An Olefin Metathesis Approach to 36- and 72-Membered Archaeal Macrocyclic Membrane Lipids

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Received March 12, 1998

An olefin metathesis approach, which has been successfully applied to an efficient synthesis of archaeal 36- and 72-membered macrocyclic membrane lipids (**1**, **2a**, and **2b**), is reported. In the presence of a Grubbs' ruthenium−alkylidene complex, $RuCl_2(=CHPh)(PCy_3)_2$ (**3**), a ring-closing metathesis (RCM) reaction of α,ω-diene **5** efficiently proceeded in 79% yield under high dilution conditions to give 36-membered **6**. By changing the reaction conditions, a acyclic diene metathesis (ADM) product **7** was predominantly formed from the same substrate **5**. The acyclic product **7** was subsequently subjected to the RCM reaction under high dilution conditions to provide 72-membered compound **8** in 45% yield. Final catalytic hydrogenation of **6** and **8** afforded the 36-membered lipid **1** and a mixture of the 72-membered lipid **2a** and **2b**, respectively. The present synthetic method appears to be of significant advantage for the synthesis of such giant ring structures of the 36- and 72-membered lipids, because both of the macrocylic lipids can be obtained in a short step at will from the same starting material only by changing the order and conditions of the metathesis reaction.

Introduction

Transition metal catalyzed carbon−carbon bond formation is an important reaction in organic synthesis. Among such transition metal-catalyzed reactions is olefin metathesis, which involves the exchange reaction of alkylidene moieties between two alkenes.[1] While the metathesis reaction has long been used in polymer chemistry, recently developed homogeneous catalysts, such as the molybdenum−alkylidene complexes introduced by Schrock et al.[2] as well as the ruthenium−alkylidene complexes of Grubbs et al.,[3] facilitated significant improvement of the olefin metathesis as a useful synthetic method. Especially, ring-closing metathesis (RCM) with these catalysts provides an efficient and widely applicable way for constructing varieties of ring sizes, and as a result, the RCM methodology has increasingly been used for natural product synthesis.[4]

Archaea (archaebacteria) have been attracting wide attention from biochemical and evolutionary viewpoints. It has now been established that the archaea are distinct from bacteria and eukarya and are classified in the third independent domain.[5] Among the major interests in archaea are the unique chemical structures of the membrane core lipids, that is, glycerol is linked to isoprenoid chains with ethereal bonding, in contrast to ester linkage with fatty acids in the bacterial and eukaryotic membrane lipids.[6] The most striking feature of the archaeal membrane lipids is found in the presence of macrocyclic structures as large as 36- and 72-membered rings (**1** and **2ab**), as shown in Figure 1.[6] The former was discovered from a methanogen *Methanococcus jannaschii* isolated from a deep-sea hydrothermal vent and the latter being found in methanogenic and thermophilic archaea such as *Methanobacterium thermoautotrophicum*, *Thermoplasma*, and *Sulfolobus*.[5] In addition, Arigoni et al. recently reported that the 72-membered lipids exist as a mixture of regioisomers in terms of the glycerol arrangements such as **2a** and **2b**.[7] These unusual lipids have attracted attention in connection with their physicochemical properties, including high stability under extreme conditions. Modeling and synthetic studies of the archaeal membrane lipids have so far been reported in order to shed light on the stability,

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S0022-3263(98)00472-1 CCC: $15.00
Published on Web 06/11/1998

