Supplementary Information

Synthesis of a Spiroketone Intermediate Featuring a Green and Sustainable Telescoped Flow Process

Shuoxun Wang,*[a] Hao Wu, [a] Yongda Zhang, [a] Frederic Buono*[a]

[a] Chemical Development, Boehringer Ingelheim Pharmaceuticals Inc., 900 Ridgebury Road, Ridgefield, Connecticut 06877 United States

* Corresponding authors:

shuoxun.wang@boehringer-ingelheim.com, frederic.buono@boehringer-ingelheim.com

Table of Contents

General Information

The substrate **1** ((R)-1,4-dioxadispiro[4.0.56.45]pentadecan-7-one) was supplied by a third party vendor. The Grubbs 1st generation (G1) catalyst and the Hoveyda-Grubbs 2nd generation (HG2) catalyst were purchased from Sigma-Aldrich. The Pd/C catalyst was purchased from Johnson Matthey (S4336). The commercially available reagents were used as received without further purification. Manufacturers and modes of instruments used are described in corresponding sections below.

RCM Step Optimization in Batch

RCM reactions for conditions optimization in batch were conducted in sealed glass vials (20 mL) at ambient pressure with 2.5 mL of 0.16 M substrate **1** solution in 2-MeTHF or toluene. Substrate preheating was done in a temperature-controlled oil bath and catalyst solution (0.5 mL) was added by a syringe with needle into the sealed glass vial while stirring at 900 rpm.

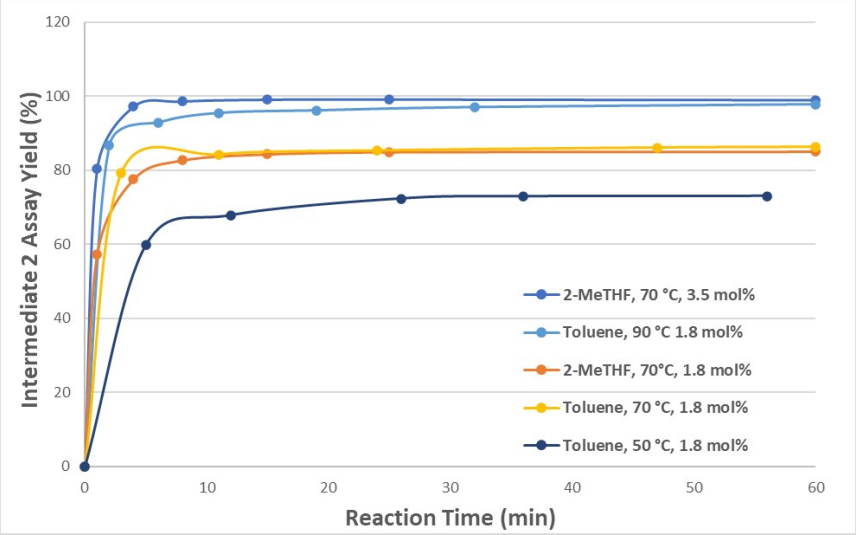

*Figure S1 Key results for temperature impact with Grubbs 1st catalyst (G1) in batch conditions. Reaction conditions: 0.16 M substrate **1** solution, no substrate preheating, one shot addition of catalyst.*

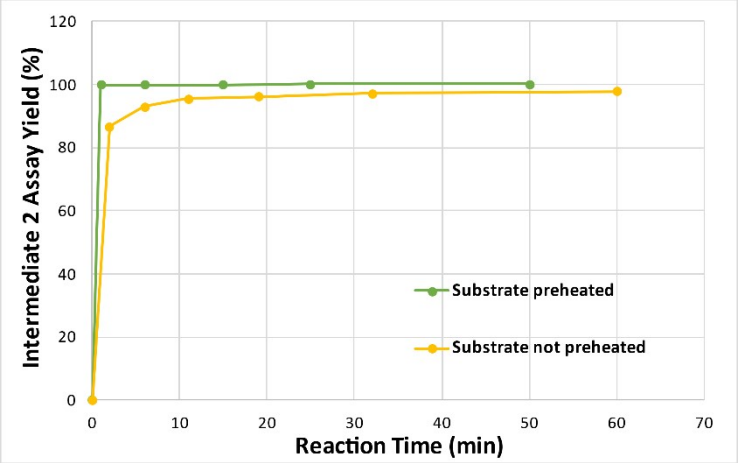

*Figure S2 RCM reaction performance with or without preheating. Reaction conditions: 0.16 M substrate **1** solution in toluene, 90 °C, 1.8 mol% G1 added in one shot.*

