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A Scalable L-α-Glycerophosphorylcholine Synthesis through the Automatic pH-Controlled (R)-Glycidol Ring Opening with Phosphorylcholine

Antonio Massa,* Mauro Anibaldi, and Lorenzo De Ferra*

The investigation of epoxide ring opening of (*R*)-glycidol with phosphorylcholine in water leads to the development of an effective synthesis of L-α-glycerophosphorylcholine (L-α-GPC), a commercially available drug. The precise control of reaction pH with an automatic titrator proves to be crucial for achieving conversions of up to 98% and limiting byproduct formation. Additionally, an effective method for the synthesis of phosphocholine as inner salt is reported for the first time, which is also essential for achieving the described results.

1. Introduction

L-α-Glycerophosphorylcholine (L-α-GPC) **1**, also known with the name of *sn*-glycero-3-phosphocholine, is a water-soluble phospholipid metabolite that is naturally present in the body. It can cross the blood–brain barrier and serves as a source for the synthesis of acetylcholine neurotransmitter, which plays a fundamental role in cognition and memory, and as precursors of glycerophospholipids biosynthesis.[1] L-α-GPC is a commercially available drug with several applications. As a parasympathetic acetylcholine precursor, it is used to treat Alzheimer's disease and dementia, as well as to enhance cognitive function in individuals with degenerative conditions.[2] L-α-GPC has been shown to improve these functions in the elderly and may also help to protect blood vessels.[2] Beyond its neurological benefits, L-α-GPC serves as a key building block in the industrial production of glycerophospholipids.[3] These compounds are widely used in liposomal nanoparticles technology for mRNA delivery in SARS-COV-2 vaccines and other drug delivery systems.[3]

The traditional method for producing L-α-GPC is based on biological or chemical cleavage of the linkages between fatty acids and the glycerol backbone of phosphatidylcholine from soybeans or other natural sources. However, this approach has several drawbacks for large-scale production due to high costs, complex purification procedures, and low L-α-GPC yields.[4] To overcome these limitations, several chemical synthetic routes have been investigated.[5,6] These approaches typically utilize readily available chiral building blocks such as (*R*) or (*S*)-glycidol[5] **2** or (*R*)-3-halo-1,2-propanediol[6] (see Scheme S1 of supporting information for a literature overview). However, these routes also present challenges for large-scale production. They usually yield only moderate or low quantities of L-α-GPC, require complex purification processes, involve organic solvents, or rely on multistep synthesis that requires elaborate purification procedures, such as column chromatography, rendering them poorly suitable for industrial application.

In this context, we focused on (*R*)-glycidol epoxide ring opening by phosphocholine, as it offers the most direct pathway to L-α-GPC synthesis. Additionally, (*R*)-glycidol is readily available on a large scale at low cost through Sharpless asymmetric epoxidation in high enantiomeric purity.[7] Although this approach has already been investigated, the outcomes have been rather disappointing.[5] As described in a Korean patent application,[5a] commercially available phosphorylcholine chloride calcium salt was first reacted with an alkali metal base in an aqueous solution, followed by the addition of (*R*)-glycidol without isolating the alkali metal-substituted salt (Scheme S1a, Supporting Information). The reaction was carried out under reflux at high temperatures in an aqueous solution. However, under these conditions, (*R*)-glycidol was unstable, leading to a low reaction yield, and it was difficult to obtain L-α-GPC with high purity,[5a] as also highlighted in another patent.[6a]

In a method disclosed in ref. [5b] (Scheme S1b), phosphorylcholine chloride calcium tetrahydrate was treated with oxalic acid, sulfuric acid, or EDTA in an aqueous solution to remove the calcium salt (see also ref. [6a]). The resulting phosphorylcholine chloride was subsequently reacted with (*R*)-glycidol in an organic solvent. Impurities were removed via solvent extraction, and the product was further purified using ion exchange chromatography, yielding L-α-GPC in moderate yield. While the reported process is of interest, some aspects of the procedure and data presentation could benefit from further clarification.

