Convergent Synthesis of Antiparallel Cyclobolaphiles Having Two Diacetylenes: Mimetics of Membrane Components That are Found in Archaea

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Abstract: Chiral 48-membered antiparallel cyclobolaphiles and their diastereomer having two diacetylenes were convergently synthesized utilizing both cross-coupling method (CuI, pyrrolidine) and Glaser intramolecular cyclization, starting from commercially available D- and L-1,2-*O*-isopropylidene-*sn*-glycerol as chiral sources.

Key words: caldarchaeol, diacetylene, antiparallel cyclobolaphile, convergent synthesis, mimetics

The recent finding that several thermostable archaeal membranes contain parallel and antiparallel caldarchaeol[1] with a molar ratio of ca 1:1 is of considerable interest (Figure 1).[2]

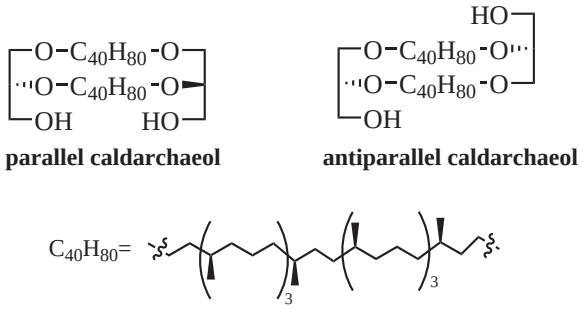

Figure 1 Backbones of typical parallel and antiparallel caldarchaeol

Such naturally-occurring membrane system stimulates us to explore the feasibility of adopting a 1:1 mixture of the parallel-antiparallel caldarchaeol analogues as an ideal composition when we turn our attention to the preparation of thermostable self-assembled lipid nanostructures.[3] At present, to our knowledge, there is only one report on the synthesis of totally artificial antiparallel analogue that contains saturated long alkyl chains,[4] although several synthetic schemes of parallel caldarchaeol analogues have previously been established.[5] Moreover, possible factors contributing to the stability in the bacterial membrane include stereospecific interactions between caldarchaeols due to inherent chirality at *syn*-2 position of their glycerol moieties. Thus, understanding how stereochemistry has an effect on molecular packing has theoretical implications.[6] With these backgrounds in mind, we have started a program for synthesizing three stereoisomers of antiparallel caldarchaeol analogues (2*R*,27*R*)-**1**, (2*S*,27*S*)-**1** and (2*R*,27*S*)-**1** that contain two diacetylene units within a long alkyl chain and phosphatidylcholine as a polar head group (Figure 2). We term such analogues antiparallel cyclobolaphiles.[7] Our construction of the thermostable cyclobolaphiles partyl hinges on the use of diacetylene units besides macrocyclic structure.[8] The expected effects of diacetylenes were 2-fold: (i) the stiffing effect of diacetylenes on alkyl chains is expected to reduce the mobility of the macrocycles to raise gel-to-liquid phase transition temperature compared to lipids having no diacetylenes, and (ii) diacetylene units have a potential of polymerization on UV-irradiation to form polymerized membranes.

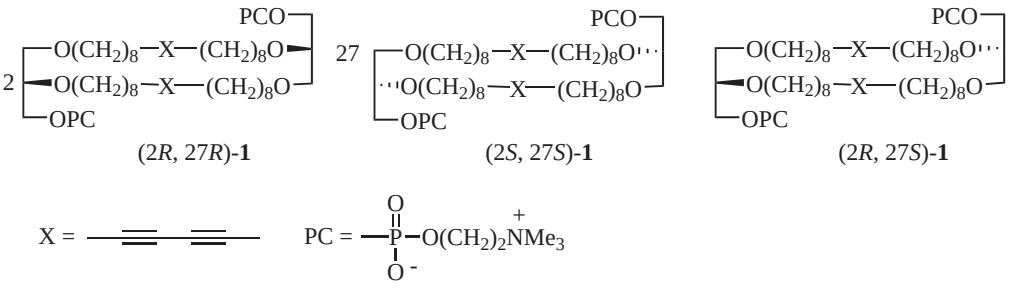

Figure 2 Structures of antiparallel cyclobolaphiles (2*R*,27*R*)-**1**, (2*S*,27*S*)-**1**, and (2*R*,27*S*)-**1**

