Electronic Supplementary Information (ESI)

3D-printed PEEK reactors and development of a complete continuous flow system for chemical synthesis

Florian Menzel,[a] Thomas Klein,[a] Thomas Ziegler[a] and Jochen M. Neumaier*[a]

[a] Institute of Organic Chemistry, University of Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany.

*E-Mail: jochen.neumaier@uni-tuebingen.de

Table of contents

3D printer setup

Two 3D printers were used for this work. 3D-printed parts out of polypropylene (PP) and polylactic acid (PLA) are printed on an A8 from Anet. In our previous paper more information and the modification of this printer can be found.[1] 3D-printed parts out of PEEK are printed on an Apium P220 from Apium Additive Technologies GmbH.

Software: The lab equipment and flow reactors used in this work were designed with Autodesk Inventor Professional 2018. After modelling, the files were exported as stl files and sliced with the software simplify3D or cura 3.7.

PP parts: The reactors were printed with Verbatim PP filament 1.75 mm - Natural Transparent on the Anet A8 3D-printer. The best results were obtained using following settings:

Print speed = 30 mm/s

Filament flow = 105%

Nozzle temp. = 200 °C

Bed temperature = 80 °C, glass plate with transparent PP packaging tape from Lyreco with a brim of 10 mm

Layer height: 0.1 mm

Wall thickness: 2.0 mm = 5 × nozzle diameter (0.4 mm)

Fan speed: 100% beginning at layer 3

PEEK parts: The reactors were printed with Apium PEEK 450 Natural filament with an Apium P220 3D-printer. The best results were obtained using following settings:

Print speed = 25 mm/s

Extrusion width: 0.48 mm

Extrusion multiplier = 0.91

Nozzle temp. = 470 °C

Bed temperature = 130 °C, glass plate coated with DimaFix pen from DIMA3D with a brim of 11.52 mm (24 perimeters)

Layer height: 0.1 mm

PLA parts: PLA 1.75 mm from Janbex was used on the Anet A8 3D-printer.

The best results for PLA were obtained using following settings:

Print speed = 60 mm/s

Filament flow = 100%

Nozzle temp. = 200 °C

Bed temperature = 60 °C, printed on a glass plate, coated with hairspray before each print.
Layer height: 0.2 mm – 0.3 mm

Continuous syringe pump

For all 3D-printed parts PLA was used. The STP and STL files of all printed parts can be found in the zip-file. **Figure S1** shows the exploded-view CAD drawing of the pump. The part numbers can be found in **Table S1**. The pump was mounted in 3 parts, the frontside with the motors and syringes, the backside with the controlling unit and the top cover with the keypad and the display. The wires were connected as shown in **Figure S2a** and all parts were put together to the bent and drilled aluminum plate. The connection of the syringes to the valve is shown in **Figure S2b**

