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Development of a Continuous Flow Scale-Up Approach of Reflux Inhibitor AZD6906

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ABSTRACT: Early scale-up work of a promising reflux inhibitor AZD6906 is described. Two steps of an earlier route were adapted to be performed in continuous flow to avoid issues related to batch procedures, resulting in a robust method with reduced cost of goods and improved product quality. Toxic and reactive reagents and starting materials could be handled in a flow regime, thereby allowing safer and more convenient reaction optimization and production.

INTRODUCTION

In AstraZeneca's program to develop efficient and safe gastroesophageal reflux inhibitors, AZD3355 (**1**), was chosen for late-stage clinical studies.[1] AZD6906 (**2**) was proposed as a follow-up to this promising $GABA_B$ receptor agonist. Both of these substances have been developed to affect peripheral receptors selectively, thereby avoiding CNS side effects associated with high doses of, among others, baclofen (**3**) (Figure 1).[2] When considering scale-up of the synthetic route

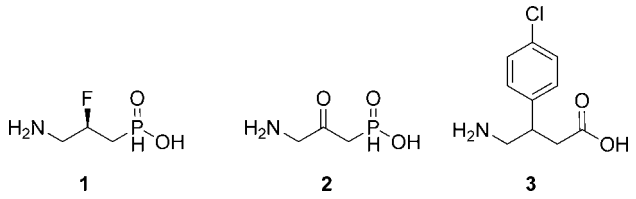

Figure 1. $GABA_B$ agonists under development or on the market.

to AZD6906 (Scheme 1) several potential problems could be identified. The first two steps are highly exothermic, the second of which requires strict cryogenic conditions and slow addition of reagents to avoid degradation of the product or side reactions. In addition, methyl dichlorophosphine (**4**) is very expensive and in short supply from commercial sources. A general problem when generating a product with acidic protons in enolate-type chemistry is the in situ quenching of the reacting anion during the reaction, often requiring excess base or reagent. By working in a different kinetic regime we hoped to be able to bypass this problem due to instant consumption of the reacting anion. An additional challenge was to produce AZD6906 in a quality suitable for pharmaceutical development. AZD6906, being a small and highly functionalized (amino-ketone, zwitterionic, and phosphinic acid) molecule, had been found to have serious stability issues, in the impure state.

It was envisioned that most of these issues could be addressed by performing the reactions in continuous flow. With the uniform conditions that are normally obtained inside narrow channels, reaction temperatures and residence times could be carefully controlled.[3] This would allow convenient examination of the effects of running the reactions at higher temperatures with continuous quenching and removal of formed product. Use of smaller-size continuous flow reactors would also make optimization of reaction conditions more efficient and allow the required stoichiometry of reagents to be explored. The conditions found to be most suitable could then directly be scaled up by simply prolonging the processing time, increasing the pump rate and the size of the reactor, or a combination thereof.

RESULTS AND DISCUSSION

The proposed synthesis of **2** is shown in Scheme 1, consisting of three steps: formation of protected phosphinate **6**, acylation of **6** with *N*-Boc-glycine methyl ester **7**, and finally deprotection and salt removal. While the third step involves heterogeneous slurries and precipitations that are inherently in conflict with the flow regime, the first two steps are known to be highly exothermic and could therefore benefit from being performed in small-size continuous flow reactors. We first set out to investigate the reaction between methyl dichlorophosphine (**4**) and triethyl orthoacetate (**5**) to form phosphinate **6**. The first step had previously been performed in a batch process, and from these experiments the reaction was known to be highly exothermic.[4] In addition, handling of the pyrophoric and toxic methyl dichlorophosphine reagent (**4**) was a cause for concern.

