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# Continuous Flow Synthesis and Purification of Atropine with Sequential In-Line Separations of Structurally Similar Impurities

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Flow chemistry has attracted significant interest in pharmaceutical development, where substantial efforts have been directed toward the design of continuous processes. Here, we report a total synthesis of atropine in flow that features an unusual hydroxymethylation and separation of several byproducts with high structural similarity to atropine. Using a combination of careful pH control in three sequential liquid-liquid extractions and a functionalized resin, atropine is delivered by the flow system with > 98% purity.

**Keywords:** continuous flow synthesis, sequential in-line extraction, atropine

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## 1. Introduction

Multi-step continuous flow synthesis combines individual synthesis and purification steps into one integrated, end-to-end system that operates at steady-state and can be computer-controlled.<sup>1</sup> High space-time throughput and accelerated scale-up are other features that can lead to great savings in time and materials involved in chemical development.<sup>2</sup> As a consequence, flow technology has been an active area of investigation for both pharmaceutical and chemical industries over the past decade.<sup>3</sup>

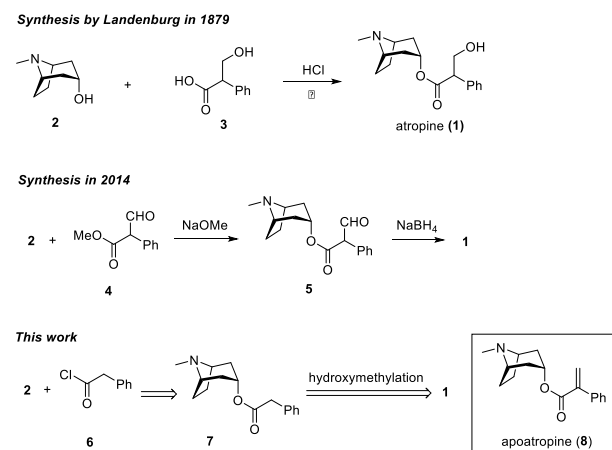
Although most flow systems have been developed for single-step reactions, recent examples have shown that flow technology can be applied to multi-step sequences.<sup>4</sup> The integrated continuous flow synthesis of complex molecules, including intermediate purification has also been achieved.<sup>5</sup> However, each additional reaction or separation implemented in the streamline increases the complexity of the flow system and can make development of an efficient flow synthesis more challenging than an individual step. Thus, development of the system requires strict tolerance and careful optimization of each step to ensure overall robustness. The reagents, intermediates, products and solvents have to be highly compatible throughout the entire process regardless of changes in temperature, pH and pressure. Meanwhile, the formation of byproducts is expected to be minimized to avoid incomplete purification. Although several purification techniques have already been developed, such as liquid-liquid extraction,<sup>6</sup> microfluidic evaporation<sup>7</sup> and distillation,<sup>8</sup> simulated moving-bed chromatography<sup>9</sup> and crystallization,<sup>10</sup> in-line separation of complex mixtures of byproducts still remains a challenge.

Our group recently reported the continuous flow synthesis of the active pharmaceutical ingredients (APIs) ibuprofen<sup>11</sup> and rufinamide.<sup>12</sup> To further investigate the synthesis of APIs in flow, we selected atropine **1**, a naturally occurring tropane alkaloid that exists as a racemic mixture of *D*-hyoscyamine and *L*-hyoscyamine.<sup>13</sup> Its sulfate salt is a core medicine in the World Health Organization's "Essential Drugs List"<sup>14</sup> and has both anticholinergic and antiparasymphathetic properties with widespread functions.<sup>15</sup> The first total synthesis of atropine was reported by Landenburg in 1879 (Scheme 1, top),<sup>16</sup> followed by a classic synthesis based on the biomimetic approach to tropine developed by Robinson in 1917.<sup>17</sup> Recently, atropine was synthesized from tropine **2** and methyl formyl phenylacetate **4**, followed by reduction with NaBH<sub>4</sub> (Scheme 1, middle).<sup>18</sup> However, current industrial manufacturing process of atropine still relies mainly on herbal extraction.<sup>19</sup> Herein, we report the first example of a continuous flow synthesis of atropine and sequential in-line separation of compounds with similar structures via pH-based liquid-liquid extractions and functionalized resin.

