

Continuous-flow microreactor multi-step synthesis of an aminonaphthalene derivative as starting material for the preparation of novel anticancer agents

Lutz F. Tietze* and Deshan Liu

*Institute of Organic and Biomolecular Chemistry of the Georg-August-University Goettingen
Tammannstr. 2, 37077 Goettingen, Germany
E-mail: ltietze@gwdg.de*

Dedicated to Professor Arlette Solladie-Cavallo on the occasion on her 70th anniversary

Abstract

A multi-step synthesis of the aminonaphthalene derivate **1** as a key intermediate in the synthesis of the duocarmycin based prodrug **2** for a selective treatment of cancer in a microreactor is described. The conditions for the synthesis in the batch mode were adjusted for application in a microreactor and the results of both methods were compared showing that the transformations in the microreactor in most cases give similar or even better results with the advantage of a continuous-flow production, higher safety and faster reactions with an empirical accelerating factor of $F = 3-10$.

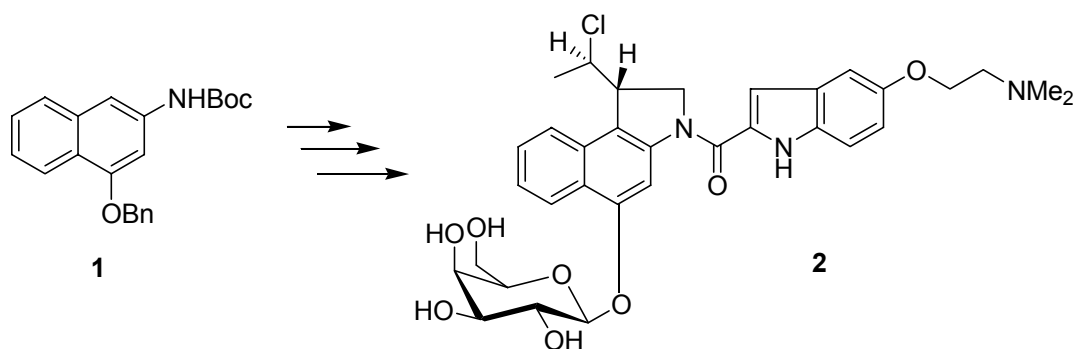
Keywords: Biphasic reactions, continuous flow reaction, Friedel-Crafts acylation, microreactor, olefination, Curtius rearrangement

Introduction

A microreactor (MR) is a miniaturized reaction system fabricated using microtechnology and precision engineering, which generally contains a small reaction volume in the nano- to microliter range with characteristic microchannel dimensions between ten and several hundred micrometers.¹ The use of microreactors in the synthesis of chemical compounds is of high interest not only for research but also for production, as reactions in microreactors have several advantages over those in the usual equipment. When two or more different fluids are introduced into microreactors, a laminar flow will dominate. As a consequence from miniaturization, the molecular diffusion path is reduced and the diffusion-controlled mixing is significantly accelerated in a way that mixing goes to completion normally within milliseconds to a few seconds at the most.^{2,3,5} Moreover, due to a highly efficient heat transfer hot spots do not occur

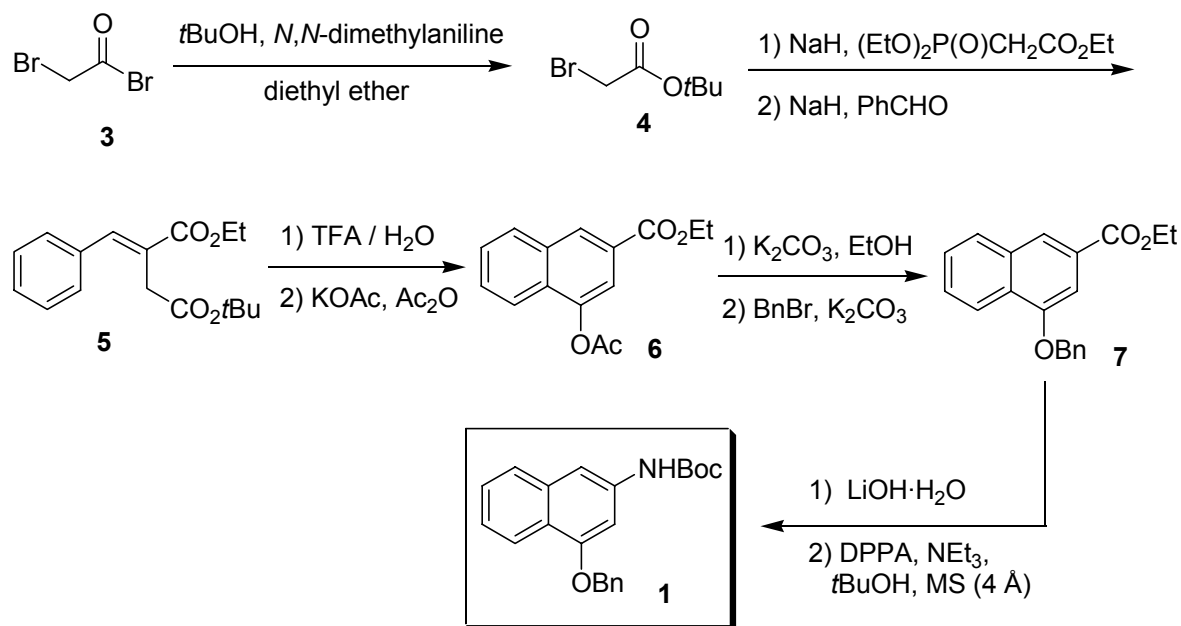
and thermally induced undesired side reactions are effectively suppressed. Thus, microreactors are especially useful for very fast and highly exothermic reactions.^{3,4,5} In addition, the continuous processing⁶ has an inherent operational safety and an economical advantage, since the synthesis of large quantities of a product can be done by numbering-up the reaction vessels instead of using a conventional time- and cost-consuming scale-up process. The use of microreactors is a subject of intensive research in industry, and one can expect that microreactors will be a promising alternative to the present chemical reactors in fine chemical production.^{7,9a}

On the other hand it should not be denied that microreactors still show several problems,^{8,9} which hamper their use. Typical among these is the chemical clogging of the tiny microchannels, since many chemical transformations involve solid handling or the formation of precipitates. In addition, multi-step syntheses using microreactors have so far seldom been reported.¹⁰



Scheme 1. Compound 1 as building block of prodrug 2 for a selective treatment of cancer.

