

Supporting Information

An Efficient Approach to Chloro(organophosphine) Gold(I) Complexes for the Synthesis of Auranofin

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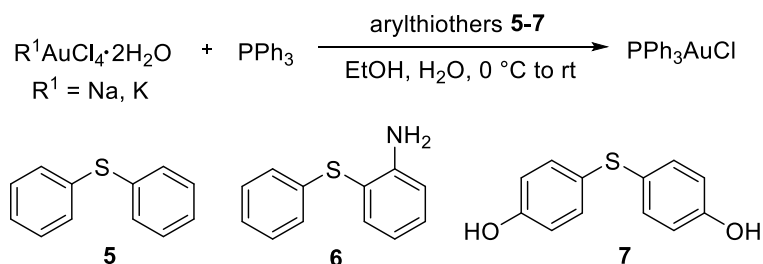
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1. General information. Commercial reagents were used without further purification except where noted. Solvents were dried and redistilled prior to use in the usual way. All reactions were performed in oven-dried glassware with magnetic stirring under an inert atmosphere unless noted otherwise. Analytical thin layer chromatography (TLC) was performed on precoated plates of Silica Gel (0.25-0.3 mm, Shanghai, China). The TLC plates were visualized with UV light and by staining with iodine vapor or sulfuric acid-ethanol solution. Silica gel column chromatography was performed on Silica Gel AR (100-200 mesh, Shanghai, China). ^1H and ^{31}P NMR spectra were measured with a Bruker Avance III 400 spectrometer. The ^1H NMR spectra were calibrated against the residual proton signals of the solvents as internal references (CDCl_3 : $\delta_{\text{H}} = 7.26$ ppm) while the ^{31}P NMR spectra were referenced to external 85% H_3PO_4 . Multiplicities are quoted as singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), triplet (t), doublet of triplets (dt), doublet of quartet (dq) or multiplet (m). All NMR chemical shifts (δ) were recorded in ppm and coupling constants (J) were reported in Hz.

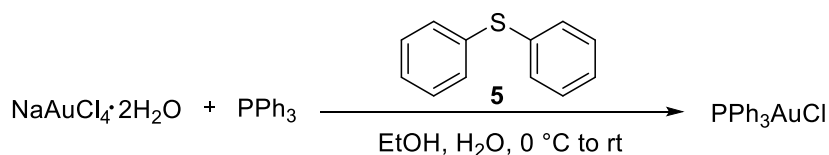
2. Experimental details and characterization data

2.1. General procedure for the synthesis of $\text{PPh}_3\text{AuCl}^{\text{I}}$



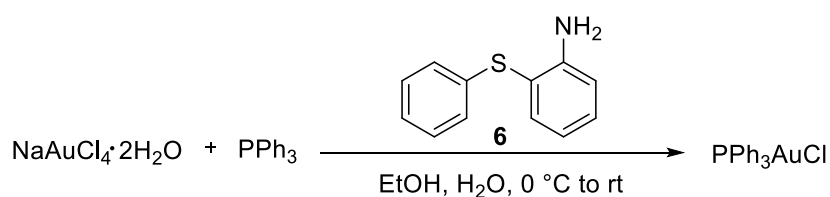
To a solution of $\text{R}^{\text{I}}\text{AuCl}_4 \cdot 2\text{H}_2\text{O}$ ($\text{R}^{\text{I}} = \text{Na}$ or K) (1 equiv.) in water/ethanol (2/3, v/v, 10 mL/mmol $\text{R}^{\text{I}}\text{AuCl}_4$) at 0 $^\circ\text{C}$, was slowly added arylthioether (**5**, **6**, or **7**) (3 equiv.). After stirring at 0 $^\circ\text{C}$ for 45 min, the mixture was added a solution of PPh_3 (1 equiv.) in ethanol (10 mL/mmol $\text{R}^{\text{I}}\text{AuCl}_4$) dropwise. The temperature was allowed to warm to room temperature and the stirring continued for 3 h. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was recrystallized from hexane- CH_2Cl_2 to afford $\text{PPh}_3\text{AuCl}^{\text{I}}$.

Example 1:



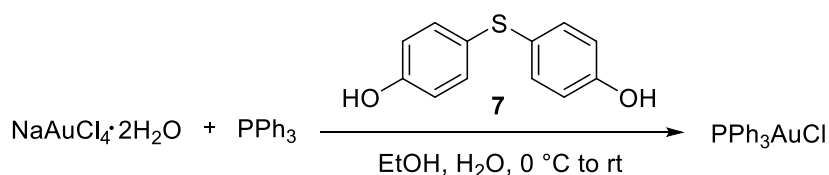
PPh_3AuCl (41% yield, white solid): ^1H NMR (400 MHz, CDCl_3) δ 7.56 – 7.44 (m, 15 H); ^{31}P NMR (162 MHz, CDCl_3) δ 33.2.

Example 2:



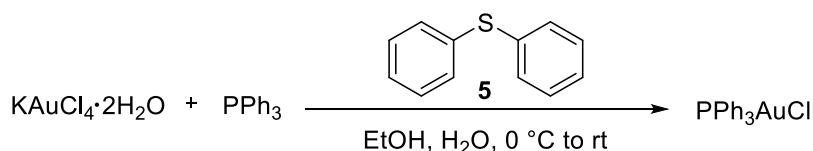
PPh_3AuCl (84% yield, dark green solid): ^1H NMR (400 MHz, CDCl_3) δ 7.56 – 7.44 (m, 15 H); ^{31}P NMR (162 MHz, CDCl_3) δ 33.2.

