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A New Approach to Archaebacterial Lipid Models

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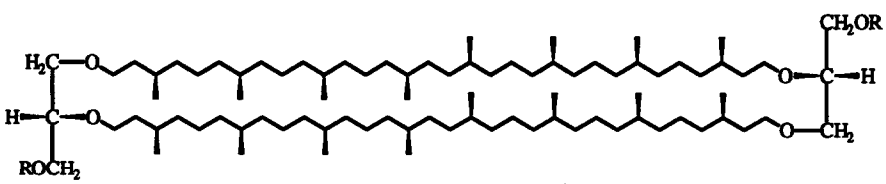
Abstract: 1,1'-(α,ω-Alkylidene)-2,2'-dialkylglycerol tetraether lipid models (**9**) have been prepared by coupling two equivalents of 1-(ω-haloalkyl)-2-alkylglycerol diethers, through silver-catalyzed coupling of the Grignard reagents **8** with iodide **7**.

Archaebacterial tetraether lipids[1] have received considerable attention due to their unusual structure and potential properties.[2] In particular the cyclic 2,3'; 3,2'-bisbiphytanyl-di-*sn*-glycerol tetraethers **1** (R = sugar, phosphate, nonitol, etc.), containing a 72-membered ring with 16 configurationally defined methyl groups, have not yet been synthesized.

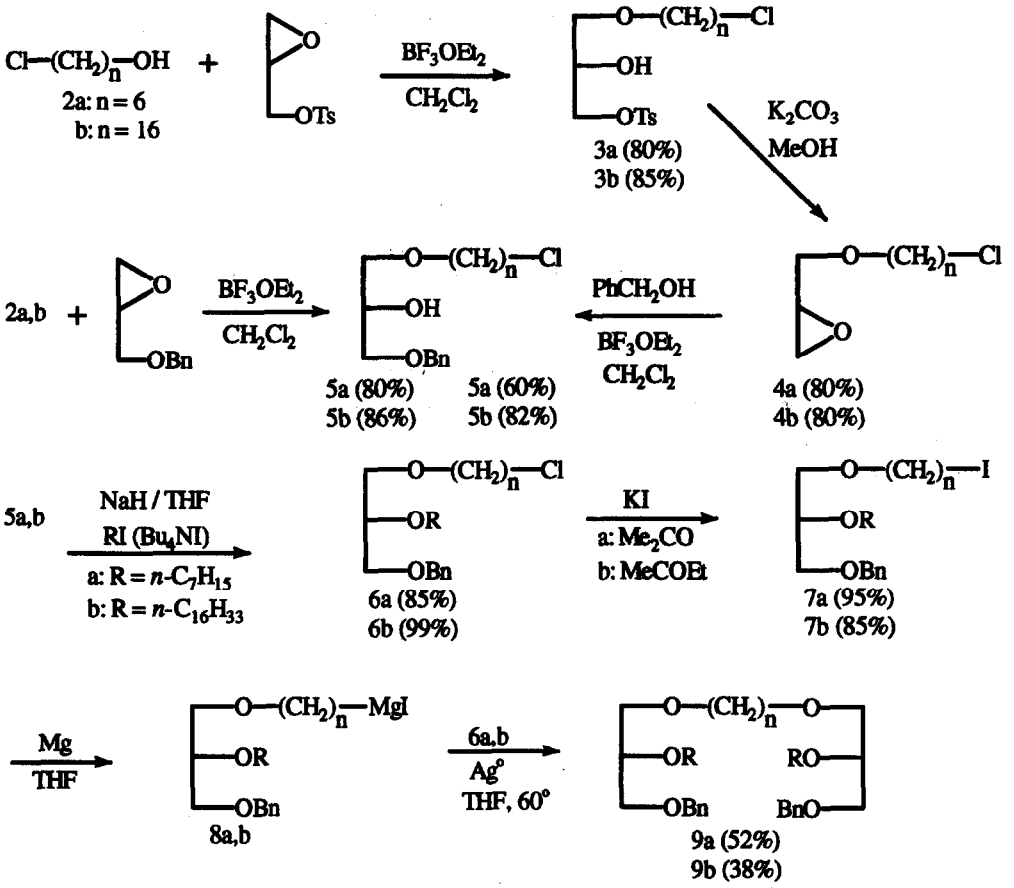


1

Previous open-chain lipid tetraethers have been prepared primarily by modifications of the Williamson ether synthesis, employing α,ω-dibromoalkanes.[3] Here we report a coupling strategy which we have successfully applied to a simpler, known, acyclic, straight-chain tetraether model. We believe this idea may be applicable to the more difficult task of assembling the cyclic tetraether.[4]