In another method, (*S*)-glycidol was first transformed into tosylate using pyridine as solvent and then underwent a

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displacement reaction with a previously prepared tetraethyl ammonium salt of phosphorylcholine (Scheme S1c, Supporting Information). The resulting epoxide was finally hydrolyzed to give L-α-GPC.[5c] However, this method also suffers from rather low yield, and the use of pyridine is a significant drawback.[5c] In another approach, L-α-GPC was obtained by displacement reaction of tosylcholine with glycidolphosphate, but this process also gave a low overall yield.[6a]

Nevertheless, the use of water in organic reactions[8] and in ring opening of epoxides[9] represents an intriguing alternative to organic solvents, not only for developing green processes but also for exploring totally new reactivities. Epoxide ring opening in water solution has been successfully achieved using several nucleophiles, including amines, thiols, and sodium azide.[9] In these cases, the pH at which the reaction has been performed is of paramount importance to prevent side processes, minimize epoxide degradation, favor regioselective ring opening,[9,10] and guarantee sufficient nucleophilic reactivity.[9a] Despite its significance, pH-controlled epoxide ring opening in the presence of phosphorylcholine or other phosphate-based nucleophiles has received little attention.[5,11] The pH control could be a key factor in epoxide ring opening of (*R*)-glycidol for the synthesis of L-α-GPC. The conceptually similar epoxide ring opening of (*R*)-glycidol with phosphoric acid and phosphate salts has already been investigated, yielding very low product formation at acidic pH and only moderate yield at pH > 10.[11]

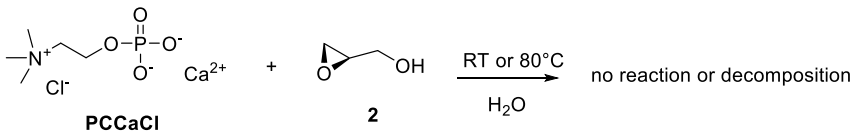
As part of recent cooperation programs between academia and industries,[12] we have first developed an effective method for the determination of the enantiopurity of L-α-GPC.[12a] Then, within our interest in the development of new synthetic methodologies,[13] herein we report an effective synthetic approach to L-α-GPC based on the epoxide ring-opening reaction of (*R*)-glycidol with phosphorylcholine as inner salt in water, facilitated by automated pH control.

2. Preliminary Experiments for L-α-GPC Synthesis

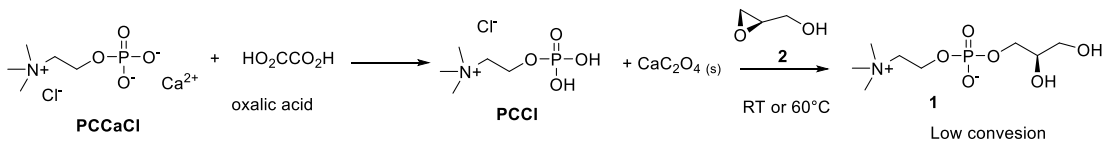
In preliminary investigations, we reconsidered the epoxide ring opening of (*R*)-glycidol (2 equiv.) using the commercially available phosphorylcholine chloride calcium salt (PCCaCl) without any treatment (**Scheme 1**).[5a] The first experiments were performed using PCCaCl as a pure salt, according to scheme 1. The reaction was carried out both at room temperature and at 80 °C (oil bath temperature), highlighting in the first case a poor reactivity, in the second very low conversion and extensive decomposition of **2**, a result somewhat in agreement with previous studies.[5a,5b,6a] The poor reactivity of PCCaCl is probably due to the presence of the Ca^{2+} ions which have high affinity with phosphate group,[5b] while the decomposition of (*R*)-glycidol at high temperature is probably due to the competitive attack of Cl^- and to polymerization reactions.

