JOC Article

Synthetic Studies on Macroviracin A: A Rapid Construction of C_{42} Macrocyclic Dilactone Corresponding to the Core

Shunya Takahashi,* Kazunori Souma, Ruri Hashimoto, Hiroyuki Koshino, and Tadashi Nakata

RIKEN (The Institute of Physical and Chemical Research), Wako-shi, Saitama 351-0198, Japan

shunyat@riken.go.jp

Received March 4, 2004

The C_2-symmetric macrodiolide core **2** of an antiviral agent, macroviracin A (**1**), was constructed in a single step by the intermolecular macrodimerization of C_{22}-hydroxy carboxylic acid **3** with 2-chloro-1,3-dimethylimidazolinium chloride and DMAP in the presence of sodium hydride (NaH). The use of potassium hydride instead of NaH caused the intramolecular cyclization, predominantly providing the corresponding monomer **26**. The acid **3** was synthesized through a series of reactions such as the coupling reaction of acetylene **5** and oxirane **6**, stereoselective glycosidation with the trichloroacetimidate method, and Jones oxidation.

In the course of a screening program for the isolation of antiviral agents from microorganisms, Hyodo et al. isolated eight types of macrocyclic compounds from the mycelium extracts of *Streptomyces* sp. BA-2836, and named them macroviracins.[1] These natural products exhibit powerful antiviral activity against herpes simplex virus type 1 (HSV-1) and varicella-zoster virus (VZV), and their potency is reported to be 10 times that of acyclovir. Macroviracin A (**1**) is a member of this family and bears a 42-membered macrodiolide core consisting of a C_{22} fatty acid dimer possessing D-glucose residues, and a long side chain attached to the core (Figure 1). Structurally, macroviracin A (**1**) is related to sugar−fatty acid lactones such as cycloviracins[2] and fattiviracins,[3] differing remarkably in the size of the macrocyclic ring systems. Recently, these lactones have attracted much attention from synthetic organic chemists owing to their architectural complexity and biological activities with significant therapeutic potential. Fürstner et al. disclosed total syntheses of cycloviracin B_1 and glucolipsin A,[4] establishing the absolute configuration.[5,6] We have been engaged in chemical studies on macroviracins, resulting in the determination of the absolute configuration of **1**.[7] In connection with our synthetic studies on macroviracin A (**1**), we describe herein a short-step synthesis of the domain structure **2** (Scheme 1).

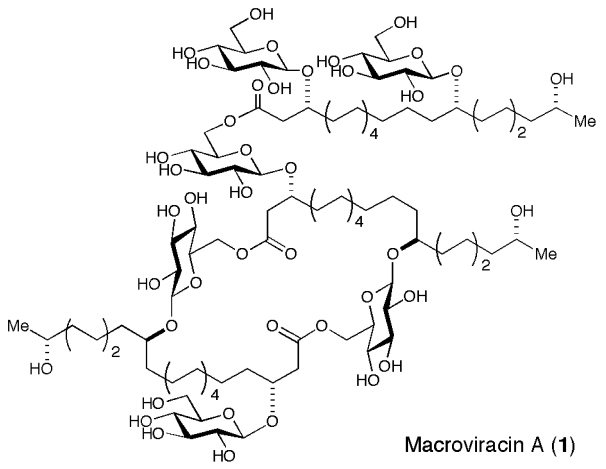


FIGURE 1. Structure of macroviracin A (**1**).

Results and Discussion

In the synthetic study of these macrocyclic sugar lactones, elaboration of the core is the most essential problem throughout the synthetic course.[8] We focused on the intermolecular macrodimerization of C_{22} carboxylic acid **3** because little is known about the cyclization of such long-chain acids.[5,6,9] Our synthetic strategy directed toward the acid **3** was based on the convergent process

* Address correspondence to this author. Phone: +81-48-467-9377. Fax: +81-48-462-4666.

(1) Hyodo, T.; Tsuchiya, Y.; Sekine, A.; Amano, T. Japanese Kokai Tokkyo Koho Japanese patent 11246587, Sept 14, 1999.

(2) Tsunakawa, M.; Komiyama, N.; Tenmyo, O.; Tomita, K.; Kawano, K.; Kotake, C.; Konishi, M.; Oki, T. *J. Antibiot.* **1992**, *45*, 1467. Tsunakawa, M.; Kotake, C.; Yamasaki, T.; Moriyama, T.; Konishi, M.; Oki, T. *J. Antibiot.* **1992**, *45*, 1472.

(3) Uyeda, M.; Yokomizo, K.; Miyamoto, Y.; Habib, E.-S. E. *J. Antibiot.* **1998**, *51*, 823. Yokomizo, K.; Miyamoto, Y.; Nagao, K.; Kumagae, E.; Habib, E.-S. E.; Suzuki, K.; Harada, S.; Uyede, M. *J. Antibiot.* **1998**, 51, 1035. Habib, E.-S. E.; Yokomizo, K.; Murata, K.; Uyeda, M. *J. Antibiot.* **2000**, *53*, 1420.

(4) Qian-Cutrone, J.; Ueki, T.; Huang, S.; Mookhtiar, K. A.; Ezekiel, R.; Kalinowski, S. S.; Brown, K. S.; Golik, J.; Lowe, S.; Pirnik, D. M.; Hugill, R.; Veitch, J. A.; Klohr, S. E.; Whitney, J. L.; Manly, S. P. *J. Antibiot.* **1999**, *52*, 245.

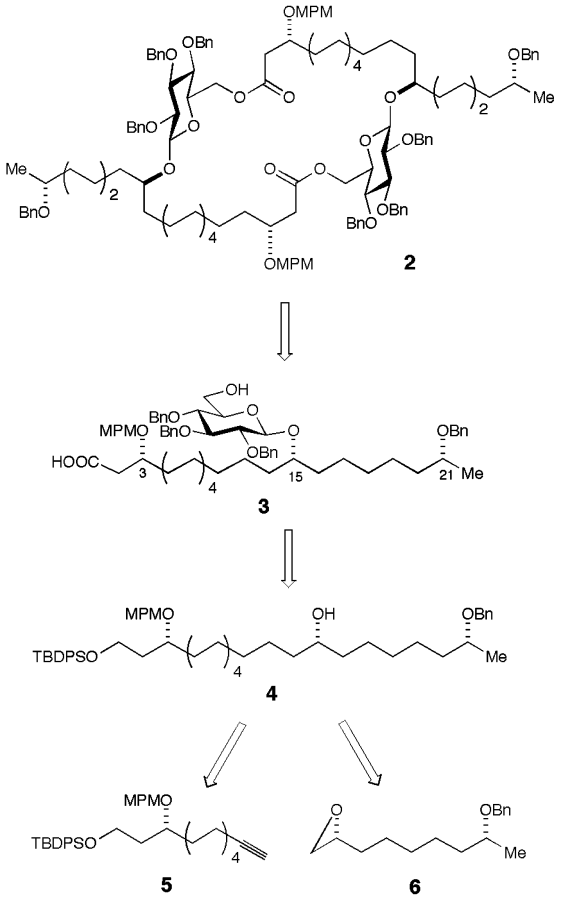
(5) (a) Fürstner, A.; Albert, M.; Mlynarski, J.; Matheu, M. *J. Am. Chem. Soc.* **2002**, *124*, 1168. (b) Fürstner, A.; Mlynarski, J.; Albert, M. *J. Am. Chem. Soc.* **2002**, *124*, 10274. (c) Fürstner, A.; Albert, M.; Mlynarski, J.; Matheu, M.; DeClercq, E. *J. Am. Chem. Soc.* **2003**, *125*, 13132.

(6) Fürstner, A.; Ruiz-Caro, J.; Prinz, H.; Waldmann, H. *J. Org. Chem.* **2004**, *69*, 459.

(7) Takahashi, S.; Hosoya, M.; Koshino, H.; Nakata, T. *Org. Lett.* **2003**, *5*, 1555.

10.1021/jo0496392 CCC: $27.50
Published on Web 05/28/2004

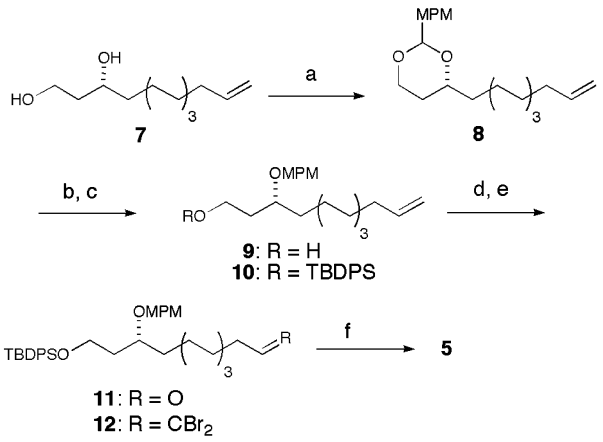
SCHEME 1. Retrosynthetic Analysis of the Domain Structure 2 of 1



previously developed by us. Thus, removal of the sugar residue from **3** and reduction of the carboxylic function led to acyclic alcohol **4**. Disconnection between the C-9 and -10 bond in **4** reverted to terminal acetylene **5**[10] and epoxide **6**. Each fragment appeared readily accessible from commercially available compounds. This approach would enable us to prepare other congeners of this family by changing the size of the acetylene unit.

