Electronic Supplementary Material (ESI) for Chemical Communications

Continuous *in-situ* generation and reaction of phosgene in a microflow system

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SUPPLEMENTARY INFORMATION

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1. General techniques

N-Boc-*O*-benzyl-L-serine was purchased from Watanabe Chemical Industries, Ltd. and used as received. *i*-Pr_2NEt was purchased from Sigma-Aldrich Corporation and it was distilled from ninhydrin, then from KOH. Octyl amine, benzyl amine and Et_2NH were purchased from Sigma-Aldrich Corporation and they were distilled from CaH. The solvents were dried on a Glass Contour Solvent dispensing system (Nikko Hansen & Co., Ltd.).

Nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR) spectra were recorded on a JEOL Model ECP-400 (400 MHz for ^{1}H, 100 MHz for ^{13}C) in $CDCl_3$. High-performance liquid chromatography (HPLC) were carried on a Waters 2695 Separation Module using a Daicel Chiralpak OD-H 0.46 cm Φ × 25 cm or Daicel Chiralpak ID 0.46 cm Φ × 25 cm with a Waters 2996 Photodiode Array Detector. T-shape mixer (Flom Co. Ltd., #9513) is made of stainless steel and it has a T-shape channel (Figure 1). Reaction tube

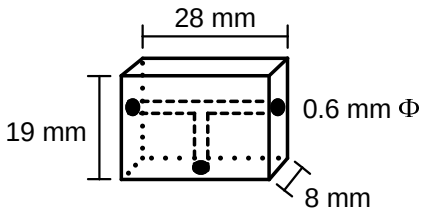


Figure 1.

was made of Teflon®. Harvard Pump 11 Plus Single Syringe (HARVARD apparatus), KDS 100 syringe pump and KDS 200 syringe pump (KD Scientific) ware used to inject compounds to the T-shape mixers. Work-up process including quenching of reaction, liquid-liquid extraction, washing and drying was performed by Zodiac CCX-1200 (Tokyo Rikakikai Co., Ltd.). Chromatographic separation was performed by Purif®-α2 (Shoko Scientific Co., Ltd.).

2. Experimental detail

2.1 General procedure for microflow synthesis of acid chloride

Figure 2 shows schematic illustration of the microflow reactor. T-shape mixer and reaction tube were immersed in water bath (20 ± 0.3 °C). Syringe pumps and a mixer were connected with Teflon tube.

N-Boc-*O*-benzyl-L-serine and triphosgene were azeotropically dried with toluene. Serine, *i*-Pr_2NEt and triphosgene were dissolved in CH_2Cl_2 in the indicated concentration under argon atmosphere and stored in the syringes. The solutions were introduced to T-shape mixer with the syringe pumps. The reaction was quenched by addition of the mixture into vigorously stirred octyl amine (550 μl) in CH_2Cl_2 (4 ml). After stirring for a couple of minutes, ethyl acetate (30 ml), NH_4Cl aq. (1.5 ml) and brine (2 ml) were added into the mixture. After vigorously stirring for 30 sec, aqueous layer was separated. Ethyl acetate (30 ml) was added into the aqueous layer and the resulting mixture was vigorously stirred for 30 sec. After removing aqueous layer, organic layers were combined, dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by Purif-α2 system using ethyl acetate in $CHCl_3$ (0% to 5%). Enantiomeric excess of product was determined by chiral HPLC with Daicel Chiralpak at 265 nm.

