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# Multiple Organolithium Generation in the Continuous Flow Synthesis of Amitriptyline

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**Abstract:** A continuous flow protocol for the preparation of the tricyclic antidepressant (TCA) amitriptyline is reported. The advantages of flow chemistry when handling organometallic agents as well as when performing reaction with gases are demonstrated. Continuous multilithiation combined with carboxylation and the Parham cyclization, a Grignard addition and thermolytic water elimination by inductive heating are key features of the multistep protocol.

**Keywords:** amitriptyline; antidepressants; carboxylation; flow chemistry; inductive heating; lithiation; Parham cyclization

Amitriptyline (Elavil) (**1**) is a tricyclic antidepressant (TCA), that among many other medical indications, also serves against migraines, tension headaches, anxiety attacks and some schizophrenic symptoms. in spite of the fact that it has been established as a drug for some time, it is as effective against depression as the newer class of selective serotonin reuptake inhibitors (SSRIs).[1] Amitriptyline (**1**) also shows strong activities on the serotonin transporter and moderate effects on the norepinephrine transporter.[2,3] It acts as a sodium, calcium, and potassium channel blocker.[4–6]

Some published syntheses[7–9] of amitriptyline exploit the inherent symmetry present in the tricyclic dibenzosuberane backbone. 10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (**3**, dibenzosuberone) can principally be approached by a one-pot Parham cyclization[10] which is initiated by a Wurtz-type dimerization of lithiated benzyl bromide **2** (Figure 1). A second lithium halogen exchange sets the stage for a monocarboxylation using carbon dioxide as electrophile. The resulting benzoic acid derivative will undergo cyclization after lithiation of the last aryl bromide moiety to furnish dibenzosuberone (**3**).[10a]

Finally, Grignard addition and elimination of water from the resulting carbinol complete the synthesis of amitriptyline (**1**).[9]

As part of our research to expand the scope of synthesis under continuous flow conditions, we developed a flow protocol that follows this principal route. The use of microstructured flow reactors is one attractive technique, among other enabling technologies for organic synthesis,[11] which shows great advantages when handling highly reactive intermediates as well as gases as reaction partners. Additionally, flow chemistry is readily amenable to multistep synthesis.[12] Often, these processes provide better yields or selectivities compared to batch processes, because only a small portion of the reactive intermediate is formed at a given time which immediately reacts under controlled conditions (control refers to reten-

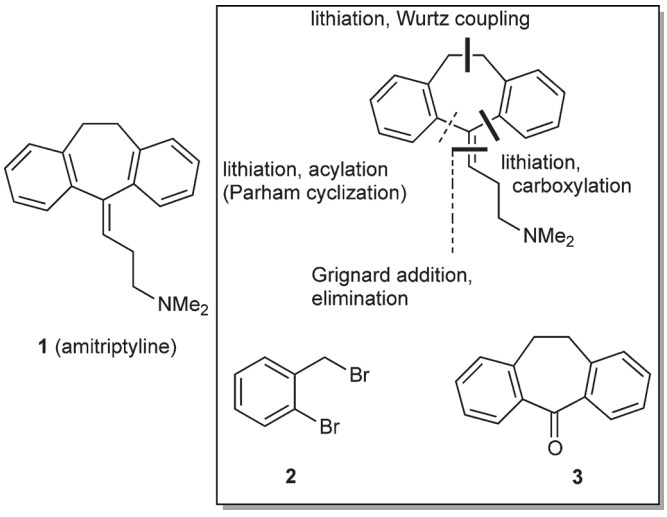



**Figure 1.** Amitriptyline (**1**) and the key C–C bond-forming processes.[9,10]

tion time/flow rate and temperature). Pioneering contributions from the Yoshida group demonstrated that sequential lithium–halogen exchange protocols with in situ trapping of aryllithium intermediates by different electrophiles in microstructured flow devices are superior to batch protocols.[13,14]

In the synthesis of amitriptyline (**1**), three different lithium–halogen exchange reactions take place with precise timing and each initiates a C–C bond-forming reaction. A second challenge of this synthesis is the controlled introduction of carbon dioxide into the flow system. This was achieved using Ley's tube-in-tube system.[15] The reaction takes place in the interstitial liquid phase between the two tubes, with the carbon dioxide gas being supplied by the outer tube, which possesses a semipermeable membrane. This set-up allows many different gases, including carbon monoxide,[16] hydrogen,[17] oxygen,[18] ammonia[19] and ethylene[20] to be employed. Importantly, the gas flow is controlled by pressure and not by metered flow, simplifying this type of gas–liquid phase reactions. Bubbles of gas are avoided entirely.