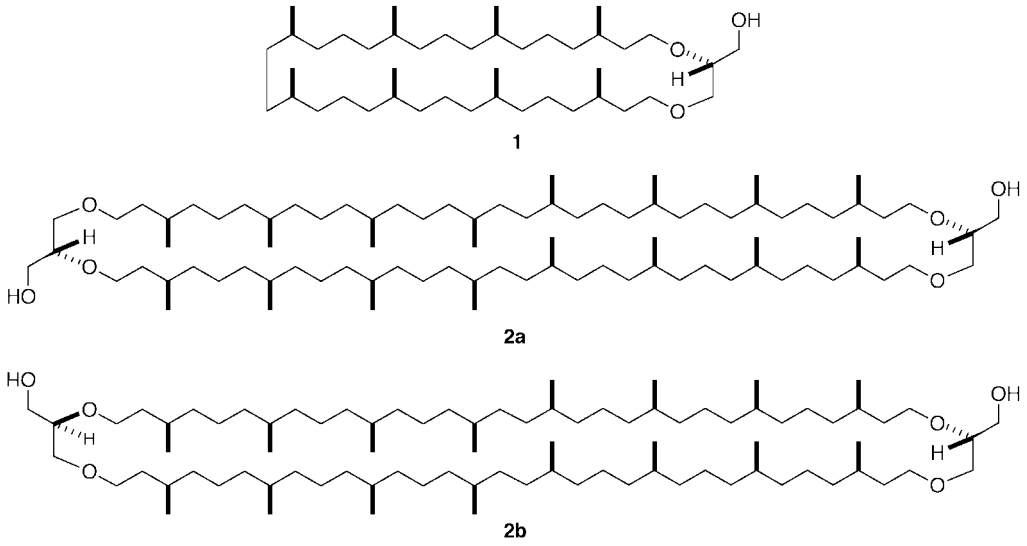

Figure 1. Core structures of archaeal macrocyclic membrane lipids (**1**, **2a**, and **2b**).

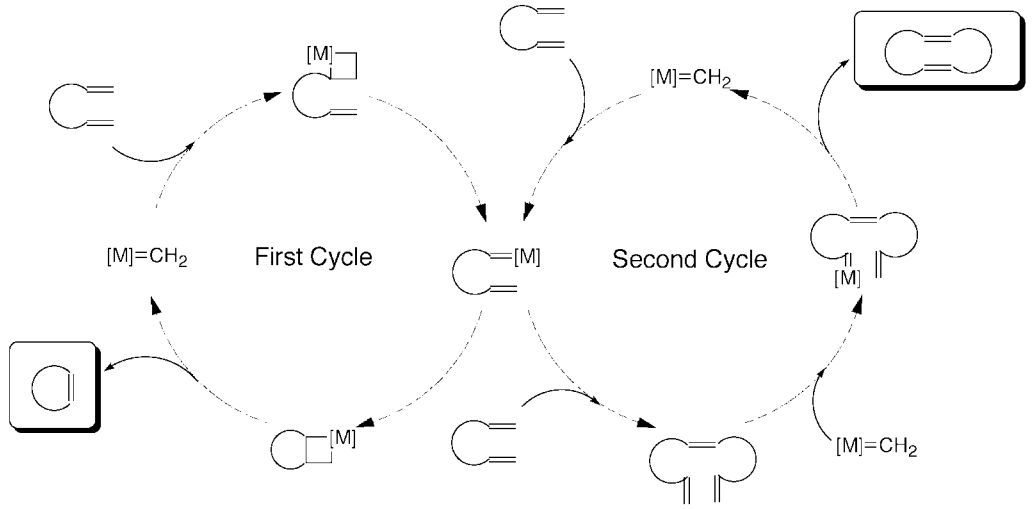

Figure 2. The concept of the metathesis approach toward the archaeal macrocyclic lipids.

fluidity, and permeability.[8] However, little is known of such a large ring as 36- and 72-membered macrocyclic lipids.

Concerning the synthetic efforts toward such macrocyclic lipids of natural form, we recently reported the first total syntheses of the macrocyclic 36-membered lipid **1** and 72-membered lipids **2a** and **2b**, where the McMurry coupling reaction[9] was a key step of macrocyclic ring formation.[10] In this paper, we wish to describe another new approach involving olefin metathesis toward the archaeal 36- and 72-membered macrocyclic lipids (**1**, **2a,** and **2b**).

