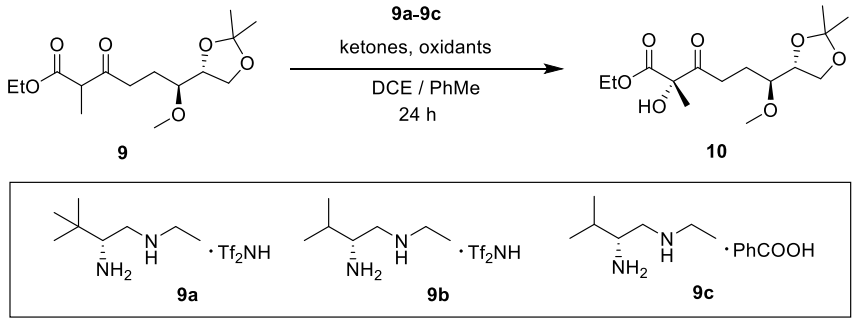
**Supporting Information**

# Convergent Synthesis of Tetrahydropyranyl Side Chain of Verucopeptin, an Antitumor Antibiotic Active against Multidrug-resistant Cancers

Yuanjun Sun, Wenhao Tang, Huxin Ni, Mei Wang, Bin Huang and Ya-Qiu Long*

Laboratory of Medicinal Chemical Biology, College of Pharmaceutical Sciences, Soochow University, Suzhou 215123, China

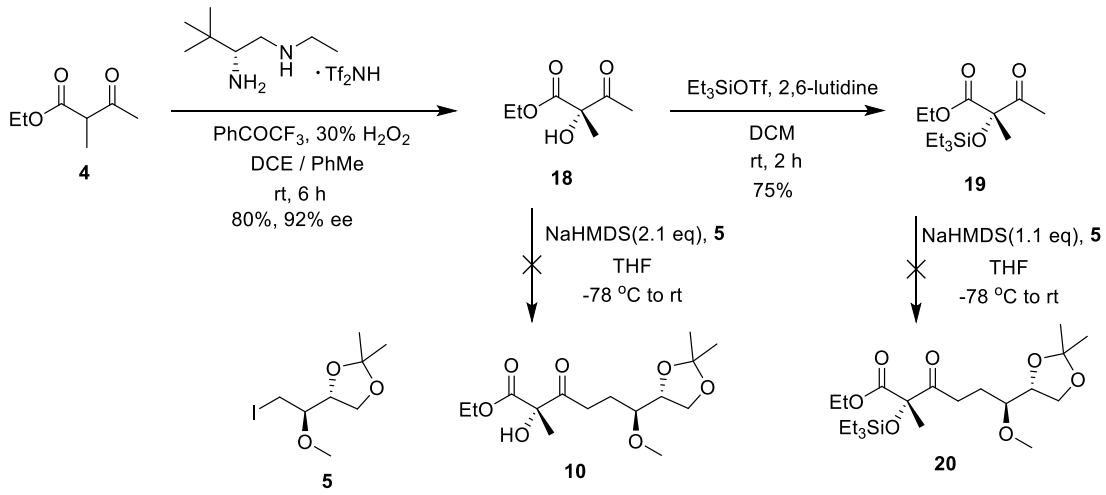
**Table S1** Optimization of the stereoselective α-hydroxylation conditions [a]




| entry | catalysts | ketones | oxidants (1.5 eq.) | temp. | conversion | yield[b] | d.r. [c] |
|---|---|---|---|---|---|---|---|
| 1 | **9a** (0.2 eq) | $PhCOCF_3$ (0.2 eq) | 30%$H_2O_2$ | rt [d] | 21%-33% | 9%-15% | >20:1 |
| 2 | **9a** (0.2 eq) | $PhCOCF_3$ (0.2 eq) | 30%$H_2O_2$ | 35 °C | 53% | trace | n.d. |
| 3 | **9a** (0.2 eq) | $PhCOCF_3$ (0.2 eq) | 30%$H_2O_2$ | 50 °C | 100%[e] | trace | n.d. |
| 4 | **9b** (0.2 eq) | $PhCOCF_3$ (0.2 eq) | 30%$H_2O_2$ | rt | 35% | 24% | >20:1 |
| 5 | **9b** (1.2 eq) | $PhCOCF_3$ (1.2 eq) | 30%$H_2O_2$ | rt | n.d. | trace | n.d. |
| 6 | **9b** (1.2 eq) | $PhCOCF_3$ (0.2 eq) | 30%$H_2O_2$ | rt | n.d. | trace | n.d. |
| 7 | **9b** (0.2 eq) | $PhCOCF_3$ (0.2 eq) | TBHP | rt | n.r. | 0% | n.d. |
| 8 | **9b** (0.2 eq) | $PhCOCF_3$ (0.2 eq) | Oxone | rt | n.r. | 0% | n.d. |
| 9 | **9b** (0.2 eq) | PhCOCOOMe (0.2 eq) | 30%$H_2O_2$ | rt | n.d. | trace | n.d. |
| 10 | **9c** (0.2 eq) | $PhCOCF_3$ (0.2 eq) | 30%$H_2O_2$ | rt | n.r. | 0% | n.d. |

[a]Reactions were performed with **9** (0.2 mmol) in 0.5 mL PhMe/DCE (1/1) for 24 h. [b]Yield of isolated product. [c]The d.r. values were determined by $^1$H NMR. [d]Room temperature (rt) ranged from 23 to 26 °C. [e]High conversion was observed because of deprotection of acetonide at 50 °C.

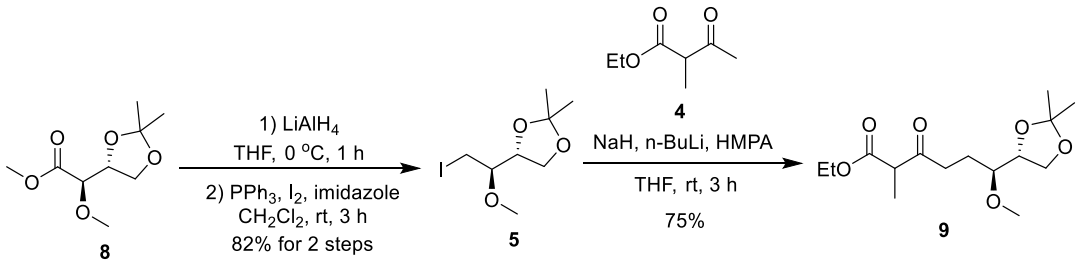
n.r.=not reacted, n.d.= not detected.




**Scheme S1** Synthetic exploration towards **10** and **20**.

**Experimental Section:**

**General remarks:** Solvents (THF and $CH_2Cl_2$) were dried via FLEANO® Solvent Purification Systems before use. Petroleum ether (60-90 °C) and ethyl acetate were distilled prior to use. The products were purified by chromatography on silica gel (0.063-0.2 mm or 0.04-0.063 mm). Preparative HPLC was performed on a Agilent® 1260 Infinity II using a Agilent® PLRP-S 300 Å column (300 x 25 mm, 8 μm). Analytical TLC was performed on pre-coated silica gel plates. TLC staining was accomplished with $KMnO_4$ solution or phosphomolybdic acid solution. NMR spectra were recorded with Bruker® AVANCE NEO 400. Chemical shifts are reported in ppm (δ) with respect to TMS, and $CHCl_3$ was used as the internal standard. Peaks were assigned using $^1H$,$^1H$ COSY and NOESY spectra. Diastereomeric ratios were determined by HPLC on Agilent® 1260 Infinity II [Agilent® EC-C18 (100 x 4.6 mm, 2.7 μm)] or by $^1H$ NMR. Optical rotations were measured with a Rudolph ® Autopol III at the sodium D line (589 nm). Mass spectra were recorded with a Agilent® 6540QTOF(HRMS).



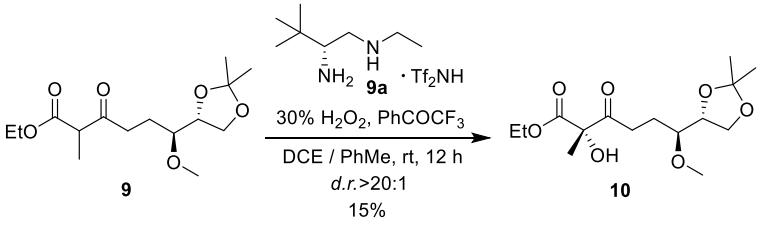

To a suspension of $LiAlH_4$ (490 mg, 13.0 mmol) in THF (12 mL) stirred at 0 °C was added a solution of methyl ester **8**[1-2] (2.20 g, 10.8 mmol) in THF (2 mL) dropwise. The resulting mixture was stirred at 0 °C for 1 h before $H_2O$ (0.5 mL), 15% NaOH (0.5 mL) and $H_2O$ (1.5 mL) were added at 0 °C respectively to quench the reaction. Then the mixture was allowed to stir at rt for 15 min and $MgSO_4$ was added. After stirring for another 15 min, the mixture was filtered through a thin layer of celite and the filtrate was concentrated to obtain primary alcohol (1.60 g) as a colorless oil which was directly used in the next step. To a solution of $I_2$ (3.12 g, 12.2 mmol) in $CH_2Cl_2$ (20 mL) stirred 0 °C under Ar atmosphere was added $PPh_3$ (3.08 g, 11.8 mmol) and imidazole (0.80 g, 11.8 mmol). The mixture was stirred at 0 °C for 15 min before a solution of primary alcohol (1.60 g, 9.08 mmol) obtained above in THF (8 mL) was added dropwise. The resulting mixture was allowed to stir at rt for 3 h. The mixture was washed with saturated aqueous $Na_2S_2O_3$ solution (15 mL) and the organic phase was dried over $Na_2SO_4$. After being

concentrated, the residue was purified by silica gel chromatography (Petroleum ether : EtOAc = 10:1) to obtain iodide **5** (2.01 g, 82% over 2 steps) as a colorless liquid.

To a flask containing NaH (60% dispersion in mineral oil, 840 mg, 20.8 mmol) was added THF (20 mL) and HMPA (1.2 mL). The mixture was cooled to 0 °C before ethyl 2-methylacetoacetate **4** (3.0 g, 20.8 mmol) was added dropwise, and stirred at 0 °C for 10 min. Then n-butyllithium (2.5 M in n-Hexane, 8.4 mL, 20.8 mmol) and iodide **5** (2.01 g, 7.02 mmol) were added respectively at 0 °C. The mixture was allowed to stir at rt for 3 h. The reaction mixture was quenched by saturated aqueous $NH_4Cl$ solution (20 mL) and extracted with EtOAc (50 mL × 2). The organic phases were dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography (Petroleum ether : EtOAc = 20:1→5:1) to obtain **9** (1.60 g, 75% yield) as a colorless oil.

$^1$H NMR (400 MHz, Chloroform-*d*, as a mixture of epimers) δ 4.17 (q, *J* = 7.1 Hz, 2H), 4.06 – 3.95 (m, 2H), 3.88 – 3.77 (m, 1H), 3.52 (qd, *J* = 7.2, 5.2 Hz, 1H), 3.36 (s, 1.5H), 3.34 (s, 1.5H), 3.26 – 3.18 (m, 1H), 2.78 – 2.56 (m, 2H), 2.00 – 1.87 (m, 1H), 1.79 – 1.68 (m, 1H), 1.39 (s, 3H), 1.34 – 1.30 (m, 6H), 1.25 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, Chloroform-*d*, as a mixture of epimers) δ 205.8, 205.8, 170.7, 109.4, 80.5, 80.4, 66.8, 66.7, 61.5, 58.5, 58.4, 53.0, 36.6, 36.5, 26.7, 25.4, 24.3, 24.2, 14.2, 13.0, 12.9; ESI-HRMS calcd for $C_{15}H_{26}NaO_6$ $[M+Na]^+$: 325.1622, found: 325.1621.

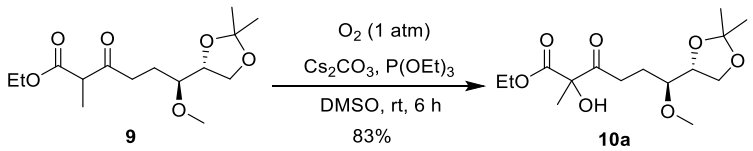
**General procedure for α-Hydroxylation Reactions:**




An oven-dried tube was charged with **9** (0.2 mmol) and aminocatalyst **9a-9c** and mixed solvent of toluene and 1,2-dichloroethane (0.5 mL). Then ketones and oxidants (0.3 mmol) was added to the vial. The reaction was conducted at specified temperatures for 24 hours. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (Petroleum ether : EtOAc = 20:1→5:1) to give product **10**.

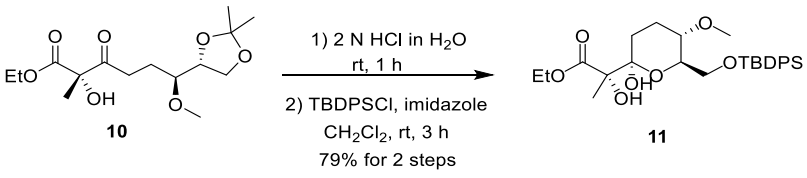
$[\alpha]_D^{23}$ = -14.3 (*c*=0.1, $CHCl_3$); IR $_{max}$ cm$^{-1}$: 2923, 1731, 1724, 1382, 1102, 1014, 890; $^1$H NMR (400 MHz, Chloroform-*d*) δ 4.30 – 4.19 (m, 2H), 4.19 (s, 1H), 4.07 – 3.98 (m, 2H), 3.87 – 3.78 (m, 1H), 3.34 (s, 3H), 3.25 – 3.19 (m, 1H), 2.72 (t, *J* = 7.2 Hz, 2H), 2.06 – 1.93 (m, 1H), 1.83 – 1.70 (m, 1H), 1.58 (s, 3H),

1.40 (s, 3H), 1.33 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 207.4, 171.7, 109.4, 81.1, 80.5, 76.7, 66.9, 62.7, 58.3, 31.5, 26.7, 25.3, 24.2, 22.0, 14.2. ESI-HRMS calcd for $C_{15}H_{27}O_7$ $[M+H]^+$: 319.1751, found: 319.1745.




To a solution of **9** (1.58 g, 5.23 mmol) in DMSO (20 mL) was added $Cs_2CO_3$ (0.34 g, 1.05 mmol) and $P(OEt)_3$ (1.86 mL, 10.5 mmol). The mixture was stirred at rt under $O_2$ atmosphere (1 atm) for 6 h. The mixture was diluted $Et_2O$ (40 mL) with and washed with $H_2O$ (40 mL). The aqueous phase was back-extracted with $Et_2O$ (40 mL×2). The combined organic phases were washed with brine (20 mL×2), dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography (Petroleum ether : EtOAc = 20:1→5:1) to obtain **10a** (1.39 g, 83% yield) as a light-yellow oil.

$^1$H NMR (400 MHz, Chloroform-*d*, as a mixture of epimers) δ 4.30 – 4.20 (m, 2H), 4.19 (s, 1H), 4.08 – 3.97 (m, 2H), 3.87 – 3.79 (m, 1H), 3.35 (s, 3H), 3.26 – 3.18 (m, 1H), 2.84 (ddd, *J* = 18.1, 8.3, 6.7 Hz, 0.5H), 2.75 – 2.70 (m, 1H), 2.63 (ddd, *J* = 18.1, 8.2, 5.8 Hz, 0.5H), 2.04 – 1.92 (m, 1H), 1.84 – 1.71 (m, 1H), 1.60 – 1.58 (m, 3H), 1.40 (s, 3H), 1.33 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, Chloroform-*d*, as a mixture of epimers) δ 207.4, 207.1, 171.7, 171.6, 109.4, 81.1, 81.1, 80.5, 80.4, 66.9, 66.8, 62.7, 62.7, 58.3, 31.5, 31.5, 26.7, 25.3, 24.2, 24.1, 22.2, 22.0, 14.2; ESI-HRMS calcd for $C_{15}H_{27}O_7$ $[M+H]^+$: 319.1751, found: 319.1742.

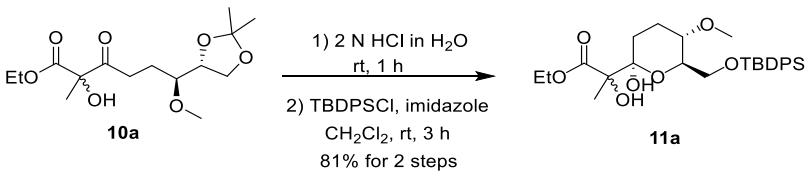



To a solution of **10** (7.5 mg, 0.0235 mmol) in THF (0.5 mL) was added aqueous 2 N HCl solution (0.5 mL). The mixture was stirred at rt for 1 h. The mixture was extracted with EtOAc (1 mL×10). The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution (2 mL) to avoid further intramolecular ketal formation between hemiketal and primary hydroxyl in an acidic condition of residual HCl, and the aqueous phase was back-extracted with EtOAc (1 mL×10). The combined organic

phases were dried over $Na_2SO_4$ and concentrated in vacuo to obtain a yellow oil which was directly used in the next step.

The yellow oil obtained above and imidazole (3.2 mg, 0.047 mmol) were dissolved in $CH_2Cl_2$ (1 mL). TBDPSCl (9.7 mg, 0.0353 mmol) was added and the resulting mixture was stirred at rt for 3 h. MeOH (0.05 mL) was added to quench the reaction, then the mixture was washed with 1% HCl (1 mL) and saturated aqueous $NaHCO_3$ solution (1 mL). The organic phase was dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography (Petroleum ether: EtOAc = 20:1→10:1→5:1) to obtain hemiketal **11** (9.6 mg, 79% for 2 steps) as a colorless oil.

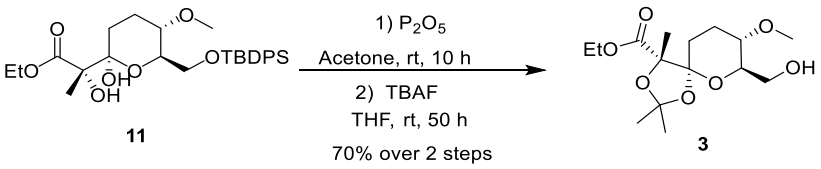
$[\alpha]_D^{23}$ = +12.1 (*c*=0.1, $CHCl_3$); IR $_{max}$ $cm^{-1}$: 2991, 1746, 1731, 1454, 1372, 1127, 1074, 955; $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.75 – 7.59 (m, 4H), 7.46 – 7.31 (m, 6H), 4.51 (d, *J* = 2.6 Hz, 1H), 4.32 – 4.11 (m, 2H), 3.93 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.78 – 3.73 (m, 1H), 3.69 (dd, *J* = 11.1, 1.8 Hz, 1H), 3.44 – 3.38 (m, 1H), 3.36 (s, 3H), 3.14 (d, *J* = 1.0 Hz, 1H), 2.18 – 2.09 (m, 1H), 2.07 – 1.95 (m, 1H), 1.85 (dt, *J* = 13.3, 3.7 Hz, 1H), 1.80 – 1.70 (m, 1H), 1.44 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.05 (s, 9H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 175.8, 135.7, 135.7, 135.7, 133.9, 133.7, 129.8, 129.7, 127.8, 127.8, 99.2, 78.3, 74.5, 74.1, 63.2, 62.3, 56.6, 27.0, 26.9, 26.3, 23.5, 20.2, 19.5, 14.2; ESI-HRMS calcd for $C_{28}H_{40}O_7SiNa$ $[M+Na]^+$: 539.2436, found: 539.2441.




**11a** (5.1 g, 81% over 2 steps) as colorless oil was synthesized from **10a** according to the same procedure to **11**

$^1$H NMR (400 MHz, Chloroform-*d*, as a mixture of epimers) δ 7.77 – 7.62 (m, 4H), 7.48 – 7.34 (m, 6H), 4.31 – 4.09 (m, 2H), 3.94 (dd, *J* = 11.0, 3.5 Hz, 0.5H), 3.85 (dd, *J* = 10.8, 3.9 Hz, 0.5H), 3.80 – 3.66 (m, 3H), 3.45 – 3.26 (m, 1H), 3.37 (s, 3H), 2.21 – 1.94 (m, 2H), 1.90 – 1.64 (m, 2H), 1.44 (s, 1.5H), 1.41 (s, 1.5H), 1.22 (t, *J* = 7.1 Hz, 1.5H), 1.21 (d, *J* = 7.1 Hz, 1.5H), 1.06 – 1.03 (m, 9H); $^{13}$C NMR (100 MHz, Chloroform-*d*, as a mixture of epimers) δ 175.8, 173.5, 135.8, 135.8, 135.7, 135.7, 135.7, 135.6, 133.9, 133.8, 133.7, 133.7, 129.7, 129.7, 129.6, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 99.2, 97.5, 78.8, 78.3,

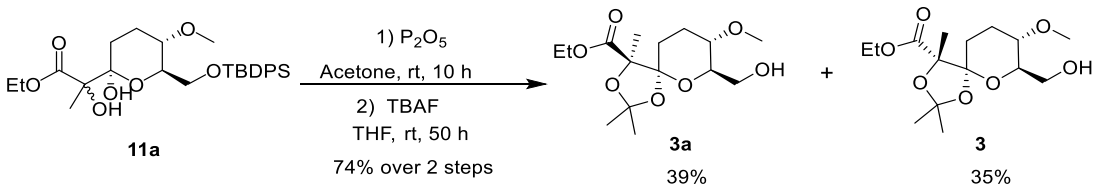
77.5, 74.5, 74.4, 74.2, 74.0, 63.3, 63.2, 62.3, 62.1, 56.6, 56.5, 28.1, 27.0, 26.9, 26.9, 26.3, 24.2, 23.4, 20.2, 20.0, 19.5, 19.4, 14.4, 14.2.



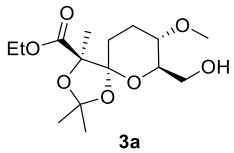

To a solution of **11a** (9 mg, 0.0174 mmol) in acetone (1 mL) was added $P_2O_5$ (3.7 mg, 0.0261 mmol) a. The mixture was stirred for 10 h. The mixture was quenched with saturated aqueous $NaHCO_3$ solution (2 mL) and extracted with EtOAc (2 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated in vacuo to obtain a yellow oil which was directly used in the next step.

The yellow oil obtained above was dissolved in THF (1 mL). TBAF (13.6 mg, 0.052 mmol) was added and the mixture was stirred at rt for 50 h. The mixture was diluted with saturated aqueous $NH_4Cl$ solution (2 mL) and extracted with EtOAc (2 mL×2). The combined organic phases were dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography (Petroleum ether : EtOAc = 5:1→2:1) to obtain alcohol **3** (3.9 mg, 70% for 2 steps) as a colorless oil.

$[\alpha]_D^{23}$ = +109.0 (*c*=0.1, $CHCl_3$); IR $_{max}$ $cm^{-1}$: 2940, 1746, 1730, 1369, 1109, 1013, 968; $^1H$ NMR (400 MHz, Chloroform-*d*) δ 4.15 (p, *J* = 7.0 Hz, 2H), 3.77 – 3.66 (m, 3H), 3.35 (s, 3H), 3.29 – 3.19 (m, 1H), 2.20 – 2.10 (m, 1H), 1.78 – 1.63 (m, 2H), 1.59 – 1.53 (m, 1H), 1.56 (s, 3H), 1.48 (s, 3H), 1.47 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); $^{13}C$ NMR (100 MHz, Chloroform-*d*) δ 172.6, 111.7, 104.1, 88.2, 74.9, 73.6, 63.0, 61.6, 56.5, 29.8, 28.9, 27.4, 24.8, 19.9, 14.2; ESI-HRMS calcd for $C_{15}H_{26}O_7Na$ $[M+Na]^+$: 341.1571, found: 341.1560.

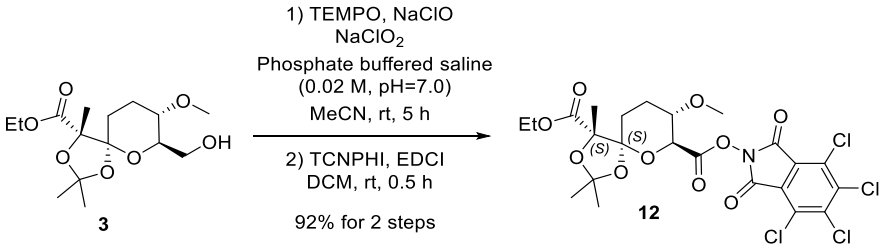



**3a** (1.22 g, 39% for 2 steps) and **3** (1.10 g, 35% for 2 steps) as colorless oil were synthesized from **11a** according to the same procedure to **3** and separated by silica gel chromatography.