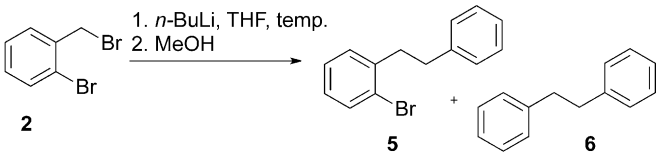
The synthesis of the dibenzosuberone (**3**) under batch conditions was described and it requires very low temperature (−100 °C) for the lithiation step.[10a] In order to be able to judge the efficiency of our flow protocol we first established the batch protocol. [2-(2-Bromophenethyl)phenyl]lithium was generated from 1-bromo-2-(bromomethyl)benzene (**2**) using one equivalent of *n*-butyllithium at −100 °C for 1 h. A stream of carbon dioxide gas was bubbled through the mixture for 1.5 h. Then the cooling was removed and at room temperature a stream of dry nitrogen was bubbled through the mixture over 1.5 h. The solution was again cooled to −100 °C and *n*-butyllithium was added. After 30 min at −100 °C and 6 h at room temperature dibenzosuberone (**3**) was isolated in 38–56% yield.[10a,21]

The key step of this process is the generation of [2-(2-bromophenethyl)phenyl]lithium. We found that even at −100 °C complete lithiation occurs resulting in the formation of the by-product 1,2-diphenylethane (**6**) in 31% yield (see Table 1, entry 4) besides the expected bromide **5**. At higher temperatures this process prevails (Table 1, entries 1–3). In essence, the practicability of this process has limitations, especially when up-scaling is envisaged.

We assumed that flow conditions would improve the handling of organolithium reagents and intermediates as only a small portion of the *n*-BuLi is subjected to the reaction conditions at a given time at a temperature that we hoped to be well above −100 °C.

We devised a flow system that consists of a T-shaped micromixer **M1** (Ø = 0.4 mm; PEEK) and a microtube reator **R1** (Ø = 1 mm, *V* = 0.5 mL; steel). Two solutions of 1-bromo-2-(bromomethyl)benzene (**2**) (0.2 M in THF; flow rate = 4 mL min$^{-1}$) and of *n*-butyllithium (0.4 M in hexane; flow rate = 2 mL min$^{-1}$) were independently fed into the reactor using two HPLC pumps. The reaction mixture was hydrolyzed with methanol at the reactor outlet. The transformation proceeded with complete conversion irrespective of whether it was conducted at −90 °C or at room temperature (Table 2, part A) providing a mixture of the desired 1-bromo-2-phenethylbenzene (**5**), 1,2-bis(2-bromophenyl)ethane (**4**) as well as **6**. Additionally, we detected 1-bromo-2-pentylbenzene (**7**) which resulted from the direct substitution reaction of *n*-butyllithium with the starting material.

**Table 1.** Wurtz coupling under batch conditions.




| Entry | Temp. [°C] | Yield [%][a] of **5** | Yield [%][a] of **6** |
|---|---|---|---|
| 1 | 0 | 6 | 55 |
| 2 | −40 | 13 | 78 |
| *3* | *−90* | *59* | *43* |
| 4 | −100 | 62 | 31 |

[a] Isolated yields.

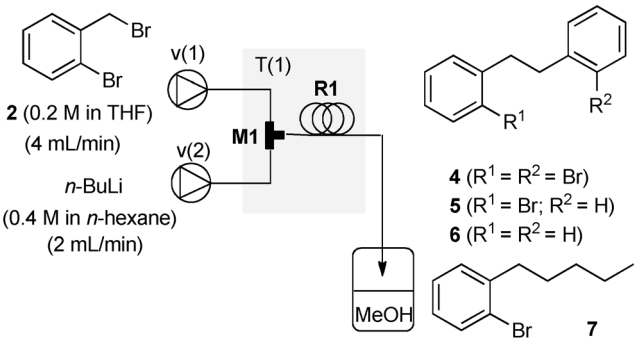
We also investigated the influence of the inner diameter of the micromixer on the outcome of lithiation and Wurtz-type coupling (Table 2, part B). A smaller diameter (Ø = 0.25 mm) favours formation of the desired aryl bromide **5**, supposedly, because it guarantees more rapid mixing of both reactants. Thus, it was possible to achieve excellent conversions at −50 °C, within 5 s, providing product **5** in 79% isolated yield.

