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Efficient tin-mediated synthesis of lysophospholipid conjugates of a TLR7/8-active imidazoquinoline

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ABSTRACT

The chemical synthesis of lysophospholipids often involves multiple synthetic and chromatographic steps due to the incorporation of the fatty acyl group onto the glycerol scaffold early in the synthesis. We report herein a new protocol for the lysophosphatidylation of alcohols and its application to the synthesis of lysophospholipid conjugates of TLR7/8-active imidazoquinoline **3**. This new procedure, which is based on the tin-mediated regioselective acylation of late-stage phosphoglycerol intermediate **17**, overcomes many of the drawbacks of conventional lysophosphatidylation methods and allows introduction of different fatty acyl groups in the penultimate step.

The immune stimulating ability of certain antiviral/antitumor 1*H*-imidazo[4,5-*c*]quinolines[1] such as imiquimod (**1**, R-837; Fig. 1), which is marketed in the USA as Aldara® and Zyclara®, has been attributed primarily to the activation of Toll-like receptor (TLR) 7 in plasmacytoid dentritic cells (DCs) and B cells and the induction of type I interferons (IFN-α/β) and IFN-regulated cytokines.[2] The structurally related imidazoquinoline resiquimod (**2**, R-848) is also a ligand for TLR7 on human cells, but—in marked contrast to imiquimod—potently activates TLR8 on myeloid and monocyte-derived DCs, leading to production of proinflammatory cytokines. Since TLR7 and TLR8 are broadly expressed in DCs and other antigen presenting cells, TLR7/8 agonists may be especially useful as adjuvants in human vaccines.[3,4] However, both oral and topical preparations of imiquimod (**1**) and resiquimod (**2**) and other small-molecule TLR7/8 agonists can exhibit serious side effects.[5] Further, since TLR7 and TLR8 receptors are located in endosomal/lysosomal compartments,[6] cellular uptake is prerequisite for cellular activation by TLR7/8 ligands. Thus, strategies that would increase the penetration of the TLR7/8 ligand into DCs and reduce toxicity are of great interest. Lipid conjugation of nucleoside drugs[7] is one useful strategy for membrane targeting and intracellular delivery, and is known to decrease toxic side effects, as well as facilitate incorporation of the nucleolipid into liposomes and other biodegradable nanoparticle formulations.

To our knowledge, the effect of conjugating small-molecule TLR7/8 agonists to lysophospholipids on immune cell activation has not been investigated. We were particularly interested in the synthesis of lysophospholipid conjugates of TLR7/8-active imidazoquinolines possessing different acyl groups to evaluate the effect of fatty acid structure on immunostimulatory activity. Varying the nature of the acyl chain in this phospholipid class should permit optimization of a particular formulation and route of administration.

The synthesis of lysophospholipids often involves multiple synthetic and chromatographic steps due to the introduction of the fatty acyl group onto the glycerol scaffold early in the synthesis and the potential for intramolecular acyl group migration. While acyl migration leading to regioisomers and other by-products has been mitigated by orthogonal protection of the *sn*-2- and *sn*-3-glycerol positions,[8–10] these multi-step approaches preclude the use of a common advanced intermediate (CAI) and the introduction of different acyl groups near the end of the synthesis. Herein, we describe an efficient synthesis of lysophosphatidyl derivatives of imidazoquinoline **3** via regioselective tin-mediated mono-acylation of the *sn*-1-position of a late-stage phosphoglycerol CAI with different acid chlorides in the penultimate step. Imidazoquinoline **3** was selected as a test compound for initial phospholipidation studies due to its known TLR7/8 activity and simplified structure relative to resiquimod **2**.