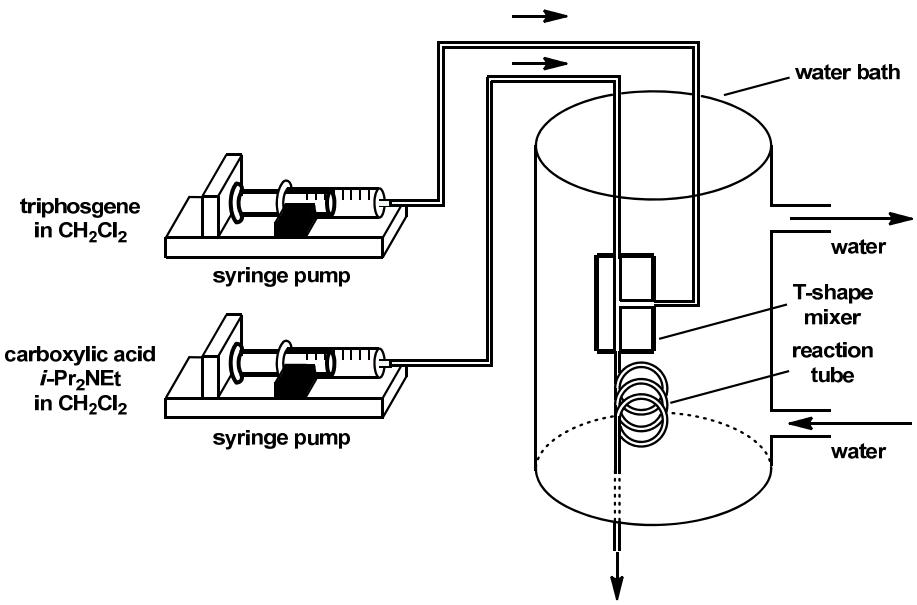


Figure 2

2.2 General procedure for continuous-flow synthesis of amide

Figure 3 shows schematic illustration of the microflow reactor. T-shape mixer and reaction tube were stored in water bath (20 ± 0.3 °C). Syringe pump and mixer were connected with Teflon tube.

N-Boc-*O*-benzyl-L-serine and triphosgene were azeotropically dried with toluene. Serine, *i*-Pr_2NEt, triphosgene and amine were dissolved in CH_2Cl_2 in the indicated concentration under argon atmosphere and stored in the syringes. A solution of serine and a solution of triphosgene were introduced to the first T-shape mixer with the syringe pumps. The resulting mixture and a solution of amine were introduced into the second T-shape mixer. The reaction was quenched by addition of the mixture into vigorously stirred NH_4Cl aq. (1.5 ml) and CH_2Cl_2 (2 ml) suspension. After stirring for a couple of minutes, ethyl acetate (30 ml) and brine (2 ml) were added into the mixture. After vigorously stirring for 30 sec, aqueous layer was separated. Ethyl acetate (30 ml) was added into the aqueous layer and the resulting mixture was vigorously stirred for 30 sec. After removing aqueous layer, organic layers were combined, dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by Purif-α2 system using ethyl acetate in $CHCl_3$ (0% to 5%). Enantiomeric excess of product was determined by chiral HPLC with Daicel Chiralpak at 265 nm.

