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TADDOL-based *P,S*-bidentate diastereomeric ligands in asymmetric allylation and hydrogenation reactions

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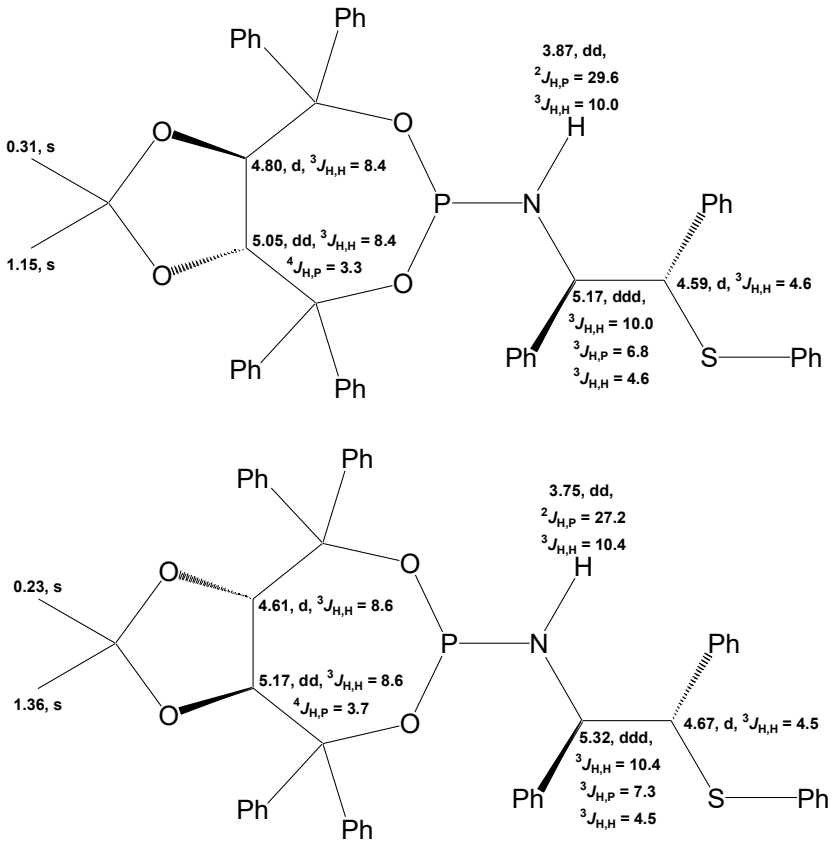

Figure S1 Assignment of non-aromatic ^{1}H resonances for ligands (*R*,*R*)-**L1** (up) and (*S*,*S*)-**L1** (down).

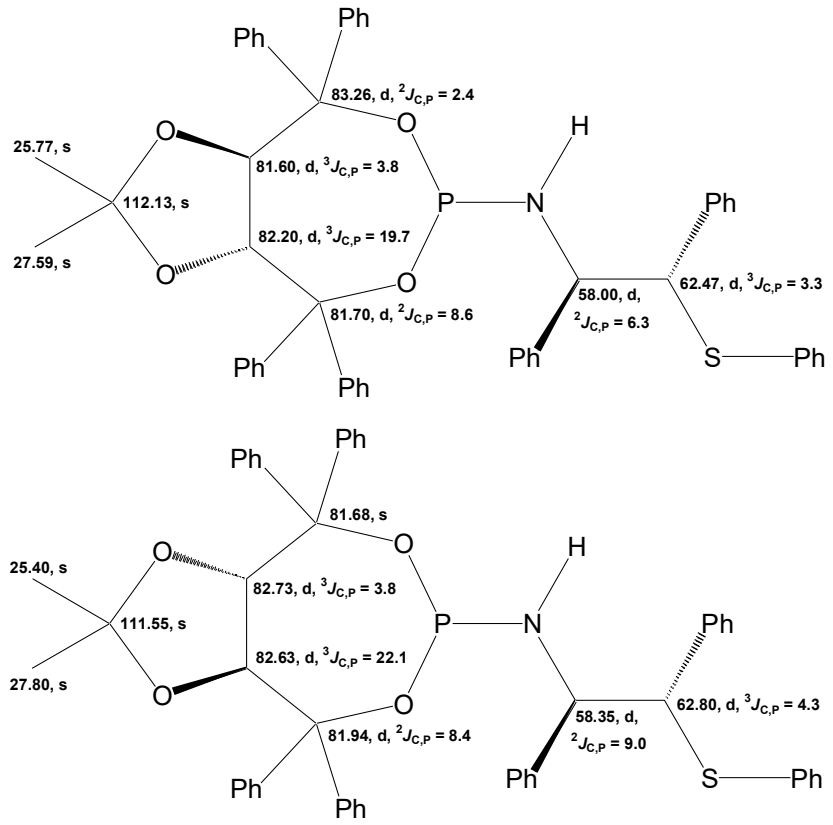

Figure S2 Assignment of non-aromatic ^{13}C{^{1}H} resonances for ligands (*R*,*R*)-**L1** (up) and (*S*,*S*)-**L1** (down).

Experimental Section

General Remarks. $^{31}P\{^1H\}$, $^{13}C\{^1H\}$ and ^1H NMR spectra were recorded with Bruker Avance 600 for (*R*,*R*)-**L1** (242.9 MHz for $^{31}P\{^1H\}$, 150.9 MHz for $^{13}C\{^1H\}$ and 600.1 MHz for ^1H) and Varian Inova 500 (*S*,*S*)-**L1** (202.3 MHz for $^{31}P\{^1H\}$, 125.7 MHz for $^{13}C\{^1H\}$ and 499.8 MHz for ^1H) instruments at room temperature in $CDCl_3$. ^1H and $^{13}C\{^1H\}$ NMR signals were attributed using APT, DEPT, $^1H,^1H$ – COSY, $^{13}C,^1H$ – HSQC techniques. The chemical shifts are referenced to residual solvent peaks (^1H, $^{13}C\{^1H\}$ NMR) or H_3PO_4 85% as external standard ($^{31}P\{^1H\}$ NMR). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, m = multiplet). Enantiomeric analysis of the products of catalytic reactions was performed with a Staier HPLC system. Elemental analysis was carried out on a Carlo Erba EA1108 CHNS-O CHN analyzer.

All reactions were carried out in anhydrous solvents under dry argon. The following compounds were synthesized according to literature procedures: ((4*R*,5*R*)- and ((4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(diphenylmethanol) ((*R*,*R*)- and (*S*,*S*)-TADDOL),[S1] (1*R*,2*S*)-1,2-diphenyl-2-(phenylthio)ethan-1-amine,[S2] (*E*)-1,3-diphenylallyl acetate (**1**) and $[Pd(\pi\text{-allyl})Cl]_2$,[S3] methyl (*Z*)-2-acetamido-3-phenylacrylate (**4b**),[S4] methyl (*Z*)-2-acetamido-3-(4-fluorophenyl)acrylate (**4c**),[S5] methyl (*Z*)-2-acetamido-3-(naphthalen-2-yl)acrylate (**4d**)[S6] and $[Rh(Cod)_2]BF_4$.[S7]

Pd-catalyzed allylic alkylation of **1** with dimethyl malonate, its amination with pyrrolidine and Rh-catalyzed hydrogenation of **4a-d** were performed according to the appropriate procedures.[S8]

Dimethyl malonate, *N*,*O*-bis(trimethylsilyl)acetamide (BSA), triethylamine, pyrrolidine and dimethyl itaconate (**4a**) were purchased from Fluka and Aldrich.

General Procedure for the Preparation of Ligands: A solution of the appropriate (*R*,*R*)- or (*S*,*S*)-TADDOL (1.87 g, 4.0 mmol) in THF (30 ml) was added dropwise at - 10 °C over 10 min to a vigorously stirred solution of PCl_3 (0.37 ml, 4.2 mmol) and Et_3N (1.17 ml, 8.4 mmol) in THF (12 ml). The reaction mixture was brought to 20°C and allowed to stir for 2 h. Solid $Et_3N{\cdot}HCl$ was filtered off, and the filtrate was concentrated in vacuum (40 Torr). The residue was triturated in pentane and dried in vacuum (10^{-3} Torr) for 8 h.

(1*R*,2*S*)-1,2-Diphenyl-2-(phenylthio)ethan-1-amine (0.61 g, 2 mmol) was added at 20 °C in one portion to a vigorously stirred solution of the obtained phosphorylating reagent (1.06 g, 2 mmol) and Et_3N (0.56 ml, 4 mmol) in toluene (15 ml). The reaction mixture was stirred during 24 h at 20°C and filtered through a short column with SiO_2/Al_2O_3, the column was washed with toluene (2 x 20 ml), and the solvent was evaporated under reduced pressure (40 Torr). Products were additionally purified by crystallization from heptane. The obtained ligands were dried in vacuum (10^{-3} Torr) for 8 h.

For the preparation of analytically pure samples, the obtained compounds were additionally dried in high vacuum (10^{-3} Torr) for 16 h.

(3a*R*,8a*R*)-6-[(1*R*,2*S*)-1,2-Diphenyl-2-(phenylthio)ethan-1-amino]-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine ((*R*,*R*)-**L1**). Yield 1.18 g (74%), white powder. ^{1}H NMR: 0.31 (s, 3H; CH_3), 1.15 (s, 3H; CH_3), 3.87 (dd, $^{2}J_{H,P}$ = 29.6, $^{3}J_{H,H}$ = 10.0, 1H; NH), 4.59 (d, $^{3}J_{H,H}$ = 4.6, 1H; CH), 4.80 (d, $^{3}J_{H,H}$ = 8.4, 1H; CH), 5.05 (dd, $^{3}J_{H,H}$ = 8.4, $^{4}J_{H,P}$ = 3.3, 1H; CH), 5.17 (ddd, $^{3}J_{H,H}$ = 10.0, $^{3}J_{H,P}$ = 6.8, $^{3}J_{H,H}$ = 4.6, 1H; CH), 6.95-6.97 (m, 4H; CH(Ph)), 7.00-7.02 (m, 2H; CH(Ph)), 7.05-7.12 (m, 6H; CH(Ph)), 7.14-7.31 (m, 23H; CH(Ph) + CH(toluene)), 7.44-7.46 (m, 2H; CH(Ph)), 7.48-7.49 (m, 2H; CH(Ph)), 7.62-7.63 (m, 2H; CH(Ph)) ppm.^{13}C{^{1}H} NMR: 25.77 (s; CH_3), 27.59 (s; CH_3), 58.00 (d, $^{2}J_{C,P}$ = 6.3; CH), 62.47 (d, $^{3}J_{C,P}$ = 3.3; CH), 81.60 (d, $^{3}J_{C,P}$ = 3.8; CH), 81.70 (d, $^{2}J_{C,P}$ = 8.6; C), 82.20 (d, $^{3}J_{C,P}$ = 19.7; CH), 83.26 (d, $^{2}J_{C,P}$ = 2.4; C), 112.13 (s; C), 126.71 (s; CH(Ph)), 126.92 (s; CH(Ph)), 126.97 (s; CH(Ph)), 127.26 (s; CH(Ph)), 127.33 (s; CH(Ph)), 127.35 (s; CH(Ph)), 127.40 (s; CH(Ph)), 127.42 (s; CH(Ph)), 127.45 (s; CH(Ph)), 127.55 (s; CH(Ph)), 127.59 (s; CH(Ph)), 127.70 (s; CH(Ph)), 127.84 (s; CH(Ph)), 127.95 (s; CH(Ph)), 128.17 (s; CH(Ph)), 128.91 (s; CH(Ph)), 129.03 (s; CH(Ph)), 129.16 (s; CH(Ph)), 129.25 (s; CH(Ph)), 131.04 (s; CH(Ph)), 135.96 (s; C(Ph)), 138.72 (s; C(Ph)), 141.24 (d, $^{3}J_{C,P}$ = 2.0; C(Ph)), 141.31 (d, $^{3}J_{C,P}$ = 1.7; C(Ph)), 142.26 (d, $^{3}J_{C,P}$ = 1.8; C(Ph)), 146.55 (d, $^{3}J_{C,P}$ = 1.7; C(Ph)), 146.88 (s; C(Ph)) ppm. ^{31}P{^{1}H} NMR: 136.49 (s) ppm. Calcld. for $C_{51}H_{46}NO_4PS$: C, 76.57; H, 5.80; N, 1.75. Found: C, 76.80; H, 5.85; N, 1.68.