In the development of the duocarmycin based prodrugs of type 2 for a selective treatment of cancer using the ADEPT approach (Scheme 1),¹¹ the aminonaphthalene derivate 1 serves as an important building block and its synthesis has been carried out according to a classical route (Scheme 2).¹² Due to the need of large amounts of the prodrug 2 for clinical trials an efficient continuous synthesis of 1 was needed to allow the preparation of 2 in a kg-scale. We assumed that the use of a microreactor would open a reasonable way to achieve this aim with good reproducibility of product quality by precise control of reaction conditions in a continuous way. Here we report on a multi-step synthesis of the aminonaphthalene derivate 1 in a microreactor (CYTOS[®] 13 College, Figure 1). First we focused on the modification of the classical reaction conditions in order to allow the use of a microreactor by avoiding the employment and formation of solid material. At last the results using the batch mode and the microreactor were compared in respect to yield, reaction time and temperature.



Scheme 2. Classical synthetic route of the aminonaphthalene derivative 1.

The following symbols are used, t : reaction time in the batch mode at a given reaction temperature; τ : residence time in the microreactor (residence volume / total flow rate); rt (room temperature): 22–25°C; T : reaction temperature in the batch mode (internal temperature) and in the microreactor (controlled by an external thermostat); F : empirical accelerating factor which characterizes in which extent the use of a microreactor can accelerate a chemical reaction, defined as $F = t$ (reaction time) / τ (residence time). It should be noted that throughout the manuscript the given F values are only estimations, since an exact determination of the kinetics of the transformation using GC has not been performed. Furthermore, the given yields for the transformations in the microreactor refer to the results under steady-state conditions; thus, the production before that time is usually lost, which however is of no importance, if the total production time is much longer than the start-up time.

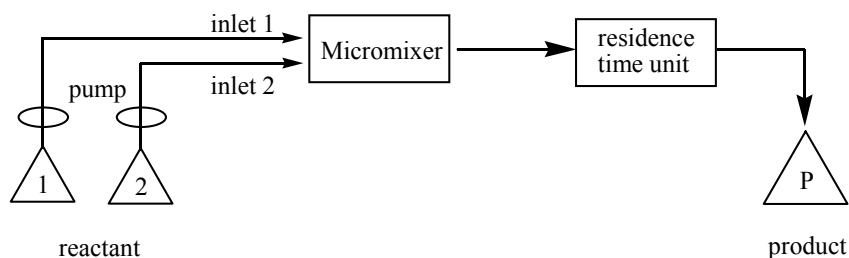
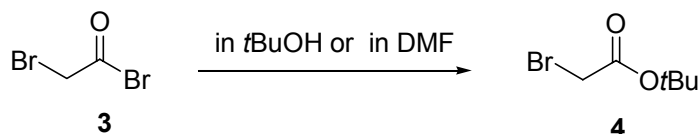


Figure 1. Microreactor system (CYTOS[®] College, heat exchanger not drawn here).

Results and Discussion

For the synthesis of the *tert*-butyl ester **4** using the bromoacetyl bromide **3** as starting material the solvent diethylether employed in the batch mode was not suitable for the microreactor due to the formation of an ammonium salt as precipitate.^{14a} THF proved also not to be appropriate due to a side reaction with **3**.¹⁵ Among other solvents investigated as CH₃CN, DMSO, *t*BuOH and DMF, *t*BuOH and DMF showed an overall homogeneous reaction with moderate to high yields (Table 1, entry 2–4). The use of *t*BuOH as solvent afforded a yield of 81% in the batch mode within 20 h at room temperature, whereas in the microreactor with 34 min residence time at 25°C only 50% yield of **4** was obtained. It is possible to increase the yield by reducing the total flow rate to prolong the residence time, which however is less desirable due to a lower efficiency and limited flow rate control. The addition of catalytic amounts of DMAP as additive did not improve the conversion neither in the batch mode nor in the microreactor (entry 2 and 3); thus, under these conditions after 5.5 h **4** was formed in the batch mode in 43% yield. A better result was obtained employing DMF as solvent with 34 min residence time using catalytic amounts of DMAP and a reaction temperature of 35°C to give **4** in 66% yield. A comparison of the reaction rates under the different conditions revealed that the transformation in the microreactor proceeds with an accelerating factor of about 10.



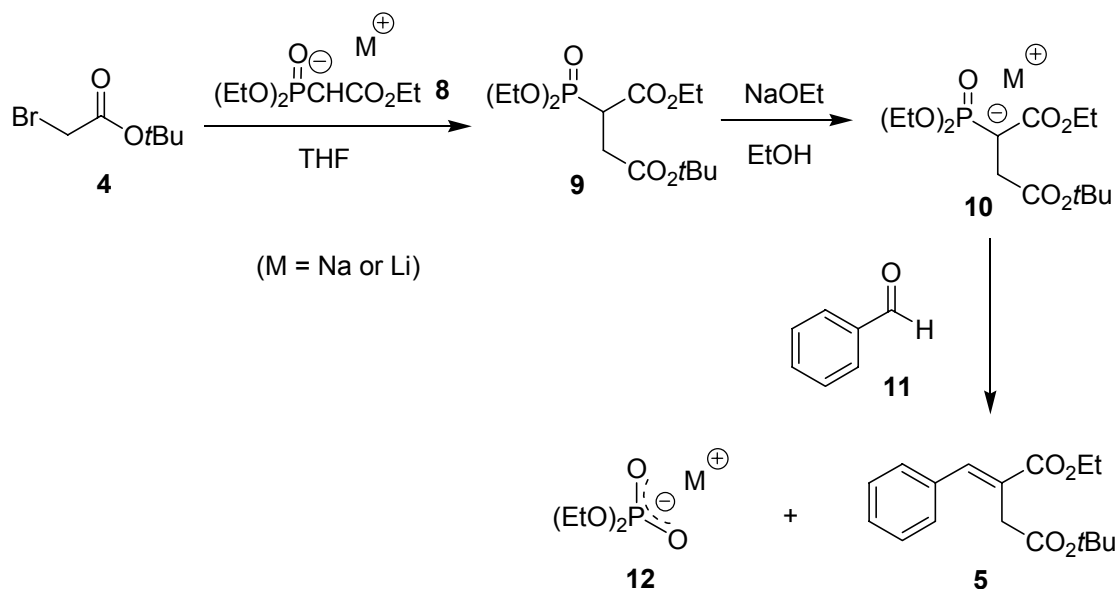
Scheme 3. Synthesis of the *tert*-butylester **4**.

