# A one-pot selective homodimerisation/hydrogenation strategy for sequential dicarba bridge formation

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**Contents:**



## Reaction screening

### S1: Assessment of AM

The dimerisation of (*S*)-methyl 2-benzamidohex-4-ynoate (**12**) was assessed according to the two following procedures:

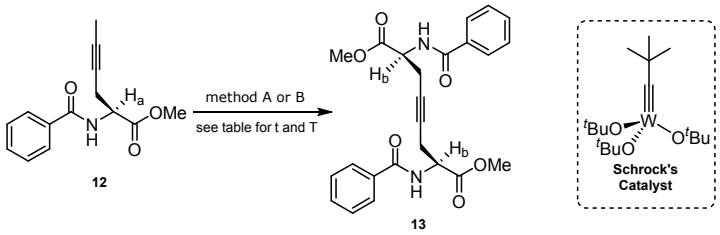
Method A: A solution of Schrock's catalyst (tri-*tert*-butoxy(2,2-dimethylpropylidyne)tungsten (100 mg/10 mL) was prepared, in dry, degassed toluene to give a clear pale yellow solution (0.02 M).

In a dry box the catalyst solution (1.00 mL, 0.02 mmol, 10 mol%) was added to (*S*)-methyl 2-benzamidohex-4-ynoate (**12**) (52.0 mg, 0.20 mmol) and optionally 5 Å sieves (100 mg) to give a red solution (0.20 M). The resulting mixtures were heated at the specified temperature and time. The solvent was evaporated *in vacuo* and the residue dissolved in $CDCl_3$, filtered through celite® then examined by $^1H$ NMR spectroscopy.

Method B: Anhydrous manganese dichloride (9.0 mg, 0.08 mmol) and Fürstner's catalyst (**7**) (103 mg, 0.08 mmol) in toluene (4 mL) were heated at 80 $^oC$ for 30 minutes to give a brown/green solution (0.02 M).

In a dry box the catalyst solution (1.00 mL, 0.02 mmol, 10 mol%) was added to (*S*)-methyl 2-benzamidohex-4-ynoate (**12**) (52 mg, 0.20 mmol) and 5 Å sieves to give a brown solution (0.20 M). The resulting mixtures were heated at the specified temperature and time. The solvent was evaporated *in vacuo* and the residue dissolved in $CDCl_3$, filtered through celite® then examined by $^1H$ NMR spectroscopy.

In each case the conversion was assessed by integration of $\delta H_a$ 4.87 (starting material (**12**)) to $\delta H_b$ 5.00 (dimer (**13**)).

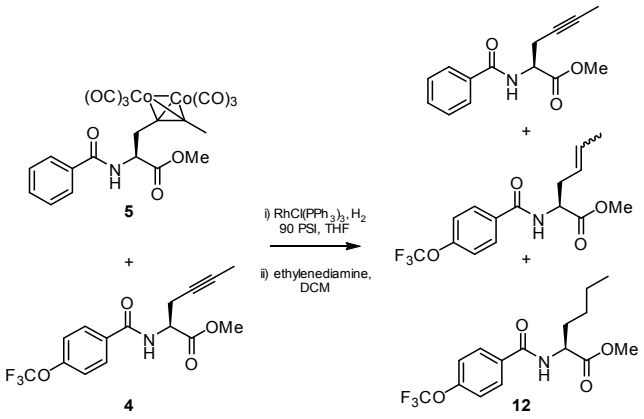


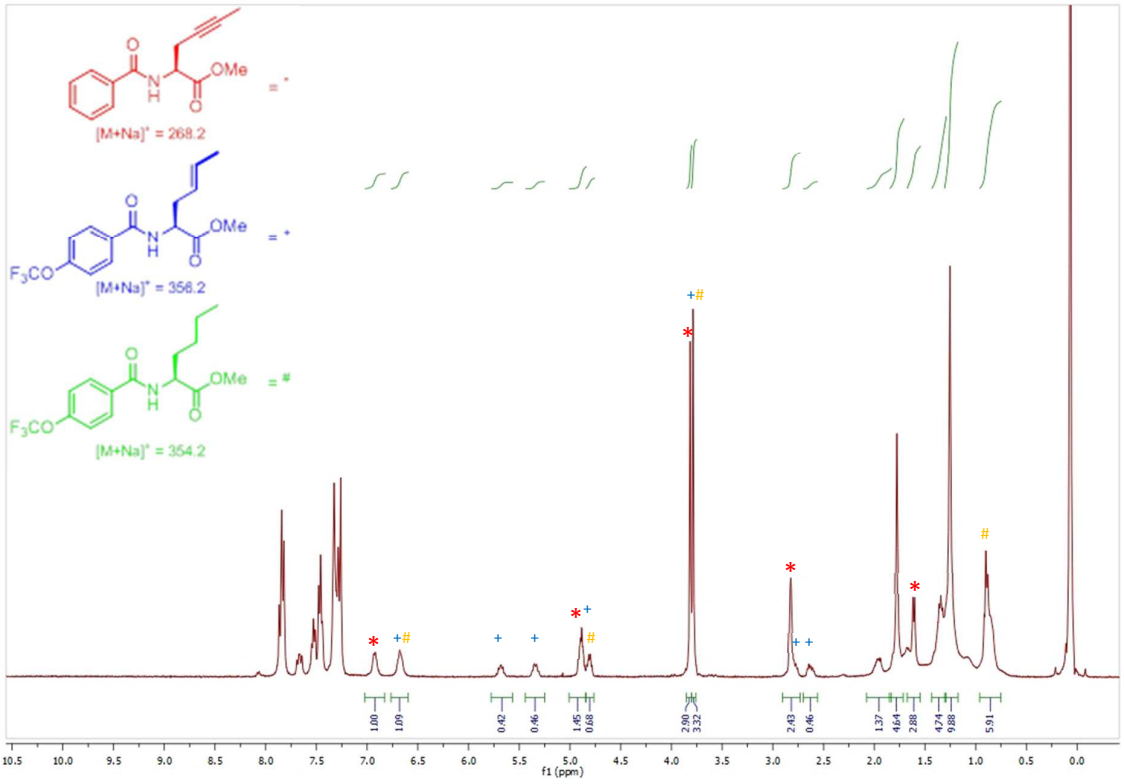

| Entry | Conversion/% | Method | T/ °C | t/ h | (100 mg) 5 Å sieves |
|---|---|---|---|---|---|
| 1 | 68[#] | A | 25 | 4 | No |
| 2 | 59[#] | A | 50 | 4 | No |
| 3 | 73[#] | A | 25 | 4 | Yes |
| 4 | 59[#] | A | 50 | 4 | Yes |
| 5 | 88 | A | 25 | 18 | Yes |
| 6 | 42 | B | 25 | 4 | Yes |
| 7 | 89 | B | 50 | 4 | Yes |
| ***8*** | ***95*** | ***B*** | ***25*** | ***18*** | ***Yes*** |

[#]Average of two runs.

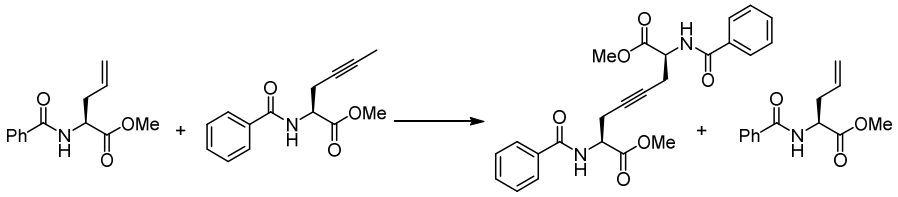
## S2: Reduction/deprotection

(*S*)-Methyl 2-(4-(trifluoromethoxy)benzamido)hex-4-ynoate (**4**) (50.0 mg, 0.16 mmol), cobalt carbonyl protected (*S*)-methyl 2-benzamidohex-4-ynoate (**5**) (52.0 mg, 0.16 mmol) and Wilkinson's catalyst (**8**) (15.0 mg, 0.16 µmol) were dissolved in THF (1.6 mL) and hydrogen was reintroduced *via* 3 purge refill cycles (-20 PSI to 90 PSI) and a final pressure of 90 PSI was attained for a further 2 h. The solvent was removed *in vacuo* and ethylenediamine:DCM (5 mL, 1:9) was added and the mixture stirred for 4 h. Water (10 mL) was then added to the mixture and the biphasic solution stirred for 1 h. The mixture was extracted with DCM (3 x 10 mL) and the combined organic extracts washed with brine (10 mL). The resulting organic solvent was dried with sodium sulphate, evaporated *in vacuo* and the residue dissolved in $CDCl_3$, filtered through celite® then examined by $^1$H NMR spectroscopy and low resolution mass spectrometry.