(3a*S*,8a*S*)-6-[(1*R*,2*S*)-1,2-Diphenyl-2-(phenylthio)ethan-1-amino]-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine ((*S*,*S*)-**L1**). Yield 1.10 g (69%), white powder. ^{1}H NMR: 0.23 (s, 3H; CH_3), 1.36 (s, 3H; CH_3), 3.75 (dd, $^{2}J_{H,P}$ = 27.2, $^{3}J_{H,H}$ = 10.4, 1H; NH), 4.61 (d, $^{3}J_{H,H}$ = 8.6, 1H; CH), 4.67 (d, $^{3}J_{H,H}$ = 4.5, 1H; CH), 5.17 (dd, $^{3}J_{H,H}$ = 8.6, $^{4}J_{H,P}$ = 3.7, 1H; CH), 5.32 (ddd, $^{3}J_{H,H}$ = 10.4, $^{3}J_{H,P}$ = 7.3, $^{3}J_{H,H}$ = 4.5, 1H; CH), 7.08-7.25 (m, 34H; CH(Ph) + CH(toluene)), 7.42-7.43 (m, 2H; CH(Ph)), 7.48-7.50 (m, 2H; CH(Ph)), 7.71-7.72 (m, 2H; CH(Ph)) ppm.^{13}C{^{1}H} NMR: 25.40 (s; CH_3), 27.80 (s; CH_3), 58.35 (d, $^{2}J_{C,P}$ = 9.0; CH), 62.80 (d, $^{3}J_{C,P}$ = 4.3; CH), 81.68 (s; C), 81.94 (d, $^{2}J_{C,P}$ = 8.4; C), 82.63 (d, $^{3}J_{C,P}$ = 22.1; CH), 82.73 (d, $^{3}J_{C,P}$ = 3.8; CH), 111.55 (s; C), 126.79 (s; CH(Ph)), 126.83 (s; CH(Ph)), 127.12 (s; CH(Ph)), 127.22 (s; CH(Ph)), 127.32 (s; CH(Ph)), 127.47 (s; CH(Ph)), 127.48 (s; CH(Ph)), 127.58 (s; CH(Ph)), 127.61 (s; CH(Ph)), 127.65 (s; CH(Ph)), 127.75 (s; CH(Ph)), 127.97 (s; CH(Ph)), 128.13 (s; CH(Ph)), 128.24 (s; CH(Ph)), 128.78 (s; CH(Ph)), 128.82 (s; CH(Ph)), 128.92 (s; CH(Ph)), 129.42 (s; CH(Ph)), 129.47 (s; CH(Ph)), 131.31 (s; CH(Ph)), 136.11 (s; C(Ph)), 138.69 (s; C(Ph)), 141.67 (d, $^{3}J_{C,P}$ = 1.7; C(Ph)), 141.78 (d, $^{3}J_{C,P}$ = 1.2; C(Ph)), 142.62 (d, $^{3}J_{C,P}$ = 1.6; C(Ph)), 146.29 (d, $^{3}J_{C,P}$ = 2.6; C(Ph)), 147.13 (s; C(Ph)) ppm. ^{31}P{^{1}H} NMR: 136.01 (s) ppm. Calcld. for $C_{51}H_{46}NO_4PS$: C, 76.57; H, 5.80; N, 1.75. Found: C, 76.85; H, 5.90; N, 1.65.

Palladium-Catalyzed Asymmetric Allylic Alkylation of (*E*)-1,3-Diphenylallyl Acetate (1) with Dimethyl Malonate: A solution of $[Pd(\pi\text{-allyl})Cl]_2$ (1 mg, 0.0025 mmol) and ligand (*R,R*)-**L1** or (*S,S*)-**L1** (4.0 mg, 0.005 mmol or 8.0 mg, 0.01 mmol) in the appropriate solvent (1.5 ml) was stirred for 40 min. (*E*)-1,3-Diphenylallyl acetate (**1**) (0.05 ml, 0.25 mmol) was added, and the solution was stirred for 15 min. Dimethyl malonate (0.05 ml, 0.44 mmol), BSA (0.11 ml, 0.44 mmol), and KOAc (2 mg) were added. The reaction mixture was stirred for 24 h, diluted with CH_2Cl_2 (2 ml) and filtered through a thin layer of SiO_2. The filtrate was evaporated at reduced pressure (40 Torr) and dried in vacuum (10^{-3} Torr) affording a residue containing dimethyl (*E*)-2-(1,3-diphenylallyl)malonate (**2**).[S9] In order to evaluate *ee* and conversion, the obtained residue was dissolved in an appropriate eluent mixture (8 ml) and a sample was taken for HPLC analysis.

Palladium-Catalyzed Asymmetric Allylic Amination of (*E*)-1,3-Diphenylallyl Acetate (1) with Pyrrolidine: A solution of $[Pd(\pi\text{-allyl})Cl]_2$ (1 mg, 0.0025 mmol) and ligand (*R,R*)-**L1** or (*S,S*)-**L1** (4.0 mg, 0.005 mmol or 8.0 mg, 0.01 mmol) in the appropriate solvent (1.5 ml) was stirred for 40 min. (*E*)-1,3-Diphenylallyl acetate (**1**) (0.05 ml, 0.25 mmol) was added, and the solution was stirred for 15 min, then freshly distilled pyrrolidine (0.06 ml, 0.75 mmol) was added. The reaction mixture was stirred for 24 h, diluted with CH_2Cl_2 (2 ml) and filtered through a thin layer of SiO_2. The filtrate was evaporated at reduced pressure (40 Torr) and dried in vacuum (10^{-3} Torr) affording a residue containing (*E*)-1-(1,3-diphenylallyl)pyrrolidine (**3**).[S10] In order to evaluate *ee* and conversion, the obtained residue was dissolved in an appropriate eluent mixture (8 ml) and a sample was taken for HPLC analysis.

Rhodium-Catalyzed Asymmetric Hydrogenation of Dimethyl Itaconate, Methyl (*Z*)-2-Acetamido-3-phenylacrylate, Methyl (*Z*)-2-Acetamido-3-(4-fluorophenyl)acrylate or Methyl (*Z*)-2-Acetamido-3-(naphthalen-2-yl)acrylate: A solution of $[Rh(Cod)_2]BF_4$ (1 mg, 0.0025 mmol) and ligand (*R,R*)-**L1** or (*S,S*)-**L1** (2.0 mg, 0.0025 mmol) in CH_2Cl_2 (2 ml) was stirred for 40 min. Then appropriate substrate (0.25 mmol) was added. Catalytic vessel containing the resulting solution was filled with hydrogen to a pressure of 6.0 atm, and the reaction mixture was stirred for 24 h and then decompressed. The solvent was evaporated at reduced pressure (40 Torr), the residue was dissolved in diethyl ether (2 ml) and filtered through a thin layer of SiO_2. The filtrate was evaporated at reduced pressure (40 Torr) and dried in vacuum (10 Torr, 12 h) affording a residue containing dimethyl 2-methylsuccinate (**5a**), methyl 2-acetamido-3-phenylpropanoate (**5b**), methyl 2-acetamido-3-(4-fluorophenyl)propanoate (**5c**) or methyl 2-acetamido-3-(naphthalen-2-yl)propanoate (**5d**).[S11] In order to evaluate *ee* and conversion, the obtained residue was dissolved in an appropriate eluent mixture (8 mL) and a sample was taken for HPLC analysis.

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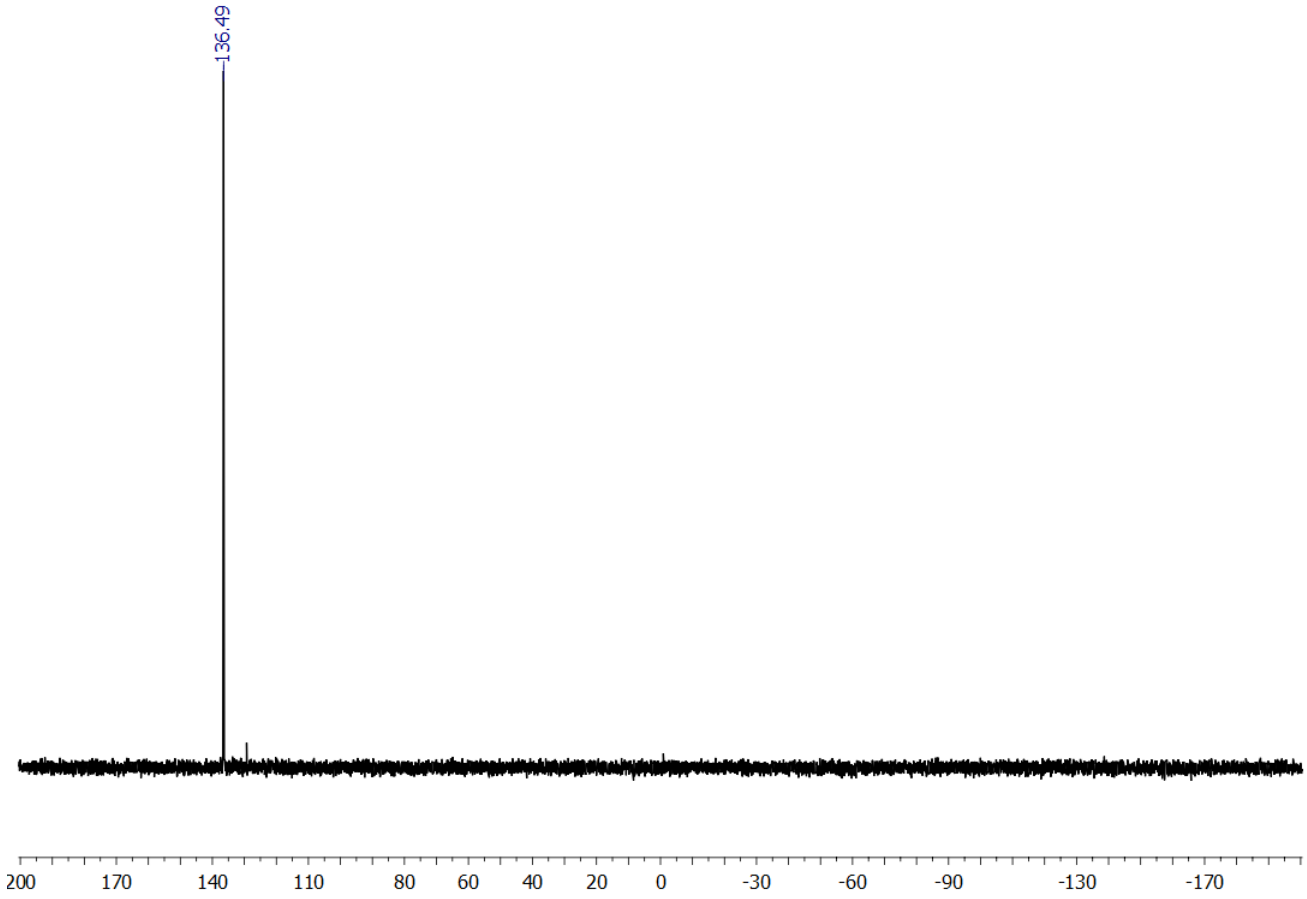