Example 3:



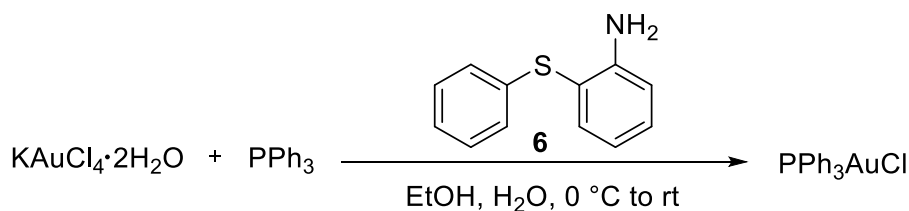
PPh_3AuCl (90% yield, pale pink solid): ^1H NMR (400 MHz, CDCl_3) δ 7.56 – 7.44 (m, 15 H); ^{31}P NMR (162 MHz, CDCl_3) δ 33.2.

Example 4:



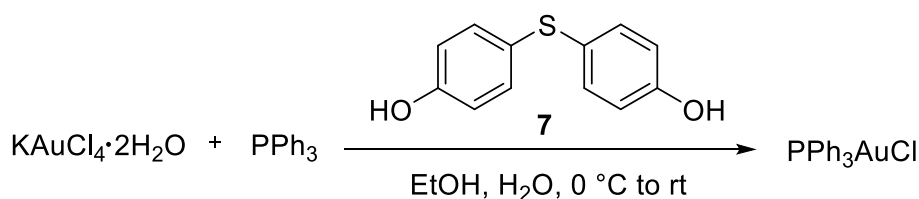
PPh_3AuCl (43% yield, white solid): ^1H NMR (400 MHz, CDCl_3) δ 7.56 – 7.44 (m, 15 H); ^{31}P NMR (162 MHz, CDCl_3) δ 33.2.

Example 5:



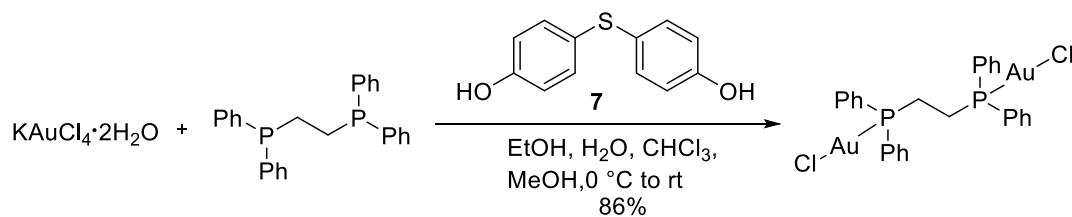
PPh_3AuCl (94% yield, dark green solid): ^1H NMR (400 MHz, CDCl_3) δ 7.56 – 7.44 (m, 15 H); ^{31}P NMR (162 MHz, CDCl_3) δ 33.2.

Example 6:



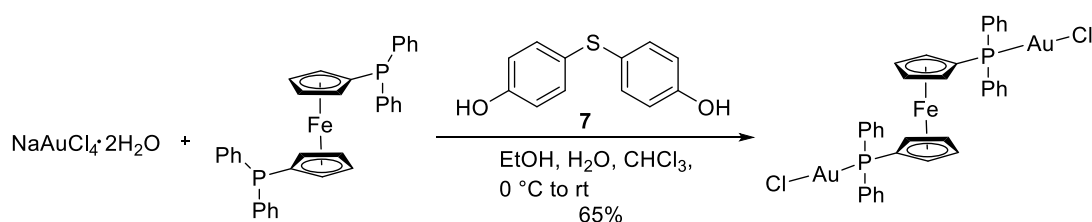
PPh_3AuCl (95% yield, pale pink solid): ^1H NMR (400 MHz, CDCl_3) δ 7.56 – 7.44 (m, 15 H); ^{31}P NMR (162 MHz, CDCl_3) δ 33.2.

2.2. Synthesis of $\text{dppe}(\text{AuCl})_2$ ²⁻⁵



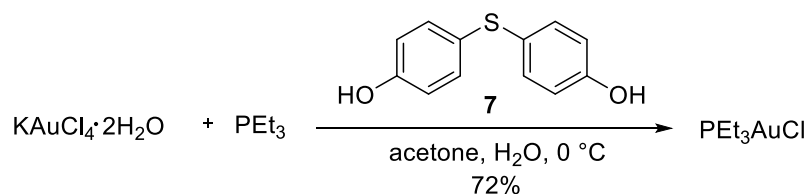
To a solution of $\text{NaAuCl}_4 \cdot 2\text{H}_2\text{O}$ (200 mg, 0.48 mmol) in water/ethanol (2/3, v/v, 5 mL) at 0 °C, was slowly added 4,4'-dihydroxydiphenyl sulfide **7** (316 mg, 1.44 mmol). After stirring at 0 °C for 45 min, the mixture was added a solution of 1,2-bis(diphenylphosphino)ethane (dppe) (92 mg, 0.24 mmol) in chloroform/methanol (1/1, v/v, 2.8 mL) dropwise. The temperature was allowed to warm to room temperature and the stirring continued for 3 h. The mixture was filtered and washed with methanol. The residue was dried to afford $\text{dppe}(\text{AuCl})_2$ (177 mg, 86%) as a pale pink solid: ^1H NMR (400 MHz, CDCl_3) δ 7.66 – 7.61 (m, 8 H), 7.58 – 7.48 (m, 12 H), 2.63 (s, 4 H); ^{31}P NMR (162 MHz, CDCl_3) δ 31.8.