In a second set of experiments, PCCaCl was treated with oxalic acid to remove Ca^{2+} ions by filtration as an insoluble salt (**Scheme 2**).[5b] The obtained phosphorylcholine chloride (PCCl) was preliminary reacted with (*R*)-glycidol (2.0 equiv.) at pH = 1 at both room temperature and at 60 °C (Scheme 2). The reactions were monitored by ^1H and ^{31}P NMR analysis. At room temperature, no reaction was observed. At 60 °C, low phosphorylcholine (PC) conversion was observed with the concomitant decrease of glycidol amount and the formation of decomposition products. This result is somewhat in agreement with the ring opening of glycidol in the presence of phosphoric acid under low pH conditions, which also resulted in very low conversions.[11]

Then, we conducted further experiments at pH around 8. Given the acidity of PCCl, the initial pH (≈1) was first adjusted to the desired value with NaOH, at which a buffer solution was formed (**Scheme 3**). The nucleophilic ring opening of **2** yields L-α-GPC **1a** as an alcoholate, which subsequently reacts with water, releasing hydroxide ions and causing an increase in the pH, as experimentally observed. The formation of hydroxide ions can also contribute to (*R*)-glycidol decomposition.[9] For this reason, $HClO_4$ solution was manually added during the reaction using a syringe. Perchloric acid was chosen because of the poor nucleophilicity of the perchlorate anion, which minimizes competition in epoxide ring-opening reactions and reduces the formation of decomposition products. Under these conditions, no reaction was observed at room temperature, while at 60 °C conversions of up to 35% were observed after 24 h, with residual (*R*)-glycidol and some decomposition products. However, these results represent an improvement with respect to the use of PCCaCl (Scheme 1). Extending the reaction time for further



Scheme 1. Investigation with phosphorylcholine chloride calcium salt.

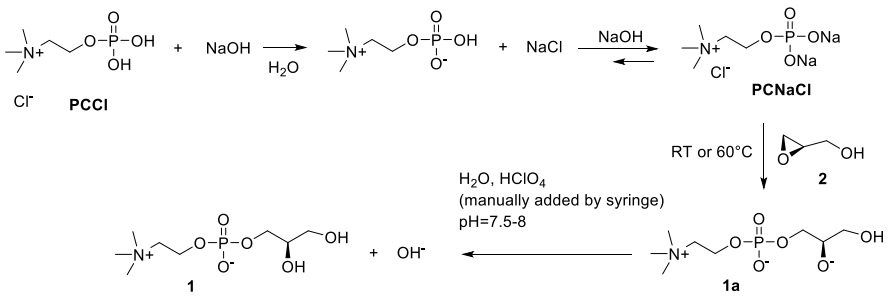


Scheme 2. Preparation of phosphorylcholine chloride.

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Scheme 3. Phosphorylcholine chloride in the epoxide ring opening of (*R*)-glycidol.

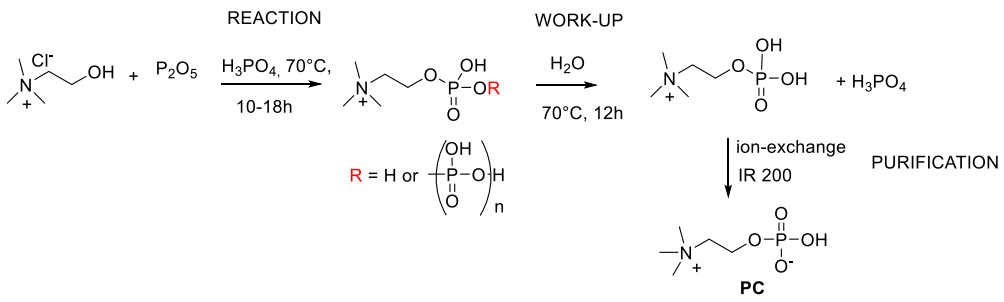
48 h led to a conversion of about 50%, along with the disappearance of (*R*)-glycidol and the formation of a series of decomposition products, results which appear in agreement with previous studies.[5b] The decomposition of **2** was probably due to the competitive nucleophilic attack of Cl^- and OH^-. These preliminary experiments highlighted the need to remove both Ca^{2+} and Cl^- and the necessity of a careful pH control.

