Tin-mediated synthesis of *lyso*-phospholipids†

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1-*O*-Acyl-*sn*-glycero-3-phosphocholine and 1-*O*-acyl-*sn*-glycero-3-phosphoric acid have been prepared selectively and with high yields from the corresponding diols, glycerophosphoryl choline and glycerol-3-phosphate. Starting from the diols, the activated tin ketals were prepared in 2-propanol by reaction with dialkyltin oxide. The intermediates were acylated in the same solvent with long-chain fatty acid chlorides, giving the corresponding 1-acyl-*lyso*-phospholipids in high yield and with complete regioselectivity. The catalytic nature of the tin-mediated acylation and the relevance of the solvent are discussed.

Introduction

Lysophospholipids (LPL) are glycerophospholipids in which one hydroxyl group in the glycerol backbone is acylated. The combination of hydrophilic and lypophilic parts in one molecule in the presence of a free hydroxyl group confers special properties to LPLs. Their presence modulates the rigidity and stability of cell wall structure as well as that of model artificial membranes.[1] LPLs are widely distributed in Nature both in animals and plants, even though they represent only a small fraction of the cellular lipid component.[2] Phosphocholines bearing an acyl chain in the *sn*-1-position, 1-*O*-acyl-*sn*-glycero-3-phosphocholine (1-*O*-Acyl-PC), or in the *sn*-2 position, 2-*O*-acyl-*sn*-glycero-3-phosphocholine (2-*O*-Acyl-PC), have been studied and synthesised.[3]

LPLs have recently become the focus of special attention, after it was discovered that in addition to their role in phospholipid metabolism they also function as secondary messengers, exhibiting a broad range of biological activities in their own right.[4–7]

It is widely accepted that availability of synthetic natural products is of fundamental importance for solving biomedical problems.[8] Thus synthetic LPC, lysophosphatidic acid (LPA) and related LPL analogues are needed to elucidate their mechanism of action, and to study the enzymes involved in their metabolism. Moreover, they are the key intermediates in the synthesis of all structured phospholipids. Total synthesis of 1-LPC, LPA and 1-*O*-acyl-*sn*-glycero-3-phosphoinositol (1-LPI)[9] have been reported. A general method for the preparation of these compounds is the phospholipase A_2 (PLA_2) catalyzed removal of the acyl chain in position *sn*-2 of a naturally occurring or synthetic phospholipid. When natural phosphatidylcholine (PC) is used as a starting material, LPLs with mixed fatty acid compositions at position 1 are obtained. Alternatively, the removal of a fatty acid chain from structured phospholipids of synthetic origin allows the formation of compounds with a defined composition of the acyl chain at position *sn*-1. However, synthesis of structured phospholipids is a multi-step process in itself, starting from enantiomerically pure glycerol derivatives, through tedious protection–deprotection steps and then the introduction of the phosphoryl group.[10,11] Such a complex synthetic strategy is not suitable for large-scale preparation, and hence the use of deacylated glycero-phospholipids, easily obtainable by alcoholysis of abundant natural phospholipids (PC or phosphatidyl ethanolamine, PE), as a more viable strategy.[11] A convenient procedure then, is the mono-acylation at position 1 of glycerophosphoryl choline (GPC) **2** (Scheme 1).[12] Compounds of type **2** can be transformed into phospholipids of general structure **5**, through **4** → **3**.[9h,12a] However, a direct, selective method of mono-acylation is not available. As a complement to this strategy, we wish to report the synthesis of 1-*O*-acyl-phospholipids starting from glycerophospholipids, exploiting the high reactivity and selectivity of stannylene ketals formed *in situ* (Scheme 1, dashed arrow).

Results and discussion

Tin-mediated mono-functionalisation of polyols allows us to achieve two main objectives: high regio- and chemo-selectivity and rate enhancement.

