Supporting Information for:

"A New Selective Synthesis of the Ile-*allo*-Thr-Gly Tripeptide Fragment of Lysobactin"

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Full experimental details and analytical data for all new compounds (**3-12**) and representative ^{1}H NMR spectra for compound **3**, **4**, **7**, **8**, and **12**.

Experimental

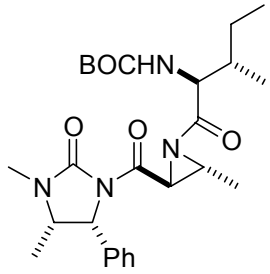
General information.

^{1}H NMR spectra were recorded on Varian spectrometers at 300 MHz. Proton chemical shifts are reported in ppm (δ) relative to the solvent peak of $CHCl_3$, defined to be δ 7.27 ppm. ^{13}C NMR spectra were recorded on Varian spectrometers at 75 MHz. Carbon chemical shifts are reported in ppm (δ) relative to the solvent peak of $CHCl_3$, defined to be δ 77.0 ppm. NMR data were collected at 25°C. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh). THF was distilled from sodium benzophenone ketyl. Dichloromethane was distilled from P_2O_5. Unless stated otherwise, chemicals were obtained from commercial sources and used without further purification. Compound **2** was prepared following the procedure reported in ref. 4c.

Preparation of (4R,5S,2'S,3'R)-1,5-Dimethyl-3-[(1'-BOCisoleucyl-3'-methyl-2'-aziridinyl)carbonyl]-4-phenylimidazolidin-2-one (3)

To a stirred solution of *N*-BOC-isoleucine (1.5 mmol, 0.35 g) and dicyclohexylcarbodiimide (1.5 mmol, 0.31 g) in CH_2Cl_2 (10 mL), a solution of aziridine **2** (1 mmol, 0.27 g) in CH_2Cl_2 (10 mL) was added dropwise at room temperature. The mixture was allowed to stir at room temperature for 12 h. After filtration of dicyclohexylurea, the solution was diluted with CH_2Cl_2 (20 mL) and washed with water (10 mL). The organic layer was then dried over Na_2SO_4 and solvent removed under reduced pressure. Compound **3** was obtained in 90% yield (0.43 g) after purification by flash chromatography on silica gel (cyclohexane/ethyl acetate 1:1). ATTENTION:

aziridine **3** spontaneously rearranges to oxazoline **4** when is left for long periods in solution of dichloromethane or chloroform.



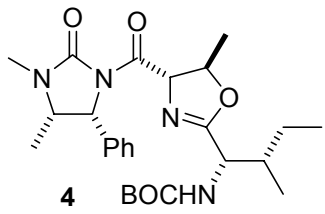
3

3: ^{1}H NMR ($CDCl_3$) δ 0.79 (d, 3H, *J*=6.6 Hz); 0.90 (t, 3H, *J*=6.9 Hz); 0.93 (d, 3H, *J*=6.6 Hz); 1.07-1.25 (m, 1H); 1.39 (d, 3H, *J*= 5.4 Hz); 1.44 (s, 9H); 1.41-1.57 (m, 1H); 1.78-1.92 (m, 1H); 2.81 (dq, 1H, *J* = 2.5, 5.4 Hz); 2.86 (s, 3H); 4.01-4.10 (m, 2H); 4.57 (d, 1H, *J*= 2.5 Hz); 5.22 (d, 1H, *J*= 9.3 Hz); 5.27 (d, 1H, *J*=8.7 Hz); 7.03-7-34 (m, 5H).^{13}C NMR ($CDCl_3$) δ 11.8, 14.8, 15.4, 17.0, 24.7, 28.1, 28.4, 39.2, 39.9, 54.2, 59.6, 60.0, 79.0, 126.8, 128.1, 128.5, 135.9, 147.1, 155.4, 166.0, 171.8. $[\alpha]^{20}_{D}$ = -63.0° (*c* =1.3, $CHCl_3$).

For the ^{1}H NMR spectra see Figure 1

Preparation of (4R,5S,4'S,5'R,1"S,2"S)-4,5-Dihydro-2-(1"-tertbutoxycarbonylamino-2"-methyl-1"-butyl)-4-[(1',5'-dimethyl-4'-phenylimidazolidin-2'-on-3'-yl)carbonyl]-5-methyloxazole (4).

To a stirred solution of aziridine **3** (0.8 mmol, 0.39 g) in dry CH_2Cl_2 (10 mL), under an atmosphere of N_2, $BF_3{\cdot}Et_2O$ (0.8 mmol, 0.1 mL) was added at room temperature. After 2h the mixture was diluted with CH_2Cl_2 (10 mL) and washed twice with a 0.1M solution of Na_2CO_3 (2×10 mL). The organic layer was dried over Na_2SO_4 and solvent removed under reduced pressure. Oxazoline **4** was obtained in 90%yield (0.35 g) after flash chromatography on silica gel (cyclohexane/ethyl acetate 8:2).