**3a**

$[\alpha]_D^{23}$ = +108.0 (*c*=0.1, $CHCl_3$); IR $_{max}$ $cm^{-1}$: 2951, 1740, 1715, 1365, 1074, 957, 724; $^1H$ NMR (400 MHz, Chloroform-*d*) δ 4.18 (qd, *J* = 7.1, 5.2 Hz, 2H), 3.71 – 3.64 (m, 2H), 3.63 – 3.56 (m, 1H), 3.33 (s, 3H), 3.15 (ddd, *J* = 11.1, 8.8, 4.6 Hz, 1H), 2.17 (dq, *J* = 12.2, 4.0 Hz, 1H), 1.93 – 1.85 (m, 2H), 1.73 – 1.59 (m, 1H), 1.52 (s, 3H), 1.43 (s, 3H), 1.40 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); $^{13}C$ NMR (100 MHz, Chloroform-*d*) δ 170.7, 111.3, 105.5, 87.6, 75.2, 73.6, 63.0, 61.2, 56.4, 29.2, 28.5, 28.2, 24.6, 22.5, 14.3; ESI-HRMS calcd for $C_{15}H_{26}O_7Na$ $[M+Na]^+$: 341.1571, found: 341.1563.

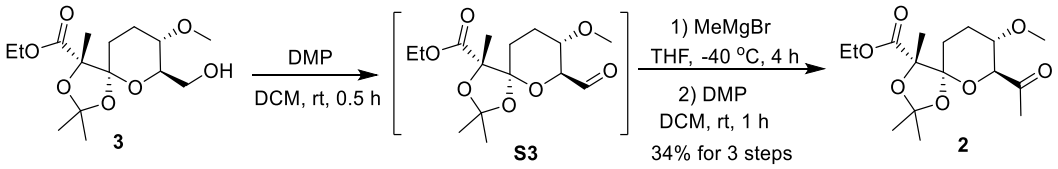



To a mixture of **3** (208 mg, 0.65 mmol) and TEMPO (10 mg, 0.065 mmol) in phosphate buffered saline (0.02 M, pH=7.0 , 2 mL) and MeCN (2 mL) stirred at 0 °C was added 80% $NaClO_2$ (148 mg, 1.31 mmol), followed by the addition of 10% $NaClO_2$ solution (0.2 mL). The resulting mixture was allowed to stir at rt for 5 h. The pH was adjusted to 10 with the addition of 1 M NaOH solution and the mixture was washed with $Et_2O$ (3 mL×2). The aqueous solution was added 2 N HCl solution until pH=1 and extracted with EtOAc (3 mL×3). The combined organic phases were dried over $Na_2SO_4$ and concentrated in vacuo to obtain the resulting carboxylic acid as a colorless oil.

To a mixture of resultant carboxylic acid and *N*-hydroxytetrachlorophthalimide (216 mg, 0.72 mmol) in $CH_2Cl_2$ (5 mL) was added DIC (0.12 mL, 0.79 mmol) dropwise. The resulting mixture was stirred at rt for 30 min and evaporated. The residue was purified by silica gel chromatography (Petroleum ether : EtOAc = 10:1→8:1) to obtain **12** (0.37 g, 92% for 2 steps) as a white solid.

$[\alpha]_D^{23}$ = +25.4 (*c*=0.1, $CHCl_3$); IR $_{max}$ $cm^{-1}$: 2939, 1750, 1729, 1371, 1127, 1014, 968; $^1H$ NMR (400 MHz, Chloroform-*d*) δ 4.57 (d, *J* = 9.7 Hz, 1H), 4.32 – 4.02 (m, 2H), 3.62 – 3.52 (m, 1H), 3.46 (s, 3H), 2.29 – 2.19 (m, 1H), 1.99 – 1.75 (m, 2H), 1.70 – 1.56 (m, 1H), 1.61 (s, 3H), 1.59 (s, 3H), 1.57 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); $^{13}C$ NMR (100 MHz, Chloroform-*d*) δ 172.3, 165.9, 157.2 141.2, 130.7, 124.8,

112.5, 104.7, 88.5, 75.3, 72.0, 61.8, 57.7, 29.2, 28.8, 27.4, 25.5, 19.8, 14.2. ESI-HRMS calcd for $C_{23}H_{23}Cl_4NO_{10}Na$ $[M+Na]^+$: 635.9968, found: 635.9970.

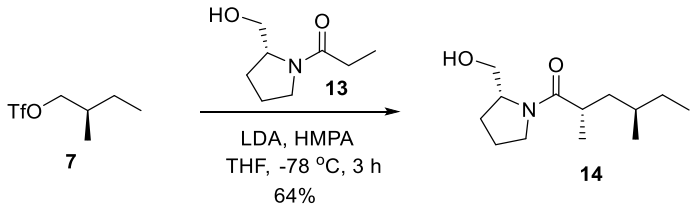



To a mixture of **3** (1.39 g, 4.36 mmol) in $CH_2Cl_2$ (20 mL) was added Dess-Martin periodinane (2.22 g, 5.24 mmol). The resulting mixture was allowed to stir at rt for 0.5 h. Then 10 mL of sat. aqueous $NaHCO_3$ solution and 10 mL of sat. aqueous $Na_2S_2O_3$ solution were added to quench the reaction. The resulting mixture was extracted with $CH_2Cl_2$ (30 mL×2). The combined organic phases were dried over $Na_2SO_4$ and concentrated under reduced pressure to obtain aldehyde **S3** as a colorless oil.

Aldehyde **S3** was dissolved in THF (12 mL) and the solution was cooled to -40 °C. MeMgBr (1.0 M in THF, 4.5 mL, 4.50 mmol) was added dropwise to the mixture under $N_2$. The resulting mixture was stirred at -40 °C for 4 h and sat. aqueous $NH_4Cl$ solution (10 mL) was added at -40 °C to quench. The mixture was warmed to rt and extracted with EtOAc (20 mL). The organic phase was dried over $Na_2SO_4$ and concentrated in vacuo to obtain the resultant alcohol as a colorless oil.

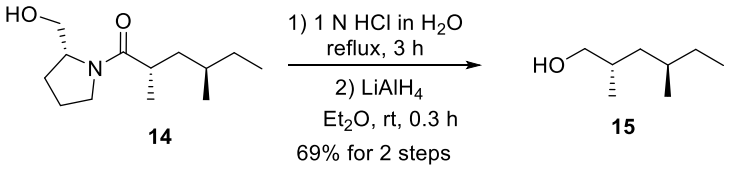
To a mixture of resultant alcohol in $CH_2Cl_2$ (20 mL) was added Dess-Martin periodinane (2.22 g, 5.24 mmol). The resulting mixture was allowed to stir at rt for 1 h. Then 10 mL of sat. aqueous $NaHCO_3$ solution and 10 mL of sat. aqueous $Na_2S_2O_3$ solution were added to quench the reaction. The resulting mixture was extracted with EtOAc (30 mL×2). The combined organic phases were dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Petroleum ether : EtOAc = 10:1→2:1) to obtain **2** (0.49 g, 34% for 3 steps) as a colorless oil.

$[\alpha]_D^{23}$ = +74.3 (*c*=0.1, $CHCl_3$); IR $_{max}$ $cm^{-1}$: 2987, 2943, 1748, 1732, 1448, 1369, 1125, 1072, 1013, 955, 939; $^1H$ NMR (400 MHz, Chloroform-*d*) δ 4.27 – 4.08 (m, 2H), 4.12 (d, *J* = 9.7 Hz, 1H), 3.39 – 3.29 (m, 1H), 3.33 (s, 3H), 2.24 (s, 3H), 2.22 – 2.16 (m, 1H), 1.87 – 1.71 (m, 2H), 1.65 – 1.59 (m, 1H), 1.58 (s, 3H), 1.53 (s, 3H), 1.48 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H); $^{13}C$ NMR (100 MHz, Chloroform-*d*) δ 205.3, 172.5, 112.0, 104.3, 88.4, 78.1, 75.1, 61.7, 56.7, 29.5, 29.0, 27.6, 27.4, 25.2, 20.0, 14.2; ESI-HRMS calcd for $C_{16}H_{26}O_7Na$ $[M+Na]^+$: 353.1571, found: 353.1556.




To a solution of **13** (8.65 g, 55.04 mmol) in THF (150 ml) stirred at -78 °C under Ar was added HMPA (9.6 ml, 55.04 mmol) and LDA (58 ml, 114.68 mmol). The mixture was stirred at -78 °C for 30 min before **7**[3,4] (11.02 g, 50.04 mmol) in THF (10 ml) was added. The mixture was stirred at -78 °C for 3.5 h before sat. aqueous $NH_4Cl$ solution was added to quench the reaction. The resulting mixture was evaporated to remove the THF and extracted with DCM. The organic phase was combined and dried over $Na_2SO_4$. The organic phase was then concentrated under reduced pressure to afford an oil, which was purified via silica gel column chromatography to yield 6.6 g (64%) of **14** as a brown oil.

$[\alpha]_D^{23}$ = +26.3 (*c*=0.1, $CHCl_3$); IR $_{max}$ $cm^{-1}$: 3367 2958, 2925., 2873, 1614, 1460, 1433, 1377, 1052; $^1H$ NMR (400 MHz, Chloroform-*d*) δ 5.24 (d, *J* = 7.4 Hz, 1H), 4.23 (tdd, *J* = 8.3, 5.6, 2.7 Hz, 1H), 3.71 – 3.45 (m, 4H), 2.62 (h, *J* = 6.7 Hz, 1H), 2.10 – 1.83 (m, 3H), 1.58 (dt, *J* = 12.5, 6.4 Hz, 1H), 1.43 – 1.27 (m, 4H), 1.20 – 1.14 (m, 1H), 1.12 (d, *J* = 6.7 Hz, 3H), 0.86 (td, *J* = 6.7, 6.0, 3.7 Hz, 6H).$^{13}C$ NMR (100 MHz, Chloroform-*d*) δ 178.9, 68.0, 61.3, 47.9, 40.3, 35.9, 32.2, 30.1, 28.4, 24.6, 19.1, 17.4, 11.5. ESI-HRMS calcd for $C_{13}H_{26}NO_2$ $[M+H]^+$: 228.1958, found: 228.1959.

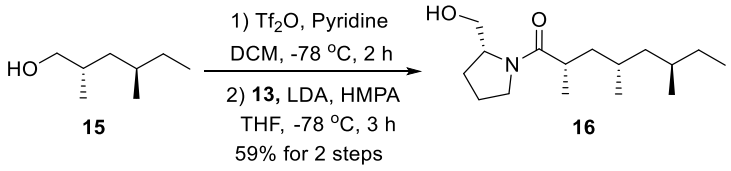



To a flask containing **14** (6.6 g, 29.03 mmol) was added 1 M HCl (100 ml), the mixture was stirred at 110 °C and was heated to reflux at this temperature for 3 h. The resulting mixture was cooled to room temperature and extracted with ethyl acetate. The organic phase was combined and dried over $Na_2SO_4$. The organic phase was then concentrated under reduced pressure to afford an oil, which was purified via silica gel column chromatography to yield 3.3 g of the acid as a brown oil.

To a solution of $LiAlH_4$ (1.7 g, 45.80 mmol) in $Et_2O$ (100 ml) was slowly added the acid (3.3 g, 22.90 mmol) at 0 °C, The mixture was stirred at 0 °C for 0.3 h. Then $H_2O$ (1.7 ml) and 10% NaOH aqueous solution (1.7 ml) was added, and then $H_2O$ (5.0 ml) was added. The resulting mixture was stirred at room temperature for 15 min and then dried with $MgSO_4$. The organic phase was then concentrated under

reduced pressure to afford an oil, which was purified via silica gel column chromatography to yield 2.59 g (69% for 2 steps) of **15** as a brown oil.

$[\alpha]_D^{23}$ = -18.4 (*c*=0.1, $CHCl_3$); IR $_{max}$ $cm^{-1}$: 2953, 2922, 2853. 1742, 1670, 1458, 1377, 1187, 1082, 969; $^1$H NMR (400 MHz, Chloroform-*d*) δ 3.48 (dd, *J* = 10.4, 5.7 Hz, 1H), 3.40 (dd, *J* = 10.3, 6.6 Hz, 1H), 1.71 (m, 1H), 1.37 – 1.23 (m, 1H), 1.23 – 1.03 (m, 3H), 0.91 – 0.80 (m, 9H).$^{13}$C NMR (100 MHz, Chloroform-*d*) δ 69.2, 40.4, 33.4, 31.7, 30.6, 19.0, 16.5, 11.6. HRMS calcd for $C_8H_{18}NaO$ $[M+Na]^+$: 153.1250, found: 153.1243. Spectral data matched the reported data[5].

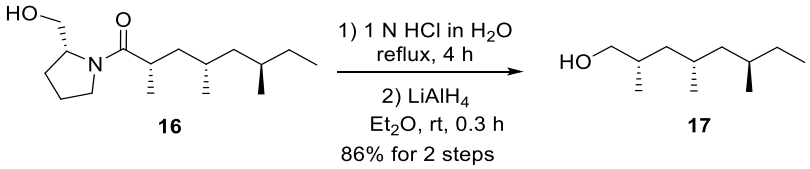



To a solution of **15** (1.68 g, 12.90 mmol) in DCM (50 ml) stirred under -78 °C under Ar was added pyridine (1.5 ml, 18.07 mmol) and $Tf_2O$ (2.5 ml, 18.07 mmol). The resulting mixture was stirred at -78 °C for 2 h before saturated NaCl aqueous solution was added to quench the reaction. The mixture was washed with 1% HCl three times to remove the pyridine. The organic phase was combined and dried over $Na_2SO_4$. The organic phase was then concentrated under reduced pressure to yield 3.04 g of the triflates as a brown oil.

To a solution of **13** (2.19 g, 13.93 mmol) in THF (60 ml) stirred under -78 °C under Ar was added HMPA (2.4 ml, 13.93 mmol) and LDA (14 ml, 27.86 mmol). The mixture was stirred at -78 °C for 30 min before the triflates (3.04 g, 11.60 mmol) in THF (5 ml) was added. The resulting mixture was stirred at -78 °C for 3 h before sat. aqueous $NH_4Cl$ solution was added to quench the reaction. The mixture was evaporated to remove the THF and extracted with DCM. The organic phase was combined and dried over $Na_2SO_4$. The organic phase was then concentrated under reduced pressure to afford an oil, which was purified via silica gel column chromatography to yield 2.06 g (59% for 2 steps) of **16** as a pale yellow oil.

$[\alpha]_D^{23}$ = +20.3 (*c*=0.1, $CHCl_3$); IR $_{max}$ $cm^{-1}$: 3387, 2957, 2923, 2872, 1617, 1460, 1433, 1377, 1052;$^1$H NMR (400 MHz, Chloroform-*d*) δ 5.25 (d, *J* = 7.4 Hz, 1H), 4.23 (ddt, *J* = 8.4, 5.7, 2.7 Hz, 1H), 3.68 – 3.43 (m, 4H), 2.74 – 2.54 (m, 1H), 2.09 – 1.83 (m, 3H), 1.70 – 1.54 (m, 2H), 1.47 (dt, *J* = 13.5, 6.7 Hz, 1H), 1.43 – 1.35 (m, 1H), 1.33 – 1.26 (m, 1H), 1.23 – 1.14 (m, 2H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.06 – 0.98 (m, 2H), 0.89 – 0.77 (m, 9H).$^{13}$C NMR (100 MHz, Chloroform-*d*) δ 178.7, 68.0, 61.2, 48.0, 44.2, 41.9,

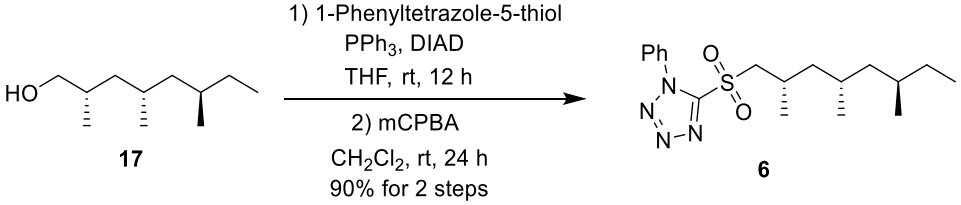
35.8, 31.7, 30.6, 28.4, 28.1, 24.6, 20.2, 19.0, 18.1, 11.5. HRMS calcd for $C_{16}H_{32}NO_2$ $[M+H]^+$: 270.2428, found: 270.2429.




To a flask containing **16** (2.7 g, 10.03 mmol) was added 1 M HCl (50 ml), and the mixture was stirred at 110 °C and heated to reflux at this temperature for 4 h. The resulting mixture was cooled to room temperature and extracted with ethyl acetate. The organic phase was combined and dried over $Na_2SO_4$. The organic phase was then concentrated under reduced pressure to afford an oil, which was purified via silica gel column chromatography to yield 1.67 g (89%) of the acid as a brown oil.

To a solution of $LiAlH_4$ (0.68 g, 17.94 mmol) in $Et_2O$ (60 ml) was slowly added the acid (1.67 g, 8.97 mmol) at 0 °C, The mixture was stirred at 0 °C for 0.3 h. Then $H_2O$ (0.68 ml) and 10% NaOH aqueous solution (0.68 ml) was added and then $H_2O$ (2 ml) was added. The resulting mixture was stirred at room temperature for 15 min and then dried with $Mg_2SO_4$. The organic phase was then concentrated under reduced pressure to afford an oil, which was purified via silica gel column chromatography to yield 1.5 g (86% for 2 steps) of **17** as a colorless oil.

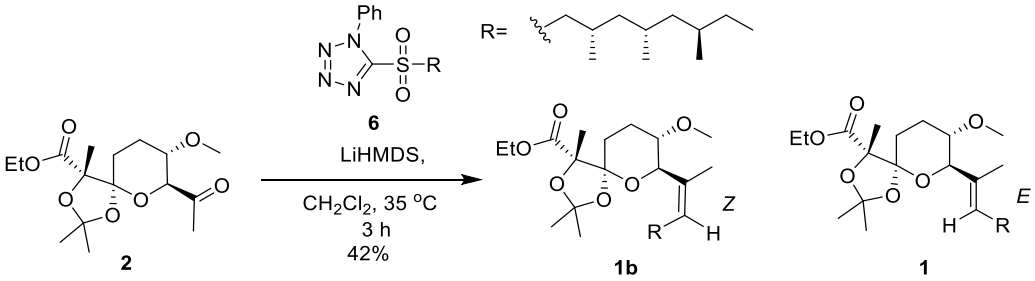
$[\alpha]_D^{23}$ = -33.7 (*c*=0.1, $CHCl_3$); IR $_{max}$ $cm^{-1}$: 3335, 2957, 2912, 2873, 1459, 1377, 1037; $^1H$ NMR (400 MHz, Chloroform-*d*) δ 3.52 (dd, *J* = 10.4, 5.2 Hz, 1H), 3.38 (dd, *J* = 10.4, 6.8 Hz, 1H), 1.73 (m, 1H), 1.58 (m, 1H), 1.37 (m, 2H), 1.26 (m, 2H), 1.19 – 0.95 (m, 4H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.87 – 0.80 (m, 9H).$^{13}C$ NMR (100 MHz, Chloroform-*d*) δ 68.7, 44.1, 42.1, 33.2, 31.9, 30.8, 27.5, 20.4, 19.0, 17.2, 11.6. HRMS calcd for $C_{11}H_{24}NaO$ $[M+Na]^+$: 195.1719, found: 195.1723. Spectral data matched the reported data.[6]



To a mixture of alcohol **17** (1.05 g, 6.09 mmol), 1-Phenyltetrazole-5-thiol (1.14 g, 6.39 mmol) and $PPh_3$ (1.92 g, 7.31 mmol) in THF (30 mL) was added DIAD (1.48 g, 7.31 mmol) dropwise at 0 °C. The resulting mixture was allowed to stir at rt for 12 h. Then 20 mL of sat. aqueous $NH_4Cl$ solution was added to quench the reaction. The resulting mixture was extracted with EtOAc (30 mL). The organic phase was dried over $Na_2SO_4$ and concentrated under reduced pressure to obtain a thioether as a colorless oil.

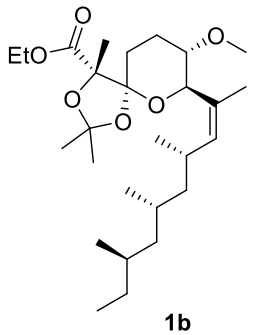
To a mixture of resultant thioether in $CH_2Cl_2$ (40 mL) was added 80% mCPBA (2.60 g, 17.0 mmol) at 0 °C. The resulting mixture was allowed to stir at rt for 24 h. Then sat. aqueous $Na_2S_2O_3$ solution was added to quench the reaction and the mixture was washed with sat. aqueous $NaHCO_3$ solution (20 mL). The organic phase was dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Petroleum ether : EtOAc = 50:1→20:1) to obtain sulfone **6** (2.0 g, 90% for 2 steps) as a colorless oil.

$[\alpha]_D^{23}$ = -8.3 (*c*=0.3, $CHCl_3$); IR $_{max}$ $cm^{-1}$: 2954, 2917, 2874, 1459, 1377; $^1H$ NMR (400 MHz, Chloroform-*d*) δ 7.72 – 7.64 (m, 2H), 7.65 – 7.54 (m, 3H), 3.79 (dd, *J* = 14.4, 4.2 Hz, 1H), 3.55 (dd, *J* = 14.4, 8.5 Hz, 1H), 2.51 – 2.37 (m, 1H), 1.66 – 1.53 (m, 1H), 1.47 – 1.09 (m, 5H), 1.15 (d, *J* = 6.7 Hz, 3H), 1.07 – 1.00 (m, 2H), 0.87 – 0.82 (m, 6H), 0.81 (d, *J* = 6.5 Hz, 3H); $^{13}C$ NMR (100 MHz, Chloroform-*d*) δ 154.2, 133.2, 131.6, 129.8, 125.3, 62.1, 45.5, 43.7, 31.7, 30.7, 27.3, 25.9, 20.4, 19.9, 18.9, 11.6; ESI-HRMS calcd for $C_{18}H_{28}N_4O_2SNa$ $[M+Na]^+$: 387.1825, found: 387.1825.



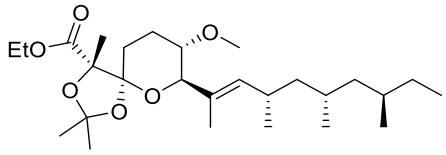

To a solution of sulfone **6** (303 mg, 0.83 mmol) in $CH_2Cl_2$ (2 mL) was added LiHMDS (1.0 M in THF, 0.91 mL, 0.91 mmol) dropwise at -40 °C. The resulting mixture was allowed to warm to 35 °C. Then a solution of methyl ketone **2** (250 mg, 0.78 mmol) in $CH_2Cl_2$ (1 mL) was added and the mixture was stirred at 35 °C for 3 h. Then 2 mL of sat. aqueous $NH_4Cl$ solution was added to quench the reaction. The resulting mixture was extracted with EtOAc (5 mL). The organic phase was dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Petroleum ether : EtOAc = 40:1→8:1) to obtain a mixture of *E*-*Z* isomers **1b** and **1** (163 mg, 42%) as a colorless

oil. The *E*-*Z* isomers were separated via prepared HPLC [PLRP-S 300 Å column (300 x 25 mm, 8 μm) 97% MeCN and 3% $H_2O$] to obtain *Z* isomer **1b** (75 mg, 19%) and *E* isomer **1** (60 mg, 15%).