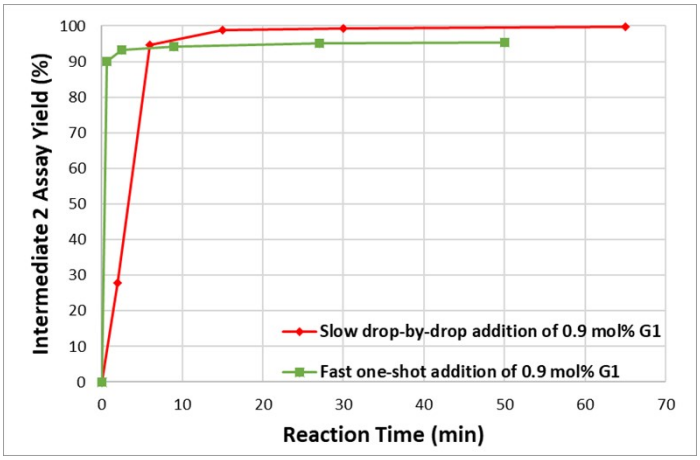

*Figure S3 – Catalyst addition protocol impact on the RCM reaction assay yield. Reaction conditions: 0.16 M substrate **1** solution in toluene, 90 °C, 0.9 mol% G1, preheated substrate **1**.*

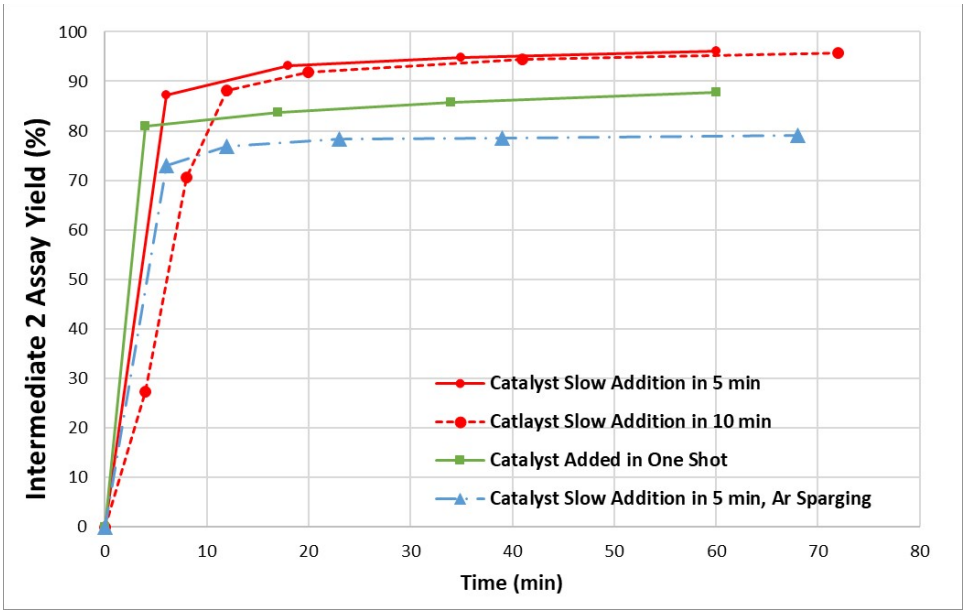

Figure S4 – Catalyst addition and inert gas sparging impact on RCM performance. Reaction conditions: 90 °C, preheated 0.16 M substrate **1** in toluene, 0.5 mol% G1 catalyst.

RCM Step in Flow Reactors

1. Membrane-in-Frame Reactor

The pervaporation membrane is sandwiched between two stainless steel modules (on the left side in Figure S5), its upper half is the retentate chamber for the liquid reaction mixture and its down half is the permeate chamber sweeping with nitrogen gas to provide driving force for the permeated ethylene gas to be removed. A HPLC mixer with volume of 250 µL was found critical to the reaction performance as its tiny inner volume allows the substrate solution to quickly mix with the catalyst solution without prolonged residence time required. The tubing on the right of the figure is for substrate preheating before it reaches the mixer. The whole system was wrapped with a heating tape and alumina foil.