With these results in hand we commenced with the continuous multistep synthesis of 10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-one (**3**). Positioned directly behind **R1**, a tube-in-tube reactor allowed us to introduce carbon dioxide into the stream of reactants. In a second microtube reator **R2** (Ø = 1 mm, *V* = 0.5 mL; PTFA) the carboxylation took place (Table 3: set-up A, bottom left). Then, a second solution of *n*-butyllithium (0.4 M in hexane) was mixed in **M2** (Ø = 0.4 mm) with the reaction stream that left **R2** and the resulting mixture was passed through **R3** (Ø = 1 mm, *V* = 0.5 mL; PTFA). A back-pressure regulator was installed behind **R3** to pressurize the system. All test samples were finally hydrolyzed in a flask that contained methanol.

Carboxylation in **R2** was inefficient at −50 °C, providing ketone **3** in only low yield. Instead, double halogen–lithium exchange and formation of 1,2-diphenylethane (**6**) occurred (Table 3, entries 1–5). When the reactor temperature was raised to room temperature, the yield of ketone **3** improved (entries 6–8). An in-

**Table 2.** Optimization of Wurtz coupling under flow conditions.[a]




| Temp. [°C] | Time [sec] | Yield [%][b] of | | | | |
|---|---|---|---|---|---|---|
| | | **2** | **4** | **5** | **6** | **7** |
| **A: Influence of temperature** | | | | | | |
| r.t. | 5 | 0 | 37 | 26 | 2 | 29 |
| 0 | 5 | 0 | 24 | 47 | 4 | 23 |
| –20 | 5 | 0 | 19 | 54 | 4 | 20 |
| –50 | 5 | 0 | 16 | 60 | 3 | 10 |
| –70 | 5 | 0 | 14 | 69 | 3 | 7 |
| *–90* | *5* | *0* | *10* | *76* | *3* | *4* |
| **B: Influence of T-mixer (Temp. = –50 °C)** | | | | | | |
| mixer M1 | ∅ [mm] | | | | | |
| steel | 1.0 | 8 | 25 | 3 | 0 | 59 |
| PEEK | 0.4 | 0 | 16 | 60 | 3 | 10 |
| steel | 0.25 | 0 | 5 | 82 (79)[c] | 4 | 6 |

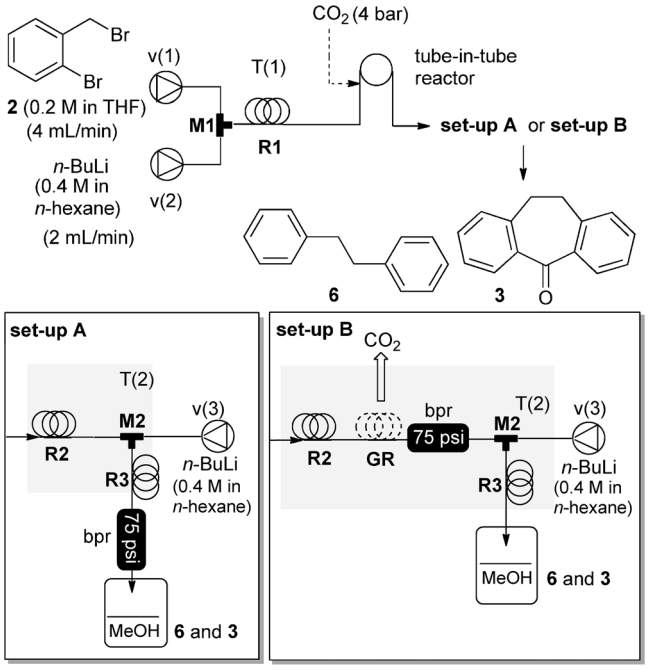
[a] T-Shaped micromixer **M1** (if not otherwise noted Ø = 0.4 mm; PEEK), microtube reactor **R1** (Ø = 1 mm, *V* = 0.5 mL; steel); best results are printed in italics [T(1) = temperature in **R1**].
[b] Determined by GC-MS analysis.
[c] Isolated yield.