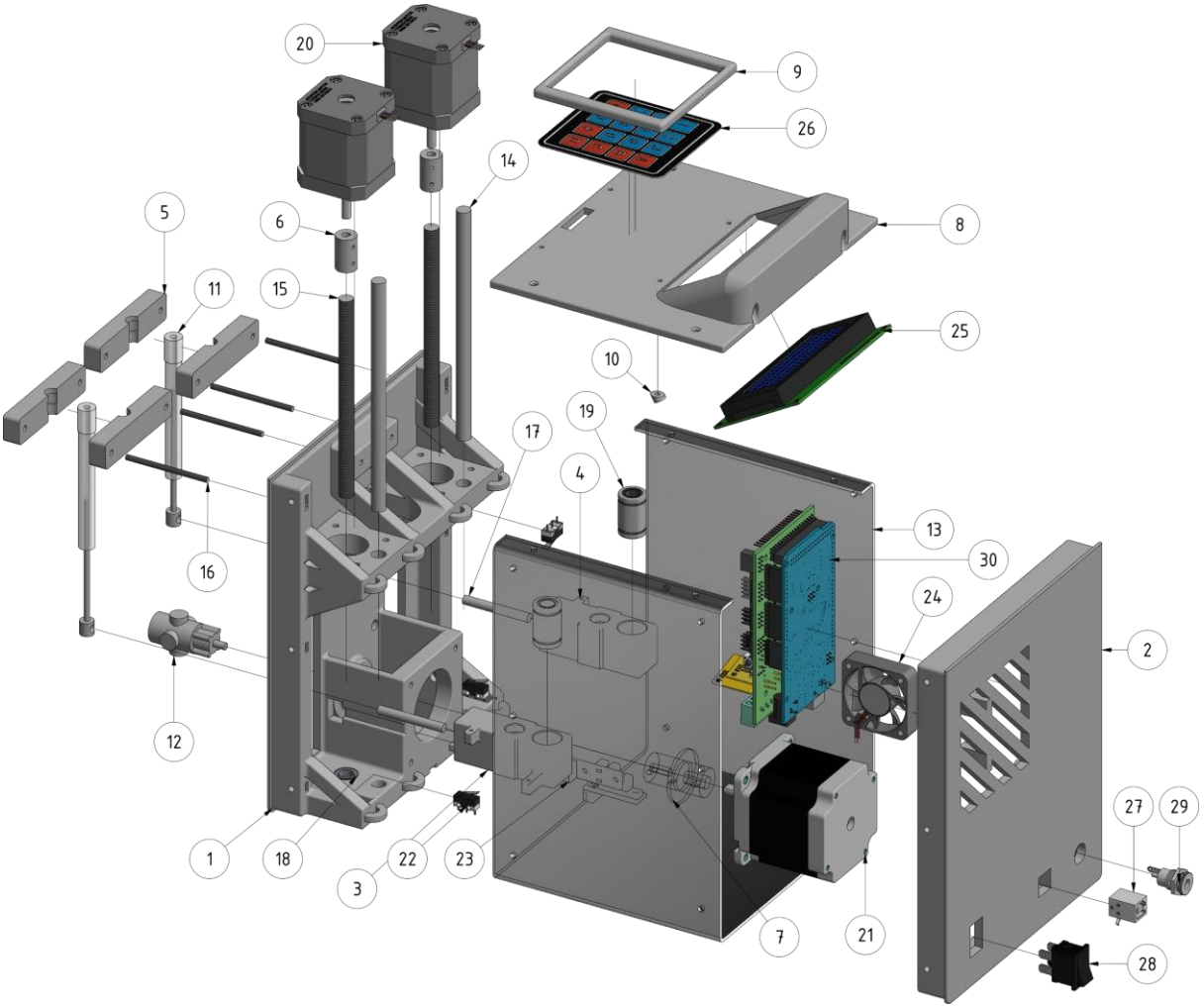


Figure S1: Exploded-view CAD drawings of the pump.

Table S1: Part list for continuous syringe pump with integrated Arduino controller, in brackets the screws and nuts are given, which are needed for mounting of each part