(OC)3Co—Co(CO)3
OMe
5
+
F3CO
4
i) RhCl(PPh3)3, H2
90 PSI, THF
ii) ethylenediamine,
DCM
OMe
+
F3CO
+
OMe
12


OMe
= *
[M+Na]+ = 268.2
F3CO
OMe
= +
[M+Na]+ = 358.2
F3CO
OMe
= #
[M+Na]+ = 354.2
f1 (ppm)

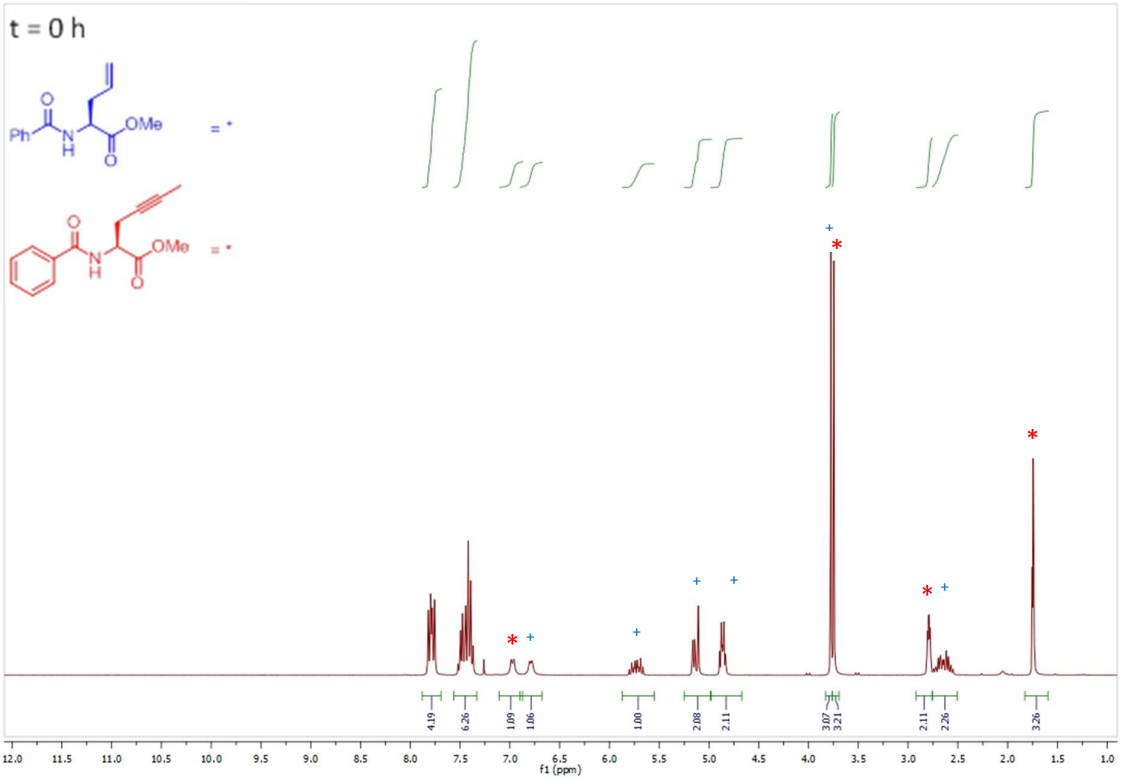
## S3: Alkene/alkyne selectivity

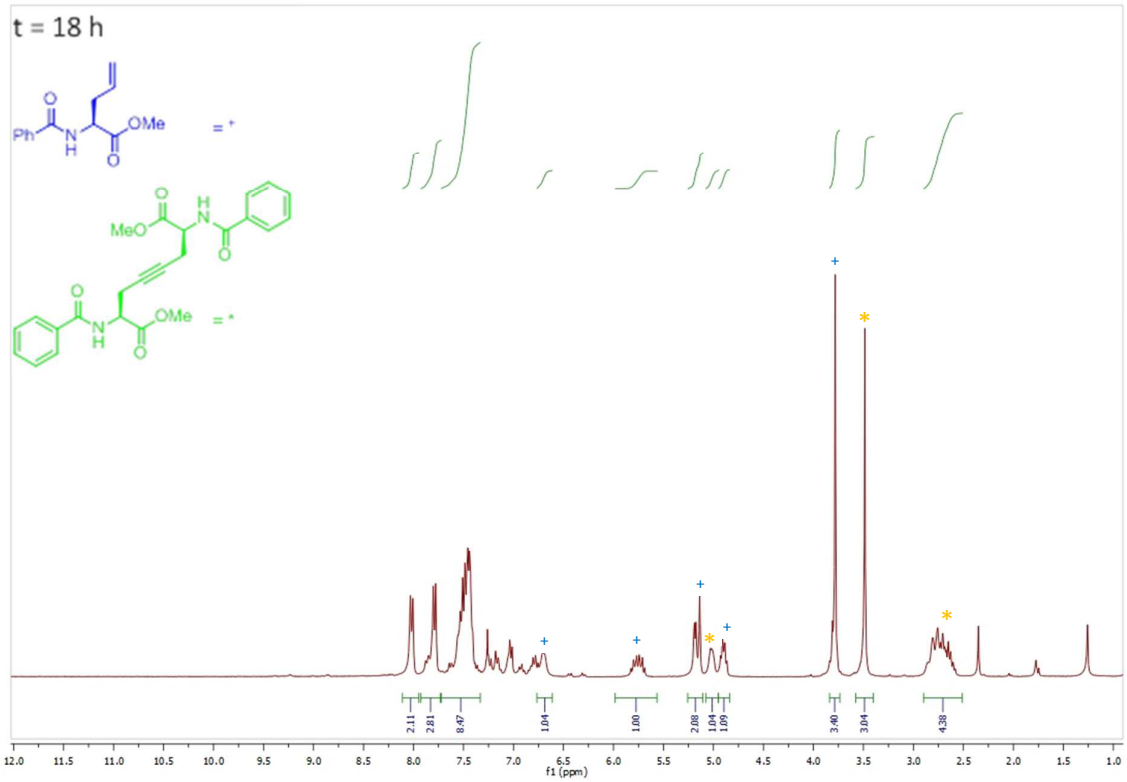


**12** **13**

Anhydrous manganese dichloride (9.0 mg, 0.08 mmol) and Fürstner's catalyst (**7**) (103 mg, 0.08 mmol) in toluene (4 mL) were heated at 80 $^{o}$C for 30 minutes to give a brown/green solution (0.02 M).

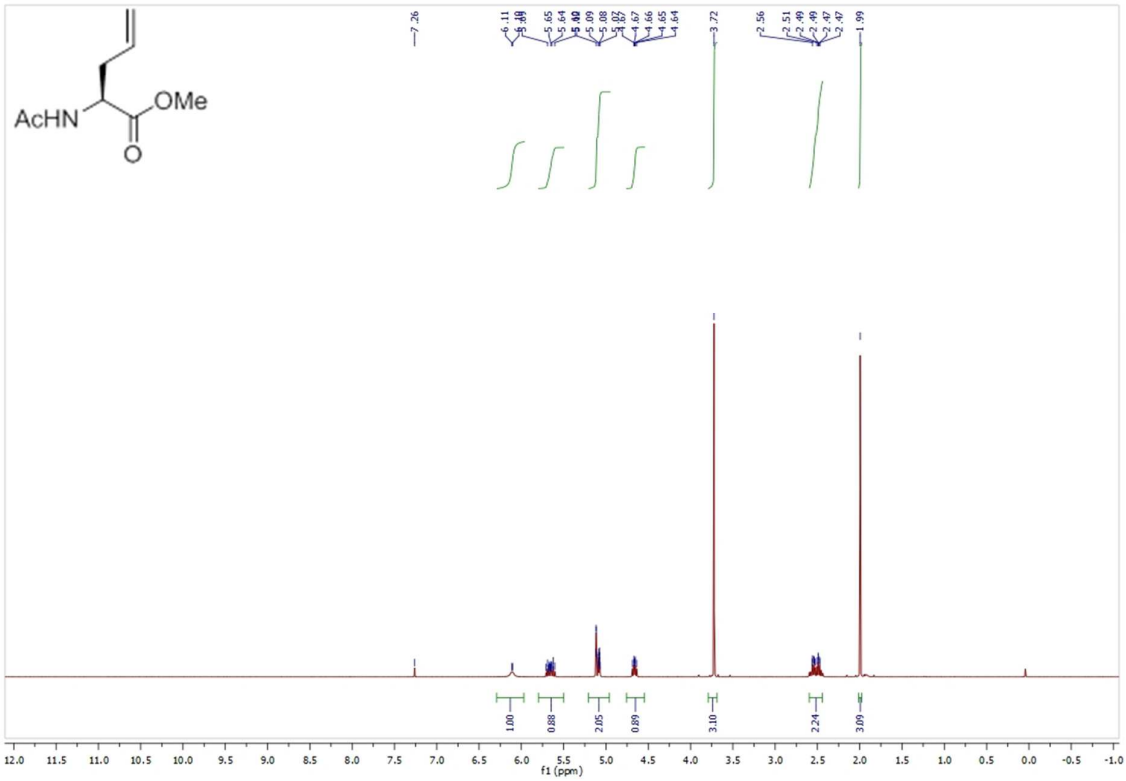
In a dry box, the above catalyst solution (1.0 mL, 0.02 mmol, 10 mol%) was added to (*S*)-methyl 2-benzamidohex-4-ynoate (**12**) (52.0 mg, 0.20 mmol), (S)-methyl 2-benzamidopent-4-enoate (46.7 mg, 0.20 mmol) and 5 Å sieves to give a brown solution (0.20 M). The resulting mixture was stirred at room temperature for 18 h. The solvent was evaporated *in vacuo* and the residue dissolved in $CDCl_3$, filtered through celite® then examined by $^{1}$H NMR spectrocopy and low resolution mass spectrometry.