Table 1. Synthesis of **4** in the batch mode and in MR: [a] Isolated product by distillation. [b] Dry dichloromethane was used to dilute **3** (*V/V*=1:1). [c] Reaction without addition of DMAP

Entry	Solvent additive	Batch mode yield ^[a] (<i>t</i> , <i>T</i>)	MR yield ^[a] (<i>τ</i> , <i>T</i>)
1 ^[14b]	Et ₂ O	78% (4 h, rt)	—
2 ^[b]	3.0 eq <i>t</i> BuOH	81% (20 h, rt)	50% (34 min, 25°C)
3 ^[b]	3.0 eq <i>t</i> BuOH + 10-mol% DMAP	43% (5.5 h, rt)	50% (34 min, 25°C)
4 ^[b]	DMF + 10-mol% DMAP	62% (19.5 h, rt) ^[c]	66% (34 min, 35°C)

To prepare the phosphonosuccinate **9** and its anion **10** for the olefination of benzaldehyde **11** to give **5**, sodium hydride is commonly used as base (Scheme 4).¹⁶ However, the intermediate **8** (M = Na) has a low solubility in THF and the by-product NaBr formed by the following nucleophilic substitution was almost insoluble in THF. On the other hand, LiBr dissolves well in THF, we therefore used the organic lithium reagents Li-HMDS, LDA and *n*-BuLi for the

deprotonation. *n*-BuLi was most suitable to obtain an overall homogeneous reaction mixture and for that reason was employed in the microreactor (Table 2, entry 2–4 to give the desired compound **9** in a yield of 70% already after 24 min at 40°C, whereas in the batch mode only 57% of **9** after 36 h at room temperature were formed. Other approaches using phase transfer conditions (aqueous NaOH/TBABr) or the combination of LiCl/NEt₃¹⁷ have failed completely.



Scheme 4. Synthesis of **9** by nucleophilic substitution and of **5** by *Wittig-Horner* olefination.

Table 2. Synthesis of **9**: [a] Isolated product after distillation. [b] Isolated product after column chromatography

Entry	Base	Batch mode yield (<i>t</i> , <i>T</i>) ^[a]	MR yield (<i>τ</i> , <i>T</i>) ^[a]
1	NaH	91% (24 h, rt)	—
2	Li-HMDS	87% ^[b] (12 h, rt)	not performed
3	LDA	70% ^[b] (15 h, rt)	not performed
4	<i>n</i> -BuLi	57% (36 h, rt)	70% (24 min, 40°C)

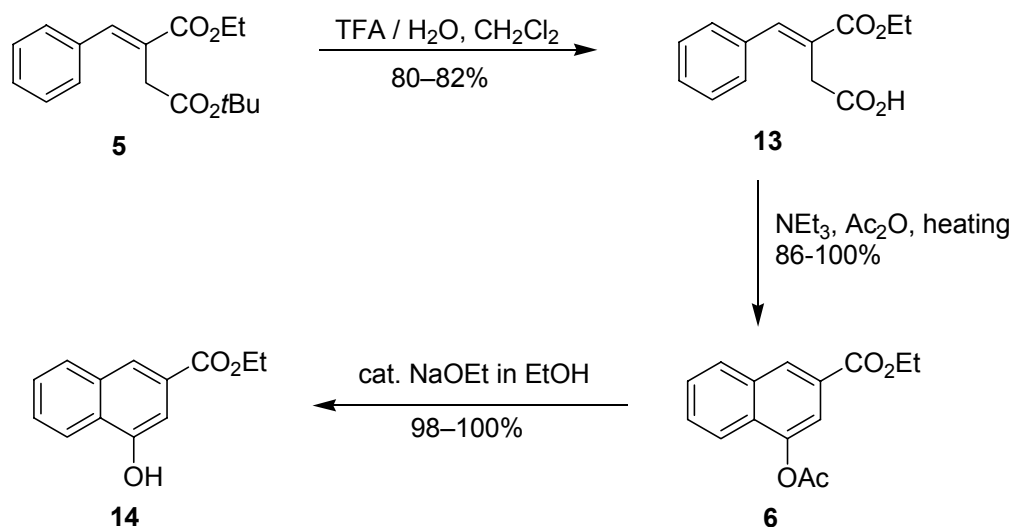
In the following *Wittig-Horner* olefination¹⁸ conventionally performed in two stages,¹⁶ again we searched for an overall homogenous reaction. In the microreactor NaH and *n*-BuLi with THF as solvent could not be used, due to the formation of the in THF insoluble intermediate **10** (M = Na) and the by-product **12** (M = Li) (Scheme 4 and Table 3, entry 1 and 2). Using DMSO as solvent with *n*-BuLi allowed a transformation in the microreactor at elevated temperature, but the yield was much lower as in the batch mode. However, the olefination using NaOEt¹⁹ in the microreactor gave a yield of 89% of the desired compound **5** with a residence time of 47 min at 25°C, while a shorter residence time afforded a mixture of **5** and the starting material (entry 4).

Compared to the batch mode the accelerating Factor F is about 6. It is worthwhile to note that **5** formed in the microreactor has an excellent purity and that the reaction proceeds with high stereoselectivity; thus, the *Z*-isomer of **5** could not be detected (NMR). The *in situ* generation of the intermediate **10** seems to be very beneficial, since another approach in the microreactor using a separate deprotonation with NaOEt under otherwise the same conditions as in entry 4 afforded only a mixture. Noteworthy, for reactions in the microreactor the collection period is important. The following different yields were obtained using different times to start the collection (conditions, entry 4): Collection from 1.0 τ over 21 min: 57%, collection from 1.5 τ over 20 min: 78%, collection from 1.9 τ over 30 min: 89%. Obviously, even after a time of 1.9 τ the steady state conditions have not been ensured, which resulted in an overall lower yield in the microreactor compared to the batch mode. Usually, a collection beginning time of 1.5 τ is suggested.^{13c,d}

Table 3. Synthesis of **5**: [a] Crude product. [b] Isolated product after column chromatography

Entry	Base / solvent	Batch mode yield ^[a] (t , T)	MR yield ^[b] (τ , T)
1	NaH / THF	92% (12 h, rt)	—
2	<i>n</i> -BuLi / THF	84% (17 h, rt)	—
3	<i>n</i> -BuLi / DMSO	81% (11 h, 45°C)	35% (54 min, 40°C)
4	NaOEt / EtOH	97% (5 h, rt)	i) 80% (23.5 min, 25°C) ii) 89% (47 min, 25°C)

In the following acid-catalyzed cleavage of the *tert*-butyl ester function in **5** the neat substrate **5** as solid needed to be dissolved in dichloromethane as additional solvent. By this way it could be separately pumped into the microreactor to react with TFA. In the batch mode the addition of dichloromethane had no influence on the yield. The transformation is a fast reaction and was completed in just 5 min at 34°C in the microreactor (Table 4), which is in accordance with data from the literature.^{16b,20}



Scheme 5. Synthesis of **13** by cleavage of the *tert*-butylester in **5**, of **6** by *Friedel-Crafts* acylation and of **14** by solvolysis.