creased flow rate for *n*-BuLi provided improved yields of **3**. However, an excess of *n*-butyllithium [v(3)] was always required, likely due to the presence of excess carbon dioxide which destroys some of the reagent. Therefore, a set-up B with a gas remover (**GR**) located behind **R2** was employed. Here, the reaction stream passed through a Teflon AF-2400 tube (50 cm).

We found that the back-pressure regulator should be placed directly behind **GR** and not behind **R3**. With this set-up the amount of *n*-BuLi required could be reduced. This flow set-up allows the preparation of ketone **3** from dibromide **2** with an overall residence time of approximately 33 s at −50 °C, compared to about 2 h at −100 °C, under batch conditions.[10a] The isolated yield was 76%, compared to the batch yield of 38–56%.

Next, the Grignard addition was investigated (Table 4).[9] A solution of ketone **3** and [3-(dimethylamino)propyl]magnesium chloride was mixed in a T-shaped micromixer **M3** (Ø = 0.4 mm, PEEK) and pumped through a microtube reactor **R4** (Ø = 1 mm, *V* = 0.5 mL, PTFE). Hydrolysis took place at the outlet by injecting the stream into a flask filled with methanol. Best results were obtained when 1.5 equivalents of the Grignard reagent in THF or toluene at room temperature were employed. Under these conditions the residence time was only about 30 s (Table 4, entries 3 and 4).

**Table 3.** Multistep flow synthesis to ketone **3** without (set-up A) and with (set-up B) gas remover **GR**.[a]

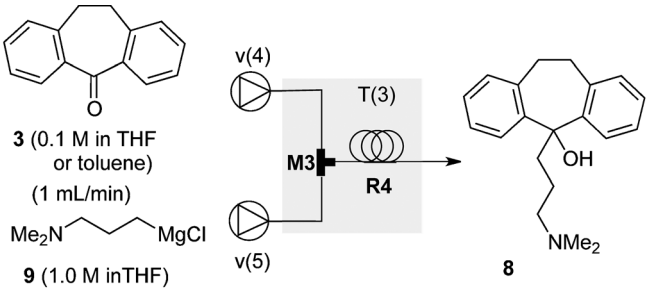



| Entry | T(1) [°C] | T(2) [°C] | v(3) [mL·min$^{-1}$] | Yield [%] of | |
|---|---|---|---|---|---|
| | | | | **3** | **6** |
| **set-up A** | | | | | |
| 1 | –50 | –50 | 2.5 | 11 | 21 |
| 2 | –50 | –50 | 3.0 | 19 | 20 |
| 3 | –50 | –50 | 3.5 | 23 | 24 |
| 4 | –50 | –50 | 3.7 | 24 | 25 |
| 5 | –50 | –50 | 4.0 | 35 | 20 |
| 6 | –50 | r.t. | 2.1 | 35 | 18 |
| 7 | –50 | r.t. | 2.5 | 51 | 20 |
| *8* | *–50* | *r.t.* | *4.0* | *62 (50)*[c] | *15* |
| **set-up B** | | | | | |
| 9 | –50 | r.t. | 2.1 | 62 | 9 |
| 10 | –50 | r.t. | 2.5 | 75 | 8 |
| *11* | *–50* | *r.t.* | *3.0* | *79 (76)*[c] | *5* |

[a] A gas remover **GR**: **M1** (Ø = 0.25 mm; steel), microtube reactor **R1** (Ø = 1 mm, *V* = 0.5 mL; steel), tube-in-tube (Ø = 2 mm/0.8 mm, *V* = 1 mL, PTFE/Teflon AF-2400); **R2** (Ø = 0.8 mm, *V* = 0.5 mL; PTFE), *R3* (Ø = 0.8 mm, *V* = 0.5 mL, PTFE), T(1), T(2) = reactor temperatures, **GR** (Ø = 0.8 mm, *V* = 1 mL, Teflon AF-2400); best results are printed in italics.
[b] Determined by GC-MS analysis.
[c] Isolated yield.

