# Efficient Synthesis of Parallel Cyclobolaphiles Having Two Diacetylenes: Mimetics of Archaeal Membrane Lipids

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**Abstract:** Chiral 48-membered parallel cyclobolaphiles and their diastereomer having two diacetylenes were efficiently synthesized by utilizing both the selective deprotection and the cross-coupling method of two distinct acetylenic compounds.

**Key words:** archaeal lipid, diacetylene, chirality, parallel cyclobolaphile, mimetics

Unusual resistance to harsh environmental conditions displayed by the archaea has received much attention in the synthesis and properties of macrocyclic and bola-amphiphilic membrane lipids similar to those found in the bacterial membranes.[1] Many groups have focused on physicochemical properties of their membrane, such as fluidity, permeability and stability.[2] While interest in their lipids within our group has centered on a new challenge aiming at making self-assembled nanostructures that are composed of the lipids, since the nanostructures, especially tubules, would have much promise as advanced materials.[3] Based on the report that both chirality and diacetylene are essential to tubule formation,[3a] we hypothesized that the formation of tubules might be accomplished via incorporation of two diacetylenes into a chiral archaeal lipid analogue and subsequent self-assembly process. With the hypothesis in mind, we have designed novel cyclobolaphiles[4] having two diacetylenes [(2*R*,27*R*)-**1**, (2*S*,27*S*)-**1** and (2*R*,27*S*)-**1**], mimics of parallel caldarchaeol[5] (Figure). Here, we report the accomplishment of the stereoselective construction of such parallel cyclobolaphiles by firstly adopting both the selective deprotection and the acetylenic cross-coupling method for the construction of macrocyclic structure.[6]

Scheme 1 outlines the synthetic approach to prepare (2*R*,27*R*)-**1** and (2*S*,27*S*)-**1**. In brief, alcohol (–)-**2** was obtained from D-1,2-*O*-isopropylidene-*sn*-glycerol according to the method described in the literature.[7] Alkylation of the resultant alcohol (–)-**2** with $MsO(CH_2)_8CCH$[8] gave terminal acetylene (–)-**3** in quantitative yield.[9] Subsequent subjection of (–)-**3** to a classical Glaser acetylene coupling method afforded diacetylene **4** in 93% yield. The synthetic strategy that we have used for the stereoselective construction of the cyclobolaphiles features selective removal of the protective groups of **4** without reduction of diacetylene unit. Removal of the trityl groups was accomplished using *p*-toluenesulfonic acid (*p*-TsOH) to give diol **5** in 86% yield, while selective deprotection of the *p*-methoxybenzyl (PMB) groups with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded the desired alcohol **6** in 88% yield.[10] Alkylation of **5** and **6** with $MsO(CH_2)_8CCH$ gave alkylated products, which were the precursors for intramolecular cyclization, in 93 and 58% yields, respectively. A significant task which remained was the construction of macrocyclic structure. Our first attempt employed high-dilution Glaser acetylene coupling (1 mM solution in acetone, 60 °C), resulting in failure. In the modified procedure, a solution of the precursor in acetone was added to a stirred solution of CuCl–TMEDA complex in *p*-xylene over 7 hours at 130 °C. The procedure successfully led to the formation of **7** and **9** in 43 and 46% yields, respectively. Thus a critical point in the present synthesis has been passed. Debenzylation of **7**

