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Direct Closure of a 36-Membered Ring Using the McMurry Coupling: Synthetic Studies on the Macrocyclic Archaebacterial Membrane Lipids

Tadashi Eguchi, Takumi Terachi, and Katsumi Kakinuma*

Department of Chemistry, Tokyo Institute of Technology
O-okayama, Meguro-ku, Tokyo 152, Japan

Abstract: *The synthesis of a desmethylated archaebacterial membrane lipid featuring the 36-membered ring using the McMurry coupling, a low-valent titanium induced coupling reaction of a dialdehyde, is reported.*

Archaebacteria including methanogens, extreme halophiles, extreme thermophiles and thermoacidophiles grow under rather extraordinary conditions and have structurally unique membrane lipids to adapt the extreme environments.[1] The lipids are consisted of hydrophobic isoprenoid chains linked to glycerol with the ether bonds, which are well contrast to the ester linkage of the eubacterial and eukaryotic membrane lipids.[2] The second feature is the stereochemistry of the glycerol portion in the archaebacterial lipids, *i.e.*, the hydrophobic phytanyl groups are attached to the hydroxyl groups at the *sn*-2- and 3-positions of glycerol. In contrast, the fatty acyl groups are substituted at the *sn*-1- and 2-positions in the eubacterial and eukaryotic lipids.[2]

The third and most striking feature of the archaebacterial ether lipid is found in the macrocyclic (36 or 72-membered) ring structures,[2,3] as shown in Figure 1. These unusual lipids have been interested quite sometime in connection with the physicochemical properties based on the lipid bilayer theory.[4] Several modeling and synthetic studies have been reported in order to investigate the stability and permeability of the archaebacterial membrane lipids, especially, in terms of thermostability of extreme thermophiles.[5]

We have been interested in the chemical and biochemical features of these archaebacterial lipids. Recently, we have postulated the pathway and stereochemistry of the lipid biosynthesis in the halophiles and the thermoacidophiles.[6] Our another interest in these lipids focuses the biochemical significance of the macrocyclic molecular structures. Prerequisite is to develop synthetic methods of the macrocyclic lipids, because it is difficult to obtain the archaebacterial lipids in pure form from natural sources.

In this paper, we describe the first synthesis of a desmethylated analog of the 36-membered archaebacterial cyclic lipid. Although there are relatively few methods available for the synthesis of macrocyclic ring systems,[7] various ring sizes of cycloalkenes up to the 22-membered ring have been prepared in good yield based on the low-valent titanium induced intramolecular dicarbonyl coupling, known as the McMurry coupling.[8] We, therefore, decided to assess the applicability of this coupling reaction for the synthesis of the desmethylated 36-membered cyclic lipid.

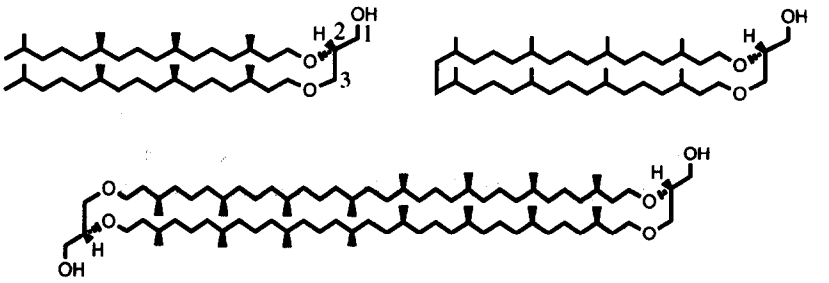
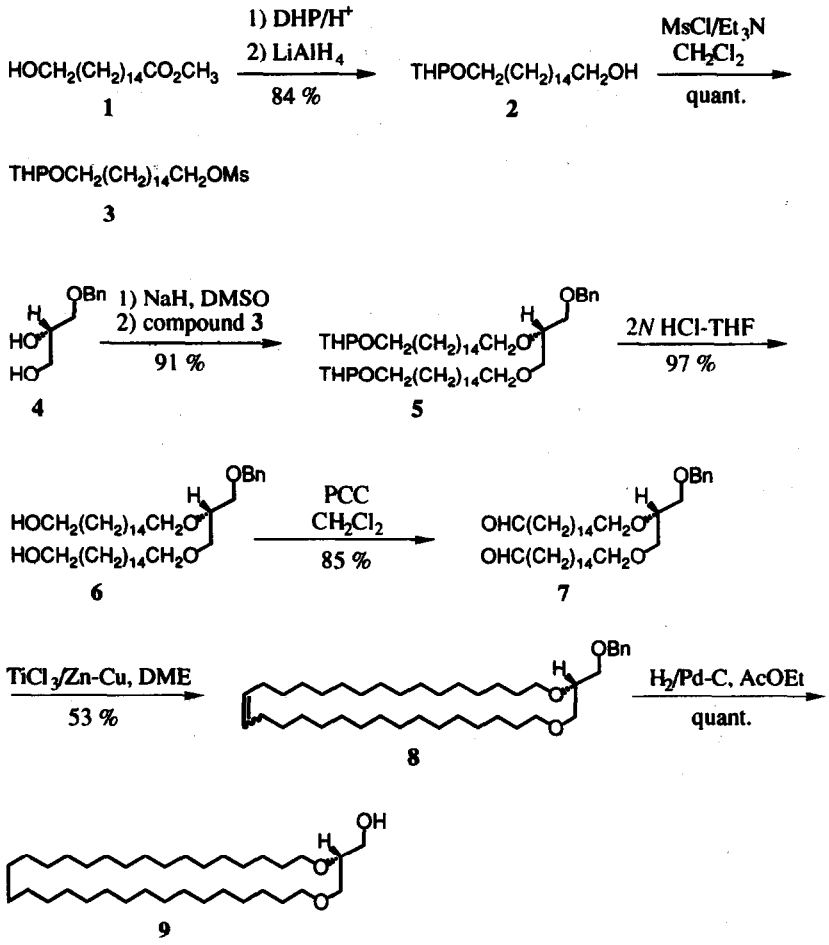