**Table 4.** Grignard addition.[a]




| Entry | Solvent | T(3) [°C] | v(5) [mL·min$^{-1}$] | Yield [%][b] of **8** |
|---|---|---|---|---|
| 1 | THF | 0 | 0.1 | 67 |
| 2 | THF | 0 | 0.15 | 78 |
| *3* | *THF* | *r.t.* | *0.15* | *80* |
| 4 | toluene | r.t. | 0.15 | 77 |

[a] **M3** (Ø = 0.25 mm, steel), **R4** (Ø = 1 mm, $V$ = 0.5 mL, PTFE), T(3) = reactor temperature; the best result is printed in italics.
[b] Isolated yield.

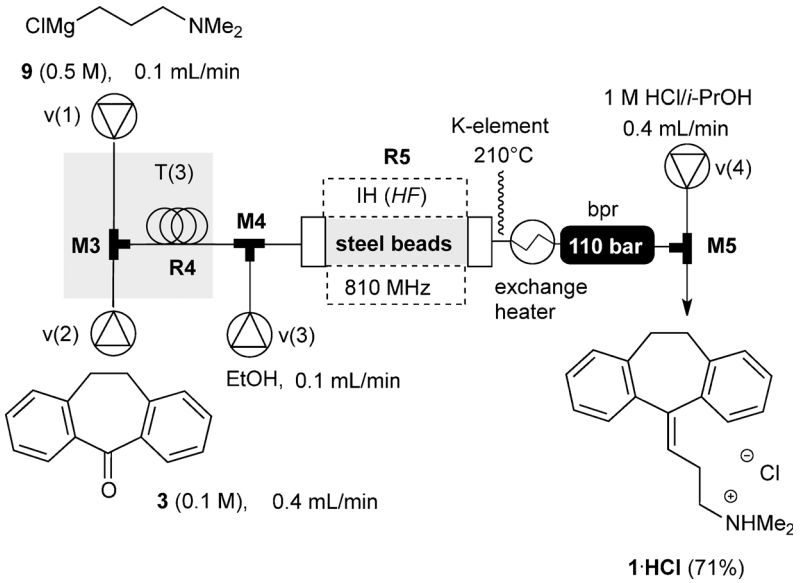
Elimination of the tertiary alcohol with HCl (7 M) in ethanol provides amitriptyline hydrochloride in 63% yield.[9] These highly corrosive conditions are deleterious for reactor and pump materials so we alternatively pursued a high temperature high/pressure elimination using inductive heating (IH).[22]

During inductive heating an external oscillating electromagnetic field induces heat in superparamagnetic nanostructured iron oxide particles or in other conductive materials. These materials may serve as a fixed bed material in flow devices.[23] Consequently, copper or steel reactors can directly be heated under these conditions.

Here, we chose a cartridge reactor (60 mm length, Ø = 4 mm, $V$ = 0.3 mL, steel) filled with steel beads (Ø = 0.8 mm) which was incased in a high frequency (hf) inductor (810 Hz).[23f] An injection loop was positioned between the pump and the reactor for injecting amine **8**.

The temperature of the reaction stream was measured with a K-element at the outlet of the flow reactor. Next to the K-element we set up a heat-exchanger (Ø = 1.0 mm, $V$ = 0.5 mL, steel) for rapid cooling to room temperature. The pressure was controlled by a back-pressure regulator. To our delight, elimination of water proceeded smoothly (36 s residence time) in ethanol at 200 °C (810 MHz, 8% energy input) in the absence of any acid and quantitatively yielded amitriptyline (**1**) (see the Supporting Information, Table S2).[24] After having optimized the Grignard addition and the elimination, we focused on telescoping these two steps (Scheme 1).[25]

Thus, the Grignard product that left **R4** was protonated by diluting the reaction mixture with ethanol and the resulting carbinol was directly pumped into an inductively heated cartridge reactor **R5** ($V$ = 0.3 mL, residence time = 30 s). At the outlet the crude elimination product was mixed in **M5** with a 1 M solution of HCl in isopropyl alcohol to yield the HCl salt of amitriptyline. One recrystallization (ethanol-ether) provided pure **1**·HCl in 71% yield. Salt formation has