4

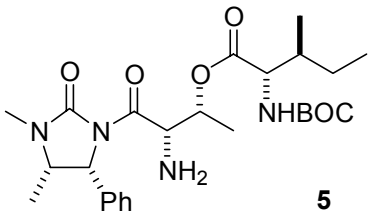
4: ^{1}H NMR ($CDCl_3$) δ 0.79 (d, 3H, *J*=6.6 Hz); 0.84 (d, 3H, *J*=7.2 Hz); 0.88 (d, 3H, *J*= 6.9 Hz); 1.02-1.19 (m, 1H); 1.41 (s, 9H); 1.42 (d, 3H, *J*=6.0 Hz); 1.41-1.57 (m, 1H); 1.71-1.83 (m, 1H); 2.83 (s, 3H); 3.96 (dq, 1H, *J*=6.6, 8.4 Hz); 4.33 (dd, 1H, *J*=4.8, 8.4 Hz); 4.73 (dq, 1H, *J*=6.0, 5.7 Hz); 5.24 (d, 1H, *J*=8.4 Hz); 5.72 (d, 1H, *J*=5.7 Hz); 7.08-7-37 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 11.6, 14.7, 14.8, 20.5, 24.6, 27.9, 28.2, 38.6, 53.2, 54.0, 59.6, 72.2, 79.3, 79.8, 126.7,

127.0, , 128.3, 128.5, 136.2, 155.3, 168.6, 169.8, 170.0. $[\alpha]^{20}_{D}$ = -16.0° (*c* = 1.2, $CHCl_3$).

For the ^{1}H NMR spectra see Figure 2

Preparation of (4R,5S,2'S,3'R)-1,5-Dimethyl-3-(2'-amino-3'-BOCisoleucyloxy butanoyl)-4-phenylimidazolidin-2-one (5).

To a stirred solution of oxazoline **4** (0.8 mmol, 0.39 g) in THF (10 ml), 0.1M HCl (2 mL) was added at room temperature. The mixture was stirred for 2h and then the organic solvent was removed under reduced pressure. The aqueous residue was diluted with water (5 mL) and extracted twice with CH_2Cl_2 (2×10 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Compound **5** was isolated after flash chromatography on silica gel (ethyl acetate) in 90% yield (0.36 g).

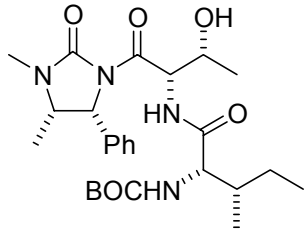


5

5: ^{1}H NMR ($CDCl_3$) δ 0.74 (d, 3H, *J*=6.9 Hz); 0.79 (d, 3H, *J*=6.6 Hz); 0.80 (d, 3H, *J*=7.2 Hz); 0.97-1.34 (m, 2H); 1.31 (d, 3H, *J*=6.0 Hz); 1.45 (s, 9H); 1.62-1-88 (m, 3H); 2.83 (s, 3H); 3.88-3.96 (m, 2H); 4.84 (d, 1H, *J*=3.3 Hz); 5.05 (d, 1H, *J*=8.4 Hz); 5.31 (d, 1H, *J*=9.0 Hz); 5.38 (dq, 1H, *J*=3.3, 6.0 Hz); 7.07-7.32 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 11.5, 14.2, 14.9, 15.1, 25.1, 26.9, 28.4, 37.9, 54.2, 57.8, 59.2, 60.4, 79.4, 127.0, 128.3, 128.5, 135.9, 155.2, 155.3, 170.9, 171.1. $[\alpha]^{20}_{D}$ = -46.2° (*c* = 0.6, $CHCl_3$).

Preparation of (4R,5S,2'S,3'R)-1,5-Dimethyl-3-(2'-BOCisoleucylamino-3'-hydroxybutanoyl)-4-phenylimidazolidin-2-one (6).

A solution of **5** (0.71 mmol, 0.36 g) in toluene (5 mL) was refluxed for 2h. After cooling to r.t., the mixture was concentrated under reduced pressure and compound **6** was obtained in 95% yield (0.34 g) from purification by flash chromatography (ethyl acetate as eluant).

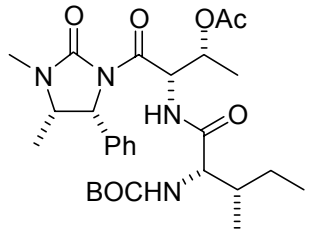


6

6: ^{1}H NMR ($CDCl_3$) δ 0.80 (d, 3H, *J*=6.6 Hz); 0.88 (t, 3H, *J*=7.5 Hz); 0.89 (d, 3H, *J*=7.5 Hz); 1.03-1.31 (m, 2H); 1.19 (d, 3H, *J*=6.3 Hz); 1.41 (s, 9H); 1.75-1.93 (m, 1H); 2.83 (s, 3H); 3.91-3.98 (m, 1H); 3.98 (dq, 1H, *J*=6.6, 9.3 Hz); 4.33 (dq, 1H, *J*=2.1, 6.3 Hz); 5.05 (d, 1H, *J*= 8.1 Hz); 5.34 (d, 1H, *J*= 9.3 Hz); 5.95 (dd, 1H, *J*=2.1, 8.7 Hz); 6.67 (d, 1H, *J*=8.7 Hz); 7.13-7.37 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 11.4, 15.1, 15.5, 19.5, 24.8, 28.2, 28.3, 37.3, 54.2, 55.7, 59.2, 59.4, 68.5, 79.8, 126.8, 128.3, 128.7, 136.1, 155.2, 169.9, 171.5. $[\alpha]^{20}_{D}$ = -45.0° (*c* = 1, $CHCl_3$).

