

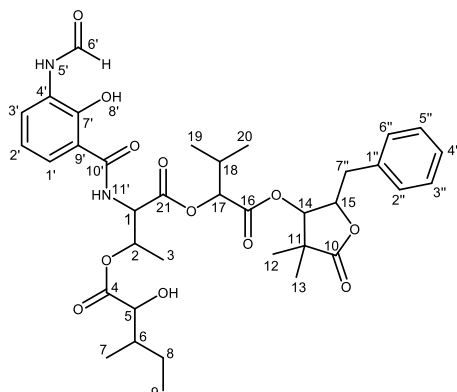
Supporting Information

Total Synthesis of Isoneoantimycin

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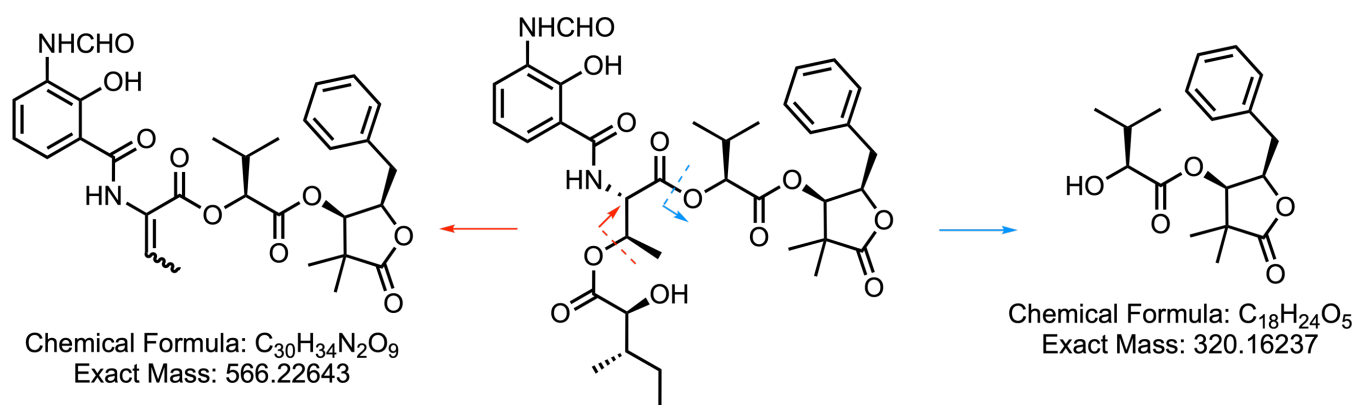
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Table S1 Comparison of ^1H and ^{13}C NMR data between natural and synthetic isoneoantimycin.

position	Natural 1			Synthetic 4		
	$(^1\text{H}$ 400 MHz, ^{13}C 100 MHz in CDCl_3)			$(^1\text{H}$ 600 MHz, ^{13}C 150 MHz in CDCl_3)		
	δ_{C} (ppm)	δ_{H} (ppm)	multiplicity ^a	δ_{C} (ppm)	δ_{H} (ppm)	multiplicity ^a
1	55.5	5.14	dd (8.8, 3.1)	55.28	5.14	dd (8.8, 3.1)
2	71.7	5.69	dq (3.1, 6.4)	71.7	5.68	dq (3.0, 6.5)
3	17.0	1.43	d (6.4)	16.94	1.42	d (6.4)
4	173.8			173.8		
5	74.5	4.1	br s	74.43	4.10	d (4.0)
6	39.1	1.80 ^b	m	38.97	1.81	m
7	15.2	0.97	d (6.9)	15.13	0.97	d (6.9)
8	24.3	1.27, 1.68	m	24.24	1.27, 1.41	m
9	11.6	0.92	t (7.5)	11.81	0.91	t (7.4)
10	178.7			178.79		
11	44.6			44.55		
12	22.8	1.33	s	22.76	1.32	s
13	18.4	1.20	s	18.27	1.19	s
14	79.4	5.32	d (3.6)	79.29	5.32	d (3.7)
15	80.1	4.77	dt (9.5, 3.5)	80.18	4.77	dt (9.5, 3.5)
16	168.1			168.15		
17	77.8	5.03	d (2.9)	77.71	5.02	d (2.9)
18	29.9	2.34 ^b	m	29.85	2.34	m
19	16.3	1.13	d (6.9)	16.2	1.13	d (6.9)
20	19.4	1.00	d (6.9)	19.4	1.00	d (6.9)
21	168.8			168.87		
1'	120.1	7.23	dd (8.1, 1.3)	120.04	7.22	d (8.2, 1.4)
2'	119.1	6.92	t (8.1)	119.09	6.92	t (8.1)
3'	124.9	8.53	dd (8.1, 1.3)	124.86	8.54	dd (8.1, 1.3)
4'	127.5			127.42		
5' NH		7.94	br s		7.91	s
6'	158.9	8.48	d (1.7)	158.94	8.49	d (1.7)
7'	150.6			150.7		
8' OH		12.54	s		12.54	s
9'	112.9			112.74		
10'	170.1			170.13		
11' NH		7.03	d (8.8)		7.01	d (8.8)
1''	136.5			136.51		
2'', 6''	129.2	7.22-7.34	n.a.	129.21	7.22	dd (8.2, 1.4)
3'', 5''	128.7	7.22-7.34	n.a.	128.7	7.33	t (7.5)
4''	127.0	7.22-7.34	n.a.	127.04	7.27	t (7.5)
7''	35.4	2.83	dd (14.6, 3.5)	35.29	2.83	dd (14.6, 3.5)
		3.02	dd (14.6, 9.5)		3.02	dd (14.7, 9.5)

^a Coupling constants J (in Hz) are in parentheses.

^b H6 and H18 were reported in the other way around in *J. Nat. Prod.* **1998**, *61*, 978.



[Mass Spectrum]

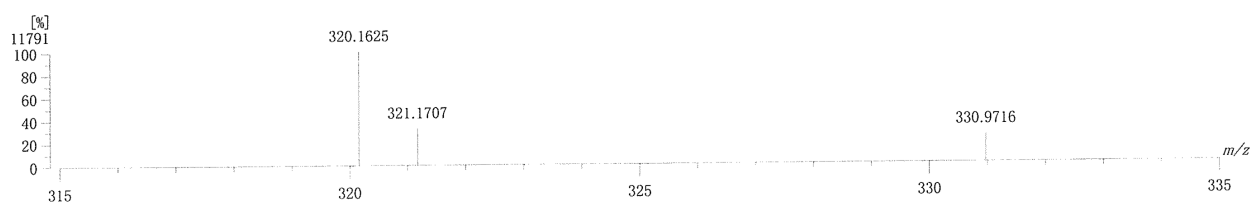
Data : YT2005-High003 Date : 06-Sep-2021 16:54

RT : 0.90 min Scan# : 19

Elements : C 18/18, H 24/24, O 5/5

Mass Tolerance : 1000ppm, 5mmu if $m/z < 5$, 50mmu if $m/z > 50$

Unsaturation (U.S.) : -0.5 - 10.0



Observed m/z	Int%	Err [ppm / mmu]	U.S. Composition
1 320.1625	100.00	+0.4 / +0.1	7.0 C18 H24 O5

[Mass Spectrum]

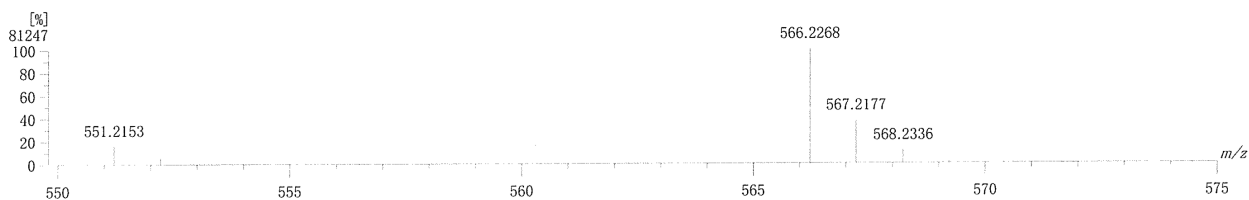
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RT : 0.45 min Scan# : 10

Elements : C 30/30, H 34/34, N 2/2, O 9/9

Mass Tolerance : 1000ppm, 5mmu if $m/z < 5$, 50mmu if $m/z > 50$

Unsaturation (U.S.) : -0.5 - 20.0

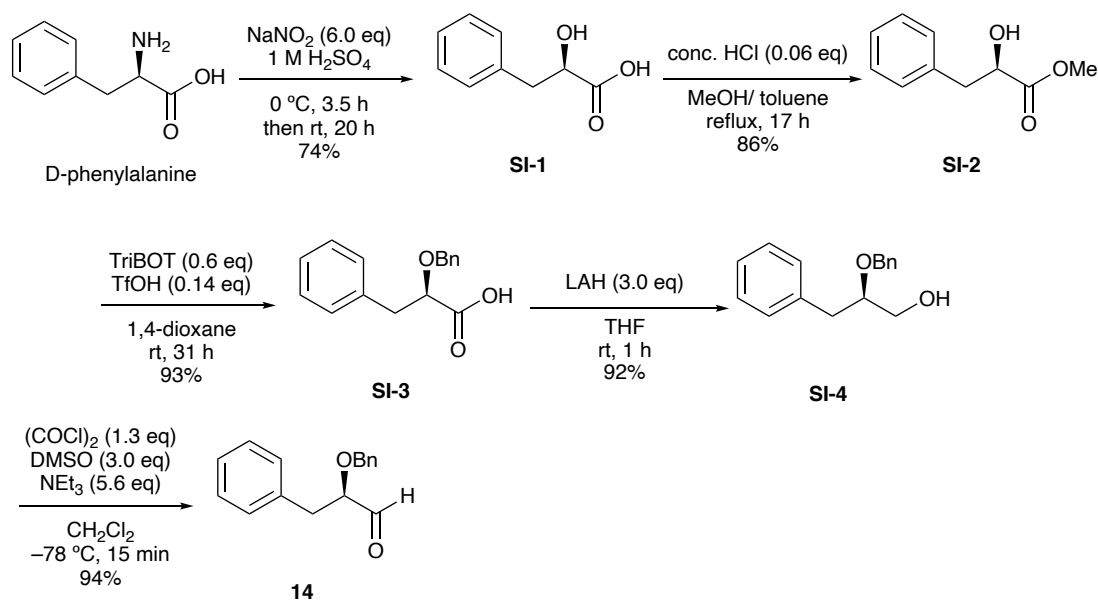


Observed m/z	Int%	Err [ppm / mmu]	U.S. Composition
1 566.2268	100.00	+0.7 / +0.4	15.0 C30 H34 N2 O9

Fig S1. Fragmentation in the HREIMS of synthetic isoneoantimycin 4.

Experimental Section for known compounds **14**, **11**, **9**, **10** and **5**

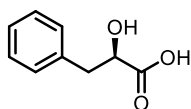
(*R*)-2-Benzyloxy-3-phenylpropanal **14** was obtained from (*R*)-D-phenylalanine as shown in Scheme SI-1, see ref 13: H. W. Yang and D. Romo, *J. Org. Chem.* **1998**, *63*, 1344; H. Lubin, A. Tessier, G. Chaume, J. Pytkowicz and T. Brigaud *Org. Lett.* **2010**, *12*, 1496.



Scheme SI-1 Synthesis of (*R*)-2-benzyloxy-3-phenylpropanal **14**

Compound SI-1:

(*R*)-2-Hydroxy-3-phenylpropanoic acid



To a stirred and cooled (0 °C) solution of D-phenylalanine (6.59 g, 39.9 mmol) in 1 M H₂SO₄ (180 mL) was added a solution of NaNO₂ (16.4 g, 238 mmol) in water (46 mL) dropwise. The mixture was stirred at 0 °C for 3.5 h, then allowed to warm up to room temperature and stirred for overnight. The resulting mixture was extracted with Et₂O. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered. The filtrate was concentrated to give **SI-1** (4.88 g, 29.4 mmol, 74%) as cream-colored solid.

¹H NMR (400 MHz, CDCl₃) δ 7.46–7.16 (m, 5H), 4.53 (dd, *J* = 7.2, 4.2 Hz, 1H), 3.22 (dd, *J* = 14.0, 4.2 Hz, 1H) 3.01 (dd, *J* = 14.0, 7.2 Hz, 1H).

[α]_D = +27.7 (*c* 1.1, acetone).

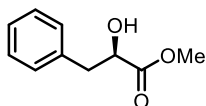
Lit [α]_D = +26.95 (*c* 1.0, acetone, 98% ee). Lit [α]_D = –28.8 (*c* 0.90, acetone), *S* isomer.