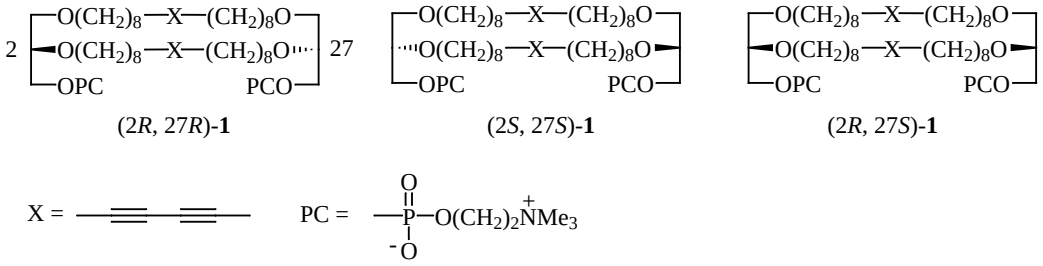


**Figure** Structures of parallel cyclobolaphiles (2*R*,27*R*)-**1**, (2*S*,27*S*)-**1**, and (2*R*,27*S*)-**1**.

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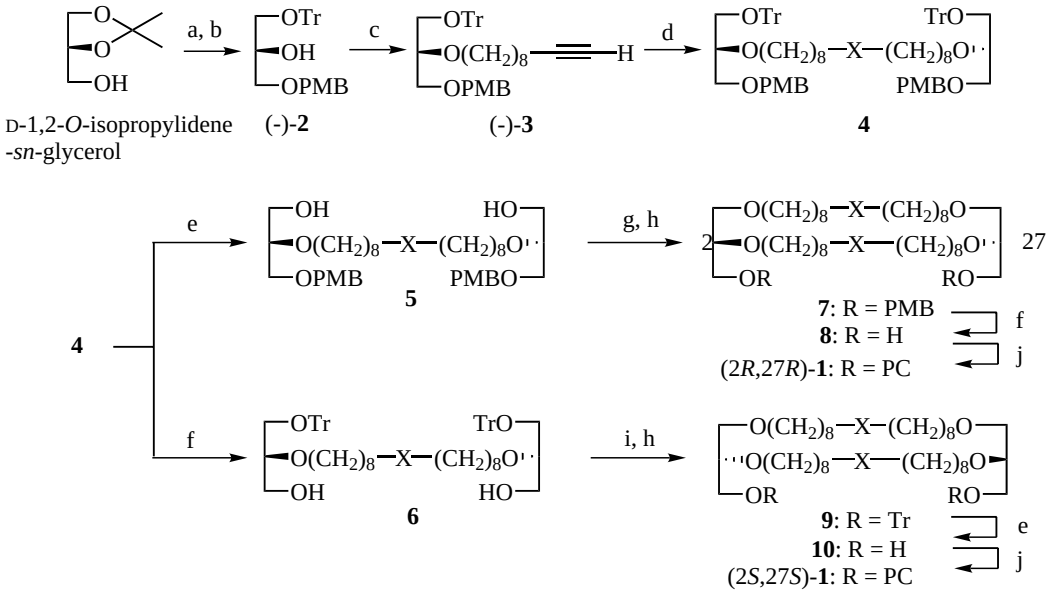
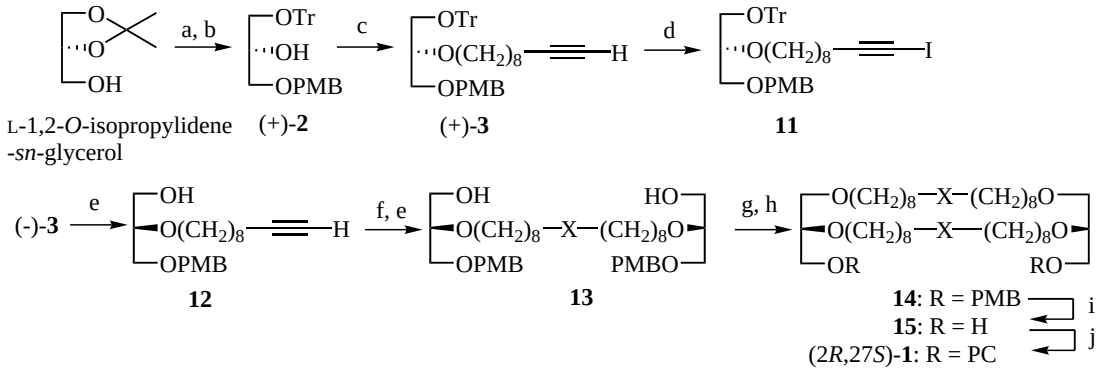
with DDQ gave diol **8**, $[\alpha]_D^{28}$ –9.80 (*c* 0.60, $CHCl_3$), in 64% yield, and detritylation of **9** with *p*-TsOH gave diol **10**, $[\alpha]_D^{28}$ +9.67 (*c* 0.30, $CHCl_3$), in 77% yield. As expected, the spectral data of **8** were identical with those of **10**, and their specific rotation values were very close in absolute values but with opposite sign.[11] Finally, phosphorylation of **8** and **10**, followed by exchange of the bromine with trimethylamine, afforded (2*R*,27*R*)-**1** and (2*S*,27*S*)-**1** in 62 and 76% yields, respectively.[12] The structures of (2*R*,27*R*)-**1** and (2*S*,27*S*)-**1** were confirmed on the basis of $^1H$, $^{13}C$ and $^{31}P$ NMR spectra, mass spectra and elemental analyses.[11]