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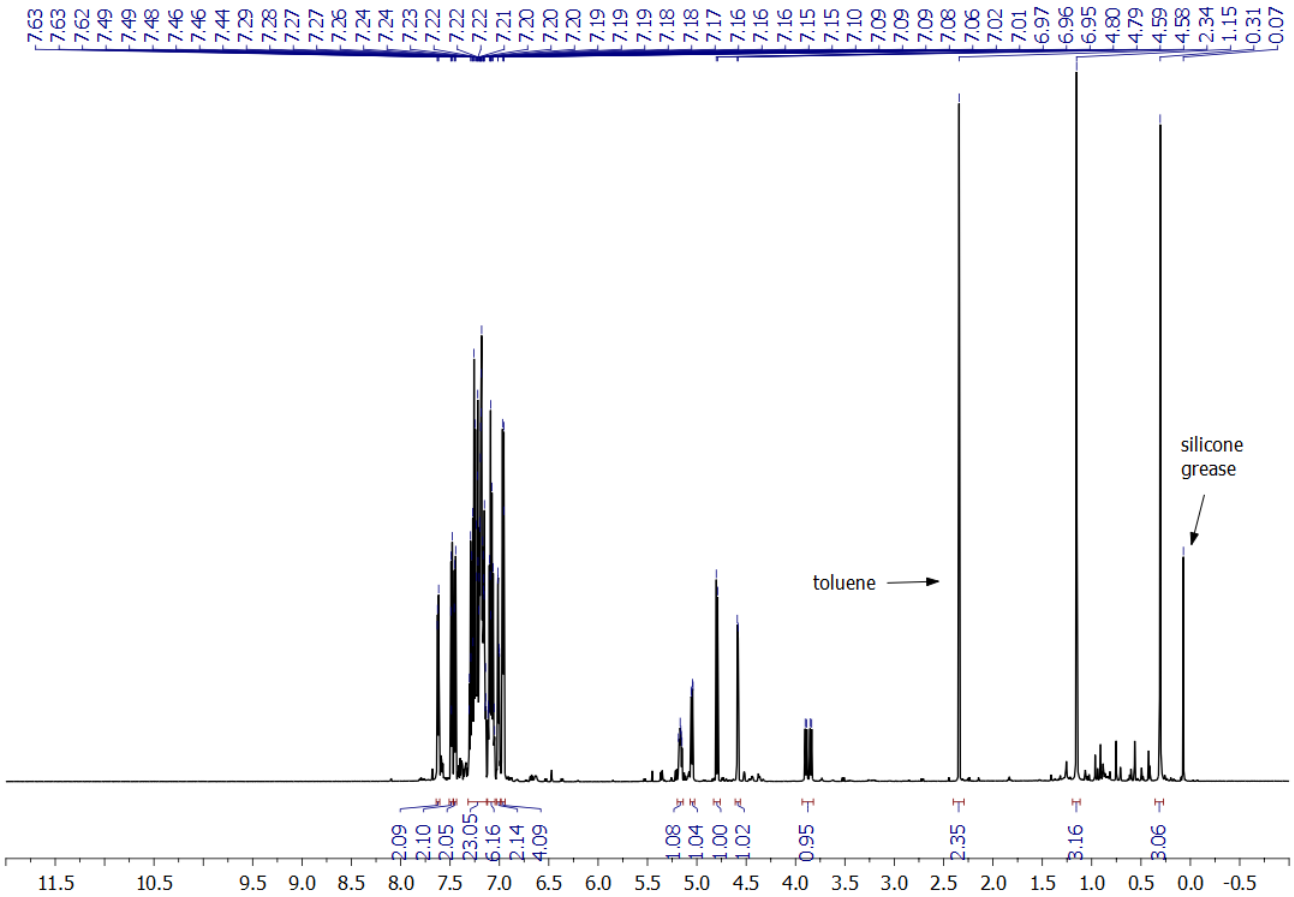

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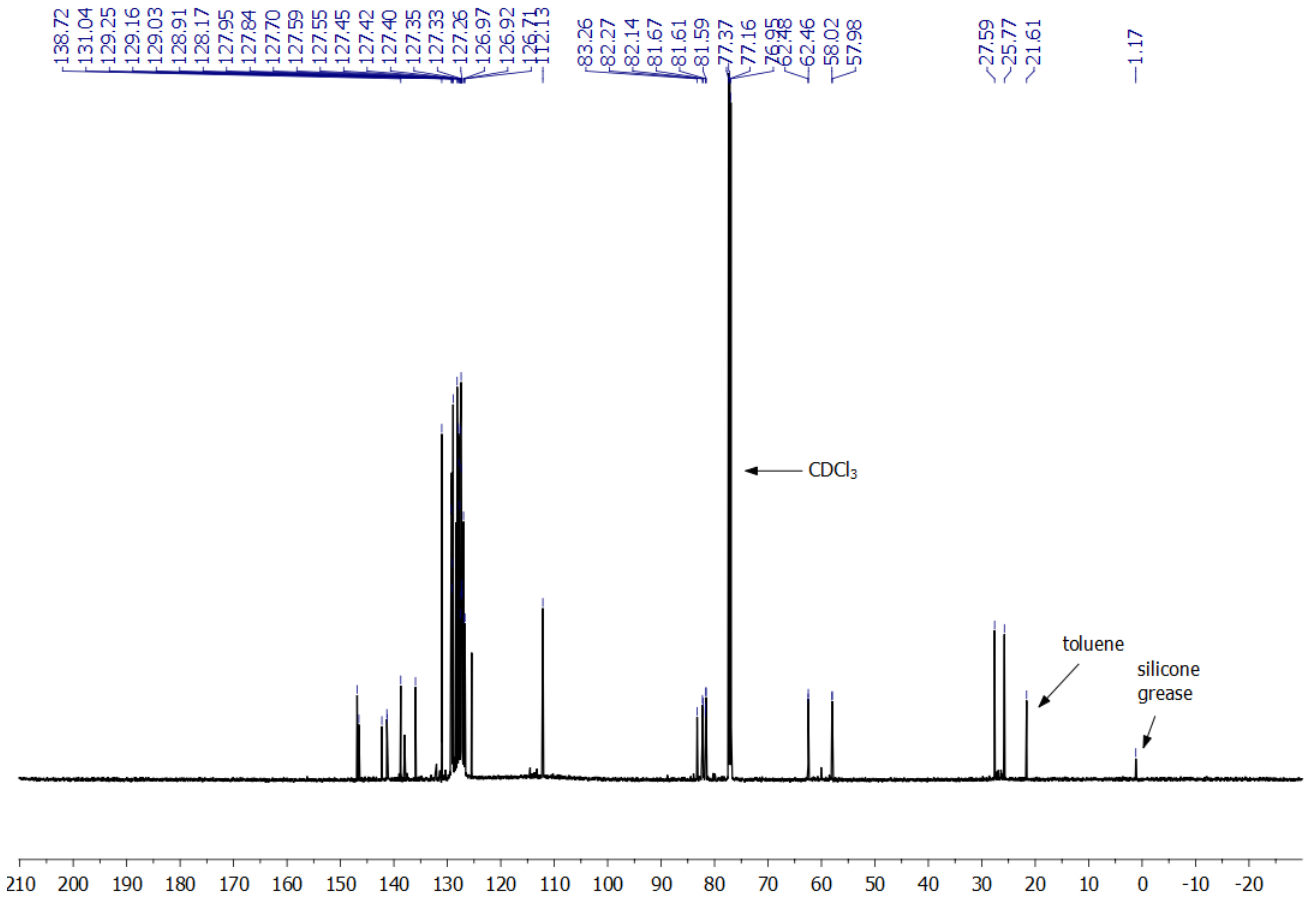