B. Larissegger-Schnell, S. M. Glueck, W. Kroutil and K. Faber, *Tetrahedron*, **2006**, *62*(12), 2912.

S. Li, S.-F. Zhu, J.-H. Xie, S. Song, C.-M. Zhang, Q.-L. Zhou, *J. Am. Chem. Soc.* **2010**, *132*, 1172.

Compound SI-2:

Methyl (*R*)-2-hydroxy-3-phenylpropanoate



To a solution of **SI-1** (4.38 g, 26.4 mmol) in toluene (18 mL) and MeOH (9.8 mL) was added conc. HCl (0.14 mL). The reaction mixture was refluxed at 90 °C for overnight. After the resulting mixture was cooled to room temperature and neutralized with sat. aq. NaHCO₃, MeOH was removed *in vacuo*. The residue was diluted with water (20 mL) and extracted with toluene (20 mL×3). The combined organic layer was washed with brine, dried over Na₂SO₄, filtered. The filtrate was concentrated to give **SI-2** (4.10 g, 22.7 mmol, 86%) as white solid.

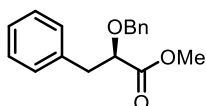
¹H NMR (400 MHz, CDCl₃) δ 7.43–7.12 (m, 5H), 4.46 (td, *J* = 6.5, 4.4 Hz, 1H), 3.78 (s, 3H), 3.13 (dd, *J* = 13.9, 4.4 Hz, 1H), 2.97 (dd, *J* = 13.9, 6.8 Hz, 1H), 2.69 (dd, *J* = 6.2, 0.7 Hz, 1H).

[α]_D = +8.0 (*c* 1.80, CHCl₃). Lit [α]_D = +6.4 (*c* 1.82, CHCl₃).

S. Ley, E. Diez, D. Dixon, R/ Guy, P. Michel, G. Nattrass and T. Sheppaer, *Org. Biomol. Chem.*, **2004**, *2*, 3608.

Compound SI-3:

Methyl (*R*)-2-benzyloxy-3-phenylpropanoate



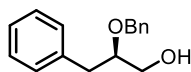
To a solution of **SI-2** (4.10 g, 22.7 mmol), TriBOT (3.47 g, 8.68 mmol) and MS4A (3.01 g) in 1,4-dioxane (97 mL) was added TfOH (0.28 mL, 3.16 mmol) dropwise. After being stirred for 1 h at room temperature, additional TriBOT was added (1.817 g, 4.55 mmol) and then the solution was stirred for 30 h. The reaction mixture was quenched by addition of NEt₃ (4.0 mL), diluted with *n*-hexane and filtered through a pad of Celite®. The filtrate and washings were concentrated. The residue was purified by flash column chromatography (30% AcOEt in *n*-hexane) to give **SI-3** (5.71 g, 21.1 mmol, 93%) as pale-yellow oil.

¹H NMR (300 MHz, CDCl₃) δ 7.40–7.07(m, 10H), 4.67 (dd, *J* = 11.9, 0.9 Hz, 1H), 4.37 (d, *J* = 11.9 Hz, 1H), 4.20–4.08 (m, 1H), 3.73 (s, 3H), 3.09 (dd, *J* = 13.9, 4.9 Hz, 1H), 3.03 (dd, *J* = 13.9, 8.3 Hz, 1H).

[α]_D = +66.5 (*c* 0.96, CHCl₃).

Compound SI-4

(R)-2-benzyloxy-3-phenylpropanol



To a suspension of LAH (874 mg, 23 mmol) in THF (9 mL) was added a solution of **SI-3** (2.06 g, 7.62 mmol) in THF (11 mL) at 0 °C. After being stirred for 1 h at room temperature, the reaction mixture was quenched by addition of water (5 mL) and 1 M HCl (70 mL). The resulting mixture was extracted with Et₂O (25 mL×3). The combined organic layer was washed with sat aq. NaHCO₃ and brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (30% AcOEt in *n*-hexane) to give **SI-4** (1.70 g, 7.02 mmol, 92%) as colorless oil.

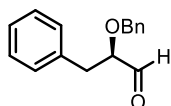
¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.16 (m, 10H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.50 (d, *J* = 11.5 Hz, 1H), 3.75 – 3.69 (m, 1H), 3.66 (dtd, *J* = 7.0, 4.0, 1.2 Hz, 1H), 3.51 (dtd, *J* = 11.7, 5.8, 1.2 Hz, 1H), 2.96 (dd, *J* = 13.5, 6.2 Hz, 1H), 2.82 (dd, *J* = 13.5, 7.1 Hz, 1H), 1.99 – 1.90 (m, 1H).

[α]_D = +15.1 (c 0.84, CH₂Cl₂). Lit [α]_D = +22.2 (c 1.00, CH₂Cl₂).

G. Cardillo, *Tetrahedron*, **1989**, *45*. 1501.

Compound 14:

(R)-2-Benzyloxy-3-phenylpropanal



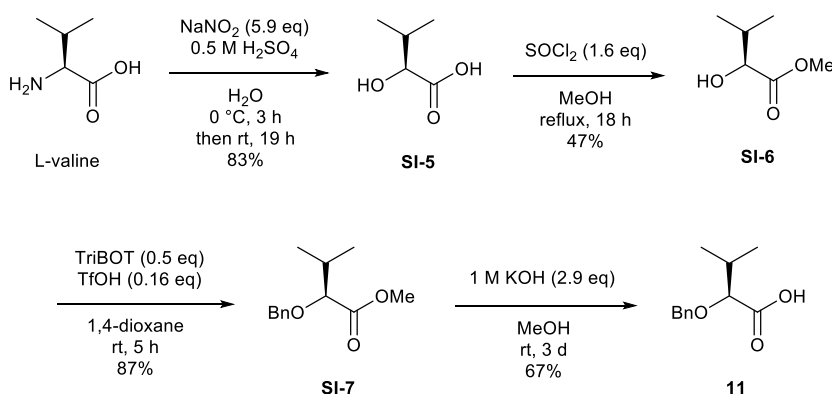
To a solution of **SI-4** (1.49 g, 6.15 mmol), DMSO (1.3 mL, 18.3 mmol) in CH₂Cl₂ (6.5 mL) was added a solution of oxalyl chloride (0.66 mL, 7.69 mmol) in CH₂Cl₂ (15 mL) at –78 °C dropwise. After being stirred for 20 min at –78 °C. The reaction mixture was quenched by NEt₃ (4.8 mL, 34.4 mmol). After being stirred for 15 min at –78 °C, the resulting mixture was allowed to warm up to room temperature and diluted with CH₂Cl₂ (60 mL). The organic layer was washed with sat aq. NH₄Cl and brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (10% AcOEt in *n*-hexane) to give **14** (1.38 g, 5.76 mmol, 94%) as yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 9.68 (d, *J* = 1.9 Hz, 1H), 7.36 – 7.09 (m, 10H), 4.58 (d, *J* = 11.8 Hz, 1H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.00 – 3.91 (m, 1H), 3.02 (dd, *J* = 14.2, 4.7 Hz, 1H), 2.92 (dd, *J* = 14.2, 8.4 Hz, 1H).

[α]_D = +39.9 (c 0.83, CHCl₃). Lit [α]_D = –84.9 (c 1.1, CH₂Cl₂) for *S*-isomer.

D. A. Evans, V. J. Cee and S. J. Siska, *J. Am. Chem. Soc.*, **2006**, *128*. 9433.

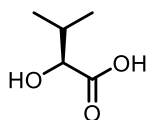
(S)-2-Benzyloxy-3-methylbutanoic acid **11** was obtained from (S)-L-valine as shown in Scheme SI-2, see ref 12: G. J. Hanson, Q. Wei and M. Zhou, US Patent 0163446, Jun. 25, 2009.



Scheme SI-2 Synthesis of **11**.

Compound SI-5:

(S)-2-Hydroxy-3-methylbutanoic acid



To a stirred and cooled (0 °C) solution of L-valine (2.33 g, 19.9 mmol) in 0.5 M H₂SO₄ (80 mL) was added a solution of NaNO₂ (8.13 g, 118 mmol) in water (30 mL) dropwise. The mixture was stirred at 0 °C for 3 h, then allowed to warm up to room temperature and stirred for overnight. The resulting mixture was extracted with Et₂O. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated to give **SI-5** (1.95 g, 16.5 mmol, 83%) as colorless oil.

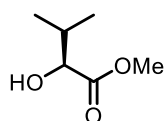
¹H NMR (400 MHz, CDCl₃) δ 4.15 (dd, *J* = 3.4, 0.9 Hz, 1H), 2.17 (dtd, *J* = 13.8, 6.8, 3.4 Hz, 1H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.93 (dd, *J* = 6.9 Hz, 3H).

[α]_D = +17.7 (*c* 1.0, CHCl₃). Lit [α]_D = +17.3 (*c* 1.06, CHCl₃).

T. Bauer and J. Gajewiak, *Tetrahedron*, **2004**, 60(41), 9163.

Compound SI-6:

Methyl (S)-2-hydroxy-3-methylbutanoate



To a stirred and cooled (0 °C) solution of **SI-5** (1.60 g, 13.6 mmol) in MeOH (13.5 mL) was added a solution of thionyl chloride (1.6 mL, 22.0 mmol) dropwise. The reaction mixture was refluxed for 18

h. After the resulting mixture was cooled to room temperature and MeOH was removed *in vacuo*. The residue was diluted with ether (60 mL) and washed with sat aq. NaHCO₃ and brine, dried over Na₂SO₄, filtered, and concentrated to give **SI-6** (851 mg, 6.44 mmol, 47%) as yellow oil.

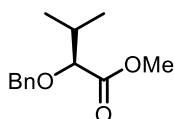
¹H NMR (400 MHz, CDCl₃) δ 4.05 (dd, *J* = 6.3, 3.5 Hz, 1H), 3.79 (s, 3H), 2.67 (dd, *J* = 6.3, 2.2 Hz, 1H), 2.07 (hd, *J* = 6.9, 3.5 Hz, 1H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H).

[α]_D = +15.4 (c 0.96, CHCl₃). Lit [α]_D = +23.7 (c 1.00, CHCl₃)

D. Shklyaruck, E. Matiushenkov, *Tetrahedron: Asymmetry*, **2011**, 22, 1448.

Compound SI-7:

Methyl (S)-2-benzyloxy-3-methylbutanoate



To a mixture of **SI-6** (851 mg, 6.44 mmol), TriBOT (1.10 g, 2.75 mmol) and MS4A (1 g) in 1,4-dioxane (27 mL) was added TfOH (0.09 mL, 1.02 mmol) dropwise. After being stirred for 1 h at room temperature, TriBOT was added (0.212 g, 0.53 mmol) and then the resulting mixture was stirred for 4 h. The reaction mixture was quenched by addition of NEt₃ (0.70 mL), diluted with *n*-hexane and filtered through a pad of Celite[®]. The filtrate was concentrated. The residue was purified by flash column chromatography (10% AcOEt in *n*-hexane) to give **SI-7** (1.24 g, 6.39 mmol, 87%) as orange oil.

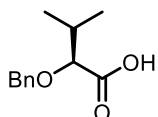
¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.22 (m, 5H), 4.70 (d, *J* = 11.8 Hz, 1H), 4.38 (d, *J* = 11.8 Hz, 1H), 3.75 (s, 3H), 2.09 (pd, *J* = 6.8, 5.6 Hz, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H).

[α]_D = –61.2 (c 1.44, MeOH). Lit [α]_D = –73.5 (c 2.44, CHCl₃).

T. Yakura, T. Tanaka, M. Ikeda, J.-i. Uenishi, *Chem. Pharm. Bull.*, **2003**, 51(4), 471.

Compound 11:

(S)-2-benzyloxy-3-methylbutanoic acid

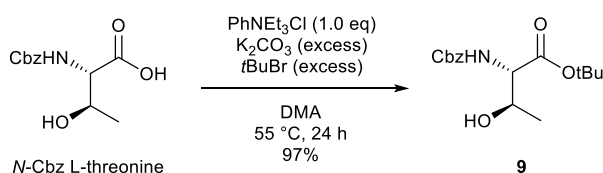


To a stirred and cooled (0 °C) solution of **SI-7** (0.895 g, 4.03 mmol) in MeOH (26 mL) was added an aqueous of KOH (1M, 12 mL, 12 mmol) dropwise and then the mixture was stirred for overnight at room temperature. After being stirred, the resulting mixture was diluted with water (44 mL) and MeOH was removed *in vacuo*. The aqueous layer was extracted with ether (30 mL×2), and neutralized with 1 M HCl (11 mL, 11 mmol) to reach pH 3. The cloudy aqueous layer was extracted with ether (50 mL×4). The combined organic phase was washed brine, dried over anhydrous Na₂SO₄ and filtered and concentrated to give yellow oil **11** (0.566 g, 2.7 mmol, 67%).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.40 – 7.24 (m, 5H), 4.73 (d, $J = 11.6$ Hz, 1H), 4.49 (d, $J = 11.6$ Hz, 1H), 3.80 (d, $J = 4.7$ Hz, 1H), 2.16 (pd, $J = 6.9, 4.7$ Hz, 1H), 1.02 (d, $J = 5.8$ Hz, 3H), 1.00 (d, $J = 5.8$ Hz, 3H). $[\alpha]_{\text{D}} = -79.2$ (c 0.78, EtOH). Lit $[\alpha]_{\text{D}} = -84.0$ (c 1.0, THF).