The resulting acid **13** was used as crude product for the following *Friedel-Crafts* acylation; for this transformation the conventionally employed reagents Ac_2O and KOAc or NaOAc ²¹ were not suitable for the application in the microreactor due to the poor solubility of the salts in organic solvents. Looking for modifications we realized that the transformation is base-accelerated. In the absence of a base using only Ac_2O the desired product was not formed. Therefore, NEt_3 was employed and proved to be more suitable than KOAc giving a yield of 86%–96% in the batch mode (Table 5). For the reaction in the microreactor the substrate **13** and Ac_2O as well as NEt_3 were premixed at room temperature and then pumped into the preheated microreactor (130°C) by one inlet to give **6** with a yield of 100%, while at lower temperatures (about 100°C) only mixtures of the substrate and the product were observed (Table 5, entry 2 and 3).

Table 4. Synthesis of **13**: [a] Crude product

Entry	Solvent	Batch mode yield ^[a] (<i>t</i> , <i>T</i>)	MR yield ^[a] (τ , <i>T</i>)
1	CH_2Cl_2	80% (16 h, rt)	82% (5 min, 34°C)

The subsequent solvolysis of **6** was performed in the microreactor using NaOEt ²² in catalytic amounts instead of K_2CO_3 as used in the batch mode. The best yield of almost 100% was achieved by using 30-mol% of NaOEt at 72°C for 23.5 min (Table 6, entry 3). With a smaller amount of NaOEt the reaction was incomplete under these conditions. However, it is also possible to obtain good results by using a lower flow rate with 20-mol% of NaOEt or less, while the reaction temperature can not be increased over 70°C, since EtOH would then form gas

bubbles, which is not desirable using a microreactor. The accelerating factor in the microreactor was estimated as about 3.

Table 5. Synthesis of **6**: [a] Crude product. [b] Isolated product after recrystallization from diethylether and pentane

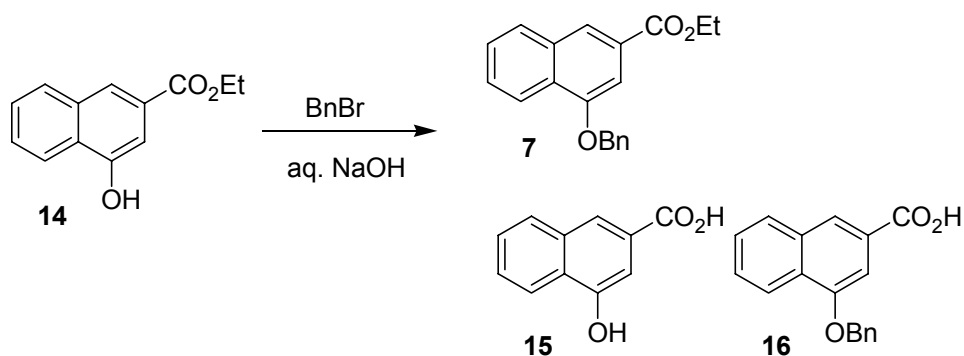
Entry	Base in Ac ₂ O	Batch mode yield ^[a] (<i>t</i> , <i>T</i>)	MR yield ^[a] (<i>τ</i> , <i>T</i>)
1	KOAc	78% (2.5 h, 136°C)	—
2	NEt ₃	86–96% (3 h, 136°C)	100% (47 min, 130°C)
3	NEt ₃	69% ^[b] (7 h, 92°C)	mixture (47 min, 95°C) or (78 min, 98°C)

The protection of the naphthol **14** as its benzyl ether **7** could conventionally be achieved using K₂CO₃ as base in 89% yield (Table 7, entry 1). To allow a homogeneous reaction mixture LiOEt and (*i*Pr)₂NEt²³ were used as base, but under these conditions only an incomplete conversion was observed (entry 2 and 3), and with aqueous NaOH (>2.0 eq) a mixture of the undesired acid **15**²⁴ and the desired product **16** was formed.

Table 6. Synthesis of **14**: [a] Crude product. [b] In addition, 10% of the starting material was found

Entry	Base in EtOH	Batch mode yield ^[a] (<i>t</i> , <i>T</i>)	MR yield ^[a] (<i>τ</i> , <i>T</i>)
1 ^[21a]	K ₂ CO ₃	90% (15 min, reflux)	—
2	20-mol% NaOEt	98% (1 h, 78°C)	87% ^[b] (72°C, 23.5 min)
3	30-mol% NaOEt	—	100% (72°C, 23.5 min)

However, by using aqueous NaOH (1.2 eq), the phase transfer catalyst TBABr and the water-insoluble organic solvent 2-methyltetrahydrofuran (MTHF),²⁵ a liquid-liquid biphasic reaction in the micro-reactor gave the benzyl ether **7** in 72% yield within 31 min at 40°C. As also observed on other occasions, microreactors are especially suitable for liquid-liquid biphasic reactions.^{3,26}

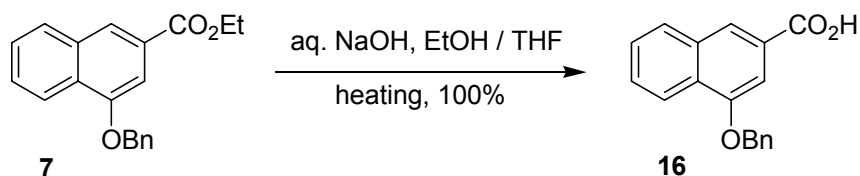


Scheme 6. Synthesis of **7** by benzylation.

Table 7. Synthesis of **7**: [a] Crude product. [b] Isolated product by column chromatography. In addition, 19% of the substrate **14** was reisolated. [c] In the batch mode 23-mol% TBABr and in MR 40-mol% TBABr were used. [d] Isolated product after recrystallization from ethanol

Entry	Base	Batch mode yield (<i>t</i> , <i>T</i>)	MR yield (<i>τ</i> , <i>T</i>)
1	K ₂ CO ₃	89% ^[a] (12.5 h, rt)	—
2	LiOEt	75% ^[b] (30.5 h, rt)	—
3	(<i>i</i> Pr) ₂ NEt	mixture (3 h, rt; then 12 h, 50°C)	—
4 ^[c]	aq. NaOH (1.2 eq)	70% ^[d] (40°C, 2 h)	72% ^[d] (40°C, 31 min)

For the hydrolysis of the ethyl ester **7** at first LiOH was used, which however formed a suspension and the reaction proceeded rather slowly (Table 8, entry 1). In contrast, using NaOH at elevated temperature the reaction was complete in the batch mode in a much shorter time (entry 2). Employing these biphasic conditions without the addition of a phase transfer catalyst in the microreactor, the acid **16** was obtained in 100% yield in 48 min at 68°C.