Results and Discussion

The concept of our new approach toward the archaeal macrocyclic lipids employing olefin metathesis is outlined in Figure 2. Although an intramolecular metathesis reaction usually competes with an intermolecular reaction, the 36-membered lipid can conceivably be available from α,ω-diene by RCM under high dilution conditions through the first catalytic cycle. In contrast, acyclic diene metathesis (ADM) may predominantly proceed to afford an intermediary triene derivative as the concentration of α,ω-diene is increased. It should be pointed out, therefore, that the second RCM reaction can be facilitated by changing the reaction conditions after the ADM reaction, as shown in the second cycle to give rise to

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Table 1. Results of RCM reaction of 5[a]

entry	substrate concn (mM)	catalyst (mol %)	conditions	yield (%)[b] 6	7	8
1[c]	5.1	10	rt, 115 h			
2	3.8	29	reflux, 42 h	79	trace	6
3	7.8	22	reflux, 36 h	55	6	11
4	29	20	reflux, 12 h	15	12	11

[a] All reactions were carried out in CH_2Cl_2 under an Ar atmosphere. [b] Isolated yield. [c] The starting **5** was quantitatively recovered.

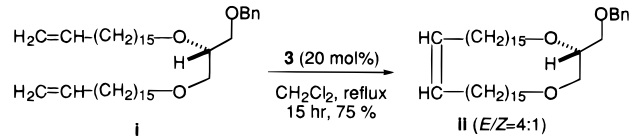
dimerized 72-membered lipids. Thus, this strategy should allow us to obtain the 36-membered lipid as well as the 72-membered compounds stepwise or in one pot from the same starting material. Although this reaction sequence ultimately provides an isomeric mixture of the 72-membered lipids **2a** and **2b**, the state of mixture is by no means problematic. Actually, Arigoni et al. recently reported that the 72-membered lipids exist as a mixture of regioisomers in terms of the glycerol arrangements such as **2a** and **2b** in several archaea,[7] and we have deduced that the physicochemical as well as polymorphismic properties of the synthesized **2a** and **2b** in pure form are indistinguishable.[10d] What is important is, therefore, the better availability of the chemically defined 72-membered lipids even as a mixture, especially for the various physicochemical analyses, in order to understand their behavior.

We first explored the possibility of a RCM reaction leading to the 36-membered lipid **1**. The substrate for the metathesis reaction, α,ω-diene **5,** was prepared from the known dialdehyde **4**[10b] by treatment with $Ph_3P{=}CH_2$ in 95% yield. Among the several olefin metathesis catalysts tested, a ruthenium−alkylidene complex, $RuCl_2(=CHPh)(PCy_3)_2$ (**3**), developed by Grubbs et al.,[3] was found to be effective for the metathesis of **5**. The results of the RCM reaction of **5** under various reaction conditions are summarized in Table 1.[11]

While the RCM reaction of **5** did not occur at room temperature under high dilution conditions at all (entry 1), the RCM reaction took place by raising the reaction temperature to reflux to afford the 36-membered compound **6** (entries 2−4). This may be due to facilitation of the release of highly volatile ethylene. In the case of entry 2, the RCM product **6** was obtained in yields as high as 79%.[12] The geometry of the newly formed double bond of **6** was found to be a mixture of approximately 7:1 (*E*/*Z*), deduced by ^1H and ^{13}C NMR analyses. As one can see from Table 1, an increase of the substrate concentration seemed to diminish the RCM reaction, probably due to a competitive polymerization reaction. It should be noteworthy that the RCM product was obtained along with a small amount of the ADM product **7** and the tandem ADM−RCM product **8**. The contents of these products tended to increase as the substrate

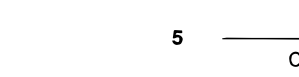
(11) Methylene chloride was the most effective solvent for the metathesis reaction of **5** and was used throughout the present study.