C. Palomo, M. Oiarbide, J. M. García, A. González, R. Pazos, J. M. Odriozola, P. Bañuelos, M. Tello and A. Linden, *J. Org. Chem.*, **2004**, *69*, 4126.

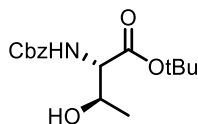
N-Cbz *L*-threonine *tert*-butyl ester **9** was obtained from *N*-Cbz *L*-threonine as shown in Scheme SI-3, see ref 10: I. Wilson and R. F. W. Jackson, *J. Chem. Soc., Perkin Trans. 1*, **2002**, 2845.



Scheme SI-3 Synthesis of **9**.

Compound 9:

tert-Butyl-*N*-benzyloxycarbonyl-*L*-threoninate



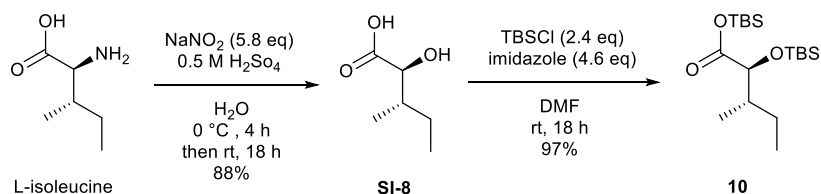
N-Benzyloxycarbonyl-*L*-threonine (2.53 g, 10.0 mmol) was dissolved in *N,N*-Dimethylacetamide (75 mL) at room temperature in the presence of benzyltriethylammonium chloride (2.29 g, 10.1 mmol). Anhydrous potassium carbonate (36.0 g, 490 mmol) was added to the stirred solution, followed by the addition of *tert*-butyl bromide (55 mL, 490 mmol). The mixture was stirred at 55°C for 24 h. The reaction mixture was allowed to be cooled and poured into water (1 L) and extracted with AcOEt (150 mL \times 2). The organic layer was separated, washed with water, dried over MgSO_4 and concentrated under the reduced pressure to give **9** (2.99 g, 9.67 mmol, 97%) as a white solid.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.43 – 7.28 (m, 5H), 5.51 (d, $J = 9.0$ Hz, 1H), 5.13 (s, 2H), 4.27 (t, $J = 6.4$ Hz, 1H), 4.21 (d, $J = 9.1$ Hz, 1H), 2.00 – 1.91 (m, 1H), 1.47 (s, 9H), 1.24 (d, $J = 6.4$ Hz, 3H).

$[\alpha]_{\text{D}} = -8.3$ (c 0.90, CH_2Cl_2). Lit $[\alpha]_{\text{D}}^{20} = -10.3$ (c 1.0, CHCl_3).

D. Wiegmann, A. P. Spork, G. Niro and C. Ducho, *Synlett*, **2018**, *29*, 440.

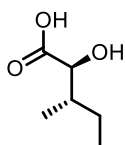
tert-Butyldimethylsilyl (2*S*, 3*S*)-2-*tert*-butyldimethylsilyloxy-3-methylpentanoate **10** was obtained from L-isoleucine as shown in Scheme SI-4, see ref 11: A. Murai, Y. Amino and T. Ando, *J. Antibiot.*, **1985**, *38*, 1610.



Scheme SI-4 Synthesis of **10**.

Compound SI-8:

(2*S*, 3*S*)-2-hydroxy-3-methylpentanoic acid



To a solution of L-isoleucine (2.621 g, 20.0 mmol) in 0.5 M H₂SO₄ (80 mL) was slowly added a solution of NaNO₂ (8.017 g, 116 mmol) in water (30 mL) with stirring at 0 °C, while the temperature of mixture was kept below 0 °C. The resulting mixture was stirred at this temperature for 4 h, and then allowed to warm up to room temperature and stirred for 18 h. The reaction mixture was extracted with ethyl ether (65 mL × 3) and the combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to give **SI-8** as white solid (2.330 g, 17.6 mmol, 88%).

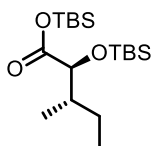
¹H NMR (400 MHz, CDCl₃) δ 4.19 (d, *J* = 3.6 Hz, 1H), 1.97 – 1.82 (m, 1H), 1.51 – 1.37 (m, 1H), 1.37 – 1.23 (m, 1H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H).

[α]_D = +19.7 (c 0.98, CHCl₃). Lit [α]_D = +20.8 (c 1.02, CHCl₃).

M. Poterala and J. Pleniewicz, *Tetrahedron: Asymmetry*, **2011**, *22*(3), 294.

Compound 10:

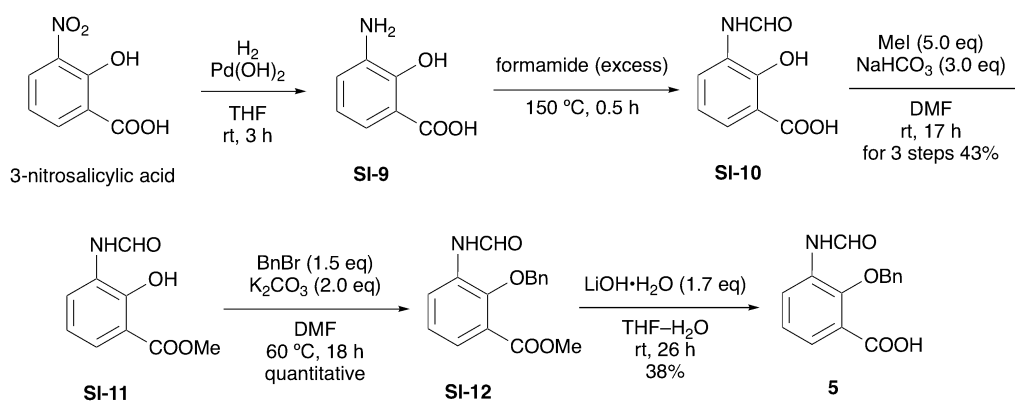
tert-Butyldimethylsilyl (2*S*, 3*S*)-2-*tert*-butyldimethylsilyloxy-3-methylpentanoate



To a solution of (2*S*, 3*S*)-hydroxy carboxylic acid **SI-8** (1.31 g, 9.9 mmol) in DMF (19 mL) at room temperature were added imidazole (3.09 g, 45.4 mmol) and TBSCl (3.58 g, 23.7 mmol) successively. After being stirred for 18 h, the reaction mixture was diluted with water (60 mL) and extracted with 4:1 mixture

of *n*-Hexane and AcOEt (60 mLx3). The combined organic layers were washed with sat aq. NaHCO₃ and brine, dried over MgSO₄, and concentrated *in vacuo*. The crude silyl ester **10** (3.47 g) was used in the next step without further purification.

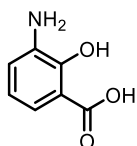
2-Benzyloxy-3-formylaminobenzoic acid was obtained from 3-nitrosalicylic acid as shown in Scheme SI-5, see ref 9: G. R. Pettit, T. H. Smith, S. Feng, J. C. Knight, R. Tan, R. K. Pettit and P. A. Hinrichs, *J. Nat. Prod.*, 2007, **70**, 1073.



Scheme SI-5 Synthesis of **5**.

Compound SI-9:

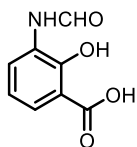
3-Aminosalicylic acid



To a stirred solution of 3-nitrosalicylic acid (2.98 g, 16.3 mmol) in THF (94 mL) was added 10% Pd(OH)₂ (502 mg). The resulting suspension was applied with H₂ gas at 1 atm and stirred vigorously at room temperature for 3 h. Then the mixture was filtered through a pad of Celite® and the filtrate was concentrated to give the **SI-9** (2.41 g, 15.7 mmol, quantitative yield). This was used for the next reaction without further purification.

Compound SI-10:

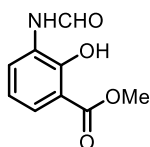
3-Formylamino-2-hydroxybenzoic acid



A suspension of 3-aminosalicylic acid **SI-9** (2.41 g, 15.7 mmol) in formamide (33 mL) was stirred for 30 min at 150 °C. The resulting solution was cooled to room temperature, diluted with sat. aq. NaHCO₃, and neutralized by adding 1 M KHSO₄ aq., and extracted with AcOEt. The combined extracts were washed with brine, dried over Na₂SO₄, concentrated and co-evaporated with toluene. This was used for the next reaction without further purification.

Compound SI-11:

Methyl 3-formylamino-2-hydroxybenzoate

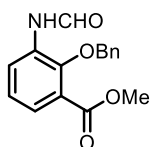


MeI (6.4 mL, 103 mmol) was added to a solution of **SI-10** (crude, 3.72 g) and NaHCO₃ (4.36 g, 51.9 mmol) in DMF (49 mL) at rt. The mixture was stirred for 17 h at rt, diluted with water, and extracted with AcOEt. The combined extracts were washed with sat. aq. NaHCO₃ water and brine, dried over Na₂SO₄, concentrated, and purified by flash column chromatography (30% AcOEt in Hexane) to give **SI-11** (1.26 g, 6.44 mmol, 43% for 3 steps) as a 5:1 mixture of rotamers.

¹H NMR (400 MHz, CDCl₃) Major isomer δ 11.30 (s, 3H), 8.57 (dd, *J* = 8.1, 1.6 Hz, 1H), 8.50 (d, *J* = 1.8 Hz, 1H), 7.85 (br s, 1H), 7.58 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.91 (t, *J* = 8.1 Hz, 1H), 3.97 (s, 3H); Minor isomer δ 11.17 (s, 1H), 8.76 (d, *J* = 11.5 Hz, 1H), 7.65 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.39 (d, *J* = 7.9 Hz, 1H), 3.98 (s, 3H).

Compound SI-12:

Methyl 2-benzyloxy-3-formylaminobenzoate



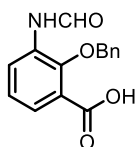
BnBr (1.15 mL, 9.61 mmol) was added to a stirred mixture of **SI-11** (1.26 g, 6.43 mmol) and K₂CO₃ (1.81 g, 13.1 mmol) in DMF (25 mL). The mixture was stirred for 18 h at 60 °C, diluted with water, and extracted with AcOEt. The combined extracts were washed with brine, dried over Na₂SO₄, concentrated, and purified by flash column chromatography (30% AcOEt in Hexane) to give **SI-12**

(1.90 g, 6.67 mmol, quantitative yield) as a 5:1 mixture of rotamers.

¹H NMR (400 MHz, CDCl₃) Major δ 8.53 (dd, *J* = 8.1, 1.6 Hz, 1H), 8.19 (d, *J* = 1.8 Hz, 1H), 7.66 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.46 – 7.34 (m, 5H), 7.21 – 7.16 (m, 1H), 5.02 (s, 2H), 3.93 (s, 3H); Minor δ 8.62 (d, *J* = 11.5 Hz, 1H), 8.24 (s, 1H), 7.78 (dd, *J* = 7.6, 2.0 Hz, 1H), 3.89 (s, 3H).

Compound 5:

2-Benzyloxy-3-formylaminobenzoic acid

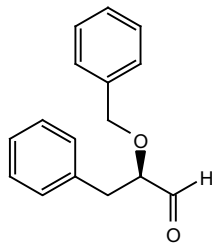


To a stirred solution of methyl ester **SI-12** (816 mg, 2.86 mmol) in THF-H₂O (3 : 1, 16 mL) was added dropwise a solution of LiOH•H₂O (445 mg, 4.76 mmol) in H₂O (11.5 mL) at 0 °C. The mixture was stirred for 26 h at room temperature, acidified (pH 3) with 1 M KHSO₄ aq., and extracted with AcOEt. The combined extracts were washed with brine, dried over Na₂SO₄, concentrated, and recrystallized from AcOEt-hexane to give **5** (294 mg, 1.08 mmol, 38%) as a 5:1 mixture of rotamers.