To demonstrate that lysophosphatidyl derivatives of imidazoquinoline **3** are isolable and stable, we first carried out the synthesis of lysophospholipids **5** and **6** using a known orthogonal

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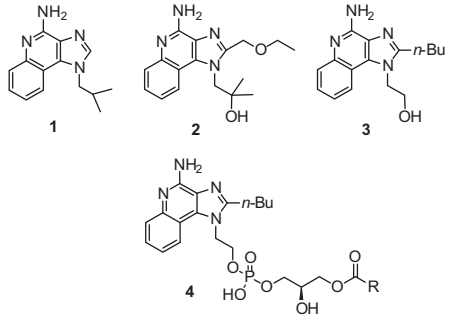
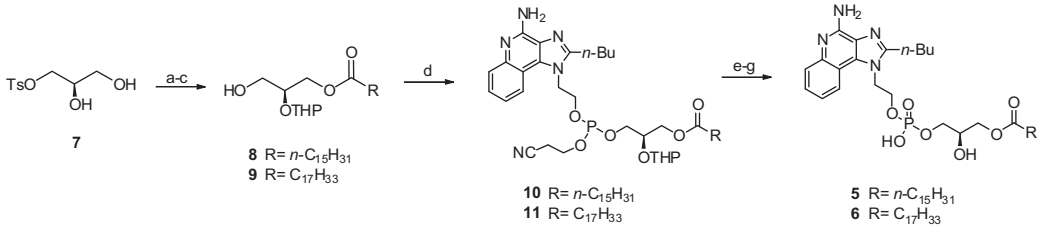


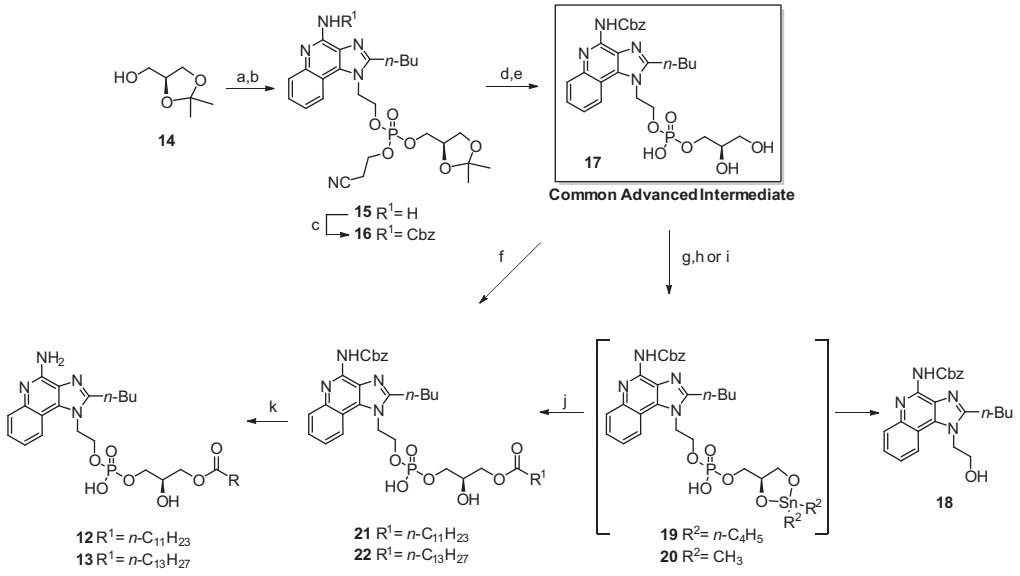
Figure 1. Structures of TLR7/8-active imidazoquinolines and lysophospholipid conjugate **4**.

