Supporting Information

Two-Step Continuous Flow Aerobic Oxidation of Cannabidiol to Cannabinoquinone Derivatives

Manuel Zielke,[ab] Christof Aellig,[c] Dominique Roberge,*[c] Christopher A. Hone,*[ab] and C. Oliver Kappe*[ab]

[a] Center for Continuous Synthesis and Processing (CC FLOW), Research Center Pharmaceutical Engineering GmbH (RCPE), Inffeldgasse 13, 8010 Graz, Austria

[b]Institute of Chemistry, University of Graz, NAWI Graz, Heinrichstrasse 28, A-8010 Graz, Austria

[c] Advanced Chemistry Technologies, Lonza AG, CH-3930 Visp, Switzerland.

Contents

1. Materials and Methods 3
   1.1. Solvents and reagents 3
   1.2. Flow Equipment 3
   1.3. NMR spectra 3
   1.4. HPLC Analysis 3
2. Experimental Details 4
   2.1. Optimized Synthesis of (6'R)-6-hydroxy-3'-methyl-4-pentyl-6'-(prop-1-en-2-yl)-[1,1'-bi(cyclohexane)]-2',3,6-triene-2,5-dione (2) 4
   2.2. Thermal Profile for the Synthesis of HU-331 (2) 6
   2.3. Optimized Synthesis of (1'R,6'R)-3-(benzylamino)-6-hydroxy-3'-methyl-4-pentyl-6'-(prop-1-en-2-yl)-[1,1'-bi(cyclohexane)]-2',3,6-triene-2,5-dione (3a) 8
   2.4. Thermal Profile of the Synthesis of Etrinabdione (3a) 10
   2.5. (6'R)-6-hydroxy-3'-methyl-4-pentyl-6'-(prop-1-en-2-yl)-3-(propylamino)-[1,1'-bi(cyclohexane)]-2',3,6-triene-2,5-dione (3b) 11
   2.6. (6'R)-6-hydroxy-3'-methyl-3-(methylamino)-4-pentyl-6'-(prop-1-en-2-yl)-[1,1'-bi(cyclohexane)]-2',3,6-triene-2,5-dione (3c) 13
3. ^{1}H-NMR and ^{13}C-NMR Spectra 15
4. References 20

1. Materials and Methods

1.1. Solvents and reagents

All solvents and reagents were obtained from standard commercial vendors (Sigma-Aldrich/Merck or VWR) and were used without any further purification, unless otherwise noted. Cannabidiol (CBD, **1**) was obtained from Lonza Group AG.

1.2. Flow Equipment

In the flow setup, standard PFA tubing (0.8 mm or 1.6 mm i.d.), fittings, T-pieces manufactured from PTFE or PEEK were used as connectors. A modular microreactor system manufactured by Ehrfeld, containing a base plate, temperature and pressure sensors, two capillary reactors, a Lonza FlowPlate™, inlets and outlets was used. The back pressure regulator (BPR-10) was obtained from Zaiput Flow Technologies. Temperature was controlled by a Huber Minstat 240.

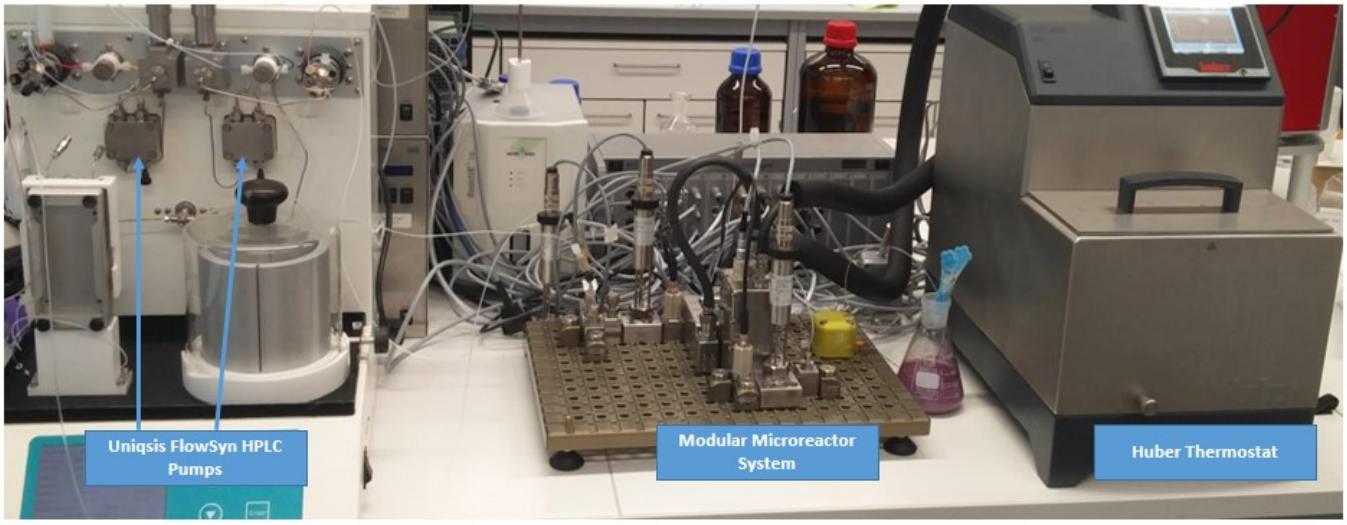


Figure S1. Continuous flow setup consisting of Uniqsis FlowSyn HPLC pumps, a modular microreactor system (Ehrfeld) and a Huber thermostat.

1.3. NMR spectra

^{1}H NMR spectra were recorded on a Bruker 300 MHz instrument. ^{13}C NMR spectra were recorded on the 300 MHz instrument at 75 MHz. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, dd, t, q, and m are used to indicate singlet, doublet, doublet of doublets, triplet, quadruplet, and multiplet.

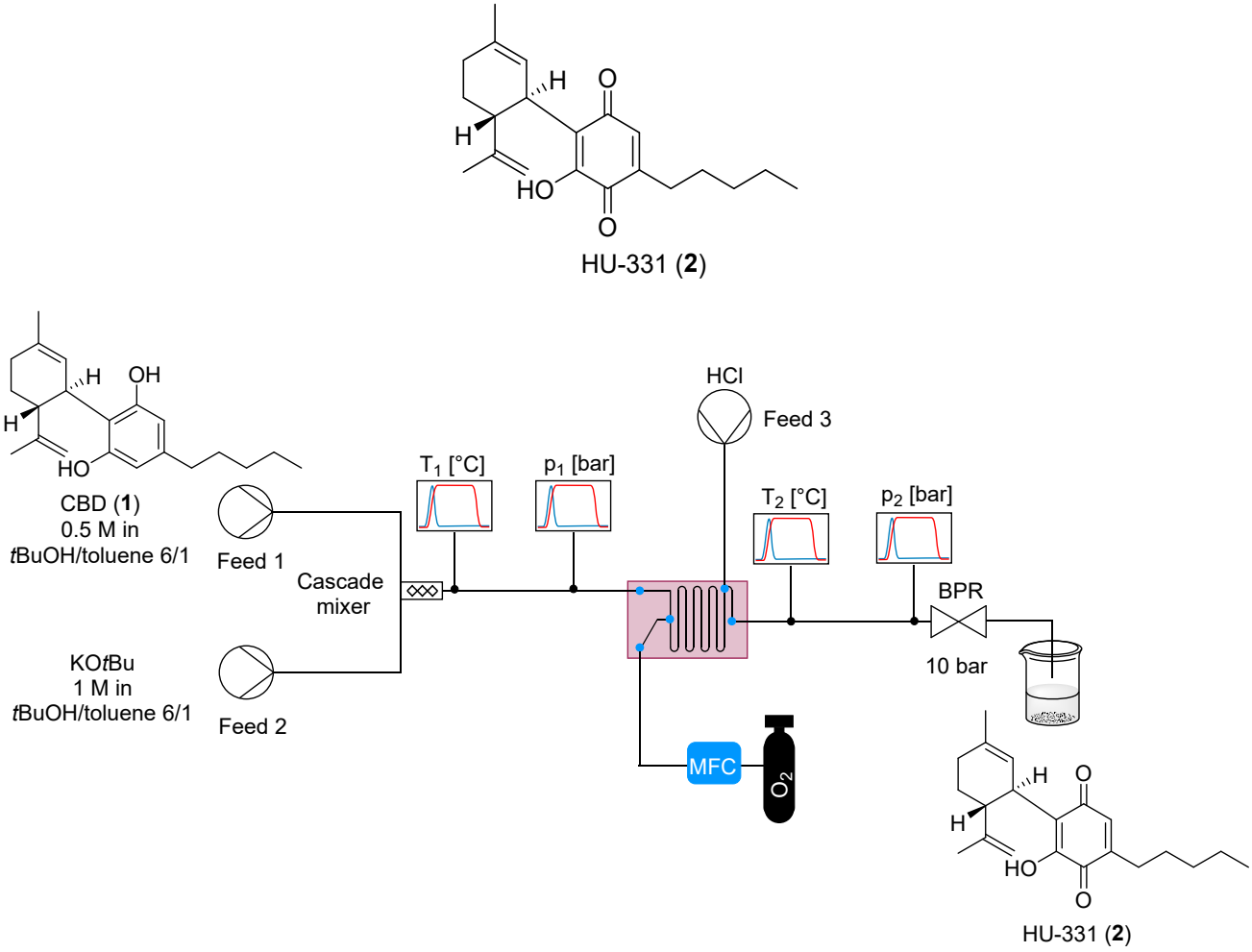
1.4. HPLC Analysis

Analytical HPLC (Shimadzu LC20) analysis was carried out on a C18 reversed-phase (RP) analytical column (150 mm × 4.6 mm, particle size 5 µm) at 37 °C using mobile phases A (H_2O/MeCN (90:10 = v:v) + 0.1% TFA) and B (MeCN + 0.1% TFA) at a flow rate of 1.5 mL/min. The following gradients were applied: A: linear increase from 30% B to 100% B within 10 min, for the separation of VCE-004 and

derivatives. B: linear increase from 30% B to 100% B within 10 min for all other separation problems.