2.1. Synthesis of Phosphorylcholine (PC) as Inner Salt

Based on the previous considerations, we first focused on the preparation of PC as inner salt, a goal that, to our knowledge, has never been achieved. This was accomplished by removing Ca^{2+} and Cl^- ions from the commercially available PCCaCl, using ion exchange chromatography (see Supporting Information for further details). Then, considering also the relatively high cost of PCCaCl, we investigated the synthesis of phosphorylcholine from readily available starting materials. To this purpose, we focused on a procedure reported in the literature, based on the phosphorylation of choline chloride in the presence of P_2O_5 and H_3PO_4.[14] In this method, the PC is isolated as PCCaCl salt after a long and tedious purification.[14] We decided to combine this synthetic method, with ion exchange chromatography purification to obtain PC as inner salt. Under the optimized conditions described in **Scheme 4**, 10 g of dry choline chloride was first reacted and then purified using 250 mL of IR200 resin, giving 82% overall yield (see Supporting Information for further details). The purification was adapted to remove the excess of phosphoric acid, which is a byproduct of the reaction and may give competitive (*R*)-glycidol ring opening in the subsequent L-α-GPC synthesis. The purity of all the fractions was carefully checked by ^{31}P NMR analysis. The NMR spectra showed an assay of >99%. This method largely improves recent attempts in the synthesis, purification, and use of phosphorylcholine.[6b]

2.2. Development of L-α-GPC Synthesis Using PC as Inner Salt: Kinetic Experiments

The obtained PC, which gives solutions with a pH of ≈4, was then reacted with (*R*)-glycidol (2 equiv.) for 24 h at 60 °C. However, the reaction proceeded with low efficiency, indicating limited reactivity under these conditions. Then, the initial pH was adjusted with NaOH (10M) to favor epoxide ring opening under weakly basic conditions.[9,11] When it was fixed at about 7–8, an increase of the pH was observed as the reaction proceeded, reaching values above 11, as measured with a pH meter. Under these new conditions, we observed promising conversions but also decomposition products. Based on these experiments, the initial pH seems to be a crucial factor in determining the effective concentration of the nucleophilic active species, PCNa. If the concentration of PCNa is insufficient, the reaction fails to initiate. Conversely, too basic conditions can lead to the decomposition of **2**, resulting in glycerol formation and polymerization reactions. To control the pH and maintain it around 8, aliquots of 0.5M $HClO_4$ were manually added using a syringe. ^1H-NMR spectra of samples taken from these reaction mixtures showed promising conversion to L-α-GPC (50% after 6.5 h) along with significant (*R*)-glycidol decomposition. However, this approach is not only impractical but also fails to ensure optimal pH control, particularly during overnight hours. Indeed, samples collected after 24 h showed a conversion of 65% with no remaining (*R*)-glycidol, and the solution's pH had risen to ≈12. By readjusting the pH to around 8 and adding an additional



Scheme 4. Synthesis and purification of phosphorylcholine (PC) as inner salt.

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equivalent of **2** (for a total of 3 equivalents), the reaction resumed, reaching about 90% L-α-GPC conversion after approximately other 6 h. However, the ^{31}P-NMR spectrum revealed, in addition to the main L-α-GPC peak at 5 ppm, several other signals. The ^{1}H-NMR spectrum also revealed the formation of L-α-GPC and a series of decomposition products.