Preparation of (4R,5S,2'S,3'R)-1,5-Dimethyl-3-(3'-acetyloxy-2'-BOCisoleucylamino butanoyl)-4-phenylimidazolidin-2-one (7).

To a solution of **6** (0.6 mmol, 0.3 g) in CH_2Cl_2, acetic anhydride (0.66 mmol, 0.06 mL), pyridine (0.66 mmol, 0.04 mL) and a catalytic amount of dimethylaminopyridine were added at room temperature under stirring. After 1h, the mixture was washed with 0.5M HCl (10 mL) and the organic layer was dried over Na_2SO_4 and concentrated. Compound **7** was isolated through flash chromatography on silica gel (cyclohexane/ethyl acetate 3:7) in 95% yield (0.31 g).



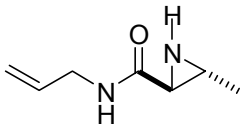
7

7: ^{1}H NMR ($CDCl_3$) δ 0.80 (d, 3H, *J*=6.6 Hz); 0.89 (t, 3H, *J*=7.5 Hz); 0.90 (d, 3H, *J*=6.6 Hz); 1.03-1.25 (m, 2H); 1.29 (d, 3H, *J*= 6.3 Hz); 1.41 (s, 9H); 1.78-1.83 (m, 1H); 2.08 (s, 3H); 2.83 (s, 3H); 3.91-4.01 (m, 2H); 5.14 (d, 1H, *J*=8.7 Hz; 5.30 (d, 1H, *J*= 9.0 Hz); 5.56 (dq, 1H, *J*=2.2, 6.3 Hz); 5.98 (dd, 1H, *J*= 2.2, 9.6 Hz); 6.53 (d, 1H, *J*= 9.6 Hz); 7.01-7.30 (m, 5H). $[\alpha]^{20}_{D}$ = -32.0° (*c* = 1, $CHCl_3$).

For the ^{1}H NMR spectra see Figure 3

Preparation of (2S,3R)- 3-methylaziridine-2-allylamide (8).

A solution of aziridine **2** (1 mmol, 0.27 g) in allylamine (5 mL) was stirred at room temperature for 12h. After removing the excess of allylamine under reduced pressure, the residue was purified through flash chromatography on silica gel (ethyl acetate as eluant). Compound **8** was isolated in 95% yield.



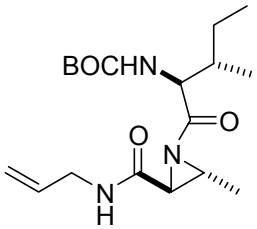
8

8: ^{1}H NMR ($CDCl_3$) δ 1.26 (d, 3H, *J*= 7.2 Hz); 2.08-2.30 (m, 2H); 3.88 (m, 2H); 5.16 (m, 2H); 5.82 (m, 1H); 6.34 (bs, 1H). ^{13}C NMR ($CDCl_3$) δ 18.5, 37.9, 41.8, 116.3, 128.5, 133.7, 170.4. $[\alpha]^{20}_{D}$ = +15.7 (*c* = 1.0 $CHCl_3$).

For the ^{1}H NMR spectra see Figure 4

Preparation of (2S,3R)-1-BOCisoleucyl-3-methylaziridine-2-allylamide (9).

To a stirred solution of *N*-BOC-isoleucine (1.5 mmol, 0.35 g) and dicyclohexylcarbodiimide (1.5 mmol, 0.31 g) in CH_2Cl_2 (10 mL) at room temperature, a solution of aziridine **8** (1 mmol, 0.14 g) in CH_2Cl_2 (10 mL) was added dropwise. The mixture was allowed to stir at room temperature for 12 h. After filtration of dicyclohexylurea, the solution was diluted with CH_2Cl_2 (20 mL) and washed twice with water (2 × 10 mL). The organic layer was then dried over Na_2SO_4 and solvent removed under reduced pressure. Compound **9** was obtained in 90% yield (0.47 g) after purification by flash chromatography on silica gel (cyclohexane/ethyl acetate 1:1).

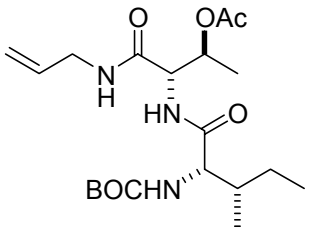


9

9: ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3H, *J*= 7.2 Hz); 0.95 (d, 3H, *J*=6.6 Hz); 1.07-1.25 (m, 1H); 1.41 (s, 9H); 1.42 (d, 3H, *J*=5.7 Hz); 1.43-1.57 (m, 1H); 1.80-2.00 (m, 1H); 2.83 (dq, 1H, *J*=2.7, 5.7 Hz); 2.92 (d, 1H, *J*=3.0 Hz); 3.87 (m, 2H); 4.11 (dd, 1H, *J*=6.0, 9.3 Hz); 5.08 (d, 1H, *J*=9.3 Hz); 5.11-5.20 (m, 2H); 5.74-5.87 (m, 1H); 6.60-6.70 (bs, 1H). ^{13}C NMR ($CDCl_3$) δ 11.6, 15.7, 16.0, 24.7, 28.2, 38.2, 41.7, 42.3, 60.2, 79.7, 99.9, 116.6, 133.5, 155.4, 166.7, 181.3. $[\alpha]^{20}_{D}$ = -30.1 (*c* = 2.9, $CHCl_3$).