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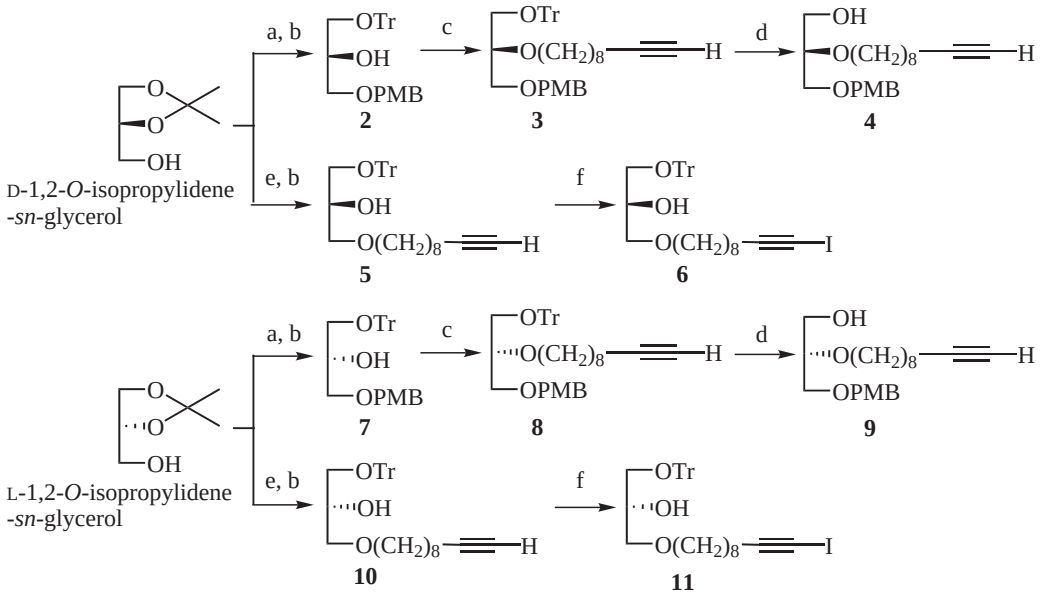


Scheme 1 *Reagents and conditions*: (a) (i) KOH, PMBCl, DMSO, r.t., 24 h; (ii) *p*-TsOH, MeOH, r.t., 36 h, 78–80%; (b) TrCl, DMAP, pyridine, 80 °C, 13 h, 80–89%; (c) $MsO(CH_2)_8CCH$, NaH, TBAI, DMF, r.t., 19 h, 92–99%; (d) *p*-TsOH, $CHCl_3$/MeOH (2:1, v/v), r.t., 4 h, 89–90%; (e) (i) $MsO(CH_2)_8CCH$, KOH, DMSO, r.t., 20 h; (ii) *p*-TsOH, MeOH, r.t., 17 h, 92%; (f) NIS, $AgNO_3$, acetone, 0 °C, 4 h, 89–99%. PMBCl = *p*-methoxybenzyl chloride, *p*-TsOH = *p*-toluenesulfonic acid, DMAP = 4-(dimethylamino)pyridine, TBAI = tetrabutylammonium iodide, NIS = *N*-iodosuccinimide, TrCl = trityl chloride