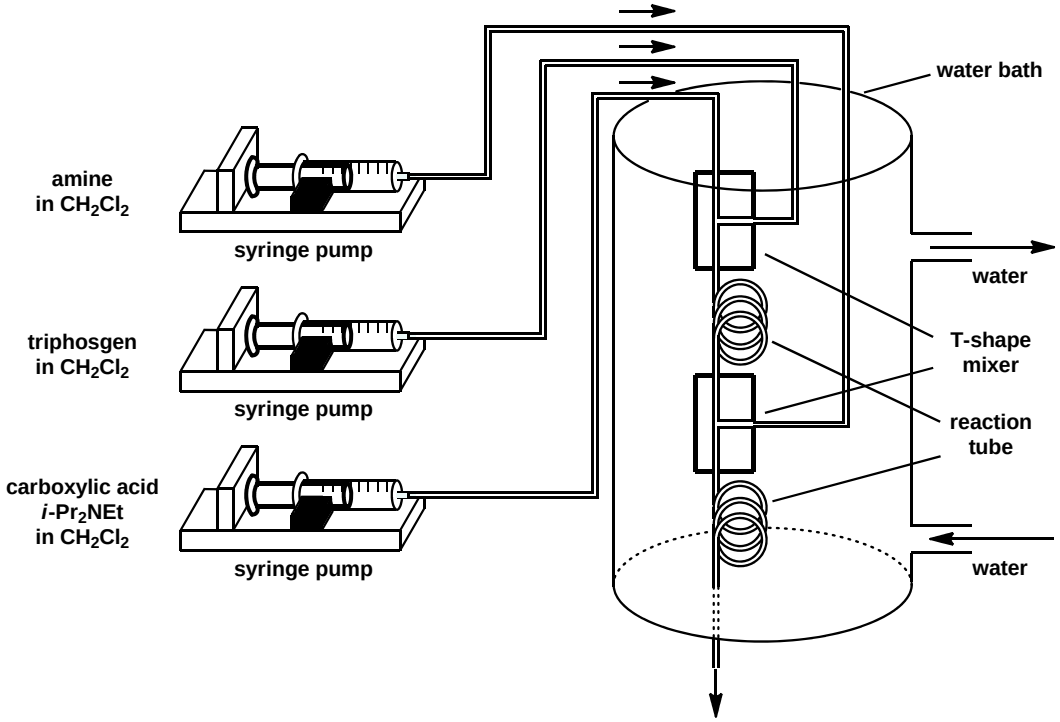


Figure 3

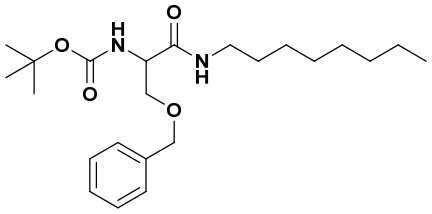
3. Physical data

N-Boc-*O*-benzyl-L-serine-octyl amide

colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.28(m, 5H), 6.39(bs, 1H), 5.39(bs, 1H), 4.57(d, *J* = 7.3 Hz, 1H), 4.50(d, *J* = 7.3 Hz, 1H), 4.23(bs, 1H), 3.91(dd, *J* = 2.4, 5.8 Hz, 1H), 3.56(dd, *J* = 4.2, 5.8 Hz, 1H), 3.25(dt, *J* = 4.2, 4.6 Hz, 2H), 1.47(s, 9H) 1.25(bs, 12H), 0.88(t, *J* = 4.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 155.5, 137.5, 128.5, 127.9, 127.7, 80.2, 73.4, 67.0, 53.8, 39.6, 31.8, 29.4, 29.2, 29.1, 28.3, 26.8, 22.6, 14.0; FT-IR (neat) 2929, 2857, 1716, 1657, 1498, 1366, 1249, 1169, 1111 cm^{-1}.

HPLC condition; Daicel chiralpak OD-H, 2% *i*-PrOH in hexane (flow rate 1 ml/min).

Retention time (min): 17.68 (*N*-Boc-*O*-benzyl-D-serine-octyl ester),
21.45 (*N*-Boc-*O*-benzyl-L-serine-octyl ester).



N-Boc-*O*-benzyl-L-serine-benzyl amide

slightly yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.23(m, 10H), 6.73(bs, 1H), 5.40(bs, 1H), 4.56(d, *J* = 7.3 Hz, 2H), 4.49(d, *J* = 7.3 Hz, 2H), 4.31(bs, 1H), 3.97(dd, *J* = 2.1, 5.5 Hz, 1H), 3.61(dd, *J* = 4.0, 5.8 Hz, 1H), 1.43(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 155.4, 137.9, 137.3, 128.6, 128.4, 127.8, 127.7, 127.4, 127.3, 80.2, 73.4, 69.9, 54.1, 43.4, 28.1; FT-IR (neat) 3089, 3064, 3031, 2978, 2931, 2868, 1717, 1664, 1497, 1454, 1367, 1249, 1167, 1106, 1027 cm^{-1}.

HPLC condition: Daicel chiralpak OD-H, 1.5% *i*-PrOH in hexane (flow rate 1 ml/min).

Retention time (min): 75.28 (*N*-Boc-*O*-benzyl-D-serine-benzyl ester),
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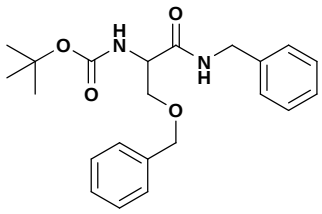
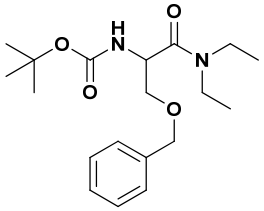