2. Experimental Details

2.1. Optimized Synthesis of (6'R)-6-hydroxy-3'-methyl-4-pentyl-6'-(prop-1-en-2-yl)-[1,1'-bi(cyclohexane)]-2',3,6-triene-2,5-dione (2)



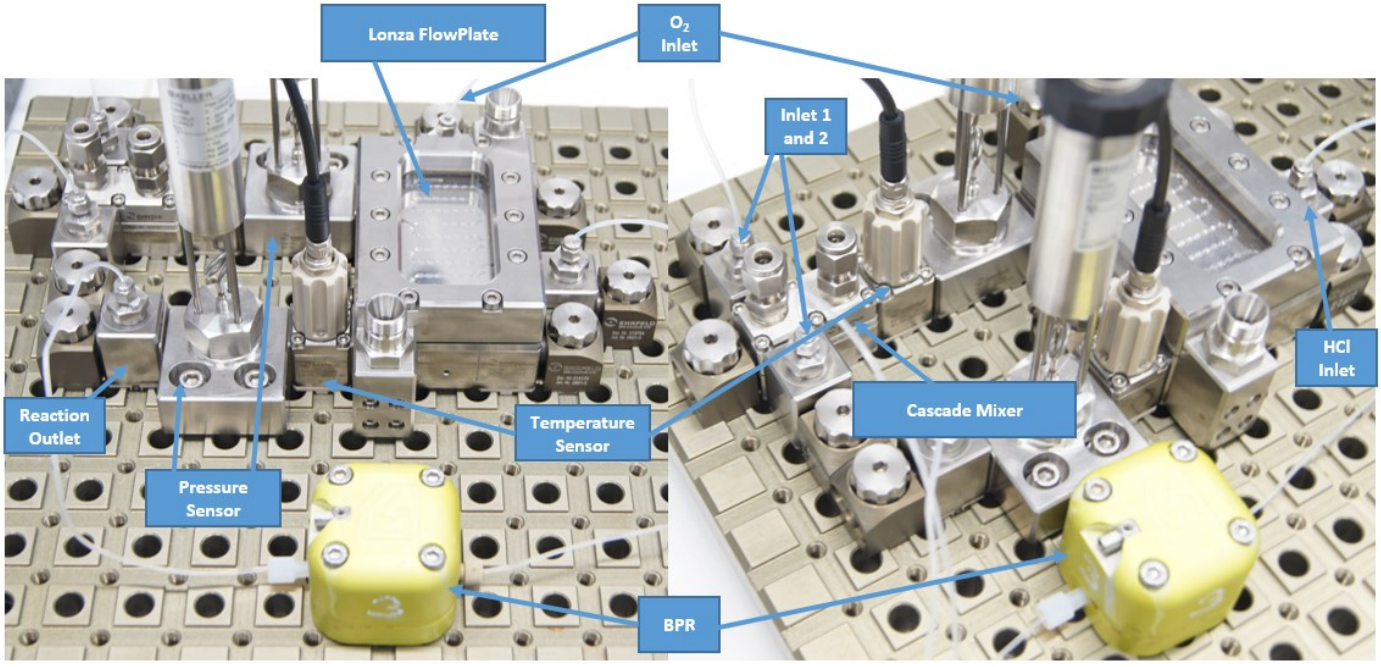


Figure S2. Modified flow configuration for inline temperature and pressure monitoring.

The flow setup consisted of two HPLC pumps (Uniqsis FlowSyn, Feed 1 and 2) and one continuous syringe pump (HighTec Zhang Syrdos, Feed 3).

Input solutions for feeds 1 and 2 were prepared with dry *tert*-Butanol/toluene (6:1 = v:v), in oven-dried volumetric flasks as follows:

Feed 1: 0.5 M Cannabidiol (CBD, **1**) (31.4 g, 100 mmol) in dry *tert*-Butanol/toluene (6:1 = v:v) within a 200 mL volumetric flask.

Feed 2: 1.0 M KO*t*Bu (28.1 g, 250 mmol) in dry *tert*-Butanol/toluene (6:1 = v:v) within a 250 mL volumetric flask.

Feed 3 was made up from 0.5 M HCl in water.

Feeds 1, 2 and 3 were directly pumped through the pumps.

Before commencing the experiment, the reactor setup was flushed by pumping dry *tert*-Butanol/toluene (6:1 = v:v) with a flow rate of 1.05 mL/min; using the pump for feed 1; and 1.1 mL/min using the pump for feed 2. Oxygen was introduced into the reactor with a flow rate of 13.00 mL/min (1.1 equiv) using a calibrated mass flow controller (MFC, Bronkhorst, EL-FLOW). Subsequently, aqueous HCl (Feed 3) was introduced into the flow system with a flow rate of 2.7 mL/min (2.5 equiv).

To commence the experiment, the pumping of dry *tert*-Butanol/toluene (6:1 = v:v) at pumps 1 and 2 was switched to their respective input solution whilst maintaining their flow rate.

Feed 1 and 2 were combined within a split and recombine mixer (Ehrfeld Cascade Mixer 06 HC, volume V1 = 103 µL) at room temperature. The mixture was passed through a temperature sensor T_1 (Ehrfeld Temperature Sensor Xyfluor 0501-1: volume V2 = 165 µL) and a pressure sensor p_1 (Ehrfeld p-Sensor Module HC: volume V3 = 560 µL) before it was combined with oxygen within a microreactor (Ehrfeld FlowPlate Lab Microreactor HC, Process plate LL, channel width = 2 mm, mixer nominal width = 0.2 mm, volume V = 0.35 mL) for three mixing zones (V4 = 166 µL). The Ehrfeld FlowPlate was heated to 30 °C by using a thermostat (Huber Ministat 240, 4000 rpm). Feed 3 was introduced within the flow plate after mixing zone 3 before leaving the reactor (V5 = 179 µL). The reaction stream was passed through a temperature sensor T_2 (Ehrfeld Temperature Sensor Xyfluor 0501-1: volume V6 = 165 µL), a pressure sensor p_2 (Ehrfeld p-Sensor Module HC: volume V7 = 560 µL) before flowing through an outlet (Ehrfeld MMRS, Fitok 1/16" HC, volume V8 = 410 µL). After passing a back pressure regulator (Zaiput BPR-10); maintaining a back pressure of 9-10 bar; the process stream was collected.

The effluent was collected over 180 min (corresponding to 94.5 mmol of material) and extracted with EtOAc (3x100 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford HU-331 (**2**) as orange crystals. (30.99 g, 94.4 mmol, 99% yield). Mp. = 55 °C. ^{1}H NMR (300.36 MHz, $CDCl_3$): δ = 7.07 (s, 1H), 6.41 (t, J = 1.5 Hz, 1H), 5.15 (s, 1H), 4.55 (q, J = 1.3 Hz, 2H), 3.80 – 3.65 (m, 1H), 2.77 (ddd, J = 11.9, 10.8, 3.1 Hz, 1H), 2.48 – 2.33 (m, 2H), 2.30 – 2.14 (m, 1H), 2.06 – 1.94 (m, 1H), 1.86 – 1.70 (m, 1H), 1.70 – 1.66 (m, 3H), 1.64 (d, J = 1.1 Hz, 3H), 1.51 (ddd, J = 9.1, 5.3, 2.0 Hz, 2H), 1.33 (td, J = 4.4, 2.2 Hz, 4H), 0.95 – 0.84 (m, 3H) ppm.^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.3, 184.2, 151.4, 148.5, 144.6, 134.8, 134.1, 122.9, 122.5, 110.8, 44.8, 35.8, 31.5, 31.3, 30.6, 28.9, 28.2, 27.2, 23.5, 22.5, 18.8, 14.0 ppm. The obtained data match those reported in the literature.[1,2]

2.2. Thermal Profile for the Synthesis of HU-331 (2)

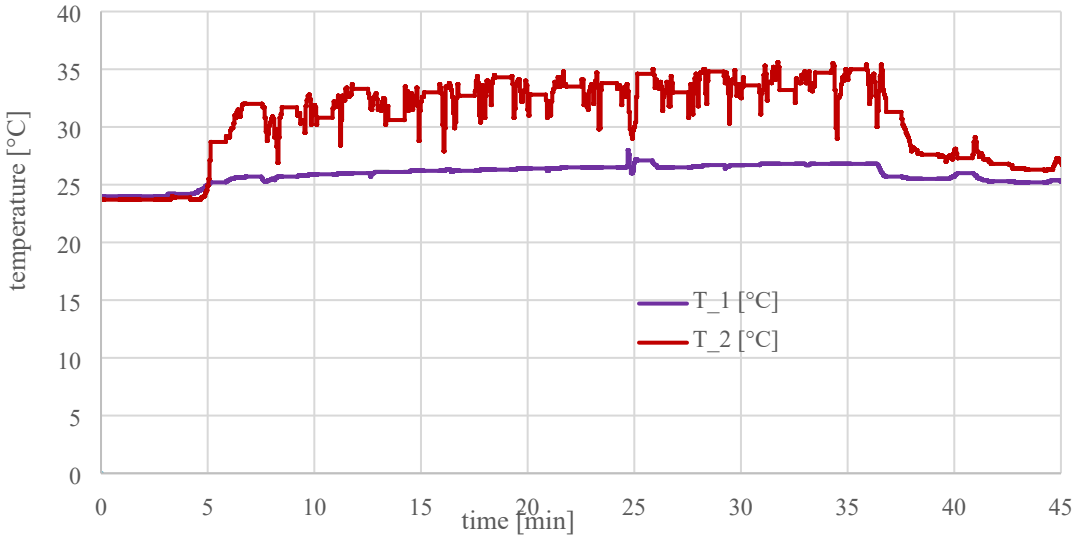


Figure S3. Thermal profile of the reaction stream for the synthesis of HU-331 (**2**) before and after addition of oxygen in the LL mixing plate when using 7 mixing structures.