Three equivalents of triethyl orthoacetate was reacted with methyl dichlorophosphine in a simple T-mixer (PTFE, 1 mm inner diameter) and a PTFE-tube reactor (inner diameter of 1 mm and a total reactor size of 2 mL)[5] set to 20 °C with a retention time of 2 min to give a clean conversion to product (**6**). The temperature increased only a few degrees during the reaction, demonstrating the outstanding heat dissipation of a small dimension tube reactor. Rinsing of the reactor with toluene followed concentration in vacuo afford the desired product in 79% yield.[6] However, it was deemed that the exotherm associated with the reaction could just as well be safely controlled at this scale (<100 g of methyl dichlorophosphine) in a batch operation by careful addition and external cooling to below 10 °C using dry ice/acetone.[7] In this batchwise manner, 75 g of methyl dichlorophosphine **4** was

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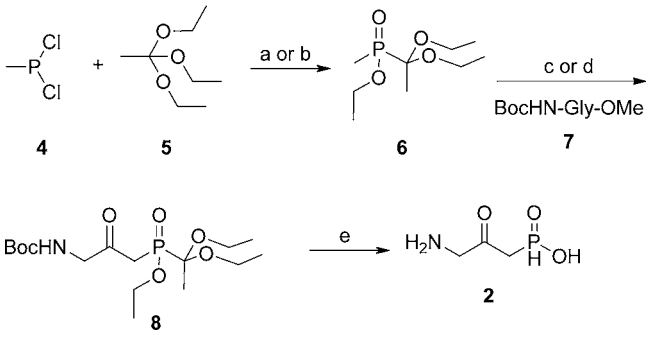
Scheme 1. Synthesis of API 2[a]



[a]Reagents and conditions: a) *In batch*: 0 °C, addition of **4** during 4 h, stirred for 2 h. b) *In continuous flow*: 25−55 °C, **4** and **5** continuously mixed, 2 min retention time. c) *In batch*: THF, −78 °C, slow addition of **6** to LDA, stirred for 1 h, dropwise addition of **7**, stirred for 45 min.[1] d) *In continuous flow*: 2-MeTHF, 35 °C, **6** and **7** continuously mixed with LDA, 1.5 or 2 min retention time . e) *i*. HCl, *i* PrOH, rt, 14 h; *ii* propylene oxide (13 equiv), MeOH, rt, 14 h; *iii* charcoal, MeOH, rt, 30 min; *iv* recrystallization from H_2O/EtOH.

converted into intermediate **6**. Due to difficulties transporting the pyrophoric and highly toxic phosphine, the remainder of the required material (an additional 700 g of methyl dichlorophosphine) was processed, using the batch protocol, by the supplier and was delivered as the protected intermediate **6**.[8]

The key acylation step, in which the carbon framework is constructed, had several limitations for batch processing. First, according to the original procedure a 2-fold excess of the costly phosphinate **6** was used.[1,4,9] The extra equivalent of the anion of **6** is consumed by deprotonation of the more acidic product **8**. In addition, cryogenic conditions had to be used to control the strongly exothermic reaction. Aiming at reducing the need for the costly phosphinate **6** we set up the reaction conditions to get instant reaction of the phosphinate anion with the glycine substrate **7** directly followed by quenching to minimize the time for side reactions. On the basis of conditions known from the previously performed reaction using a batch protocol[1,4] (addition of 1 equiv of *N*-Boc-glycine methyl ester to 2 equiv of phosphinate **6** deprotonated with 3.5 equiv LDA in THF at −78 °C), we attempted the same stoichiometry but at a higher temperature and shorter reaction times in a continuous flow reactor. Thus, a solution of *N*-Boc-glycine methyl ester (**7**, 1 equiv) and methyl phosphinate (**6**, 2 equiv) was mixed with a solution of freshly prepared LDA (3 equiv) in a T-mixer at room temperature and reacted in a PTFE tube reactor (2 mL) thermostatted at 25 °C. The flow rates were adjusted to achieve a retention time of 5 min (see Figures 2 and 3). After workup and monitoring by TLC, the reaction appeared to have gone to completion.[10] The experiment was repeated using excess (2 equiv) of *N*-Boc-glycine methyl ester, pleasingly with the same apparent result. However, when running a ^{1}H NMR assay (against benzyl benzoate as internal standard), it turned out that typical yields for the reaction using 2 equiv of *N*-Boc-glycine methyl ester was 40−50% based on **6**. Still this was already on par with the previously used batch conditions based on limiting **6**. We noticed that the temperature of the reaction reached 80 °C when measured directly after the T-mixer, but after only a few seconds after entering the temperate reaction zone the temperature was measured to 25 °C, again displaying the superior heat transfer

