Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Micro-Total Process System Machine (μ-TPSM) for Rapid Synthesis of antiretroviral Darunavir

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Table of contents:

1. General

1.1. Materials. Most of the reagents and chemicals are bought from Sigma-Aldrich and used as such without any further purification. Common organic chemicals and salts were purchased from Avra chemicals, India. Deionized water (18.2 mS conductivity) was used in all experiments wherever required. All work-up and purification procedures were carried out with reagent-grade solvents in air. Analytical thin-layer chromatography (TLC) was performed using analytical chromatography silica gel 60 F254 precoated plates (0.25 mm). The developed chromatogram was analysed by UV lamp (365 nm). PTFE (id = 1000 μm) tubing, T-junction, high-purity PFA tubing was purchased from Upchurch IDEX HEALTH & SCIENCE. Homemade photo-batch reactor bought from Lelesil Mumbai, India was slightly modified for the continuous photo flow reaction.

1.2. Analysis. High-resolution mass spectra (HRMS) were obtained from a JMS-T100TD instrument (DART) and Thermo Fisher Scientific Exactive (APCI). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 600, 500, 400 or 300 MHz in $CDCl_3$ or DMSO-d_6 solvent. Chemical shifts for ^1H NMR are expressed in parts per million (ppm) relative to tetramethylsilane (δ 0.00 ppm). Chemical shifts for ^{13}C NMR are expressed in ppm relative to $CDCl_3$ (δ 77.0 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, quin = quintet, sext = sextet, m = multiplet), coupling constant (Hz), and integration. GC/MS analysis was conducted on an Shimadzu technology GCMS-QP2010 instrument equipped with a HP-5 column (30 m × 0.25 mm, Hewlett-Packard) and inbuilt MS 5975C VL MSD system with triple axis detector.

2. HIV protease inhibitors derived from α-halogenated ketone.

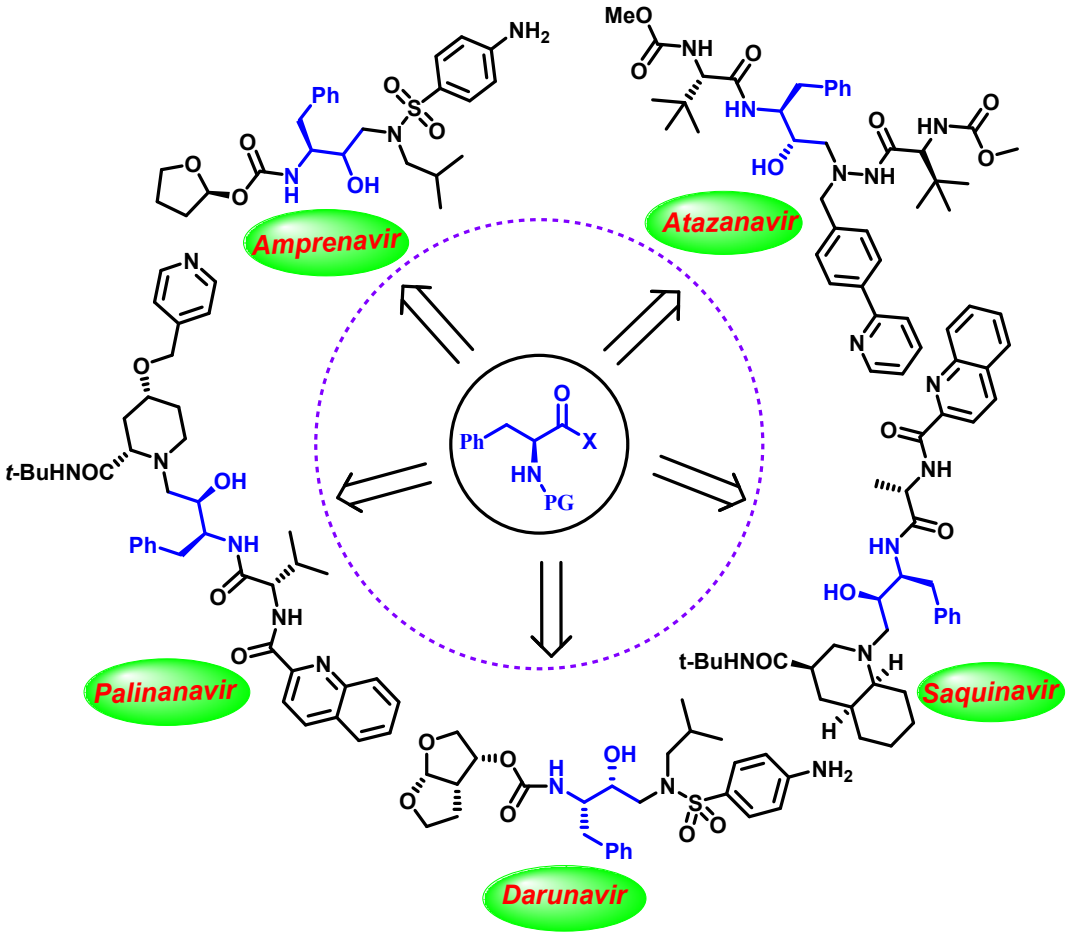


Figure S1. Examples of amino acid containing APIs derived from halogenated ketone.

3. Batch process synthesis of Darunavir.

3.1. First generation.

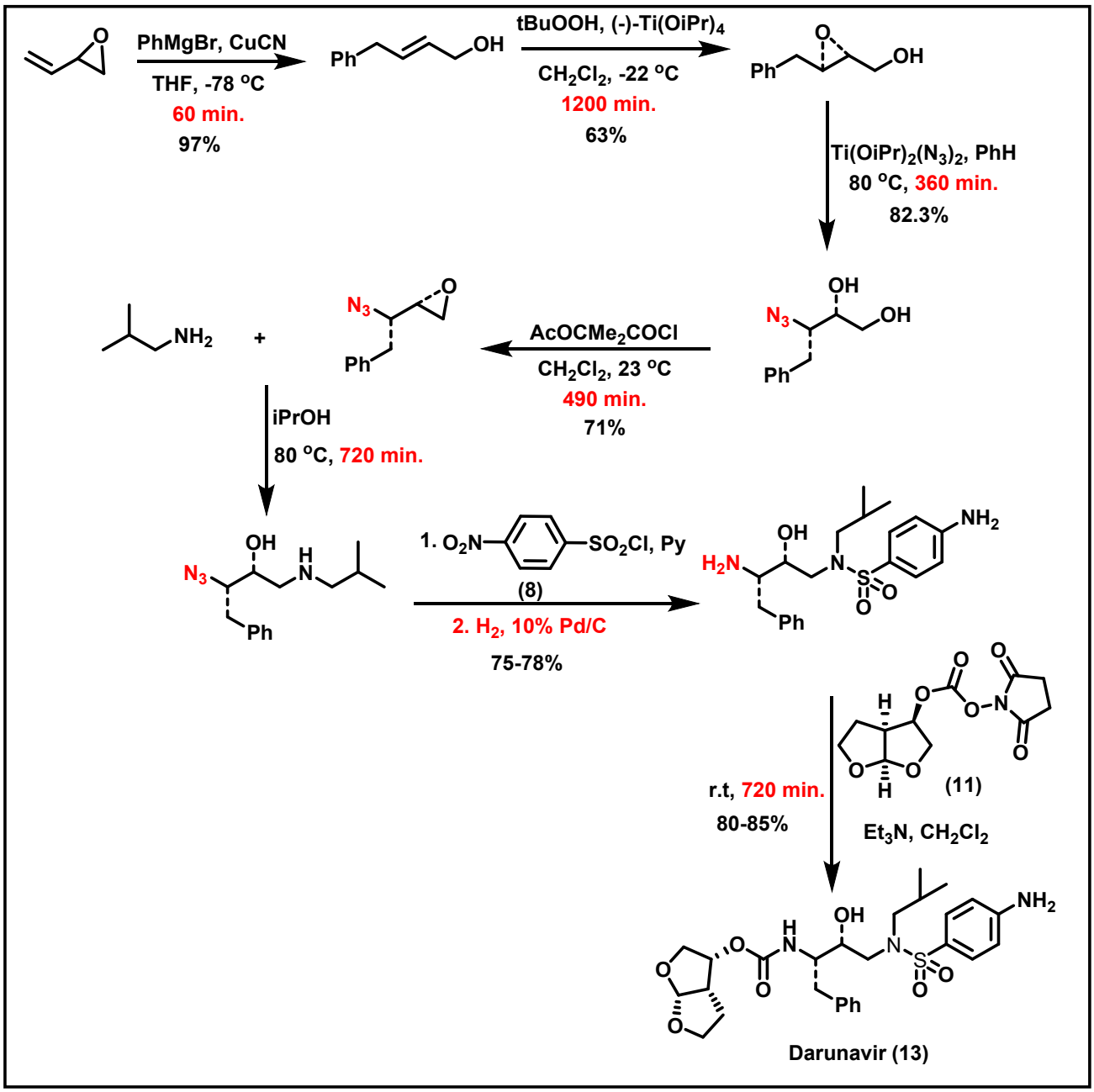


Figure S2. First generation hazardous azide epoxide assisted synthesis of darunavir with total reaction time 3550 min., overall yield 27% (1998). [1, 2]

3.2. Second generation.

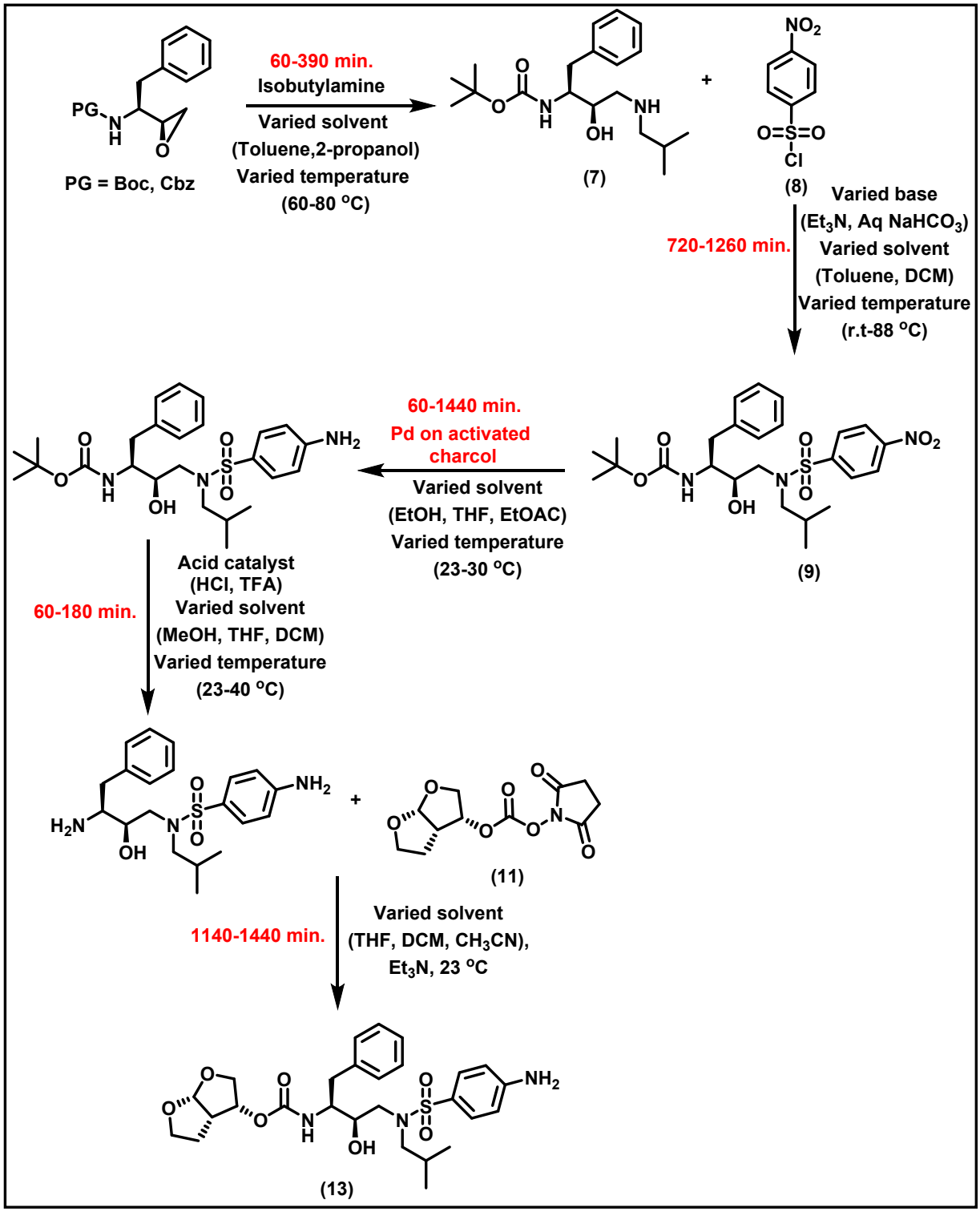
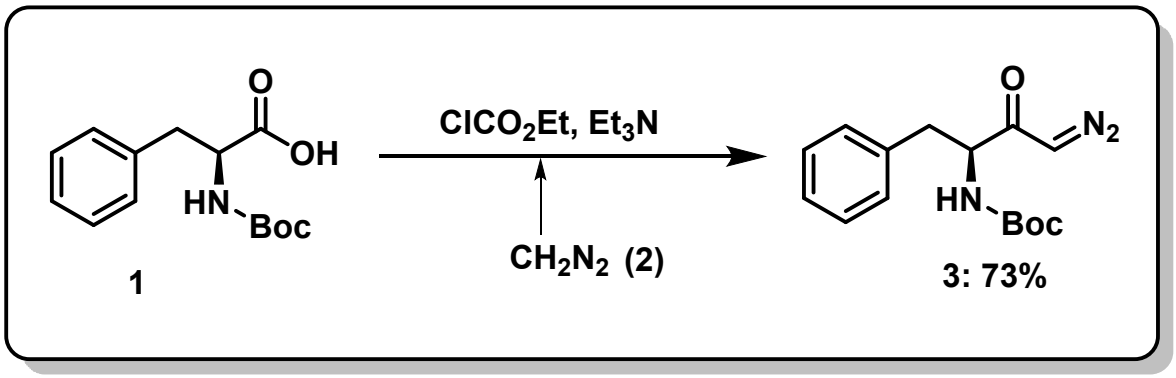


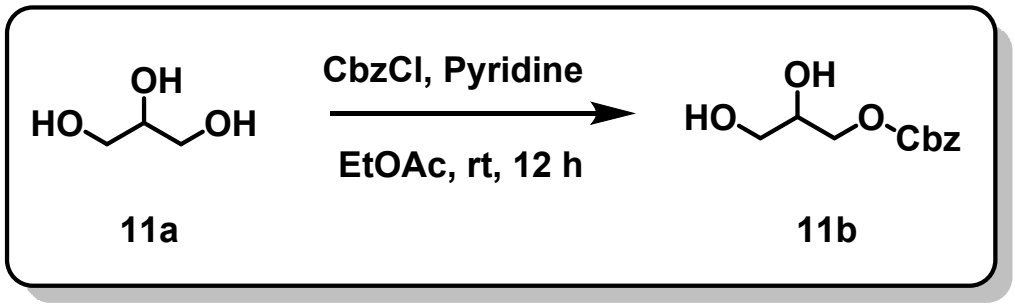
Figure S3. Second generation scale up and costly Pd catalyst assisted synthesis of darunavir with total reaction time 1602-4320 min., overall yield (37-80%).[3, 4] Epoxide is commercially available CAS No 98737-29-2(Boc protected) and CAS No 128018-44-0 (Cbz protected).

4. Batch process synthesis of Darunavir.

4.1. Synthesis of *tert*-butyl (*S*)-(4-diazo-3-oxo-1-phenylbutan-2-yl) carbamate **(3)**. Reported procedure[5] has been applied to synthesize the intermediate **3**.

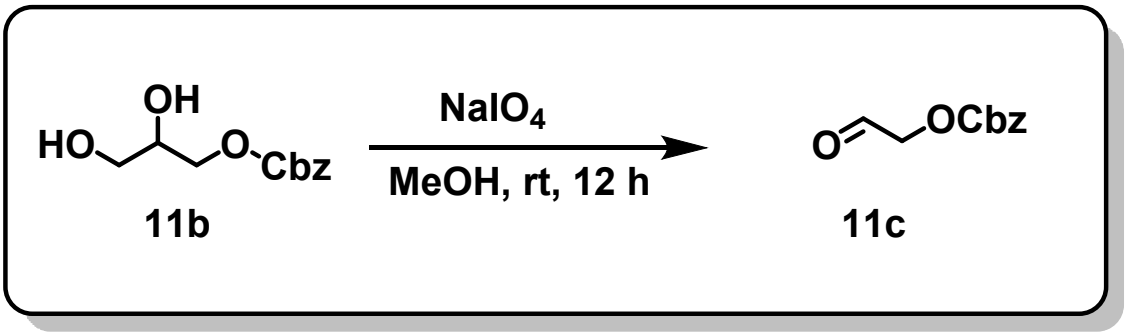


4.2. Synthesis of benzyl (2,3-dihydroxypropyl) carbonate **(11b).**



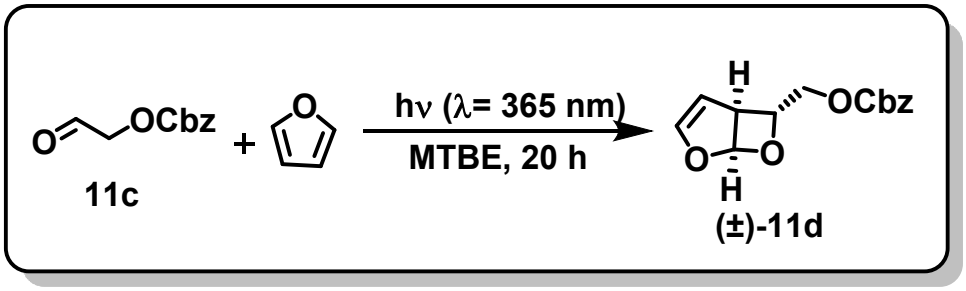
Ethylene glycol **11a** (20 g, 217 mmol) was dissolved in ethyl acetate (120 mL) and pyridine (1.9 mL, 23.89 mmol) was added and then the reaction mixture stirred at room temp for 5 min. and then cooled to 0 °C before adding benzyl chloroformate (Cbz) (3.1 mL, 21.7 mmol) dropwise over 15 min. After complete addition, the reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was extracted through reported procedure to yield Cbz-protected glycerol **11b** as a colorless oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.39 – 7.34 (m, 5H), 5.17 (s, 2H), 4.27 – 4.18 (m, 2H), 3.99 – 3.84 (m, 1H), 3.73 – 3.59 (m, 2H), 2.69 (d, *J* = 5.2 Hz, 1H), 2.27 – 2.17 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 155.3, 135.0, 128.8, 128.8, 128.5, 70.1, 70.0, 68.8, 63.2. **IR (ν_{max}):** 3473.54, 3426.14, 1746.83 cm^{-1}. **HRMS (ESI):** *m/z* calcd for **$C_{11}H_{13}NaO_5$** $(M+Na)^+$ 249.0733, Found 249.0734. Analytical data are well matched with reported literature.[6]

4.3. Synthesis of benzyl (2-oxoethyl) carbonate **(11c).**



Cbz-protected glycerol **11b** (8 g, 35.3 mmol) was dissolved in methanol, and to this was added sodium metaperiodate ($NaIO_4$) (11.3 g, 53.0 mmol) portion wise at 0 ^oC. After addition reaction the mixture was warmed to room temperature and stirred overnight. The reaction mixture was then filtered to remove the formed precipitate and concentrated give to aldehyde **11c**, which was used further without any purification in next step.

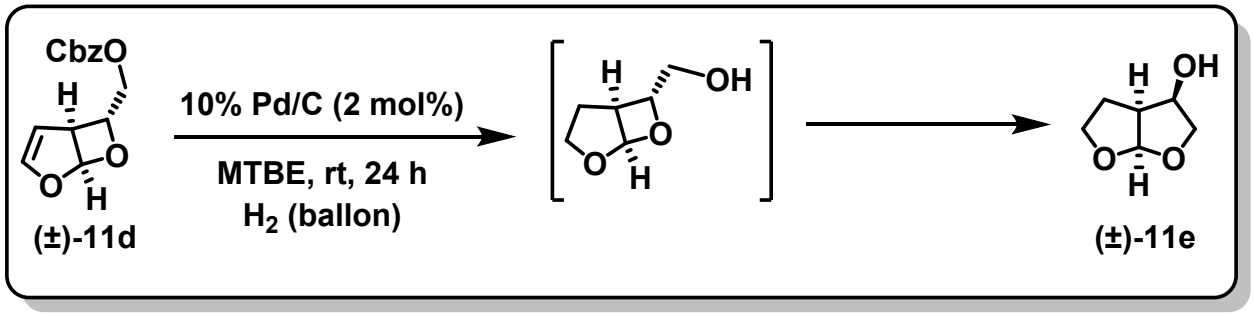
4.4. Synthesis of (1*R*,5*S*,6*R*)-2,7-dioxabicyclo[3.2.0]hept-3-en-6-yl)methyl benzyl carbonate (±)-**(11d)**



Cbz-protected aldehyde **11c** (2 g, 10.3 mmol) and furan (3.7 mL, 51.5 mmol) in MTBE (15 mL) were dissolved in 50 mL photolysis glass tube equipped with a magnetic stir bar and placed in a photochemical reactor. The reaction mixture was stirred for 20 h under UV light. After reaction completion reaction mixture was concentrated and purified through reported procedure to yield

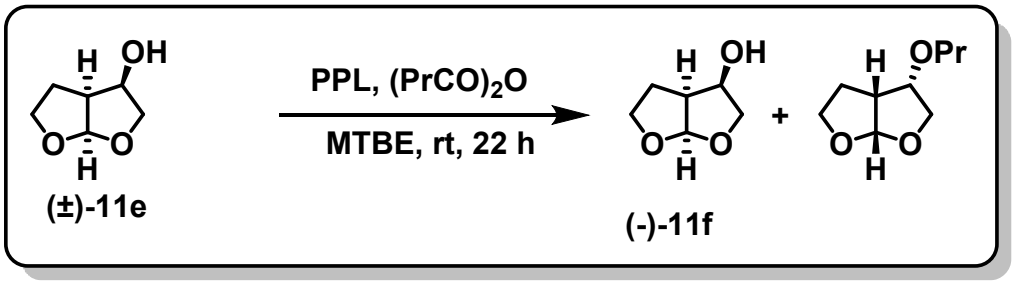
compound **(±)-11d** as a colorless oil (2.43 g, 90%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.40 – 7.36 (m, 5H), 6.64 – 6.63 (m, 1H), 6.31 (d, *J* = 4.0 Hz, 1H), 5.34 (t, *J* = 2.9 Hz, 1H), 5.20 (s, 2H), 4.74 – 4.70 (m, 1H), 4.42 (dd, *J* = 12.2, 3.6 Hz, 1H), 4.32 (dd, *J* = 12.2, 3.6 Hz, 1H), 3.70 – 3.67 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 155.2, 148.6, 135.1, 128.8, 128.6, 127.1, 108.1, 103.7, 88.1, 70.2, 69.0, 46.7. **IR (ν_{max}):** 1750.84 cm^{-1}. **HRMS (ESI):** *m/z* calcd for **$C_{14}H_{13}NaO_5$** $(M+Na)^+$ 285.0733, Found 285.0735. Analytical data are well matched with reported literature.[6]