Synthesis of the left-half segment **5** started with hydroxy protection of diol **7**[7] (Scheme 2). Thus, 1,3-diol **7** was treated with benzaldehyde dimethylacetal in the presence of D-camphorsulfonic acid (CSA) in DMF at 60 °C under reduced pressure to give benzylidene derivative **8** in 99% yield. DIBAL reduction of **8** afforded primary alcohol **9** in 92% yield. The liberated hydroxyl group was protected as the corresponding *tert*-butyldiphenylsilyl (TBDPS) ether, giving **10** (96%). Lemieux−Johnson oxidation of **10** afforded aldehyde **11** in good yield. This was transformed into dibromoolefin **12** and then **5** according to Corey's procedure.[11]

SCHEME 2. Synthesis of Acetylene 5[a]



[a] Reagents and conditions: (a) *p*-anisealdehyde dimethylacetal, CSA, DMF, 60 °C, 99%; (b) DIBAL, CH_2Cl_2, 0 °C, 92%; (c) TBDPSCl, imidazole, DMF, rt, 96%; (d) OsO_4, $NaIO_4$, THF−H_2O, rt, 80%; (e) CBr_4, Ph_3P, Et_3N, CH_2Cl_2, 0 °C, 92%; (f) *n*-BuLi, THF, −78 °C, 94%.

In previous studies,[7] synthesis of a right-half epoxide corresponding to **6** required 14 steps from methyl 3-tetrahydropyranyloxy butyrate. For large-scale preparation of the benzyl analogue **6**, we newly developed a short-step synthesis based on the hydrolytic kinetic resolution of a terminal epoxide reported by Jacobsen et al (Scheme 3).[12] Thus, methyl ester **13**[9f] was initially reduced (94%), and the resulting alcohol **14**[13] was sulfonylated to afford tosylate **15** in 77% yield. The chain extension from **15** was performed by the action of 1-pentenylmagnesium bromide in the presence of CuI to give olefin **16** in 99% yield. This was oxidized with mCPBA in CH_2Cl_2 to provide a ca. 1:1 diastereomeric mixture of terminal epoxides **17** in 87% yield. The epoxide **17** was treated with 0.9 mol % of (*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)1,2-cyclohexadiamino cobalt in the presence of water (0.65 equiv) at room temperature, giving epoxide **6** in 44% and diol **18** (44%). The optical purity of the epoxide **6** was determined to be >99% de by NMR and HPLC analyses, using a chiral column.[14] The resolved diol **18** was also transformed into **6** via the corresponding benzoyl mesylate **19**.

(8) For recent synthetic studies on complex glycolipids see: (a) Brito-Arias, M.; Pereda-Miranda, R.; Heathcock, C. H. *J. Org. Chem*. p ublished online Jan 6, 2004, http://dx.doi.org/10.1021/jo030244c. (b) Fürstner, A. *Eur. J. Org. Chem*. **2004**, 943. (c) Fürstner, A.; Jeanjean, F.; Razon, P.; Wirtz, C.; Mynott, R. *Chem. Eur. J*. **2003**, *9*, 307. (d) Fürstner, A.; Jeanjean, F.; Razon, P.; Wirtz, C.; Mynott, R. *Chem. Eur. J*. **2003**, *9*, 320. (e) Fürstner, A.; Radkowski, K.; Grabowski, J.; Wirtz, C.; Mynott, R. *J. Org. Chem*. **2000**, *65*, 8758. (f) Furukawa, J.; Kobayashi, S.; Nomizu, M.; Nishi, N.; Sakairi, N. *Tetrahedron Lett*. **2000**, *41*, 3453 and references therein.

(9) For relative small dilactones, see: (a) Su, Q.; Beeler, A. B.; Lobkovsky, E.; Porco, J. A., Jr.; Panek, J. S. *Org. Lett*. **2003**, *5*, 2149. (b) Garcia, D. M.; Yamada, H.; Hatakeyama, S.; Nishizawa, M. *Tetrahedron Lett*. **1994**, *35*, 3325. (c) Plattner, D. A.; Brunner, A.; Dobler, M.; Muller, H.; Petter, W.; Zinden, P.; Seebach, D. *Helv. Chim. Acta* **1993**, *76*, 2004. (d) Zhi-wei, G.; Ngooi, T. K.; Scilimati, A.; Fülling, G.; Sih, C. J. *Tetrahedron Lett*. **1988**, *29*, 5583. (e) Yoshida, M.; Harada, N.; Nakamura, H.; Kanematsu, K. *Tetrahedron Lett*. **1988**, *29*, 6129. (f) Seebach, D.; Braendli, U.; Schnurrenberger, P.; Przybylski, M. *Helv. Chim. Acta* **1988**, *71*, 155. (g) Velarde, S.; Urbina, J.; Peña, M. R. *J. Org. Chem*. **1996**, *61*, 9541.

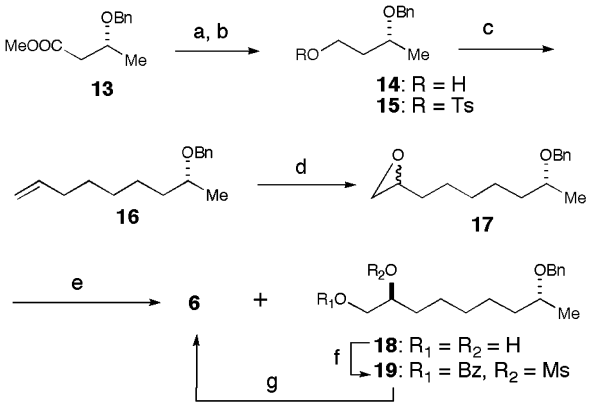
(10) In previous work,[7] alkyl iodide was employed as a nucleophilic precursor. However, we did not adopt this route for the large-scale synthesis of **4** because of the lack of reproducibility of the coupling reaction with **6**.

(11) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett*., **1972**, 3769.

(12) (a) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2002**, *124*, 1307. (b) Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem*. **1998**, *63*, 6776. (c) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *227*, 936 and references therein.

(13) (a) Izquierdo, I.; Plaza, M. T.; Rodriguez, M.; Tamayo, J. A.; Martos, A. *Tetrahedron: Asymmetry*, **2001**, *12*, 293. (b) Yang, Q.; Toshima, H.; Yoshihara, T. *Tetrahedron*, **2001**, *57*, 5377.

SCHEME 3. Synthesis of Terminal Epoxide 6[a]



[a] Reagents and conditions: (a) $LiAlH_4$, ether, 0 °C, 94%; (b) *p*-TsCl, pyridine, 0 °C, 77%; (c) 1-pentenylmagnesium bromide, CuI, THF, 0−50 °C, 99%; (d) MCPBA, CH_2Cl_2, 0 °C to rt, 87%; (e) (*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt, H_2O, *tert*-butyl methyl ether, rt, 44% for **6**, 44% for **18**; (f) BzCl, pyridine, CH_2Cl_2, −15 °C, and then MsCl, −15 °C to rt, 74%; (g) 4M NaOH, THF−MeOH, −10 °C to rt, 84%.