In compounds containing three or more hydroxyl groups, the regioselectivity is the prevalent aspect of the reaction and it has been applied in the selective functionalisation of carbohydrates.[13] In compounds containing primary and secondary hydroxyl groups, functionalisation at the primary group prevails. Advantages over conventional chemical acylation are the short reaction time and the higher selectivity.[14] In most reaction protocols, usually on model substrates, dibutyltin oxide (DBTO) is used in a stoichiometric amount in a solvent which must be able to dissolve the diol. For this reason methanol has usually been employed as a medium, particularly in carbohydrate chemistry. Under these conditions, large amounts of acylating agent are consumed by reaction with the solvent. In some cases the catalytic function of the tin ketal has been demonstrated on model compounds (phenylethanediol), but the application to very polar compounds

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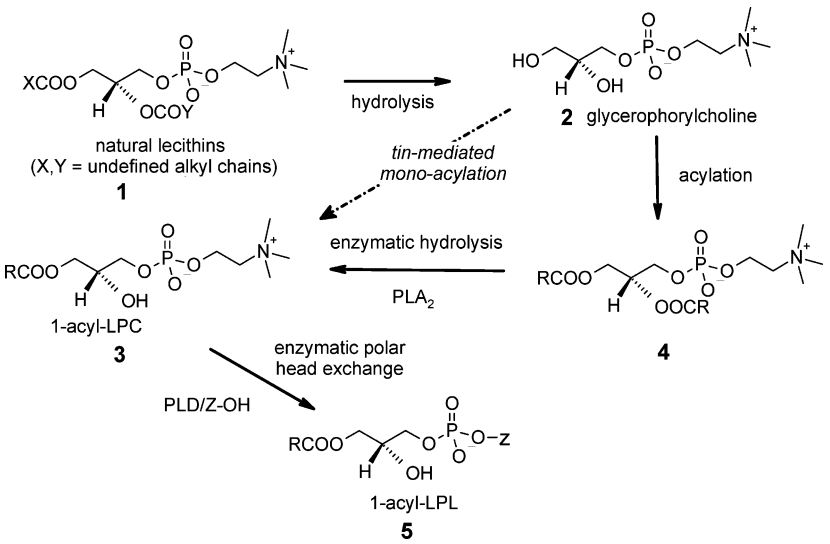


Scheme 1 Possible ways from natural lecithins to 1-acyl-LPL.

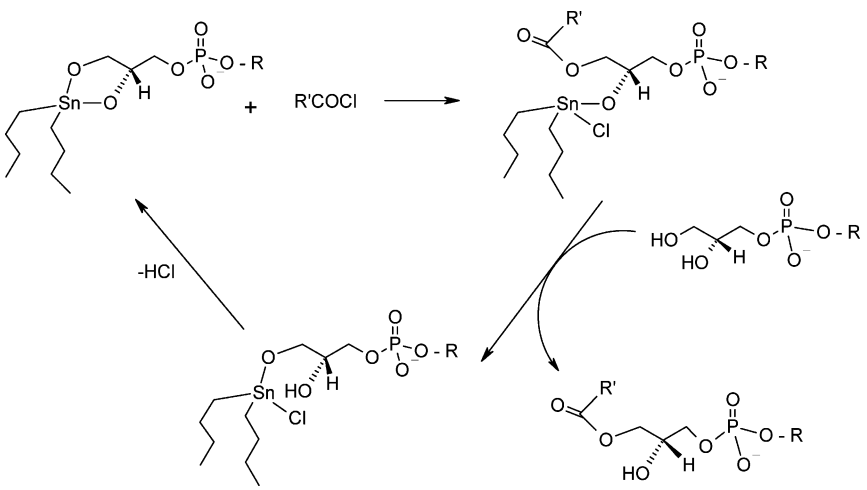
is hampered by the low solubility and low reaction rates when a non-polar medium is used. We have recently shown that in the benzoylation of phenylethanediol in the presence of DBTO, the initially formed tin ketal acts in subsequent steps as the active catalyst of the reaction.[15] Several tin ketals obtained from DBTO and different alcohols (MeOH, 2-PrOH) undergo exchange in the presence of 1,2-diols, forming primarily the corresponding diol ketal, which becomes the catalytically active species. If the diol is not appreciably soluble in the reaction mixture, the formation of the active ketal is limited and the reaction does not proceed with the expected mechanism. Applied to the acylation of a glycerophospholipid, the catalytic cycle can be represented as in Scheme 2.

The same mechanism has previously been proposed for the tin-catalysed sulfonylation of diols.[16] We present here a reaction protocol based on the generation of a diol–tin ketal derived from a glycero-phospholipid in a protic solvent and its reaction with an acyl chloride to give the 1-LPLs with absolute selectivity and high yield.

