Novel bipolar phospholipids with different headgroups

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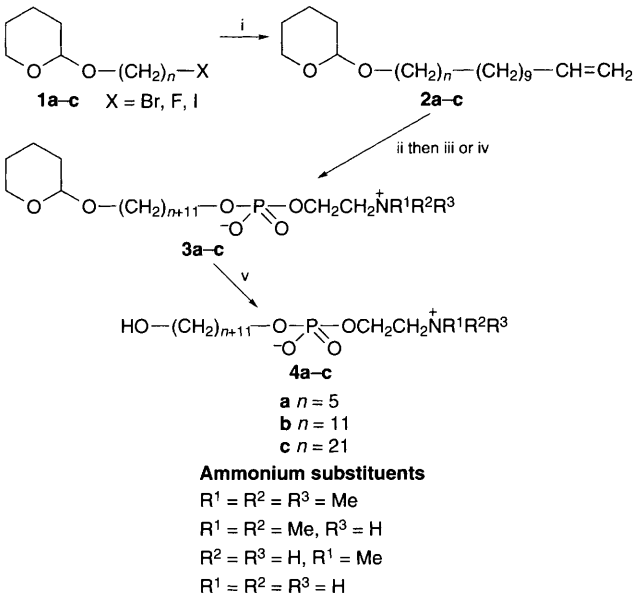
The synthesis of long chain bipolar phospholipids with different polar headgroups and chain lengths of 16, 22 and 32 carbon atoms is described, using a Li_2CuCl_4-catalysed cross-coupling of Grignard reagents with ω-functionalised halogenoalkanes in order to synthesise unsymmetric bolaamphiphiles.

Bolaamphiphiles[1] are bipolar compounds containing one or two alkyl chains with polar head groups in the α- and ω-positions. These substances are interesting with regard to the synthetic, biological and practical viewpoint.[2–4] The natural equivalent to these compounds are the lipids found in archaebacterial membranes, which are an important subject of biotechnological research. The high stability of the membranes of archaebacteria under extreme environmental conditions is due to the unusual structure of these compounds[5] (Fig. 1). Yet, simple bipolar lipids are also of interest, as shown in the recent publication of the structure elucidation and synthesis of irlbacholin, a 1,22-bisphosphocholin with antifungal activity.[6] Unsymmetric bolaamphiphiles are of particular concern, as the different sized headgroups can induce membrane curvature.[1]

Here we present our results concerning the synthesis of unsymmetric bolaform phospholipids. These compounds are part of our programme to study the physicochemical and biophysical properties of archaebacterial lipid models.

The synthesis is outlined in Scheme 1. Starting with the compounds **1a–c** the terminal alkenes **2a–c** were obtained in 81% yield using Li_2CuCl_4-catalysed cross-coupling[7] with the Grignard reagent of 11-bromoundec-1-ene. For the coupling of the C-21 units with 11-bromundec-1-ene the iodides were most suitable, giving a 74% yield of the C-32 unit, whereas the bromides led to a maximum yield of 20%. After hydroboration with 9-BBN followed by oxidative hydrolysis, monoprotected diols were obtained. The phospholipids **3** resulted from the reaction of these alcohols with 2-bromoethylphosphoric acid dichloride[8] and subsequent quarternation with various amines. In doing so the standard conditions were slightly changed by increasing the pH value of the reaction media to 8. The removal of the THP group using standard methods[9] led to the ω-hydroxy-substituted bipolar compounds **4**.† The terminal hydroxy group is now suitable for either further phosphorylation or other functionalisation. It is also possible to use 2-chloro-2-oxo-1,3,2-dioxaphospholane in combination with lithium bromide[10] instead of 2-bromoethylphosphoric acid dichloride. This method, although including an additional step, also gives good yields and it has proved to be a good alternative for phosphorylation of long chained compounds.



Scheme 1 *Reagents and conditions*: i, 11-bromundec-1-ene, Mg, diethyl ether, then THF, Li_2CuCl_4, 3 h, 0 °C; ii, 9-BBN, THF, H_2O_2, NaOH, 3 h, room temp.; iii, $Cl_2P(O)OCH_2CH_2Br$, $CHCl_3$, triethylamine, 24 h, room temp., then $NR^1R^2R^3$, $CHCl_3$, 8 h, 40 °C; iv, 2-chloro-2-oxo-3,2-dioxaphospholane, $CHCl_3$, triethylamine, then LiBr, acetone, then $NR^1R^2R^3$, $CHCl_3$; v, pyridinium toluene-*p*-sulfonate, MeOH, reflux, 2 h

