{-1}; IR (neat): 3027, 2930, 1825, 1496, 1455, , 1412, 1133, 829, 750, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.18 (m, 5 H), 4.51-4.48 (m, 1 H), 3.48 (dd, *J* = 16.5, 5.5 Hz, 1 H), 3.03 (dd, *J* = 16.5, 4.5 Hz, 1 H), 2.84-2.80 (m, 1 H), 2.76-2.70 (m, 1 H), 2.22-2.18 (m, 1 H), 2.12-2.07 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 140.0, 128.5, 128.2, 126.2, 70.3, 42.7, 36.2, 31.1; MS (EI, 70 eV): *m/z* 176 (M^+), 158, 131, 117, 104, 91, 84; HRMS *m/z* calcd for $C_{11}H_{12}O_2$: 176.0838; found: 176.0839; Anal. calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86; found: C, 74.97; H, 7.07.

24. Separation of the enantiomers by chiral HPLC (Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 10% ^{i}PrOH, 90% hexane, T_r 14.3 (*S*) and 16.5 (*R*) min) provided the enantiomer ratio: 4(*S*):4(*R*) = 96.1:3.9 (92% ee).

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

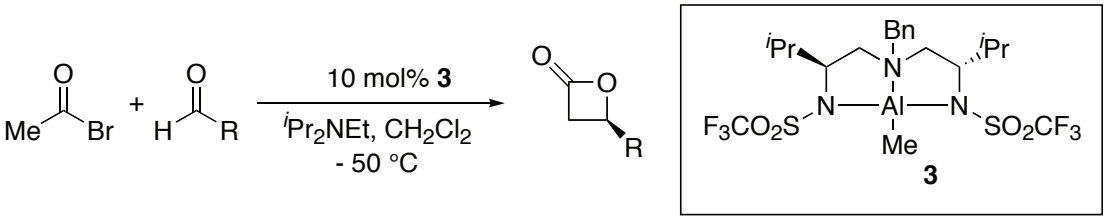
Recent success in developing *de novo* asymmetric syntheses of enantioenriched β-lactones has created renewed interest in these heterocycles as versatile platforms for asymmetric organic synthesis.[3,4] β-Lactones are direct progenitors of numerous useful building blocks

including enantioenriched β-amino acids,[5] allenes[6] and β,β-disubstituted carboxylic acids.[7] β-Lactones are also functional equivalents of ester aldol addition products.[8] In this latter context, we developed acyl halide-aldehyde cyclocondensation (AAC) reactions that deliver enantioenriched β-lactone acetate aldol surrogates from commercially available starting materials (eq 1).

We have recently described Al(III)-catalyzed cyclocondensations of acyl halides and aldehyde electrophiles as an operationally simple route to highly enantioenriched 4-substituted 2-oxetanones. The easily prepared Al(III)-triamine catalyst **3** is uniquely effective in mediating highly enantioselective [2+2] cycloadditions of *in situ* generated ketene and aldehydes. The enantioenriched triamine ligand **2** required for preparing the AAC catalyst is obtained in two high yielding steps from (*S*)-valinol. The AAC catalyst **3** is prepared from the triamine ligand *in situ* by reacting **2** with $AlMe_3$; the acetyl bromide, aldehyde and diisopropylethylamine required for the AAC reaction are then simply added to the resulting catalyst solution. The enantioenriched β-lactones emerging from the AAC reactions are typically sufficiently pure to be used in subsequent transformations without purification.

The catalyst complex **3** renders a variety of structurally diverse aldehydes as effective electrophiles for the catalyzed asymmetric AAC reactions. The procedure described herein highlights the reactivity of enolizable aliphatic aldehydes under the AAC reactions. The examples compiled in Table 1 are indicative of other aldehyde substrates that participate in efficient AAC reactions. Aromatic aldehydes bearing alkyl or electron-withdrawing substituents, functionalized aldehydes bearing common oxygen protecting groups and conjugated ynals are all very reactive electrophiles in the asymmetric AAC reactions. Aldehydes that are not useful AAC substrates include conjugated enals and α-branched aldehydes (c.f., cyclohexanecarboxaldehyde); these types of aldehydes afford little to no β-lactone product under the AAC reaction conditions.

Table 1



Aldehyde (R)	% yield	% ee
-$(CH_2)_8CH=CH_2$	91	91
-$CH_2CH(CH_3)_2$	80	93
-CH_2OCH_2Ph	91	92
-CH_2OSiPh_2tBu	74	89
-$CH_2CH_2OCH_2Ph$	90	91
-$C\equiv CCH_2OCH_2Ph$	86	93
-$C_6H_4NO_2$	93	95

1. Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania, 15260.