Therefore, we decided to carry out the reaction at three different pH values, 7, 8, and 9, using a dual-burette automatic titrator for better pH regulation with $HClO_4$ and NaOH solutions (Trials FC 1-7, **Table 1** and **Scheme 5**). After adjusting the initial pH with concentrated 10M NaOH, the PCNa solution was placed in an oil bath at 65 °C, and (*R*)-glycidol **2** was added. At this stage, the preselected automated addition program on the titrator was initiated, correcting the pH as it overcomes the setpoint. Samples were taken at regular intervals to monitor the reaction kinetics via ^{1}H-NMR analysis (**Figure 1**, see also supporting information). Over time, the data showed a decrease in the intensity of the peak at $\delta = 4.07$ ppm, corresponding to a CH_2 group of PC, accompanied by an increase in the peak at $\delta = 4.24$ ppm, belonging to a CH_2 group in the newly formed L-α-GPC. The proton spectrum also revealed a progressive decrease of (*R*)-glycidol, as indicated by the diminishing signals at $\delta = 2.81$ ppm and $\delta = 2.66$ ppm.

In particular, two experiments were conducted at pH = 8 with a tolerance of ±0.3 units (Table 1 and Figure 1). In the first trial (FC1) performed with 2 equivalents of compound **2**, an initial program was set to add 0.040 mL of 0.5M $HClO_4$ solution every 20 s of delay time. A delay time of 20 s means that, even if the pH value of 8.3 (8.0 + 0.3) is overcome, the new addition will occur not before 20 s from the previous one. This program effectively controlled the initial pH increase during the early stages of the reaction. However, after ≈3 h, the 0.040 mL additions frequently caused the pH to drop below the set point, requiring corrections with NaOH. To prevent an unnecessary increase in reaction volume, the program was then adjusted to add 0.020 mL every 20 s. This setting worked well for up to 7 h, ensuring high conversion rates of up to 80%. However, during the night, the pH regulation system did not work efficiently, and by the following morning, the reaction volume had doubled due to additional NaOH additions. Despite this, the analysis revealed a very high conversion exceeding 90%. Interestingly, about 30% of unreacted (*R*)-glycidol was still present, highlighting the critical role of pH control in maintaining reaction selectivity and reducing byproduct formation.

In the second trial (FC2), 2 g of PC and 1.5 equiv. of compound **2** (instead of 2 equiv.) were used; pH correction was performed with 2M $HClO_4$. The kinetic profile (see Supporting Information for further details) was very similar to that of FC1. However, the used 2M $HClO_4$ solution proved to be too concentrated, occasionally causing excessive pH drops that required NaOH corrections. Notably, this experiment also left a residual (*R*)-glycidol content of around 20%, and the ^{31}P-NMR spectrum was particularly clean.

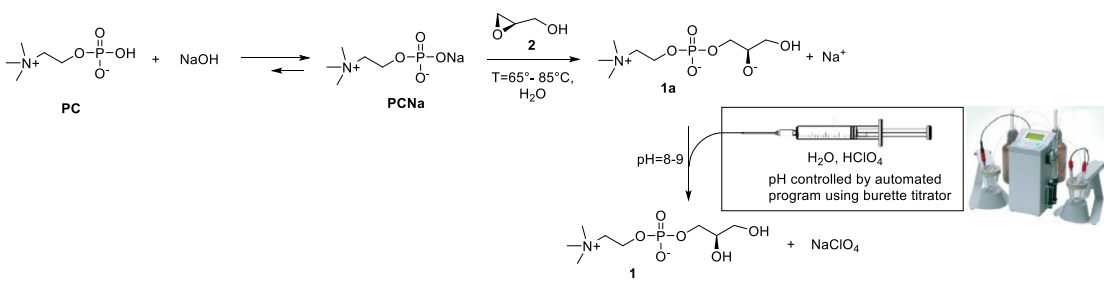
Subsequently, a synthesis was carried out at pH 7 using 630 mg of PC and 0.8M $HClO_4$ for pH correction (FC3 trial). The reaction exhibited an irregular progression and a noticeably lower reaction rate compared to those conducted at pH 8.