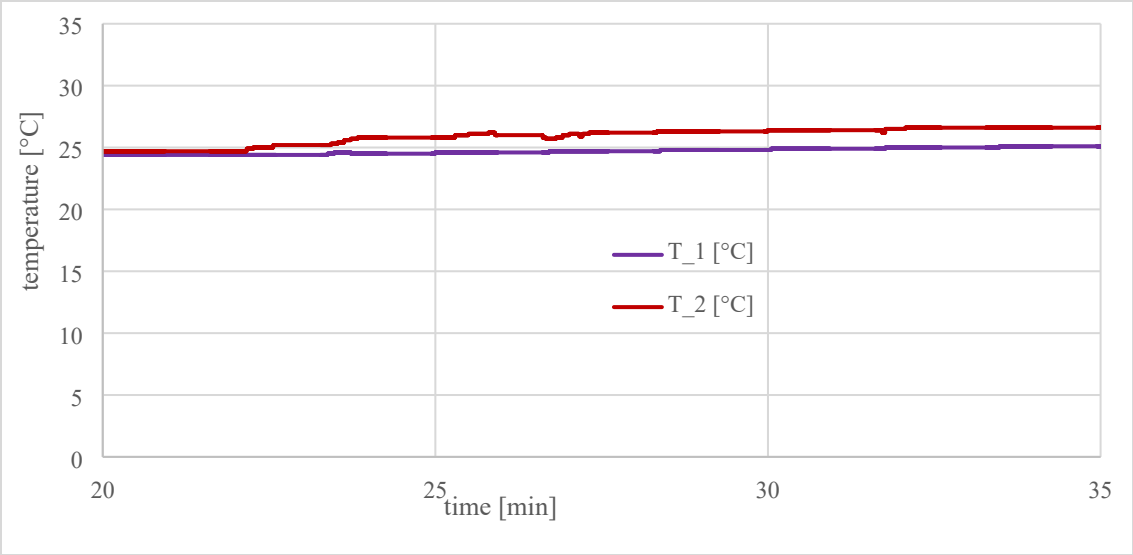
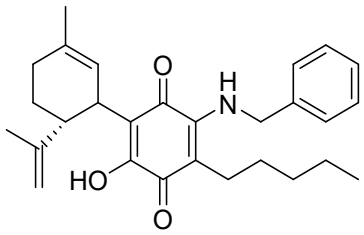
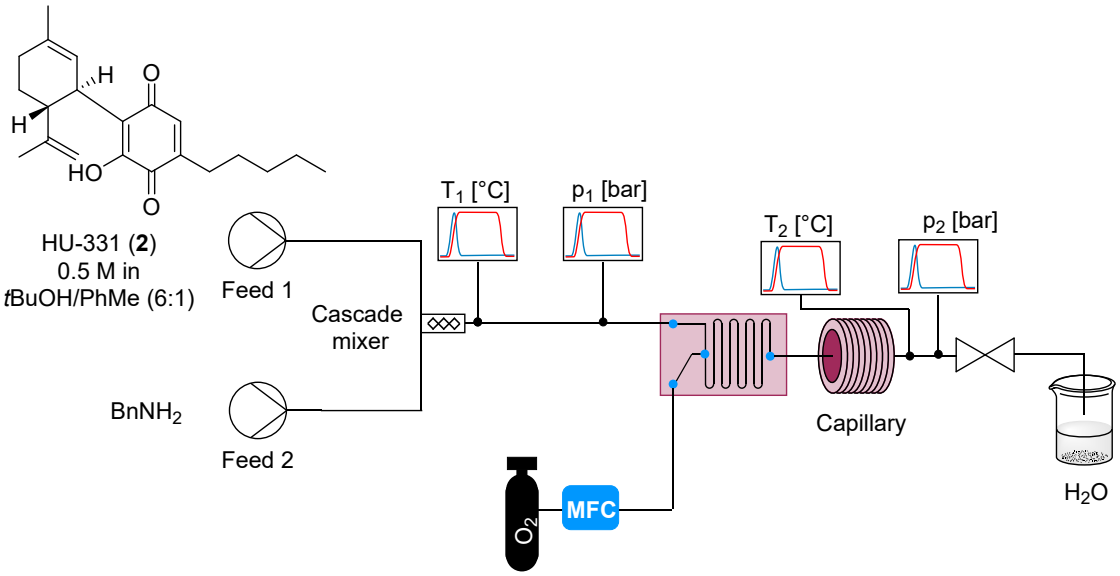


Figure S4. Thermal profile of the reaction stream for the synthesis of HU-331 (**2**) before and after addition of oxygen in the LL mixing plate when using all 70 mixing structures.

2.3. Optimized Synthesis of (1'R,6'R)-3-(benzylamino)-6-hydroxy-3'-methyl-4-pentyl-6'-(prop-1-en-2-yl)-[1,1'-bi(cyclohexane)]-2',3,6-triene-2,5-dione (3a)



3a



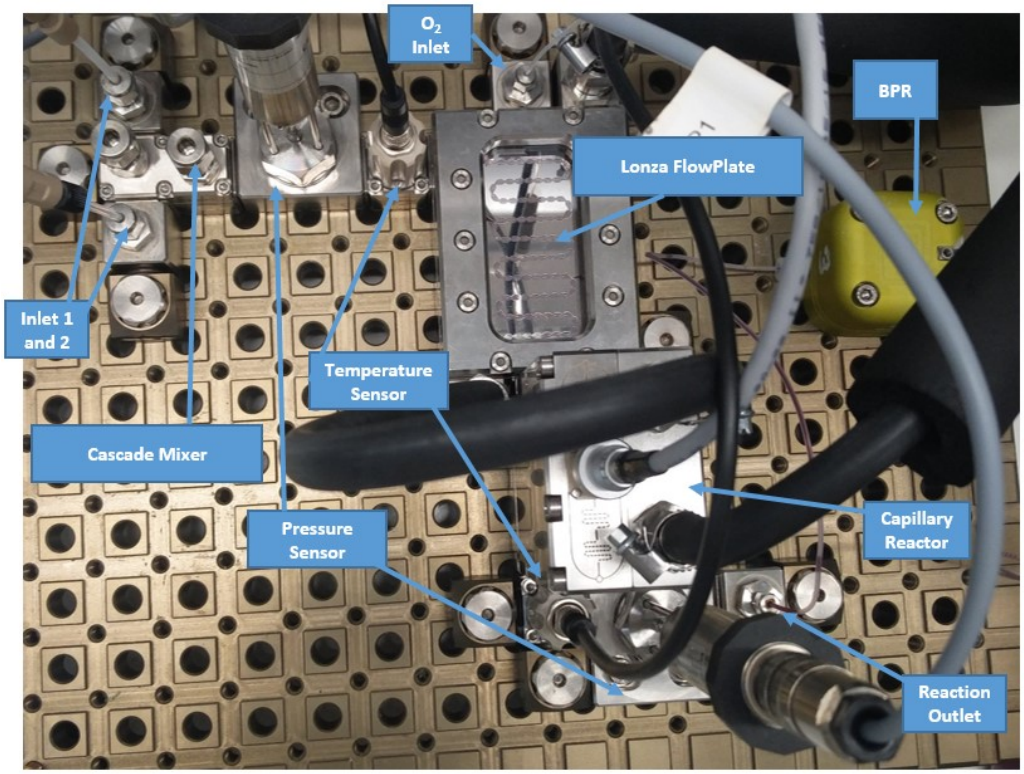


Figure S5. Continuous flow configuration for the oxidative amination of HU-331 (**2**) to **3a**

The flow setup consisted of two HPLC pumps (Uniqsis FlowSyn, Feed 1 and 2).

The input solution for feed 1 was prepared with dry *tert*-Butanol/toluene (6:1 = v:v), in an oven-dried volumetric flask as follows:

Feed 1: 0.5 M HU-331 (**2**) (16.4 g, 50 mmol) in dry *tert*-Butanol/toluene (6:1 = v:v) within a 100 mL volumetric flask.

Feed 2: Benzylamine (9.15 M) in a 250 mL glass flask.

Before commencing the experiment, the reactor setup was flushed by pumping dry *tert*-Butanol/toluene (6:1 = v:v) with a flow rate F1 = 0.75 mL/min; using the pump for feed 1; and neat benzylamine with F2 = 0.41 mL/min using the pump for feed 2. Oxygen was introduced into the reactor with a flow rate of 12.5 mL/min (1.5 equiv) using a calibrated Bronkhorst MFC.

To commence the experiment, the pumping of dry *tert*-Butanol/toluene (6:1 = v:v) at pump 1 was switched to the respective input solution whilst maintaining the flow rate.

Feed 1 and 2 were combined within a split and recombine mixer (Ehrfeld Cascade Mixer 06 HC, volume V1 = 103 µL) at room temperature. The mixture was passed through a temperature sensor T_1 (Ehrfeld Temperature Sensor Xyfluor 0501-1: volume V2 = 165 µL), a pressure sensor p_1 (Ehrfeld p-Sensor Module HC: volume V3 = 560 µL) before it was combined with oxygen within a microreactor (Ehrfeld FlowPlate Lab Microreactor HC, Process plate LL, channel width = 2 mm, mixer nominal width = 0.2 mm, volume V4 = 0.35 mL). After leaving the microreactor, the reaction stream passed through two capillary reactors (Ehrfeld F348 HC, total volume V5 = 10.01 mL), a temperature sensor T_2 (Ehrfeld Temperature Sensor Xyfluor 0501-1: volume V6 = 165 µL) and a pressure sensor p_2 (Ehrfeld p-Sensor Module HC: volume V7 = 560 µL). After passing through a back pressure regulator (Zaiput BPR-10); maintaining a back pressure of 13-14 bar; the process stream was collected in a water bath. The Ehrfeld FlowPlate and the capillary reactors were heated to 30 °C by using a thermostat (Huber Ministat 240, 4000 rpm).