Quant.	Part	Source	No.
1	Frontside (6 × countersunk screws PH, M3 × 16 mm, 6 × M3 nuts)	3D-printed	1
1	Backside (6 × countersunk screws PH, M3 × 16 mm, 6 × M3 nuts)	3D-printed	2
1	Plunger carrier (2 × cheese head screw, M2 × 16 mm for manual justification of the endstops)	3D-printed	3
1	Plunger carrier, mirrored (2 × cheese head screw, M2 ×16 mm for manual justification of the endstops)	3D-printed	4
4	Syringe holder	3D-printed	5
2	Motor coupling	3D-printed	6
1	Motor coupling for valve (2 × set screw, M3 ×6 mm)	3D-printed	7
1	Top cover (4 × countersunk screws PH, M3 × 8 mm)	3D-printed	8
1	Keypad frame (4 × countersunk screws PH, M2.5 × 4 mm)	3D-printed	9
2	Display seat	3D-printed	10
2	Syringe, 500 µl SYR H-XL PTFE-seal	ILS, Innovative Labor Systeme GmbH	11
1	V-100 D, 4-Way valve PEEK diagonal flow IDEX H&S V-100D	Roland Vetter Laborbedarf OHG	12
1	Aluminium plate 586 × 140 mm × 2mm, bended	In-house workshop	13
2	Round rod, 8 × 146 mm	In-house workshop	14
2	Trapezium thread spindle, Tr8×1.5 × 120 mm	HFB-Gewindetechnik	15
2	Hexagon nut, Tr8×1.5, inprinted in part No. 3 and 4	HFB-Gewindetechnik	
4	Threaded rod, M3 × 50 mm (Wing nut, M3)	In-house workshop	16
2	Round rod, 5 × 40 mm	In-house workshop	17
2	Plain bearing, 8 mm	Igus	18
2	RJ4JP-01-08 drylin® R - bearing 8mm	Igus	19
2	ACT 17HM5417 hybrid stepper motor NEMA 17, 0.9 °, 1.7 A, 3.06 V (8 × cheese head screw with hexagon socket, M3 ×12 mm)	Reichelt elektronik GmbH & Co. KG	20

Quant.	Part	Source	No.
1	ACT 23HS6430 stepper motor, 4 pole, 1.8 °, 2.4 V DC (4 × cheese head screw with hexagon socket, M3 ×16 mm, 4 × M3 nuts)	Reichelt elektronik GmbH & Co. KG	21
4	Pololu mini snap-action switch with 13.5mm lever (8 × cheese head screw with hexagon socket, M2 ×10 mm)	Eckstein GmbH	22
2	Optical endstop switch (4 × cheese head screw with hexagon socket, M2.5 ×8 mm)	Eckstein GmbH	23
1	Fan, 40x40x10 mm, 12 VDC (2 × cheese head screw with hexagon socket, M3 × 20 mm, 2 × M3 nuts)	Reichelt elektronik GmbH & Co. KG	24
1	Character 20x4 LCD display module (4 × countersunk screws PH, M2.5 × 6 mm)	Eckstein GmbH	25
1	4x4 matrix array keypad 8 pin 16 key membrane keyboard for Arduino	Eckstein GmbH	26
1	USB panel socket, series B (cheese head screw with hexagon socket, M3 ×8 mm)	Reichelt elektronik GmbH & Co. KG	27
1	Rocker switch, 3-Pin	Eckstein GmbH	28
1	DC-socket 2.1/5.5mm	Reichelt elektronik GmbH & Co. KG	29
1	HIMALAYA basic MEGA 2560	Eckstein GmbH	30
1	Ramps 1.4 controller (3 × countersunk screws PH, M3 × 20 mm)	Eckstein GmbH	30
3	DRV8825 stepper motor driver	Eckstein GmbH	
1	Single output power supply 12 V, 3 A	Reichelt elektronik GmbH & Co. KG	
	4-Pin 20 cm jumper wire cable female to female	Eckstein GmbH	

Wiring of the Arduino and motors: For controlling the motors of the syringes and valve we use a RAMPS 1.4 controller, which was attached to the Arduino Mega 2560. The DRV8825 Stepper Motor Driver was clipped to the RAPMS controller at X, Y, Z position and the jumper settings was set to half steps (MS1 jumpered). The current limiting was adjusted to around 1.6 A with the integrated trimmer potentiometer (0.8 V). The assignment of the stepper motors, end stop switches, display and keypad are shown in **Figure S2a**. The RAPMS controller was connected to a standard 12 V DC, 3 A power supply over a rocker switch and a DC socket. Be careful, not to connect the power supply and the USB of the Arduino at the same time! All

parts were connected using female-to-female or female-to-male jumper wires to minimize soldering operations.

