# Total Synthesis of (+)-Chaetocin and its Analogs: Their Histone Methyltransferase G9a Inhibitory Activity

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## Supporting Information

**(A) Complete Ref. 3c.**

**(B) General**

**(C) Total synthesis of (+)-chaetocin**

**(D) Conversion and structural determination of tetracyclic DKP 10.**

**(E) Total synthesis of *ent*-chaetocin**

**(F) Synthesis of *S*-deficient analogs**

**(G) HMT G9a–inhibitory activity assay**

**(H) Additional note-1: Dimerization of 10 and α-oxidation of the obtained octacyclic ring system**

**(I) Additional note-2: Details of the synthesis of DKP 9.**

**(J) Additional note-3: Stereochemical model of bromocyclization (9 -> 10)**

**(K) Additional note-4: Details of radical bromination**

**(L) Additional note-5: On the stereochemistry of diols**

**(M) Additional note-6: Stereochemical models of $H_2S$-substitution.**

**(N) NMR spectra**

## (A) Complete Ref. 3c

Liu, F.; Chen, X.; Allali-Hassani, A.; Quinn, A. M.; Wasney, G. A.; Dong, A.; Barsyte, D.; Kozieradzki, I.; Senisterra, G.; Chau, I.; Siarheyeva, A.; Kireev, D. B.; Jadhav, A.; Herold, J. M.; Frye, S. V.; Arrowsmith, C. H.; Brown, P. J.; Simeonov, A.; Vedadi, M.; Jin, J. *J. Med. Chem.* **2009**, *52*, 7950.

## (B) General

NMR spectra were recorded on a JEOL JNM-ECP500 spectrometer operating at 500 MHz for $^1$H NMR, 125 MHz for $^{13}$C NMR or a JEOL JNM-ECP400 spectrometer operating at 400 MHz for $^1$H NMR. Chemical shifts were reported downfield from TMS (= 0) or in a scale relative to the solvent signal as an internal reference for $^1$H NMR. For $^{13}$C NMR, chemical shifts were reported in a scale relative to the solvent signal as an internal reference. IR was measured on a Thermo Nicolet AVATAR 370 FT-IR. Optical rotations were measured on a JASCO DIP-370 polarimeter. In some cases, purification was carried out using Yamazen medium-pressure liquid chromatography (MPLC) systems [pump, 580-D; UV-detector, prepUV-10VW; column, Yamazen HI-FLASH$^{TM}$ or Ultra Pack$^{TM}$ SI-40A or KUSANO pre-packed $SiO_2$ column; eluent, *n*-hexane/ethyl acetate or chloroform/methanol]. Column chromatography was performed with silica gel 60 (40-100 μm) purchased from KANTO CHEMICAL Co., INC. Dehydrated *N*,*N*-dimethylformamide (DMF), acetonitrile, stabilizer-free tetrahydrofuran (THF), and dichloromethane were purchased from KANTO CHEMICAL Co., INC. Dehydrated acetone was purchased from Wako Pure Chemical Industries, Ltd. *N*-Bromosuccinimide was recrystallized from water and dried over $P_2O_5$ under vacuum before use. Other solvents and reagents used in this paper were purchased and used as received. *N*-Benzyloxycarbonyl-*N*-methyl-D-serine (**7**) was synthesized from D-serine according to the reported procedure.[1] Natural (+)-chaetocin was purchased from Sigma-Aldrich.

**Numbering system**:

Based on a numbering system employed in Movassaghi's paper,[2] we employ the following numbering system in this Supporting Information. The numbers assigned for early synthetic intermediates to specify positions of interest are in accord with the corresponding carbons in (+)-chaetocin.

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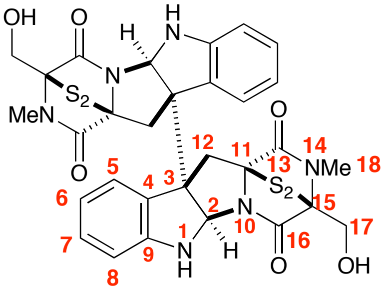
[1] Aurelio, L.; Box, J. S.; Brownlee, R. T. C.; Hughes, A. B.; Sleebs, M. M. *J. Org. Chem.* **2003**, *68*, 2652.

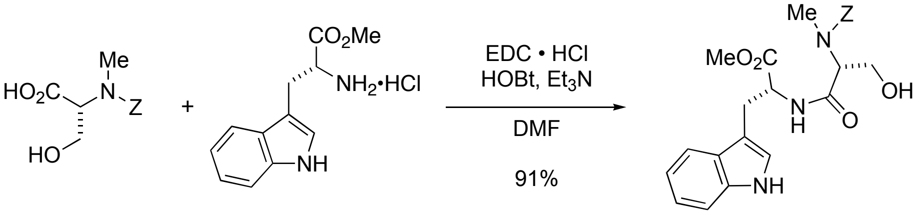
[2] Kim, J.; Ashenhurst, J. A.; Movassaghi, M. *Science* **2009**, *324*, 238.



(+)-Chaetocin (**1**)

## (C) Total synthesis of (+)-chaetocin

### (C-1) Synthesis of DKP 9



**7** **8** **S-15**

To a solution of **7** (14.3 g, 56.4 mmol) and D-tryptophan methyl ester hydrochloride **8** (14.4 g, 56.4 mmol) and triethylamine (7.9 mL, 56.7 mmol) in *N*,*N*-dimethylformamide (180 mL) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (11.9 g, 62.1 mmol) and 1-hydroxybenzotriazole monohydrate (9.15 g, 67.7 mmol) at –20 °C. The reaction mixture was allowed to warm up to room temperature and then stirred over night. After removal of the solvent in vacuo, the obtained residue was diluted with ethyl acetate (700 mL). The organic layer was washed with 5% aqueous sodium bicarbonate solution (4 x 500 mL), 10% aqueous citric acid solution (4 x 500 mL), and water (3 x 500 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. Further purification was performed by flash column chromatography (chloroform/methanol = 99/1 to 95/5) to give **S-15** (23.4 g, 91%) as colorless gum.

**S-15**:

$^1$H NMR (500 MHz, $CDCl_3$, 55 °C) δ: 2.59 (br s, 1H, O**H**), 2.65 (s, 3H, $C_{18}\mathbf{H}_3$), 3.21 (dd, *J* = 6.6 Hz, 14.9 Hz, 1H, $C_{12}\mathbf{H}$), 3.29 (dd, *J* = 5.3 Hz, 14.9 Hz, 1H, $C_{12}\mathbf{H}$), 3.69 (s, 3H, $OC\mathbf{H}_3$), 3.78 (br s, 1H, $C_{17}\mathbf{H}$), 3.95-4.00 (m, 1H, $C_{15}\mathbf{H}$), 4.58 (br s, 1H, $C_{17}\mathbf{H}$), 4.83-4.87 (m, 1H, $C_{11}\mathbf{H}$), 5.07 (br s, 2H, $PhC\mathbf{H}_2$), 6.50 (br s, 1H, $N_{10}\mathbf{H}$), 6.84 (s, 1H, $C_2\mathbf{H}$), 7.08 (t, *J* = 7.6 Hz, 1H, $C_6\mathbf{H}$), 7.15 (t, *J* = 7.6 Hz, 1H, $C_7\mathbf{H}$), 7.28 (d, *J* = 7.6 Hz, 1H, $C_5\mathbf{H}$), 7.25-7.40 (m, 5H, $\mathbf{Ph}CH_2OCON$), 7.80 (d, *J* = 7.6 Hz, 1H, $C_8\mathbf{H}$), 7.84 (br s, 1H, $N_1\mathbf{H}$).

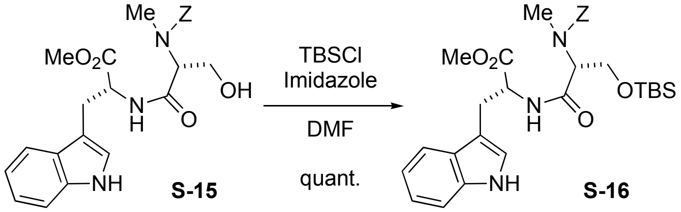
$^{13}$C NMR (125 MHz, $CDCl_3$, 55 °C) δ: 27.6 ($\mathbf{C}_{12}$), 31.8 ($\mathbf{C}_{18}$), 52.5 ($O\mathbf{C}H_3$), 52.8 ($\mathbf{C}_{11}$), 60.6 ($\mathbf{C}_{15}$), 61.1 ($\mathbf{C}_{17}$), 67.9 ($Ph\mathbf{C}H_2OCON$), 109.9 ($\mathbf{C}_3$), 111.5 ($\mathbf{C}_5$), 118.5 ($\mathbf{C}_8$), 119.9 ($\mathbf{C}_6$), 122.5 ($\mathbf{C}_7$), 123.0 ($\mathbf{C}_2$), 127.5 ($\mathbf{C}_4$), 128.1 ($\mathbf{Ph}CH_2OCON$), 128.4 ($\mathbf{Ph}CH_2OCON$), 128.7 ($\mathbf{Ph}CH_2OCON$), 136.5 ($\mathbf{C}_9$ and

PhCH$_2$O**C**ON), 170.3 (**C**$_{16}$), 172.2 (**C**$_{13}$).

[α]$_D$: +6.8 (CHCl$_3$, c 1.0, 25 °C)

FTIR (neat) cm$^{-1}$: 3321 (br), 2953 (m), 1666 (s), 744 (s).

LRMS (ESI) (m/z): 476 [M+Na]$^+$



To a solution of **S-15** (38.7 g, 85.2 mmol) and imidazole (13.9 g, 204 mmol) in dry *N*,*N*-dimethylformamide (0.4 M, 210 mL) was added *tert*-butyldimethylchlorosilane (15.4 g, 226 mmol) under nitrogen atmosphere. After stirring over night at room temperature, the reaction mixture was concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (400 mL), then washed with water (3 x 200 mL) and brine (150 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give crude **S-16** (48.8 g, quant.) as pale yellow gum. A small crude sample was further purified by GPC for spectroscopic analysis.

**S-16**:

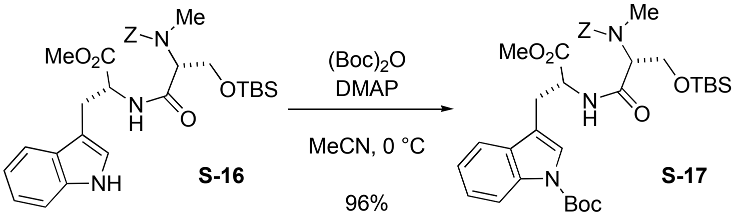
$^1$H NMR (500 MHz, CDCl$_3$, 55 °C) δ: –0.01 (s, 3H, Si(C**H**$_3$)$_2$), 0.00 (s, 3H, Si(C**H**$_3$)$_2$), 0.82 (9H, s, SiC(C**H**$_3$)$_3$), 2.72 (s, 3H, C$_{18}$**H**$_3$), 3.23 (dd, *J* = 5.5 Hz, 11.9 Hz, 1H, C$_{12}$**H**), 3.31 (dd, *J* = 5.5 Hz, 11.9 Hz, 1H, C$_{12}$**H**), 3.67 (s, 3H, OC**H**$_3$), 3.84 (br s, 1H, C$_{17}$**H**), 4.03 (dd, *J* = 6.4 Hz, 10.5 Hz, 1H, C$_{17}$**H**), 4.08 (br s, 1H, C$_{15}$**H**), 4.88 (br s, 1H, C$_{11}$**H**), 5.10 (br s, 2H, PhC**H**$_2$OCON), 6.89 (br s, 1H, C$_2$**H**), 7.08 (t, *J* = 7.5 Hz, 1H, C$_6$**H**), 7.16 (t, *J* = 7.5 Hz, 1H, C$_7$**H**), 7.29 (d, *J* = 7.5 Hz, 1H, C$_5$**H**), 7.20-7.40 (m, 5H, **Ph**CH$_2$OCON), 7.51 (br d, *J* = 6.9 Hz, 1H, C$_8$**H**), 7.96 (br, 1H, N$_1$**H**).

$^{13}$C NMR (125 MHz, CDCl$_3$, 55 °C) δ: –5.53 (Si**C**H$_3$), –5.45 (Si**C**H$_3$), 18.1 (Si**C**(CH$_3$)$_3$), 25.8 (SiC(**C**H$_3$)$_3$), 27.8 (**C**$_{12}$), 31.6 (**C**$_{18}$), 52.3 (O**C**H$_3$), 52.9 (**C**$_{11}$), 60.8 (**C**$_{17}$), 61.4 (**C**$_{15}$), 67.7 (Ph**C**H$_2$OCON), 110.3 (**C**$_4$), 111.4 (**C**$_5$), 118.7 (**C**$_8$), 119.9 (**C**$_6$), 122.4 (**C**$_7$), 122.9 (**C**$_2$), 127.8 (**Ph**CH$_2$OCON), 128.1 (**Ph**CH$_2$OCON), 128.2 (**Ph**CH$_2$OCON), 128.7 (**Ph**CH$_2$OCON), 136.5 (**C**$_9$), 136.9 (PhCH$_2$O**C**ON), 169.3 (**C**$_{16}$), 172.2 (**C**$_{13}$).

[α]$_D$: –8.2 (c 0.86, CHCl$_3$, 23 °C)

FTIR (neat) cm$^{-1}$: 3338 (br), 2952 (m), 2930 (m), 1741 (s), 1690 (s), 1676 (m), 1154 (s), 1112 (s), 839 (s), 742 (s).

LRMS (ESI) (m/z): 590 [M+Na]$^+$



To a solution of **S-16** (17.6 g, 30.9 mmol) in dry acetonitlile (80 mM, 390 mL) was added 4-dimethylaminopyridine (378 mg, 3.09 mmol) at 0 °C. Then di-*tert*-butyl dicarbonate (7.44 g, 34.0 mmol) in dry acetonitrile (30 mL) was added dropwise over 25 min. The reaction mixture was stirred at 0 °C for 5 h. Then additional di-*tert*-butyl dicarbonate (733 mg, 3.36 mmol) in dry acetonitrile (30 mL) was added dropwise. After further stirring for 90 min, the reaction mixture was concentrated in vacuo. Further purification by flash column chromatography (hexane/acetone = 20/80) was carried out to give **S-17** (19.9 g, 96%) in a white amorphous form.

**S17:**

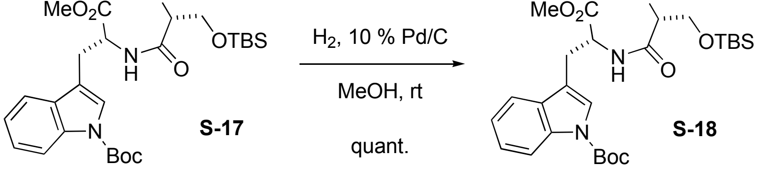
$^1$H NMR (400 MHz, CDCl$_3$, 50 °C) δ: 0.00 (s, 3H, SiC**H**$_3$), 0.01 (s, 3H, SiC**H**$_3$), 0.81 (s, 9H, SiC(C**H**$_3$)$_3$), 1.66 (s, 9H, (C**H**$_3$)$_3$COCON), 2.80 (s, 3H, C$_{18}$**H**$_3$), 3.17 (dd, *J* = 5.6 Hz, 14.6 Hz, 1H, C$_{12}$**H**), 3.26 (dd, *J* = 5.6 Hz, 14.6 Hz, 1H, C$_{12}$**H**), 3.69 (s, 3H, OC**H**$_3$), 3.84 (br s, 1H, C$_{17}$**H**), 4.05 (dd, *J* = 6.6, 10.7 Hz, 1H, C$_{17}$**H**), 4.63 (br s, 1H, C$_{15}$**H**), 4.91 (app. br d, *J* = 5.6 Hz, 1H, C$_{11}$**H**), 5.10 (m, 2H, PhC**H**$_2$OCON), 7.00 (br s, 1H, N$_{10}$**H**), 7.21 (t, *J* = 7.7 Hz, 1H, C$_6$**H**), 7.27-7.36 (m, 7H, C$_2$**H**, C$_7$**H**, **Ph**CH$_2$OCON), 7.46 (br s, 1H, C$_5$**H**), 8.10 (d, *J* = 7.7 Hz, 1H, C$_8$**H**).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ: –5.56 (Si**C**H$_3$), –5.50 (Si**C**H$_3$), 18.1 (Si**C**(CH$_3$)$_3$), 25.8 (SiC(**C**H$_3$)$_3$), 27.6 (**C**$_{12}$), 28.4 ((**C**H$_3$)$_3$COCON), 32.1 (**C**$_{18}$), 52.4 (O**C**H$_3$), 52.7 (**C**$_{11}$), 61.0 (**C**$_{17}$), 61.4 (**C**$_{15}$), 67.7 (Ph**C**H$_2$OCON), 83.8 ((CH$_3$)$_3$**C**OCON), 115.2 (**C**$_3$), 115.5 (**C**$_5$), 118.9 (**C**$_8$), 122.8 (**C**$_6$), 124.2 (**C**$_2$), 124.7 (**C**$_7$), 128.0 (**Ph**CH$_2$OCON), 128.1 (**Ph**CH$_2$OCON), 128.6 (**Ph**CH$_2$OCON), 130.7 (**C**$_4$), 135.6 (**C**$_9$), 136.7 (PhCH$_2$O**C**ON), 149.7 ((CH$_3$)$_3$CO**C**ON), 169.4 (**C**$_{16}$), 171.8 (**C**$_{13}$).

[α]$_D$: –18 (c 1.0, CHCl$_3$, 26 °C)

FTIR (neat) cm$^{-1}$: 3322 (br), 2953 (m), 2929 (m), 2856 (m), 1729 (s), 1691 (s), 1678 (s), 1255 (s), 1158 (s), 839 (s), 748 (s).

LRMS (ESI) (m/z): 690 [M+Na]$^+$



To a solution of **S-17** (21.4 g, 32.1 mmol) in ethanol (100 mM, 320 mL) was added 10% Pd/C (3.39 g, 10 mol% Pd). After replacement of the inner gas with hydrogen (balloon), the resulting mixture was stirred for 5 h. The reaction mixture was diluted with ethyl acetate, then filtered through Celite® with ethyl acetate washing. Concentration in vacuo gave crude **S-18** (18.9 g, quant.) as colorless gum. A small crude sample was further purified by MPLC (column: Yamazen High Flash, chloroform/methanol = 63/37 to 95/5) for spectroscopic analysis.

**S18:**

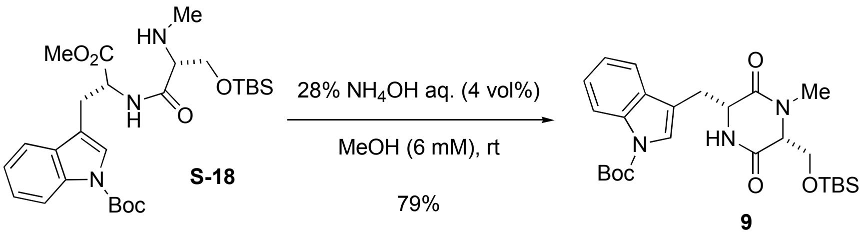
$^1$H NMR (500 MHz, CDCl$_3$, 50 °C) δ: 0.02 (s, 3H, SiC**H**$_3$), 0.04 (s, 3H, SiC**H**$_3$), 0.85 (s, 9H, SiC(C**H**$_3$)$_3$), 1.66 (s, 9H, (C**H**$_3$)$_3$COCON), 2.38 (s, 3H, C$_{18}$**H**$_3$), 3.05 (dd, *J* = 4.2 Hz, 7.8 Hz, 1H, C$_{15}$**H**), 3.19 (dd, *J* = 6.0 Hz, 14.8 Hz, 1H, C$_{12}$**H**), 3.22 (dd, *J* = 6.0 Hz, 14.8 Hz, 1H, C$_{12}$**H**), 3.52 (dd, *J* = 7.8 Hz, 10.1 Hz, 1H, C$_{17}$**H**), 3.67 (s, 3H, OC**H**$_3$), 3.81 (dd, *J* = 4.2 Hz, 10.1 Hz, 1H, C$_{17}$**H**), 4.92 (dt, *J* = 6.0 Hz, 8.3 Hz, 1H, C$_{11}$**H**), 7.21 (t, *J* = 7.8 Hz, 1H, C$_6$**H**), 7.29 (t, *J* = 7.8 Hz, 1H, C$_7$**H**), 7.39 (s, 1H, C$_2$**H**), 7.50 (d, *J* = 7.8 Hz, 1H, C$_5$**H**), 7.86 (d, *J* = 8.3 Hz, 1H, N$_{10}$**H**), 8.10 (d, *J* = 7.8 Hz, 1H, C$_8$**H**).

$^{13}$C NMR (125 MHz, CDCl$_3$, 50 °C) δ: –5.40 (Si**C**H$_3$), –5.32 (Si**C**H$_3$), 18.3 (Si**C**(CH$_3$)$_3$), 25.9 (SiC(**C**H$_3$)$_3$), 27.9 (**C**$_{12}$), 28.3 ((**C**H$_3$)$_3$COCON), 35.3 (**C**$_{18}$), 52.1 (O**C**H$_3$), 52.3 (**C**$_{11}$), 63.2 (**C**$_{17}$), 66.9 (**C**$_{15}$), 83.6 ((CH$_3$)$_3$**C**OCON), 115.4 (**C**$_3$ and **C**$_8$), 119.0 (**C**$_5$), 122.6 (**C**$_6$), 124.1 (**C**$_2$), 124.6 (**C**$_7$), 130.7 (**C**$_4$), 135.6 (**C**$_9$), 149.6 ((CH$_3$)$_3$CO**C**ON), 171.8 (**C**$_{16}$), 172.1 (**C**$_{13}$).

[α]$_D$: –22 (c 1.4, CHCl$_3$, 26 °C)

FTIR (neat) cm$^{-1}$: 3348 (br), 2952 (m), 2931 (m), 2884 (m), 2857 (s), 1735 (s), 1372 (s), 1255 (s), 1158 (s), 1088 (s), 838 (s).

LRMS (ESI) (m/z): 556 [M+Na]$^+$



To a solution of **S-18** (184 mg, 345 μmol) in methanol (6 mM, 54 mL) was added 28% aqueous NH$_4$OH solution (2.0 mL) at room temperature. After stirring for 27 h, additional 28% aqueous NH$_4$OH solution (2.0 mL) was added and the mixture was stirred for additional 31 h, after which time TLC indicated complete consumption of the starting material. The reaction mixture was concentrated in vacuo, and further purification by flash column chromatography (hexane/ethyl acetate = 30/70 to 0/100) gave **9** (136 mg, 79%) as white solid.

**DKP 9**:

$^1$H NMR (500 MHz, CDCl$_3$, 50 °C) δ: 0.13 (s, 6H, Si(C**H$_3$**)$_2$), 0.94 (s, 9H, SiC(C**H$_3$**)$_3$), 1.67 (s, 9H, (C**H**$_3$)$_3$COCON), 3.02 (s, 3H, C$_{18}$**H**$_3$), 3.07 (dd, *J* = 11.0 Hz, 14.2 Hz, 1H, C$_{12}$**H**), 3.58 (dd, *J* = 2.8, 14.2 Hz, 1H, C$_{12}$**H**), 3.87 (t, *J* = 2.6 Hz, 1H, C$_{15}$**H**), 3.98 (dd, *J* = 2.6 Hz, 10.6 Hz, 1H, C$_{17}$**H**), 4.08 (dd,

$J$ = 2.6 Hz, 10.6 Hz, 1H, C$_{17}$**H**), 4.20 (dd, $J$ = 2.8 Hz, 11.0 Hz, 1H, C$_{11}$**H**), 5.95 (s, 1H, N$_{10}$**H**), 7.25 (dt, $J$ = 0.9 Hz, 8.1 Hz, 1H, C$_{6}$**H**), 7.33 (dt, $J$ = 0.9, 8.1 Hz, 1H, C$_{7}$**H**), 7.46 (s, 1H, C$_{2}$**H**), 7.61 (app. d, $J$ = 8.1 Hz, 1H, C$_{5}$**H**), 8.16 (app. d, $J$ = 8.1 Hz, 1H, C$_{8}$**H**).

$^{13}$C NMR (125 MHz, CDCl$_3$, 50 °C) δ: –5.20 (Si**C**H$_3$), –5.13 (Si**C**H$_3$), 18.8 (Si**C**(CH$_3$)$_3$), 26.2 (SiC(**C**H$_3$)$_3$), 28.3 ((**C**H$_3$)$_3$COCON), 32.5 (**C**$_{18}$), 32.8 (**C**$_{12}$), 55.7 (**C**$_{11}$), 62.3 (**C**$_{17}$), 64.4 (**C**$_{15}$), 84.0 ((CH$_3$)$_3$**C**OCON), 115.4 (**C**$_3$), 115.7 (**C**$_8$), 119.3 (**C**$_5$), 123.0 (**C**$_6$), 124.7 (**C**$_2$), 125.1 (**C**$_7$), 129.8 (**C**$_4$), 136.1 (**C**$_9$), 149.5 ((CH$_3$)$_3$CO**C**ON), 165.8 (**C**$_{16}$), 166.2 (**C**$_{13}$).

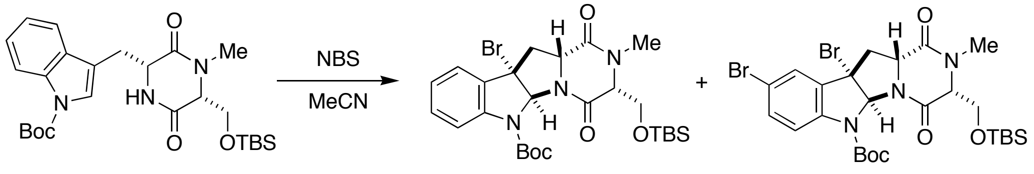
[α]$_D$: +79 (c 1.7, CHCl$_3$, 26 °C)

FTIR (neat) cm$^{-1}$: 3229 (br), 2931 (m), 2857 (m), 1732 (s), 1660 (s), 1158 (s), 1086 (s), 837 (s), 749 (s).

LRMS (ESI) (m/z): 524 [M+Na]$^+$

HRMS (ESI) (m/z): calcd. for C$_{26}$H$_{39}$N$_3$NaO$_5$Si [M+Na]$^+$: 524.25567,
found: 524.25358.

**(C-2) Bromocyclization of 9 to give tetracyclic bromide 10**



**9** **10** (88%) **S-19** (6%)

To a solution of **9** (426 mg, 849 μmol) in acetonitrile (40 mM, 21 mL) was added *N*-bromosuccinimide (182 mg, 102 μmol) at –30 °C. After stirring for 9.5 h at –30 °C, the reaction mixture was diluted with dichloromethane (50 mL), and then quenched with aqueous 5% sodium bicarbonate (16 mL). The reaction mixture was warmed up to room temperature. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (50 mL). The combined organic layers were washed with brine (20 mL), and then dried over anhydrous sodium sulfate. After concentration in vacuo, purification by flash column chromatography (chloroform), followed by purification by MPLC (column: Yamazen Ultra Pack, hexane/ethyl acetate = 63/37) gave **10** (211.8 mg, 88%, white amorphous form) and dibromide **S-19** (35.2 mg, 6%, white amorphous form).

Tetracyclic bromide **10**:

$^1$H NMR (500 MHz, CDCl$_3$, 24 °C) δ: 0.11 (s, 6H, Si(C**H**$_3$)$_2$), 0.90 (s, 9H, SiC(C**H$_3$**)$_3$), 1.57 (s, 9H, (C**H**$_3$)$_3$COCON), 2.83 (app. t, $J$ = 11.9 Hz, 12.4 Hz, 1H, C$_{12}$**H**), 2.91 (s, 3H, C$_{18}$**H**$_3$), 3.12 (dd, $J$ = 4.1 Hz, 11.9 Hz, 1H, C$_{12}$**H**), 3.77 (dd, $J$ = 4.1 Hz, 12.4 Hz, 1H, C$_{11}$**H**), 3.92 (dd, $J$ = 2.8 Hz, 10.1 Hz, 1H, C$_{17}$**H**), 3.98 (app. s, 1H, C$_{15}$**H**), 4.27 (dd, $J$ = 1.0 Hz, 10.1 Hz, 1H, C$_{17}$**H**), 6.83 (s, 1H, C$_2$**H**), 7.09 (dt, $J$ = 0.9 Hz, 7.8 Hz, 1H, C$_6$**H**), 7.27 (dt, $J$ = 0.9 Hz, 7.8 Hz, 1H, C$_7$**H**), 7.40 (app. d, $J$ = 7.8 Hz, 1H,

$C_5$**H**), 7.70 (br s, 1H, $C_8$**H**).

$^{13}$C NMR (125 MHz, $CDCl_3$, 26 °C) δ: –5.27 (Si$CH_3$), –5.12 (Si$CH_3$), 18.7 (Si**C**$(CH_3)_3$), 26.2 (SiC(**CH**$_3$)$_3$), 28.4 ((**C**H$_3$)$_3$COCON), 31.7 (**C**$_{18}$), 50.5 (**C**$_{12}$), 58.4 (**C**$_{11}$), 59.6 (**C**$_3$), 61.4 (**C**$_{17}$), 64.3 (**C**$_{15}$), 83.0 $(CH_3)_3$**C**OCON), 84.0 (**C**$_2$), 115.4 (**C**$_8$), 124.2 (**C**$_6$), 125.3 (**C**$_5$), 130.9 (**C**$_7$), 131.0 (**C**$_4$), 142.2 (**C**$_9$), 151.6 ($(CH_3)_3$CO**C**ON), 163.9 (**C**$_{16}$), 164.6 (**C**$_{13}$).

$[\alpha]_D$: +132 (c 1.0, $CHCl_3$, 25 °C)

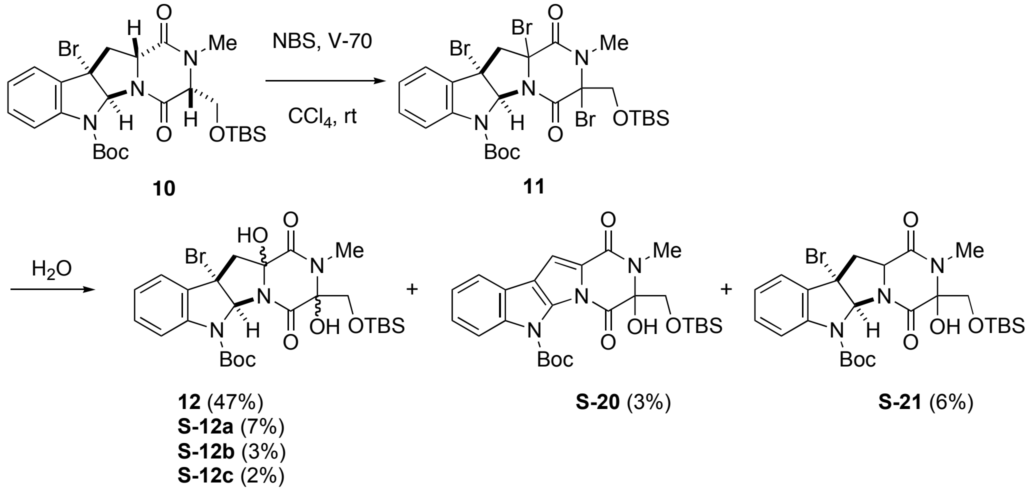
FTIR (neat) cm$^{-1}$: 2953 (m), 2931 (m), 2886 (m), 2857 (m), 1717 (s), 1689 (s), 1668 (s), 1374 (s), 1152 (s), 754 (s).

LRMS (ESI) (m/z): 602 $[M+Na]^+$

HRMS (ESI) (m/z): calcd. for $C_{26}H_{38}BrN_3NaO_5Si$ $[M+Na]^+$: 602.16618,

found: 602.16369.

### (C-3) Radical bromination and substitution with water



**10**

**11**

**12** (47%)
**S-12a** (7%)
**S-12b** (3%)
**S-12c** (2%)

**S-20** (3%)

**S-21** (6%)

To a solution of **10** (2.02 g, 3.48 mmol) and *N*-bromosuccinimide (1.26 g, 7.06 mmol) in carbontetrachloride (30 mM, 115 mL) was added V-70 (2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile),[3] 255 mg, 0.83 mmol) at room temperature. After stirring for 5 h at room temperature, the reaction mixture was filtered through cotton plug and the remaining solid was washed with carbontetrachloride. After removal of the solvent in vacuo, crude tribromide **11** was obtained almost quantitatively.

The crude product **11** was dissolved in MeCN/10 mM pH 7.0 phosphate buffer = 1/1 (140 mL, 25 mM) at room temperature. After stirring for 3 h, the reaction mixture was diluted with ethyl acetate (3 x 100 mL). The separated organic layer was washed with brine (100 mL) and then dried over anhydrous sodium sulfate. After concentration in vacuo, purification by flash column

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[3] Kita, Y.; Sano, A.; Yamaguchi, T.; Oka, M.; Gotanda, K.; Matsugi, M. *Tetrahedron Lett.* **1997**, *38*, 3549.

chromatography (chloroform/ethyl acetate = 80/20) was carried out to give a mixture of two diastereomers **12**, **S-12a** (**12**/**S-12a** = 87/13, 1.15 g, 54%, white solid). Recovered unpurified mixture of more polar compounds was subjected to MPLC (column: Yamazen High Flash, hexane/ethyl acetate = 20/80 and KUSANO pre-packed $SiO_2$ column, hexane/ethyl acetate = 50/50) to give other diastereomers **S-12b** (53.4 mg, 3%), **S-12c** (39.3 mg, 2%), and byproducts **S-20** (64.4 mg, 3%), **S-21** (102 mg, 6%). Being subjected to preparative chiral HPLC (Chiralpak IC (2 cm ϕ x 25 cm), hexane/2-propanol = 95/5, 6 mL/min), stereoisomers **12** and **S-12a** could be separated. The major compound **12** was obtained in 47% yield as a white solid, which was used in the following step.

**Tribromide 11**: $^1$H NMR of the crude product is given in Section M.

$^1$H NMR (400 MHz, $CDCl_3$, 23 °C) δ: 0.09 (s, 3H), 0.13 (s, 3H), 0.85 (9H, s), 1.62 (s, 9H), 3.21 (s, 3H), 3.46 (d, *J* = 15.0 Hz, 1H), 3.83 (d, *J* = 15.0 Hz, 1H), 4.10 (d, *J* = 10.9 Hz, 1H), 4.65 (d, *J* = 10.9 Hz, 1H), 6.74 (s, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 1H).

**Diol 12**:

$^1$H NMR (500 MHz, $CDCl_3$, 25 °C) δ: 0.13 (s, 3H, $SiC\mathbf{H}_3$), 0.14 (s, 3H, $SiC\mathbf{H}_3$), 0.90 (s, 9H, $SiC(C\mathbf{H}_3)_3$), 1.60 (s, 9H, $(C\mathbf{H}_3)_3COCON$), 3.00 (s, 3H, $C_{18}\mathbf{H}_3$), 3.18 (d, *J* = 14.2 Hz, 1H, $C_{12}\mathbf{H}$), 3.43 (d, *J* = 14.2 Hz, 1H, $C_{12}\mathbf{H}$), 3.82 (br s, 1H, O**H**), 4.09 (d, *J* = 11.0 Hz, 1H, $C_{17}\mathbf{H}$), 4.14 (d, *J* = 11.0 Hz, 1H, $C_{17}\mathbf{H}$), 4.57 (br s, 1H, $C_{15}O\mathbf{H}$), 6.63 (s, 1H, $C_2\mathbf{H}$), 7.14 (t, *J* = 7.8 Hz, 1H, $C_6\mathbf{H}$), 7.31 (dt, *J* = 0.9 Hz, 7.8 Hz, 1H, $C_7\mathbf{H}$), 7.44 (app. d, *J* = 7.8 Hz, 1H, $C_5\mathbf{H}$), 7.66 (d, *J* = 7.8 Hz, 1H, $C_8\mathbf{H}$).