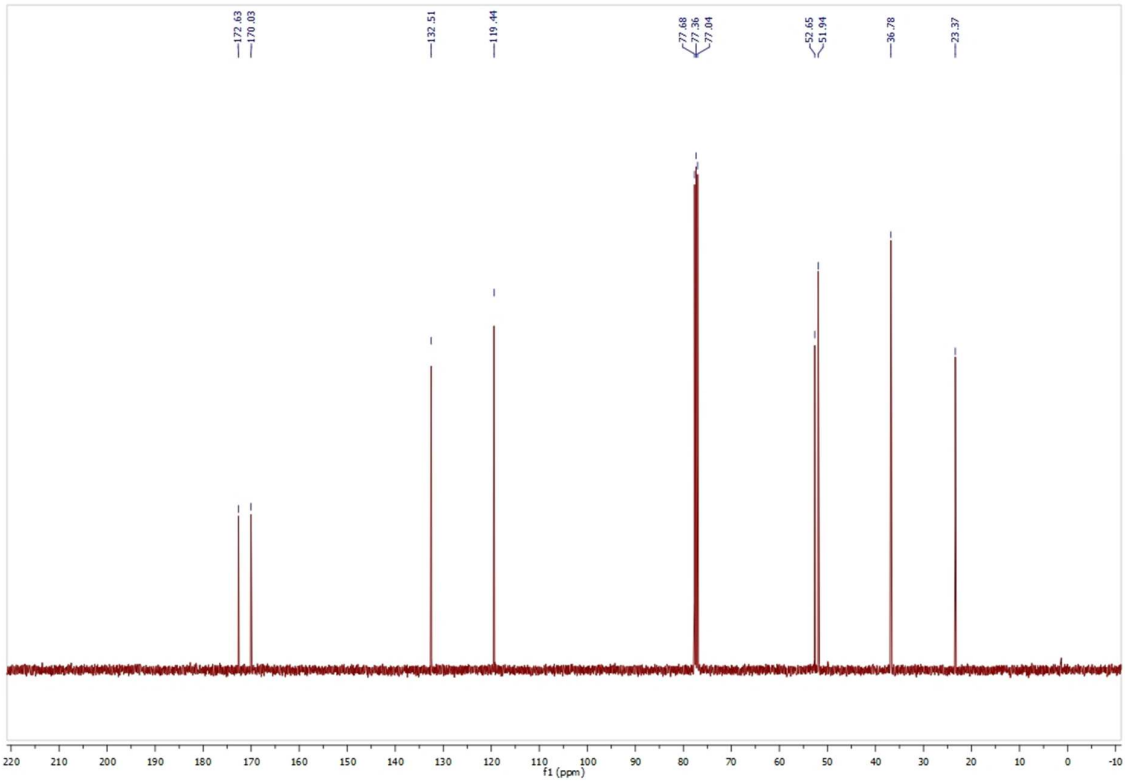


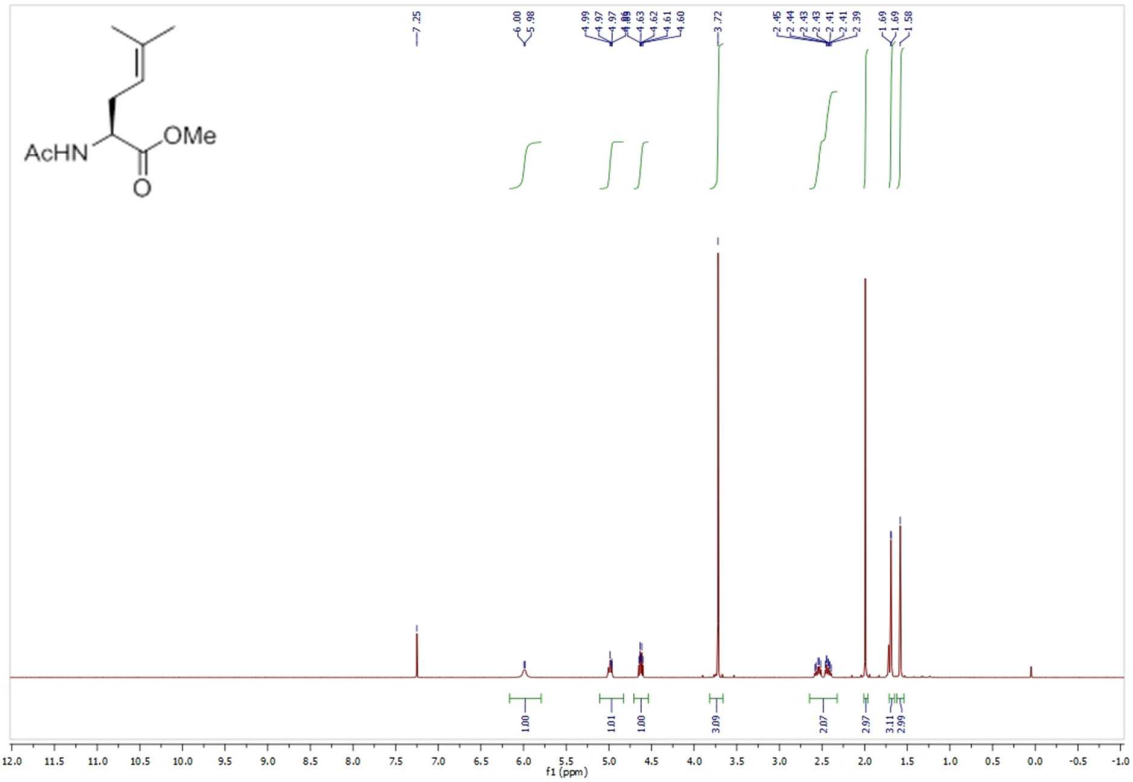

**Copies of proton and carbon NMR spectra for compounds**

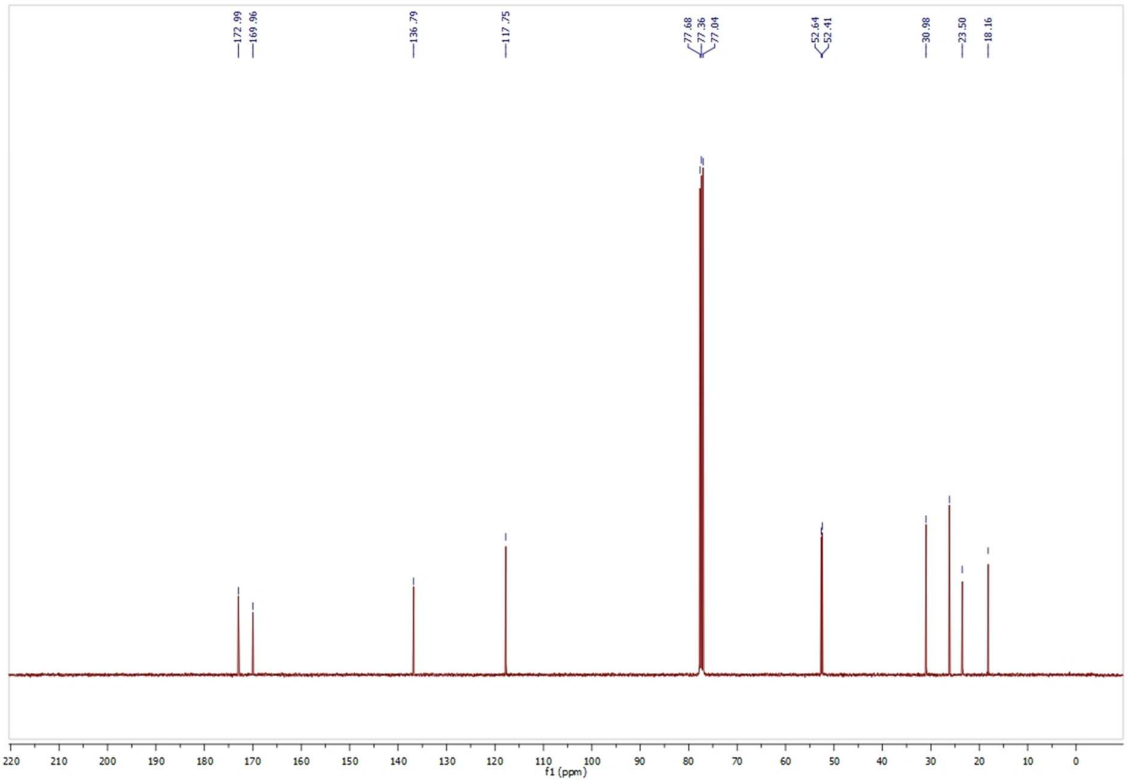
(*S*)-Methyl 2-acetamidopent-4-enoate



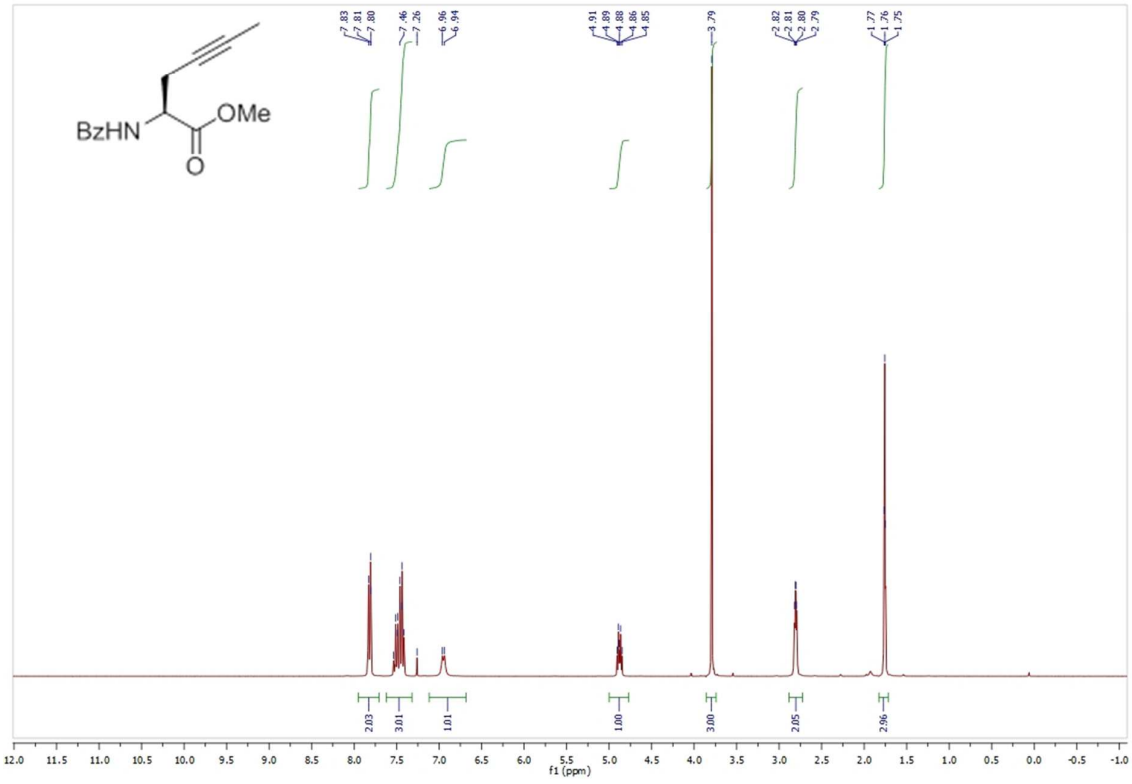



