The First Total Synthesis of (+)-Bullatacin, a Potent Antitumor *Annonaceous* Acetogenin, and (+)-(15,24)-*bisepi*-Bullatacin†

Hiroyuki Naito, Eiji Kawahara, Katsunori Maruta, Minoru Maeda, and Shigeki Sasaki*

Faculty of Pharmaceutical Sciences, Kyushu University 3-1-1 Maidashi, Higashi-ku, Fukuoka 812, Japan

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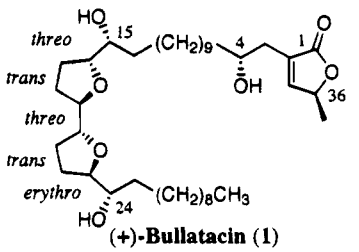
This paper reports the first total synthesis of the natural product (+)-bullatacin (**1**), a representative of potent antitumor *Annonaceous* acetogenins, as well as a stereoisomer (+)-(15,24)-*bisepi*-bullatacin (**2**). In this synthesis, a new, efficient method has been developed to introduce the γ-lactone into the bistetrahydrofuran skeleton through *in situ* alkylation of epoxide **4** by the α-sulfonyl carbanion of phenyl sulfone **5**. The methylated γ-lactone was successfully synthesized by a sequence of reactions comprising an aldol reaction, an acidic lactonization, and elimination under mild, basic condition.

Introduction

In recent years, a number of new natural products in the family of *Annonaceous* acetogenins have been isolated from the genera of *Annonoceae* plants. They have several structural characteristics: (1) more than one tetrahydrofuran ring, (2) relatively long unbranched alkyl chains functionalized with hydroxyl groups, acetoxyl groups, or a ketone, and (3) an α,β-unsaturated or saturated γ-lactone attached to the end of a long alkyl chain.[1] Their absolute and relative structures have been elucidated mainly from spectral studies such as those of the MTPA esters.[2] These tetrahydrofuranic acetogenins have attracted much attention because of their diverse biological effects.[1] In particular, they are expected to be new candidates for anticancer agents based on the promising antitumor effects shown by *in vitro* as well as *in vivo* studies.[3,4] Biochemical studies have revealed their inhibitory effects toward mitochondrial respiration and NADH oxidase of tumor cells,[3] and their calcium-selective binding nature has also been reported.[5] Such biological and chemical effects are significantly influenced by their absolute and relative structures, and therefore an efficient and stereocontrolled synthesis is desired.

Structure of (+)-Bullatacin (1). (+)-Bullatacin (**1**), a representative of *Annonaceous* acetogenins, has a hydroxylated bistetrahydrofuran (bis-THF) and an α,β-unsaturated γ-lactone and exhibits quite potent antitumor activity.[6] The structure of (+)-squamocin G has been reported to be the same as that of **1**.[7] As a result of many



(+)-Bullatacin (1)
(Squamocin G)

synthetic studies on *Annonaceous* acetogenins,[8] (−)-bullatacin, the enantiomer of the natural product, has been synthesized.[8b] The previous syntheses of the acetogenins have entailed (1) construction of the THF ring through acid-catalyzed opening of a chiral epoxide[8a-c,e,f] or asymmetric haloetherification,[8d] (2) introduction of a γ-lactone unit by cross-coupling with a Pd(0) catalyst[8a-c] or Grignard reaction,[8e] and (3) formation of a methylated γ-lactone through aldol addition with a chiral aldehyde[8d] or alkylation with a chiral epoxide.[8b,e] We developed a new and efficient method for the coupling of the bis-THF skeleton and the γ-lactone through *in situ* alkylation of epoxide **4** with an α-sulfonyl carbanion of phenyl sulfone **5** and succeeded in the total synthesis of (+)-bullatacin (Figure 1). In this paper, we report in detail the first total synthesis of natural (+)-bullatacin (**1**) and its stereoisomer (+)-(15,24)-*bisepi*-bullatacin (**2**).

Results

The synthesis of key intermediate **6** started with diethyl 2,3-*O*-isopropylidene-D-tartrate (Scheme 1). Diethyl 2,3-*O*-isopropylidene-D-tartrate was reduced with DIBALH to give the corresponding aldehyde, followed by a Wittig–Horner reaction[9] without isolation, and then catalytic hydrogenation of the α,β-unsaturated ester over

* Author to whom correspondences should be addressed. Phone: +81-92-641-1151 (ex. 6192). Fax: +81-92-641-8154. E-mail: sasaki@chemgate.phar.kyushu-u.ac.jp.

† For a recent total synthesis of (+)-bullatacin, see: Hoye, T. R.; Tan, L. *Tetrahedron Lett.* **1995**, in press.

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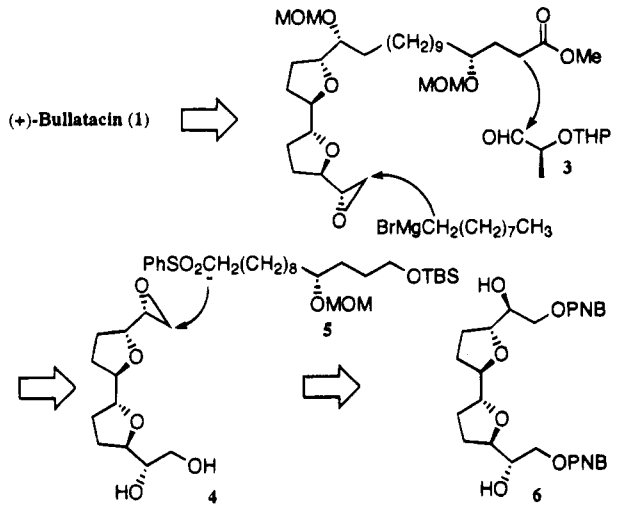

Figure 1.

Pd/C afforded **7** (86%). The same sequence of reactions with DIBALH and the ylide provided *trans-trans* diester **8** in 78% purified yield. Diallyl alcohol **9** was obtained by the reduction of **8** with DIBALH in 86% yield. According to the Sharpless protocol, catalytic asymmetric epoxidation of diallyl alcohol **9** was performed using L-(+)-diisopropyl tartrate as the chiral ligand,[10] followed by *in situ* protection of the primary alcohol with *p*-nitrobenzoyl chloride[11] to afford **10** (96%). Acid-catalyzed removal of the acetonide and simultaneous opening of the epoxide to construct the hydroxylated bis-THF skeleton **6** were most effectively achieved using a catalytic amount of $BF_3{\cdot}Et_2O$ in the presence of a small amount of water (10 mol % of $BF_3{\cdot}Et_2O$) in CH_2Cl_2–MeOH at rt (92%).[12] No isomer peaks were detected in the ^{13}C-NMR spectrum of **6**. The above method demonstrated efficient synthesis of key intermediate **6** in 51% overall yield from diethyl D-tartrate.

The intermediate **6** has the *erythro-trans-threo-trans-erythro* configuration and is C_2-symmetric. Therefore, stereochemical inversion of one of the hydroxy groups of **6** was required to construct (+)-bullatacin (**1**). Thus, **6** was monomesylated with 1.5 equiv of MsCl and TEA in THF to give the desired **11** in 86% yield, after repeating the same reaction three times using the recovered **6**. Hydrolysis of the *p*-nitrobenzoyl ester of **11** with *n*-Bu_4NOH and simultaneous epoxide formation afforded **4** with the desired *threo-trans-threo-trans-erythro* configuration, in quantitative yield.

The synthetic route to sulfone **5**, which is the precursor of the alkyl chain with the γ-lactone, is shown in Scheme 2. The aldehyde **12** was prepared in 43% yield from decamethylene glycol and subjected to Brown's asymmetric allylation with allyl-B(^{d}Ipc)$_2$[13] to provide (*R*)-**13** in 66% yield with 92% ee.[14] Alcohol **13** was treated as follows: protection (MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to rt), hydroboration (BH_3·THF, THF, −20 °C to rt, then NaOH, H_2O_2, 0 °C to rt), protection (TBDMSCl, TEA, imidazole, CH_2Cl_2, 0 °C to rt), deprotection (Li/NH_3, −78 °C), tosylation (TsCl, pyridine, 0 °C), thioetherification (PhSH, NaH, THF, 0 °C to rt), and oxidation (magnesium monoperoxyphthalate (MMPP), EtOH–H_2O, rt)[15] to give sulfone **5** in 18% overall yield from decamethylene glycol.

As a result of several investigations of the nucleophilic epoxide opening of **4** by the α-sulfonyl carbanion of **5**, it was deduced that the reaction is most efficiently performed by *in situ* trapping of the α-sulfonyl carbanion with epoxide **4** (Scheme 3). Thus, 4.0 equiv of *n*-BuLi was added dropwise into a mixture of **4** and 2.0 equiv of **5** in DME at rt, and the reaction was complete immediately after the addition (83%).[16] Desulfonation with sodium amalgam afforded the desired alkylated product **15** in 80% purified yield. Epoxide **16** was prepared in 57% yield in two steps (TsCl, pyridine, −20 °C, then K_2CO_3/MeOH–H_2O, rt). A nonyl chain was introduced onto the epoxide of **16** (CuBr, $CH_3(CH_2)_8MgBr$, THF, 0 °C), and the subsequent protection of hydroxy groups with MOMCl afforded **17** in 64% yield, which furnished the desired structure with the same stereochemistry as (+)-bullatacin (**1**) except for the α,β-unsaturated γ-lactone.

