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Efficient Synthesis of 40- and 48-Membered Tetraether Macrocyclic Bisphosphocholines

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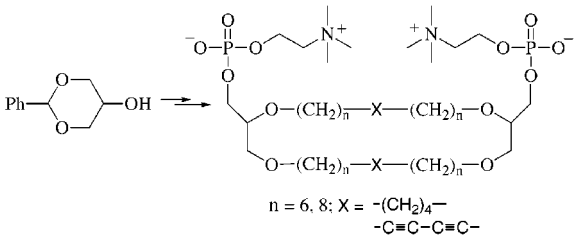
ABSTRACT



An efficient route toward the synthesis of unsaturated (bis-diacetylenic) and saturated 40- and 48-membered macrocyclic bisphosphocholines has been developed using 2-phenyl-5-hydroxy-1,3-dioxane as a common glycerol synthon. Ring closure was accomplished using either high-dilution Glaser oxidation or $[(Cy_3P)_2Ru{=}CHPh]Cl_2$-catalyzed olefin metathesis conditions. Deprotection of benzyl ethers using trimethylsilyl iodide (TMS-I) in the presence of diacetylenic moieties has also been demonstrated for the first time.

Archaeabacteria have recently been categorized as a third domain organism.[1] Their ability to survive under harsh environmental conditions has been attributed in part to their unique membrane structural features.[2,3] Their membrane lipid components differ from their eukaryotic counterparts in the type of glycerolipids that are present. The most unusual features of archaebacterial lipids are (i) alkyl chains that are ether linked instead of ester linked to the glycerol backbone, (ii) isoprenyl-based alkyl chains that occasionally include cyclopentane ring modifications, and (iii) macrocyclic lipid structures that contain two, presumably membrane-spanning, alkyl chains that connect the two glycerol backbones. The unique thermotropic properties of these membrane lipids have led to the synthesis[4] of structural mimics (e.g., bola-amphiphiles) and their application in supported membrane biosensor devices.[5] Synthetic bolaamphiphiles have also been used as design elements for coupled electron/ion charge transfer across thin membrane vesicles.[6,7] Interest in the synthesis of these compounds has arisen from the difficulties encountered in isolating gram quantities of naturally occurring archaebacterial lipids and from the desire to study structure−property relationships in this novel class of membrane materials.[8] Large quantities of bolaamphiphiles are required to conduct such studies; however, the natural product total syntheses are labor-intensive.[9−14] As a result,

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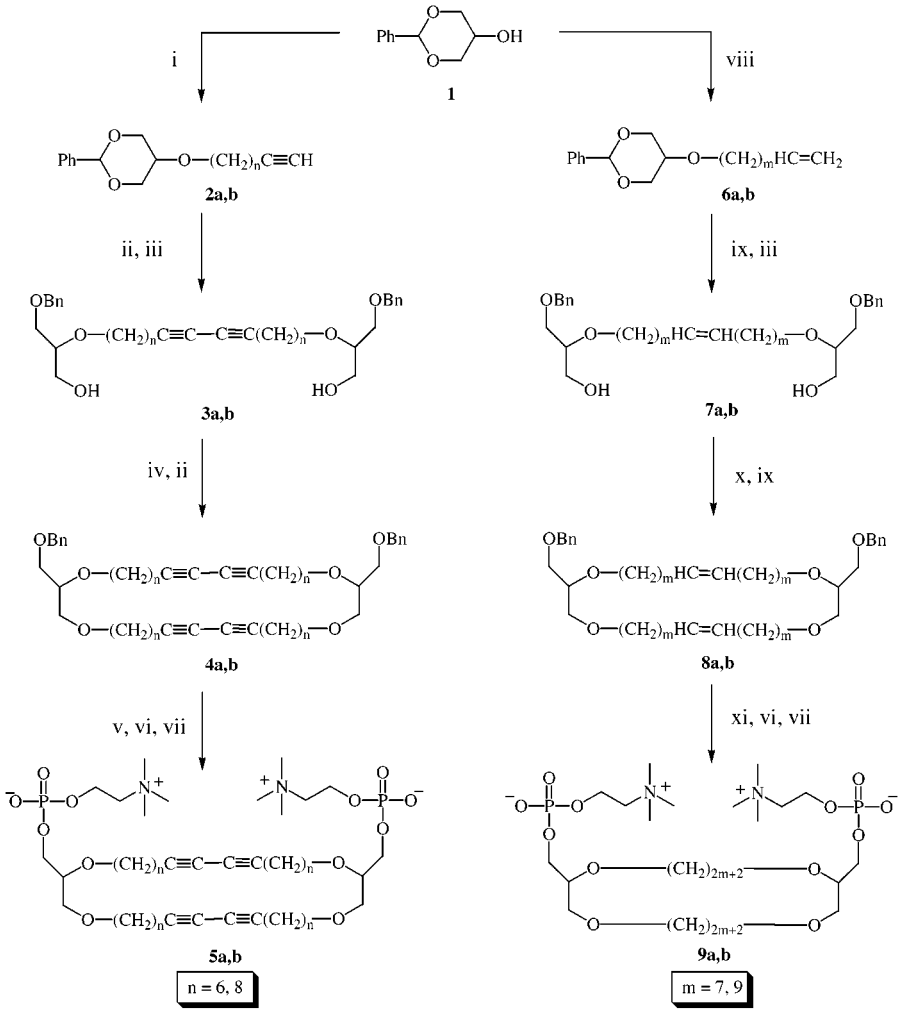
Scheme 1[a]