2.3. Synthesis of $\text{dppf}(\text{AuCl})_2$ ⁶



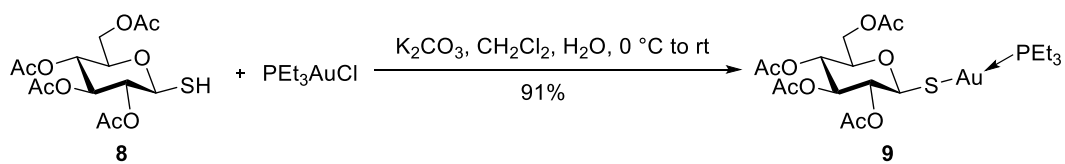
To a solution of $\text{NaAuCl}_4 \cdot 2\text{H}_2\text{O}$ (200 mg, 0.48 mmol) in water/ethanol (2/3, v/v, 5 mL) at 0 °C, was slowly added 4,4'-dihydroxydiphenyl sulfide **7** (316 mg, 1.44 mmol). After stirring at 0 °C for 45 min, the mixture was added a solution of 1,1'-bis(diphenylphosphino)ferrocene (dppf) (134 mg, 0.24 mmol) in chloroform (1.4 mL) dropwise. The temperature was allowed to warm to room temperature and the stirring continued for 3 h. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was recrystallized from hexane- CH_2Cl_2 to afford $\text{dppf}(\text{AuCl})_2$ (158 mg, 65%) as a yellow solid: ¹H NMR (400 MHz, CDCl_3) δ 7.53 – 7.42 (m, 20 H), 4.72 (m, 4 H), 4.27 (m, 4 H); ³¹P NMR (162 MHz, CDCl_3) δ 27.7.

2.4. Synthesis of PEt_3AuCl ⁷



To a solution of $\text{KAuCl}_4 \cdot 2\text{H}_2\text{O}$ (200 mg, 0.48 mmol) in water (2.9 mL) at 0 °C, was slowly added 4,4'-dihydroxydiphenyl sulfide **7** (210 mg, 0.96 mmol). After 10 min, the mixture was added a solution of Et_3P (65 μl , 0.48 mmol) in acetone (4 drops). After stirring at 0 °C for 3 h, the mixture was concentrated *in vacuo*. Elution through silica gel column chromatography (CH_2Cl_2) and recrystallized from ethanol-water gave PEt_3AuCl (121 mg, 72%) as a white needle: ¹H NMR (400 MHz, CDCl_3) δ 1.84 (dq, $J = 7.6, 10.0$ Hz, 6 H, CH_2CH_3), 1.19 (dt, $J = 7.6, 19.2$ Hz, 9 H, CH_2CH_3); ³¹P NMR (162 MHz, CDCl_3) δ 31.4.

2.5. Synthesis of auranofin **9**⁸⁻¹⁰



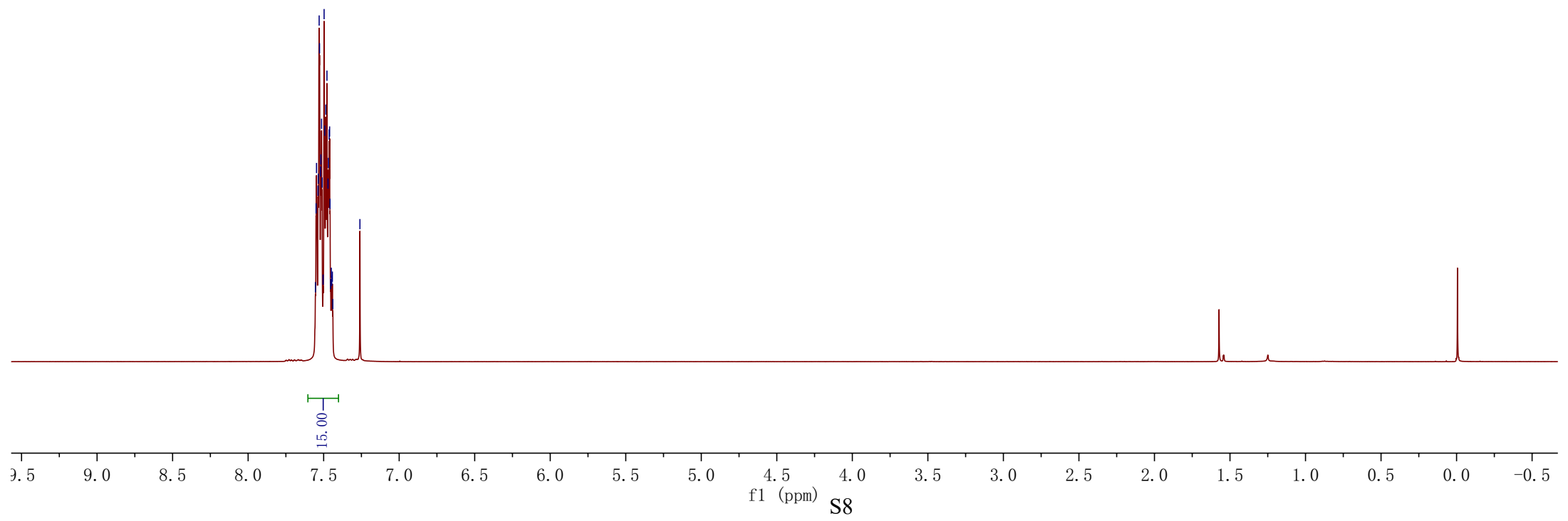
To a solution of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose **8** (318 mg, 0.87 mmol) and PEt₃AuCl (306 mg, 0.87 mmol) in CH₂Cl₂ (1.6 mL) at 0 °C, was added a solution of potassium carbonate (145 mg, 1.04 mmol) in water (1 mL). The temperature was allowed to warm to room temperature and the stirring continued for 2 h. The CH₂Cl₂ layer was separated and the aqueous layer was extracted four times with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was recrystallized from methanol-water to provide auranofin **9** (538 mg, 91%) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 5.17 – 5.07 (m, 3 H, H-1, H-3, H-4), 4.97 (m, 1 H, H-2), 4.23 (dd, *J* = 4.8, 12.4 Hz, 1 H, H-6a), 4.08 (dd, *J* = 2.4, 12.4 Hz, 1 H, H-6b), 3.72 (m, 1 H, H-5), 2.07 (s, 3 H, C(O)CH₃), 2.05 (s, 3 H, C(O)CH₃), 2.01 (s, 3 H, C(O)CH₃), 1.98 (s, 3 H, C(O)CH₃), 1.84 (dq, *J* = 7.6, 9.6 Hz, 6 H, CH₂CH₃), 1.20 (dt, *J* = 7.6, 18.4 Hz, 9 H, CH₂CH₃); ³¹P NMR (162 MHz, CDCl₃) δ 37.2.