**1b**

$[\alpha]_D^{23}$ = +38.3 (*c*=0.35, $CHCl_3$); IR $_{max}$ $cm^{-1}$: 2956, 2925, 1751, 1732, 1458, 1377, 1118, 1059, 1010, 881; $^1$H NMR (400 MHz, Chloroform-*d*) δ 5.14 (dd, *J* = 9.9, 1.6 Hz, 1H), 4.50 (d, *J* = 9.5 Hz, 1H), 4.27 – 4.08 (m, 2H), 3.31 (s, 3H), 3.20 – 3.09 (m, 1H), 2.56 (dq, *J* = 9.7, 6.7 Hz, 1H), 2.19 – 2.04 (m, 1H), 1.81 – 1.74 (m, 2H), 1.72 (d, *J* = 1.4 Hz, 3H), 1.61 – 1.53 (m, 1H), 1.57 (s, 3H), 1.54 – 1.38 (m, 1H), 1.49 (s, 3H), 1.48 (s, 3H), 1.44 – 1.29 (m, 1H), 1.34 – 0.99 (m, 6H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.6 Hz, 3H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 173.0, 138.0, 130.2, 111.5, 104.0, 88.6, 75.8, 72.7, 61.5, 57.4, 46.7, 44.4, 31.8, 30.7 30.2, 29.7, 29.2, 27.6, 27.5, 26.1, 21.3, 20.8, 19.9, 19.1, 19.0, 14.2, 11.6; ESI-HRMS calcd for $C_{27}H_{48}O_6Na$ $[M+Na]^+$: 491.3343, found:491.3349.



**1**

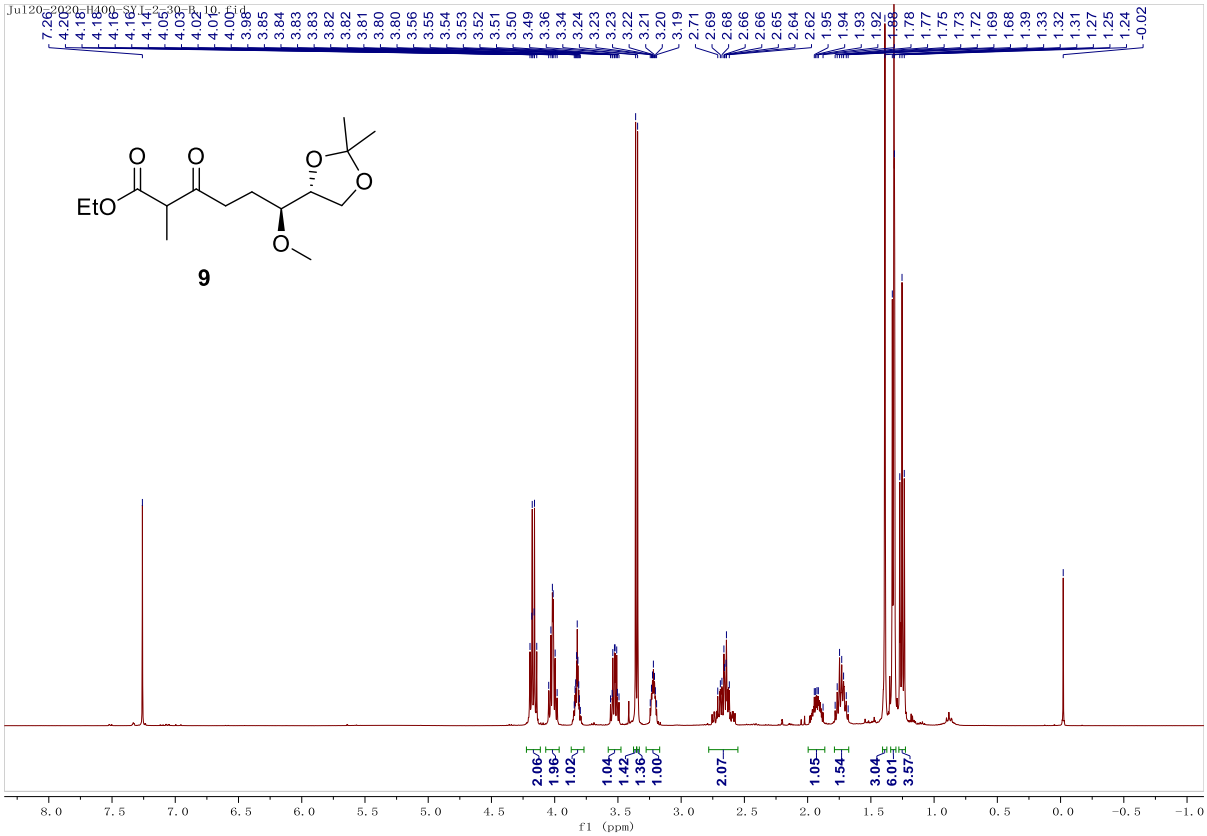
$[\alpha]_D^{23}$ = +53.3 (*c*=0.15, $CHCl_3$); IR $_{max}$ $cm^{-1}$: 2957, 2923, 1751, 1732, 1457, 1376, 1119, 1059, 1009, 881; $^1$H NMR (400 MHz, Chloroform-*d*) δ 5.19 (dd, *J* = 9.8, 1.7 Hz, 1H), 4.25 – 4.10 (m, 2H), 3.98 (d, *J* = 9.5 Hz, 1H), 3.30 (s, 3H), 3.15 – 3.08 (m, 1H), 2.59 – 2.47 (m, 1H), 2.14 – 2.04 (m, 1H), 1.81 – 1.67 (m, 2H), 1.67 (d, *J* = 1.3 Hz, 2H), 1.59 – 1.28 (m, 3H), 1.57 (s, 3H), 1.49 (s, 3H), 1.46 (s, 3H), 1.32 – 0.93 (m, 6H), 1.30 (t, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.85 (t, 3H), 0.80 (d, *J* = 6.6 Hz, 3H), 0.78 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 173.0, 137.1, 130.6, 111.4, 103.9, 88.3, 80.3, 76.1, 61.5, 57.2, 46.2, 45.3, 31.8, 30.5, 30.1, 29.7, 28.5, 28.0, 27.5, 26.2, 21.6, 19.7, 19.3, 19.1, 14.2, 12.4, 11.6; ESI-HRMS calcd for $C_{27}H_{48}O_6Na$ $[M+Na]^+$: 491.3343, found:491.3346.

## Reference:

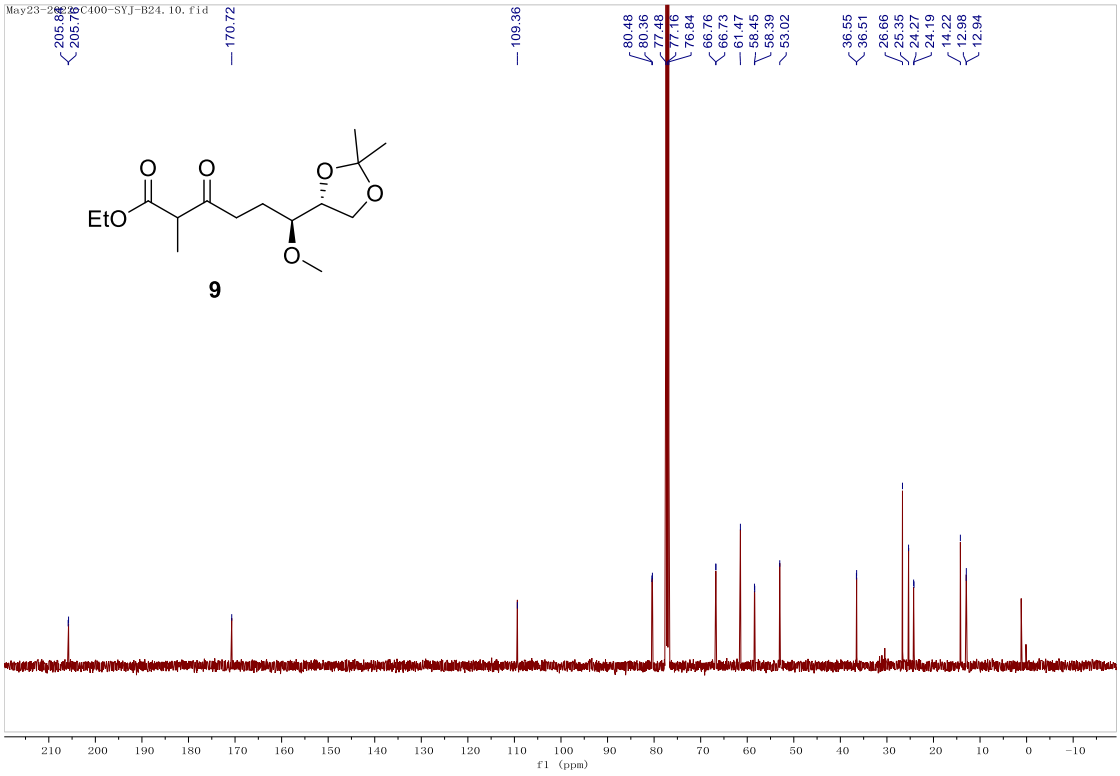
(1) Andre, C.; Bolte, J.; Demuynck, C. Syntheses of L-threose and D-erythrose analogues modified at position 2. *Tetrahedron: Asymmetry* **1998**, *9*, 1359-1367.
(2) Chiu, D. C.; Lin, T. C.; Huang, W. I.; Cheng, T. J.; Tsai, K. C.; Fang, J. M. Peramivir analogues bearing hydrophilic side chains exhibit higher activities against H275Y mutant than wild-type influenza virus. *Org. Biomol. Chem.* **2017**, *15*, 9910-9922.
(3) Organ, M. G.; Bilokin, Y. V.; Bratovanov, S. Approach toward the total synthesis of orevactaene. 2. convergent and stereoselective synthesis of the C18−C31 domain of orevactaene. evidence for the relative configuration of the side chain. *J. Org. Chem.* **2002**, *67*, 5176-5183.
(4) Ding, F.; William, R.; Leow, M. L.; Chai, H.; Fong, J. Z. M.; Liu, X.-W. Directed orthometalation and the asymmetric total synthesis of N-deoxymilitarinone A and torrubiellone B. *Org. Lett.* **2014**, *16*, 26-29.
(5) Tokuyama, H.; Yamada, K.; Fujiwara, H.; Sakata, J.; Okano, K.; Sappan, M.; Isaka, M. Structural Determination of (−)-SCH 64874 and Hirsutellomycin by Semisynthesis. *J. Org. Chem.* 2017, 82, 353-371.
(6) Takahashi, N.; Hayashi, H.; Poznaks, V.; Kakeya, H. Total synthesis of verucopeptin, an inhibitor of hypoxia-inducible factor 1 (HIF-1). *Chem. Commun.* **2019**, *55*, 11956-11959.

# NMR spectra:

## $^{1}$H NMR (400 MHz, $CDCl_3$):




## $^{13}$C NMR (100 MHz, $CDCl_3$):



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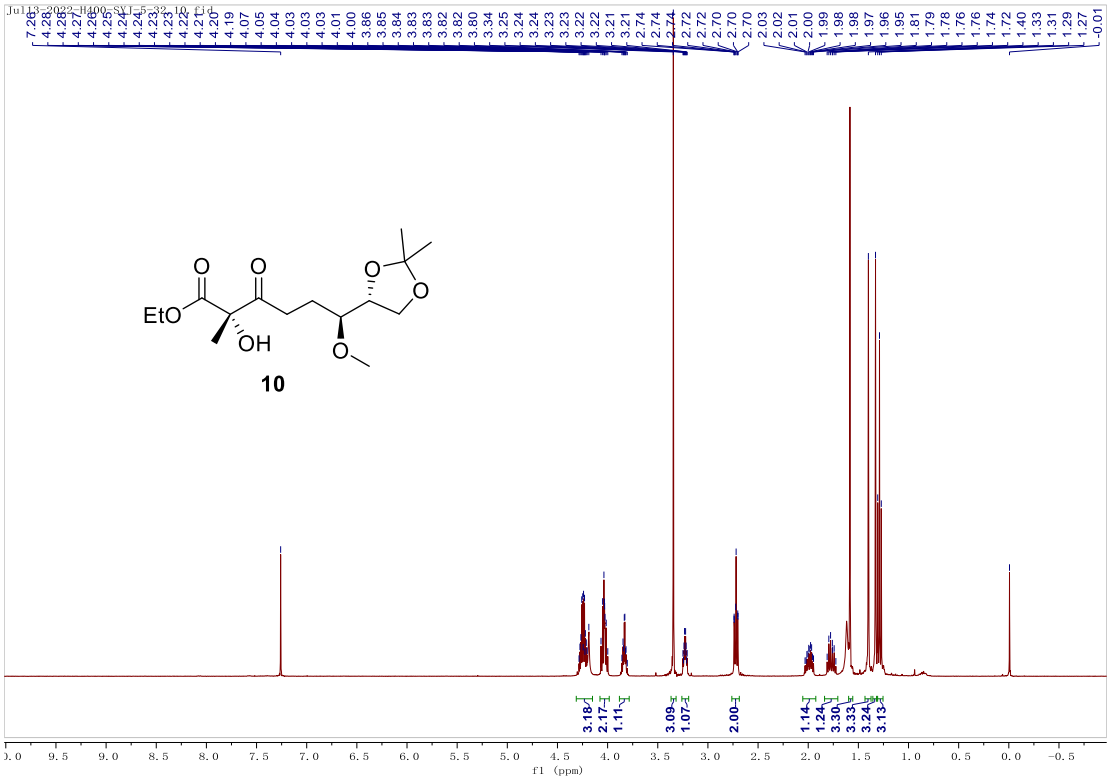


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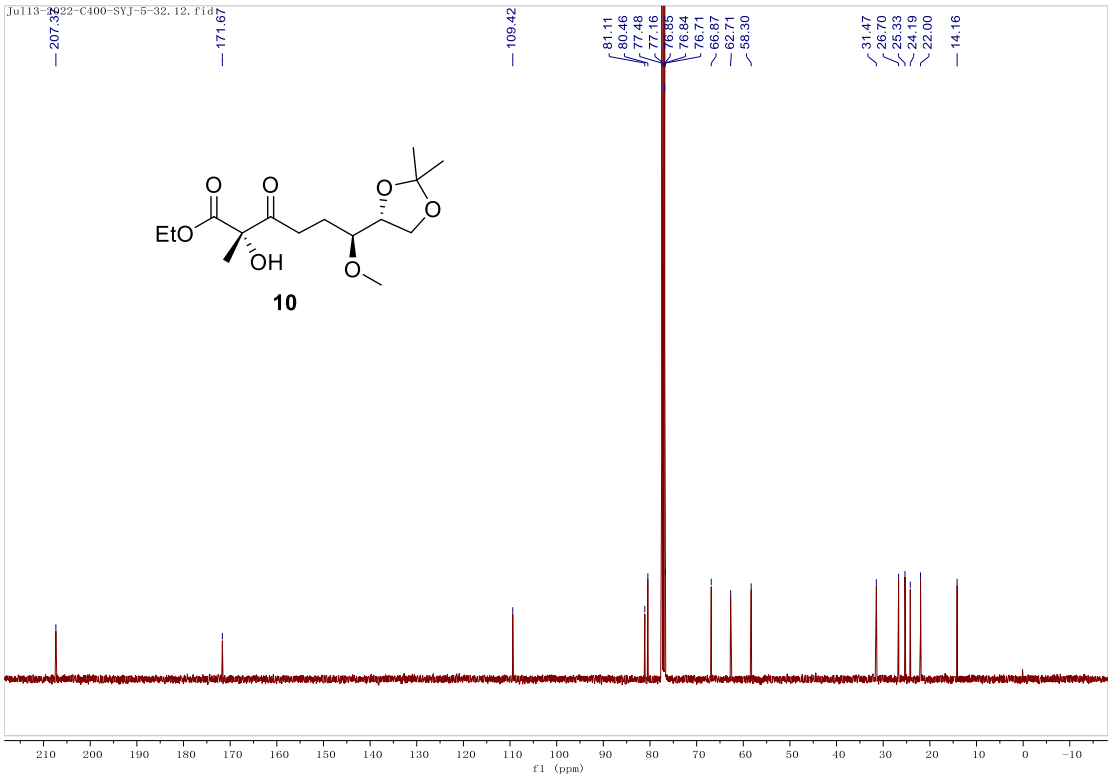

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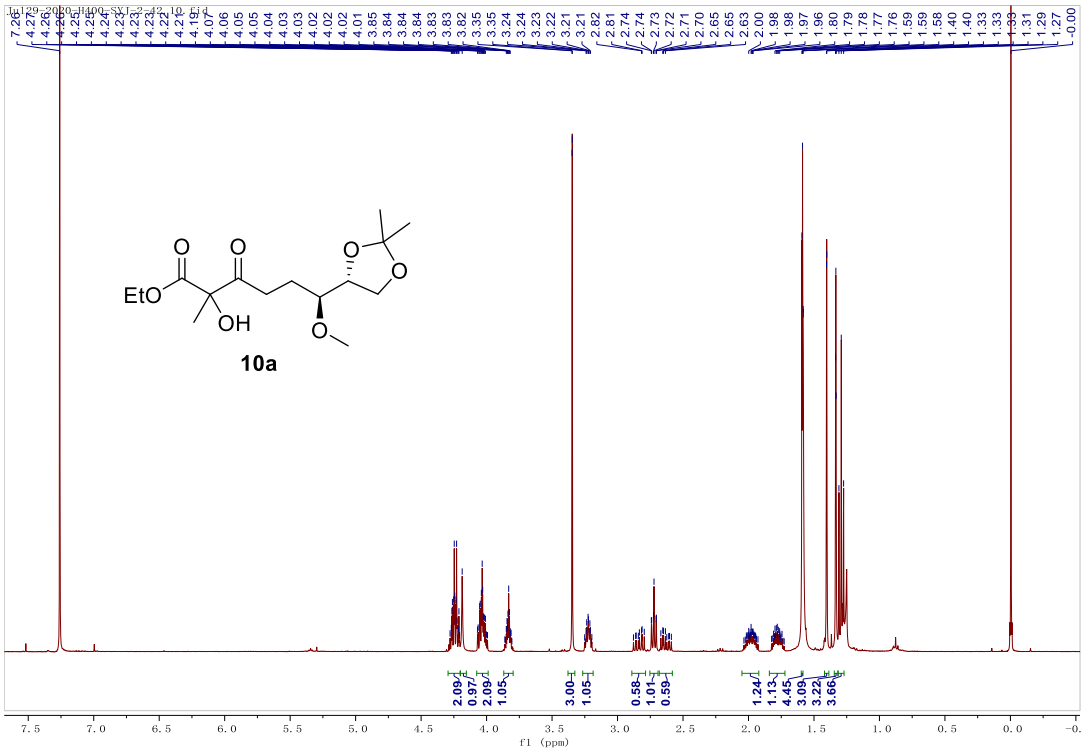
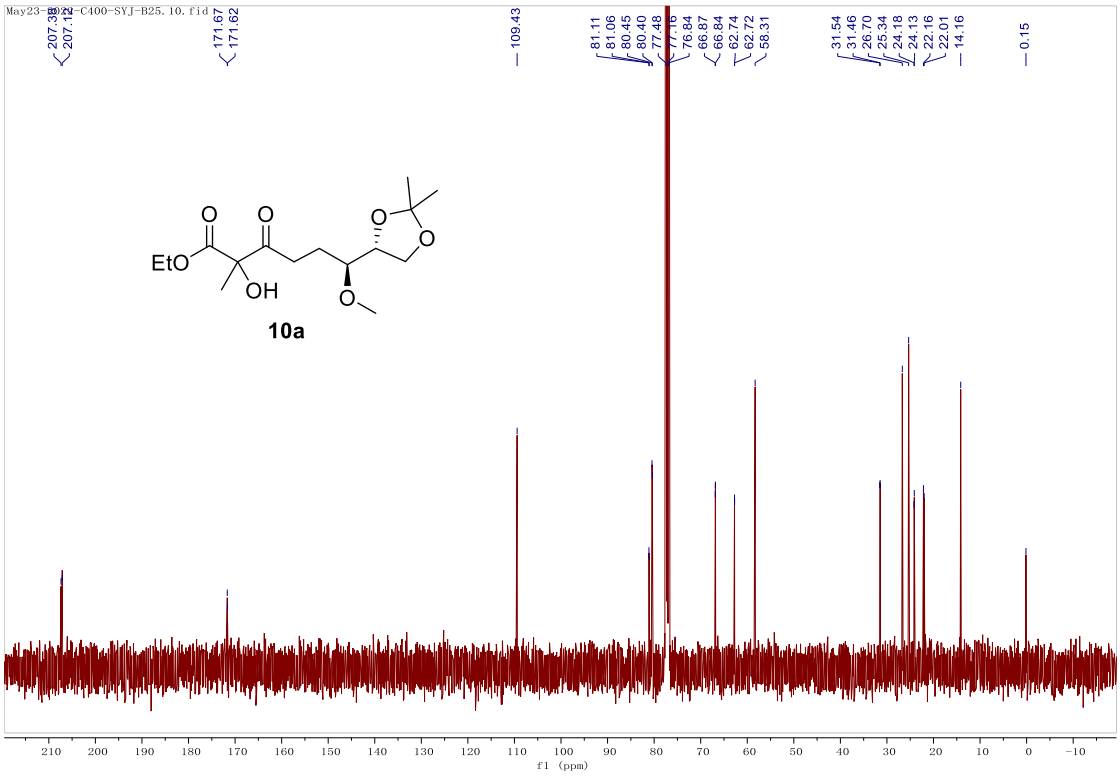
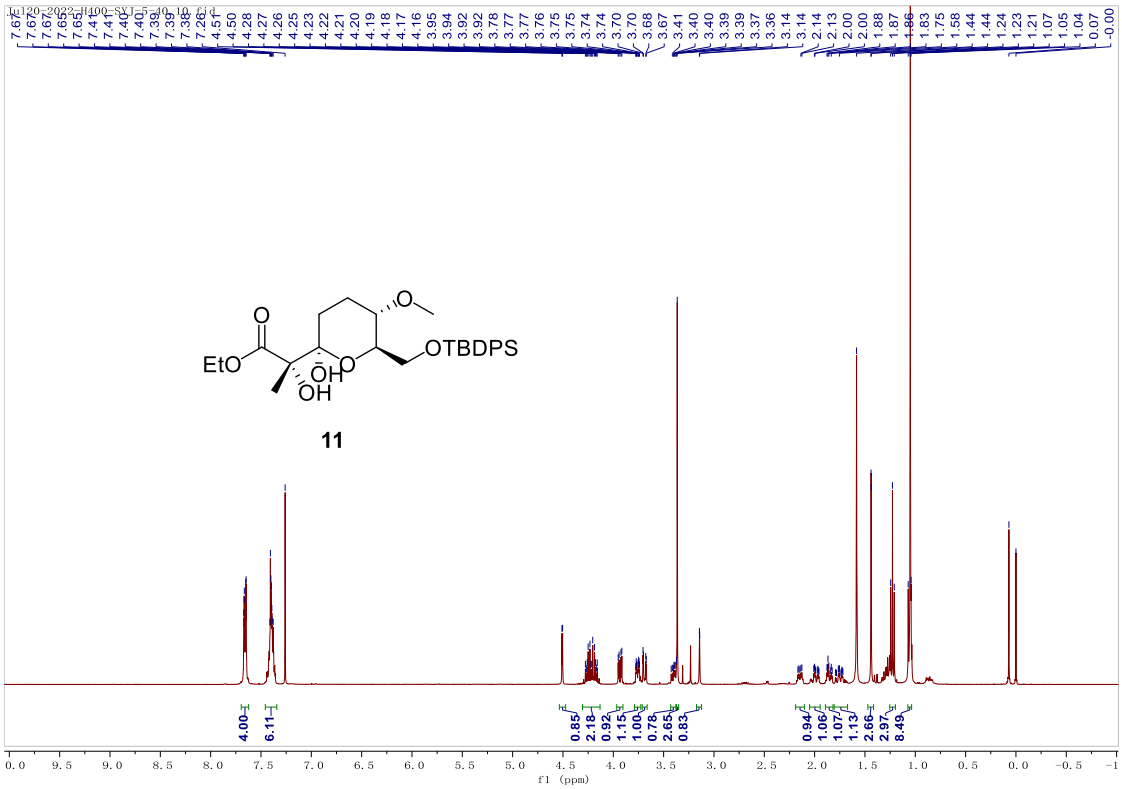