(12) In our preliminary experiments using desmethylated model compound **i**, the RCM reaction occurred more rapidly than for **5**. The acyclic diene **i** was converted to **ii** under high dilution conditions (substrate concentration, 2.9 mM).



i ii (*E*/*Z*=4:1)

Table 2. Results of the ADM reaction of 5[a]



entry	substrate concn (mM)	catalyst (mol %)	conditions	yield (%)[b] recovered 5	7[c]
1	40	7	rt, 63 h	60	28 (70)
2	78	20	rt, 22 h	59	26 (63)
3	108	20	rt, 9 h	57	35 (81)
4	408	20	rt, 20 h	43	19 (33)

[a] All reactions were carried out in CH_2Cl_2 under an Ar atmosphere. [b] Isolated yield. [c] Conversion yields (%) of **7** were estimated by subtracting the recovered **5** and are shown in parentheses.

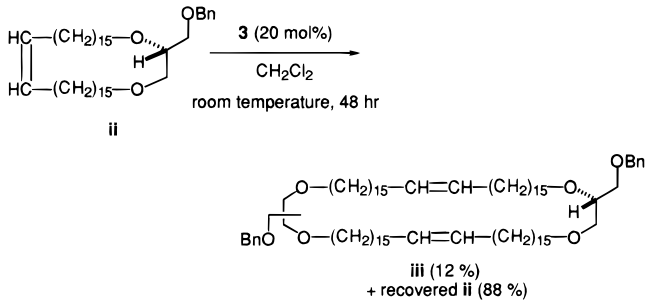
concentration increased. The possibility of the formation of **7** and **8** via a ring-opening metathesis[13] from **6** was ruled out, since no reaction was observed when the isolated **6** was subjected to the same metathesis conditions and the starting **6** was quantitatively recovered. Therefore, the internal olefin in this case is not reactive enough for metathesis, probably due to a steric factor.[14] The importance of steric effect for the reactivity in metathesis was previously reported.[4a] Apparently, the ADM and the subsequent RCM processes took place. These observations clearly demonstrated the possibility of 72-membered ring formation from **5** by the olefin metathesis approach.

The next was to optimize the reaction conditions for the ADM reaction starting from **5**. As was mentioned above, the RCM reaction of **5** preferentially proceeded under high dilution conditions and an increase of the concentration of **5** led to polymerization under reflux conditions; however, we observed at the same time that lowering the reaction temperature to room temperature diminished the undesired polymerization, even at higher concentration. To optimize the reaction conditions, we attempted the ADM reaction of **5** in various substrate concentrations, and the results are shown in Table 2. In all cases, the reactions were not completed; however, the high conversion yield of 81% was observed in entry 3. The recovered starting material **5** can be recycled after chromatographic separation. Under these reaction conditions, the RCM product **6** and the tandem ADM−RCM product **8** were not obtained. Prolonged reaction time led to a lower yield of the desired **7**, probably due to polymerization.