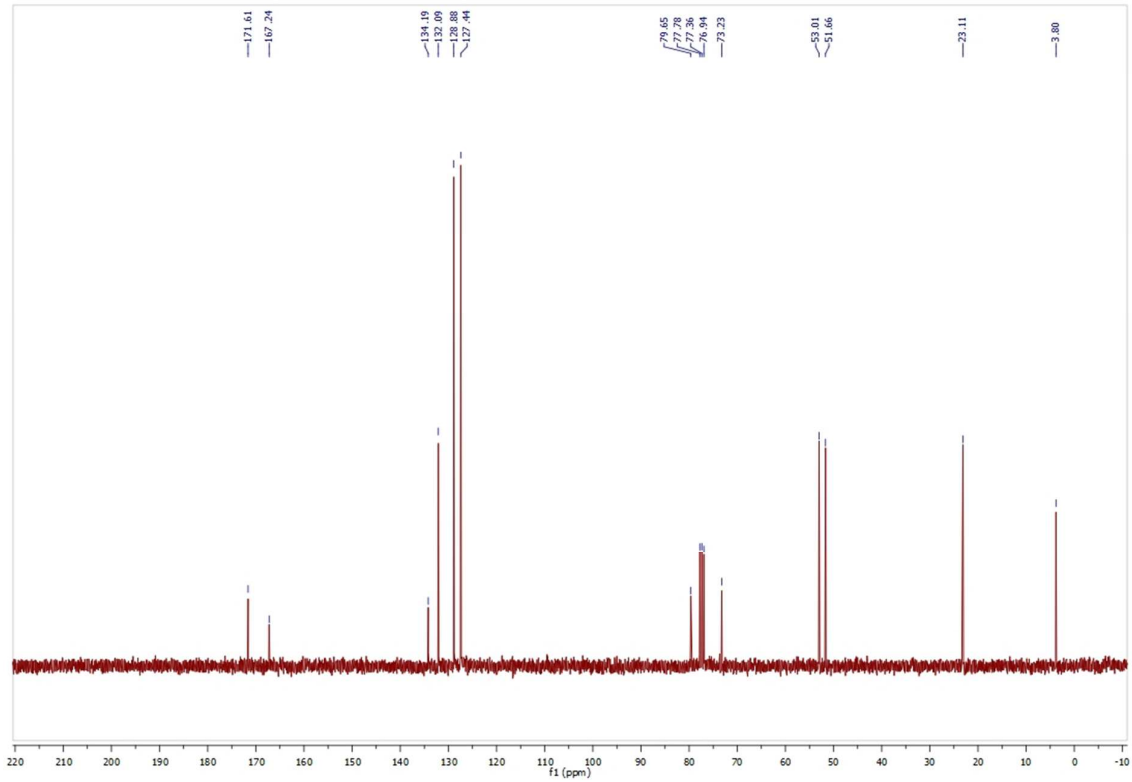

(*S*)-Methyl 2-acetamido-5-methylhex-4-enoate (**6**)


AcHN
OMe
O
7.25
6.00
5.98
4.99
4.97
4.97
4.63
4.62
4.61
4.60
3.72
2.45
2.44
2.43
2.43
2.41
2.41
2.39
1.69
1.69
1.58
1.00
1.01
1.00
3.09
2.07
2.97
3.11
2.99
f1 (ppm)