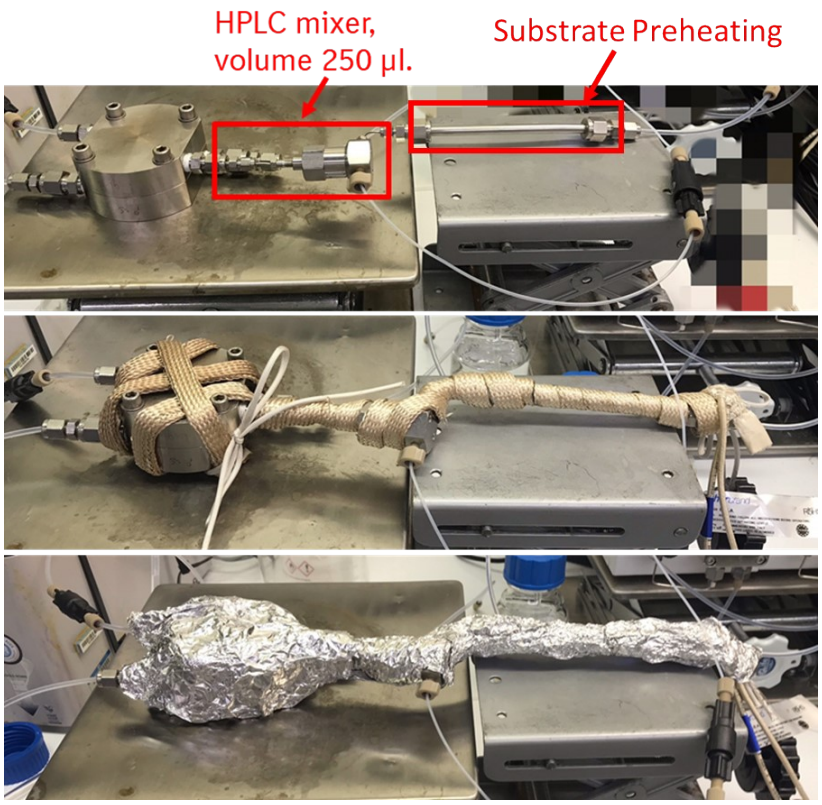

Figure S5 Membrane-in-Frame reactor setup with a HPLC mixer (top) wrapped with heating tape (middle) and alumina foil (bottom).

Table S1 summaries the select reaction results using the membrane-in-frame reactor setup as mentioned above with different types of mixers. With the HPLC mixer, 99% assay yield for the RCM step was reached with 1.8 mol% G1 catalyst, but furtherly decreased catalyst loading caused compromised reaction performance. However, the HPLC mixer is not scalable, and they are not suitable for high temperature. The 3D-printed mixer has an inner volume of ~1mL. Because of its larger inner volume and its relatively low mixing efficiency, the RCM reaction assay yield reached ~80%. The T-shape mixer has caused a diminished reaction performance as well.

*Table S1 Select RCM reaction results with the membrane-in-frame reactor and different types of mixers. Reaction conditions: preheated 0.16 M substrate **1** solution in toluene, 90 °C.*

Mixer Type	Mixer Pic.	G1 Equiv.	Intermediate 2 Assay Yield
HPLC Mixer		1.8 mol%	99%
		1.3 mol%	91%

3D-printed Mixer		1.8 mol%	80%
T-shape Mixer		1.8 mol%	78%

2. Tube-in-Tube Membrane Reactor

The instrument setup for a tube-in-tube membrane reactor is shown in Figure S6. The tube-in-tube reactor is assembled with a 1/8" O.D. stainless steel outer tubing and an AF2400 gas permeable membrane inner tubing. The setup tested for the RCM reaction was with a HPLC mixer and a piece of ¼" tube for substrate preheating warped with a heating tape. The reaction mixture flew through the inner tubing while the outer space between the inner tubing and the housing tubing is connected to vacuum to vent the permeated ethylene gas continuously. This pattern of fluid flows could cause lower actual temperature of the reaction mixture than desired, therefore lower assay yield of the reaction. Though a reverse pattern with the liquid reaction mixture flowing through the outer space and the inner tubing connect to vacuum would result in a better thermal transfer for the reaction, this operation is not recommended by the membrane manufacturer as it exposes the risk to the inner tubing to be collapsed from the outside due to pressure difference.