The ring opening at pH 9 using 1 g of PC exhibited a kinetic profile very similar to those at pH 8, with a comparable amount of residual (*R*)-glycidol (FC4). This is an encouraging result, as it provides a reasonable degree of flexibility in reaction conditions without affecting the starting materials and thereby limiting the formation of byproducts.

Table 1. Condition for the automated controlled ring opening of (*R*)-Glycidol with PC.

Trial	PC [g]	(*R*)-Glycidol [g]	Initial water amount [mL]	pH set point	T oil bath [°C]	Acid [M]	End time [h]	Conversion [%][a)]
FC1	1.31	1.06	3	8	65	$HClO_4$ (0.5)	20	92
FC2	2.07	1.23	4	8	65	$HClO_4$ (2)	22	87
FC3	0.625	0.378	1.5	7	65	$HClO_4$ (0.8)	24	69
FC4	0.925	0.561	2.2	9	65	$HClO_4$ (0.5)	24	90
FC5	1.0	0.606	2.4	8.5	65	H_2SO_4 (0.5)	24	90
FC6	0.945	0.573	2.3	8.5	75	$HClO_4$ (0.8)	22	95
FC7	2.72	1.675	6.6	8.5	85	$HClO_4$ (1)	6	98

[a)]Evaluated by ^{1}H NMR analysis on the crude.



Scheme 5. Automated control in ring opening of (*R*)-glycerol in the synthesis of L-α-GPC.

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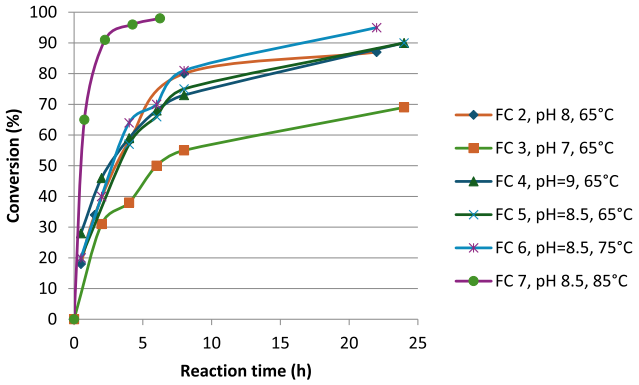


Figure 1. Kinetic experiments (Table 1). Conversion was determined by relative integration of ^{1}H NMR signals of PC and L-α-GPC. Curve for FC1 trial is not reported for brevity: see Supporting Information for further details.

For these reasons, in the next experiment (FC5 trial), the target pH was set at 8.5 with a tolerance of 0.5 units (regulating the reaction pH between 8 and 9) instead of 0.3 units of the previous ones. Additionally, 0.5M H_2SO_4 was considered as a pH regulator in a reaction conducted at 65 °C on a 1 g scale of PC. The data presented in the graph indicate a kinetic profile very similar to those observed with $HClO_4$ at pH 8 and 9. However, ^{1}H NMR analysis revealed some (*R*)-glycidol decomposition. In fact, in the spectrum recorded after 24 h, the residual (*R*)-glycidol content was nearly zero.