$^{13}$C NMR (125 MHz, $CDCl_3$, 25 °C) δ: –5.44 ($Si\mathbf{C}H_3$), –5.24 ($Si\mathbf{C}H_3$), 18.3 ($Si\mathbf{C}(CH_3)_3$), 25.9 ($SiC(\mathbf{C}H_3)_3$), 27.9 ($\mathbf{C}_{18}$), 28.3 ($(\mathbf{C}H_3)_3COCON$), 51.7 ($\mathbf{C}_{12}$), 58.3 ($\mathbf{C}_3$), 63.2 ($\mathbf{C}_{17}$), 83.1 ($(CH_3)_3\mathbf{C}OCON$), 85.4 ($\mathbf{C}_{15}$), 85.5 ($\mathbf{C}_2$), 87.6 ($\mathbf{C}_{11}$), 117.3 ($\mathbf{C}_8$), 124.1 ($\mathbf{C}_5$), 124.6 ($\mathbf{C}_6$), 130.5 ($\mathbf{C}_7$), 134.3 ($\mathbf{C}_4$), 141.0 ($\mathbf{C}_9$), 152.1 ($(CH_3)_3CO\mathbf{C}ON$), 163.7 ($\mathbf{C}_{16}$), 167.9 ($\mathbf{C}_{13}$).

$[\alpha]_D$: +139 (c 1.0, $CHCl_3$, 25 °C)

FTIR (neat) cm$^{-1}$: 3402 (br), 2954 (m), 2923 (m), 2883 (m), 2847 (m), 1710 (s), 1389 (s), 1155 (s), 842 (s).

LRMS (ESI) (m/z): 634 $[M+Na]^+$

HRMS (ESI) (m/z): calcd. for $C_{26}H_{38}BrN_3NaO_7Si$ $[M+Na]^+$: 634.15601,
found: 634.15453.

**Diol 12a**:

$^1$H NMR (500 MHz, tetrahydrofuran-$d_8$, 25 °C) δ: –0.27 (s, 3H, $SiC\mathbf{H}_3$), –0.11 (s, 3H, $SiC\mathbf{H}_3$), 0.59 (s, 9H, $SiC(C\mathbf{H}_3)_3$), 1.58 (s, 9H, $(C\mathbf{H}_3)_3COCON$), 2.84 (s, 3H, $C_{18}\mathbf{H}_3$), 3.10 (d, *J* = 15.1 Hz, 1H, $C_{12}\mathbf{H}$), 3.56 (d, *J* = 10.1 Hz, 1H, $C_{17}\mathbf{H}$), 3.62 (d, *J* = 15.1 Hz, 1H, $C_{12}\mathbf{H}$), 4.08 (d, *J* = 10.1 Hz, 1H, $C_{17}\mathbf{H}$), 5.74 (br s, 1H, $C_{15}O\mathbf{H}$), 6.47 (s, 1H, $C_2\mathbf{H}$), 6.52 (s, 1H, $C_{11}O\mathbf{H}$), 6.98 (dt, *J* = 0.9 Hz, 7.8 Hz, 1H, $C_7\mathbf{H}$), 7.16 (dt, *J* = 1.4 Hz, 7.8 Hz, 1H, $C_6\mathbf{H}$), 7.36 (dd, *J* = 0.9 Hz, 7.8 Hz, 1H, $C_5\mathbf{H}$), 7.62 (br s, 1H,

$C_8$**H**).

$^{13}$C NMR (125 MHz, tetrahydrofuran-$d_8$, 25 °C) δ: –5.47 (Si**C**H$_3$), –5.02 (Si**C**H$_3$), 19.0 (Si**C**(CH$_3$)$_3$), 26.4 (SiC(**C**H$_3$)$_3$), 27.2 (**C**$_{18}$), 28.7 ((**C**H$_3$)$_3$COCON), 51.7 (**C**$_{12}$), 60.0 (**C**$_3$), 65.1 (**C**$_{17}$), 82.7 ((CH$_3$)$_3$**C**OCON), 86.6 (**C**$_2$), 87.7 (**C**$_{11}$), 87.7 (**C**$_{15}$), 118.1 (**C**$_8$), 125.1 (**C**$_7$), 125.6 (**C**$_5$), 131.1 (**C**$_6$), 136.0 (**C**$_4$), 141.7 (**C**$_9$), 152.3 ((CH$_3$)$_3$CO**C**ON), 166.4 (**C**$_{16}$), 167.7 (**C**$_{13}$).

[α]$_D$: +27 (c 1.3, CHCl$_3$, 26 °C)

FTIR (neat) cm$^{-1}$: 3358 (br), 2953 (m), 2931 (m), 2883 (m), 2857 (m), 1710 (s), 1368 (s), 1156 (s), 841 (s).

LRMS (ESI) (m/z): 634 [M+Na]$^+$

HRMS (ESI) (m/z): calcd. for $C_{26}H_{38}BrN_3NaO_7Si$ [M+Na]$^+$: 634.15601,

found: 634.15722.

**Diol 12b**:

$^1$H NMR (500 MHz, CDCl$_3$, 25°C) δ: –0.11 (s, 3H, SiC**H**$_3$), –0.06 (s, 3H, SiC**H**$_3$), 0.75 (s, 9H, SiC(C**H**$_3$)$_3$), 1.62 (s, 9H, (C**H**$_3$)$_3$COCON), 2.98 (s, 3H, $C_{18}$**H**$_3$), 3.14 (dd, *J* = 2.3 Hz, 13.8 Hz, 1H, $C_{12}$**H**), 3.49 (d, *J* = 13.8 Hz, 1H, $C_{12}$**H**), 3.61 (d, *J* = 10.6 Hz, 1H, $C_{17}$**H**), 3.76 (d, *J* = 10.6 Hz, 1H, $C_{17}$**H**), 4.41 (d, *J* = 2.3 Hz, 1H, $C_{11}$O**H**), 4.44 (s, 1H, $C_{15}$O**H**), 6.76 (s, 1H, $C_2$**H**), 7.13 (dt, *J* = 0.9 Hz, 7.6 Hz, 1H, $C_6$**H**), 7.26 (dt, *J* = 1.4 Hz, 7.6 Hz, 1H, $C_7$**H**), 7.45 (dd, *J* = 1.4 Hz, 7.6 Hz, 1H, $C_5$**H**), 7.58 (br s, 1H, $C_8$**H**).

$^{13}$C NMR (125 MHz, CDCl$_3$, 25 °C) δ: –5.88 (Si**C**H$_3$), –5.75 (Si**C**H$_3$), 18.7 (Si**C**(CH$_3$)$_3$), 26.0 (SiC(**C**H$_3$)$_3$), 27.0 (**C**$_{18}$), 28.3 ((**C**H$_3$)$_3$COCON), 51.3 (**C**$_{12}$), 58.3 (**C**$_3$), 65.9 (**C**$_{17}$), 82.9 ((**C**H$_3$)$_3$**C**OCON), 84.7 (**C**$_{15}$), 85.2 (**C**$_2$), 88.0 (**C**$_{11}$), 117.2 (**C**$_8$), 124.3 (**C**$_5$), 124.7 (**C**$_6$), 130.1 (**C**$_7$), 134.6 (**C**$_4$), 140.6 (**C**$_9$), 151.8 ((CH$_3$)$_3$CO**C**ON), 164.9 (**C**$_{13}$), 166.3 (**C**$_{16}$).

[α]$_D$: +121 (c 1.2, CHCl$_3$, 24 °C)

FTIR (neat) cm$^{-1}$: 3366 (br), 2953 (m), 2931 (m), 2884 (m), 2859 (m), 1719 (s), 1677 (s), 1389 (s), 1156 (s), 838 (s).

LRMS (ESI) (m/z): 634 [M+Na]$^+$

HRMS (ESI) (m/z): calcd. for $C_{26}H_{38}BrN_3NaO_7Si$ [M+Na]$^+$: 634.15601,

found: 634.15445.

**Diol 12c**:

$^1$H NMR (500 MHz, CDCl$_3$, 23 °C) δ: 0.16 (s, 6H, Si(C**H**$_3$)$_2$), 0.92 (s, 9H, SiC(C**H**$_3$)$_3$), 1.63 (s, 9H, (C**H**$_3$)$_3$COCON), 2.87 (s, 3H, $C_{18}$**H**$_3$), 3.32 (d, *J* = 15.1 Hz, 1H, $C_{12}$**H**), 3.67 (d, *J* = 15.1 Hz, 1H, $C_{12}$**H**), 3.70 (d, *J* = 10.6 Hz, 1H, $C_{17}$**H**), 3.77 (d, *J* = 10.6 Hz, 1H, $C_{17}$**H**), 4.04 (s, 1H, $C_{15}$O**H**), 5.28 (s, 1H, $C_{11}$O**H**), 6.57 (s, 1H, $C_2$**H**), 7.10 (t, *J* = 7.4 Hz, 1H, $C_6$**H**), 7.28 (t, *J* = 7.4 Hz, 1H, $C_7$**H**), 7.39 (d, *J* = 7.4 Hz, 1H, $C_5$**H**), 7.64 (br s, 1H, $C_8$**H**).

$^{13}$C NMR (125 MHz, CDCl$_3$, 25 °C) δ: –5.49 (Si**C**H$_3$), –5.46 (Si**C**H$_3$), 18.8 (Si**C**(CH$_3$)$_3$), 26.0 (SiC(**C**H$_3$)$_3$), 27.0 (**C**$_{18}$), 28.4 ((**C**H$_3$)$_3$COCON), 49.9 (**C**$_{12}$), 57.3 (**C**$_3$), 65.7 (**C**$_{17}$), 83.0 ((CH$_3$)$_3$**C**OCON), 85.0 (**C**$_{15}$), 85.5 (**C**$_2$), 87.2 (**C**$_{11}$), 116.8 (**C**$_8$), 124.7 (**C**$_5$), 124.7 (**C**$_6$), 130.6 (**C**$_7$), 134.8 (**C**$_4$), 139.8 (**C**$_9$), 151.7 ((CH$_3$)$_3$CO**C**ON), 165.0 (**C**$_{13}$), 166.6 (**C**$_{16}$).

[α]$_D$: +21 (c 0.97, CHCl$_3$, 25 °C)

IR (neat) cm$^{-1}$: 3344 (br), 2954 (m), 2932 (m), 2886 (m), 2859 (m), 1725 (s), 1687 (s), 1391 (s), 1158 (s), 838 (s).

LRMS (ESI) (m/z): 634 [M+Na]$^+$

HRMS (ESI) (m/z): calcd. for $C_{26}H_{38}BrN_3NaO_7Si$ [M+Na]$^+$: 634.15601,

found: 634.15600.

**S-20**:

$^1$H NMR (500 MHz, CDCl$_3$, 23 °C) δ: –0.14 (s, 3H, SiC**H**$_3$), –0.04 (s, 3H, SiC**H**$_3$), 0.60 (s, 9H, SiC(C**H**$_3$)$_3$), 1.68 (s, 9H, (C**H**$_3$)$_3$COCON), 3.11 (s, 3H, C$_{18}$**H**$_3$), 3.87 (d, *J* = 10.3 Hz, 1H, C$_{17}$**H**), 4.09 (d, *J* = 10.3 Hz, 1H, C$_{17}$**H**), 5.61 (br s, 1 H, C$_{15}$O**H**), 7.10 (s, 1H, C$_{12}$**H**), 7.12-7.19 (m, 2H, C$_6$**H,** C$_7$**H**), 7.34- 7.35 (m, 1H, C$_5$**H**), 7.82 (d, *J* = 8.3 Hz, 1H, C$_8$**H**).

$^{13}$C NMR (125 MHz, CDCl$_3$, 25 °C) δ: –5.76 (Si**C**H$_3$), –5.64 (Si**C**H$_3$), 17.8 (Si**C**(CH$_3$)$_3$), 25.5 (SiC(**C**H$_3$)$_3$), 26.6 (**C**$_{18}$), 28.2 ((**C**H$_3$)$_3$COCON), 64.7 (**C**$_{17}$), 85.3 ((CH$_3$)$_3$**C**OCON), 87.5 (**C**$_{15}$), 110.0 (**C**$_{12}$), 115.5 (**C**$_8$), 115.6 (**C**$_2$), 119.6 (**C**$_5$), 121.3 (**C**$_4$), 123.6 (**C**$_6$), 124.9 (**C**$_7$), 125.4 (**C**$_3$), 134.4 (**C**$_{11}$), 140.2 (**C**$_9$), 148.7 ((CH$_3$)$_3$CO**C**ON), 157.9 (**C**$_{13}$), 163.5 (**C**$_{16}$).

[α]$_D$: +1.2 (c 1.00, CHCl$_3$. 24 °C)

IR (neat) cm$^{-1}$: 3260 (br, m), 2932 (m), 1741 (s)

LRMS (ESI) (m/z): 536 [M+Na]$^+$

HRMS (ESI) (m/z): calcd. for $C_{26}H_{35}N_3NaO_6Si$ [M+Na]$^+$: 536.21928,

found: 536.21851.

**S-21**:

$^1$H NMR (500 MHz, CDCl$_3$, 25 °C) δ: 0.13 (s, 6H, Si(C**H**$_3$)$_2$), 0.91 (s, 9H, SiC(C**H**$_3$)$_3$), 1.60 (s, 9H, (C**H**$_3$)$_3$COCON), 2.84 (t, *J* = 12.2 Hz, 1H, C$_{12}$**H**), 2.96 (s, 3H, C$_{18}$**H**$_3$), 3.24 (dd, *J* = 4.8 Hz, 12.2 Hz, 1H, C$_{12}$**H**), 3.46 (br s, 1H, C$_{15}$O**H**), 3.81 (d, *J* = 9.6 Hz, 1H, C$_{17}$**H**), 3.91 (dd, *J* = 4.8 Hz, 12.2 Hz, C$_{11}$**H**), 4.05 (d, *J* = 9.6 Hz, 1H, C$_{17}$**H**), 6.73 (s, 1H, C$_2$**H**), 7.13 (t, *J* = 7.4 Hz, 1H, C$_6$**H**), 7.31 (dt, *J* = 0.93 Hz, 7.4 Hz, 1H, C$_7$**H**), 7.43 (app. d, *J* = 7.4 Hz, 1H, C$_5$**H**), 7.67 (br s, 1H, C$_8$**H**).

$^{13}$C NMR (125 MHz, CDCl$_3$, 25 °C) δ: –5.31 (Si**C**H$_3$), –5.19 (Si**C**H$_3$), 18.5 (Si**C**(CH$_3$)$_3$), 26.0 (SiC(**C**H$_3$)$_3$), 27.2 (**C**$_{18}$), 28.3 ((**C**H$_3$)$_3$COCON, 49.0 (**C**$_{12}$), 58.3 (**C**$_{11}$), 58.9 (**C**$_3$), 64.7 (**C**$_{17}$), 83.2 ((CH$_3$)$_3$**C**OCON), 84.3 (**C**$_2$), 85.9 (**C**$_{15}$), 116.0 (**C**$_8$), 124.5 (**C**$_6$), 124.9 (**C**$_5$), 131.0 (**C**$_7$), 131.1 (**C**$_4$), 142.1 (**C**$_9$), 151.6 ((CH$_3$)$_3$CO**C**ON), 164.6 (**C**$_{16}$), 165.1 (**C**$_{13}$).

$[\alpha]_D$: +132 (c 0.95, $CHCl_3$, 26 °C)

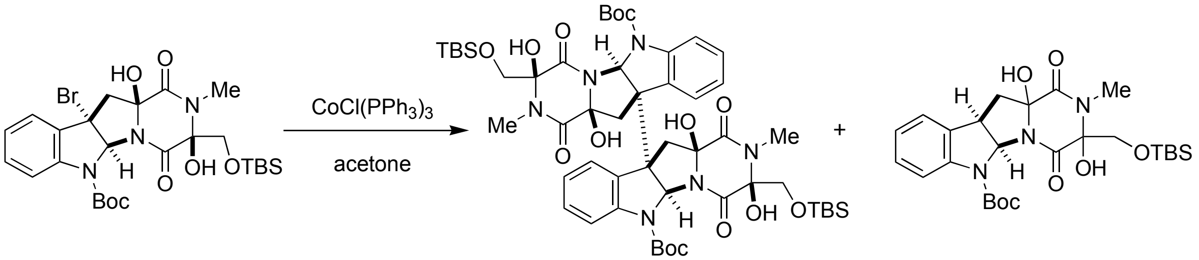
FTIR (neat) $cm^{-1}$: 3365 (br), 2949 (m), 2931 (m), 2883 (m), 2857 (m), 1711 (s), 1374 (s), 1153 (s), 842 (s).

LRMS (ESI) (m/z): 618 $[M+Na]^+$

HRMS (ESI) (m/z): calcd. for $C_{26}H_{38}BrN_3NaO_6Si$ $[M+Na]^+$: 618.16109,

found: 618.15806.

### (C-4) Radical dimerization reaction to give 13.



**12** **13** (55%) **S-22** (3%)

Stereochemistry at the α-position is tentatively assigned.

Freshly prepared tris(triphenylphosphine)cobalt chloride ($CoCl(PPh_3)_3$, 509 mg, 578 μmol)[4] was added as a solid quickly to a degassed (nitrogen babbling for 10 min) solution of **12** (182 mg, 300 μmol) in dry acetone (3.0 mL) at room temperature under nitrogen atmosphere. After 90 min, the reaction mixture was diluted with dichloromethane (10 mL) and quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine (10 mL) and then dried over anhydrous sodium sulfate. After removal of the solvent in vacuo, purification by flash column chromatography (chloroform/ethyl acetate = 80/20 to 70/30) gave the crude product of **13** and **S-22** (2.4 mg, 3%). The obtained crude compound was subjected to purification with MPLC system (column: High Flash M, hexane/ethyl acetate = 70/30 to 50/50) to give pure **13** (86.6 mg, 55%) as white solid.

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[4] (a) Baysdon, S. L.; Liebeskind, L. S. *Organometallics* **1982**, *1*, 771.

(b) Yamada, Y. ;Momose, D. *Chem. Lett.* **1981**, 1277.

(c) Movassaghi, M.; Schmidt, M. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 3725.

(d) Schmidt, M. A.; Movassaghi, M. *Synlett* **2008**, 313.

(e) Movassaghi, M.; Schmidt, M. A.; Ashenhurst, J. A. *Angew. Chem. Int. Ed.* **2008**, *47*, 1485.

(f) Kim, J.; Ashenhurst, J. A.; Movassaghi, M. *Science* **2009**, *324*, 238.

(g) Pérez-Balado, C.; Rodríguez-Grana, P.; de Lera, Á. R. *Chem. Eur. J.* **2009**, *28*, 9928.

(h) Pérez-Balado, C.; de Lera, Á. R. *Org. Lett.* **2008**, 10, 3701-3704.

**Dimeric tetraol 13**:

$^1$H NMR (400 MHz, $CDCl_3$, 55 °C) δ: 0.17 (s, 6H, SiC**H**$_3$), 0.18 (s, 6H, SiC**H**$_3$), 0.94 (s, 18H, SiC(C**H**$_3$)$_3$), 1.66 (s, 18H, (C**H**$_3$)$_3$COCON), 2.83 (d, *J* = 14.1 Hz, 2H, $C_{12}$**H**), 2.91 (d, *J* = 14.1 Hz, 2H, $C_{12}$**H**), 3.08 (s, 6H, $C_{18}$**H**$_3$), 3.37 (s, 2H, $C_{11}$O**H**), 4.15 (d, *J* = 11.0 Hz, 2H, $C_{17}$**H**), 4.22 (d, *J* = 11.0 Hz, 2H, $C_{17}$**H**), 4.28 (s, 2H, $C_{15}$O**H**), 6.89 (dt, *J* = 1.0 Hz, 7.4 Hz, 2H, $C_6$**H**), 7.10 (app. dt, *J* = 1.1 Hz, 7.4 Hz, 2H, $C_7$**H**), 7.26 (app. d, *J* = 7.4 Hz, 2H, $C_5$**H**), 7.51 (app. d, *J* = 7.4 Hz 2H, $C_8$**H**),

$^{13}$C NMR (125 MHz, $CDCl_3$, 25 °C) δ: –5.57 (Si**C**H$_3$), –5.14 (Si**C**H$_3$), 18.4 (Si**C**(CH$_3$)$_3$), 25.9 (SiC(**C**H$_3$)$_3$), 27.9 (**C**$_{18}$), 28.1 ((**C**H$_3$)$_3$COCON), 42.6 (**C**$_{12}$), 56.7 (**C**$_3$), 62.5 (**C**$_{17}$), 79.7 (**C**$_{15}$), 82.7 ((CH$_3$)$_3$**C**OCON), 85.4 (**C**$_2$), 86.8 (**C**$_{11}$), 117.0 (**C**$_8$), 122.4 (**C**$_5$), 123.3 (**C**$_6$), 129.7 (**C**$_7$), 131.6 (**C**$_4$), 141.7 (**C**$_9$), 151.2 ((CH$_3$)$_3$CO**C**ON), 163.1 (**C**$_{13}$), 169.1 (**C**$_{16}$).

$[\alpha]_D$: +182 (c 1.0, $CHCl_3$, 24 °C)

IR (neat) cm$^{-1}$ = 3367 (br), 2954 (m), 2932 (m), 2890 (m), 2858 (m), 1717 (s), 1390 (s), 1367 (s), 1157 (s), 841 (s).

LRMS (ESI) (m/z): 1087 [M+Na]$^+$

HRMS (ESI) (m/z): calcd. for $C_{52}H_{76}N_6NaO_{14}Si_2$ [M+Na]$^+$: 1087.48557,
found: 1087.48134.

**Reduced byproduct S-22**:

$^1$H NMR (500 MHz, $CDCl_3$, 23 °C) δ: 0.06 (s, 3H, SiC**H**$_3$), 0.09 (s, 3H, SiC**H**$_3$), 0.85 (s, 9H, SiC(C**H**$_3$)$_3$), 1.56 (s, 9H, (C**H**$_3$)$_3$COCON), 2.47 (dd, *J* = 8.7 Hz, 13.8 Hz, 1H, $C_{12}$**H**), 2.67 (d, *J* = 13.8 Hz, 1H, $C_{12}$**H**), 2.94 (s, 3H, $C_{18}$**H**$_3$), 3.84 (d, *J* = 10.4 Hz, 1H, $C_{17}$**H**), 3.99 (app. t, *J* = 7.8 Hz, 1H, $C_3$**H**), 4.09 (s, 1H, $C_{11}$O**H**), 4.23 (d, *J* = 10.4 Hz, 1H, $C_{17}$**H**), 5.00 (s, 1H, $C_{15}$O**H**), 6.60 (d, *J* = 7.8 Hz, 1H, $C_2$**H**), 7.01 (t, *J* = 7.8 Hz, 1H, $C_6$**H**), 7.18 (d, *J* = 7.8 Hz, 1H, $C_5$**H**), 7.21 (t, *J* = 7.8 Hz, 1H, $C_7$**H**), 7.68 (d, *J* = 7.8 Hz, 1H, $C_8$**H**).

$^{13}$C NMR (125 MHz, $CDCl_3$, 25 °C) δ: –5.50 (Si**C**H$_3$), –5.27 (Si**C**H$_3$), 18.3 (Si**C**(CH$_3$)$_3$), 25.9 (SiC(**C**H$_3$)$_3$), 27.7 (**C**$_{18}$), 28.3 ((**C**H$_3$)$_3$COCON), 41.6 (**C**$_3$), 42.3 (**C**$_{12}$), 63.5 (**C**$_{17}$), 77.5 (**C**$_2$), 82.3 ((CH$_3$)$_3$**C**OCON), 86.0 (**C**$_{15}$), 87.6 (**C**$_{11}$), 116.6 (**C**$_8$), 123.6 (**C**$_6$), 123.8 (**C**$_5$), 128.3 (**C**$_7$), 132.9 (**C**$_4$), 142.2 (**C**$_9$), 152.4 ((CH$_3$)$_3$CO**C**ON), 163.9 (**C**$_{16}$), 168.5 (**C**$_{13}$).

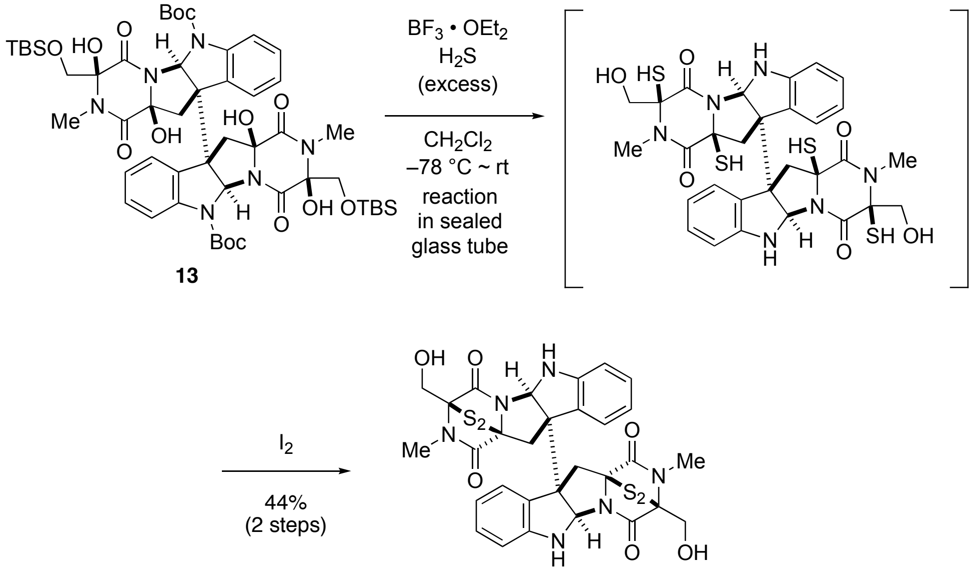
$[\alpha]_D$: +99 (c 0.59, $CHCl_3$, 25 °C)

IR (neat) cm$^{-1}$ = 3256 (br), 2953 (m), 2931 (m), 2883 (m), 2857 (m), 1710 (s), 1391 (s), 1156 (s), 839 (s).

LRMS (ESI) (m/z): 556 [M+Na]$^+$

HRMS (ESI) (m/z): calcd. for $C_{26}H_{39}N_3NaO_7Si$ [M+Na]$^+$: 556.24550,
found: 556.24623.

**(C-5) Substitution reaction with $H_2S$.**



13

(+)-Chaetocin (**1**)

Hydrogen sulfide (bp –60 ºC, ca.1 mL) was condensed at –78 ºC in a sealed-tube capped with a rubber septam. A solution of **13** (20.0 mg, 18.8 μmol) in dichloromethane (0.76 mL) and boron trifluoride diethyl ether complex (23 μL, 186 μmol) were added to the liquid hydrogen sulfide. Then rubber septum was replaced with a sealed-tube stopper, and the resulting mixture was allowed to warm up to room temperature. The reaction apparatus was placed behind a blast shield in a fume hood. After stirring for 90 min at room temperature, the reaction mixture was cooled to –78 ºC again, and the sealed-tube stopper was replaced by a rubber septum having a needle connected to two traps linearly, which are filled with 20% aqueous sodium hydroxide. The cooling bath was removed, and the solution was warmed up to room temperature. After purging with nitrogen gas, the reaction mixture was diluted with ethyl acetate (3 mL) and washed with saturated aqueous ammonium chloride (2 mL). The separated aqueous layer was extracted with ethyl acetate (3 x 2 mL). To the combined organic layers was added a solution of 2 equivalents of $I_2$ in ethyl acetate (50 mM, 0.73 mL) at room temperature. The organic solution turned red immediately. After strirring for 1 min, 10% aqueous sodium thiosulfate solution was added for quenching. Separated aqueous phase was further extracted with ethyl acetate (3 x 3 mL) and combined all organic phase was dried over anhydrous sodium sulfate. After concentration in vacuo, purification by preparative-TLC (Merck HPTLC Diol $F_{254s}$, 0.25 mm x 10 cm x 10 cm, EtOAc) gave (+)-chaetocin (**1**) (5.8 mg, 44%) as a white solid.

**(+)-Chaetocin (1):**

$^1$H NMR (500 MHz, $CDCl_3$, 24 °C) δ: 2.74 (d, *J* = 15.1 Hz, 2H, $C_{12}\mathbf{H}$), 3.08 (s, 6H, $C_{18}\mathbf{H}_3$), 3.29 (dd, *J* = 6.0 Hz, 9.2 Hz, 2H, $C_{17}O\mathbf{H}$), 3.84 (d, *J* = 15.1 Hz, 2H, $C_{12}\mathbf{H}$), 4.18 (dd, *J* = 9.2 Hz, 12.8 Hz, 2H, $C_{17}\mathbf{H}$), 4.25 (dd, *J* = 6.0 Hz, 12.8 Hz, 2H, $C_{17}\mathbf{H}$), 5.25 (s, 2H, $C_2\mathbf{H}$), 5.25 (s, 2H, N**H**), 6.74 (app. d, *J*

= 7.5 Hz, 2H, C$_5$**H**), 6.92 (dt, *J* = 0.9 Hz, 7.5 Hz, 2H, C$_6$**H**), 7.25 (dt, *J* = 1.4 Hz, 7.5 Hz, 2H, C$_7$**H**), 7.42 (app. d, *J* = 7.5 Hz, 2H, C$_8$**H**).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ: 27.5 (**C**$_{18}$), 39.4 (**C**$_{12}$), 60.0 (**C**$_3$), 60.7 (**C**$_{17}$), 73.5 (**C**$_{11}$), 76.0 (**C**$_{15}$), 80.7 (**C**$_2$), 110.9 (**C**$_5$), 120.5 (**C**$_6$), 125.4 (**C**$_8$), 127.6 (**C**$_4$), 130.6 (**C**$_7$), 149.3 (**C**$_9$), 163.0 (**C**$_{16}$), 165.8 (**C**$_{13}$).

[α]$_D$: +537 (c 0.20, CHCl$_3$, 26 °C)

IR (neat) cm$^{-1}$ = 3374 (br), 2928 (m), 1677 (s), 751 (s).

HRMS (ESI) (m/z): calcd. for $C_{30}H_{28}N_6NaO_6S_4$ [M+Na]$^+$: 719.08508,
found: 719.08494.

**(+)-Chaetocin (1, from *Chaetomium minutum*):**

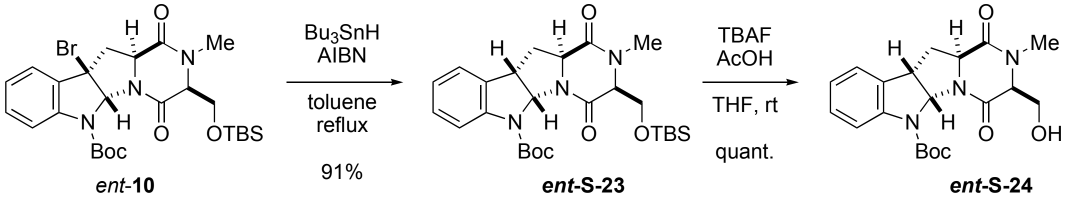
$^1$H NMR (500 MHz, CDCl$_3$, 24 °C) δ: 2.74 (d, *J* = 15.2 Hz, 2H, C$_{12}$**H**), 3.08 (s, 6H, C$_{18}$**H**$_3$), 3.26 (dd, *J* = 6.0 Hz, 9.6 Hz, 2H, C$_{17}$O**H**), 3.84 (d, *J* = 15.1 Hz, 2H, C$_{12}$**H**), 4.18 (dd, *J* = 9.6 Hz, 12.8 Hz, 2H, C$_{17}$**H**), 4.25 (dd, *J* = 6.0 Hz, 12.8 Hz, 2H, C$_{17}$**H**), 5.23 (s, 2H, N**H**), 5.25 (s, 2H, C$_2$**H**), 6.74 (app. d, *J* = 7.8 Hz, 2H, C$_5$**H**), 6.92 (t, *J* = 7.8 Hz, 2H, C$_6$**H**), 7.25 (t, *J* = 7.8 Hz, 2H, C$_7$**H**), 7.42 (app. d, *J* = 7.8 Hz, 2H, C$_8$**H**).

[α]$_D$: +530 (c 0.04, CHCl$_3$, 26 °C)

## (D) Conversion and structural determination of tetracyclic DKP 10.

### (D-1) Conversion of 10

For the determination of the relative stereochemistry of the tetracyclic DKP, the antipode of **10** was converted to **S-24** for the X-ray analysis. This revealed that the bromine atom of **10** is positioned *trans* to the α-protons of the DKP ring.



A solution of *ent*-**10** (332 mg, 570 μmol), tri-*n*-butyltin hydride (180 μL, 690 μmol), and 2,2'-azobisisobutyronitrile (11.5 mg, 69 μmol) in toluene (5.8 mL) was heated to reflux for 3.5 h under nitrogen atmosphere. The reaction mixture was concentrated in vacuo. The resulting residue was purified by flash column chromatography (chloroform) to give reduced ***ent*-S-23** (261 mg, 91%) as a white solid.

To a solution of ***ent*-S-23** (198 mg, 0.39 mmol) in dry tetrahydrofuran (10 mM, 4 mL) were added acetic acid (60 μL, 1.0 mmol) and tetrabutylammonium fluoride (1M tetrahydrofuran solution, 800 μL, 0.8 mmol) at 0 °C. After stirring for 4 h at room temperature under nitrogen atmosphere, the reaction mixture was concentrated in vacuo. The obtained residue was purification by column chromatography (chloroform/methanol = 100/0 to 98/2) to give ***ent*-S-24** (180 mg, quant.) as a white solid. Recrystallization from hexane-ethyl acetate afforded a crystal suitable for an X-ray structural analysis.

***ent*-S-23**:

$^1$H NMR (500 MHz, CDCl$_3$, 25 °C) δ: 0.07 (s, 3H, SiC**H**$_3$), 0.09 (s, 3H, SiC**H**$_3$), 0.89 (9H, s, SiC(C**H**$_3$)$_3$), 1.58 (s, 9H, (C**H**$_3$)$_3$COCON), 2.26 (ddd, *J* = 8.3 Hz, 11.8 Hz, 11.8 Hz, 1H, C$_{12}$**H**), 2.45 (dd, *J* = 4.8 Hz, 11.8 Hz, 1H, C$_{12}$**H**), 2.94 (s, 3H, C$_{18}$**H**$_3$), 3.89-3.95 (m, 3H, C$_3$**H,** C$_{11}$**H,** C$_{17}$**H**), 3.98 (app. s, 1H, C$_{15}$**H**), 4.26 (dd, *J* = 1.4 Hz, 10.1 Hz, 1H, C$_{17}$**H**), 6.77 (d, *J* = 7.8 Hz, 1H, C$_2$**H**), 7.02 (t, *J* = 7.5 Hz, 1H, C$_6$**H**), 7.19 (d, *J* = 7.5 Hz, 1H, C$_5$**H**), 7.22 (t, *J* = 7.5 Hz, 1H, C$_7$**H**), 7.71 (br s, 1H, C$_8$**H**).

$^{13}$C NMR (125 MHz, CDCl$_3$, 25 °C) δ: –5.24 (Si(**C**H$_3$)$_2$), –5.21 (Si(**C**H$_3$)$_2$), 18.7 (Si**C**(CH$_3$)$_3$), 26.1 (SiC(**C**H$_3$)$_3$), 28.6 ((**C**H$_3$)$_3$COCON), 31.8 (**C**$_{18}$), 39.8 (**C**$_{12}$), 42.7 (**C**$_3$), 57.1 (**C**$_{11}$), 61.6 (**C**$_{17}$), 64.6 (**C**$_{15}$), 75.5 (**C**$_2$), 82.3 ((CH$_3$)$_3$**C**OCON), 115.1 (**C**$_8$), 123.5 (**C**$_6$), 125.0 (**C**$_5$), 128.7 (**C**$_7$), 130.3 (**C**$_4$), 143.3 (**C**$_9$), 152.2 ((CH$_3$)$_3$CO**C**ON), 163.8 (**C**$_{16}$), 166.2 (**C**$_{13}$).