Our attention was next turned to assembling the long alkyl chain. Generation of a lithium acetylide derived from **5** (*n*-BuLi, THF, −78 °C) followed by addition of the epoxide **6** and $BF_3{\cdot}Et_2O$ in THF at −78 °C cleanly provided coupling product **20** in 91% yield.[14] Selective hydrogenation of the triple bond in **20** was conducted by the use of Wilkinson catalyst in benzene, giving saturated compound **4** in 99% yield. Introduction of a sugar residue into the carbon backbone was performed by the use of 1.5 equiv of trichloacetimide **21**[5,15] in the presence of trimethylsilyl trifluoromethanesulfonate (0.15 equiv) in acetonitrile/CH_2Cl_2 at −40 °C to give the desired β-glycoside **23** in 62% yield along with the corresponding α-anomer **22** (17%). $BF_3{\cdot}Et_2O$-promoted glycosidation resulted in a mixture of anomers in low yield (30−40%). In the ^1H NMR spectra of **23**, the large coupling constant value ($J = 7.0$ Hz) indicates the presence of the equatorial oriented glycosidic linkage of **23**. The TBDPS group in **23** was removed by TBAF to afford **24** in good yield. Jones oxidation of **24** followed by alkaline hydrolysis provided seco acid **3** in good overall yield. Macrocycliztion from **3** into **2** was investigated under a variety of conditions (Table 1).[16] Lactonization of **3** under Yamaguchi's conditions[17] led to monomer **26** in very high yield, while the Mitsunobu reaction[18] of **3** afforded a 1:1 mixture of the desired dimeric compound **2** and **26** (total 20% yield). The use of 2-chloro-1,3-dimethylimidazolinium chloride[19] and (*N*,*N*-dimethylamino)pyridine (DMAP) in the presence of alkaline metal improved the reaction.[20] In particular, addition of sodium hydride in toluene was effective in this system to provide **2** in 35% yield (44% yield based on the starting acid **3** consumed) along with **26** (30%). On the other hand, the use of potassium hydride as a base again afforded monomer **26** as a major product (77%). The structures of both compounds were confirmed by the NMR analyses coupled with MS spectra. This type of macrodilactonization has been well-documented to proceed efficiently in a template-directed manner assisted by admixed metal cations by Fürstner et al.[5] In our case, interesting results were obtained by changing the metal cations (Table 1). In the case of sodium cations, the cyclization of **3** afforded a ca. 1:1 mixture of the desired dimer **2** and the corresponding monomer **26** (entry 4−6). The formation of a considerable amount of **26** suggests that the cations could not preorganize the substrate efficiently in a head-to-tail arrangement suitable for dimerization. Although the carboxylic acid **3** is regarded as a molecule with some degree of ionophoric character, the alkyl chain in **3** may be too long. In the case of KH, the product distribution was similar to that in other conditions (e.g., entry 1). Therefore, the possibility of nontemplating cyclization cannot be ruled out, either. In any case, however, the conformational flexibility of the cyclization precursor interfered with the simple rationalization of the mechanism.

TABLE 1. Macrodimerization[a]

entry	reagents	added metal	solvent	molarity (M)	yield (%) 2	26	3
1	ArCl,[b] DMAP, Et_3N		toluene	0.02	16	83	
2	DEAD, Ph_3P		THF	0.08	10	10	
3	DMC,[c] DMAP		CH_2Cl_2	0.02	trace	24	
4	DMC, DMAP	NaH	CH_2Cl_2	0.02	25	22	19
5	DMC, DMAP	NaH	CH_2Cl_2	0.05	33	33	29
6	DMC, DMAP	NaH	toluene	0.05	35	30	19
7	DMC, DMAP	KH	CH_2Cl_2	0.02	20	77	
8	DMC, DMAP	Cs_2CO_3	CH_2Cl_2	0.02	7	16	48

[a] All reactions were performed at rt. [b] ArCl = 2,4,6-trichlorobenzoyl chloride. [c] DMC = 2-chloro-1,3-dimethylimidazolinium chloride.

In summary, we have succeeded in rapid entry to the core of macroviracin A (**1**) from the hydroxy carboxylic acid **3** through one-step macrocyclization. Work on the total synthesis of **1** from **2** is currently under way.

Experimental Section

(*R*)-4-Dec-9-enyl-2-(4-methoxyphenyl)[1,3]dioxane (8). A mixture of **7** (3.00 g, 14.0 mmol), *p*-methoxybenzaldehyde dimethylacetal (3.39 mL, 19.9 mmol), and camphorsulfonic acid (324 mg, 1.4 mmol) in *N*, *N*-dimethylformamide (15 mL) was heated at 60 °C with stirring under reduced pressure (100 mmHg) for 2 h, cooled, and then poured into sat. $NaHCO_3$ solution. The resulting mixture was extracted with ether. The extracts were washed with water and brine, dried, and concentrated. The residue was chromatographed on silica gel (*n*-hexane:EtOAc = 10:1) to give **8** (4.59 g, 99%) as a white

(14) The optical purity of **6** and the stereochemistry at the C-8 position in **20** were also confirmed by the modified Moshers' method[21] of the corresponding MTPA esters of **20**. Differences in the chemical shifts (Δ_{S-R}) values in δ (400 MHz) between (*R*)- and (*S*)-MTPA esters of **20** are as follows: Me-2 (−0.01), H-2 (−0.02), H-7 (−0.11, −0.09), H-9 (+0.02, +0.07), H-12 (+0.04).

(15) (a) Hoch, M.; Heinz, E.; Schmidt, R. R. *Carbohydr. Res.* **1989**, *191*, 21. (b) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212. (c) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21.

(16) Attempts for macrodimerization of **3** with distannoxane transesterification catalysts[9a,22] failed.

(17) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. (b) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *Tetrahedron* **1990**, *46*, 4613.

(18) Mitsunobu, O. *Synthesis* **1981**, 1.

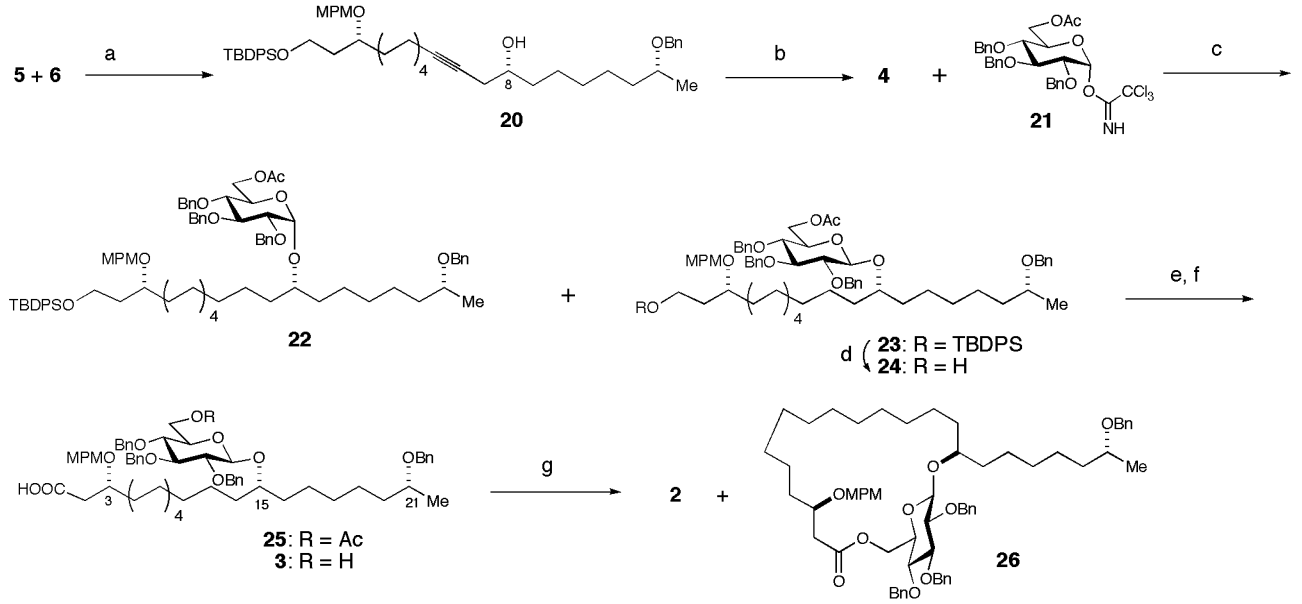
(19) (a) Fujisawa, T.; Mori, T.; Fukumoto, K.; Sato, T. *Chem. Lett.* **1982**, 1891. (b) Isobe, T.; Ishikawa, T. *J. Org. Chem.* **1999**, *64*, 6984.

(20) In these conditions several minor products that seemed to be higher oligomers were also detected as judged by TLC analysis. However, such compounds were not characterized.

(21) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(22) Otera, J. *Chem. Rev.* **1993**, *93*, 1449.

SCHEME 4. Coupling Reaction of 5 with 6 and Macrodimerization[a]



[a] Reagents and conditions: (a) *n*-BuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C, 91%; (b) H_2, $(Ph_3P)_3RhCl$, H_2, benzene, rt, 99%; (c) TMSOTf, MS4A, $CH_3CN-CH_2Cl_2$, −40 °C, 17% for **22**, 62% for **23**; (d) TBAF, THF, rt, 82%; (e) Jones reagent, 0 °C; (f) 1 M NaOH, THF−MeOH, 0 °C, 85% in 2 steps; (g) 2-chloro-1,3-dimethylimidazolinium chloride, NaH, DMAP, toluene, rt, 35% for **2**, 30% for **26**.

glass: $[\alpha]^{22}_D$ +18.6 (*c* 1.05, $CHCl_3$); IR (neat) 2926, 2854, 1616, 1518, 1249, 1170, 1107, 1037, 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.81 (m, 1H), 5.46 (s, 1H), 5.00 (dq, J = 17.2, 1.2 Hz, 1H), 4.93 (dq, J = 10.4, 1.2 Hz, 1H), 4.25 (dd, J = 12.0, 5.2 Hz, 1H), 3.94 (td, J = 12.0, 2.4 Hz, 1H), 3.83−3.78 (m, 1H), 3.80 (s, 3H), 2.04 (q, J = 6.8 Hz, 2H), 1.78−1.26 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 139.0, 131.4, 127.1, 114.0, 113.4, 100.9, 77.2, 67.0, 55.2, 52.5, 36.1, 33.8, 31.4, 29.6, 29.5 (2×), 29.2, 29.0, 25.0.