Scheme 1 outlines our coupling studies. $BF_3 \cdot OEt_2$ catalyzed[5] reaction of *rac*-benzyl glycidyl ether with hexamethylene chlorohydrin[6] **2a** gave **5a** in one step in 80% isolated yield. This sequence was repeated using 16-chlorohexadecanol analogs. 16-Hydroxyhexadecanoic acid was converted to 16-chlorohexadecanoyl chloride and reduced without purification by alane[7] to the 16-chloro alcohol **2b** (94%). BF_3-catalyzed alcoholysis of (*R*)-glycidyl benzyl ether with the chlorohydrin gave the corresponding primary ether, (*S*)-**5b**, in 86% yield.

As an alternative route to **5**, BF_3 catalyzed ring opening of *rac*-glycidyl tosylate with hexamethylene chlorohydrin (**2a**) gave the ether-tosylate **3a** in 80% yield. Treatment with potassium carbonate[8] gave 6-chlorohexyl glycidyl ether **4a** (80%) which was opened regioselectively in a similar manner with benzyl alcohol/BF_3 etherate to give the benzyl 6-chlorohexyl diether **5a** (60%). This sequence was also repeated using the 16-chlorohexadecanol analogs. BF_3-catalyzed alcoholysis of (*R*)-glycidyl tosylate[9] with the chlorohydrin **2b** gave the corresponding primary ether **3b** in 85% yield. Ring closure with base (80%) followed by ring opening with benzyl alcohol and BF_3 etherate (82%), as before, gave 3-*O*-benzyl-1-*O*-(16-chlorohexadecyl)-*sn*-glycerol, diether (*R*)-(+)-**5b** in 82% yield.



Scheme 1

Alkylation of the free hydroxyl group of **5a** with *n*-heptyl iodide in the presence of a catalytic amount of tetra-*n*-butylammonium iodide[10] afforded triether **6a** in 85% yield. The chloride was replaced by iodide (**7a**, 95%), then dimerized to **9a** (52%) using Kochi's procedure:[11] one equivalent of iodide **7a** was converted to the Grignard reagent (**8a**) then coupled with a second equivalent of iodide using "soluble silver" catalyst.[12] Similarly, Williamson coupling of the free secondary hydroxyl group of (*R*)-**5b** with hexadecyl iodide gave triether **6b** (99%). Again, conversion to the iodide (**7b**, 85%) and Kochi coupling with Grignard reagent **8b** (38%) gave the known[3a,b] 1,32-di-(3-benzyloxy-(2*R*)-2-hexadecyloxypropanoxy)-dotridecane (**9b**). The overall yield of the benzyl protected *sn*-1,2-glycerol tetraether **9b** for the 6 steps, starting with the hydroxy acid **2b**, was 25.9%. Considering the low yield coupling step, this reaction sequence compares favorably with published procedures which employed the Williamson reaction exclusively for acyclic tetraethers (9-15%). It is worth noting the lengthy preparation of 1,32-dibromodotridecane[4b,13] required by the Williamson route. The overall yield of benzyl protected *sn*-2,3-glycerol tetraether **9b** for the 8 steps starting with the tosylate would be 16.7% using this route.

In conclusion, the method reported here allows the preparation of protected 1,2 or 2,3-*sn*-glycerol tetraethers via BF_3-catalyzed alcoholysis of glycidyl derivatives and Kochi-type coupling.[14] Attempts to construct and couple appropriately substituted haloalkyl glycerol derivatives to form cyclic diglycerol tetraethers are in progress.

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14. All compounds were characterized by IR, ^{1}H and ^{13}C NMR, low and high resolution mass spectrometry, and elemental analysis as appropriate. $[\alpha]_D^{25}$ ($CHCl_3$): (*R*)-**3b**, -3.04°; (*R*)-**4b**, +1.60°; (*S*)-**5b**, -1.34°; (*R*)-**5b**, +1.33°; (*R*)-**6b**, +0.19°; (*R*)-**7b**, +0.17°; (*R*)-**9b**, +0.23°.

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