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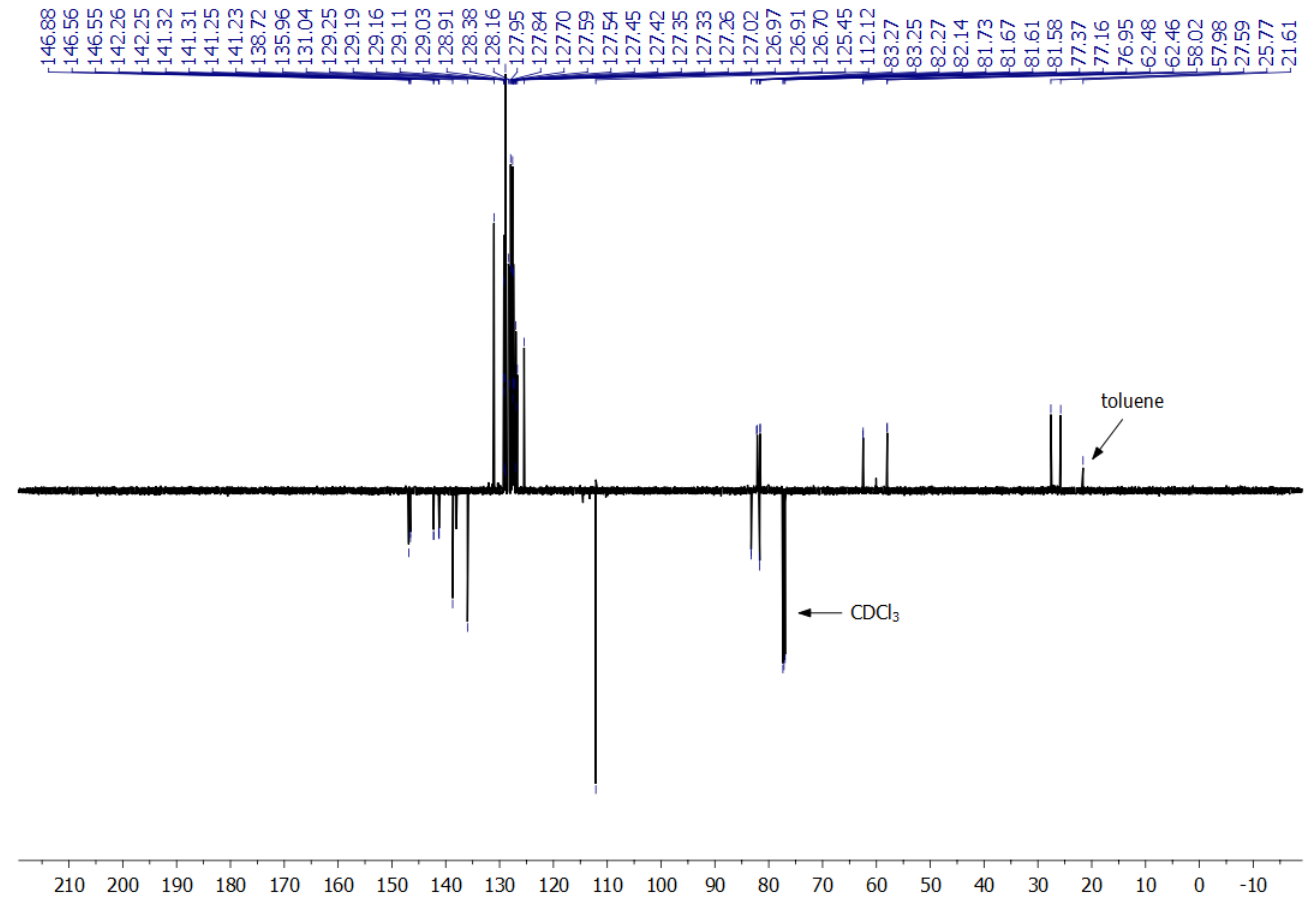

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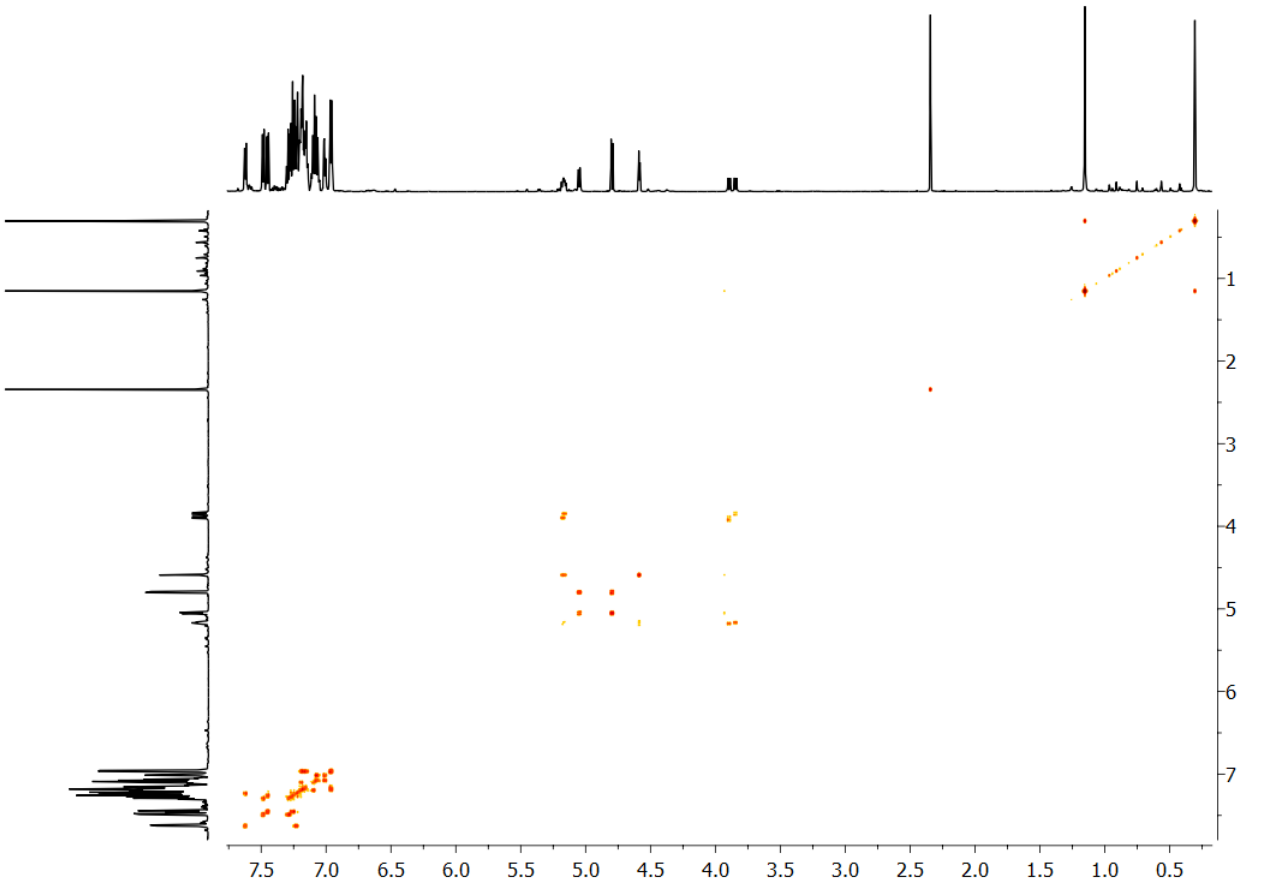

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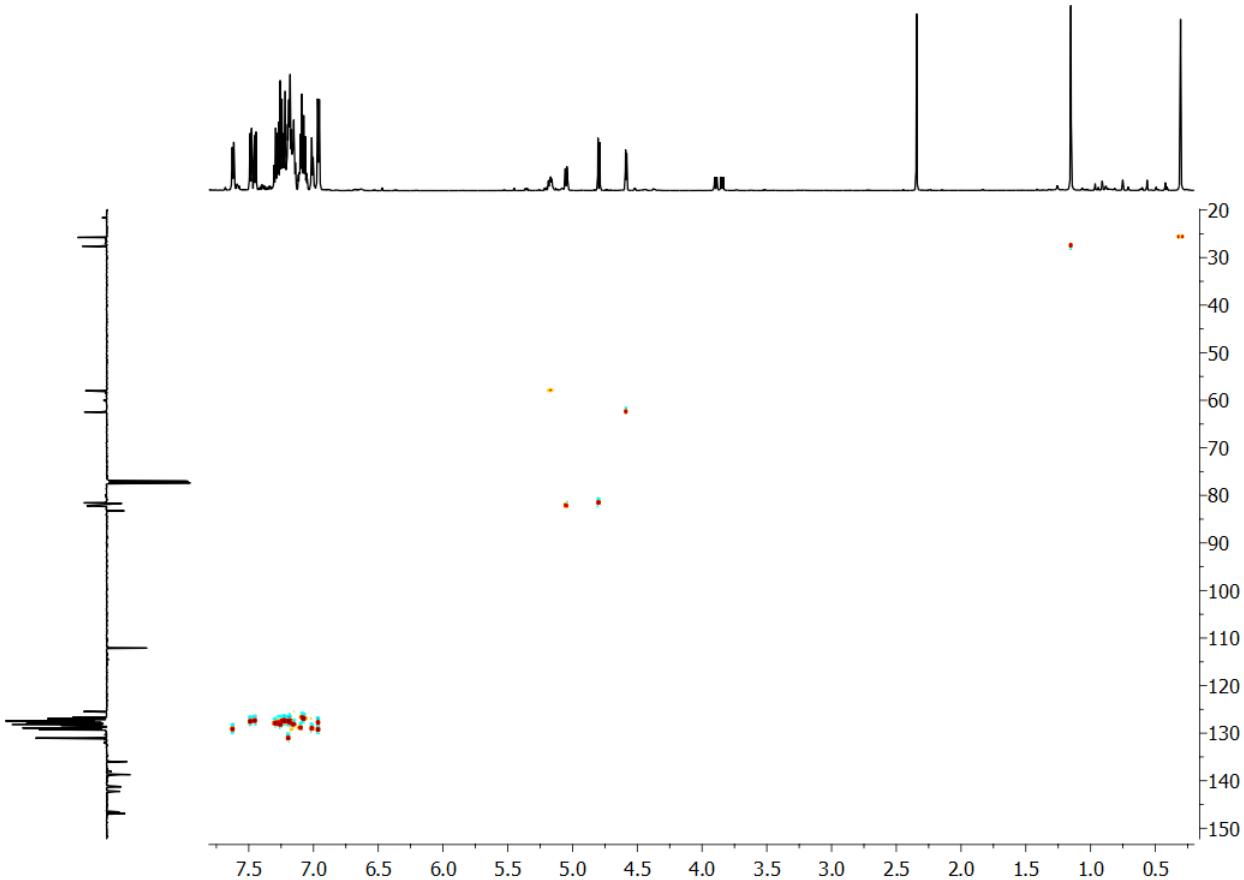