Anal. Found: C, 75.53; H, 9.63. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H.9.70.

(*R*)-3-(4-Methoxybenzyloxy)tridec-12-en-1-ol (9). To a stirred solution of **8** (4.27 g, 12.8 mmol) in dichloromethane (28 mL) was added dropwise a 0.93 M solution of DIBAL (27.5 mL, 25.6 mmol) in hexane at 0 °C. After the mixture was stirred at 0 °C for 45 min, 2-methyl-2-propanol (7 mL), water (7 mL), and silica gel were sequentially added at the same temperature with stirring. The resulting mixture was stirred at room temperature for 30 min, filtered through a pad of Celite, and then concentrated. The residue was chromatographed on silica gel (*n*-hexane:EtOAc = 4:1 → 2:1) to give **9** (3.96 g, 92%) as a colorless liquid: $[\alpha]^{20}_D$ −29.2 (*c* 1.57, $CHCl_3$); IR (neat) 3421, 3075, 2928, 2855, 1614, 1514, 1249, 1039, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.82 (m, 1H), 4.99 (dq, J = 17.2, 1.2 Hz, 1H), 4.94 (dq, J = 10.4, 1.2 Hz, 1H), 4.54 (d, J = 11.2 Hz, 1H), 4.42 (d, J = 11.2 Hz, 1H), 3.84−3.70 (m, 2H), 3.80 (s, 3H), 3.66−3.60 (m, 1H), 2.45 (t, J = 5.6 Hz, 1H), 2.05 (q, J = 7.2 Hz, 3H), 1.84−1.50 (m, 4H), 1.40−1.25 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 139.0, 130.4, 129.2, 114.0, 113.7, 78.1, 70.5, 60.7, 55.2, 35.9, 33.8, 33.5, 29.8, 29.6, 29.4, 29.1, 28.9, 25.2.

Anal. Found: C, 75.08; H, 10.29. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H.10.29.

(*R*)-*tert*-Butyl-[3-(4-methoxybenzyloxy)tridec-12-enyloxy]diphenylsilane (10). To a stirred solution of **9** (683 mg, 2.04 mmol) and imidazole (278 mg, 4.08 mmol) in *N*,*N*-dimethylformamide (3.7 mL) was added dropwise chloro-*tert*-butyldiphenylsilane (637 μL. 2.45 mmol) at 0 °C. After the mixture was stirred at 0 °C for 1 h, ice water was added. The resulting mixture was stirred at room temperature for 1.5 h, then extracted with ether. The extracts were washed successively with water snd brine, dried, and concentrated. The residue was chromatographed on silica gel (*n*-hexane:EtOAc = 20:1) to give **10** (1.12 g, 96%) as a colorless syrup: $[\alpha]^{23}_D$ −4.2 (*c* 1.13, $CHCl_3$); IR (neat) 3072, 2930, 2856, 1614, 1514, 1428, 1248, 1112, 1087, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73−7.64 (m, 4H), 7.44−7.35 (m, 6H), 7.19 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 5.82 (m, 1H), 4.99 (dq, J = 17.2, 1.2 Hz, 1H), 4.94 (dq, J = 10.4, 1.2 Hz, 1H), 4.42 (d, J = 11.2 Hz, 1H), 4.37 (d, J = 11.2 Hz, 1H), 3.84−3.70 (m, 2H), 3.78 (s, 3H), 3.59 (m, 1H), 2.07−2.02 (m, 2H), 1.75 (m, 2H), 1.59−1.17 (m, 14H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 139.1, 135.5, 134.7, 133.8, 131.1, 129.5, 129.2, 127.5, 114.0, 113.6, 75.7, 70.7, 60.7, 55.3, 37.2, 34.2, 33.9, 29.9, 29.7, 29.6, 29.2, 29.0, 27.0, 26.7, 25.4, 19.7, 19.1

Anal. Found: C, 77.54; H, 9.28. Calcd for $C_{37}H_{52}O_3Si$: C, 77.57; H, 9.15.

(*R*)-12-(*tert*-Butyldiphenylsilanyloxy)-10-(4-methoxybenzyloxy)dodecanal (11). To a stirred solution of **10** (7.26 g, 12.7 mmol) in tetrahydrofuran (160 mL) and water (128 mL) was added dropwise a solution of OsO_4 (ca. 0.84 mmol) in 2-methyl-2-propanol (10.5 mL) at room temperature. After the mixture was stirred for 15 min, $NaIO_4$ (13.6 g, 63.5 mmol) was added over 30 min. After being stirred for an additional 1.8 h, the mixture was filtered through a pad of Celite, and the filtrate was extracted with EtOAc. The extracts were washed successively with 5% Na_2S solution, water, and brine and concentrated. The residue was chromatographed on silica gel (*n*-hexane:EtOAc = 6:1) to give **11** (5.85 g, 80%) as a colorless liquid: $[\alpha]^{23}_D$ −3.8 (*c* 0.97, $CHCl_3$); IR (neat) 3071, 2931, 2857, 2710, 1726, 1514, 1248, 1112, 1087, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, J = 2.0 Hz, 1H), 7.73−7.64 (m, 4H), 7.44−7.35 (m, 6H), 7.18 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 4.41 (d, J = 11.2 Hz, 1H), 4.37 (d, J = 11.2 Hz, 1H), 3.84−3.71 (m, 2H), 3.79 (s, 3H), 3.59 (m, 1H), 2.42 (td, J = 7.6, 2.0 Hz, 2H), 1.75 (m, 2H), 1.68−1.42 (m, 2H), 1.35−1.21 (m, 12H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 158.8, 135.4, 134.6, 133.8, 131.0, 129.5, 129.4, 129.2, 127.6, 113.6, 75.6, 70.6, 60.7, 55.3, 43.9, 37.2, 34.2, 29.8, 29.5, 29.4, 29.2, 27.0, 26.6, 25.4, 22.2, 19.3, 19.1.

Anal. Found: C, 75.19; H, 8.76. Calcd for $C_{36}H_{50}O_4Si$: C, 75.22; H, 8.77.

(*R*)-*tert*-Butyl[13,13-dibromo-3-(4-methoxybenzyloxy)-tridec-12-enyloxy]diphenylsilane (12). To a stirred solution

of carbon tetrabromide (1.02 g, 3.08 mmol) in dichloromethane (6.6 mL) was added dropwise a solution of triphenylphosphine (1.62 g, 6.16 mmol) in dichloromethane (2.0 mL) at 0 °C. After the mixture was stirred for 15 min, triethylamine (1.71 mL, 12.3 mmol) was added. To the resulting mixture was added a solution of **11** (885 mg, 1.54 mmol) in dichloromethane (1.0 mL) at 0 °C with stirring. The mixture was stirred at 0 °C for 21 h, poured into sat. $NaHCO_3$−$Na_2S_2O_3$ (1:1) solution, and then extracted with ether. The extracts were washed successively with sat. $Na_2S_2O_3$ solution, water, and brine and concentrated. The residue was chromatographed on silica gel (*n*-hexane:EtOAc = 15:1) to give **12** (1.03 g, 92%) as a light-yellow syrup: $[\alpha]^{21}_D$ −3.2 (*c* 1.27, $CHCl_3$); IR (neat) 3071, 2930, 2856, 1614, 1513, 1428, 1248, 1112, 1086, 822, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−7.65 (m, 4H), 7.44−7.35 (m, 6H), 7.19(d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 6.39 (t, J = 7.2 Hz, 1H), 4.41 (d, J = 11.2 Hz, 1H), 4.37 (d, J = 11.2 Hz, 1H), 3.85−3.71 (m, 2H), 3.79 (s, 3H), 3.60 (m, 1H), 2.09 (q, J = 7.2 Hz, 2H), 1.75 (m, 2H), 1.58−1.21 (m, 14H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 138.7, 135.4, 134.6, 133.8, 131.0, 129.5, 129.2, 127.5, 113.6, 88.4, 75.6, 70.7, 60.7, 55.3, 37.2, 34.2, 33.1, 29.8, 29.6, 29.4, 29.1, 27.9, 27.0, 26.6, 25.4, 19.3.