4.5. Synthesis of anti-hexahydrofuro[2,3-b] furan-3-ol ((±)-**(11e).**



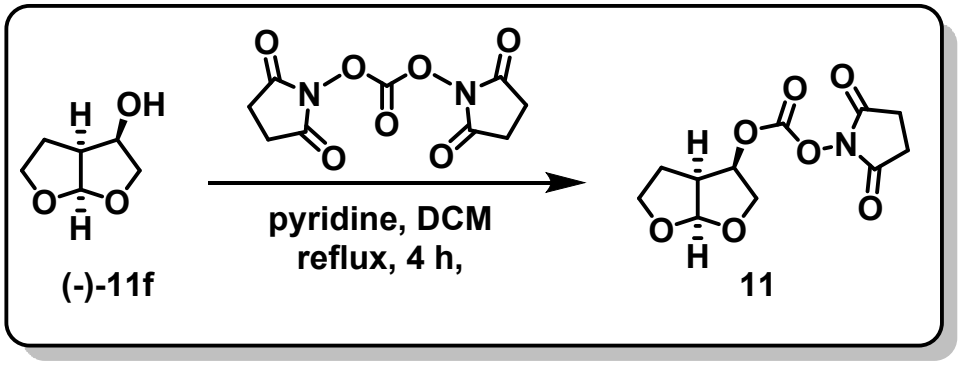
The compound (±)-**11d** (2.1 g, 8.00 mmol) was dissolved in MTBE, 10% Pd/C (168 mg, 0.2 mmol w/w) was added to the reaction mixture and then reaction vessel was evacuated and refilled with hydrogen at room temp. The reaction mixture stirred at this temperature for 24 h. The resulting mixture filtered and extracted through reported procedure to yield compound (±)-**11e** as a colorless oil (930 mg, 89%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.70 (d, *J* = 5.2 Hz, 1H), 4.48 – 4.43 (m, 1H), 4.02 – 3.97 (m, 2H), 3.94 – 3.88 (m, 1H), 3.65 (dd, *J* = 9.2, 7.0 Hz, 1H), 2.90 – 2.83 (m, 1H), 2.34 – 2.28 (m, 1H), 1.93 – 1.83 (m, 1H), 1.78 (br s, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 109.6, 73.2, 71.1, 69.9, 46.6, 24.9. Analytical data are well matched with reported literature.[6]

4.6. Synthesis of (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-b]furan-3-ol ((–)-**(11f).**



The compound (±)-**11e** (1 g, 7.69 mmol) was dissolved in MTBE, Porcine Pancreatic Lipase (PPL) (1.0 g, 10% w/w) and propionic anhydride (1.0 g, 7.69 mmol) were added to the reaction mixture and stirred for 22 h at room temp. The reaction mixture was filtered and extracted through reported procedure to give compound (–)-**11f** (433 mg, 43%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 5.69 (d, *J* = 5.2 Hz, 1H), 4.45 (dd, *J* = 13.3, 6.4 Hz, 1H), 4.01 – 3.97 (m, 2H), 3.93 – 3.88 (m, 1H), 3.65 (dd, *J* = 9.2, 7.0 Hz, 1H), 2.89 – 2.83 (m, 1H), 2.33 – 2.28 (m, 1H), 1.92 – 1.84 (m, 1H), 1.80 (br s, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 109.6, 73.1, 70.8, 70.0, 46.6, 24.9. **IR (ν_{max}):** 3473.46, 2952.87 cm^{-1}. Analytical data are well matched with reported literature.[6]

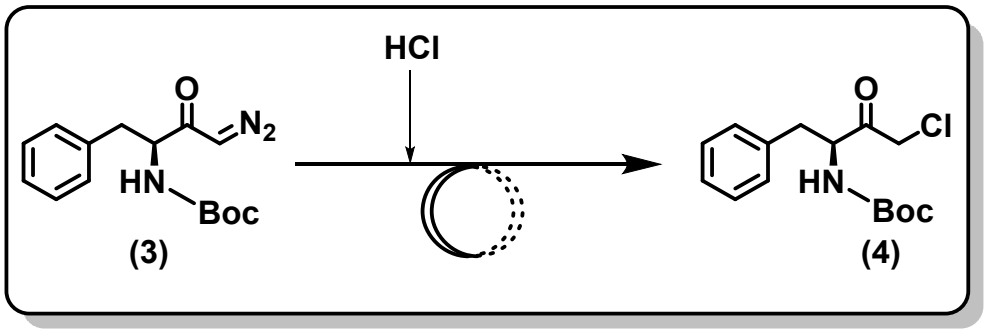
4.7. Synthesis of 2,5-Dioxopyrrolidin-1-yl ((3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-b]furan-3-yl) carbonate **(11).**



The compound (–)-**11f** (3.8 g, 29.2 mmol) was dissolved in DCM (40 mL), *N,N*-Disuccinimidyl carbonate (11.2 g, 43.84 mmol), pyridine (6 mL, 73.07 mmol) were added to reaction mixture at room temperature and then reaction mixture was heated to reflux for 4 h. After the completion of reaction, DCM (75 mL) and water (75 mL) were added to reaction mixture at room temperature, resultant biphasic mixture was stirred for 30 min. The reaction mixture was extracted through reported procedure to give compound **11** (5.9 g, 75%) as a white solid, **mp**: 115-116 °C. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 5.75 (d, *J* = 5.2 Hz, 1H), 5.27 – 5.23 (m, 1H), 4.13 – 4.10 (m, 1H), 4.06 – 4.02 (m, 1H), 3.97 – 3.92 (m, 2H), 3.16 – 3.10 (m, 1H), 2.86 (s, 4H), 2.18 – 2.13 (m, 1H), 2.03 – 1.95 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.5, 151.3, 109.3, 79.8, 70.2, 69.8, 45.2, 26.1, 25.6. **IR (ν_{max}):** 1789.54, 1739.93 cm^{-1}. **HRMS (ESI):** *m/z* calcd for $\mathbf{C_{11}H_{14}NO_7}$ $(M+H)^+$ 272.0765, Found 272.0769. Analytical data are well matched with reported literature.[7]

5. Continuous flow process Darunavir synthesis.

5.1. Preparation of compound **(4).**



A solution of compound **3** in DEE (diethyl ether) was charged in one syringe. HCl in dioxane: DEE was charged in another syringe. The two solutions were pumped by varying flow rate and molar ratio to maintain the stoichiometry and mixing at T- mixer and passing through PFA tubular reactor (figure S4). Optimization conditions were varied depending on the molar solutions, temperature, and pressure etc (Table 1).

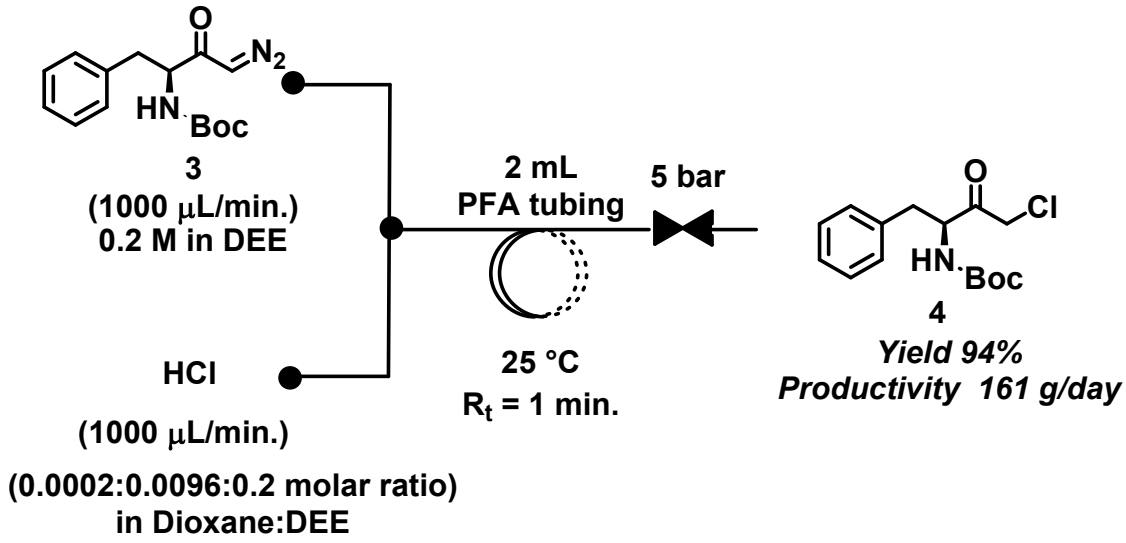


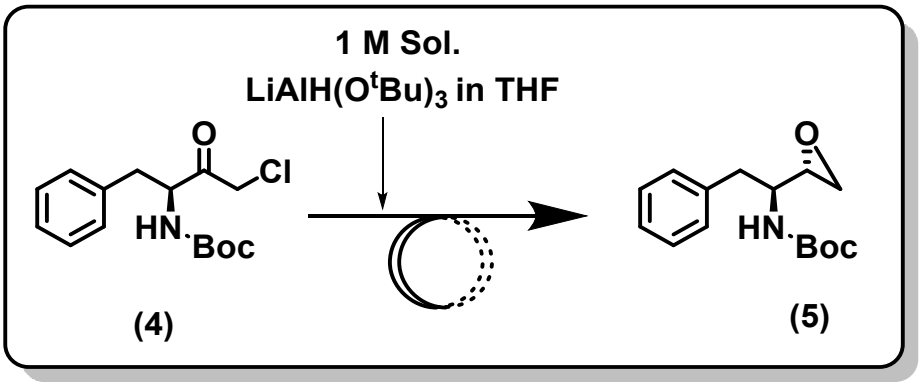
Figure S4. Schematic presentation of continuous flow synthesis of compound **4**.

A 0.2 M solution of **3** in DEE was charged in one syringe and solution of HCl in dioxane: DEE (0.0002:0.0096:0.2 molar ratio) charged in another syringe (figure S4). The two solutions were introduced to a T-mixer with same flow rate 1000 µL/min. with the ratio of 1:1 (compound **3**: HCl) to maintain the stoichiometry, and then passed through a PFA tubing (id = 1000 µm, l = 2.6 m, vol. = 2 mL) to occur the reaction in 1 min. residence time at 25 °C and 5 bar pressure (Table 1, entry 9). After completion the resulting solution was extracted through the regular process to yield intermediate **4,** as a white solid having yield 94% and **mp**: 102-103 °C. Under the stable condition the product was collected for 1 h and experiment was repeated for three times. The yield is based on average of three analysis. $[a]_D^{25}$ -34.29 (*c* = 1.00, MeOH). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.34 – 7.27 (m, 3H), 7.17 – 7.11 (m, 2H), 5.02 (br s, 1H), 4.69 – 4.64 (m, 1H), 4.16 (d, *J* = 16.2 Hz, 1H), 3.98 (d, *J* = 16.2 Hz, 1H), 3.11 – 2.98 (m, 2H), 1.41 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 201.6, 155.4, 135.7, 129.4, 129.3, 129.1, 127.5, 80.7, 58.6, 47.7, 37.9, 28.4. **IR (ν_{max}):** 3355.01, 2937.77, 1738.36, 1688.23 cm^{-1}. **HRMS (ESI):** *m/z* calcd for **$C_{15}H_{19}ClNNaO_3$** $(M+Na)^+$ 320.1029, Found 320.1030. Analytical data are well matched with reported literature.[8]

Table S1: Comparison table for synthesis of **4** in batch and continuous flow process

Entry	Process	Time (min.)	Temp. (0 °C)	Yield (%)	Ref.
1	batch	60	0	92	[9]
2	Semi batch	10	25	80	[8]
3	**flow**	**1**	**25**	**94**	**this study**

5.2. Preparation of compound **(5).**



A solution of intermediate **4** in ethanol: THF was taken in one syringe and solution of lithium tri-*tert*-butoxyaluminum hydride (LTBA) in THF in another syringe. The two solutions were introduced into a T-mixer in a varied flow rate and ratio to maintain stoichiometry, and then passed through SS tubular reactor, out coming solution was collected in round bottom flask for quenching purpose (figure S5). Optimization conditions were varied depending on the molar solutions, temperature, and pressure etc. (Table 2).

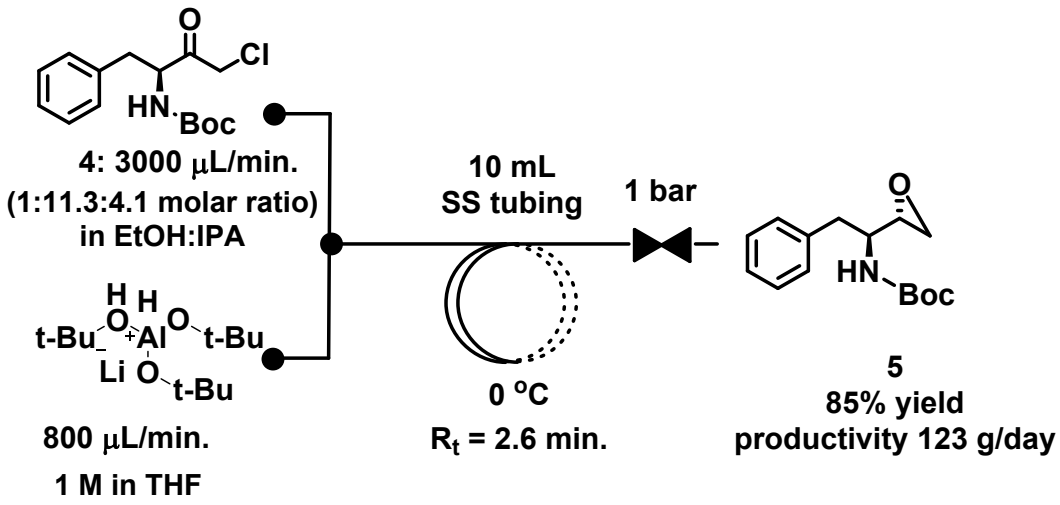


Figure S5. Schematic presentation of continuous flow synthesis of compound **5**.

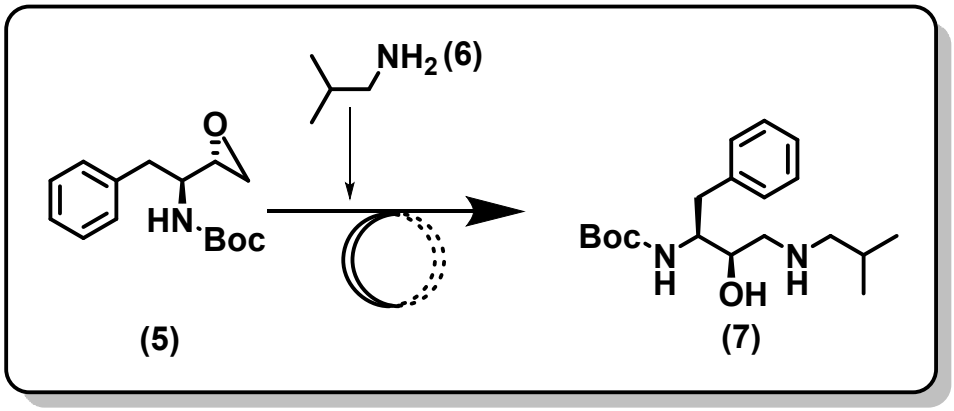
A solution of intermediate **4** in EtOH: THF (1:11.3:4.1 molar ratio) was charged in one syringe and another syringe was charged with 1 M LTBA solution in THF (figure S5). The two solutions were pumped and mixing at T-mixer with flow rate 3000 µL/min. for compound **4** and flow rate of LTBA is 800 µL/min. in the ratio of 1:3.3 (intermediate **4**: LTBA) to maintain the stoichiometry, and then passed through SS tubular reactor (id = 1000 µm, l = 12.8 m, vol. = 10 mL) to complete the reaction in 2.6 min. residence time at 0 °C and 1 bar pressure (Table 2, entry 7). Under stable condition, product was collected in a round bottom flask having Rochelle salt solution (solution of potassium sodium tartrate and potassium carbonate) for quenching the outcome reaction mixture. The resulting solution was extracted to yield of intermediate **5** as a white solid having yield 85% and **mp**: 121-122 °C. Under the stable condition, the product was collected for 1 h and experiment was repeated for three times. The yield is based on average of three analysis. $[a]_D^{25}$ -8.80 (c = 1.00, MeOH). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.33 – 7.21 (m, 5H), 4.45 (s, 1H), 3.69 (s, 1H), 2.99 – 2.76 (m, 5H), 1.38 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 155.2, 136.7, 129.5, 128.6, 126.7, 79.7, 53.2, 52.6, 46.9, 37.6, 28.3. **IR (ν_{max}):** 3377.02, 2983.25, 1681.72, 1524.25 cm^{-1}. **HRMS**

(ESI): *m/z* calcd for $C_{15}H_{22}NO_3$ $(M+H)^+$ 264.1594, Found 264.1595. Analytical data are well matched with reported literature.[10]

Table S2. Comparison of batch and continuous flow process for synthesis of **5**.

Entry	Process	Time (min.)	Temp. (°C)	Yield (%)	Ref.
1	batch	180	-78	82	[10]
2	**flow**	**2.6 min.**	**0**	**85**	**this study**

5.3. Preparation of compound **(7).**



A solution of intermediate **5** in IPA (isopropyl alcohol) was charged in one syringe. Isobutyl amine **6** dissolved in IPA was charged in another syringe. Mixing at T- mixer and passing through PFA tubular reactor placed in heating condition (figure S6). The two solutions were pumped by varying flow rate and molar ratio to maintain the stoichiometry. Optimization conditions were varied depending on the molar solutions, temperature, and pressure etc. (Table 3).

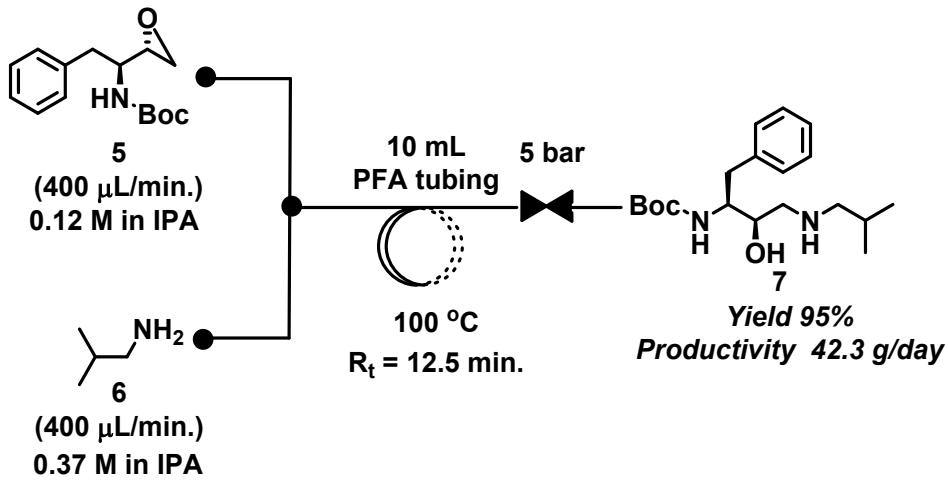


Figure S6. Schematic presentation of continuous flow synthesis of compound **(7)**.

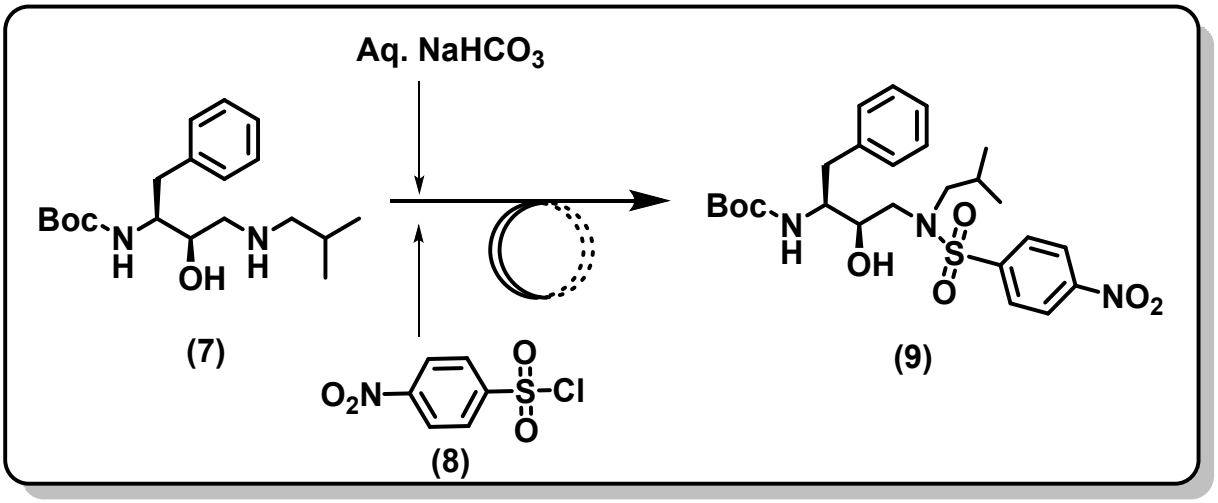
A 0.12 M solution of intermediate **5** in isopropyl alcohol (IPA) was charged in one syringe. Another syringe was filled with 0.37 M solution of reagent **6** (isobutyl amine) solution in IPA (figure S6). The two solutions were pumped to a T-mixer at same flow rate 400 µL/min. with the ratio of 1:3 (intermediate **5**: reagent **6**) to maintain the stoichiometry, and then passed through a PFA tubing (id = 1000 µm, l = 12.8 m, vol. = 10 mL) to complete the reaction in 12.5 min. residence time and 100 °C and 5 bar pressure (Table 3, entry 5). The resulting solution was extracted and purified by column chromatography with DCM/Methanol (95:05) to yield intermediate **7** as a white solid having yield 95% and **mp**: 106 –107 °C. Under the stable condition the product was collected for 1 h and experiment was repeated for three times. The yield is based on average of three analysis. $[a]_D^{25}$ = +7.70 (c = 1.00, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.31 – 7.27 (m, 2H), 7.24 – 7.19 (m, 3H), 4.70 (d, J = 8.6 Hz, 1H), 3.81 (br s, 1H), 3.48 – 3.43 (m, 1H), 2.99 (dd, J = 14.0, 4.7 Hz, 1H), 2.88 – 2.83 (m, 1H), 2.68 (d, J = 4.7 Hz, 2H), 2.41 (d, J = 6.7 Hz, 2H), 1.76 – 1.66 (m, 1H), 1.35 (s, 9H), 0.92 (d, J = 2.2 Hz, 3H), 0.90 (d, J = 2.2 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 156.1, 138.0, 129.7, 128.5, 126.5, 79.6, 70.8, 58.1, 54.3, 51.6, 36.8,

28.4, 20.7. **IR (ν_{max}):** 3366.93, 2955.62, 2877.81, 1683.71 cm^{-1}. **HRMS (ESI):** *m/z* calcd for **$C_{19}H_{33}N_2O_3$** $(M+H)^+$ 337.2486, Found 337.2495. Analytical data are well matched with reported literature.[11]

Table S3. Comparison of batch and continuous flow process synthesis **7**.

Entry	Process	Time (min.)	Temp. °C	Yield %	Ref
1	batch	360	60	100	[12]
2	batch	60	78	99.8	[13]
3	batch	120	90	99	[3]
4	batch	180	80	91	[14]
5	batch	390	80	91.5	[15]
6	batch	300	50	90	[16]
7	batch	360	80	83	[17]
8	batch	360	80	83	[18]
9	**flow**	**12.5**	**100**	**95**	**this study**

5.4. Preparation of compound **(9).**



A solution of intermediate **7** in DCM, reagent **8** (nosyl chloride) was dissolved in DCM, and sodium bicarbonate dissolved in water were charged in three different syringes. Mixed through X-mixer and passed through PFA tubular reactor placed in heating condition (figure S7). The three solutions were pumped by varying flow rate and molar ratio to maintain the stoichiometry. Optimization conditions were varied depending on the molar solutions, temperature, and pressure etc. (Table 4).