Preparation of (2S,3R) N-allyl-3-acetyloxy-2-BOCisoleucylaminobutanamide (10).

A solution of aziridine **9** (1 mmol, 0.35 g) in acetic acid (5 mL) was stirred at 65°C for 2h. The mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 1:1 as eluant). Compound **10** was isolated in 95% yield (0.39 g).

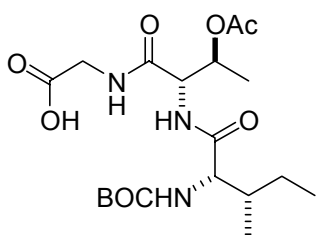


10

10: ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3H, *J*= 7.5 Hz); 0.94 (d, 3H, *J*= 6.9 Hz); 1.12-1.19 (m, 1H); 1.32 (d, 3H, *J*= 6.3 Hz); 1.44 (s, 9H); 1.46-1.53 (m, 1H); 1.82-1.98 (m, 1H); 2.02 (s, 3H); 3.87 (m, 2H); 3.95 (t, 1H, *J*= 5.5 Hz); 4.76 (dd, 1H, *J*= 3.5, 8.1 Hz); 4.9 bs, 1H); 5.06 (dd, 1H, *J*= 3.5, 6.3 Hz); 5.15 (m, 2H); 5.78 (m, 1H); 6.52 (bs, 1H); 7.21 (d, 1H, *J*= 8.1 Hz). ^{13}C NMR ($CDCl_3$) δ 11.5, 15.7, 22.4, 24.7, 28.3, 36.8, 41.9, 55.7, 59.8, 63.1, 71.1, 80.2, 116.4, 133.6, 156.0, 167.9, 170.8, 171.6. $[\alpha]^{20}_{D}$ = -14.7 (*c* = 0.8, $CHCl_3$)

Preparation of N-BOC-Ile-allo-Thr-Gly (11).

To a stirred solution of compound **10** (0.1 mmoli, 0.041 g) in water/acetone (7:1, 8 mL), acetic acid (0.87 mmol, 0.05 mL) and $KMnO_4$ (0.35 mmol) were added at 0°C. After stirring for 1.5h at room temperature, the mixture was cooled to 0°C and a solution of Na_2SO_3 (5 mL) was added. The solution was then acidified by adding 6M HCl was dropwise until pH=3 was reached. Acetone was removed under reduced pressure and the residue was diluted with ethyl acetate (15 mL), washed with water and then with a saturated solution of NaCl, dried over Na_2SO_4 and concentrated. Compound **11** was obtained in 95% yield (0.041 g).



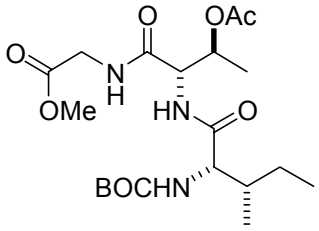
11

11: ^{1}H NMR ($CDCl_3$) δ 0.91 (m, 6H); 1.20-1.40 (m, 1H); 1.25 (m, 3H); 1.39 (s, 9H); 1.41-1.60 (m, 1H); 1.80-2.00 (m, 1H); 2.05 (s, 3H); 3.95-4.18 (m, 3H); 4.92-5.04 (m, 1H); 5.05-5.21 (m, 1H); 5.23-5.40 (m, 1H); 7.30-7.45 (m, 1H); 7.46-7.60 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 11.8, 14.8, 17.0, 20.5, 24.7, 28.3, 33.9, 39.2, 54.2, 59.7, 65.8, 79.0, 155.4, 163.7, 166.4, 181.5.

$[\alpha]^{20}_D$ = -22.0 (*c* = 1.0, $CHCl_3$).

Preparation of N-BOC-Ile-allo-Thr-Gly methyl ester (12).