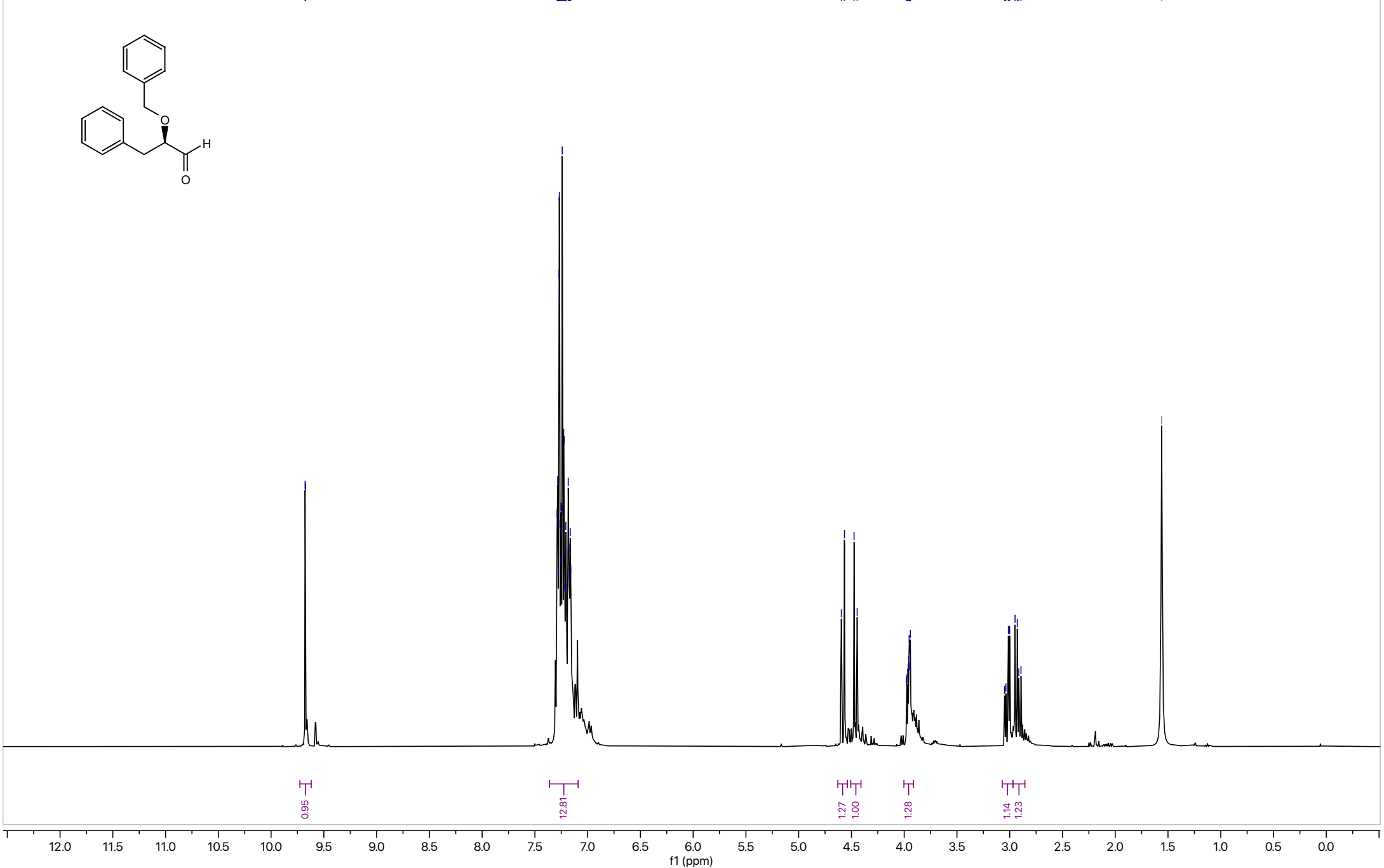
¹H NMR (400 MHz, CDCl₃) δ 13.09 (s, 1H), 9.77 (s, 1H), 8.34 (d, *J* = 1.8 Hz, 1H), 8.30 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.55 – 7.30 (m, 5H), 7.19 (t, *J* = 8.0 Hz, 1H), 4.95 (s, 2H); Minor (diagnostic peaks only) δ 9.68 (d, *J* = 11.1 Hz, 1H), 8.50 (d, *J* = 10.9 Hz, 1H), 4.92 (s, 2H).

¹H NMR Spectrum of **14** (400 MHz, CDCl₃)

S13

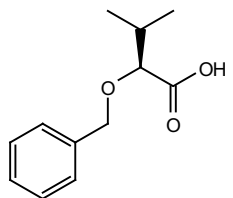


9.68
9.67
7.29
7.28
7.28
7.27
7.27
7.27
7.26
7.26
7.25
7.25
7.24
7.24
7.23
7.22
7.22
7.21
7.21
7.20
7.18
7.18
7.17
7.17
7.16
4.60
4.57
4.48
4.45
3.98
3.97
3.97
3.96
3.96
3.95
3.95
3.95
3.94
3.05
3.04
3.01
3.00
2.95
2.93
2.91
2.89
1.56 CDCl₃



¹H NMR Spectrum of **11** (400 MHz, CDCl₃)

S14

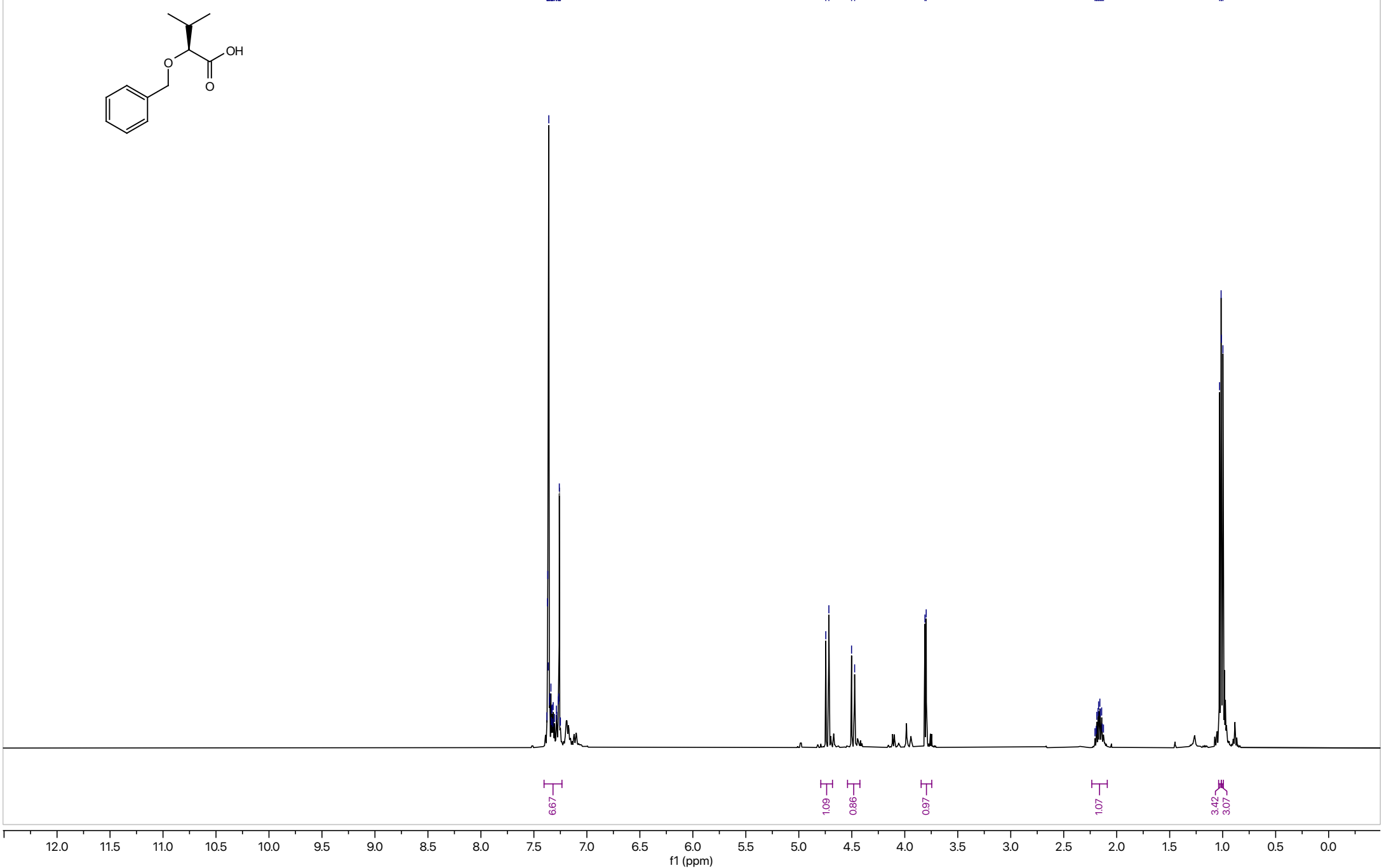


7.38
7.37
7.37
7.36
7.36
7.35
7.35
7.34
7.33
7.33
7.33
7.32
7.32
7.31
7.29
7.28
7.27
7.27
7.26
7.26 CDCl₃
7.25
7.25

4.75
4.72
4.50
4.47

3.81
3.80

2.21
2.19
2.19
2.18
2.17
2.16
2.15
2.14
2.14
2.12
1.03
1.01
1.01
1.00



6.67

1.09

0.86

0.97

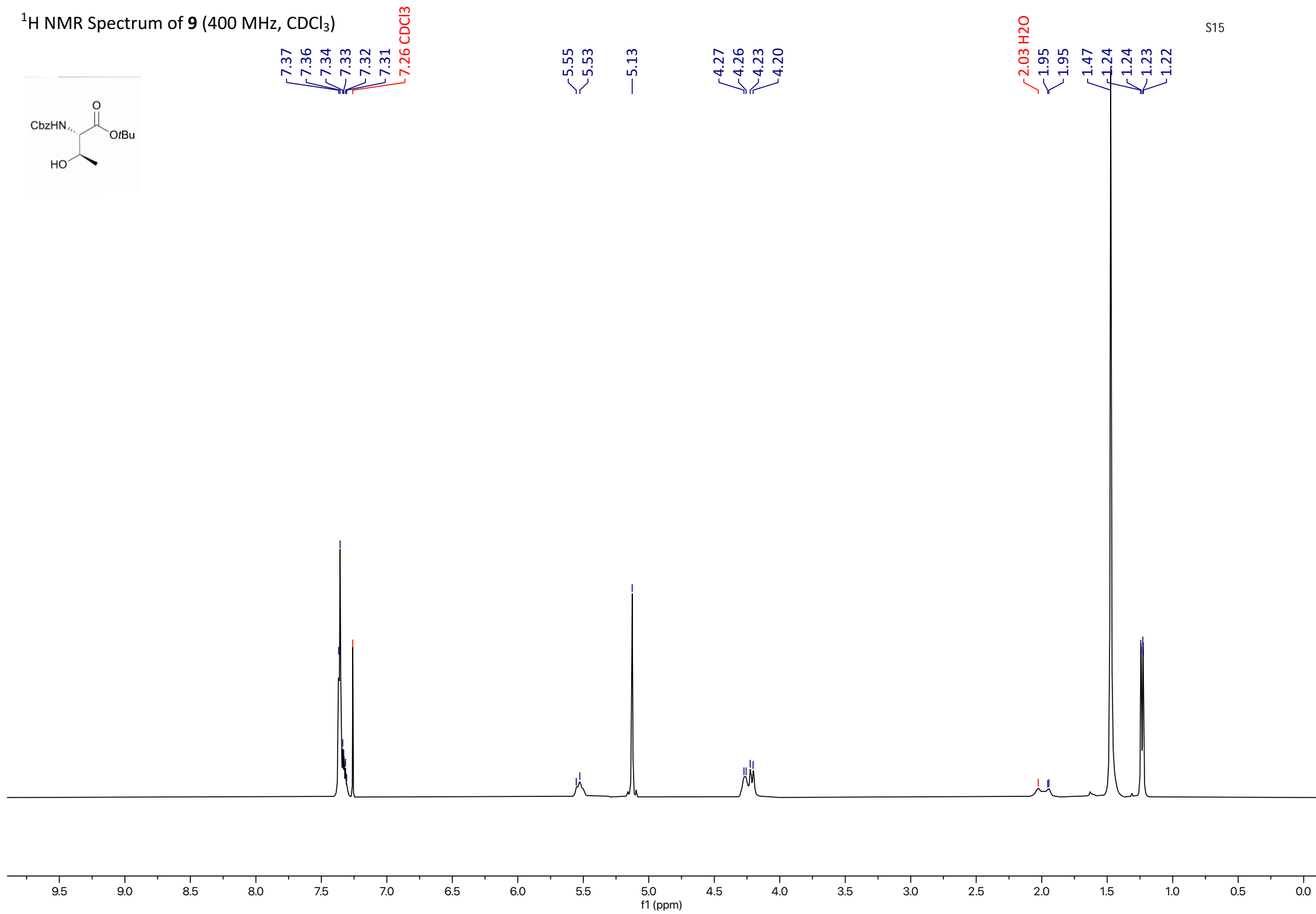
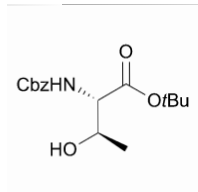
1.07

3.42

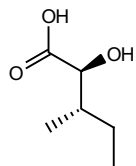
3.07

f1 (ppm)