Anal. Found: C, 60.67; H, 6.98; Br, 22.01. Calcd for $C_{37}H_{50}O_3Br_2Si$: C, 60.82; H, 6.90; Br, 21.87.

(*R*)-*tert*-Butyl[3-(4-methoxybenzyloxy)tridec-12-ynyloxy]diphenylsilane (5). To a stirred solution of **12** (1.03 g, 1.41 mmol) in tetrahydrofuran (8.4 mL) was added dropwise a 1.59 M solution of *n*-BuLi (1.86 mL, 2.96 mmol) in hexane at −78 °C. The mixture was stirred at −78 °C for 3 h and 0 °C for 40 min. After being quenched with sat. NH_4Cl solution, the resulting mixture was extracted with ether. The extracts were washed with water and brine, dried, and concentrated. The residue was chromatographed on silica gel (*n*-hexane:EtOAc = 10:1) to give **5** (760 mg, 94%) as a light-yellow syrup: $[\alpha]^{23}_D$ −3.6° (*c* 1.06, $CHCl_3$); IR (neat) 3309, 3071, 2932, 2857, 1612, 1514, 1428, 1248, 1112, 1085, 822, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.67−7.64 (m, 4H), 7.46−7.35 (m, 6H), 7.19 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 4.41 (d, J = 11.2 Hz, 1H), 4.37 (d, J = 11.2 Hz, 1H), 3.84−3.71 (m, 2H), 3.79 (s, 3H), 3.59 (m, 1H), 2.19 (td, J = 7.2, 2.4 Hz, 2H), 1.94 (t, J = 2.4 Hz, 1H), 1.75 (m, 2H), 1.57−1.21 (m, 14H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 135.4, 133.8, 131.0, 129.4, 129.2, 127.5, 113.6, 84.7, 75.6, 70.6, 68.1, 60.7, 55.3, 37.2, 34.2, 29.8, 29.5, 29.1, 28.8, 28.6, 27.0, 25.4, 19.3, 18.5.

Anal. Found: C, 77.51; H, 8.86. Calcd for $C_{37}H_{50}O_3Si$: C, 77.84; H, 8.83.

(*R*)-3-Benzyloxybutan-1-ol (14). To a stirred suspension of lithium aluminum hydride (1.38 g, 36.4 mmol) in ether (80 mL) was added dropwise a solution of **13** (10.0 g, 48.0 mmol) in ether (30 mL) at 0 °C, and the mixture was stirred at 0 °C for 2 h. Water (1.4 mL), 10% NaOH solution (1.4 mL), and water (4.2 mL) were sequentially added at 0 °C with stirring. The resulting mixture was filtered through a pad of Celite, and then concentrated. The residue was chromatographed on silica gel (*n*-hexane:EtOAc = 4:1 → 2:1) to give **14** (8.11 g, 94%) as a colorless liquid: $[\alpha]^{23}_D$ −63.8 (*c* 2.09, $CHCl_3$) {$[\alpha]^{23}_D$ −57.5 (*c* 1.0, $CHCl_3$),[13a] $[\alpha]^{23}_D$ −48.1 (*c* 8.3, $CHCl_3$)[13b]}; IR (neat) 3401, 3032, 2969, 2932, 2873, 1455, 1375, 1094, 1054, 737, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29−7.16 (m, 5H), 4.55 (d, J = 11.6 Hz, 1H), 4.37 (d, J = 11.6 Hz, 1H), 3.72−3.65 (m, 3H), 2.63 (br s, 1H), 1.72−1.68 (m, 2H), 1.18 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 128.3, 127.5, 127.4, 74.4, 70.4, 60.6, 38.8, 19.4.

Anal. Found: C,73.02; H, 8.92. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H.8.95.

(*R*)-3-Benzyloxybutyl *p*-Toluenesulfonate (15). To a stirred solution of **14** (3.99 g, 22.1 mmol) in pyridine (25 mL) was added *p*-TsCl (6.03 g, 31.6 mmol) at 0 °C, and the mixture was stirred at 0 °C for 3 h. After addition of crashed ice, the resulting mixture was stirred vigorously for 30 min, poured into ice water, and then extracted with ether. The extracts were washed successively with water, cold HCl solution, water, sat. $NaHCO_3$ solution, water, and brine and concentrated. The residue was chromatographed on silica gel (*n*-hexane:EtOAc = 6:1) to give **15** (5.65 g, 77%) as a white solid: $[\alpha]^{24}_D$ −37.0 (*c* 1.03, $CHCl_3$); IR (KBr) 2974, 2889, 1597, 1462, 1370, 1357, 1191, 1180, 1064, 1026, 939, 888 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 2H), 7.34−7.28 (m, 5H), 7.23 (d, J = 8.0 Hz, 2H), 4.51 (d,J = 11.2 Hz, 1H), 4.27 (d, J = 11.2 Hz, 1H), 4.22−4.07 (m, 2H), 3.54 (m, 1H), 2.42 (s, 3H), 1.84 (m, 1H), 1.18 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 138.3, 132.9, 130.0, 128.2, 127.7, 127.4 (2x), 71.0, 70.6, 67.6, 36.2, 21.7, 19.6.

Anal. Found: C, 64.92; H, 6.69; S, 9.43. Calcd for $C_{18}H_{22}O_4S$: C, 64.64; H, 6.63; S, 9.59.

(*R*)-8-Benzyloxynonan-1-ene (16). To a stirred solution of pentenylmagnesium bromide prepared from magnesium turnings (3.68 g, 0.15 mol) and 5-bromo-1-pentene (19.9 mL, 0.17 mol) in tetrahydrofuran (300 mL) was added a solution of **15** (18.7 g, 55.9 mmol) in tetrahydrofuran (40 mL) at 0 °C over 30 min. Then CuI (1.28 g, 6.72 mmol) was added and the resulting mixture was stirred at 0 °C for 1.5 h, 50 °C for 1.5 h, and room temperature for 12 h. After being quenched with the addition of sat. NH_4Cl solution, the mixture was extracted with ether. The extracts were washed with water and brine and concentrated. The residue was chromatographed on silica gel (*n*-hexane:EtOAc = 50:1) to give **16** (12.8 g, 99%) as a light-yellow liquid: $[\alpha]^{22}_D$ −18.0 (*c* 1.23, $CHCl_3$); IR (neat) 3067, 3030, 2930, 2858, 1640, 1455, 1373, 1069, 910, 733, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25−7.15 (m, 5H), 5.73 (ddt, J = 17.2, 10.4, 6.8 Hz, 1H), 4.91 (dq, J = 17.2, 1.2 Hz, 1H), 4.85 (dq, J = 10.4, 1.2 Hz, 1H), 4.48 (d, J = 12.0 Hz, 1H), 4.37 (d, J = 12.0 Hz, 1H), 3.42 (m, 1H), 1.95−1.88 (m, 2H), 1.57−1.22 (m, 8H), 1.11 (s, J = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 138.9, 128.1, 127.5, 127.2, 114.0, 74.8, 70.3, 36.7, 33.8, 29.3, 29.0, 25.5, 19.7.

Anal. Found: C, 82.52; H, 10.43. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41.

(2*RS*,6*R*)-2-(6-Benzyloxyheptyl)oxirane (17). To a stirred solution of **16** (12.8 g, 55.3 mmol) in dichloromethane (300 mL) was added *m*-chloroperoxybenzoic acid (>65% assay, 33.4 g, 194 mmol) at 0 °C, and the mixture was stirred for 1 d. Triethylamine was added and the mixture was stirred for an additional 30 min and concentrated. The residue was chromatographed on silica gel (*n*-hexane:EtOAc = 20:1) to give **17** (12.0 g, 87%) as a ca. 1:1 diastereomeric mixture: IR (neat) 3032, 2970, 2933, 2859, 1455, 1374, 1136, 1068, 736, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.31 (m, 5H), 4.57 (d, J = 12.0 Hz, 1H), 4.45 (d, J = 12.0 Hz, 1H), 3.51 (m, 1H), 2.92−2.85 (m, 1H), 2.74 (t, J = 4.8 Hz, 1H), 2.46 (dd, J = 4.8, 2.0 Hz, 1H), 1.61−1.27 (m, 8H), 1.19 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 128.1, 127.4, 127.1, 74.7, 70.2, 52.3, 47.0, 36.6, 32.4, 29.5, 26.0, 25.5, 19.7.

Anal. Found: C, 77.34; H, 9.79. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74.