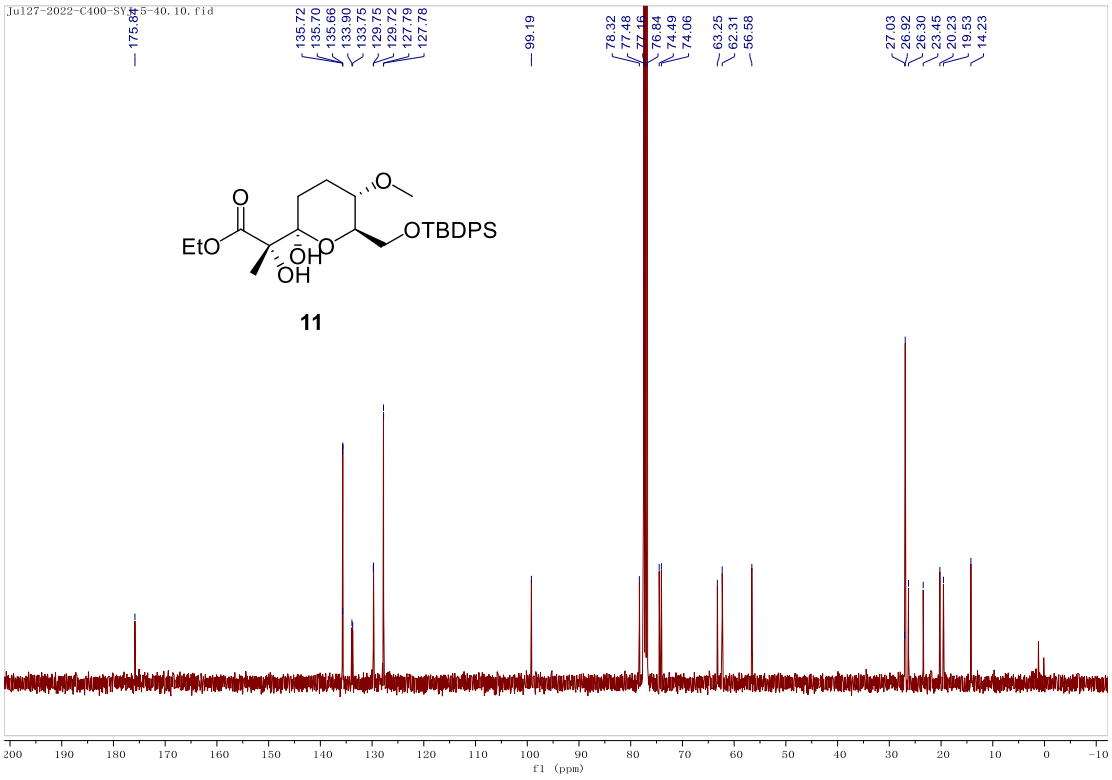

**$^{13}$C NMR (100 MHz, $CDCl_3$):**



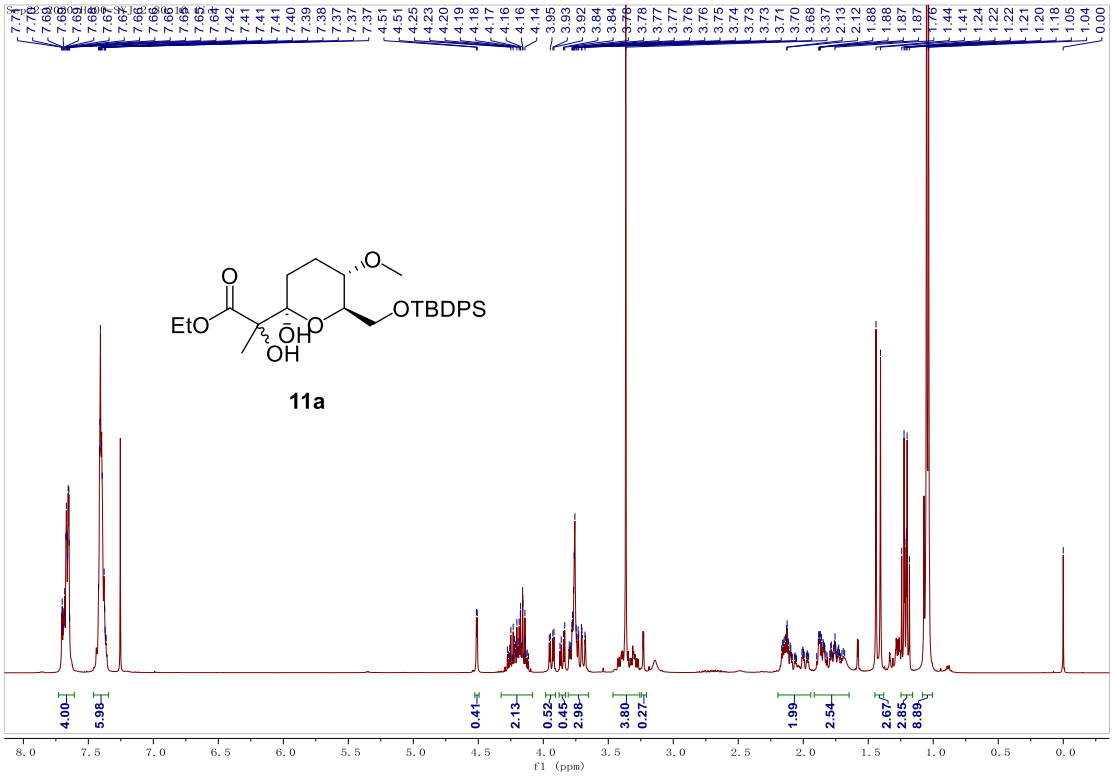
**$^{1}$H NMR (400 MHz, $CDCl_3$):**



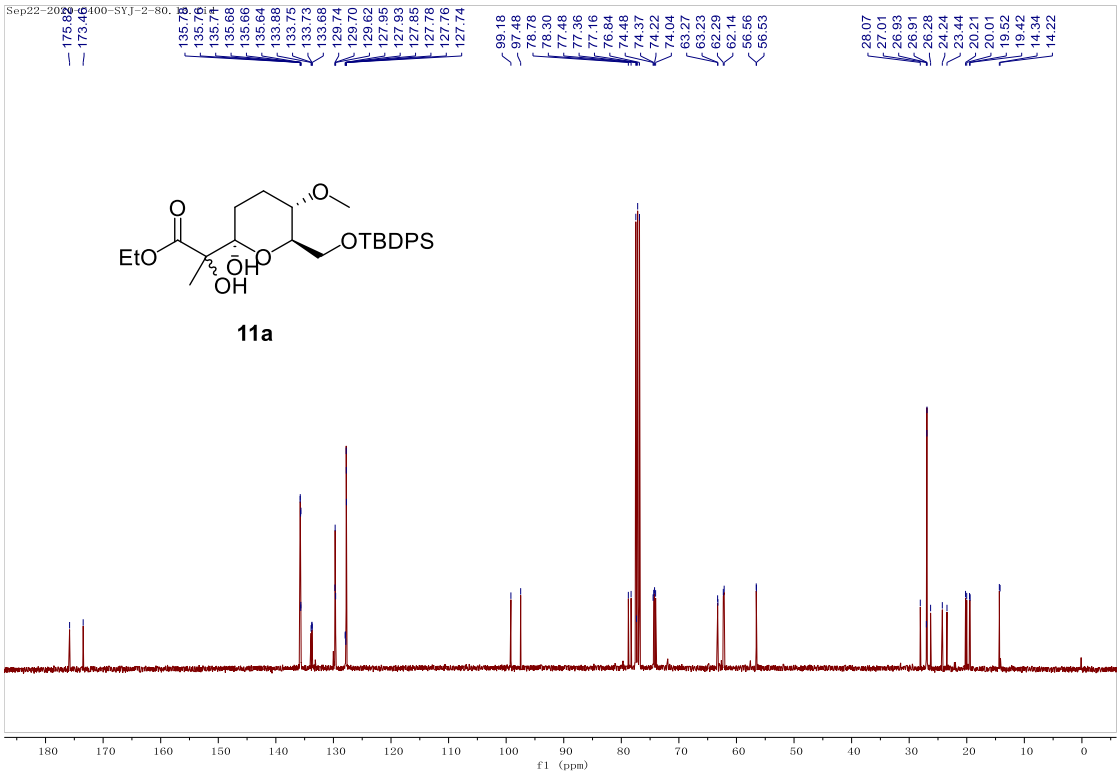

**$^{13}$C NMR (100 MHz, $CDCl_3$):**



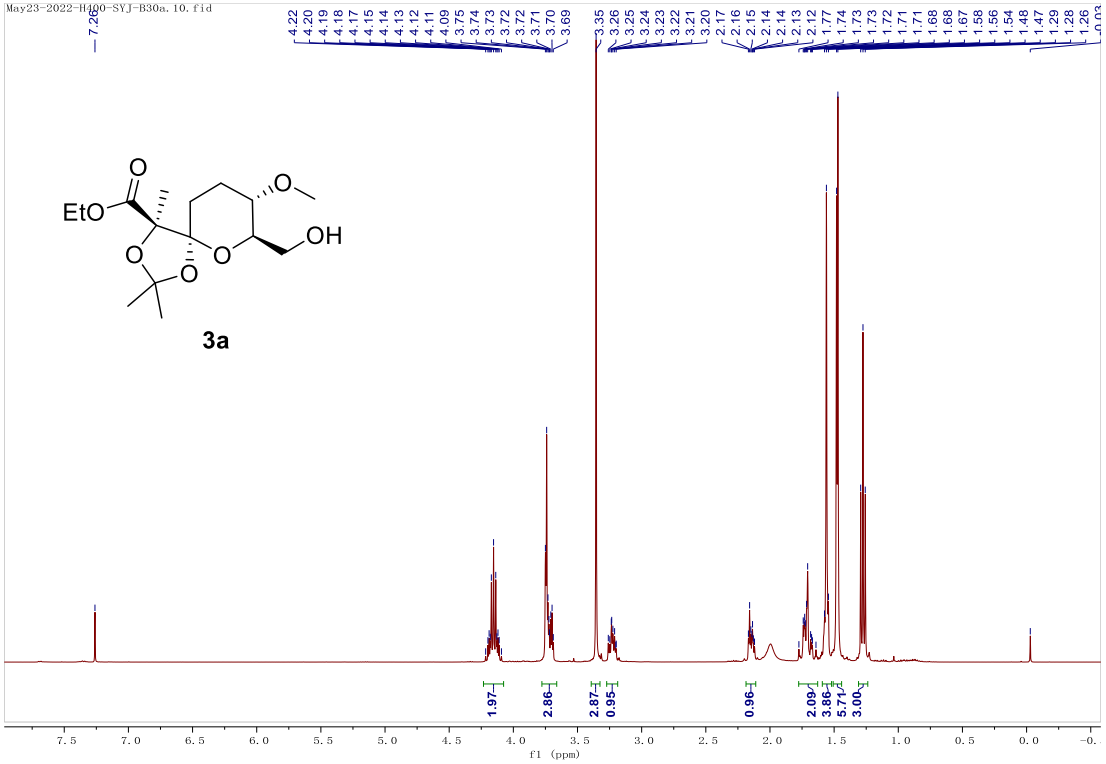
**$^{1}$H NMR (400 MHz, $CDCl_3$):**



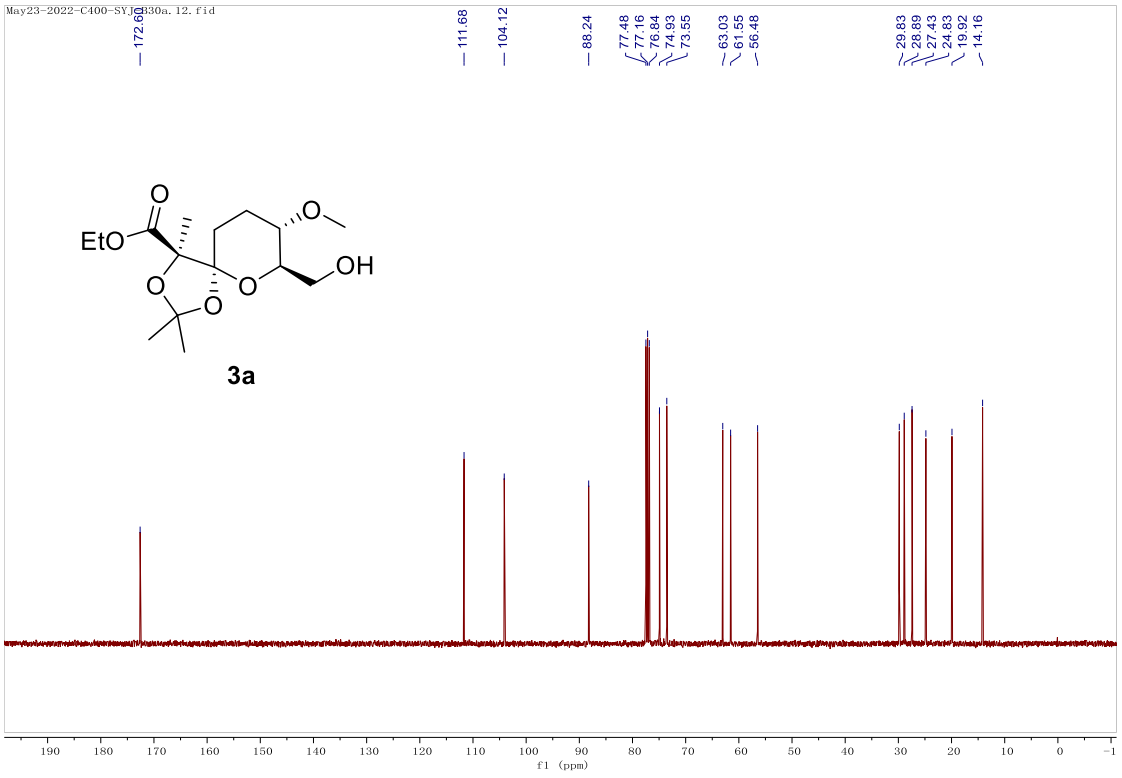

**$^{13}$C NMR (100 MHz, $CDCl_3$):**



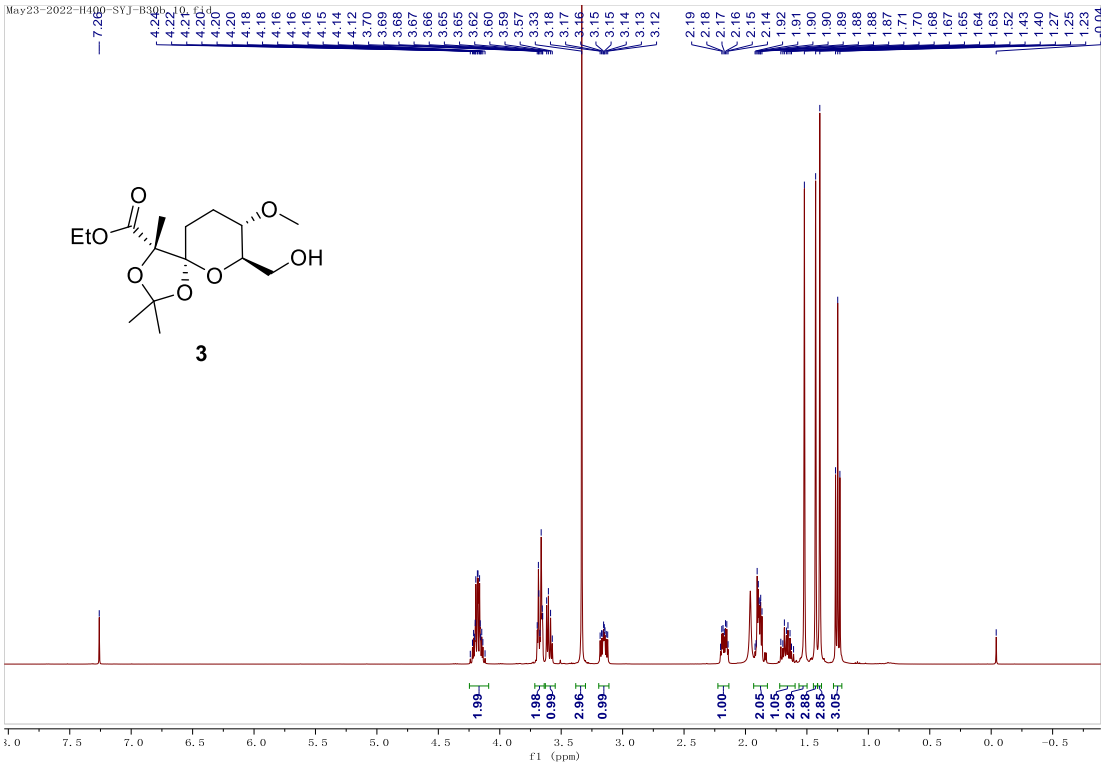
**$^{1}$H NMR (400 MHz, $CDCl_3$):**



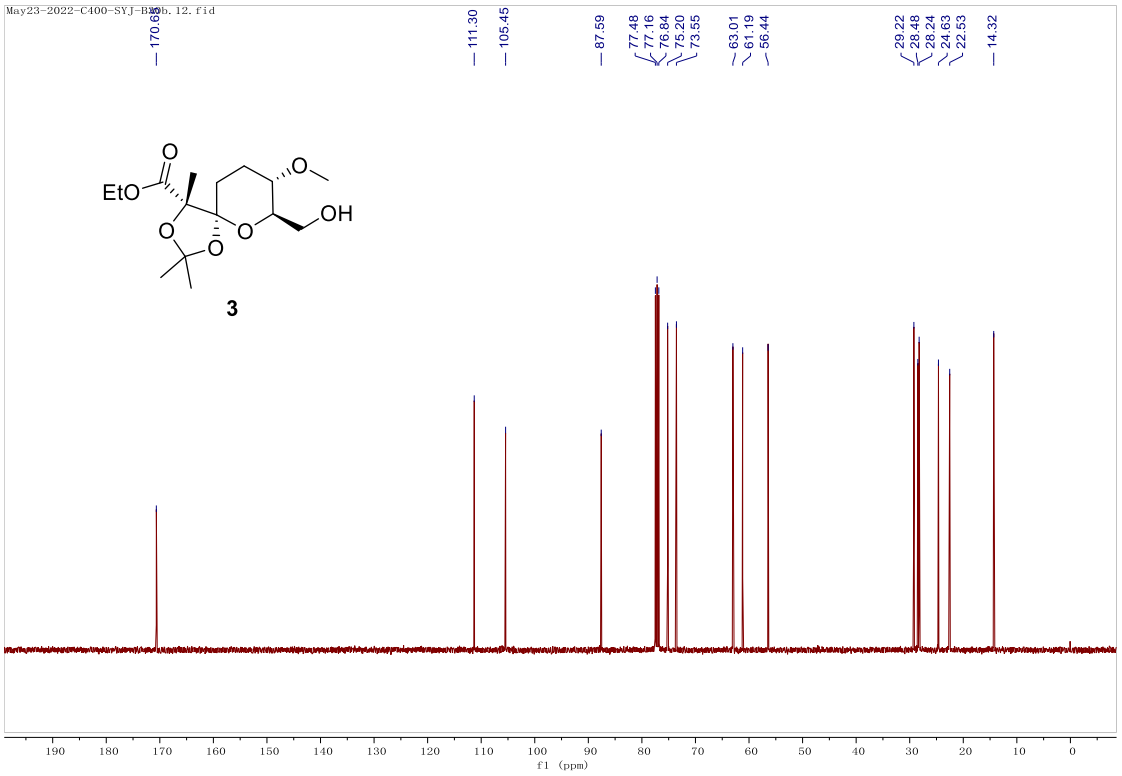

**$^{13}$C NMR (100 MHz, $CDCl_3$):**



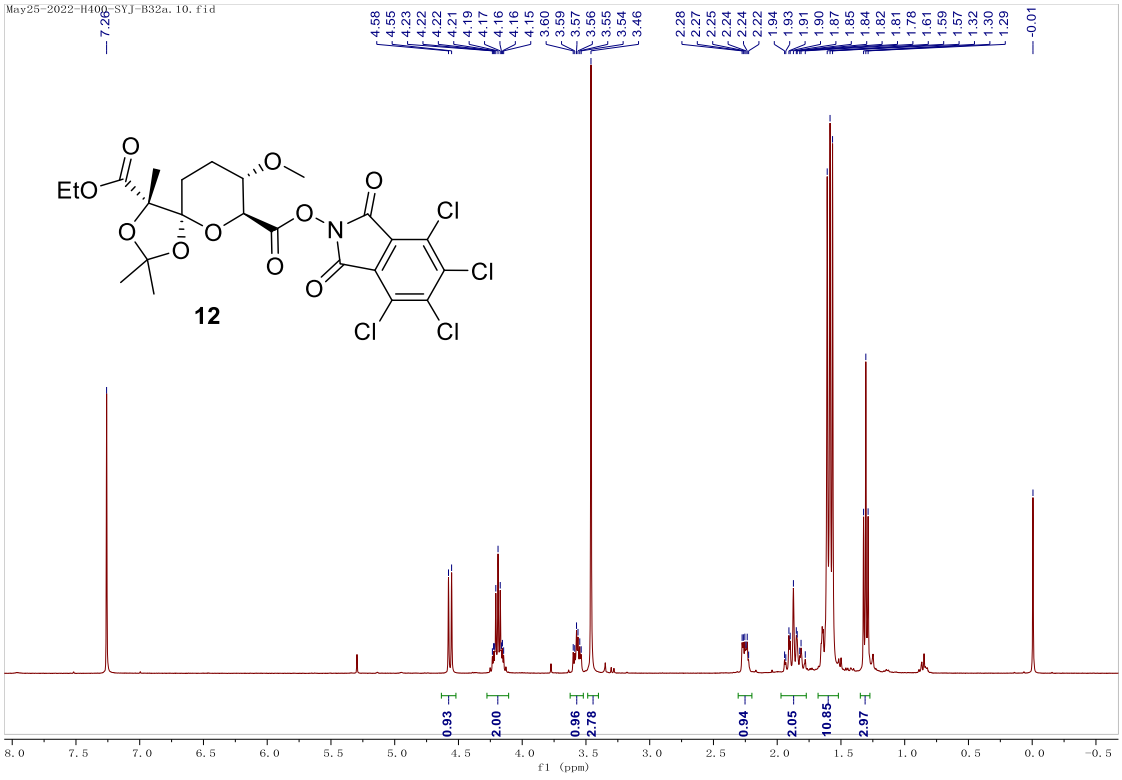
**$^{1}$H NMR (400 MHz, $CDCl_3$):**



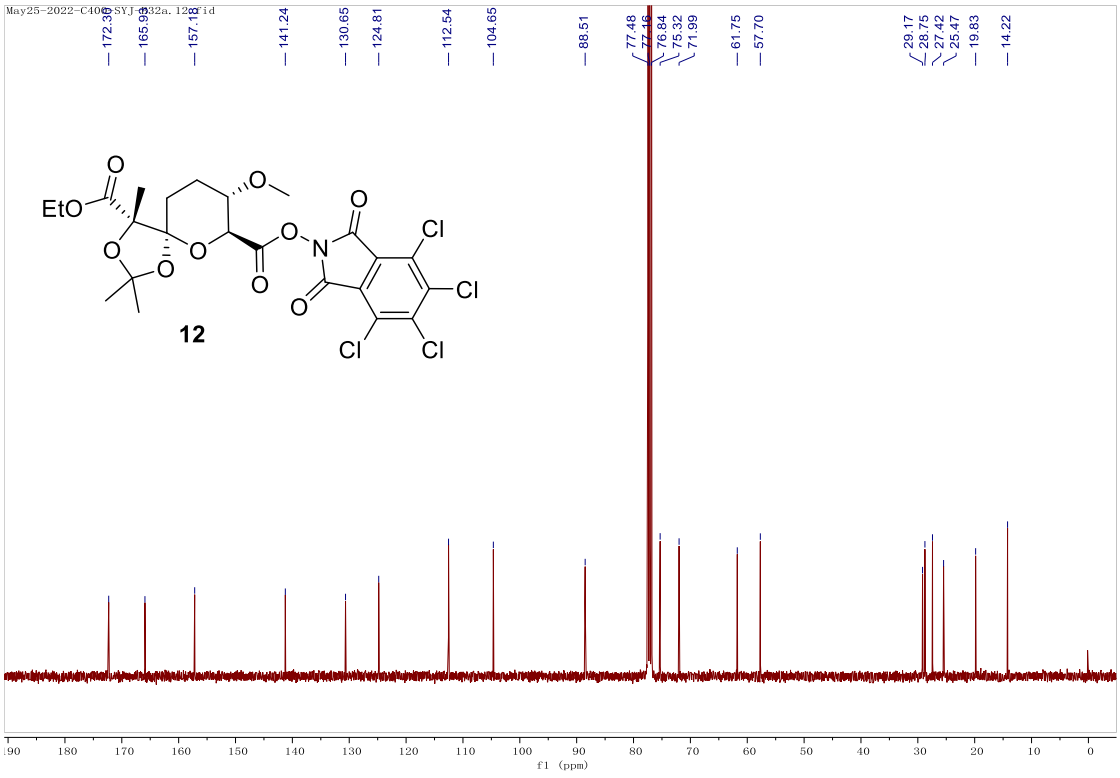

**$^{13}$C NMR (100 MHz, $CDCl_3$):**



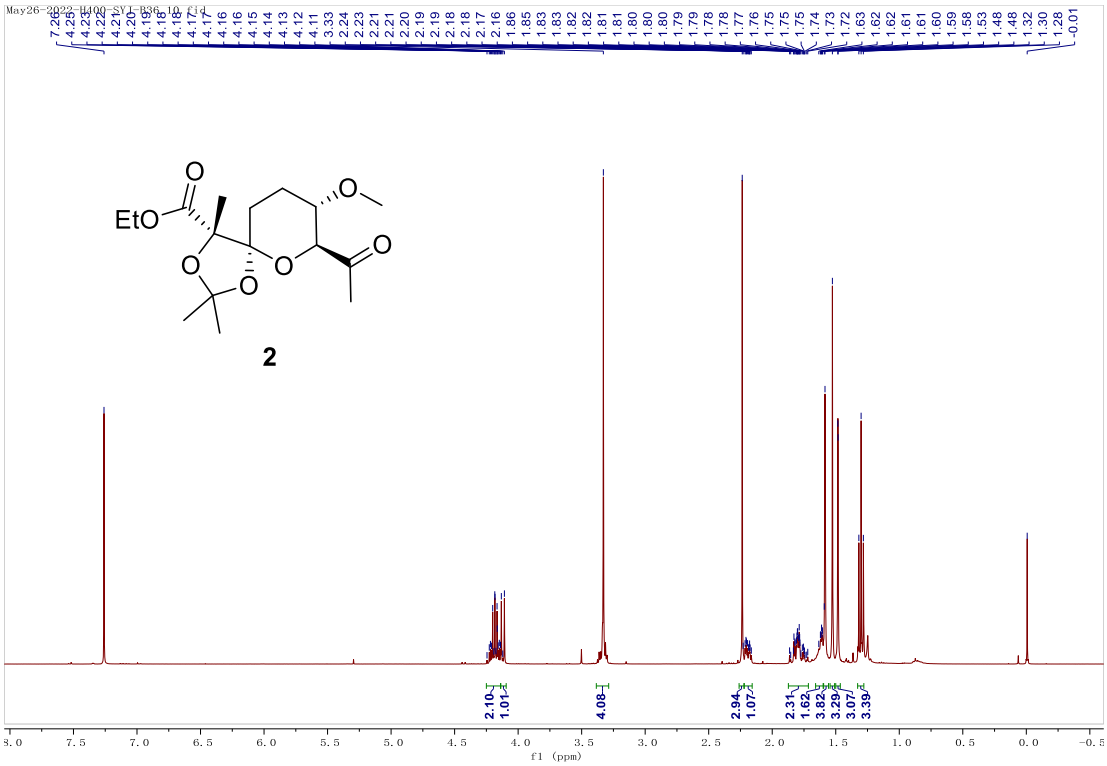
**$^{1}$H NMR (400 MHz, $CDCl_3$):**



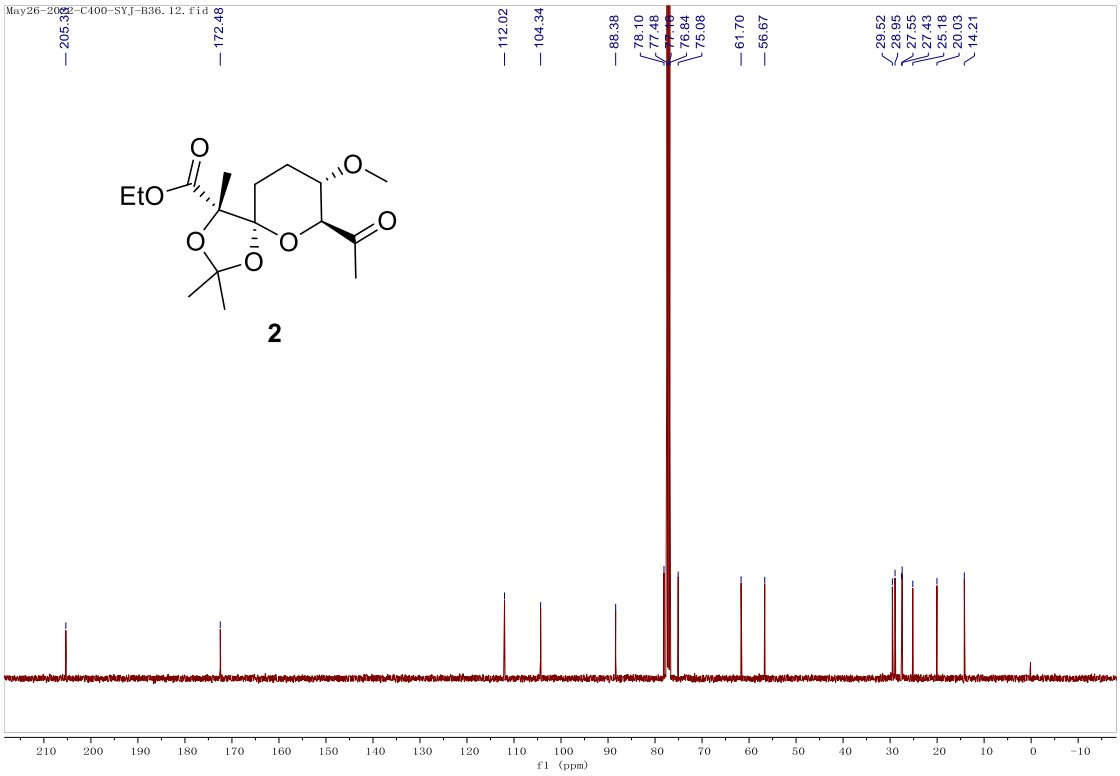

**$^{13}$C NMR (100 MHz, $CDCl_3$):**



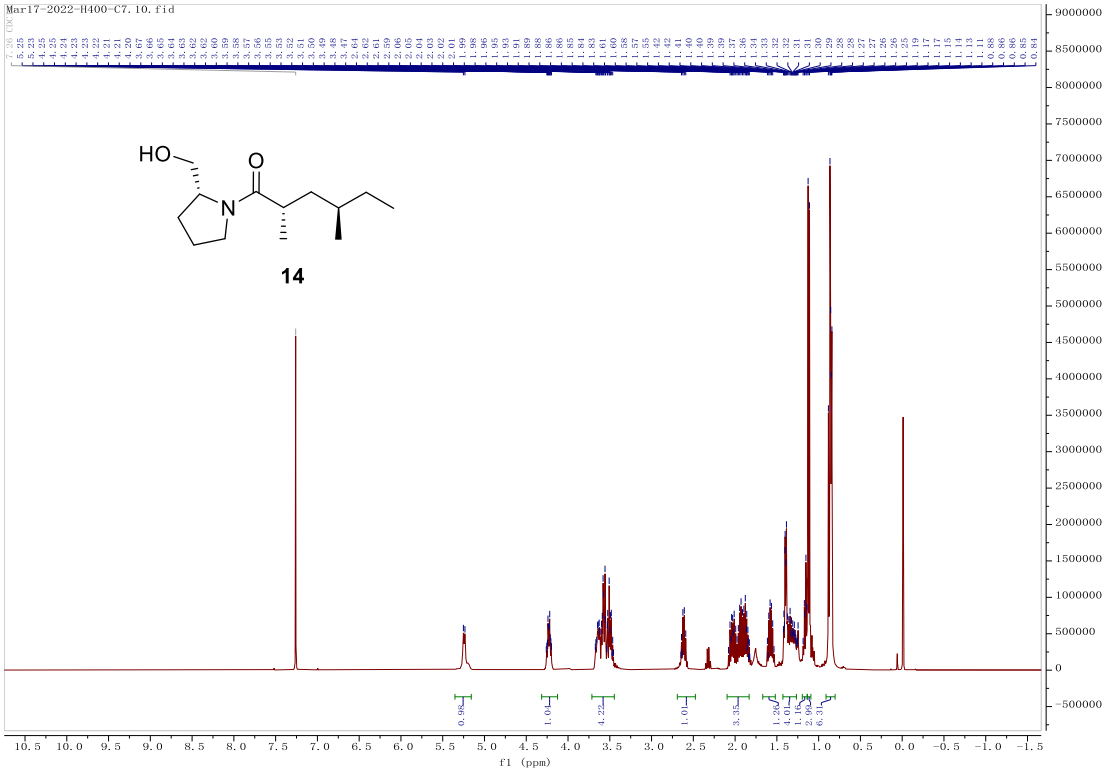
**$^{1}$H NMR (400 MHz, $CDCl_3$):**



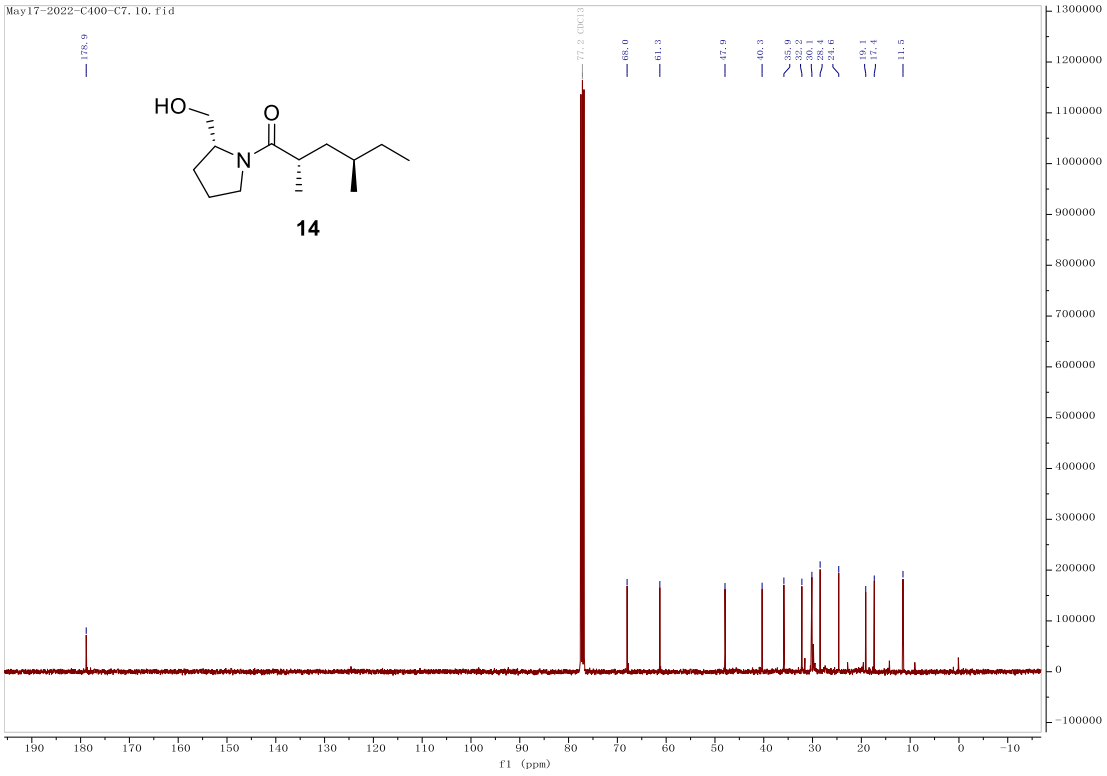

**$^{13}$C NMR (100 MHz, $CDCl_3$):**



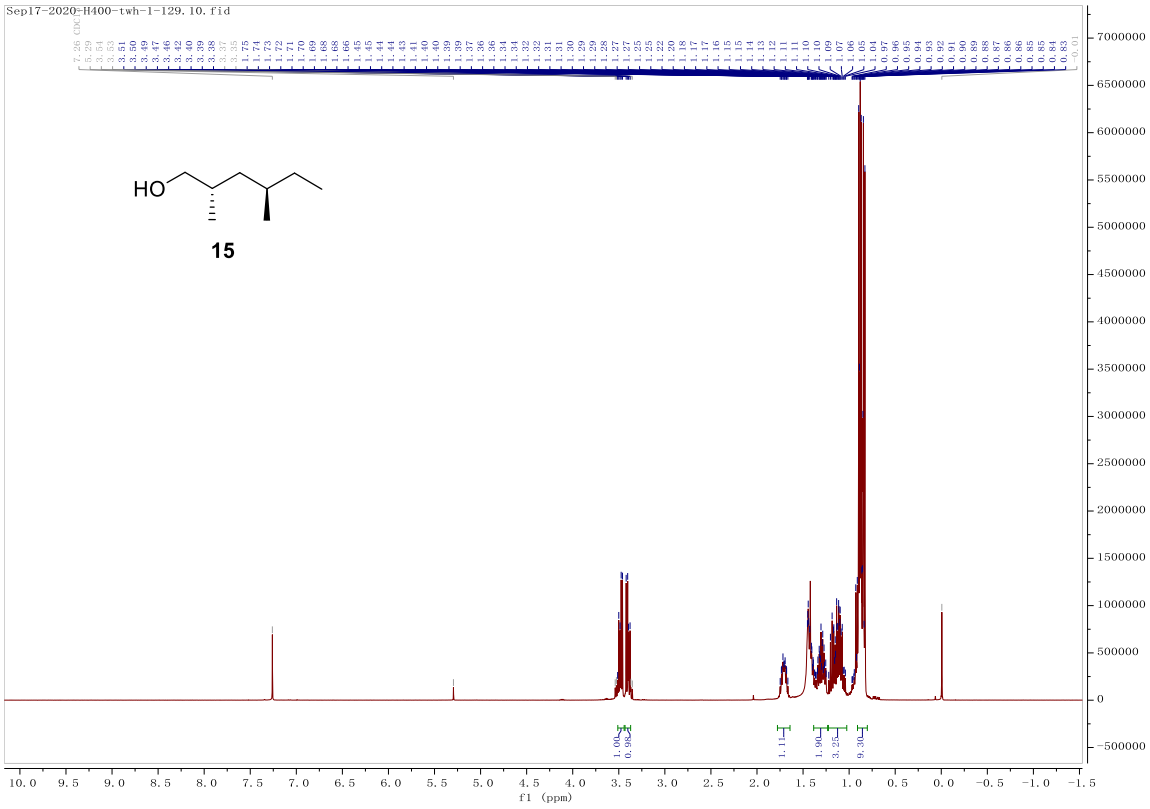
**$^{1}$H NMR (400 MHz, $CDCl_3$):**



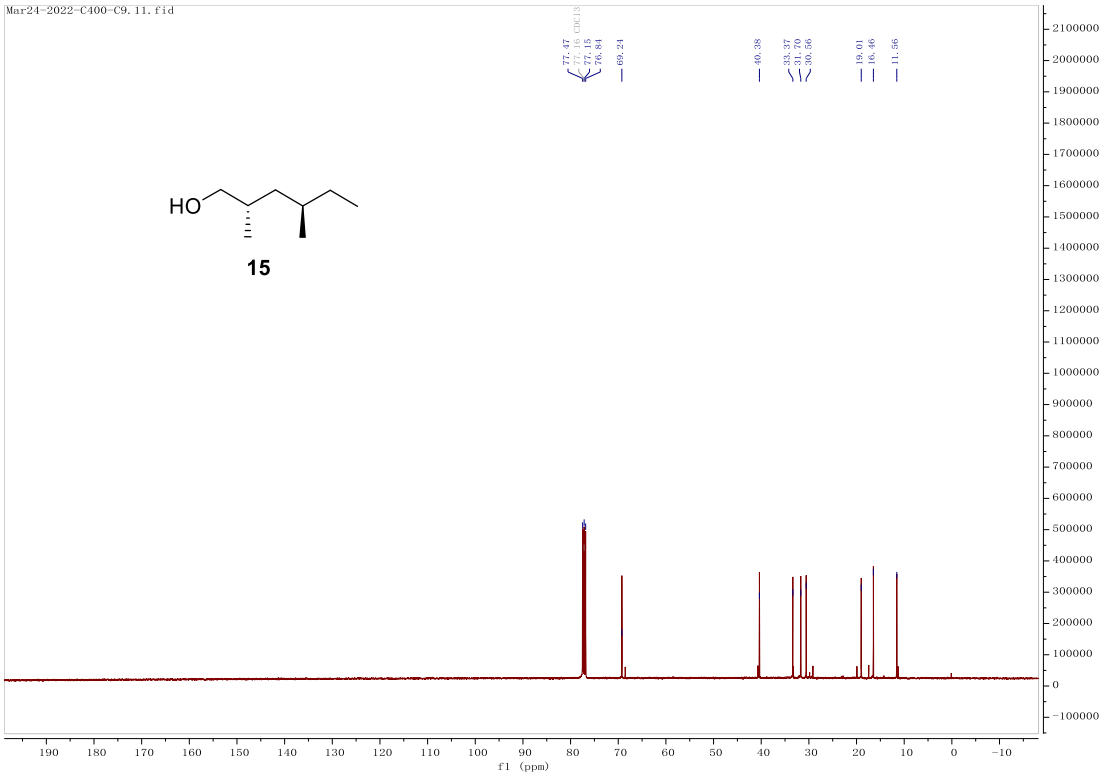

**$^{13}$C NMR (100 MHz, $CDCl_3$):**



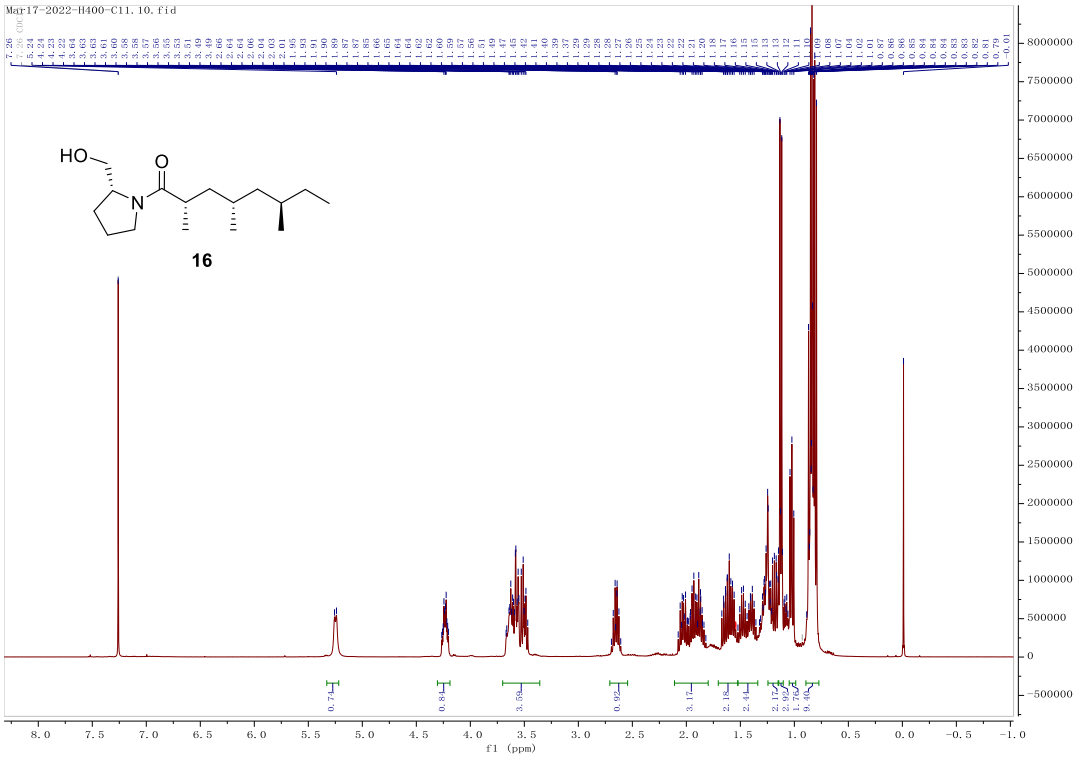
**$^{1}$H NMR (400 MHz, $CDCl_3$):**



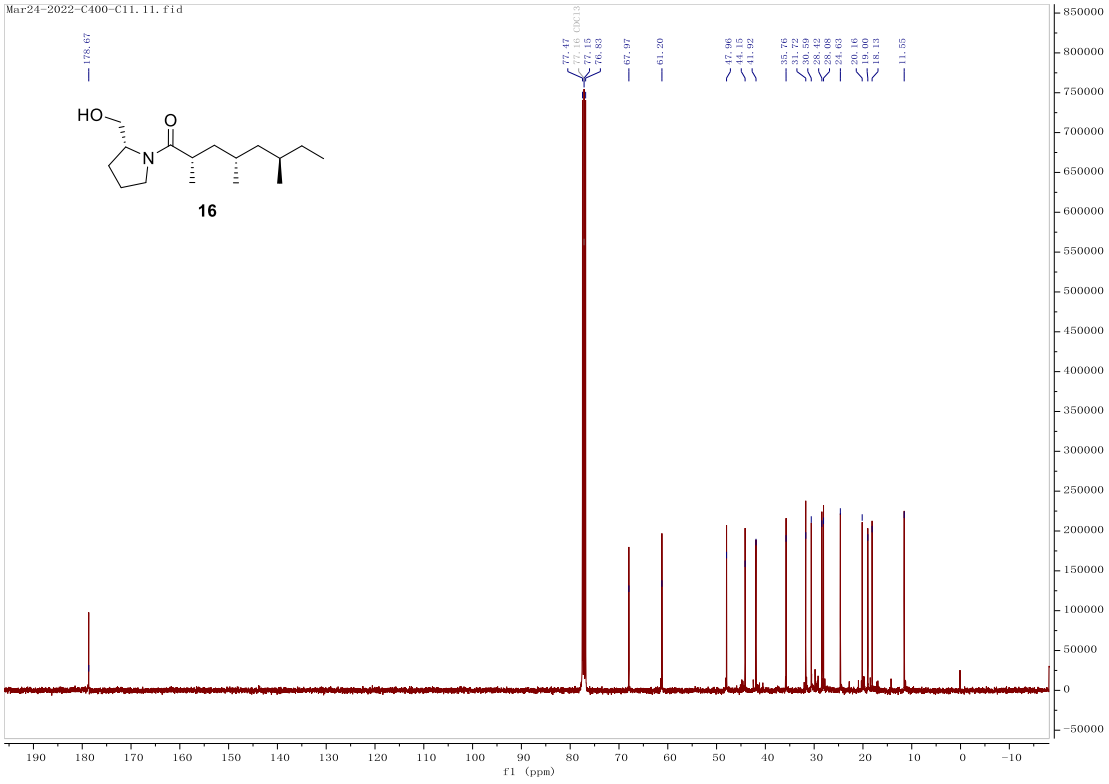

**$^{13}$C NMR (100 MHz, $CDCl_3$):**



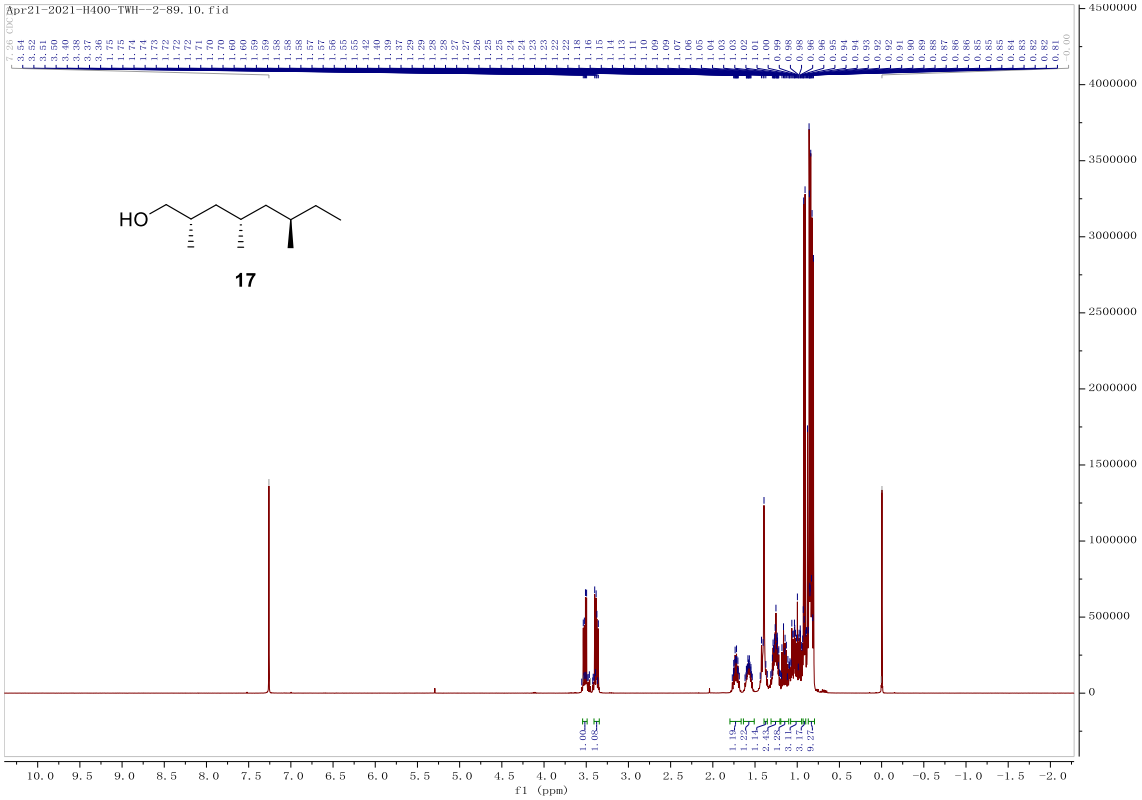
**$^{1}$H NMR (400 MHz, $CDCl_3$):**



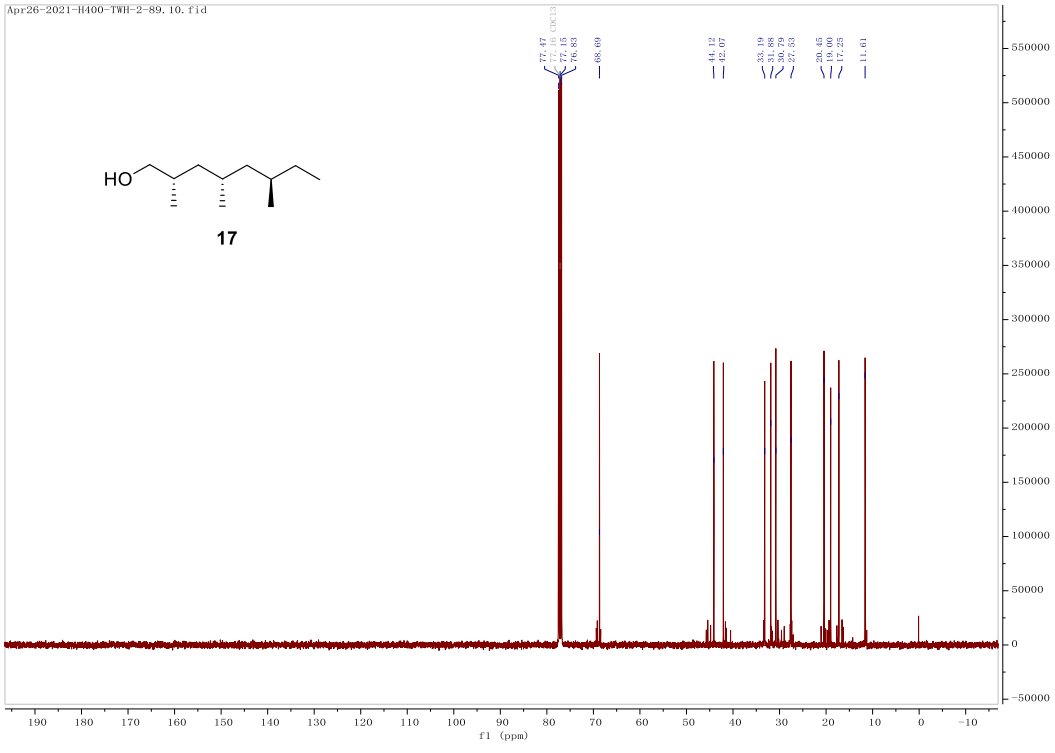