Scheme 7. Synthesis of **16** by hydrolysis.

Table 8. Synthesis of **16**: [a] Crude product

Entry	Base	Batch mode yield ^[a] (<i>t</i> , <i>T</i>)	MR yield ^[a] (<i>τ</i> , <i>T</i>)
1	LiOH·H ₂ O	92% (40 h, rt)	—
2	aq. NaOH	100% (3.5 h, 74°C)	100% (48 min, 68°C)

The obtained carboxylic acid **16** was directly used for the reaction with the *Shioiri-Yamada* reagent (DPPA)²⁷ in the presence of *tert*-butanol to give the desired final product **1** via a *Curtius* rearrangement. According to the proposed mechanism^{27a} the intermediate azide **17** would lead to the isocyanate **18** which further reacts with *tert*-butanol to give **1** (Scheme 8). It was expected that the nitrogen formation in the *Curtius* rearrangement would have a negative influence on the steady state situation in the microreactor. Thus, for a reproducible reaction we prepared the isocyanate **18** using 1,4-dioxane as solvent in the batch mode. After the gas evolution had finished, the resulting solution was introduced into the microreactor together with *tert*-butanol containing a little of 1,4-dioxane. However, even under these conditions the obtained yield of 52% of **1** was much lower than those in the batch mode (Table 9). This seems to be a result of the instability of the isocyanate **18**; we first thought that the use of molecular sieves in the batch mode, which are clearly unsuitable for reactions in the micro reactor, has caused the difference; but a reaction in the batch mode without the addition of molecular sieves gave the same results.^{12b} It is noteworthy that a homogenous solution could be collected at the outlet of the microreactor, while the formation of a suspension was observed in the batch mode. This phenomenon can be explained by the finer size of the particles obtained in the microreactor.

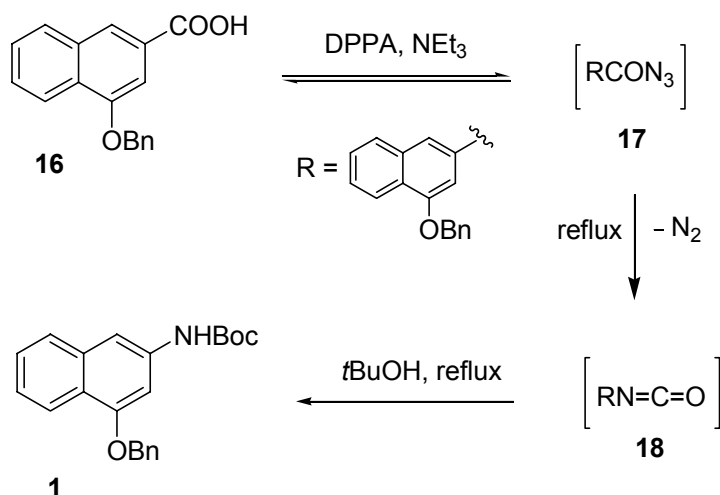
**Scheme 8.** Proposed *Curtius* rearrangement for the synthesis of **1**.

Table 9. Synthesis of **1** via *Curtius* rearrangement: [a] Crude product. [b] Formation of **18** in the batch mode followed by reaction with *tert*-butanol in the MR

Entry	Additive	Batch mode yield ^[a] (<i>t</i> , <i>T</i>)	MR ^[b] yield ^[a] (τ , <i>T</i>)
1 ^[12a]	molecular sieve 4 Å	85% (72 h, reflux)	—
2 ^[12b]	no additive	83% (3 h, reflux)	52% (34 min, 80°C)

Conclusions

In conclusion, a nine-step synthesis of the aminonaphthalene **1** was accomplished using a microreactor as reaction vessel in a continuous-flow mode, allowing a large-scale production in an easier and safer way as in the batch mode. Moreover, an accelerating factor for the different reactions of $F = 3$ –10 and mostly similar and sometimes even better yields using the microreactor were found.

Experimental Section

General Procedures. All reagents obtained from commercial sources were normally used without further purification. All solvents were dried by standard methods. Thin-layer chromatography (TLC) was performed on precoated silica gel plates (SIL G/UV₂₅₄, Macherey-Nagel GmbH & Co. KG). Silica gel 60 (0.032–0.064 mm) (Merck) was used for column chromatography. ¹H-NMR spectra were recorded on Varian mercury-200 or Unity-300. All reactions in the batch mode were performed in normal laboratory glassware. As microreactor the CYTOS[®] College System (MR, CPC Systems) was used consisting of one micromixer (core structure) with 2 mL residence volume and a residence unit with 45 mL volume. The flow rates of 0.4–20 mL/min were controlled by two integrated ISMATEC ceramic piston pumps. The temperature in the microreactor and the attached residence unit was regulated by an external thermostat (Lauda RKS-20 or Lauda Integral T1200). It was set at least 5°C lower than the boiling point of solvent used.

MR-Setup^{4,10b,13c}: Before the reaction the MR was purged with the solvent used in the transformation (at least a 2-fold volume of the microreactor). The pumps A (for inlet A) and B (for inlet B) of the MR were calibrated to the desired flow rates. The residence time τ was defined by the equation: τ (min) = volume (mL) / total flow rate (mL/min). After preparation of the solution of the substrates (one or two) the transformation was started by pumping the solution(s) into the micromixer. Product collection started after at least 1.5-fold residence time to ensure steady state conditions.^{4,13c} The accuracy of the flow rate was verified by measuring the consumed volume of the solutions of the substrates after a given time period.

Procedure: Only the experiments with the best results in the batch mode and the MR are described.