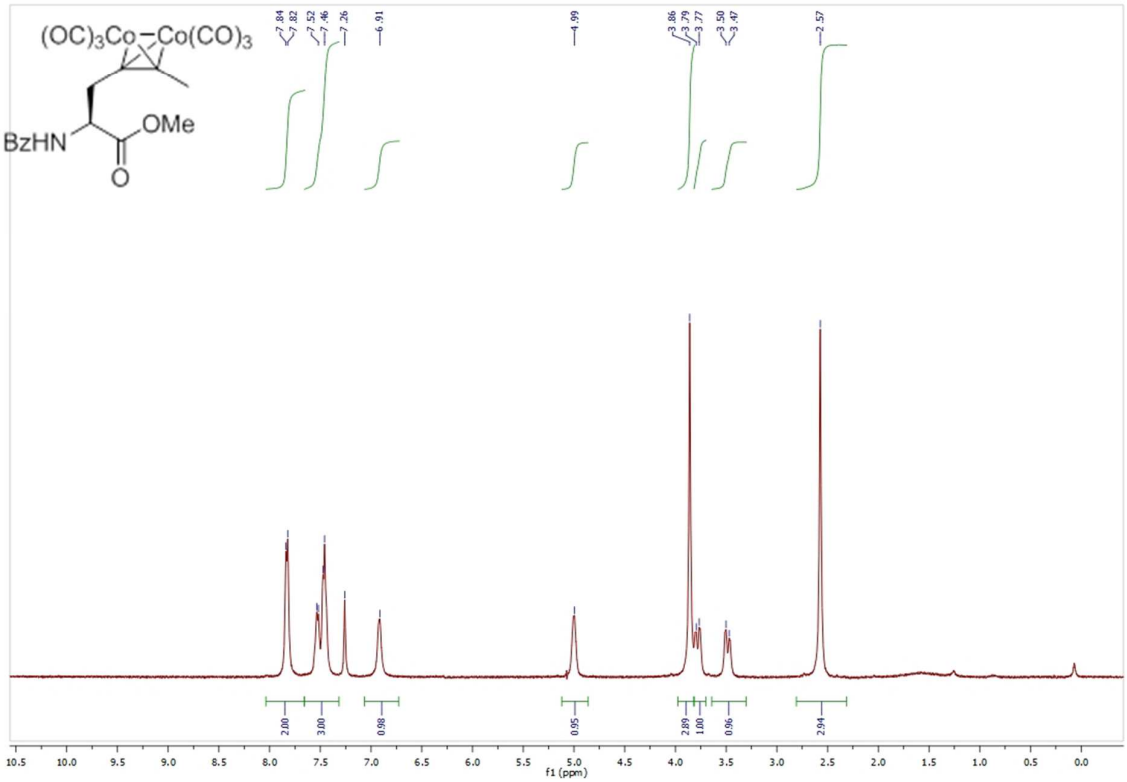

172.99
169.96
136.79
117.75
77.68
77.36
77.04
52.64
52.41
30.98
23.50
18.16
f1 (ppm)

(*S*)-Methyl 2-benzamidohex-4-ynoate (**12**)



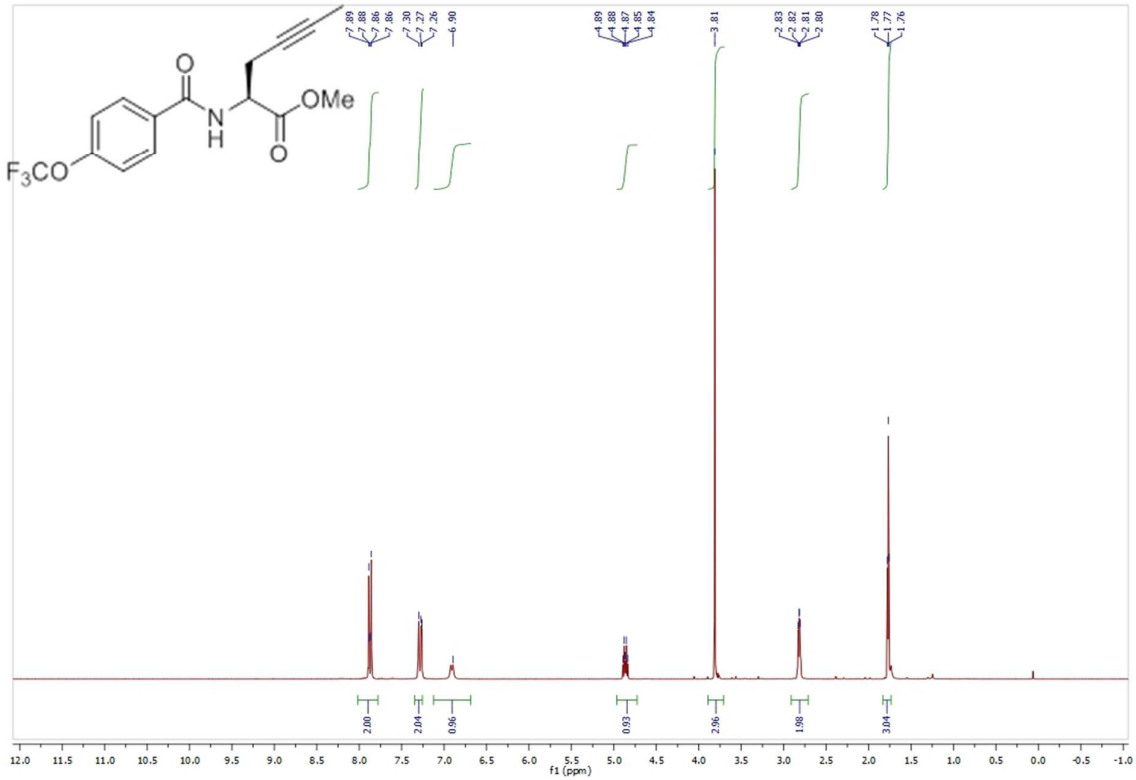



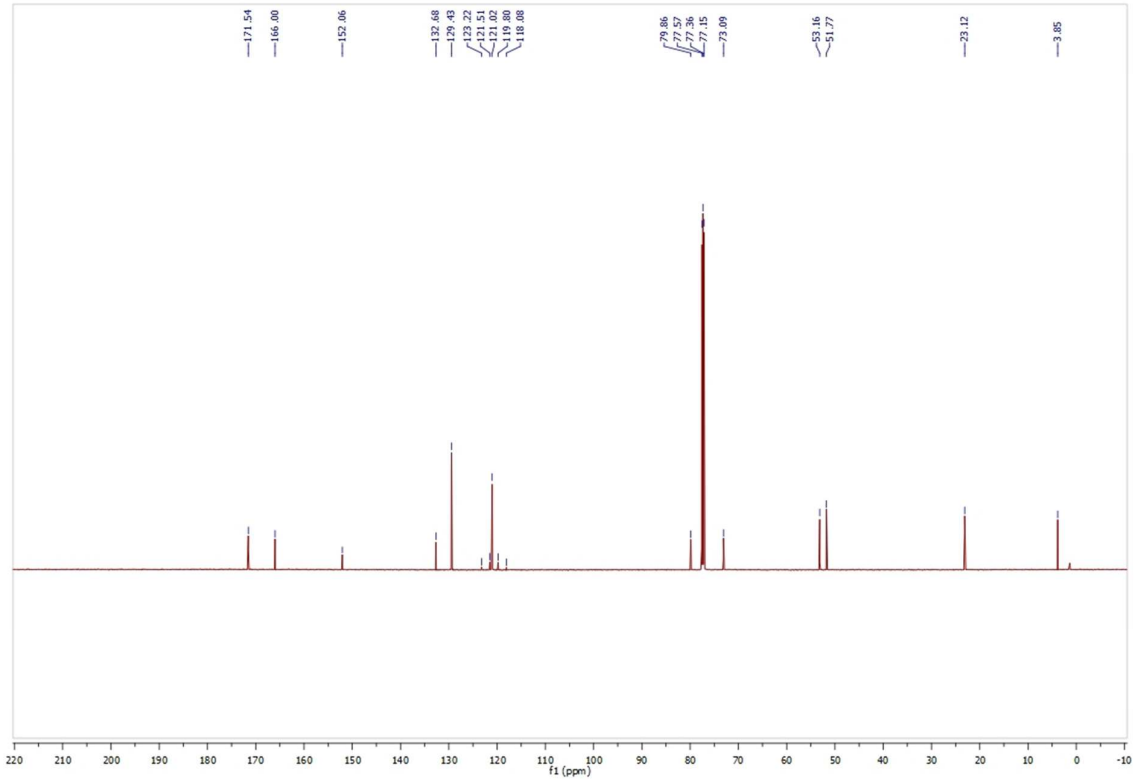
Cobalt-carbonyl protected (*S*)-methyl 2-benzamidohex-4-ynoate (**5**)