3. References

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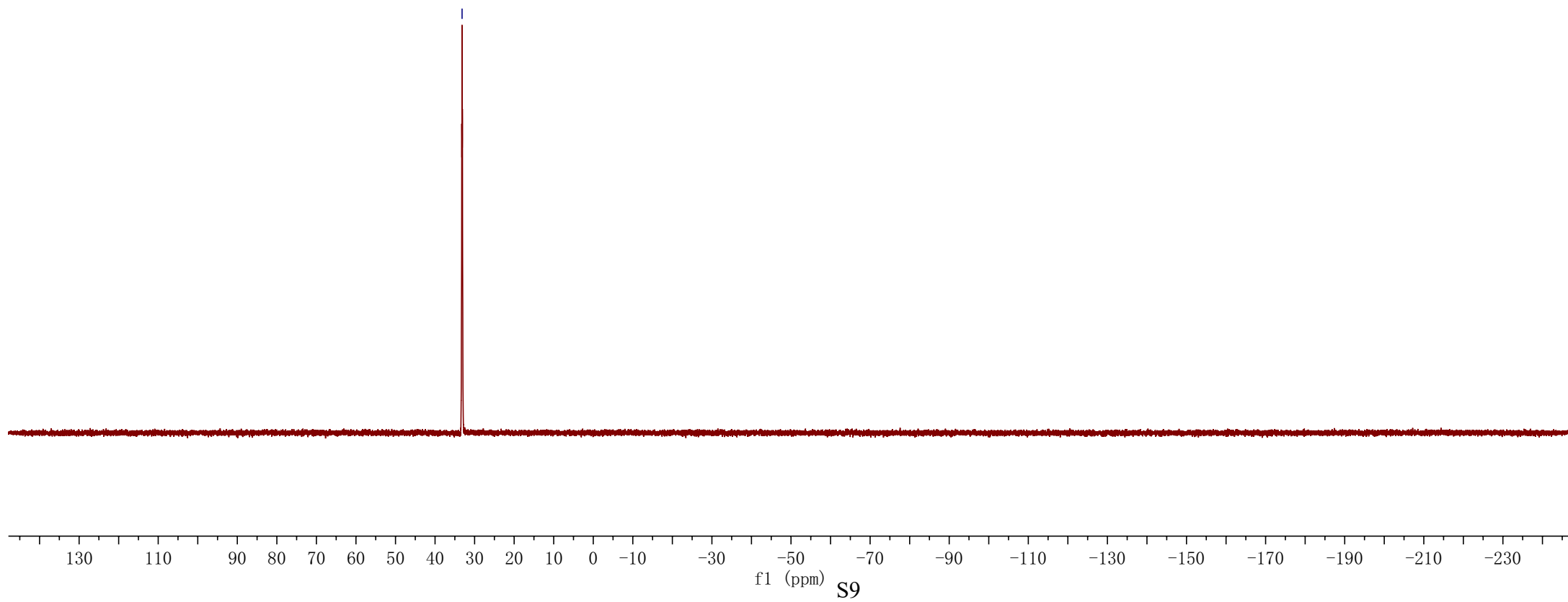
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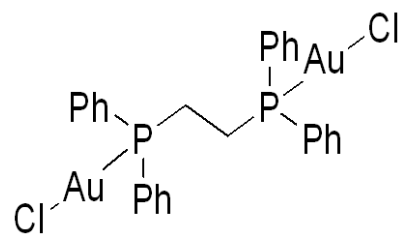
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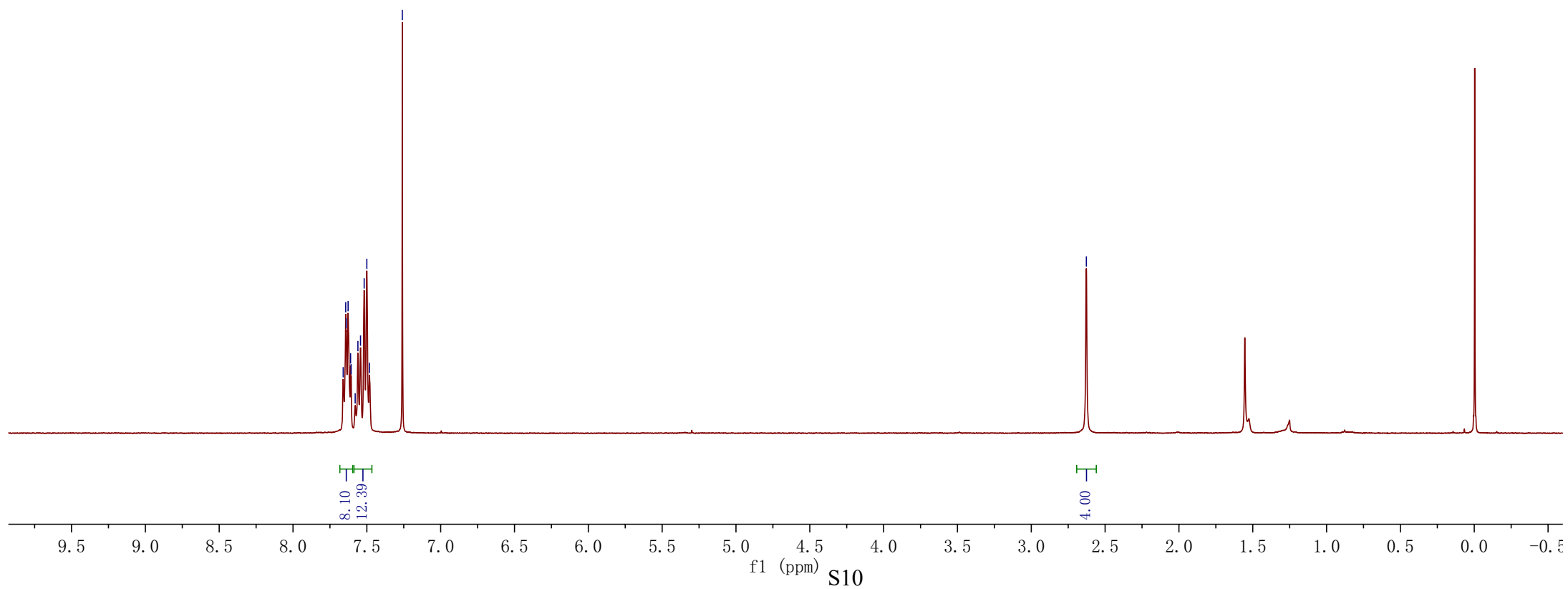
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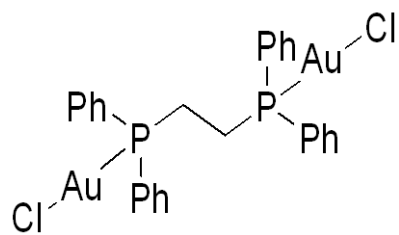