**$^{13}$C NMR (100 MHz, $CDCl_3$):**



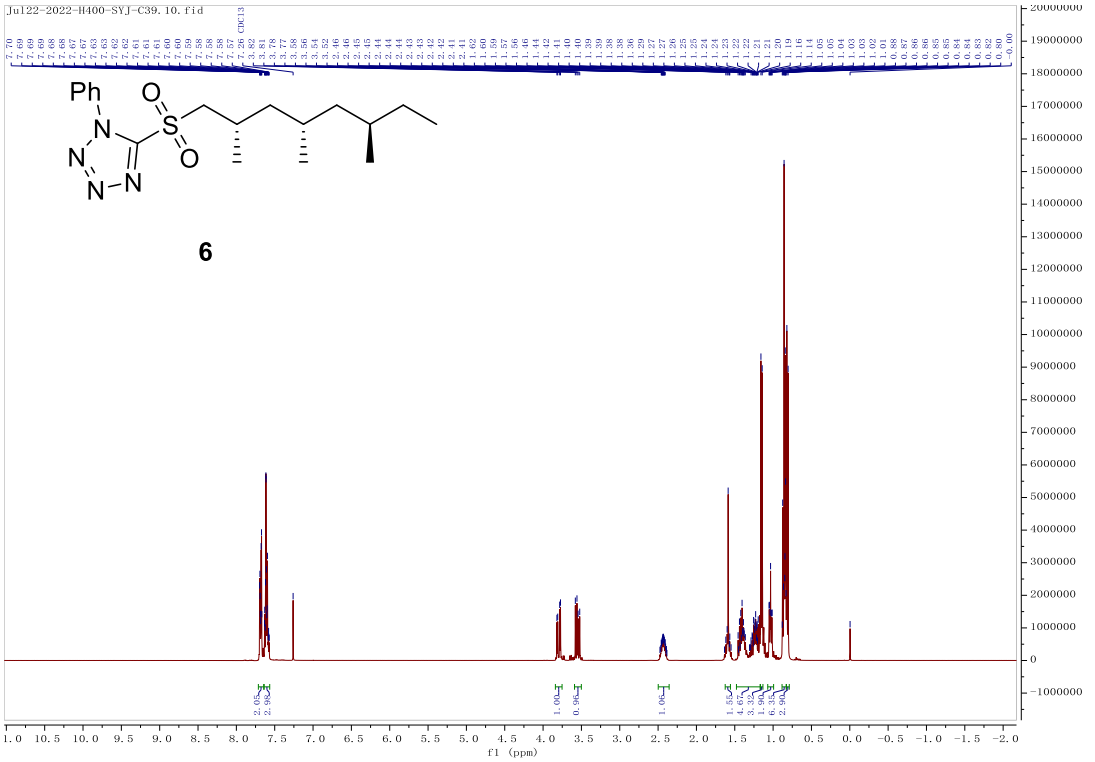
**$^{1}$H NMR (400 MHz, $CDCl_3$):**



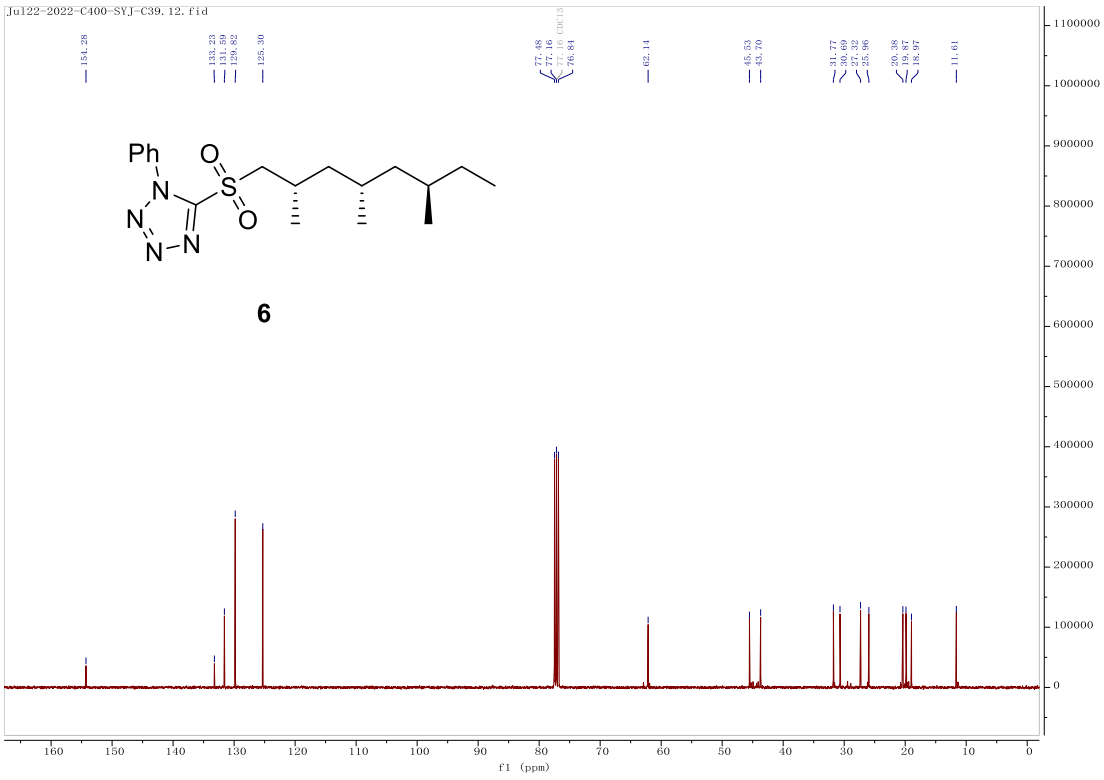

**$^{13}$C NMR (100 MHz, $CDCl_3$):**



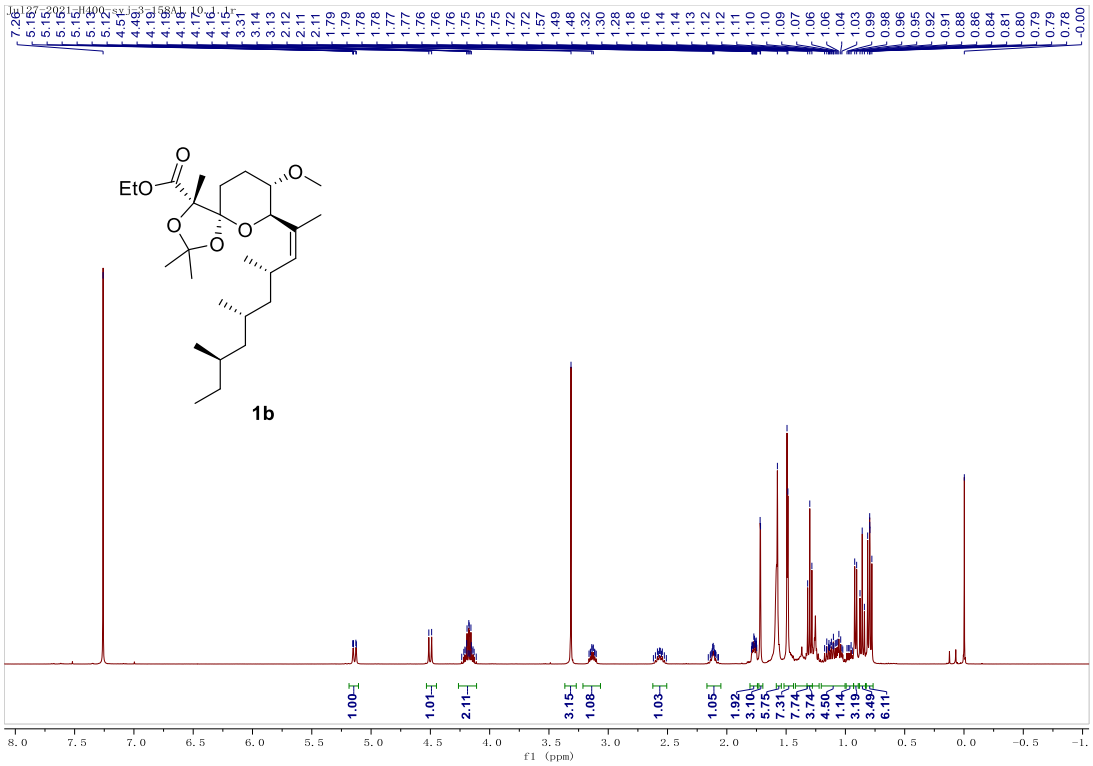
**$^{1}$H NMR (400 MHz, $CDCl_3$):**



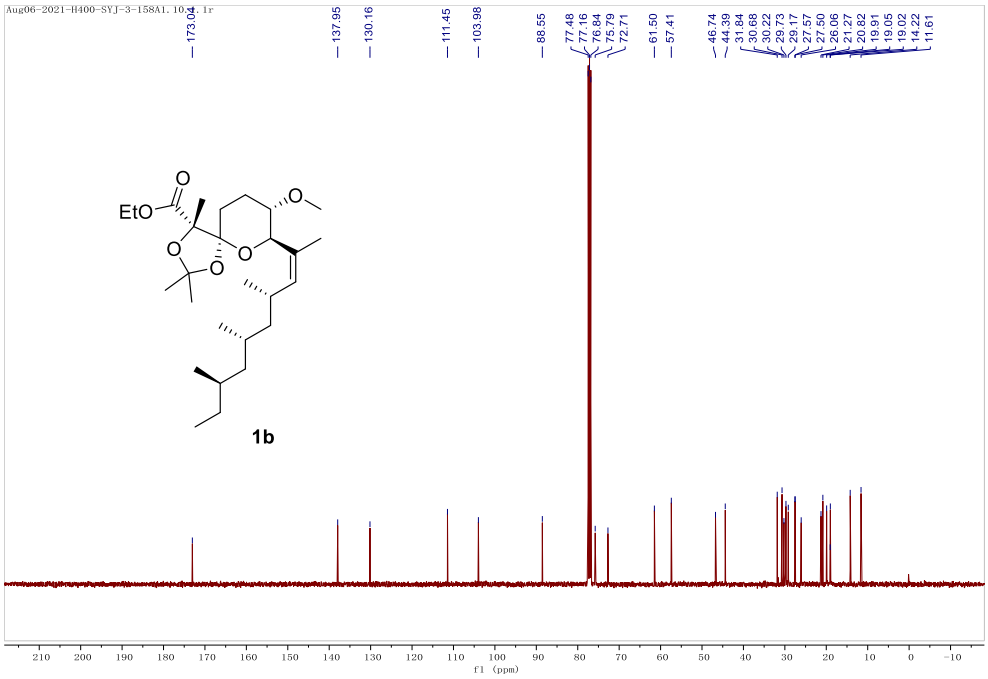

**$^{13}$C NMR (100 MHz, $CDCl_3$):**



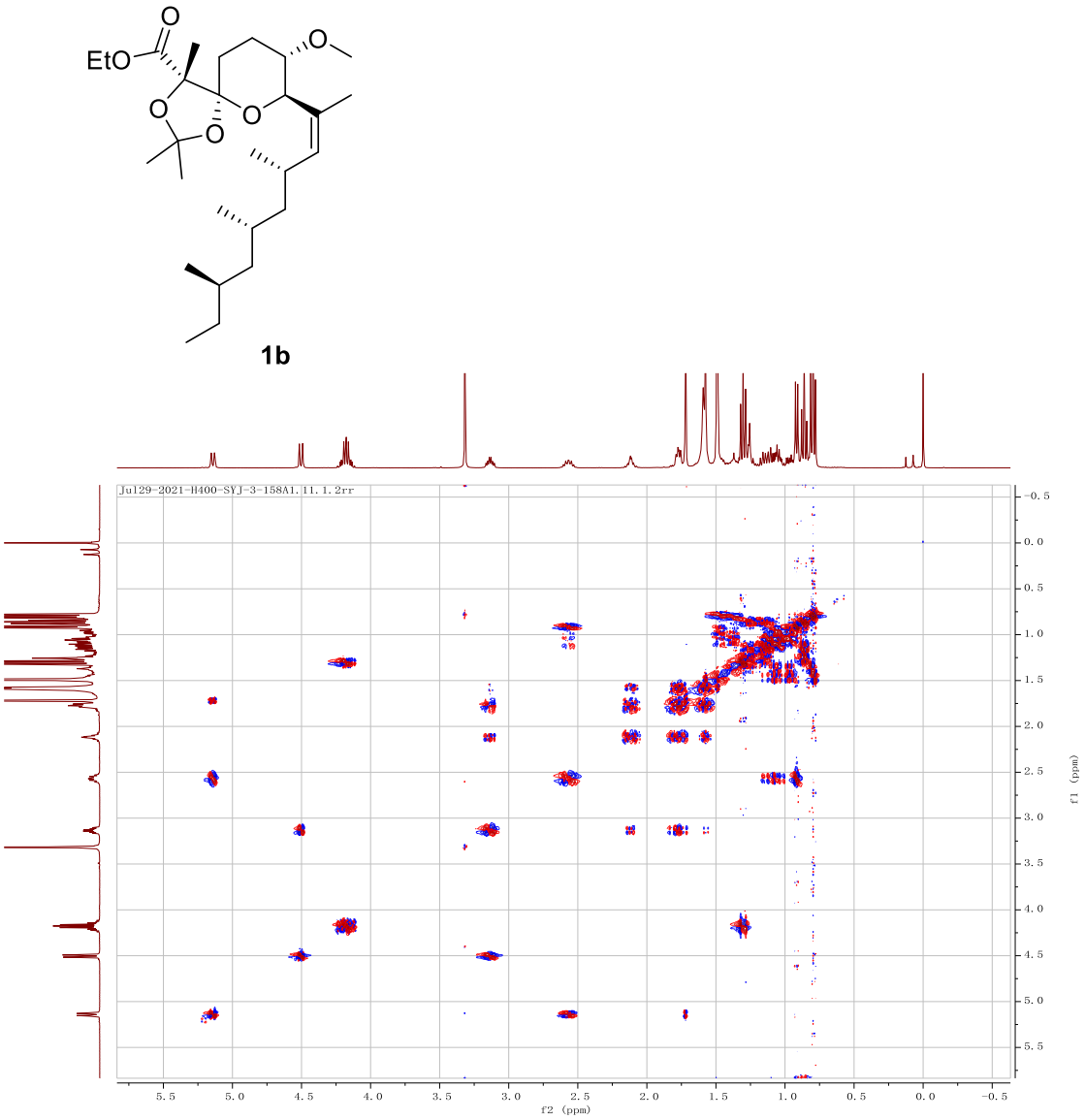
**$^{1}$H NMR (400 MHz, $CDCl_3$):**



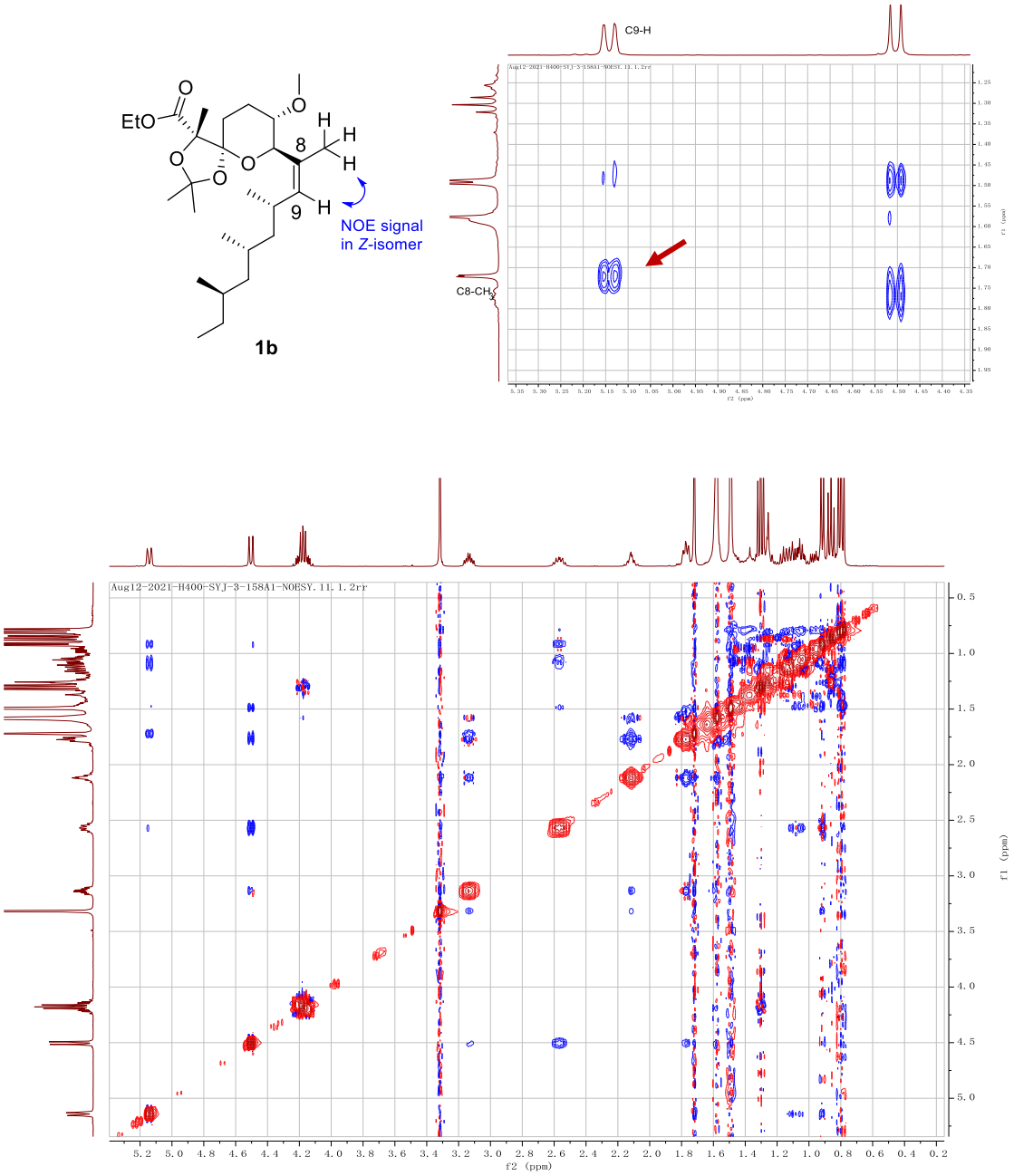

**$^{13}$C NMR (100 MHz, $CDCl_3$):**



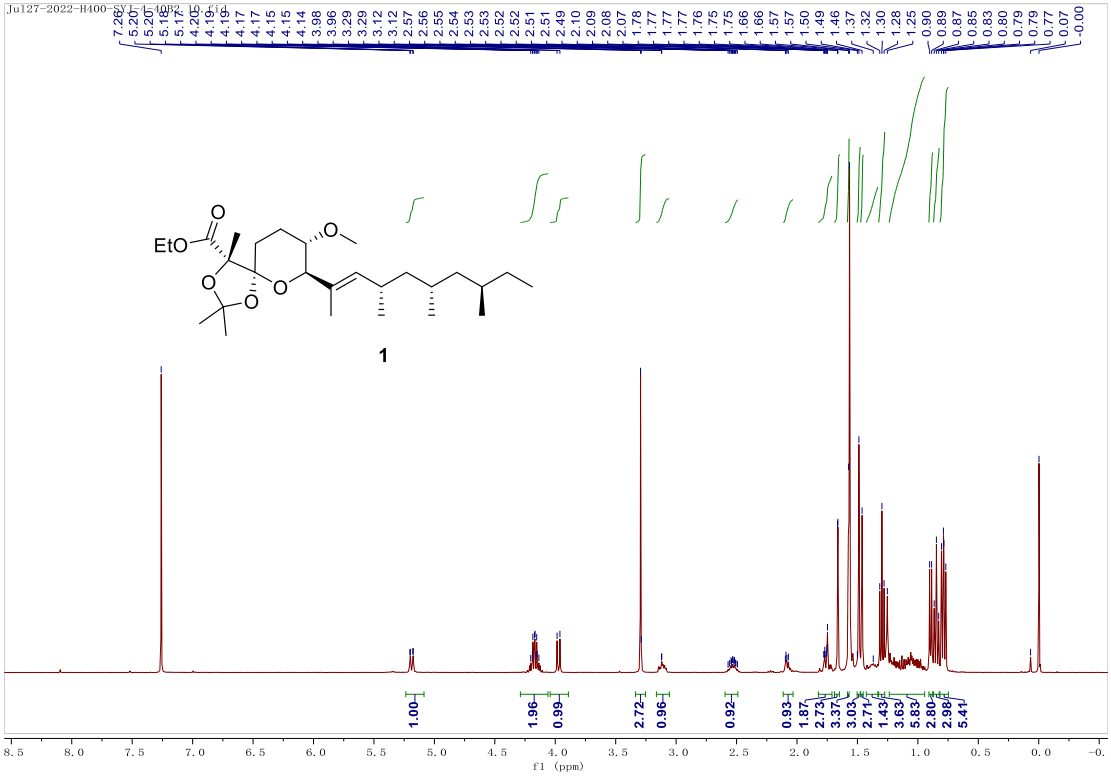
**$^{1}$H, $^{1}$H COSY of 1b:**



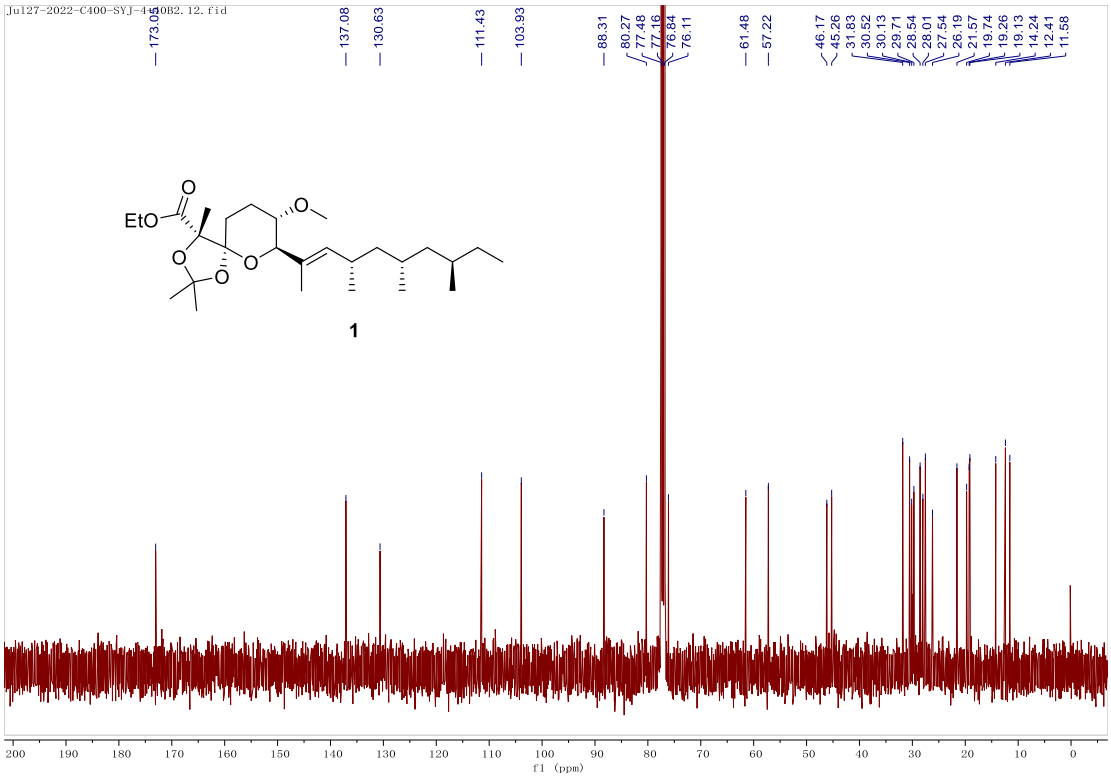
**NOESY of 1b:**


EtO
O
O
O
O
O
8
9
H
H
H
H
NOE signal
in Z-isomer
1b
C9-H
C8-CH
Aug12-2021-H400-SYJ-3-158A1-NOESY. 11. 1. 2rr
f2 (ppm)
f1 (ppm)

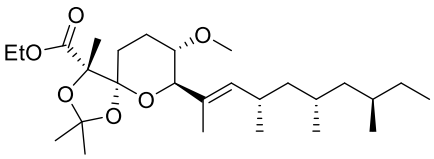
**$^{1}$H NMR (400 MHz, $CDCl_3$):**



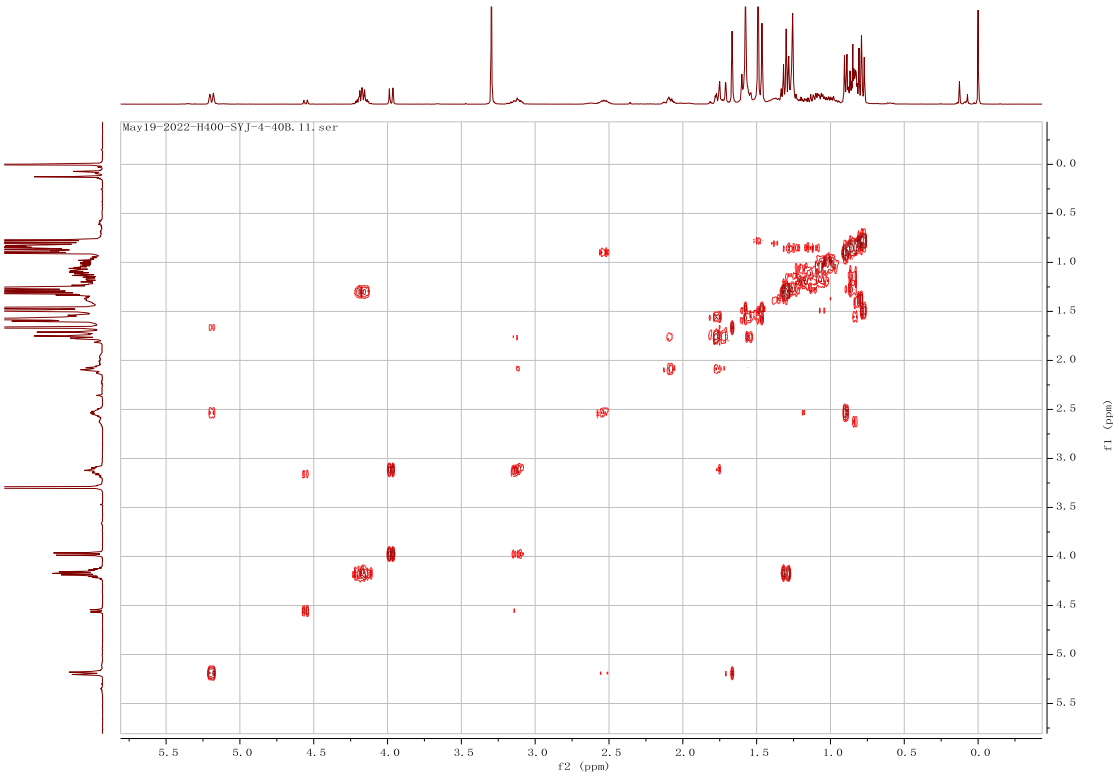

**$^{13}$C NMR (100 MHz, $CDCl_3$):**



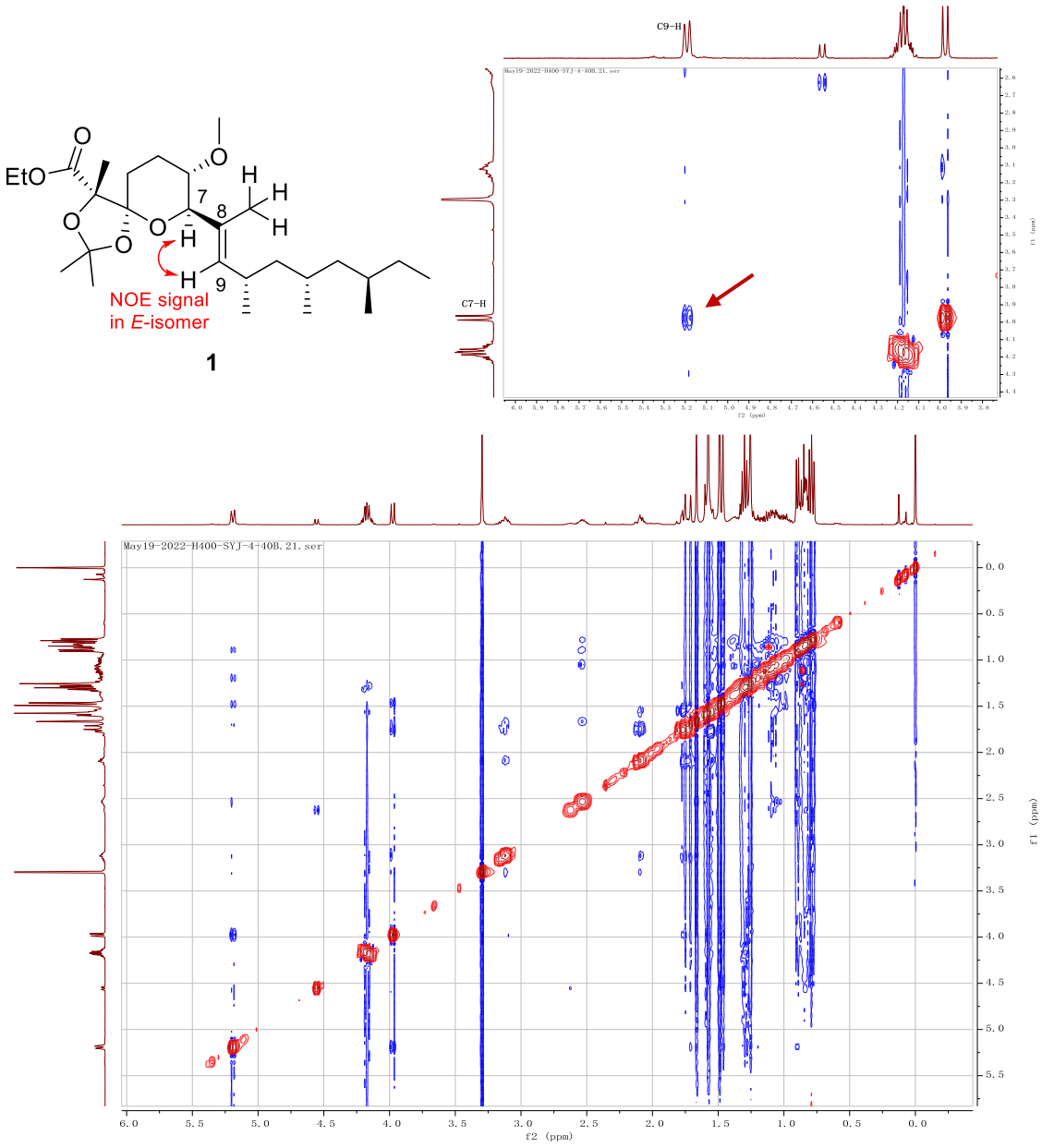
**$^{1}$H, $^{1}$H COSY of 1:**




**1**



**NOESY:**

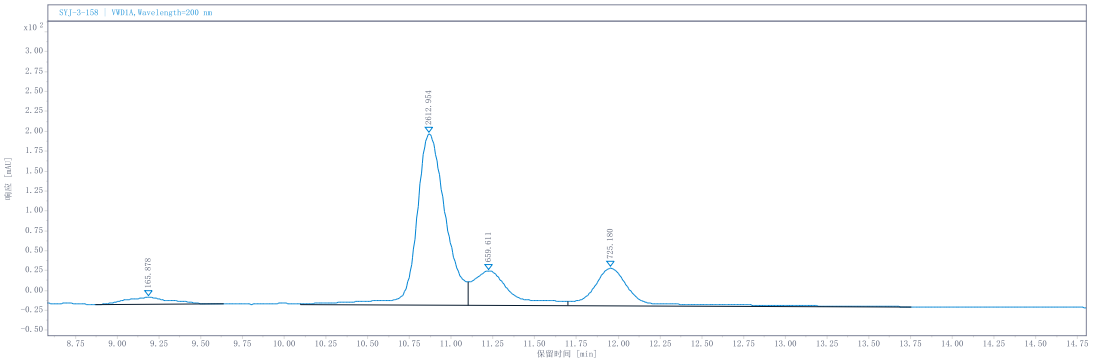

EtO
O
O
O
O
O
H
H
H
H
H
7
8
9
NOE signal
in E-isomer
1
C9–H
C7–H
May19-2022-H400-SYJ-4-40B.21.ser
f2 (ppm)
f1 (ppm)

# HPLC chromatographic condition for the detection of 1b and 1

**Column:** Agilent® EC-C18 (100 x 4.6 mm, 2.7 µm)

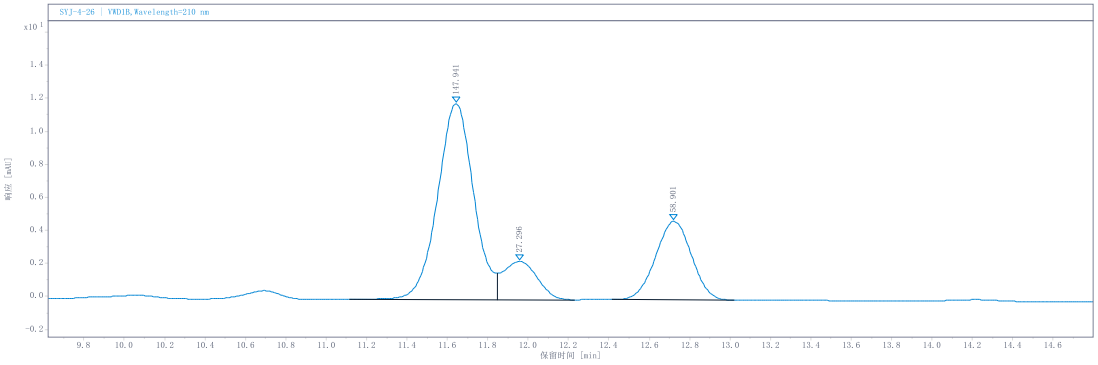
**Eluent:** $H_2O$, MeCN 10:90, 0.8 ml/min, 25 °C, 200 or 210 nm

# HPLC chromatograms of 1b and 1 (entry 3 in Table 1)



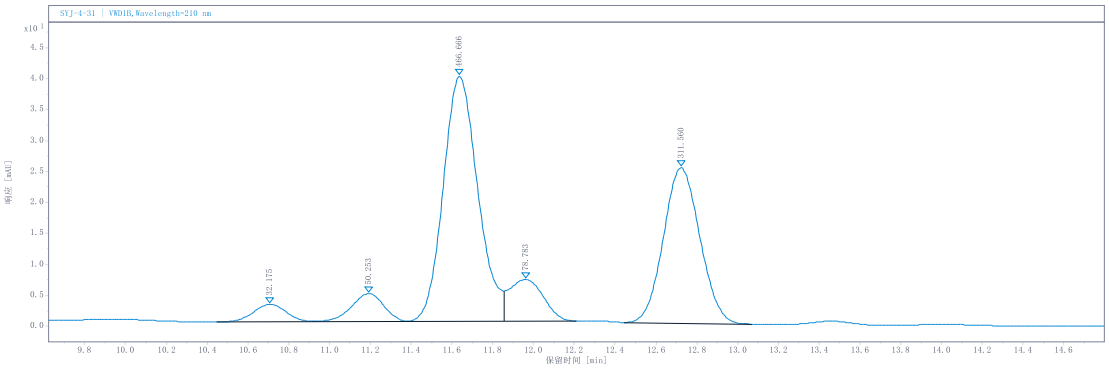