## 2. Results and discussion

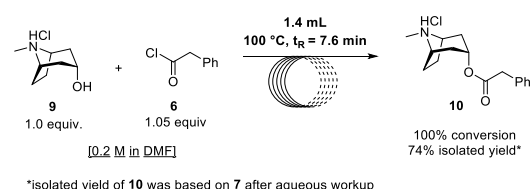
We envisioned that the flow synthesis of atropine could be achieved from the readily available starting materials: tropine **2** and phenylacetyl chloride **6** in two steps. The coupling reaction will give ester intermediate **7**, and without any separation of the intermediate, this ester can be used directly for the hydroxymethylation by treating with base and formaldehyde (Scheme 1, bottom). This route offers high degree of cost efficiency and application feasibility. However, in the presence of base, the generated atropine is prone to E1cB elimination, giving the conjugated byproduct apoatropine **8**, which is also present in the extraction of natural atropine.<sup>20</sup> Due to the close structural similarity, separation of atropine from apoatropine presents an exceptional challenge, particularly in flow. In order to minimize the generation of apoatropine, we undertook a systematic evaluation of the base and formaldehyde source.

### Scheme 1. Synthesis of atropine



We first examined the coupling reaction of tropine **2** and phenylacetyl chloride **6** in batch. When using 1.0 equivalent of phenylacetyl chloride, we were only able to obtain the maximum isolated yield of 50%. It is speculated that other than the hydroxyl group, the tertiary amine in tropine ring could also react with phenylacetyl chloride, resulting in undesired consumption of phenylacetyl chloride. The generated quaternary ammonium salt seemed quite stable under the reaction conditions and didn't react with another molecule of tropine. In order to achieve full conversion of the first step, there are two options. One is to use the hydrogen chloride salt of tropine (**9**), and the other is to use 2.0 equivalents of phenylacetyl chloride. In the end, we decided to choose the first solution since excess amounts of phenylacetyl chloride might cause unpredictable problems in the subsequent hydroxymethylation and purification steps. Re-examination of the coupling reaction in batch using the tropine hydrogen chloride salt as starting material gave quantitative conversion. We then conducted this reaction in flow, where a solution of tropine hydrogen chloride and phenylacetyl chloride in DMF was pumped into a 1.4 mL reactor at a flow rate of 180  $\mu\text{L}/\text{min}$ . The reaction was completed in 7.6 min at 100  $^{\circ}\text{C}$  (Scheme 2).

### Scheme 2. Synthesis of intermediate 10 in flow

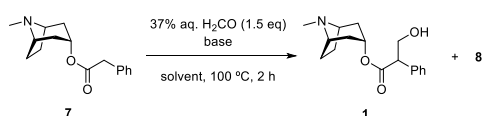


Next, we examined the hydroxymethylation step. Various formaldehyde sources and bases were tested. Among all the formaldehyde reagents, only 37% aq. formaldehyde solution gave promising results. 1,3,5-Trioxane failed to provide the product and paraformaldehyde was insoluble in DMF at

room temperature which makes it unavailable for use in the flow synthesis. We also tried to obtain pure formaldehyde gas by cracking paraformaldehyde at high temperature.<sup>21</sup> However, it is difficult to control the flow rate of formaldehyde gas generated in this way and safely handle such a highly toxic and reactive gas. Making a formaldehyde solution (such as in THF) from polyoxymethylene is another option, although its storage requires a specific cooling system.<sup>22</sup>

Due to the usage of an aqueous formaldehyde solution, water-sensitive organic bases, such as LiO<sup>t</sup>Bu, LiHMDS and <sup>n</sup>BuLi, are therefore not compatible. Other organic bases, such as pyridine and triethylamine failed to provide atropine even at 100 °C (Table 1, entries 1-2), while DBU gave an equal mixture of atropine and apoatropine in low conversion at 60 °C (entry 3). We therefore decided to screen inorganic bases in batch. Na<sub>2</sub>CO<sub>3</sub> only delivered a 61% conversion (entry 4). pH = 10 Buffer led to higher conversions upon heating (entries 5-8). Excess amounts of formaldehyde (5.0 equiv) increased the conversion, but produced apoatropine **8** as the major product (entry 6). Interestingly, when catalytic amounts of NaOH were used, 97% conversion was obtained (entry 9). This result indicated that an intermolecular deprotonation occurs between the generated alkoxide and another molecule of **7**. While stoichiometric amounts of NaOH gave full conversion at room temperature but with a complex mixture of byproducts (entry 10).