[a] (i) NaH/ toluene, **12a** or **12b**, reflux; (ii) CuCl, TMEDA, *p*-xylene, air, 140 °C; (iii) DIBAL-H, CH_2Cl_2, −78 °C; (iv) NaH/ THF, **11a** or **11b**, reflux; (v) TMS-I, MeOH; (vi) $Cl(O)P(OCH_2)_2$, benzene, Et_3N; (vii) CH_3CN, Me_3N, 3 days, 65 °C; (viii) NaH/toluene, **15a** or **15b**, reflux; (ix) $[(PCy_3)_2Ru{=}CHPh]Cl_2$ (Grubbs catalyst), CH_2Cl_2, reflux; (x) NaH/ THF, **14a** or **14b**, reflux; (xi) H_2/ 10% Pd−C, EtOAc.

many model compounds that retain some of the essential structural features of archea membrane lipids, such as ether linkages and membrane-spanning hydrophobic chains, have been reported.[8,15−20] Previous synthetic studies of model tetraether-linked bolaamphiphiles have been mostly limited to acyclic bisphosphocholines[15,17,18] and macrocyclic phosphocholines.[19,21] Menger and co-workers[22] have synthesized 72-membered saturated macrocyclic bisphosphocholines; however, their synthesis required multiple protection−deprotection steps. Routes to the synthesis of bolaamphiphiles have typically exploited glycidol,[17] epichlorohydrin,[18] or solketal[15,18−20] as glycerol synthons. In our previous report,[17,18] acid-catalyzed ring opening of glycidyl *m*-nitrobenzenesulfonate or epichlorohydrin using 1,16-hexandecanediol gave good yields of diethers bearing free hydroxyls at the *sn*2 and *sn*2′ positions of the glycerol backbones. A similar strategy has been employed to synthesize macrocyclic bisphosphocholines by alkylating the *sn*2 and *sn*2′ hydroxyls with 1,*ω*-bromoalkynes which then allows intramolecular ring closure via high-temperature copper-mediated Glaser oxidation.[22−24] Since this intramolecular cyclization did not

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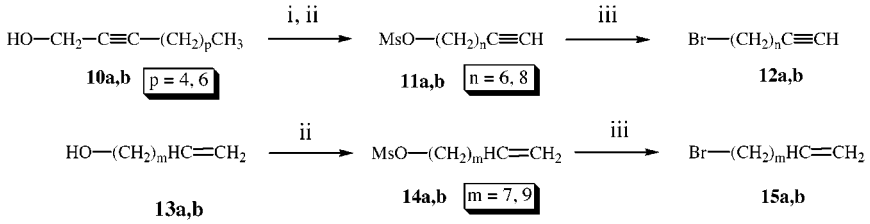
Scheme 2[a]



[a] (i) Li, 1,3-diaminopropane, t-BuOK, 70 °C;[29] (ii) MsCl, Et_3N, CH_2Cl_2; (iii) LiBr, THF, reflux.