[α]$_D$: –95 (c 0.35, CHCl$_3$, 25 °C)

FTIR (neat) cm$^{-1}$: 2949 (m), 2930 (m), 2857 (m), 1711 (s), 1678 (s), 1382 (s), 1149 (s), 836 (s).

LRMS (ESI) (m/z): 524 [M+Na]$^+$

HRMS (ESI) (m/z): calcd. for $C_{26}H_{39}N_3NaO_5Si$ [M+Na]$^+$: 524.25567,
found: 524.25414.

***ent*-S-24**:

$^1$H NMR (500 MHz, CDCl$_3$, 24 °C) δ: 1.58 (s, 9H, (C**H**$_3$)$_3$COCON), 2.30 (ddd, *J* = 8.1, 11.9, 11.9 Hz, 1H, C$_{12}$**H**), 2.52 (dd, *J* = 5.1, 11.9 Hz, 1H, C$_{12}$**H**), 2.57 (br s, 1H, O**H**), 3.00 (s, 3H, C$_{18}$**H**$_3$), 3.88-3.94 (m, 2H, C$_{11}$**H** and C$_{17}$**H**), 4.00-4.03 (m, 2H, C$_3$**H** and C$_{15}$**H**), 4.23 (ddd, *J* = 2.3, 6.9, 11.0 Hz, 1H, C$_{17}$**H**), 6.76 (d, *J* = 7.8 Hz, 1H, C$_2$**H**), 7.03 (t, *J* = 7.4 Hz, 1H, C$_6$**H**), 7.20 (d, *J* = 7.4 Hz, 1H, C$_7$**H**), 7.22 (t, *J* = 7.4 Hz, 1H, C$_5$**H**), 7.68 (br s, 1H, C$_8$**H**).

$^{13}$C NMR (125 MHz, CDCl$_3$, 25 °C) δ: 28.5 ((**C**H$_3$)$_3$COCON), 31.8 (**C**$_{18}$), 39.1 (**C**$_{12}$), 42.8 (**C**$_3$), 57.2 (**C**$_{11}$), 60.3 (**C**$_{17}$), 64.0 (**C**$_{15}$), 75.5 (**C**$_2$), 82.4 ((CH$_3$)$_3$**C**OCON), 115.2 (**C**$_8$), 123.5 (**C**$_6$), 124.8 (**C**$_5$), 128.7 (**C**$_7$), 130.3 (**C**$_4$), 143.1 (**C**$_9$), 152.1 ((CH$_3$)$_3$CO**C**ON), 164.4 (**C**$_{16}$), 166.8 (**C**$_{13}$).

[α]$_D$: –125 (c 0.12, CHCl$_3$, 26 °C)

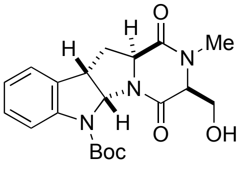
FTIR (neat) cm$^{-1}$: 3408 (br), 2977 (m), 2927 (m), 1710 (s), 1659 (s), 1381 (s), 1149 (s), 753 (s).

LRMS (ESI)(m/z): 410 [M+Na]$^+$

HRMS (ESI) (m/z): calcd. for $C_{20}H_{25}N_3NaO_5$ [M+Na]$^+$: 410.16919,
found: 410.17098.

### (D-2) X-ray crystal structure analysis of *ent*-S-24

CCDC-764669 contains the supplementary crystallographic data for ***ent*-S-24**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



**S-24**

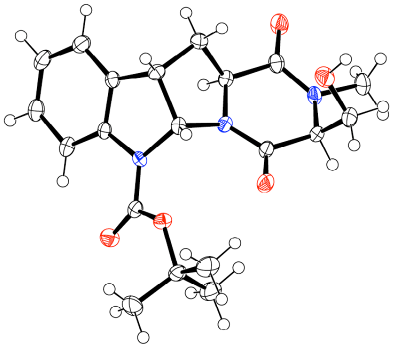


**Figure S-1.** Molecular structure of **S-24**.

### (E) Total synthesis of *ent*-chaetocin

According to the synthetic procedures for (+)-chaetocin (**1**), its antipode was successfully synthesized starting from L-serine and L-tryptophan. Optical rotations of each compound are listed below.

***ent*-9**: $[\alpha]_D$: –78 (c 1.0, $CHCl_3$, 25 °C)

***ent*-10**: $[\alpha]_D$: –112 (c 1.0, $CHCl_3$, 25 °C)

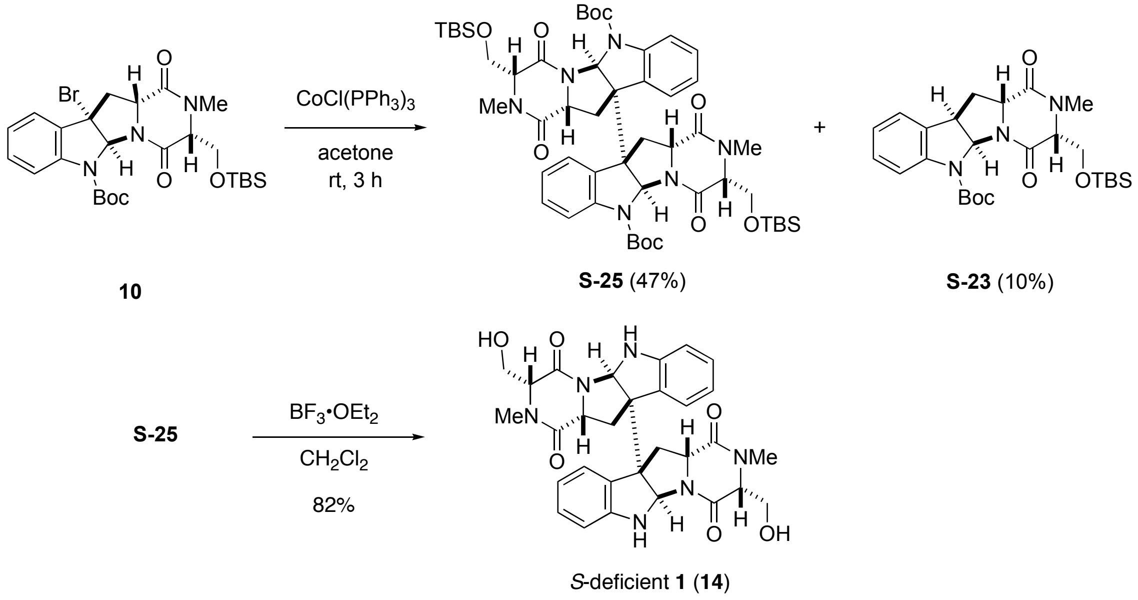
***ent*-12**: $[\alpha]_D$: –134 (c 1.0, $CHCl_3$, 26 °C)

***ent*-13**: $[\alpha]_D$: –217 (c 1.0, $CHCl_3$, 25 °C)

***ent*-1**: $[\alpha]_D$: –554 (c 0.20, $CHCl_3$, 24 °C)

## (F) Synthesis of *S*-deficient analogs

### (F-1) Synthesis of *S*-deficient analog of 1 (14).



To a solution of **10** (377 mg, 650 μmol) in dry acetone saturated with nitrogen was added $CoCl(PPh_3)_3$ (1.14 g, 1.29 mmol) at room temperature under nitrogen atmosphere. After stirring for 3 h at room temperature, water (20 mL) was added for quenching. The organic solvent was removed in vacuo. The obtained suspension was extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with water (50 mL) and brine (30 mL), and then dried over anhydrous sodium sulfate. After concentration in vacuo, purification by flash column chromatography (hexane/ethyl acetate = 70/30) and GPC was carried out to give **S-25** (152 mg, 47%, white amorphous form) and reduced byproduct **S-23** (31.2 mg, 10%, white amorphous form.).

**S-25**:

$^1$H NMR (500 MHz, $CDCl_3$, 60 °C) δ: 0.10 (s, 6H, $SiC\mathbf{H}_3$), 0.12 (s, 6H, $SiC\mathbf{H}_3$), 0.91 (18H, s, $SiC(C\mathbf{H}_3)_3$), 1.61 (s, 18H, $(C\mathbf{H}_3)_3COCON$), 2.39 (t, *J* = 11.9 Hz, 2H, $C_{12}\mathbf{H}$), 2.81 (dd, *J* = 4.9, 11.9 Hz, 2H, $C_{12}\mathbf{H}$), 2.97 (s, 6H, $C_{18}\mathbf{H}_3$), 3.82 (dd, *J* = 4.9 Hz, 11.9 Hz, 2H, $C_{11}\mathbf{H}$), 3.86 (app. br s, 2H, $C_{15}\mathbf{H}$), 4.08 (dd, *J* = 2.5 Hz, 11.0 Hz, 2H, $C_{17}\mathbf{H}$), 4.28 (dd, *J* = 2.8 Hz, 11.0 Hz, 2H, $C_{17}\mathbf{H}$), 6.47 (s, 2H, $C_2\mathbf{H}$), 6.83 (t, *J* = 7.4 Hz, 2H, $C_6\mathbf{H}$), 7.05 (t, *J* = 7.4 Hz, 2H, $C_7\mathbf{H}$), 7.23 (d, *J* = 7.4 Hz, 2H, $C_5\mathbf{H}$), 7.48 (d, *J* = 7.4 Hz, 2H, $C_8\mathbf{H}$).

$^{13}$C NMR (125 MHz, $CDCl_3$, 60 °C) δ: –5.24 ($Si\mathbf{C}H_3$), –5.00 ($Si\mathbf{C}H_3$), 18.6 ($Si\mathbf{C}(CH_3)_3$), 26.2 ($SiC(\mathbf{C}H_3)_3$), 28.5 ($(\mathbf{C}H_3)_3COCON$), 31.1($\mathbf{C}_{18}$), 38.8 ($\mathbf{C}_{12}$), 58.4($\mathbf{C}_{11}$), 58.7($\mathbf{C}_3$), 61.7($\mathbf{C}_{17}$), 63.8($\mathbf{C}_{15}$), 78.5 ($\mathbf{C}_2$), 82.5 ($(CH_3)_3\mathbf{C}OCON$), 116.1 ($\mathbf{C}_8$), 122.7 ($\mathbf{C}_5$), 123.4 ($\mathbf{C}_6$), 129.8 ($\mathbf{C}_7$), 130.1 ($\mathbf{C}_4$), 143.4 ($\mathbf{C}_9$), 151.4 ($(CH_3)_3CO\mathbf{C}ON$), 162.6 ($\mathbf{C}_{16}$), 166.2 ($\mathbf{C}_{13}$).

$[\alpha]_D$: +213 (c 1.8, $CHCl_3$, 25 °C)

FTIR (neat) cm$^{-1}$: 2953 (m), 2931 (m), 2887 (m), 2857 (m), 1715 (s), 1678 (m), 1155 (s), 752 (s).

LRMS (ESI) (m/z): 1023 $[M+Na]^+$

HRMS (ESI) (m/z): calcd. for $C_{52}H_{76}N_6NaO_{10}Si_2$ $[M+Na]^+$: 1023.50591,

found: 1023.50647.

**S-23**: $[\alpha]_D$: +96 (c 1.3, $CHCl_3$, 26 °C)

To a solution of **S-25** (30.0 mg, 0.30 mmol) in dry dichloromethane (20 mM, 1.5 mL) was added boron trifluoride diethyl ether complex (32 μL, 0.240 mmol) at 0 °C under nitrogen atmosphere. After stirring for 2 h at room temperature, the reaction mixture was quenched with saturated aqueous ammonium chloride (1.5 mL), and the separated aqueous layer was extracted with ethyl acetate (4 x 3 mL). The combined organic layers were dried over sodium sulfate. After concentration in vacuo, purification by flash column chromatography (chloroform/methanol = 90/10) afforded **14** (14.1 mg, 82%) as white solid.

***S*-deficient analog 14**:

$^1$H NMR (500 MHz, $CDCl_3$, 25 °C) δ: 2.43-2.52 (m, 4H, $C_{12}\mathbf{H}$), 2.99 (s, 6H, $C_{18}\mathbf{H}_3$), 3.94-3.96 (m, 4H, $C_{15}\mathbf{H}$ and $C_{17}\mathbf{H}$), 4.05 (dd, *J* = 6.4 Hz, 11.5 Hz, 2H, $C_{11}\mathbf{H}$), 4.24-4.30 (m, 4H, $C_{17}\mathbf{H}$ and O**H**), 4.92 (s, 2H, N**H**), 5.73 (s, 2H, $C_2\mathbf{H}$), 6.61 (app. d, *J* = 7.6 Hz, 2H, $C_5\mathbf{H}$), 6.82 (t, *J* = 7.6 Hz, 2H, $C_6\mathbf{H}$), 7.13 (dt, *J* = 0.9 Hz, 7.6 Hz, 2H, $C_7\mathbf{H}$), 7.31 (d, *J* = 7.6 Hz, 2H, $C_8\mathbf{H}$).

$^{13}$C NMR (125 MHz, $CDCl_3$, 25 °C) δ: 31.6 ($\mathbf{C}_{18}$), 39.1 ($\mathbf{C}_{12}$), 58.2 ($\mathbf{C}_{11}$), 60.0 ($\mathbf{C}_{17}$), 61.1 ($\mathbf{C}_3$), 64.2 ($\mathbf{C}_{15}$), 78.7 ($\mathbf{C}_2$), 109.8 ($\mathbf{C}_5$), 119.2 ($\mathbf{C}_6$), 126.0 ($\mathbf{C}_8$), 127.1 ($\mathbf{C}_4$), 129.8 ($\mathbf{C}_7$), 150.8 ($\mathbf{C}_9$), 164.4 ($\mathbf{C}_{16}$), 166.3 ($\mathbf{C}_{13}$).

$[\alpha]_D$: +217 (c 1.0, $CHCl_3$, 25 °C)

FTIR (neat) cm$^{-1}$: 3342 (br), 2997 (m), 2948 (m), 2887 (m), 1642 (s), 1465 (m), 748 (s).

LRMS (ESI) (m/z): 595 $[M+Na]^+$

HRMS (ESI) (m/z): calcd. for $C_{30}H_{32}N_6NaO_6$ $[M+Na]^+$: 595.22810,

found: 595.22761.

### (F-2) Synthesis of *S*-deficient analog of *ent*-1 (*ent*-14).

*Ent*-**14** was synthesized according to the same protocol for the synthesis of **14**. Optical rotations of each intermediate are provided below.

***ent*-25:** –210 (c 1.0, $CHCl_3$, 26 °C)

***ent*-14:** –239 (c 0.51, $CHCl_3$, 24 °C)

### (G) HMT G9a–inhibitory activity assay

G9a inhibition assay of the synthesized compounds was carried out according to a reported ELISA method.[5]

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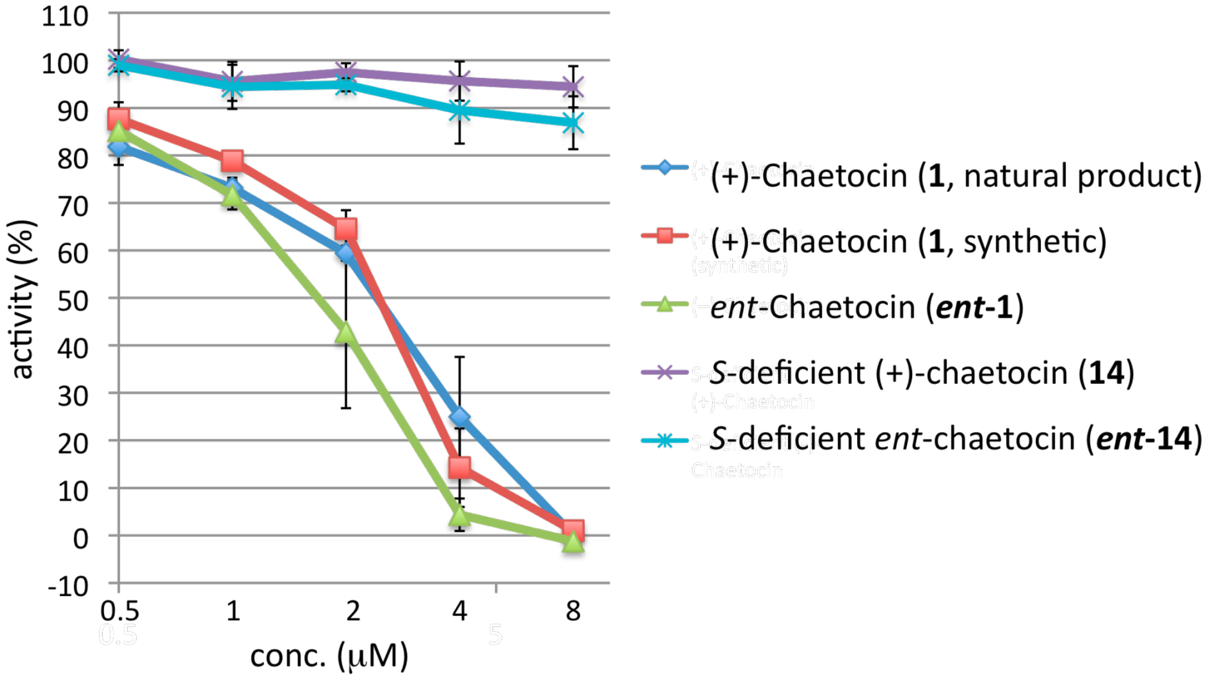
[5] Kubicek, S.; O'Sullivan, R. J.; August, E. M.; Hickey, E. R.; Zhang, Q.; Teodoro, M. L.; Rea, S.; Mechtler,

## Inhibition assay

A mixture of 1 μL of GST-G9a (200 ng), 1 μL of BSA (150 ng), 25 μL of 2xHMT activity buffer (100 mM Tris-HCl (pH 8.5), 20 mM $MgCl_2$, 40 mM KCl, 20 mM 2-mercaptoethanol, 500 mM sucrose), 1 μL of a DMSO solution of a compound of interest, and 20 μL of $H_2O$ was incubated at room temperature for 1 h in a total volume of 48 μL/well. After the addition of 1 μL of *S*-adenosylmethionine (SAM) (50 ng) and 1 μL of biotinylated H3 peptide (50 ng) into this reaction mixture, the resulting mixture was further incubated at 37 °C for 2 h and boiled at 96 °C for 30 min. The supernatant of the mixture was transferred to a streptavidin-coated plate and incubated at room temperature for 1 h. The supernatant was removed, and the remaining plate was washed with 300 μL of PBS containing 0.5% Tween20 (PBST) 3 times. Then, the plate was treated with 14.6 ng/mL of an anti-methylated-lysine antibody MEK3D7[6] in PBST. After incubation at room temperature for 1h, the supernatant was removed, and the remaining plate was washed with 300 μL of PBST 3 times. Subsequently, the secondary antibody conjugated with mouse HRP in PBST (100 μL/well) was added to the plate, and the resulting mixture was incubated at room temperature for 1 h. After the removal of the supernatant, the plate was washed with 300 μL of PBST 5 times. A substrate of TMB peroxidase (3,3',5,5'-tetramethylbenzidine) was added to the plate and the reaction was run at room temperature for 30 min. Finally, the inhibitory activity was evaluated by measuring the absorption of each well at 650 nm using a plate reader.

In the case of the compounds **14** and *ent*-**14**, no inhibition was observed even at the concentration of 50 μM.



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K.; Kowalski, J. A.; Homon, C. A.; Kelly, T. A.; Jenuwein, T. Molecular Cell 2007, 25, 473.

[6] Iwabata, H.; Yoshida, M.; Komatsu, Y. *Proteomics*, **2005**, *18*, 4653.

**Table. IC$_{50}$ values for G9a inhibitory activity**

| Compound | IC$_{50}$ (μM) |
|---|---|
| (+)-Chaetocin (**1**, natural product) | 2.4 |
| (+)-Chaetocin (**1**, synthetic) | 2.4 |
| *ent*-Chaetocin (***ent*-1**) | 1.7 |
| *S*-deficient (+)-chaetocin (**14**) | >50 |
| *S*-eficient *ent*-chaetocin (***ent*-14**) | >50 |

**Results and comments**:

As shown above, synthetic (+)-chaetocin showed inhibitory activity comparable to that of natural (+)-chaetocin, confirming that (+)-chaetocin is directly involved in the inhibition of histone methyltransferase (HMT) G9a. The IC$_{50}$ value observed in our study was in good accord with the value determined by a standard radioactive filter-binding assay.[7] Surprisingly, *ent*-chaetocin also inhibited G9a equally effectively, indicating that HMT G9a does not strictly recognize the absolute stereochemistry of the inhibitor, and that the binding site of chaetocin is flexible.

On the other hand, we also tested sulfur atom-deficient analogs **14** and ***ent*-14**. The spatial arrangement of all substituents of these compounds, other than the disulfide bonds, matches well with that of the parent compounds. Therefore, biological assay of **14** and ***ent*-14** should allow for direct evaluation of the influence of the sulfur functionality within chaetocin. Interestingly, these compounds were completely inactive, indicating that either disulfide bond or reduced dithiol moiety participates in the inhibition of G9a. These results are not surprising, because disulfide bonds have been proposed to play critical roles in interfering with the physiological events. In the previous paper[7], Imhof and coworkers reported that the addition of a large excess of DTT to reduce the disulfide bond within chaetocin did not lead to a significant decrease in its activity towards SU(VAR)3-9. They speculated that chaetocin simply binds to a SAM-binding cleft, based on their observation that chaetocin acts as a competitive inhibitor for *S*-adenosylmethionine (SAM), and they did not considered possible interaction of sulfur groups with histone methyltransferases. Although their conclusion seems reasonable, our assay results, including the effect of the absolute stereochemistry and, most importantly, the inactivity of the sulfur-deficient analogs, imply a more complicated scenario of how chaetocin interaction with HMT G9a and SU(VAR)3-9. In case that the disulfide bonds are reduced by the addition of DTT as discussed in Imhof's paper, our present results suggest that the reduced dithiol moiety may be involved in the interaction with the enzyme. Further investigation to clarify the molecular mechanism is under way in our laboratory.

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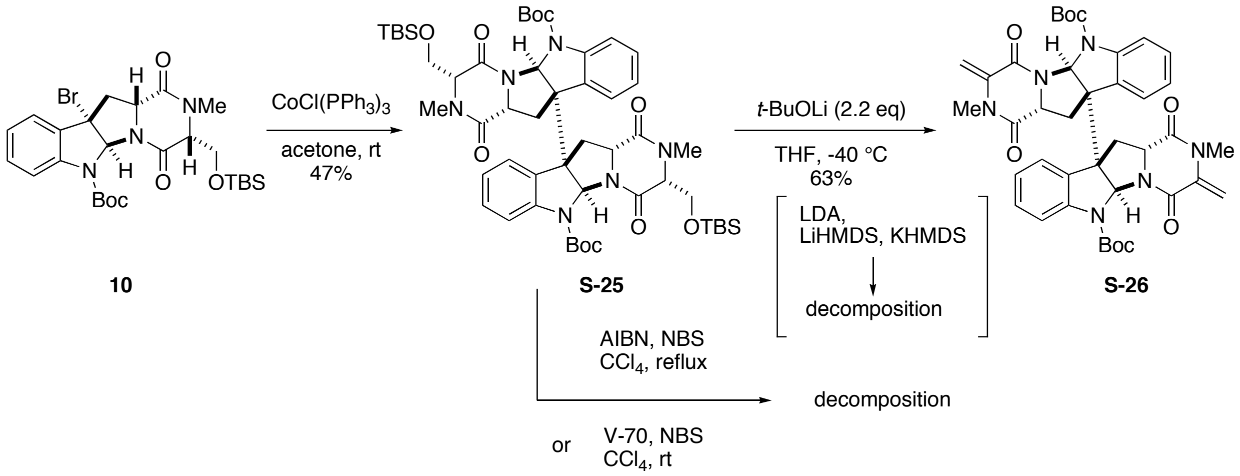
[7] Greiner, D.; Bonaldi, T.; Eskeland, R.; Roemer, E.; Imhof, A. *Nat. Chem. Biol.* **2005**, *1*, 143.

## (H) Additional note-1: Dimerization of 10 and α-oxidation of the obtained octacyclic ring system



Based on classical enolate strategy to introduce a sulfur functionality, which was originally applied to DKPs by Schmidt et al.[8], we first examined reactions of the tetracyclic compound **S-25** with various bases to form the corresponding di- or tetra anions. All attempts with commonly-used strong bases, including LDA, LiHMDS, and KHMDS, were unsuccessful, and only decomposition of **S-25** was observed even at -78 °C regardless of the presence or absence of electrophilc sulfur compounds. Although the reaction with *t*-BuOLi was clean, β-elimination of the TBS-oxy group readily occurred to give exo-methylene compound **S-26** in 63% yield.

Next, we examined α-bromination reaction under radical conditions. Such reactions of diketopiperazines (DKPs) with molecular bromine or NBS are known to be useful to selectively brominate the α-position of DKPs.[9] In the preceding examples, however, non-substituted DKPs derived from glycine or sarcosine alone were employed for the radical bromination reaction. Nevertheless, we tried the reaction of **S-25** using NBS. Unfortunately, reaction of dimeric compound **S-25** either at reflux or at ambient temperature gave a complex mixture, resulting in complete decomposition of the dimeric core structure.

Based on these experimental results, it was concluded that the dimeric core structure is highly unstable under radical conditions. Therefore, we abandoned the late stage oxidation of the dimeric core framework and instead planned the early stage radical bromination of the tetracyclic compound

---

[8] (a) Öhler, E.; Poisel, H.; Tataruch, F.; Schmidt, U. *Chem. Ber.* **1972**, 104, 1714.

(b) Öhler, E.; Poisel, H.; Tataruch, F.; Schmidt, U. *Chem. Ber.* **1972**, 105, 635.

(c) Hino, T.; Sato, T. *Tetrahedron Lett.* **1971**, *12*, 3127.

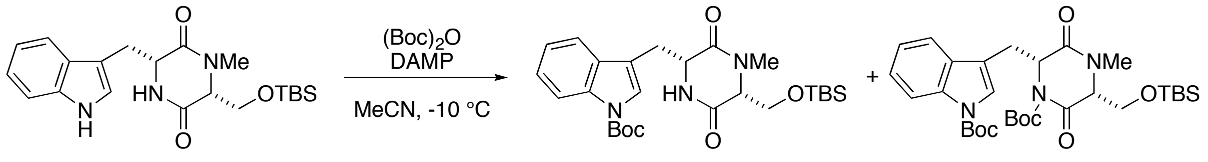
[9] (a) Trown, P. W. *Biochem. Biophys. Res. Commun.* **1968**, *33*, 402.

(b) Kishi,Y.; Nakatsuka, S.; Fukuyama, T.; Havel, M. *J. Am. Chem. Soc.* **1973**, *95*, 6493.

(c) Fukuyama, T.; Nakatsuka, S.; Kishi, Y. *Tetrahedron* **1981**, *37*, 2045-2078.

**10** as discussed in the main text. See also Additional note 4 below.

## (I) Additional note-2: Details of the synthesis of DKP 9.



**S-27** **9** (32%) **S-28** (22%)

Although *N*-Boc-protected compound **9** was accessible from DKP **S-27**, the chemical yield was not satisfactory. This is because di-Boc-protected compound **S-28** was also formed significantly. In contrast to acyclic dipeptide **S-16**, the nitrogen atom of the lactam ring seems more nucleophilic than that of the amide in **S-16** probably due to the rigid conformation of the DKP ring.

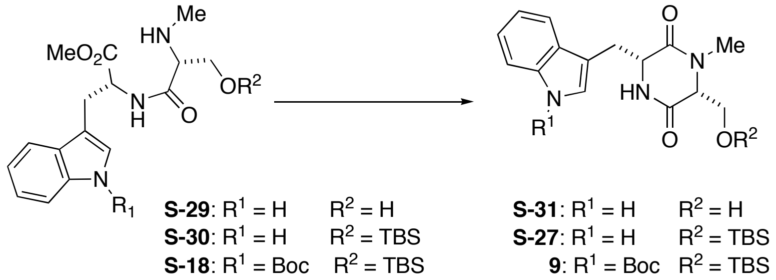
The table below summarizes our optimization of the ring closure to afford diketopiperazines from dipeptides. Normally, the addition of weak base is necessary for intramolecular condensation reaction between an ester and a secondary amine.[10] Initially, we selected compound **S-29** as a substrate. When triethylamine was used as a base, the target reaction did not proceed even under reflux (entry 1). In contrast, ammonium hydroxide promoted the reaction efficiently even at room temperature, affording the cyclized compound **S-31** in good yield. However, the corresponding diastereomer, presumably generated by the epimerization at the $\alpha$-position of the serine moiety during prolonged exposure to basic conditions, was formed in an appreciable amount (entry 2). In contrast, when the reaction time was reduced to 6 h, the desired compound was obtained quantitatively, and the diastereomer ratio was greatly improved (entry 3). To our delight, we found that protection of the hydroxyl group efficiently suppressed the epimerization (entry 4). Thus, TBS-protected **S-30** underwent the cyclization reaction without epimerization under the same conditions as shown in entry 3. Although a prolonged reaction time was necessary for completion of the reaction, the desired product **S-27** was produced in excellent yield. We applied this condition to **S-18** for the preparation of **9** (entry 5).

We normally kept the concentration of 28% ammonium hydroxide below 7 vol%. Otherwise, nucleophilic attack of ammonia to the methyl ester occurred, giving the corresponding amide in an appreciable amount.

---

[10] (a) Chai, C. L. L.; King, A. R. *J. Chem. Soc., Perkin Trans. 1*, **1999**, 1173.
(b) Kawasaki, T.; Enoki, H.; Matsumura, K.; Ohyama, M.; Inagawa, M.; Sakamoto, M. *Org. Lett.* **2000**, *2*, 3027.

**Table S-1**



**S-29**: $R^1$ = H $R^2$ = H
**S-30**: $R^1$ = H $R^2$ = TBS
**S-18**: $R^1$ = Boc $R^2$ = TBS

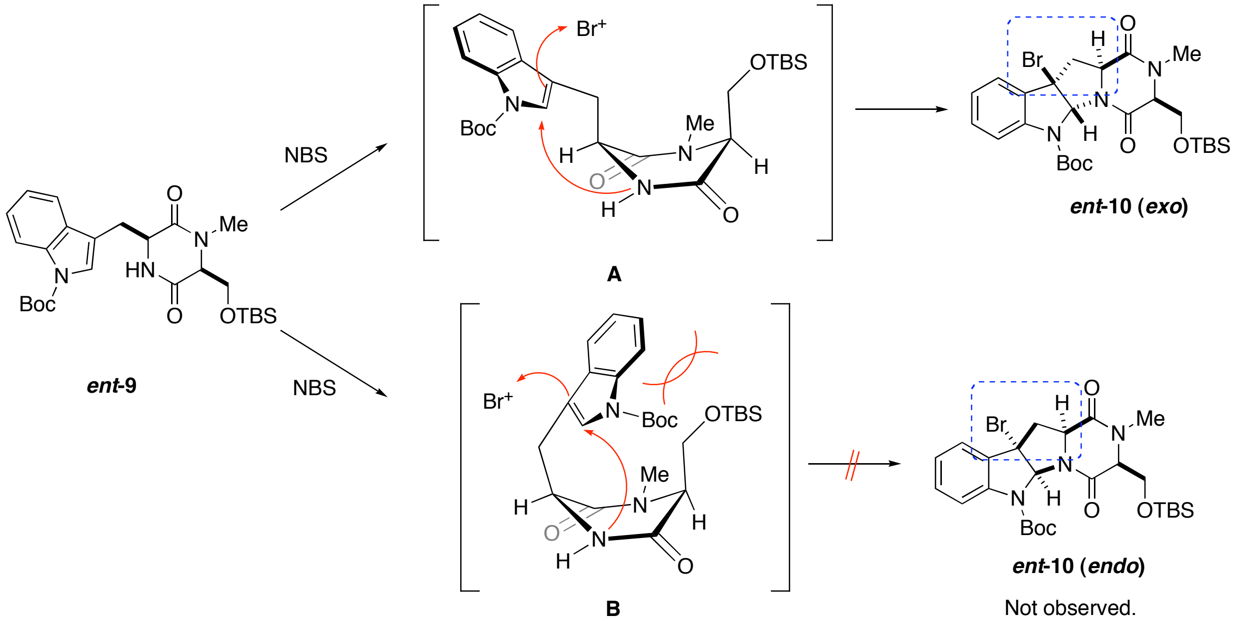
**S-31**: $R^1$ = H $R^2$ = H
**S-27**: $R^1$ = H $R^2$ = TBS
**9**: $R^1$ = Boc $R^2$ = TBS

| entry | material | solvent (concentration) | base | temp. | time | yield | distereomer ratio[a] |
|---|---|---|---|---|---|---|---|
| 1 | **S-29**: $R^1$ = H, $R^2$ = H | toluene | $Et_3N$ | reflux | 36 h | 13% | ——[b] |
| 2 | **S-29**: $R^1$ = H, $R^2$ = H | MeOH (6 mM) | 28% $NH_4OH$ aq. (7 vol%) | rt | 27 h | quant. | 1 : 0.23 |
| 3 | **S-29**: $R^1$ = H, $R^2$ = H | MeOH (6 mM) | 28% $NH_4OH$ aq. (7 vol%) | rt | 6 h | quant. | 1 : 0.05 |
| 4 | **S-30**: $R^1$ = H, $R^2$ = TBS | MeOH (6 mM) | 28% $NH_4OH$ aq. (7 vol%) | rt | 67 h | 94% | ——[c] |
| 5 | **S-18**: $R^1$ = Boc, $R^2$ = TBS | MeOH (6 mM) | 28% $NH_4OH$ aq. (4 vol%) | rt | 58 h | 79% (isolated) | ——[c] |

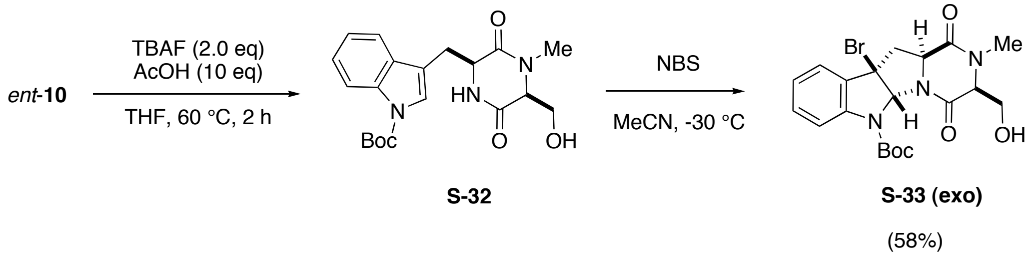
a) Yield and distereomer ratio were estimated by $^1H$ NMR. b) Not determined. c) Not detected.

## (J) Additional note-3: Stereochemical model of bromocyclization (9 -> 10)

As discussed above, the relative configuration of the tetracyclic bromide **10** was determined by X-ray analysis of *ent*-**S-24**. This bromocyclization reaction was highly stereoselective, and the corresponding epimer was not detected. The excellent exo-selectivity observed in this reaction can be explained as follows: The DKP ring being co-planar, the *N*-Me group is considered to be on the same plane. In order to avoid steric interaction with the *N*-Me group, it is likely that the TBS-oxymethyl group is located at the pseudo-axial position. This idea is also supported by the X-ray analysis (Figure S-1). For the formation of the *endo*-oriented product, the indole ring must point to the TBS-oxymethyl group, which may cause severe steric repulsion. As a result, the transition state model **B** should be destabilized considerably, thereby minimizing the formation of *endo*-**10**. In contrast, it seems that reaction via transition state model **A** proceeds smoothly to afford *exo*-**10**.