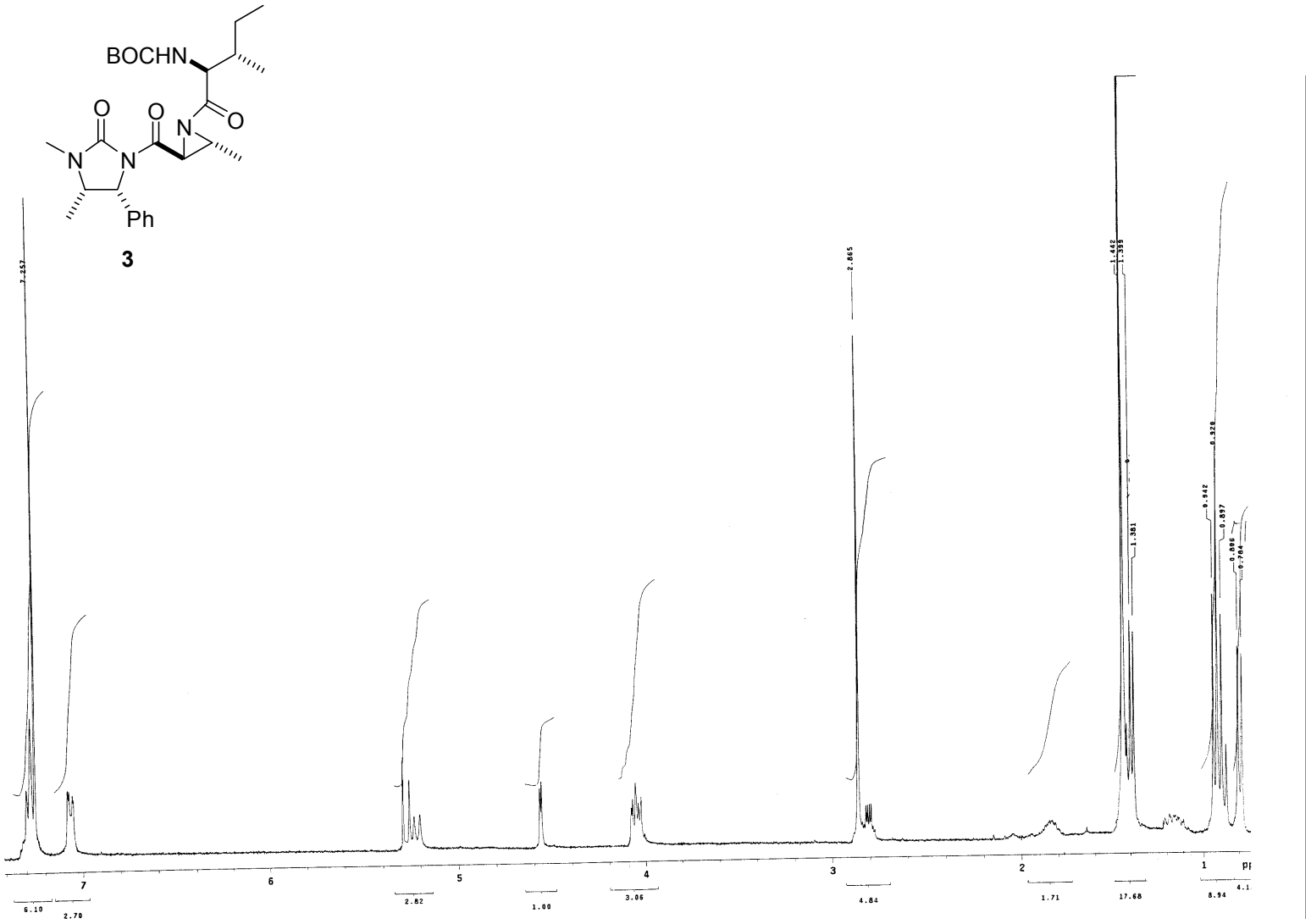
To a stirred solution of tripeptide derivative **11** in diethyl ether (5 mL), a solution of CH_2N_2 in diethyl ether was added dropwise until the mixture reached a yellow coloration. After stirring 30 minutes at room temperature, the solution was concentrated under reduced pressure and methyl ester **12** was obtained in 95% yield.



12

12: ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 3H, *J*= 7.5 Hz); 0.95 (d, 3H, *J*= 7.2 Hz); 1.05-1.25 (m, 1H); 1.33 (d, 3H, *J*= 6.6 Hz); 1.43 (s, 9H); 1.45-1.53 (m, 1H); 1.82-1.98 (m, 1H); 2.06 (s, 3H); 3.73 (s, 3H); 3.94 (m, 2H); 4.05 (m, 1H); 4.80 (dd, 1H, *J*= 3.9, 9 Hz); 4.97 (d, 1H, *J*= 6.6); 5.09 (dq, 1H, *J*= 3.9, 6.6 Hz); 7.03 (bs, 1H); 7.14 (d, 1H, *J*= 8.1 Hz). ^{13}C NMR ($CDCl_3$) δ 11.5, 15.7, 21.1, 24.8, 28.3, 29.7, 36.8, 41.1, 52.3, 55.6, 60.0, 70.9, 71.2, 80.5, 156.3, 168.7, 169.7, 171.3, 171.6. $[\alpha]^{20}_D$ = -16.0 (*c* = 1.2, $CHCl_3$).