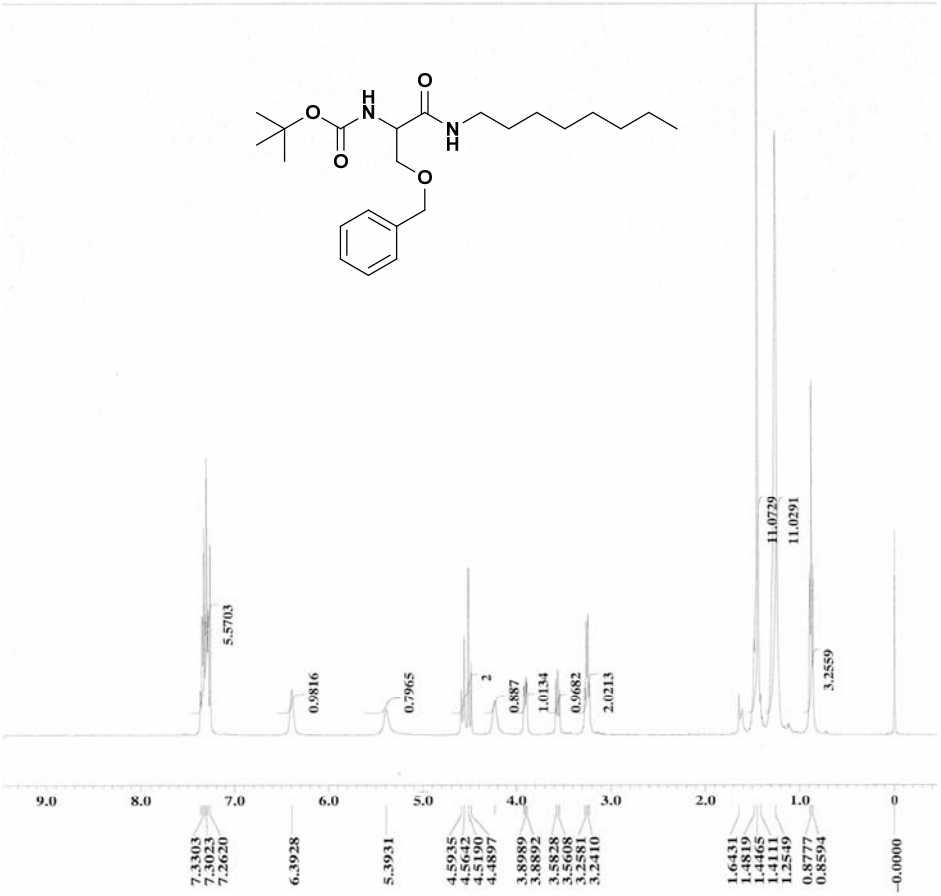
***N*-Boc-*O*-benzyl-L-serine-diethyl amide**

slightly yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26(m, 5H), 5.37(bs, 1H), 4.82(bs, 1H), 4.51(dd, *J* = 7.6, 12.2 Hz, 2H), 3.65-3.50(m, 4H), 3.31-3.21(m, 2H), 1.43(s, 9H), 1.17(t, *J* = 4.6 Hz, 3H) 1.12(t, *J* = 4.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 155.1, 137.9, 128.3, 127.6, 127.5, 79.7, 73.2, 71.3, 49.8, 41.9, 40.5, 28.3, 14.4, 12.8; FT-IR (neat) 2977, 2934, 2873, 1710, 1638, 1497, 1455, 1366, 1248, 1170, 1116, 1099 cm^{-1}.

HPLC condition: Daicel chiralpak ID, 10% *i*-PrOH in hexane (flow rate 1 ml/min).

Retention time (min): 14.60 (*N*-Boc-*O*-benzyl-L-serine-diethyl ester),
19.23 (*N*-Boc-*O*-benzyl-D-serine-diethyl ester).