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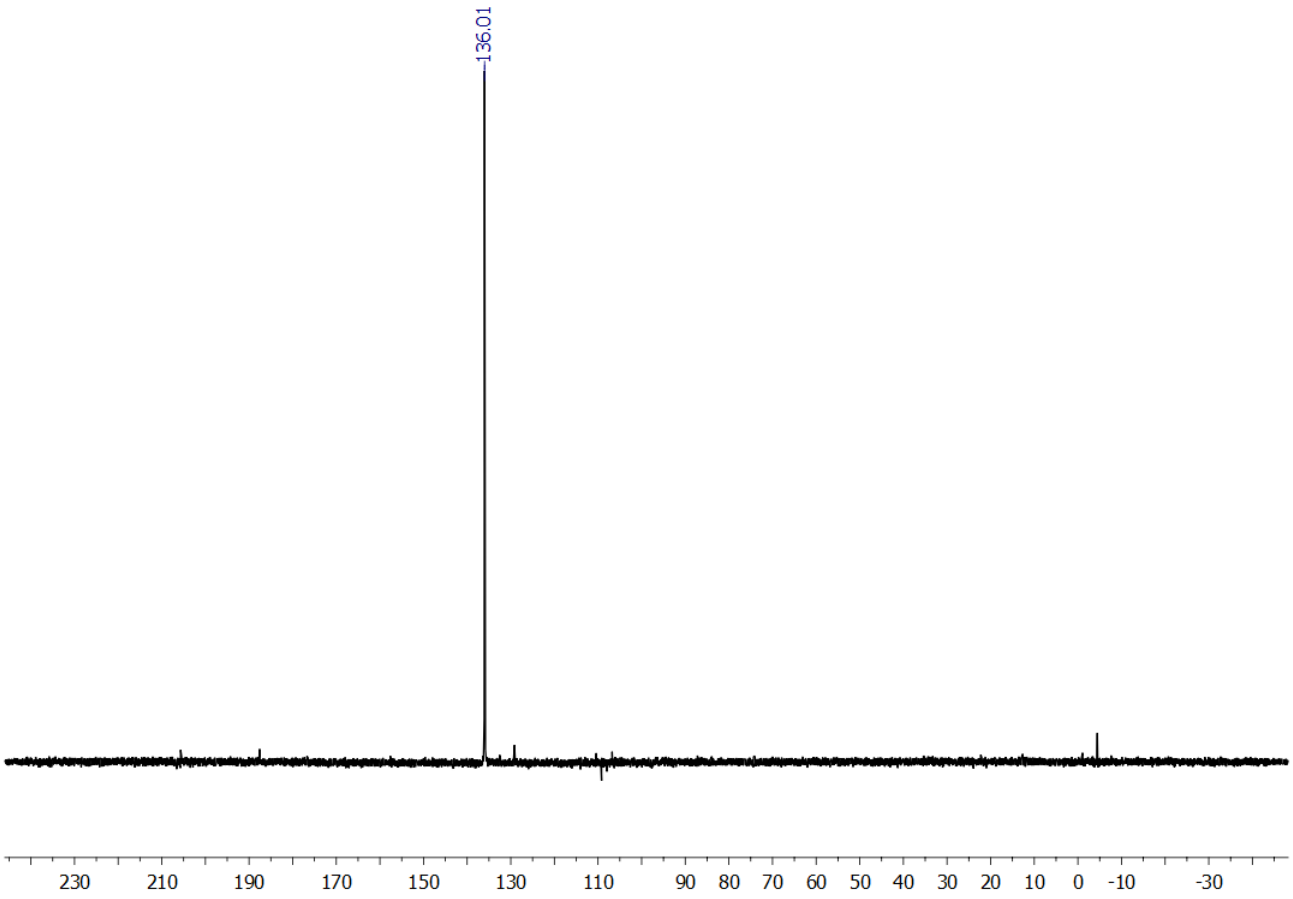

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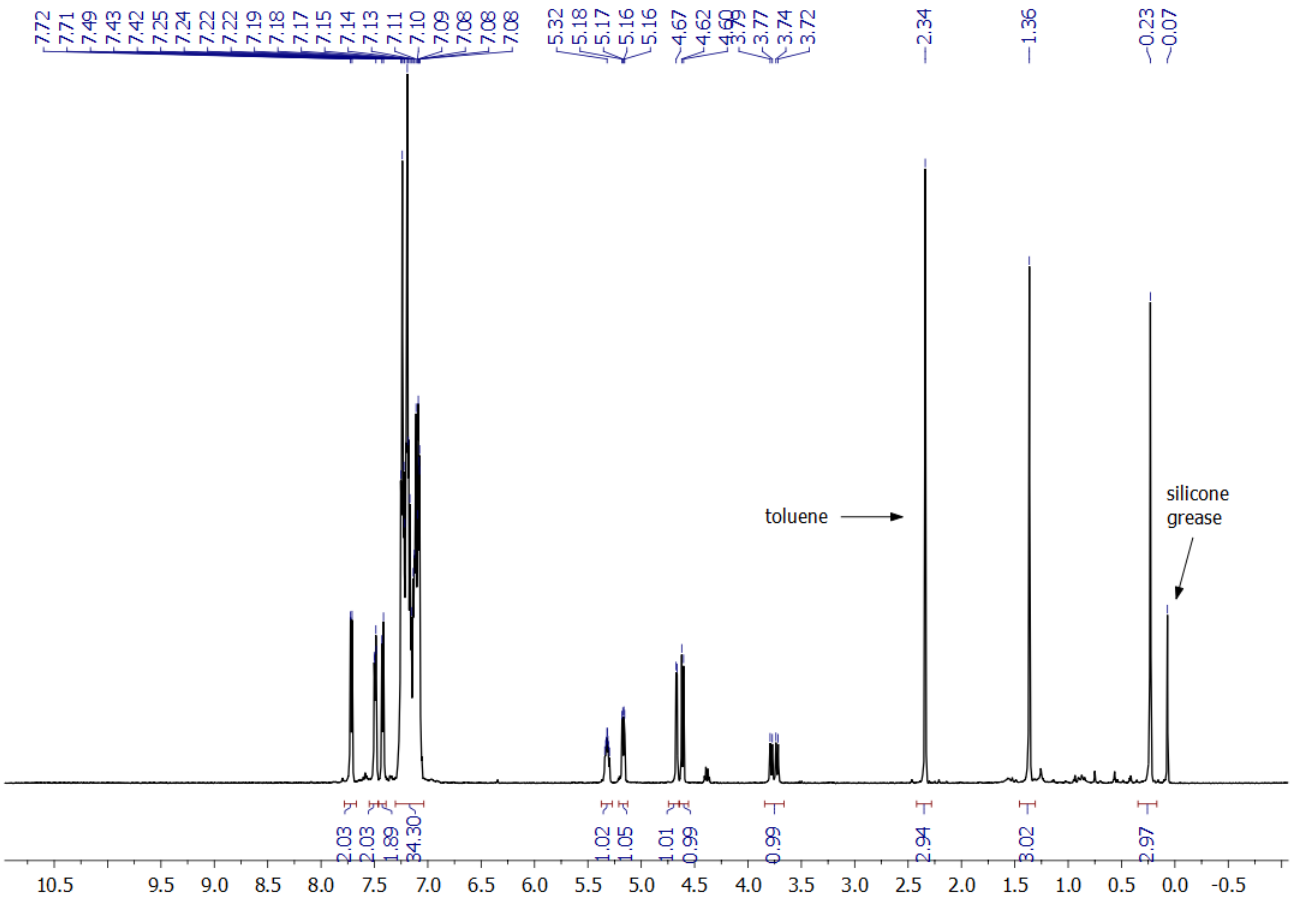

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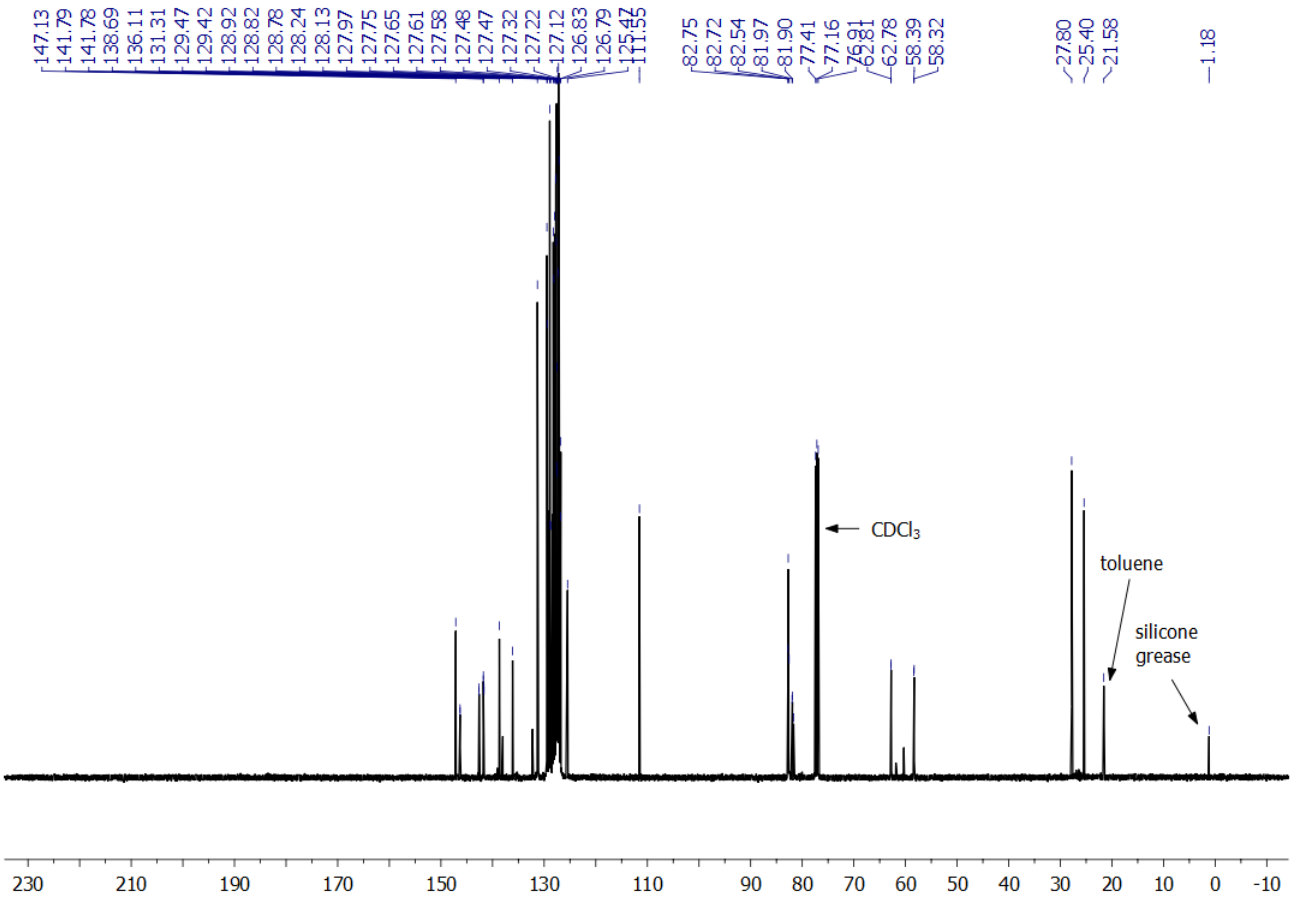