protection strategy starting from 3-*p*-toluenesulfonyl-*sn*-glycerol (**7**)[10] and employing a one-pot, two-step phosphitylation reaction recently developed in our laboratory to install the lysophosphatidyl group (Scheme 1). Accordingly, monoacyl glycerols **8** and **9**, prepared in 3 steps from **7**, were treated with 2-cyanoethyl *N*,*N*,*N*′,*N*′-tetraisopropylphosphordiamidite in the presence of tetrazole to give the corresponding glycerol phosphoramidites (not isolated), which were reacted in situ with imidazoquinoline **3** in the presence of imidazolium triflate (Im-OTf) to afford the desired phosphite intermediates **10** and **11** in 97% and 73% yield, respectively, after chromatographic purification. Subsequent oxidation of phosphites **10** and **11** to the corresponding phosphates with *t*-butyl peroxide and sequential removal of the cyanoethyl and tetrahydropyranyl (THP) protecting groups provided the desired lysonucleolipids **5** and **6** in 66% and 52% yield, respectively, after chromatography. Reversing the order in which the protecting groups are removed leads to the regeneration of starting material **3**, presumably via initial intramolecular attack of the *sn*-2-hydroxyl group on the phosphotriester moiety. In this way, lysophospholipids **5** and **6** could be prepared in 8 steps and 19–33% overall yield from known tosyl glycerol **7** using the linear synthetic route shown in Scheme 1.

Next, we turned our attention to carrying out the convergent synthesis of homologous lysonucleolipids **12** and **13** via monoacylation of a phosphoglycerol intermediate toward the end of the synthesis (Scheme 2). While regioselective monoacylation of the *sn*-1-position of late-stage phosphoglycerol intermediates using carbodiimide-mediated or mixed anhydride acylation protocols has typically led to low yields of lysophosphatidylated products, the regioselective derivatization of vicinal diols using reactive stannylene acetal intermediates has been widely applied in organic synthesis.[11] Thus, we envisioned that the differentially acylated nucleolipids **12** and **13** could be assembled by first, constructing the protected phosphoglycerol **15** through tandem phosphitylation of alcohols **3** and **14**, and then—subsequent to protecting group manipulation—selective tin-mediated monoacylation[12] of the *sn*-1-position of the phosphoglycerol **17**.



Scheme 1. Reagents and conditions: (a) RCO_2H, DCC, DMAP, CH_2Cl_2, rt; (b) dihydropyran, *p*-TsOH, CH_2Cl_2, rt; (c) (i) $CH_3OCH_2CO_2^-Bu_4N^+$, CH_3CN, rt, (ii) *t*-$BuNH_2$, $CHCl_3$, CH_3OH, 0 °C, 52% (R = *n*-$C_{15}H_{31}$), 49% (R = $C_{17}H_{33}$); (d) (i) 1*H*-tetrazole, (*i*-$Pr_2N)_2POEtCN$, CH_2Cl_2, rt; (ii) **3**, Im-OTf, 0 °C to rt, 97% (R = *n*-$C_{15}H_{31}$), 73% (R = $C_{17}H_{33}$); (e) *t*-BuO_2H, CH_2Cl_2, rt; (f) Et_3N, CH_2Cl_2, rt; (g) 0.15 N HCl, $CHCl_3$, CH_3OH, 0 °C, 66% (R = *n*-$C_{15}H_{31}$), 52% (R = $C_{17}H_{33}$).



Scheme 2. Reagents and conditions: (a) (i) 1*H*-tetrazole, (*i*-$Pr_2N)_2POEtCN$, CH_2Cl_2, rt; (ii) **3**, Im-OTf, 0 °C to rt, 87%; (b) *t*-BuO_2H, CH_2Cl_2, rt; (c) Rapoport's reagent, CH_2Cl_2, rt, 80%; (d) Et_3N, CH_2Cl_2, rt; (e) TMSOTf, CH_2Cl_2, rt, 90% (2 steps); (f) RCO_2H, EDC, DMAP, CH_2Cl_2, rt, <35% yield); (g) Bu_2SnO, refluxing *i*-PrOH; (h) Me_2SnCl_2, K_2CO_3, THF, rt; (i) Me_2SnCl_2, TEA, CH_2Cl_2, rt; (j) RCO_2Cl, 59% (**21**), 80% (**22**); (k) 10% Pd/C, H_2, THF, 59% (**12**), 65% (**13**).