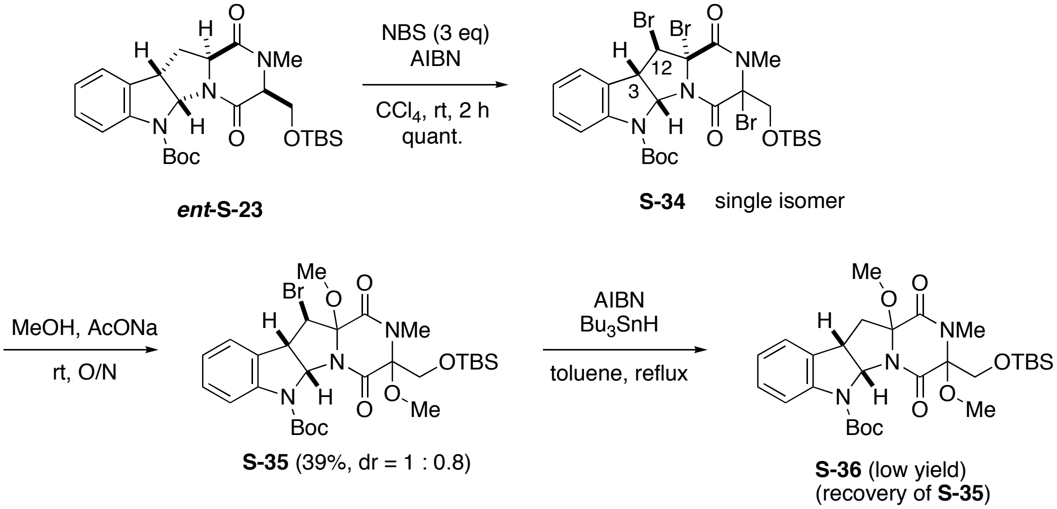
We also tested the reaction of less sterically hindered **S-32**. After the removal of the TBS group under acidic conditions, the obtained alcohol was subjected to bromocyclization reaction. Again, **S-33** with exo-stereochemistry was isolated as a single isomer in 58% yield.



In contrast, the stereoselectivity of the bromocyclization reaction was found to vary depending on the size of the substituents on the DKP ring in previous reports on total syntheses of (-)-ditryptophenaline (**2**) and (+)-11,11'-dideoxyverticillin (**4**). However, those reactions were carried out before *N*-methylation of the DKP substrates. Although a tosyl group was used as a protecting group of the indole ring and $Br_2$ as an electrophile in place of NBS, we speculate that the difference in stereoselectivity observed between our case and the previous examples depends upon whether or not an *N*-methyl group is present, since it may considerably affect the conformation of the DKP substrates.

## (K) Additional note-4: Details of radical bromination of tetracyclic DKP.

As discussed in the main text, the desired radical bromination of **10** proceeded smoothly to give tribromide **11** almost quantitatively. A model study indicated that the bulky bromine atom at the benzylic position played an important role in this reaction. Thus, when reduced compound **S-23** was subjected to the same radical reaction, overbromination occurred at the methylene part of the tryptophan unit, affording tribromide **S-34** as a single isomer. Interestingly, the tribromide was always a major product, even when the amount of NBS was reduced, indicating that the undesired bromination reaction was fast.



***ent*-S-23**

**S-34** single isomer

**S-35** (39%, dr = 1 : 0.8)

**S-36** (low yield)
(recovery of **S-35**)

Molecular modeling and careful analysis of the $^1H$ NMR spectrum of crude **S-34** revealed the relative stereochemistry of two hydrogen atoms at C-3 and C-12 positions to be *trans*, and that of two neighboring bromine atoms to be *trans,* since no coupling was observed between the C-3 and C-12 hydrogen atoms. Similar overbromination was previously well documented in the literature.[11] It is known that a hydrogen atom next to the bromine atom can be readily abstracted by a radical species to give a carbon radical, because the generated carbon radical is stabilized by the next bromine atom as a result of the positive interaction of the bonding orbital of the C-Br bond.[12] Such a mechanism allows stereoselective bromination reaction to proceed, which is in accord with the orientation of two bromine atoms within **S-34**. Although the obtained tribromide was converted to the corresponding methyl ethers **S-35** with a diastereomeric ratio of about 1:1, the subsequent removal of the remaining bromine atom was difficult probably because of the steric repulsion caused by the neighboring methoxy group. Taken together with this difficulty, the stereoselective nature of the bromination

---

[11] (a) Yoshimura, J.; Sugiyama, Y.; Nakamura, H. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2850.

(b) Yoshimura, J.; Nakamura, H.; Matsunari, K. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 605.

(c) Caballeroa,E.; Avendañoa, C.; Menéndeza, J. C. *Tetrahedron: Asymmetry* **1998**, *9*, 967.

(d) Caballero,E.; Avendaño. C.; Menéndez, J. C. *Tetrahedron* **1999**, *55*, 14185.

[12] (a) J. March. In Advanced Organic Chemistry (5th edition) John Wiley and Sons, New York, 1992, pp899–900.

(b) Thaler, W. *J. Am. Chem. Soc.* **1963**, *85*, 2607.

(c) Skell, P. S.; Pavlis, R. R.; Lewis, D. C.; Shea, K. J. *J. Am. Chem. Soc.* **1973**, *95*, 6735.

(d) Skell, P. S.; Traynham, J. G. *Acc. Chem. Res*. **1984**, *17*, 160.

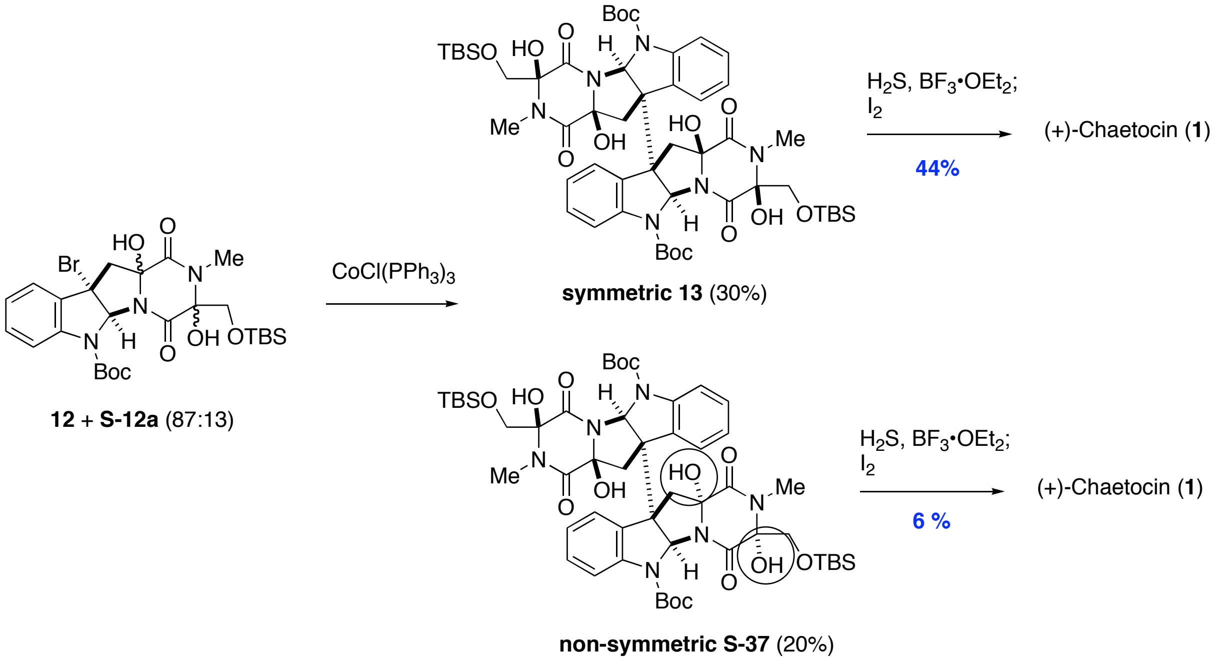
reaction led us to envision that the undesired third bromination would be suppressed if a bulky substituent shielded the convex face of the 5,5-fused ring system. As we hoped, the bulky bromine atom in compound **10** effectively minimized the undesired over-bromination at the methylene part, and the di-brominated product was exclusively formed.

## (L) Additional note-5: On the stereochemistry of diols

Although the exact stereochemistry at the aminal moiety has not been determined, we tentatively assign the stereochemistry of **12** on the basis of the following experimental results.

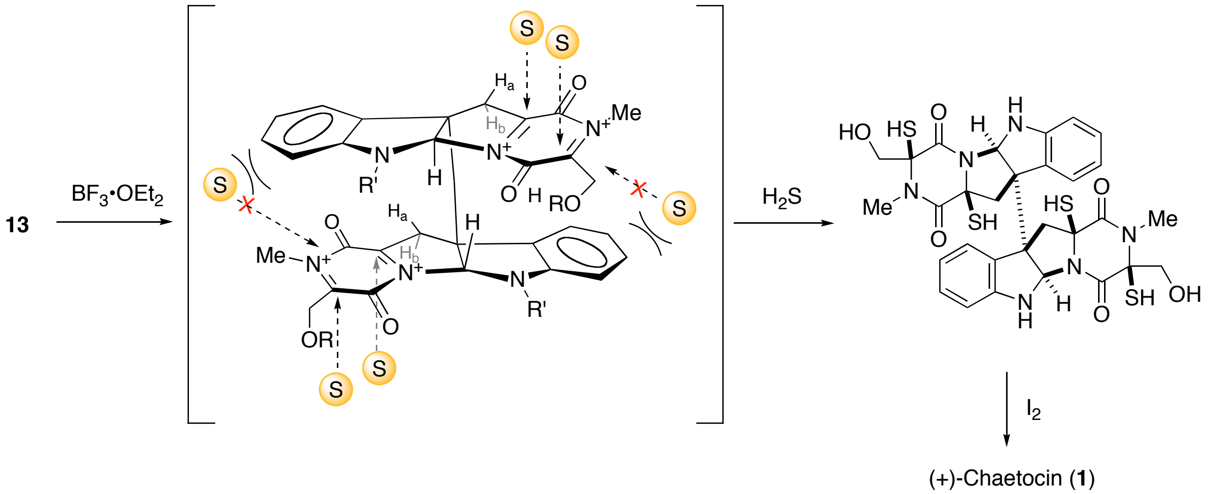
When a mixture of **12** and its stereoisomer **S-12a** was treated with Co(I) complex, symmetric **13** and non-symmetric **S-37** were obtained in 30% and 20% yield, respectively. In this reaction, three isomers can be in principle formed, but the coupling product of minor **S-12a** and **S-12a** was not isolated. It is likely that symmetric **13** arises from coupling of two molecules of **12**, and non-symmetric **S-37** is formed from the coupling reaction between **12** and **S-12a**.

While symmetric **13** underwent substitution reaction with $H_2S$ in a reasonable yield (see the main text), **S-37** was less reactive, so only a 6% yield of the final product was obtained. These results indicate that $BF_3$•$OEt_2$ could access to the hydroxyl groups of **13**, and the substitution reaction proceeded without difficulty. *We speculate that all of the hydroxyl groups within **13** point away to the outer surface of the double-decker core structure.* In the case of **S-37**, however, it is considered that at least one hydroxyl group is oriented into the inside of the core structure. This may prevent the access of the Lewis acid to the hydroxyl group, resulting in the low yield. Based on these results, we tentatively assigned the stereochemistry of diol **12** as shown in Scheme 2 (main text).



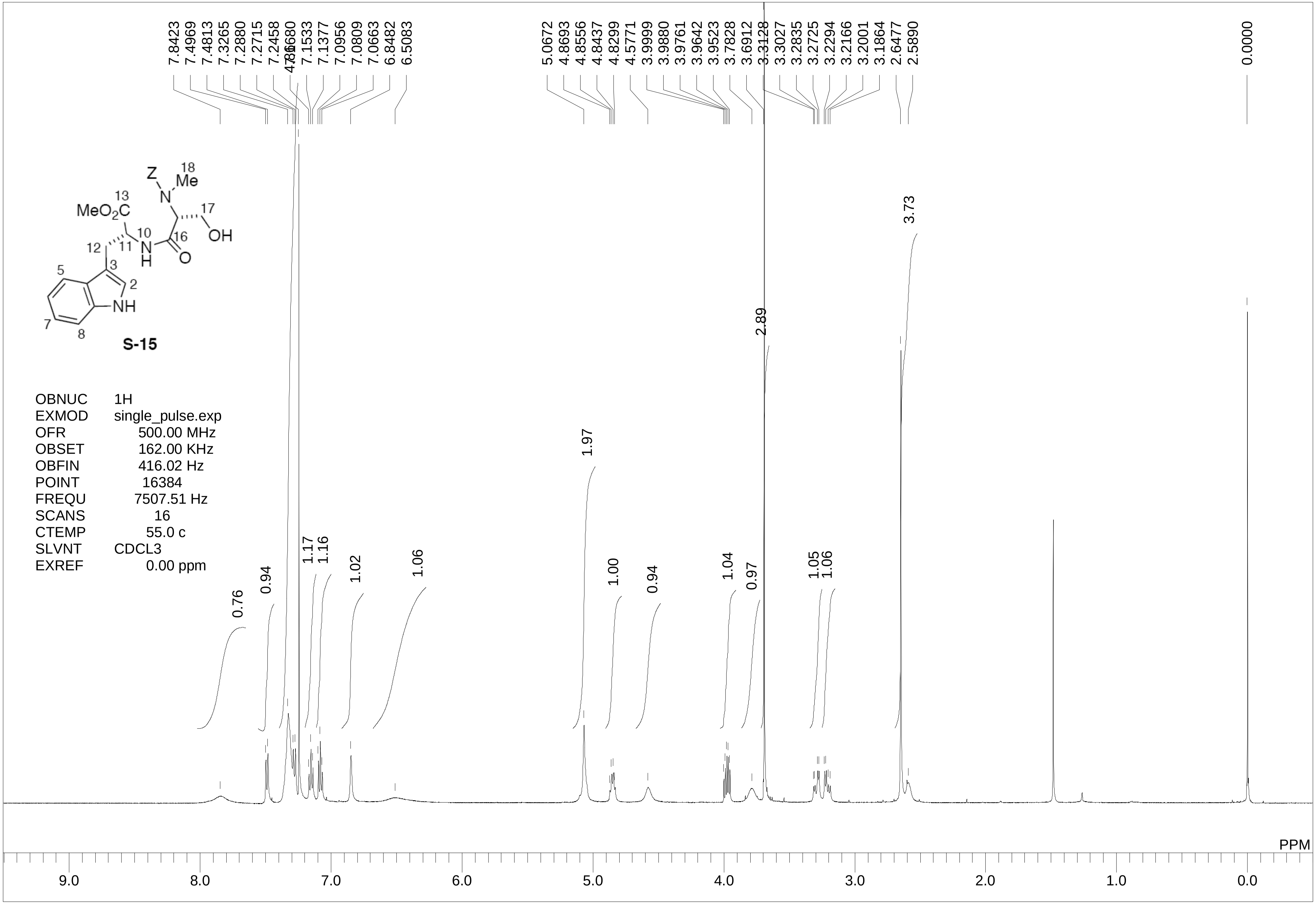
### (M) Additional note-6: Stereochemical models of $H_2S$-substitution reaction.

Because $BF_3$•$OEt_2$ is a widely used Lewis acid for the activation of aminals, we employed it here. Considering the intrinsic nature of borane as a hard Lewis acid, we expected that the resulting thiol would be stable under such Lewis acidic conditions. The activation of the hemiaminal **13** by $BF_3$•$OEt_2$ should give an iminium ion intermediate, so that the stereochemistry at the $\alpha$-position would be cancelled. However, *it seems that hydrogen sulfide mainly attacked from the outer surface of the double-decker core structure, affording the tetrathiol precursor stereoselectively.* Clean formation of the tetrathiol was supported by the $^1H$ NMR analysis of the crude product.



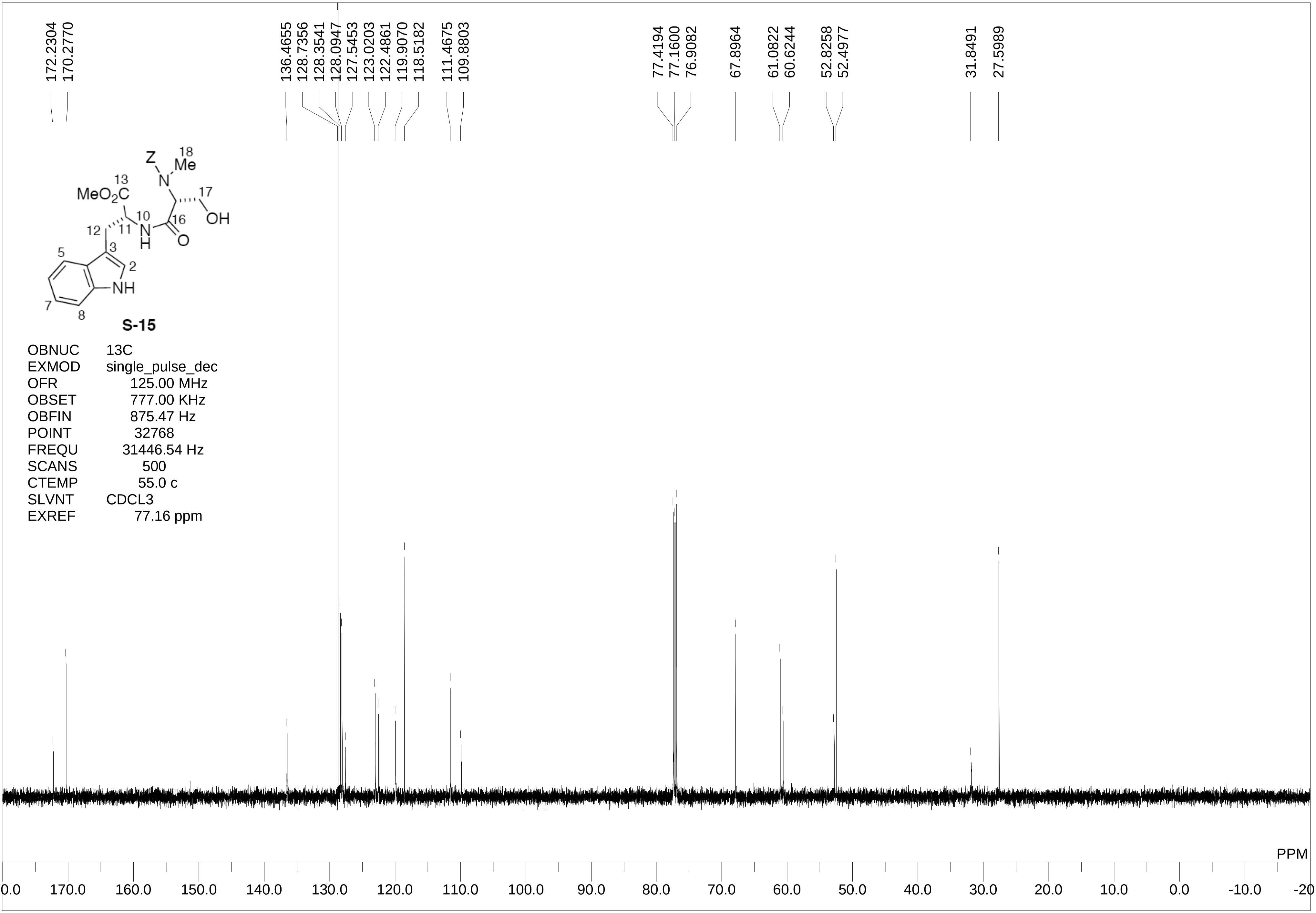
We also tested $ZnCl_2$ as a Lewis acid. Matsunari et al. reported $ZnCl_2$–promoted substitution reaction of methyl aminal with $H_2S$ in good yield.[9] According to Matsunari's protocol, we tested the reaction of tetraol **13** using $ZnCl_2$. However, the substitution reaction with $H_2S$ did not occur.

### (N) NMR spectra



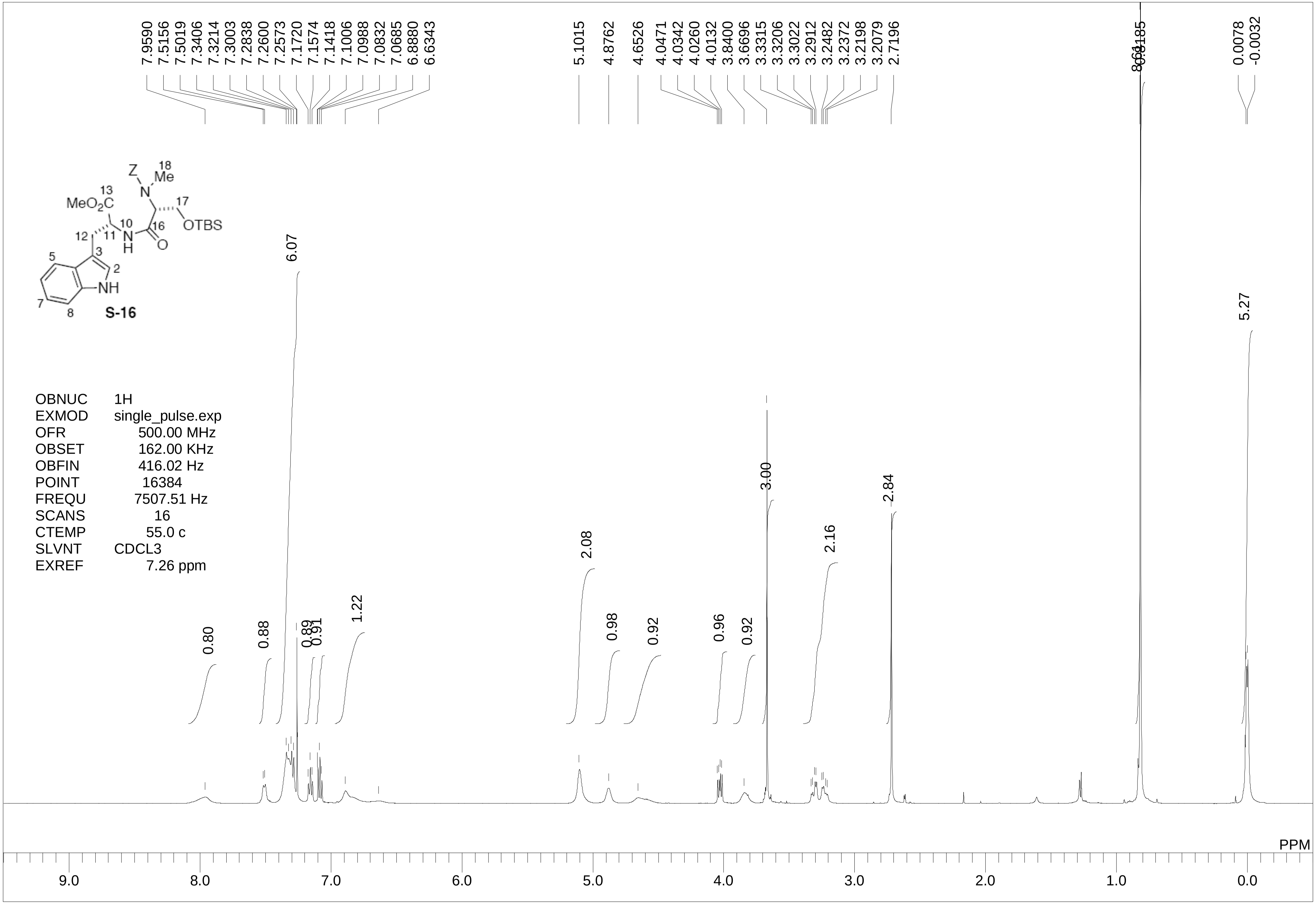
**S-15**

| | |
|---|---|
| OBNUC | 1H |
| EXMOD | single_pulse.exp |
| OFR | 500.00 MHz |
| OBSET | 162.00 KHz |
| OBFIN | 416.02 Hz |
| POINT | 16384 |
| FREQU | 7507.51 Hz |
| SCANS | 16 |
| CTEMP | 55.0 c |
| SLVNT | CDCL3 |
| EXREF | 0.00 ppm |



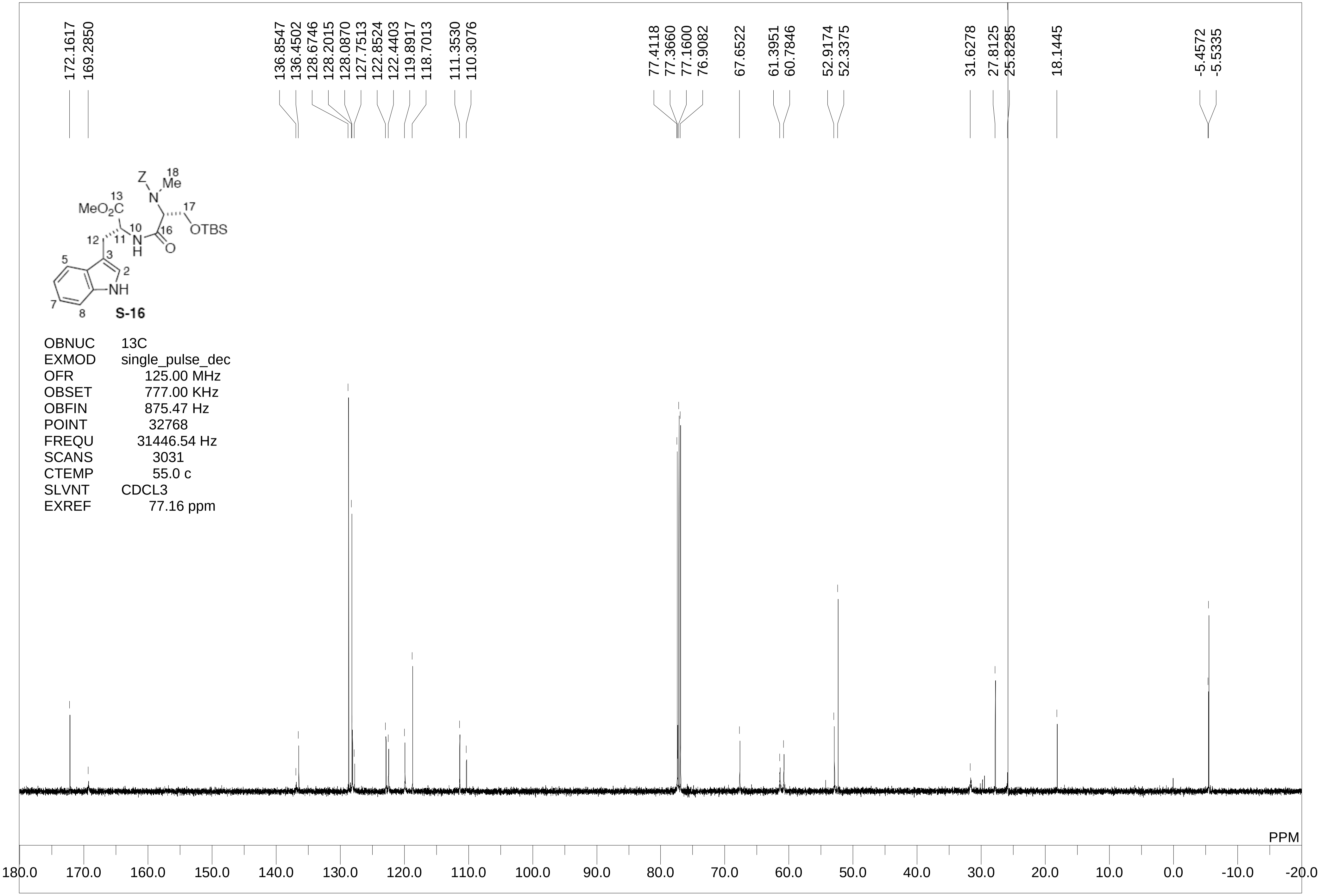
**S-15**

| | |
|---|---|
| OBNUC | 13C |
| EXMOD | single_pulse_dec |
| OFR | 125.00 MHz |
| OBSET | 777.00 KHz |
| OBFIN | 875.47 Hz |
| POINT | 32768 |
| FREQU | 31446.54 Hz |
| SCANS | 500 |
| CTEMP | 55.0 c |
| SLVNT | CDCL3 |
| EXREF | 77.16 ppm |



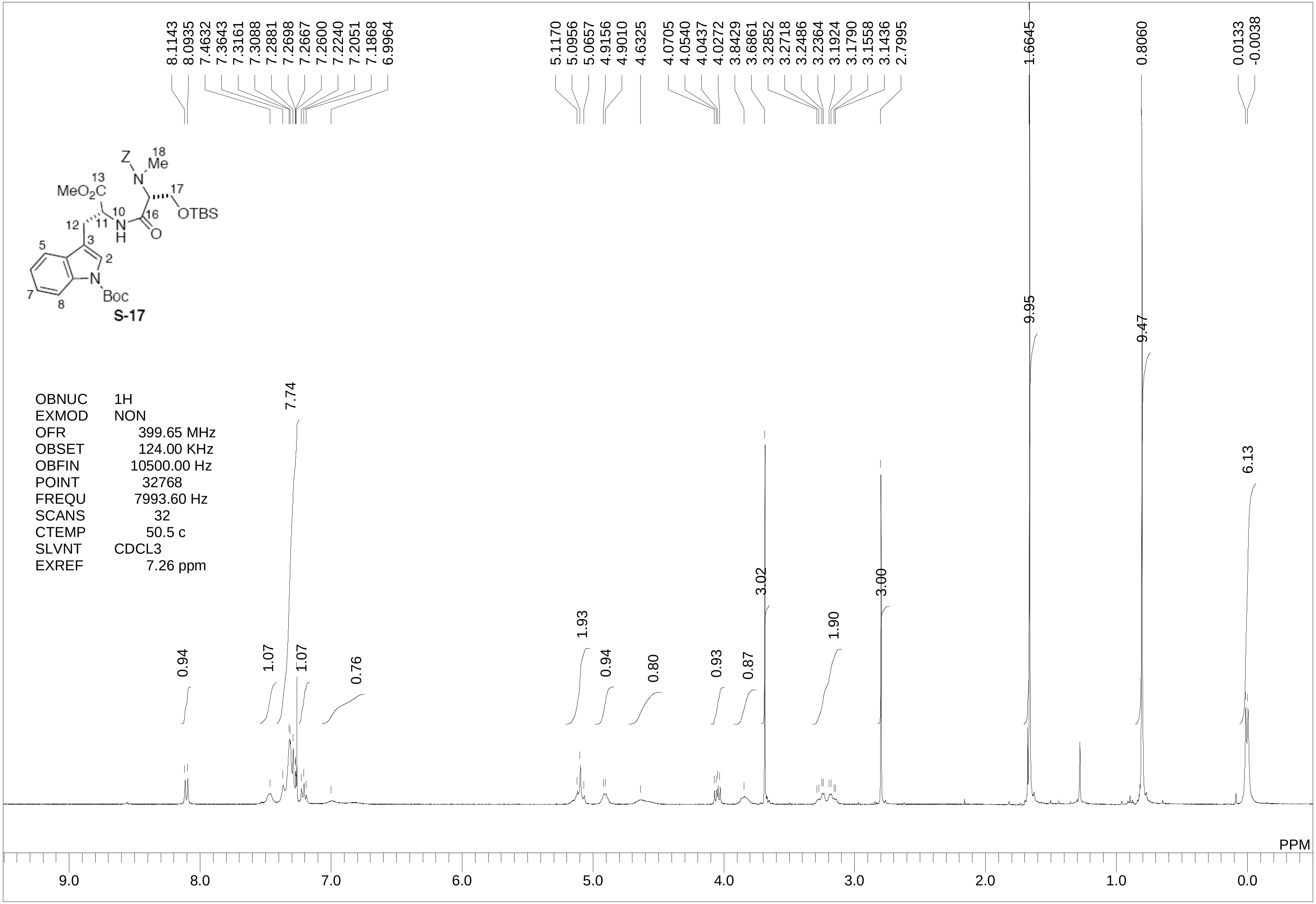
**S-16**

| | |
|---|---|
| OBNUC | 1H |
| EXMOD | single_pulse.exp |
| OFR | 500.00 MHz |
| OBSET | 162.00 KHz |
| OBFIN | 416.02 Hz |
| POINT | 16384 |
| FREQU | 7507.51 Hz |
| SCANS | 16 |
| CTEMP | 55.0 c |
| SLVNT | CDCL3 |
| EXREF | 7.26 ppm |



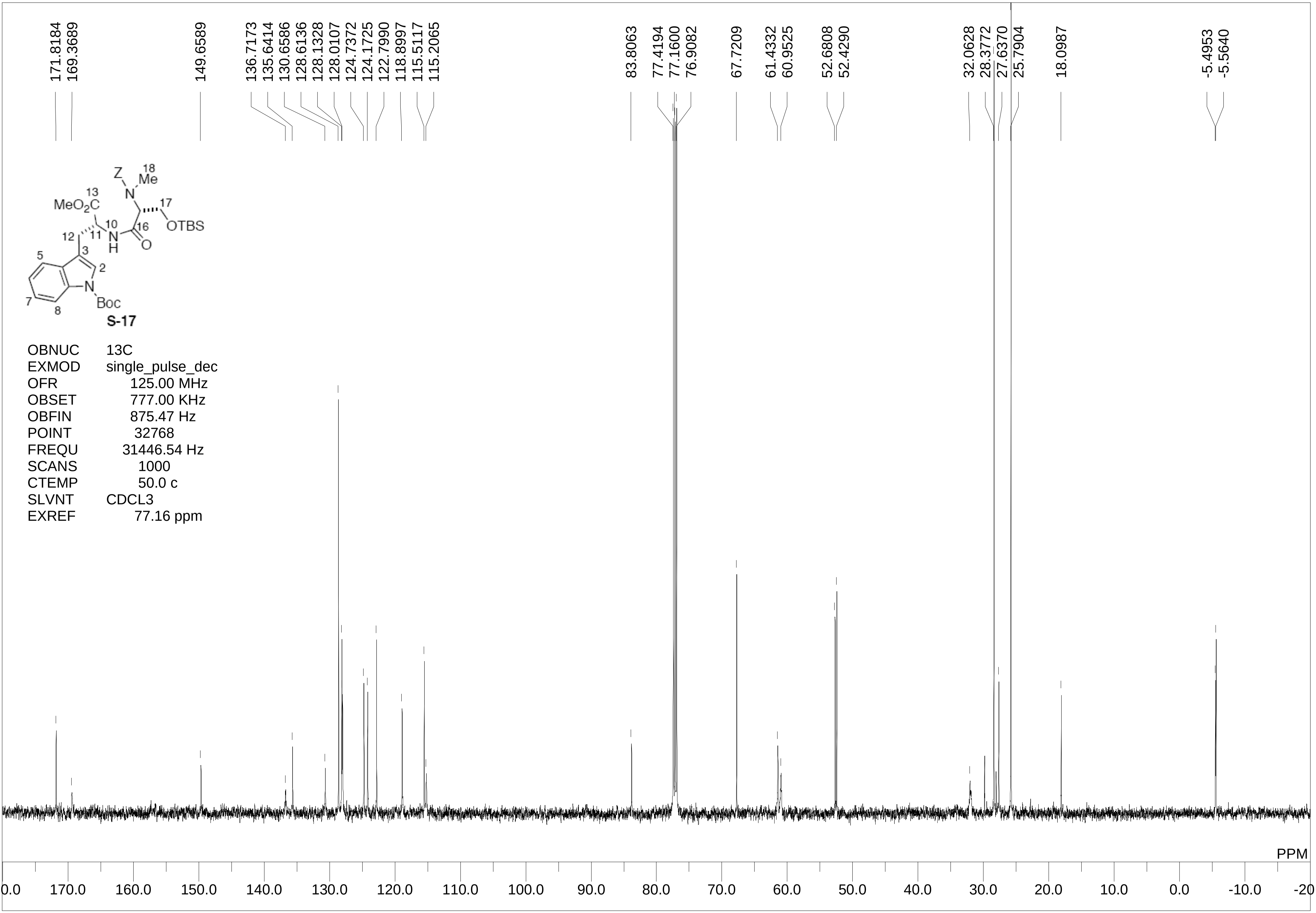
**S-16**

| | |
|---|---|
| OBNUC | 13C |
| EXMOD | single_pulse_dec |
| OFR | 125.00 MHz |
| OBSET | 777.00 KHz |
| OBFIN | 875.47 Hz |
| POINT | 32768 |
| FREQU | 31446.54 Hz |
| SCANS | 3031 |
| CTEMP | 55.0 c |
| SLVNT | CDCL3 |
| EXREF | 77.16 ppm |