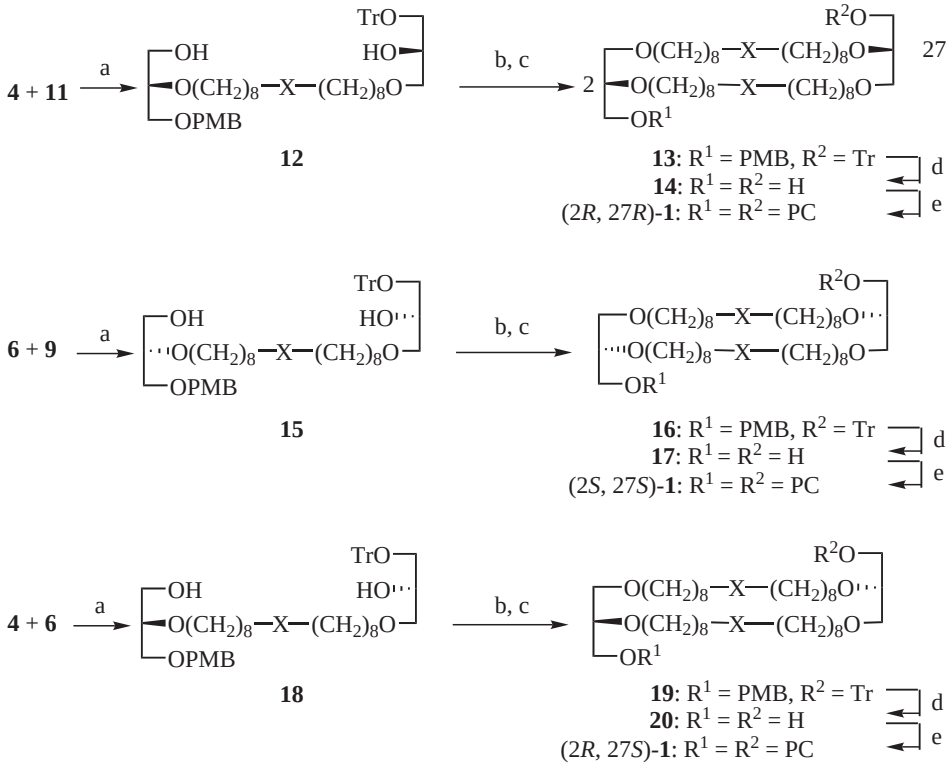
Here we report the accomplishment of the synthesis of the diacetylene-containing antiparallel cyclobolaphiles by firstly adopting cross-coupling method of alkynes with 1-iodoalkynes for the construction of macrocyclic structure.[9]

Chiral building blocks **4**, **6**, **9** and **11** were synthesized via the reaction sequence shown in Scheme 1. In brief, detritylation (*p*-TsOH) of terminal acetylene **3** that was prepared according to the method described in the literature,[10–12] afforded the desired alcohol **4** in 90% yield. Next, iodination (*N*-iodosuccinimide, $AgNO_3$) of **5**, prepared by use of procedures described in the literature,[4] provided the desired iodide **6** in 89% yield. Finally, the synthesis of **9** and **11** followed the same strategy that was employed for the preparation of **4** and **6**, respectively.

(2*R*,27*R*)-**1**, (2*S*,27*S*)-**1** and (2*R*,27*S*)-**1** were synthesized as shown in Scheme 2. Terminal acetylene **4** was coupled with iodide **11** by Alami procedure employing CuI-pyrrolidine,[13] to furnish diacetylene **12**, $[\alpha]_D^{26}$ +6.7 (*c* 0.45, $CHCl_3$), in 79% yield. By use of the same procedure for the preparation of **12**, coupling of **9** and **4** with **6** provided diacetylenes **15**, $[\alpha]_D^{26}$ –6.7 (*c* 0.48, $CHCl_3$), and **18**, $[\alpha]_D^{26}$ +2.5 (*c* 0.57, $CHCl_3$), in 64 and 73% yields, respectively. Subsequent alkylation of **12**, **15** and **18** with $MsO(CH_2)_8CCH$, followed by intramolecular cyclization by applying high dilution Glaser protocol,[4,14] afforded macrocyclic compounds **13**, $[\alpha]_D^{23}$ +6.1 (*c* 3.0, $CHCl_3$), **16**, $[\alpha]_D^{26}$ –6.9 (*c* 2.0, $CHCl_3$), and **19**, $[\alpha]_D^{28}$ –4.1 (*c* 1.7, $CHCl_3$), in 26%, 27% and 27% overall yields for the two steps, respectively. Detritylation (*p*-TsOH), followed by debenzylation (DDQ)[15] afforded diols **14**, $[\alpha]_D^{25}$ –9.0 (*c* 0.61, $CHCl_3$), **17**, $[\alpha]_D^{25}$ +7.8 (*c* 0.85, $CHCl_3$), and **20**, $[\alpha]_D^{28}$ 0.0 (*c* 0.50, $CHCl_3$), in 50%, 69% and 55% overall yields for two steps, respectively. Finally, Phosphorylation, followed by replacement of bromine with trimethylamine yielded the desired products (2*R*,27*R*)-**1**, (2*S*,27*S*)-**1**, and (2*R*,27*S*)-**1** in 67%, 60% and 59% yields for two steps, respectively.[16,17] The structures of the cyclobolaphiles were confirmed on the basis of ^1H, ^{13}C and ^{31}P NMR spectra, mass spectra and elemental analyses.[18]