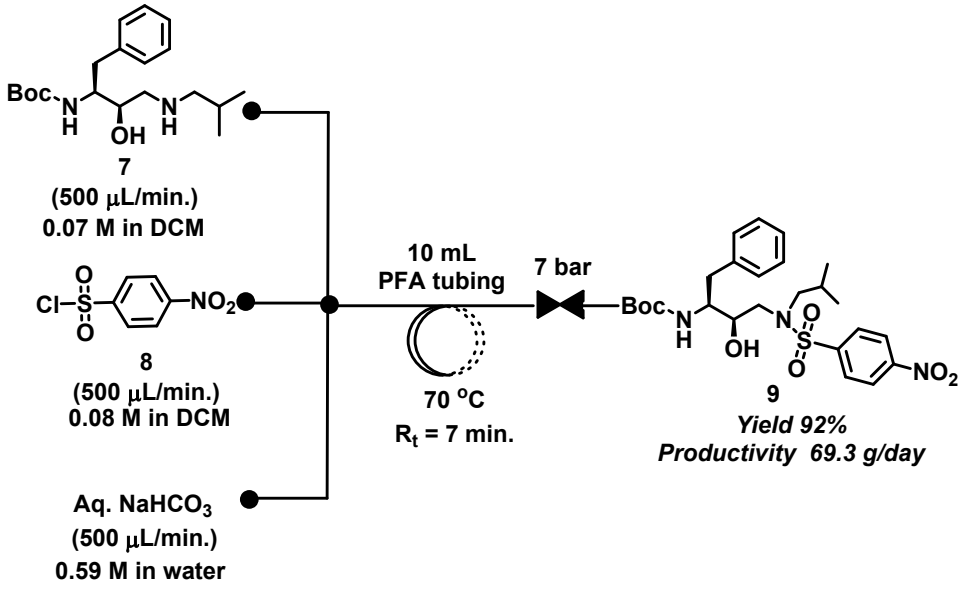


Figure S7. Schematic presentation of continuous flow synthesis of compound **9**.

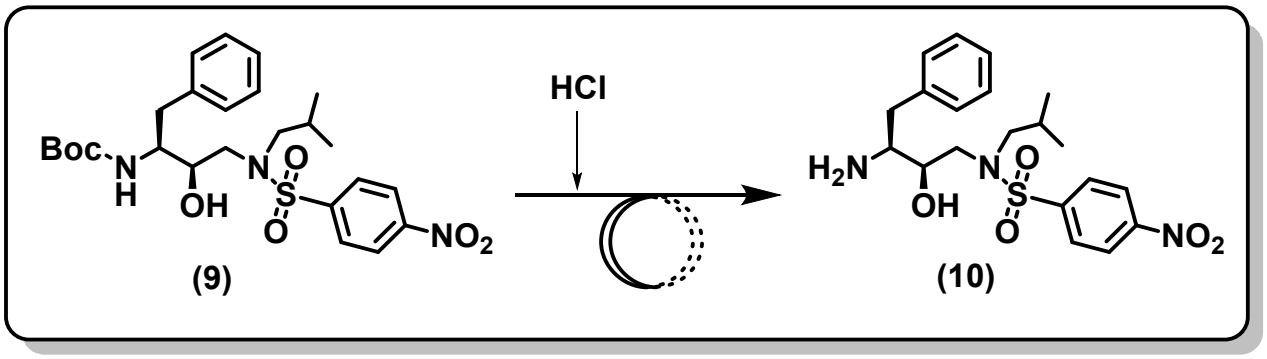
A 0.07 M solution of intermediate **7** in DCM, 0.08 M solution of reagent **8** (nosyl chloride) in DCM and 0.59 M solution of sodium bicarbonate in water were charged in three different syringes (figure S7). The three solutions were pumped to a X-mixer in a flow rate with the ratio of 1:1.1:8.4 (intermediate **7**: reagent **8**: aq. $NaHCO_3$) to maintain the stoichiometry, and then passed through a PFA tubing (id = 1000 µm, l = 12.8 m, vol. = 10 mL) to complete reaction in 7 min. residence time and 70 °C and 7 bar pressure (Table 4, entry 6). The resulting solution was extracted through the regular process and was purified by column chromatography with DCM/Methanol (99:1) to yield intermediate **9** as a pale-yellow solid having yield 92% and **mp**: 169-170 °C. Under the stable condition the product was collected for 1 h and experiment was repeated for three times. The yield is based on average of three analysis. $[a]_D^{25}$ = +10.20 (c = 1.00, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.33 (d, J = 8.9 Hz, 2H), 7.96 (d, J = 8.9 Hz, 2H), 7.33 – 7.29 (m, 2H), 7.24 – 7.22 (m, 3H), 4.63 (d, J = 7.1 Hz, 1H), 3.82 – 3.76 (m, 3H), 3.20 (d, J = 5.5 Hz, 2H), 2.99 (d, J = 7.6 Hz, 2H), 2.95 – 2.86 (m, 2H), 1.93 – 1.83 (m, 1H), 1.36 (s, 9H), 0.88 (dd, J = 6.6, 4.9 Hz, 6H). **^{13}C**

NMR (101 MHz, $CDCl_3$) δ 156.5, 150.1, 145.1, 137.6, 129.5, 128.8, 128.7, 126.8, 124.4, 80.3, 72.4, 57.7, 55.4, 52.7, 35.8, 28.4, 27.1, 20.1, 20.0. **IR (ν_{max}):** 3560.01, 3358.99, 2975.62, 1696.61 cm^{-1}. **HRMS (ESI):** *m/z* calcd for **$C_{25}H_{34}N_3NaO_7S$** $(M+Na)^+$ 544.2088, Found 544.2099. Analytical data are well matched with reported literature.[3]

Table S4. Comparative synthesis of intermediate **9** in batch and continuous flow process.

Entry	Process	Base	Time (min.)	Yield %	Ref
1	batch	Aq. $NaHCO_3$	1260	100	[3]
2	batch	DIEA, DMAP	240	98	[15]
3	batch	Aq. $NaHCO_3$	720	96	[19]
4	batch	DIEA, DMAP	330	91	[18]
5	batch	TEA	750	88	[16]
6	batch	DIEA, DMAP	300	91	[17]
7	**flow**	**Aq. $NaHCO_3$**	**7**	**92**	**this study**

5.5. Preparation of compound **(10).**



A solution of intermediate **9** in DCM was charged in one syringe. And solution of HCl in water: IPA was charged in another syringe. After mixing at T- mixer and passed through PFA tubular reactor placed in heating condition (figure S8). The two solutions were introduced by varying flow rate and molar ratio to maintain the stoichiometry. Optimization conditions were varied depending on the molar solutions, temperature, and pressure etc. (Table 5)

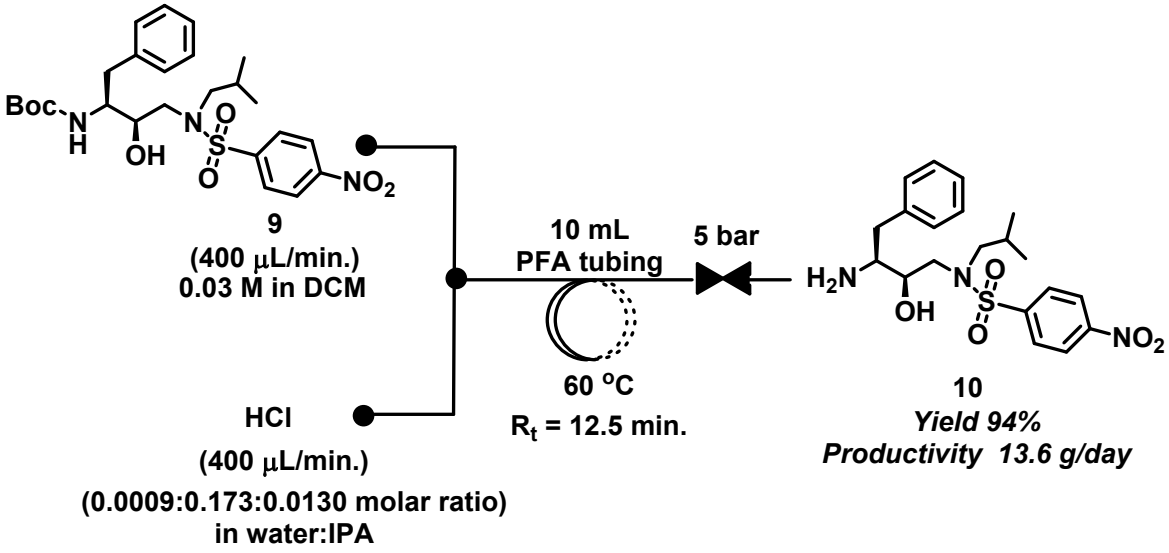


Figure S8. Schematic presentation of continuous flow synthesis of compound **10**.

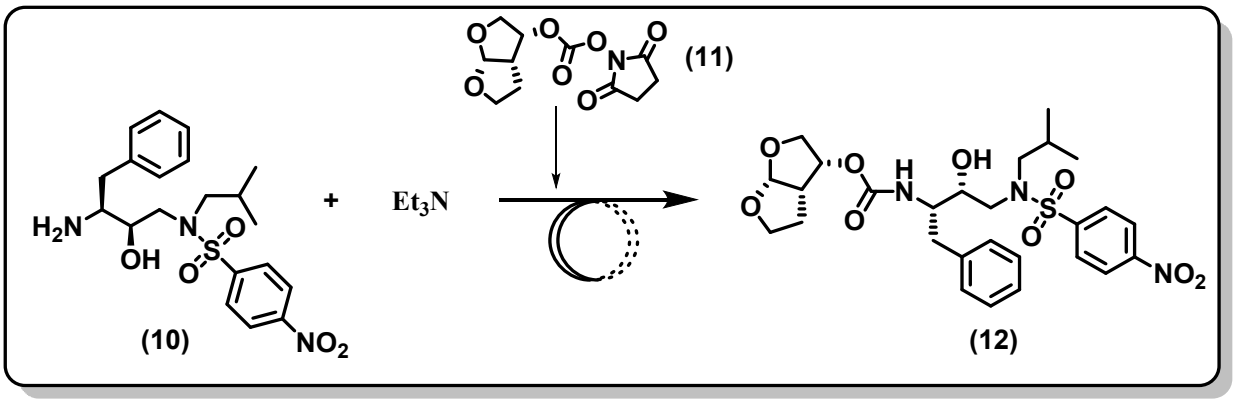
A 0.03M solution of intermediate **9** in DCM was charged in one syringe and another syringe was charged with solution of HCl in water: IPA (0.0009:0.173:0.0130 molar ratio) (figure S8). The two solutions were pumped to a T-mixer at same flow rate 400 µL/min. with the ratio of 1:30 (intermediate **9**: HCl) to maintain the stoichiometry, and then passed through a PFA tubing (id = 1000 µm, l = 12.8 m, vol. = 10 mL) to occur the reaction in 12.5 min. residence time and 60 °C and 5 bar pressure (Table 5, entry 10). The resulting solution was extracted through the actual reported procedure and was purified by column chromatography with DCM/Methanol (85:15) to yield intermediate **10** as a white solid having yield 94% and **mp**: 88-89 °C. Under the stable condition the product was collected for 1 h and experiment was repeated for three times. The yield is based on average of three analysis. $[a]_D^{25}$ = +10.50 (*c* = 1.00, $CHCl_3$). **^{1}H NMR (400 MHz, DMSO-d_6)** δ 8.38 (d, *J* = 8.9 Hz, 2H), 8.06 (d, *J* = 8.9 Hz, 2H), 7.93 (br s, 2H), 7.38 – 7.27 (m, 5H), 5.66 (d, *J* = 5.7 Hz, 1H), 3.97 – 3.90 (m, 1H), 3.48 – 3.36 (m, 2H), 3.09 – 2.97 (m, 3H), 2.89 – 2.77 (m, 2H), 1.92 – 1.85 (m, 1H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.76 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR (101 MHz, DMSO-d_6)** δ 151.6, 146.1, 137.2, 130.5, 130.2, 129.9, 128.5, 125.4, 70.0, 58.6, 56.8, 52.1, 33.6, 28.0, 20.3, 20.3. **IR (ν_{max}):** 3695.23, 3441.09, 2929.09 cm^{-1}. **HRMS (ESI):** *m/z* calcd for **$C_{20}H_{28}N_3O_5$ S** $(M+H)^+$ 422.1744, Found 422.1747. Analytical data are well matched with reported literature.[11]

Table S5. Comparative synthesis of intermediate **10** in batch and continuous flow process.

Entry	Process	Reagent	Time (min.)	Yield %	Ref
1	batch	TFA	180	100	[3]
2	batch	TFA	180	83	[18]
3	batch	TFA	120	69	[15]
4	batch	HCl	60	94	[4]

5	batch	TFA	180	83	[17]
6	**flow**	**HCl**	**12.5**	**94**	**this study**

5.6. Preparation of compound **(12).**



A solution of intermediate **10** and triethylamine (Et_3N) in DCM (dichloromethane) was charged in one syringe. Furfuranol **11** dissolved in DCM was charged in another syringe. The two solutions were introduced by varying flow rate and molar ratio to maintain the stoichiometry into the T-mixer and passed through PFA tubular reactor placed in heating condition (figure S9). Optimization conditions were varied depending on the molar solutions, temperature, and pressure etc. (Table 6).

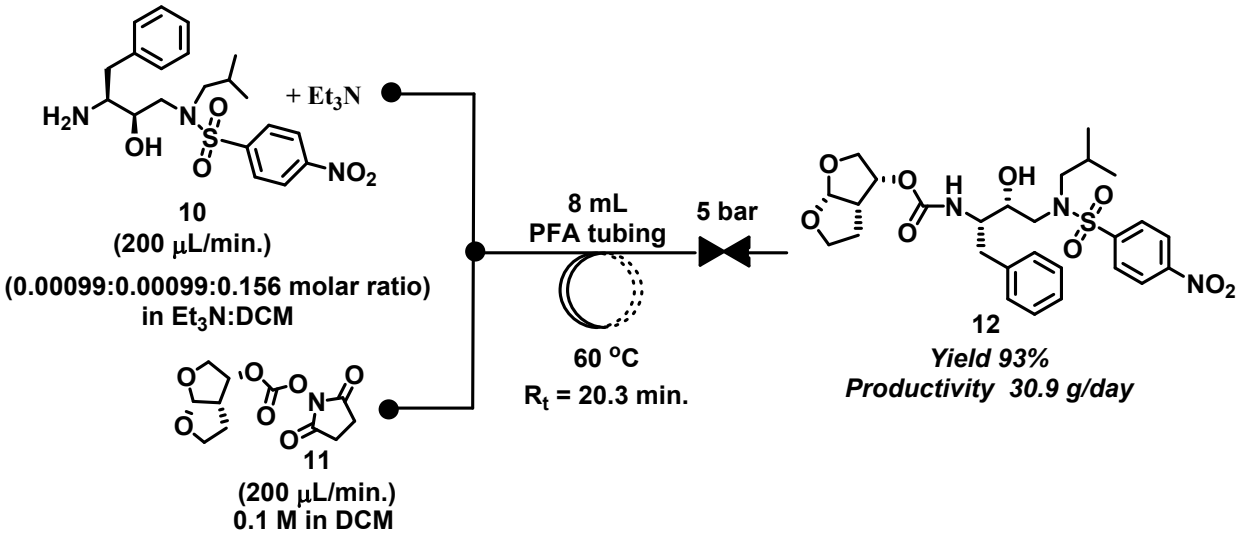


Figure S9. Schematic presentation of continuous flow synthesis of compound **(12)**.

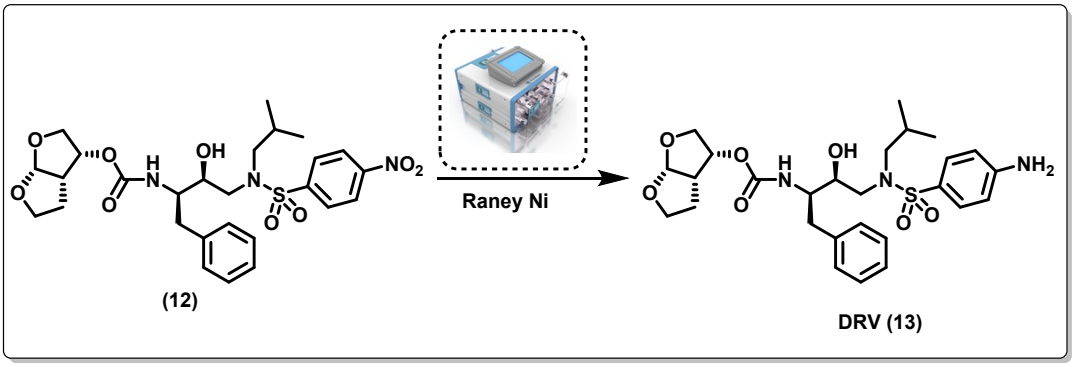
A 0.1 M solution of intermediate **10** in Et_3N: DCM (0.00099:0.00099:0.156 molar ratio) was charged in one syringe and another syringe was charged with solution of 0.1 M **11** in DCM (figure S9). The two solutions were introduced to a T-mixer in a flow rate with the ratio of 1:1 (intermediate **10**:**11**) to maintain the stoichiometry, and then passed through a PFA tubing (id = 1000 µm, l = 10.2 m, vol. = 8 mL) to occur the reaction in 20.3 min. residence time at 60 °C and 5 bar pressure (Table 6, entry 9). The resulting solution was extracted through the regular process and was purified by column chromatography with DCM/Methanol (95:05) to yield intermediate **12** as a white solid having yield 93% and **mp**: 114-115 °C. Under the stable condition the product was collected for 1 h and experiment was repeated for three times. The yield is based on average of three analysis. $[a]_D^{25}$ = -12.9 (*c* = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.36 (d, *J* = 8.9 Hz, 2H), 7.97 (d, *J* = 8.9 Hz, 2H), 7.32 – 7.20 (m, 5H), 5.65 (d, *J* = 5.2 Hz, 1H), 5.06 – 4.95 (m, 2H), 3.97 – 3.82 (m, 4H), 3.74 – 3.65 (m, 2H), 3.43 (br s, 1H), 3.26 – 3.14 (m, 2H), 3.10 – 2.88 (m, 4H), 2.82 – 2.77 (m, 1H), 1.93 – 1.83 (m, 1H), 1.71 – 1.65 (m, 1H), 1.50 – 1.45 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 155.8, 150.3, 144.6,

137.5, 129.4, 128.8, 128.7, 126.9, 124.6, 109.4, 73.8, 72.7, 71.0, 69.7, 58.2, 55.5, 53.2, 45.5, 35.7, 27.2, 26.0, 20.2, 20.0. **IR (ν_{max}):** 3343.73, 2960.96, 2873.66, 1701.10, 1530.17 cm^{-1}. **HRMS (ESI):** *m/z* calcd for **$C_{27}H_{36}N_3O_9S$** $(M+H)^+$ 578.2167, Found 578.2170. Analytical data are well matched with reported literature.[3]

Table S6. Comparative synthesis of intermediate **12** in batch and continuous flow process..

Entry	Process	Time (min.)	Temp. (°C)	Yield (%)	Ref.
1	batch	1140	25	95	[3]
2	batch	1440	25	90	[4]
3	**flow**	**20.3**	**60**	**93**	**this study**

5.7. Preparation of compound Darunavir **(13)**.



A solution of intermediate **12** in protic solvent was charged in one syringe. Solution was passed through H-cube (cartridge filled with Raney Ni) for nitro reduction reaction. The solution was introduced in a varied flow rate and ratio to maintain the stoichiometry, the solution passed metal cartridge filled with Raney Ni for hydrogenation and reduction (figure S10). Optimization conditions were varied depending on the molar solutions, temperature, and pressure etc. (Table 7)

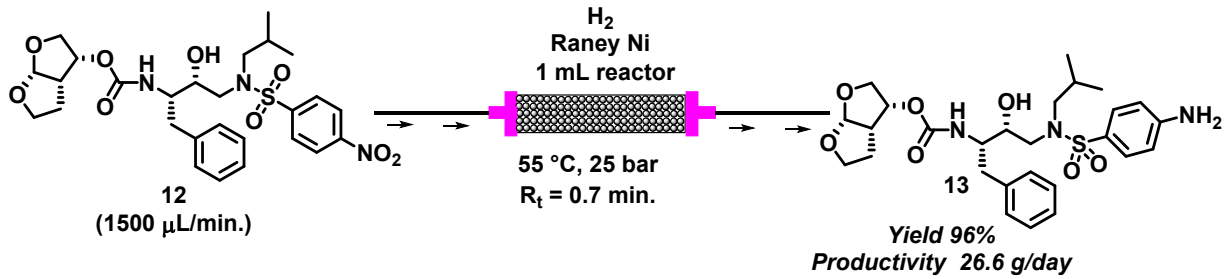


Figure S10. Schematic presentation of continuous flow hydrogenation of darunavir intermediate **12**.

A 0.02 M solution of intermediate **12** in methanol (MeOH) was charged in one syringe. Solution passed through H-cube wherein the metal cartridge was filled with Raney Ni, for hydrogenation reaction for 0.7 min. of residence time at 55 °C and 25 bar pressure (Table 7, entry 5). The resulting solution was extracted through the regular process and was purified by column chromatography with hexane/ethyl acetate (10:90) to yield **DRV (13)** as a white solid having yield 96% and **mp**:

78-79 °C. Under the stable condition the product was collected for 1 h and experiment was repeated for three times. The yield is based on average of three analysis. $[a]_D^{25}$ = +1.00 (*c* = 1.00, $CHCl_3$). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.54 (d, *J* = 8.7 Hz, 2H), 7.29 – 7.26 (m, 2H), 7.22 – 7.18 (m, 3H), 6.68 (d, *J* = 8.7 Hz, 2H), 5.64 (d, *J* = 5.2 Hz, 1H), 5.03 – 4.95 (m, 2H), 4.17 (br s, 2H), 3.97 – 3.83 (m, 4H), 3.71 – 3.66 (m, 3H), 3.17 – 3.06 (m, 2H), 2.98 – 2.87 (m, 3H), 2.82 – 2.76 (m, 2H), 1.85 – 1.79 (m, 1H), 1.61 – 1.59 (m, 1H), 1.49 – 1.45 (m, 1H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 155.6, 150.9, 137.8, 129.7, 129.5, 128.7, 126.7, 126.2, 114.3, 109.4, 73.5, 73.0, 71.0, 69.8, 59.1, 55.3, 53.9, 45.5, 35.8, 27.5, 26.0, 20.3, 20.1. **IR (ν_{max}):** 3469.61, 3364.95, 2927.01, 1709.62, 1597.78 cm^{-1}. **HRMS (ESI):** *m/z* calcd for **$C_{27}H_{38}N_3O_7S$** $(M+H)^+$ 548.2425, Found 548.2431. Analytical data are well matched with reported literature.[3]

Table S7. Comparative synthesis of intermediate **13** in batch and continuous flow process.