| Peak# | RT (min) | Area (mAU·s) | Area % | Height (mAU) |
|---|---|---|---|---|
| 1 | 10.869 | 2612.954 | 12.997 | 215.232 |
| 2 | 11.225 | 659.611 | 3.281 | 43.042 |
| 3 | 11.954 | 725.180 | 3.607 | 46.988 |

# HPLC chromatograms of 1b and 1 (entry 4 in Table 1)



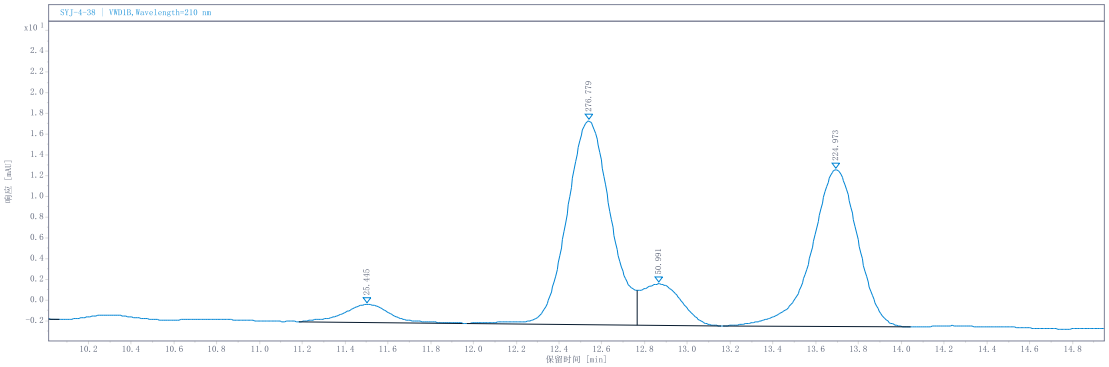

| Peak# | RT (min) | Area (mAU·s) | Area % | Height (mAU) |
|---|---|---|---|---|
| 1 | 11.643 | 147.941 | 2.611 | 11.887 |
| 2 | 11.959 | 27.296 | 0.482 | 2.317 |
| 3 | 12.722 | 58.901 | 1.040 | 4.752 |

## HPLC chromatograms of 1b and 1 (entry 5 in Table 1)




| Peak# | RT (min) | Area (mAU·s) | Area % | Height (mAU) |
|---|---|---|---|---|
| 1 | 11.637 | 466.666 | 2.338 | 39.547 |
| 2 | 11.961 | 78.783 | 0.395 | 6.746 |
| 3 | 12.722 | 311.560 | 1.561 | 25.110 |

## HPLC chromatograms of 1b and 1 (entry 6 in Table 1)




| Peak# | RT (min) | Area (mAU·s) | Area % | Height (mAU) |
|---|---|---|---|---|
| 1 | 12.538 | 276.779 | 1.472 | 19.612 |
| 2 | 12.867 | 50.991 | 0.271 | 3.965 |
| 3 | 13.695 | 224.973 | 1.196 | 15.114 |

## Crystal Structure of **12** $C_{23}H_{23}Cl_4NO_{10}$

The room temperature (290±2°K) single-crystal X-ray experiments were performed on a Rigaku diffractometer with Cu $K_\alpha$ radiation. Unit cell was obtained and refined by 4060 reflections with $4.6° < \theta < 77.3°$. No decay was observed in data collection. Raw intensities were corrected for Lorentz and