Hydrolytic Kinetic Resolution of 17. A mixture of (*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt (91 mg, 0.15 mmol) and acetic acid (17 μL, 0.30 mmol) in toluene (0.4 mL) was stirred while open to the air for 1 h at room temperature. The solvent was removed by rotary evaporation to leave a brown solid. The resulting catalyst residue and **17** (4.0 g, 16.1 mmol) were dissolved in *tert*-butylmethyl ether (3.8 mL), the mixture was cooled to 0 °C, and water (0.19 mL, 10.5 mmol) was added dropwise at 0 °C with stirring. The resulting mixture was allowed to warm to room temperature with stirring over 20 h, and concentrated. The residue was chromatographed on silica gel (*n*-hexane:EtOAc = 10:1 → 6:1 → 1:1 → 1:0) to give **6** (1.77 g, 44%) and **18** (1.90 g, 44%).

6: light-yellow liquid; $[\alpha]^{26}_D$ −11.6 (*c* 1.27, $CHCl_3$); IR (neat) 2970, 2933, 2859, 1455, 1374, 1136, 1068, 735, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.31 (m, 5H), 4.57 (d, J = 12.0

Hz, 1H), 4.45 (d, J = 12.0 Hz, 1H), 3.51 (m, 1H), 2.89 (m, 1H), 2.74 (t, J = 4.7 Hz, 1H), 2.46 (dd, J = 4.8, 2.7 Hz, 1H), 1.61−1.28 (m, 8H), 1.19 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 128.0, 127.4, 127.1, 74.6, 70.2, 52.2, 46.9, 36.5, 32.4, 29.5, 25.9, 25.4, 19.6.

Anal. Found: C, 77.42; H, 9.84. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74.

18: light-yellow liquid; $[\alpha]^{22}_D$ −19.6 (c 1.09, $CHCl_3$); IR (neat) 3378, 2933, 2860, 1454, 1277, 1069, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.29 (m, 5H), 4.57 (d, J = 12.0 Hz, 1H), 4.45 (d, J = 12.0 Hz, 1H), 3.74−3.63 (m, 2H), 3.50 (m, 1H), 3.43 (ddd, J = 11.2, 7.6, 5.2 Hz, 1H), 2.00 (d, J = 4.4 Hz, 1H), 1.86 (t, J = 6.0 Hz, 1H), 1.60−1.28 (m, 10H), 1.19 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 128.1, 127.5, 127.2, 72.2, 71.6, 70.3, 66.7, 36.6, 33.1, 29.7, 25.5, 25.3, 19.7.

Anal. Found: C, 70.75; H, 9.70. Calcd for $C_{16}H_{26}O_3 \cdot 0.3H_2O$: C, 70.71; H, 9.87.

Transformation of 18 into 6 via 19. To a stirred solution of **18** (1.8 g, 6.8 mmol) in dichloromethane (10 mL) and pyridine (5 mL) was added dropwise benzoyl chloride (0.82 mL, 7.1 mmol) at −15 °C, and the mixture was stirred for 1.5 h. Methanesulfonyl chloride (1.05 mL, 13.5 mmol) was added at −15 °C and stirring was continued for 1 d at −15 °C to rt. After addition of crashed ice, the resulting mixture was stirred vigorously for 6 h, and then extracted with ether. The extracts were washed successively with water, cold HCl solution, water, sat. $NaHCO_3$ solution, water, and brine and concentrated. The residue was chromatographed on silica gel (n-hexane:EtOAc = 20:1 → 10:1 → 4:1) to give **19** (2.25 g, 74%) as a light-yellow syrup; $[\alpha]^{23}_D$ −2.7° (c 1.13, $CHCl_3$); IR (neat) 3032, 2937, 2862, 1725, 1453, 1344, 1274, 1176, 1114, 918, 714 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.0 Hz, 2H), 7.59 (t, J = 8.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 2H), 7.34−7.23 (m, 5H), 5.02 (dtd, J = 7.6, 6.0, 2.8 Hz, 1H), 4.57 (d, J = 12.0 Hz, 1H), 4.53 (dd, J = 12.4, 2.8 Hz, 1H), 4.44(d, J = 12.0 Hz, 1H), 4.39 (dd, J = 12.4, 7.6 Hz, 1H), 3.51 (m, 1H), 3.03 (s, 3H), 1.87−1.71 (m, 2H), 1.61−1.36 (m, 8H), 1.19 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 138.9, 133.2, 129.6, 129.3, 128.4, 128.2, 127.5 (2×), 127.2, 80.2, 74.6, 70.3, 65.5, 38.8, 65.5, 38.8, 36.5, 31.7, 29.3, 25.3, 25.0, 19.7.

Anal. Found: C, 64.27; H, 7.19; S, 7.12. Calcd for $C_{24}H_{32}O_6S$: C, 64.26; H, 7.19; S, 7.15.

To a stirred solution of **19** (2.03 g, 4.53 mmol) in tetrahydrofuran (10 mL) and methanol (10 mL) was added dropwise 4 M NaOH solution (2.3 mL, 9.1 mmol) at −10 °C, and the mixture was stirred for 20 h at −10 °C to rt. After addition of crashed ice, the resulting mixture was extracted with ether. The extracts were washed successively with water and brine and concentrated. The residue was chromatographed on silica gel (n-hexane:EtOAc = 20:1) to give **6** (946 mg, 84%).

(2*R*,8*R*,20*R*)-2-Benzyloxy-22-(*tert*-butyldiphenylsilanyloxy)-20-(4-methoxybenzyloxy)docos-10-yn-8-ol (20). To a stirred solution of **5** (3.00 g, 5.25 mmol) in tetrahydrofuran (30 mL) was added dropwise a 1.59 M solution of n-BuLi (3.1 mL, 4.85 mmol) in hexane at −78 °C, and the mixture was stirred at the same temperature for 1 h. A solution of **6** (1.00 g, 4.04 mmol) in tetrahydrofuran (4.0 mL) was added dropwise at −78 °C, followed by addition of $BF_3 \cdot Et_2O$ (0.61 mL, 4.85 mmol). After being stirred for 1.5 h, the mixture was quenched with sat. NH_4Cl solution and extracted with ether. The extracts were washed with water and brine and concentrated. The residue was chromatographed on silica gel (n-hexane:EtOAc = 20:1 → 10:1 → 2:1) to give **20** (3.02 g, 91%) as a light-yellow syrup. The acetylene **5** (891 mg, 30%) was also recovered.

20: $[\alpha]^{24}_D$ −7.2 (c 0.98, $CHCl_3$); IR (neat) 3449, 3070, 2931, 2857, 1613, 1513, 1248, 1112, 735, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.66 (m, 4H), 7.44−7.35 (m, 9H), 7.24−7.26 (m, 2H), 7.20 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 4.58 (d, J = 12.0 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.45 (d, J = 11.2 Hz, 1H), 4.39 (d, J = 11.2 Hz, 1H), 3.86−3.73 (m, 2H), 3.78 (s, 3H), 3.62 (m, 1H), 3.58 (m, 1H), 3.52 (m, 1H), 2.42 (ddt, J = 16.8, 4.4, 2.4 Hz, 1H), 2.28 (ddt, J = 16.8, 6.8, 2.4 Hz, 1H), 2.19 (m, 2H), 1.99 (d, J = 4.8 Hz, 1H), 1.77 (m, 2H), 1.67−1.26 (m, 24H), 1.20 (d, J = 6.0 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 139.0, 135.4, 133.8, 131.0. 129.4, 129.2, 128.1, 127.5(2x), 127.2, 113.6, 83.2, 76.1, 75.6, 74.8, 70.6, 70.3, 70.1, 60.7, 55.3, 37.2, 36.6, 36.2, 34.2, 29.8, 29.7, 29.6, 29.2, 29.1, 29.0, 27.9, 27.0, 25.7, 25.6, 25.4, 19.7, 19.3, 18.9.

Anal. Found: C, 77.49; H, 9.24. Calcd for $C_{53}H_{74}O_5Si$: C, 77.70; H, 9.10.

(2*R*,8*S*,20*R*)-2-Benzyloxy-22-(*tert*-butyldiphenylsilanyloxy)-20-(4-methoxybenzyloxy)docosan-8-ol (4). A mixture of **20** (200 mg, 0.24 mmol) and tris(triphenylphosphine)-rhodium chloride (11.3 mg, 12.2 μmol) in benzene (1.0 mL) was stirred at rt under hydrogen atmosphere for 10 h, and concentrated. The residue was chromatographed on silica gel (n-hexane:EtOAc = 4:1) to give **4** (201 mg, 99%) as a colorless syrup: $[\alpha]^{25}_D$ −6.5 (c 0.99, $CHCl_3$); IR (neat) 3448, 2929, 2856, 1613, 1514, 1464, 1248, 1112, 735, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.65 (m, 4H), 7.44−7.32 (m, 9H), 7.28−7.26 (m, 2H), 7.19 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 4.57 (d, J = 12.0 Hz, 1H), 4.46 (d, J = 12.0 Hz, 1H), 4.42 (d, J = 11.2 Hz, 1H), 4.37 (d, J = 11.2 Hz, 1H), 3.85−3.72 (m, 2H), 3.80 (s, 3H), 3.60 (m, 2H), 3.51 (m, 1H), 1.76 (m, 2H), 1.64−1.23 (m, 32H), 1.20 (d, J = 6.0 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 135.4, 133.9, 131.1, 129.4, 129.2, 128.2, 127.5, 127.2, 113.6, 75.7, 74.8, 72.0, 70.7, 70.3, 60.7, 55.3, 37.6, 37.5, 37.2, 36.7, 34.3, 29.9 (2×), 29.8 (2×), 29.7, 27.0, 25.8, 25.7, 25.6, 25.4, 19.7, 19.3.