The construction of the γ-lactone and the completion of the total synthesis are shown in Scheme 3. Methyl ester **18** was obtained in 71% yield in three steps from **17** by the following sequence of reactions: desilylation with *n*-Bu_4NF, oxidation with Jones' reagent, and then esterification with diazomethane. The ester **18** was treated with LDA and subjected to an aldol reaction with aldehyde **3**, which was prepared from (*S*)-(−)-methyl lactate. During the deprotection of THP with CSA in MeOH–H_2O, the lactone was simultaneously formed to afford the hydroxy lactone, which was transformed into the α,β-unsaturated γ-lactone **19** through benzoylation followed by elimination with ammonia in methanol.[17] The overall yield of **19** from **18** was 48% in four steps. Finally, deprotection of the MOM groups of **19** with $BF_3{\cdot}Et_2O$ in DMS provided (+)-bullatacin (**1**) in quantitative yield. The obtained compound is identical with natural (+)-squamomcin G,[7] *i.e.*, (+)-bullatacin (**1**), with respect to spectroscopic properties and analysis by reverse-phase HPLC.

The same method of alkylation through *in situ* trapping of the α-sulfonyl carbanion by an epoxide was applied to the synthesis of (+)-(15,24)-*bisepi*-bullatacin (**2**) with an *erythro-trans-threo-trans-threo* configuration as shown in Scheme 4. The monomesylate **11** was protected with MOMCl and then treated with *n*-Bu_4NOH followed by silylation with *t*-$BuPh_2SiCl$ to afford the protected epoxide **20** in 84% overall yield from **11**. Alkylation of **20** with a Grignard reagent (CuBr, $CH_3(CH_2)_8MgBr$, THF, 0 °C) gave **21**, which was converted to the epoxide **22** in 74% yield (five steps from **20**). The alkylation of **22** by the α-sulfonyl carbanion of **5** was carried out in the same manner as described above, and protection of the resulting alcohol followed by desulfona-

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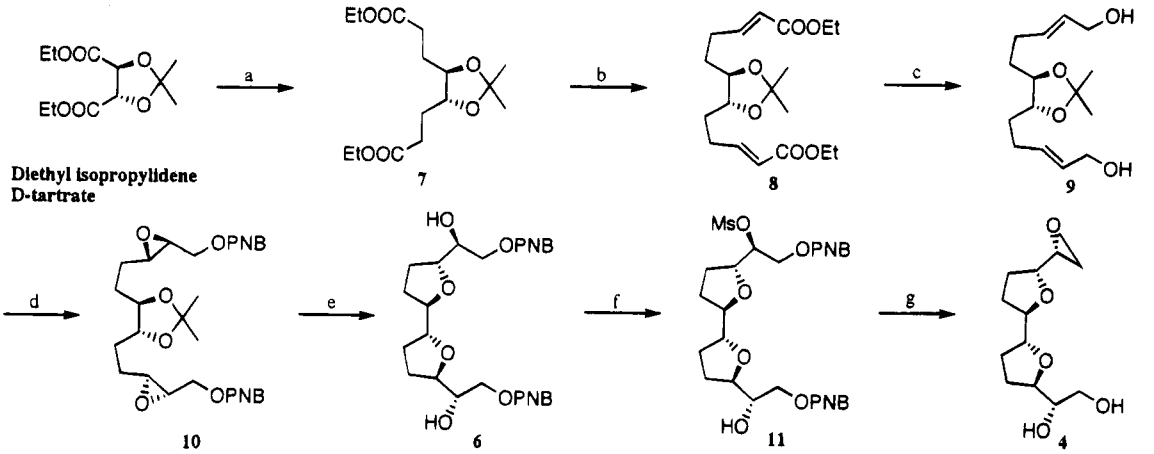
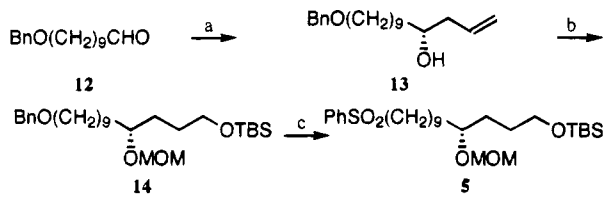
(16) These reaction conditions were most effective because the α-sulfonyl carbanion turned out to be labile and easily decomposed.
(17) No epimerization was observed during the formation of 4-methyl 2-buten-4-olides: Takahata, H.; Uchida, Y.; Momose, T. *Tetrahedron Lett.* **1994**, *35*, 4123. We did not succeed in eliminating the MOM ether of the hydroxyl lactone with DBU, although this method was reported in ref 8d.

Scheme 1[a]



[a] (a) (1) DIBALH, toluene, −78 °C, (2) $(EtO)_2P(O)CH_2CO_2Et$, NaH, DME, −78 °C to rt, (3) H_2, 5% Pd/C, EtOH, rt; (b) (1) DIBALH, toluene, −78 °C, (2) $(EtO)_2P(O)CH_2CO_2Et$, NaH, DME, −78 °C to rt; (c) DIBALH, CH_2Cl_2, toluene, −78 °C; (d) (1) (+)DIPT, Ti(O-*i*-Pr)$_4$, TBHP, 4 Å MS, CH_2Cl_2, −30 °C to −20 °C, (2) PNBCl, TEA, 0 °C; (e) BF_3·Et_2O, MeOH−CH_2Cl_2, H_2O, 0 °C to rt; (f) MsCl, TEA, THF, 0 °C; (g) *n*-Bu_4NOH, THF, 0 °C.

Scheme 2[a]



[a] (a) (1) allyl-B(^{d}Ipc)$_2$, Et_2O, −78 °C, (2) NaOH, H_2O_2, −78 °C to rt; (b) (1) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to rt, (2) BH_3·THF, THF, −20 °C to rt, (3) NaOH, H_2O_2, 0 °C to rt, (4) TBDMSCl, TEA, imidazole, CH_2Cl_2, 0 °C to rt; (c) (1) Li, liquid NH_3, −78 °C, (2) TsCl, pyridine, 0 °C, (3) PhSH, NaH, THF, 0 °C to rt, (4) MMPP, EtOH−H_2O, rt.

tion gave **23** in 74% yield. (+)-(15,24)-*bisepi*-Bullatacin (**2**) was obtained from **23** according to the same procedure as described for (+)-bullatacin (**1**) in 41% overall yield (8 steps).

The *in vitro* antitumor activities of eight compounds against P388 are shown in Table 1.[18] Natural product **1** shows a more potent antitumor activity than unnatural stereoisomer **2**. A comparison of the antitumor activities of the natural products (**1**, **2**) and the model compounds (**24**−**28**) indicates that the γ-lactone and 4-hydroxy groups are essential for high antitumor activity.

In conclusion, we have established an efficient method for the total synthesis of the natural product (+)-bullatacin (**1**) and related tetrahydrofuranic acetogenins. This method is applicable to the synthesis of unnatural derivatives of the acetogenins, and further study is ongoing to develop more potent antitumor agents.

Experimental Section

General. ^{1}H NMR spectra were taken at 500, 270, or 60 MHz. ^{13}C NMR spectra were run at 68 MHz and referenced to the central line of the solvent. Analytical TLC was carried out on Merck precoated TLC plates (Kieselgel 60 F_{254}, 0.2 mm). Column chromatography was done using silica gel BW200 (150−350 mesh, Fuji Devision) and medium-pressure chromatography was done by using silica gel FL60D or silica gel CQ.3 (Fuji Devision). Reverse phase HPLC was performed using nacalai tesque COSMOSIL 5C18-MS (4.6 × 250 mm) as a column and methanol/water (93:7) as an eluent with monitoring at 220 nm.