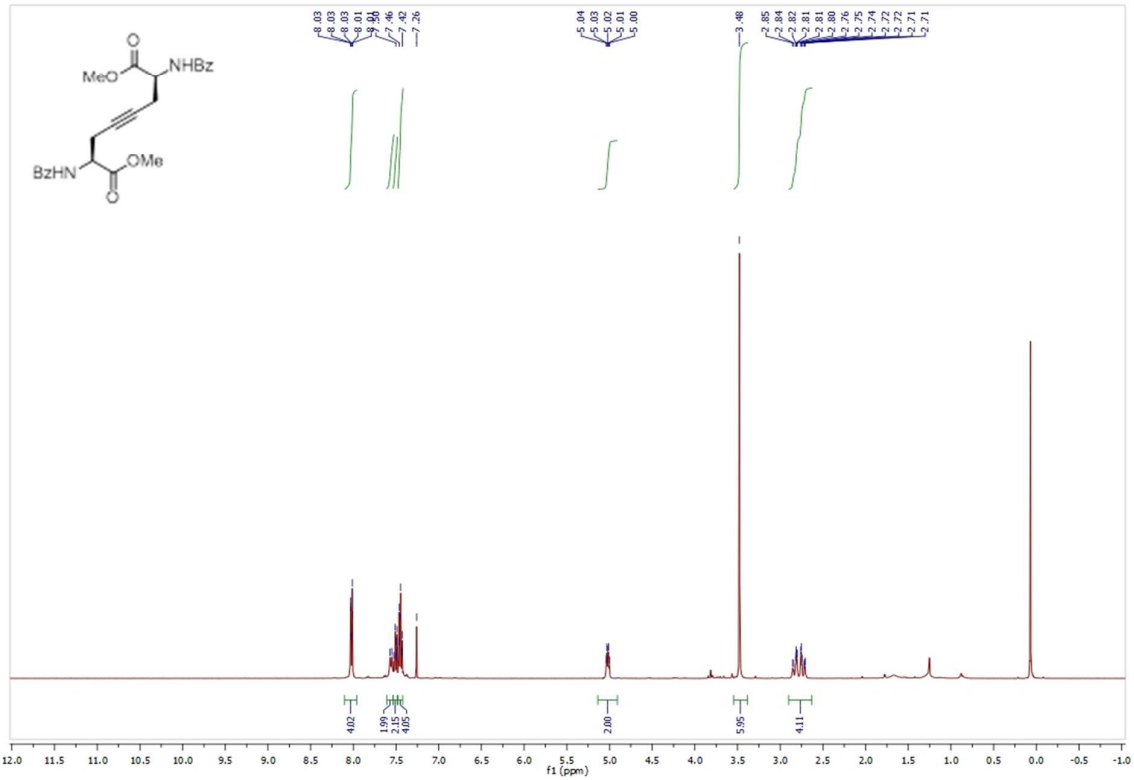

Carbon not obtainable due to peak broadening **5**.

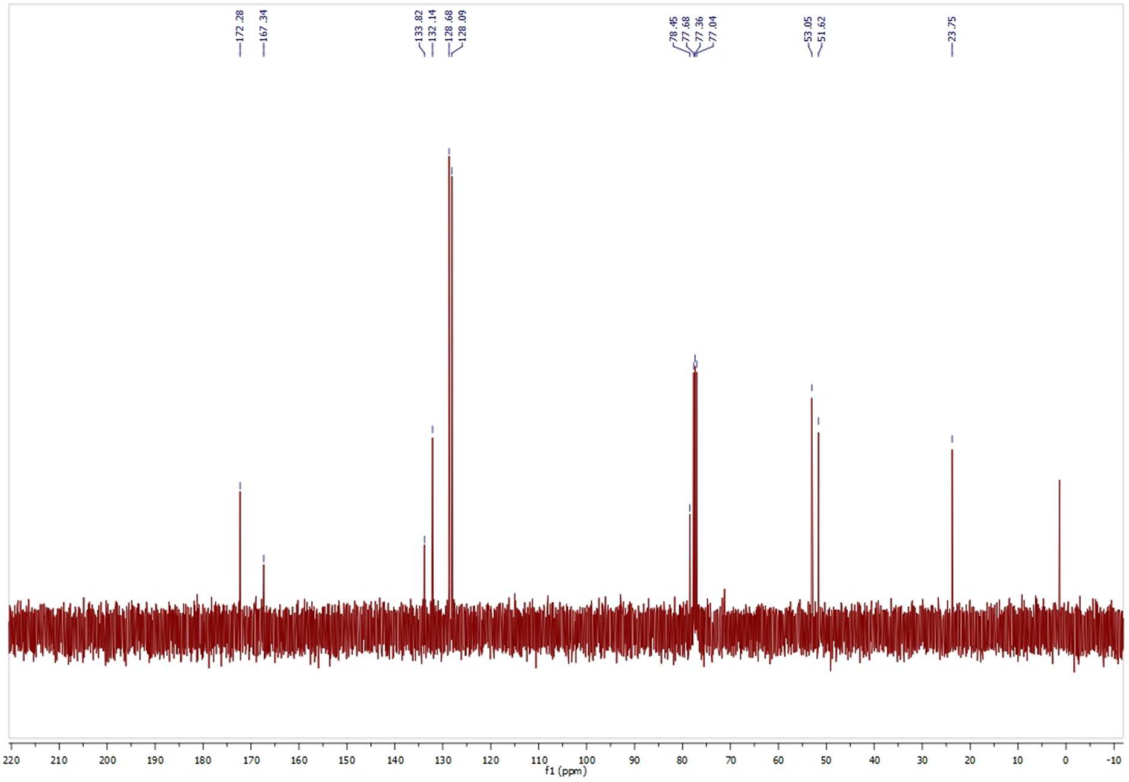
(*S*)-Methyl 2-(4-(trifluoromethoxy)benzamido)hex-4-ynoate (**4**)



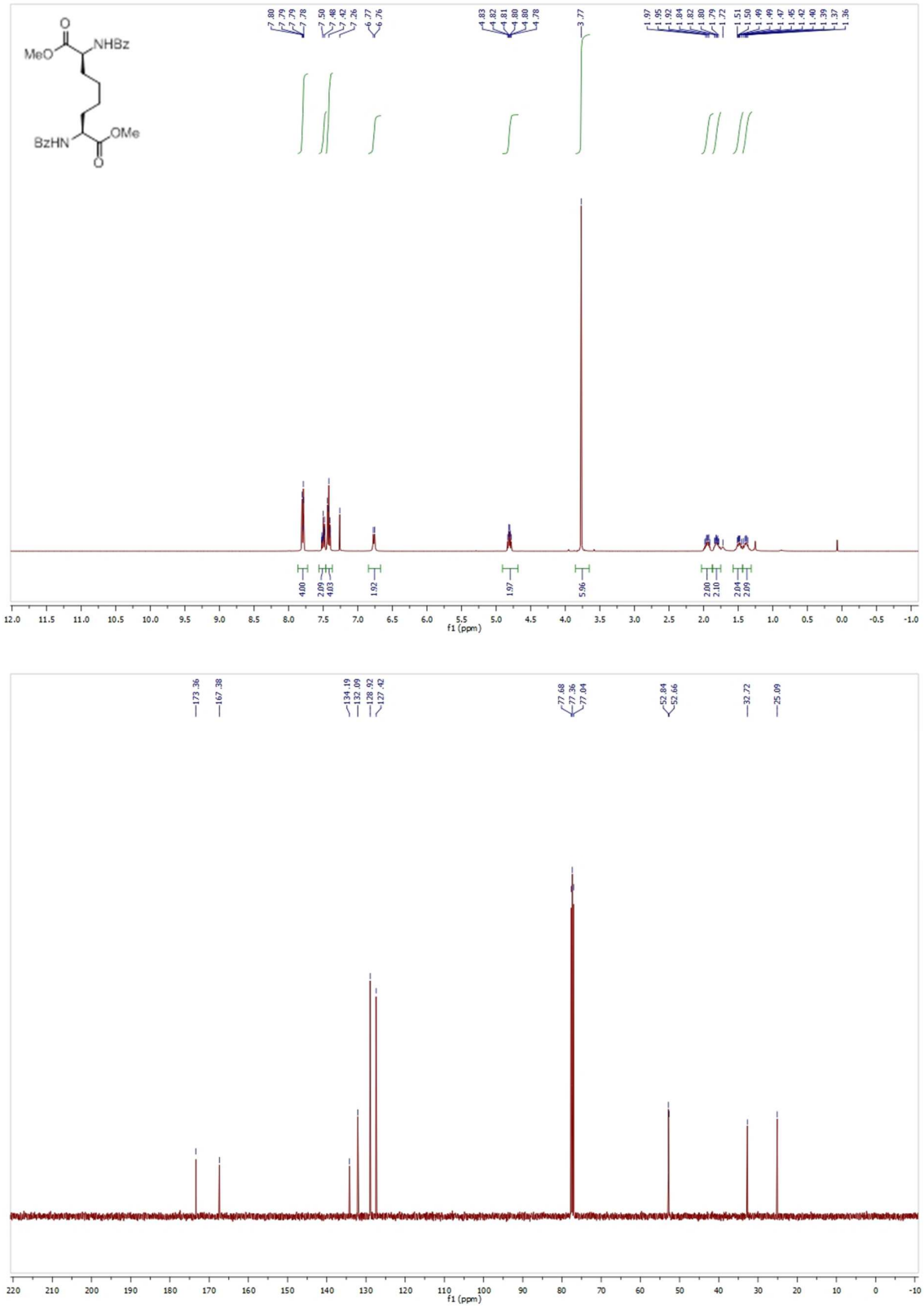




(2*S*,7*S*)-Dimethyl 2,7-bis(benzamido)oct-4-ynedioate (**13**)