For the ^{1}H NMR spectra see Figure 5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5
4
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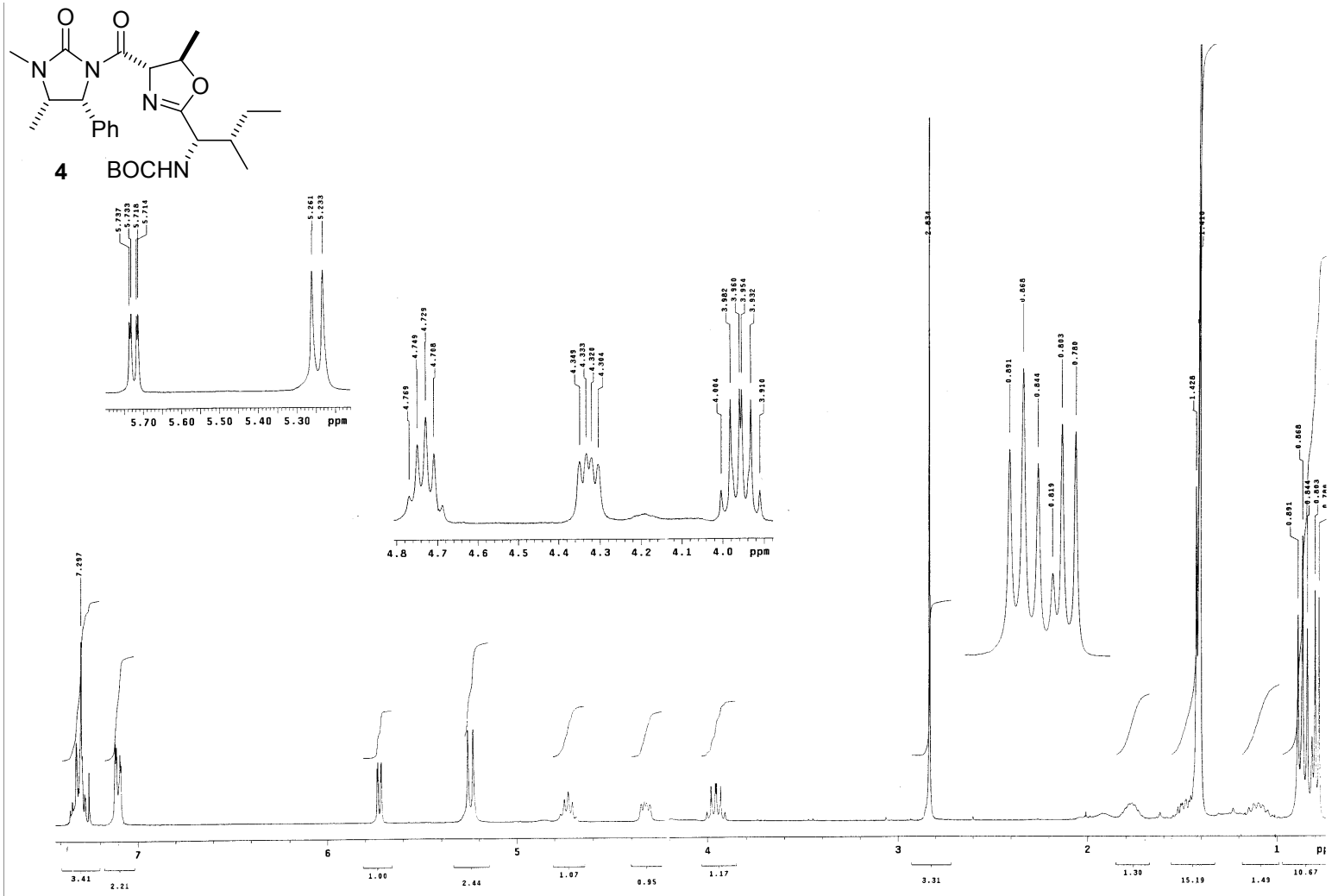
4.1