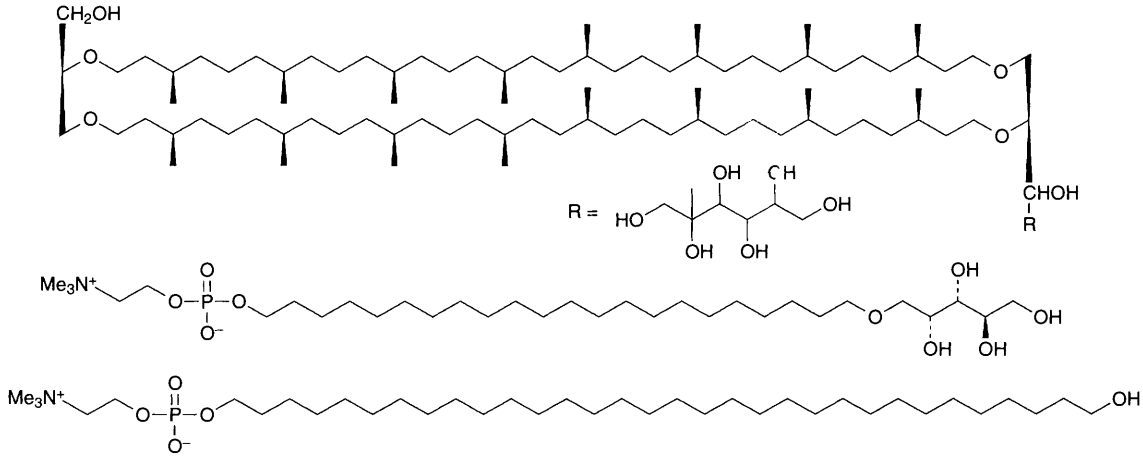
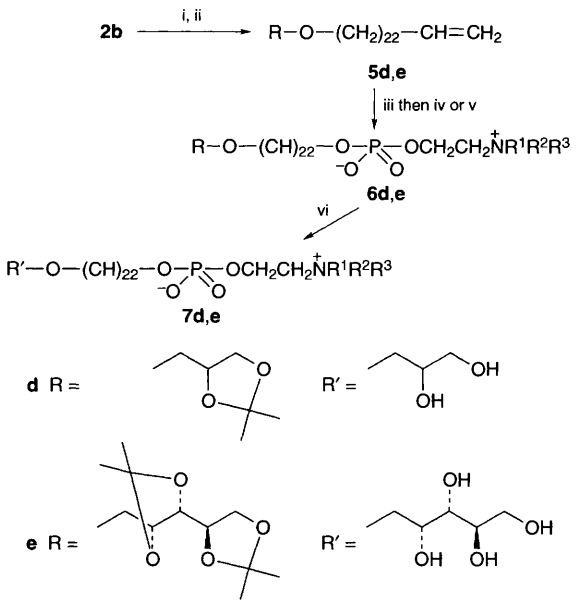


Fig. 1 Typical structure of an archaebacterial lipid and model lipids

The hydroxy end of the bola compound **4** was then substituted with (*R*)- and (*S*)-glycerol or an open chain polyol residue, in order to introduce both chiral headgroups and more hydroxy functions. This was done as follows: compound **2b** was converted into the ω-bromoalkene,[11] which gave, after alkylation with (*R*)- or (*S*)-1,2-isopropylideneglycerol, the alkene **5d** and, after hydroboration, the monoprotected alcohol (Scheme 2). After phosphorylation and deprotection, the bola compounds **7d**‡ were obtained. 2,3 : 4,5-Diisopropylidene-D-arabit was synthesised starting with gluconic acid methylester.[12] The protected polyol residue was alkylated in the usual manner after isopropylidenation, periodate oxidation and reduction of the 2,3 : 4,5-diisopropylidene-D-arabinose. Hydroboration, phosphorylation and deprotection resulted in the bola compounds **7e**.§



Scheme 2 *Reagents and conditions*: i, PPh_3, Br_2, CH_2Cl_2, 16 h; ii, (*R*)- or (*S*)-1,2-isopropylidineglycerol, 2,3 : 4,5-diisopropylidene-D-arabit, $KOBu^t$, THF; iii, 9-BBN, THF, H_2O_2, NaOH, 3 h, room temp.; iv, $Cl_2P(O)OCH_2CH_2Br$, $CHCl_3$, triethylamine, 24 h, room temp., then $NR^1R^2R^3$, $CHCl_3$, 8 h, 40 °C; v, 2-chloro-2-oxo-3,2-dioxaphospholane, $CHCl_3$, triethylamine, then LiBr, acetone, then $NR^1R^2R^3$, $CHCl_3$; vi, pyridinium toluene-*p*-sulfonate, MeOH, reflux, 2 h

All intermediate products were checked for purity by HPLC and elemental analysis. The final structures were confirmed by ES-MS, NMR (^1H, ^{13}C) and checked for purity as mentioned above.

The bipolar phospholipids with unsymmetric headgroups are new compounds that offer manifold possibilities for application in membrane research and biotechnology.

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Footnotes

† *Selected data* for **4c** ($R^1 = R^2 = R^3$ = Me): ES-MS: *m/z* 648 (M + H), 670 (M + Na).

‡ *Selected data* for **7d** ($R^1 = R^2 = R^3$ = Me): δ_H($CDOD_3$, 500 MHz) 1.26 (40 H, s), 1.59–1.64 (4 H, m), 3.2 (9 H, s), 3.39–3.55 (5 H, m), 3.59–3.61 (3 H, m), 3.74 (1 H, m), 3.84–3.87 (2 H, m), 4.22 (2 H, m); ES-MS: *m/z* 582 (M + H), 604 (M + Na).

§ *Selected data* for **7e** ($R^1 = R^2 = R^3$ = Me): ES-MS: *m/z* 642 (M + H), 665 (M + Na).

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