**Scheme 1.** Continuous two-step Grignard addition, elimination and synthesis of **1**·HCl. a) **M3** (Ø = 0.4 mm, PEEK), **R4** (Ø = 1 mm, $V$ = 0.5 mL, PTFE); **M4** (Ø = 0.4 mm, PEEK), **R5** (length = 60 mm, Ø = 4 mm, steel, filled with steel beads Ø = 0.8 mm, $V$ = 0.3 mL), IH(hf) = high frequency inductive heating (8%, 810 kHz), heat exchanger ($V$ = 0.5 mL), **M5** (Ø = 0.4 mm, PEEK).

several advantages: (i) it provides crystalline material avoiding chromatographic purification steps and (ii) the salt form is commonly employed in medical applications. The simple recrystallization procedure principally allows to us reach an impurity profile that corresponds well with USP requirements.

In conclusion, we have disclosed a multistep flow synthesis of the hydrochloride salt of the tricyclic antidepressant amitriptyline (**1**·HCl). The process involves low temperature, as well as high temperature/high pressure transformations. Intermediate ketone **3** was formed at a rate of about 127 mg min$^{-1}$, while the second sequence provided about 8.9 mg min$^{-1}$ of amitriptyline (**1**·HCl). The flow protocols developed clearly demonstrate the power of microreactor synthesis when highly reactive intermediates such as organolithium species are generated. Metallations can be operated at higher temperatures than for the corresponding batch processes and therefore proceed more rapidly. This flow protocol reduces concerns on safety issues compared to the corresponding batch protocol because only a small portion of *n*-BuLi needs to be subjected to the lithiation and coupling conditions at a given time.

Additionally, we have shown that high temperature reactions with short residence times can be strategically implemented in a synthetic sequence. In this context, inductive heating of flow reactors can be regarded as a powerful and safe[26] enabling technology.

## Experimental Section

### Multistep Flow Synthesis to 10,11-Dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (3)

A solution of 1-bromo-2-(bromomethyl)benzene (**2**) [0.20 M, v(1) = 4 mL min$^{-1}$] in THF and a solution of *n*-butyllithium [0.4 M, v(2) = 2 mL min$^{-1}$] in hexane were mixed in **M1** (Ø = 0.25 mm, steel) and the mixture was passed through **R1** (Ø = 1 mm, *V* = 0.5 mL; steel) at −50 °C. The reaction stream was directed through a tube-in-tube reactor (Ø = 0.8 mm, *V* = 1 mL, Teflon AF-2400) at room temperature to saturate the reaction mixture with carbon dioxide. At the outlet of **R2** (Ø = 0.8 mm, *V* = 0.5 mL; PTFE) a gas remover **GR** (Ø = 0.8 mm, *V* = 1 mL, Teflon AF-2400) was installed. A back-pressure regulator (75 psi) was placed immediately after the gas remover, which allowed a more rapid outgassing of carbon dioxide. The resulting solution was mixed with a solution of *n*-butyllithium [0.4 M, v(3) = 3 mL min$^{-1}$] in hexane at room temperature and passed through **R3** (Ø = 0.8 mm, *V* = 0.5 mL, PTFE). When including this microreactor flow system, an overall residence time of 33 s was calculated. After a steady state had been reached, the product was collected over a period of 30 min. After diluting the solution with hydrochloric acid (5%, 60 mL), the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 60 mL). The combined organic phases were washed with an aqueous sodium hydroxide solution (5%), dried over $MgSO_4$ and concentrated under reduced pressure. Ketone **3** was obtained as a yellow oil; yield: 126.6 mg min$^{-1}$ (0.61 mmol min$^{-1}$, 76%); $^1$H NMR (400 MHz, $CDCl_3$,): $\delta$ = 8.02 (2H, dd, *J* = 1.4, 7.8 Hz), 7.44 (2H, dt, *J* = 1.5, 7.4 Hz), 7.33 (2H, dt, *J* = 1.3, 7.6 Hz), 7.23 (2H, dd, *J* = 0.9, 7.5 Hz), 3.22 (4H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 195.6, 141.9, 138.6, 132.3, 130.5, 129.2, 126.6, 34.9; HR-MS (ESI): *m/z* = 209.0944, calculated for $C_{15}H_{13}O^+$ $[M+H]^+$: 209.0961. All data were in accordance with published values.[27]