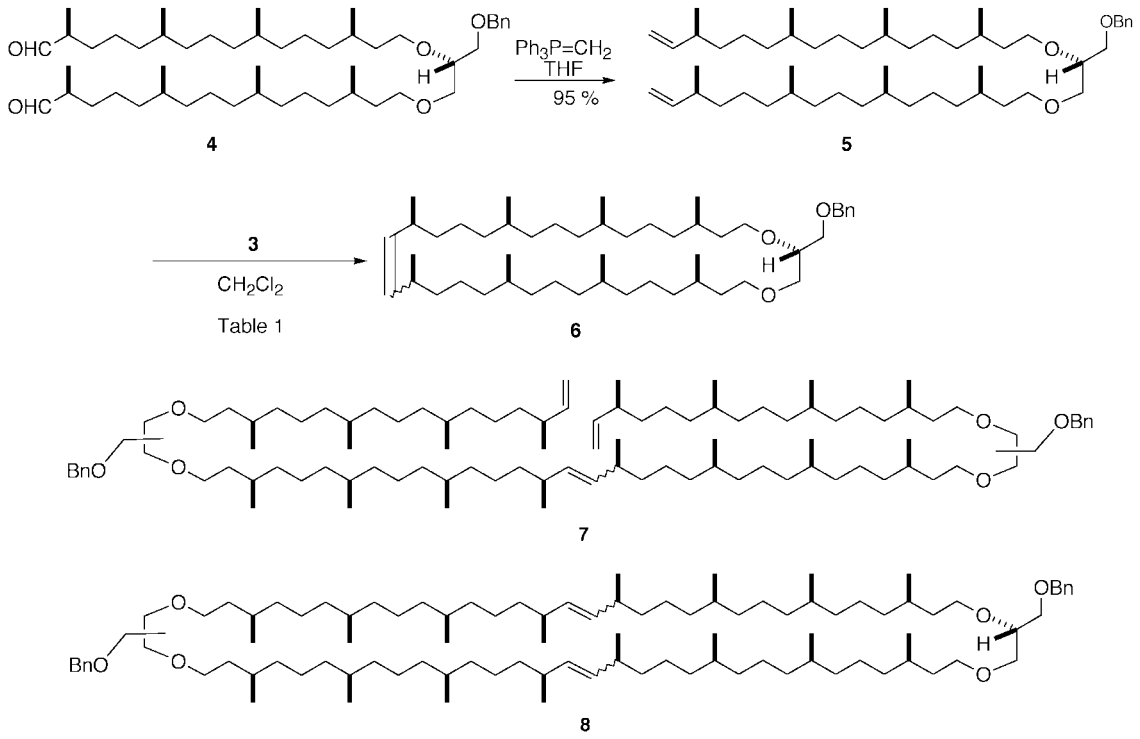
With an efficient route to **7** in hand, we next turned our attention to the RCM reaction from the intermediary **7**. Thus, the isolated **7** was subjected to the RCM

(13) Warwel, S.; Kätker, H. *Synthesis* **1987**, 935.

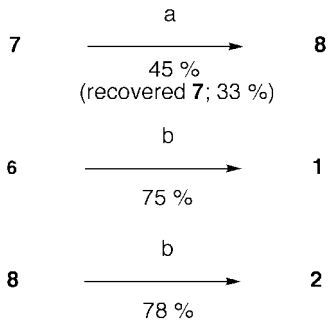
(14) The ring-opening metathesis in the case of the compound **ii** proceeded in 12% yield to afford **iii**, together with the recovered **ii** (88%). The different reactivities of **ii** and **6** are probably due to a steric factor.



Scheme 1



Scheme 2[a]



[a] Reagents and conditions: (a) substrate concentration, 1.0 mM, **3** (20 mol %), CH_2Cl_2, reflux, 72 h; (b) H_2, 10% Pd−C/EtOAc.

reaction with **3** under high dilution conditions. As illustrated in Scheme 2, the RCM reaction of **7** in a concentration of 1.0 mM proceeded smoothly to afford the 72-membered **8** in 45% yield, along with the recovered **7** (33%). The latter can of course be recycled. The geometrical isomer ratio of **8** was almost similar (E/Z = 10:1) to the case of **6**.

Finally, the obtained **6** and **8** were separately converted by catalytic hydrogenation to the 36-membered lipid **1** and to a mixture of 72-membered lipids **2a** and **2b**, respectively (Scheme 2). All spectroscopic data of the synthesized **1** and the mixture of **2a** and **2b** were completely identical with those reported.[10]

In summary, we have successfully shown a convenient synthesis of both 36- and 72-membered lipids from the same starting material via the olefin metathesis reaction, while the efficiency of the cyclization steps by RCM leading to these macrocyclic lipids is comparable to the McMurry coupling.[10] The present synthetic strategy for the 72-membered lipids is the first example toward natural products by means of the conceptual tandem ADM−RCM reaction.

Experimental Section

General Information. All reactions, except for catalytic hydrogenation reactions, were carried out in an inert (Ar or N_2) atmosphere. THF was distilled from sodium/benzophenone ketyl. CH_2Cl_2 was distilled from calcium hydride. The metathesis catalyst **3** was prepared in our laboratory according to the literature.[3b] Coupling constants (J) are reported in hertz.