**Table 1. Base screen for hydroxymethylation in batch**

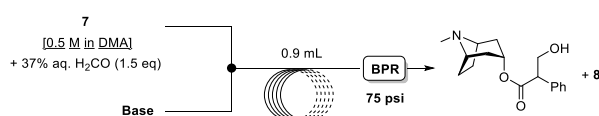


entry	base	solvent (v/v)	conversion <sup>a</sup>	<b>1</b> : <b>8</b>
1	Pyridine (1.0 eq)	DMF	0%	N/A
2	Et <sub>3</sub> N (1.0 eq)	DMF	0%	N/A
3	DBU (1.0 eq) <sup>b</sup>	THF	33%	1:1
4	Na <sub>2</sub> CO <sub>3</sub> (1.0 eq)	DMF/H <sub>2</sub> O (1:1)	61%	4:1
5	pH = 10 buffer <sup>c</sup>	DMA/buffer (1:1)	86%	2:1
6	pH = 10 buffer <sup>c,d</sup>	DMA/buffer (1:1)	97%	1:1.4
7	pH = 10 buffer <sup>c</sup>	DMA/buffer (3:1)	92%	6:1
8	pH = 10 buffer <sup>c</sup>	DMA/buffer (5:1)	79%	16:1
9	1 M NaOH (0.17 eq)	DMA/aq. NaOH (9:1)	97%	1.4:1
10	1 M NaOH (1.0 eq) <sup>e</sup>	DMA/aq. NaOH (2.3:1)	100%	complex mixture

<sup>a</sup>Reaction conversions are based on <sup>1</sup>H NMR after aqueous workup. <sup>b</sup>The reaction was running at 60 °C. At 100 °C, the reaction only gave apoatropine **8** with 100% conversion. <sup>c</sup>pH = 10 Buffer (blue) is purchased from VWR (catalog No: 2309670). Contents: NaHCO<sub>3</sub>/Na<sub>2</sub>CO<sub>3</sub>/H<sub>2</sub>O. <sup>d</sup>The reaction was running with 5.0 equiv of H<sub>2</sub>CO. <sup>e</sup>The reaction was running with 1.0 equiv of H<sub>2</sub>CO at room temperature.

When performing the hydroxymethylation reaction in flow, pH = 10 buffer only provided high conversion (82%) at 100 °C (Table 2, entry 1), while NaOH delivered full conversion at room temperature with a 5:1 ratio of atropine to apoatropine. Increased flow rate (shorter *t<sub>r</sub>*) provided a higher ratio (8:1, entry 2), but in slightly attenuated conversion (90%, entry 3).

**Table 2. Base screen for hydroxymethylation in flow**

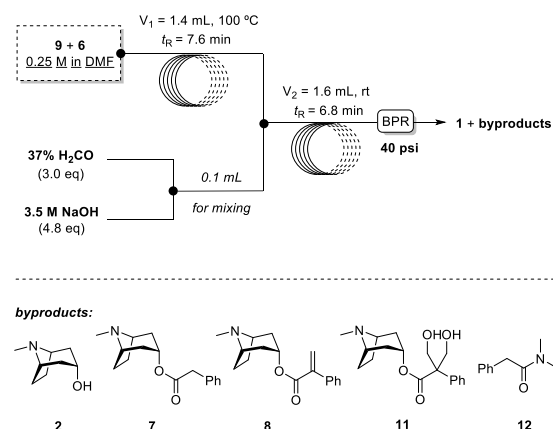


entry	base	$t_R^a$	T	conversion <sup>b</sup> (1:8)
1	pH = 10 buffer	23 min	100 °C	82% (4:1)
2	1 M NaOH (1.0 eq)/ DMA (1:1) <sup>c</sup>	9 min	rt	100% (5:1)
3	1 M NaOH (1.0 eq)/ DMA (1:1) <sup>c</sup>	6 min	rt	90% (8:1)

<sup>a</sup>The residence time was calculated based on pumping flow rates of two feeds. <sup>b</sup>Reaction conversions are based on <sup>1</sup>H NMR after aqueous workup. <sup>c</sup>Reactions were running without a BPR at the end of the reactor.