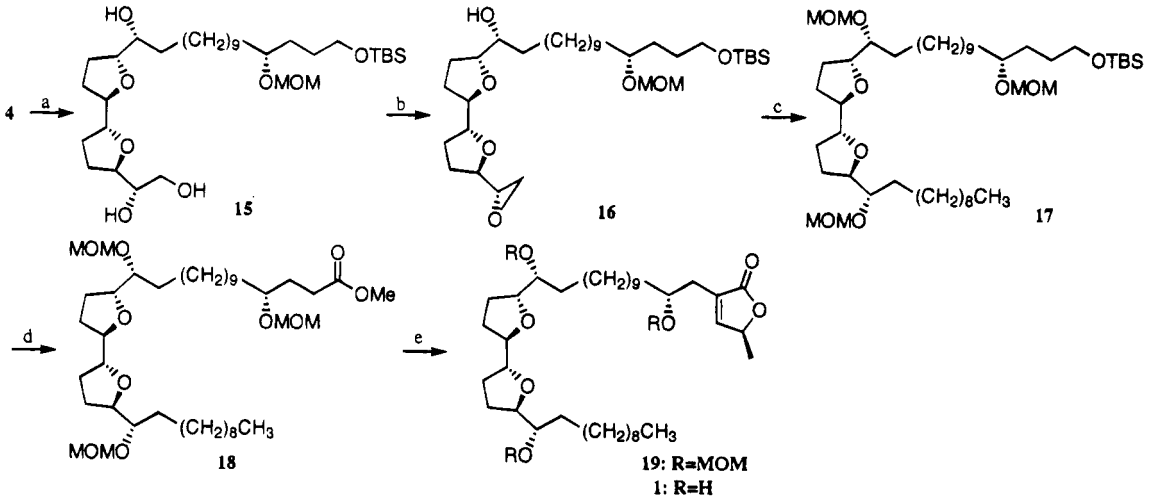
Diethyl (+)-(4*R*,5*R*)-4,5-*O*-Isopropylidene-4,5-dihydroxyoctanedioate (7). A solution of DIBALH (95 mL of a 1.5 M solution in toluene, 0.143 mol) was added dropwise to a solution of diethyl 2,3-*O*-isopropylidene-D-tartrate (16.0 g, 0.065 mol) in anhyd toluene (200 mL) at −78 °C under an argon atm, and the mixture was stirred for 2.5 h at −78 °C. On the other hand, ethyl (diethylphosphono)acetate (39 mL, 0.195 mol) was added to a suspension of NaH (7.80 g of 60% in mineral oil, 0.195 mol) in anhyd DME (180 mL) at 0 °C under argon atm. The mixture was stirred for 30 min at rt. This solution was added dropwise to the reaction mixture of the DIBALH at −78 °C during 1 h, and the mixture was stirred at rt for 12 h. Water (100 mL), diethyl ether (500 mL), and Celite (100 g) were successively added to the reaction mixture, and the whole was filtered through a Celite pad. The filtrate was washed with water and brine and then dried over $MgSO_4$. Filtration and evaporation of the solvent afforded the crude mixture which was chromatographed on a silica gel column (hexane/AcOEt = 6/1) to give the corresponding α,β-unsaturated diester (17.0 g, 88%). The diester (16.5 g, 0.055 mol) was dissolved in ethanol (300 mL) and hydrogenated with 5% Pd/C (1.5 g) under H_2 atm for 2 h at rt. The reaction mixture was filtered through a Celite pad, and the filtrate was evaporated to afford the crude mixture which was distilled (bp_{7mmHg} 175−180 °C) to give **7** (16.4 g, 98%) as a colorless oil: $[\alpha]^{24}_D$ = +33.7° (*c* 1.05, $CHCl_3$); IR (neat) 1720 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 4.14 (4 H, q, *J* = 7.2 Hz), 3.74−3.56 (2 H, m), 2.62−2.36 (4 H, m), 2.08−1.86 (4 H, m), 1.36 (6 H, s), 1.26 (6 H, t, *J* = 7.2 Hz); FDMAS *m*/*z* 303 (M + H), 302 (M$^+$), 287 (M − Me), 244 (M − 2Et). Anal. Calcd for $C_{15}H_{26}O_6$: C, 59.58; H, 8.67. Found: C, 59.56; H, 8.57.

Diethyl (+)-(6*R*,7*R*)-6,7-*O*-Isopropylidene-6,7-dihydroxy-2,10-dodecadienedioate (8). **7** (14.0 g 0.046 mol) was subjected to the same sequence of the reactions as descrived above, and the crude product was chromatograped on a silica gel column (hexane/AcOEt = 6/1) to give pure **8** as a colorless oil (13.0 g, 79%): $[\alpha]^{27}_D$ = +32.2° (*c* 0.99, $CHCl_3$); IR (neat) 1720, 1660 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.97 (2 H, dt, *J* = 15.5, 6.9 Hz), 5.85 (2 H, dt, *J* = 15.5, 1.7 Hz), 4.19 (4 H, q, *J* = 6.9 Hz), 3.62 (2 H, ddd, *J* = 8.7, 5.3, 3.3 Hz), 2.47−2.25 (4 H, m), 1.74−1.61 (4 H, m), 1.38 (6 H, s), 1.29 (6 H, t, *J* = 7.3 Hz); FDMAS *m*/*z* 354 (M$^+$), 339 (M − Me). Anal. Calcd for $C_{19}H_{30}O_6$: C, 64.38; H, 8.53. Found: C, 64.37; H, 8.46.

(+)-(6*R*,7*R*)-6,7-*O*-Isopropylidene-1,6,7,12-tetrahydroxy-2,10-dodecadiene (9). A solution of DIBALH (54 mL of a 1.5 M solution in toluene, 0.081 mol) was added dropwise to a solution of **8** (5.08 g, 16.2 mmol) in anhyd CH_2Cl_2 (60 mL) at

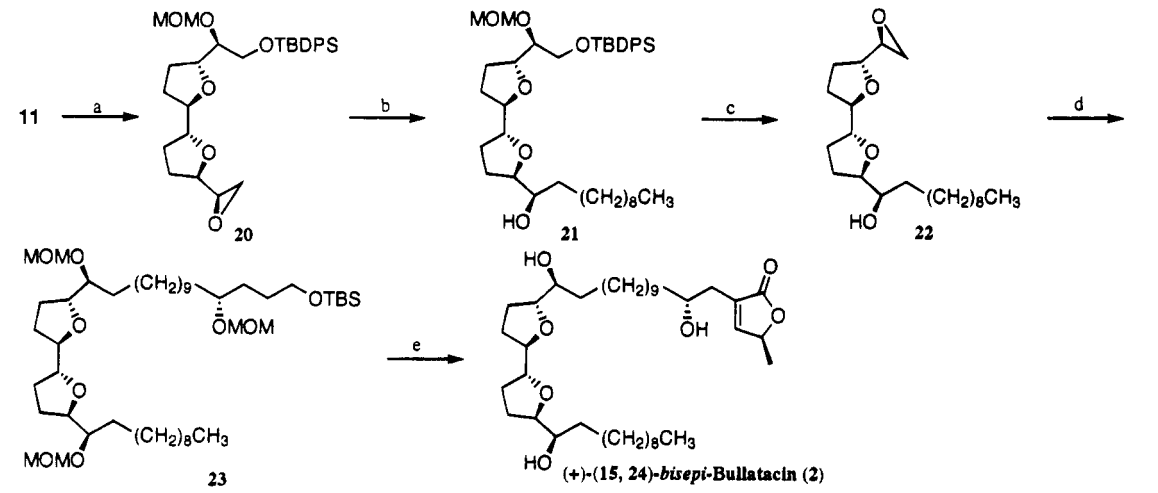
(18) The syntheses of the model compounds (**24**−**28**) from D-tartrate have been summarized in ref 5. These antitumor activities were tested at the Exploratory Research Laboratories I, Daiichi Pharmaceutical CO., LTD., Japan, for which we are grateful.

Scheme 3[a]



[a] (a) (1) **5**, *n*-BuLi, DME, rt, (2) Na–Hg, EtOH, rt; (b) (1) TsCl, pyridine, −20 °C, (2) K_2CO_3, EtOH–H_2O, rt; (c) (1) CuBr, $CH_3(CH_2)_8MgBr$, THF, 0 °C, (2) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to rt; (d) (1) *n*-Bu_4NF, THF, 0 °C, (2) CrO_3–H_2SO_4, acetone, −20 °C, (3) CH_2N_2, Et_2O–AcOEt, 0 °C; (e) (1) LDA, (2) **3**, THF, −78 °C, (3) CSA, MeOH–H_2O, rt, (4) BzCl, pyridine, 0 °C to rt, (5) NH_3 in MeOH, rt, (6) BF_3·Et_2O, DMS, rt.

Scheme 4[a]



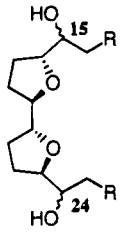
[a] (a) (1) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to rt, (2) *n*-Bu_4NOH, THF, 0 °C, (3) TBDPSCl, TEA, imidazole, CH_2Cl_2, rt; (b) CuBr, $CH_3(CH_2)_8MgBr$, THF, 0 °C; (c) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to rt, (2) *n*-Bu_4NF, THF, 0 °C to rt, (3) TsCl, pyridine, 0 °C, (4) BF_3·Et_2O, DMS, 0 °C, (5) K_2CO_3, EtOH–H_2O, rt; (d) (1) **5**, *n*-BuLi, DME, rt, (2) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to rt, (3) Na–Hg, EtOH, rt; (e) (1) *n*-Bu_4NF, THF, 0 °C, (2) CrO_3–H_2SO_4, acetone, −20 °C, (3) CH_2N_2, Et_2O–AcOEt, 0 °C, (4) LDA, **3**, THF, −78 °C, (5) CSA, MeOH–H_2O, rt, (6) BzCl, pyridine, 0 °C to rt, (7) NH_3 in MeOH, rt, (8) BF_3·Et_2O, DMS, rt.

−78 °C under an argon atm. The mixture was stirred for 2.5 h at −78 °C, then diluted with THF (180 mL), and quenched with methanol (12 mL). Celite was added to the reaction mixture, and the whole was filtered through a Celite pad. The filtrate was evaporated to afford the crude mixture which was chromatographed on a silica gel column (AcOEt) to give **9** (3.77 g, 86%) as a colorless oil: $[\alpha]^{25}_D$ = +30.0° (*c* 0.82, $CHCl_3$); IR (neat) 3700–3100, 1670 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.77–5.62 (4 H, m), 4.09 (4 H, dd, *J* = 3.3, 1.0 Hz), 3.63 (2 H, ddd, *J* = 10.5, 6.6, 5.9 Hz), 2.30–2.09 (4 H, m), 1.73 (2 H, bs), 1.65–1.57 (4 H, m), 1.38 (6 H, s); FABMAS *m*/*z* 271 (M + H), 255 (M − Me), 253 (M − OH); HRFABMS calcd for $C_{15}H_{27}O_4$ 271.1909, found 271.1872. Anal. Calcd for $C_{15}H_{27}O_4$: C, 66.64; H, 9.69. Found: C, 66.77; H, 9.67.