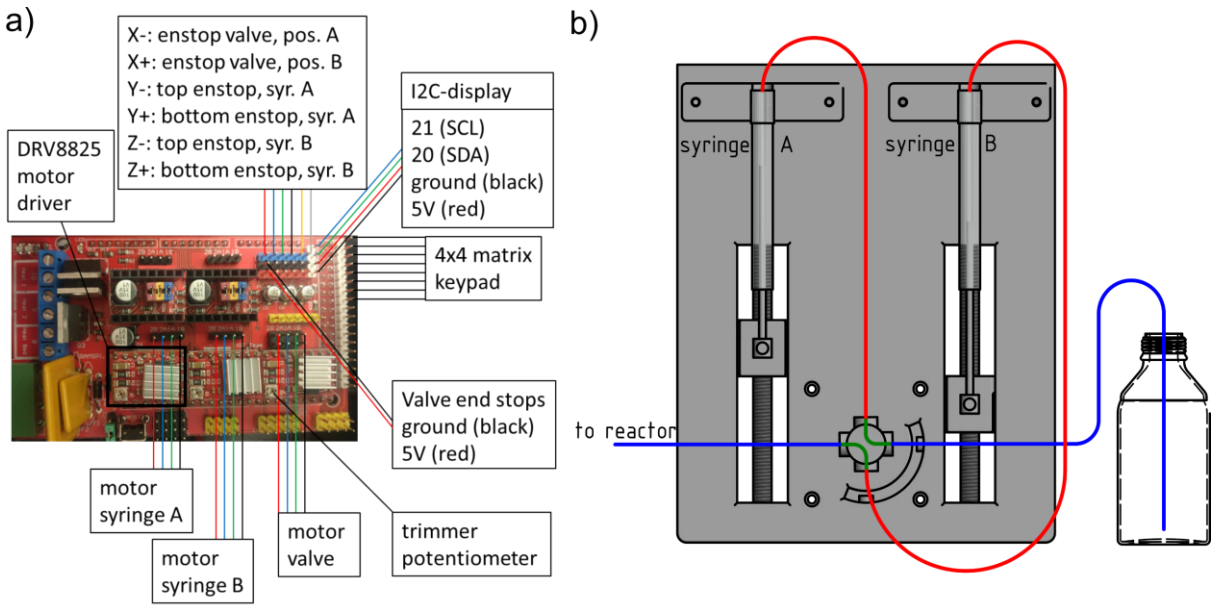


Figure S2: a) Wiring diagram of the Arduino. b) Connection of the syringes and valve

Programming with Arduino software: The software was written on the open-source Arduino software. If the motor and end stop ports are connected with the Arduino as mentioned above, the written software can be used instantly, otherwise the pins of the Arduino have to be edited to the corresponding pins. We choose 500 µL syringes with a stroke of 60 mm which results in a syringefactor of 120 mm/mL. This factor is as defined in the program code as “float syringefactor”, which could easily be modified, if other syringes are used. After the first accuracy test (see below) the syringefactor was corrected corresponding to the measured volumes to give a final syringefactor of 120.69. With this method different syringes can be inserted in the code and a very accurate dispensing is achieved. The complete program code can be found in the zip-file.

Accuracy test of the syringe pump: The pump was tested with flow rates from 2.5 to 1000 µL/min. Distilled water was dispensed at room temperature for 1 to 10 min, weight and compared to the theoretical volume. **Table S2** shows the measured weight after correction of the syringefactor. In all flow rates a deviation between 0 and 1.7% were measured.

Table S2: Accuracy test of the used syringes.

Flow rate [µL/min]	Time [min]	Weight [g]	Deviation
1000	1	1.017	+1.7%
500	3	1.503	+0.2%
200	3	0.599	–0.16%
100	4	0.401	+0.25%
50	12	0.597	-0.5%
20	20	0.400	0%
2.5	30	0.076	+1.33%

Brief instruction for using the syringe pump: After starting up the pump, the syringes go to their starting position. By pressing the key C, a loading program can be started to remove air from the syringes and load the syringes with the desired solution. By pressing the key D, a purging program could be started. With the key 1 the flow rates can be set with one decimal place in µL/min. The key A starts and stops the pump. During change of the flow rate the pump stops! Due to a delay in the program loop during actualization of the display, the display will not refresh automatically. The 0-key has to be pressed to refresh the display manually. After refresh, it shows the actual dispensed volume. With the key 5 the dispensed volume can be reset to 0.