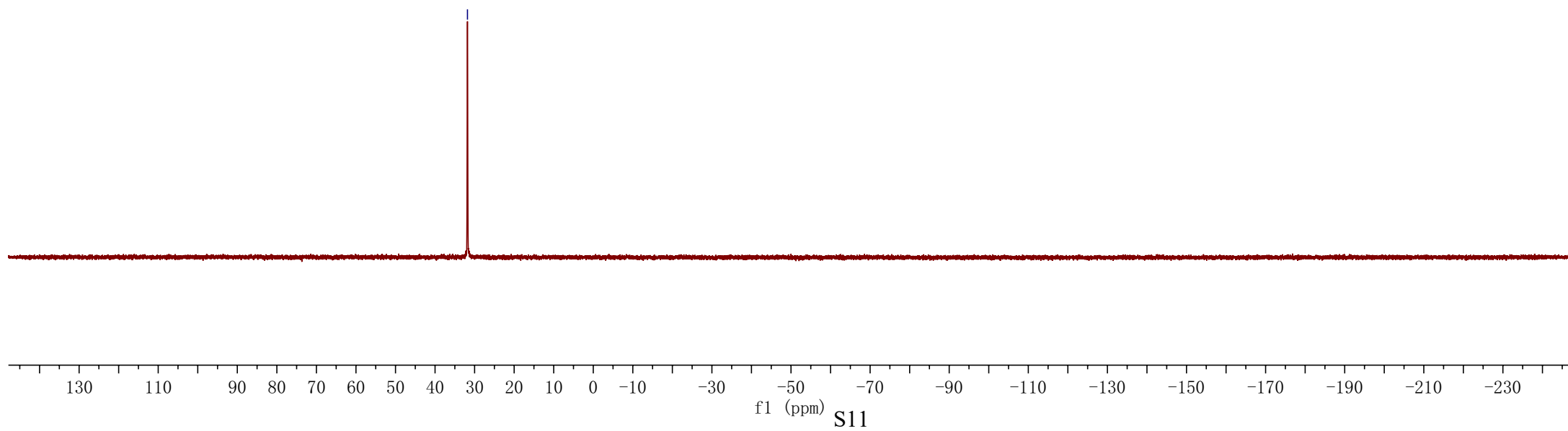
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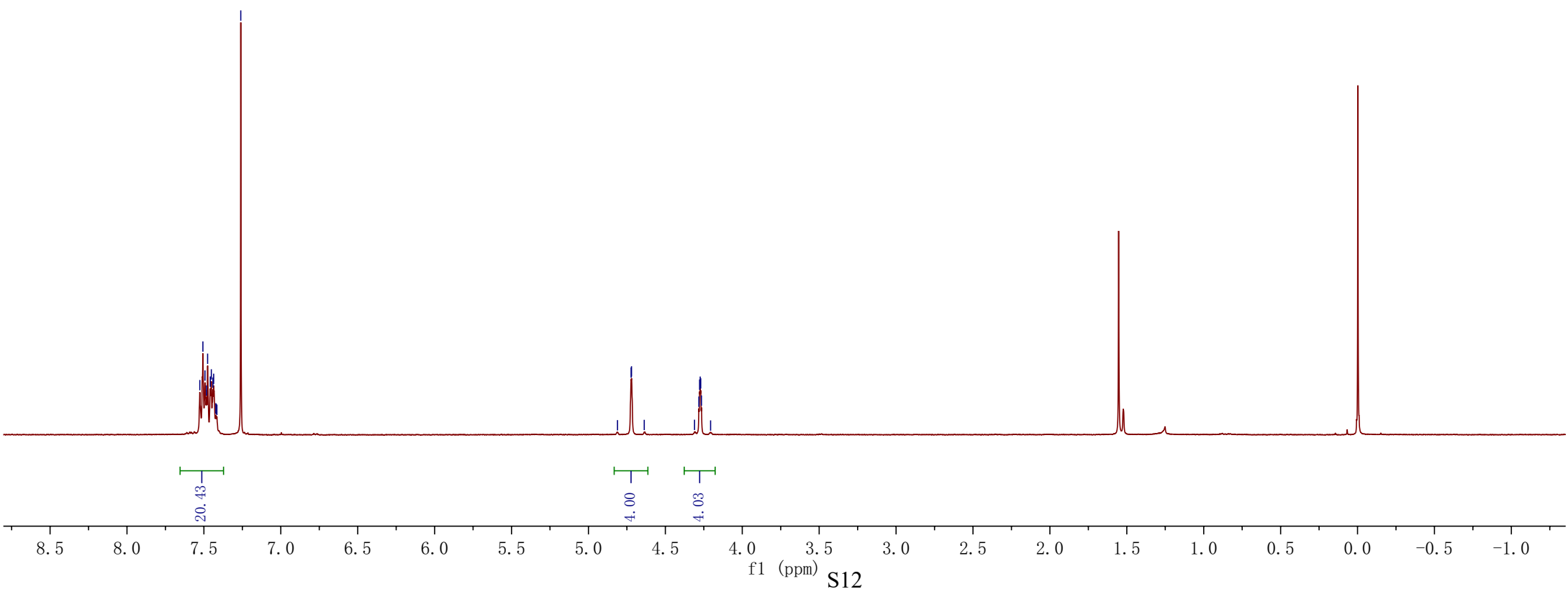
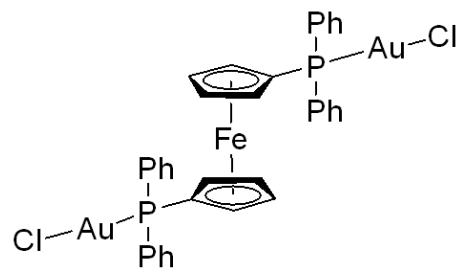
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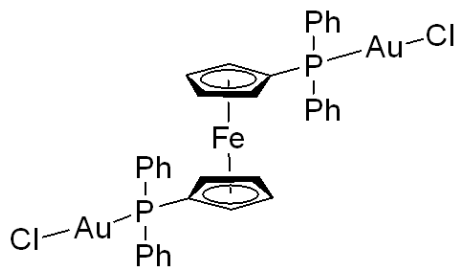