Diastereomer (2*R*,27*S*)-**1** was synthesized as shown in Scheme 2. Iodide **11** was obtained, in 91% yield, by iodination of (+)-**3** that was prepared from L-1,2-*O*-isopropylidene-*sn*-glycerol according to the same synthetic method as (–)-**3**, while terminal acetylene **12** was obtained by detritylation of (–)-**3** in 90% yield. Cross-coupling of **12** with **11**, followed by detritylation, gave diol **13** in 69% overall yield for the two steps.[13] The resultant diol **13** was converted to (2*R*,27*S*)-**1** in four steps according to the same synthetic method as (2*R*,27*R*)-**1**. The structure of (2*R*,27*S*)-**1** was confirmed on the basis of $^1H$, $^{13}C$ and $^{31}P$ NMR spectra, mass spectra and elemental analyses by comparing with the spectral data of (2*R*,27*R*)-**1**.[11]




**Scheme 1** *Reagents and conditions*: (a) (i) KOH, PMBCl, DMSO, r.t., 24 h; (ii) *p*-TsOH, MeOH, r.t., 36 h, 80%; (b) TrCl, DMAP, pyridine, 80 °C, 13 h, 80%; (c) $MsO(CH_2)_8CCH$, NaH, TBAI, DMF, r.t., 19 h, 99%; (d) CuCl, $O_2$, acetone, TMEDA, 60 °C, 15 h, 93%; (e) *p*-TsOH, $CHCl_3$/MeOH (2:1, v/v), r.t., 4 h, 77–86%; (f) DDQ, $CH_2Cl_2$/phosphate buffer solution (pH 7.2) (18:1, v/v), 0 °C, 1.5 h, 64–88%; (g) $MsO(CH_2)_8CCH$, NaH, DMSO, r.t., 14 h, 93%; (h) CuCl, TMEDA, $O_2$, *p*-xylene, 130 °C, 43–46%; (i) $MsO(CH_2)_8CCH$, NaH, DMSO, 60 °C, 6 h, 58%; (j) (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, 62–76%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TMEDA = tetramethylethylenediamine, PMBCl = *p*-methoxybenzyl chloride, *p*-TsOH = *p*-toluenesulfonic acid, DMAP = 4-(dimethylamino)pyridine, TBAI = tetrabutylammonium iodide, TrCl = trityl chloride.




**Scheme 2** *Reagents and conditions*: (a) (i) KOH, PMBCl, DMSO, r.t., 24 h; (ii) *p*-TsOH, MeOH, r.t., 36 h, 78%; (b) TrCl, DMAP, pyridine, 80 °C, 13 h, 89%; (c) $MsO(CH_2)_8CCH$, NaH, TBAI, DMF, r.t., 19 h, 92%; (d) $I_2$, morpholine, benzene, 40 °C, 11 h, 91%; (e) TsOH, $CHCl_3$/MeOH (2:1, v/v), r.t., 19 h, 90–95%; (f) **11**, CuI, pyrrolidine, –20 °C, 62%; (g) $MsO(CH_2)_8CCH$, NaH, DMSO, r.t., 14 h, 53%; (h) CuCl, TMEDA, $O_2$, *p*-xylene, 130 °C, 19%; (i) DDQ, $CH_2Cl_2$/phosphate buffer solution (pH 7.2) (18:1, v/v), 0 °C, 1.5 h, 59%; (j) (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, 79%.

In conclusion, the synthetic strategy that highlights both the selective deprotection of compound **4** and cross-coupling of intermediates **11** and **12** should permit the efficient construction of chiral cyclobolaphiles and the diastereomer having two diacetylenes. This strategy also could be wide applicable to the synthesis of the analogous compounds. Work is currently in progress to develop their self-assemblies and will be reported elsewhere.

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(4) (a) Amphiphilic molecules containing 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. (b) Also termed 'bolaphile': Jayasuriya, N.; Bosak, S.; Regen, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5844. (c) While amphiphiles having a macrocyclic ring as a hydrophobic segment have been termed 'macrocyclic bolaamphiphiles' (see Ref.[2a]), we prefer to adopt the abbreviated and more readily pronounceable term, 'cyclobolaphile'.