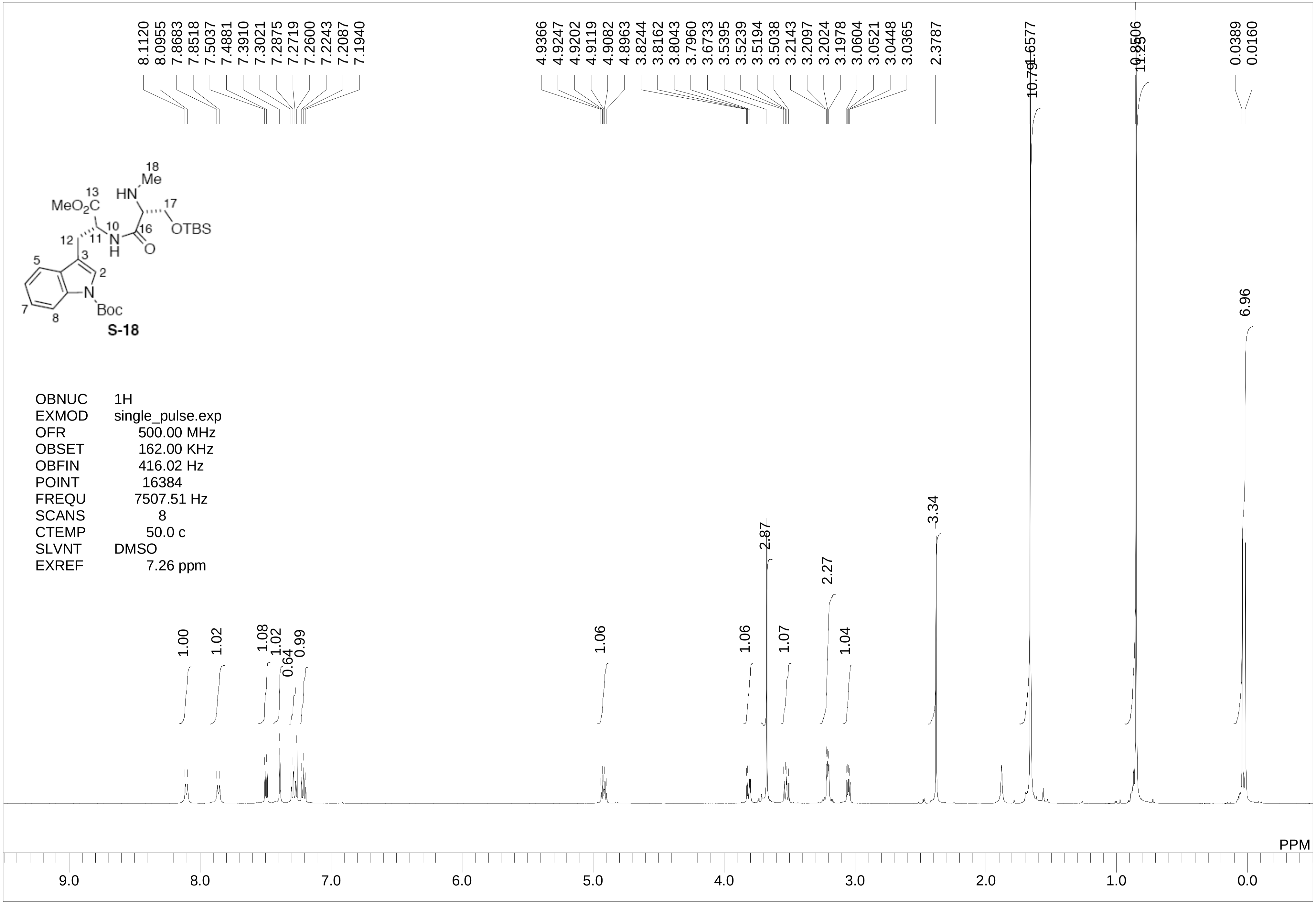
**S-17**

| | |
|---|---|
| OBNUC | 1H |
| EXMOD | NON |
| OFR | 399.65 MHz |
| OBSET | 124.00 KHz |
| OBFIN | 10500.00 Hz |
| POINT | 32768 |
| FREQU | 7993.60 Hz |
| SCANS | 32 |
| CTEMP | 50.5 c |
| SLVNT | CDCL3 |
| EXREF | 7.26 ppm |



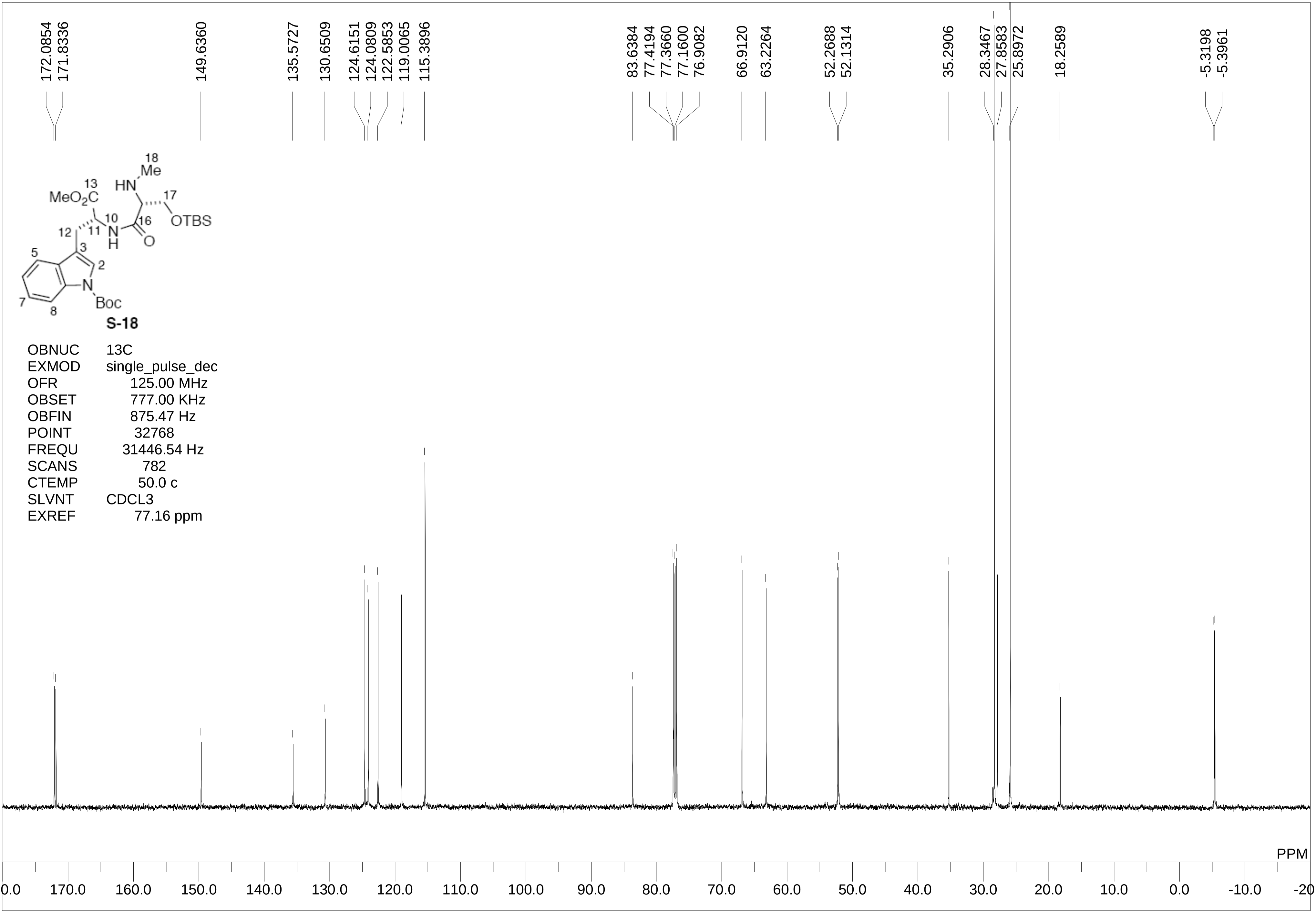
**S-17**

| | |
|---|---|
| OBNUC | 13C |
| EXMOD | single_pulse_dec |
| OFR | 125.00 MHz |
| OBSET | 777.00 KHz |
| OBFIN | 875.47 Hz |
| POINT | 32768 |
| FREQU | 31446.54 Hz |
| SCANS | 1000 |
| CTEMP | 50.0 c |
| SLVNT | CDCL3 |
| EXREF | 77.16 ppm |



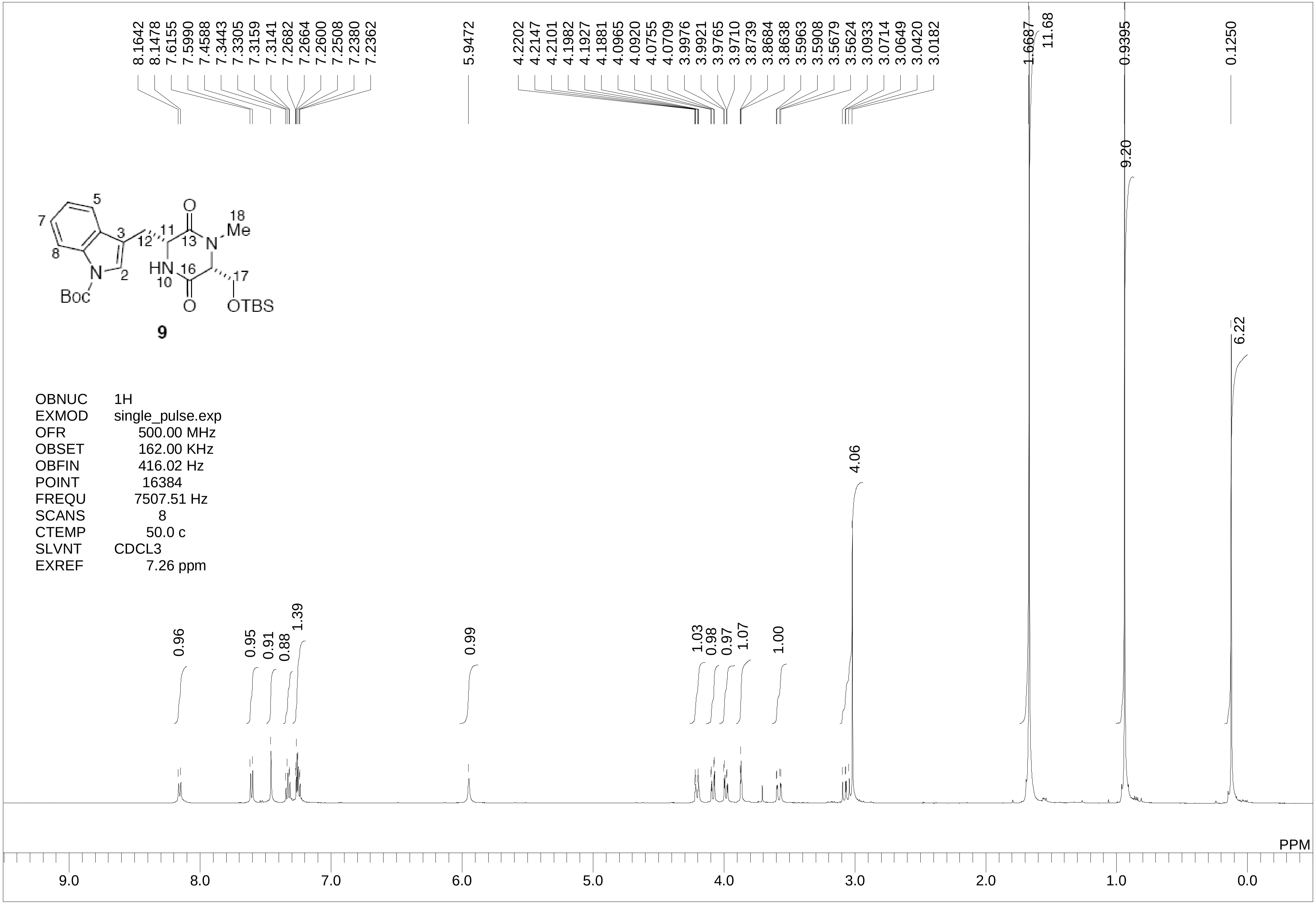
**S-18**

OBNUC 1H
EXMOD single_pulse.exp
OFR 500.00 MHz
OBSET 162.00 KHz
OBFIN 416.02 Hz
POINT 16384
FREQU 7507.51 Hz
SCANS 8
CTEMP 50.0 c
SLVNT DMSO
EXREF 7.26 ppm



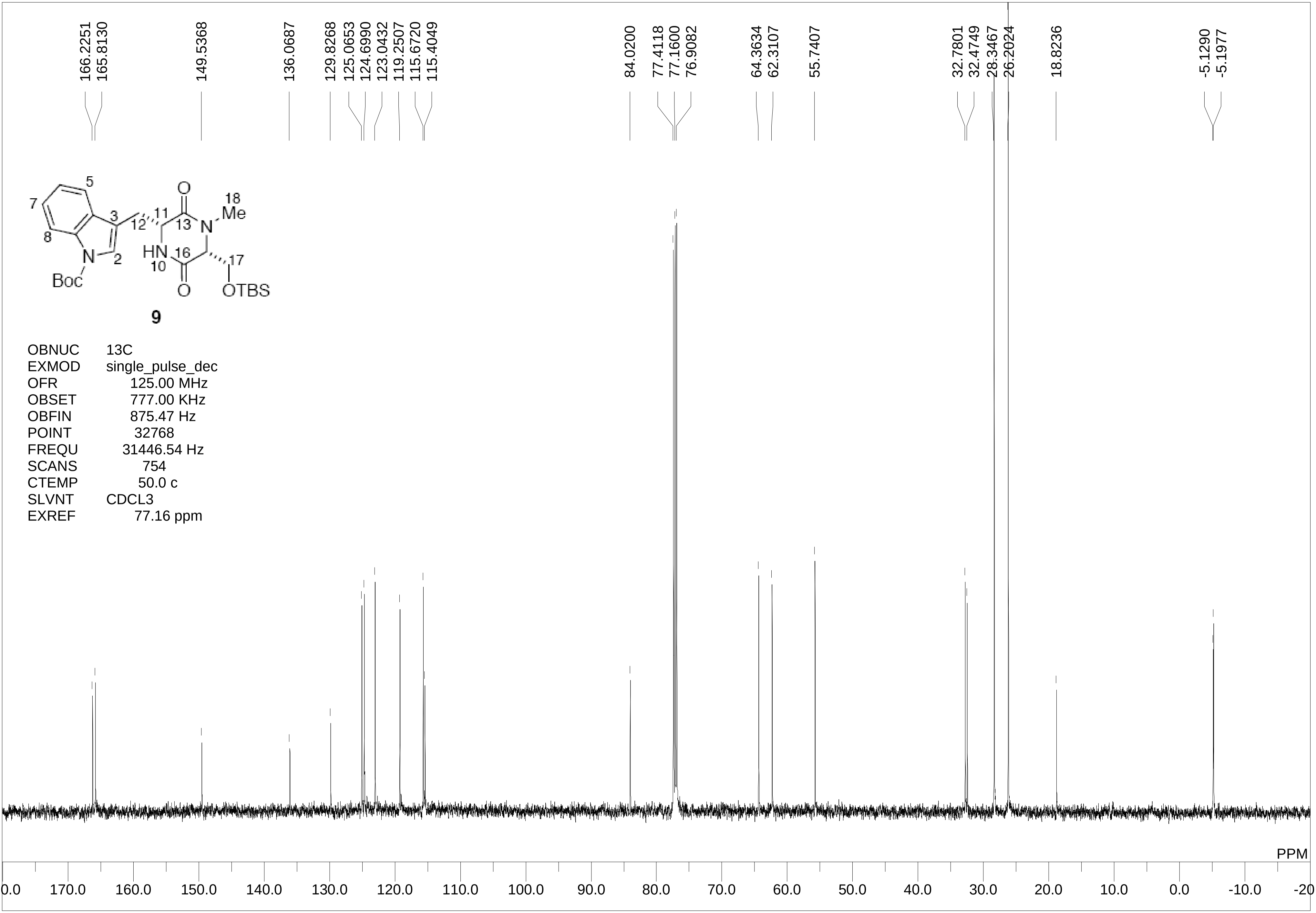
**S-18**

| | |
|---|---|
| OBNUC | 13C |
| EXMOD | single_pulse_dec |
| OFR | 125.00 MHz |
| OBSET | 777.00 KHz |
| OBFIN | 875.47 Hz |
| POINT | 32768 |
| FREQU | 31446.54 Hz |
| SCANS | 782 |
| CTEMP | 50.0 c |
| SLVNT | CDCL3 |
| EXREF | 77.16 ppm |



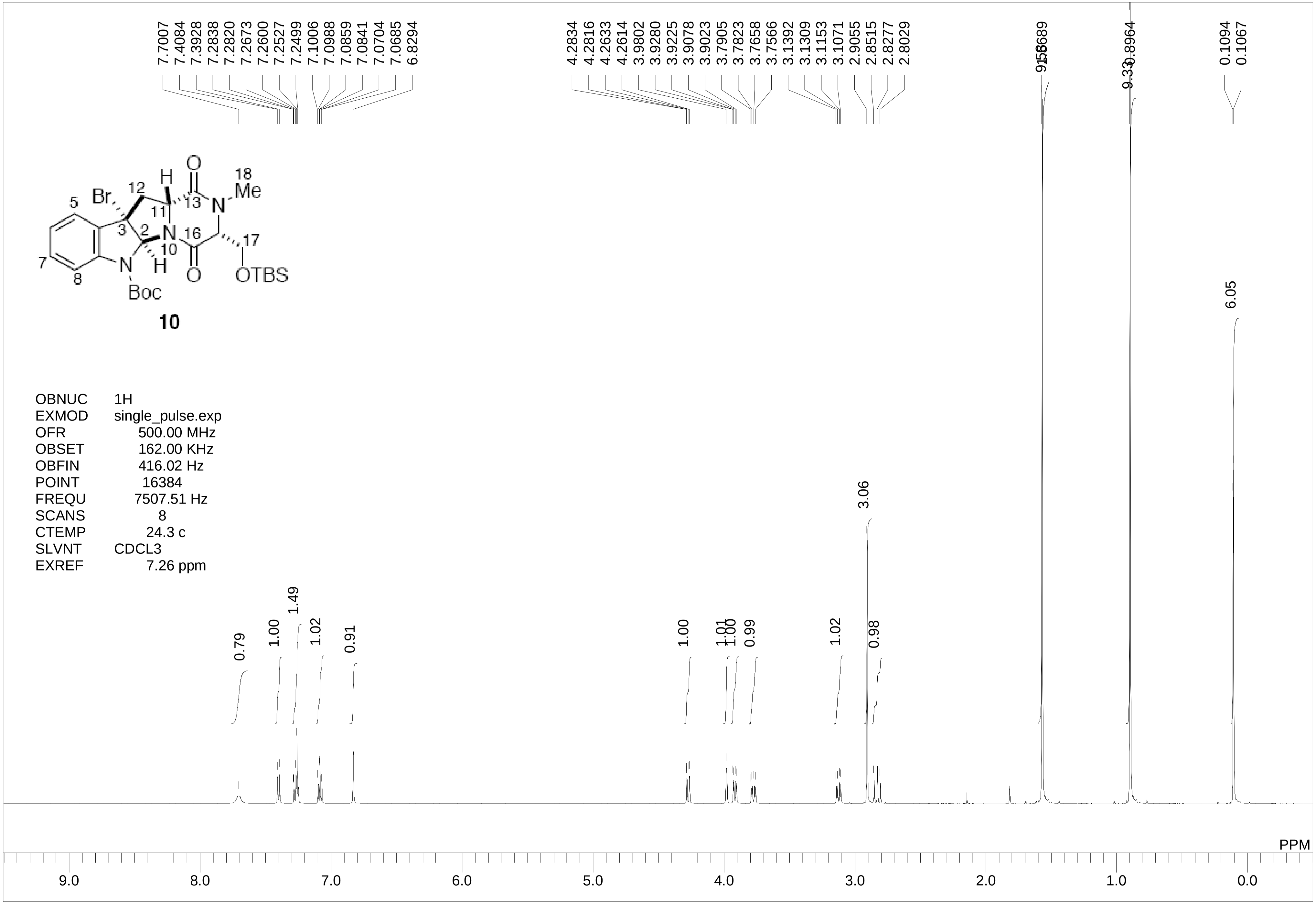
**9**

OBNUC 1H
EXMOD single_pulse.exp
OFR 500.00 MHz
OBSET 162.00 KHz
OBFIN 416.02 Hz
POINT 16384
FREQU 7507.51 Hz
SCANS 8
CTEMP 50.0 c
SLVNT CDCL3
EXREF 7.26 ppm



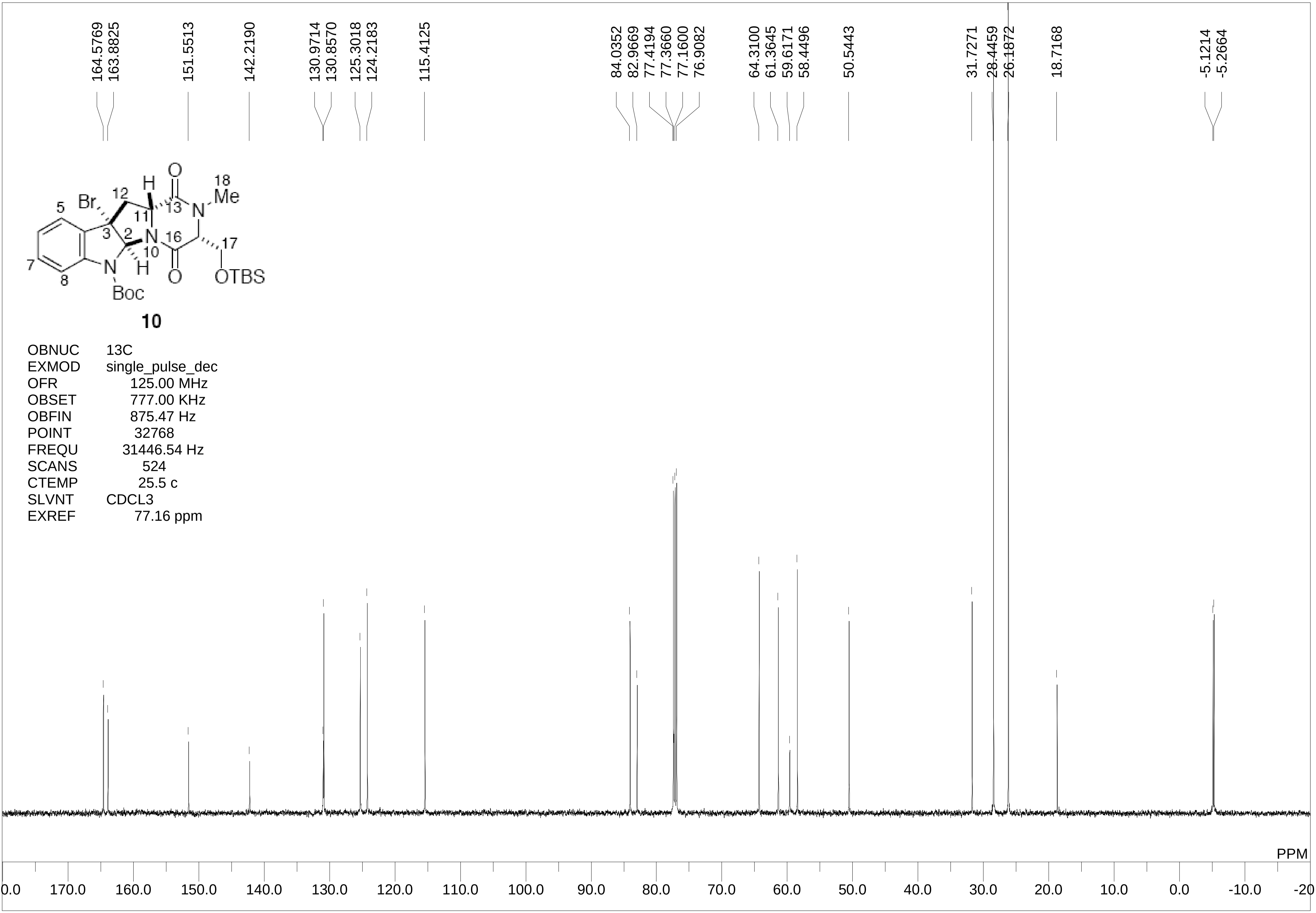
**9**

| | |
|---|---|
| OBNUC | 13C |
| EXMOD | single_pulse_dec |
| OFR | 125.00 MHz |
| OBSET | 777.00 KHz |
| OBFIN | 875.47 Hz |
| POINT | 32768 |
| FREQU | 31446.54 Hz |
| SCANS | 754 |
| CTEMP | 50.0 c |
| SLVNT | CDCL3 |
| EXREF | 77.16 ppm |



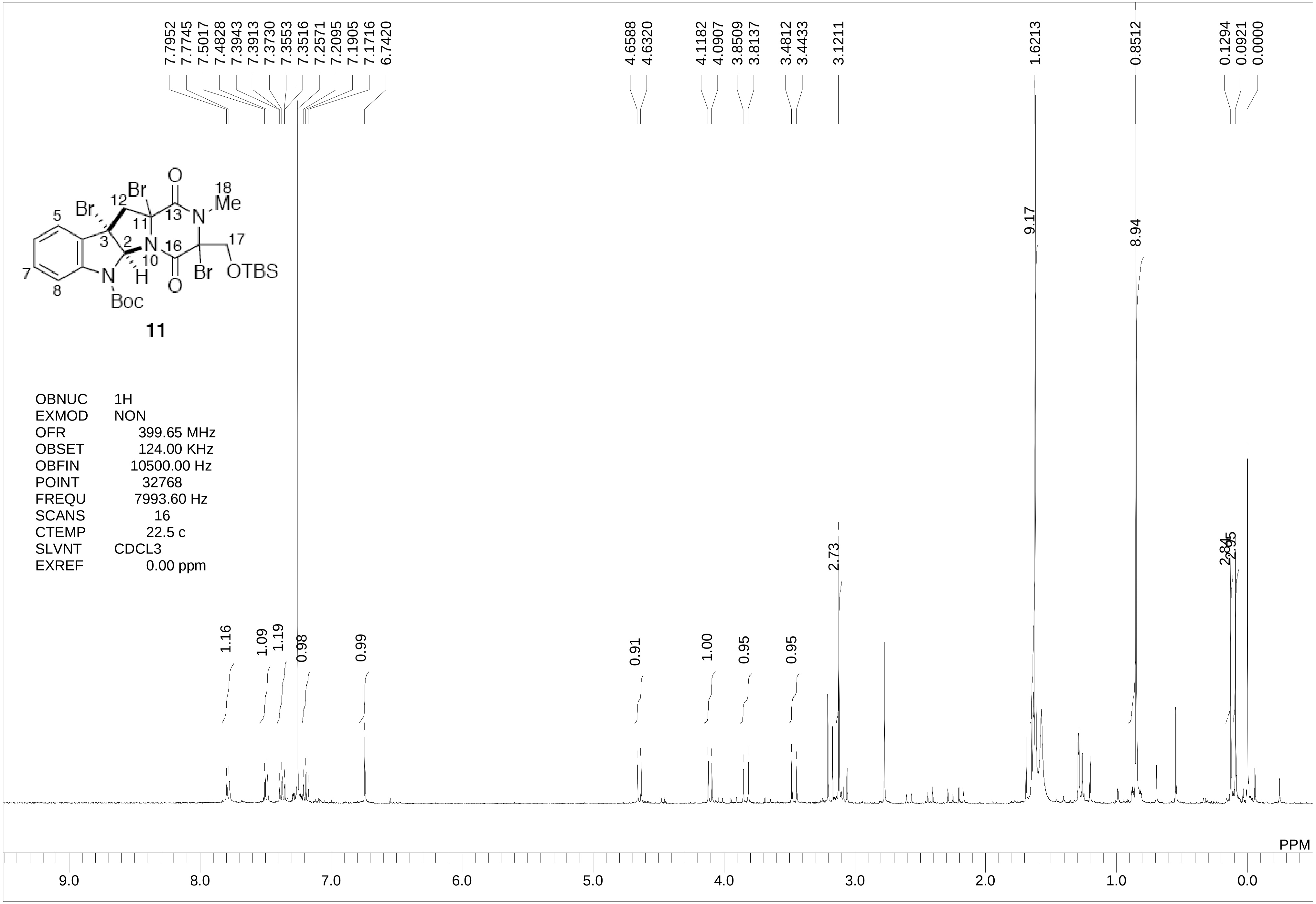
**10**

OBNUC 1H
EXMOD single_pulse.exp
OFR 500.00 MHz
OBSET 162.00 KHz
OBFIN 416.02 Hz
POINT 16384
FREQU 7507.51 Hz
SCANS 8
CTEMP 24.3 c
SLVNT CDCL3
EXREF 7.26 ppm



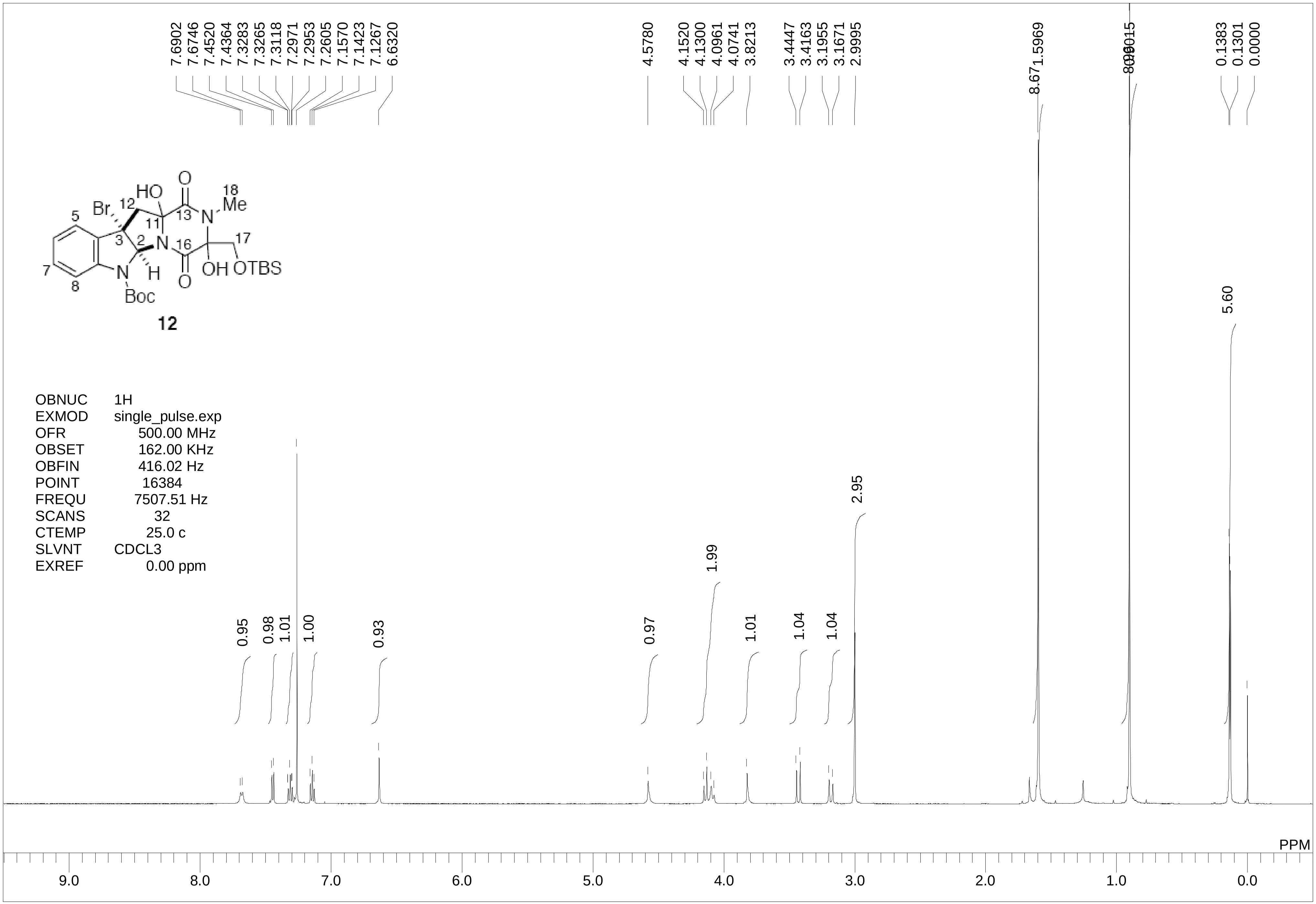
**10**

| | |
|---|---|
| OBNUC | 13C |
| EXMOD | single_pulse_dec |
| OFR | 125.00 MHz |
| OBSET | 777.00 KHz |
| OBFIN | 875.47 Hz |
| POINT | 32768 |
| FREQU | 31446.54 Hz |
| SCANS | 524 |
| CTEMP | 25.5 c |
| SLVNT | CDCL3 |
| EXREF | 77.16 ppm |