Figure 1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4.320
4.304
4.004
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3.954
3.932
3.910
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0.803
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7 6 5 4 3 2 1
3.41
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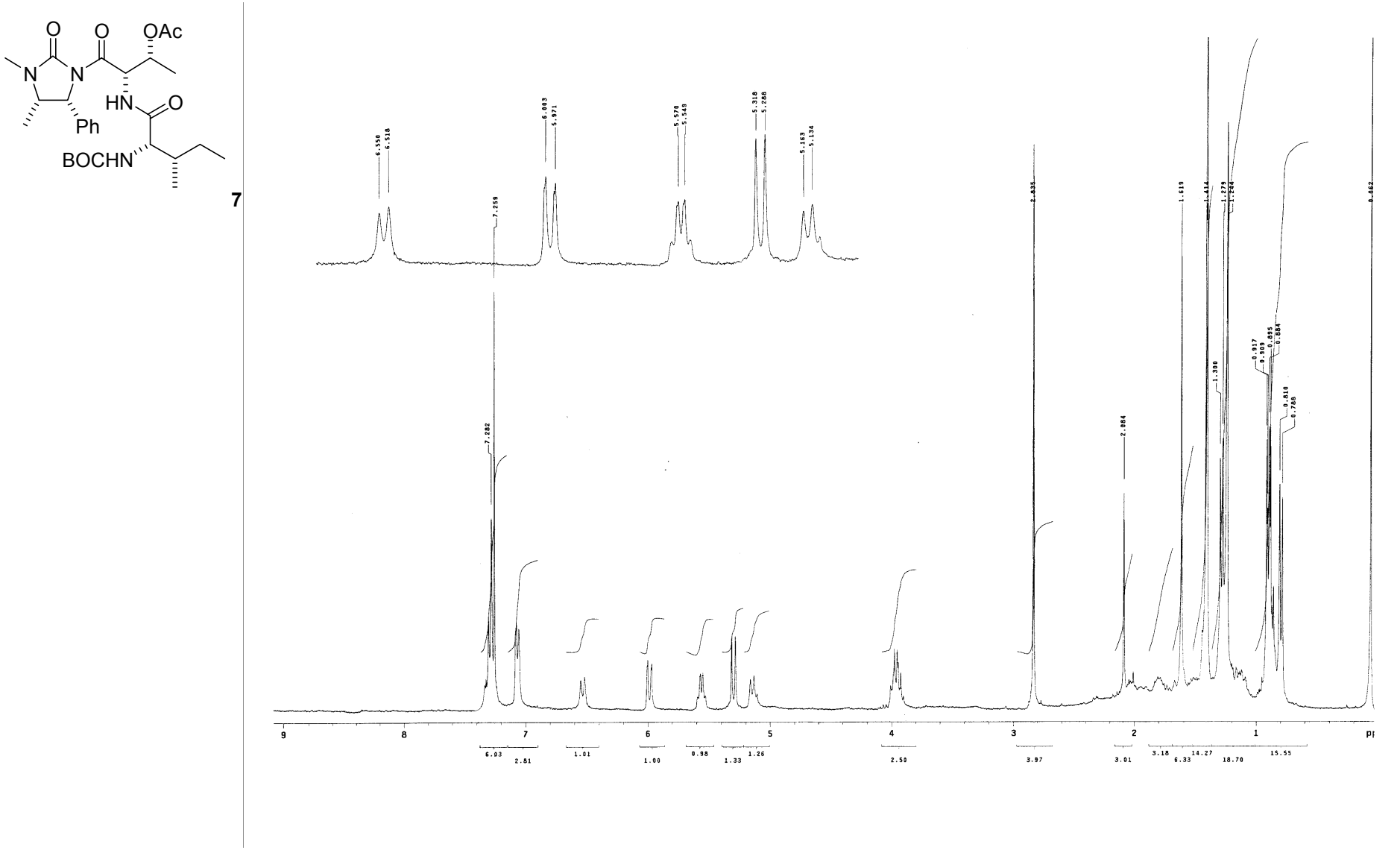
Figure 2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5.163
5.134
7.282
2.835
2.084
1.619
1.300
0.917
0.909
0.885
0.864
0.810
0.788
0.062
9
8
7
6
5
4
3
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1
ppm
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2.81
1.01
1.00
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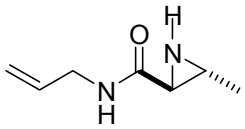
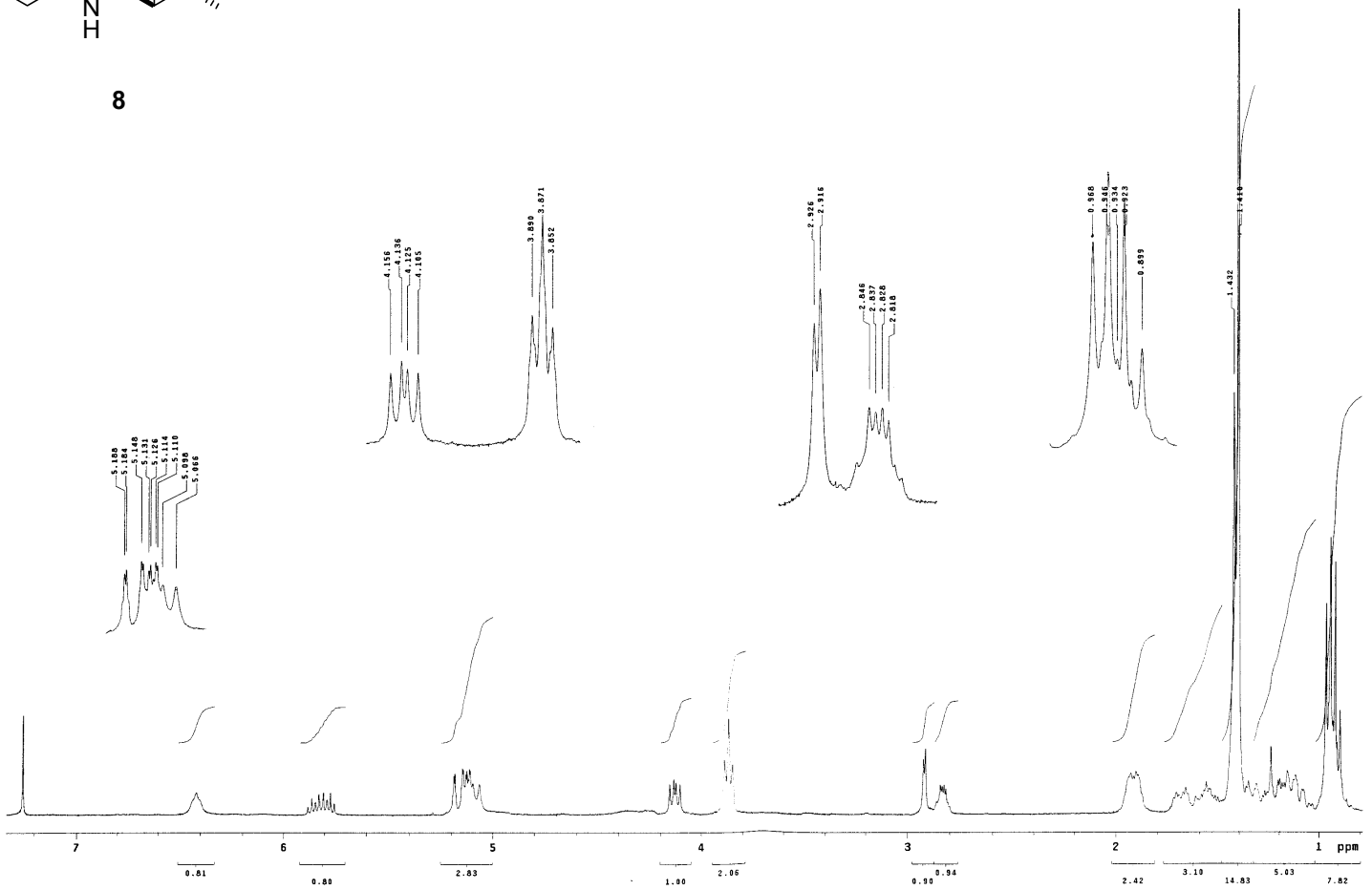
Figure 3