Choice of the solvent

Since non-acylated glycerophospholipids are not soluble in non-protic organic solvents, the choice of the solvent is critical. This observation finds proof in the different reaction yields obtained with the use of different solvents.

In the first experiment, GPC was suspended in a solvent of low polarity (MTBE, toluene) in the presence of 1 eq. of DBTO, and the suspension refluxed for 24 h. The mixture was cooled to 0 °C and treated with 1.2 eq. of acylating agent (acid chloride) and 1.2 eq. of triethylamine (TEA). After 15 min at rt, the mixture was analyzed: only a low conversion was observed (3–15%), comparable to the one obtained in the absence of the tin compound. When the experiment was repeated in methanol and in 2-propanol, the conversions were 40% and >90% respectively. These results suggest that in non-protic solvents, there is no catalytic effect from the presence of the tin compound, since either the ketal is not formed due to the low solubility of the diol or it is not appreciably soluble. In protic solvents, the tin ketal is readily



Scheme 2 Catalytic cycle for the tin-mediated monoacylation of glycerophospholipids.

formed and the reaction proceeds at a higher rate than in the absence of the tin species. In methanol the conversion is limited due to the competitive acylation of the solvent.

In a second set of experiments, GPC was treated with 1 eq. of DBTO in methanol (2.5 g in 100 ml) and the suspension refluxed for 3 h. This treatment afforded a clear solution, presumably containing the corresponding tin-ketal.[17] The solvent was removed from the clear solution and the residue resuspended in the series of non-protic solvents as above, and treated with the acylating agent under the same conditions as described before. The conversions observed with this procedure are between 3% (MTBE) and 22% (DMF), suggesting that the solubility of the ketal controls the entire reaction cycle. Suspending the crude material obtained from the above treatment in 2-propanol and treating it further with acid chloride and base led to an excellent yield of the mono-acylated compound, with an excellent selectivity as well. Thus, the synthesis of tin-ketal was then performed directly in 2-propanol, and these conditions proved to be the most efficient for the mono-acylation of GPC; in fact, esterification of the solvent does not occur at a comparable rate. GPC was refluxed for 1 h in 2-propanol in the presence of 1 eq. of DBTO at a concentration of 2.5 g in 100 ml. The reaction was cooled to 25 °C and treated with 1.2 eq. of acylating agent and 1.2 eq. of TEA. The mixture was stirred at rt for 15 min. HPLC analysis of the reaction showed a 95% yield of 1-LPC. The product was purified by extraction and crystallisation, as described in the Experimental section. The positional purity was evaluated from HPLC, ^{1}H and ^{13}C NMR, and showed no detectable trace of the isomeric mono-acyl derivative.[10b,g,h] The thermodynamic mixture of 1-LPC and 2-LPC obtained by acyl migration of one fatty acid chain from the *sn*-1 to the *sn*-2 position and *vice versa* was formed in slightly acidic conditions or in methanol solution in a time-dependent manner. On the other hand, acylation of GPC without the formation of tin ketal gave the usual ratio of isomers with a much lower reaction rate. The amount of acylating agent determines the conversion when methanol is used as a solvent. In the case of 2-propanol, an optimum of conversion was obtained with 1.2 eq. of palmitoyl chloride at rt (97%). As an alternative to the acid chloride, palmitoyl anhydride, palmitic acid and methyl palmitate were used. In the case of anhydride, 15% conversion was observed, while there was no reaction with the ester or the carboxylic acid. Using 4-(dimethylamino)pyridine (DMAP) as the base had no advantages over TEA, which was required in a 1 : 1 ratio with the acyl chloride.

Acylation of the preformed tin intermediate obtained as described was strongly dependent on the solvent used. Using 1.2 eq. of palmitoyl chloride in 40 volumes of solvent at rt for 15 min, the conversions ranged from 3% for MTBE to 22% for DMF, the remaining solvents giving conversions in the following order: $CHCl_3$ < *t*-BuOH < CH_3CN < CH_2Cl_2 < Tol < THF < DMF.