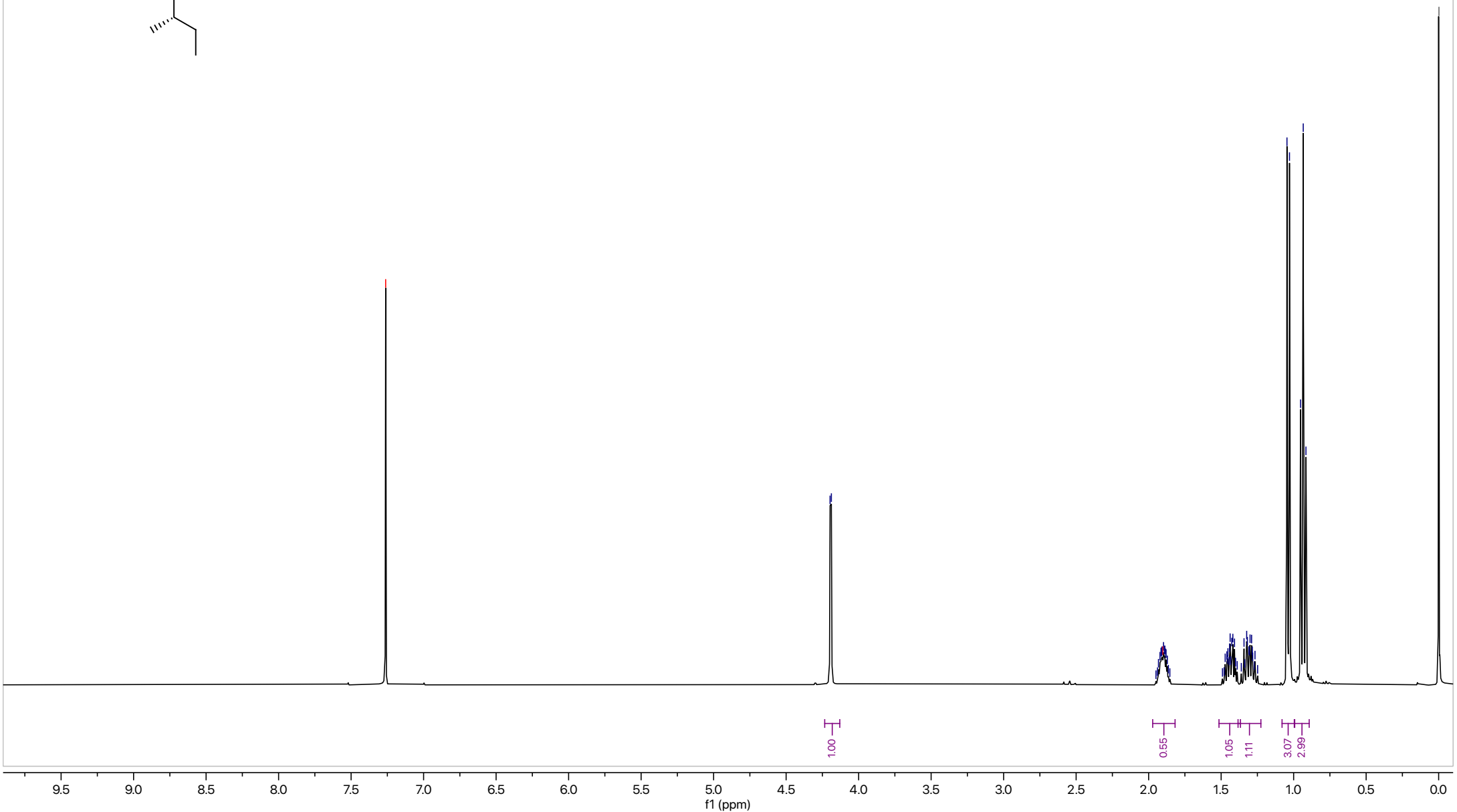
¹H NMR Spectrum of **9** (400 MHz, CDCl₃)



¹H NMR Spectrum of **SI-8** (400 MHz, CDCl₃)

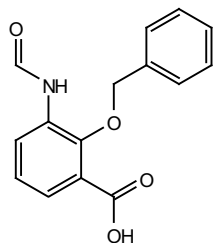


7.26 CDCl₃
4.20
4.19
1.95
1.94
1.93
1.92
1.91
1.91
1.91
1.90 H₂O
1.90
1.89
1.89
1.88
1.88
1.87
1.86
1.85
1.49
1.48
1.47
1.46
1.46
1.45
1.45
1.44
1.44
1.43
1.43
1.42
1.41
1.40
1.39
1.36
1.34
1.34
1.32
1.32
1.31
1.31
1.30
1.29
1.29
1.28
1.27
1.27
1.25
1.05
1.03
0.95
0.93
0.92
0.00 TMS
-0.00



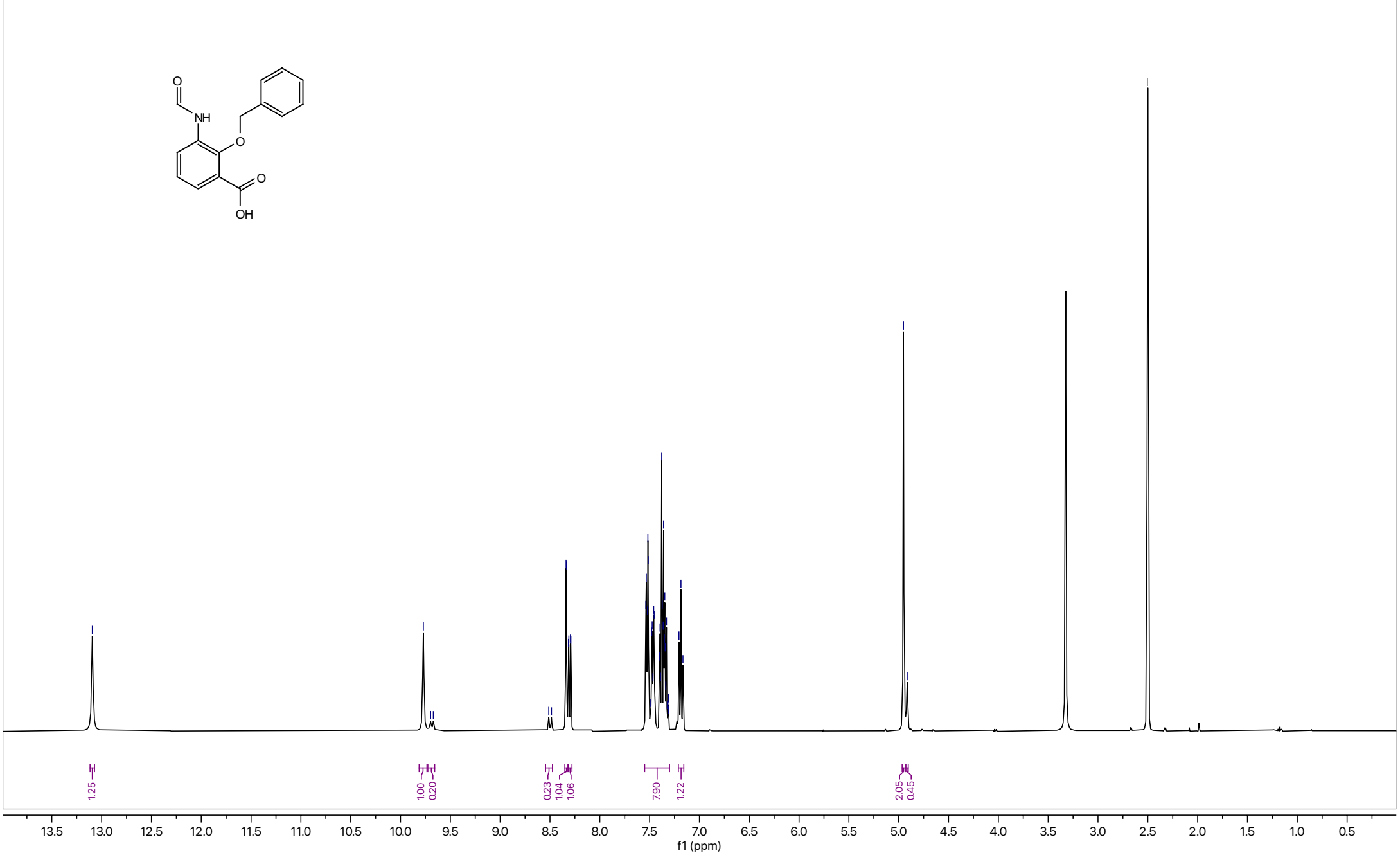
¹H NMR Spectrum of 5 (400 MHz, CDCl₃)

