Synthetic studies of archaeal macrocyclic tetraether lipids—a versatile approach to desmethylated analogues of the 72-membered macrocycle dibiphytanyldiglycerol

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The regioisomeric desmethylated analogues of the archaeal tetraether lipid featuring its 72-membered ring are synthesized with McMurry coupling as a key step.

Archaea (archaebacteria) including extreme halophiles, extreme thermophiles, thermoacidophiles and methanogens grow under the rather extraordinary conditions of high salt, low pH, high temperature, or complete lack of oxygen and significantly differ from other forms of life.[1] These unusual microorganisms have distinctive biochemical features, especially the membrane lipid structures. Archaeal membrane core lipids are unique in that they consist of saturated isoprenoid chains attached to glycerol at the *sn*-2- and -3-positions by ether linkages.[1,2] These ether lipids are completely absent in eubacteria and eukarya which contain predominantly *sn*-1,2-diacylglycerol-derived lipids.

The most striking feature of archaeol lipids is the large macrocyclic ring sizes—as big as 36- and 72-membered (**1** and dibiphytanyldiglycerol **2**).[2,3] The physical nature of the membrane composed of these macrocyclic lipids is quite intriguing. Several modelling studies have so far been reported that investigate the stability and permeability of the archaeal membrane lipids, especially the thermotolerance of extreme thermophiles.[4] We have been interested in the biochemical significance of the macrocyclic molecular structures. A prerequisite is to develop synthetic methods for the macrocyclic lipids on a significant scale.

Here we describe the synthesis of the desmethylated analogues of the regioisomeric 72-membered tetraether lipids **3a** and **3b**. Although Menger *et al.* briefly commented on the synthesis of such a 72-membered lipid by Glaser coupling,[4] no details have been reported. The structure of the natural archaeal 72-membered tetraether lipid has usually been illustrated as **2**. However, since the relative arrangement of the two glycerol units in **2** has not been rigorously determined, it apparently remains a possibility that the natural 72-membered archaeal tetraether lipid is either one of the regioisomers in terms of the glycerol arrangement or a mixture of them, as shown in the model structures **3a** and **3b**, Fig. 1. We therefore undertook a distinctive synthetic route for both regioisomeric models **3a** and **3b**. As to this point, Arigoni *et al.* have recently clearly demonstrated that the 72-membered tetraether lipids from several archaeal organisms are actually a regioisomeric mixture.[5]