Figure 1. Typical Structures of Archaebacterial Membrane Lipids

Synthesis of the desmethylated 36-membered cyclic lipid by the McMurry coupling required a dialdehyde such as **7**. The preparation of the required dialdehyde **7** was straightforward starting from methyl 16-hydroxyhexadecanoate **1** as outlined in Scheme 1.[9] Thus, the readily available **1** was transformed in 84 % yield to the diol mono-THP ether **2** by treatment with 2,3-dihydropyran in the presence of p-toluenesulfonic acid in THF, followed by $LiAlH_4$ reduction in one pot. Upon treatment with methanesulfonyl chloride-triethylamine in CH_2Cl_2, **2** was quantitatively converted to the corresponding mesylate **3**. The alkoxide generated from 1-*O*-benzyl-*sn*-glycerol **4**[10] with NaH in DMSO was treated with 2.3 equivalent of the mesylate **3** to give the diether derivative **5** in 91 % yield, along with a minute amount of mono ethers. Acid hydrolysis of **5** with 2*N* HCl-THF afforded the diol **6**, which was subsequently oxidized to the desired dialdehyde **7** by reaction with PCC in 82 % overall yield.

The next was the crucial stage where the direct carbon-carbon bond formation to the 36-membered ring using McMurry coupling reaction could be performed. To our surprise, the McMurry coupling leading to the 36-membered ring underwent quite easily. The dialdehyde **7** in dimethoxyethane was added by a motor-driven syringe pump over a period of 100 h to a refluxing slurry of $TiCl_3$/Zn-Cu in dimethoxyethane.[11] After the mixture was stirred under reflux for an additional 14 h, chromatographical work-up led in 53 % yield to the 36-membered cyclic product **8** as a white crystalline solid.[12] The coupling product **8** was a mixture (*ca.* 4:1) of two geometrical isomers of the double bond, as evidenced by the ^{13}C-NMR signals of the olefinic carbons (δ 130.59 for the major isomer, δ 130.01 for the minor isomer) and the allylic carbons (δ 32.27 for the major isomer, δ 26.95 for the minor isomer). The major product was assigned to *trans*-isomer based on the comparison with the standard ^{13}C-NMR chemical shifts of long chain internal alkenes.[13] Deprotection of the benzyl group and the final reduction of the double bond of **8** were quantitatively performed by catalytic hydrogenation over Pd-C to give the desmethylated archaebacterial 36-membered cyclic diether lipid **9**.[12]

In summary, we have developed a highly efficient synthetic method of the 36-membered macrocyclic diether lipid based on the McMurry coupling. It now appears, from this and other studies,[8] that the McMurry coupling is one of the most powerful method for constructing macrocyclic ring systems. Investigation of the properties of the synthesized lipid and the synthesis of natural macrocyclic ether lipids are currently underway.



Scheme 1

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12. **8**: mp 72-73°C (hexane). IR ($CHCl_3$): 670, 725, 1105, 1210, 2855, 2930 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.29 (m), 1.55 (m, 4H), 2.02 (m, 4H), 3.40-3.67 (m, 9H), 4.55 (s, 2H), 5.35 (m, 2H), 7.26-7.35 (m, 5H). ^{13}C-NMR ($CDCl_3$) (major isomer) : δ 26.12, 26.19, 28.48, 29.19, 29.34, 29.45, 29.54, 29.59, 29.65, 29.69, 30.08, 32.27, 70.28, 70.59, 71.46, 71.54, 73.37, 78.07, 127.51, 127.58, 128.31, 130.59, 138.41. EI-MS *m/z* (rel intensity): 626 (M^+, 1.3), 443 (0.7), 517 (0.8), 535 (1.5), 91 (100). **9**: mp 58-59°C (methanol). IR ($CHCl_3$): 665, 720, 1205, 2855, 2935, 3450 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.27 (m), 1.57 (m, 4H), 3.40-3.75 (m, 9H). ^{13}C-NMR ($CDCl_3$): δ 26.00, 26.04, 28.96, 28.98, 29.05, 29.11, 29.20, 29.28, 29.35, 29.40, 29.46, 29.54, 29.69, 30.00, 63.04, 70.40, 71.20, 71.74, 78.46. EI-MS; *m/z* (rel intensity): 538 (M^+, 0.4), 508 (1.9), 489 (1.3), 111 (5.0), 97 (9.2), 83 (21.6), 69 (37.0), 57 (80.0), 43 (100).
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