The First Synthesis of an Archaebacterial 36-Membered Macrocyclic Diether Lipid

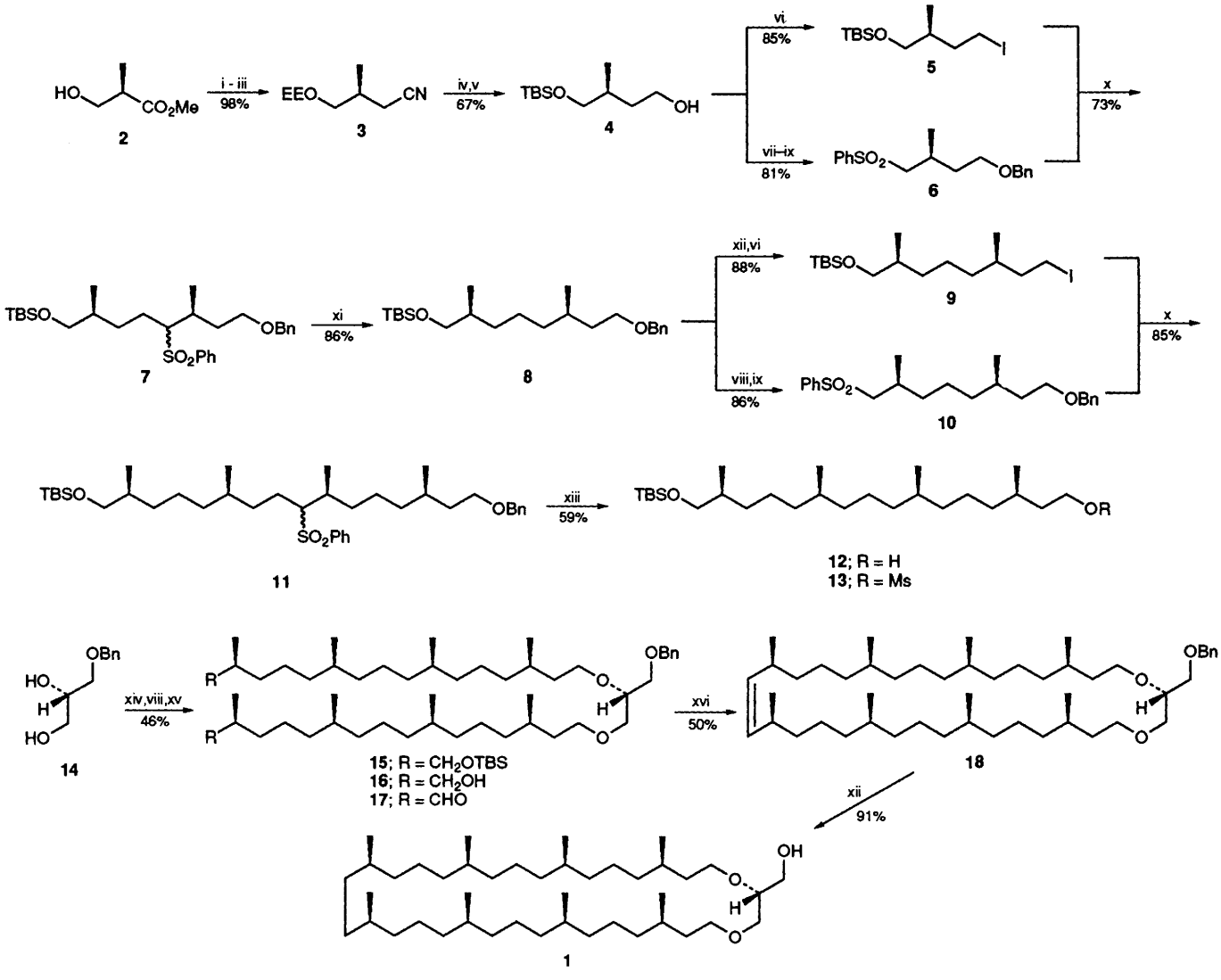
Tadashi Eguchi, Takumi Terachi and Katsumi Kakinuma*

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

The archaebacterial macrocyclic diether lipid featuring a 36-membered ring is synthesized by the McMurry coupling as a key step.