Back pressure regulator (BPR) and membrane phase separator

The STP and STL files of all printed parts can also be found in the zip-file. **Figure S3** shows the exploded-view CAD drawing of the BPR and the membrane separator. The part numbers can be found in **Table S3**.

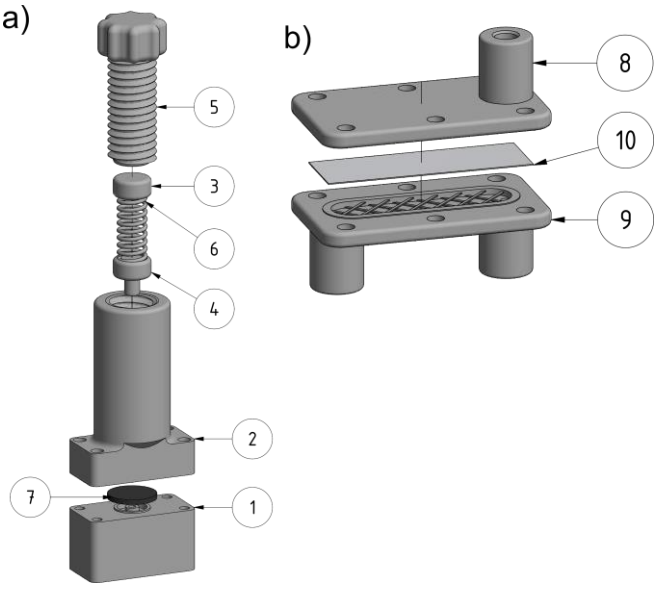


Figure S3: a) BPR b) membrane phase separator

The parts No. 8 and 9 were printed of PEEK with the connectors facing to the build plate. This is important, because warping during the print do not provide a flat surface which is necessary for a tight fit of the two plates. Also, the flat side was sanded with 1000 grit abrasive paper.

Table S3: Part list for BPR and membrane phase separator

Quant.	**Part**	**Source**	**No.**
1	Bottom part	3D-printed out of PEEK	1
1	Top part	3D-printed out of PLA	2
1	Top spring holder	3D-printed out of PLA	3
1	Stamp	3D-printed out of PLA	4
1	Top screw	3D-printed out of PLA	5
1	Spring 0.5 × 6.5 × 25 mm	IVO Industriebedarf	6
1	Spring 0.8 × 7,7 × 25 mm	IVO Industriebedarf	6
1	PTFE foil (100 µm) + silicone sheet (500 µm)	In-house workshop	7
1	Separator part 1	3D-printed out of PEEK	8
1	Separator part 2	3D-printed out of PEEK	9
1	PTFE membrane, pore size 1 µm, 100 µm thickness	Pieper Filter GmbH	10

Pressure test

For the pressure test of the two different springs in the BPR a HPLC pump S1100 from Sykam was used with isopropanol as solvent. The pressure was measured with two types of manometer. For pressures between 1 and 6 bar a manometer Cl 2.5 from WIKA was used, for pressures up to 30 bar a manometer from Messer Griesheim was used.