(−)-(2*S*,3*S*,6*R*,7*R*,10*S*,11*S*)-2,3:10,11-Diepoxy-6,7-*O*-isopropylidene-1,12-*O*-bis(4-nitrobenzoyl)-1,6,7,12-tetrahydroxydodecane (10). L-(+)-Diisopropyl tartrate (0.04 mL, 0.23 mmol), Ti(O-*i*-Pr)$_4$ (0.03 mL, 0.09 mmol) and TBHP (1.0 mL of a 3.9 M solution in toluene, 3.90 mmol) were successively added to a suspension of molecular sieves 4 Å (0.43 g) in anhyd CH_2Cl_2 (15 mL) at −20 °C under an argon atm, and the mixture was stirred at −20 °C for 30 min. A solution of **9** (0.43 g, 1.60 mmol) in anhyd CH_2Cl_2 (2 mL) was added dropwise to the above mixture at −30 to −20 °C, and the mixture was stirred for 17 h at −30 to −15 °C. $(MeO)_3P$ (0.35 mL, 2.9 mmol) was added to the reaction mixture between −30 and −20 °C. Triethylamine (0.90 mL, 6.3 mmol) was then added, followed by the addition of *p*-nitrobenzoyl chloride (1.05 g, 5.8 mmol). The mixture was stirred for 1 h at 0 °C and filtered through a Celite pad. The filtrate was successively washed with 10% aqueous tartaric acid, saturated aqueous $NaHCO_3$, and brine and then dried over Na_2SO_4. The filtrate was evaporated to afford the crude mixture, which was chromatographed on a silica gel column ($CHCl_3$/ether = 9/1) to give **10** (0.85 g, 96%) as a yellow oil: $[\alpha]^{24}_D$ = −26.3° (*c* 1.40, $CHCl_3$); IR (neat) 1720, 1520, 1270 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.33–8.21 (8 H, m), 4.72 (2 H, dd, *J* = 12.2, 6.6 Hz), 4.19 (2 H, dd, *J* = 12.2, 6.6 Hz), 3.63–3.61 (2 H, m), 3.15 (2 H, ddd, *J* = 6.6, 3.3, 3.0 Hz), 3.00 (2 H, ddd, *J* = 5.9, 3.3, 2.3 Hz), 2.03–1.58 (8 H, m), 1.38 (6 H, s); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 163.4, 150.7, 135.1, 130.9, 123.8, 108.5, 80.7, 66.0, 56.4, 55.4, 29.1, 28.7, 27.3; FABMAS *m*/*z* 601 (M^+), 543 (M − C_3H_6O), 526 (M − $C_3H_6O_2$); HRFABMS calcd for $C_{29}H_{33}O_{12}N_2$ 601.2034,

Table 1. *In Vitro* Antitumor Activities against P388[18]

Compound	GI_{50}(ng/ml)
1	0.08
2	2.23
24[5]	2.71×10^2
25[5]	1.16×10^4
26[5]	1.11×10^2
27[5]	1.40×10^2
28[5]	$> 2.50 \times 10^4$



compounds	configuration		R
	15	24	
24	*R*	*R*	$(CH_2)_8CH_3$
25	*R*	*R*	CH_3
26	*R*	*S*	$(CH_2)_8CH_3$
27	*S*	*S*	$(CH_2)_8CH_3$
28	*S*	*S*	CH_3

found 601.2036. Anal. Calcd for $C_{29}H_{33}O_{12}N_2$: C, 58.00; H, 5.37; N, 4.66. Found: C, 57.79; H, 5.42; N, 4.54.

(−)-(2*S*,3*R*,6*R*,7*R*,10*R*,11*S*)-1,12-*O*-Bis(4-nitrobenzoyl)-3,6:7,10-diepoxy-1,2,11,12-tetrahydroxydodecane (6). MeOH (3.0 mL), water (18 μL), and $BF_3{\cdot}Et_2O$ (0.18 mL, 1.45 mmol) were added dropwise to a solution of **10** (1.52 g, 2.54 mmol) in anhyd CH_2Cl_2 (8.0 mL) at 0 °C, and the mixture was stirred at rt for 5 h. The mixture was diluted with AcOEt, successively washed with saturated aqueous $NaHCO_3$, water, and brine, and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture, which was chromatographed on a silica gel column ($CHCl_3$/AcOEt = 2/1) to give **6** (1.31 g, 92%) as a yellow caramel: $[\alpha]^{22}_D = -2.22°$ (*c* 0.64, $CHCl_3$); IR (neat) 3600−3200, 1720, 1520 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.32−8.20 (8 H, m), 4.50 (2 H, dd, *J* = 11.6, 3.6 Hz), 4.37 (2 H, dd, *J* = 11.6, 6.6 Hz), 4.20 (2 H, dt, *J* = 6.6, 4.2 Hz), 4.10 (2 H, ddd, *J* = 11.2, 5.2, 4.2 Hz), 3.96 (2 H, ddd, *J* = 10.6, 5.8, 5.0 Hz), 2.51−2.40 (2 H, bs), 2.13−1.60 (8 H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 164.8, 150.6, 135.3, 130.8, 123.5, 82.6, 80.1, 70.8, 66.9, 28.7, 26.6; FABMAS *m*/*z* 561 (M^+), 543 (M − H_2O); HRFABMS calcd for $C_{26}H_{29}O_{12}N_2$ 561.1721, found 561.1702.

(−)-(2*S*,3*R*,6*R*,7*R*,10*R*,11*S*)-1,12-*O*-Bis(4-nitrobenzoyl)-3,6:7,10-diepoxy-2-*O*-methanesulfonyl-1,2,11,12-tetrahydroxydodecane (11). MsCl (26 μL, 0.336 mmol) was added to a solution of **6** (191.1 mg, 0.341 mmol) and triethylamine (0.1 mL, 0.717 mmol) in anhyd THF (3.0 mL) at 0 °C under an argon atm. The reaction mixture was diluted with AcOEt (50 mL), successively washed with saturated aqueous NH_4Cl, water, and brine, and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column (hexane/AcOEt = 3/1) to give **11** (80.6 mg, 37%) and recovered **6** (109.2 mg, 57%) as a yellow caramel: $[\alpha]^{26}_D = -5.44°$ (*c* 1.44, $CHCl_3$); IR (neat) 3600−3200, 1720, 1520, 1350, 1280 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.35−8.20 (8 H, m), 5.10−5.04 (1 H, m), 4.69 (2 H, dd, *J* = 11.6, 3.6 Hz), 4.37 (2 H, dd, *J* = 11.6, 6.6 Hz), 4.20 (2 H, dt, *J* = 6.6, 4.2 Hz), 4.10 (2 H, ddd, *J* = 11.2, 5.2, 4.2 Hz), 4.55−3.92 (7 H, m), 3.09 (3 H, s), 2.45−2.35 (1 H, bs), 2.13−1.95 (4 H, m), 1.80−1.58 (4 H, m); FDMAS *m*/*z* 639 (M^+); HRFABMS calcd for $C_{27}H_{31}O_{14}N_2S$ 639.1496, found 639.1489.

(−)-(2*R*,3*R*,6*R*,7*R*,10*R*,11*S*)-11,12-Dihydroxy-1,2:3,6:7,10-triepoxydodecane (4). A solution of *n*-Bu_4NOH (69 μL of a 1.0 M solution in methanol, 69 μmol) was added dropwise to a solution of **11** (21 mg, 32.9 μmol) in anhyd THF (1.0 mL) at 0 °C, and the mixture was stirred for 60 min at rt. The reaction mixture was diluted with AcOEt, washed with brine, and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column (AcOEt) to give **4** (7.4 mg, quantative yield) as a colorless oil: $[\alpha]^{25}_D = -0.13°$ (*c* 1.59, $CHCl_3$); IR (neat) 3700−3100, 1270, 1060 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.05−3.80 (5 H, m), 3.80−3.55 (2 H, m), 2.99 (1 H, dt, *J* = 7.0, 3.0 Hz), 2.85−2.73 (2 H, m), 2.60−2.50 (1 H, m), 2.40−2.25 (1 H, bs), 2.20−1.55 (8 H, m); HRFABMS calcd for $C_{12}H_{21}O_5$ 245.1389, found 245.1384.

10-(Benzyloxy)-1-decanal (12). A solution of decamethylene glycol (10.0 g, 57.4 mmol) in anhyd DMF (30 mL) was added dropwise to a suspension of NaH (2.98 g of 60% in mineral oil, 74.6 mmol) in anhyd DMF (300 mL), and the mixture was stirred for 3 h at 40−55 °C under an argon atm. BnCl (6.6 mL, 57.4 mmol) was added dropwise to the above mixture at 0 °C. The reaction mixture was stirred for 13 h at rt. Water/brine (1/1) was added to the mixture, and the whole was extracted with AcOEt/hexane (10/1). The organic layer was washed with water/brine (1/1) and dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column (hexane/AcOEt, 5/1 to 2/1) to give the corresponding monobenzyl ether (7.68 g, 51%) and dibenzyl ether (5.02 g, 25%). Next, PDC (8.5 g, 22.7 mmol) was added to a suspension of the monobenzyl ether (5.0 g, 18.9 mmol) and Celite (17 g) in CH_2Cl_2 (10 mL), and the mixture was stirred for 24 h at rt. Filtration through a Celite pad and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column (hexane/AcOEt = 1/1) to give **12** (4.09 g, 82%) as a colorless oil: IR (neat) 3020, 1720, 1495, 700 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 9.79 (1 H, t, *J* = 1.7 Hz), 7.35 (5 H, s), 4.51 (2 H, s), 3.48 (2 H, t, *J* = 6.2 Hz), 2.50−2.20 (2 H, m), 1.80−1.15 (14 H, m); FDMAS *m*/*z* 263 (M + H), 262 (M^+).