Bromoacetic acid *tert*-butyl ester (4). Batch mode. Bromoacetyl bromide (20.0 mL, 229 mmol, 1.00 eq) was added dropwise to a stirred solution of *tert*-butanol (28.3 mL, 298 mmol, 1.30 eq), *N,N*-dimethylaniline (31.8 mL, 252 mmol, 1.10 eq) in DMF (80 mL) at 0°C. Stirring was continued at rt for 19.5 h before water (100 mL) and chloroform (200 mL) were added. The aqueous layer was separated and extracted with chloroform (2 × 100 mL). The combined organic layers were washed with 10% sulfuric acid (2 × 150 mL) and brine, dried (MgSO₄) and filtered. The solvent was removed and the residue distilled under reduced pressure to give **4** as a colorless liquid (27.8 g, 62%). *MR*: Residence volume 47 mL, $\tau = 34$ min, $T = 35^\circ\text{C}$. Solution A, bromoacetyl bromide (50.0 mL, 572 mmol) in dry dichloromethane (total volume 100 mL) was introduced into inlet A at a flow rate of 0.4 mL/min. Solution B, *N,N*-dimethylaniline (79.5 mL, 629 mmol), *tert*-butanol (70.7 mL, 744 mmol), DMAP (7.00 g, 57.2 mmol) in DMF (total volume 260 mL) was simultaneously introduced into inlet B at a flow rate of 1.0 mL/min. The product solution corresponding to 59 mL of used solution A was collected over 150 min beginning after a run time of 1.6 τ . It was treated with water (150 mL) and extracted with diethylether (4 × 80 mL). The combined organic layers were washed with 10% aqueous sulfuric acid (3 × 100 mL), an aqueous saturated NaHCO₃-solution (100 mL) and brine, dried (NaSO₄) and filtered. The solvent was removed and the residue distilled under reduced pressure to give **4** as a colorless liquid (43.4 g, 66%). ; b.p. 60°C at 20 mbar. ¹H-NMR (200 MHz, CDCl₃): $\delta = 1.48$ (s, 9 H, C(CH₃)₃), 3.75 (s, 2 H, CH₂Br).

2-(Diethoxyphosphoryl)succinic acid 4-*tert*-butyl-1-ethyl diester (9). Batch mode. To a stirred solution of *n*-butyllithium (2.5 M in hexane, 90.0 mL) in dry THF (155 mL) was added dropwise at -78°C triethyl phosphonoacetate (48.0 g, 214 mmol, 1.00 eq) and stirring of the resulting yellow solution was continued at rt for 3 h. Then a solution of **4** (44.1 g, 226 mmol, 1.05 eq) in dry THF (18 mL) was added dropwise at 0°C. Stirring was continued at rt for 36 h, then the solvent evaporated in vacuo and the residue carefully treated with EtOAc (200 mL) and water (250 mL) with cooling. The aqueous layer was separated and extracted with EtOAc (2 × 70 mL). The combined organic layers were washed with water (100 mL) and brine, dried (MgSO₄) and filtered. After removal of the solvent the residue was distilled under reduced pressure to afford **9** as a colorless liquid (41.1 g, 57%). *MR*: Residence volume 47 mL, $\tau = 24$ min, $T = 40^\circ\text{C}$. Solution A, a yellow solution of the intermediate product **8** (total volume 332 mL) prepared with *n*-butyllithium (2.5 M in hexane, 110 mL), dry THF (170 mL) and triethyl phosphonoacetate (58.7 g, 262 mmol) as described for the batch mode was introduced into inlet A at a flow rate of 1.56 mL/min. Solution B, **4** in anhydrous THF (total volume 87 mL) was simultaneously introduced into inlet B at a flow rate of 0.40 mL/min. The product solution corresponding to 57.5 mL of used solution B was collected over 150 min beginning from a run time of 1.7 τ . Work up and purification as described for the batch mode afforded **9** as a colorless liquid (41.9 g, 70%); b.p. 143°C at 0.17 mbar. ¹H-NMR (200 MHz, CDCl₃): $\delta = 1.24$ – 1.38 (m,

9 H, 3 × CH₂CH₃), 1.43 (s, 9 H, C(CH₃)₃), 2.72 (ddd, $J = 17.1, 8.8, 3.4$ Hz, 1 H, 3-H_a), 2.88–3.10 (m, 1 H, 2-H), 3.40 (ddd, $J = 23.9, 11.8, 3.4$ Hz, 1 H, 3-H_b), 4.03–4.35 (m, 6 H, 3 × CH₂CH₃).

(E)-2-Benzylidenesuccinic acid 4-tert-butyl-1-ethyl diester (5). Batch mode. A solution of NaOEt (21%wt, 2.30 mL, 6.16 mmol, 1.04 eq) in EtOH was added slowly by syringe to a stirred solution of freshly distilled benzaldehyde (659 mg, 6.21 mmol, 1.05 eq) and **9** (2.00 g, 5.91 mmol, 1.00 eq) in dry EtOH (15 mL) at 0°C. After stirring for 15 min at 0°C stirring was continued at rt for 5 h. The solvent was evaporated in vacuo and the residue taken up in EtOAc (40 mL) and water (10 mL). The organic layer was separated, washed with water (10 mL) and brine, dried (MgSO₄) and filtered. The solvent was removed in vacuo to provide **5** as a yellow oil (1.67 g, 97%). *MR*: Residence volume 47 mL, $\tau = 47$ min, $T = 25^\circ\text{C}$. Solution A, a solution of **9** (16.3 g, 48.3 mmol) and freshly distilled benzaldehyde (5.38 g, 50.7 mmol) in dry EtOH (total volume 70 mL) was introduced into inlet A at a flow rate of 0.5 mL/min. Solution B, a NaOEt-solution in EtOH prepared by dilution of a NaOEt-solution (21%wt 18.9 mL, 50.7 mmol) with dry EtOH to a total volume of 70 mL, was simultaneously introduced into inlet B at a flow rate of 0.5 mL/min. The product solution corresponding to 10.5 mL, 10 mL and 15 mL of used solution A were successively collected over 21 min beginning from the run time of 1.0 τ , over 20 min beginning from the run time of 1.5 τ and over 30 min beginning from the run time of 1.9 τ . Work up and purification as described for the batch mode provided **5** as a yellow oil (1.19 g, 57%; 1.57 g, 78%; 2.66 g, 89%, respectively). ¹H-NMR (200 MHz, CDCl₃): $\delta = 1.34$ (t, $J = 7.1$ Hz, 3 H, OCH₂CH₃), 1.45 (s, 9 H, C(CH₃)₃), 3.45 (s, 2 H, 3-H₂), 4.28 (q, $J = 7.1$ Hz, 2 H, OCH₂CH₃), 7.36 (s, 5 H, 5 × Ph-H), 7.85 (s, 1 H, PhCH).