S11

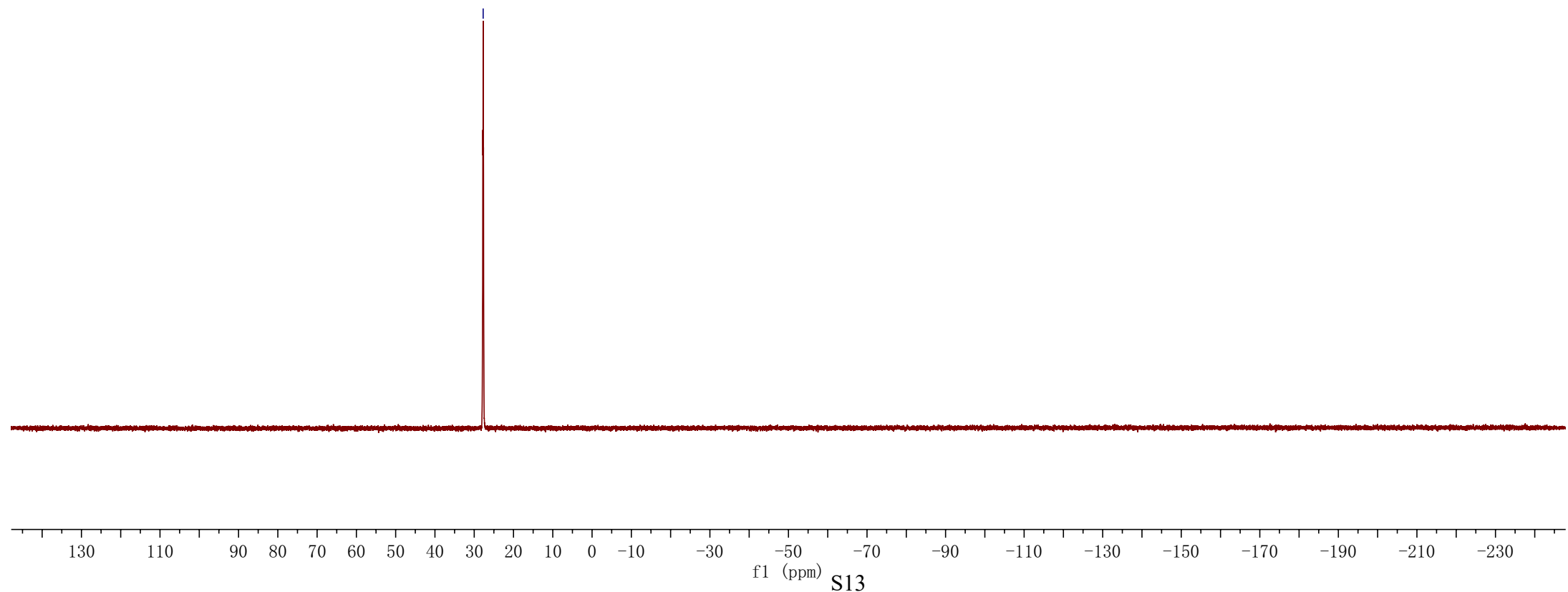
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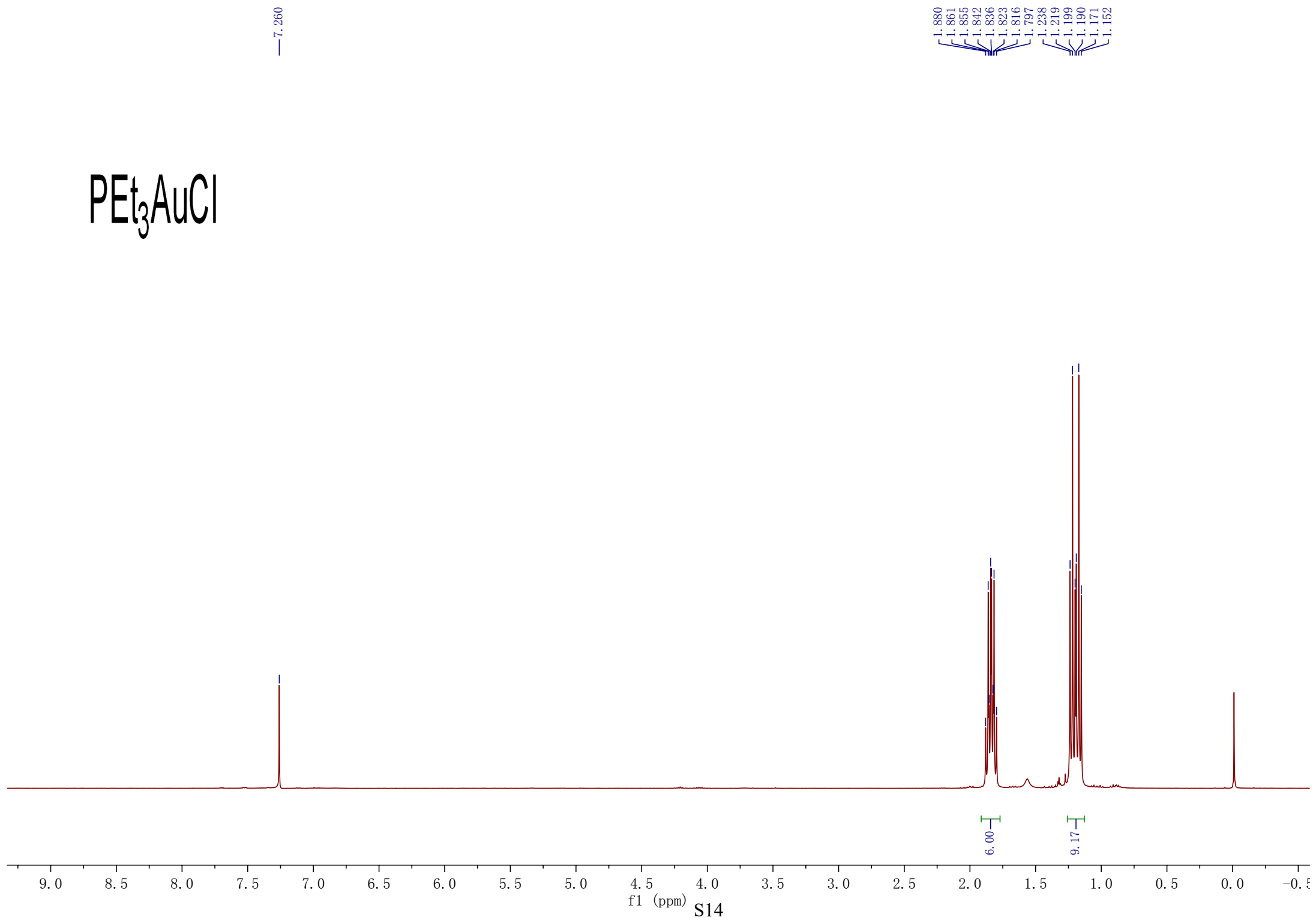