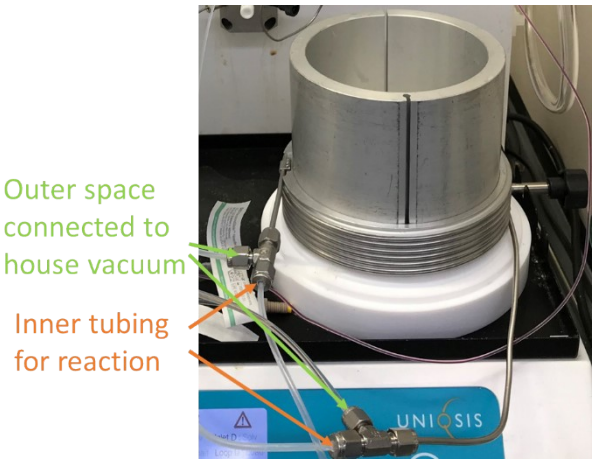

Figure S6 Tube-in-tube membrane flow reactor setup on Uniqsis FlowSyn system for heating.

3. Tube Plug Flow Reactor

The photo for the tube plug flow reactor system setup is as shown in Figure S7. Solutions of reaction substrate **1** and G1 catalyst were pumped into the HPLC mixer via Kanuer pumps. The substrate preheating and the HPLC mixer were wrapped with a heating tape of which temperature was controlled by a J-Kem thermal controller. The coil reactor is made of a 1/16" tubing with total volume of 2.5 mL.

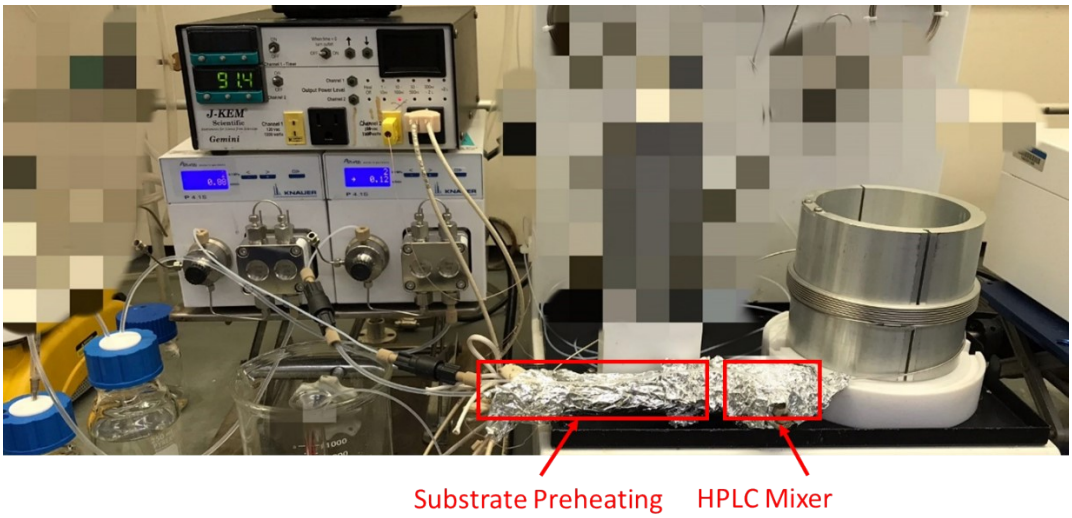

Figure S7 Plug flow reactor setup with stainless steel coil heating on the Uniqsis FlowSyn Unit.

4. Glass Mixing Chip

The glass static mixing chip (1.6 mL or 10 mL) was found promising for the RCM step. This type of reactor integrated preheating path and mixing/reacting path into one plate therefore no additional mixer nor preheating setup is required. A small-scale reaction was first tested with a 1.6 mL glass plate, then with a 10 mL plate, and both reached 99% assay yield with 1.8 mol% G1 at 90 °C. Figure S8 shows the setup for a 10 mL glass mixing chip with the heating device that is suitable for two parallel 1.6 mL plates as well.

Figure S8 The glass static mixing chip setup with a Polar Bear Plus heating and cooling system.

Hydrogenation Step in Trickle Bed reactor with Pd Catalyst

Hydrogenation reaction with Pd catalyst in flow condition was performed on a HEL FlowCAT trickle bed reactor (cartridge with 12 mm I.D. and 150 mm length) with 5% Pd/C granular catalyst from Johnson Matthey (S4336, 6.6 g). The catalyst was loaded in the middle of the cartridge with sands in the bottom and quartz wool on the top. The catalyst activity and stability were first tested in batch at 70 °C, 100 psi H_2 for 30 min or 60 min (Table S2). The Pd/C catalyst remained active for the hydrogenation reaction after long term exposure to the reaction mixture indicates no significant inhibitive compounds generated to the catalyst from the reaction.