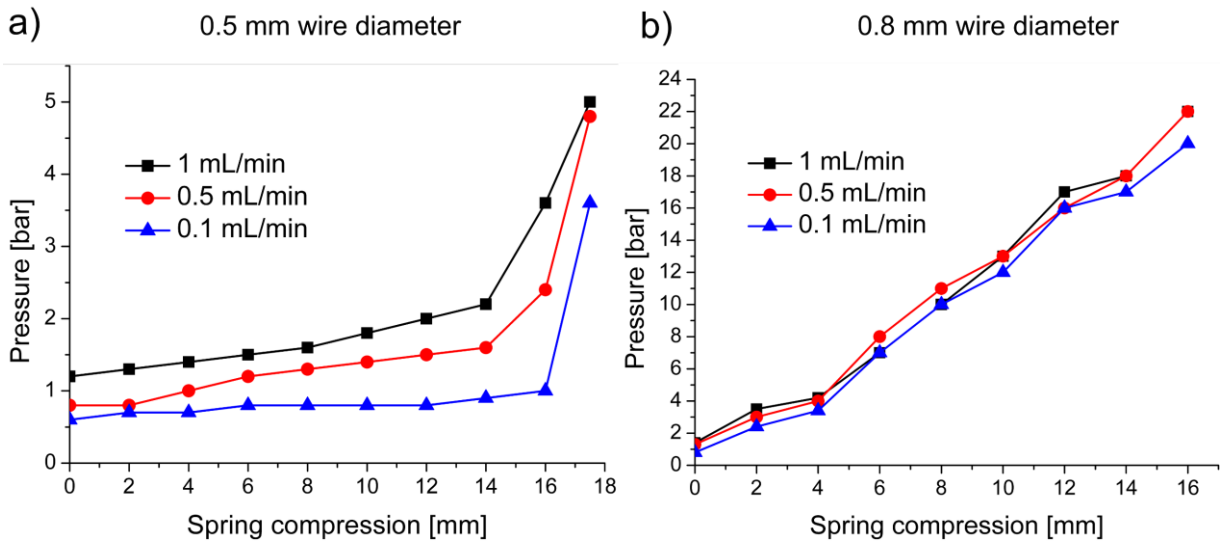


Figure S4: Back pressure regulator with two springs (a: 0.5 mm wire diameter, b: 0.8 mm wire diameter) at different flow rates.

The pressure test with a weaker spring (0.5 × 6.5 × 25 mm) in the BPR shows, that in the range of 0 to 14 mm spring compression the pressure rises very constantly. Beyond 14 mm compression the pressure rises dramatically, probably because it's beyond the maximum travel of the spring. It is possible to adjust the pressure with the stronger spring (0.8 × 7.7 × 25 mm) very precisely, due to the almost linear increase.

Mixing tests

Every mixing geometry was tested with equal flow rates for both syringes. The combined flow rates were 10, 5, 3, 1.5 and 0.5 mL/min. We started with the highest flowrate and took 3 × 20 measurements after reaching a reasonably constant absorption. The mean value of the 60 measurements was used to calculate the segregation index. We used a reactor outlet tube with a length of 1 m to ensure the completion of the VD reaction. As tubes we used 1/16'' ETFE tubes with 1 mm ID. The chemicals for the mixing tests were obtained from Applichem, Honeywell, Merck and Sigma-Aldrich.

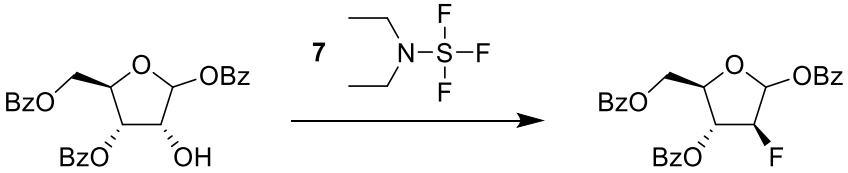
Printing tests

The volumes of the mixers and the test reactors were measured by pumping a dye solution (brilliant blue) through the channels with a 250 µL gas tight glass syringe from Hamilton and observing the volume dispensed when the solution reaches the outlet. The dimensions of wider channels of the open test piece we measured with a caliper and a digital microscope, the narrower channels (0.8 mm and smaller) with a microscope that has a built-in scale.