The mixture was collected over 120 min (corresponding to 45 mmol of material) in water. After adjusting the pH of the aqueous phase to 2 with HCl the product was extracted with EtOAc (3x100 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained solid was grinded and dried under vacuo to afford Etrinabdione (**3a**) as purple amorphous solid. (19.4 g, 44.95 mmol, 99% yield). Mp. = 91-92 °C.^{1}H NMR (300.36 MHz, $CDCl_3$): δ = 7.07 (s, 1H), 6.41 (t, J = 1.5 Hz, 1H), 5.15 (s, 1H), 4.55 (q, J = 1.3 Hz, 2H), 3.80 – 3.65 (m, 1H), 2.77 (ddd, J = 11.9, 10.8,

3.1 Hz, 1H), 2.48 – 2.33 (m, 2H), 2.30 – 2.14 (m, 1H), 2.06 – 1.94 (m, 1H), 1.86 – 1.70 (m, 1H), 1.70 – 1.66 (m, 3H), 1.64 (d, J = 1.1 Hz, 3H), 1.51 (ddd, J = 9.1, 5.3, 2.0 Hz, 2H), 1.33 (td, J = 4.4, 2.2 Hz, 4H), 0.95 – 0.84 (m, 3H) ppm.^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.3, 184.2, 151.4, 148.5, 144.6, 134.8, 134.1, 122.9, 122.5, 110.8, 44.8, 35.8, 31.5, 31.3, 30.6, 28.9, 28.2, 27.2, 23.5, 22.5, 18.8, 14.0 ppm. The obtained data match those reported in the literature.[2]

2.4. Thermal Profile of the Synthesis of Etrinabdione (3a)

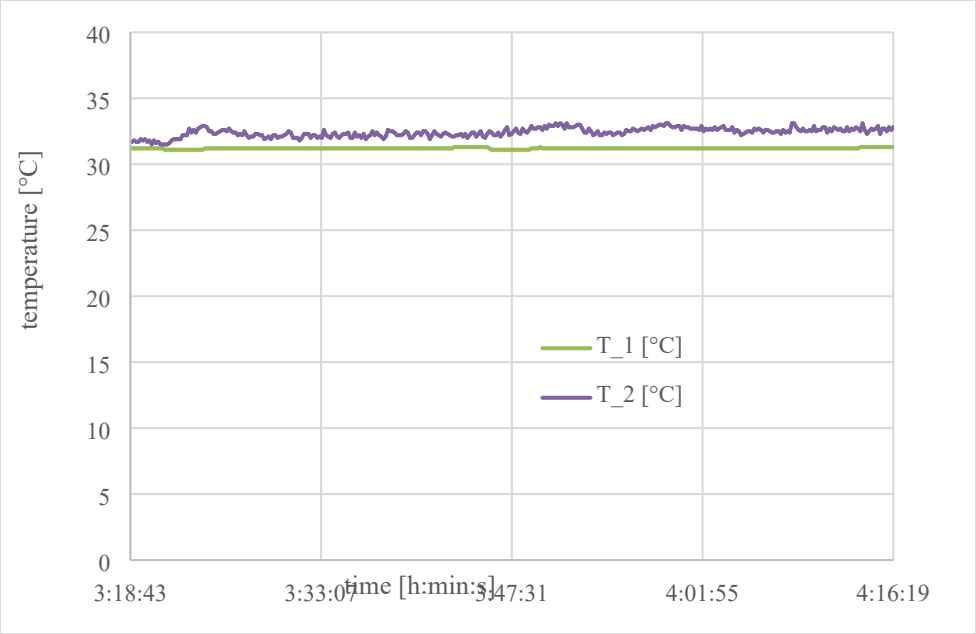
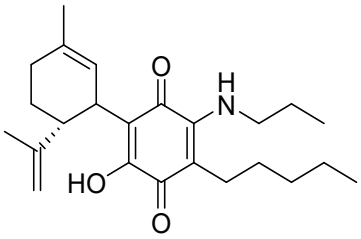
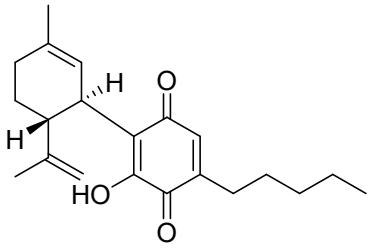


Figure S6. Thermal profile of the reaction stream for the synthesis of VCE-004.8 (**3a**) before and after addition of oxygen in a Lonza FlowPlate when using all 70 mixing structures.

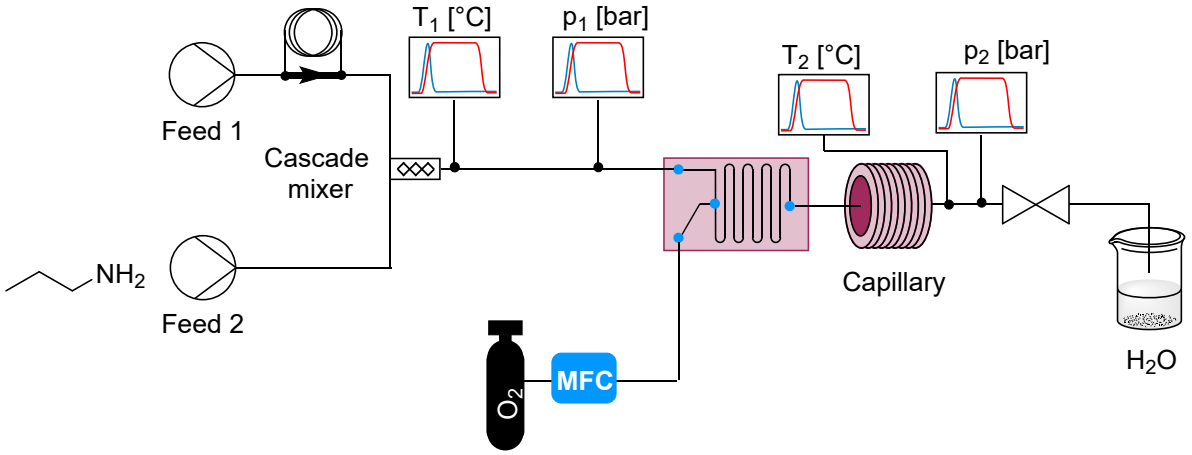
2.5. (6'R)-6-hydroxy-3'-methyl-4-pentyl-6'-(prop-1-en-2-yl)-3-(propylamino)-[1,1'-bi(cyclohexane)]-2',3,6-triene-2,5-dione (3b)



3b



HU-331 (**2**)
0.5 M in *t*BuOH/PhMe (6:1)



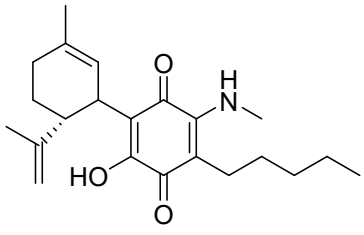
The flow setup consisted of two HPLC pumps (Uniqsis FlowSyn, Feed 1 and 2).

Before commencing the experiment, the reactor setup was flushed by pumping dry *tert*-Butanol/toluene (6:1 = v:v) with a flow rate F1 = 0.75 mL/min; using the pump for feed 1; and neat Propylamine (12.1 M) with F2 = 0.41 mL/min using the pump for feed 2. Oxygen was introduced into the reactor with a flow rate of 12.5 mL/min (1.5 equiv) using a calibrated Bronkhorst MFC. A sample loop (3 mL) was loaded with HU-331 (0.5 M in *t*BuOH:toluene = 6:1). To commence the experiment, the sample loop was injected into feed 1 whilst maintaining the flow rate of feed 1.

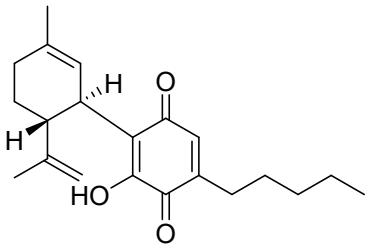
Feed 1 and 2 were combined within a split and recombine mixer (Ehrfeld Cascade Mixer 06 HC, volume V1 = 103 µL) at room temperature. The mixture was passed through a temperature sensor T_1 (Ehrfeld Temperature Sensor Xyfluor 0501-1: volume V2 = 165 µL), a pressure sensor p_1 (Ehrfeld p-Sensor Module HC: volume V3 = 560 µL) before it was combined with oxygen within a microreactor (Ehrfeld

FlowPlate Lab Microreactor HC, Process plate LL, channel width = 2 mm, mixer nominal width = 0.2 mm, volume V4 = 0.35 mL). After leaving the microreactor, the reaction stream passed through two capillary reactors (Ehrfeld F348 HC, total volume V5 = 10.01 mL) a temperature sensor T_2 (Ehrfeld Temperature Sensor Xyfluor 0501-1: volume V6 = 165 µL), and a pressure sensor p_2 (Ehrfeld p-Sensor Module HC: volume V7 = 560 µL). After passing through a back pressure regulator (Zaiput BPR-10); maintaining a back pressure of 13-14 bar; the process stream was collected in a water bath. The Ehrfeld FlowPlate and the capillary reactors were heated to 30 °C by using a thermostat (Huber Ministat 240, 4000 rpm). The reaction mixture was collected in water. After adjusting the pH of the aqueous phase to 2 with HCl the product was extracted with EtOAc (3x25 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained solid was grinded and dried under vacuo to afford **3b** as purple amorphous solid. (550 mg, 1.43 mmol, 95% yield). Mp. 97-98 °C; ^{1}H NMR (300.36 MHz, $CDCl_3$): δ = 7.99 (s, 1H), 6.45 (t, J = 5.9 Hz, 1H), 5.10 (s, 1H), 4.53 (s, 2H), 3.69 – 3.52 (m, 1H), 3.46 – 3.33 (m, 2H), 2.69 (ddd, J = 12.0, 10.7, 3.0 Hz, 1H), 2.51 – 2.37 (m, 2H), 2.25 – 2.08 (m, 1H), 1.99 – 1.88 (m, 1H), 1.78 – 1.68 (m, 2H), 1.64 (dd, J = 4.5, 2.7 Hz, 5H), 1.59 (d, J = 1.2 Hz, 4H), 1.45 – 1.21 (m, 7H), 0.96 (t, J = 7.4 Hz, 3H), 0.91 – 0.80 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.9, 179.5, 154.9, 148.5, 145.5, 133.4, 123.2, 116.1, 110.6, 106.4, 46.4, 44.5, 36.1, 31.8, 30.5, 29.0, 23.8, 23.7, 23.5, 22.5, 18.8, 14.1, 11.2 ppm. HRMS (ESI+) m/z calcd. for $C_{24}H_{35}NO_3$:386.2689; found: 386.2687. The obtained data match those reported in the literature.[2]