Entry	Process	Reagent	Time (min.)	Temp. (°C)	Yield (%)	Ref
1	batch	Pd/C	1440	25	95	[3]
2	batch	Pd/C	60	25	99	[4]
3	**Flow**	**Raney Ni**	**0.7**	**55**	**96**	**This study**

6. Integrated multistep synthesis of darunavir without intermediate purification:

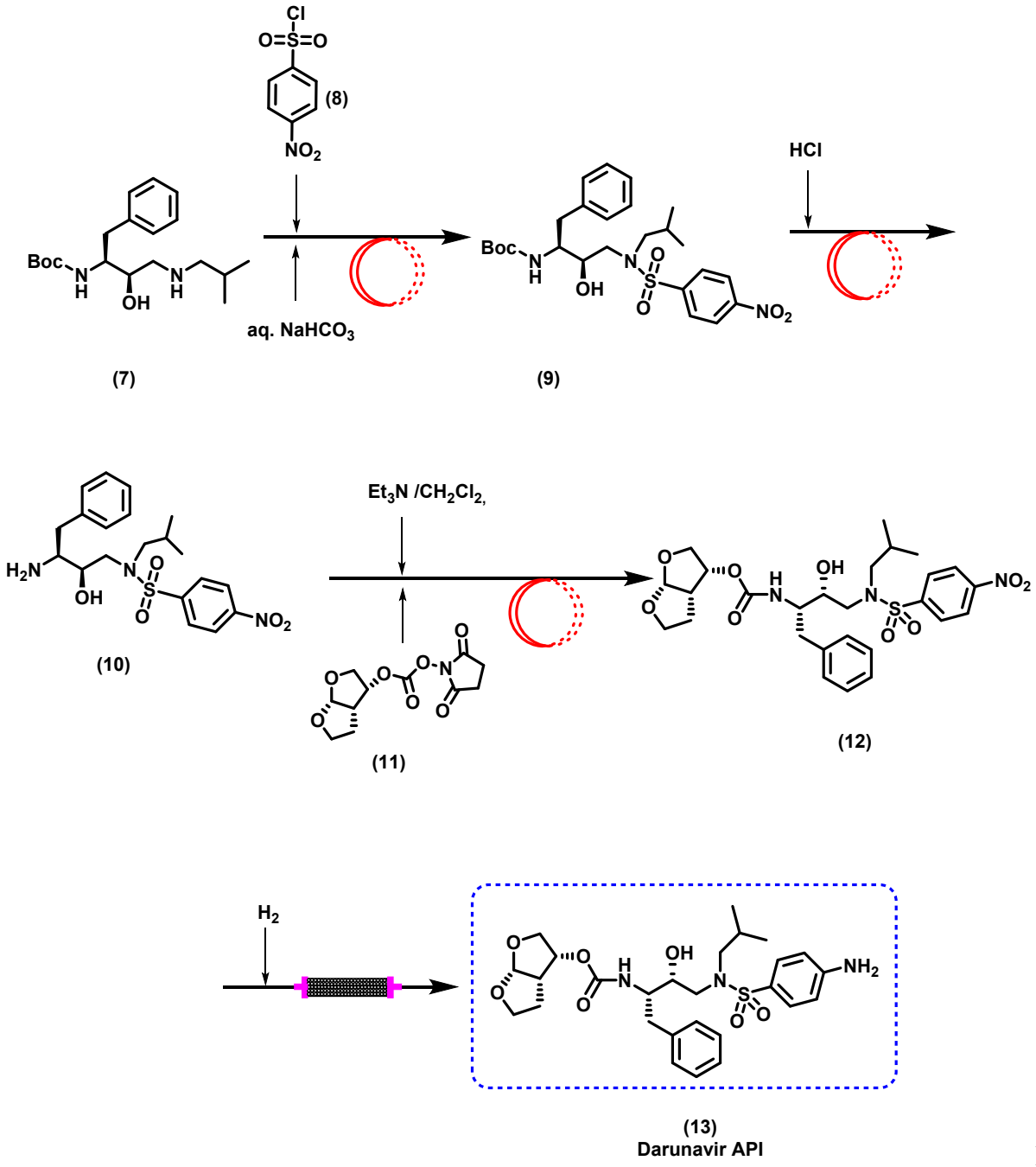


Figure S11. Schematic presentation of integrated continuous flow process for the synthesis of Darunavir.

A solution of compound **7** in DCM, solution of intermediate **8** in DCM and solution of $NaHCO_3$ in water were pumped through pumps. The three solutions were introduced into X_1-mixer in an optimized flow rate and ratio to maintain stoichiometry, and then passed through PFA tubular reactor for the reaction to occur. Then the solution was passed through a liquid-liquid separator $\mathbf{S_1}$ to separate aqueous and organic layer. The out coming crude reaction mixture **9** was interconnected with pump and pre-optimized solution of HCl in water: IPA was pumped through another pump, mixing at T_1- mixer in an optimized flow rate and ratio to maintain stoichiometry, and then passed through PFA tubular reactor. The crude reaction mixture **10** was quenched with water by mixing water at T_2-mixer to remove remaining HCl in reaction mixture and then passed through second liquid-liquid separator $\mathbf{S_2}$ to separate aqueous and organic layer. Now out-coming crude reaction mixture **10** (organic layer) was interconnected with pump and pre-optimized solution of furfuranol **11** in DCM and TEA in DCM were pumped through syringe pump and mixed at X_2- mixer in an optimized flow rate and ratio to maintain stoichiometry, and then further passed through PFA tubular reactor following optimized parameters. To the out coming crude reaction mixture **12**, MeOH was added at pre optimized flow rate and then the total reaction mixture was pumped through a pump and passed through H-cube having metal cartridge with reducing agent in a varied flow rate and ratio to maintain stoichiometry, and then the outgoing reaction mixture was collected in conical flask.

6.1. Integrated DRV synthesis machine process system. A solution of intermediate **7** in dichloromethane (DCM; 0.07 M) , solution of reagent **8** (0.08 M nosyl chloride in DCM) and a solution of $NaHCO_3$ (0.59 M in water) were introduced into the microreactor with a X_1-mixer using three separate pumps. The flow rate of the intermediate **7** solution was 500 μL/min., flow rate of the reagent **8** solution was 500 μL/min. and the flow rate of solution of $NaHCO_3$ was 500 μL/min. The three solutions were introduced to a X_1-mixer in a flow rate with the ratio of 1:1.1:8.4 (intermediate **7**: reagent **8**: Aq. $NaHCO_3$) to maintain the stoichiometry, and then passed through a PFA tubing (id = 1000 μm, l = 12.8 m, vol. = 10 mL) to occur the sulfonylation during 6.66 min. of residence time and 70 ^oC temperature and 7 bar pressure. Further the aqueous and DCM continuous flow droplet was separated through micro-separator S_1 which is reported by our labs previously.[20] A residence time of 0.5 min., 1 bar pressure was found to be enough for the aqueous waste removal of the crude organic solution of intermediate **9**. Out-flowing crude mixture of intermediate **9** from first step and premixed solution of HCl in water: IPA (0.0009:0.173:0.0130 molar ratio), were mixed in a T_1-shaped mixer and the combined mixture went through PFA tubing (id = 1000 μm, l = 12.2 m, vol. = 10 mL). The flow rate of crude reaction mixture intermediate **9** was 1000 μL/min., and flow rate of HCl was 150 μL/min., A residence time of 12.5 min., temperature 60 ^oC, and 5 bar pressure was found enough for the *N*-Boc deprotection and synthesis of intermediate **10**. A residence time of 2.3 min., 25 ^oC was found to be enough for the quenching of the intermediate **10** with water at 1000 μL/min. flow rate. Further the aqueous and DCM continuous flow droplet were separated through our labs previously reported micro-separator S_2. A residence time of 0.5 min., 1 bar pressure was found to be enough for the aqueous waste removal of the crude organic solution of intermediate **10**. The outflowing crude solution of intermediate **10** from above in DCM, solution intermediate **11 (**0.1 M in DCM) and trimethylamine were dissolved

in DCM (0.1 M). Crude organic solution of intermediate **10**, intermediate **11**, and trimethylamine were mixed in a X_2-shaped mixer and the combined mixture went through PFA tubing (id = 1000 μm, l = 38 m, vol. = 30 mL). The flow rates of crude reaction mixture intermediate **10** are 1000 μL/min., flow rate of intermediate **11** and trimethylamine are 280 μL/min., each shown above in the figure S11. A residence time of 20.3 min. temperature 60 ^{o}C, and 5 bar pressure was found enough for the synthesis of intermediate **12**. The processed mixture left the flow reactor as a one phase DCM solution. The outflowing crude reaction mixture of intermediate **12** from above is in DCM, with 1000 μL/min. flow rate MeOH was mixed and the resulting reaction mixture passes through 2560 μL/min. flow rate and passed through H-cube and cartridge filled with Raney Ni. A 0.4 min. of residence time, temperature of 55 ^{o}C, and 25 bar pressure was found enough for the synthesis of darunavir in ultra-rapid manner within 41 min. of total time. Under the stable condition the out-flowing reaction mixture from the H-cube was collected for 1 h time (volume 153 ml). The solvent was removed under reduced pressure and additional 20 mL DCM were added. The reaction mixture further washed with water (30 mL) then washed with brine solution (30 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure.

Crude mixture HPLC yield = 86±1%

The product was purified using flash column chromatography on 200–300-mesh silica gel with hexane/ethyl acetate as an eluent.

The obtained product weight (mg/h) = 815

Theoretical weight (mg/h) = 0.07 × 0.5 × 60 × 547 = 1148

isolated yield (%) = 815/1148 = 71

Productivity (mmol/h) = 815/547 = 1.48

Table S8. Comparison of Integrated Darunavir synthesis with Batch and Continuous Flow Process.

Entry	Process	Overall time (min.)	Overall yield (%)	Reference
1	batch	4320	90	[3]
2	batch	1602	82	[19]
3	batch	1320	38	[21]
4	**Continuous flow**	**41**	**71**	**This study**

7. Spectra

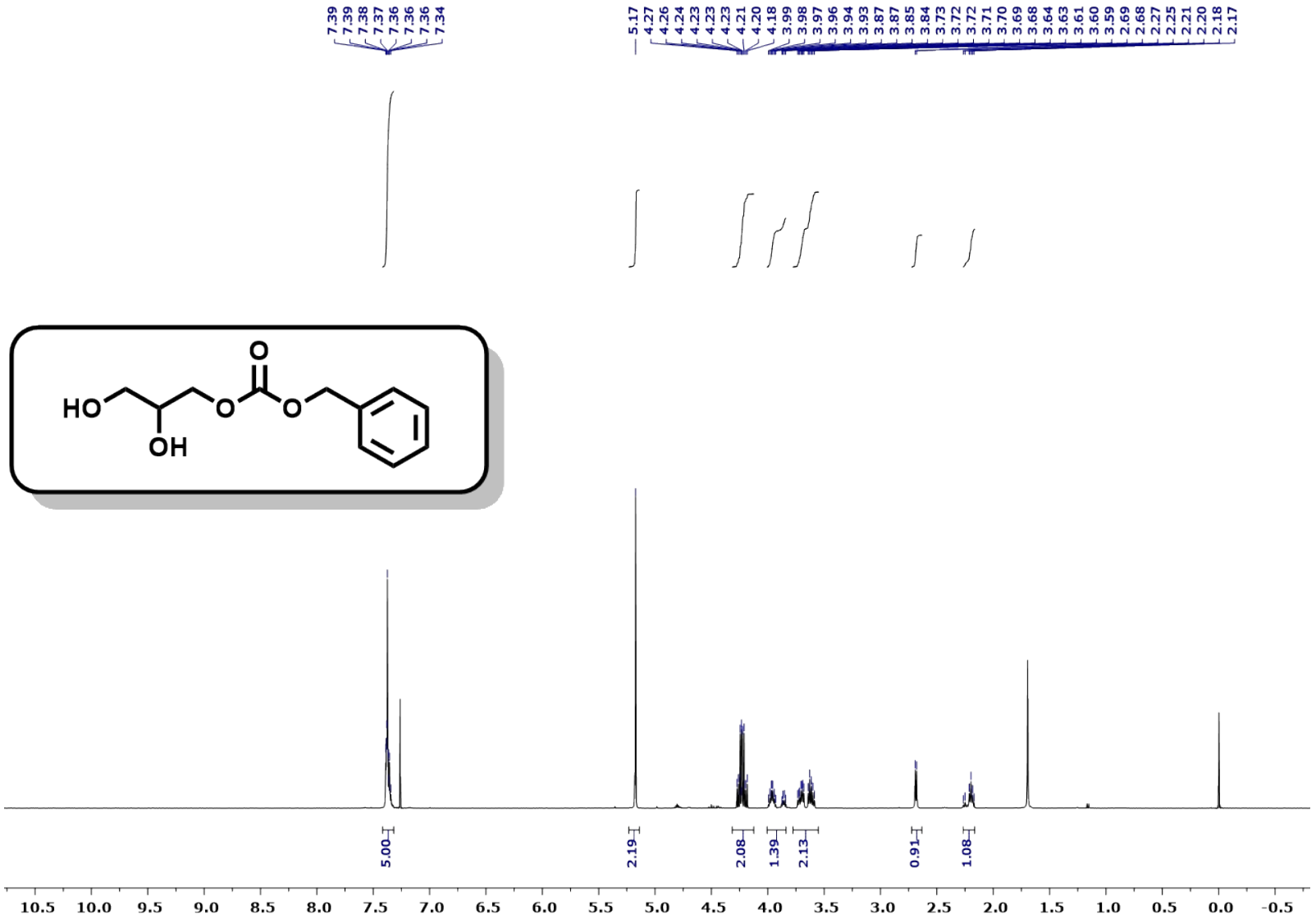


Fig. S12. ^{1}H NMR (400 MHz, $CDCl_3$) spectra of Benzyl (2,3-dihydroxypropyl) carbonate **(11b)**.

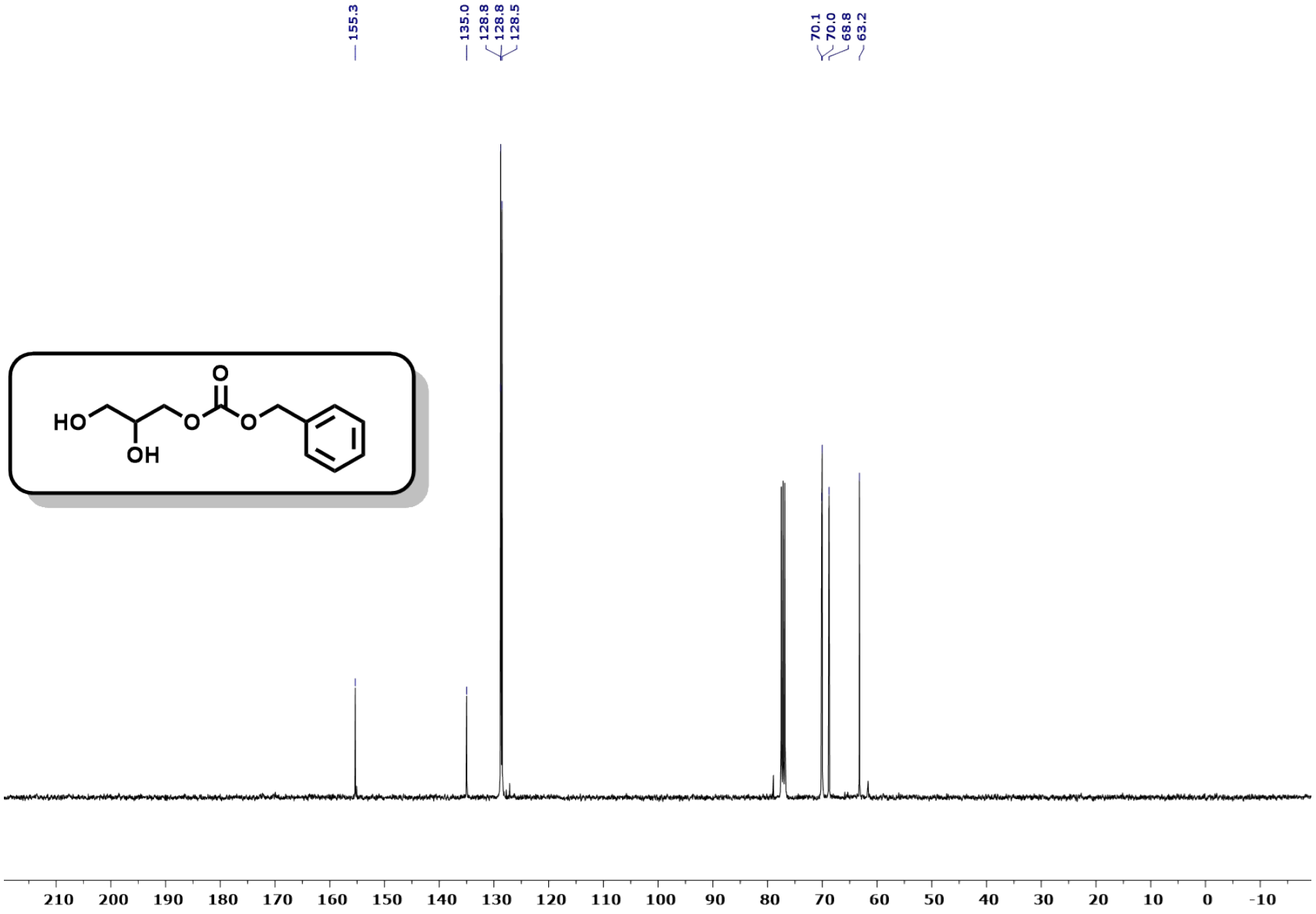


Fig. S13. ^{13}C NMR (101 MHz, $CDCl_3$) spectra of Benzyl (2,3-dihydroxypropyl) carbonate **(11b)**.

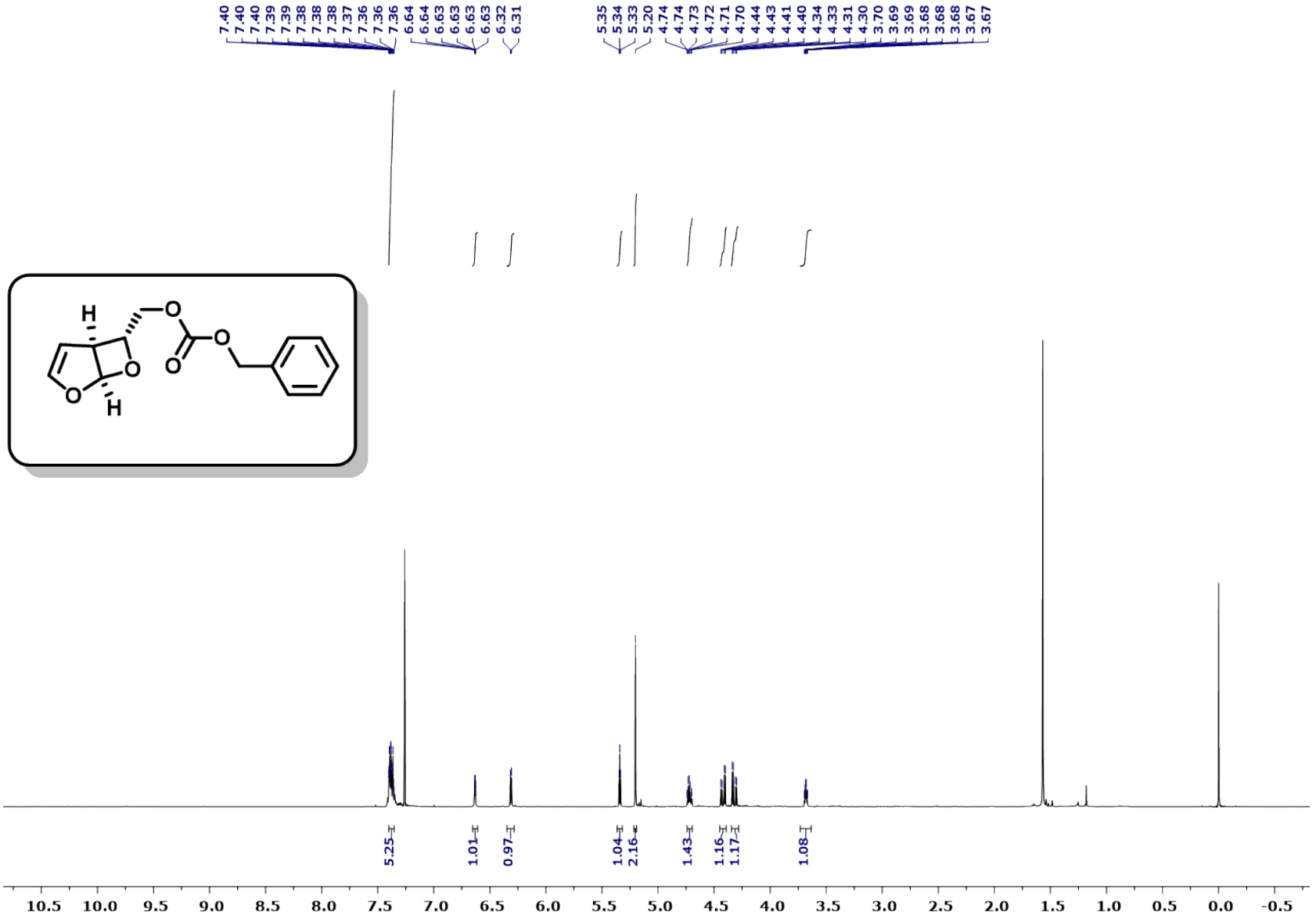


Fig. S14. ^{1}H NMR (400 MHz, $CDCl_3$) spectra of exo-2,7-Dioxabicyclo[3.2.0]hept-3-en-6-yl)methyl benzyl carbonate((±)-**11d)**.

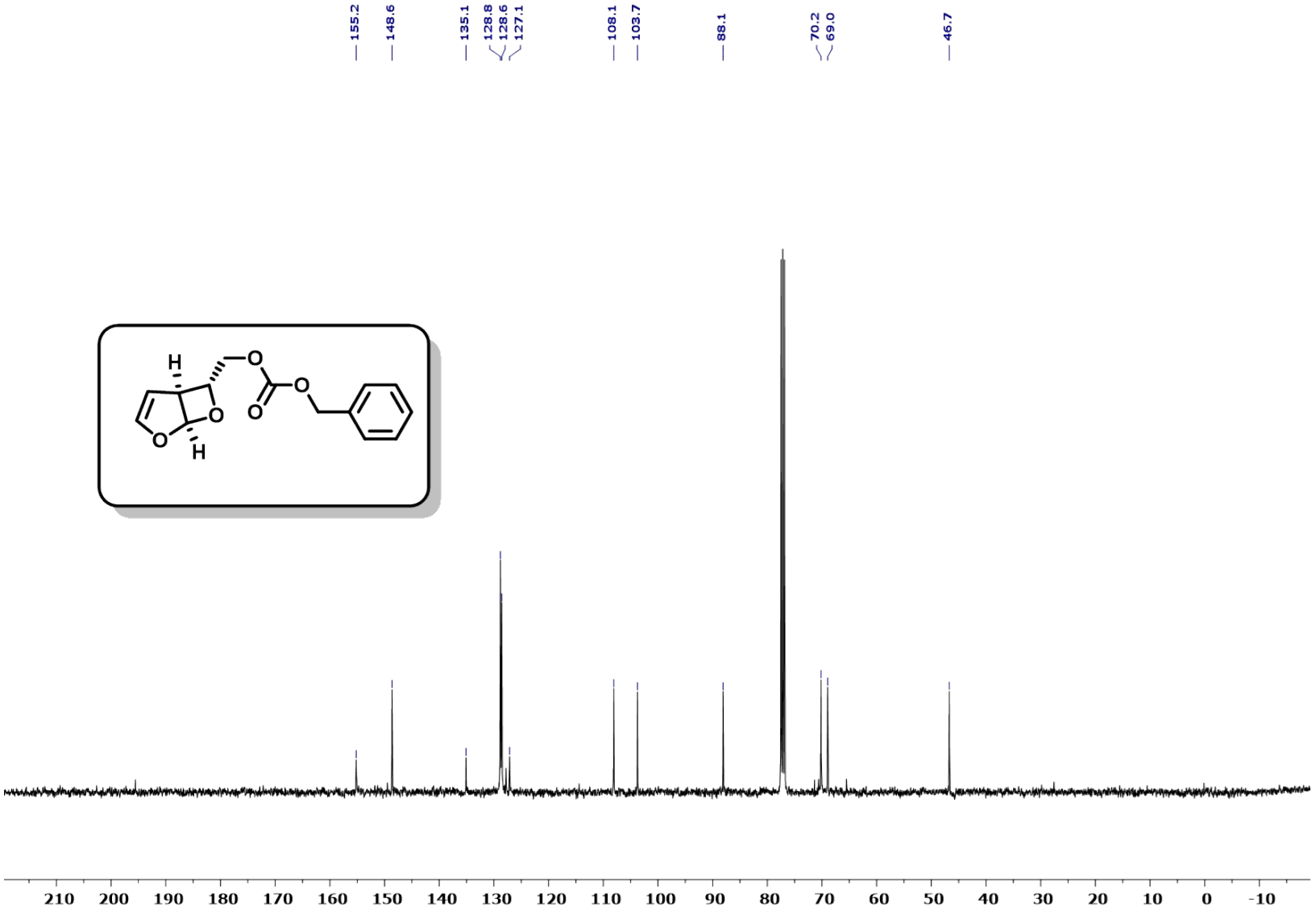


Fig. S15. ^{13}C NMR (101 MHz, $CDCl_3$) spectra of exo-2,7-Dioxabicyclo[3.2.0]hept-3-en-6-yl)methyl benzyl carbonate ((±)-**11d)**.