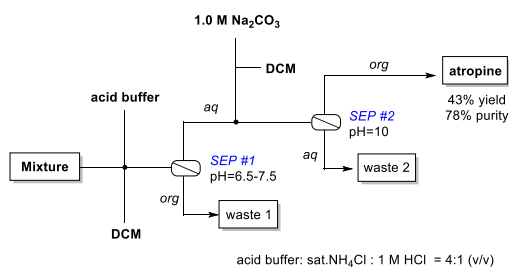
Based on the results we obtained so far, we set up the flow system and obtained the optimized conditions to synthesize atropine in-line. Tropine hydrogen chloride salt **9** reacted with phenylacetyl chloride **6** in reactor 1 ( $V_1 = 1.4$  mL,  $t_R = 7.6$  min) at 100 °C. Without purification of the intermediate, the reaction mixture flowed into reactor 2 ( $V_2 = 1.6$  mL,  $t_R = 6.7$  min), where it met a mixture of pre-mixed solution of 3.5 M NaOH solution and 37% aq. formaldehyde solution at room temperature. A 40 psi BPR was attached to the outline of reactor 2 (Scheme 3). It is worth mentioning that the ratio of water from the inorganic reagents to DMF is important since it affects the solubility of salts in the reaction mixture, which can lead to potential clogging issues in flow. This condition was shown to give the best combination of conversion and selectivity of atropine to apoatropine. In the product mixture, several other byproducts besides apoatropine have been identified as: tropine **2**, intermediate (**7**), diol (**11**) from double hydroxymethylations, and byproduct (**12**). It is known that DMF can undergo decomposition under basic condition at high temperature.<sup>23</sup> The generated dimethylamine functioned as a scavenger of phenylacetyl chloride and gave **12**. All of these byproducts are structurally similar to atropine, and thus are difficult to separate. Therefore, the main challenge at this stage was to develop an effective purification method of atropine in flow.

### Scheme 3. Flow synthesis of atropine



The strategy we developed to purify atropine involves a sequential extraction sequence by taking advantage of the different pKa values of the byproducts (Scheme 4). After the reaction, the mixture was washed with an acidic solution (prepared from  $\text{NH}_4\text{Cl}$  and  $\text{HCl}$ ), and the pH of the aqueous outline after separator 1 was adjusted to 6.5-7.5. In this case, byproducts **2**, **8**, **12** and partial **7** were removed by the organic phase, while atropine, **11** and remnants of **7** were extracted to the aqueous outline. Then a basic solution (prepared from  $\text{Na}_2\text{CO}_3$ ) was introduced to the aqueous line and the pH of the aqueous outline after separator 2 was adjusted to 10. This time, atropine was extracted to the organic line in an overall isolated yield of 43%. The purity of atropine was only 78% with impurities **7**, **8** and **11** still presented to some degree.

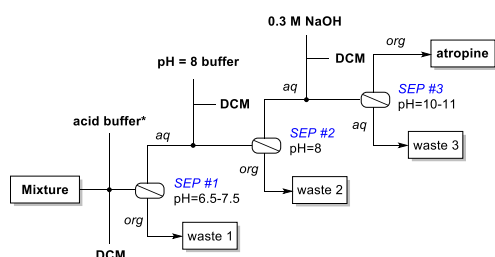
### Scheme 4. Flow separation of atropine using 2-separator strategy



The appearance of apoatropine in the isolated product is surprising, since during the batch workup using separation funnel, apoatropine was removed completely by the same acidic/basic extraction sequence. Further examination of the flow system revealed that the incomplete separation was due to the mechanical dissonance of all the pumps we used to flow the feeds. Because our separation relies on accurate pH control, any fluctuation of the flow rates, especially the flow rates of the reaction mixture before separator 1 and the acidic solution would affect the pH adjustment, leading to the incomplete removal of impurities.

In order to solve this problem, we decided to add an extra separation using a pH = 8 buffer solution<sup>24</sup> between the acidic and basic separations (Scheme 5). Therefore, excess amounts of acid or base passing through separator 1 will be buffered and impurities can be further removed under this pH condition. By using this three-separation strategy, apoatropine was removed completely. However, approximately 10% atropine was also sacrificed at this stage of development. The final impurities left with atropine were only **7** and **11**.