O
H
N
N
H

8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5.184
5.148
5.138
5.126
5.114
5.110
5.066
4.156
4.136
4.125
4.105
3.899
3.871
3.852
2.926
2.916
2.846
2.837
2.828
2.818
0.968
0.946
0.934
0.923
0.899
1.432
1.416
7
6
5
4
3
2
1 ppm
0.81
0.80
2.83
1.00
2.06
0.90
0.94
2.42
3.10
14.83
5.03
7.82

Figure 4

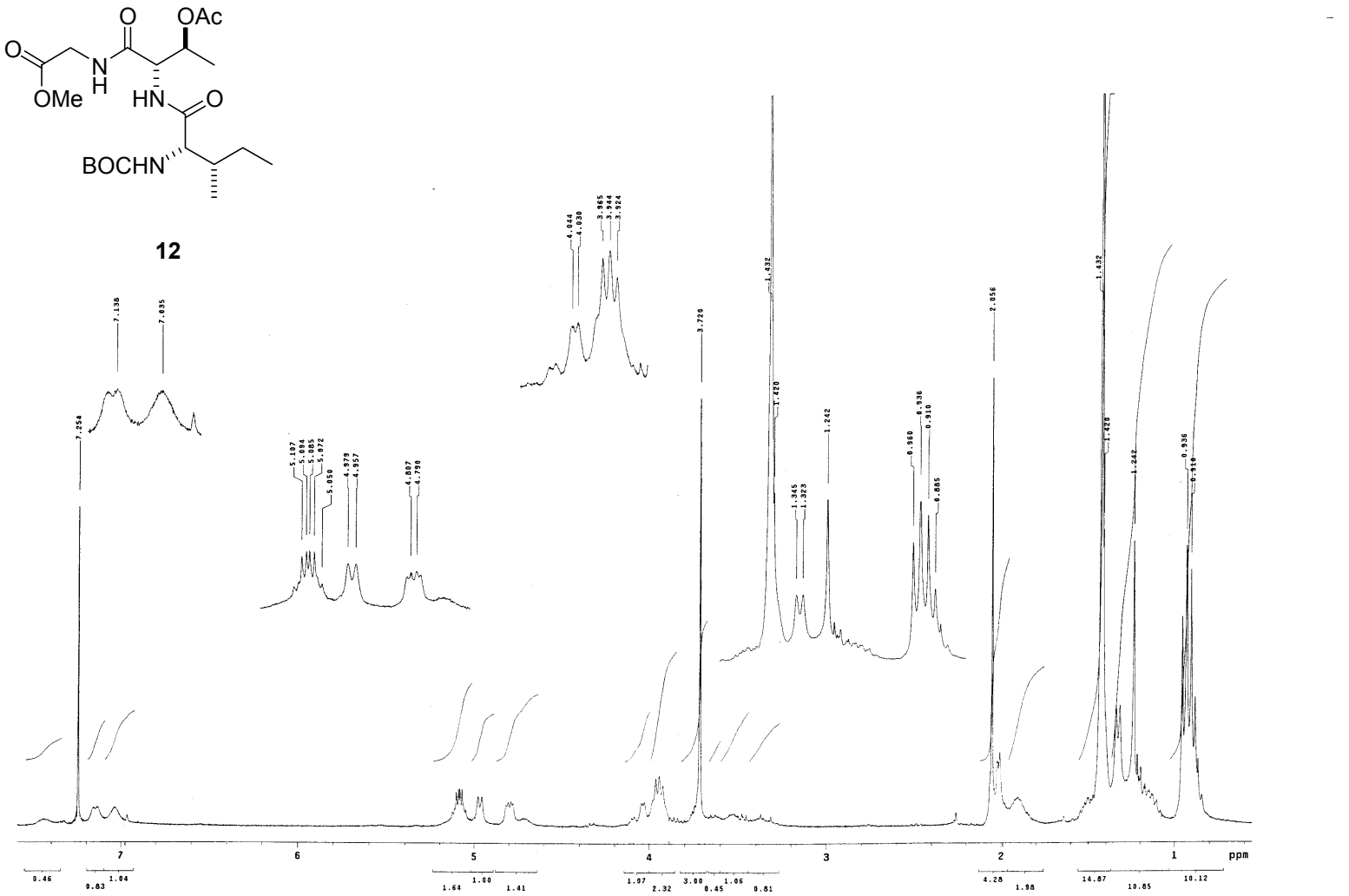
O
OAc
O
N
H
OMe
HN
O
BOCHN
12
7.138
7.035
7.254
5.187
5.084
5.065
5.072
5.050
4.979
4.957
4.807
4.790
4.044
4.030
3.965
3.944
3.924
3.726
1.432
1.420
1.345
1.323
1.242
0.960
0.936
0.910
0.885
2.056
ppm

Figure 5