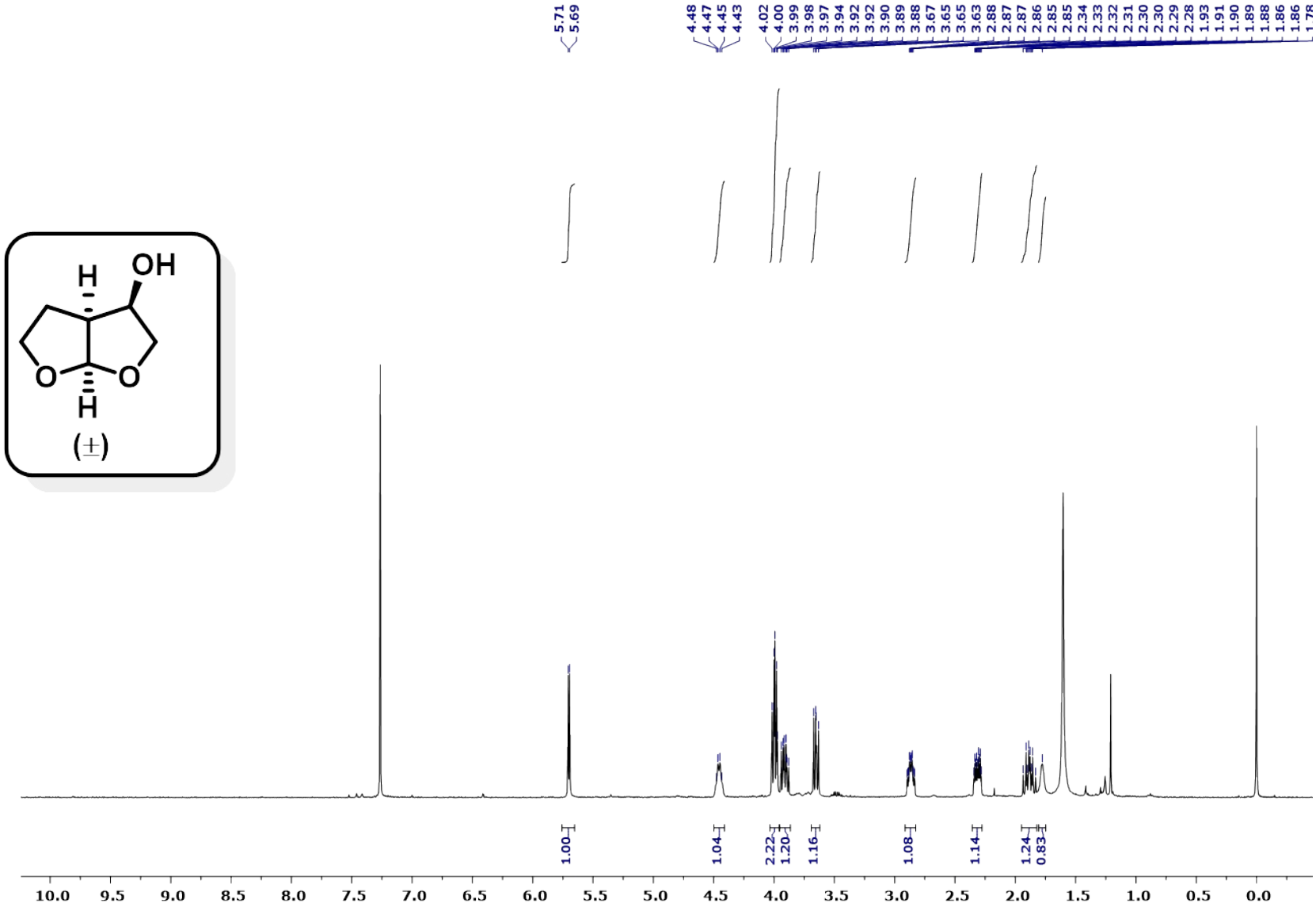


Fig. S16. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of anti-hexahydrofuro[2,3-b] furan-3-ol ((±)-(**11e**).

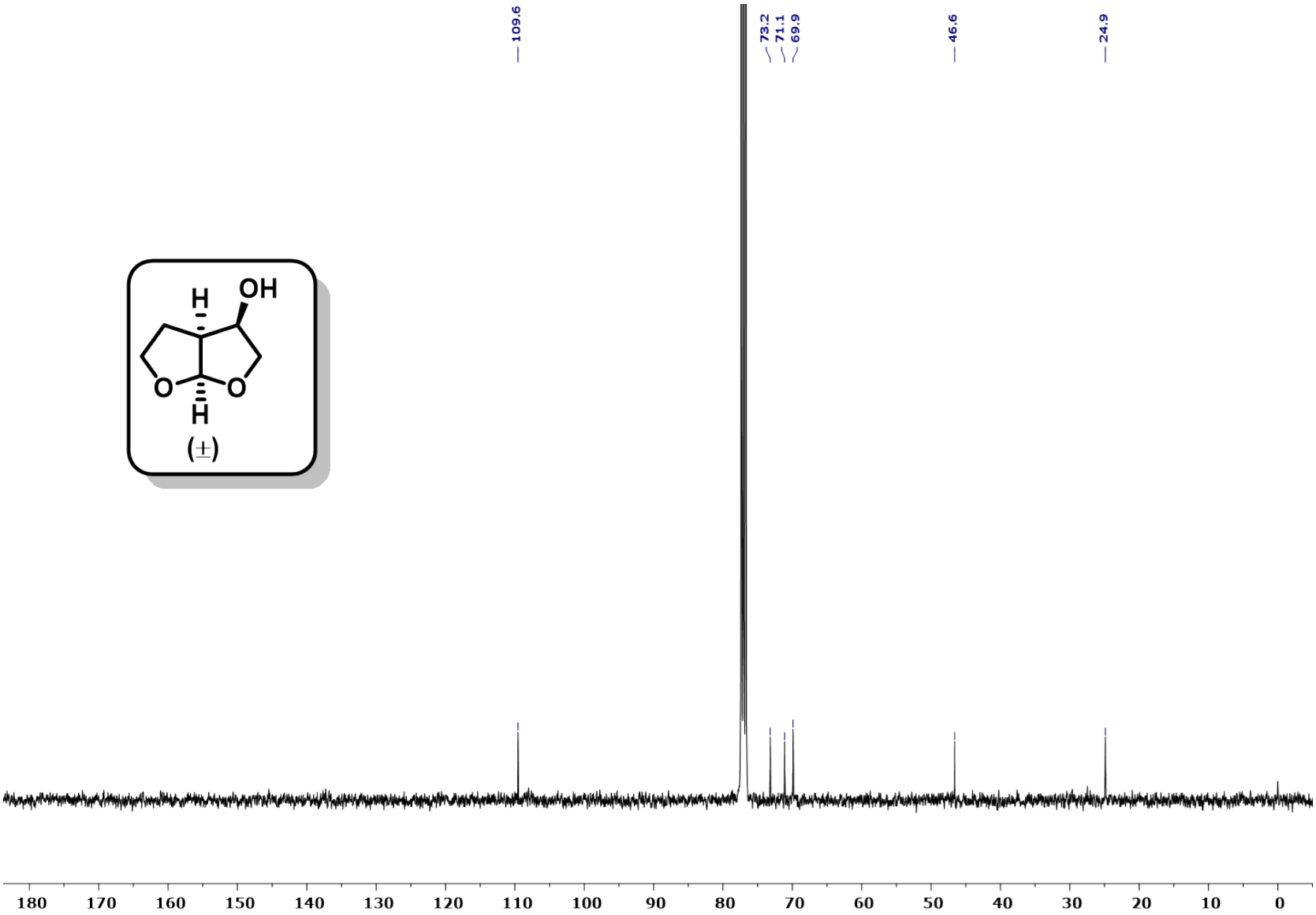


Fig. S17. ^{13}C NMR (101 MHz, $CDCl_3$) spectra of anti-hexahydrofuro[2,3-b] furan-3-ol ((±)-(**11e**).

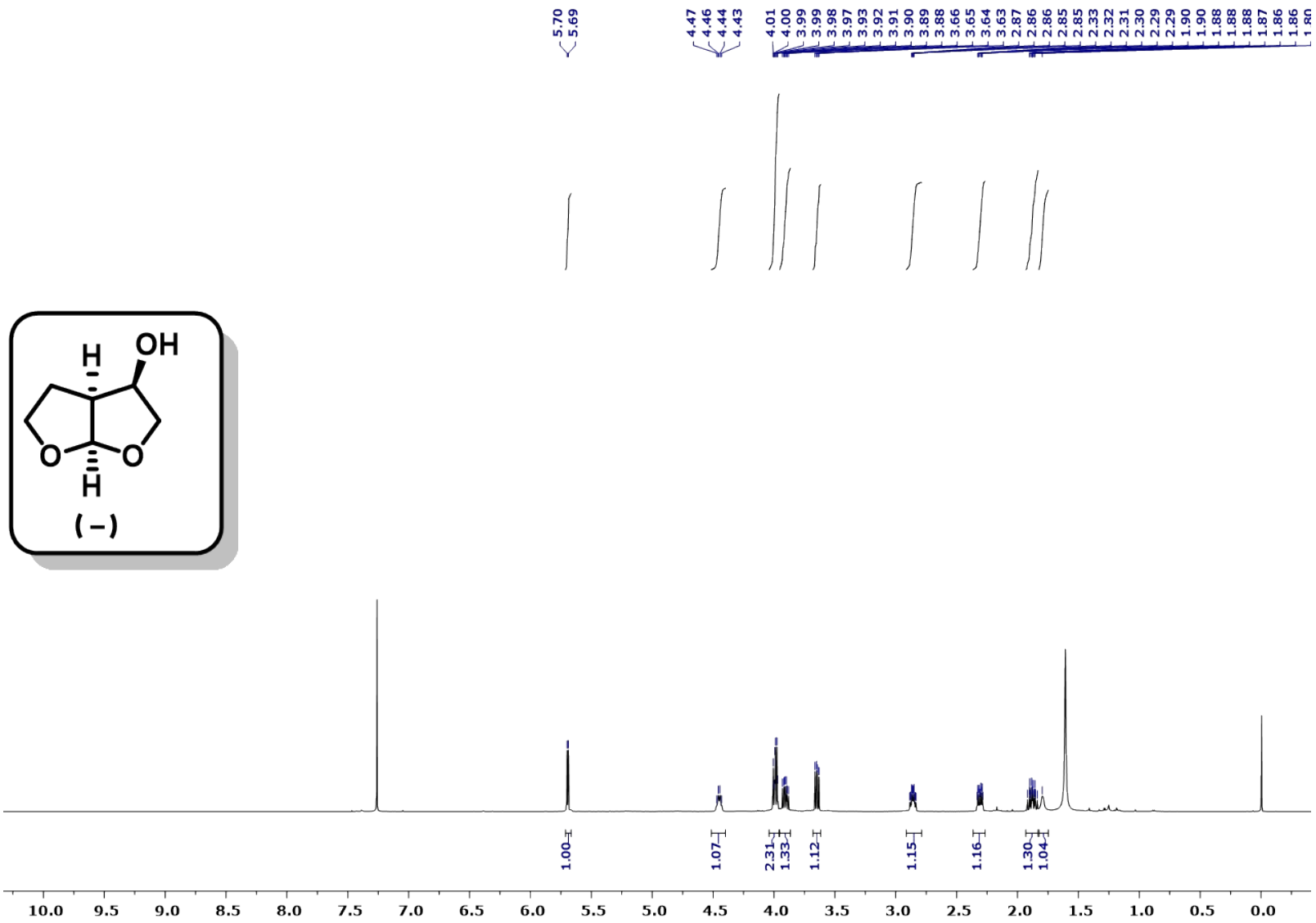


Fig. S18. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of (3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-b]furan-3-ol ((**–**)-**11f**).

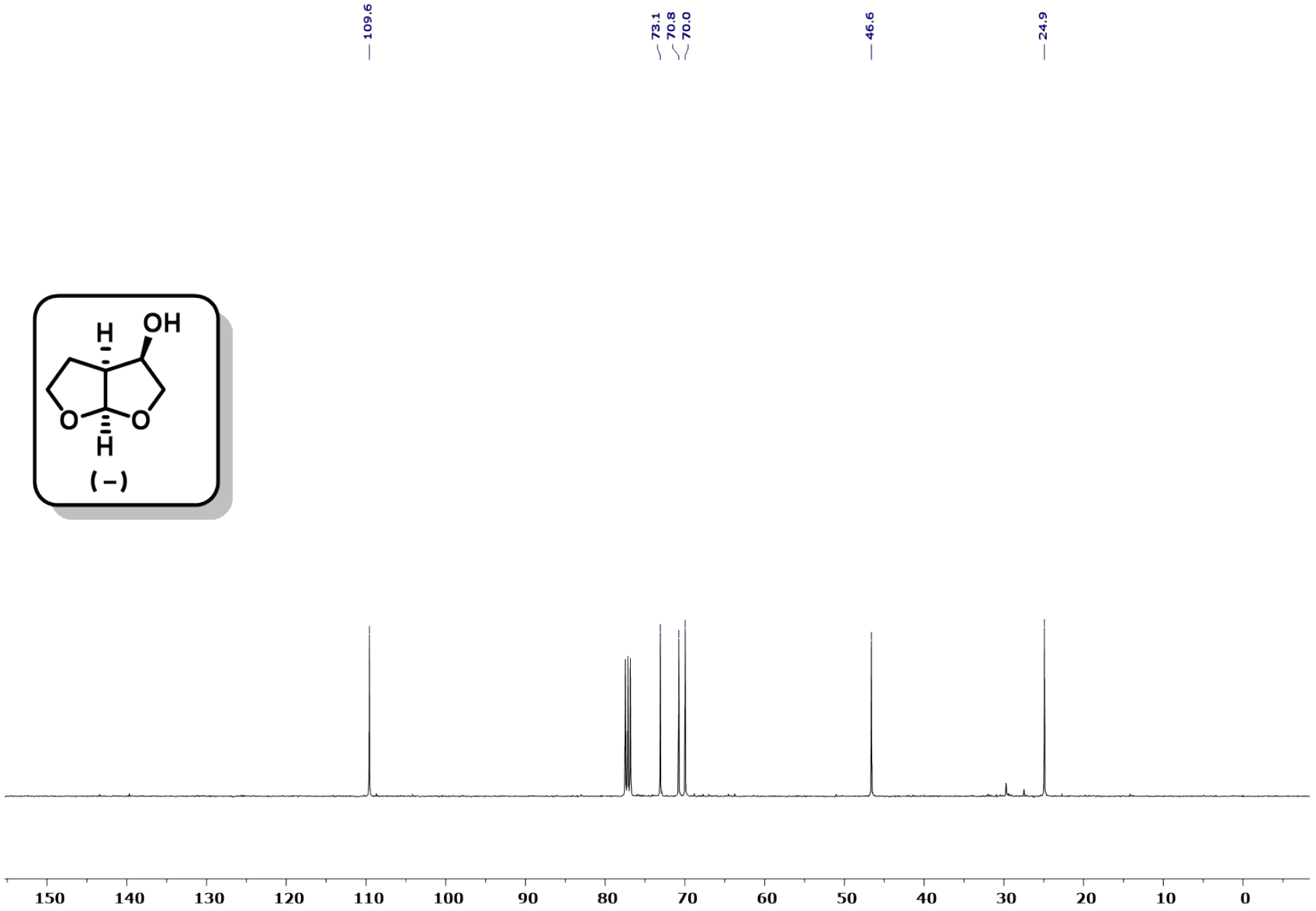


Fig. S19. ^{13}C NMR (101 MHz, $CDCl_3$) spectra of (3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-b]furan-3-ol ((**–**)-**11f)**.

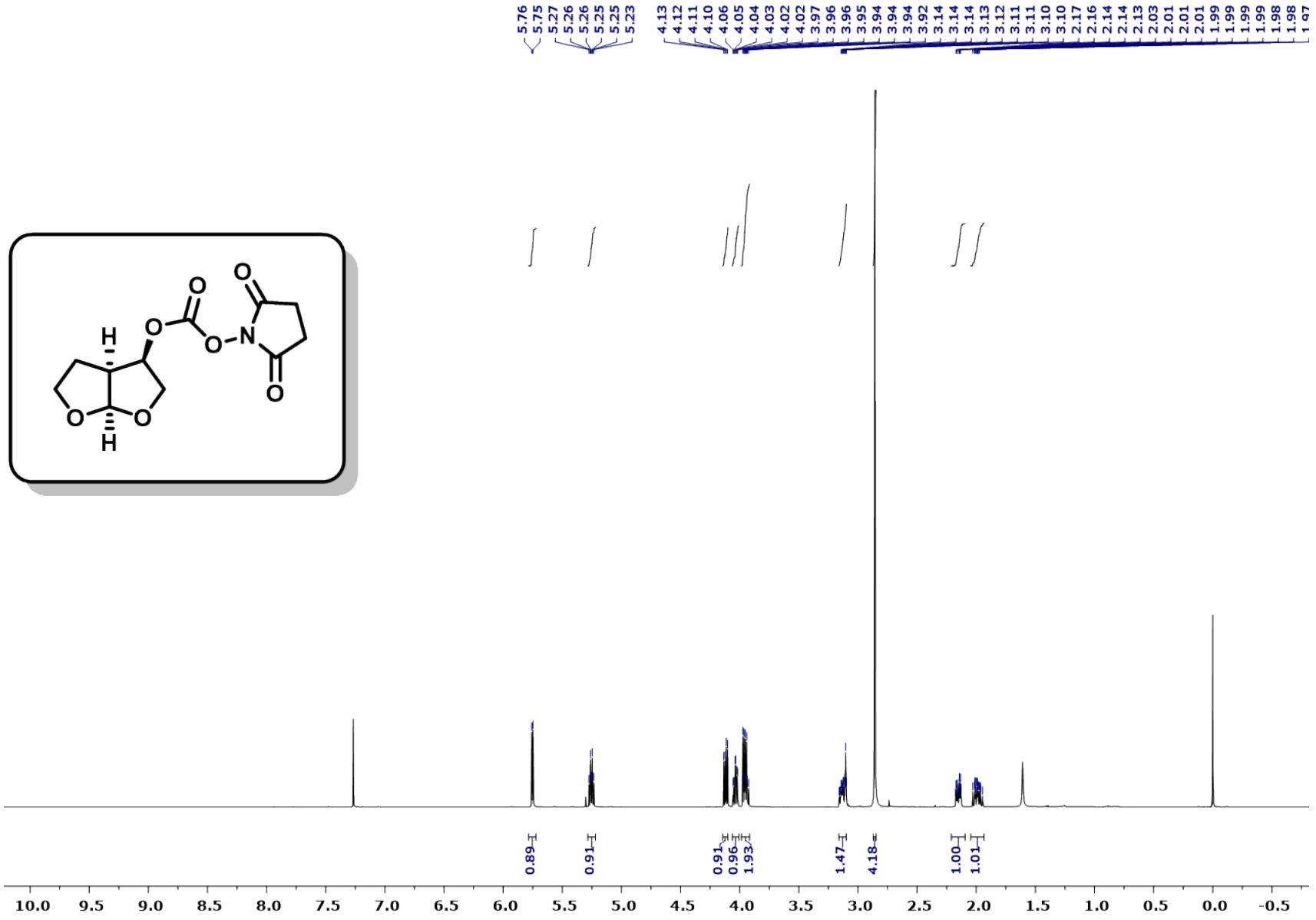


Fig. S20. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of 2,5-Dioxopyrrolidin-1-yl ((3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-b]furan-3-yl) carbonate **(11)**.

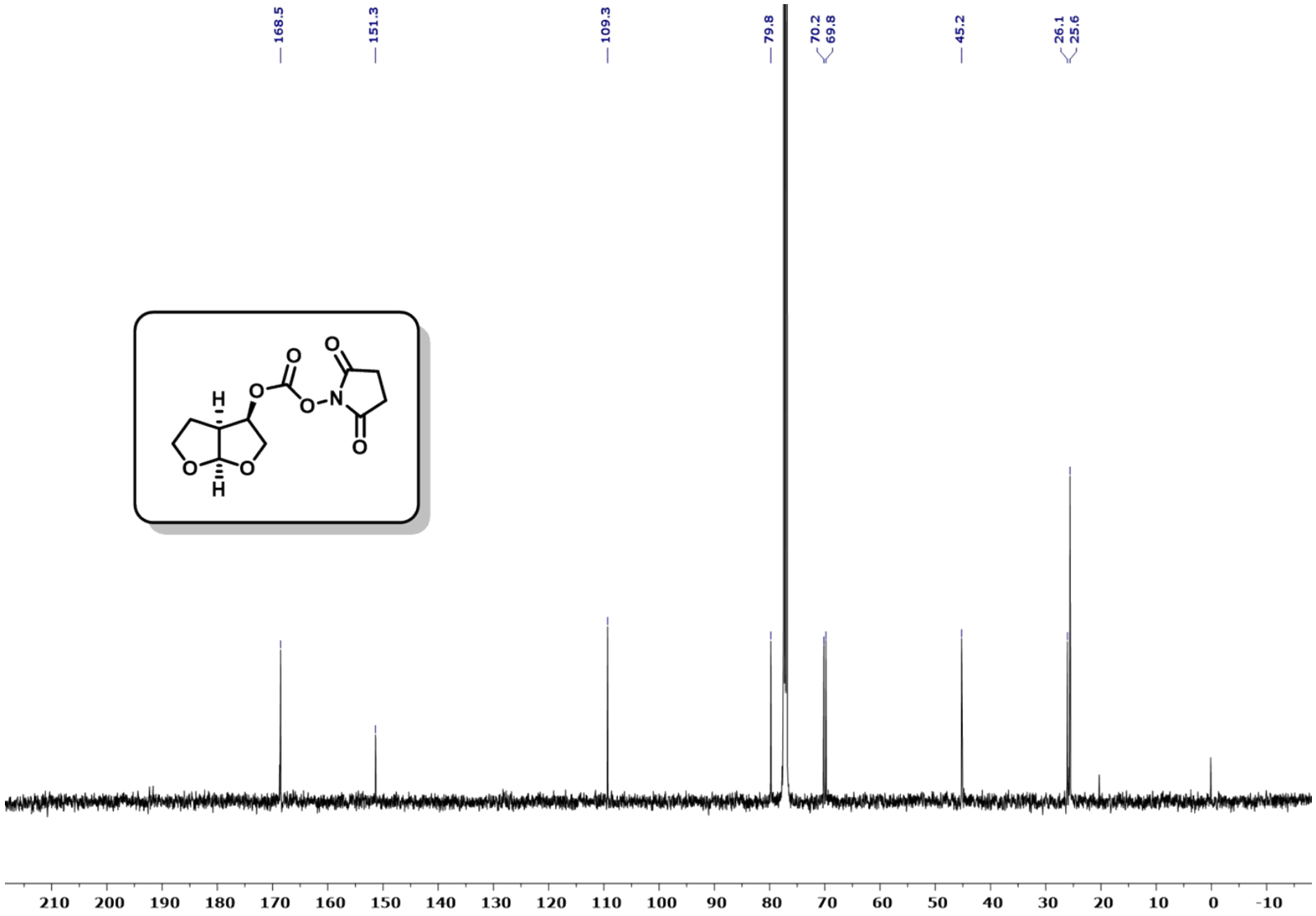


Fig. S21. ^{13}C NMR (101 MHz, $CDCl_3$) spectra of 2,5-Dioxopyrrolidin-1-yl ((3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-b]furan-3-yl) carbonate **(11)**.