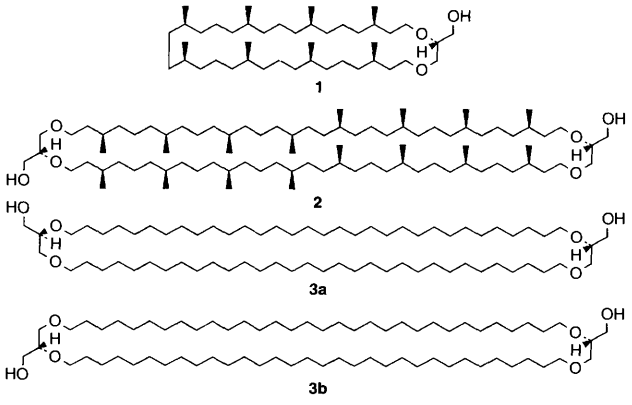


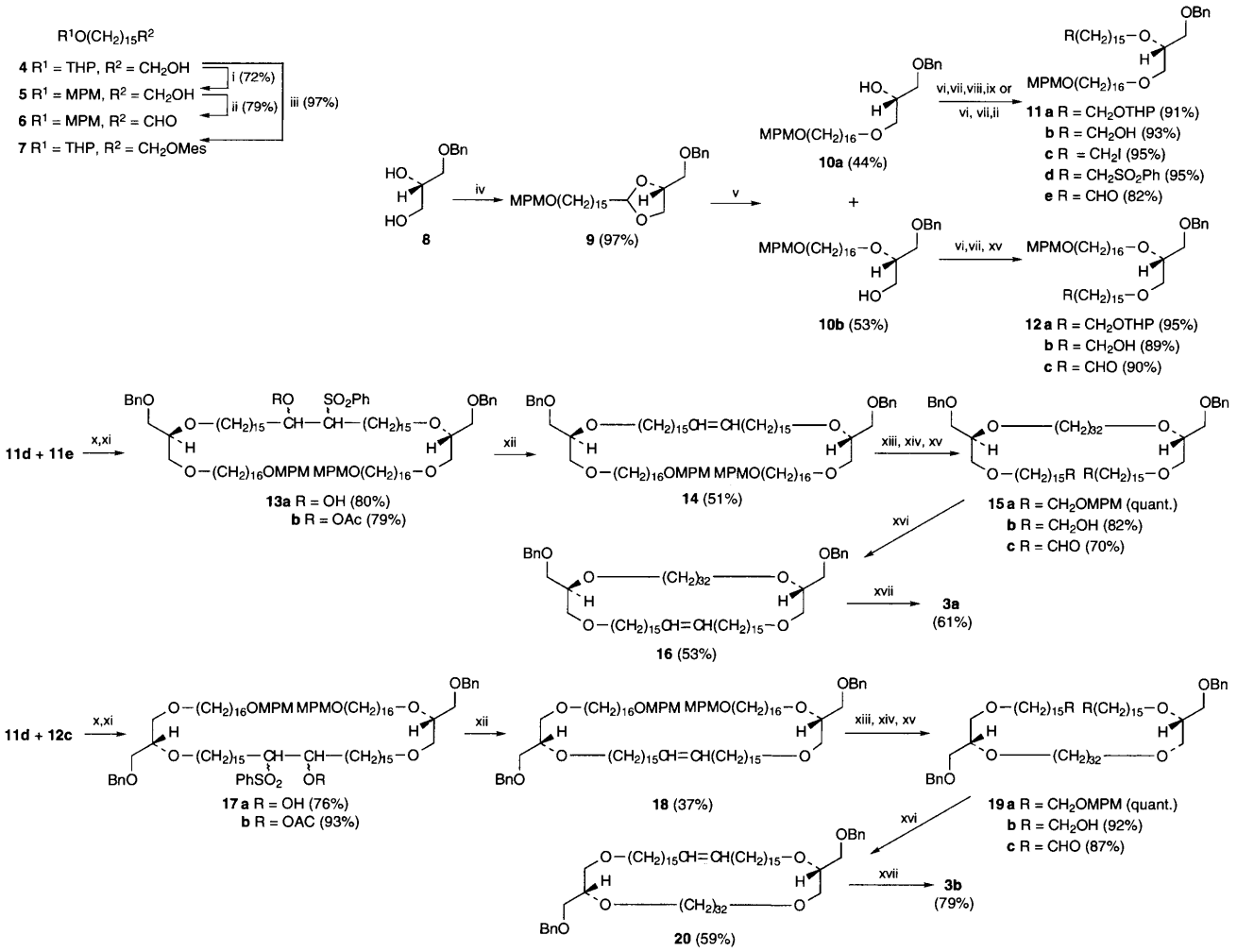
Fig. 1 Typical structures of archaeal membrane lipids and desmethylated analogue of 72-membered tetraether lipids

We recently reported a highly efficient method for macrocyclic ring formation based on McMurry coupling[6] leading towards the 36-membered macrocyclic archaeal membrane lipids.[7] Synthetic studies of the 72-membered ring skeletons based on the same strategy have thus been pursued. The basic strategy was first to prepare suitable half-sized diether precursors and then to stepwise couple (or possibly dimerize) these precursors together.