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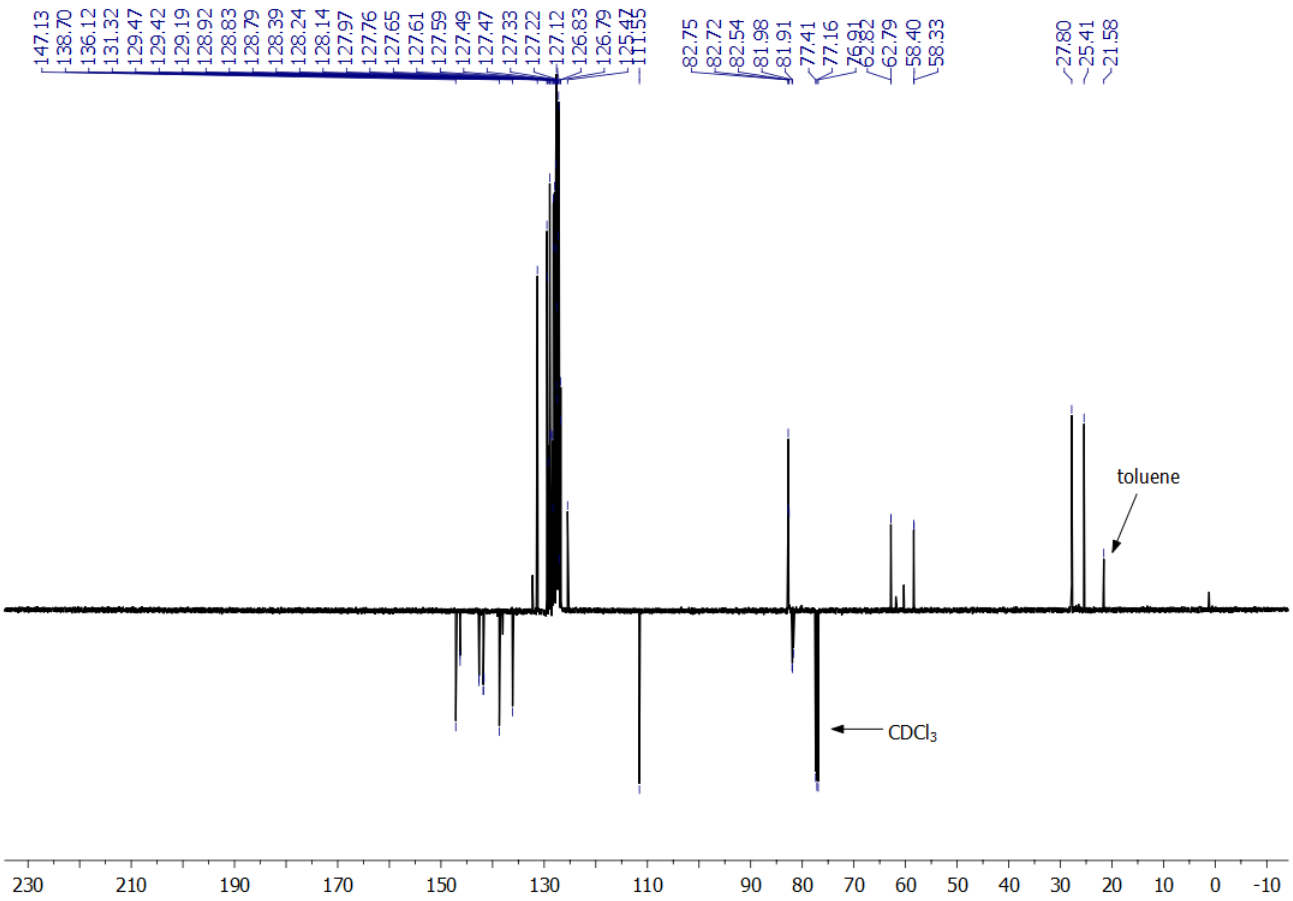

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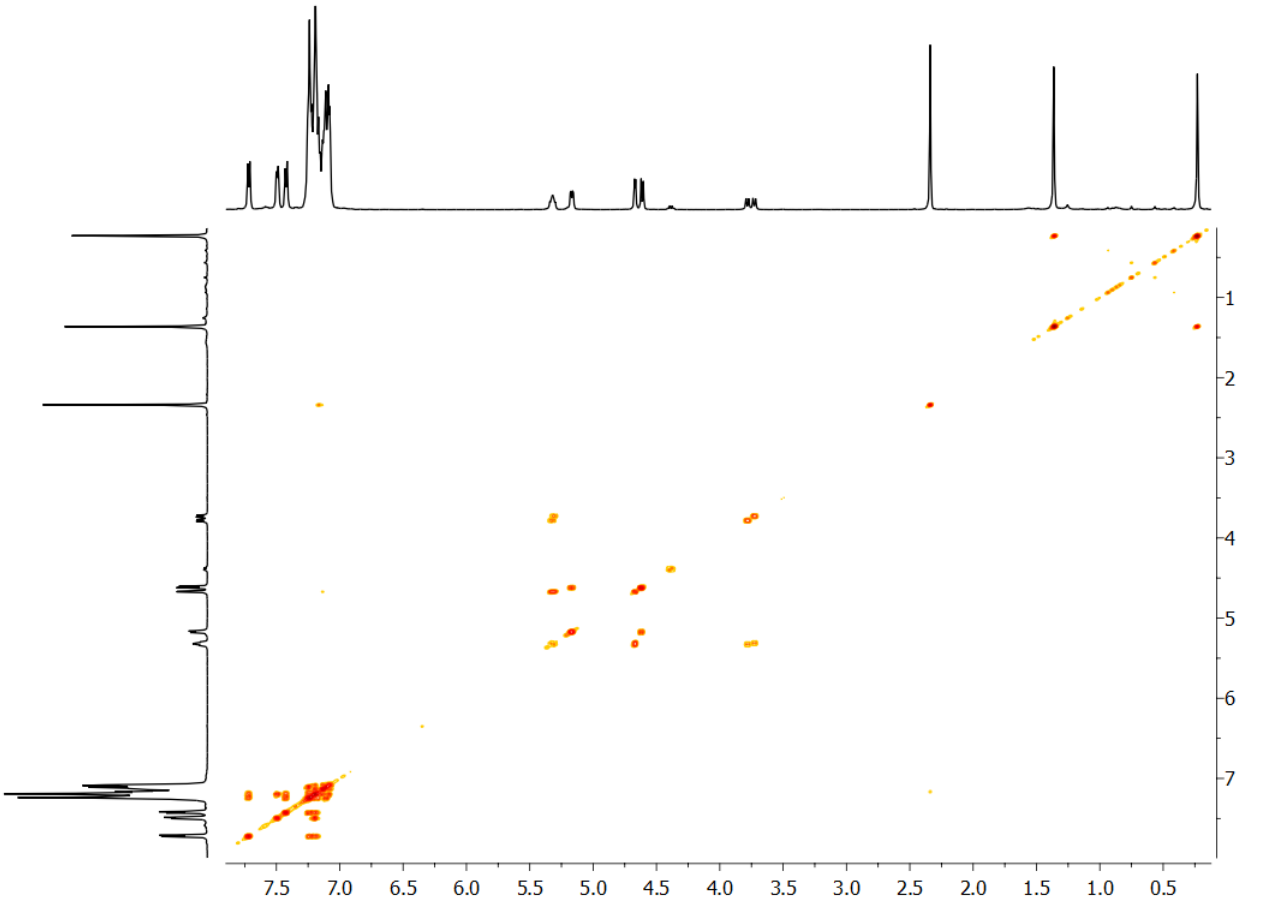

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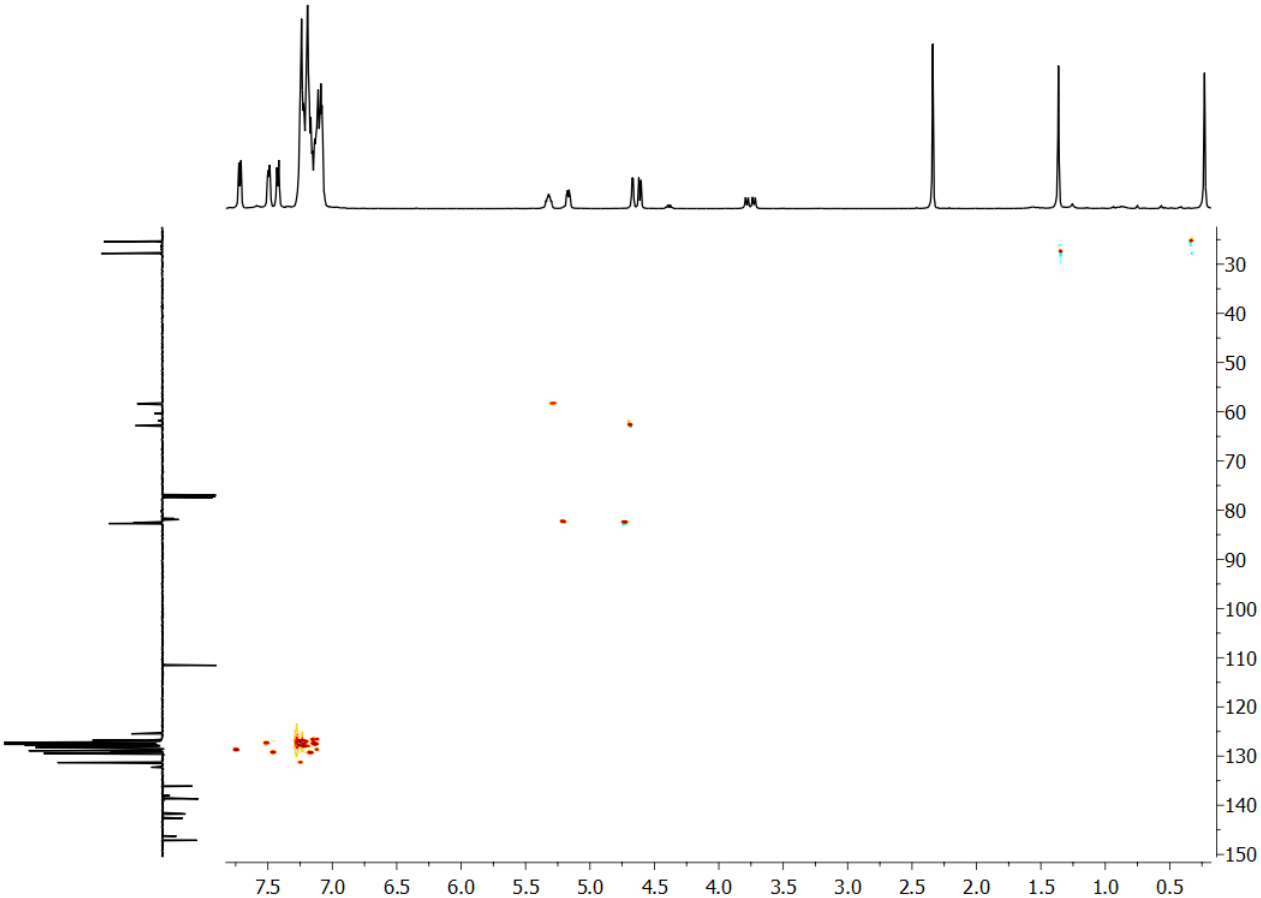