(E)-2-Benzylidene-succinic acid 1-ethyl ester (13). Batch mode. A mixture of TFA/H₂O ($V/V = 9:1$, total volume 62 mL) was added to a stirred solution of **5** (13.1 g, 45.1 mmol, 1.00 eq) in dichloromethane (40 mL) at rt and stirring was continued for 16 h. The solvent was evaporated in vacuo and for azeotropic removal of TFA the residue was taken up in toluene and concentrated in vacuo again (3 times with 25 mL). Then an aqueous saturated NaHCO₃-solution (48 mL) was added carefully. After being stirred for 1 h the mixture was washed with pentane (2 × 30 mL) and acidified to pH 1 with 2 N HCl (36 mL). The resulting mixture was extracted with EtOAc (2 × 50 mL) and the combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated in vacuo to afford **13** as a pale yellow solid (8.42 g, 80%). *MR*: Residence volume 2 mL, $\tau = 5$ min, $T = 34^\circ\text{C}$. Solution A, a solution of **5** (10.8 g, 37.2 mmol) in dichloromethane (total volume 35 mL) was introduced into inlet A at a flow rate of 0.2 mL/min. Solution B, a mixture of TFA/H₂O ($V/V = 9:1$, total volume 45 mL) was simultaneously introduced into inlet B at a flow rate of 0.2 mL/min. The product solution corresponding to 23.6 mL of used solution A was collected over 130 min beginning from a run time of 6 τ . Work up and purification as described for the batch mode afforded **13** as a pale yellow solid (3.73 g, 82%). ¹H-NMR (200 MHz, CDCl₃): $\delta = 1.35$ (t, $J = 7.1$ Hz, 3 H, OCH₂CH₃), 3.58 (s, 2 H, 3-H₂), 4.30 (q, $J = 7.1$ Hz, 2 H, OCH₂CH₃), 7.28–7.49 (m, 5 H, 5 × Ph-H), 7.93 (s, 1 H, PhCH), 11.12 (s_{br}, 1 H, CO₂H).

4-Acetoxy-naphthalene-2-carboxylic acid ethyl ester (6). Batch mode. A solution of **13** (35.2 g, 150 mmol, 1.00 eq) in Ac₂O (770 mL) was stirred at rt for 16.5 h. Then NEt₃ (29.3 mL, 210 mmol, 1.40 eq) was added and the mixture heated to reflux (T = 136°C, oil bath: 155°C) for 3 h. The solvent was evaporated in vacuo and the residue taken up in EtOAc (200 mL) and water (200 mL). After basification to pH = 9 with solid NaHCO₃ the aqueous layer was separated and extracted with EtOAc (100 mL). The combined organic layers were washed successively with an aqueous saturated NaHCO₃-solution (2 × 150 mL), 2 N HCl (2 × 100 mL) and brine, dried (MgSO₄), filtered and concentrated in vacuo to yield **6** as a brown solid (37.3 g, 96%). *MR*: Residence volume 47 mL, τ = 47 min, T = 130°C. Solution A, a solution of **13** in Ac₂O (total volume 190 mL) prepared by mixing a solution of **13** (8.24 g, 35.2 mmol) in Ac₂O (132 mL) with a solution of NEt₃ (4.98 g, 49.2 mmol, 1.40 eq) in Ac₂O (50 mL), was introduced into inlet A at a flow rate of 1.0 mL/min. The product solution corresponding to 30 mL of used solution A was collected over 30 min beginning from a run time of 2 τ and over 30 min from the run time of 2.6 τ. Work up and purification as described for the batch mode yielded **6** as a brown solid (1.45 g, 100%; 1.44 g, 100% respectively). ¹H-NMR (200 MHz, CDCl₃): δ = 1.42 (t, J = 7.1 Hz, 3 H, OCH₂CH₃), 2.46 (s, 3 H, COCH₃), 4.42 (q, J = 7.1 Hz, 2 H, OCH₂CH₃), 7.58 (m_c, 2 H, 6-H, 7-H), 7.82 (d, J = 1.4 Hz, 1 H, 3-H), 7.83–7.90 (m, 1 H, 8-H), 7.93–8.01 (m, 1 H, 5-H), 8.50 (s, 1 H, 1-H).

4-Hydroxy-naphthalene-2-carboxylic acid ethyl ester (14). Batch mode. A solution of NaOEt (21%wt, 15.0 mL, 39.9 mmol, 0.277 eq) in EtOH was added to a solution of **6** (37.3 g, 144 mmol, 1.00 eq) in dry EtOH (1000 mL). The mixture was heated to reflux (T_{internal} = 78°C) using an oil bath for 1 h. After removal of the solvent in vacuo the resulting residue was taken up in EtOAc (300 mL) and washed with an aqueous saturated NH₄Cl-solution (2 × 100 mL) and brine. The organic solution was dried (MgSO₄), filtered and concentrated in vacuo to furnish **14** as a brown solid (30.4 g, 141 mmol, 98%). *MR*: Residence volume 47 mL, τ = 23.5 min, T = 72°C. Solution A, a solution of **6** (5.24 g, 20.2 mmol) in dry EtOH (total volume 97 mL) was introduced into inlet A at a flow rate of 1.0 mL/min. Solution B, a NaOEt-solution in EtOH prepared by dilution of a NaOEt-solution (21%wt, 3.00 mL, 8.04 mmol) with dry EtOH to a total volume of 97 mL, was simultaneously introduced into inlet B at a flow rate of 1.0 mL/min. The product solution corresponding to 40 mL of the used solution A was collected over 40 min beginning from a run time of 1.5 τ. Work up and purification as described for the batch mode furnished **14** as a brown solid (1.81 g, 100%). ¹H-NMR (200 MHz, CDCl₃): δ = 1.38 (t, J = 7.2 Hz, 3 H, OCH₂CH₃), 4.38 (q, J = 7.2 Hz, 2 H, OCH₂CH₃), 6.42 (s_{br}, 1 H, OH), 7.42–7.57 (m, 3 H, 3-H, 6-H, 7-H), 7.79–7.89 (m, 1 H, 8-H), 8.13 (s, 1 H, 1-H), 8.15–8.22 (m, 1 H, 5-H).