(+)-(4*R*)-13-(Benzyloxy)-4-hydroxy-1-tridecene (13). Allylmagnesium bromide (12.3 mL of a 1.0 M solution in ether, 12.3 mmol) was added to a solution of $^dIpc_2BOMe$ (14.3 mmol) at 0 °C under an argon atm, and the reaction mixture was vigorously stirred at rt. A solution of **12** (2.33 g, 8.9 mmol) in anhyd ether (5 mL) was added dropwise to the above solution at −78 °C, and the mixture was stirred for 1.5 h at the same temperature. Then, aqueous NaOH (7.0 mL of a 4.0 N solution in water) was added to the reaction mixture, and the whole was warmed up to rt. H_2O_2 (10 mL of a 30% solution in water) was added dropwise to the above mixture, and the mixture was stirred for 10 h at rt and then refluxed for 30 min. The reaction mixture was extracted with ether, and the organic layer was washed with water/brine (1/1) and dried over magnesium sulfate. Filtration and evaporation of the solvents afforded the crude mixture, which was chromatographed on a silica gel column (hexane/AOEt, 12/1 to 4/1) to give **13** (1.77 g, 66%) as a colorless oil: $[\alpha]^{22}_D = +2.01°$ (*c* 1.37, $CHCl_3$); IR (neat) 3400, 3020, 1640, 910, 735, 700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.35−7.25 (5 H, m), 5.91−5.15 (1 H, m), 5.18−5.15 (1 H, m), 5.12−5.09 (1 H, m), 4.50 (2 H, s), 3.66−3.60 (1 H, m), 3.46 (2 H, t, *J* = 6.6 Hz), 2.35−2.25 (1 H, m), 2.19−2.08 (1 H, m), 1.66−1.17 (16 H, m); FABMAS *m*/*z* 305 (M + H), 287 (M − OH), 288 (M − C_6H_5); HRFABMS calcd for $C_{20}H_{33}O_2$ 305.2481, found 305.2484.

(+)-(4*R*)-13-(Benzyloxy)-1-[(*tert*-butyldimethylsilyl)oxy]-4-[(methoxymethyl)oxy]tridecane (14). MOMCl (0.11 mL, 1.45 mmol) was added to a solution of **13** (225 mg, 0.74 mmol) and *i*-Pr_2NEt (0.6 mL, 3.67 mmol) in anhyd CH_2Cl_2 (2.0 mL) at 0 °C, and the mixture was stirred for 17 h at rt. The reaction mixture was quenched with saturated aqueous NH_4Cl and then extracted with ether. The organic layer was washed with water and brine and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column (hexane/AcOEt = 4/1) to give the protected allyl alcohol (252 mg, 98%) as a colorless oil: $[\alpha]^{24}_D = +5.37°$ (*c* 1.60, $CHCl_3$); IR (neat) 3020, 1640, 730, 700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.36−7.24 (5 H, m), 5.82 (1 H, ddt, *J* = 17.2, 10.2, 7.1 Hz), 5.07 (1 H, m), 5.06 (1 H, m), 4.68 (1 H, d, *J* = 6.9 Hz), 4.50 (2 H, s), 3.60 (1 H, ddt, *J* = 5.9, 5.8, 5.6 Hz), 3.46 (2 H, t, *J* = 6.6 Hz), 3.38, (3 H, s), 2.30 (1 H, dt, *J* = 5.9, 1.3 Hz), 2.27 (1 H, dt, *J* = 5.9, 1.3 Hz), 1.66−1.28 (18 H, m); FABMAS *m*/*z* 349 (M + H), 348 (M^+), 317 (M − OMe), 214 (M − $C_8H_{10}O$); HRFABMS calcd for $C_{22}H_{37}O_3$ 349.2743, found 349.2729.

$BH_3{\cdot}THF$ complex (22 mL of a 1.0 M solution in THF, 22 mmol) was added to a solution of the protected allyl alcohol

(5.15 g, 14.8 mmol) in anhyd THF (50 mL) at 0 °C under argon atm. The mixture was stirred at rt for 12 h and carefully quenched with water (0.4 mL) at 0 °C. Aqueous NaOH (20 mL of a 4.0 N solution in water) and H_2O_2 (20 mL of a 30% solution in water) were added to the reaction mixture, and the whole was stirred for 1 h at room temprature. The mixture was extracted with ether, and the organic layer was washed with water and brine and then dried over $MgSO_4$. Filtration and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column (hexane/AcOEt = 4/1 to 2/1) to give the primary alcohol (4.23 g, 78%) as a colorless oil: $[\alpha]^{24}_D = -6.27°$ (*c* 0.86, $CHCl_3$); IR (neat) 3400, 3020, 730, 700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.35–7.24 (5 H, m), 4.66 (2 H, s), 4.50 (2 H, s), 3.67–3.62 (2 H, m), 3.49–3.44 (2 H, m), 3.46 (2 H, t, J = 6.6 Hz), 3.38, (3 H, s), 1.98 (1 H, br), 1.19–0.70 (20 H, m); FABMAS m/z 367 (M + H), 335 (M − OMe), 305 (M − MOM), 214 (M − $C_9H_{13}O$); HRFABMS calcd for $C_{22}H_{39}O_4$ 367.2848, found 367.2851.

TBDMSCl (0.286 g, 1.9 mmol) was added to a solution of the primary alcohol (0.551 g, 1.5 mmol), triethylamine (0.33 mL, 2.37 mmol), and imidazole (0.16 g, 2.37 mmol) in anhyd CH_2Cl_2 (8.0 mL) at 0 °C, and the mixture was stirred for 18 h. Saturated aqueous $NaHCO_3$ was added to the mixture, and the whole was extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous NH_4Cl and brine and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture, which was chromatographed on a silica gel column (hexane/AcOEt = 2/1) to give **14** (0.716 g, 99%) as a colorless oil: $[\alpha]^{23}_D = -0.65°$ (*c* 0.92, $CHCl_3$); IR (neat) 3020, 1250, 1100, 730, 700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.36–7.25 (5 H, m), 4.65 (2 H, s), 4.50 (2 H, s), 3.57–3.52 (1 H, m), 3.61 (2 H, t, J = 5.3 Hz), 3.46 (2 H, t, J = 6.6 Hz), 3.38, (3 H, s), 1.64–1.28 (20 H, m), 0.89 (9 H, s), 0.05 (6 H, s); FABMAS m/z 481 (M + H), 479 (M − H), 449 (M − OMe), 423 (M − *t*-Bu); HRFABMS calcd for $C_{28}H_{51}O_4Si$ 479.3557, found 479.3537.

(+)-(4*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-4-[(methoxymethyl)oxy]-13-benzenesulfonyltridecane (5). A solution of **14** (3.51 g, 7.3 mmol) in anhyd ether (14 mL) was added dropwise to a solution of Li (0.21 g, 0.053 mol) in liquid ammmonia (300 mL) at −78 °C, and the mixture was stirred for 30 min at −78 °C. The reaction mixture was then stirred at ambient temperature for 3 h, and the reaction was quenched with saturated aqueous NH_4Cl. After evaporation of ammmonia, the residue was extracted with ether, and the organic layer was washed with brine and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column (hexane/AcOEt = 1/1) to give the primary alcohol (2.81 g, 99%) as a colorless oil: $[\alpha]^{23}_D = +1.43°$ (*c* 1.54, $CHCl_3$); IR (neat) 3400, 1250, 1100 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.65 (2 H, s), 3.64 (2 H, t, J = 6.6 Hz), 3.63–3.60 (2 H, m), 3.57–3.53 (1 H, m), 3.38, (3 H, s), 1.70–1.23 (20 H, m), 0.89 (9 H, s), 0.05 (6 H, s); FABMAS m/z 391 (M + H), 373 (M − OH), 359 (M − OMe), 333 (M − *t*-Bu), 271 (M − $C_5H_{12}O$); HRFABMS calcd for $C_{21}H_{47}O_4Si$ 391.3243, found 391.3230.

A solution of TsCl (217 mg, 2.13 mmol) in anhyd pyridine (0.5 mL) was added dropwise to a solution of the primary alcohol (112 mg, 0.29 mmol) in anhyd pyridine (1.0 mL) at 0 °C, and the mixture was stored at −20 °C for 41 h. The mixture was diluted with ether, washed with saturated aqueous NH_4Cl, water, and brine, and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column (hexane/AcOEt = 8/1) to give the corresponding tosylate (152 mg, 97%). On the other hand, PhSH (14 μL, 0.136 mmol) was added to a suspension of NaH (25 mg of 60% in mineral oil, 0.625 mmol) in anhyd THF (2.0 mL) at 0 °C, and the mixture was stirred for 30 min. A solution of the tosylate (51 mg, 0.094 mmol) in anhyd THF (1.0 mL) was added dropwise to the above solution, and the mixture was stirred for 2 h at rt. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The organic layer was washed with 10% aqueous NaOH and brine and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column (hexane/AcOEt = 10/1) to give the corresponding thioether (41 mg, 92%) as a colorless oil: $[\alpha]^{25}_D = +1.05°$ (*c* 1.14, $CHCl_3$); IR (neat) 1580, 1485, 1480, 1250, 1100, 1020, 840, 785, 740, 690 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 7.41–7.23 (5 H, m), 4.64 (2 H, s), 3.75–3.40 (3 H, m), 3.37, (3 H, s), 3.08–2.75 (2 H, m), 1.82–1.19 (20 H, m), 0.90 (9 H, s), 0.05 (6 H, s).