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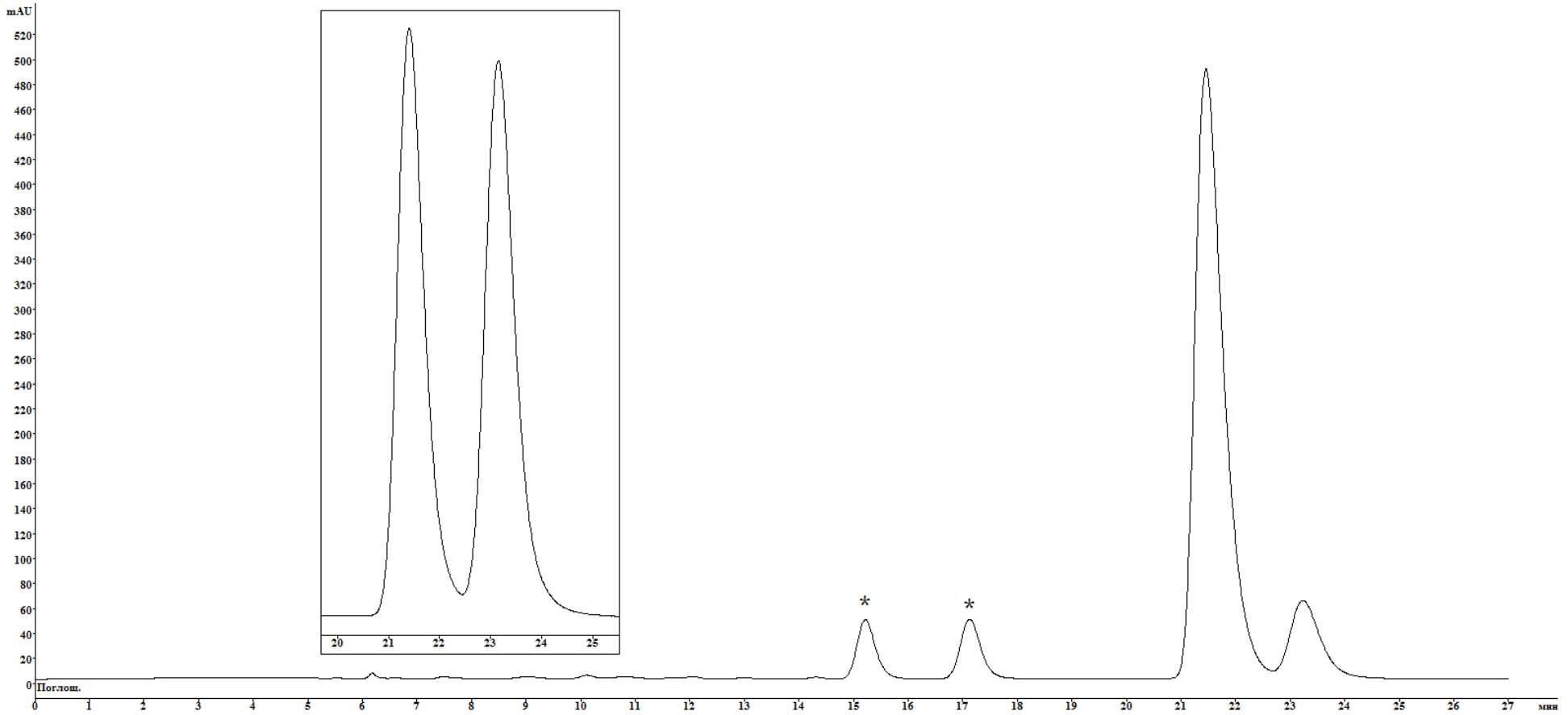
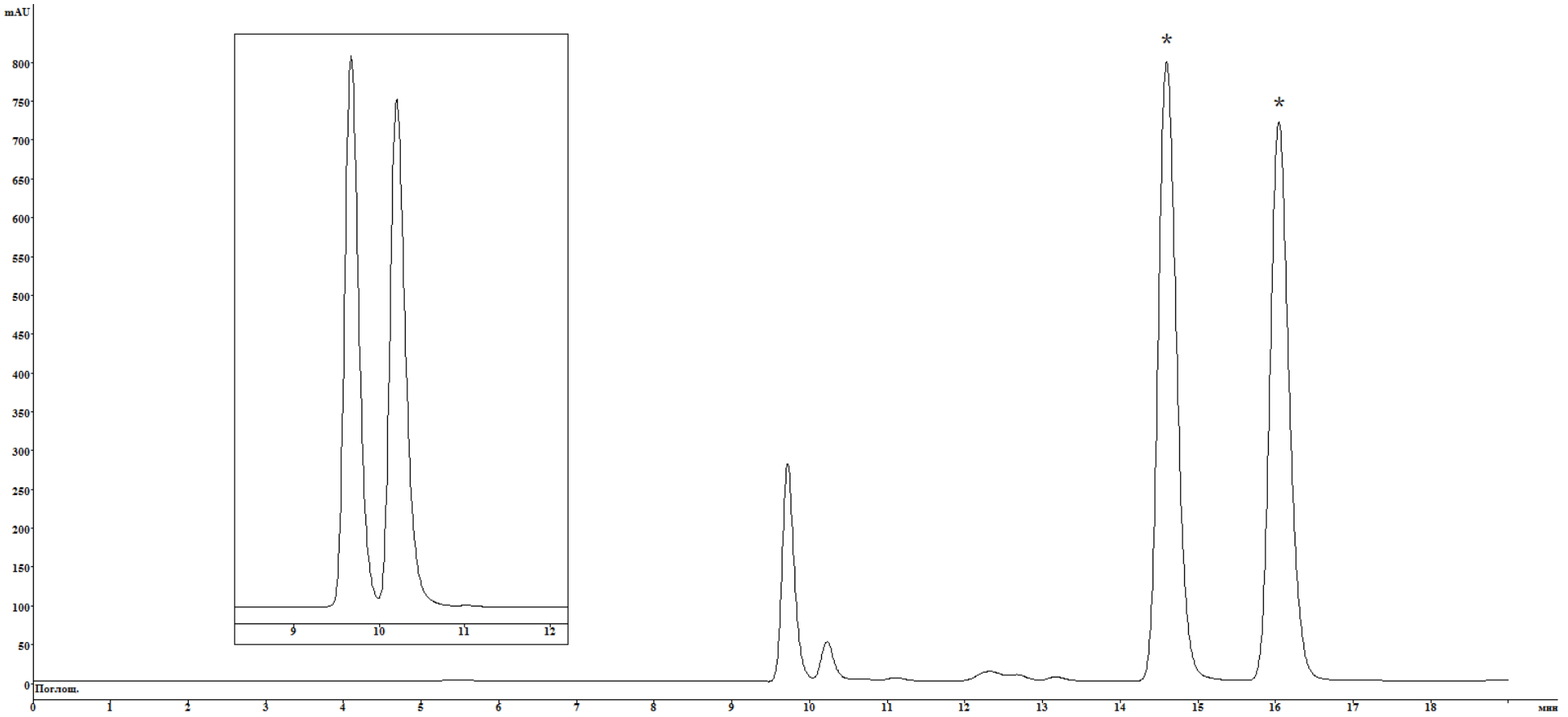


Chiral HPLC profile for the Pd-catalyzed asymmetric allylic alkylation of 1 with dimethyl malonate (entry 2 in Table 1) and for a racemic mixture of 2 (in the frame).

* starting substrate **1**



Chiral HPLC profile for the Pd-catalyzed asymmetric allylic amination of 1 with pyrrolidine (entry 4 in Table 2) and for a racemic mixture of 3 (in the frame).