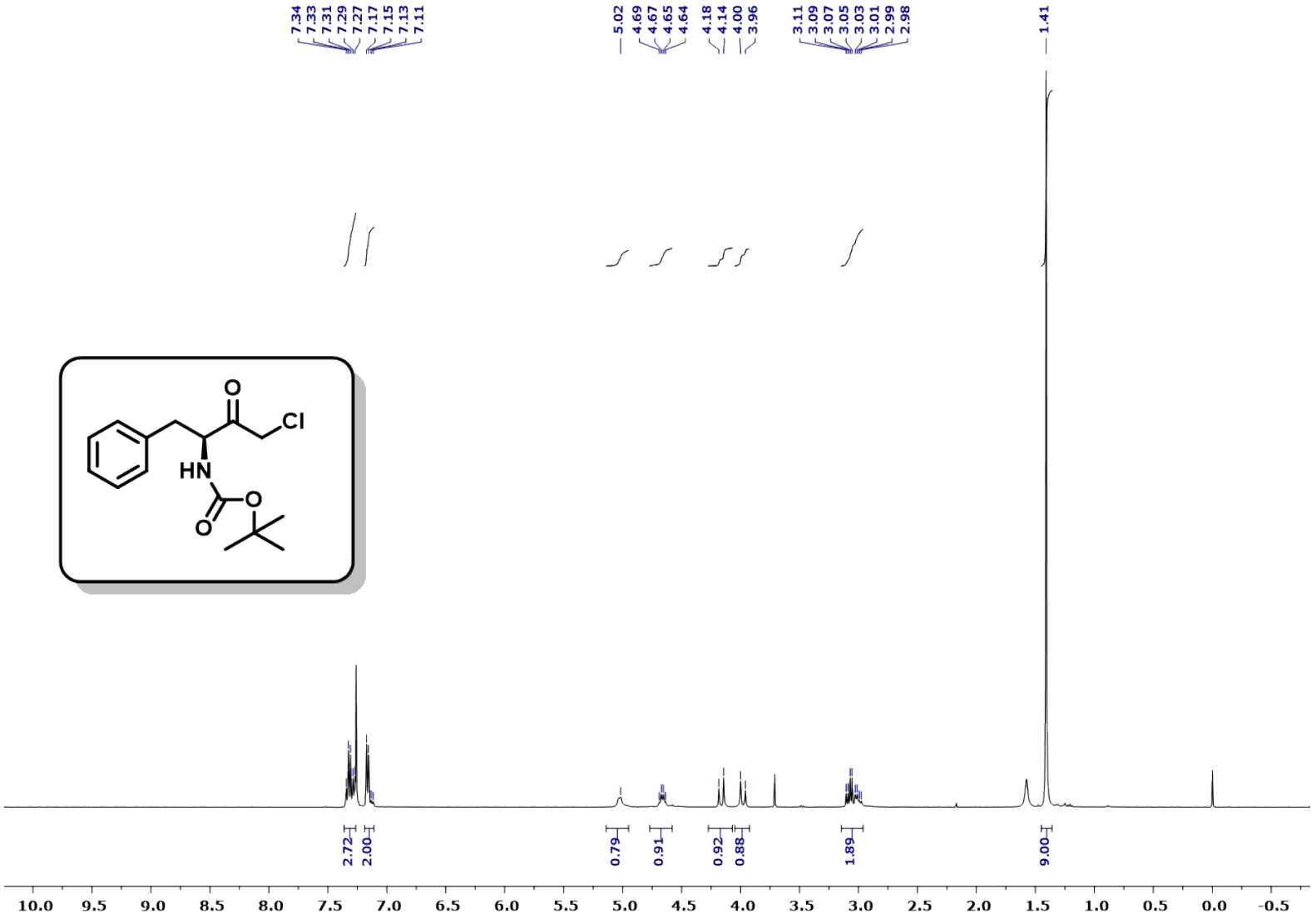


Fig. S22. ^{1}H NMR (400 MHz, $CDCl_3$) spectra of *tert*-Butyl (*S*)-(4-chloro-3-oxo-1-phenylbutan-2-yl) carbamate **(4)**.

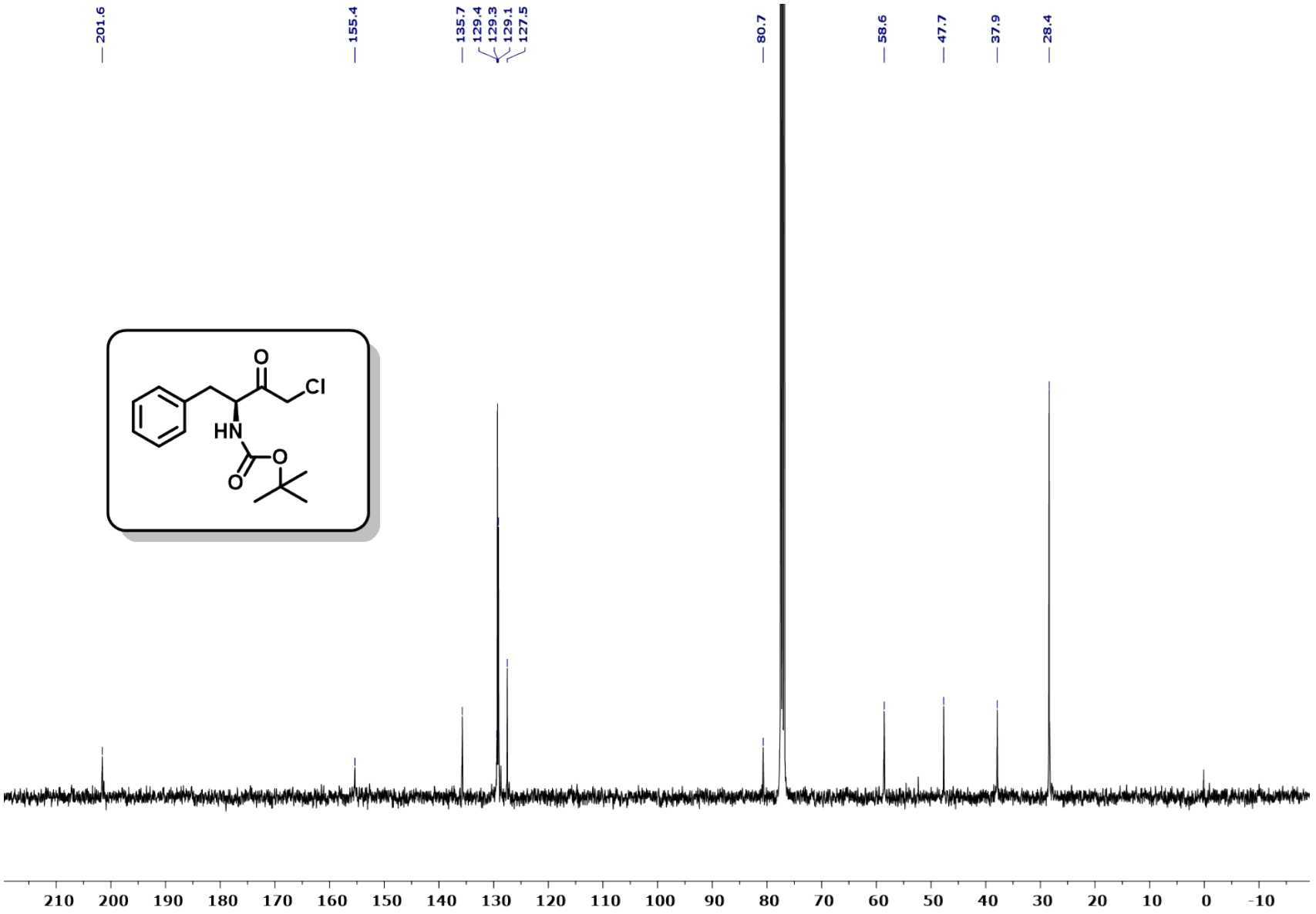


Fig. S23. ^{13}C NMR (101 MHz, $CDCl_3$) spectra of *tert*-Butyl (*S*)-(4-chloro-3-oxo-1-phenylbutan-2-yl) carbamate **(4)**.

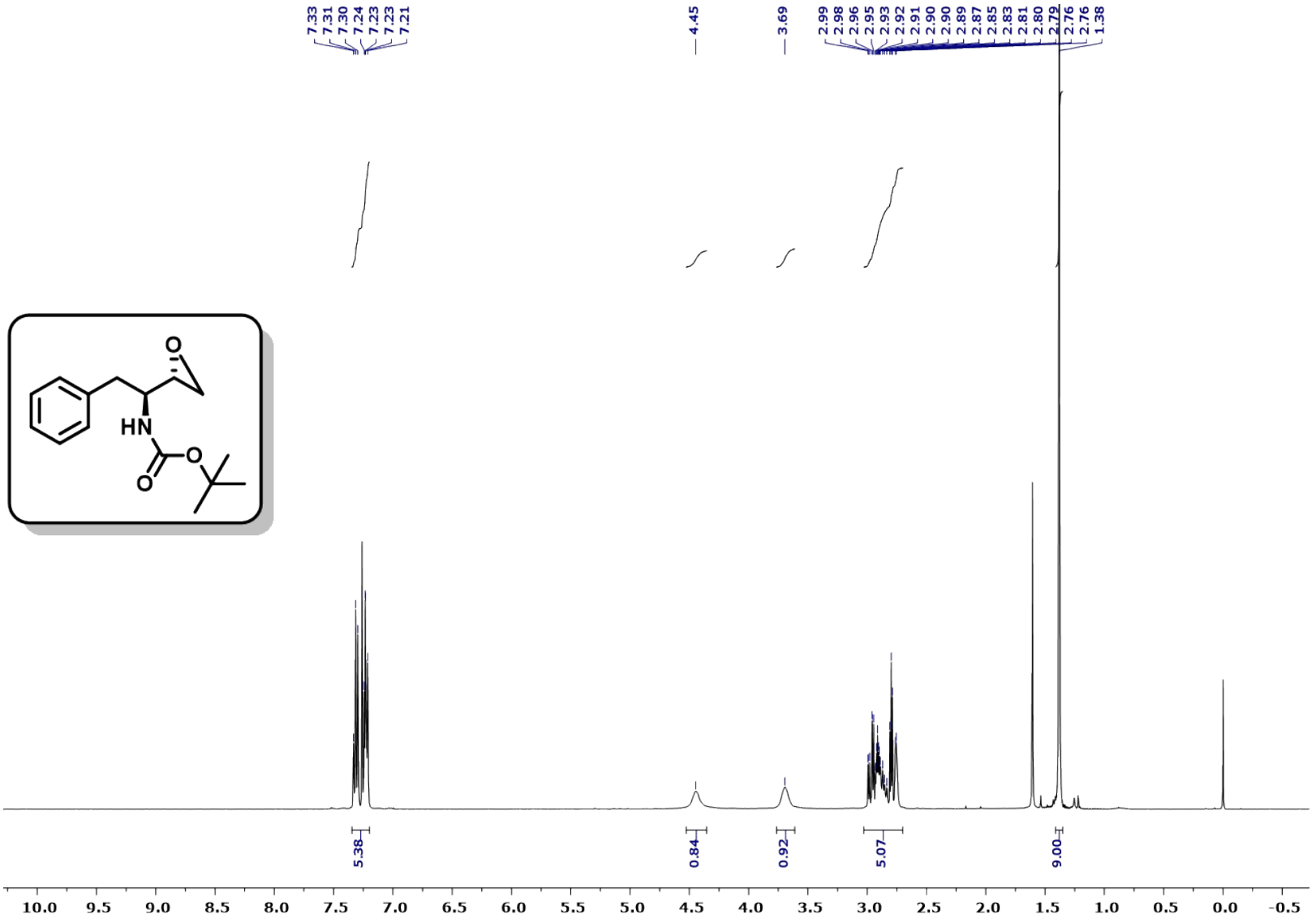


Fig. S24. ^{1}H NMR (400 MHz, $CDCl_3$) spectra of *tert*-Butyl ((*S*)-1-((*S*)-oxiran-2-yl)-2-phenylethyl) carbamate **(5)**.

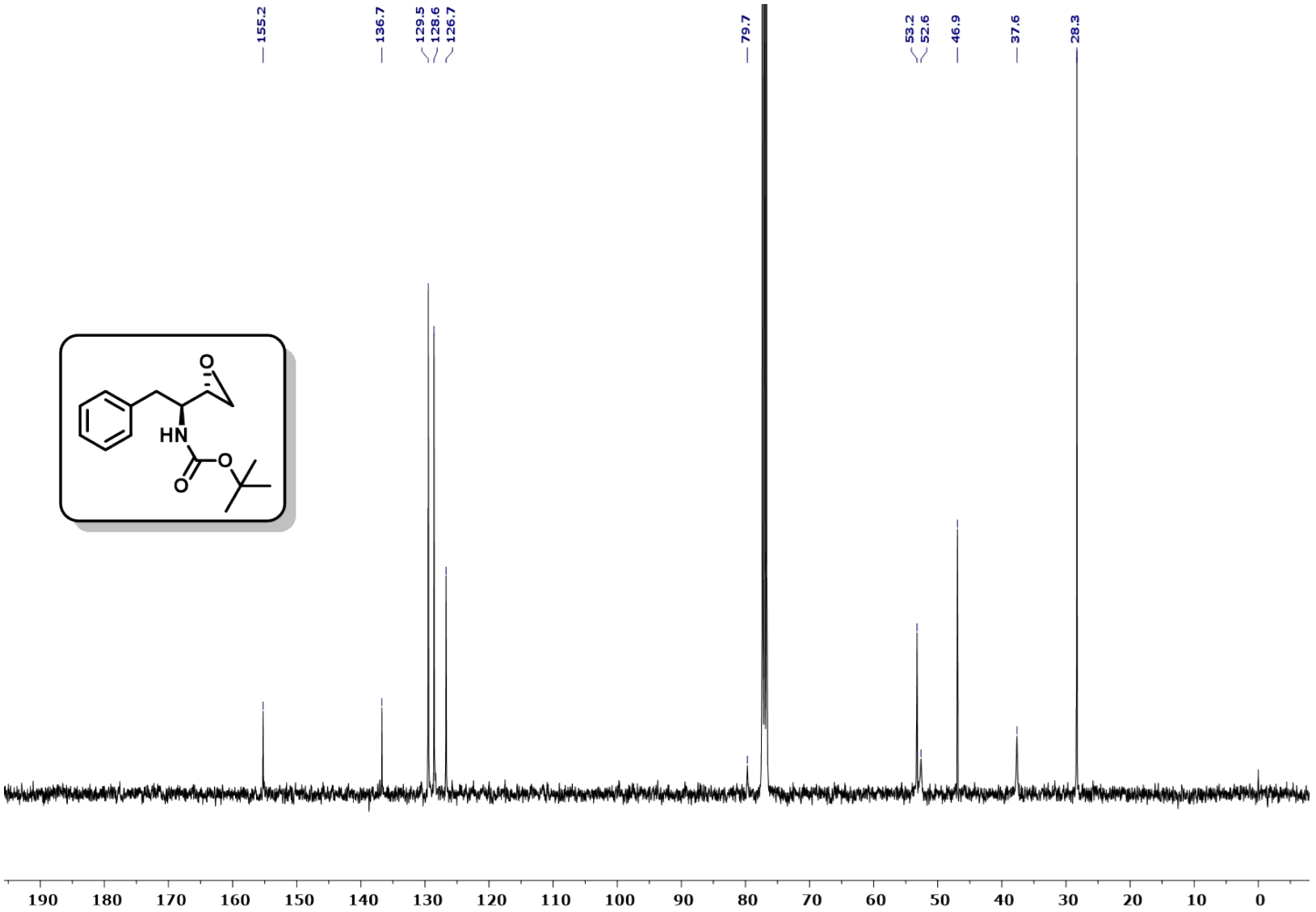
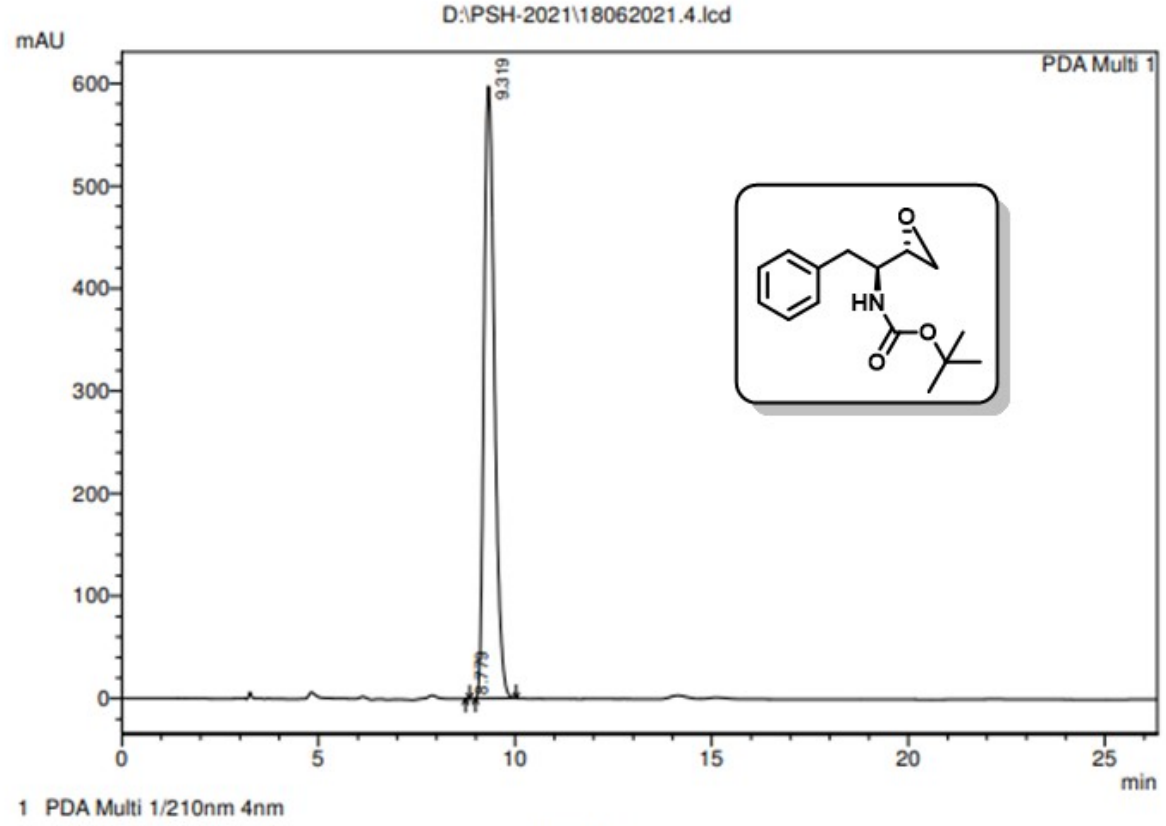


Fig. S25. ^{13}C NMR (101 MHz, $CDCl_3$) spectra of *tert*-Butyl ((*S*)-1-((*S*)-oxiran-2-yl)-2-phenylethyl) carbamate **(5).**

Acquired by : Manjula
Sample Name : PSH-AB-EPOXIDE-A
Sample ID : PSH-AB-EPOXIDE-A
Tray# : 1
Vail # : 77
Injection Volume : 5 uL
Data File Name : 18062021.4.lcd
Method File Name : 18062021.lcm
Batch File Name :
Report File Name : Default.lcr
Data Acquired : 6/18/2021 12:21:52 PM
Data Processed : 6/18/2021 1:09:25 PM
COLUMN: CHIRALCEL-01 250X4.6mm 5u
MOBILE PHASE: 98% HEPTANE: 1% MEOH: 1% ETOH
FLOW RATE : 1ml/min

<Chromatogram>



1 PDA Multi 1/210nm 4nm

PeakTable

PDA Ch1 210nm 4nm

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2	9.319	11102969	597263	99.999	99.993
Total		11103081	597303	100.000	100.000

Fig. S26. HPLC data of the epoxide **(5)**.

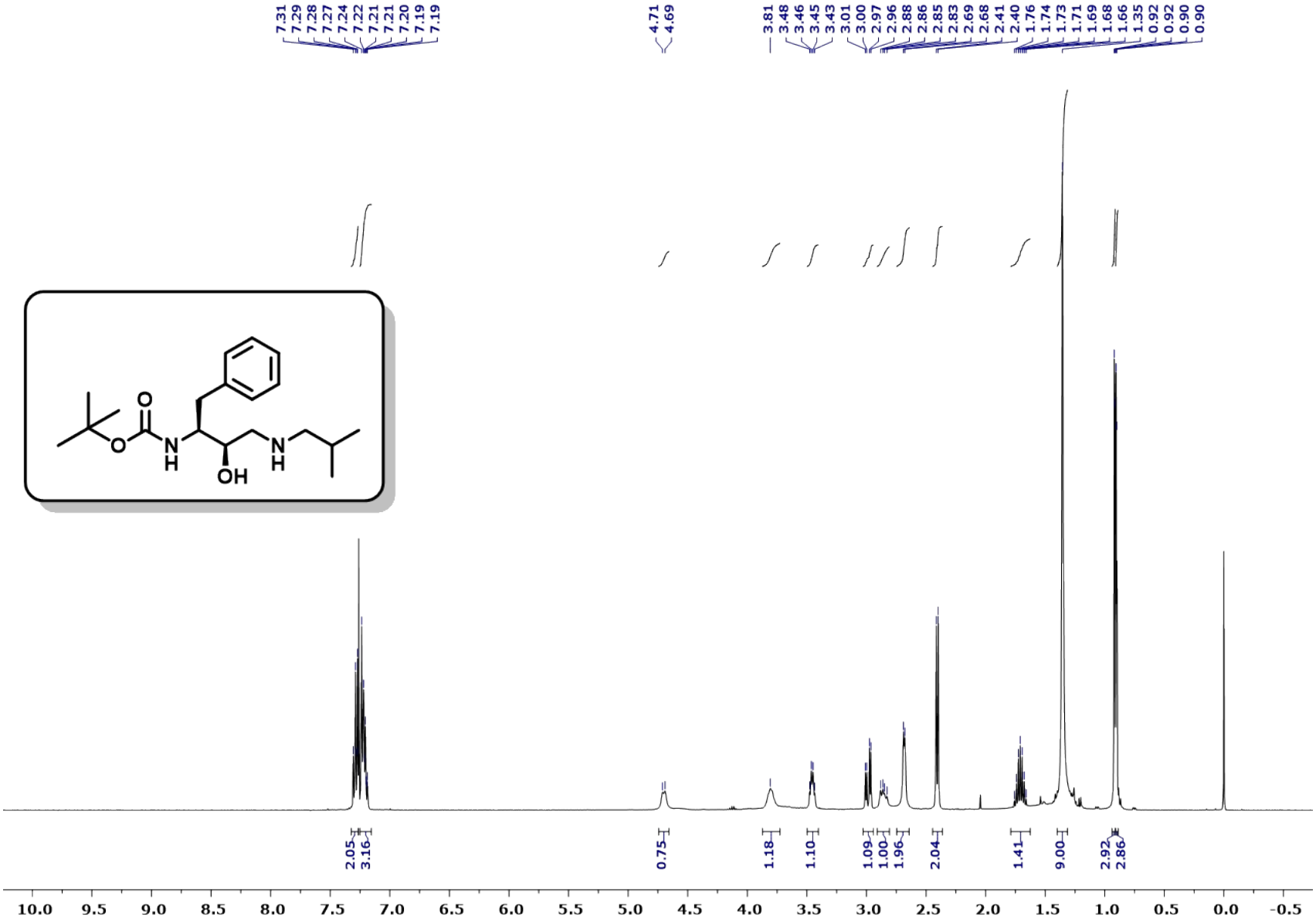


Fig. S27. ^{1}H NMR (400 MHz, $CDCl_3$) spectra of *tert*-butyl ((2*S*,3*R*)-3-hydroxy-4-(isobutylamino)-1-phenylbutan-2-yl)carbamate **(7)**.