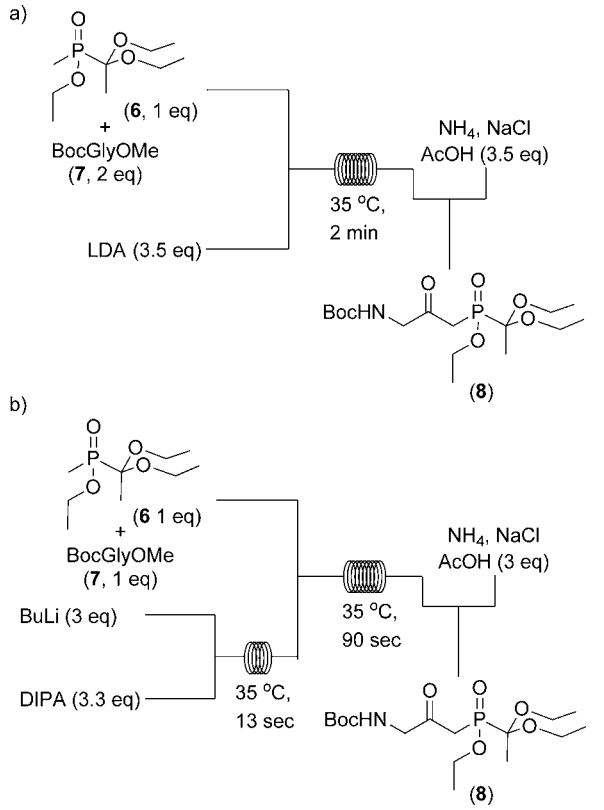


Figure 2. Schematics of reactor. (a) first generation; (b) second generation.

abilities of miniaturized reactors. Knowing that the reaction can tolerate high temperatures for at least short periods of time, the effect of the reaction temperature was examined in the range of 25−55 °C and was found to be of little consequence for the reaction. The reactor temperature was therefore increased to 35 °C, reasoning that this might reduce problems with viscosity-related clogging during longer processing times.[11] The retention time was examined, and it was found that the same results were achieved after 90 s as there were after 15 min; i.e. the reaction proceeds very quickly at these temperatures. Initially, commercial-grade LDA[12] was used. It was found that the final concentration of LDA in the reaction mixture had to be higher than 1 M to ensure fast reactions. At LDA concentrations higher than 1.4 M the operation of the HPLC pumps was unreliable due to clogging of the check valves, leaving an optimal concentration of about 1.25 M LDA in 2-methyltetrahydrofuran. Commercial- grade LDA was later abandoned since the quality was found to be too unreliable between batches.[13] Instead, LDA was prepared by adding 2.5 M *n*-BuLi to a 2.75 M solution of diisopropyl amine in 2-MeTHF at a temperature below 0 °C. The LDA solution was degassed at 10 °C, and a pressure of 350 mmHg was applied to avoid loss of pressure in the pumps due to the in situ formed *n*-butane. The reaction was continuously quenched by mixing the reactor output solution with an aqueous solution of NH_4Cl (5%), NaCl (15%), and AcOH in an equimolar amount to LDA (3.5 equiv) in a batch reactor set at 10 °C. This mixture, together with using 2-methyltetrahydrofuran as the reaction solvent aided phase separation and made further extractions or drying of the reaction mixture unnecessary.