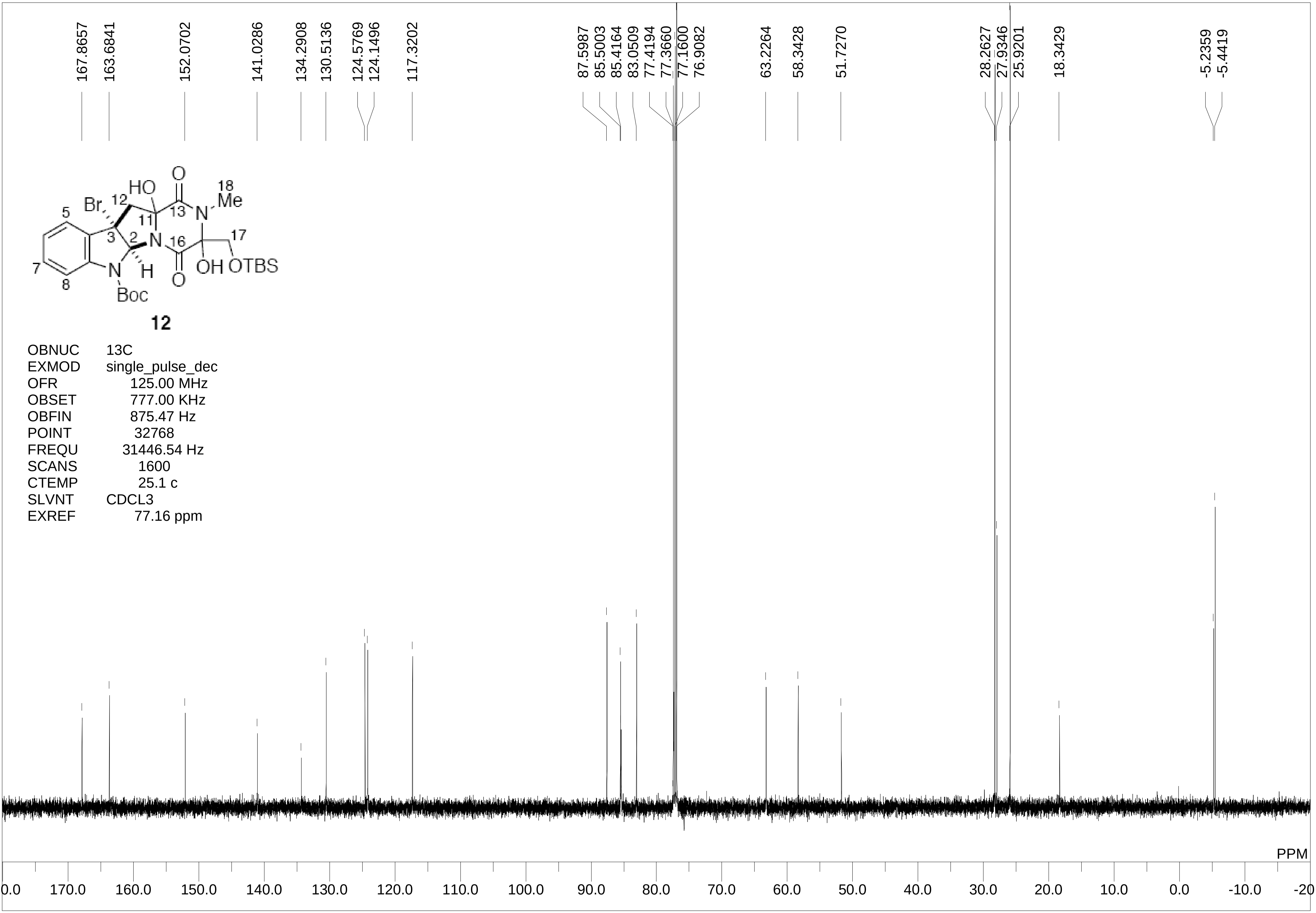
**11**

OBNUC 1H
EXMOD NON
OFR 399.65 MHz
OBSET 124.00 KHz
OBFIN 10500.00 Hz
POINT 32768
FREQU 7993.60 Hz
SCANS 16
CTEMP 22.5 c
SLVNT CDCL3
EXREF 0.00 ppm



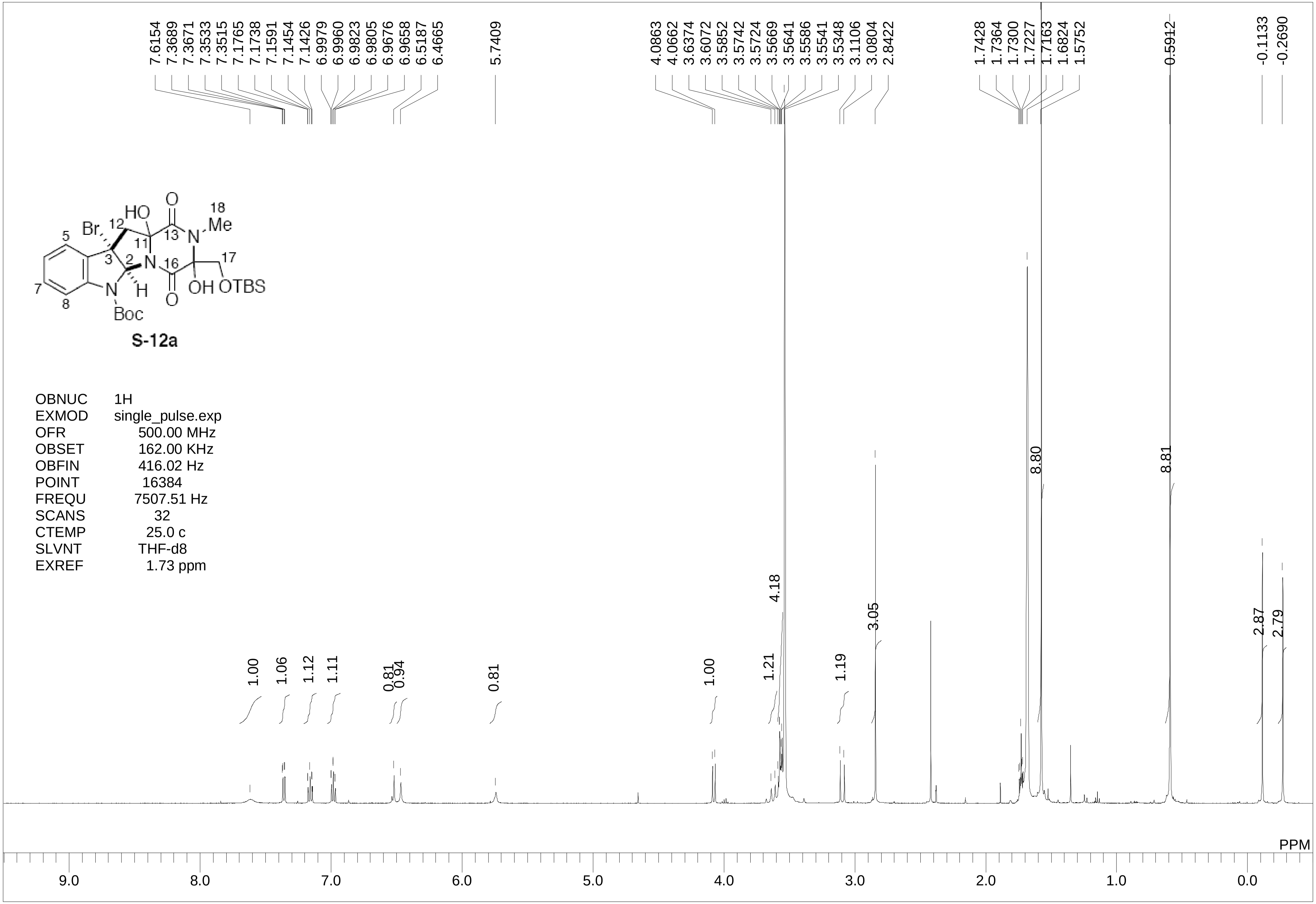
**12**

OBNUC 1H
EXMOD single_pulse.exp
OFR 500.00 MHz
OBSET 162.00 KHz
OBFIN 416.02 Hz
POINT 16384
FREQU 7507.51 Hz
SCANS 32
CTEMP 25.0 c
SLVNT CDCL3
EXREF 0.00 ppm



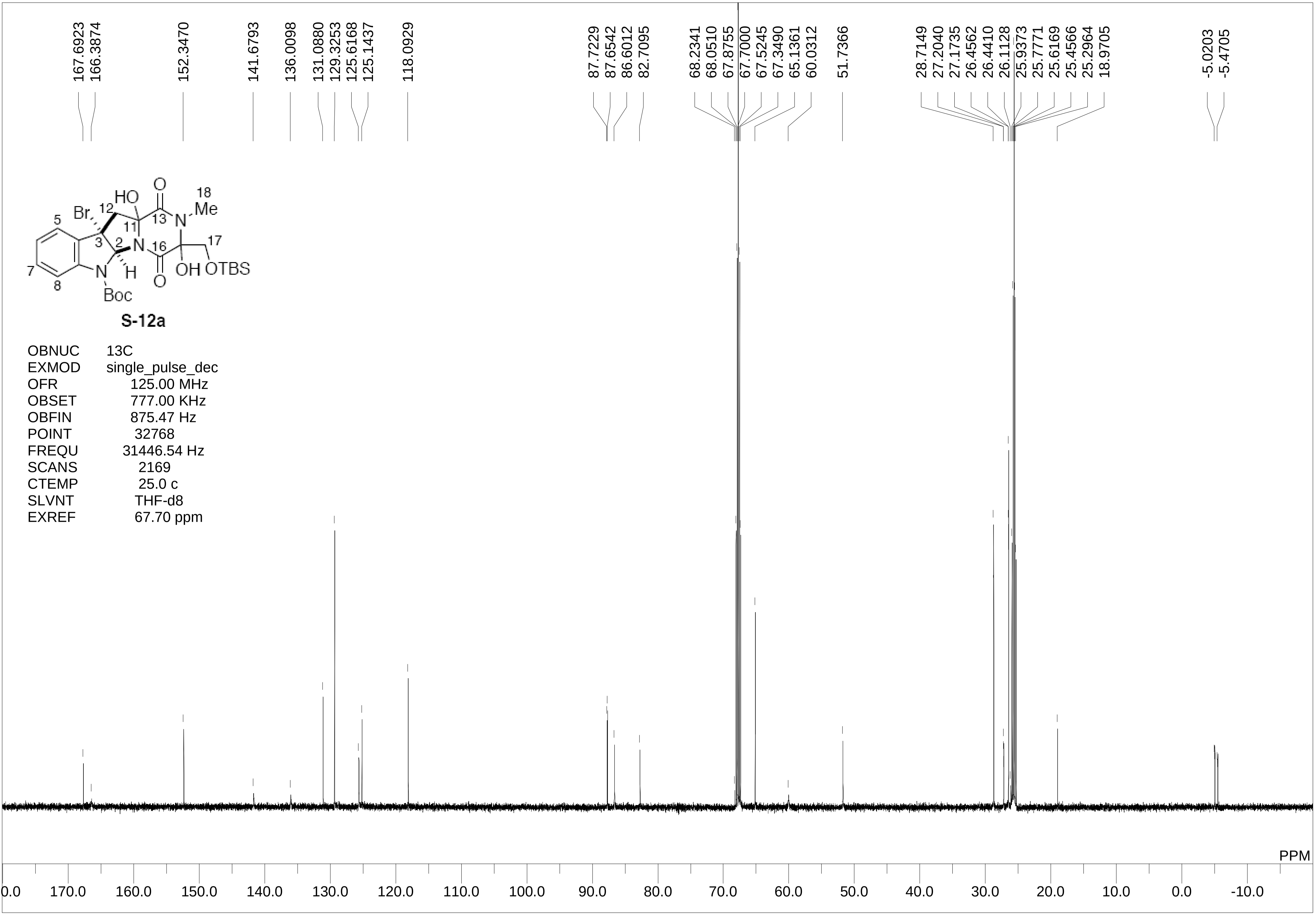
**12**

| | |
|---|---|
| OBNUC | 13C |
| EXMOD | single_pulse_dec |
| OFR | 125.00 MHz |
| OBSET | 777.00 KHz |
| OBFIN | 875.47 Hz |
| POINT | 32768 |
| FREQU | 31446.54 Hz |
| SCANS | 1600 |
| CTEMP | 25.1 c |
| SLVNT | CDCL3 |
| EXREF | 77.16 ppm |



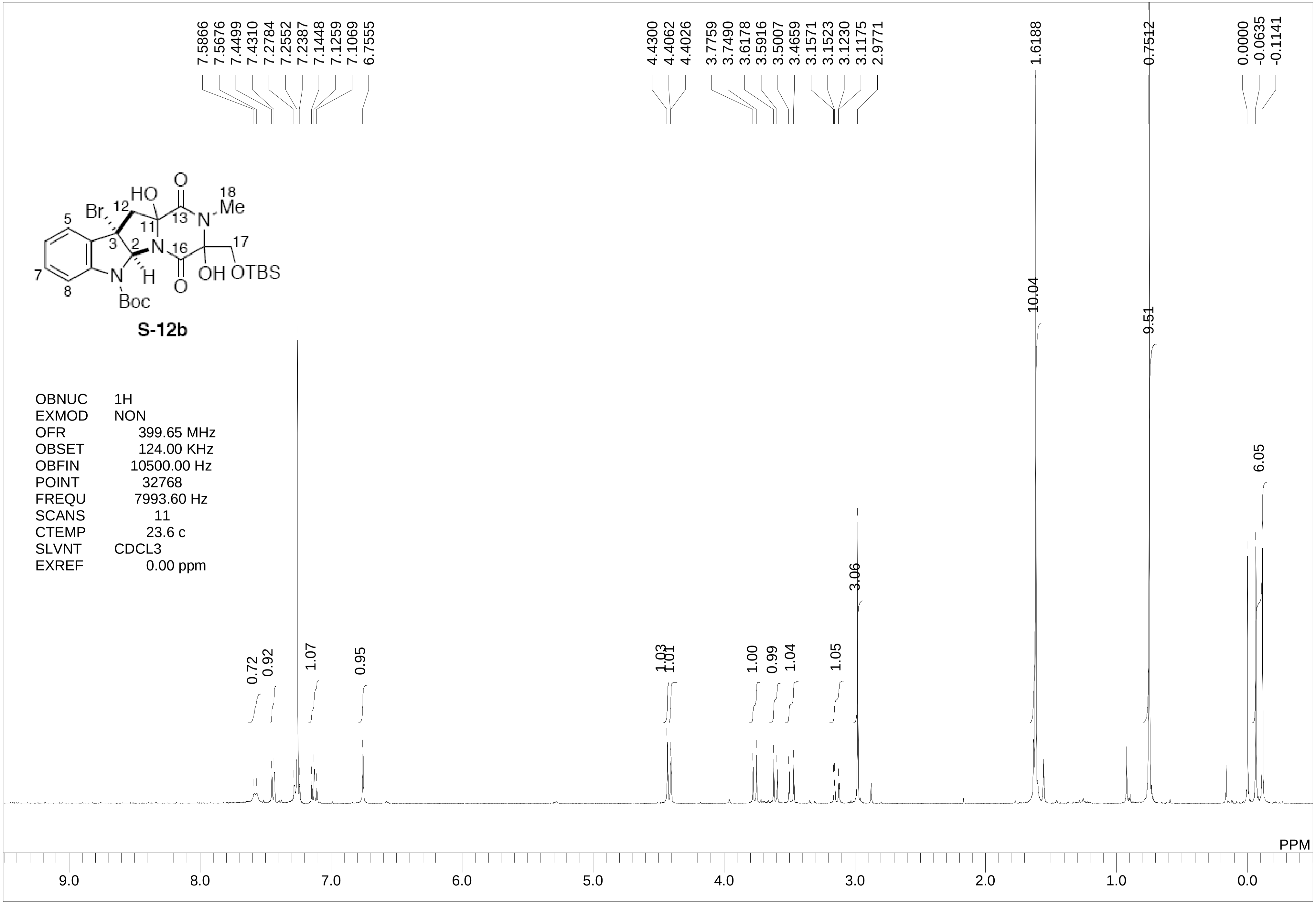
**S-12a**

| | |
|---|---|
| OBNUC | 1H |
| EXMOD | single_pulse.exp |
| OFR | 500.00 MHz |
| OBSET | 162.00 KHz |
| OBFIN | 416.02 Hz |
| POINT | 16384 |
| FREQU | 7507.51 Hz |
| SCANS | 32 |
| CTEMP | 25.0 c |
| SLVNT | THF-d8 |
| EXREF | 1.73 ppm |



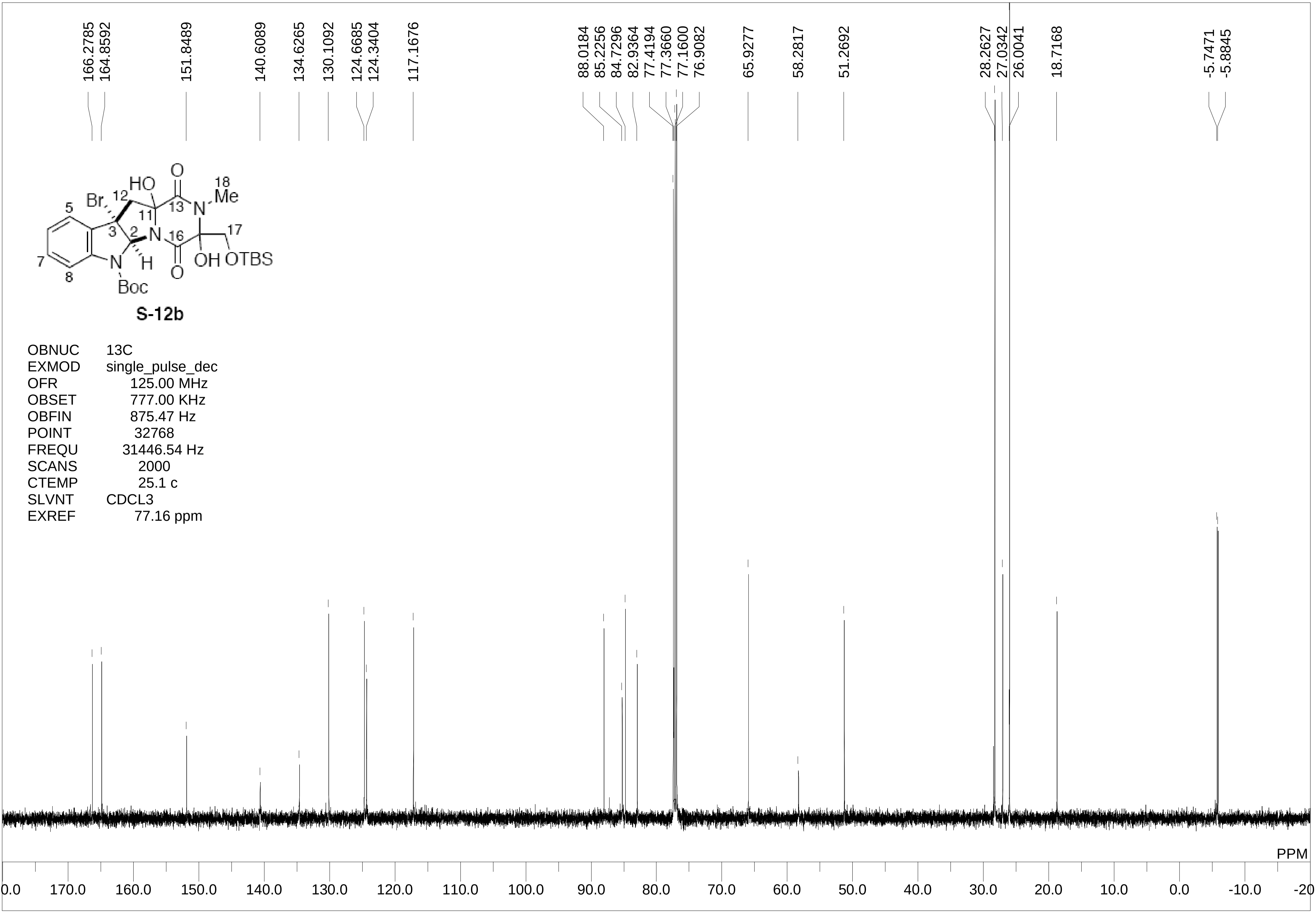
**S-12a**

| | |
|---|---|
| OBNUC | 13C |
| EXMOD | single_pulse_dec |
| OFR | 125.00 MHz |
| OBSET | 777.00 KHz |
| OBFIN | 875.47 Hz |
| POINT | 32768 |
| FREQU | 31446.54 Hz |
| SCANS | 2169 |
| CTEMP | 25.0 c |
| SLVNT | THF-d8 |
| EXREF | 67.70 ppm |



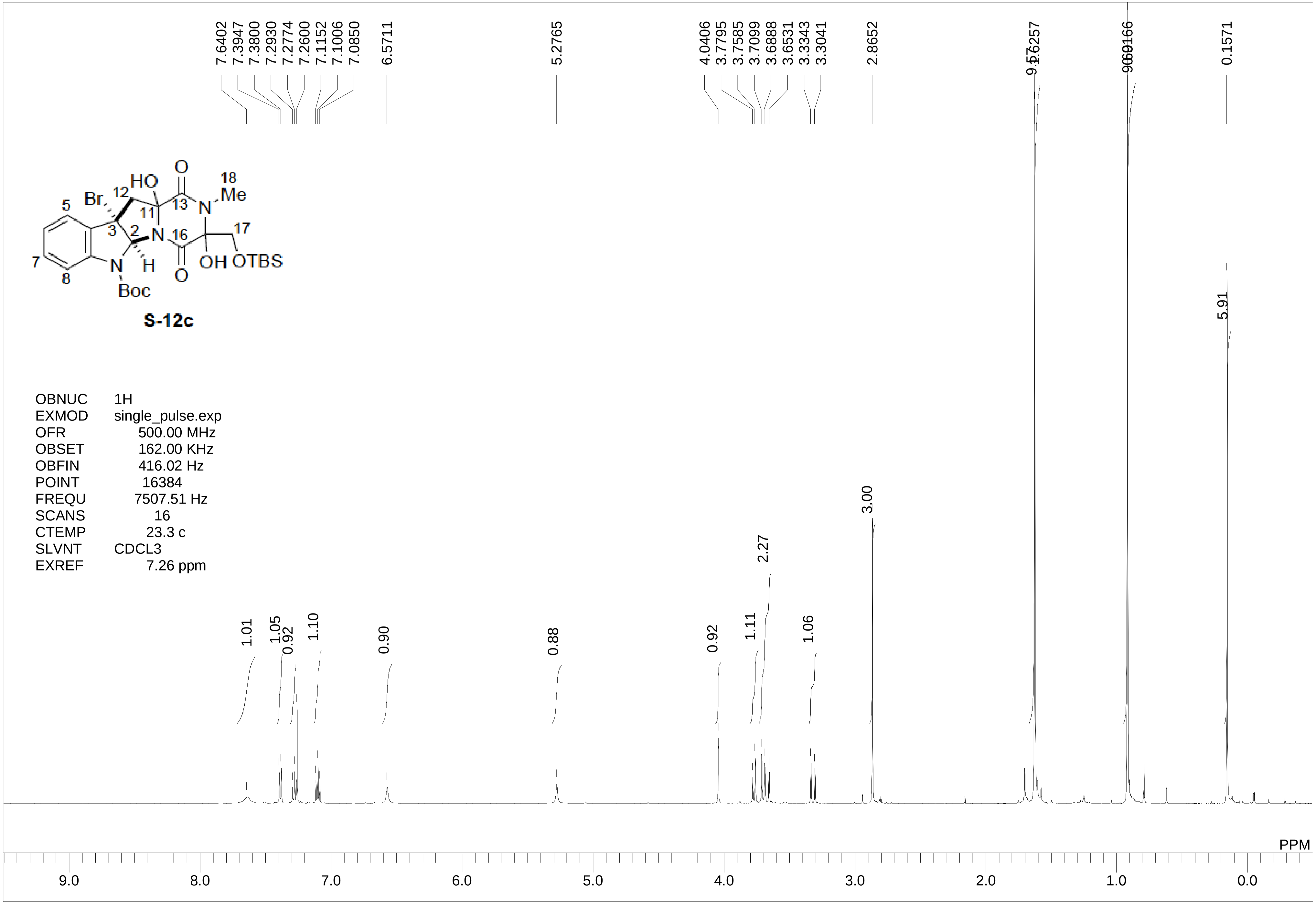
**S-12b**

OBNUC 1H
EXMOD NON
OFR 399.65 MHz
OBSET 124.00 KHz
OBFIN 10500.00 Hz
POINT 32768
FREQU 7993.60 Hz
SCANS 11
CTEMP 23.6 c
SLVNT CDCL3
EXREF 0.00 ppm



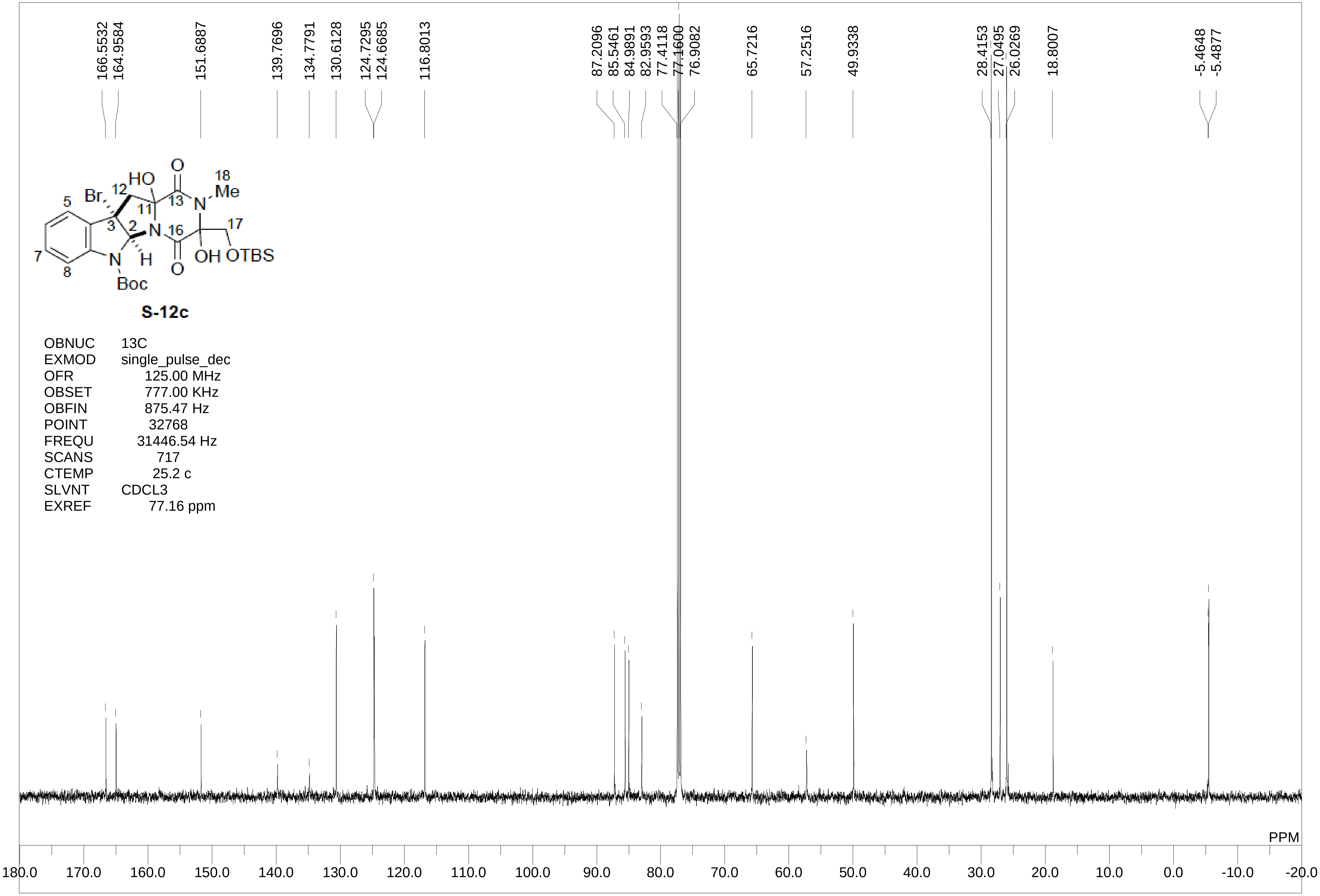
**S-12b**

| | |
|---|---|
| OBNUC | 13C |
| EXMOD | single_pulse_dec |
| OFR | 125.00 MHz |
| OBSET | 777.00 KHz |
| OBFIN | 875.47 Hz |
| POINT | 32768 |
| FREQU | 31446.54 Hz |
| SCANS | 2000 |
| CTEMP | 25.1 c |
| SLVNT | CDCL3 |
| EXREF | 77.16 ppm |



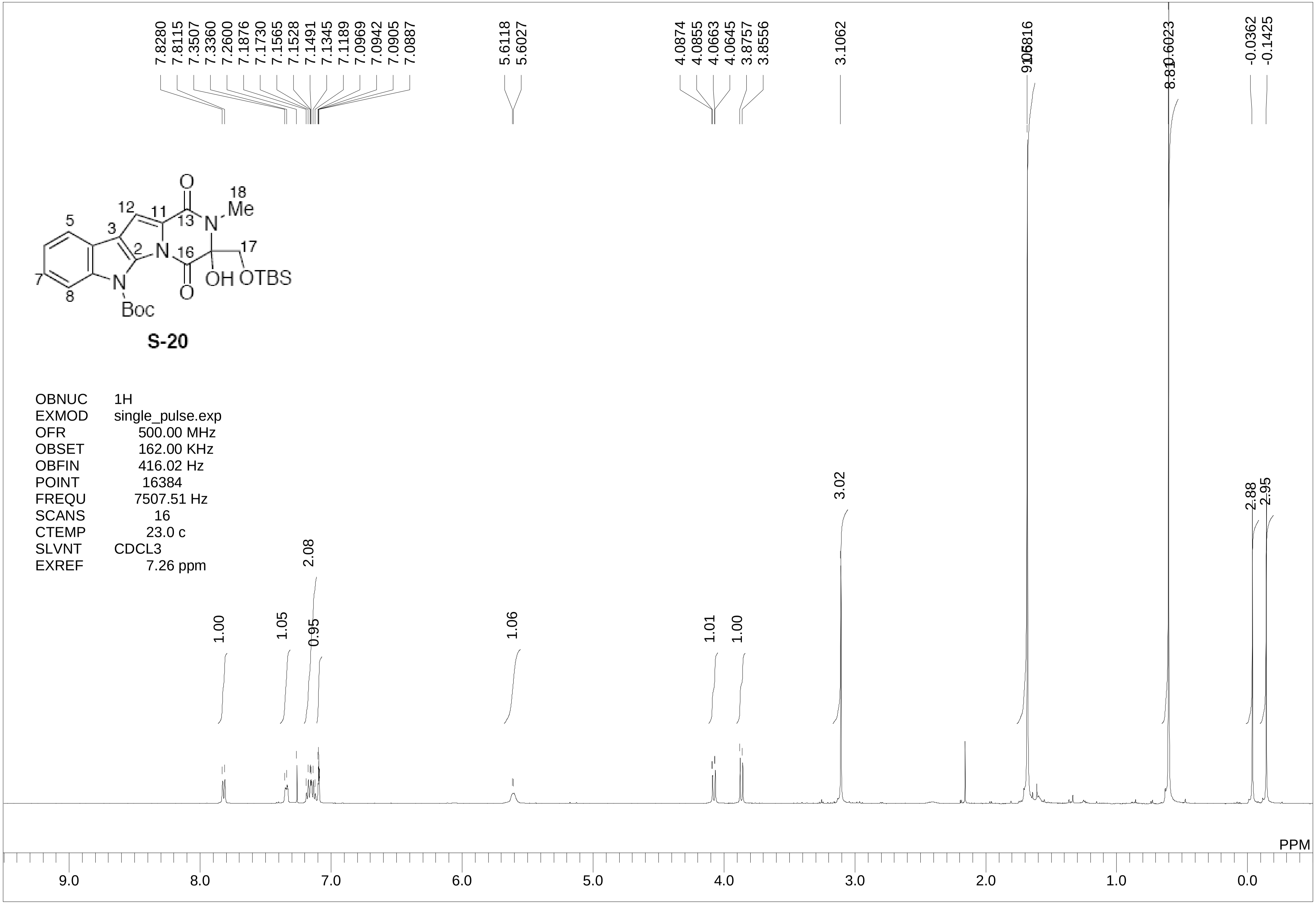
**S-12c**

| | |
|---|---|
| OBNUC | 1H |
| EXMOD | single_pulse.exp |
| OFR | 500.00 MHz |
| OBSET | 162.00 KHz |
| OBFIN | 416.02 Hz |
| POINT | 16384 |
| FREQU | 7507.51 Hz |
| SCANS | 16 |
| CTEMP | 23.3 c |
| SLVNT | CDCL3 |
| EXREF | 7.26 ppm |



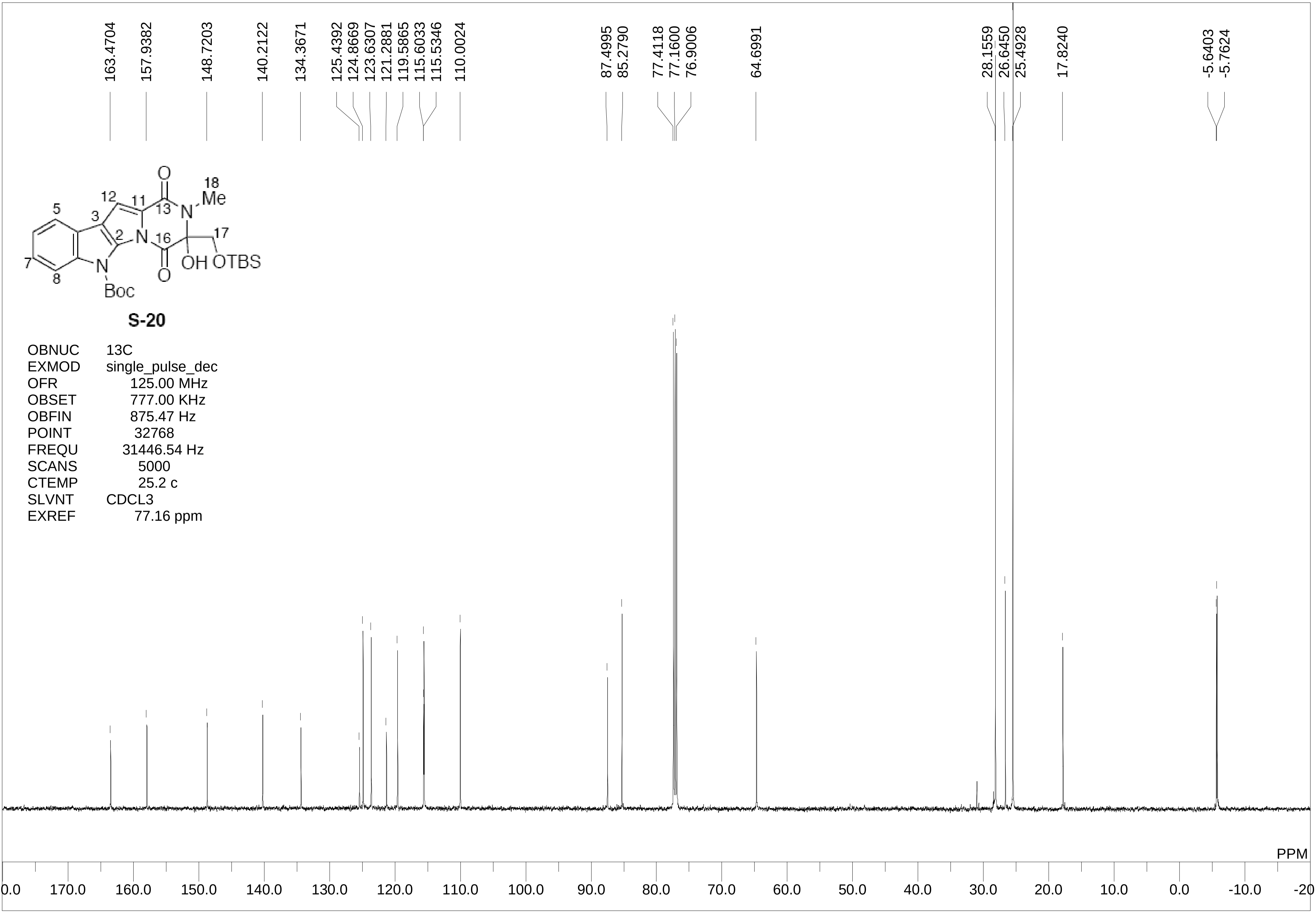
**S-12c**

OBNUC 13C
EXMOD single_pulse_dec
OFR 125.00 MHz
OBSET 777.00 KHz
OBFIN 875.47 Hz
POINT 32768
FREQU 31446.54 Hz
SCANS 717
CTEMP 25.2 c
SLVNT CDCL3
EXREF 77.16 ppm



