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Demonstration of a convergent approach to UV-polymerizable lipids bisDenPC and bisSorbPC

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ABSTRACT

Lipids containing UV-polymerizable diene moieties, such as BisDenPC **1** and BisSorbPC **2**, have been extremely useful for the construction of micelles and lipid bilayers. The published syntheses have yielded lipids with only a trimethylamine head group. We have improved the syntheses of these monomers by a convergent method employing the Chabrier reaction of trimethylamine with a cyclic phospholane. This method can be extended to a variety of dialkylamine derivatives.

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1. Introduction

For the past 25 years, the synthetic lipids bisDenPC **1** and bisSorbPC **2** have been utilized by a number of groups, including our own, to form vesicles which undergo polymerization to impart stability.[1] Polymerization of the conjugated dienes in **1** and **2** via UV and/or redox techniques yields a poly[lipid] covalently bonded via poly-olefin chains. For a time, **1** was commercially available from Wako Chemicals and Nippon Oil & Fats Co.;[2] unfortunately, these companies are no longer suppliers. Previously published syntheses of **1** coupled the appropriate dienoic fatty acids to the commercially available *syn*-glycero-3-phosphocholine cadmium chloride adduct.[3–5] These procedures can only yield lipids with a trimethylamine head group. We decided to try the convergent methodology[6] to construct the phosphocholine head group onto the glycerol backbone already containing the fatty acid components. The Chabrier reaction[7] involving displacement on a cyclic phospholane by dialkylamine derivatives has been demonstrated to be very general by Nakaya and Li[6] for the synthesis of other linear-polymerizable lipids; however, this method has not been extended to vesicle-forming monomers. While this Letter is a preliminary report on the successful synthesis of two known lipids, this methodology is envisioned to be used to synthesize related lipids with potentially polymerizable hydrophilic head groups.[8] Various improvements in the synthesis of the required intermediates are included in our Letter.

2. Results/discussion

The first improvement in the synthesis of bisDenPC **1** concerned the synthesis and purification of dienoic acid **3**.[9–12] Previously, after PCC oxidation of tetradecanol, subjecting the resulting tetradecanal to Horner–Wadsworth–Emmons (HWE) reaction conditions with triethylphosphonocrotonate led to a variable ratio of desired (*E*,*E*) and unusable (*E*,*Z*) isomers;[13] similar results were obtained with either commercially available or freshly prepared methyl or ethyl HWE reagent. Urea inclusion had been the preferred separation method to isolate the pure (*E*,*E*) isomer.[14] We have now observed that saponification of the intermediate methyl or ethyl ester in refluxing alkali overnight gave only the desired (*E*,*E*) dienoic acid **3**, presumably due to base-catalyzed olefin isomerization (Scheme 1).

Attention then turned to diacylation of commercially available (R)-(+)-3-benzyloxy-1,2-propanediol **4** with dienoic acid **3** (Scheme 2). When the coupling reagent DCC was used, even under reflux, only the primary monoacylated product **5** and the unreacted DCC-fatty acid adduct were isolated. With the acid chloride or acid bromide[15] from **3**, only **5** was observed, even when **4** was first treated with 2.2 equiv of *n*BuLi. When the acid was activated with carbonyl-diimidazole,[16] again only **5** was isolated. Some mixed success was achieved using a catalytic amount of scandium(III) triflate,[17] with both monoacyated **5** and diacylated **6** being isolated from the reaction mixture.

Finally, Yamaguchi esterification conditions[18] yielded the one-pot diacylation product **6** with no observed **5**; addition of 2,4,6-trichlorobenzoyl chloride to acid **3** in toluene with triethylamine followed by addition of **4** with DMAP gave the diacylated **6** in acceptable yield (Scheme 3). Following careful deprotection with BCl_3, the installation of the phosphocholine head group was achieved in two-steps using 2-chloro-2-oxo-1,3,2-dioxaphospholane followed by trimethylamine in acetonitrile.[19] This model reaction improved the synthesis of our "workhouse" bisDenPC by a convergent method which can be extended to a variety of dialkylamine derivatives.

As to bisSorbPC **2**, the synthesis of the fatty acid component turned out to be the difficult step. The more recent approach of