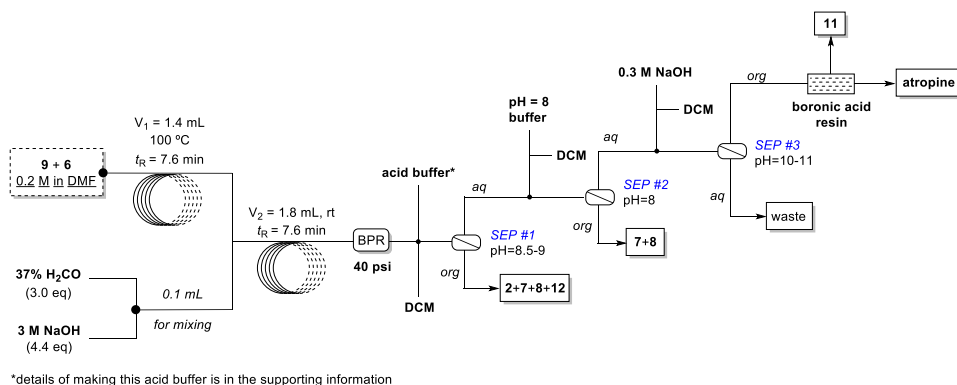
#### Scheme 5. Flow separation of atropine using 3-separator strategy



\*details of making this acid buffer is in the supporting information

Attempts to separate intermediate (**7**) and diol byproduct (**11**) from atropine by pH-based extractions were unsuccessful, possibly because their pKa values are close to atropine and would require extreme tuning of pH for their separation. Therefore, adjustment to the system was necessary to obtain a high purity of atropine. We envisioned that nearly complete consumption of intermediate (**7**) could be achieved by using a larger reactor for the hydroxymethylation step, although the longer reaction time would lead to hydrolysis of atropine and higher conversion to diol (**11**). Indeed, when using a 1.8 mL reactor, the amount of unreacted **7** was minimized to 5-8% prior to purification. A cartridge packed with wet boronic acid resin was also attached to the last organic line to capture the diol byproduct (Scheme 6). Finally, by using this adjusted continuous flow system we were able to obtain atropine with >98% purity, while successfully running for over 12 h.<sup>25</sup>

#### Scheme 6. Continuous flow synthesis of atropine using sequential extractions and functionalized resin



### 3. Conclusion

A continuous total synthesis of atropine in flow has been achieved in two steps featuring hydroxymethylation using an inorganic base (NaOH) and aqueous formaldehyde solution. Most notably, compounds with very similar structures were successfully separated by multiple-stage in-line liquid-liquid separation with careful pH control. To our knowledge, this is the first example of pH-based continuous in-line separation using membrane-based separators in this fashion. In addition, the application of the boronic acid resin facilitates the separation of the desired atropine from a diol byproduct. Pure atropine was obtained with >98% purity in 7.7% overall yield.

### 4. Experimental section

**General information.** Chemicals and solvents were purchased from Sigma-Aldrich and used without further purification unless mentioned specifically. Tropine was purchased from Alfa. pH = 10 Buffer was purchased from VWR.

All pieces of the flow system were purchased from IDEX Health & Science Technologies unless mentioned specifically. The reactors were constructed from high-purity PFA tubing with 1/16" o.d. and 0.03" i.d. Liquid-liquid separators were purchased from Zaiput Flow Technologies and the PTFE microfiltration membranes were bought from Pall Zefluor with 0.5  $\mu$ m pore size. All feeds were delivered using either a PhD syringe pump from Harvard Apparatus or Asia syringe pumps from Syrris. A 8-mL high-pressure stainless steel syringe with 1/16" SWAGELOCK® from Harvard Apparatus was used for the Harvard pump, while SGE airtight glass syringes from Syrris were used for Asia pumps. All reagent and solvent streams were mixed using Tefzel T-mixers with 0.02" thru for reactions and Tefzel cross-mixers with 0.02" thru for extractions. Pressure was controlled using a 40 psi back-pressure regulator (BPR). The packed-bed scavenger was assembled by packing immobilized boronic acid resin (purchased from ThermoFisher Scientific, product#: 20244) into a stainless steel tube (1/4 in x 4.6 mm x 10 cm) and stainless steel 1/16" female nut from Swagelok.