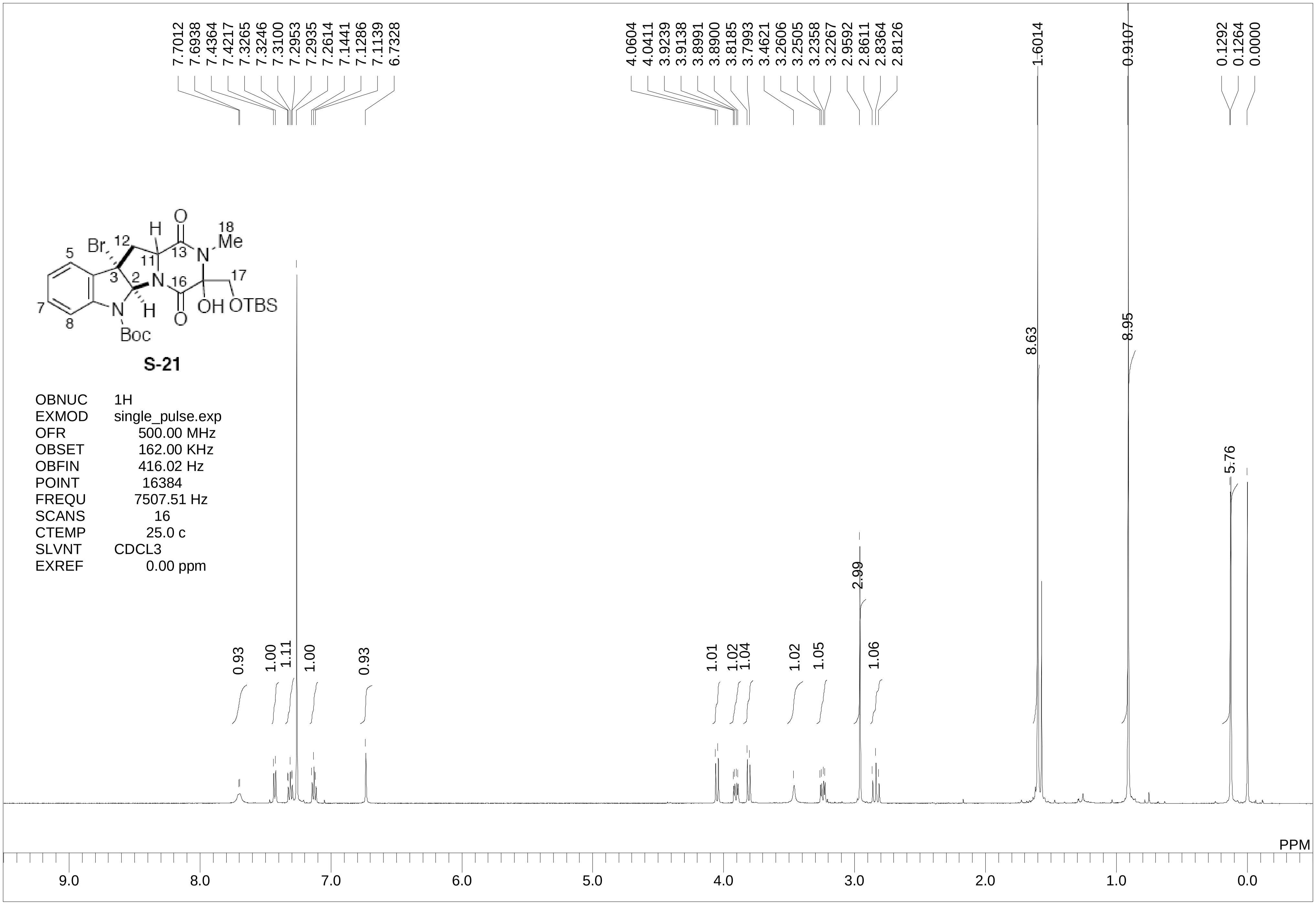
**S-20**

OBNUC 1H
EXMOD single_pulse.exp
OFR 500.00 MHz
OBSET 162.00 KHz
OBFIN 416.02 Hz
POINT 16384
FREQU 7507.51 Hz
SCANS 16
CTEMP 23.0 c
SLVNT CDCL3
EXREF 7.26 ppm



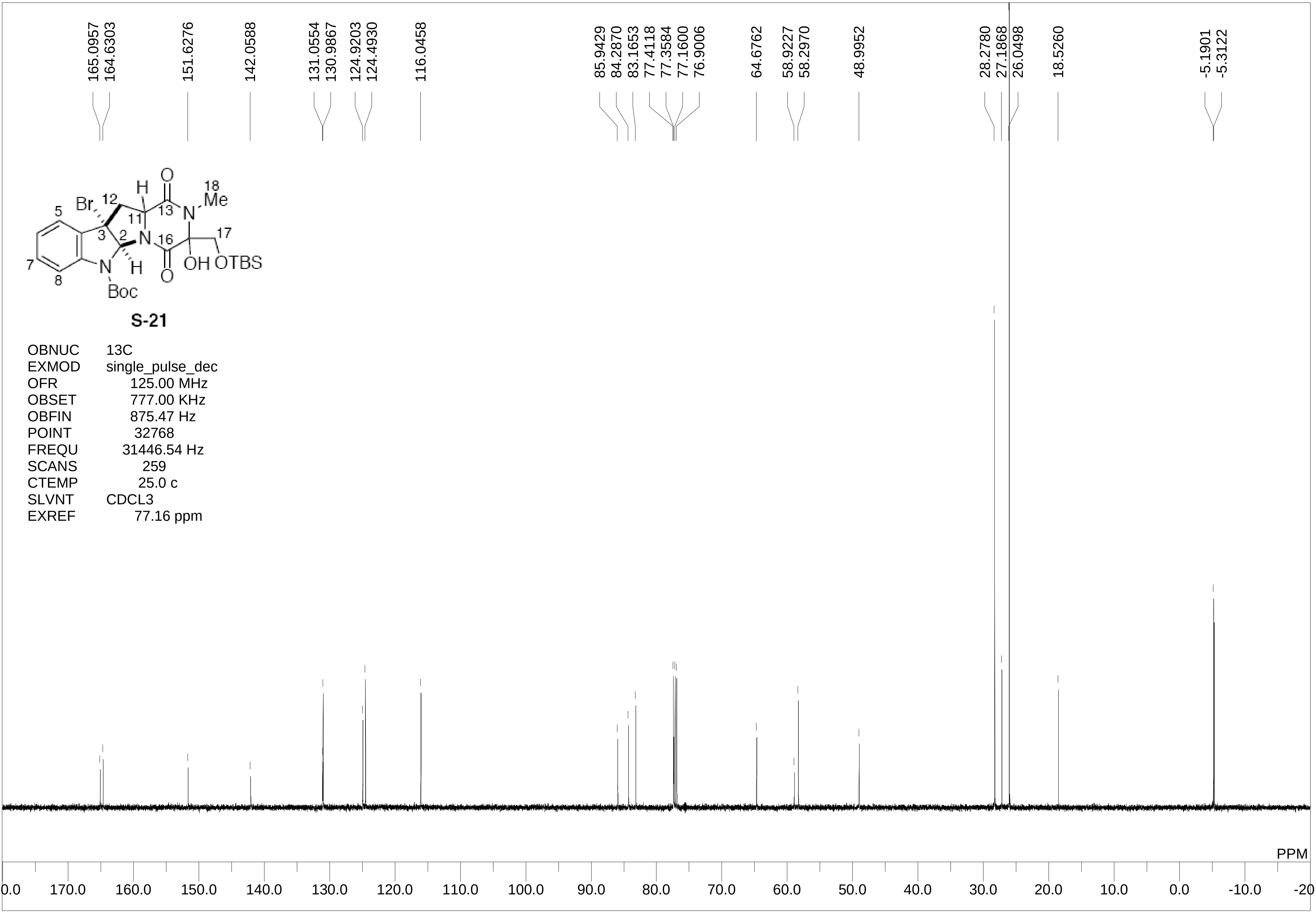
**S-20**

| | |
|---|---|
| OBNUC | 13C |
| EXMOD | single_pulse_dec |
| OFR | 125.00 MHz |
| OBSET | 777.00 KHz |
| OBFIN | 875.47 Hz |
| POINT | 32768 |
| FREQU | 31446.54 Hz |
| SCANS | 5000 |
| CTEMP | 25.2 c |
| SLVNT | CDCL3 |
| EXREF | 77.16 ppm |



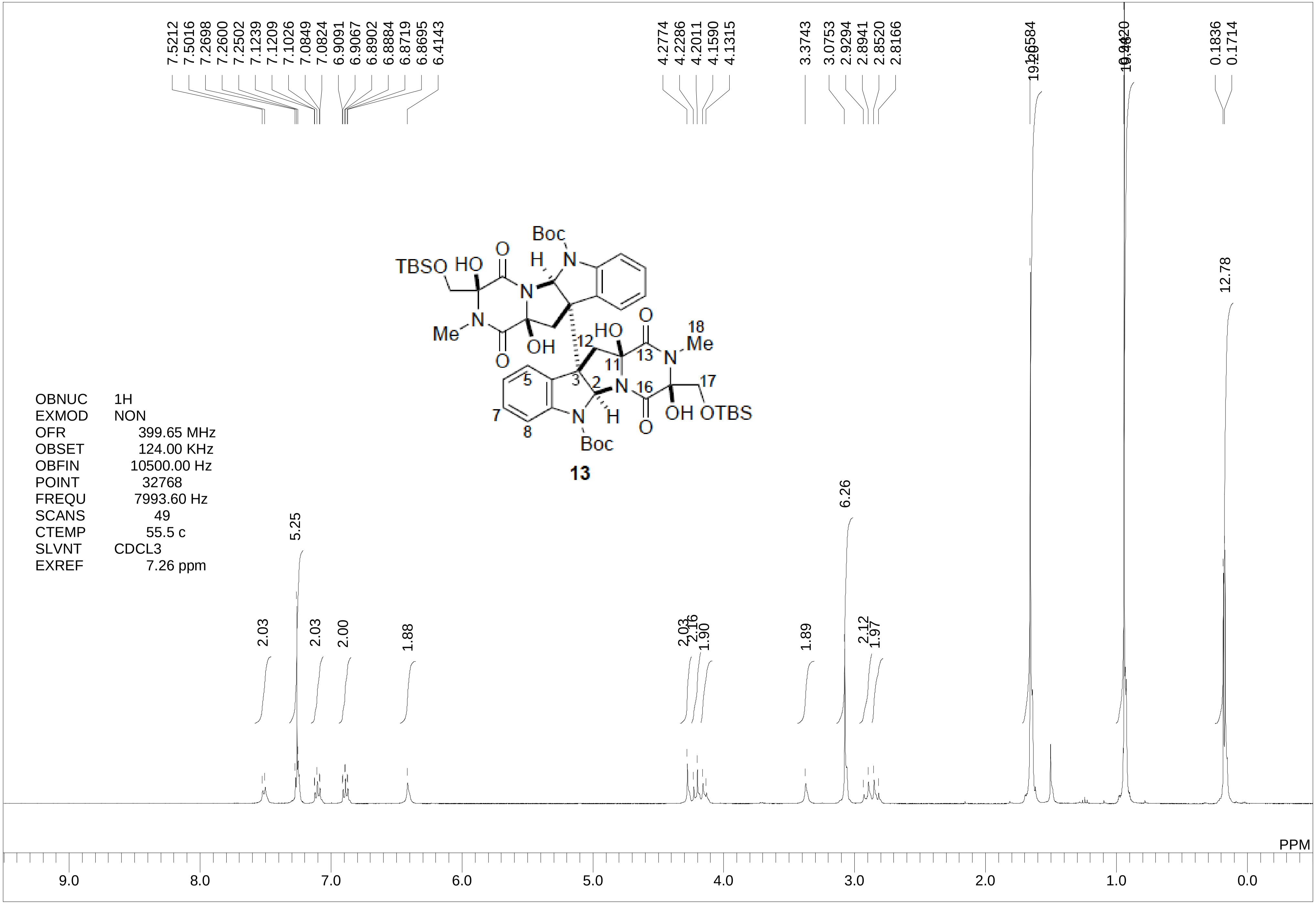
**S-21**

| | |
|---|---|
| OBNUC | 1H |
| EXMOD | single_pulse.exp |
| OFR | 500.00 MHz |
| OBSET | 162.00 KHz |
| OBFIN | 416.02 Hz |
| POINT | 16384 |
| FREQU | 7507.51 Hz |
| SCANS | 16 |
| CTEMP | 25.0 c |
| SLVNT | CDCL3 |
| EXREF | 0.00 ppm |



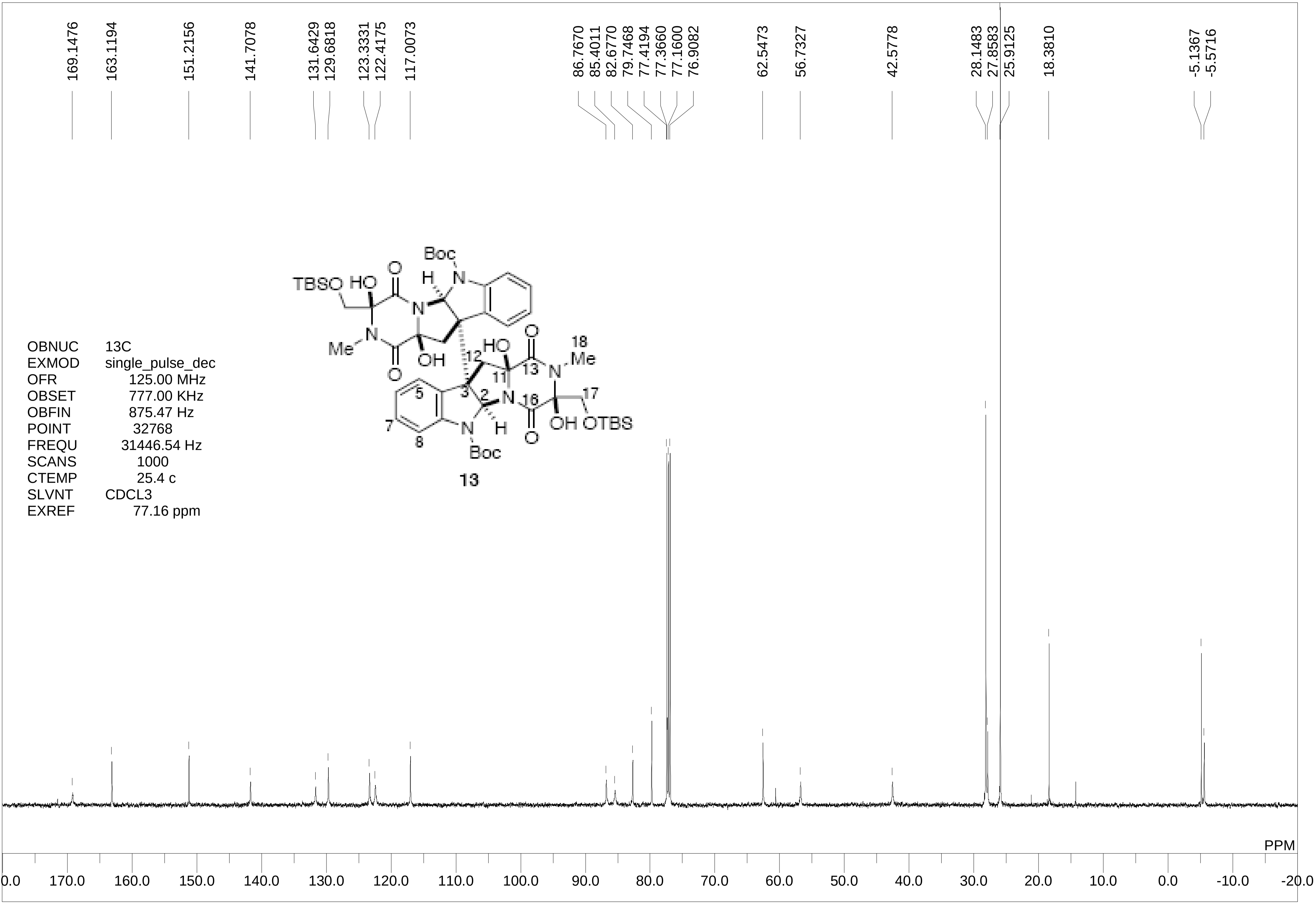
**S-21**

OBNUC 13C
EXMOD single_pulse_dec
OFR 125.00 MHz
OBSET 777.00 KHz
OBFIN 875.47 Hz
POINT 32768
FREQU 31446.54 Hz
SCANS 259
CTEMP 25.0 c
SLVNT CDCL3
EXREF 77.16 ppm



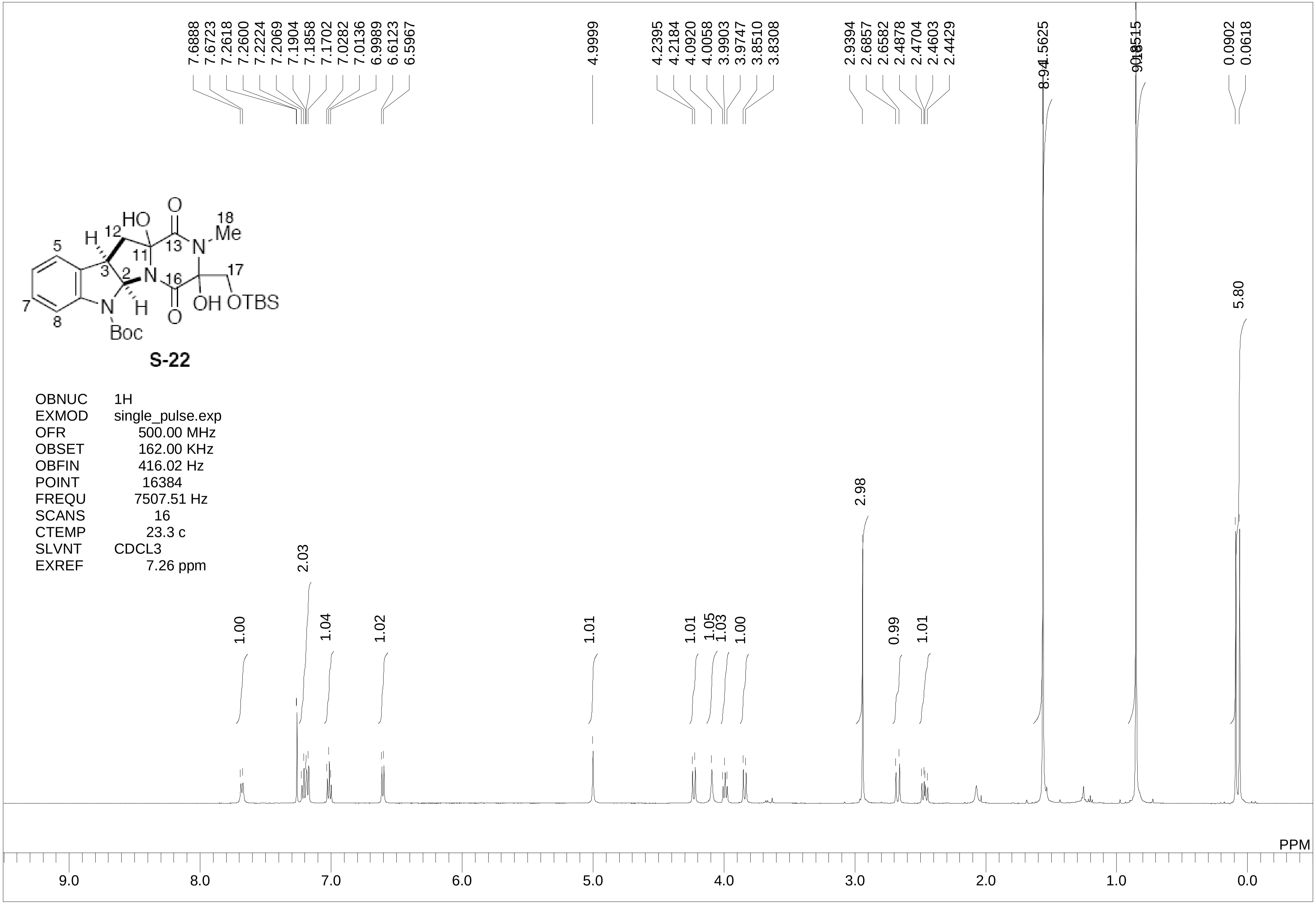
**13**

OBNUC 1H
EXMOD NON
OFR 399.65 MHz
OBSET 124.00 KHz
OBFIN 10500.00 Hz
POINT 32768
FREQU 7993.60 Hz
SCANS 49
CTEMP 55.5 c
SLVNT CDCL3
EXREF 7.26 ppm



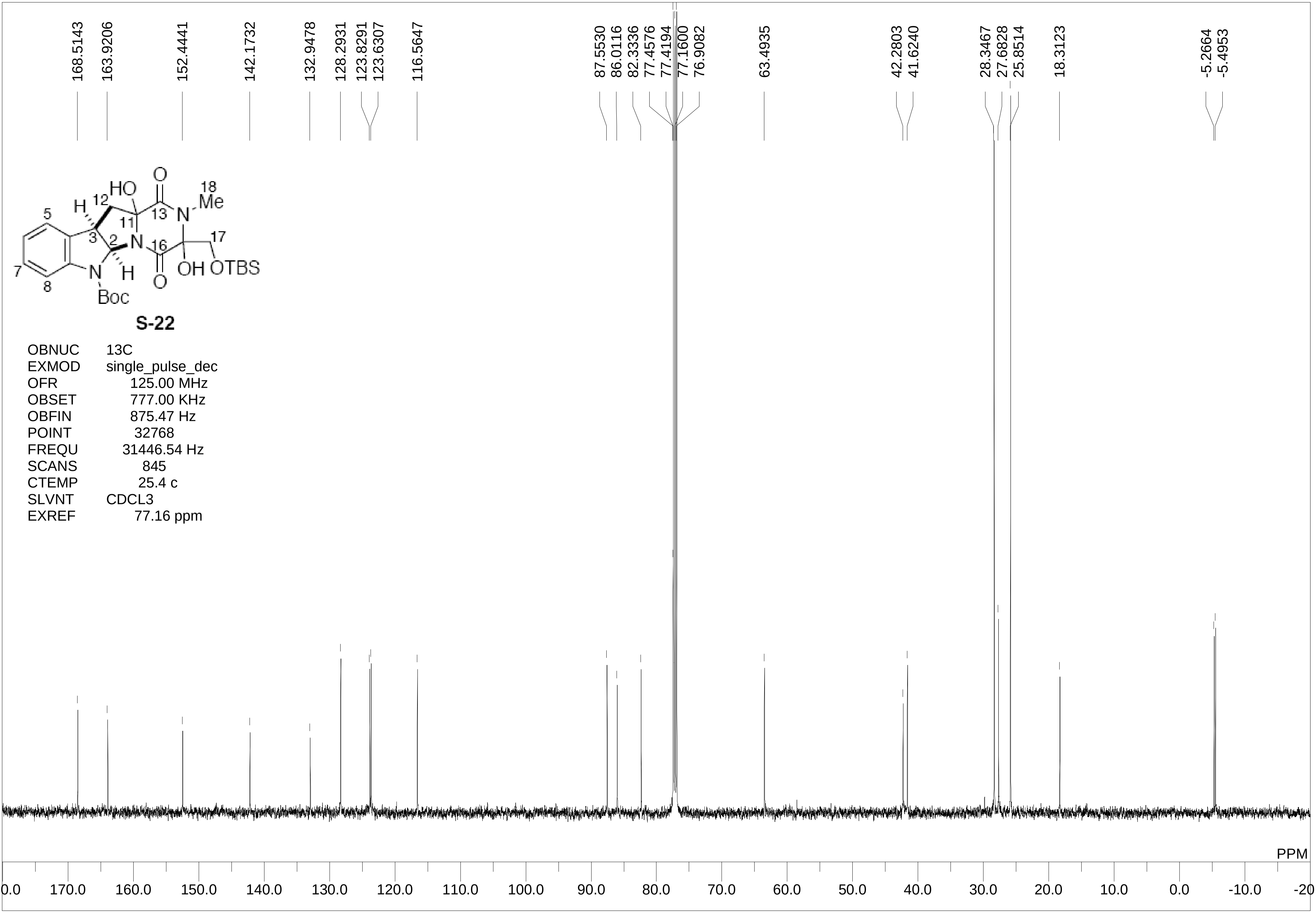
13

OBNUC 13C
EXMOD single_pulse_dec
OFR 125.00 MHz
OBSET 777.00 KHz
OBFIN 875.47 Hz
POINT 32768
FREQU 31446.54 Hz
SCANS 1000
CTEMP 25.4 c
SLVNT CDCL3
EXREF 77.16 ppm



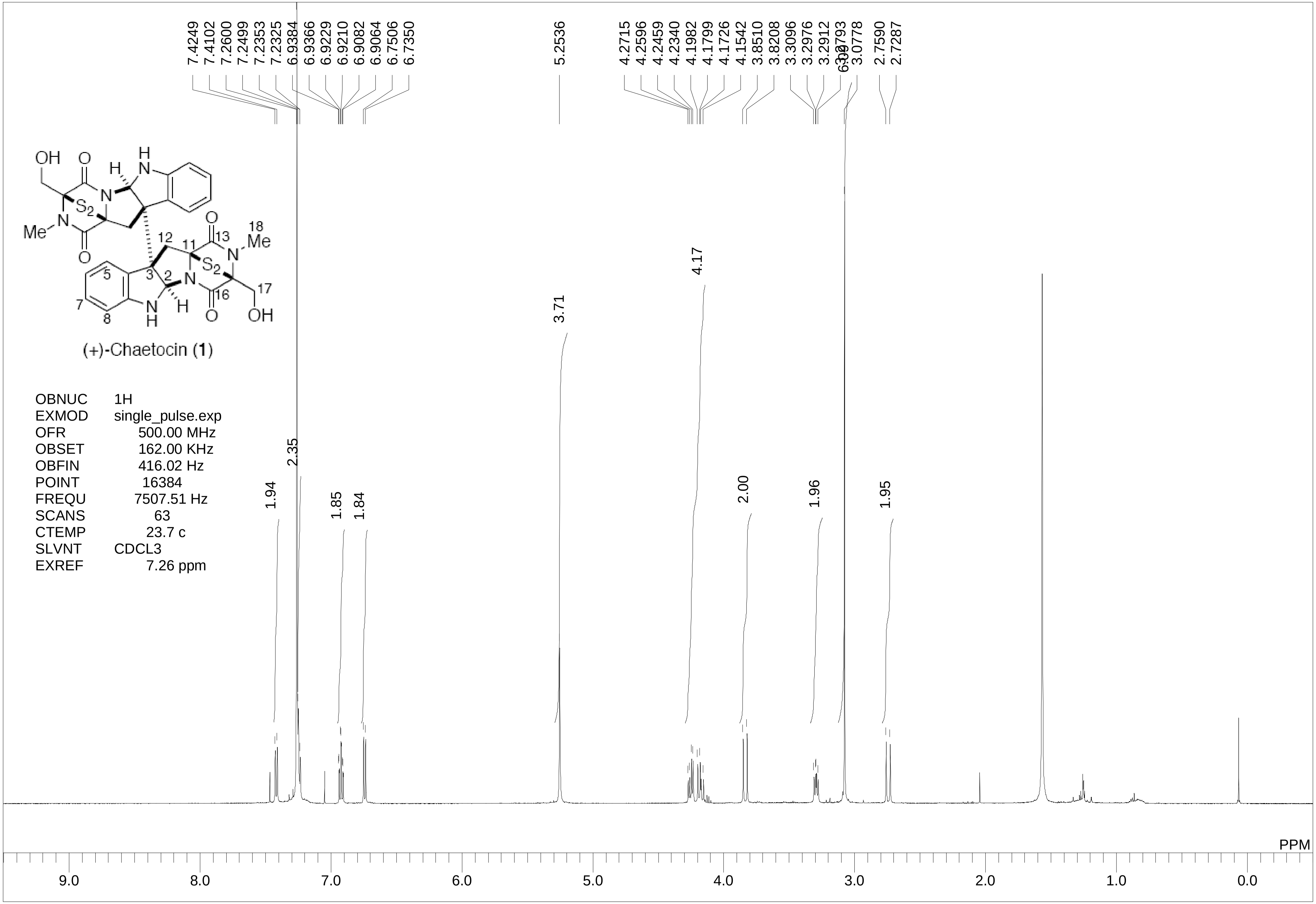
**S-22**

| | |
|---|---|
| OBNUC | 1H |
| EXMOD | single_pulse.exp |
| OFR | 500.00 MHz |
| OBSET | 162.00 KHz |
| OBFIN | 416.02 Hz |
| POINT | 16384 |
| FREQU | 7507.51 Hz |
| SCANS | 16 |
| CTEMP | 23.3 c |
| SLVNT | CDCL3 |
| EXREF | 7.26 ppm |



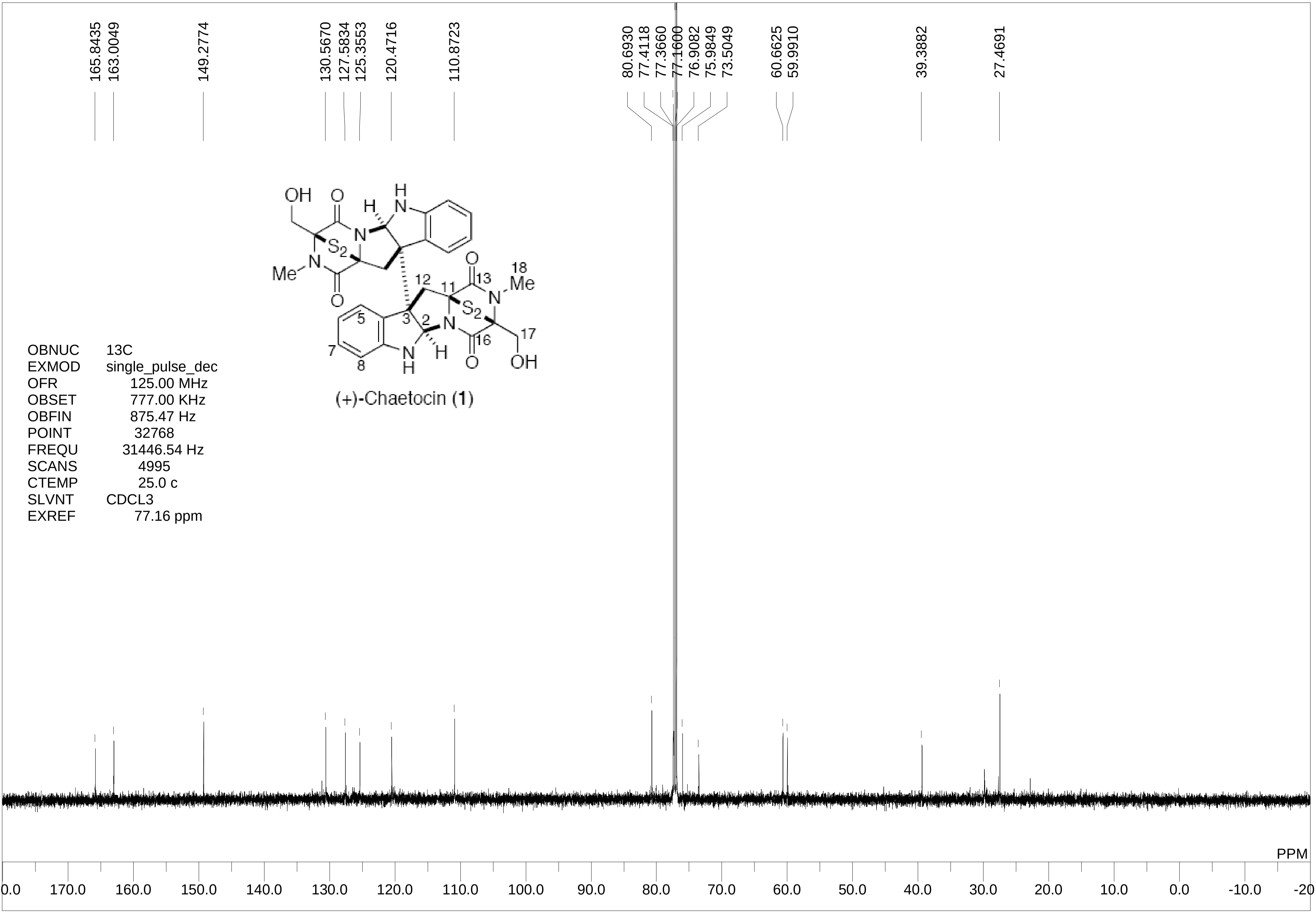
**S-22**

| | |
|---|---|
| OBNUC | 13C |
| EXMOD | single_pulse_dec |
| OFR | 125.00 MHz |
| OBSET | 777.00 KHz |
| OBFIN | 875.47 Hz |
| POINT | 32768 |
| FREQU | 31446.54 Hz |
| SCANS | 845 |
| CTEMP | 25.4 c |
| SLVNT | CDCL3 |
| EXREF | 77.16 ppm |



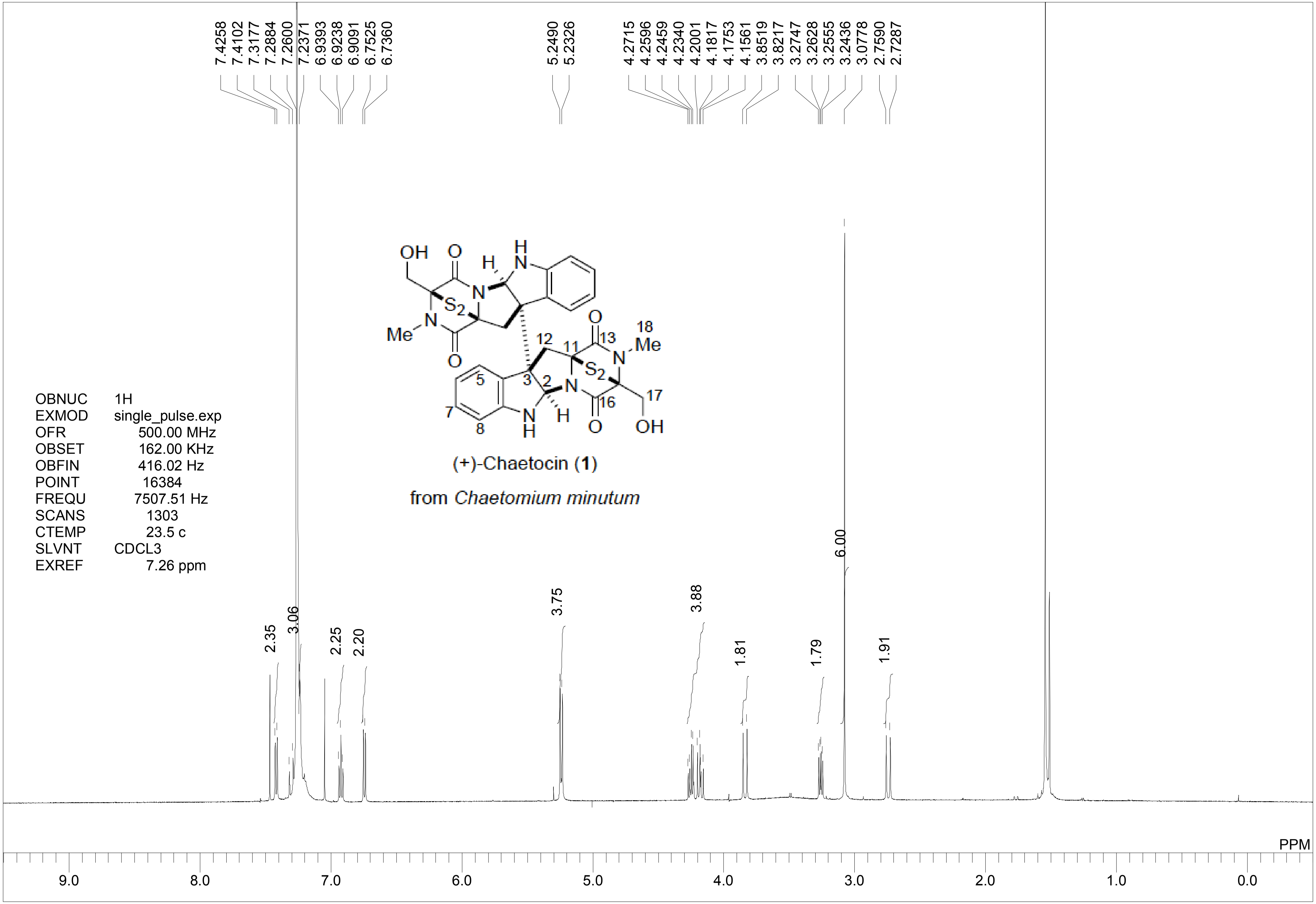
(+)-Chaetocin (**1**)