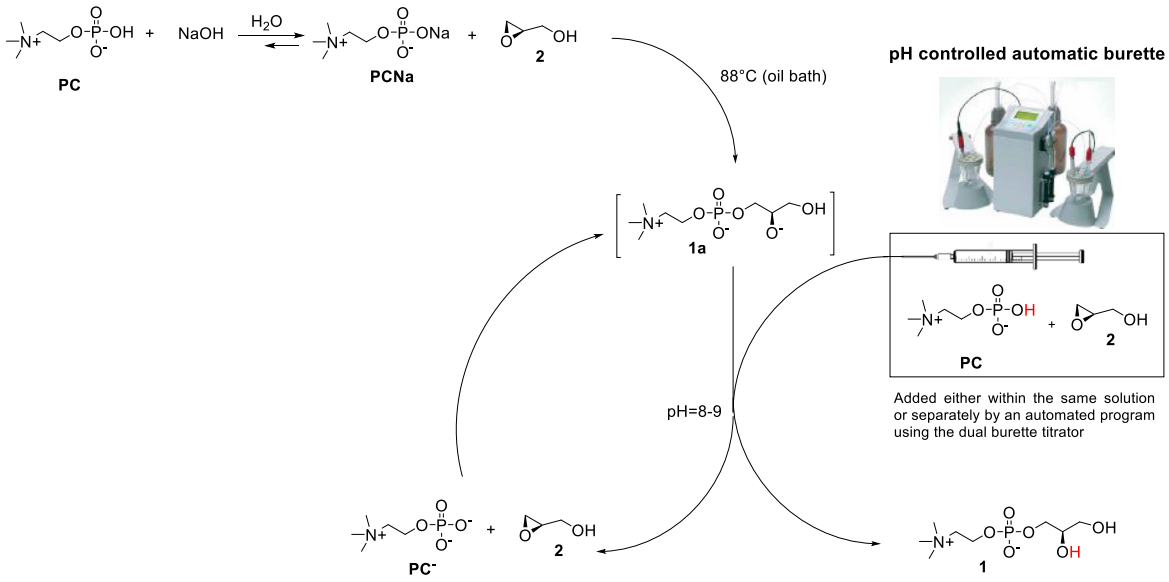
We, then, evaluated the effect of the temperature, relying on the assumption that (*R*)-glycidol decomposition would be minimized with careful pH control, since H_2O itself is a poor nucleophile in epoxide ring opening.[9a] Nicely, at 75 °C, using 0.8M $HClO_4$ for pH correction, the reaction exhibited a faster kinetic profile compared to previous experiments, achieving 80% conversion after 10 h and 95% conversion after 22 h (FC6).

Considering the positive effect of temperature on the reaction rate, we decided to further increase the temperature to 85 °C and scale-up the reaction at 2.7 g of purified PC (FC7 trial). The initial pH was set at 8.5 with a tolerance of ±0.5 unit. Considering the larger scale of the PC used, the pH correction was carried out by adding 0.10 mL 1M $HClO_4$ every 10 s of delay time. These values were progressively adjusted (smaller amounts of 1M $HClO_4$ were added at longer reaction times), as the reaction proceeds, and the concentration of the reactants became lower. These conditions proved to be particularly effective, leading to 98% conversion in 6 h of reaction time, without evident formation of decomposition products and with a percentage of residual (*R*)-glycidol of ≈20% (see Supporting Information for details). The conversion and selectivity were also confirmed by ^{31}P NMR spectrum.

2.3. An Optimized Automated Synthesis of L-α-GPC

The evolution of the pH-controlled ring opening of (*R*)-glycidol was guided by the goal of eliminating the use of $HClO_4$ and drastically reducing the salts formation as byproducts. This is also a key aspect for a greener approach to large-scale production of L-α-GPC. The objective was to improve atom economy, sustainability, and safety, avoiding the use of large amounts of strong base and acid. It is noteworthy that, under the conditions of FC1–7 experiments (with the exception of FC5 trial), sodium perchlorate is produced in almost stoichiometric amounts. This poses also significant environmental drawbacks, especially for large-scale industrial production.[15]

The reduction of waste was achieved progressively through a series of experiments, as described below. Since the purified PC, as inner salt, is weakly acidic, we investigated a possible dual role as both reactant and pH corrector, replacing perchloric or sulfuric acid. To achieve this, we developed a system in which the reaction was initially triggered by NaOH, as described in Scheme 6, using only a small portion of PC and (*R*)-glycidol (15% or 20% of the total), while the remaining quantities were automatically added by dual-burette automatic titrator as the reaction



Scheme 6. Optimized automated synthesis of L-α-GPC.