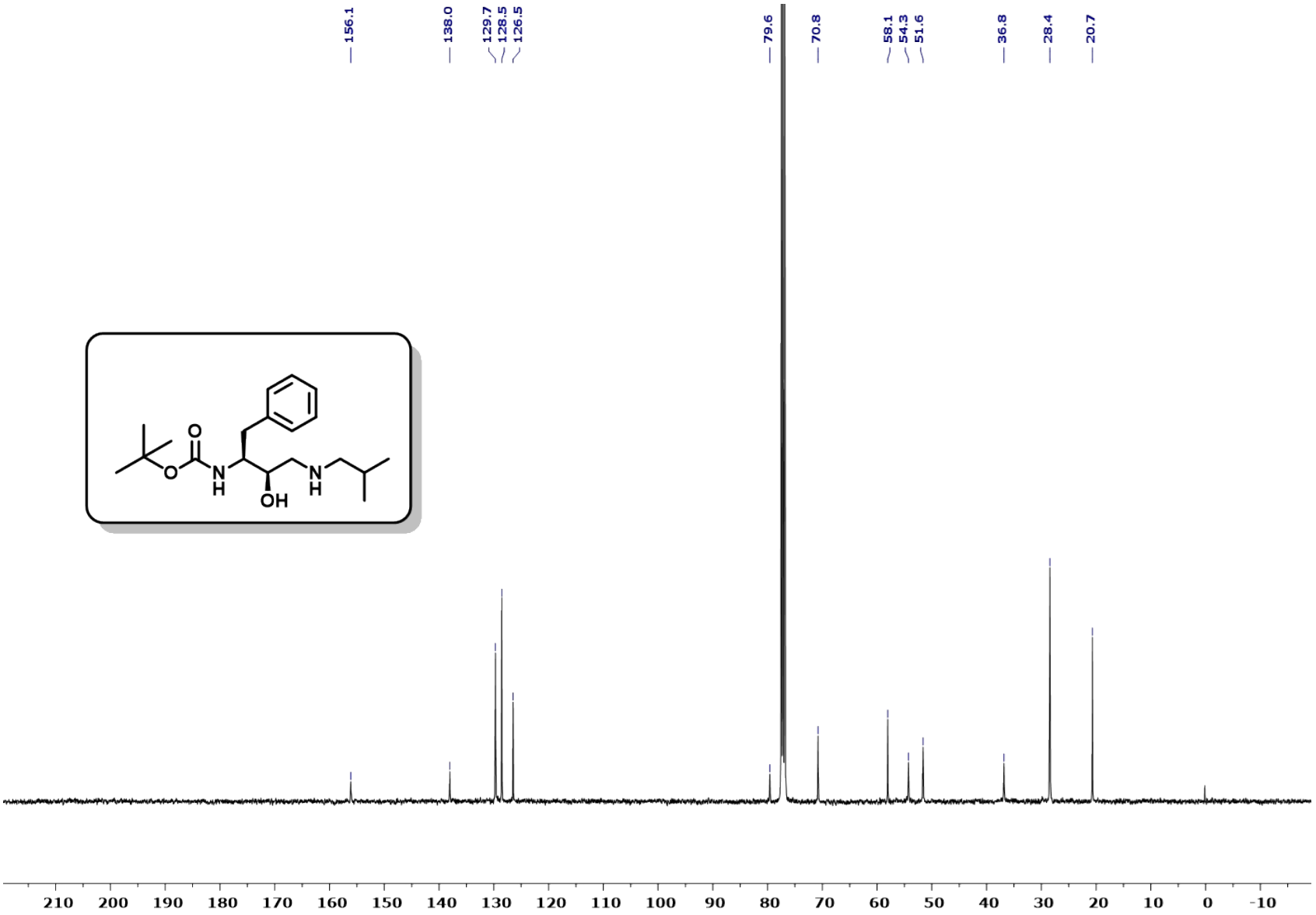


Fig. S28. ^{13}C NMR (101 MHz, $CDCl_3$) spectra of *tert*-butyl ((2*S*,3*R*)-3-hydroxy-4-(isobutylamino)-1-phenylbutan-2-yl)carbamate **(7).**

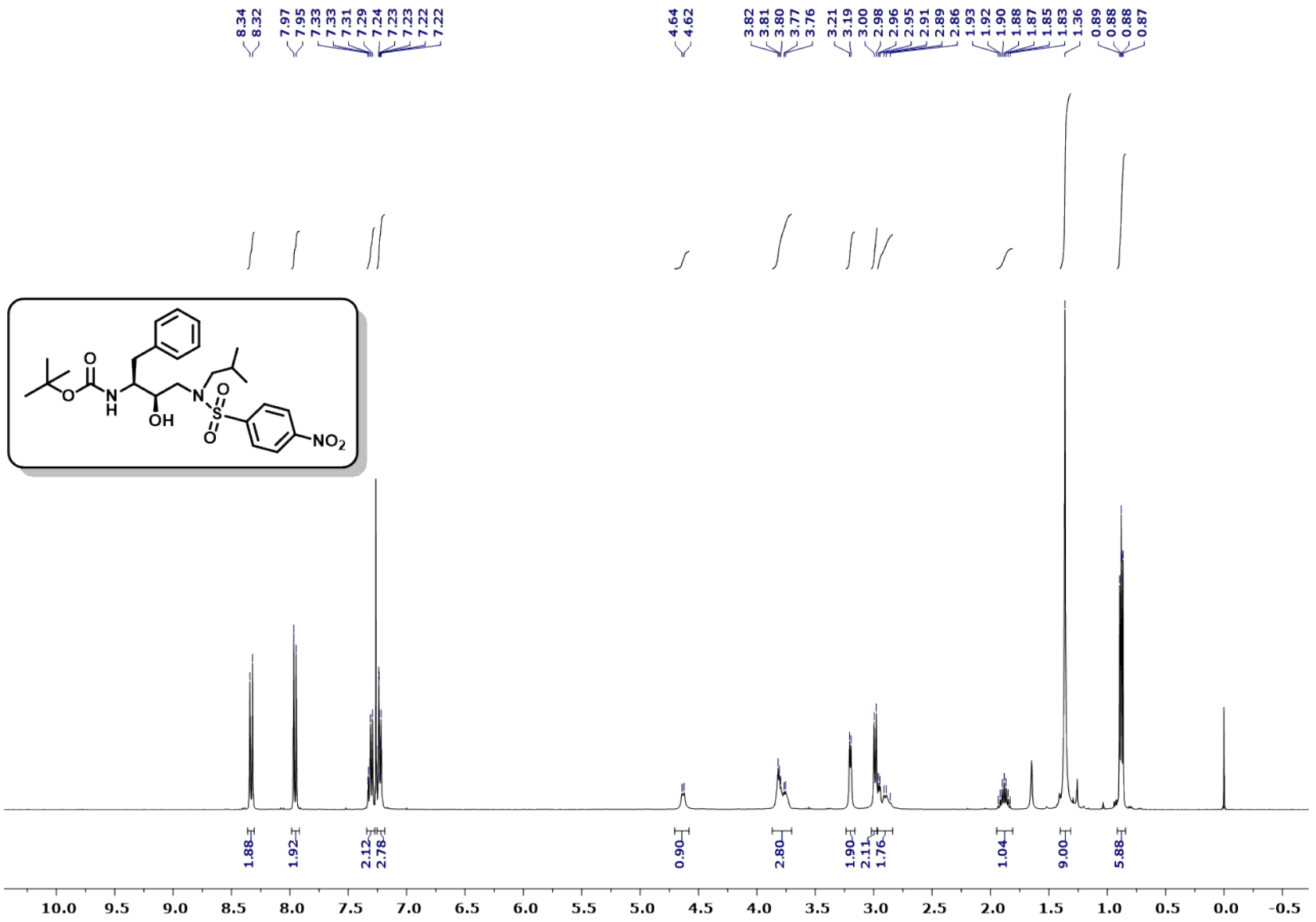


Fig. S29. ^{1}H NMR (400 MHz, $CDCl_3$) spectra of *tert*-butyl ((2*S*,3*R*)-3-hydroxy-4-((*N*-isobutyl-4-nitrophenyl)sulfonamido)-1- phenylbutan-2-yl)carbamate **(9).**

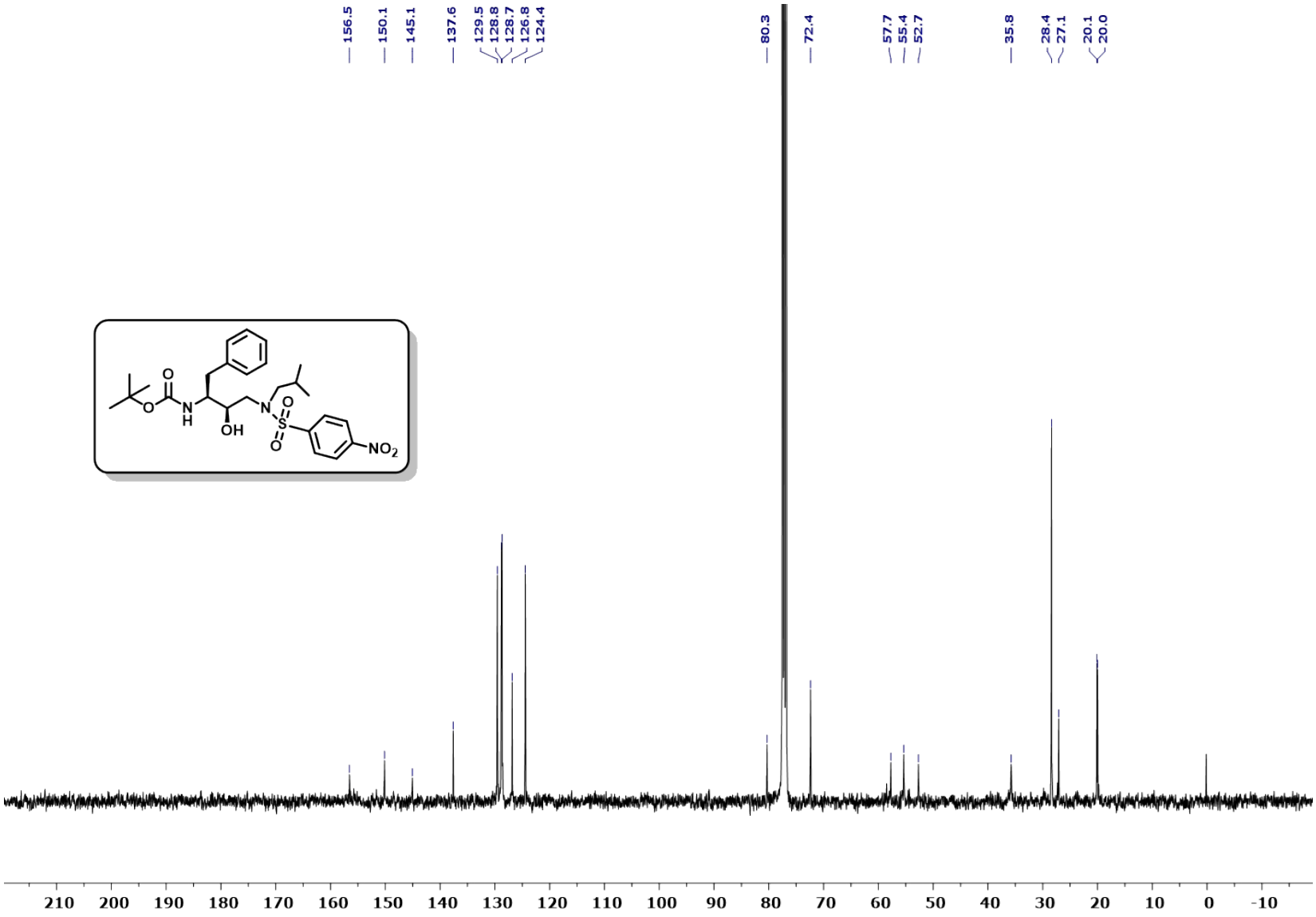


Fig. S30. ^{13}C NMR (101 MHz, $CDCl_3$) spectra of *tert*-butyl ((2*S*,3*R*)-3-hydroxy-4-((*N*-isobutyl-4-nitrophenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate **(9)**.

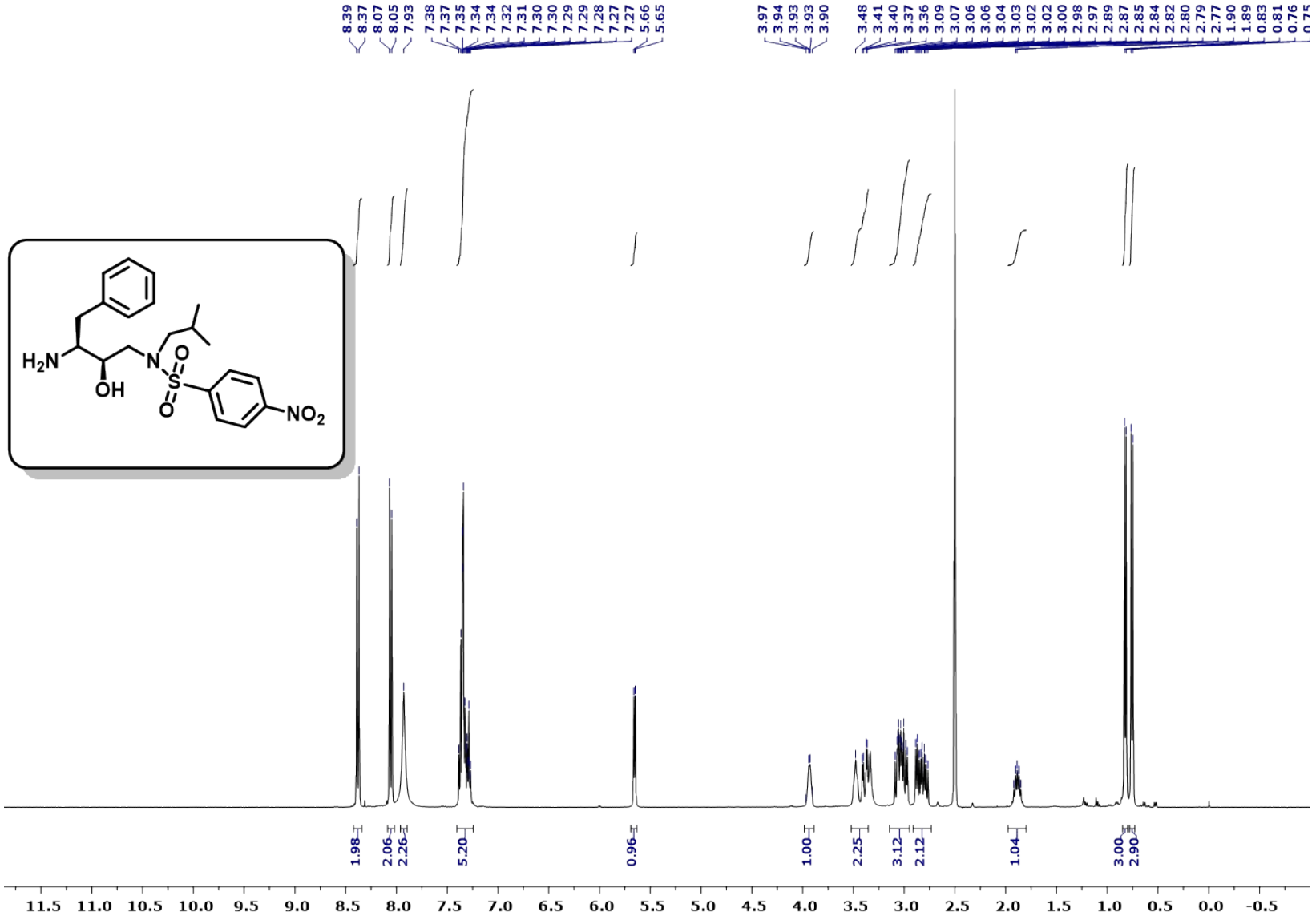


Fig. S31. ^{1}H NMR (400 MHz, DMSO-d_6) spectra of *N*-((2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-4-nitrobenzenesulfonamide **(10)**.

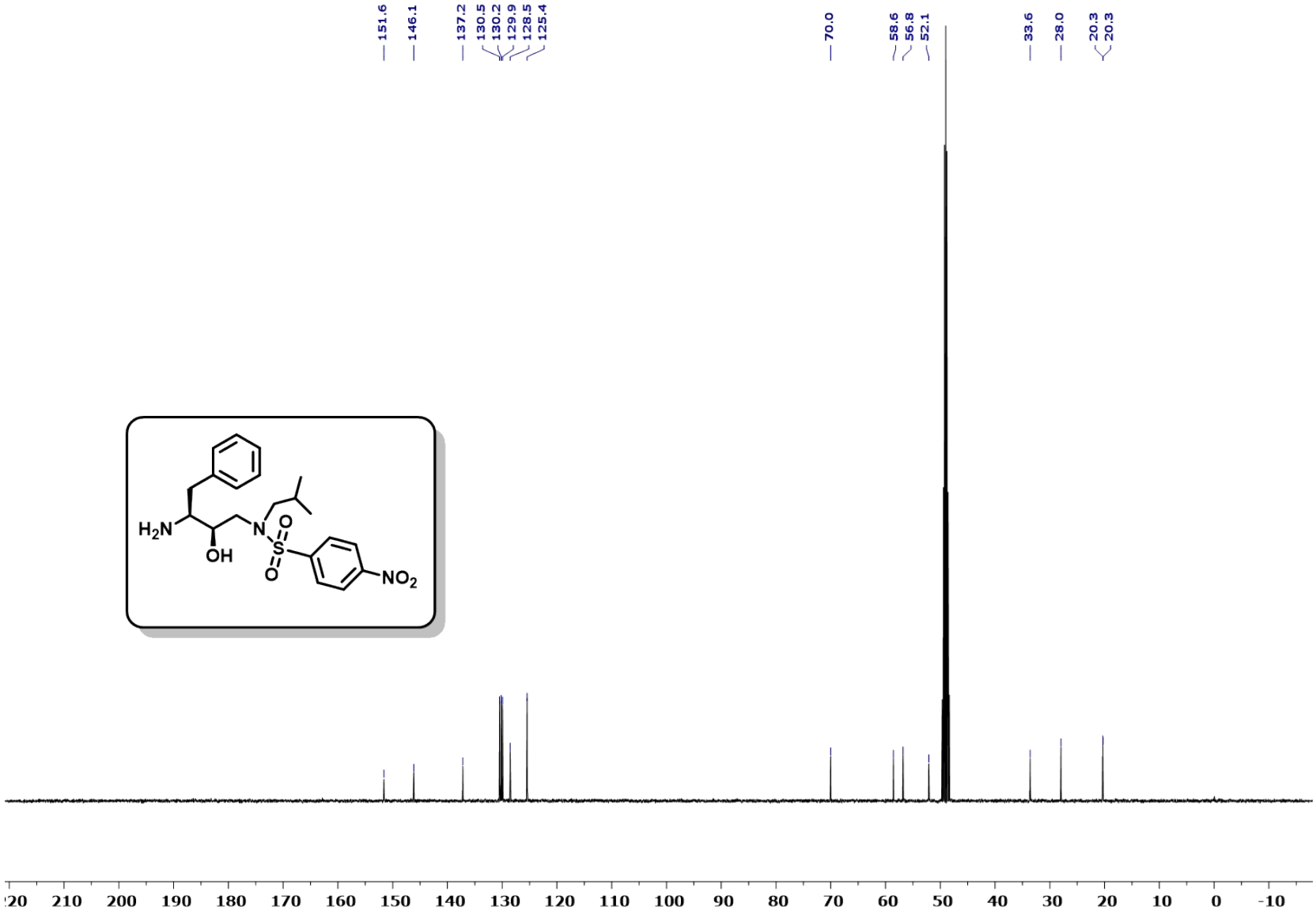


Fig. S32. ^{13}C NMR (101 MHz, DMSO-d_6) spectra of *N*-((2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-4-nitrobenzenesulfonamide. **(10)**.

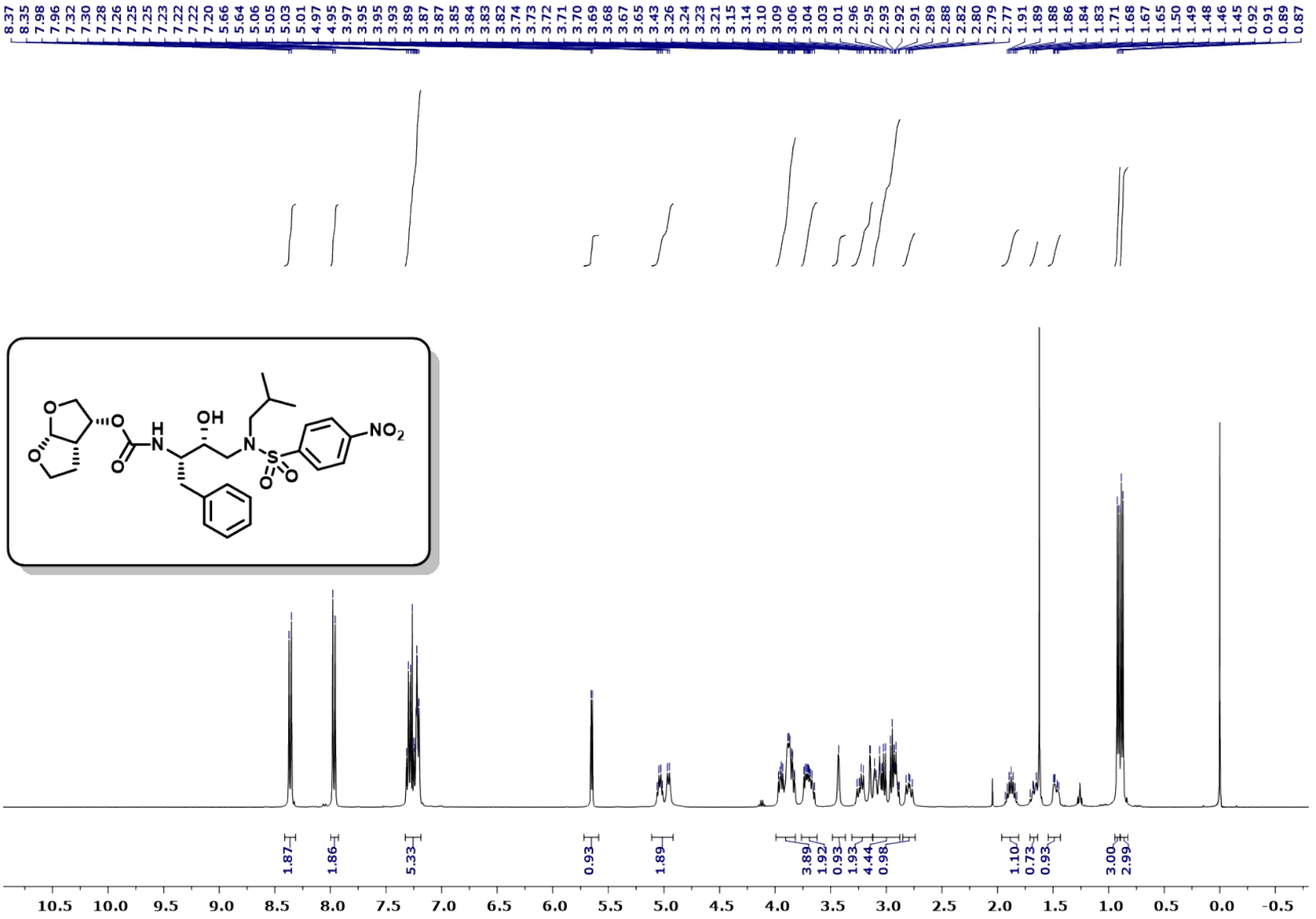


Fig. S33. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-b]furan-3-yl ((2*S*,3*R*)-3-hydroxy-4-((*N*-isobutyl-4-nitrophenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate **(12)**.