Accordingly, commercially available (*S*)-1,2-isopropylidene glycerol (**14**) was treated with 2-cyanoethyl *N*,*N*,*N*′,*N*′-tetraisopropylphosphordiamidite in the presence of tetrazole to give the corresponding glycerol phosphoramidite, which was reacted in situ with imidazoquinoline **3** in the presence of imidazolium triflate to afford the desired phosphite intermediate in 87% yield after chromatographic purification. Subsequent oxidation of the intermediate phosphite led to phosphate **15** in quantitative yields after chromatography. Due to the incompatibility of the primary aromatic amino group of **15** with stannylene and other O-acylation protocols as well as the susceptibility of the cyanoethyl group of **15** to β-elimination in the presence of the unprotected amino group,[13] the amine was protected as the benzyl carbamate **16** in 80% yield using 1-carbobenzoxy-3-methylimidazolium trifuoromethanesulfonate (Rapoport's reagent).[14] Sequential removal of the cyanoethyl and acetonide groups of **16** with triethylamine and trimethylsilyl triflate (TMSOTf)[15] then gave the phosphoglycerol common advanced intermediate **17**[16] in excellent yields. Reversing the order of protecting group removal or simultaneous deprotection of the 2-cyanoethyl and acetonide groups with TMSOTf/*N*,*N*-diisopropylethylamine (DIPEA)[17] resulted in significantly lower yields of **17** and the formation of imidazoquinoline **18** as a significant by-product.

Consistent with literature reports with other phosphoglycerols, attempts to selectively acylate the *sn*-1-hydroxy group of key intermediate **17** under carbodiimide-mediated conditions with lauric or myristic acid or with the corresponding acid anhydrides in the presence of base led to low yields (<35%) of monoacylated products **21** and **22** accompanied by significant amounts of di-acylated and other by-products, which were difficult to separate chromatographically. Not unexpectedly, phosphoglycerol **17** could be readily diacylated under standard conditions (fatty acid/DCC, DMAP) in high yields (data not shown).

Since dibutyltin oxide (DBTO) was recently employed to selectively mono-acylate the *sn*-1-position of a glycerophosphoryl choline,[12] we attempted to prepare **21** via acylation of dibutylstannylene acetal **19** with lauroyl chloride. However, under the conditions of the reaction (1 equiv DBTO, refluxing *i*-PrOH; then lauroyl chloride, Et_3N) the intermediate stannylene **19** was converted to imidazoquinoline **18** in nearly quantitative yields, presumably via intramolecular attack of the reactive stannylene on the phosphodiester group. Similarly, treatment of **17** with catalytic amounts of dimethyltin dichloride reagent[18] in the presence of potassium carbonate in anhydrous tetrahydrofuran (THF) at room temperature to form **20** also led to the formation of **18** as the major product, despite the milder reaction conditions. Gratifyingly, by employing an organic base (Et_3N) in place of potassium carbonate as demonstrated by Onomura[19] in the mono-silylation of diols via dimethylstannylene intermediates, the CAI **17** was converted to the desired mono-acyl products **21** and **22** in 59% and 80% overall yield,[20] respectively, after treating the in situ-prepared stannylene **20** with the requisite acyl chlorides in dichloromethane at room temperature. Hydrogenolysis of the *N*-Cbz group then provided the desired lysophospholipids **12** and **13** in 59% and 65% yield,[21] respectively, after chromatographic purification.

In summary, a short and convergent synthesis of lysophospholipid conjugates of TLR7/8-active imidazoquinoline **3** was developed utilizing a common advanced intermediate strategy and a reactive tin acetal to incorporate different acyl residues in the penultimate step. The synthesis of nucleolipids **12** and **13** in 2 steps and in 35–52% overall yield from CAI **17** by this method compares very favorably to the linear preparation of the homologous lysophospholipids **5** and **6** in 8 steps and 19–33% overall yield from tosylate **7**. The biological activity of these lysophosphatidylated imidazoquinolines will be reported elsewhere.