A solution of MMPP (500 mg, 0.813 mmol) in water (0.5 mL) was added to a solution of the thioether (110 mg, 0.228 mmol) in ethanol (0.5 mL), and the mixture was stirred for 12h at rt. The reaction mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$, water, and brine, and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture, which was chromatographed on a silica gel column (hexane/AcOEt = 3/1) to give **5** (112 mg, 95%) as a colorless oil: $[\alpha]^{25}_D = +0.60°$ (*c* 1.0, $CHCl_3$); IR (neat) 1580, 1470, 1460, 1450, 1320, 1255, 1040, 840, 780, 690 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.91 (2 H, ddd, J = 8.3, 3.6, 2.3 Hz), 7.70–7.54 (3 H, m), 4.64 (2 H, s), 3.61–3.59 (2 H, m), 3.56–3.54 (1 H, m), 3.37, (3 H, s), 3.11–3.03 (2 H, m), 1.76–1.18 (20 H, m), 0.89 (9 H, s), 0.04 (6 H, s); FABMAS m/z 515 (M + H), 483 (M − OMe), 457 (M − C_4H_9); HRFABMS calcd for $C_{27}H_{47}O_4SiS$ 495.2964, found 483.2973.

(+)-(4*R*,15*R*,16*R*,19*R*,20*R*,23*R*,24*S*)-1-*O*-(*tert*-Butyldimethylsilyl)-16,19:20,23-diepoxy-4-*O*-(methoxymethyl)-1,4,15,24,25-pentahydroxypentacosane (15). A solution of *n*-BuLi (90 μL of a 1.63 M solution in hexane, 0.15 mmol) was added dropwise to a solution of **4** (5.5 mg, 0.025 mmol) and **5** (37.7 mg, 0.073 mmol) in DME (50 mL) at rt under argon atm, and the mixture was stirred for 10 min at rt. Then the reaction mixture was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether, washed with water and brine, and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column (AcOEt) to give the corresponding alkylated product (14.2 mg, 83%). Next, sodium amalgam (400 mg) was added to a solution of this product (30.0 mg, 0.040 mmol) in ethanol (0.5 mL), and the mixture was stirred for 24 h at rt and then quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether, washed with water and brine, and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column (AcOEt) to give **15** (20.0 mg, 60%). The unreacted sulfone was recovered (8.2 mg, 20%) as a colorless oil: $[\alpha]^{27}_D = +4.89°$ (*c* 0.94, $CHCl_3$); IR (neat) 3700–3100, 1280, 1100, 1040 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.65 (2 H, s), 3.99–3.40 (14 H, m), 3.38 (3 H, s), 2.14–1.06 (33 H, m), 0.89 (9 H, s), 0.05 (6 H, s); FABMAS m/z 641 (M + Na), 587 (M − OMe), 557 (M − MOMO); HRFABMS calcd for $C_{33}H_{66}O_8SiNa$ 641.4424, found 641.4419.

(+)-(4*R*,15*R*,16*R*,19*R*,20*R*,23*R*,24*S*)-1-*O*-(*tert*-Butyldimethylsilyl)-4-*O*-(methoxymethyl)-16,19:20,23:24,25-triepoxy-1,4,15-trihydroxypentacosane (16). TsCl (6.0 mg, 0.031 mmol) was added to a solution of **15** (20.6 mg, 0.033 mmol) in anhyd pyridine (100 μL) at −30 °C, and the mixture was stored at −20 °C for 48 h. The mixture was diluted with AcOEt, washed with water and brine, and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column ($CHCl_3$/methanol, 100/1 to 50/1) to give the corresponding tosylate (11.0 mg, 42%) and recovered **15** (7.0 mg, 33%). Next, aqueous K_2CO_3 (1.2 mL of a 1.0 N aqueous solution) was added to a solution of the above tosylate (10.0 mg, 0.013 mmol) in ethanol (0.5 mL), and the mixture was stirred for 10 min at rt. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with AcOEt. The organic layer was washed with water and brine and then dried over Na_2SO_4. Filtration through a Celite pad and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column ($CHCl_3$/methanol = 30/1) to give **16** (7.0 mg, 90%) as a colorless oil: $[\alpha]^{27}_D = +4.16°$ (*c* 0.77, $CHCl_3$); IR (neat) 3600–3200, 1280, 1100, 1040 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.64 (2 H, s), 4.02–3.80 (4 H, m), 3.70–3.60 (2 H, m), 3.60–3.50 (1 H, m), 3.45-3.35 (1 H, m), 3.37 (3 H, s), 3.03 (1 H, ddd, J = 5.0, 4.0, 2.6 Hz), 2.79 (1 H,

dd, J = 5.0, 4.0 Hz), 2.59 (1 H, dd, J = 5.0, 2.6 Hz), 2.15−1.20 (33 H, m), 0.88 (9 H, s), 0.04 (6 H, s); FABMAS m/z 623 (M + Na), 539 (M − MOMO), 481 (M − $C_5H_{11}O_3$); HRFABMS calcd for $C_{33}H_{64}O_7SiNa$ 623.4319, found 623.4318.

(+)-(4*R*,15*R*,16*R*,19*R*,20*R*,23*R*,24*S*)-1-*O*-(*tert*-Butyldimethylsilyl)-16,19:20,23-diepoxy-1,4,15,24-tetrahydroxy-4,15,24-*O*-tris(methoxymethyl)tetratriacontane (17). A solution of nonylmagnesium bromide (0.11 mL of a 0.41 M solution in THF, 0.045 mmol) was added dropwise to a suspension of CuBr (1.0 mg, 0.007 mmol) in anhyd THF (0.5 mL) at 0 °C. A solution of **16** (5.8 mg, 0.010 mmol) in anhyd THF (0.1 mL) was added dropwise to the above mixture at 0 °C, and the mixture was stirred for 1 h at 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl/aqueous ammonia (9/1) and diluted with ether. The organic layer was washed with water and brine and then dried over Na_2SO_4. Filtration and evaporation of the solvent afforded the crude mixture, which was chromatographed on a silica gel column ($CHCl_3$/methanol = 20/1) to give the alkylated product (7.3 mg, quantitative). Next, MOMCl (0.3 mL, 4.09 mmol) was added to a solution of the above product (7.0 mg, 0.010 mmol) and i-PrNEt (0.5 mL, 28.8 mmol) in anhyd CH_2Cl_2 (50 μL) at 0 °C, and the mixture was stirred for 24 h at rt. The reaction mixture was diluted with ether, washed with saturated aqueous NH_4Cl, water, and brine, and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture, which was chromatographed on a silica gel column (hexane/AcOEt = 6/1) to give **17** (5.0 mg, 64%) as a colorless oil: $[\alpha]^{27}_D$ = +4.24° (c 0.66, $CHCl_3$); IR (neat) 1300, 1100, 1040 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.80 (2 H, dd, J = 8.5, 6.9 Hz), 4.65 (2 H, t, J = 6.3 Hz), 4.63 (2 H, s), 4.08−3.94 (2 H, m), 3.94−3.85 (2 H, m), 3.75−3.45 (5 H, s), 3.39 (3 H, s), 3.38 (3 H, s), 3.37 (3 H, s), 2.05−1.20 (50 H, m), 0.90 (9 H, m), 0.88 (3 H, t, J = 6.6 Hz), 0.04 (6 H, s); FABMAS m/z 839 (M + Na), 785 (M − OMe), 539 (M − $C_3H_8O_3$), 661 (M − $C_5H_{13}O_5$), 539 (M − 3MOMO), 499 (M − $C_{12}H_{30}O_6Si$); HRFABMS calcd for $C_{46}H_{92}O_9SiNa$ 839.6408, found 839.6406.

(+)-(4*R*,15*R*,16*R*,19*R*,20*R*,23*R*,24*S*)-16,19:20,23-Diepoxy-1,4,15,24-tetrahydroxy-4,15,24-*O*-tris(methoxymethyl)-tetratriacontanoic Acid Methyl Ester (18). A solution of n-Bu_4NF (50 μL of a 1.0 M solution in THF, 50 μmol) was added to a solution of **17** (5.5 mg, 6.73 μmol) in anhyd THF (0.5 mL) at 0 °C, and the mixture was stirred for 2 h at rt and then quenched with saturated aqueous NH_4Cl. The mixture was diluted with diethyl ether, washed with water and brine, and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column (hexane/AcOEt = 2/1) to give the corresponding alcohol (4.1 mg, 87%). Next, a solution of Jones' reagent (CrO_3−H_2SO_4, 0.1 mL) was added to a solution of the above alcohol (3.5 mg, 4.98 μmol) in anhyd acetone (25 μL) at −20 °C, and the mixture was stirred at −20 °C for 20 min. Then the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with AcOEt, and the organic layer was washed with water and brine and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude product, which was dissolved in AcOEt (2 mL) and treated with diazomethane at 0 °C. The reaction mixture was quenched with acetic acid, and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column ($CHCl_3$/AcOEt = 8/1) to give **18** (3.2 mg, 88%) as a colorless oil: $[\alpha]^{25}_D$ = +6.73° (c 0.60, $CHCl_3$); IR (neat) 1740, 1460, 1280, 1140, 1100, 1040, 920 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.80 (2 H, dd, J = 8.6, 6.9 Hz), 4.66 (2 H, t, J = 6.3 Hz), 4.63 (2 H, s), 4.08−3.94 (2 H, m), 3.94−3.85 (2 H, m), 3.75−3.65 (1 H, m), 3.67 (3 H, s), 3.64−3.45 (2 H, m), 3.39 (3 H, s), 3.38 (3 H, s), 3.37 (3 H, s), 2.41 (2 H, dt, J = 6.9, 2.0 Hz), 2.05−1.20 (48 H, m), 0.88 (3 H, t, J = 6.6 Hz); FABMAS m/z 753 (M + Na), 699 (M − OMe), 623 (M − $C_4H_8O_3$); HRFABMS calcd for $C_{41}H_{78}O_{10}Na$ 753.5492, found 753.5502.