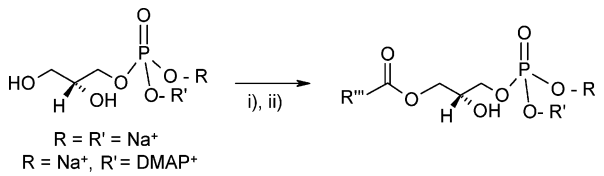
Catalytic nature of the tin-mediated acylation

During the reaction of GPC with DBTO, the ^{31}P NMR spectra of the mixture showed a peak attributed to the tin ketal, which never exceeded 40%.[18] Since in these conditions the conversion with respect to the acylating agent was close to 100%, the data confirms a catalytic mechanism.

We have recently shown in the simple benzoylation of phenylethanediol that the tin ketal formed *in situ* by reaction of an alkyltin oxide with the diol (or preformed in a separate reaction and treated with the acylating agents in the presence of a base) is itself the catalyst of the acylation. Thus GPC was refluxed in 2-propanol in the presence of 5 mol% of DBTO and the mixture then treated as previously described. After 15 min reaction, the conversion in this case also exceeded 90%.

Significance of the tin-mediated acylation of glycerophospholipids

When compared to other methods of mono-functionalisation of GPCs, the present approach gives mono-acyl derivatives free from the regioisomer usually produced by reaction protocols involving the use of acidic conditions during the reaction or in the isolation procedure. The possibility of forming the stannylene ketal and the successive acylation reaction in a protic solvent that does not interfere with the acylation reaction is the key point of the procedure. The method is general, giving comparable yields with saturated and unsaturated fatty acid derivatives of different lengths. Thus, in completely identical procedures, 1-stearoyl-, 1-lauroyl- and 1-oleyl-LPCs were obtained. The method is applicable also to the acylation of 3-glycerophosphate (GPA). Glycerophosphoric acid disodium salt, insoluble in 2-propanol, was transformed into the mono-DMAP salt to improve its solubility. This was suspended in 2-propanol and refluxed in the presence of Bu_2SnO, leading to a soluble tin ketal derivative. Palmitoylation with 1.2 eq. of the acid chloride in the presence of 1.2 eq. of TEA was rapid, complete and selective, giving 1-palmitoyl-LPA with more than 90% yield (Scheme 3) and again free from the regioisomer. The selectivity and reaction rate observed in this case are particularly surprising due to the highly functionalised nature of the molecule. Removal of the tin-containing material from the products was achieved with a selective extraction/precipitation procedure followed by crystallisation (see Experimental). The use of catalytic amounts of tin reagents or an immobilised catalyst should allow an easier and complete removal of tin from the reaction mixture.[19]



Scheme 3 *Reagents and conditions*: i) 2-PrOH, DBTO, reflux; ii) TEA, R‴COCl, rt.

Conclusions

Glycerophosphorylcholine, easily obtained from natural lecithins by purification-hydrolysis, is the natural synthon from which most structured phospholipids can be obtained, through the sequential introduction of acyl chains and eventual modification of the polar head *via* transphosphatidylation reaction catalysed by phospholipase D. However, mono-functionalisation of glycerophosphate derivatives is not efficient due to their low solubility in organic solvents and the low selectivity of the acylation step. We have shown in this paper that mono-acylation of the tin ketal (easily prepared from either a stoichiometric or a catalytic amount of dialkyltin oxides or their equivalent), can be performed in 2-propanol, in which the solubility and reactivity of GPC is

appreciable, and the acylation of the solvent by the long-chain fatty acid chlorides of little significance. Under these conditions, the formation of 1-acyl-LPC is rapid and complete. The reaction has also been applied to the preparation of 1-acyl-LPA from (*R*)-glycerophosphate with high yields and selectivity.

Experimental

1-*O*-Hexadecanoyl-*sn*-glycero-3-phosphocholine (1-*O*-Palm-PC)

GPC (10 g, 39 mmol) and DBTO (10.65 g, 43 mmol) were suspended in 2-propanol (400 ml) and refluxed for 1 h. The mixture was cooled to 25 °C, and treated with TEA (6.5 ml, 47 mmol) and palmitoyl chloride (12.8 g, 47 mmol). The formation of the lysoPC and the disappearance of GPC was followed by HPLC. After 15 min at rt, a sample from the reaction mixture was analysed (HPLC) and shown to contain 1-palmitoyl-*sn*-2-*lyso*-phosphatidylcholine (97%) and GPC (3%) as the only phospholipids. The solution was treated with water (400 ml) and extracted with heptane (400 ml). The water–alcohol solution was extracted again with heptane (3 × 250 ml). The heptane phase contained the tin compounds and the product of reaction between excess palmitoyl chloride and the solvent (isopropyl palmitate). The water–alcohol solution was evaporated, the residue dissolved in ethanol (100 ml) and precipitated with acetone (400 ml) at −10 °C, leading to 15 g of a white powder (80%). The product was crystallised from ethanol (7.5 g, 40%). Elemental analysis showed a tin content of 90 ppm. ^{1}H NMR and ^{13}C NMR spectra were identical to those reported in the literature[9e,20]