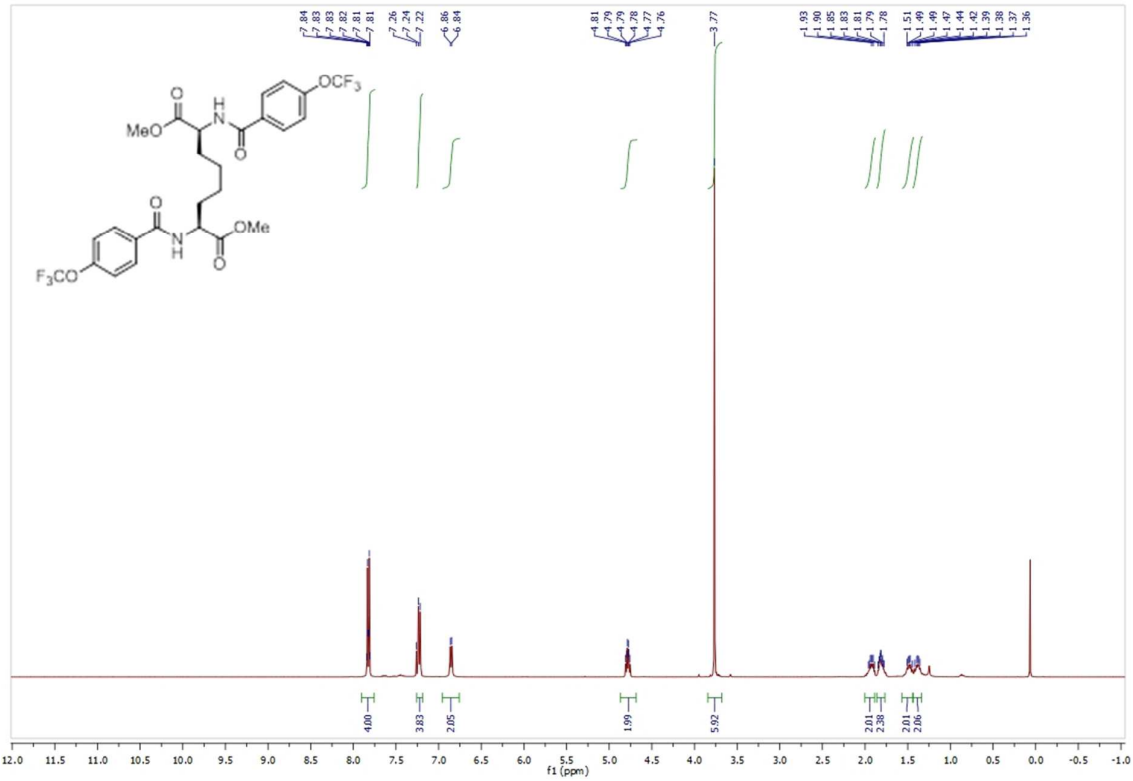


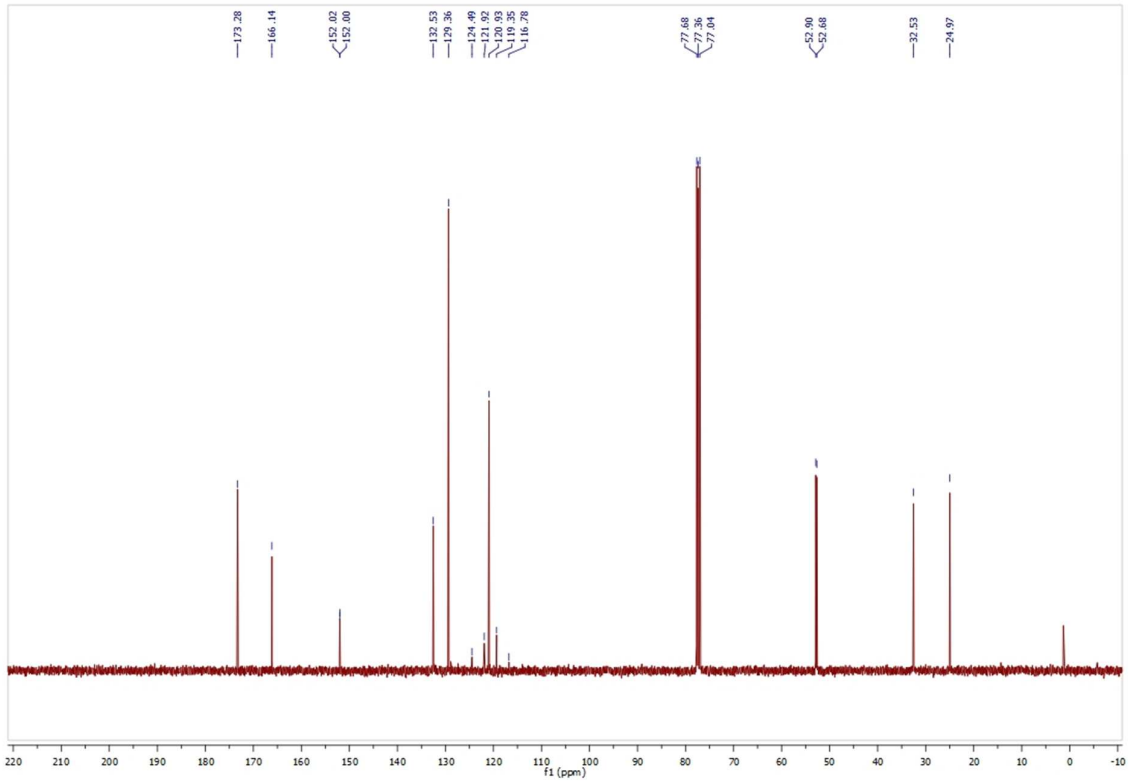




(2*S*,7*S*)-Dimethyl 2,7-bis(benzamido)octanedioate (**2**)