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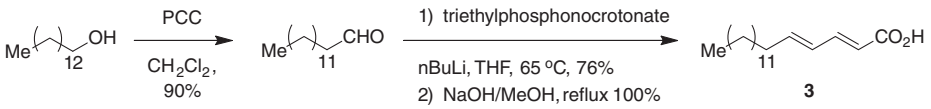
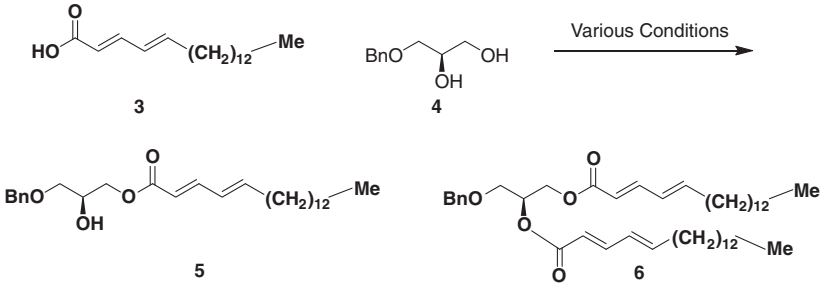
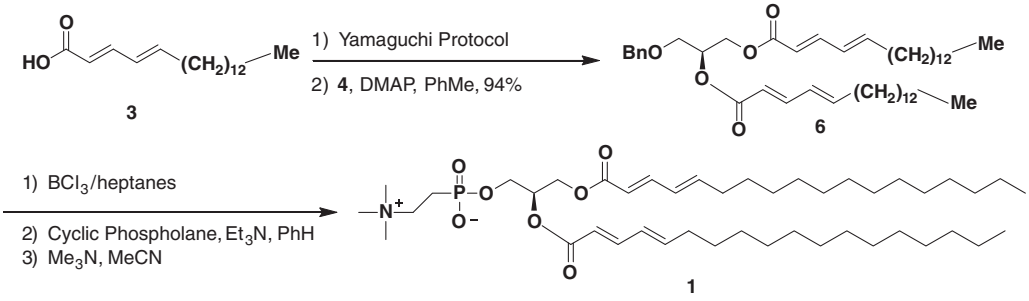


Scheme 1. Synthesis of (*E*,*E*)-2,4-octadecadienoic acid **3**.

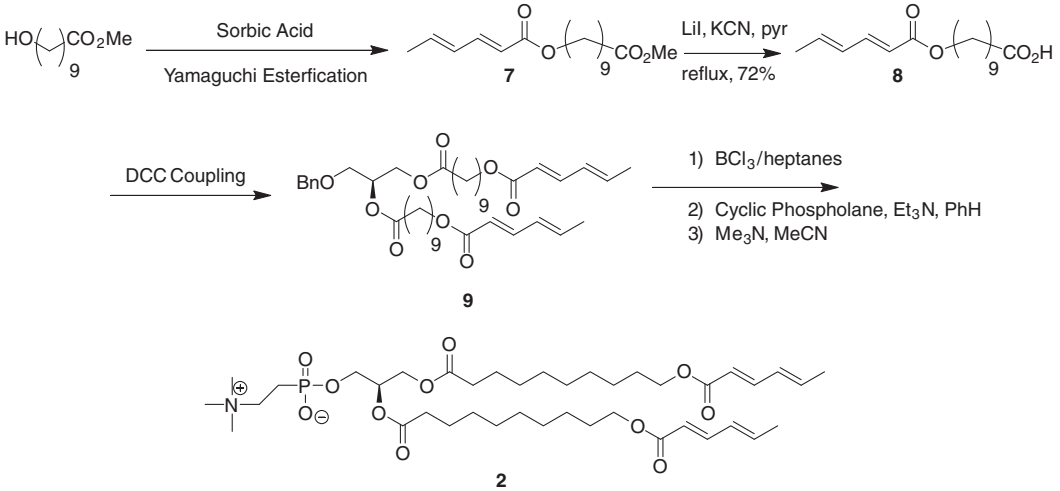


Scheme 2. Synthesis of diacylated benzyloxy protected propanediol **6**.



Scheme 3. Synthesis of bisDenPC **1**.

Bae et al. failed in our hands; however, we did take inspiration from their work. Sorbic acid was coupled to methyl 10-hydroxydecanoate under standard Yamaguchi esterification conditions to give the mixed ester **7** (Scheme 4). We expected that saponification should occur much faster with a methyl group as opposed to a sorboyl group; yet traditional saponifications with alkali in alcohol or mixed alcohol–solvent systems were either too sluggish or not specific enough for the methyl ester. By subjecting **7** to lithium iodide and potassium cyanide in refluxing pyridine[20], an S_N2-type demethylation yielded the corresponding fatty acid **8**. With this saturated acid, DCC coupling of **8** to chiral diol **4** cleanly gave the diacylated product **9**. Deprotection with BCl_3 gave the expected alcohol, which was used without purification to suppress ester group migration. Subjecting the alcohol to 2-chloro-2-oxo-1,3,2-dioxaphospholane followed by trimethylamine in acetonitrile gave bisSorbPC **2**. Again, we have improved the synthesis of our extensively used monomer using a convergent approach which can be generalized with other dimethylamine derivatives.[21]



Scheme 4. Synthesis of bisSorbPC **2**.

Acknowledgments

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Supplementary data

Supplementary data (the synthesis, characterization, and NMR spectra of compounds **1**, **2**, **3**, **6**, **7**, **8**, and **9**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.090.

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