1-*O*-Hexadecanoyl-*sn*-glycero-3-phosphoric acid DMAP salt (1-*O*-Palm-PA)

Glycerol-3-phosphate disodium salt (10 g) was dissolved in H_2O (20 ml) and passed through a column of acidic sulfonic resin DOWEX 50X8. The solution was treated with DMAP to adjust the pH to 6, and the solution lyophilised, giving glycerol-3-phosphate mono-DMAP salt.

GPA mono-DMAP salt (1 g, 5.4 mmol) and DBTO (1.35 g, 3.4 mmol) in 2-propanol (50 ml) were heated under reflux for 2 h. The resulting suspension was then cooled to 25 °C in an ice bath and TEA (1.3 ml, 8.1 mmol) and palmitoyl chloride (2.2 g, 8.1 mmol) were added dropwise. The reaction was stirred for 15 min at room temperature. After 15 min, a sample of the reaction mixture was analysed (HPLC) and found to contain 1-palmitoyl-LPA and GPA in the ratio 91 : 9. The water–alcohol mixture was treated with 400 ml of water and extracted with heptane. The water–alcohol solution was extracted again with heptane (3 × 250 ml). The heptane phase contained the tin compounds and the palmitoyl ester. The water–alcohol solution was evaporated, the residue dissolved in ethanol (100 ml) and precipitated with acetone (400 ml) at −10 °C, yielding a white powder (12 g, 75%). The product was crystallised from ethanol (6 g, 35%). Elemental analysis showed a tin content of 90 ppm.

1-*O*-Octadecanoyl-*sn*-glycero-3-phosphocholine (1-*O*-Stear-PC)

A suspension of GPC (1.85 g, 7.2 mmol) and DBTO (1.90 g, 7.6 mmol) in 2-propanol (30 ml) was heated under reflux for 1 h. The resulting suspension was then cooled to 25 °C in an ice bath, and TEA (1.2 ml, 7.9 mmol) and stearoyl chloride (2.3 g, 7.9 mmol) were added. The reaction was stirred for 35 min at room temperature. A sample from the reaction mixture was analysed (HPLC) and shown to contain 1-stearoyl-LPC and GPC in the ratio 95 : 5. Isolation of the product was performed as previously described for the palmitoyl analogue.

1-*O*-Oleoyl-*sn*-glycero-3-phosphocholine (1-*O*-Oleo-PC)

A suspension of GPC (1.85 g, 7.2 mmol) and DBTO (1.90 g, 7.6 mmol) in 2-propanol (30 ml) was heated under reflux for 6 h. The resulting suspension was then cooled to 25 °C in an ice bath, and TEA (1.2 ml, 7.9 mmol) and oleoyl chloride (2.1 g, 7.9 mmol) were added. The reaction was stirred for 35 min at room temperature. A sample from the reaction mixture was analysed (HPLC) and shown to contain 1-oleoyl-LPC and GPC in the ratio 95 : 5. Isolation of the product was performd as previously described for the palmitoyl analogue.

1-*O*-Dodecanoyl-*sn*-glycero-3-phosphocholine (1-*O*-Laur-PC)

A suspension of GPC (1.85 g, 7.2 mmol) and DBTO (1.90 g, 7.6 mmol) in 2-propanol (30 ml) was heated under reflux for 2 h. The resulting suspension was then cooled to 25° C in an ice bath, and TEA (1.2 ml, 7.9 mmol) and lauroyl chloride (1.6 g, 7.9 mmol) were added. The reaction was stirred for 35 min at room temperature. A sample from reaction mixture was analysed (HPLC) and shown to contain 1-lauroyl-LPC and GPC in the ratio 95 : 5. Isolation of the product was performed as previously described for the palmitoyl analogue.

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