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Yang, H. W.; Zhao, C.; Wright, G. D. *Bioorg. Med. Chem.* **1998**, *6*, 1255. (c) Tennyson, R.; Romo, D. *J. Org. Chem*. **2000**, *65*, 7248. (d) Evans, D. A.; Janey, J. M. *Org. Lett*. **2001**, *3*, 2125. (e) Cortez, G. S.; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc*. **2001**, *123*, 7945. (f) Calter, M. A.; Liao, W. *J. Am. Chem. Soc*. **2002**, *124*, 13127 and references therein.

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6. Wan, Z.; Nelson, S. G. *J. Am. Chem. Soc*. **2000**, *122*, 10470.

7. Nelson, S. G.; Wan, Z.; Stan, M. A. *J. Org. Chem*. **2002**, *67*, 4680.

8. Nelson, S. G.; Wan, Z.; Peelen, T. J.; Spencer, K. L. *Tetrahedron Lett.* **1999**, *40*, 6535.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

(*S*)-Valinol: (2*S*)-2-Amino-3-methyl-1-butanol; (2026-48-4)

Triethylamine: *N,N*-Diethylethanamine,; (121-44-8)

Trifluoromethanesulfonic anhydride; (358-23-6)

(*S*)-*N*-Trifluoromethylsulfonyl-2-isopropylaziridine: (*S*)-2-(1-Methylethyl)-1-[(trifluoromethyl)sulfonyl]-aziridine; (196520-85-1)

Benzylamine: Benzenemethanamine; (100-46-9)

(*2S,6S*)-4-Benzyl-1,7-bis(trifluoromethylsulfonyl)-2,6-diisopropyl-1,4,7-triazaheptane: *N,N′*-[[(Phenylmethyl)imino]bis[(1*S*)-1-(1-methylethyl)-2,1-ethanediyl]]bis[1,1,1-trifluoro]-methanesulfonamide; (200351-80-0)

Diisopropylethylamine: *N*-Ethyl-*N*-(1-methylethyl)-2-propanamine; (7087-68-5)

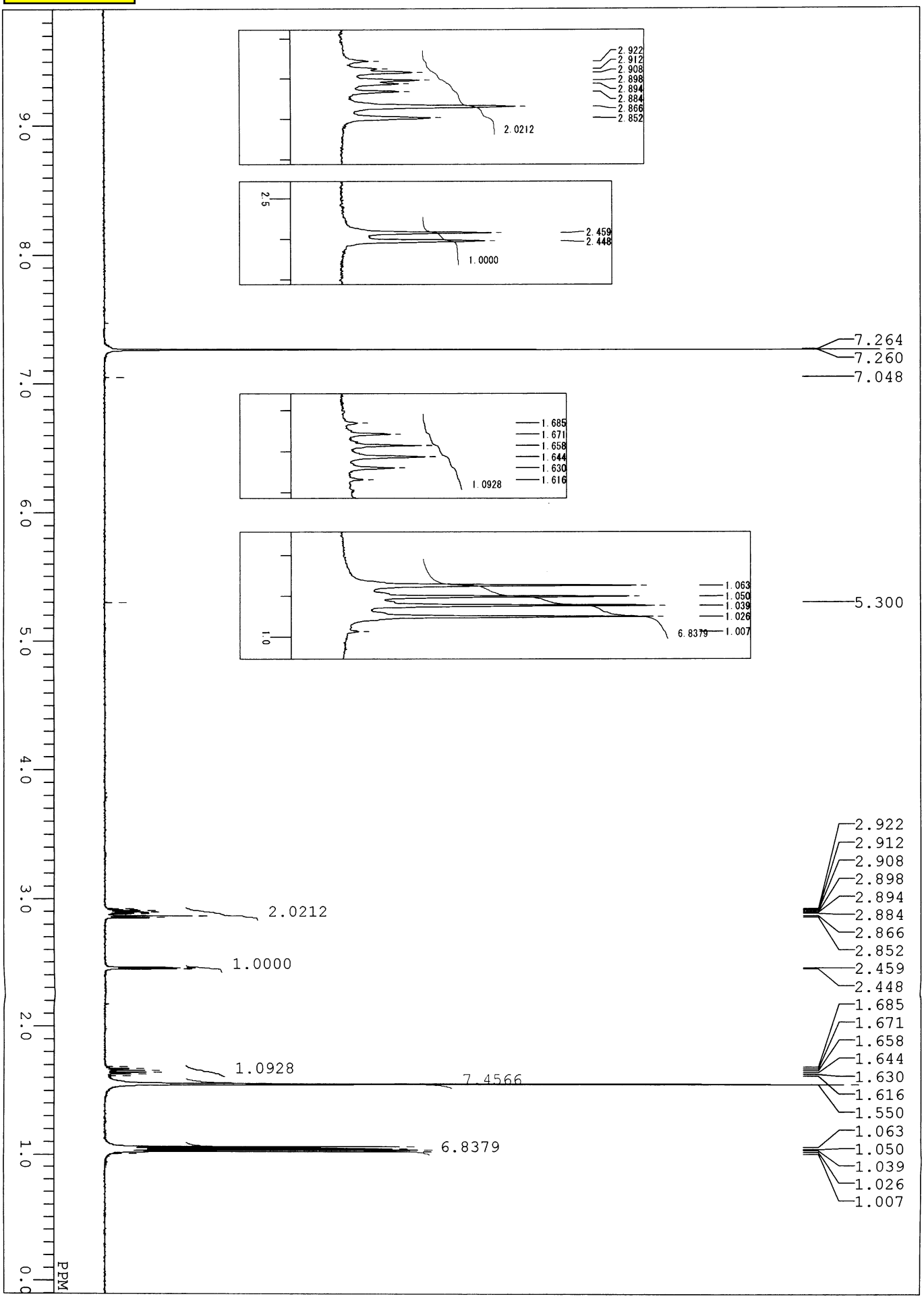
Trimethylaluminum; (75-24-1)