Archaebacterial membrane lipids are structurally unique in that the glycerol core is linked to isoprenoid chains with ethereal bonding, compared to the ester linkage with fatty acids found in eubacterial and eukaryotic membrane lipids.[1] These unusual lipids have attracted attention in connection with their physicochemical properties. Several modelling and synthetic studies have been reported in order to investigate the stability, fluidity and permeability of the archaebacterial membrane lipids.[2] The most striking feature of the archaebacterial ether lipid is found in the macrocyclic ring structures. Recently, we reported a highly efficient method for macrocyclic ring formation based on the McMurry coupling directed toward the macrocyclic archaebacterial membrane lipids.[3] From the initial stage, we have envisaged that the McMurry coupling approach can be applied to both desmethylated and methylated (naturally occurred) lipids.† Our continuing efforts have now yielded the first total synthesis of the archaebacterial 36-membered macrocyclic diether lipid isolated from the extremely thermophilic *Methanococcus jannaschii*.[1b]

Although the stereochemistry of the natural lipid from *M. jannaschii* has not been rigorously determined, we presumed the natural lipid as **1** for the following reasons. First, as to the stereochemistry of the glycerol portion, it seemed most probable that the hydrophobic alkyl chains link to *sn*-2- and 3-positions of glycerol, because all of the archaebacterial lipids



Scheme 1 *Reagents and conditions*: i, (1) ethyl vinyl ether, PPTS, THF, (2) $LiAlH_4$; ii, TsCl-py; iii, NaCN, Me_2SO; iv, (1) 2 mol dm^{-3} HCl–THF. (2) TBSCl, imidazole, DMF; v, (1) DIBAH, (2) DIBAH; vi, I_2, Ph_3P, imidazole, benzene; vii, $BnOC(=NH)CCl_3$, TfOH, diethyl ether; viii, 2 mol dm^{-3} HCl–THF; ix, (1) MsCl-py, (2) PhSH, K_2CO_3, DMF, (3) mCPBA, CH_2Cl_2; x, (1) Bu^nLi, THF–HMPA, −78 °C, (2) compound **5** (or **9**), −25 °C then room temp.; xi, 5% Na(Hg), MeOH; xii, H_2/10% Pd–C, AcOEt; xiii, (1) Li–$EtNH_2$–THF, −78% °C, (2) MsCl–Et_3N, CH_2Cl_2; xiv, (1) NaH, Me_2SO, (2) compound **13**; xv, PCC, AcONa, MS 3Å, CH_2Cl_2; xvi, $TiCl_3$–Zn–Cu, DME; PPTS = pyridinium toluene-*p*-sulfonate, DMF = dimethylformamide, DIBAH = diisobutylaluminium hydride, HMPA = hexamethylphosphoramide, DME = 1,2-dimethoxyethane

reported to date have the same configuration.[1] Secondly, since the chemical metabolism in microorganisms may well be programmed according to evolutionary or phylogenetic relations, the biphytane part of the *M. jannaschii* lipid seems likely to have similar stereochemistries to the related phytane and biphytane structures produced by other methanogenic and thermophilic archaebacteria such as *Methanobacterium thermoautotrophicum, Thermoplasma* and *Sulfolobus*. In this regard, Heathcock and coworkers were successful to show the absolute stereochemistry of the biphytane of the archaebacterial tetraether lipid by the synthetic approach.[4] We thus decided to tackle the synthesis of **1**.

The key strategy employed for the synthesis of **1** has been the McMurry coupling reaction to form a macrocycle. As shown in Scheme 1, the targeted McMurry coupling necessitated a crucial dialdehyde such as **17**. Thus, our initial target was a C_{20} intermediate **12** possessing four chiral centres. Chiral C_5 alcohol **4** was readily prepared from the commercially available methyl (*R*)-3-hydroxy-2-methylpropionate **2** by similar manipulations as reported previously.[5] Reaction of **4** with I_2–Ph_3P–imidazole gave iodide **5**. Compound **4** was really a bidirectional precursor and transformations of **4** comprising of protection of an alcohol with a benzyl group, acid hydrolysis, mesylation, displacement of the mesylate with a thiophenyl group and oxidation with MCPBA afforded C_5 sulfone **6** in good yield. Straightforward alkylation of **6** with **5** gave the coupling product **7**, which was then reduced by Na(Hg) to afford the bifunctional C_{10} synthon **8**.