1-*O*-Benzyl-2,3-bis-*O*-[(3*R*,7*R*,11*S*,15*S*)-3,7,11,15-tetramethylheptadec-16-enyl]-*sn*-glycerol (5). To a suspension of methyltriphenylphosphonium bromide (331 mg, 0.927 mmol) in THF (8 mL) was added *n*BuLi (1.59 M in hexane, 0.580 mL, 0.922 mmol) at −78 °C, and the mixture was stirred at −78 °C for 30 min and then at room temperature for 30 min. The mixture was recooled to −78 °C and a solution of dialdehyde **4**[10b] (139 mg, 0.180 mmol) in THF (5 mL) was added. The mixture was stirred at −78 °C for 15 min and at room temperature for 1 h. Saturated NH_4Cl (10 mL) was added and the mixture was extracted twice with ether. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexanes−EtOAc (50:1 v/v) to give **5** (131 mg, 95%) as an oil. $[\alpha]^{21}_D$ +6.63° (*c* 0.89, $CHCl_3$). ^{1}H NMR (400 MHz): δ 0.84 (d, J = 6.6, 9H), 0.86 (d, J = 6.6, 9H), 0.98 (d, J = 6.6, 6H), 1.00−1.70 (m, 46H), 2.10 (m, 2H), 3.42−3.66 (m, 9H), 4.55 (s, 2H), 4.93 (ddd, J = 1.7, 2.0, and 10, 2H), 4.94 (ddd, J = 1.2, 1.7, and 17, 2H), 5.69 (ddd, J = 7.6, 10, and 17, 2H), 7.25−7.34 (m, 5H). ^{13}C NMR (100 MHz): δ 19.68, 19.72, 19.76, 20.24, 24.36, 24.48, 24.62, 29.80, 29.88, 32.74, 32.80, 36.63, 36.97, 37.09, 37.39, 37.46, 37.51, 37.76, 68.87, 69.95, 70.30, 70.78, 73.34, 77.93, 112.20, 127.48, 127.56, 128.29, 138.42, 144.98. IR (neat): 908, 1462, 1639 cm^{-1}. Anal. Calcd for $C_{52}H_{94}O_3$: C, 81.40; H, 12.35. Found: C, 81.15; H, 12.61.

(2*S*,7*R*,11*R*,15*S*,19*S*,22*S*,26*S*,30*R*,34*R*)-2-Benzyloxymethyl-7,11,15,19,22,26,30,34-octamethyl-1,4-dioxacyclohexatriacont-20-ene (6). To a refluxing solution of diene **5** (32 mg, 0.042 mmol) in CH_2Cl_2 (5 mL) was added a purple solution of **3** (10 mg, 0.012 mmol, 29 mol %) in CH_2Cl_2 (6 mL). The mixture was refluxed for 42 h. After concentrating the mixture, the residue was purified by flash chromatography over silica gel with hexanes−EtOAc (25:1) to afford **6** (24 mg, 79%; E/Z = ca. 7:1) as an oil. ^{1}H NMR (400 MHz): δ 0.83 (d, J = 6.4, 6H), 0.84 (d, J = 6.4, 6H), 0.87 (d, J = 6.6, 6H), 0.94

(d, J = 6.6, 6H), 1.00−1.70 (m, 46H), 2.01 (m, 2H), 3.46−3.64 (m, 9H), 4.55 (s, 2H), 5.10 (dd, J = 2.4 and 5.1, 1.75H), 5.22 (dd, J = 2.0 and 4.2, 0.25H), 7.26−7.34 (m, 5H). ^{13}C NMR (100 MHz): δ 19.78, 19.85, 21.82, 24.50, 25.06, 29.61, 29.74, 32.85, 32.87, 36.65, 36.98, 37.23, 37.33, 37.36, 37.46, 37.49, 37.77, 68.59, 69.71, 70.30, 71.45, 73.36, 77.94, 127.52, 127.58, 128.31, 134.18, 134.98, 138.38. IR (neat): 968, 1462, 1736 cm^{-1}. EI-MS m/z (rel intensity): 739 (M^+, 7), 648 ($M^+ - CH_2$-Ph, 100), 633 (43), 556 (20). Anal. Calcd for $C_{50}H_{90}O_3$: C, 81.24; H, 12.27. Found: C, 81.02; H, 12.46.