### Synthesis of 5-[3-(Dimethylamino)propyl]-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ol (8) under Flow Conditions

A solution of 10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (**3**) [0.1 M, v(4) = 1 mL min$^{-1}$] in toluene and a solution of the Grignard reagent **9** [1 M, v(5) = 0.15 mL min$^{-1}$] in THF were mixed in **M3** (Ø = 0.25 mm, steel). The reaction solution was passed through **R4** (Ø = 1 mm, *V* = 0.5 mL; steel) at room temperature. After reaching steady state the product stream was collected over a period of 10 min. The solvent was removed and the solid was hydrolyzed with an aqueous solution of ammonium chloride (10%, 50 mL). The mixture was extracted with dichloromethane (3 × 50 mL). The combined, organic phases were dried over magnesium sulfate, filtered and concentrated under vacuum. Alcohol **8** was obtained as colourless crystals without a detectable trace of starting material; yield: 22.2 mg mL$^{-1}$ (0.076 mmol mL$^{-1}$, 77%); mp 118 °C (ref.[9] 119–120 °C); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.04 (2H, dd, *J* = 1.4, 7.9 Hz), 7.21–7.05 (6H, m), 3.52–3.42 (2H, m), 3.02–2.92 (2H, m), 2.52–2.47 (2H, m), 2.27–2.22 (2H, m), 2.22 (6H, s), 1.39–1.32 (2H, m); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 145.8, 137.4, 130.2, 126.8, 126.7, 125.9, 76.4, 59.6, 45.1, 44.2, 33.8, 22.3; HR-MS (ESI): *m/z* = 296.2112, calculated for $C_{20}H_{26}NO^+$ $[M+H]^+$: 296.2009. All data were in accordance with published values.[9]

### Two-Step Flow Synthesis towards Amitriptyline Hydrochloride (1·HCl)

A solution of 10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (**3**) [0.1 M, v(4) = 0.4 mL min$^{-1}$] in toluene and a solution of Grignard reagent **9** [0.5 M, v(5) = 0.1 mL min$^{-1}$] in THF were mixed in **M3** (Ø = 0.25 mm, steel). The resulting solution was passed through **R4** (Ø = 1 mm, *V* = 0.5 mL; steel) at room temperature and at the outlet it was mixed with ethanol [v(6) = 0.1 mL min$^{-1}$] in **M4** (Ø = 0.5 mm, PEEK). The solution of reactants was pumped into cartridge reactor **R5** (length = 60 mm, Ø = 4 mm, steel, filled with steel beads Ø = 0.8 mm, *V* = 0.3 mL) and heated inductively at high frequencies [8%, 800 kHz; T(4) = 210 °C]. The reaction stream was cooled by an exchange heater (*V* = 0.5 mL) before it reached the back-pressure regulator (110 bar). Finally, the resulting solution was mixed with a solution of HCl [1 M, v(7) = 0.5 mL min$^{-1}$] in isopropyl alcohol in **M6** (Ø = 0.5 mm, PEEK) at room temperature. The product was collected over a period of 30 min and filtered over CeliteTM. The solvent was removed under reduced pressure. Recrystallization from ethanol-ether solution (1:20) gave amitriptyline hydrochloride (**1**·HCl) as a colourless solid; yield: 8.91 mg min$^{-1}$

(0.028 mmol min$^{-1}$, 71%); mp 190 °C (ref.[S6] 193–194 °C); $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.25$–6.99 (8H, m), 5.75 (3H, t, $J = 7.1$ Hz), 3.37–3.19 (2H, m), 3.18–3.03 (1H, m), 3.00–2.81 (2H, m), 2.80–2.71 (1H, m), 2.66 (8H, br s); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 146.8$, 139.6, 138.8, 138.6, 136.7, 129.8, 128.0, 127.8, 127.3, 127.1, 126.8, 126.7, 123.0, 56.5, 42.6, 41.9, 33.2, 31.6, 23.9. All data were in accordance with published values.[9]

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