(5) (a) We term caldarchaeol with a parallel arrangement of glycerol units 'parallel caldarchaeol', and that with an antiparallel arrangement 'antiparallel caldarchaeol': Gräther, O.; Arigoni, D. *J. Chem. Soc., Chem. Commun.* **1995**, 405. (b) Nishihara, M.; Morii, H.; Koga, Y. *J. Biochem.* **1987**, *101*, 1007.

(6) Intense examination of macrocyclic synthetic methods that have been previously reported indicates that only our strategy has the potential to provide three stereoisomers of parallel cyclobolaphiles that contain diacetylene units (see Ref.[1c,d,2]).

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(11) All new compounds gave satisfactory analytical and spectral data. Selected physical data are as follows: **4**: Stage yellow oil, $R_f$ = 0.55 [hexane/ethyl acetate (2:1, v/v)], $[\alpha]_D^{28}$ –1.67 (*c* 0.24, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): δ = 7.45–7.39 (m, 12 H), 7.27–7.19 (m, 18 H), 7.16 (d, *J* = 8.8 Hz, 4 H), 6.81 (d, *J* = 8.5 Hz, 4 H), 4.44 (d, *J* = 11.6 Hz, 2 H), 4.40 (d, *J* = 11.9 Hz, 2 H), 3.77 (s, 6 H), 3.56–3.49 (m, 10 H), 3.17 (d, *J* = 4.6 Hz, 4 H), 2.19 (t, *J* = 7.2 Hz, 4 H), 1.56–1.44 (m, 8 H), 1.34–1.24 (m, 16 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 159.06, 144.09, 130.48, 129.13, 128.72, 127.70, 126.87, 113.62, 86.48, 78.29, 77.52, 72.87, 70.60, 70.09, 65.22, 63.44, 55.24, 30.06, 29.33, 29.07, 28.82, 28.32, 26.10, 19.17 ppm. Anal. Calcd for $C_{80}H_{90}O_8$: C, 81.46; H, 7.69%. Found: C, 81.43; H, 7.66%. **8**: Stage pale yellow oil, $R_f$ = 0.13 [hexane/ethyl acetate (2:1, v/v)], $[\alpha]_D^{28}$ –9.80 (*c* 0.60, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): δ = 3.72–3.48 (m, 18 H), 2.23 (t, *J* = 6.9 Hz, 8 H), 2.17 (brs, 2 H), 1.65–1.42 (m, 16 H), 1.40–1.19 (m, 32 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 78.44, 77.41, 71.60, 71.08, 70.34, 65.31, 62.90, 29.95, 29.46, 29.26, 29.10, 28.93, 28.58, 28.19, 25.93, 19.11 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, 76.19; H, 10.81%. **10**: $[\alpha]_D^{28}$ +9.67 (*c* 0.30, $CHCl_3$). **15**: $[\alpha]_D^{28}$ 0.00 (*c* 0.45, $CHCl_3$). (2*R*,27*R*)-**1**: Stage pale yellow solid, $R_f$ = 0.1 [$CHCl_3$/MeOH/$H_2O$ (65:25:4, v/v/v)]. $[\alpha]_D^{28}$ +5.81 (*c* 0.75, MeOH). $^1$H NMR [500 MHz, $CDCl_3$/$CD_3OD$ (97:3, v/v)]: δ = 4.24 (brs, 4 H), 3.84 (t, *J* = 5.3 Hz, 4 H), 3.65 (brs, 4 H), 3.58–3.51 (m, 8 H), 3.43–3.37 (m, 6 H), 3.24 (s, 18 H), 2.21 (t, *J* = 6.7 Hz, 8 H), 1.49–1.43 (m, 16 H), 1.34–1.20 (m, 32 H) ppm. $^{13}$C NMR (125 MHz, $CD_3OD$): δ = 79.50, 77.97, 72.46, 72.01, 71.49, 67.47, 66.57, 66.20, 60.37, 54.69, 31.21, 30.78, 30.41, 30.24, 29.98, 29.83, 29.58, 27.29, 19.79 ppm. $^{31}$P NMR [200 MHz, $CDCl_3$/$CD_3OD$ (99:1, v/v)]: δ = –0.50 (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, 61.59; H, 9.43; N, 2.56%. (2*S*,27*S*)-**1**: $[\alpha]_D^{28}$ –5.77 (*c* 0.70, MeOH). (2*R*,27*S*)-**1**: $[\alpha]_D^{28}$ +0.00 (*c* 0.37, 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**.

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