yield the desired intramolecular macrocyclic product, we sought to develop a more direct synthetic pathway involving inexpensive starting materials that could expand the diversity of bolaamphiphiles available. In this Letter, we report the synthesis of a diastereomeric mixture of macrocyclic bolaamphiphiles bearing two phosphocholines headgroups using 2-phenyl-5-hydroxy-1,3-dioxane as precursor. Two different coupling conditions were employed: (i) the Glaser oxidation method to synthesize 1,ω-bolaamphiphiles **5a**,**b** and (ii) olefin metathesis using $[(Cy_3P)_2Ru{=}CHPh]Cl_2$ (Grubbs catalyst) to synthesize the corresponding saturated bolaamphiphile analogues **9a**,**b**. The synthesis of 2-phenyl-5-hydroxy-1,3-dioxane **1** (Scheme 1) as the glycerol precursor utilized glycerol and benzaldehyde.[25] Alkylation at the secondary hydroxyl position with either 1,ω-bromoalkynes **12a**,**b** or 1,ω-bromoalkenes **15a**,**b** (Scheme 2) gave the corresponding ethers **2a**,**b** and **6a**,**b** in 67% yield, respectively. The alkylated 1,3-dioxanes were then dimerized to yield bis-dioxane products. Glaser oxidation of compounds **2a**,**b** produced the corresponding diacetylenic bis-dioxane in 70% yield; dimerization of **6a**,**b** via olefin metathesis yielded the corresponding olefinic bis-dioxanes in 78% yield. DIBAL-H[26] was then used to open the acetal ring, giving the bis-benzyl-protected glyceryl tetraether diols **3a**,**b** and **7a**,**b**. Subsequent alkylations of diols **3a**,**b** with 1,ω-alkyne mesylate **11a** or **11b**, and diols **7a**,**b** with 1,ω-alkene mesylate **14a** or **14b**, yielded products with alkyl chains activated for coupling between the *sn*1 and *sn*1′ positions. High-dilution Glaser oxidation[23] and olefin metathesis[9] reactions were again carried out to effect intramolecular macrocyclization in high yields, (i.e., **4a**,**b** and **8a**,**b** in 65% and 80% yields, respectively). It should be noted that the yields of macrocyclic compounds **8a**,**b** were drastically improved by very slow addition of the triolefin precursor to the ruthenium catalyst.[27] Debenzylation of **4a**,**b** without polymerization was crucial for the successful synthesis of the target tetraacetylenic lipids. Application of the most commonly used debenzylating methods such as catalytic hydrogenation, dissolving metals in ammonia, or Lewis acid mediated benzyl ether cleavage would destroy the diacetylenic moiety. Closer examination of the debenzylation literature revealed that Berk and co-workers[28,29] had previously reported the removal of benzyl protecting groups from other lipid precursors bearing saturated alkyl chains in 45% yield using trimethylsilyl iodide (TMS-I); however, there were no indications that this transformation could be effected in the presence of an electron rich diacetylenic moiety. Application of TMS-I for debenzylation of **4a** and **4b** to the corresponding diols was found to be reasonably efficient (68% isolated yield). Debenzylation of **8a** and **8b** was achieved using standard hydrogenolysis conditions with 10% Pd−C catalyst. The corresponding macrocyclic diols were then phosphorylated[17,18] using 2-chloro-2-oxo-1,3,2-dioxaphospholane, followed by trimethylamine ring opening in acetonitrile at 65 °C for 3 days, to give the tetrayne **5a**,**b** (70%) and saturated **9a**,**b** (46%) macrocyclic bisphosphocholines with overall yields of 9% and 11%, respectively.

In conclusion, we have developed a novel and versatile synthetic route using 2-phenyl-5-hydroxy-1,3-dioxane as precursor. Two different high-dilution coupling conditions were employed for the synthesis of macrocyclic bisphosphocholines in high yields. To the best of our knowledge, this route also demonstrates for the first time the debenzylation of benzyl ethers using TMS-I in the presence of diacetylenic moieties in good yields.

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Supporting Information Available: ^1H, ^{13}C, and ^{31}P NMR spectra for compounds **1**−**15b**. Elemental analysis for the diols (bisphosphocholine precursor) and mass spectral data for **5a**,**b** and **9a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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