Anal. Found: C, 77.24; H, 9.55. Calcd for $C_{53}H_{78}O_5Si$: C, 77.32; H, 9.55.

Glycosidation of 4. To a stirred solution of **4** (1.56 g, 1.93 mmol), **21** (2.01 g, 2.89 mmol), and MS 4A (600 mg) in dichloromethane (11 mL) and acetonitrile (11 mL) was added dropwise trimethylsilyl trifluoromethanesulfonate (52 μL, 289 μmol) at −40 °C, and the mixture was stirred at the same temperature for 2.5 h. After addition of sat. $NaHCO_3$ solution, the resulting mixture was filtered through a pad of Celite. The filtrate was diluted with water and extracted with dichloromethane. The extracts were washed with water and brine and concentrated. The residue was chromatographed on silica gel (n-hexane:EtOAc = 10:1 → 8:1) to give **23** (1.57 g, 62%) and the corresponding α-anomer **22** (420 mg, 17%).

22: colorless syrup; $[\alpha]^{25}_D$ +27.2 (c 0.47, $CHCl_3$); IR (neat) 3032, 2930, 2856, 1744, 1514, 1455, 1247, 1090, 1029, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.64 (m, 4H), 7.36−7.28 (m, 24H), 7.18 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 5.01 (d, J = 11.2 Hz, 1H), 4.92 (d, J = 3.2 Hz, 1H), 4.87 (d, J = 10.0 Hz, 1H), 4.82 (d, J = 10.0 Hz, 1H), 4.73 (d, J = 12.0 Hz, 1H), 4.67 (d, J = 12.0 Hz, 1H), 4.56 (d, J = 11.2 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.45 (d, J = 12.0 Hz, 1H), 4.41 (d, J = 11.2 Hz, 1H), 4.36 (d, J = 11.2 Hz, 1H), 4.29 (dd, J = 12.0, 4.0 Hz, 1H), 4.24 (d, J = 12.0 Hz, 1H), 4.01 (t, J = 9.6 Hz, 1H), 3.90 (m, 1H), 3.81−3.73 (m, 2H), 3.78 (s, 3H), 3.60−3.45 (m, 5H), 2.01 (s, 3H), 1.75 (m, 2H), 1.55−1.19 (m, 5H), 1.17 (d, J = 6.0 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 158.8, 139.0, 138.6, 138.0, 137.7, 135.4, 133.8, 131.1, 129.4, 129.2, 128.4, 128.3 (2×), 128.2, 128.1, 127.8 (2×), 127.7, 127.5, 127.2, 113.6, 95.5, 82.0, 80.1, 78.4, 77.5, 75.7, 75.6, 75.1, 74.8, 73.2, 70.7, 70.3, 68.9, 63.2, 60.7, 55.3, 37.2, 36.7, 34.5, 34.3, 33.3, 30.1, 30.0, 29.9 (2×), 29.8, 29.7, 27.0, 25.9, 25.6, 25.5, 25.1, 20.9, 19.7, 19.3.

Anal. Found: C, 75.78; H, 8.44. Calcd for $C_{82}H_{108}O_{11}Si$: C, 75.89; H, 8.39.

23: colorless syrup; $[\alpha]^{23}_D$ +3.4 (c 1.15, $CHCl_3$); IR (neat) 3032, 2930, 2856, 1745, 1613, 1513, 1455, 1361, 1247, 1071, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67−7.64 (m, 4H), 7.44−7.24 (m, 24H), 7.18 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 4.97 (d, J = 11.2 Hz, 2H), 4.94 (d, J = 11.2 Hz, 1H), 4.85 (d, J = 11.2 Hz, 1H), 4.78 (d, J = 10.8 Hz, 1H), 4.71 (d, J = 11.2 Hz, 1H), 4.55 (d, J = 10.8 Hz, 1H), 4.54 (d, J = 12.0 Hz, 1H), 4.44 (d, J = 12.0 Hz, 1H), 4.43 (d, J = 7.0 Hz, 1H),

4.41 (d, J = 11.2 Hz, 1H), 4.36 (d, J = 11.2 Hz, 1H), 4.32 (dd, J = 12.0, 2.2 Hz, 1H), 4.18 (dd, J = 12.0, 4.6 Hz, 1H), 3.84−3.71 (m, 2H), 3.78 (s, 3H), 3.68−3.56 (m, 3H), 3.53−3.40 (m, 4H), 2.05 (s, 3H), 1.75 (m, 2H), 1.58−1.19 (m, 32H), 1.16 (d, J = 6.2 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 158.8, 139.0, 138.4, 138.3, 137.7, 135.4, 133.8, 131.1, 129.4, 129.2, 128.3 (2×), 128.2 (2×), 128.0, 127.8, 127.7, 127.5 (2×), 113.6, 102.6, 84.9, 82.3, 80.3, 77.7, 75.7, 74.9, 74.8, 72.6, 70.6, 70.2, 63.3, 60.7, 55.3, 37.2, 36.7, 34.9, 34.2, 30.2, 29.9, 29.8, 29.7 (3×), 26.7, 25.6, 25.4, 25.3, 20.9, 19.7, 19.3.

Anal. Found: C, 76.11; H, 8.48. Calcd for $C_{82}H_{108}O_{11}Si$: C, 75.89; H, 8.39.

(3*R*,15*S*,21*R*)-15-(6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-*β*-D-glucopyranosyloxy)-21-benzyloxy-3-(4-methoxybenzyloxy)-docosan-1-ol (24). To a stirred solution of **23** (1.79 g, 1.32 mmol) in tetrahydrofuran (12.7 mL) was added dropwise a 1.0 M solution of *n*-tetrabutylammonium fluoride (1.98 mL, 1.98 mmol) in tetrahydrofuran at rt, and the mixture was stirred at the same temperature for 6 h. After addition of water, the resulting mixture was extracted with ether. The extracts were washed with water and brine and concentrated. The residue was chromatographed on silica gel (*n*-hexane:EtOAc = 4:1 → 2:1 → 1:1) to give **24** (1.14 g, 82%) as a colorless syrup: $[\alpha]^{26}_D$ −3.8 (*c* 1.04, $CHCl_3$); IR (neat) 3484, 3032, 2929, 2855, 1744, 1514, 1455, 1247, 1069, 736, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.23 (m, 22H), 6.87 (d, J = 8.8 Hz, 2H), 4.96 (d, J = 11.2 Hz, 1H), 4.94 (d, J = 11.2 Hz, 1H), 4.85 (d, J = 10.8 Hz, 1H), 4.78 (d, J = 11.2 Hz, 1H), 4.71 (d, J = 10.8 Hz, 1H), 4.56 (d, J = 11.2 Hz, 1H), 4.54 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 11.2 Hz, 1H), 4.44 (d, J = 11.2 Hz, 1H), 4.42 (d, J = 7.7 Hz, 1H), 4.41 (d, J = 12.0 Hz, 1H), 4.31 (dd, J = 12.0, 2.4 Hz, 1H), 4.18 (dd, J = 12.0, 5.6 Hz, 1H), 3.80−3.60 (m, 5H), 3.79 (s, 3H), 3.50−3.41 (m, 4H), 2.45 (dd, J = 6.0, 4.8 Hz, 1H), 2.02 (s, 3H), 1.58−1.19 (m, 34H), 1.16 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 159.0, 138.9, 138.3 (2×), 137.6, 130.4, 129.2, 128.3, 128.2, 128.1 (2×), 127.9, 127.7 (2×), 127.6, 127.4, 127.2, 113.7, 102.5, 84.8, 82.3, 80.2, 78.2, 77.6, 75.6, 74.9, 74.8 (2×), 72.5, 70.5, 70.2, 63.3, 60.7, 55.2, 36.7, 35.9, 34.9, 34.2, 33.5, 30.1, 29.8, 29.7 (2×), 25.5, 25.3, 25.2, 20.9, 19.7.

Anal. Found: C, 74.80; H, 8.64. Calcd for $C_{66}H_{90}O_{11}$: C, 74.82; H, 8.56.