Table S2 Hydrogenation in batch with the 5% Pd/C catalyst.

	10 mol% Pd		**5 mol% Pd**	**1 mol% Pd**	
Catalyst Condition	Fresh	Reused*	Fresh	Fresh	
Reaction Time	30 min	30 min	30 min	30 min	60 min
Conversion	100%	100%	98%	50%	88%

*The catalyst was recycled from the reaction with fresh catalyst after a week of soaking in the hydrogenation product mixture.

The residence time for packed trickled bed reactor was measured with aid of a FlowIR unit that gives real time response of the liquid composition flowing out of the reactor. The measurement was done by injecting a small amount of methanol into toluene stream flowing through the catalyst bed using a syringe pump and monitoring the time duration until the methanol peaks in FlowIR disappeared. With real-time monitoring of the composition, residence time with different combination of gas and liquid flow rates were measured. The results are shown in Table S3 indicating the residence time is mostly impacted by the liquid flow rate.

Table S3 Residence time measurement for the Pd/C packed trickle bed reactor.

N_2 Gas Flow Rate (mL/min)	**Liquid Flow Rate (mL/min)**	**Residence time (min.'sec.")**
0	0.25	10'40"
0	0.5	5'30"
0	1.0	2'40"

0	1.5	1’30”
10	1.0	2’40”
20	1.0	2’45”
40	1.0	2’40”

PAT for the RCM Step with Inline FTIR

Reaction results using HG2 catalyst in the 10 mL glass static mixing chip flow reactor is shown in Table S4. The system setup is the same as depict in Figure S8. 0.5 mol% HG2 catalyst **5** is the minimum amount for full conversion RCM reactions with 0.11 M-0.19 M mixed substrate concentration.

Table S4 RCM step results with HG2 catalyst in the 10 mL glass static mixing chip flow reactor. Reaction conditions: 90 °C, 1 mL/min total stream, residence time 10 min.

Subs. Solution	**Mixed Subs. Conc.**	**Mixed HG2 Cat. Conc.**	**HG2 Equiv.**	**RCM Conversion**
17 vol.	0.11 M	0.00057 M	0.5 mol%	100%
10 vol.	0.19 M	0.00097 M	0.5 mol%	99.8%
5 vol.	0.44 M	0.0022 M	0.5 mol%	71.4%
	0.39 M	0.0027 M	0.7 mol%	86.7%
	0.36 M	0.0031 M	0.85 mol%	96%
	0.34 M	0.0034 M	1.0 mol%	100%

Screenshots of the calibrated models for substrate **1** and intermediate **2** using the iC Quant function in the iC 7.0 software are shown in Figure S9.

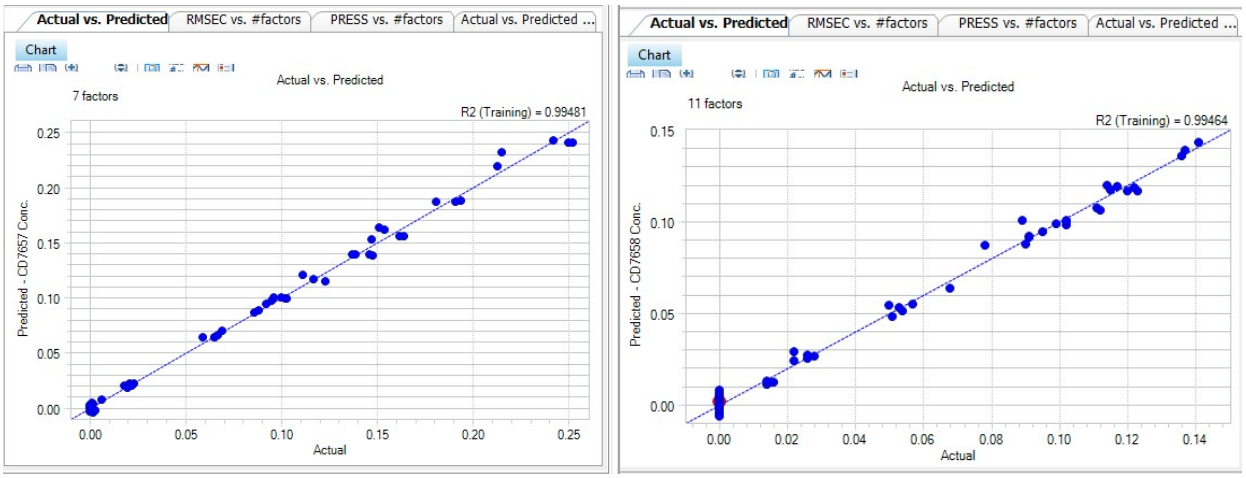

*Figure S9 Screenshots for the calibrated iC Quant models of the substrate **1** (left) and intermediate **2** (right).*