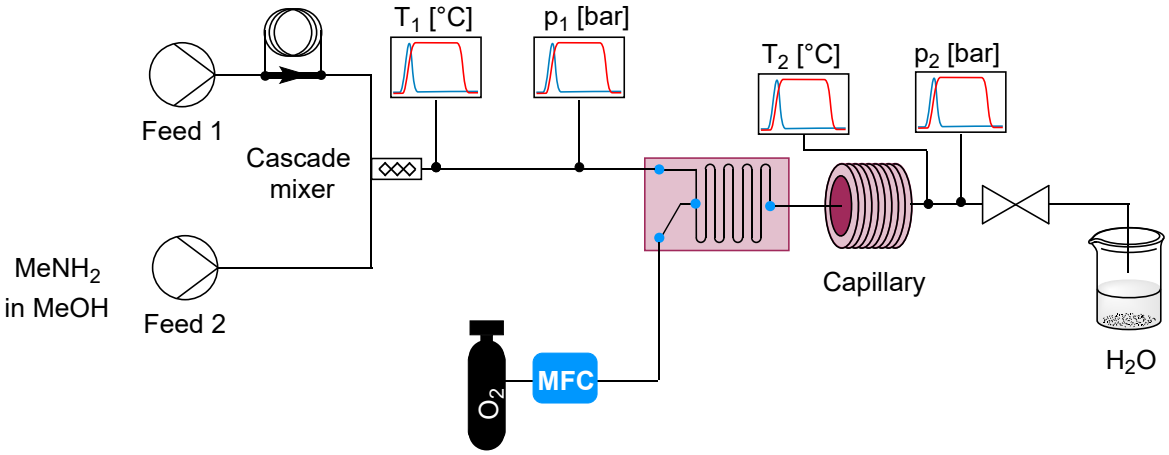
2.6. (6'R)-6-hydroxy-3'-methyl-3-(methylamino)-4-pentyl-6'-(prop-1-en-2-yl)-[1,1'-bi(cyclohexane)]-2',3,6-triene-2,5-dione (3c)



3c



HU-331 (**2**)
0.5 M in *t*BuOH/PhMe (6:1)



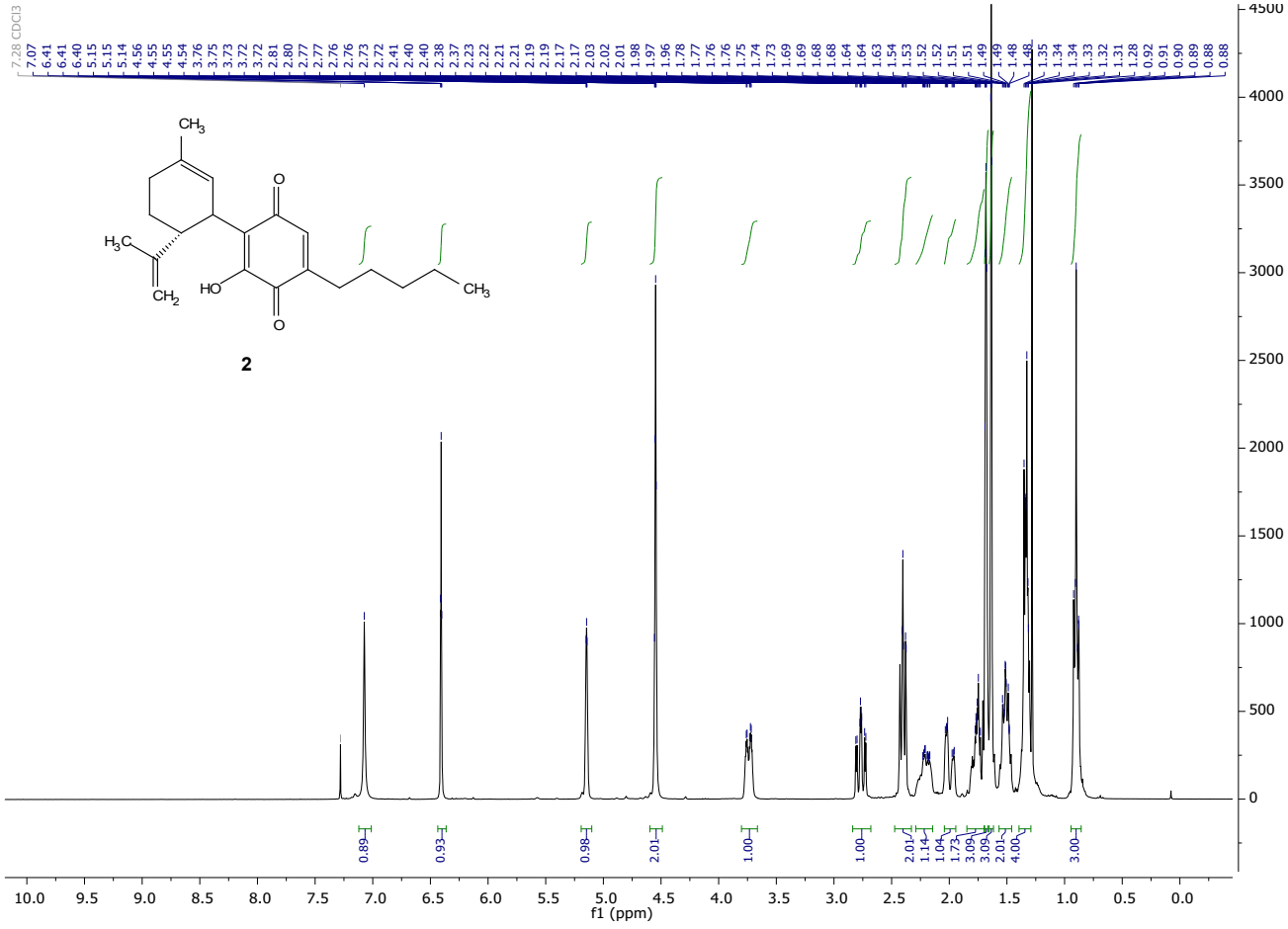
The flow setup consisted of two HPLC pumps (Uniqsis FlowSyn, Feed 1 a 2).

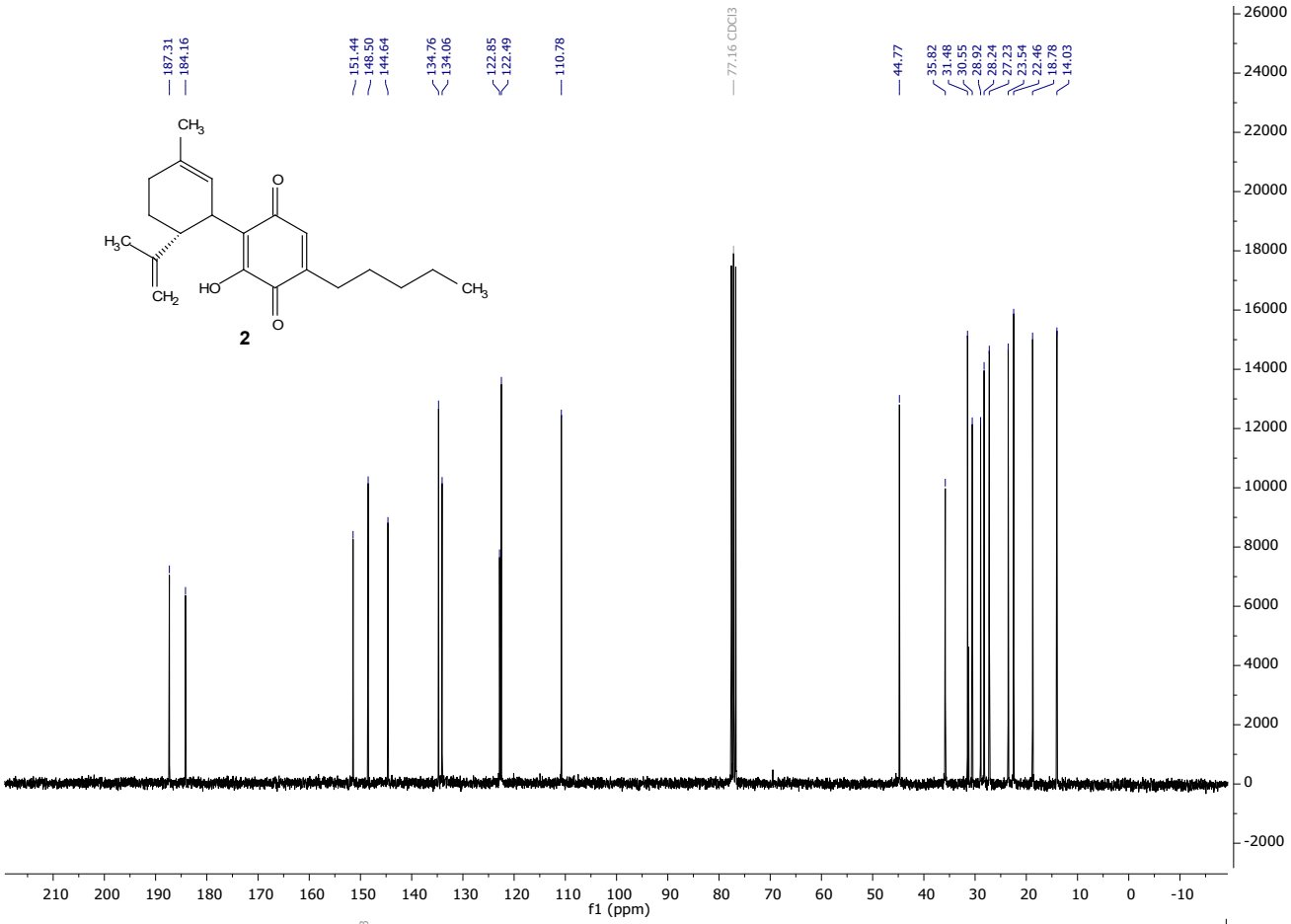
Before commencing the experiment, the reactor setup was flushed by pumping dry *tert*-Butanol/toluene (6:1 = v:v) with a flow rate F1 = 0.75 mL/min; using the pump for feed 1; and Methylamine (9.81 M in MeOH) with F2 = 0.21 mL/min using the pump for feed 2. Oxygen was introduced into the reactor with a flow rate of 12.5 mL/min (1.5 equiv) using a calibrated Bronkhorst MFC. A sample loop (3 mL) was loaded with HU-331 (0.5 M in *t*BuOH:toluene = 6:1). To commence the experiment, the sample loop was injected into feed 1 whilst maintaining the flow rate of feed 1.