The ADM Reaction of 5. To a stirred solution of diene **5** (25 mg, 0.032 mmol) in CH_2Cl_2 (0.2 mL) was added a purple solution of **3** (5.4 mg, 6.6 μmol) in CH_2Cl_2 (0.10 mL) at room temperature. The mixture was stirred at room temperature for 9 h. The solution was passed through a pad of silica gel. After concentration, the residue was chromatographed over silica gel with hexanes−EtOAc (25:1) to afford **7** (8.4 mg, 35%) and the recovered **5** (14.3 mg, 57%). **7**; ^{1}H NMR (400 MHz): δ 0.83 (d, J = 6.4, 6H), 0.84 (d, J = 6.6, 12H), 0.86 (d, J = 6.4, 12H), 0.87 (d, J = 6.8, 6H), 0.95 (d, J = 6.8, 6H), 0.98 (d, J = 6.8, 6H), 1.00−1.70 (m, 92H), 1.95−2.20 (br, 4H), 3.42−3.66 (m, 18H), 4.55 (s, 4H), 4.89 (ddd, J = 1.7, 2.0, and 10, 2H), 4.94 (ddd, J = 1.2, 2.0, and 17, 2H), 5.10 (dd, J = 2.4 and 5.4, 0.2H), 5.17 (dd, J = 2.2 and 4.6, 1.8H), 5.81 (ddd, J = 7.6, 10, and 17, 2H), 7.26−7.34 (m, 10H). ^{13}C NMR (100 MHz): δ 19.68, 19.72, 19.75, 20.23, 21.17, 24.37, 24.48, 24.51, 24.63, 24.73, 29.69, 29.83, 29.91, 32.75, 32.82, 36.65, 36.70, 36.98, 37.11, 37.40, 37.47, 37.54, 37.75, 68.89, 69.97, 70.34, 70.80, 73.35, 77.95, 112.20, 127.48, 127.57, 128.29, 134.40, 134.57, 138.44, 145.01. IR (neat): 908, 1462, 1734 cm^{-1}. EI-MS m/z (rel intensity): 1505 (M^+, 4), 1414 ($M^+ - CH_2Ph$, 100), 1308 (55). Anal. Calcd for $C_{102}H_{184}O_6$: C, 81.32; H, 12.31. Found: C, 81.19; H, 12.61.

The RCM Reaction of 7. To a refluxing solution of **7** (17 mg, 11.2 μmol) in CH_2Cl_2 (10 mL) was added a purple solution of **3** (2.0 mg, 22 mol %) in CH_2Cl_2 (1.0 mL). The mixture was refluxed for 72 h. After concentrating the mixture, the residue was chromatographed over silica gel with hexanes−EtOAc (30:1) to afford **8** (7.4 mg, 45%) and the recovered **7** (5.6 mg, 33%). **8**: ^{1}H NMR (400 MHz): δ 0.83 (d, J = 6.4, 12H), 0.84 (d, J = 6.6, 12H), 0.87 (d, J = 6.6, 12H), 0.94 (d, J = 6.8, 12H), 0.98−1.70 (m, 92H), 2.02 (br, 4H), 3.45−3.66 (m, 18H), 4.55 (s, 4H), 5.15 (dd, J = 2.2 and 4.6, 3.7H), 5.19 (dd, J = 2.0 and 4.6, 0.3H), 7.26−7.34 (m, 10H). ^{13}C NMR (100 MHz): δ 19.75, 19.81, 21.37, 24.39, 24.50, 24.80, 29.70, 29.76, 29.86, 32.77, 32.82, 36.64, 36.87, 37.10, 37.40, 37.44, 37.48, 37.51, 37.60, 68.81, 69.91, 70.32, 70.96, 73.35, 77.95, 127.49, 127.57, 128.30, 134.67, 138.42. IR (neat): 968, 1462, 1743 cm^{-1}. EI-MS m/z (rel intensity): 1477 (M^+, 4), 1386 ($M^+ - CH_2Ph$, 100), 1280 (57). Anal. Calcd for $C_{100}H_{180}O_6$: C, 81.24; H, 12.27. Found: C, 81.24; H, 12.42.