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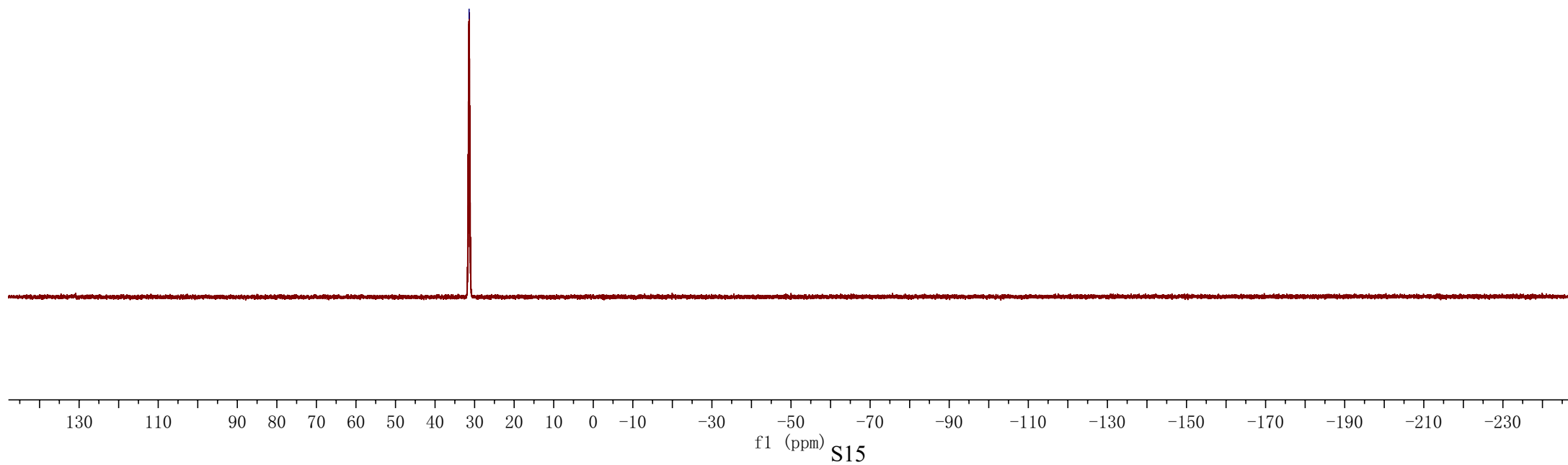