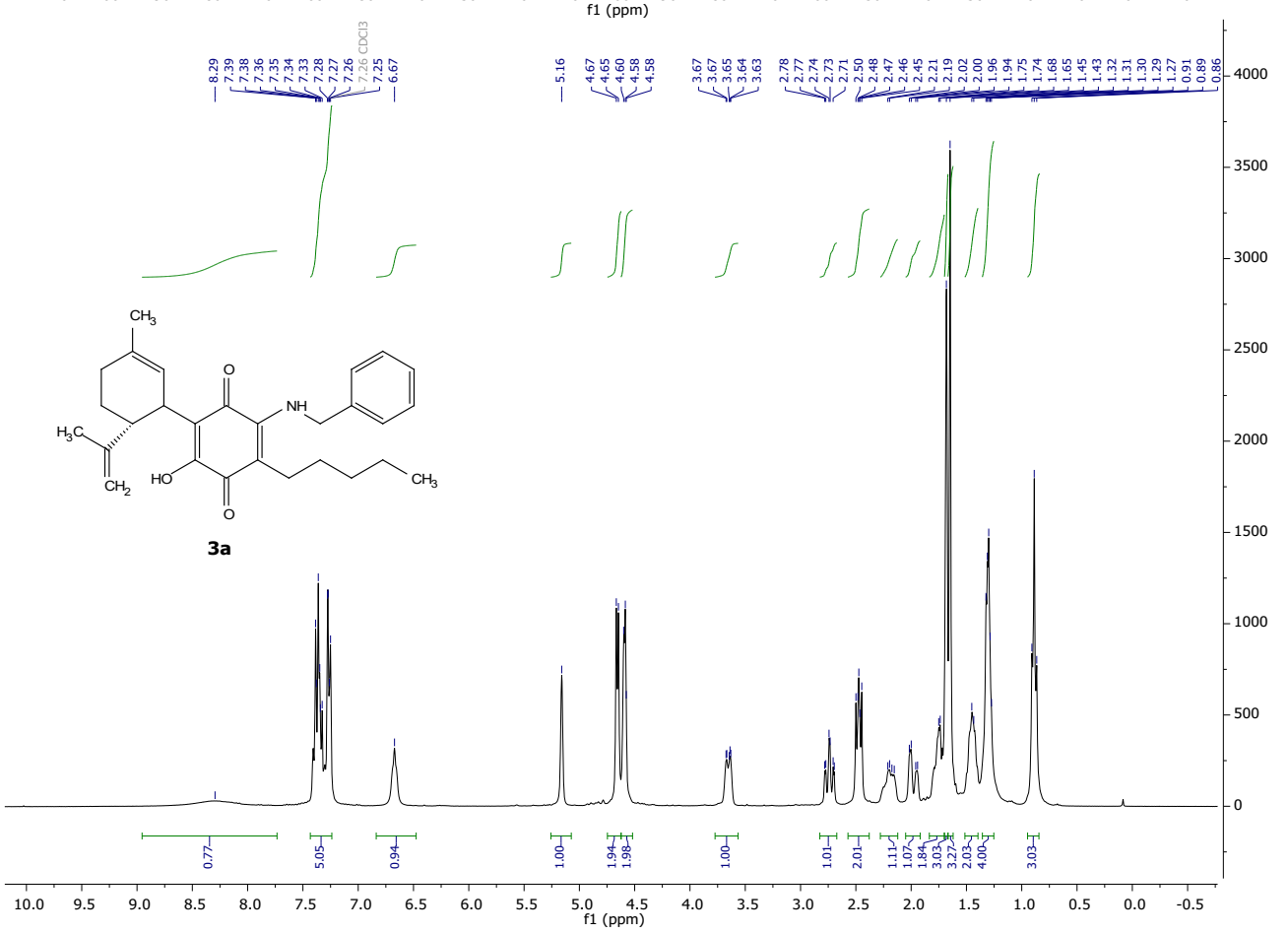
Feed 1 and 2 were combined within a split and recombine mixer (Ehrfeld Cascade Mixer 06 HC, volume V1 = 103 µL) at room temperature. The mixture was passed through a temperature sensor T_1 (Ehrfeld Temperature Sensor Xyfluor 0501-1: volume V2 = 165 µL), a pressure sensor p_1 (Ehrfeld p-Sensor Module HC: volume V3 = 560 µL) before it was combined with oxygen within a microreactor (Ehrfeld FlowPlate Lab Microreactor HC, Process plate LL, channel width = 2 mm, mixer nominal width =

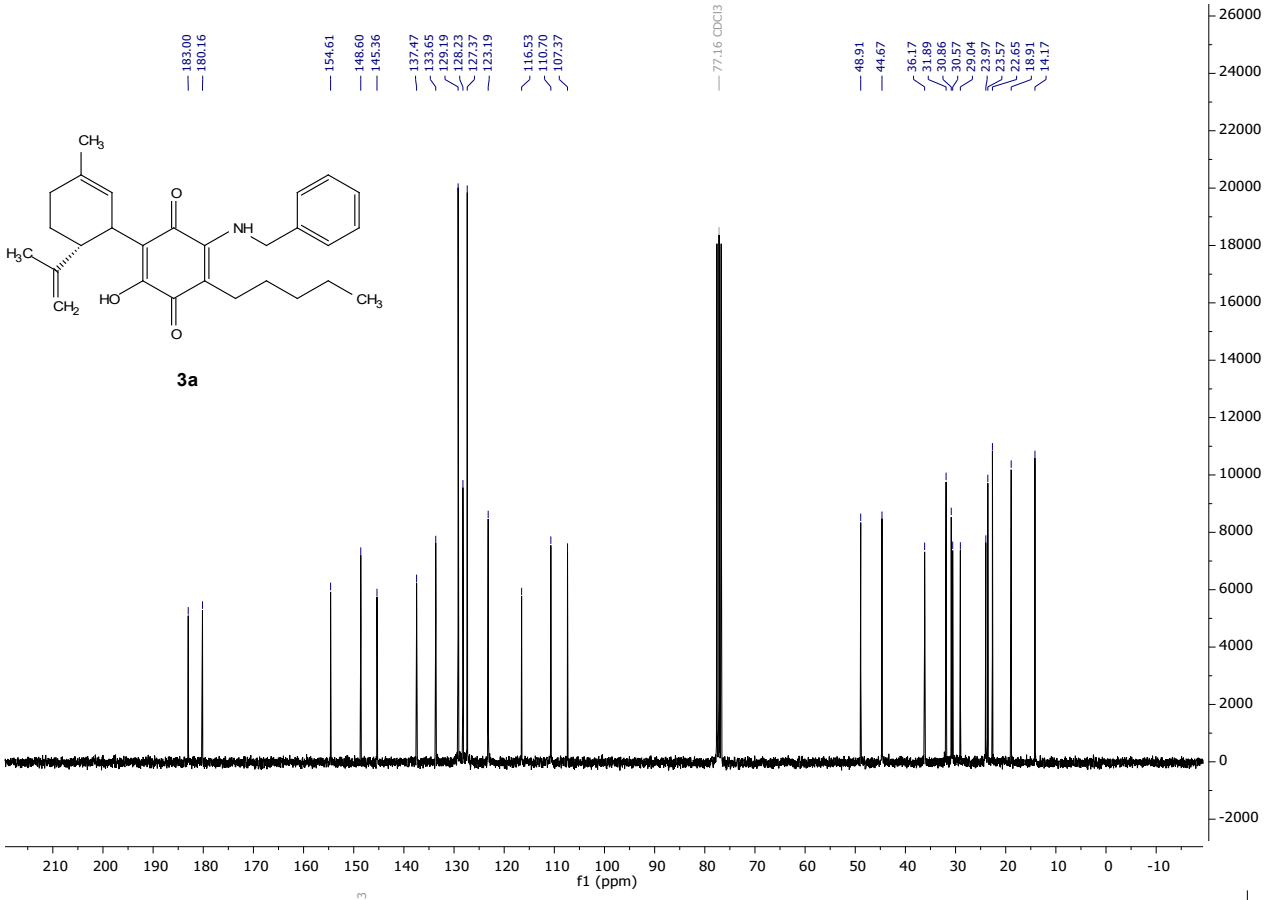
0.2 mm, volume V4 = 0.35 mL). After leaving the microreactor, the reaction stream passed through two capillary reactors (Ehrfeld F348 HC, total volume V5 = 10.01 mL), a temperature sensor T_2 (Ehrfeld Temperature Sensor Xyfluor 0501-1: volume V6 = 165 µL) and a pressure sensor p_2 (Ehrfeld p-Sensor Module HC: volume V7 = 560 µL). After passing through a back pressure regulator (Zaiput BPR-10); maintaining a back pressure of 13-14 bar; the process stream was collected in a water bath. The Ehrfeld FlowPlate and the capillary reactors were heated to 30 °C by using a thermostat (Huber Ministat 240, 4000 rpm). The reaction mixture was collected in water. After adjusting the pH of the aqueous phase to 2 with HCl the product was extracted with EtOAc (3x25 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained solid was grinded and dried under vacuo to give **3c** as purple amorphous solid. (511 mg, 1.43 mmol, 95% yield). Mp. 112-113 °C; ^{1}H NMR (300.36 MHz, $CDCl_3$): δ = 7.99 (s, 1H), 6.45 (t, J = 5.9 Hz, 1H), 5.10 (s, 1H), 4.53 (s, 2H), 3.69 – 3.52 (m, 1H), 3.46 – 3.33 (m, 2H), 2.69 (ddd, J = 12.0, 10.7, 3.0 Hz, 1H), 2.51 – 2.37 (m, 2H), 2.25 – 2.08 (m, 1H), 1.99 – 1.88 (m, 1H), 1.78 – 1.68 (m, 2H), 1.64 (dd, J = 4.5, 2.7 Hz, 5H), 1.59 (d, J = 1.2 Hz, 4H), 1.45 – 1.21 (m, 7H), 0.96 (t, J = 7.4 Hz, 3H), 0.91 – 0.80 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.9, 179.5, 154.9, 148.5, 145.5, 133.4, 123.2, 116.1, 110.6, 106.4, 46.4, 44.5, 36.1, 31.8, 30.5, 29.0, 23.8, 23.7, 23.5, 22.5, 18.8, 14.1, 11.2 ppm.