(2*R*,7*R*,11*R*,15*S*,19*S*,22*S*,26*S*,30*R*,34*R*)-2-Hydroxymethyl-7,11,15,19,22,26,30,34-octamethyl-1,4-dioxacyclohexatriacontane (1). A mixture of **6** (15 mg, 21 μmol) and 10% Pd−C (17 mg) in EtOAc (5 mL) was stirred for 21 h under a hydrogen atmosphere at room temperature. The catalyst was filtered through a pad of Celite and washed with EtOAc. The filtrate and washings were combined and concentrated to dryness. The residue was chromatographed over silica gel with hexanes−EtOAc (10:1) to give **1** (10 mg, 75%) as an oil. $[\alpha]^{20}_D$ +8.22 ° (c 1.01, $CHCl_3$). ^{1}H NMR (400 MHz): δ 0.85 (d, J = 6.6, 12H), 0.88 (d, J = 6.6, 6H), 0.89 (d, J = 6.3, 6H), 1.00−1.70 (m, 52H), 2.15 (br, 1H), 3.46−3.71 (m, 9H). ^{13}C NMR (100 MHz): δ 19.85, 19.93, 20.03, 20.09, 23.97, 24.27, 24.42, 29.72, 29.77, 32.41, 32.47, 32.60, 32.67, 32.77, 33.03, 33.58, 34.16, 36.54, 36.68, 37.00, 37.26, 63.03, 68.53, 70.00, 71.19, 78.38. IR (neat): 1462, 3446 cm^{-1}. EI-MS m/z (rel intensity): 651 (M^+, 100), 633 ($M^+ - H_2O$, 60), 621 (59). Anal. Calcd for $C_{43}H_{86}O_3$: C, 79.32; H, 13.31. Found: C, 79.03; H, 13.40.

Tetraether Lipids 2a and 2b. A mixture of **8** (7.4 mg, 5.0 μmol) and 10% Pd−C (9.4 mg) in EtOAc (5 mL) was stirred for 34 h under an hydrogen atmosphere at room temperature. The catalyst was filtered through a pad of Celite and washed with EtOAc. The filtrate and washings were combined and concentrated to dryness. The residue was purified by flash chromatography over silica gel with hexanes−EtOAc (4:1) to give a mixture of **2a** and **2b** (5.1 mg, 78%). $[\alpha]^{22}_D$ +7.31° (c 0.51, $CHCl_3$). ^{1}H NMR (400 MHz): δ 0.85 (d, J = 6.4, 24H), 0.88 (d, J = 6.6, 12H), 0.89 (d, J = 6.6, 12H), 1.00−1.70 (m, 104H), 2.17 (br, 2H), 3.46−3.75 (m, 18H). ^{13}C NMR (100 MHz): δ 19.76, 19.83, 19.85, 24.37, 24.46, 29.79, 29.84, 32.79, 33.06, 34.30, 36.57, 37.06, 37.37, 37.51, 63.08, 68.59, 70.09, 71.06, 78.34. IR (neat): 1462, 3435 cm^{-1}. EI-MS m/z (rel intensity): 1301 (M^+, 76), 1283 ($M^+ - H_2O$, 54), 1271 (61), 650 (100). Anal. Calcd for $C_{86}H_{172}O_6$: C, 79.32; H, 13.31. Found: C, 79.02 H, 13.59.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for the compounds **5**−**8**, **1,** and **2** and MS spectra for the compounds **6**−**8**, **1**, and **2** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO980472K