Chemical reactions

For flow reactions the self-built continuous syringe pump was used and additional syringe pumps LA-30 from Landgraf Laborsysteme HLL GmbH. HPLC grade $CHCl_3$ were passed through a column filled with molecular sieve (4 Å, 1 g/mL $CHCl_3$) prior use. NMR spectra were recorded on a Bruker "Avance 400" spectrometer and calibrated to the solvent signal ($CDCl_3$: ^1H 7.27 ppm, ^{13}C 77.0 ppm). HPLC measurements were made on HPLC system containing a Sykam S 1121 solvent delivering system, a Sykam S5200 sample injector and a Linear UVVIS-205 absorbance detector (254 nm). As column a GROM-SIL 120 ODS-3 CP, 5 µm column (250 × 4 mm) was used. Diethylaminosulfur trifluoride (DAST) must be handled with caution and must not be heated above 90 °C due to highly reactive decomposition products.

Procedure of the flow synthesis of 2-fluoro-1,3,5-tri-*O*-benzoyl-α-D-arabinofuranose (8) in different reactors



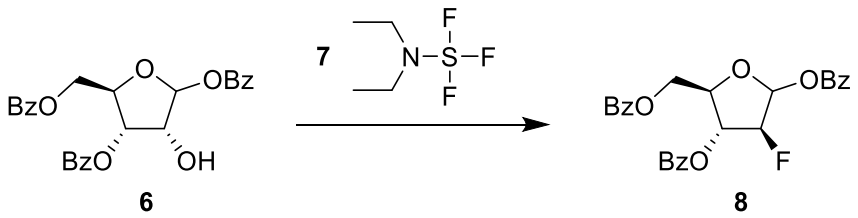
6 **8**

A solution of 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose (**6**) (0.3 M in dry $CHCl_3$, 1 eq.) and a solution of diethylaminosulfur trifluoride (**7**) (0.3 M in dry $CHCl_3$, 3 eq.) were pumped through flow reactor R1-R4, respectively, at 75 °C. The BPR was set to 2 bar. The flow rates was set according to **Table S4**. 500 µL of the reaction mixture was collected in a glass vial containing sat. $NaHCO_3$ solution (1 mL). 50 µL of the organic phase was diluted with 950 µL acetonitrile (HPLC grade) for HPLC measurements.

Table S4: Conditions for fluorination

Exp. No.	Reactor (µL)	flow rate of 6 [µL/min]	flow rate of DAST [µL/min]	Residence time [min]
1	R1 (320 µL)	40	120	2
2		16	48	5
3		8	24	10
4		5	16	15
5	R2 (480 µL)	60	180	2
6		24	72	5
7		12	36	10
8		8	24	15
9	R3 (510 µL)	64	191	2
10		26	77	5
11		13	38	10
12		9	26	15
13	R4 (290 µL)	36	109	2
14		15	44	5
15		7	22	10
16		5	14	15

Optimization procedure for the flow synthesis of 2-fluoro-1,3,5-tri-*O*-benzoyl-α-D-arabinofuranose (8)

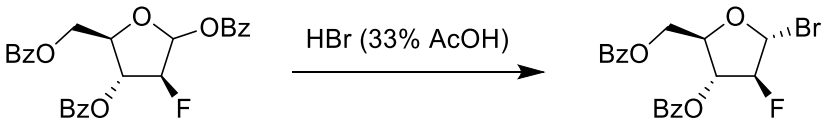


A solution of 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose (**6**) (0.3 M in dry $CHCl_3$, 1 eq.) and a solution of diethylaminosulfur trifluoride (**7**) (0.3 M in dry $CHCl_3$, 3 eq.) were pumped through flow reactor R1 (320 µL) and a BPR set to 2 bar. The temperature, the overall flow rate and the resulting residence time are shown in **Table S5**. For each experiment 500 µL of the reaction mixture was collected in a glass vial containing sat. $NaHCO_3$ solution (1 mL). 50 µL of the organic phase was diluted with 950 µL acetonitrile (HPLC grade) for HPLC measurements.