Telescoped Process for Continuous Production

Figure S10 is the instruments setup for the telescoped process, in which the intermediate **2** reservoir is not shown. The bottles of substrate **1** solution, HG2 catalyst **5** solution and the intermediate **2** reservoir are under protection in Ar atmosphere to prevent any influence by air.

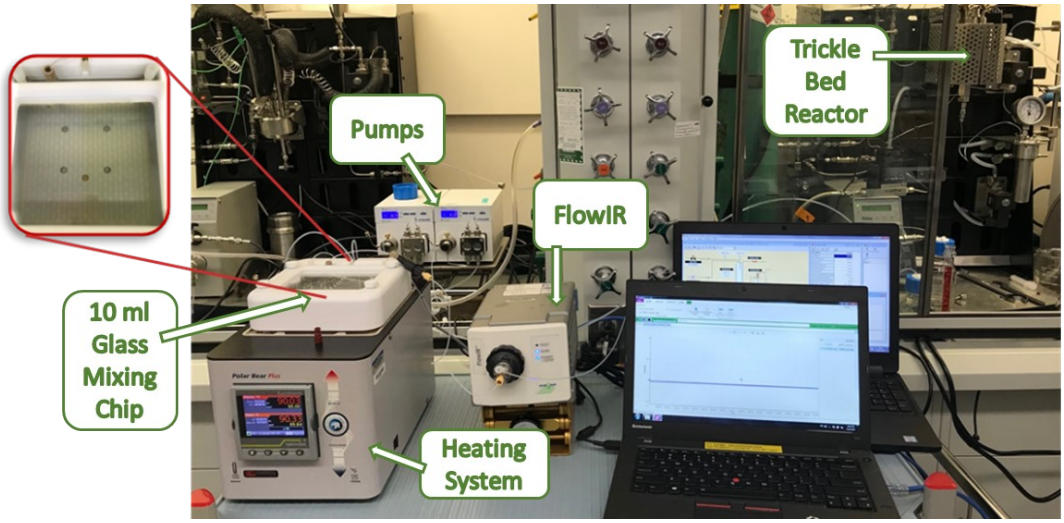

*Figure S10 The instruments setup of the telescoped process for continuous flow production of **3**.*

A total flow rate of 1 mL/min of Substrate **1** and HG2 catalyst **5** (0.5 mol% equiv.) in toluene solutions were fed into the 10 mL glass mixing chip with residence time of 10 min for the RCM reaction. The chip was heated to 90 °C by the Polar Bear Plus platform. The outlet of the glass mixing chip was connected to the FlowIR unit which analyzed the stream composition and interpreted the IR data into reaction conversion and assay yield. Liquid came out of the FlowIR

chamber was collected into a reservoir for intermediate **2** (not shown) then fed into the trickle bed reactor packed with glass beads only (150-212 μm) for hydrogenation. The trickle bed reactor was heated to 120 °C and pressurized with H_2 gas at 300 psi with residence time of 7 min for the hydrogenation step.

GC Analysis in This Study

The GC analysis was done with an Agilent 3790 unit. Reaction conversion and assay yield were calculated from a calibration curve created with purified substrate **1** (retention time = 9.342 min), intermediate **2** (rt = 9.146 min), product **3** (rt = 9.289 min), and cyclohexane as the GC internal standard. The GC column used was a HP-5ms column, 30 m in length with internal diameter of 0.25 mm and film thickness of 0.25 mm. The oven temperature was set at 100 °C for injection and hold for 2 minutes, then ramp up to 300 °C at rate of 25 °C/min and hold for 2 minutes.

NMR Spectra

Intermediate **2**:

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.73-5.77 (m, 1H), 5.60-5.65 (m, 1H), 4.01-4.07 (m, 1H), 3.91-3.98 (m, 2H), 3.83-3.89 (m, 1H), 2.95-3.03 (m, 1H), 2.80-2.86 (m, 1H), 2.61-2.68 (m, 1H), 2.24-2.36 (m, 2H), 2.10-2.18 (m, 1H), 1.42-1.71 (m, 5H), 1.10-1.20 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 210.4, 125.6, 123.1, 110.6, 65.7, 64.3, 56.2, 40.6, 33.6, 33.3, 32.0, 23.6, 22.0.