Similar manipulations of compound **8** as described above for the conversion of **4** to **8** would be well anticipated as a route to a C_{20} compound, and it was the case. Thus, compound **8** was converted into both iodide **9** and sulfone **10**, respectively. The coupling reaction of **10** with **9** was readily carried out to give sulfone **11**, which was subsequently treated with lithium in ethylamine–THF to obtain C_{20} alcohol **12**.

Having the C_{20} synthon in hand, a recently described approach was undertaken to provide the archaebacterial macrocyclic diether lipid. Thus, mesylate **13**, prepared from the alcohol **12**, was treated with a dialkoxide derived from 1-*O*-benzyl-*sn*-glycerol with NaH in Me_2SO to afford the diether derivative **15**. Acid hydrolysis of **15** afforded diol **16**, which was subsequently oxidized to the desired dialdehyde **17** by reaction with PCC (PCC = pyridinium chlorochromate). A McMurry coupling reaction of dialdehyde **17** under the standard high dilution conditions yielded the macrocyclic product **18** as a single compound in 50% yield.[6] The stereochemistry of the resulting double bond was not rigorously determined, but was tentatively assigned to be *E* according to the previous observation that such a macrocyclization by the McMurry coupling reaction predominantly afforded the *E*-double bond.[6] Deprotection of the benzyl group and the final reduction of the double bond of **18** were performed simultaneously by catalytic hydrogenation over Pd–C to give the macrocyclic diether lipid **1**, EI-MS: *m/z* 650 (M^+), high-resolution MS 650.6607 (calcd for $C_{43}H_{86}O_3$, 650.6581), $[\alpha]_D$ +8.1 (*c*. 0.98, $CHCl_3$). Unfortunately, the synthetic product was unable to be compared directly with the natural lipid, because the natural specimen is no longer available. However, the spectral properties were in good agreement with those reported.[1b] The structure of the synthetic **1** was confirmed by spectrometric analysis as well as comparison with natural 2,3-di-*O*-phytanylglycerol lipid isolated from *Halobacterium halobium*.[7]

In summary, we have achieved the synthesis of the archaebacterial 36-membered diether lipid possessing eight chiral centres in the biphytane alkyl chain by the McMurry coupling as a key step. Properties of the synthesized macrocyclic ether lipids are currently under study.

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, and by a grant from the Ciba-Geigy Foundation.

Received, 31st August 1993; Com. 3/05211G

Footnote

† During the preparation of this manuscript, we noted that Menger *et al.* have synthesized macrocyclic ethereal lipids by way of the Glaser reaction (ref. 2*c*), but the Glaser reaction seems to be impossible to apply to the synthesis of methylated natural lipids.

References

1 (*a*) S. C. Kushwaha, M. Kates, G. D. Sprott, and I. C. P. Smith, *Biochim. Biophys. Acta*, 1981, **664**, 156; (*b*) P. B. Comita, R. B. Gagosian, H. Pang and C. E. Costello, *J. Biol. Chem.*, 1984, **254**, 15234.

2 (*a*) D. H. Thompson, F. W. Kim, R. Humphry-Baker, J. J. Wheeler, J.-M. Khim and S. B. Rananavare, *J. Am. Chem. Soc.*, 1992, **114**, 9035; (*b*) R. A. Moss and J.-M. Li, *J. Am. Chem. Soc.*, 1992, **114**, 9227; (*c*) F. M. Menger, X. Y. Chen, S. Brocchini, H. P. Hopkins and D. Hamilton, *J. Am. Chem. Soc.*, 1993, **115**, 6600.

3 T. Eguchi, T. Terachi and K. Kakinuma, *Tetrahedron Lett.*, 1993, **34**, 2175.

4 C. H. Heathcock, B. L. Finkelstein, T. Aoki and C. D. Poulter, *Science*, 1985, **229**, 862; C. H. Heathcock, and P. A. Radel, *J. Org. Chem.*, 1986, **51**, 4323; C. H. Heathcock, B. L. Finkelstein, E. T. Jarvi, P. A. Radel and C. R. Hadley, *J. Org. Chem.*, 1988, **53**, 1922.

5 K. Mori, *Tetrahedron*, 1983, **39**, 3107; K. Mori and T. Ebata, *Tetrahedron*, 1986, **39**, 4413.

6 K. E. McMurry, *Chem. Rev.*, 1989, **89**, 1513.

7 K. Kakinuma, M. Yamagishi, Y. Fujimoto, N. Ikekawa and T. Oshima, *J. Am. Chem. Soc.*, 1990, **112**, 2740.