Table S5: Conditions for fluorination

Exp. No.	Temperature	Overall flow rate [µL/min]	Residence time [min]
1–16	60–90 °C	21	15
		9	27
		57	5.6
		107	3

Procedure and optimization of the flow synthesis of 2-deoxy-2-fluoro-3,5-di-*O*-benzoyl-α-D-arabinofuranosyl bromide (5)



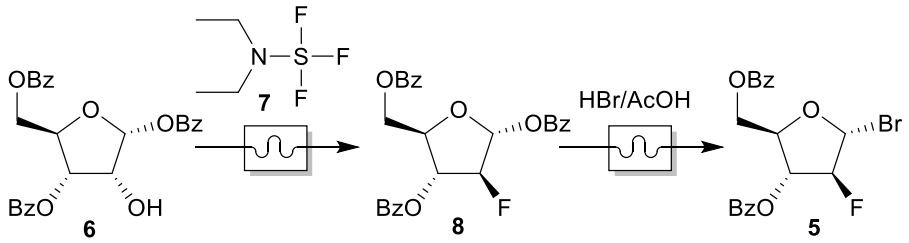
8 **5**

A solution of 2-fluoro-1,3,5-tri-*O*-benzoyl-α-D-arabinofuranose (**8**) (0.3 M in dry $CHCl_3$, 1 eq.) and a solution of HBr (33% in AcOH, 10 and 25 eq.) were pumped through flow reactor R5 (820 µL) and a BPR set to 2 bar. The temperature was set to 55 °C, the overall flow rate and the resulting residence time are shown in **Table S6**. For each experiment 500 µL of the reaction mixture was collected in a glass vial containing sat. $NaHCO_3$ solution (1 mL). 50 µL of the organic phase was diluted with 950 µL acetonitrile (HPLC grade) for HPLC measurements.

Table S6: Conditions for bromination

Exp. No.	Equivalents of HBr	flow rate of 8 [µL/min]	flow rate of HBr [µL/min]	Residence time [min]
1–3	10	107	57	5
		54	28	10
		27	14	20
4–6	25	71	93	5
		35	47	10
		18	23	20

Continuous flow procedure for the synthesis of 2-deoxy-2-fluoro-3,5-di-*O*-benzoyl-α-D-arabinofuranosyl bromide (5)



A solution of 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose (**6**) (0.4 M in dry $CHCl_3$, 1 eq.) and a solution of diethylaminosulfur trifluoride (**7**) (0.4 M in dry $CHCl_3$, 3 eq.) were pumped through flow reactor R5 (820 µL), respectively, at 75 °C. For the directly following second step, HBr (33% in dry AcOH, 25 eq.) and the reaction mixture of step one were pumped through an additional flow reactor R5 (820 µL) at 55-75 °C. The BPR was set to 2 bar. For further purification the reaction mixture of step two and H_2O were pumped through a third reactor R1 (320 µL), serving as an extractor followed by the membrane separator (150 µL). The flow rates were set according to **Table S7**. 500 µL of the organic phase was collected in a glass vial. 50 µL of the organic phase was diluted with 700 µL acetonitrile (HPLC grade) for HPLC measurements.

Table S7: Conditions for the multistep synthesis

Reaction	**Reactor (µL)**	**flow rate of 6 [µL/min]**	**flow rate of DAST [µL/min]**	**Residence time [min]**
Fluorination	R5 (820 µL)	10	31	20
		flow rate of 8 [µL/min]	**flow rate of HBr [µL/min]**	**Residence time [min]**
Bromination	R5 (820 µL)	41	17	14
		flow rate of 5 [µL/min]	**flow rate of H_2O [µL/min]**	**Residence time [min]**
Quenching	R1 (320 µL)	58	49	3
Seperation	membrane separator (150 µL)			1

Notes and references

1. J. M. Neumaier, A. Madani, T. Klein and T. Ziegler, *Beilstein J. Org. Chem.*, 2019, **15**, 558–566.