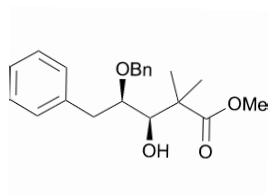
S17



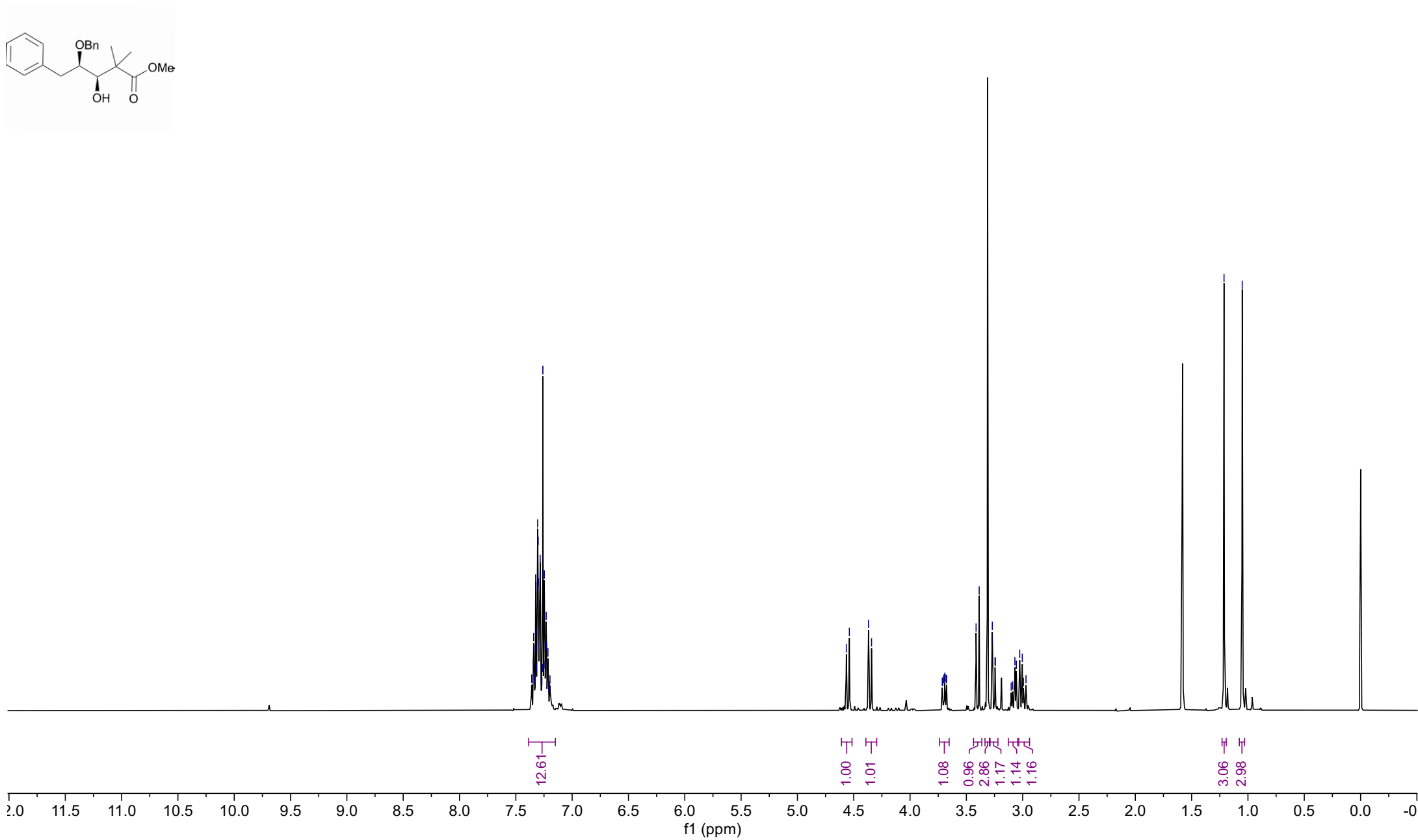
—13.09

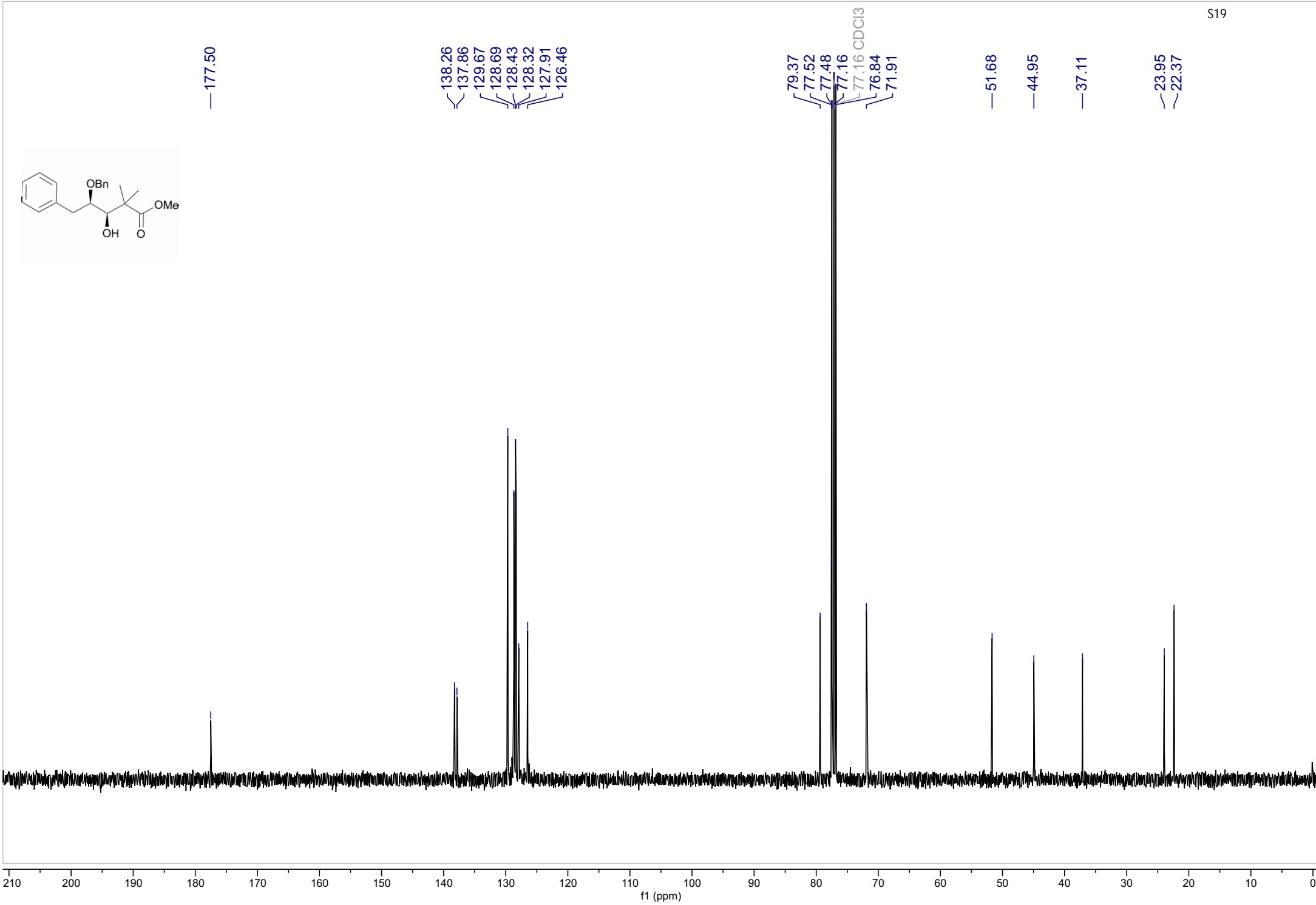
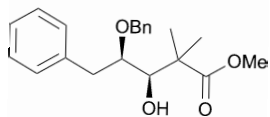
9.77
9.70
9.67
8.51
8.48
8.34
8.33
8.31
8.31
8.29
8.29
7.54
7.53
7.52
7.52
7.51
7.49
7.48
7.47
7.47
7.46
7.45
7.40
7.40
7.39
7.38
7.37
7.36
7.36
7.35
7.35
7.34
7.34
7.33
7.32
7.32
7.31
7.31
7.21
7.19
7.17
4.95
4.91
2.50 DMSO-d6



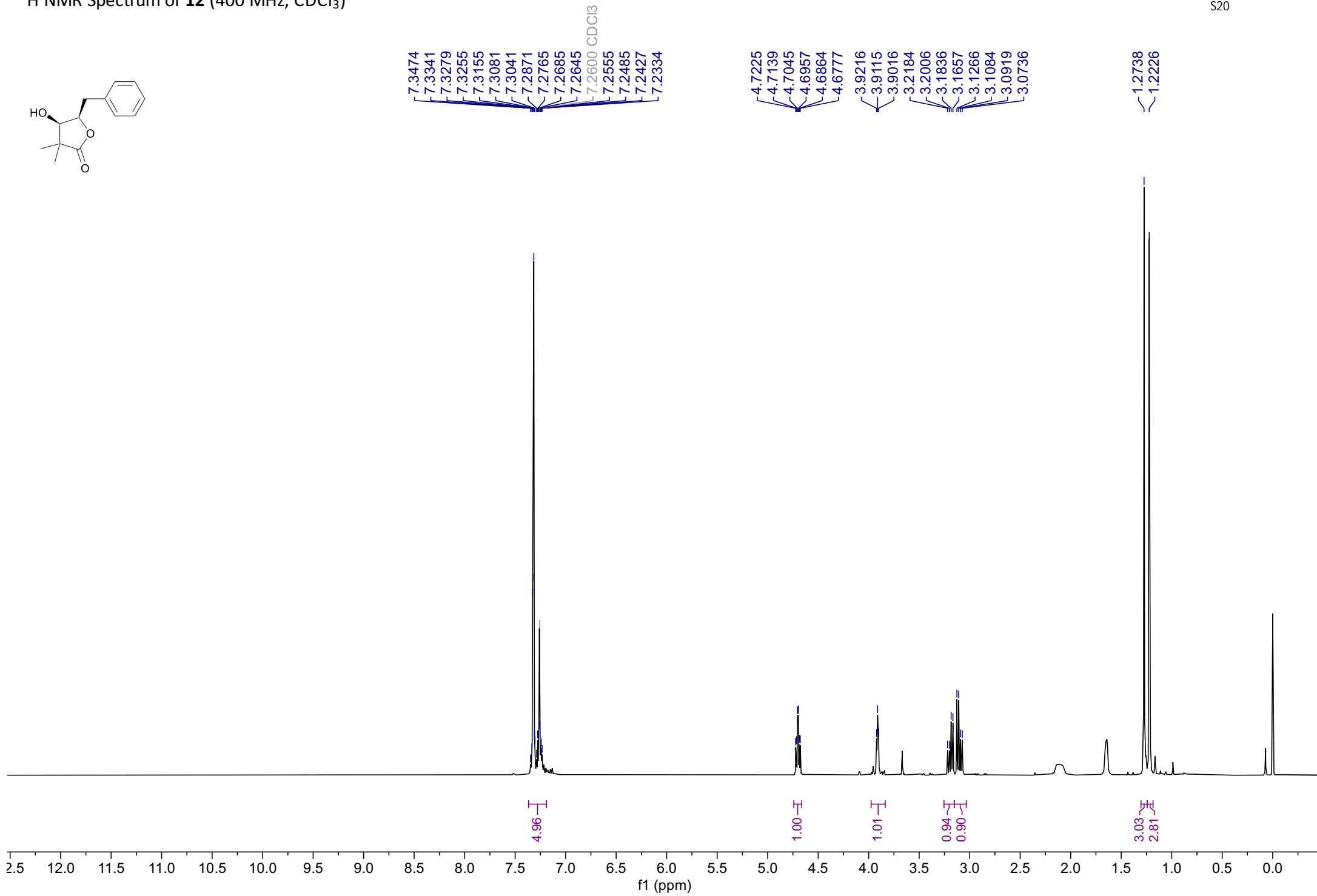
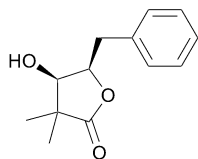


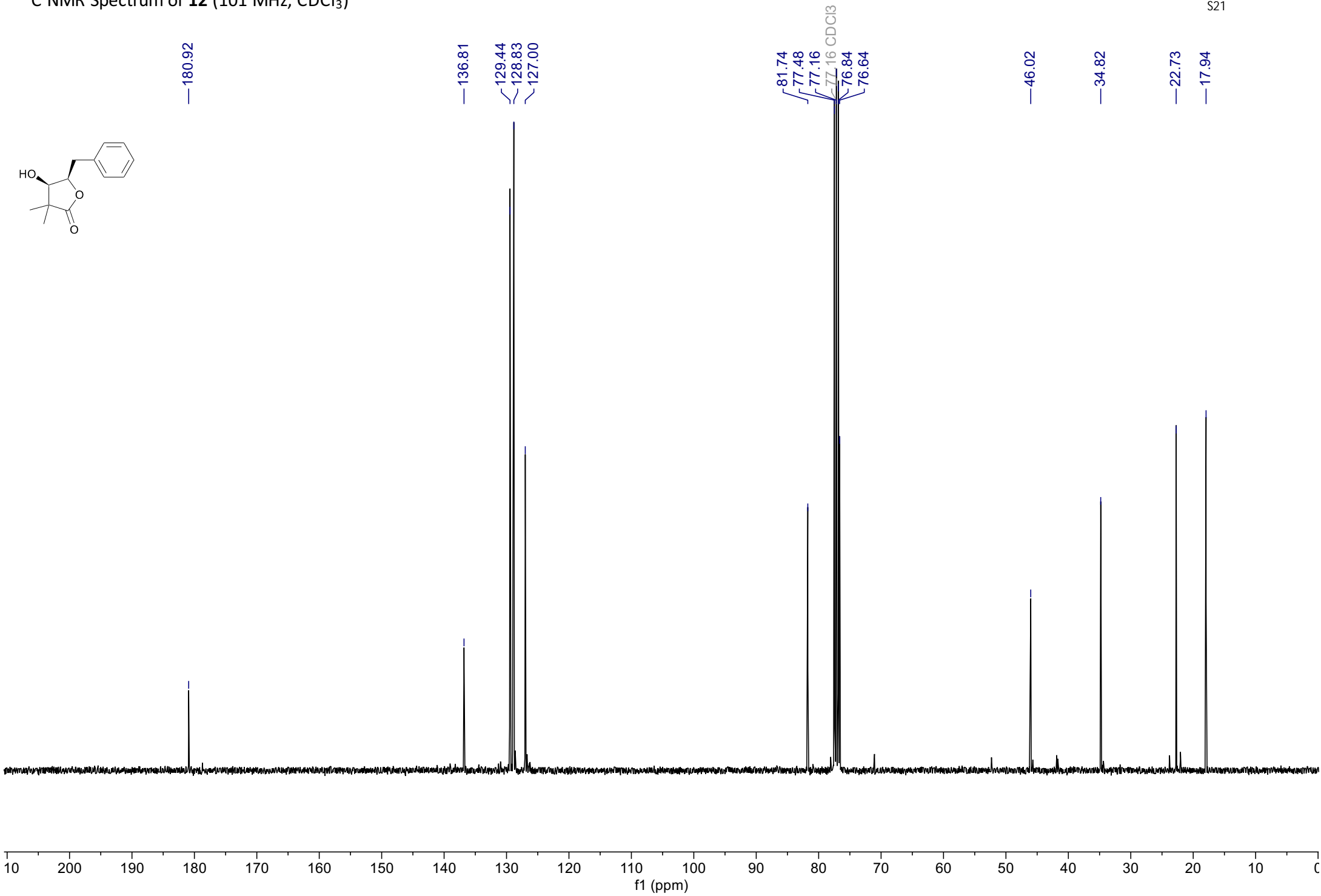
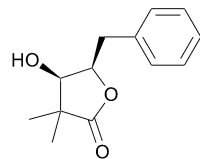
7.3593
7.3446
7.3417
7.3378
7.3343
7.3309
7.3243
7.3222
7.3200
7.3163
7.3065
7.3014
7.2992
7.2938
7.2893
7.2840
7.2818
7.2735
7.2685
7.2648
7.2601
7.2600 CDCl₃
7.2517
7.2473
7.2416
7.2348
7.2302
7.2271
7.2201
7.2147
7.2084
7.2006
7.1969
4.5657
4.5389
4.3686
4.3417
3.7141
3.7107
3.7012
3.6978
3.6917
3.6883
3.6788
3.6753
3.4138
3.3863
3.3121
3.2731
3.2698
3.2456
3.2422
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3.0262
3.0037
2.9934
2.9706
1.2124
1.0508



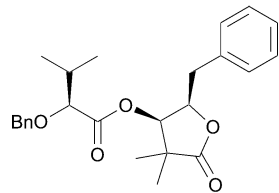


¹H NMR Spectrum of **12** (400 MHz, CDCl₃)





¹H NMR Spectrum of **16** (400 MHz, CDCl₃)



7.3403
7.3345
7.3320
7.3232
7.3096
7.3055
7.3030
7.2995
7.2962
7.2878
7.2840
7.2785
7.2750
7.2600
7.2600 CDCl₃
7.2554
7.2431
7.2395
7.2361
7.2304
7.2266
5.4022
5.3927
4.8153
4.8057
4.8026
4.7927
4.7827
4.7258
4.6967
4.4155
4.3865
3.8529
3.8420
3.0198
2.9973
2.9834
2.9609
2.8552
2.8448
2.8190
2.8085
2.1802
2.1743
2.1632
2.1572
1.3446
1.2093
1.0527
1.0355
0.9865
0.9694