polarization effects, and for absorption by empirical method. Direct phase determination yielded the positions of all non-hydrogen atoms. All non-hydrogen atoms were subjected to anisotropic refinement. All hydrogen atoms were generated geometrically with C-H bonds of 0.96-0.98 Å according to criteria described in the SHELXTL manual (Bruker, 1997). They were included in the refinement with $U_{iso}(H) = 1.2U_{eq}$ or $1.5U_{eq}$ (for methyl C) of their parent atoms. The final full-matric least-square refinement on $F^2$ converged with $R1 = 0.0753$ and $wR2 = 0.1614$ for 4637 observed reflections [$I \geq 2\sigma(I)$]. The final difference electron density map shows no features. Details of crystal parameters, data collection and structure refinement are given in Table 1.

Data collection was controlled by CrysAliPro program (Rigaku, 2013). Computations were performed using the SHELXTL NT ver. 5.10 program package (Bruker, 1997) on an IBM PC 586 computer. Analytic expressions of atomic scattering factors were employed, and anomalous dispersion corrections were incorporated (*International Tables for X-ray Crystallography*, 1989). Crystal drawings were produced with XP (Bruker, 1997).

### References


Bruker. (1997) SHELXTL. Structure Determination Programs, Version 5.10, Bruker AXS Inc.,6300 Enterprise Lane, Madison, WI 53719-1173, USA.

*International Tables for X-ray Crystallography*: (1989) Vol. C (Kluwer Academic Publishers, Dordrecht) Tables 4.2.6.8 and 6.1.1.4.