3. ^{1}H-NMR and ^{13}C-NMR Spectra

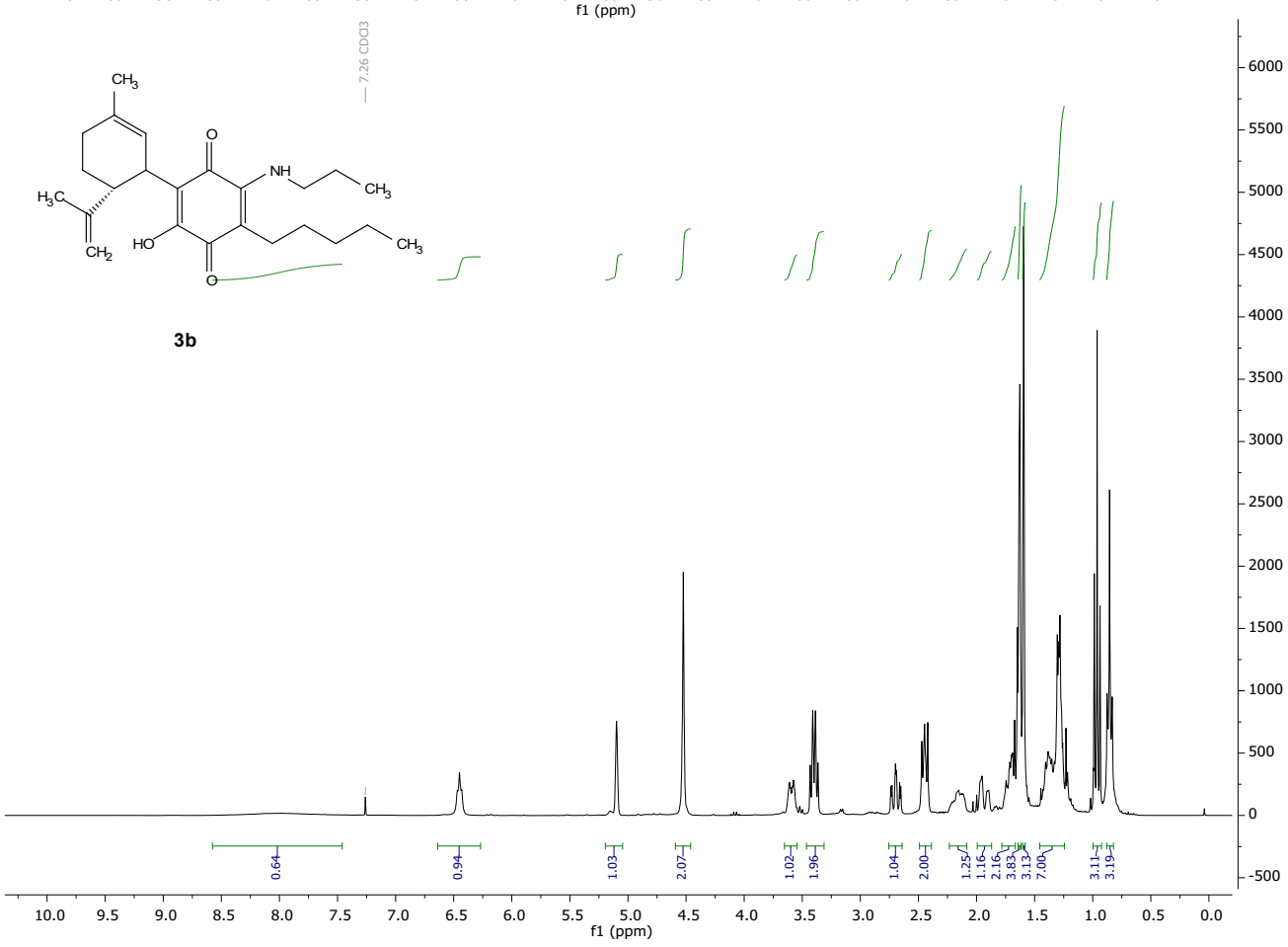



187.31
184.16
151.44
148.50
144.64
134.76
134.06
122.85
122.49
110.78
77.16 CDCl3
44.77
35.82
31.48
30.55
28.92
28.24
27.23
23.54
22.46
18.78
14.03
CH3
H3C
CH2
HO
O
O
CH3
2
f1 (ppm)

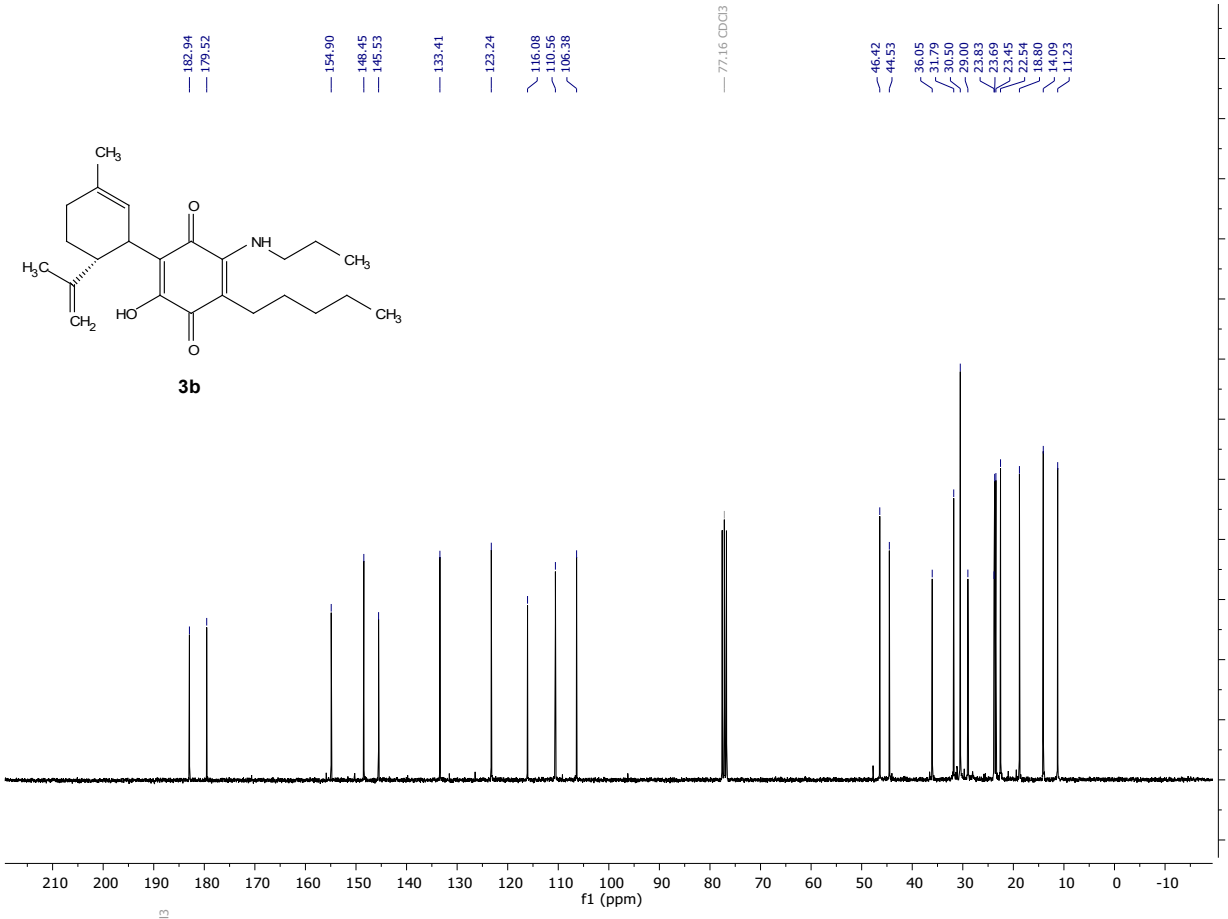

8.29
7.39
7.38
7.36
7.35
7.34
7.33
7.28
7.27
7.26
7.26 CDCl3
7.25
6.67
5.16
4.67
4.65
4.60
4.58
4.58
3.67
3.67
3.65
3.64
3.63
2.78
2.77
2.74
2.73
2.71
2.50
2.48
2.47
2.46
2.45
2.21
2.19
2.02
2.00
1.96
1.94
1.75
1.74
1.68
1.65
1.45
1.43
1.32
1.31
1.30
1.29
1.27
0.91
0.89
0.86
CH3
H3C
CH2
HO
O
O
NH
CH3
3a
0.77
5.05
0.94
1.00
1.94
1.98
1.00
1.01
2.01
1.11
1.07
1.84
3.03
3.27
2.03
4.00
3.03
f1 (ppm)


183.00
180.16
154.61
148.60
145.36
137.47
133.65
129.19
128.23
127.37
123.19
116.53
110.70
107.37
77.16 CDCl3
48.91
44.67
36.17
31.89
30.86
30.57
29.04
23.97
23.57
22.65
18.91
14.17
CH3
O
NH
H3C
HO
CH2
CH3
O
f1 (ppm)