S22

11.07

1.00

1.10

1.00

1.05

1.01

1.11

1.09

0.69

2.83

3.09

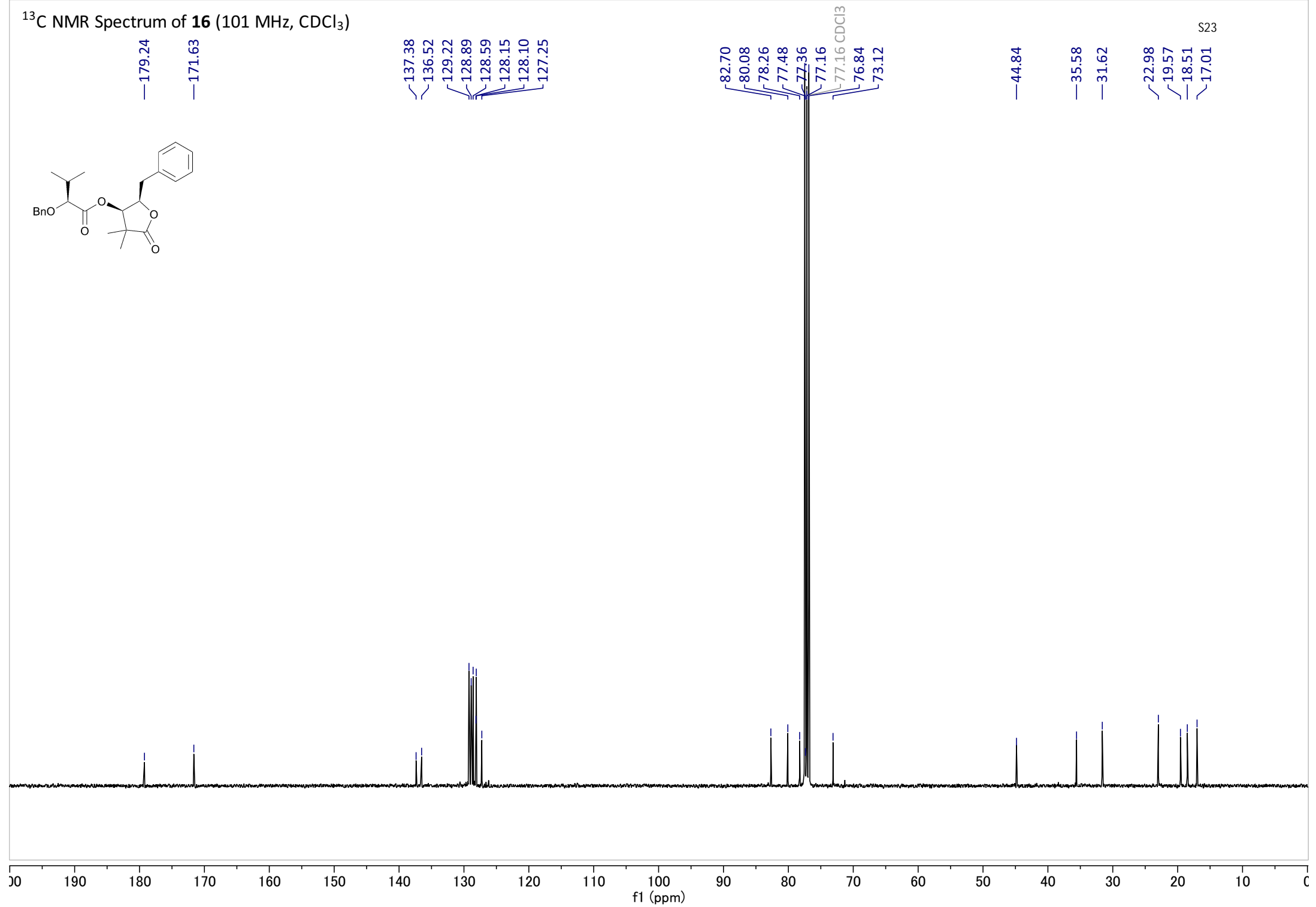
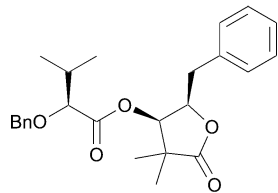
3.04

2.99

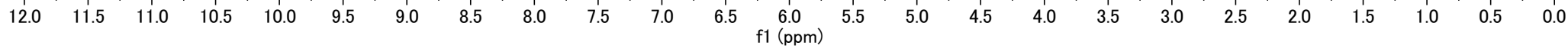
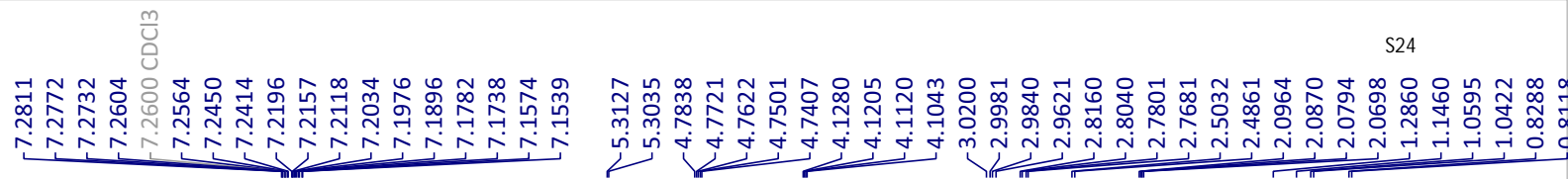
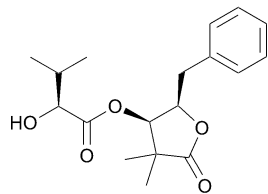
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0

f1 (ppm)

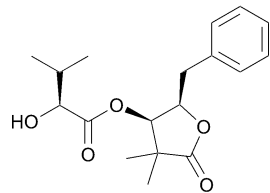
¹³C NMR Spectrum of **16** (101 MHz, CDCl₃)



¹H NMR Spectrum of **7** (400 MHz, CDCl₃)



¹³C NMR Spectrum of **7** (101 MHz, CDCl₃)



179.0354

174.2959

136.0898

129.1631

128.9439

127.3123

79.9831

79.0351

77.1600 CDCl₃

75.2390

44.7737

35.3682

32.0065

22.9615

19.5169

18.4078

15.5439

S25

190

180

170

160

150

140

130

120

110

100

90

80

70

60

50

40

30

20

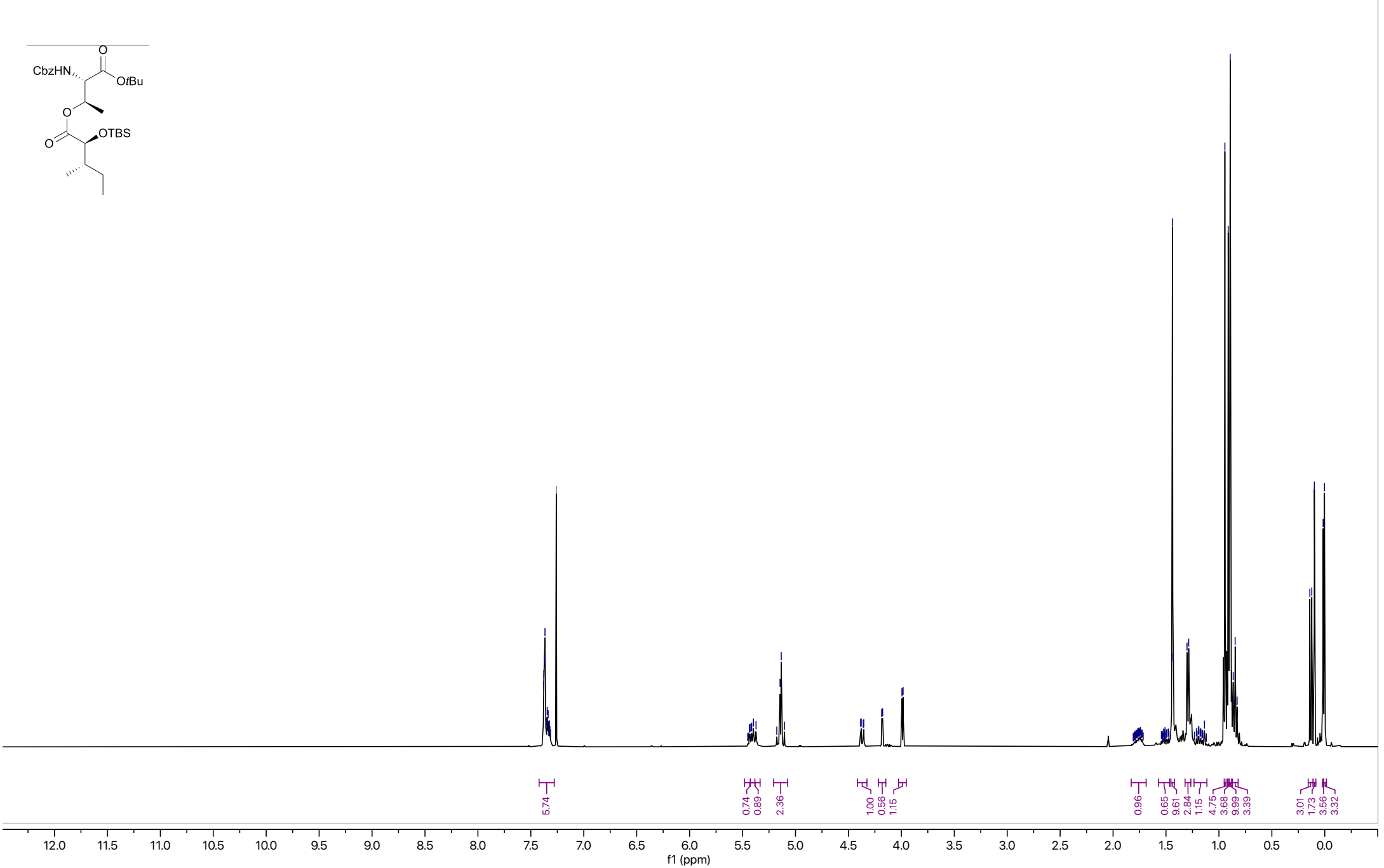
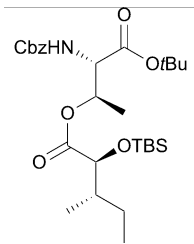
10

0

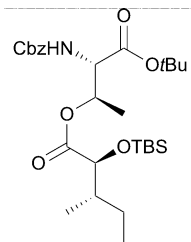
f1 (ppm)

¹H NMR Spectrum of **17** (400 MHz, CDCl₃)

7.38
7.38
7.37
7.37
7.35
7.35
7.35
7.34
7.33
7.32
7.32
7.31
-7.26 CDCl₃
-5.44
-5.43
-5.42
-5.41
-5.40
-5.37
-5.18
-5.15
-5.13
-5.10
-4.38
-4.38
-4.36
-4.35
-4.19
-4.18
-3.99
-3.98
-1.78
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-1.77
-1.77
-1.76
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-1.74
-1.74
-1.73
-1.73
-1.52
-1.51
-1.51
-1.50
-1.49
-1.48
-1.44
-1.43
-1.30
-1.29
-1.21
-1.19
-1.19
-1.18
-1.17
-1.16
-1.15
-1.14
-0.94
-0.91
-0.89
-0.86
-0.85
-0.83
-0.14
-0.12
-0.10
-0.02
0.00



¹³C NMR Spectrum of **17** (101 MHz, CDCl₃)