To examine thermal stability of the cyclobolaphiles, the thermotropic phase behavior of (2*S*,27*S*)-**1** was examined by high-sensitive differential scanning calorimetry (*hs*-DSC) (data not shown).[19] This compound exhibited a substantially broadened endotherm at 65 °C with a peak width of ca. 30 °C (four scans). Such breadth of the endotherm is an intrinsic property of cyclobolaphiles, i.e., symmetric cyclobolaphile does not allow the lipid to pack tightly in the curved vesicle membrane, resulting in the lack of cooperative melting process.[20] Thus, comparison of T_m value for (2*S*,27*S*)-**1** with 'untethered' 1,2-dialkylphosphatidylcholine suggests that both cyclic structure and two diacetylene units contribute to the raise of thermostability.[21]

In conclusion, we have developed a convergent synthetic route for cyclobolaphiles (2*R*,27*R*)-**1**, (2*S*,27*S*)-**1** and (2*R*,27*S*)-**1**. This strategy also could be wide applicable to the stereoselective construction of antiparallel cyclobolaphiles containing the same functional group at each end of a macrocyclic segment. Work is currently in progress to develop their thermostable self-assembled lipid nanostructures and will be reported elsewhere.



Scheme 2 *Reagents and conditions*: (a) CuI, pyrrolidine, –20 °C, 10 min, 64–79%; (b) $MsO(CH_2)_8CCH$, NaH, DMSO, r.t., 14 h, 57–64%; (c) CuCl, TMEDA, O_2, *p*-xylene, 130 °C, 42–45%; (d) (i) *p*-TsOH, $CHCl_3$/MeOH (2:1, v/v), r.t., 4 h; (ii) DDQ, CH_2Cl_2/phosphate buffer solution (pH 7.2) (18:1, v/v), 0 °C, 1.5 h, 50–69%; (e) (i) 2-bromoethyl dichlorophosphate, benzene, Et_3N, r.t., 12 h, and then H_2O, r.t., 9 h; (ii) Me_3N (aq), $CHCl_3$/*i*-PrOH/MeCN (3:5:5, v/v/v), 60 °C, 15 h, 59–67%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine

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(6) Our working hypothesis has been that each stereochemical combination of parallel-antiparallel caldarchaeol analogues provides a nanostructure with various degrees of thermostability, and that some optimal combinations give a considerably thermostable nanostructure that is robuster than the natural one. Our ultimate goal is to find such optimal combinations. Note that the applicability of Kakinuma’s strategy to the construction of all stereoisomers and diacetylene-containing derivatives (see in text) remains unclear, although they did not refer to such possibility (see ref. 4a and 5a). As a first step toward this goal, therefore, alternative strategy that is applicable to the synthesis of all stereoisomers is required.
(7) Amphiphilic molecules that contain a polar head group at the end of a hydrophobic segment have been termed; ‘bolaamphiphiles’ (Fuhrhop, J.-H.; Mathiewu, J. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 100) or ‘bolaphile’ (Jayasuriya, N.; Bosak, S.; Regen, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5844). While amphiphiles having a macrocyclic ring as a hydrophobic segment have been termed ‘macrocyclic bolaamphiphiles’ (see Ref. 5b), we prefer to adopt the abbreviated and more readily pronounceable term, ‘cyclobolaphile’.
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(14) A solution of the precursor of **13** (0.10 g, 0.10 mmol) in acetone (5 mL) was added to a stirred solution of CuCl (0.20 g, 2.1 mmol) and TMEDA (310 μL, 2.1 mmol) in *p*-xylene (36 mL) under oxygen over 7 h at 130 °C.

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(17) (2*R*, 27*R*)-**1**, (2*S*, 27*S*)-**1**, and (2*R*, 27S)-**1** were successfully purified by flash chromatography (SiO_2, $CHCl_3$/MeOH/H_2O, 65:25:4, v/v/v).