Using these parameters, a 20 mL tube reactor and a retention time of 2 min, 1.3 kg of phosphinate **6** (~3.4 mol) was

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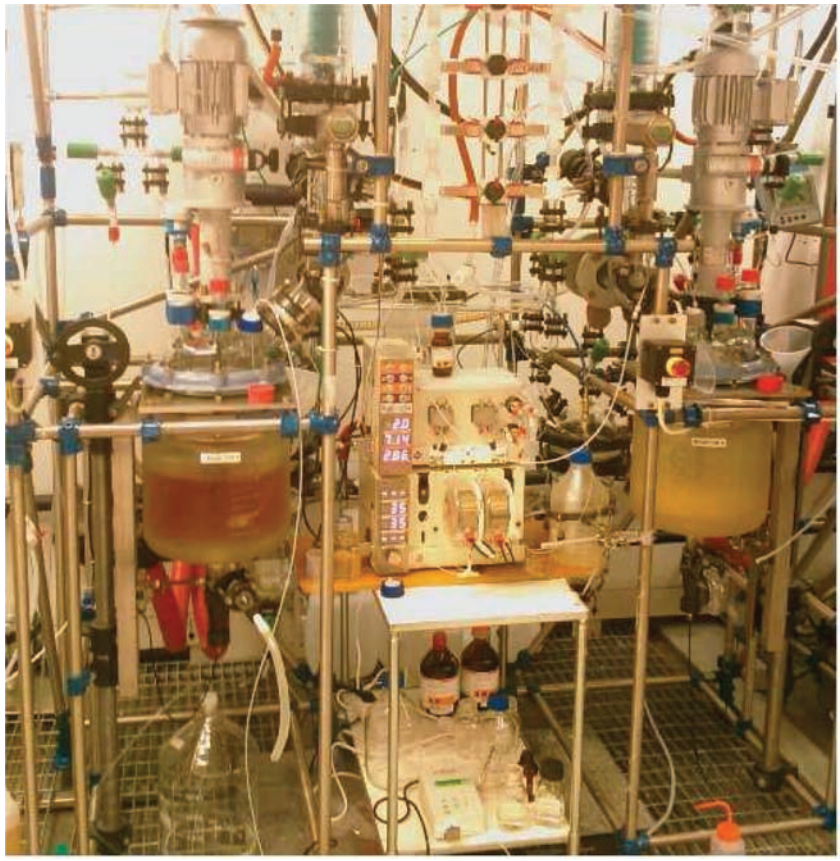

Figure 3. Photo of reactor (*first generation*).

processed during a total run time of 25 h. Unfortunately, the use of excess *N*-Boc glycine methyl ester (**7**) and formation of colored side products made chromatography necessary. It was found that the product was appreciably labile on silica, and a quick elution using straight EtOAc was used to minimize losses. Isolated yields of product **8** from the reaction varied as much as between 24 and 54% from different chromatography batches, largely depending on how rapidly the chromatography was performed. This resulted in insufficient amounts of product that could be isolated and a pressing need for further optimization. In addition to the instability of **8** on silica gel, it was also found to be thermally unstable. Within 10 min most of a sample had deteriorated at 55 °C.

Satisfyingly, small-scale (15 g phosphinate **6**) experiments showed that productivity could be maintained using a 1:1 molar ratio of glycinate **7** and phosphinate **6**, resulting in 58% yield.[14] To simplify handling the LDA solution, an in situ production of LDA was developed for the next run. Thus, 2.5 M solutions of *n*-BuLi and DIPA were mixed in a T-mixer and allowed to react for a total of 13 s in a 2 mL tube reactor at 35 °C. This saved several hours of reactor time for LDA formation, made degassing unnecessary, and reduced potential variance between LDA batches. The LDA solution (3 equiv) was directly reacted with a 1:1 mixture of glycine and phosphinate, again in a 20 mL reactor but using 90 s retention time. Another 1.3 kg of phosphinate **6** was processed in this way, delivering sufficient amounts of product **8** to proceed with the deprotection without the need for chromatographic purification.