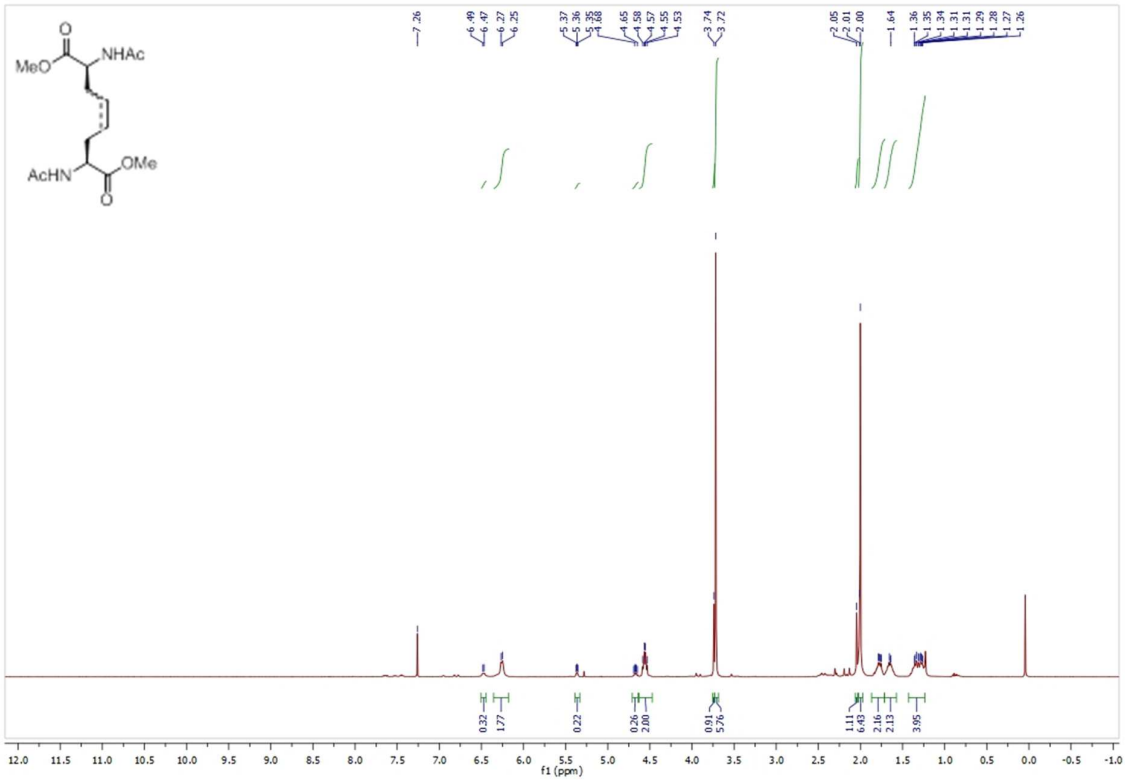


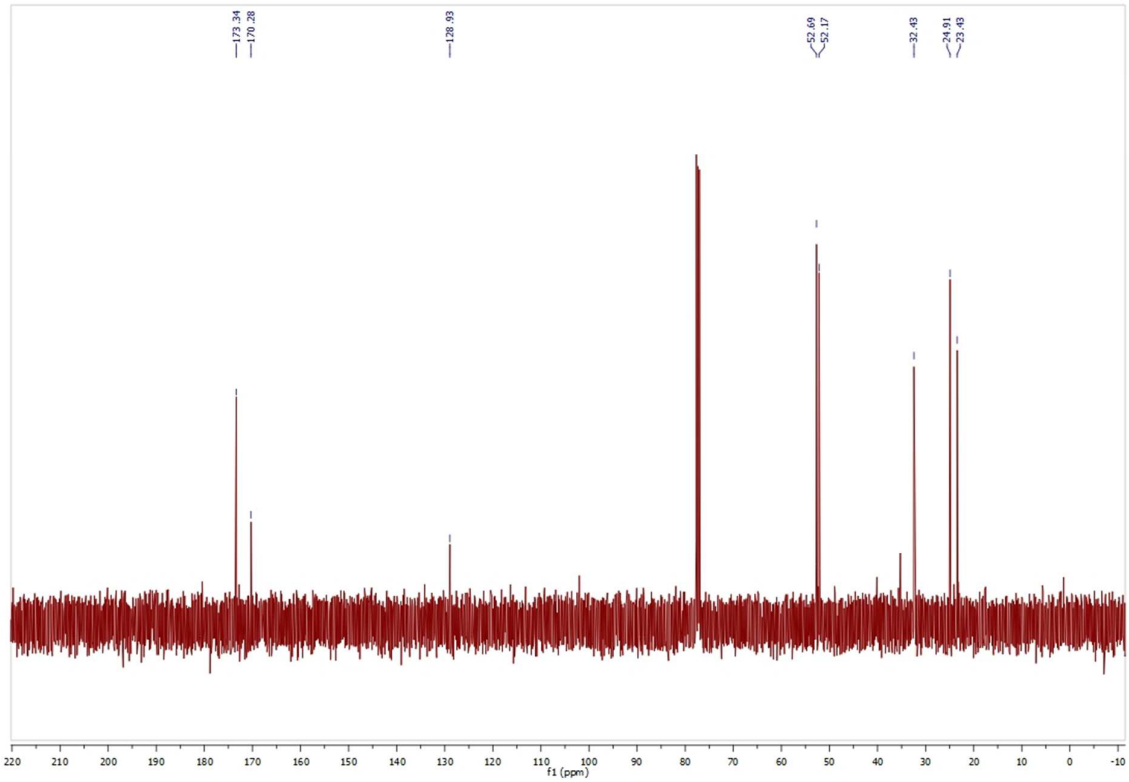

(2*S*,7*S*)-Dimethyl 2,7-bis(4-(trifluoromethoxy)benzamido)octanedioate (**1**)



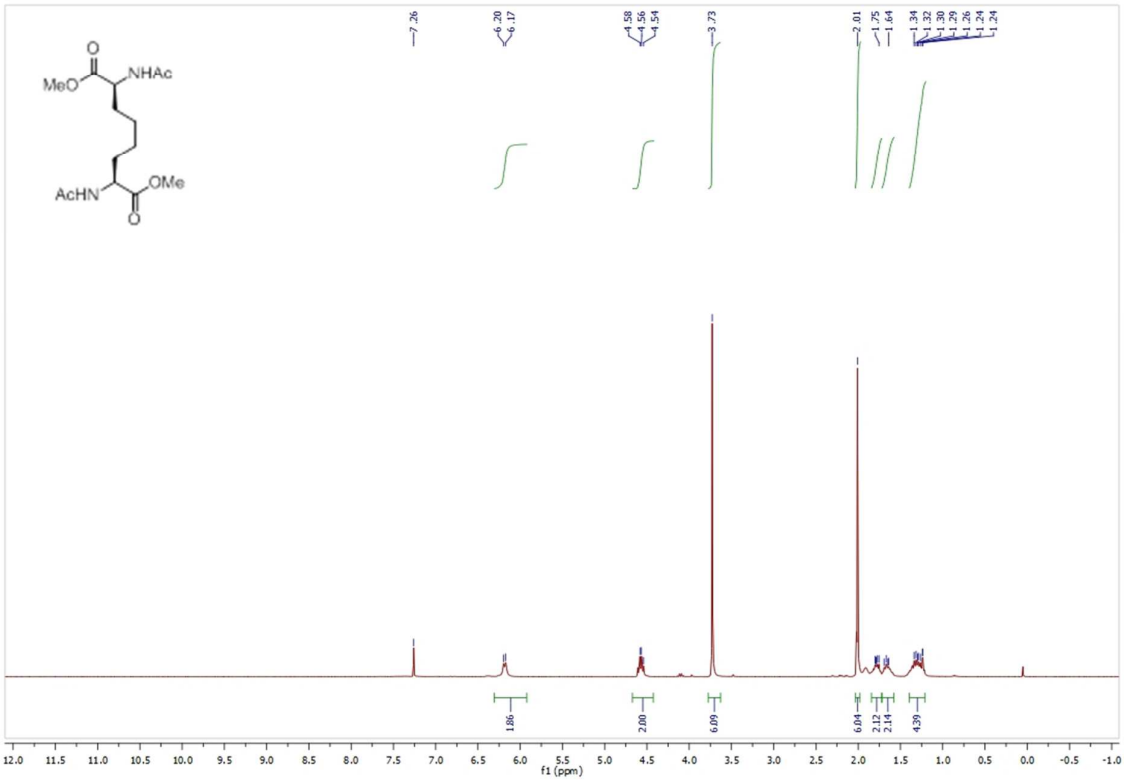



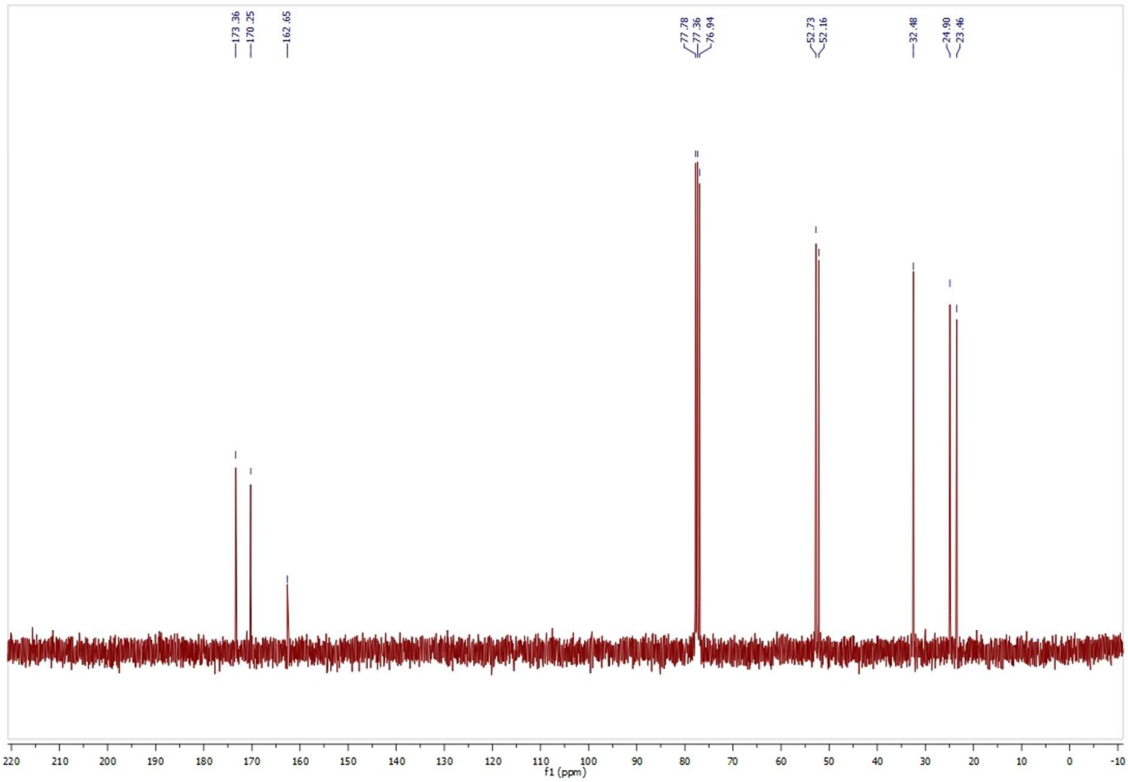

(2*S*,7*S*)-Dimethyl 2,7-diacetamidooctanedioate (**3**) + unreduced impurity **15**




(2*S*,7*S*)-Dimethyl 2,7-diacetamidooctanedioate (**3**)


MeO
NHAc
AcHN
OMe
O
7.26
6.20
6.17
4.58
4.56
4.54
3.73
2.01
1.75
1.64
1.34
1.32
1.30
1.29
1.26
1.24
1.24
1.86
2.00
6.09
6.04
2.12
2.14
4.39
f1 (ppm)


173.36
170.25
162.65
77.78
77.36
76.94
52.73
52.16
32.48
24.90
23.46
f1 (ppm)