Acknowledgments

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16. *Synthesis of* **17**: (*S*)-1,2-isopropylidene glycerol **14** (2.0 equiv) and 2-cyanoethyl *N*,*N*,*N*′,*N*′-tetraisopropylphosphordiamidite (2.1 equiv) were dissolved in anhydrous methylene chloride (0.5 M) at room temperature (rt). 1*H*-Tetrazole (2.1 equiv) was added in five portions over 20 min and the reaction mixture stirred at room temperature for one hour. The reaction mixture was cooled to 0 °C, imidazoquinoline **3** (1.0 equiv) and imidazolium triflate (1.5 equiv) were added, and the reaction mixture allowed to warm up to rt. After 1.5 h at rt, the crude was purified by chromatography on silica gel (0–10% CH_3OH in $CHCl_3$). The resulting phosphite was dissolved in anhydrous methylene chloride (0.4 M) and oxidized by addition of *t*-butyl hydroperoxide (2.0 equiv). The reaction was done after stirring at rt for 30 min. After aqueous work-up and purification by chromatography on silica gel, **15** was obtained in 89% yield. **15**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.52 (t, J = 8.8 Hz, 1H), 7.33 (t, J = 8.4 Hz, 1H), 5.44 (s, 2H), 4.83 (t, J = 5.6 Hz, 2H), 4.56 (m, 2H), 4.15–3.60 (m, 7H), 2.95 (t, J = 8.0 Hz, 2H), 2.56 (m, 2H), 1.94–1.86 (m, 2H), 1.60–1.50 (m, 2H), 1.36 (d, J = 4.4 Hz, 3H), 1.30 (s, 3H), 1.02 (t, J = 7.2 Hz, 3H); positive ES TOF-MS calc for $[M+H]^+$ 532.2326, found 532.2352. Rapoport's reagent (4 equiv) was added to a solution of **15** in CH_2Cl_2 (0.4 M) and stirred at rt for 18 h. After purification by chromatography on silica gel (0–10% CH_3OH in $CHCl_3$) **16** was obtained in 80% yield. **16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.23 (d, J = 7.2 Hz, 1H), 8.02 (d, J = 9.2 Hz, 1H), 7.61 (t, J = 6.8 Hz, 1H), 7.50 (m, 3H), 7.41–7.34 (m, 3H), 5.33 (s, 2H), 4.84 (t, J = 5.6 Hz, 2H), 4.57 (m, 2H), 4.13–3.60 (m, 7H), 2.94 (t, J = 7.6 Hz, 2H), 2.55 (m, 2H), 1.90 (m, 2H), 1.50 (m, 2H), 1.35 (d, J = 5.2 Hz, 3H), 1.29 (d, J = 2.8 Hz, 3H), 1.01 (t, J = 7.2 Hz, 3H). Triethylamine (35% v/v) was added to a solution of **16** in acetonitrile (0.4 M) and stirred at rt. After 16 h, excess triethylamine was removed and purification by chromatography on silica gel (0–30% CH_3OH in $CHCl_3$) gave the deprotected phosphate in 85% yield. Subsequent acetonide group deprotection with trimethylsilyl triflate (4.0 equiv) in CH_2Cl_2 (0.3 M) at 0 °C for two hours followed by aqueous work

up with solid $NaHCO_3$ and purification by chromatography on silica gel (0–20% $CH_3OH/H_2O/NH_4OH$ 7:2:1 in $CHCl_3$) afforded **17** in quantitative yields. **17**: ^1H NMR (400 MHz, CD_3OD/drop of NH_4OH): δ 8.25 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.62–7.49 (m, 4H), 7.41–7.33 (m, 3H), 5.32 (s, 2H), 4.89 (t, J = 5.6 Hz, 2H), 4.34 (m, 2H), 3.58–3.36 (m, 5H), 3.12 (t, J = 7.6 Hz, 2H), 1.92 (m, 2H), 1.56 (m, 2H), 1.04 (t, J = 7.2 Hz, 3H); positive ES TOF-MS calc for $[M+H]^+$ 573.2115, found 573.2148.