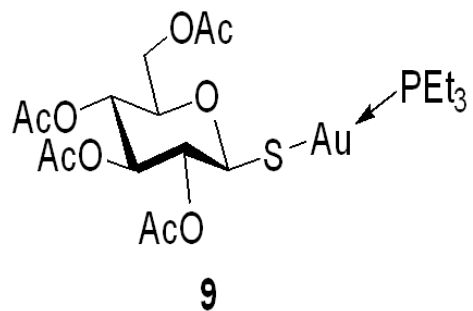
PEt₃AuCl





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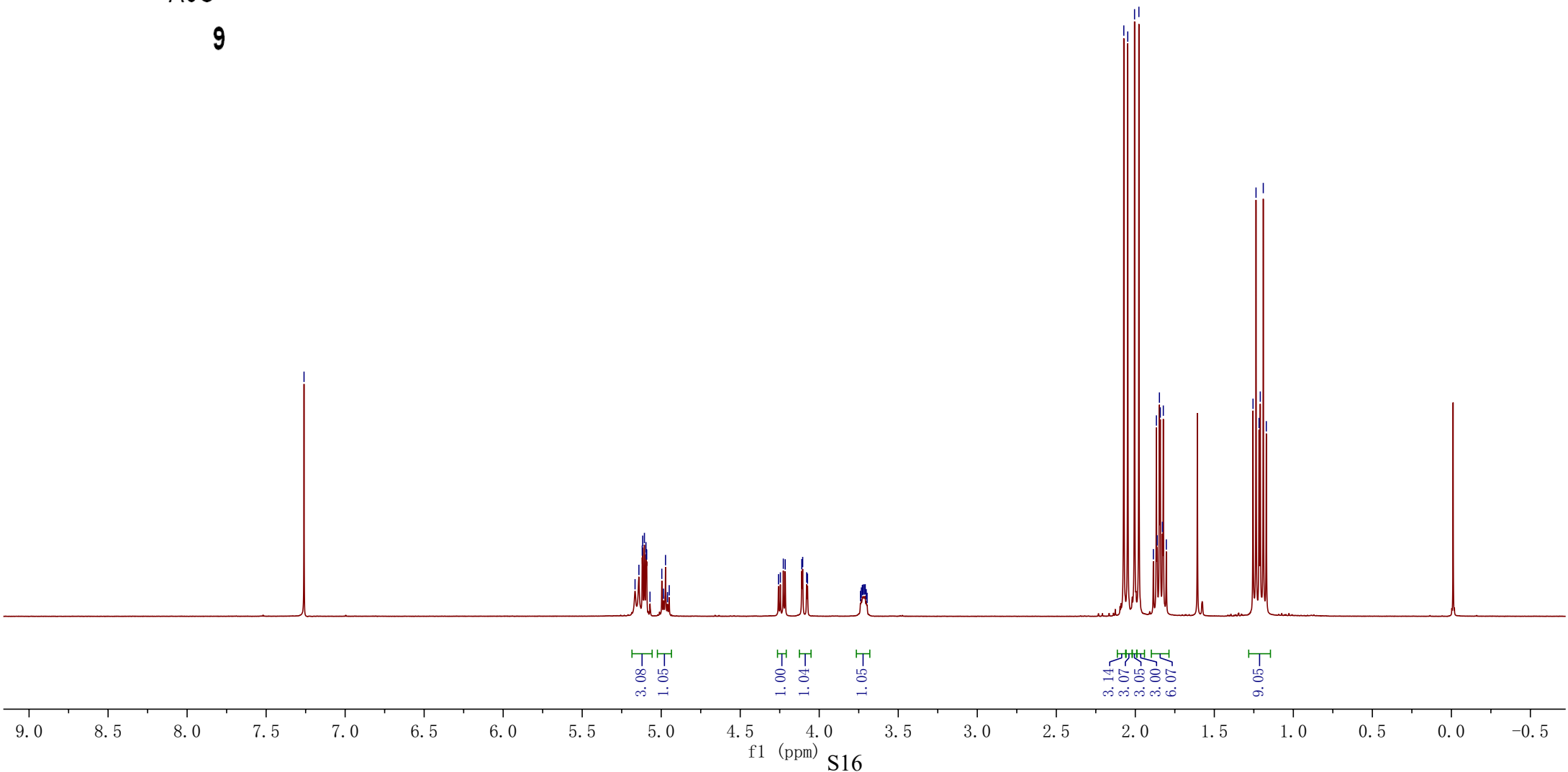


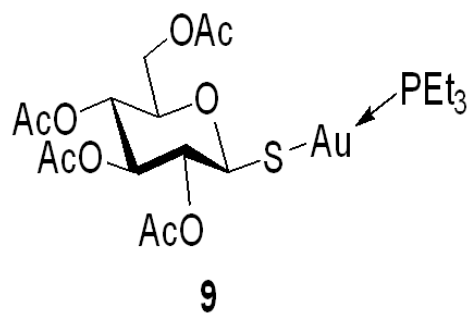


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