OBNUC 1H
EXMOD single_pulse.exp
OFR 500.00 MHz
OBSET 162.00 KHz
OBFIN 416.02 Hz
POINT 16384
FREQU 7507.51 Hz
SCANS 63
CTEMP 23.7 c
SLVNT CDCL3
EXREF 7.26 ppm



(+)-Chaetocin (**1**)

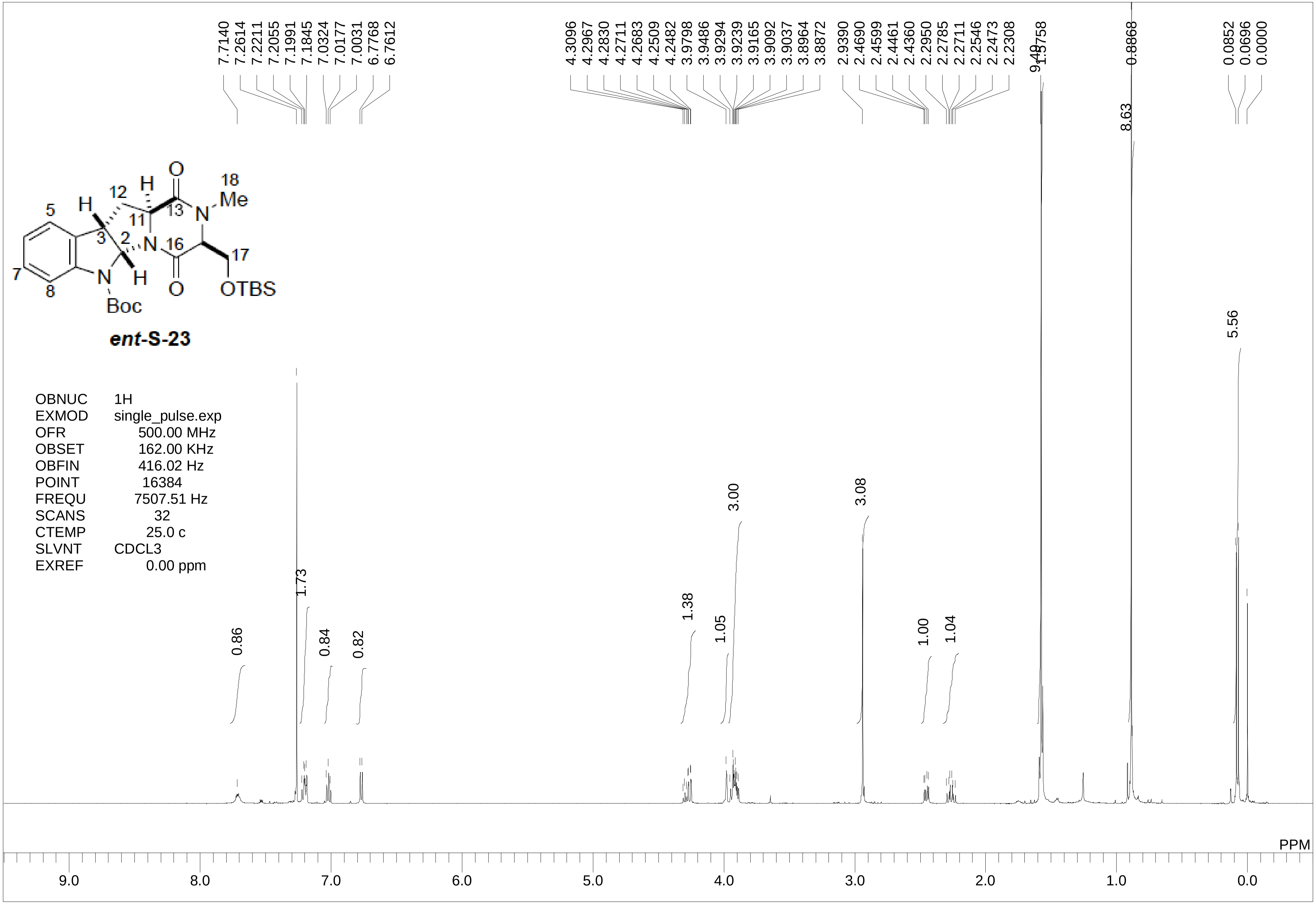
| | |
|---|---|
| OBNUC | 13C |
| EXMOD | single_pulse_dec |
| OFR | 125.00 MHz |
| OBSET | 777.00 KHz |
| OBFIN | 875.47 Hz |
| POINT | 32768 |
| FREQU | 31446.54 Hz |
| SCANS | 4995 |
| CTEMP | 25.0 c |
| SLVNT | CDCL3 |
| EXREF | 77.16 ppm |



(+)-Chaetocin (**1**)

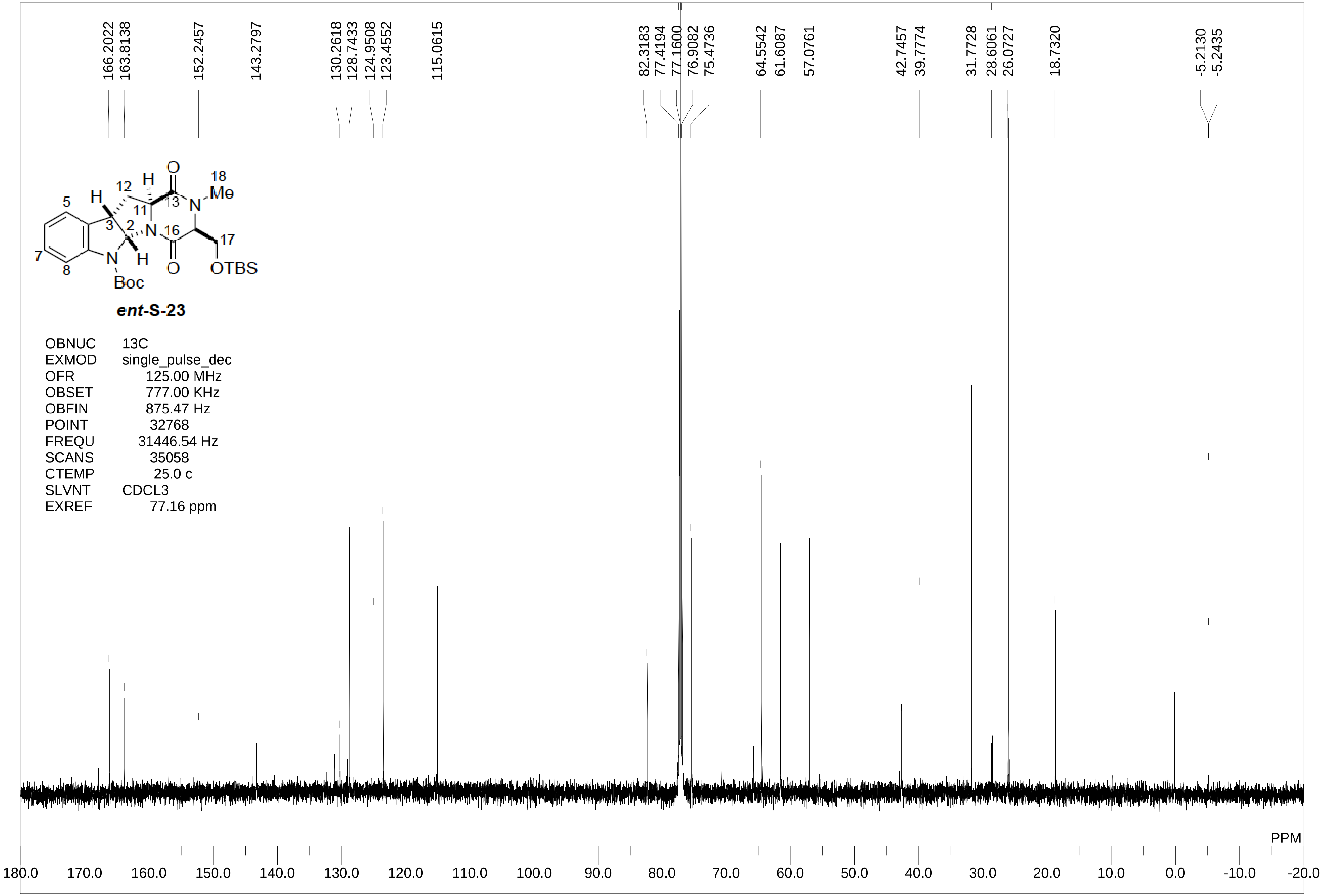
from *Chaetomium minutum*

| | |
|---|---|
| OBNUC | 1H |
| EXMOD | single_pulse.exp |
| OFR | 500.00 MHz |
| OBSET | 162.00 KHz |
| OBFIN | 416.02 Hz |
| POINT | 16384 |
| FREQU | 7507.51 Hz |
| SCANS | 1303 |
| CTEMP | 23.5 c |
| SLVNT | CDCL3 |
| EXREF | 7.26 ppm |



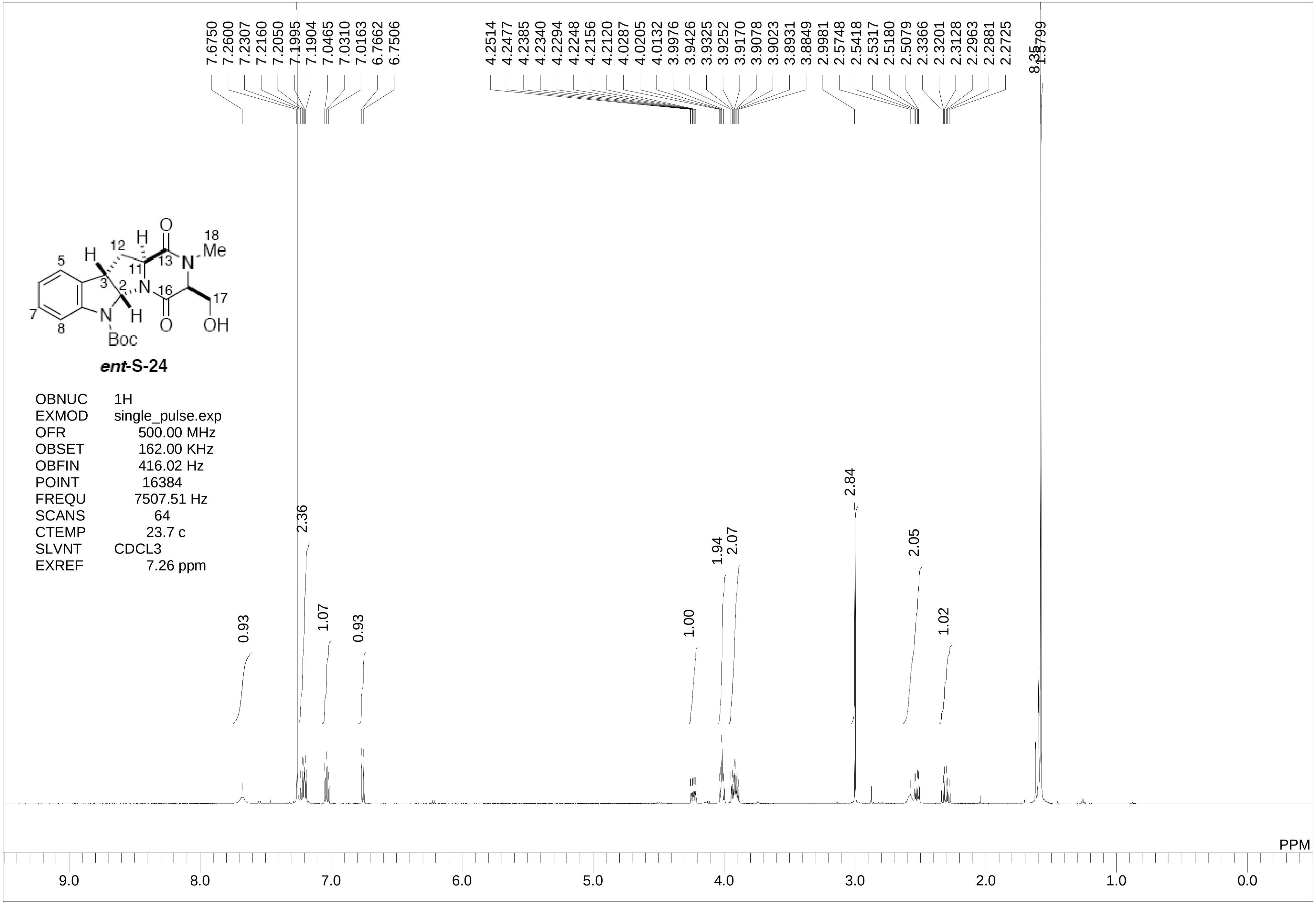
***ent*-S-23**

OBNUC 1H
EXMOD single_pulse.exp
OFR 500.00 MHz
OBSET 162.00 KHz
OBFIN 416.02 Hz
POINT 16384
FREQU 7507.51 Hz
SCANS 32
CTEMP 25.0 c
SLVNT CDCL3
EXREF 0.00 ppm



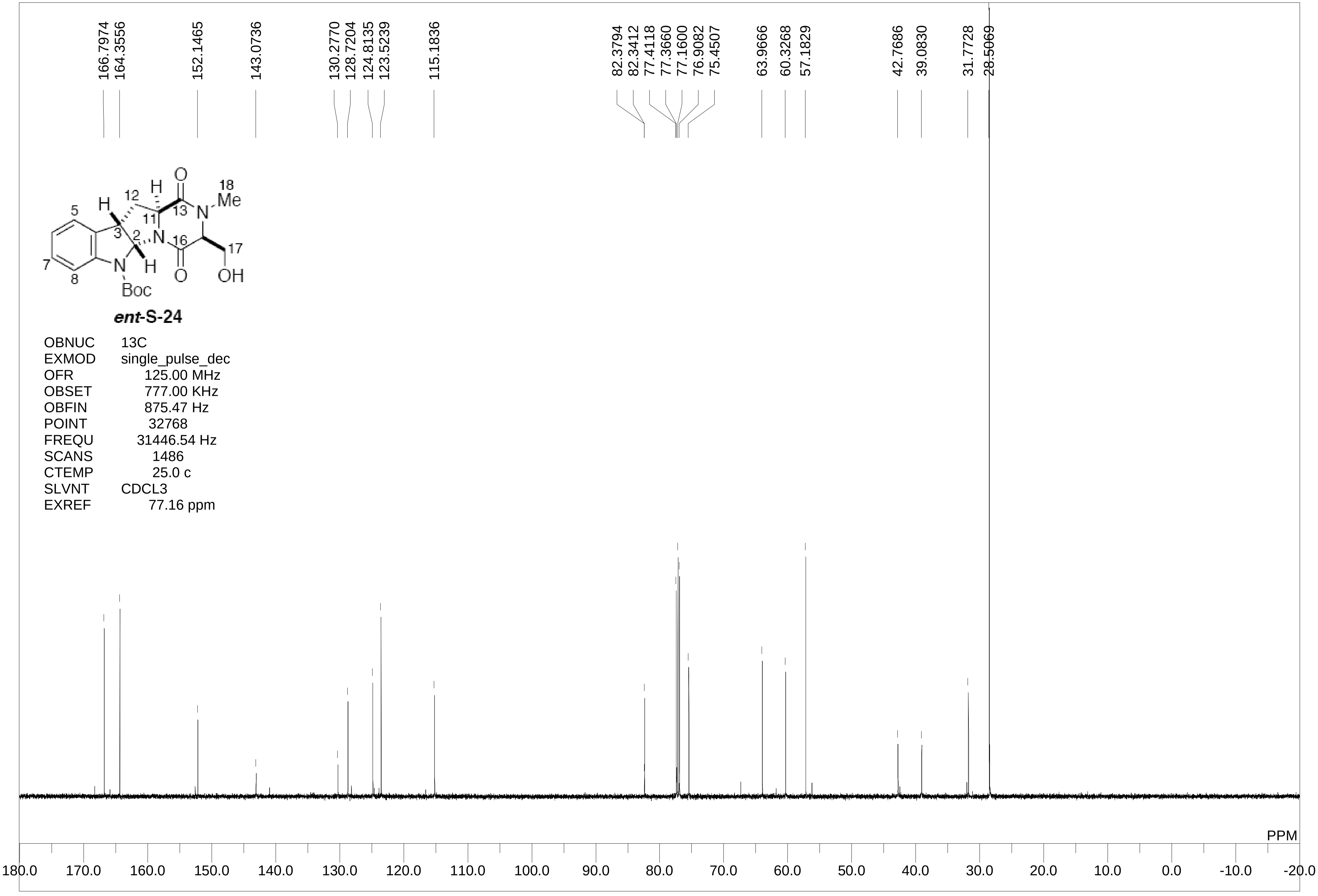
***ent*-S-23**

| | |
|---|---|
| OBNUC | 13C |
| EXMOD | single_pulse_dec |
| OFR | 125.00 MHz |
| OBSET | 777.00 KHz |
| OBFIN | 875.47 Hz |
| POINT | 32768 |
| FREQU | 31446.54 Hz |
| SCANS | 35058 |
| CTEMP | 25.0 c |
| SLVNT | CDCL3 |
| EXREF | 77.16 ppm |



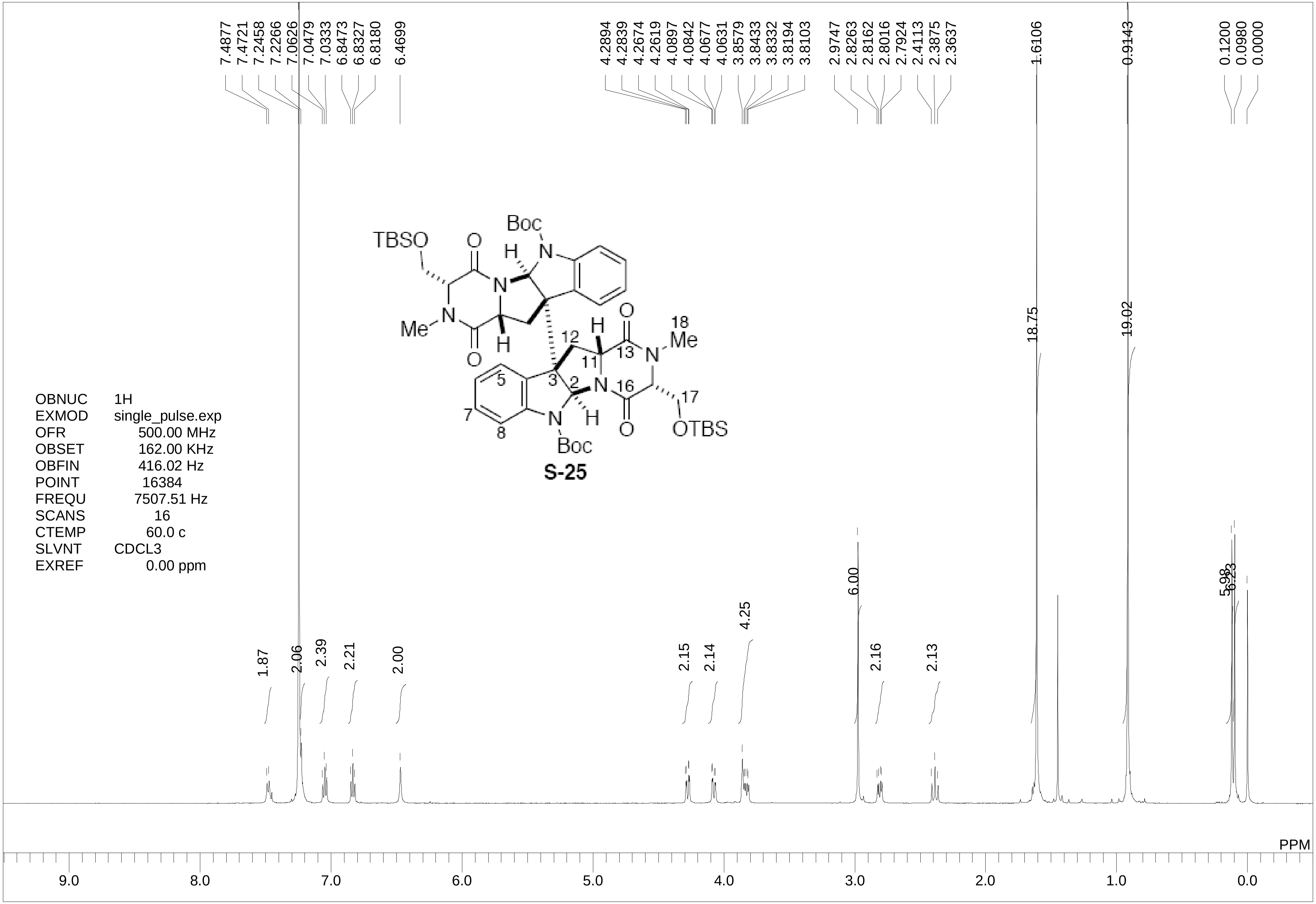
***ent*-S-24**

| | |
|---|---|
| OBNUC | 1H |
| EXMOD | single_pulse.exp |
| OFR | 500.00 MHz |
| OBSET | 162.00 KHz |
| OBFIN | 416.02 Hz |
| POINT | 16384 |
| FREQU | 7507.51 Hz |
| SCANS | 64 |
| CTEMP | 23.7 c |
| SLVNT | CDCL3 |
| EXREF | 7.26 ppm |



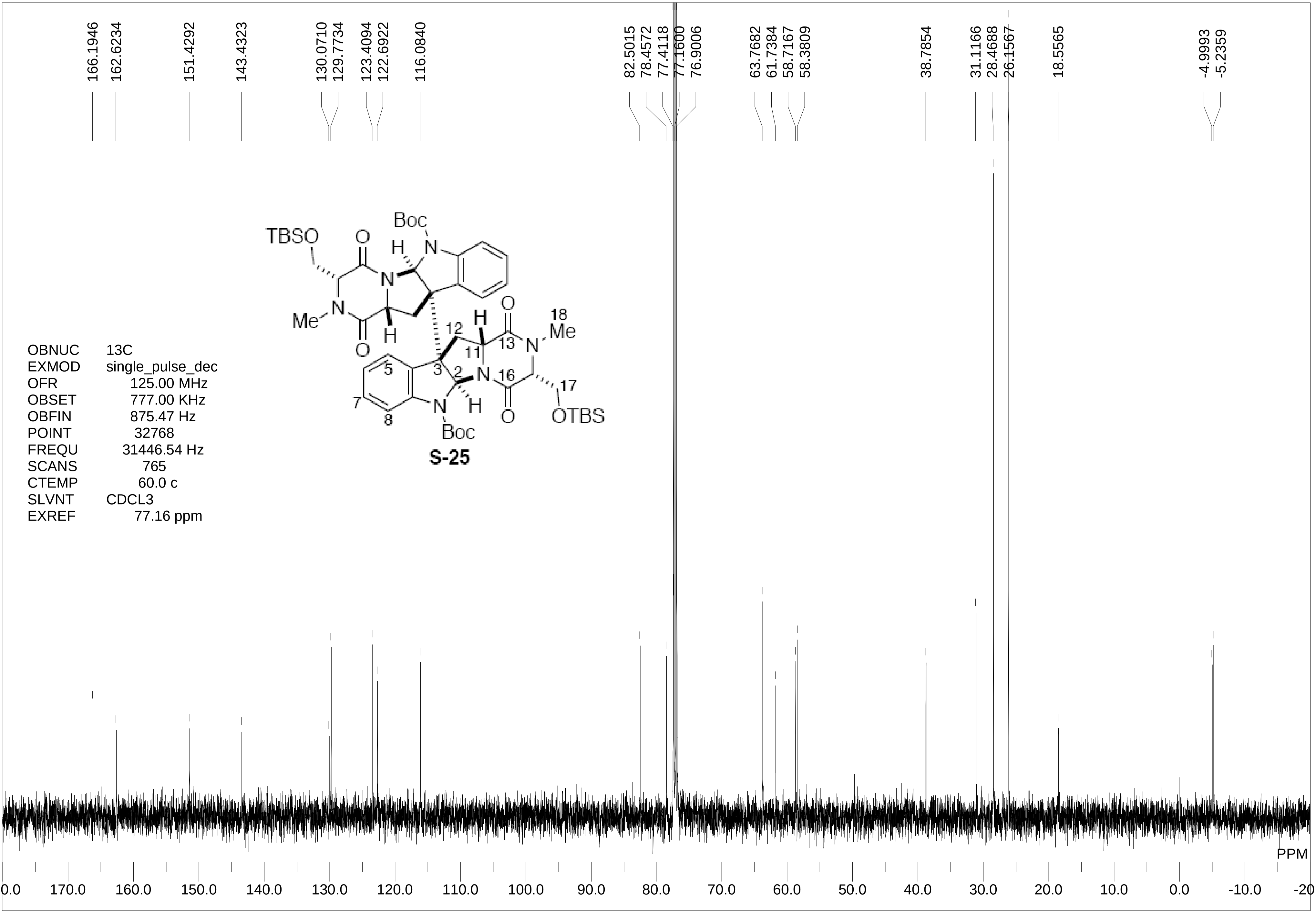
***ent*-S-24**

| | |
|---|---|
| OBNUC | 13C |
| EXMOD | single_pulse_dec |
| OFR | 125.00 MHz |
| OBSET | 777.00 KHz |
| OBFIN | 875.47 Hz |
| POINT | 32768 |
| FREQU | 31446.54 Hz |
| SCANS | 1486 |
| CTEMP | 25.0 c |
| SLVNT | CDCL3 |
| EXREF | 77.16 ppm |



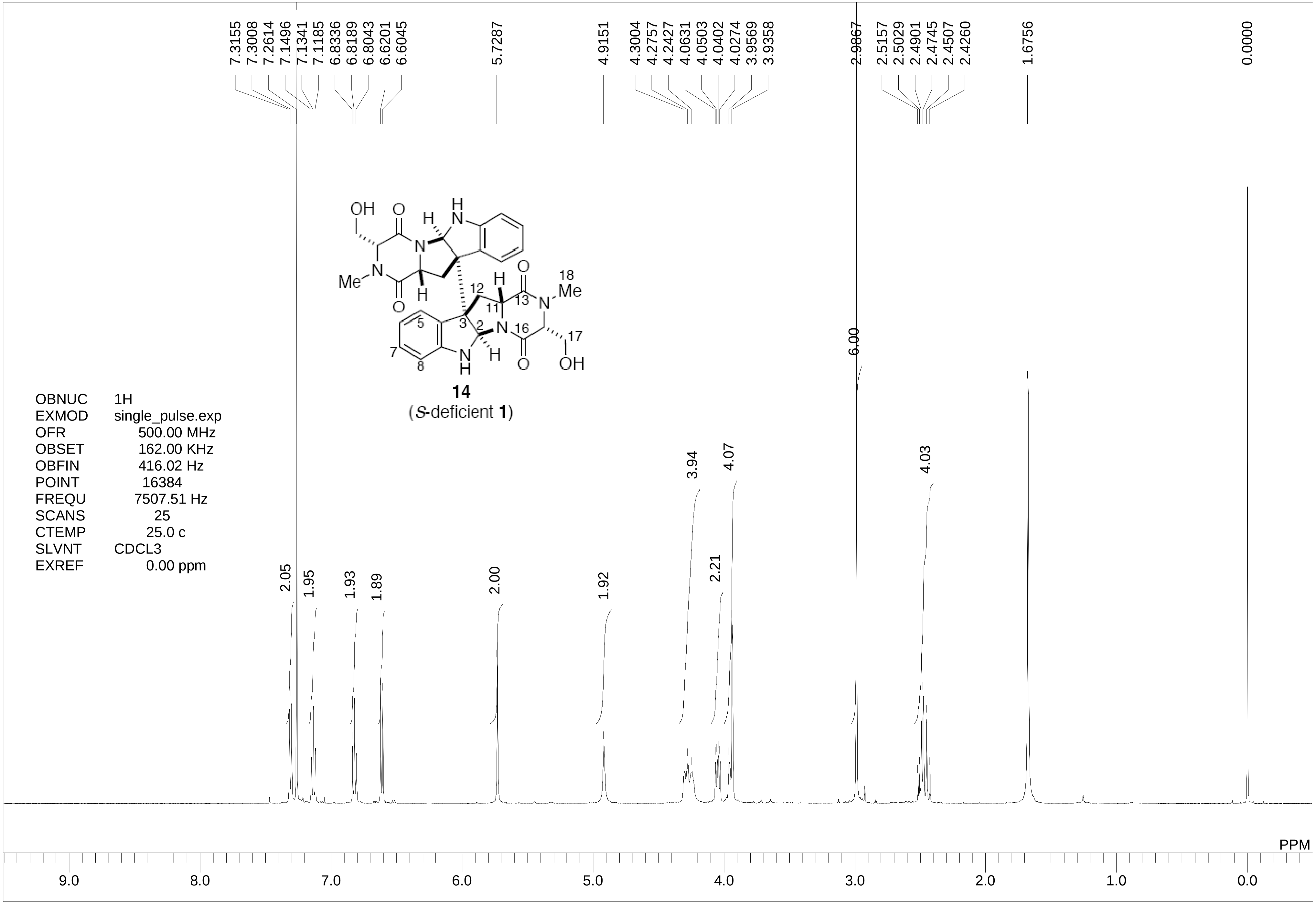
**S-25**

| | |
|---|---|
| OBNUC | 1H |
| EXMOD | single_pulse.exp |
| OFR | 500.00 MHz |
| OBSET | 162.00 KHz |
| OBFIN | 416.02 Hz |
| POINT | 16384 |
| FREQU | 7507.51 Hz |
| SCANS | 16 |
| CTEMP | 60.0 c |
| SLVNT | CDCL3 |
| EXREF | 0.00 ppm |



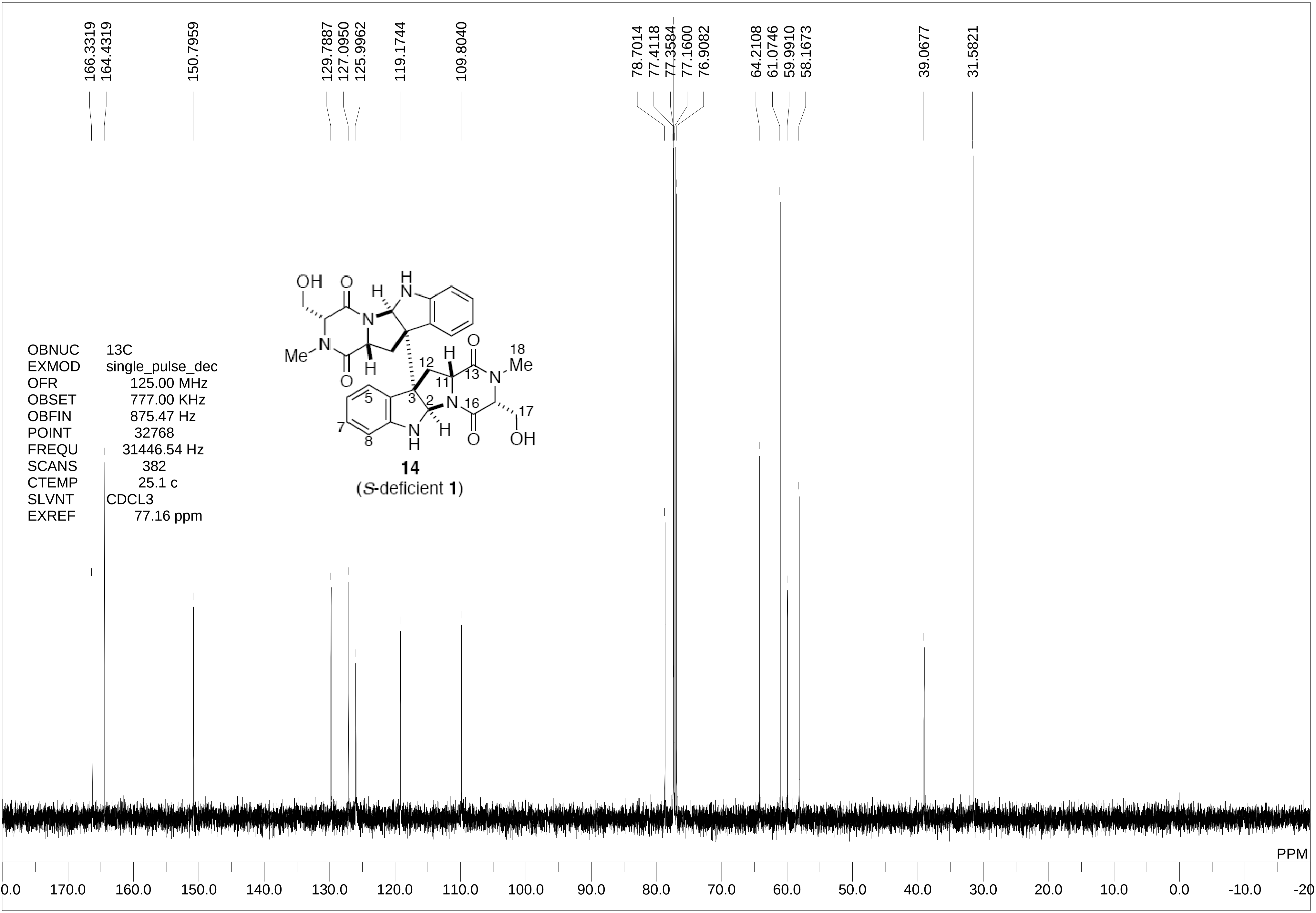
**S-25**

| | |
|---|---|
| OBNUC | 13C |
| EXMOD | single_pulse_dec |
| OFR | 125.00 MHz |
| OBSET | 777.00 KHz |
| OBFIN | 875.47 Hz |
| POINT | 32768 |
| FREQU | 31446.54 Hz |
| SCANS | 765 |
| CTEMP | 60.0 c |
| SLVNT | CDCL3 |
| EXREF | 77.16 ppm |



**14**
(*S*-deficient **1**)

| | |
|---|---|
| OBNUC | 1H |
| EXMOD | single_pulse.exp |
| OFR | 500.00 MHz |
| OBSET | 162.00 KHz |
| OBFIN | 416.02 Hz |
| POINT | 16384 |
| FREQU | 7507.51 Hz |
| SCANS | 25 |
| CTEMP | 25.0 c |
| SLVNT | CDCL3 |
| EXREF | 0.00 ppm |



```
OBNUC      13C
EXMOD      single_pulse_dec
OFR            125.00 MHz
OBSET          777.00 KHz
OBFIN          875.47 Hz
POINT           32768
FREQU        31446.54 Hz
SCANS            382
CTEMP            25.1 c
SLVNT      CDCL3
EXREF           77.16 ppm
```

**14**
(*S*-deficient **1**)