(3*R*,15*S*,21*R*)-21-Benzyloxy-15-(2,3,4-tri-*O*-benzyl-*β*-D-glucopyranosyloxy)-3-(4-methoxybenzyloxy)docosanoic Acid (3). To a stirred solution of **24** (106 mg, 0.10 mmol) in acetone (5 mL) was added dropwise Jones reagent (ca. 0.13 mL) at 0 °C, and the mixture was stirred at the same temperature for 20 min. 2-Methyl-2-propanol was added followed by addition of water, and the resulting mixture was extracted with chloroform. The extracts were washed with water and brine and concentrated to give **25** (99.5 mg), which was dissolved in methanol (0.53 mL) and tetrahydrofuran (0.53 mL). To this solution was added dropwise 1.0 M NaOH solution (0.37 mL) at 0 °C with stirring. The mixture was stirred at 0 °C for 20 min, acidified with Dowex-50W X-8 (H^+) resin, and filtered through a pad of Celite. The filtrate was evaporated to give a syrup, which was chromatographed on silica gel (*n*-hexane:EtOAc:acetic acid = 400:100:1) to give **3** (87.4 mg, 85%) as a white glass; $[\alpha]^{23}_D$ −2.7° (*c* 1.05, $CHCl_3$); IR (neat) 3434, 3032, 2922, 2850, 1717, 1614, 1515, 1455, 1350, 1251, 1072, 819, 738, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.29 (m, 22H), 6.88 (d, J = 8.8 Hz, 2H), 4.95 (d, J = 11.2 Hz, 1H), 4.93 (d, J = 10.8 Hz, 1H), 4.86 (d, J = 11.2 Hz, 1H), 4.80 (d, J = 11.2 Hz, 1H), 4.71 (d, J = 10.8 Hz, 1H), 4.63 (d, J = 11.2 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 11.2 Hz, 1H), 4.49 (d, J = 11.2 Hz, 1H), 4.48 (d, J = 7.7 Hz, 1H), 4.44 (d, J = 12.0 Hz, 1H), 3.87−3.82 (m, 2H), 3.80 (s, 3H), 3.71−3.64 (m, 3H), 3.56 (t, J = 9.6 Hz, 1H), 3.49−3.30 (m, 3H), 2.59 (dd, J = 16, 2.4 Hz, 1H), 2.55 (dd, J = 16, 1.2 Hz, 1H), 1.66−1.19 (m, 32H), 1.16 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 159.0, 138.9, 138.4, 138.3, 137.8, 130.1, 129.3, 128.3, 128.2 (2×), 128.1, 127.9, 127.7 (3×), 127.6, 127.4 (2×), 127.2, 113.7, 102.4, 84.7, 82.3, 80.1, 77.7, 77.3, 76.7, 75.6, 75.3, 74.9, 72.8 (2×), 74.7, 71.1, 70.2, 62.2, 55.2, 39.5, 39.4, 36.7, 34.9, 34.2, 30.1, 29.8, 29.7 (2×), 29.6 (2×), 25.5, 25.4, 25.2, 25.1, 19.7.

Anal. Found: C, 74.65; H, 8.57. Calcd for $C_{64}H_{86}O_{11}$: C, 74.53; H, 8.40.

Macrocyclization of 3. To a stirred solution of **3** (18.6 mg, 18.0 μmol) in toluene (0.35 mL) was added dropwise a 25% solution of 2-chloro-1,3-dimethylimidazolidium chloride (30 μL, 43.9 μmol) in dichloromethane at 0 °C. After 5 min, sodium hydride (60% suspension in mineral oil, 1.5 mg, 38 μmol) was added and the mixture was stirred at 0 °C for 1 h. (*N*,*N*-Dimethylamino)pyridine (5.2 mg, 42.5 μmol) was then added and stirring was continued for 90 h at room temperature. The reaction mixture was directly poured onto a column of silica gel (*n*-hexane:EtOAc =10:1). Elution with *n*-hexane:EtOAc = 10:1 → 4:1 gave a syrup, which was further purified by preparative TLC (*n*-hexane:EtOAc = 4:1,three developments) to give **2** (6.4 mg, 35%) and **26** (5.5 mg, 30%). In addition, starting material **3** (3.6 mg, 19%) was also recovered.

2: white solid; $[\alpha]^{23}_D$ +3.7 (*c* 1.05, $CHCl_3$); IR (neat) 3032, 2923, 2853, 1740, 1514, 1455, 1249, 1070, 743, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.28 (m, 44H), 6.83 (d, J = 8.8 Hz, 4H), 4.96 (d, J = 10.8 Hz, 2H), 4.93 (d, J = 11.2 Hz, 2H), 4.84 (d, J = 11.2 Hz, 2H), 4.78 (d, J = 11.2 Hz, 2H), 4.69 (d, J = 11.2 Hz, 2H), 4.57 (d, J = 10.8 Hz, 2H), 4.54 (d, J = 12.0 Hz, 2H), 4.49−4.41 (m, 8H), 4.37 (d, J = 7.9 Hz, 2H), 4.42−4.37 (m, 2H), 4.10 (dd, J = 11.6, 6.8 Hz, 2H), 3.86 (m, 2H), 3.74 (s, 6H), 3.64 (t, J = 8.8 Hz, 2H), 3.56 (m, 2H), 3.50−3.36 (m, 8H), 2.58 (dd, J = 15.6, 8.0 Hz, 2H), 2.43 (dd, J = 15.6, 5.6 Hz, 2H), 1.55−1.22 (m, 64H), 1.16 (d, J = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 158.9, 139.0, 138.4, 138.3, 137.6, 130.6, 129.2, 128.3, 128.2 (2×), 127.9, 127.8, 127.7 (2×), 127.5, 127.4, 127.2, 113.6, 102.9, 84.9, 82.4, 80.8, 78.0, 75.8, 75.7, 75.0, 74.8 (2×), 72.7, 71.3, 70.2, 63.5, 55.2, 39.9, 36.7, 35.1, 34.6 (2×), 30.2, 30.1 (2×), 30.0 (3×), 29.9 (2×), 25.6 (2×), 25.5, 25.3, 19.7; ESI-FTMS calcd for $C_{128}H_{168}O_{20}Na$ [M + Na]$^+$ 2049.2055, found 2049.1980.

26: colorless glass; $[\alpha]^{21}_D$ +1.9 (*c* 0.99, $CHCl_3$); IR (neat) 3032, 2926, 2855, 1741, 1513, 1455, 1355, 1248, 1071, 737, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.25 (m, 22H), 6.84 (d, J = 8.8 Hz, 2H), 4.96 (d, J = 10.8 Hz, 1H), 4.94 (d, J = 10.8 Hz, 1H), 4.86 (d, J = 11.2 Hz, 1H), 4.78 (d, J = 10.8 Hz, 1H), 4.70 (d, J = 11.2 Hz, 1H), 4.57 (d, J = 10.8 Hz, 1H), 4.55 (d, J = 11.2 Hz, 1H), 4.48 (br s, 2H), 4.45 (d, J = 12.0 Hz, 1H), 4.43 (d, J = 7.5 Hz, 1H), 4.40 (dd, J = 12, 1.5 Hz, 1H), 4.17 (d, J = 12.0, 6.8 Hz, 1H), 3.88 (m, 1H), 3.76 (s, 3H), 3.66 (t, J = 9.2 Hz, 1H), 3.60−3.56 (m, 1H), 3.53−3.37 (m, 4H), 2.62 (dd, J = 15.6, 6.8 Hz, 1H), 2.46 (dd, J = 15.6, 6.0 Hz, 1H), 1.61−1.22 (m, 32H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 158.9, 139.0, 138.4, 138.3, 137.7, 130.6, 129.2, 128.4, 128.2 (2×), 128.0, 127.9, 127.8 (3×), 127.7 (2×), 127.6, 127.5 (2×), 127.4, 127.2, 113.7, 102.9, 84.9, 82.3, 81.0, 78.2, 77.3, 75.7, 75.3, 75.0, 74.8, 72.8, 71.0, 70.2, 63.7, 55.3, 39.4, 36.7, 35.1, 34.5, 33.2, 30.2, 29.4, 28.6, 28.1, 27.5, 27.3, 26.9, 26.8, 25.6, 25.5, 25.2, 23.5, 19.7; FABMS calcd for $C_{64}H_{84}O_{10}Na$ [M + Na]$^+$ 1035.5962, found 1035.5956.

Acknowledgment. We are grateful to Mr. S. Hyoudo (Kaken Pharm. Co.) for providing us natural macroviracins. We also thank Dr. T. Nakamura (RIKEN) for mass spectral measurements and Dr. T. Chihara and his collaborators in RIKEN for the elemental analyses.

Supporting Information Available: General procedures and copies of ^{1}H and ^{13}C NMR spectra of compounds **2** and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0496392