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proceeded and the pH increased. In the first experiments, a single-titration solution containing both (*R*)-glycidol and purified PC was used (**Scheme 6**). This refined approach proved to be particularly effective, achieving conversions greater than 95% in the reasonable reaction time of ≈7 h. The only aspect that required some attention was the final phase of the reaction. In one example carried out on a scale of 2 g of PC (7.78 mmol), the reaction was initially triggered using 15% of the used PC (1.17 mmol) and (*R*)-glycidol (1.75 mmol) with almost an equimolar amount of NaOH (1 mmol). At the completion of the (*R*)-glycidol/PC solution automatic addition, the conversion reached ≈75%, while the pH tended to increase, due to the progression of the reaction. To control the reaction in the final stage, ≈2 mL of a 0.5M sulfuric acid (about 1 mmol) solution was added using the automatic system, an amount equivalent to the initial quantity of NaOH used.

In this method, PC and (*R*)-glycidol were conveyed in a single solution with a specific automatic addition program using a single syringe. As the quantities increase with scale-up, the number of single-syringe loadings would have increased considerably. The separation of PC and (*R*)-glycidol in two different solutions allowed the use of both the syringes (10 mL each) of the titrator, reducing the loading to 3 instead of 6 (see Supporting Information for further technical details). Under these modified conditions, 9 g of PC were efficiently reacted in about 7 h with a conversion of about 95%. The reaction was triggered by 1.26 g of PC (15% of the entire batch) and 0.82 g of **2**. Then, two aqueous solutions of 30 mL each, containing respectively 7.67 g of PC and 4.7 g of **2,** were placed in two separate cylinders and loaded separately into the two syringes of the titrator. The automatic regulation program was set at pH = 8.8, with a tolerance of 0.5 pH units and additions of 0.040 mL per pump every 20 s. The bath temperature was maintained at 88 °C, which corresponds to an internal temperature of ≈73–75 °C, as measured by the instrument. At the end of the process, after final pH correction with H_2SO_4, L-α-GPC was estimated by qNMR analysis, using 2-phosphonoacetic acid (PAA) as internal standard. The analysis allowed to estimate a L-α-GPC amount of about 9.96 g, corresponding to a theoretical yield of 88%. The reaction mixture was then purified by ion exchange chromatography using IRA404 resin in its acetate form, with water as eluent (see Supporting Information for further details). Notably, a limited amount of the resin was used due to the low content of impurities and salt byproducts in the crude. Additionally, the resin was easily regenerated and reused, making the entire process particularly sustainable. Finally, after water evaporation, the purified L-α-GPC was crystallized by DMSO with an overall isolated yield of 76.9%. The residual L-α-GPC amount in mother liquor, evaluated by qNMR, was about 1.2 g, furnishing an overall yield of 87.5%.

In conclusion, the reported synthetic process for L-α-GPC demonstrated high reproducibility, yielding consistent results when performed by different operators in both academic and industrial partners involved in this investigation. These optimized methods significantly reduce salt byproducts, and the reagent addition program no longer requires the adjustments previously noted in Section 2.3.

3. Conclusions

Automatic real-time regulation of the pH in the epoxide ring opening of (*R*)-glycidol with phosphorylcholine in water enabled an effective synthesis of L-α-glycerophosphorylcholine (L-α-GPC), a commercially available drug with many applications. This approach, which represents a significant advancement beyond conventional syringe pump techniques, is easily scalable with conversions up to 98%, reduces the waste, affording a product that is easily isolated in high yield and purity. The use of water in the synthesis and purification, and the low amount of produced wastes, makes this process particularly attractive for the environment and for large-scale production. In addition, a method for the obtaining of phosphorylcholine as an inner salt was developed.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: aqueous-phase reactions and purifications · automatic reaction controls · epoxide ring openings · salt-free phosphocholines · *sn*-glycero-3-phosphocholine

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