(18) All new compounds gave satisfactory analytical and spectral data. Selected physical data are as follows: **14**: Stage pale yellow oil, R_f = 0.13 [hexane/ethyl acetate (2:1, v/v)], $[\alpha]_D^{25}$ –9.0 (*c* 0.61, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.70–3.38 (m, 18 H), 2.23 (t, *J* = 6.9 Hz, 8 H), 2.17 (brs, 2 H), 1.60–1.43 (m, 16 H), 1.36–1.23 (m, 32 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 78.42, 72.40, 71.65, 71.11, 70.33, 65.32, 63.00, 29.97, 29.50, 29.30, 29.15, 28.98, 28.63, 28.22, 25.97, 19.16 ppm. LRMS (FAB): *m/z* = 725 [(M + H)$^+$]. Anal. Calcd for $C_{46}H_{76}O_6$: C, 76.20; H, 10.56%. Found: C, 75.91; H, 10.41%. **17**: $[\alpha]_D^{25}$ +7.8 (*c* 0.85, $CHCl_3$). **20**: $[\alpha]_D^{28}$ 0.0 (*c* 0.50, $CHCl_3$). The spectral data of **17** and **20** were identical with those of **14** except the optical rotations. (2*R*, 27*R*)-**1**: Stage pale yellow solid, R_f = 0.10 [$CHCl_3$/MeOH/H_2O (65:25:4, v/v/v)], $[\alpha]_D^{25}$ +4.2 (*c* 0.70, MeOH). ^{1}H NMR [500 MHz, $CDCl_3$/CD_3OD (97:3, v/v)]: δ = 4.21 (brs, 4 H), 3.83 (brs, 4 H), 3.60 (brs, 4 H), 3.56–3.51 (m, 8 H), 3.43–3.33 (m, 6 H), 3.19 (s, 18 H), 2.19 (t, *J* = 6.7 Hz, 8 H), 1.47–1.42 (m, 16 H), 1.33–1.15 (m, 32 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 79.50, 77.98, 72.50, 72.03, 71.43, 67.47, 66.60, 66.23, 60.38, 54.71, 31.13, 30.79, 30.62, 30.41, 30.26, 29.96, 29.86, 29.59, 29.52, 27.29, 19.82 ppm. ^{31}P NMR [200 MHz, $CDCl_3$/CD_3OD (99:1, v/v)]: δ = –0.69 (s)ppm. LRMS (FAB): *m/z* = 1054 [M$^+$], 995 [(M – $(Me)_3N)^+$]. Anal. Calcd for $C_{56}H_{100}N_2O_{12}P_2 \cdot 2\,H_2O$: C, 61.63; H, 9.60; N, 2.57%. Found: C, 61.62; H, 9.50; N, 2.42%. (2*S*,27*S*)-**1**: $[\alpha]_D^{27}$ –4.9 (*c* 0.49, MeOH). (2*R*,27*S*)-**1**: $[\alpha]_D^{28}$ 0.0 (*c* 0.70, MeOH). The spectral data of (2*R*,27*S*)-**1** and (2*S*,27*S*)-**1** were identical with those of (2*R*,27*R*)-**1** except the optical rotations.

(19) Multilamellar suspension for *hs*-DSC measurement was prepared as follows. First, 1 mL of methanol solution of (2*S*, 27*S*)-**1** (4.7 mM) was transferred to a test tube. The methanol was then evaporated under a stream of nitrogen, thereby leaving the lipid as a thin film on the walls of the test tube. The remaining solvent was removed by subjecting the lipid film to high vacuum for at least 2 h. 3 mL of milli-Q water was added and the mixture was sonicated for 1 h at 97±2 °C. Calorimetric measurement was performed with a MC-2 differential scanning calorimeter purchased from Microcal, Inc.

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(21) Menger, F. M.; Chen, X. F.; Brocchini, S.; Hopkins, H. P.; Hamilton, D. *J. Am. Chem. Soc.* **1993**, *115*, 6600. The 'untethered' lipids are also archaeal membrane lipid analogues, and include linear saturated long alkyl chains that are connected to the glycerol backbone by means of ether linkage. If one may take into account the "dimer-like structure" of the cyclobolaphiles, it seems reasonable to assume that (2*S*,27*S*)-**1** is comparable to the "untethered" lipid with chains of 10 carbons. Menger et al. have reported the T_m values for the 'untethered' lipids with chains of only 14–20 carbons, ranging from 26.9 to 66.5 °C in this report. Thus, we currently consider that the introduction of cyclic structure and diacetylene units leads to higher thermostability, although exact comparison between the cyclobolaphile and 10-carbon "untethered" lipid remains to be made.