**Continuous synthesis of atropine (1).** A DMF solution (3.55 g, 20.0 mmol, 1.0 equiv, 0.2 M) of tropine hydrogen chloride salt and phenylacetyl chloride (2.8 mL, 21.0 mmol, 1.05 equiv) was loaded in a pair of 2.5/5 mL glass syringes and delivered at 180  $\mu$ L/min by a Syrris pump to a 1.4 mL PFA reactor where the coupling reaction was running at 100 °C. Neat 37% aq. H<sub>2</sub>CO solution was loaded in a 8 mL stainless steel syringe and delivered at 8.03  $\mu$ L/min by a Harvard pump. Meanwhile, a 3.0 M NaOH solution was loaded in a pair of 0.5/1.0 mL glass syringes and delivered at 52.8  $\mu$ L/min by a Syrris pump. Both streams were mixed by a T-mixer and passed through a 0.1 mL PFA reactor at room temperature. Then two outlets were jointed by a T-mixer and passed through a 1.8 mL PFA reactor where the hydroxymethylation reaction was running at room temperature with a 40 psi back-pressure regulator assembled to the outlet. After the reaction, the mixture was jointed with DCM and acid buffer solution by a cross-mixer and passed through a 0.5 mL PFA reactor. Then the outlet was connected to separator 1. Both of the feeds were loaded in a pair of 2.5/5 mL glass syringes on a Syrris pump. DCM was delivered at 350  $\mu$ L/min, while the flow rate of acid buffer was adjusted (normally was about 280-285  $\mu$ L/min) until the pH of the aqueous outline after separator 1 was measured around 8.5-9 by pH test strips. The organic outlet was collected and impurities were identified as tropine **2**, intermediate (**7**), apoatropine **8** and byproduct (**12**). Meanwhile, the aqueous outlet was jointed with DCM and pH = 8 buffer solution by a cross-mixer and passed through a second 0.5 mL PFA reactor which was connected to separator 2. Both of the feeds were loaded in a pair of

2.5/5 mL glass syringes on a Syrris pump. DCM was delivered at 250  $\mu\text{L}/\text{min}$  while pH = 8 buffer was delivered at 300  $\mu\text{L}/\text{min}$ . The organic outlet was collected and impurities were identified as intermediate **7** and apotropine **8**. The aqueous outlet was jointed with DCM and 0.3 M NaOH solution by a cross-mixer and passed through a 0.1 mL PFA reactor which was connected to separator 3. Both of the feeds were loaded in a pair of 2.5/5 mL glass syringes on a Syrris pump. DCM was delivered at 250  $\mu\text{L}/\text{min}$ , while the flow rate of 0.3 M NaOH was adjusted (normally was about 200-210  $\mu\text{L}/\text{min}$ ) until the pH of the aqueous outline after separator 3 was measured around 10-11 by pH test strips. The organic outlet was then flowed into a packed-bed cartridge filled with wet phenyl boronic acid resin and product was collected for 50 min after 5-residence-times of equilibrium (76 min, calculated based on the first two reactions). The collected colorless solution was then evaporated to give atropine (40.0 mg, 0.14 mmol) as a white solid with 98% purity in overall 7.7% isolated yield.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR in  $\text{CDCl}_3$  are in accordance with reported literature values.<sup>26</sup>

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**Supporting Information Available:** Supplementary data (Experimental procedures and NMR spectra) associated with this article can be found in the online version at: doi:xxxxxxx.

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24. pH Buffers were made according to "Laboratory stock solution and equipment, common stock solutions, buffers, and media." *Curr. Protoc. Cell Biol.* **1998** Appendix 2: Appendix 2A. Solution A: 27.2 g KH<sub>2</sub>PO<sub>4</sub> per liter in water. Solution B: 34.8 g K<sub>2</sub>HPO<sub>4</sub> per liter in water. Thus, pH = 8 buffer [0.1 M]: 5.3 mL (solution A) / 94.7 mL (solution B).
25. The boronic acid resin-packed cartridge needs to be replaced every 1.5 h in order to achieve complete removal of apotatropine.
26. For <sup>1</sup>H NMR data, see: 1) Stenberg, V. I.; Narain, N. K.; Singh, S. P. *J. Heterocycl. Chem.* **1977**, *14*, 225; 2) Do Pham, D. D.; Kelso, G. F.; Yang, Y.; Hearn, M. T. W. *Green Chem.* **2012**, *14*, 1189. For <sup>13</sup>C NMR data, see: Taha, A. M.; Rücker, G. *J. Pharm. Sci.* **1978**, *67*, 775.