Product **3**:

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.01-3.82 (m, 4H), 2.50-2.44 (m, 1H), 2.38-2.34 (m, 1H), 2.28-2.22 (m, 1H), 2.11-2.05 (m, 1H), 2.01-1.95 (m, 1H), 1.92-1.86 (m, 1H), 1.81-1.58 (m, 6H), 1.54-1.43 (m, 3H), 1.27-1.18 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 213.2, 110.9, 65.0, 64.2, 57.0, 40.4, 33.3, 32.8, 31.8, 27.3, 23.3, 21.2, 20.6.

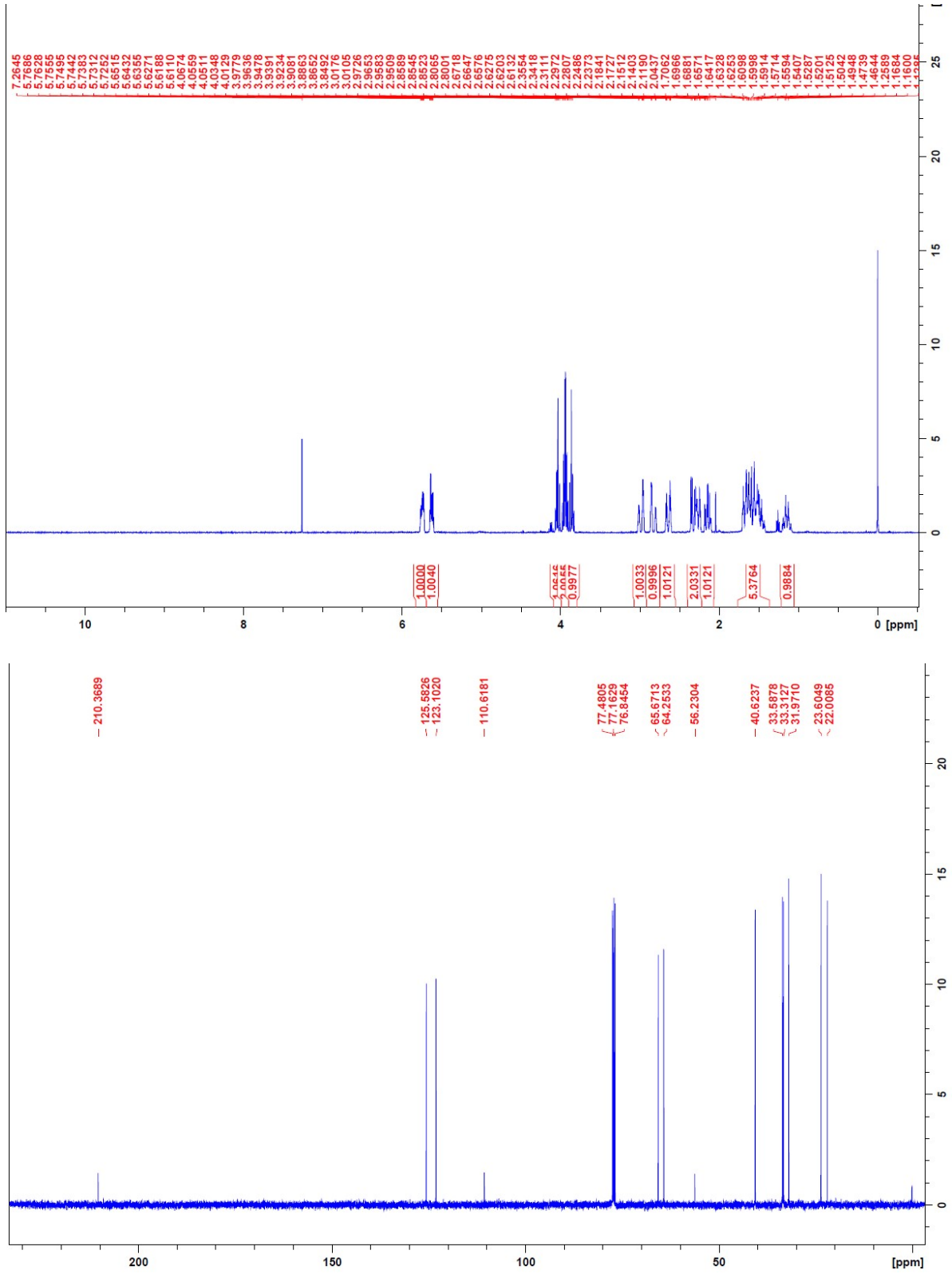

*Figure S11 ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra for the intermediate **2**.*