(−)-(2*S*)-2-*O*-(Tetrahydropyranyloxy)propanal (3). 3,4-Dihydro-2*H*-pyran (1.05 mL, 0.012 mol) was added to a solution of (*S*)-(−)-methyl lactate (1.0 mL, 0.010 mol) in anhyd CH_2Cl_2 (1.0 mL) and CSA (5.0 mg, 0.021 mmol) at 0 °C, and the mixture was stirred at the same temperature for 1 h. The reaction mixture was quenched with $NaHCO_3$ (4.0 mg) and triethylamine (10 μL) and stirred for 20 min at rt. Filtration and evaporation of the solvents afforded the crude mixture which was distilled (4 mmHg, bp 90−100 °C) to give the protected methyl lactate (1.93 g, 98%). DIBALH (0.7 mL of a 1.5 M solution in toluene, 1.05 mmol) was added dropwise to a solution of the above protected methyl lactate (195 mg, 1.04 mmol) in anhyd CH_2Cl_2 (2.0 mL) at −78 °C, and the mixture was stirred for 20 min at −78 °C. Anhyd methanol (0.1 mL) was added dropwise, and the mixture was stirred for 40 min at −78 °C to rt. Celite (2 g) was then added, and the mixture was filtered through a Celite pad. Evaporation of the solvents afforded the crude mixture which was distilled (bp_{3mmHg} 95−110 °C) to give **3** (141 mg, 79%) as a colorless oil: $[\alpha]^{26}_D$ = +25.60° (c 1.25, $CHCl_3$); IR (neat) 1730 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 9.71 (1 H, d, J = 1.7 Hz), 4.80−4.50 (1 H, m), 4.45−3.20 (3 H, m), 2.15−1.15 (6 H, m), 1.22 (1.5 H, d, J = 7.0 Hz), 1.13 (1.5 H, d, J = 7.0 Hz).

(+)-4,15,24-*O*-Tris(methoxymethyl)bullatacin (19). A solution of n-BuLi (7.0 μL of a 1.63 M solution in hexane, 0.011 mmol) was added to a solution of i-Pr_2NH (2.0 μL, 0.018 mmol) in anhyd THF (30 μL) at −78 °C under argon atm, and the mixture was stirred for 10 min at −78 °C. A solution of **18** (5.0 mg, 6.8 μmol) in anhyd THF (30 μL) was added to the above mixture, and the whole was stirred for 20 min at −78 °C. Next, a solution of **3** (2.0 mg, 0.011 mmol) in anhyd THF (30 μL) was added dropwise to the above mixture, and the mixture was stirred for 10 min at −78 °C and then quenched with saturated aqueous NH_4Cl at the same temprature. The reaction mixture was extracted with ether, and the organic layer was washed with water and brine and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column (hexane/AcOEt = 4/1) to give the adduct (3.0 mg) and recovered **18** (1.0 mg, 20%). Removal of the THP group of the adduct (3.0 mg) was done with CSA (0.5 mL of a 1.0% solution in methanol−water (9/1)) for 2 h at rt. The mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ether. The organic layer was washed with water and brine and then dried over Na_2SO_4. The crude product was dissolved in anhyd pyridine (100 μL) and treated with benzoyl chloride (30 μL) at 0 °C to rt for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ether. The organic layer was washed with water and brine and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude benzoylated product. Finally, a solution of ammonia (1.0 mL of a 22% solution in methanol) was added to the above product, and the mixture was stirred for 30 min at rt. The mixture was diluted with ether, washed with water and brine, and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column (hexane/AcOEt = 5/1) to give **19** (2.0 mg, 48% from **18**) as a colorless oil: $[\alpha]^{28}_D$ = +8.57° (c 0.18, $CHCl_3$); IR (neat) 1750−1730, 1460, 1280, 1140, 1100, 1040, 920 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.17 (1 H, d, J = 1.3 Hz), 5.02 (1 H, dq, J = 6.9, 1.3 Hz), 4.81 (2 H, dd, J = 8.6, 6.9 Hz), 4.66 (2 H, t, J = 6.3 Hz), 4.70−4.55 (2 H, m), 4.08−3.94 (2 H, m), 3.94−3.79 (3 H, m), 3.77−3.63 (2 H, m), 3.55−3.43 (1 H, m), 3.39 (3H, s), 3.38 (3 H, s), 3.35 (3 H, s), 2.50 (2 H, dd, J = 7.3, 1.3 Hz), 2.10−1.20 (46 H, m), 1.41 (3 H, d, J = 6.9 Hz), 0.88 (3 H, t, J = 6.6 Hz); FABMAS m/z 777 (M + Na), 723 (M + Na − C_3H_2O), 661 (M + Na − $C_5H_5O_2$), 647 (M − $C_6H_8O_2$), 599 (M − $C_9H_{15}O_2$); HRFABMS calcd for $C_{43}H_{78}O_{10}Na$ 777.5492, found 777.5485.

(+)-Bullatacin (1). BF_3·Et_2O (20 μL, 0.16 mmol) was added dropwise to a solution of **19** (2.0 mg, 2.65 μmol) in dimethyl sulfide (150 μL) at 0 °C, and the mixture was stirred for 30 min at rt. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and diluted with AcOEt. The mixture was washed with water and brine and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column (AcOEt) to give (+)-bullatacin (**1**) (1.6 mg, quantative yield) as white crystals. The retention time of HPLC (flow rate: 0.6 mL/min) for **1** was 13.0 min and identical with squamocin G by the co-injection experiment: mp 78−83 °C; $[\alpha]^{23}_D$ = +8.22°

(*c* 0.05, $CHCl_3$); IR (neat) 3600–3200, 1750–1720, 1460, 1280, 1140, 1100, 1040, 920 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.18 (1 H, d, J = 1.1 Hz), 5.06 (1 H, dq, J = 6.9, 1.4 Hz), 3.97–3.90 (2 H, m), 3.90–3.80 (4 H, m), 3.43–3.38 (1 H, m), 2.55 (1 H, ddd, J = 15.1, 3.3, 1.7 Hz), 2.41 (1 H, dd, J = 15.0, 8.3 Hz), 2.04–1.94 (42 H, m), 1.44 (3 H, d, J = 6.7 Hz), 0.86 (3 H, t, J = 6.6 Hz); FABMAS *m/z* 645 (M + Na), 623 (M), 605 (M − H_2O), 523 (M − $C_5H_8O_2$); HRFABMS calcd for $C_{37}H_{67}O_7$ 623.4886, found 623.4882.

(+)-(2*S*,3*R*,6*R*,7*R*,10*R*,11*R*)-1-*O*-(*tert*-Butyldimethylsilyl)-2-*O*-(methoxymethyl)-3,6:7,10:11,12-triepoxy-1,2-dihydroxydodecane (20). MOMCl (0.01 mL, 0.13 mmol) was added to a solution of **11** as mentioned above (58.2 mg, 0.092 mmol) and *i*-Pr_2NEt (0.04 mL, 0.23 mmol) in anhyd CH_2Cl_2 (1.0 mL) at 0 °C, and the mixture was stirred for 8 h at rt. The reaction mixture was quenched with saturated aqueous NH_4Cl and then extracted with ether. The organic layer was washed with water and brine and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column ($CHCl_3$/AcOEt = 9/1) to give the full-protected bis-THF (62.2 mg, quantative yield) as a yellow oil: $[\alpha]^{25}_D$ = −8.99° (*c* 0.95, $CHCl_3$); IR (neat) 1720, 1600, 1520, 1350, 1280 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.34–8.16 (8 H, m), 5.46–5.30 (1 H, m), 4.80 (1 H, d, J = 6.9 Hz), 4.74 (1 H, d, J = 7.0 Hz), 4.63 (1 H, dd, J = 11.9, 3.4 Hz), 4.56 (1 H, dd, J = 11.0, 3.3 Hz), 4.22–4.00 (2 H, m), 3.99–3.84 (2 H, m), 3.37 (3 H, s), 3.07 (3 H, s), 2.20–1.60 (8 H, m); FABMAS *m/z* 683 (M + H), 651 (M − OMe), 620 (M − MOMO), 587 (M − 95), 428 (M − 254); HRFABMS calcd for $C_{29}H_{35}O_{15}N_2S$ 683.1758, found 683.1756.