Rigaku. (2013) CrysAlisPro, Agilent Technologies, Version 1.171.36.32 (release 02-08-2013 CrysAlis171 .NET)

Table 1. Details of Data Collection, Processing and Structure Refinement

| | |
|---|---|
| Sample code | **SYJ-3-80** |
| Molecular formula | $C_{23}H_{23}Cl_4NO_{10}$ |
| Molecular weight | 615.22 |
| Color and habit | colorless block |
| Crystal size | 0.05 × 0.30 × 0.50 mm |
| Crystal system | orthorhombic |
| Space group | $P2_12_12_1$ (No. 19) |
| Unit cell parameters | $a$ = 8.1465(3) Å  α = 90.00°<br>$b$ = 8.8611(3) Å  β = 90.00°<br>$c$ = 38.0503(12) Å  γ = 90.00°<br>$V$ = 2746.74(16) Å$^3$  $Z$ = 4  $F$(000) = 1264 |
| Density (calcd) | 1.488 g/cm$^3$ |
| Diffractometer | Xcalibur, Atlas, Gemini |
| Radiation | Cu K$_\alpha$, λ = 1.54178 Å |
| Temperature | 290±2K |
| Scan type | ω-scan |
| Data collection range | $-10 < h < 9$, $-11 < k < 11$, $-35 < l < 47$; $\theta_{max}$ = 77.4° |
| Reflections measured | Total: 12532  Unique ($n$): 5481  Observed [I ≥ 2σ(I)]: 4637 |
| Absorption coefficient | 4.406 mm$^{-1}$ |
| Minimum and maximum transmission | 0.298, 1.000 |
| No. of variables, $p$ | 348 |
| Weighting scheme | $w = \frac{1}{\sigma^2(F_o^2) + (0.001P)^2 + 4.5P}$  $P = (F_o^2 + 2F_c^2)/3$ |
| $R1 = \frac{\Sigma\|\|F_o\|-\|F_c\|\|}{\Sigma\|F_o\|}$ (for all reflections) | 0.0963  0.0753 (for observed data) |
| $wR2 = \sqrt{\frac{\Sigma[w(F_o^2 - F_c^2)^2]}{\Sigma w(F_o^2)^2}}$ (for all reflections) | 0.1782  0.1614 (for observed data) |
| Goof = S = $\sqrt{\frac{\Sigma[w(F_o^2 - F_c^2)^2]}{n - p}}$ | 1.137 |
| Largest and mean Δ/σ | 0.001, 0.000 |
| Residual extrema in final difference map | -0.548 to 0.785 $e$Å$^{-3}$ |

Table 2. Atomic coordinates and equivalent isotropic temperature factors* (Å$^2$)

| Atoms | *x* | *y* | *z* | $U_{eq.}$ |
|---|---|---|---|---|
| Cl(1) | 0.6332(3) | 0.7681(2) | 0.79395(5) | 0.0471(4) |
| Cl(2) | 0.4696(3) | 0.5069(3) | 0.83655(5) | 0.0594(5) |
| Cl(3) | 0.5253(3) | 0.1730(3) | 0.81537(6) | 0.0610(6) |
| Cl(4) | 0.7436(3) | 0.0949(2) | 0.74964(6) | 0.0557(5) |
| O(1) | 1.1179(9) | 0.5845(14) | 0.48277(17) | 0.088(3) |
| O(2) | 1.3766(8) | 0.5100(9) | 0.48986(15) | 0.0611(17) |
| O(3) | 1.2897(9) | 0.3414(7) | 0.54764(17) | 0.0568(15) |
| O(4) | 1.3573(7) | 0.5580(6) | 0.57623(12) | 0.0397(10) |
| O(5) | 1.0782(7) | 0.5512(7) | 0.59020(12) | 0.0420(11) |
| O(6) | 1.1109(10) | 0.8872(10) | 0.6432(2) | 0.073(2) |
| O(7) | 0.8228(8) | 0.5709(12) | 0.63920(17) | 0.072(2) |
| O(8) | 1.0257(7) | 0.5858(8) | 0.67902(13) | 0.0491(13) |
| O(9) | 0.8648(9) | 0.7794(6) | 0.72708(14) | 0.0484(13) |
| O(10) | 0.9414(9) | 0.2878(8) | 0.69539(19) | 0.0642(18) |
| N(1) | 0.9116(10) | 0.5441(8) | 0.70370(16) | 0.0464(15) |
| C(1) | 1.1589(16) | 0.5667(18) | 0.4212(3) | 0.085(4) |
| C(2) | 1.1614(14) | 0.6782(19) | 0.4500(3) | 0.084(4) |
| C(3) | 1.2395(11) | 0.5157(13) | 0.50000(18) | 0.055(2) |
| C(4) | 1.1790(10) | 0.4532(11) | 0.53590(18) | 0.0482(19) |
| C(5) | 1.1966(9) | 0.5797(9) | 0.56390(17) | 0.0386(15) |
| C(6) | 1.4004(12) | 0.4015(11) | 0.5733(2) | 0.0504(19) |
| C(7) | 1.5750(13) | 0.3907(14) | 0.5609(3) | 0.069(3) |
| C(8) | 1.3736(19) | 0.3219(13) | 0.6079(3) | 0.083(4) |
| C(9) | 1.0083(12) | 0.3874(14) | 0.5327(2) | 0.067(3) |
| C(10) | 1.1831(10) | 0.7446(10) | 0.5517(2) | 0.0485(18) |
| C(11) | 1.2008(13) | 0.8490(10) | 0.5832(3) | 0.059(2) |
| C(12) | 1.0801(11) | 0.8090(11) | 0.6119(2) | 0.0514(19) |
| C(13) | 1.0961(9) | 0.6410(9) | 0.62044(18) | 0.0420(17) |
| C(14) | 0.9633(10) | 0.5936(11) | 0.64567(18) | 0.0463(18) |
| C(15) | 0.8879(10) | 0.3909(9) | 0.7117(2) | 0.0437(16) |
| C(16) | 0.7823(9) | 0.3974(8) | 0.74367(17) | 0.0370(14) |
| C(17) | 0.7110(10) | 0.2805(9) | 0.7624(2) | 0.0424(16) |
| C(18) | 0.6151(10) | 0.3155(9) | 0.7916(2) | 0.0438(16) |
| C(19) | 0.5904(10) | 0.4657(10) | 0.80123(17) | 0.0423(15) |
| C(20) | 0.6643(9) | 0.5818(9) | 0.78215(17) | 0.0370(14) |
| C(21) | 0.7585(8) | 0.5479(7) | 0.75337(15) | 0.0327(12) |
| C(22) | 0.8486(9) | 0.6465(8) | 0.72797(17) | 0.0358(14) |
| C(23) | 1.0209(19) | 1.0149(17) | 0.6495(5) | 0.114(6) |

*$U_{eq.}$ defined as one third of the trace of the orthogonalized **U** tensor.

Table 3. Bond lengths (Å) and bond angles (°)

| | | | |
|---|---|---|---|
| Cl(1)-C(20) | 1.730(7) | N(1)-C(15) | 1.405(11) |
| Cl(2)-C(19) | 1.705(8) | C(1)-C(2) | 1.478(18) |
| Cl(3)-C(18) | 1.716(8) | C(3)-C(4) | 1.554(11) |
| Cl(4)-C(17) | 1.735(8) | C(4)-C(9) | 1.512(13) |
| O(1)-C(3) | 1.336(13) | C(4)-C(5) | 1.553(10) |
| O(1)-C(2) | 1.539(15) | C(5)-C(10) | 1.538(12) |
| O(2)-C(3) | 1.183(11) | C(6)-C(7) | 1.502(14) |
| O(3)-C(4) | 1.412(12) | C(6)-C(8) | 1.511(12) |
| O(3)-C(6) | 1.432(12) | C(10)-C(11) | 1.522(13) |
| O(4)-C(5) | 1.404(9) | C(11)-C(12) | 1.512(13) |
| O(4)-C(6) | 1.435(11) | C(12)-C(13) | 1.529(13) |
| O(5)-C(13) | 1.406(8) | C(13)-C(14) | 1.507(10) |
| O(5)-C(5) | 1.413(8) | C(15)-C(16) | 1.491(10) |
| O(6)-C(23) | 1.369(15) | C(16)-C(17) | 1.385(11) |
| O(6)-C(12) | 1.401(11) | C(16)-C(21) | 1.397(10) |
| O(7)-C(14) | 1.187(11) | C(17)-C(18) | 1.395(12) |
| O(8)-C(14) | 1.369(10) | C(18)-C(19) | 1.395(12) |
| O(8)-N(1) | 1.372(9) | C(19)-C(20) | 1.395(11) |
| O(9)-C(22) | 1.185(10) | C(20)-C(21) | 1.371(10) |
| O(10)-C(15) | 1.187(10) | C(21)-C(22) | 1.495(9) |
| N(1)-C(22) | 1.392(9) | | |

| | | | |
|---|---|---|---|
| C(3)-O(1)-C(2) | 118.2(8) | O(4)-C(5)-O(5) | 112.1(6) |
| C(4)-O(3)-C(6) | 110.9(7) | O(4)-C(5)-C(10) | 107.3(6) |
| C(5)-O(4)-C(6) | 109.5(6) | O(5)-C(5)-C(10) | 109.6(6) |
| C(13)-O(5)-C(5) | 114.0(6) | O(4)-C(5)-C(4) | 102.5(6) |
| C(23)-O(6)-C(12) | 117.4(10) | O(5)-C(5)-C(4) | 107.1(6) |
| C(14)-O(8)-N(1) | 113.4(6) | C(10)-C(5)-C(4) | 118.1(6) |
| O(8)-N(1)-C(22) | 121.9(7) | O(3)-C(6)-O(4) | 105.0(7) |
| O(8)-N(1)-C(15) | 120.1(7) | O(3)-C(6)-C(7) | 111.0(7) |
| C(22)-N(1)-C(15) | 115.8(6) | O(4)-C(6)-C(7) | 108.5(9) |
| C(1)-C(2)-O(1) | 103.7(12) | O(3)-C(6)-C(8) | 109.3(9) |
| O(2)-C(3)-O(1) | 124.1(9) | O(4)-C(6)-C(8) | 110.4(7) |
| O(2)-C(3)-C(4) | 124.8(9) | C(7)-C(6)-C(8) | 112.4(9) |
| O(1)-C(3)-C(4) | 111.0(7) | C(11)-C(10)-C(5) | 109.4(7) |
| O(3)-C(4)-C(9) | 110.1(9) | C(12)-C(11)-C(10) | 111.4(8) |
| O(3)-C(4)-C(5) | 103.3(6) | O(6)-C(12)-C(11) | 112.5(8) |
| C(9)-C(4)-C(5) | 114.8(6) | O(6)-C(12)-C(13) | 106.6(8) |
| O(3)-C(4)-C(3) | 109.0(7) | C(11)-C(12)-C(13) | 109.0(7) |
| C(9)-C(4)-C(3) | 110.9(7) | O(5)-C(13)-C(14) | 106.8(6) |
| C(5)-C(4)-C(3) | 108.4(7) | O(5)-C(13)-C(12) | 111.6(6) |

(Table 3. continued)

| | | | |
|---|---|---|---|
| C(14)-C(13)-C(12) | 110.2(7) | C(17)-C(18)-Cl(3) | 119.7(7) |
| O(7)-C(14)-O(8) | 122.8(7) | C(19)-C(18)-Cl(3) | 120.2(6) |
| O(7)-C(14)-C(13) | 127.4(8) | C(18)-C(19)-C(20) | 120.3(7) |
| O(8)-C(14)-C(13) | 109.8(7) | C(18)-C(19)-Cl(2) | 119.6(6) |
| O(10)-C(15)-N(1) | 125.5(8) | C(20)-C(19)-Cl(2) | 120.1(6) |
| O(10)-C(15)-C(16) | 131.9(9) | C(21)-C(20)-C(19) | 119.7(7) |
| N(1)-C(15)-C(16) | 102.6(6) | C(21)-C(20)-Cl(1) | 119.9(6) |
| C(17)-C(16)-C(21) | 121.3(7) | C(19)-C(20)-Cl(1) | 120.3(6) |
| C(17)-C(16)-C(15) | 129.2(7) | C(20)-C(21)-C(16) | 119.8(6) |
| C(21)-C(16)-C(15) | 109.4(7) | C(20)-C(21)-C(22) | 131.6(7) |
| C(16)-C(17)-C(18) | 118.6(7) | C(16)-C(21)-C(22) | 108.6(6) |
| C(16)-C(17)-Cl(4) | 120.1(6) | O(9)-C(22)-N(1) | 126.0(7) |
| C(18)-C(17)-Cl(4) | 121.3(6) | O(9)-C(22)-C(21) | 130.8(7) |
| C(17)-C(18)-C(19) | 120.1(7) | N(1)-C(22)-C(21) | 103.3(6) |

Table 4. Anisotropic thermal parameters* (Å$^2$)

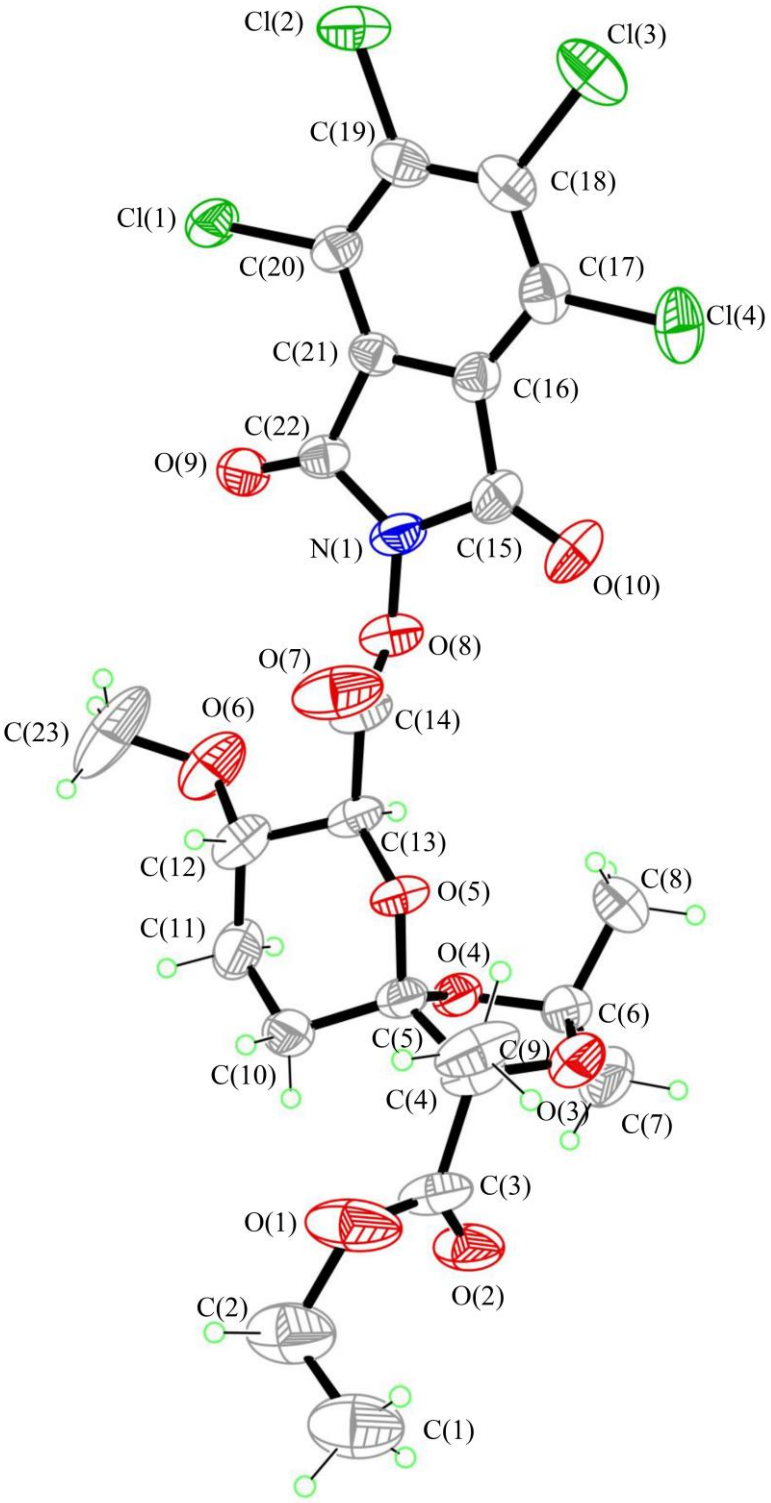
| Atoms | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| Cl(1) | 0.0604(11) | 0.0396(8) | 0.0414(8) | -0.0103(7) | 0.0119(7) | 0.0016(8) |
| Cl(2) | 0.0628(12) | 0.0752(14) | 0.0401(8) | -0.0007(9) | 0.0190(8) | -0.0103(11) |
| Cl(3) | 0.0669(13) | 0.0564(11) | 0.0597(11) | 0.0188(9) | -0.0096(10) | -0.0243(11) |
| Cl(4) | 0.0677(12) | 0.0305(7) | 0.0690(11) | -0.0065(8) | -0.0177(10) | -0.0013(8) |
| O(1) | 0.044(3) | 0.178(10) | 0.040(3) | 0.015(4) | 0.000(3) | 0.019(5) |
| O(2) | 0.043(3) | 0.099(5) | 0.041(3) | 0.007(3) | 0.012(2) | 0.014(3) |
| O(3) | 0.071(4) | 0.049(3) | 0.051(3) | -0.012(3) | 0.009(3) | 0.004(3) |
| O(4) | 0.039(3) | 0.046(3) | 0.034(2) | -0.0037(19) | 0.0052(19) | 0.006(2) |
| O(5) | 0.044(3) | 0.052(3) | 0.029(2) | -0.009(2) | 0.0106(19) | -0.002(2) |
| O(6) | 0.065(4) | 0.077(5) | 0.077(4) | -0.039(4) | -0.001(4) | 0.007(4) |
| O(7) | 0.037(3) | 0.130(7) | 0.047(3) | -0.015(4) | 0.006(2) | -0.009(4) |
| O(8) | 0.049(3) | 0.066(4) | 0.033(2) | -0.008(2) | 0.009(2) | -0.004(3) |
| O(9) | 0.069(4) | 0.036(3) | 0.040(2) | -0.002(2) | 0.010(3) | -0.005(3) |
| O(10) | 0.072(4) | 0.055(4) | 0.065(4) | -0.023(3) | 0.013(3) | 0.016(3) |
| N(1) | 0.060(4) | 0.047(3) | 0.032(3) | -0.009(3) | 0.013(3) | 0.000(3) |
| C(1) | 0.066(7) | 0.132(12) | 0.057(5) | -0.003(7) | -0.006(5) | -0.017(8) |
| C(2) | 0.052(5) | 0.148(12) | 0.053(5) | 0.000(7) | -0.007(4) | 0.012(7) |
| C(3) | 0.041(4) | 0.094(7) | 0.030(3) | -0.012(4) | 0.005(3) | 0.004(4) |
| C(4) | 0.044(4) | 0.067(5) | 0.033(3) | -0.011(3) | 0.008(3) | 0.000(4) |
| C(5) | 0.036(3) | 0.050(4) | 0.030(3) | -0.003(3) | 0.006(2) | 0.005(3) |
| C(6) | 0.059(5) | 0.053(4) | 0.039(3) | 0.002(3) | 0.004(3) | 0.016(4) |
| C(7) | 0.065(6) | 0.074(6) | 0.068(6) | -0.004(5) | 0.004(5) | 0.033(5) |
| C(8) | 0.126(11) | 0.069(6) | 0.056(5) | 0.025(5) | 0.016(6) | 0.032(8) |
| C(9) | 0.056(5) | 0.092(7) | 0.053(4) | -0.035(5) | 0.017(4) | -0.015(5) |
| C(10) | 0.046(4) | 0.060(5) | 0.040(3) | 0.008(3) | 0.006(3) | 0.015(4) |
| C(11) | 0.058(5) | 0.044(4) | 0.075(6) | -0.005(4) | 0.016(4) | 0.006(4) |
| C(12) | 0.042(4) | 0.058(5) | 0.054(4) | -0.019(4) | 0.006(3) | 0.002(4) |
| C(13) | 0.036(4) | 0.060(5) | 0.030(3) | -0.010(3) | 0.006(3) | 0.006(3) |
| C(14) | 0.044(4) | 0.062(5) | 0.033(3) | -0.015(3) | 0.008(3) | -0.002(4) |
| C(15) | 0.046(4) | 0.040(4) | 0.045(4) | -0.013(3) | 0.003(3) | 0.001(3) |
| C(16) | 0.042(4) | 0.036(3) | 0.033(3) | -0.005(3) | -0.003(3) | 0.003(3) |
| C(17) | 0.047(4) | 0.036(3) | 0.045(3) | -0.004(3) | -0.010(3) | -0.003(3) |
| C(18) | 0.043(4) | 0.049(4) | 0.040(3) | 0.006(3) | -0.012(3) | -0.009(3) |
| C(19) | 0.045(4) | 0.052(4) | 0.030(3) | 0.005(3) | -0.005(3) | -0.004(3) |
| C(20) | 0.037(3) | 0.042(4) | 0.032(3) | -0.006(3) | 0.000(2) | 0.001(3) |
| C(21) | 0.036(3) | 0.035(3) | 0.027(3) | 0.000(2) | -0.001(2) | -0.003(3) |
| C(22) | 0.037(3) | 0.041(4) | 0.030(3) | -0.005(2) | 0.002(3) | -0.004(3) |
| C(23) | 0.095(10) | 0.106(11) | 0.141(13) | -0.090(11) | -0.006(9) | 0.030(9) |

*The exponent takes the form: $-2\pi^2\Sigma\Sigma U_{ij}h_ih_j\mathbf{a}_i^*\mathbf{a}_j^*$

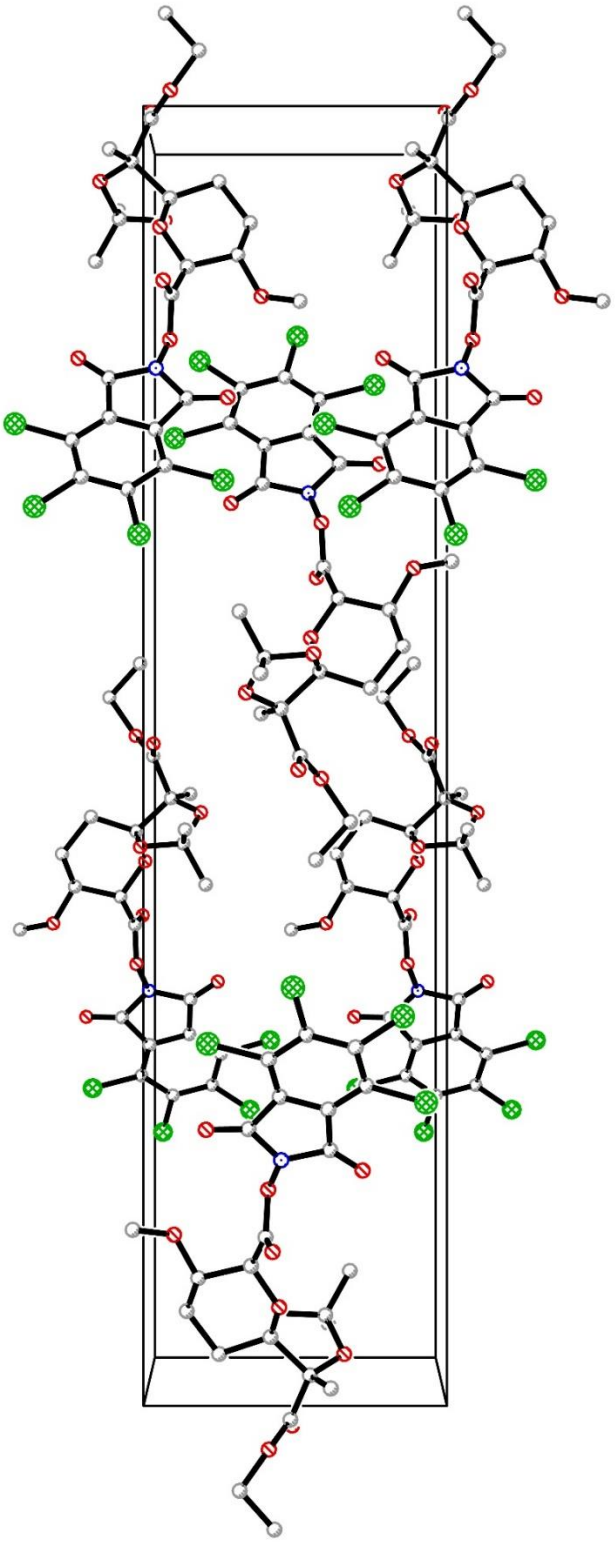
Table 5. Coordinates and isotropic temperature factors* (Å$^2$) for H atoms

| Atoms | *x* | *y* | *z* | $U_{eq.}$ |
|---|---|---|---|---|
| H(1A) | 1.0931 | 0.4817 | 0.4279 | 0.128 |
| H(1B) | 1.2688 | 0.5338 | 0.4163 | 0.128 |
| H(1C) | 1.1131 | 0.6123 | 0.4005 | 0.128 |
| H(2A) | 1.0810 | 0.7572 | 0.4461 | 0.101 |
| H(2B) | 1.2692 | 0.7237 | 0.4524 | 0.101 |
| H(7A) | 1.6464 | 0.4350 | 0.5781 | 0.104 |
| H(7B) | 1.5865 | 0.4436 | 0.5390 | 0.104 |
| H(7C) | 1.6038 | 0.2866 | 0.5576 | 0.104 |
| H(8A) | 1.2596 | 0.3275 | 0.6142 | 0.125 |
| H(8B) | 1.4386 | 0.3695 | 0.6258 | 0.125 |
| H(8C) | 1.4055 | 0.2180 | 0.6058 | 0.125 |
| H(9A) | 0.9728 | 0.3511 | 0.5552 | 0.101 |
| H(9B) | 1.0098 | 0.3054 | 0.5162 | 0.101 |
| H(9C) | 0.9341 | 0.4640 | 0.5245 | 0.101 |
| H(10A) | 1.2685 | 0.7663 | 0.5346 | 0.058 |
| H(10B) | 1.0776 | 0.7611 | 0.5405 | 0.058 |
| H(11A) | 1.3117 | 0.8418 | 0.5923 | 0.071 |
| H(11B) | 1.1826 | 0.9524 | 0.5758 | 0.071 |
| H(12) | 0.9682 | 0.8305 | 0.6039 | 0.062 |
| H(13) | 1.2038 | 0.6219 | 0.6310 | 0.050 |
| H(23A) | 0.9167 | 0.9876 | 0.6594 | 0.171 |
| H(23B) | 1.0037 | 1.0680 | 0.6278 | 0.171 |
| H(23C) | 1.0791 | 1.0787 | 0.6656 | 0.171 |

*The exponent takes the form: $-8\pi^2 U\sin^2\theta/\lambda^2$




ORTEP drawing of $C_{23}H_{23}Cl_4NO_{10}$ with 50% probability ellipsoids, showing the atomic numbering scheme.



A packing view along the *a* direction