Simultaneous deprotection of both protecting groups was done by treatment with 3 M aqueous HCl, or alternatively with HCl in an organic solvent such as isopropyl alcohol. After concentration the HCl-salt of **2** was dissolved in methanol and propylene oxide was added to precipitate the zwitterionic product. The resulting precipitate was isolated by filtration and washed with methanol before drying. The crude product was recrystallized from water and an organic solvent such as acetone, methanol or ethanol. Even though purity analysis indicated a purity of 99% the product was colored and decomposed upon standing.[15] To our satisfaction this could be resolved by treatment of an aqueous solution of the product with charcoal[16] to remove colored impurities. The colorless product obtained after charcoal treatment and crystallization was found to be stable for several months under high humidity and elevated temperatures. Thus, the required amount, 400 g, of the final API **2** could be delivered in a quality suitable for further pharmaceutical development.

■ CONCLUSION

A short and concise route that was deemed difficult to scale-up was adapted to a continuous flow regime. Two of the steps were successfully implemented while the last deprotection was well suited for batch processing. The final preparation avoided cryogenic conditions as well as had a more favorable starting material stoichiometry and allowed chromatography to be omitted. Productivity with respect to the commercially limiting starting material was maintained and the final product was obtained in a higher quality than earlier procedures, resulting in a more stable API.

■ EXPERIMENTAL SECTION

Ethyl 1,1-Diethoxyethyl(methyl)phosphinate (6).[17] *Method a (Batch Procedure).* Methyl dichlorophosphine (**4**,

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19.5 g, 0.167 mol) was added to triethyl orthoacetate (480 mL, 2.6 mol) at −3 °C. After an initiation time of about 4 min the temperature started to rise up to about 10 °C. More methyl dichlorophosphine (43.5 mL, 56.6 g) was added over a 10 min period while controlling the exothermic reaction so that the temperature did not rise above 22 °C. After complete addition the mixture was kept at 20 °C for 30 min and then all volatile components were removed at 47 °C, first at low vacuum and then at ∼1−2 mbar to give **6** (140 g, 98%) as a colorless oil.

Method b (Continuous Flow). Methyl dichlorophosphine (**4**, 19.4 g, 0.166 mol, flow rate 0.140 mL/min) and triethyl orthoacetate (81 g, 0.498 mol, flow rate 0.860 mL/min) were mixed in a T-mixer and led through a PTFE tube reactor (inner diameter 1 mm, 2 mL, 2 min retention time) at 25 °C. The reactor was rinsed with toluene (10 mL), and the mixture was concentrated under reduced pressure to give **6** (29.4 g, 79%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): d 1.06−1.13 (6 H, d, J = 7.1 Hz), 1.18−1.23 (3 H, t, J = 7.1 Hz), 1.32−1.40 (6 H, m), 3.49−3.67 (4 H, m), 4.01−4.16 (2 H, m).

***tert*-Butyl 3-((1,1-diethylethyl)(ethoxy)phosphoryl)-2-oxopropylcarbamate (8).** *First-Generation Synthesis.* A solution of *N*-Boc-glycine methyl ester (**7**, 1510 g, 8 mol) and ethyl 1,1-diethoxy(methyl)phosphinate (**6**, 897 g, 4 mol) in 2-methyltetrahydrofuran (1.6 L, total volume 4.0 L, i.e. 2 and 1 M solutions, respectively, flow rate 2.86 mL/min) was continuously mixed with lithium diisopropyl amine (10.0 L, 1.6 M in 2-methyltetrahydrofuran, flow rate 7.14 mL/min) in a T-mixer then led through a PTFE tube reactor (inner diameter 1 mm, 2 × 10 mL, 2 min retention time) at 35 °C. The reactor pressure was controlled using a pressure regulator set at 2 bar.[18] The output solution was continuously quenched with an aqueous solution of acetic acid (1.2 M), NaCl (15%) and NH_4Cl (5%) with a flow rate of 10.0 mL/min and collected in a reactor thermostatted at 10 °C. The phases were separated and the organic phase was concentrated. The crude product was purified on silica (100% EtOAc) to give **8** (360 g, 24%).