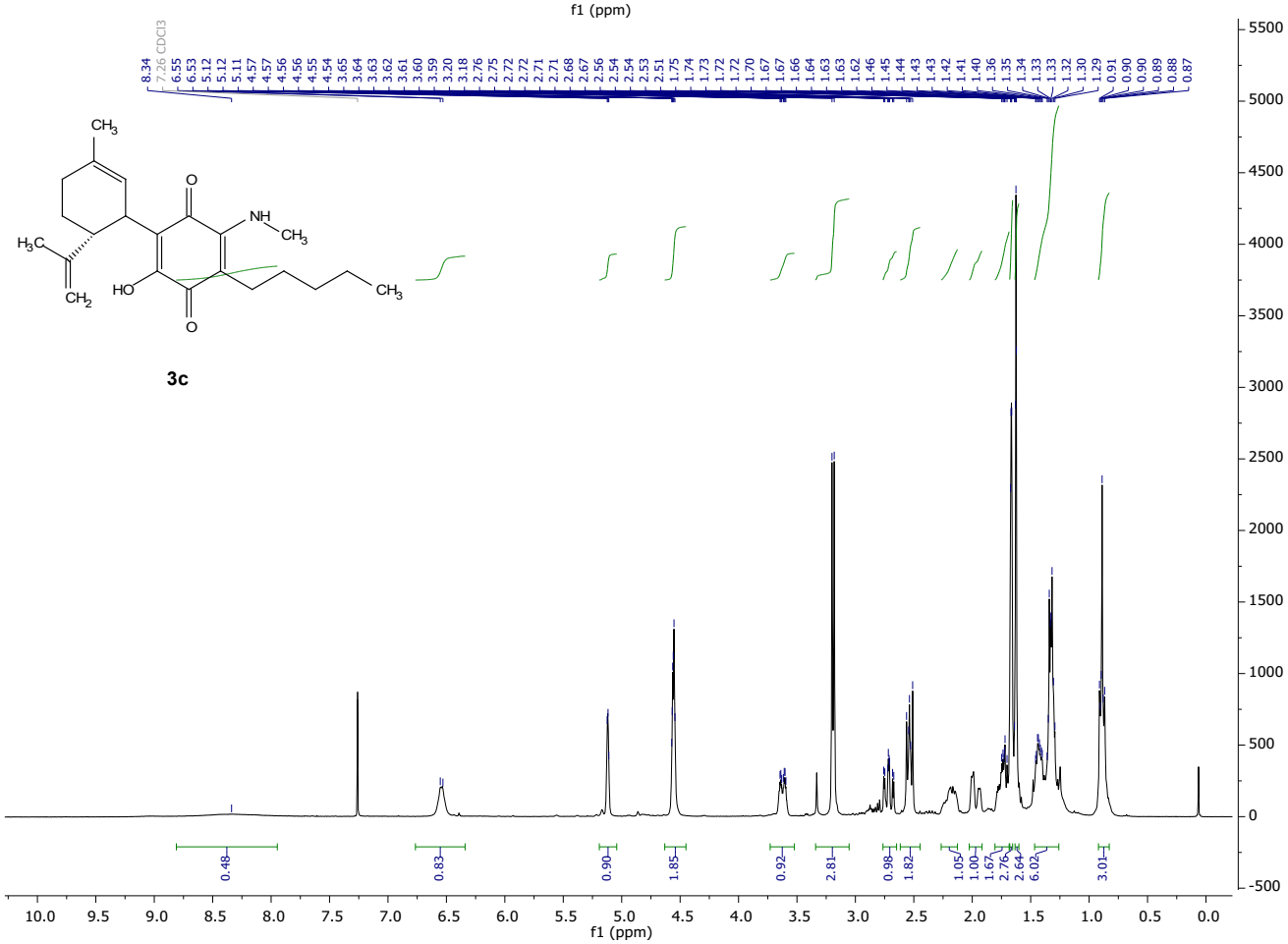
3a


7.26 CDCl3
CH3
O
NH
CH3
H3C
HO
CH2
CH3
O
0.64
0.94
1.03
2.07
1.02
1.96
1.04
2.00
1.25
1.16
2.16
3.83
3.13
7.00
3.11
3.19
f1 (ppm)

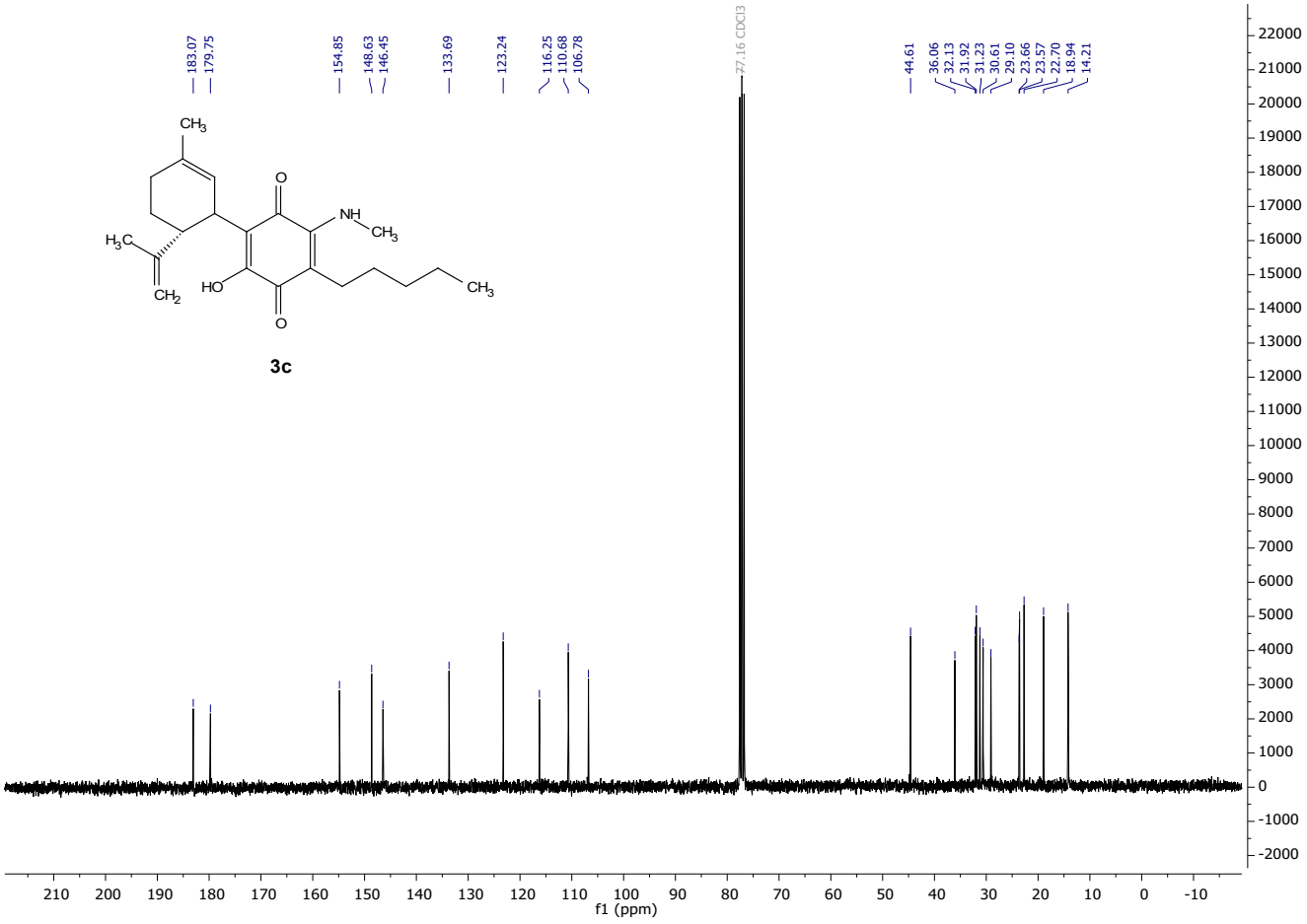
3b


182.94
179.52
154.90
148.45
145.53
133.41
123.24
116.08
110.56
106.38
77.16 CDCl3
46.42
44.53
36.05
31.79
30.50
29.00
23.83
23.69
23.45
22.54
18.80
14.09
11.23
CH3
O
NH
CH3
H3C
HO
CH2
CH3
O
f1 (ppm)

3b


8.34
7.26 CDCl3
6.55
6.53
5.12
5.12
5.11
4.57
4.57
4.56
4.56
4.55
4.54
3.65
3.64
3.63
3.62
3.61
3.60
3.59
3.20
3.18
2.76
2.75
2.72
2.72
2.71
2.71
2.68
2.67
2.56
2.54
2.54
2.53
2.51
1.75
1.74
1.73
1.72
1.72
1.70
1.67
1.67
1.66
1.64
1.63
1.63
1.62
1.46
1.45
1.44
1.43
1.43
1.42
1.41
1.40
1.36
1.35
1.34
1.33
1.33
1.32
1.30
1.29
0.91
0.90
0.90
0.89
0.88
0.87
CH3
O
NH
CH3
H3C
HO
CH2
CH3
O
0.48
0.83
0.90
1.85
0.92
2.81
0.98
1.82
1.05
1.00
1.67
2.76
2.64
6.02
3.01
f1 (ppm)

3c


183.07
179.75
154.85
148.63
146.45
133.69
123.24
116.25
110.68
106.78
77.16 CDCl3
44.61
36.06
32.13
31.92
31.23
30.61
29.10
23.66
23.57
22.70
18.94
14.21
CH3
O
NH
CH3
H3C
HO
CH2
CH3
O
f1 (ppm)

3c

4. References

(1) Kogan, N. M.; Rabinowitz, R.; Levi, P.; Gibson, D.; Sandor, P.; Schlesinger, M.; Mechoulam, R. Synthesis and Antitumor Activity of Quinonoid Derivatives of Cannabinoids. *J. Med. Chem.* **2004**, *47* (15), 3800–3806.

(2) G. Appendino, M. L. Bellido Cabello de Alba and E. Muñoz Blanco (Vivacell Biotechnology España), *Novel Cannabidiol Quinone Derivatives*, PCT/EP2014/057767, **2015.**