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20. *General procedure for the synthesis of* **21** *and* **22**: to a suspension of **17** in anhydrous CH_2Cl_2 (0.3 M) was added Me_2SnCl_2 (10 mol %) followed by TEA (1.5 equiv) and acyl chloride (1.1 equiv). The reaction was stirred at room temperature under N_2 for two hours. Purification by chromatography on silica gel (0–30% CH_3OH in $CHCl_3$) gave the monoacylated products **21** (54% yield) and **22** (80% yield). **21**: ^1H NMR (400 MHz, $CDCl_3$): δ 8.07 (br s, 1H), 7.51–7.44 (m, 3H), 7.40–7.32 (m, 5H), 5.33 (s, 2H), 4.73 (m, 2H), 4.34 (m, 2H), 4.07–3.66 (m, 5H), 2.97 (m, 2H), 2.27 (m, 2H), 1.84 (m, 2H), 1.56–1.42 (m, 4H), 1.33–1.15 (m, 16H), 0.97 (m, 3H), 0.87 (t, J = 6.8 Hz, 3H); positive ES TOF-MS calcd for $[M+H]^+$ 755.3786, Found 755.3836. **22**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (br s, 1H), 7.50 (m, 3H), 7.42–7.32 (m, 5H), 5.33 (s, 2H), 4.63 (m, 2H), 4.29 (m, 2H), 4.06–3.69 (m, 5H), 2.93 (m, 2H), 2.24 (m, 2H), 1.81 (m, 2H), 1.54–1.43 (m, 4H), 1.29–1.15 (m, 20H), 0.95 (m, 3H), 0.87 (t, J = 6.8 Hz, 3H); positive ES TOF-MS calc for $[M+H]^+$ 783.4099, Found 783.4115.
21. *General procedure for the synthesis of* **12** *and* **13**: a solution of **21** or **22** in anhydrous THF (0.1 M) was hydrogenated at rt in presence of 10% Pd/C (50% w/w) under atmospheric H_2 pressure overnight. After filtration of the catalyst and concentration of the reaction mixture, the resulting crude was purified by chromatography on silica gel (0–25% CH_3OH/H_2O 95:5 in $CHCl_3$) to afford **12** (54% yield) and **13** (65% yield). **12** ^1H NMR (400 MHz, $CDCl_3/CD_3OD$): δ 8.11 (br s, 1H), 7.32 (t, J = 7.2 Hz, 1H), 7.11 (br s, 1H), 6.80 (br s, 1H), 4.62 (br s, 4H), 4.07–3.85 (m, 5H), 2.96 (br s, 2H), 2.26 (t, J = 8.0 Hz, 2H), 1.91–1.83 (m, 2H), 1.53–1.45 (m, 4H), 1.18 (m, 16H), 0.99 (t, J = 6.8 Hz, 3H), 0.81 (t, J = 6.4 Hz, 3H); positive ES TOF-MS calcd for $[M+H]^+$ 621.3418, found 621.3481. **13** ^1H NMR (400 MHz, $CDCl_3/CD_3OD$): δ 8.10 (br s, 1H), 7.32 (br s, 1H), 7.11 (br s, 1H), 6.80 (br s, 1H), 4.62 (m, 4H), 4.07–3.83 (m, 5H), 2.90 (m, 2H), 2.26 (t, J = 7.2 Hz, 2H), 1.88 (t, J = 6.8 Hz, 2H), 1.53–1.47 (m, 4H), 1.19 (m, 20H), 0.99 (t, J = 7.2, 3H), 0.82 (t, J = 6.4 Hz, 3H); positive ES TOF-MS calcd for [$[M+H]^+$ 649.3731, found 649.3796.