Second-Generation Synthesis. A solution of diisopropylamine (2.7 L, 19.2 mol) in 2-methyltetrahydrofuran (4.3 L, total volume 7 L, flow rate 4.71 mL/min) was continuously mixed with *n*-butyllithium (7 L, 2.5 M in hexane, flow rate 4.71 mL/min) in a T-mixer and then led through a PTFE tube reactor (inner diameter 1 mm, 2 mL, 13 s retention time) at 35 °C. The resulting LDA solution (1.25 M, flow rate 9.42 mL/min) was continuously mixed with a solution of *N*-Boc-glycine methyl ester (**7**, 1046 g, 5.53 mol) and ethyl 1,1-diethoxy-(methyl)phosphinate (**6**, 1292 g (96% purity), 5.530 mol) in 2-methyltetrahydrofuran (3.2 L, total volume 5.5 L, 1.0 M solution, flow rate 3.92 mL/min) in a T-mixer then led through a PTFE tube reactor (inner diameter 1 mm, 20 mL, 90 s retention time) at 35 °C. The reactor pressure was controlled using a pressure regulator set at 2 bar.[15] The output solution was continuously quenched with an aqueous solution of acetic acid (0.85 M), NaCl (15%) and NH_4Cl (5%) with a flow rate of 14 mL/min and collected in a reactor thermostatted at 10 °C. The phases were separated, and the organic phase was concentrated in vacuo by coevaporation with heptane to give **8** (682 g with purity of 80%; based on ^{1}H NMR assay some heptane and ethyl acetate remain in the material, 26%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (6 H, dt, J = 7.0, 1.9 Hz), 1.28 (3 H, t, J = 7.1 Hz), 1.38 (9 H, s), 1.46 (3 H, d, J = 12.5 Hz), 3.01 (1 H, dd, J = 16.9, 13.2 Hz), 3.17 (1 H, t, J = 14.2 Hz), 3.48−3.76 (4 H, m), 4.02−4.25 (4 H, m).

3-Amino-2-oxopropylphosphinic Acid (2). Hydrochloric acid, 37% (1.5 L) was added to isopropanol (3.6 L) under a nitrogen atmosphere in a 10-L reactor equipped with an overhead stirrer, and the mixture was cooled to 15 °C. *tert*-Butyl 3-((1,1-diethoxyethyl)(ethoxy)phosphoryl)-2-oxopropylcarbamate (**8**, 682 g (80% purity), 1.43 mol) was dissolved in isopropanol (1.0 L), and the resulting solution was added in portions (in order to evacuate gaseous byproducts) over a period of 45 min to the mixture of hydrochloric acid and isopropanol. The mixture was heated to 20 °C and stirred overnight; the solvent was then removed in vacuo at 33 °C and the residue coevaporated with methanol (1 L) twice. The residue was dissolved in methanol (2.5 L) and cooled to −26 °C. Propylene oxide (1.3 L, 19.7 mol) was added under a nitrogen atmosphere over a period of 20 min. During the addition the temperature rose to −16 °C. The mixture was allowed to heat up to 20 °C over a period of 3 h and was then stirred overnight at 20 °C. The resulting crystals were isolated by filtration and washed with methanol (0.9 L). Drying in vacuo gave **2** (202 g, 103%[19]).

^{1}H NMR (400 MHz, D_2O): δ 3.01 (2 H, d, J = 18.1 Hz), 4.00 (2 H, s), 6.99 (1 H, d, J = 552 Hz) ^{31}P NMR (161.9 MHz, D_2O): δ 16.0.