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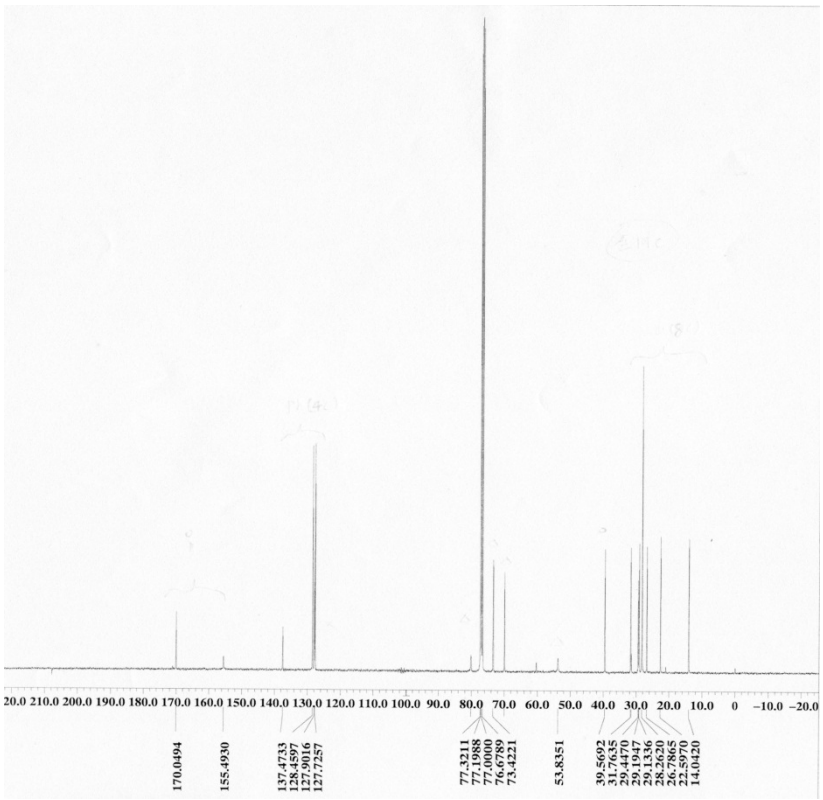
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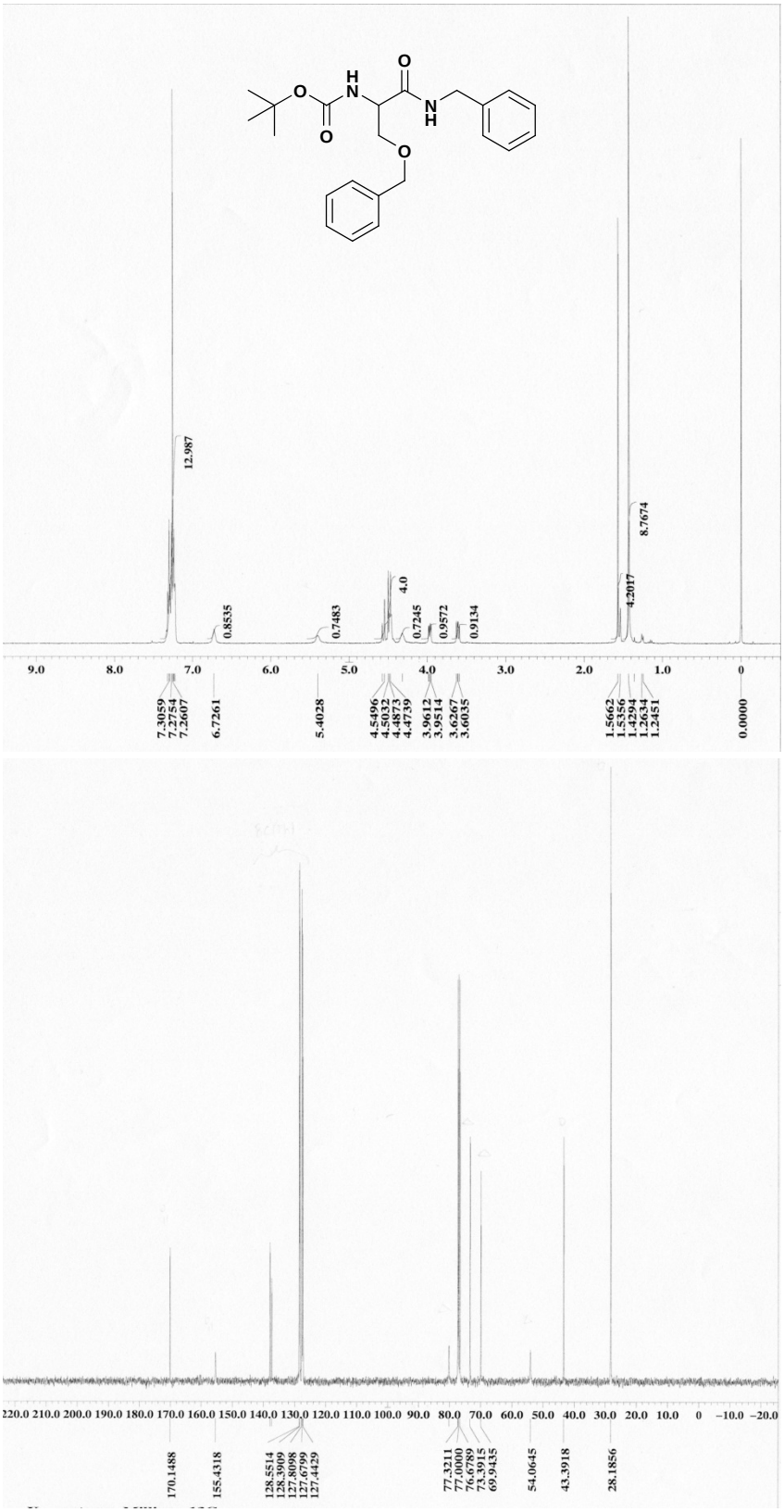