172.29
168.82
156.75

136.36

128.68
128.35
128.21

82.91
77.36
77.16 CDCl₃
76.41
71.08
67.36
58.28

39.65

28.11
25.85
24.00

18.33
17.41
15.78
11.76

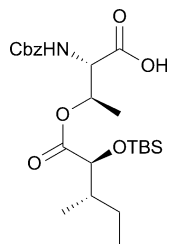
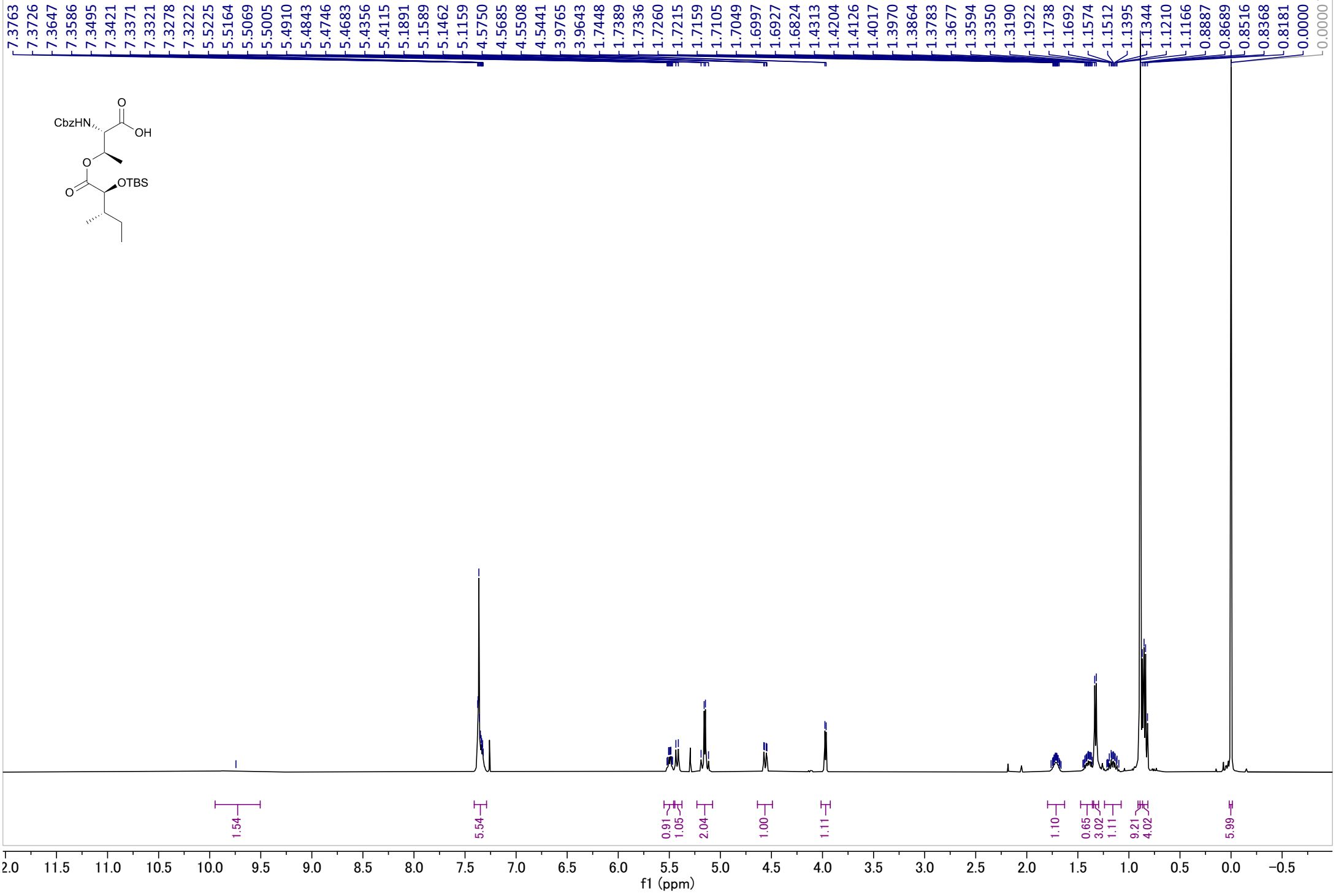
S27

-4.67
-5.20

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

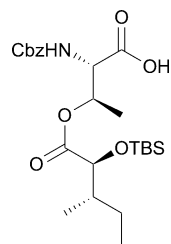
f1 (ppm)

¹H NMR Spectrum of **8** (400 MHz, CDCl₃)



¹³C NMR Spectrum of **8** (101 MHz, CDCl₃)

S29



179.04

174.30

136.09

129.16

128.94

127.31

79.98

79.04

77.96

77.16 CDCl₃

75.24

44.77

35.37

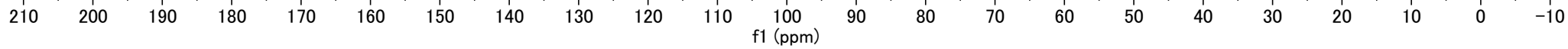
32.01

22.96

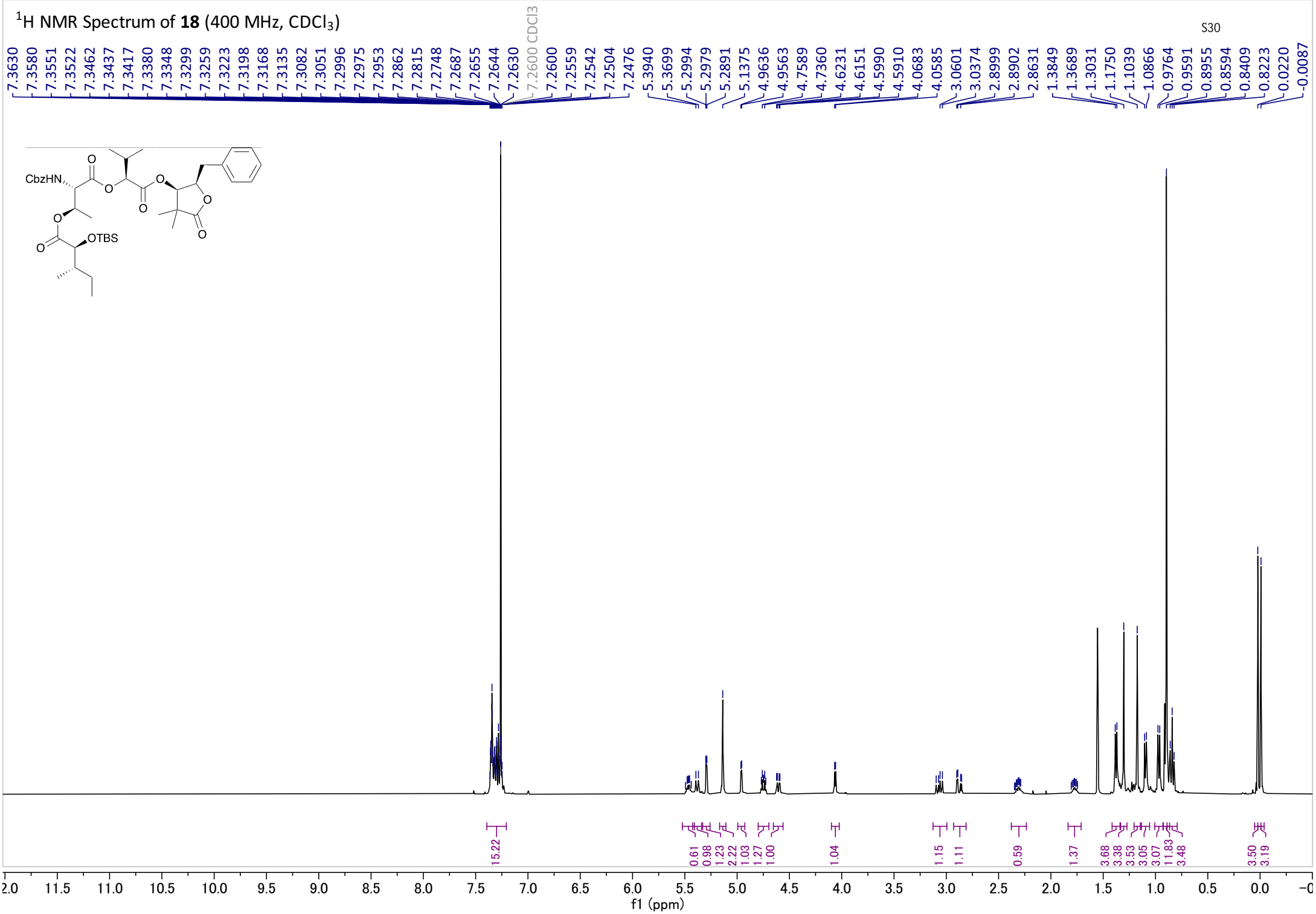
19.52

18.41

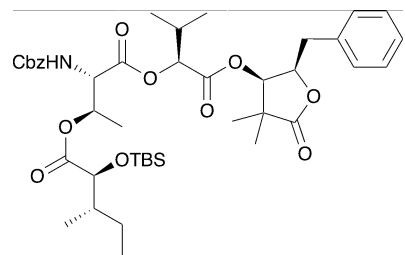
15.54



¹H NMR Spectrum of **18** (400 MHz, CDCl₃)



¹³C NMR Spectrum of **18** (101 MHz, CDCl₃)



172.29
168.82
156.75

136.36
128.68
128.35
128.21

82.91
77.36
77.16 CDCl₃
76.41
71.08
67.36

58.28

39.65

28.11
25.85
24.00

18.33
17.41
15.78
11.76

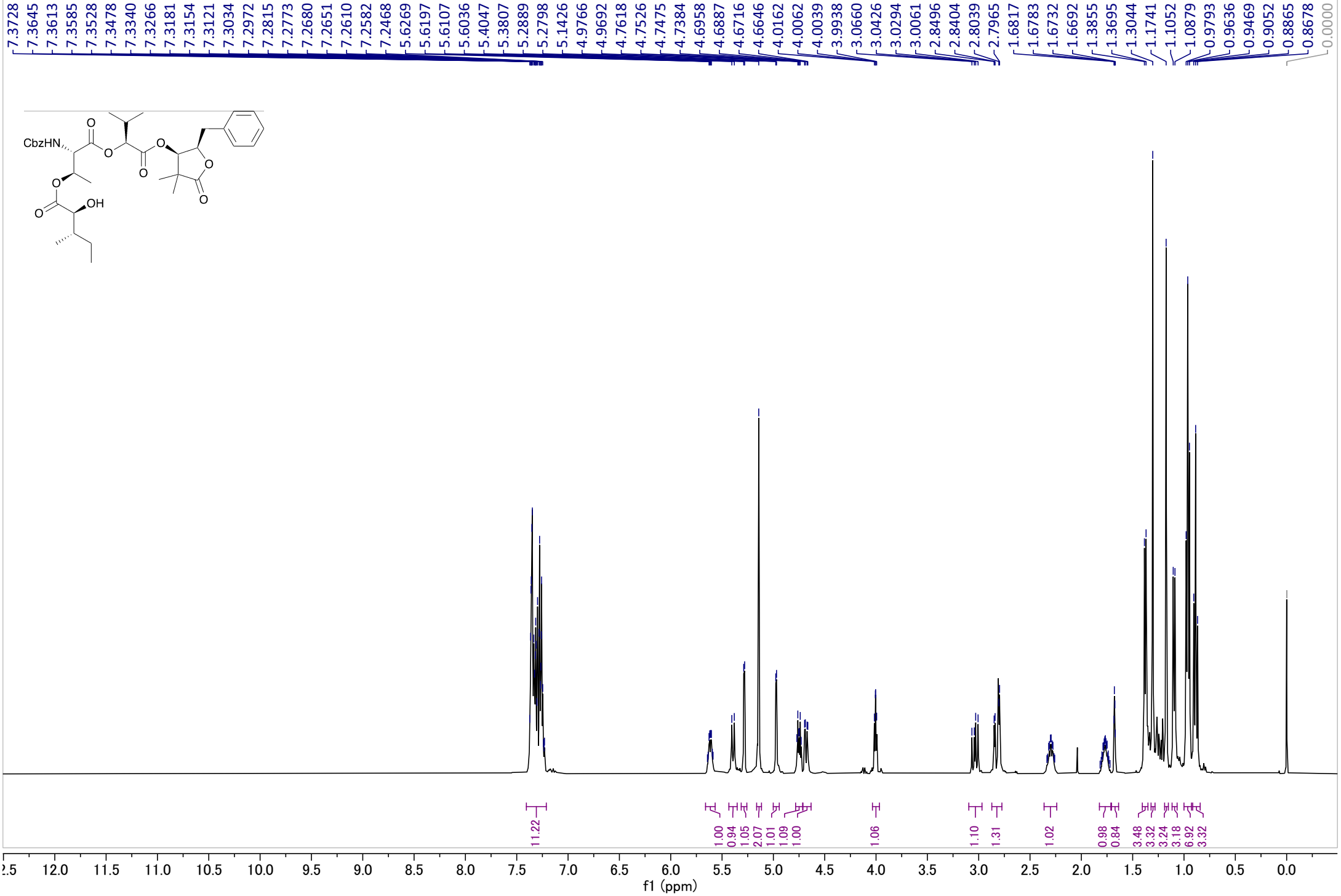
S31

-4.67
-5.20

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1

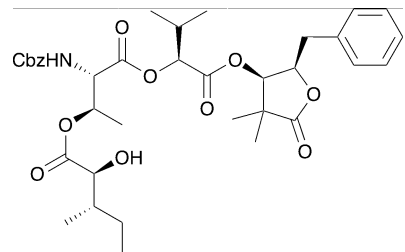
f1 (ppm)

¹H NMR Spectrum of **19** (400 MHz, CDCl₃)



¹³C NMR Spectrum of **19** (101 MHz, CDCl₃)

S33



179.00
173.88
169.43
168.34

156.66

136.64
135.97
129.37
128.81
128.72
128.51
128.30
127.11

80.39
79.20
77.54
77.48
77.16
77.16 CDCl₃
76.84
74.61
71.64
67.69
57.50

44.67
38.83
35.35
29.96
23.98
22.88
19.53
18.41
16.81
16.34
15.43
11.87

0.11

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

¹H NMR Spectrum of 4 (600 MHz, CDCl₃)

S34