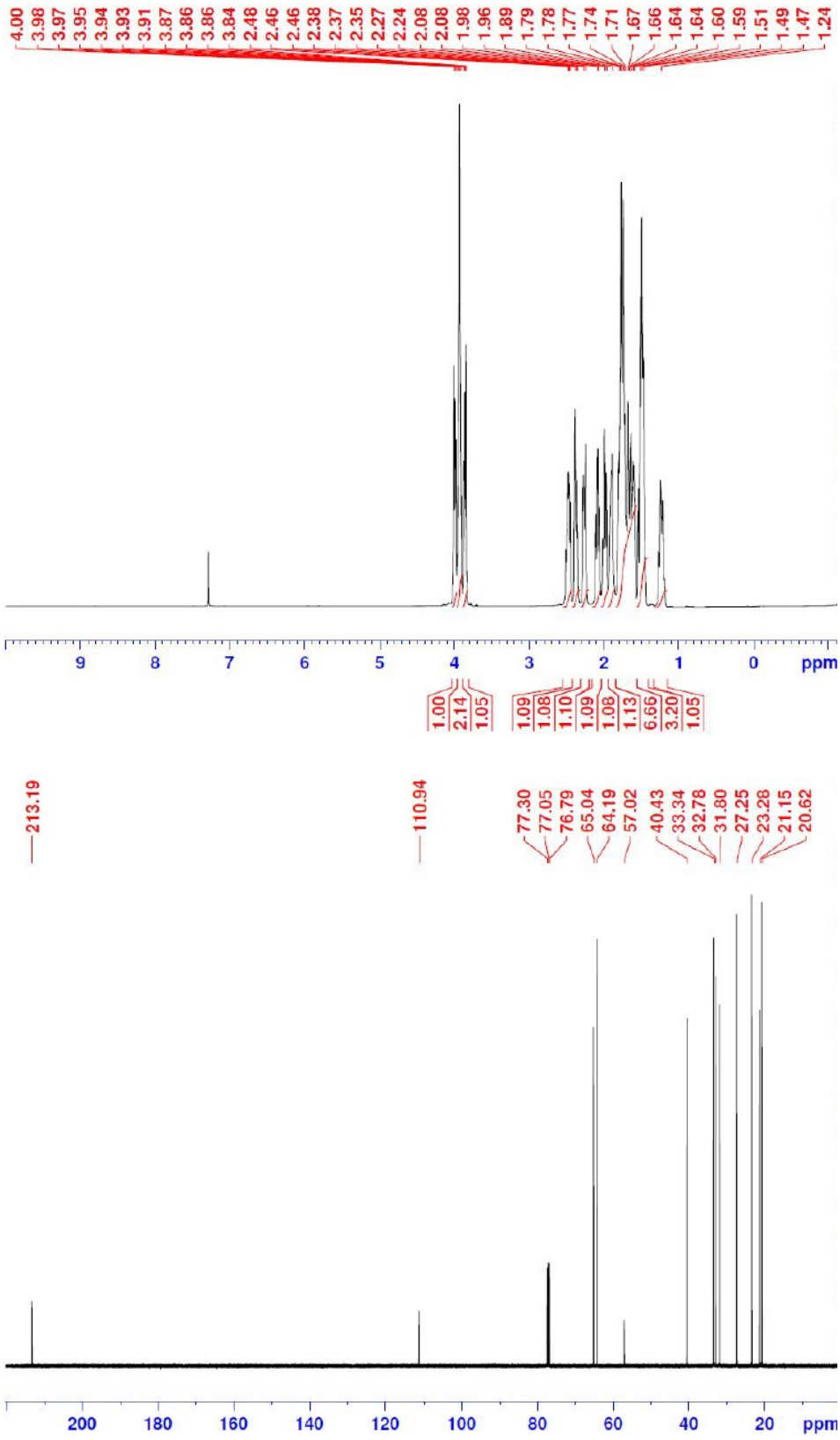

*Figure S12 ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra for the product **3**.*