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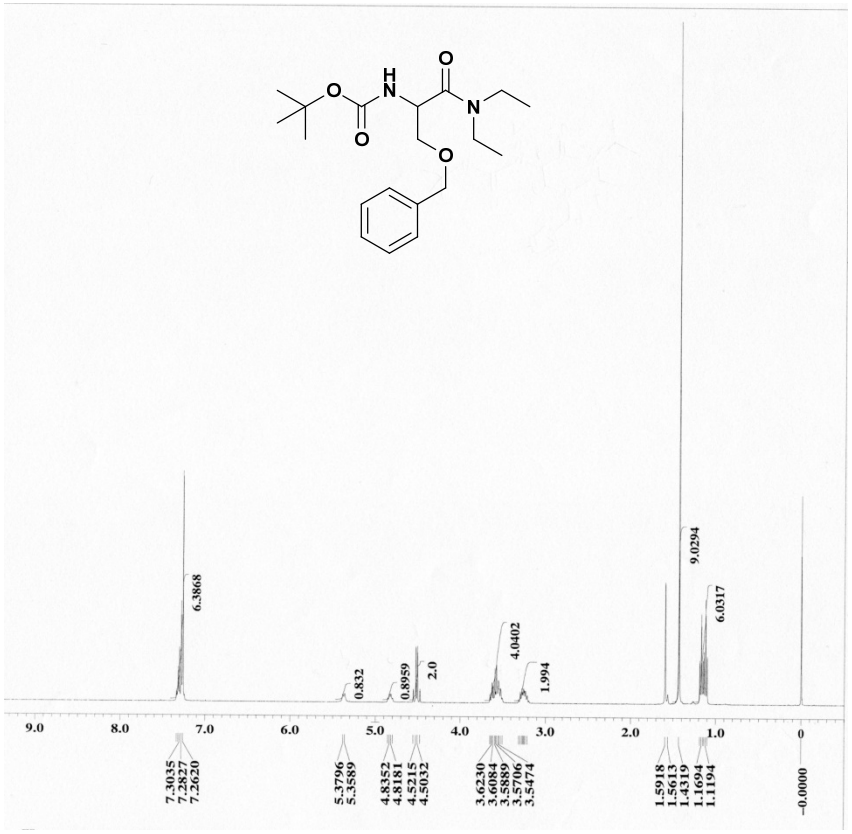
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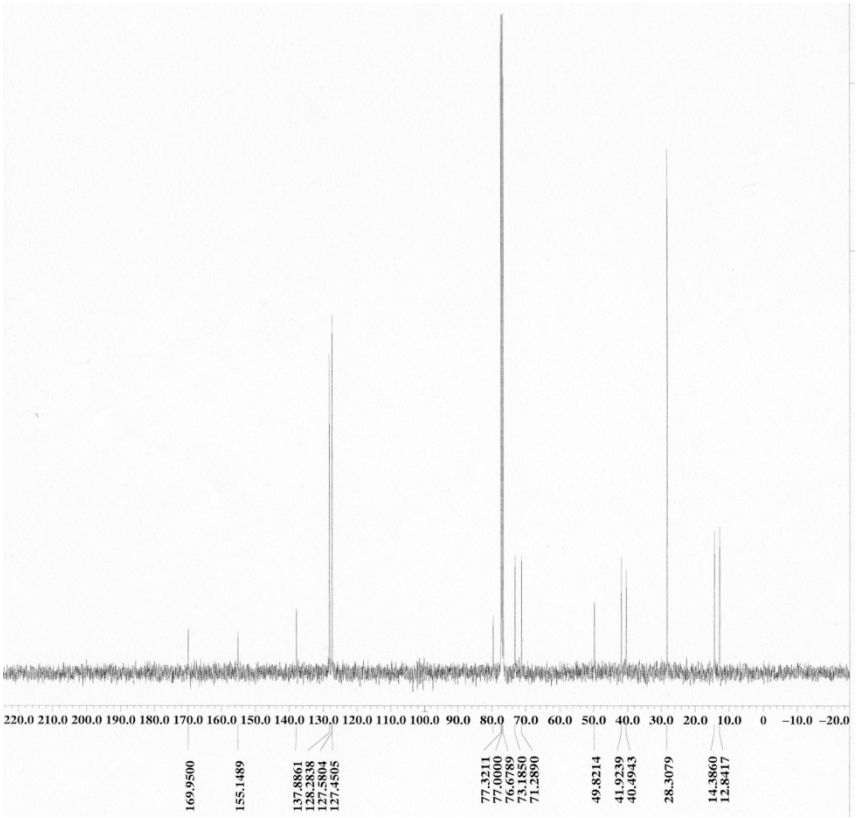
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