The desmethylated model **3a** was first synthesized. The McMurry coupling required a suitably protected dialdehyde precursor **15c**. The dialdehyde was prepared from a monoprotected hexadecane-1,16-diol **4**.[7a] After the protective group exchange of **4** shown in Scheme 1, oxidation with catalytic Pr_4NRuO_4 (TPAP) in the presence of *N*-methylmorpholine *N*-oxide (NMO) as reoxidant[8] afforded aldehyde **6**, which was then subjected to acetal formation with 1-*O*-benzyl-*sn*-glycerol in the presence of toluene-*p*-sulfonic acid (PTSA) and $MgSO_4$ to give the acetal derivative **9**. Subsequent reduction with DIBAL-H afforded a separable mixture of **10a** and **10b** (44 and 53% yields respectively).[9] To introduce the second aliphatic chain, the alkoxide derived from **10a** was treated with mesylate **7** to afford 2,3-*O*-disubstituted 1-*O*-benzyl-*sn*-glycerol **11a**, which was subsequently hydrolysed to alcohol **11b**. Reaction of **11b** with I_2–Ph_3P–imidazole gave iodide **11c**, which was further converted into sulfone **11d** by treatment with $PhSO_2Na$. Alternatively, **11b** was oxidized to aldehyde **11e**, which was coupled with an α-sulfonyl carbanion, which had been generated from **11d** with LDA, to give β-hydroxysulfone **13a**. After acetylation of **13a**, the resulting **13b** was treated with Na–Hg to afford olefin **14**.[10] Hydrogenation of the double bond of **14** leading to **15a** and subsequent oxidative deprotection of *p*-methoxyphenylmethyl (MPM) groups with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in CH_2Cl_2–H_2O afforded the diol **15b**. Finally, Swern oxidation of **15b** gave the precursor **15c** of the key McMurry coupling.

The crucial McMurry coupling reaction of dialdehyde **15c** was carried out under high dilution conditions as described previously[7] to successfully yield the 72-membered ring macrocyclic product **16**, mp 97.5–99.8 °C, EI-MS: 1255 (M^+), 1164 (M^+ − Bn), as a mixture (*E*/*Z* = 4:1) in 53% yield.[7a] Deprotection of the benzyl groups and the final reduction of the double bond of **16** was simultaneously performed by catalytic hydrogenation over Pd–C to give the desmethylated analogue **3a**, mp 129.1–129.9 °C, EI-MS: *m*/*z* 1077 (M^+) and 1059 (M^+ − H_2O).

The synthesis of the positional isomer **3b** started from sulfone **11d** and aldehyde **12c** derived from alcohol **10b**, and similar manipulations as described above gave the regioisomeric



Scheme 1 *Reagents and conditions*; i (*a*) MPMCl, NaH, THF–HMPA, (*b*) 4 mol dm^{-3} HCl–THF–MeOH; ii TPAP, NMO, MS4A, CH_2Cl_2–MeCN (9 : 1), room temp.; iii MesCl. Et_3N, CH_2Cl_2; iv **6**, PTSA, $MgSO_4$, CH_2Cl_2; v DIBAL-H, toluene, room temp.; vi NaH, **7**, Me_2SO; vii 2 mol dm^{-3} HCl–THF–MeOH; viii I_2, Ph_3P, imidazole, benzene; ix $PhSO_2Na$, DMF, room temp.; x LDA, THF, −20 °C; xi Ac_2O, DMAP, py; xii 5% Na–Hg, NaH_2PO_4, THF–MeOH, −20 °C–room temp.; xiii H_2/5% Pd–C, AcOEt; xiv DDQ, CH_2Cl_2–H_2O (18 : 1), room temp.; xv Swern oxid; xvi $TiCl_3$, Zn–Cu, DME, reflux; xvii H_2/10% Pd–C, EtOH, reflux. THP = tetrahydropyran-2-yl, MS4A = molecular sieves 4 Å.

dialdehyde **19c**. A McMurry coupling of the dialdehyde **19c** also underwent smoothly to afford the cyclized product **20** in 59% yield, mp 99.5–101.8 °C, EI-MS: *m/z* 1255 (M^+) and 1164 (M^+ − Bn), as a mixture of geometrical isomers in a similar ratio. Hydrogenation gave the desmethylated analogue **3b**, mp 131.5–133.3 °C, EI-MS: *m/z* 1077 (M^+) and 1059 (M^+ − H_2O).

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