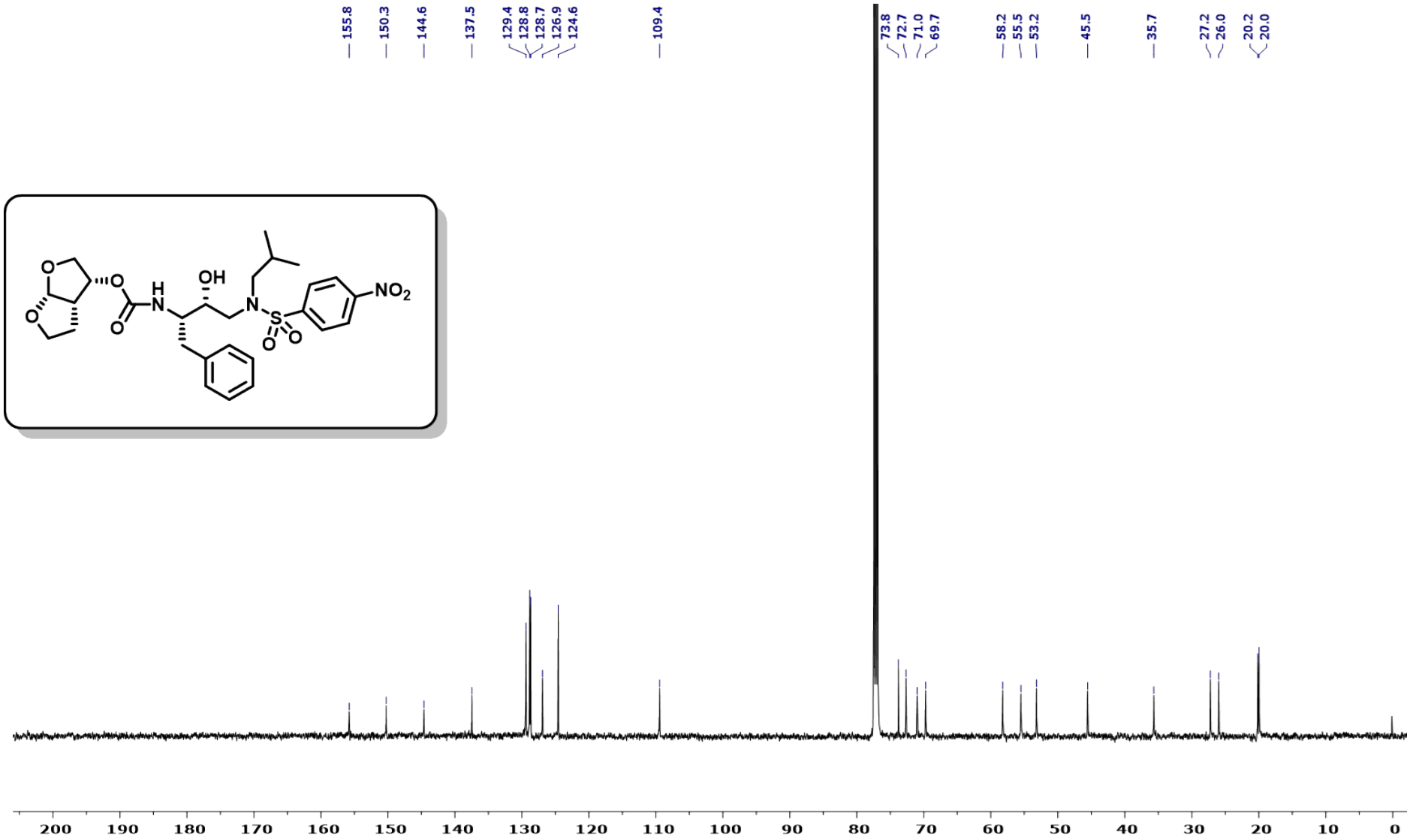


Fig. S34. ^{13}C NMR (101 MHz, $CDCl_3$) spectra of (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-b]furan-3-yl ((2*S*,3*R*)-3-hydroxy-4-((*N*-isobutyl-4-nitrophenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate **(12)**.

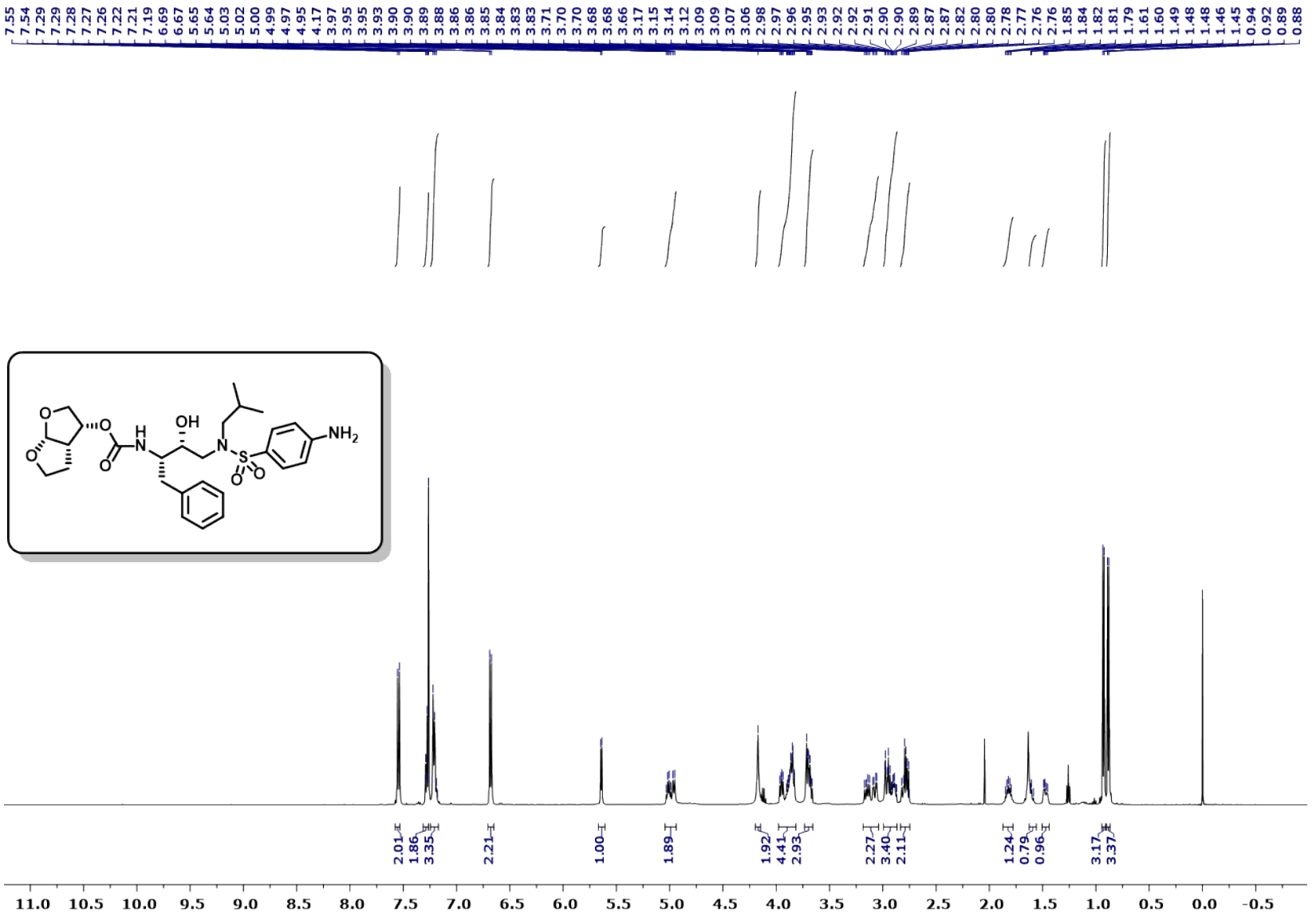


Fig. S35. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-b]furan-3-yl ((2*S*,3*R*)-4-((4-amino-N-isobutylphenyl)sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)carbamate **(13)**.

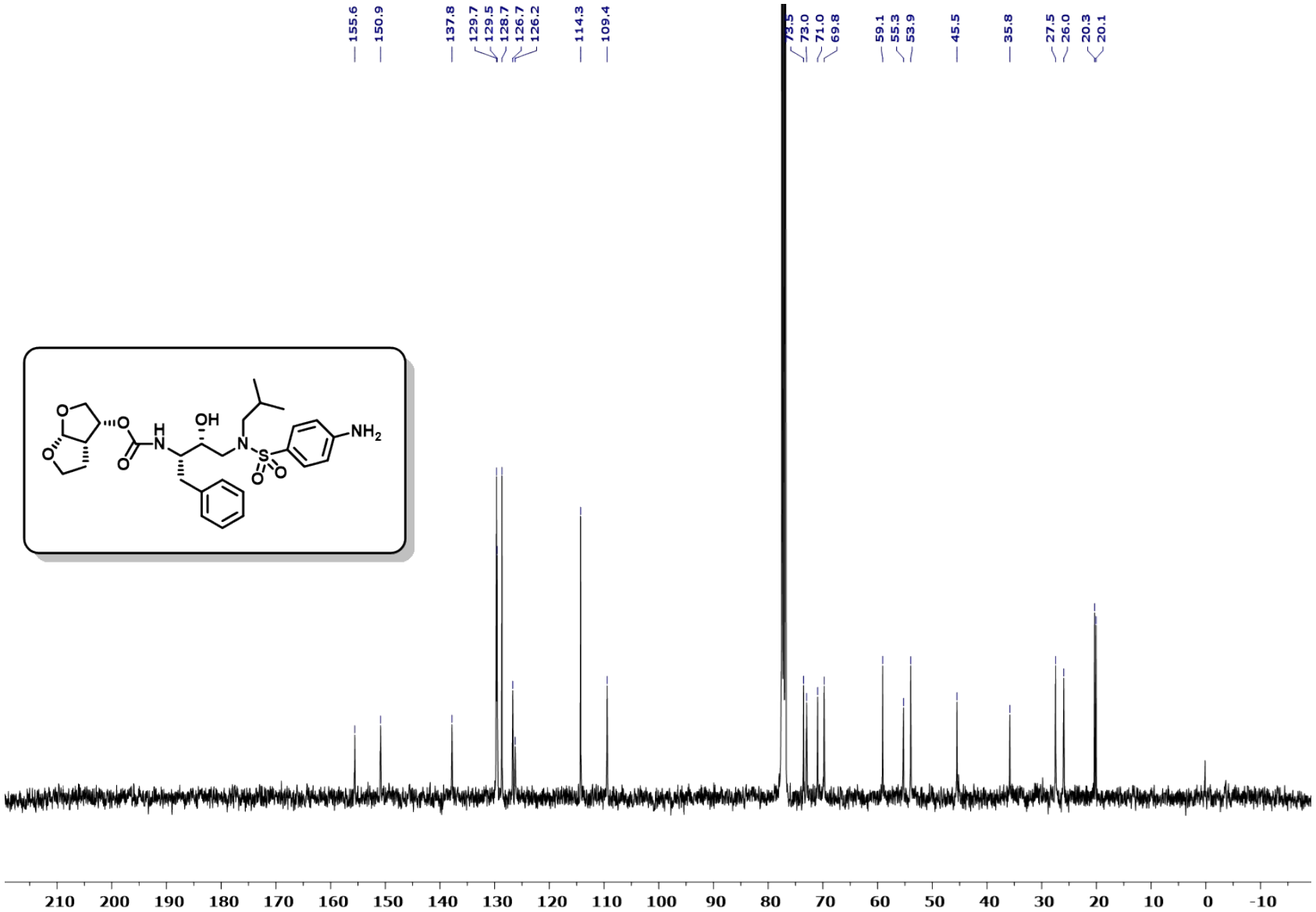
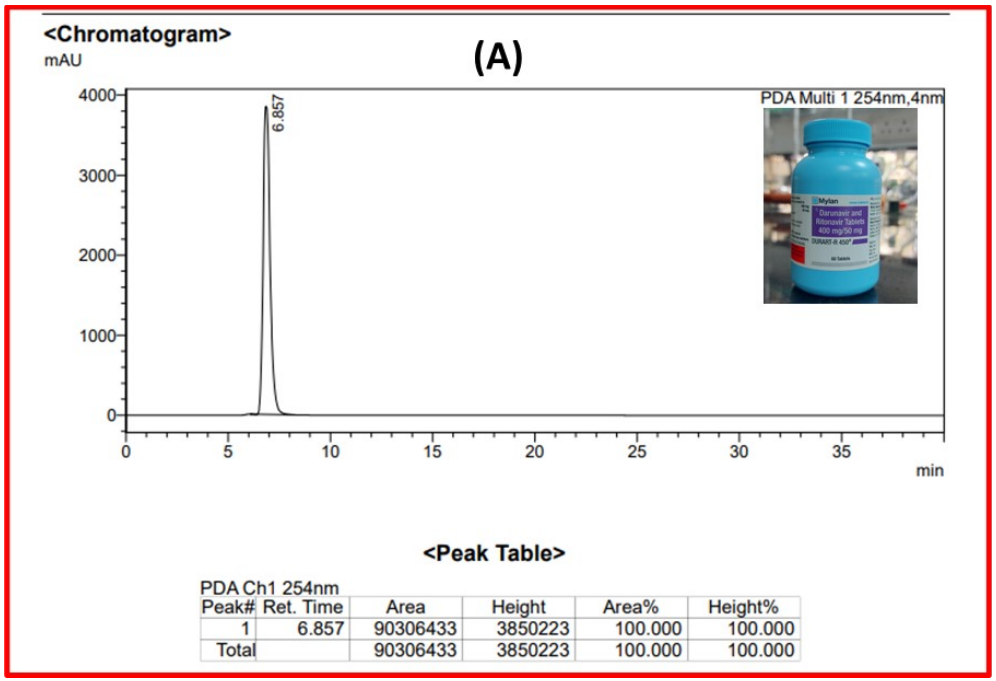


Fig. S36. ^{13}C NMR (101 MHz, $CDCl_3$) spectra of (3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-b]furan-3-yl((2*S*,3*R*)-4-((4-amino-N-isobutylphenyl)sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)carbamate **(13)**.



<Peak Table>

PDA Ch1 254nm

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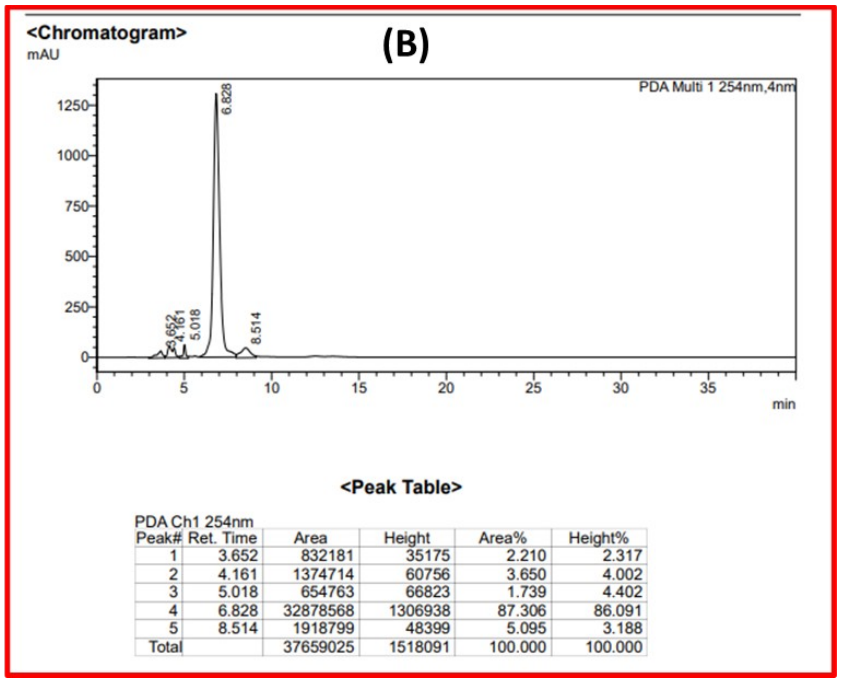
Total		90306433	3850223	100.000	100.000



<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%	Height%
1	3.652	832181	35175	2.210	2.317
2	4.161	1374714	60756	3.650	4.002
3	5.018	654763	66823	1.739	4.402
4	6.828	32878568	1306938	87.306	86.091
5	8.514	1918799	48399	5.095	3.188
Total		37659025	1518091	100.000	100.000

Fig. S37. Comparative HPLC data; (A) commercially available DRV; (B) continuous flow-process synthesized crude mixture of DRV **(13)**.

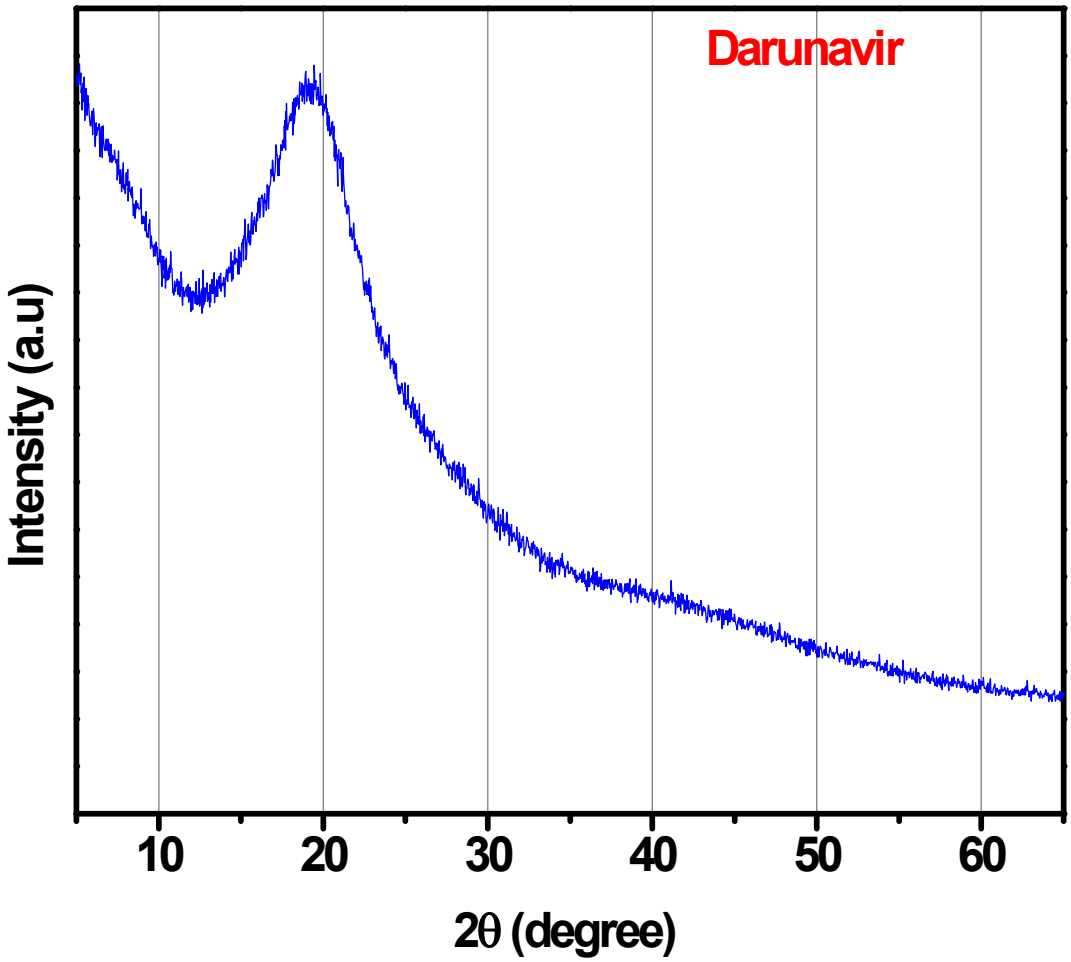


Fig. S38. Powder XRD of Darunavir **(13)**.

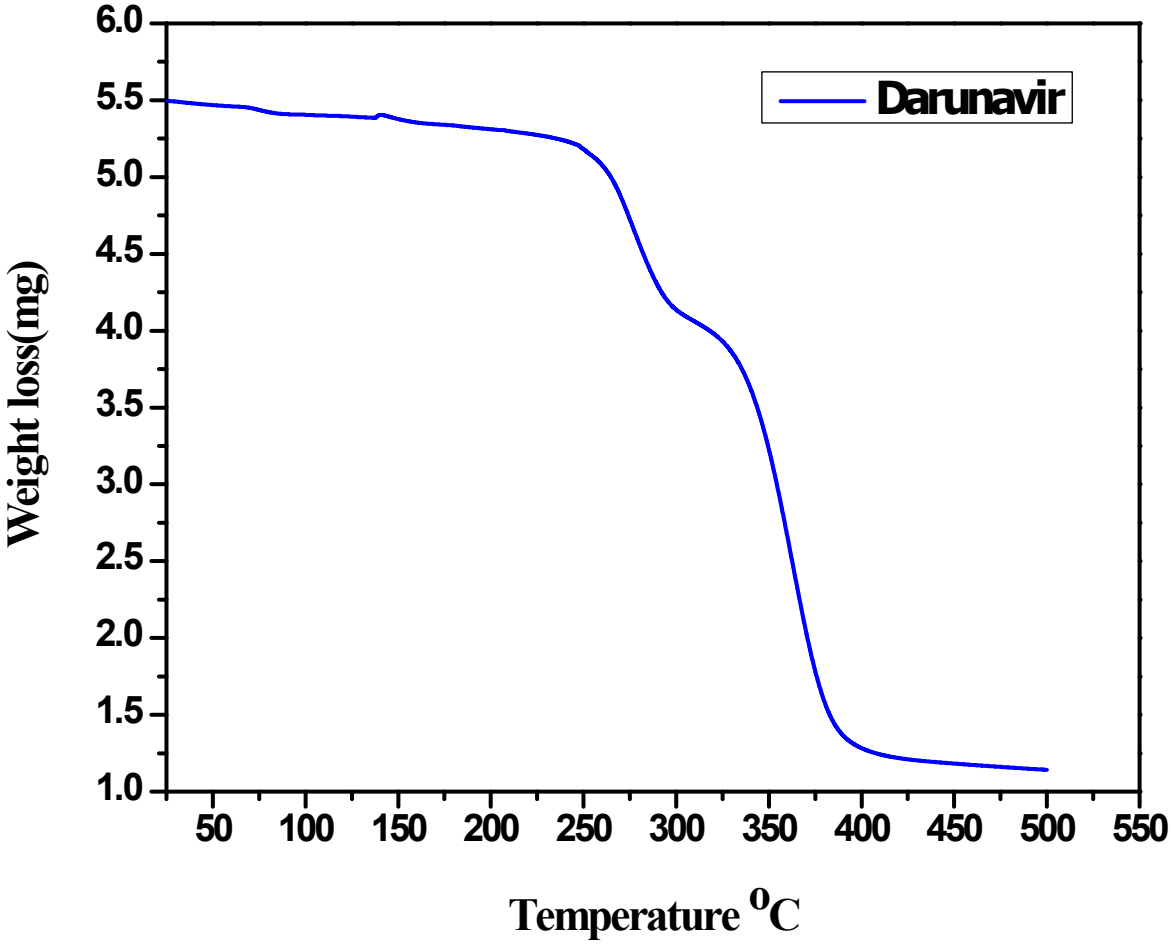


Fig. S39. Thermo-gravimetrical analysis data of the Darunavir **(13)**.

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