Acetyl bromide; (506-96-7)

Hydrocinnamaldehyde: Benzenepropanal; (104-53-0)

(4*S*)-4-(2-Phenethyl)oxetan-2-one:, (4*S*)-4-(2-phenylethyl)-2-oxetanone; (214853-90-4)

Step A (1H NMR)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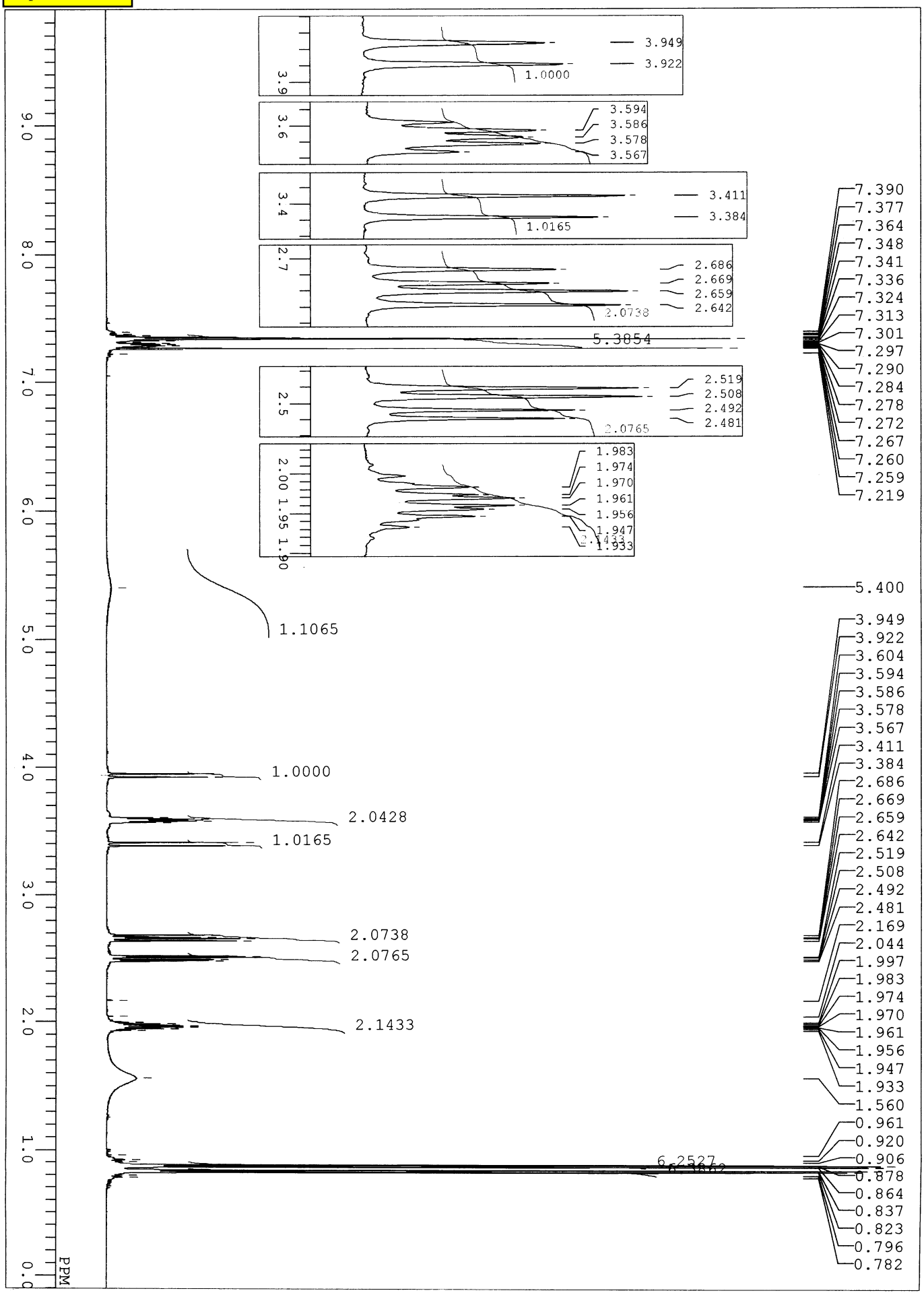
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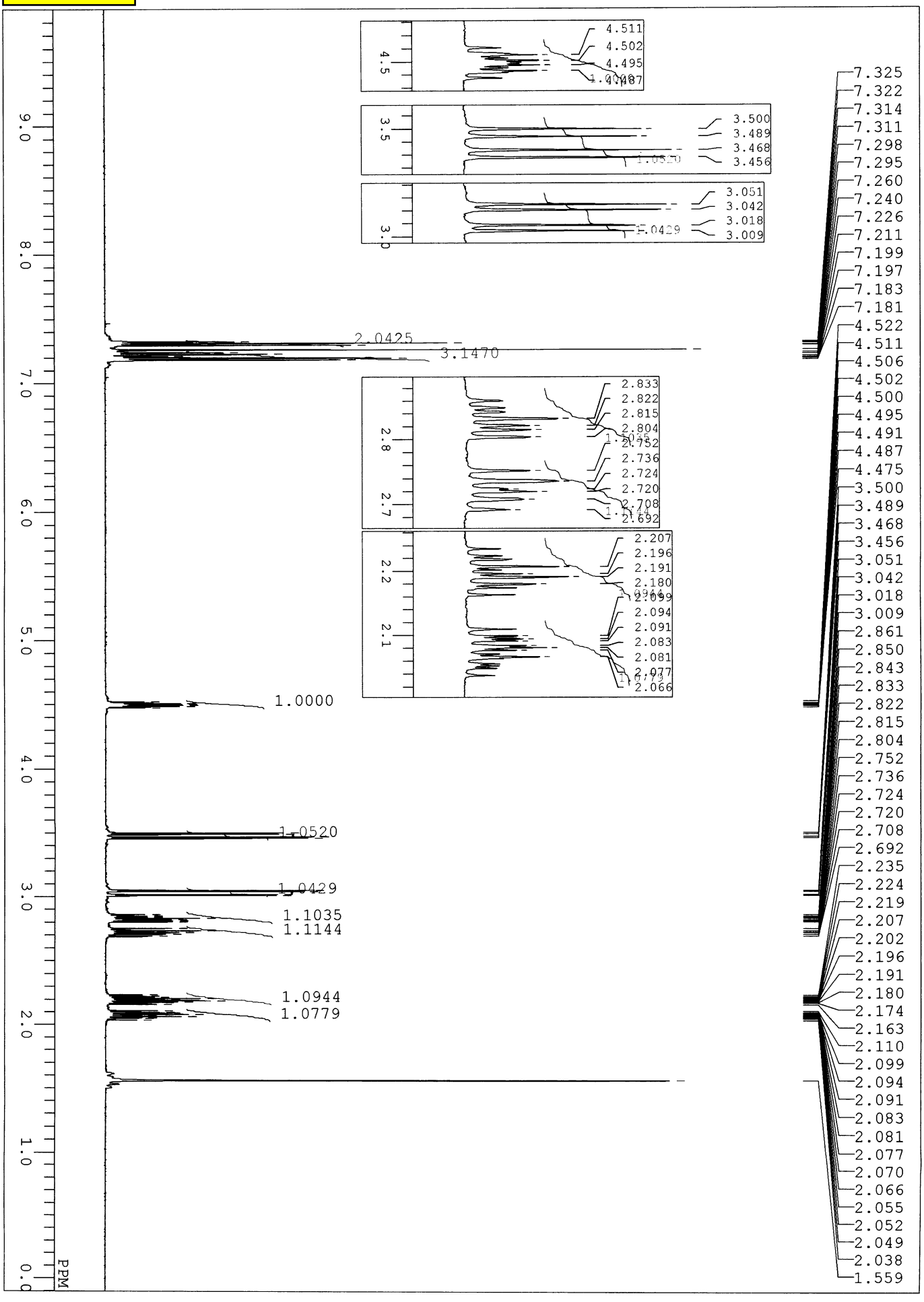
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