4-Benzoyloxy-naphthalene-2-carboxylic acid ethyl ester (7). Batch mode. To a stirred solution of **14** (0.52 g, 2.4 mmol, 1.0 eq) in 2-methyltetrahydrofuran (MTHF, 10 mL) were added benzyl bromide (0.45 g, 2.6 mmol, 1.1 eq), tetrabutylammonium bromide TBABr (0.18 g, 0.56 mmol, 0.23 eq), water (9 mL) and an aqueous 2.5 M NaOH-solution (1.2 mL, 2.9 mmol, 1.2 eq). The mixture was heated to T_{internal} = 40°C for 2 h. After cooling to room temperature the organic layer was separated, washed successively with 2 N HCl (5 mL), water (5 mL) and brine, dried

(MgSO₄), filtered and concentrated in vacuo to afford a light brown-yellow solid (0.69 g), which was recrystallized from EtOH to give **7** as a light yellow solid (0.53 g, 70%). *MR*: Residence volume 47 mL, $\tau = 31$ min, $T = 40^\circ\text{C}$. Solution A, a solution of **14** (3.5 g, 16 mmol) and benzyl bromide (3.1 g, 18 mmol) in MTHF (total volume 60 mL) was introduced into inlet A at a flow rate of 0.75 mL/min. Solution B, a solution of TBABr (2.1 g, 6.4 mmol) and aqueous 2.5 M NaOH (7.9 mL, 20 mmol) in water (total volume 60 mL) was simultaneously introduced into inlet B at a flow rate of 0.75 mL/min. The product solution corresponding to 14 mL of used solution A was collected over 19 min beginning from a run time of 1.5 τ . Work up and purification as described for the batch mode gave **7** as a light yellow solid (0.84 g, 72%). ¹H-NMR (200 MHz, CDCl₃): $\delta = 1.46$ (t, $J = 7.1$ Hz, 3 H, OCH₂CH₃), 4.45 (q, $J = 7.1$ Hz, 2 H, OCH₂CH₃), 5.31 (s, 2 H, CH₂Ph), 7.32–7.66 (m, 8 H, 3-H, 6-H, 7-H, 5 × Ph-H), 7.87–7.97 (m, 1 H, 8-H), 8.25 (s, 1 H, 1-H), 8.32–8.42 (m, 1 H, 5-H).

4-Benzyloxy-naphthalene-2-carboxylic acid (16). Batch mode. An aqueous 2.5 M NaOH-solution (9.10 mL, 22.8 mmol, 10.0 eq) was added to a stirred solution of **7** (700 mg, 2.28 mmol, 1.00 eq) in THF (6 mL) and EtOH (8 mL). The biphasic mixture was heated to reflux ($T_{\text{internal}} = 74^\circ\text{C}$) in an oil bath (80°C) for 3.5 h. The solvent was evaporated and the residue acidified with 2 N HCl (15 mL). The formed precipitate was dissolved by addition of EtOAc (50 mL) and the aqueous layer was separated and extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated in vacuo to give **16** as a pale yellow solid (634 mg, 100%). 2) *MR*: The MR system was configured as follows: residence volume 47 mL, $\tau = 48$ min, $T = 68^\circ\text{C}$. Solution A, a solution of **7** (4.91 g, 16.0 mmol) in EtOH (56 mL) and THF (42 mL) with a total volume of 99 mL was introduced into inlet A at a flow rate of 0.58 mL/min. Solution B, an aqueous solution of NaOH (2.5 M, 64.0 mL, 160 mmol) was simultaneously introduced into inlet B at a flow rate of 0.40 mL/min. The product solution corresponding to 26 mL of used solution A was collected over 45 min beginning from a run time of 1.6 τ . Work up and purification as described for the batch mode gave **16** as a pale yellow solid (1.19 g, 100%). ¹H-NMR (300 MHz, DMSO-d₆): $\delta = 5.38$ (s, 2 H, CH₂Ph), 7.33–7.48 (m, 3 H, 1 × Ph-H, 6-H, 7-H), 7.50 (d, $J = 1.2$ Hz, 1 H, 3-H), 7.55–7.70 (m, 4 H, 4 × Ph-H), 8.05–8.12 (m, 1 H, 8-H), 8.23 (s, 1 H, 1-H), 8.23–8.28 (m, 1 H, 5-H), 13.01 (s_{br}, 1 H, COOH).

(4-Benzyloxy-naphthalen-2-yl)-carbamic acid tert-butyl ester (1). Batch mode. To a stirred solution of **16** (2.86 g, 10.3 mmol, 1.00 eq) in dry 1,4-dioxane (60 mL) were added NEt₃ (1.25 g, 12.3 mmol, 1.19 eq) and DPPA (3.06 g, 11.1 mmol, 1.08 eq). The mixture was heated to reflux for 45 min with evolution of nitrogen to give the isocyanate **18** and afterwards cooled down to 40°C. Then mixture was treated with freshly distilled *tert*-butanol (192 mL) and heated to reflux ($T_{\text{internal}} = 85^\circ\text{C}$) using an oil bath (106°C) for 14 h. After being cooled to room temperature the reaction mixture was filtered to remove a white precipitate. The mother liquor was treated with EtOAc (120 mL), washed successively with 2 N HCl (2 × 70 mL), aqueous saturated NaHCO₃-solution (2 × 40 mL), water (70 mL) and brine (60 mL). The organic solution was dried (MgSO₄), filtered and concentrated in vacuo to provide a yellow solid (3.03 g) which was taken up in diethylether. Some insoluble white solid was filtered off through a sintered-

glass-fritted funnel (porosity 4). The resulting mother liquor was concentrated in vacuo and the residue was washed with EtOH to give **1** a light yellow solid (1.49 g, 53%). *MR*: Residence volume 47 mL, $\tau = 34$ min, $T = 80^\circ\text{C}$. Solution A, a solution of the intermediate isocyanate **18** in 1,4-dioxane (total volume 100 mL) prepared by heating the mixture of **16** (4.02 g, 14.4 mmol, 1.00 eq), NEt_3 (1.75 g, 17.3 mmol, 1.20 eq) and DPPA (4.19 g, 15.2 mmol, 1.06 eq) in dry 1,4-dioxane (94 mL) to reflux for 80 min and subsequent dilution with dry 1,4-dioxane, was introduced into inlet A at a flow rate of 0.40 mL/min. Solution B, a solution of dry *tert*-butanol/1,4-dioxane ($V/V = 29:1$, total volume 250 mL) was simultaneously introduced into inlet B at a flow rate of 1.0 mL/min. The product solution corresponding relating to 47 mL of used solution A was collected over 120 min beginning from a run time of 1.8τ . Work up and purification as described for the batch mode gave **1** as a light yellow solid (1.21 g, 52%). **$^1\text{H-NMR}$** (200 MHz, CDCl_3): $\delta = 1.48$ (s, 9 H, $\text{C}(\text{CH}_3)_3$), 5.15 (s, 2 H, CH_2Ph), 6.55 (s_{br}, 1 H, NH), 6.99 (d, $J = 1.7$ Hz, 1 H, 3-H), 7.19–7.50 (m, 8 H, 1-H, 6-H, 7-H, $5 \times \text{Ph-H}$), 7.61 (d, $J = 8.2$ Hz, 1 H, 8-H), 8.15 (d, $J = 8.2$ Hz, 1 H, 5-H).

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