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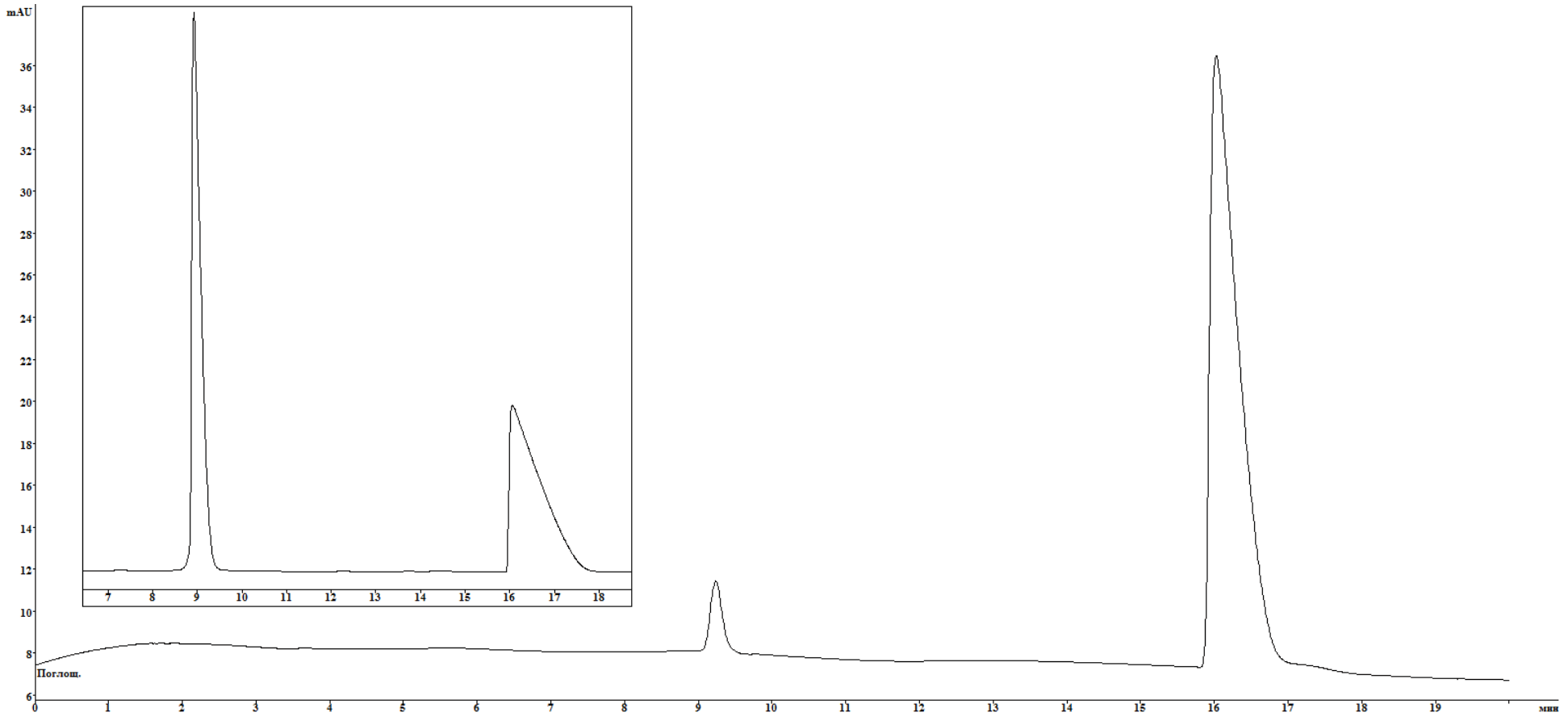
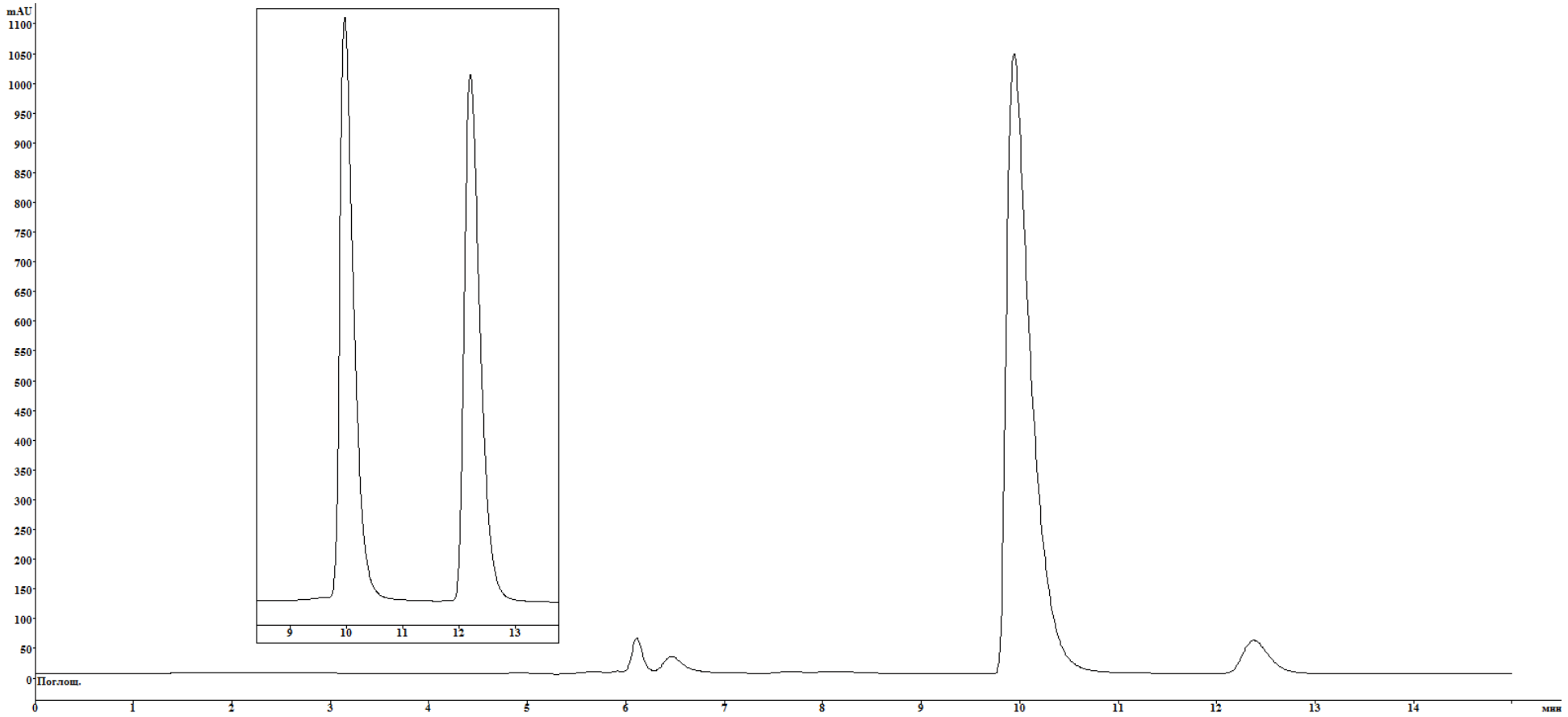
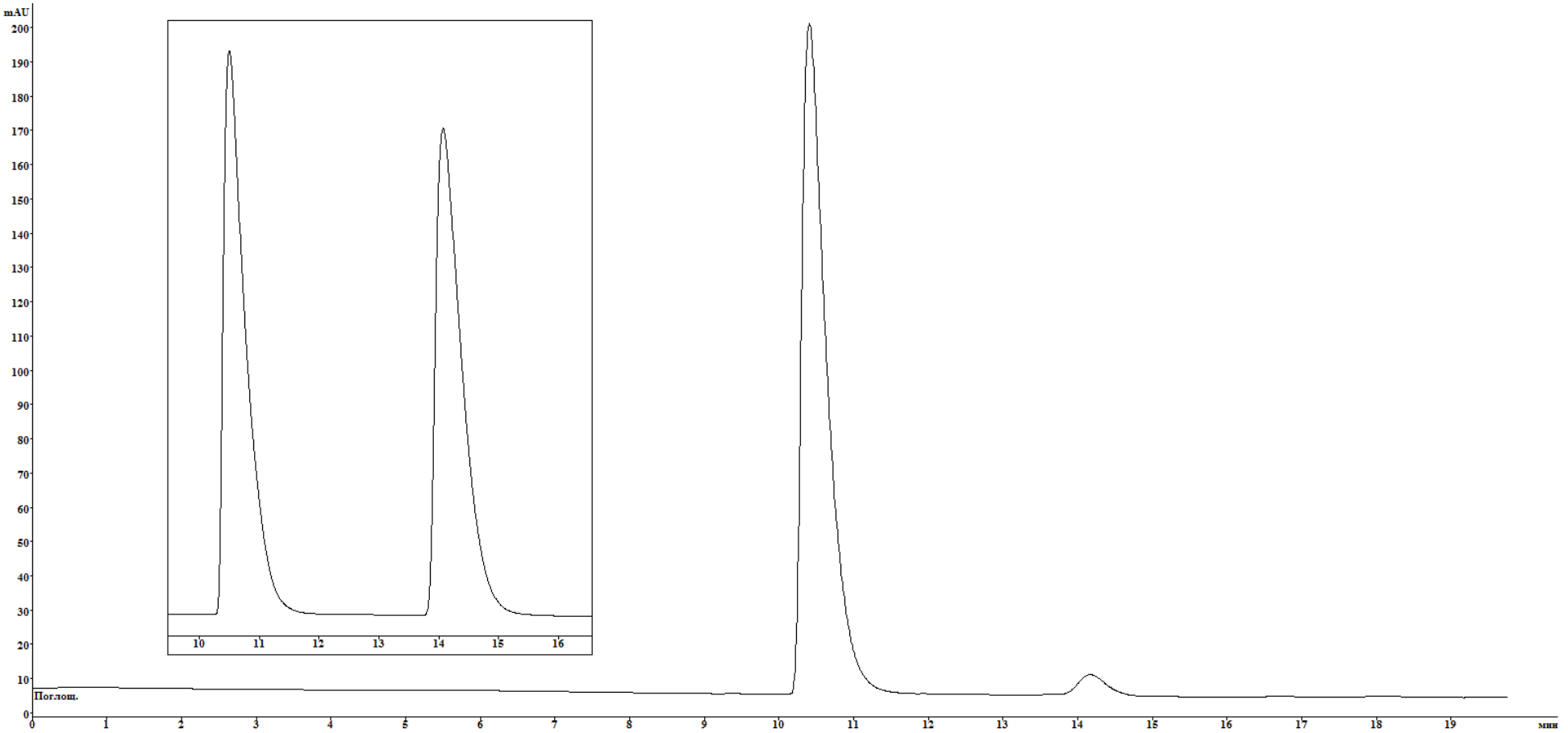


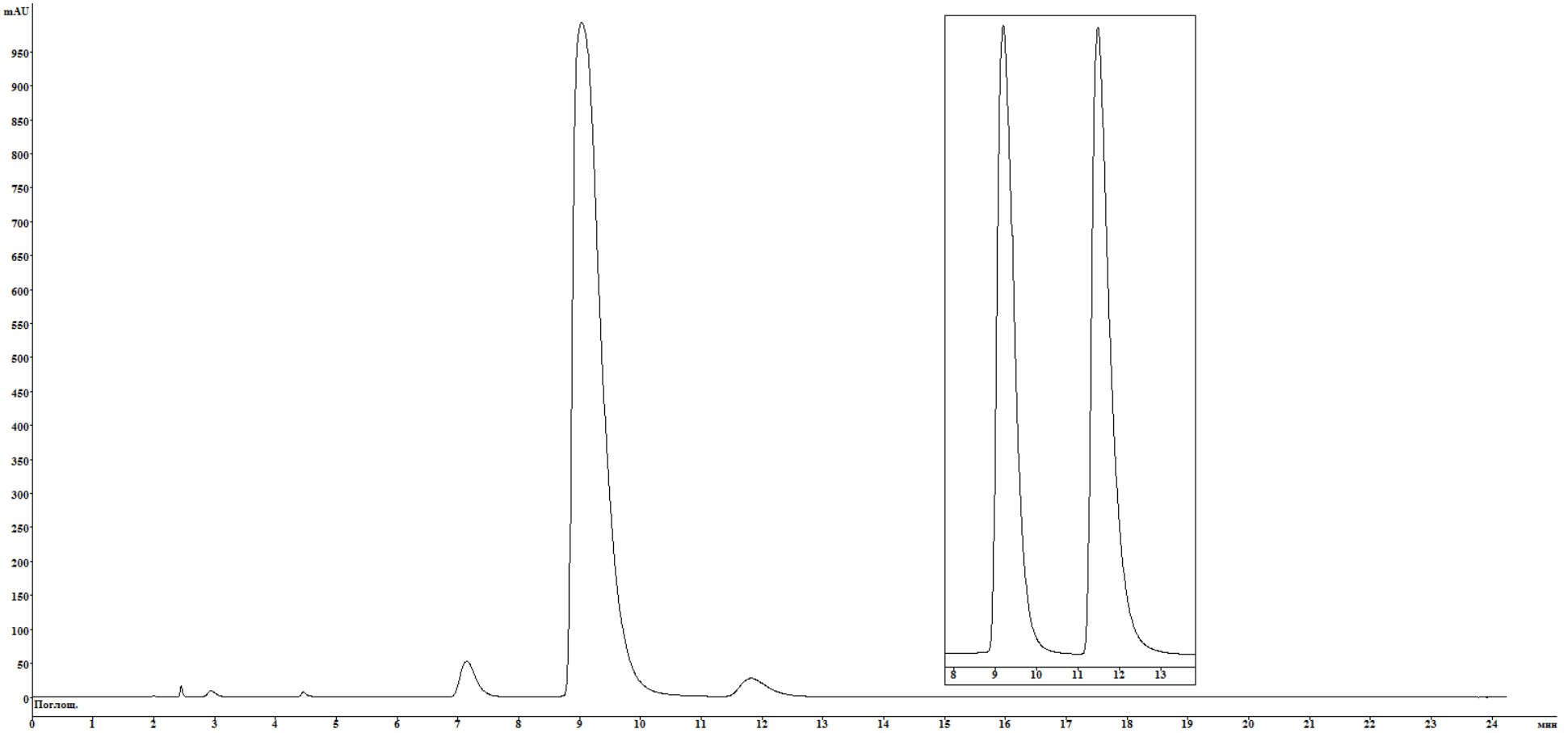
Chiral HPLC profile for the Rh-catalyzed asymmetric hydrogenation of 4a (entry 1 in Table 3) and for a racemic mixture of 5a (in the frame).



Chiral HPLC profile for the Rh-catalyzed asymmetric hydrogenation of 4b (entry 2 in Table 3) and for a racemic mixture of 5b (in the frame).



Chiral HPLC profile for the Rh-catalyzed asymmetric hydrogenation of 4c (entry 3 in Table 3) and for a racemic mixture of 5c (in the frame).



Chiral HPLC profile for the Rh-catalyzed asymmetric hydrogenation of 4d (entry 4 in Table 3) and for a racemic mixture of 5d (in the frame).