Decolorization. A solution of raw 3-amino-2-oxopropylphosphinic acid (**2**, 87 g, 0.63 mol) in water (350 mL) was filtered through a prewetted column of activated carbon (70 g).[16] The column was washed with water (400 mL), and the combined filtrates were concentrated in vacuo to give a solid residue (102 g). The material was dissolved in water (200 mL); 95% ethanol (200 mL) was added followed by some seeding crystals. Additional ethanol (350 mL) was added dropwise over a period of 30 min, and the resulting suspension was stirred at 15 °C for 1 h, filtered, and washed with ethanol (2 × 50 mL). Drying in vacuo overnight gave **2** as off-white crystals (61.99 g, 71%) in two crops.

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Notes

The authors declare no competing financial interest.

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(5) A Vapourtec R4/R2+ equipment with two or three pumps was used. For further information, see http://www.vapourtec.co.uk/.

(6) The product **6** is somewhat volatile, and the slightly lower yield in comparison to that from the batch process is presumably due to coevaporation with toluene. For physical properties of **6**, see: Zhang, D.; Yuan, C. *Chem.—Eur. J.* **2009**, *15*, 4088−4101.

(7) If the addition rate was too high, the temperature could be controlled only with difficulty. At one point, we experienced a temperature increase from 0 to 45 °C in approximately three seconds before the reaction could be stabilized by cooling in a dry ice/acetone bath.

(8) Strem Chemicals, Inc., 7 Mulliken Way, Newburyport, MA 01950-4098 U.S.A.

(9) In reference 1 the yield for the acylation step is given as 85%. However, this yield is based on glycine ester **7**, and if recalculated to reflect use of phosphinate **6**, the yield is 42.5%. It is known from later batchwise scale-up work that the yield decreases further on larger scale (unpublished results).

(10) LC or LC−MS techniques were not helpful since the product was neither UV-absorbing nor prone to ionize (positively or negatively) in the mass spectrometer.

(11) During processing, a continuous buildup of the pressure could sometimes be observed. This could be avoided by rinsing the reactor with 2-methyltetrahydrofuran when the reactor pressure approached the set cutoff limit (20 bar).

(12) A 2 M solution in tetrahydrofuran/heptane/ethylbenzene, Sigma-Aldrich, product number 361798.

(13) For the generation of **8**, other conditions such as phase transfer catalyst using sodium hydroxide/tetrabutylammonium hydrogen sulfate in dichloromethane/water or potassium hydride as base instead of LDA were tried. In our hands these experiments were unsuccessful. By using KHMDS, NaHMDS, and LiHMDS (3.5 equiv) and **7** (2 equiv), yields of 9, 12, and 15% (by ^{1}H NMR assay), respectively, were obtained.

(14) The experimental setup that was used worked well in trial experiments, up to 15 g of **6** in a 20 min run, but during prolonged processing the isolated yields dropped. It can be speculated that the thermal instability of **8** in combination with the strongly exothermic reaction generating up to 80 °C on the outer surface of the T-mixer, even though exposure was very brief, is accountable for this difference.

(15) No additional signals could be seen in ^{1}H NMR purity assays for either charcoal treated or untreated material. Since the product is a zwitterion and contains no chromophores, HPLC analysis was difficult. It was noticed that charcoal-treated product was in the form of white crystals that were stable at 75% relative moisture at 45 °C for several months, whereas untreated product was slightly tan and formed a dark oil after approximately one week at 75% moisture and 45 °C. Thus, the color, in addition to ^{1}H NMR assays, served as a fair indicator of purity.

(16) Darco G-60, Sigma-Aldrich, product number 242276.

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(18) Back Pressure Controller from Syrris FRX system. For further information, see http://www.syrris.com.

(19) The higher than theoretical yield is presumably due to an error in estimating the purity assay of **8** from the previous step.