A solution of *n*-Bu_4NOH (1.1 mL of a 1.0 M solution in methanol, 1.1 mmol) was added dropwise to a solution of the full-protected bis-THF (0.49 g, 0.74 mmol) in anhyd THF (25 mL) at 0 °C, and the mixture was stirred for 2.5 h at 0 °C. The reaction mixture was diluted with AcOEt, washed with brine, and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column (AcOEt) to give the corresponding epoxide (0.19 g, 91%). Next, to a solution of the epoxide (11 mg, 0.038 mmol) in anhyd CH_2Cl_2 (0.5 mL) were added triethylamine (8 μL, 0.057 mmol), imidazole (4.0 mg, 0.59 mmol), and *tert*-butyldiphenylsilyl chloride (12 μL, 0.046 mmol), and the mixture was stirred for 1.5 h at room temprature. The reaction was quenched with saturated aqueous NH_4Cl at the same temprature. The reaction mixture was extracted with CH_2Cl_2, and the organic layer was washed with water and brine and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column (hexane/AcOEt = 4/1 to AcOEt) to give **20** (19 mg, 96%) as a colorless oil: $[\alpha]^{25}_D$ = +16.9° (*c* 1.02, $CHCl_3$); IR (neat) 1100, 1050, 740, 710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74–7.65 (4 H, m), 7.46–7.39 (6 H, m), 4.77 (1 H, d, J = 6.6 Hz), 4.71 (1 H, d, J = 6.6 Hz), 4.15 (1 H, dt, J = 7.3, 4.0 Hz), 3.95–3.79 (4 H, m), 3.77–3.65 (2 H, m), 3.39 (3 H, s), 2.96 (1 H, ddd, J = 5.9, 4.0, 2.6 Hz), 2.73 (1 H, dd, J = 5.3, 4.0 Hz), 2.70 (1 H, dd, J = 5.3, 2.6 Hz), 2.12–1.62 (8 H, m), 1.04 (9 H, s); FABMAS *m/z* 527 (M + H), 495 (M − C_2H_2O), 465 (M + H − MOMO), 447 (465 − H_2O), 428 (M − 254); HRFABMS calcd for $C_{30}H_{43}O_6Si$ 527.2829, found 527.2812.

(+)-(2*S*,3*R*,6*R*,7*R*,10*R*,11*R*)-1-*O*-(*tert*-Butyldimethylsilyl)-2-*O*-(methoxymethyl)-3,6:7,10-diepoxy-1,2,11-trihydroxyhenicosane (21). A solution of nonylmagnesium bromide (1.6 mL of a 1.15 M solution in THF, 1.8 mmol) was added dropwise to a suspension of CuBr (51 mg, 0.36 mmol) in anhyd THF (40 mL) at 0 °C. A solution of **20** (0.26 g, 0.45 mmol) in anhyd THF (5.0 mL) was added dropwise to the above mixture at 0 °C, and the mixture was stirred for 1 h at 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl/aqueous ammonia (9/1) and diluted with ether. The organic layer was washed with water and brine and then dried over Na_2SO_4. Filtration and evaporation of the solvent afforded the crude mixture, which was chromatographed on a silica gel column (hexane/AcOEt = 2/1) to give **21** (0.26 g, 87%) as a colorless oil: $[\alpha]^{24}_D$ = +17.3° (*c* 0.96, $CHCl_3$); IR (neat) 3400–3250, 1070, 745, 690 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.69–7.64 (4 H, m), 7.46–7.33 (6 H, m), 4.78 (1 H, d, J = 6.6 Hz), 4.71 (1 H, d, J = 6.6 Hz), 4.17 (1 H, dt, J = 7.3, 4.3 Hz), 3.89–3.61 (6 H, m), 3.38–3.36 (1 H, m), 3.34 (3 H, s), 2.48 (1 H, bs), 1.94–1.63 (8 H, m), 1.47–1.22 (18 H, m), 1.04 (9 H, s), 0.88 (3 H, t, J = 6.6 Hz); FABMAS *m/z* 693 (M + K), 677 (M + Na), 623 (M − OCH_3), 597 (M − *t*-Bu); HRFABMS calcd for $C_{39}H_{62}O_6SiNa$ 677.4213, found 677.4208.

(+)-(2*S*,3*R*,6*R*,7*R*,10*R*,11*R*)-1,2:3,6:7,10-triepoxy-11-hydroxyhenicosane (22). MOMCl (8 μL, 0.105 mmol) was added to a solution of **21** (28 mg, 0.043 mmol) and *i*-Pr_2NEt (37 μL, 0.212 mmol) in anhyd CH_2Cl_2 (0.1 mL) at 0 °C, and the mixture was stirred for 12 h at rt. The reaction mixture was quenched with saturated aqueous NH_4Cl and then extracted with ether. The organic layer was washed with water and brine and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column (hexane/AcOEt = 4/1) to give the corresponding dimethoxymethylate (29.2 mg, 98%). Next, to a solution of the dimethoxymethylate (29.2 mg, 0.042 mmol) in anhyd THF (1.0 mL) was added dropwise tetrabutylammonium floride (0.17 mL of a 1.0 M solution in THF, 0.117 mmol) at 0 °C, and the mixture was stirred for 2 h at room temprature. The reaction was quenched with saturated aqueous NH_4Cl at the same temprature. The reaction mixture was extracted with ether, and the organic layer was washed with water and brine and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column (hexane/AcOEt = 2/1) to give the primary alcohol (19.0 mg, 96%) as a colorless oil: $[\alpha]^{23}_D$ = +8.52° (*c* 1.08, $CHCl_3$); IR (neat) 3400–3300, 1070, 745, 690 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.82 (1 H, d, J = 6.6 Hz), 4.75 (1 H, d, J = 6.6 Hz), 4.72 (1 H, d, J = 6.6 Hz), 4.68 (1 H, d, J = 6.6 Hz), 4.09–3.76 (8 H, m), 3.38 (3 H, s), 3.34 (3 H, s), 2.13–1.67 (8 H, m), 1.47–1.22 (18 H, m), 0.88 (3 H, t, J = 6.6 Hz); FABMAS *m/z* 483 (M + Na), 429 (M + H − OCH_3), 397 (M + H − MOM); HRFABMS calcd for $C_{25}H_{48}O_7Na$ 483.3298, found 483.3293.

TsCl (105 mg, 0.54 mmol) was added to a solution of the primary alcohol (49.8 mg, 0.108 mmol) in anhyd pyridine (26 mL) at 0 °C, and the mixture was stored at 0 °C for 24 h. The mixture was diluted with AcOEt, subsequently washed with saturated aqueous NH_4Cl, water, and brine, and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column (hexane/AcOEt = 3/1) to give the corresponding monotosylate (68.8 mg).

$BF_3{\cdot}Et_2O$ (0.25 mL, 2.0 mmol) was added dropwise to a solution of the monotosylate (54.2 mg, 0.088 mmol) in dimethyl sulfide (0.5 mL) at 0 °C, and the mixture was stirred for 10 min at 0 °C. The reaction was quenched with saturated aqueous $NaHCO_3$, and the mixture was diluted with AcOEt. The mixture was washed with water and brine and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column (hexane/AcOEt = 1/1) to give the corresponding diol (46.3 mg). Next, aqueous K_2CO_3 (1.2 mL of a 1.0 N aqueous solution) was added to a solution of the above diol (39.1 mg, 0.074 mmol) in ethanol (0.4 mL), and the mixture was stirred for 10 min at rt. The reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted with AcOEt. The organic layer was washed with water and brine and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column (hexane/AcOEt = 1/1) to give **22** (28.1 mg, quantative yield in three steps) as a colorless oil: $[\alpha]^{22}_D$ = +6.48° (*c* 1.08, $CHCl_3$); IR (neat) 3500–3400, 1250, 900 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.05–3.80 (4 H, m), 3.48–3.35 (1 H, m), 3.09–3.01 (1 H, m), 2.80 (1 H, t, J = 4.0 Hz), 2.61 (1 H, dd, J = 2.6, 6.0 Hz), 2.15–1.90 (4 H, m), 1.85–1.45 (6 H, m), 1.40–1.18 (18 H, m), 0.88 (3 H, t, J = 6.6 Hz); FABMAS *m/z* 709 (2M + H), 377 (M + Na), 355 (M + H); HRFABMS calcd for $C_{21}H_{39}O_4$ 355.2848, found 355.2847.

(+)-(4*S*,15*S*,16*R*,19*R*,20*R*,23*R*,24*R*)-1-*O*-(*tert*-Butyldimethylsilyl)-4,15,24-*O*-tris(methoxymethyl)-16,19:20,23-diepoxy-1,4,15,24-tetrahydroxytetratriacotane (23). A solution of *n*-BuLi (162 μL of a 1.63 M solution in hexane, 0.26

mmol) was added dropwise to a solution of **22** (21.6 mg, 0.061 mmol) and **5** (65.0 mg, 0.126 mmol) in DME (2.0 mL), and the mixture was stirred for 10 min at rt. The reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with ether. The mixture was washed with water and brine and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture which was chromatographed on a silica gel column (hexane/AcOEt = 2/1) to give the corresponding diol (43.3 mg, 82%). Next, MOMCl (0.2 mL, 2.73 mmol) was added dropwise to a solution of the above diol (43 mg, 0.049 mmol) and *i*-Pr_2NEt (1.0 mL, 57.6 mmol) in anhyd CH_2Cl_2 (0.3 mL) at 0 °C, and the mixture was stirred for 15 h at rt. The reaction mixture was diluted with ether, washed with saturated aqueous NH_4Cl, water and brine, and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture, which was chromatographed on a silica gel column (hexane/AcOEt = 4/1) to give the corresponding dimethoxymethylate (68.5 mg, 76%) and recovered the diol (18.8 mg, 23%) as a colorless oil: $[\alpha]^{23}_D$ = +1.60° (*c* 1.00, $CHCl_3$); IR (neat) 1300, 1255, 1100, 1040, 840, 780 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.92–7.82 (2 H, m), 7.67–7.52 (3 H, m), 4.82 (0.5 H, d, *J* = 6.9 Hz), 4.81 (0.5 H, d, *J* = 6.9 Hz), 4.75 (0.5 H, d, *J* = 6.9 Hz), 4.70 (0.5 H, d, *J* = 6.6 Hz), 4.68–4.62 (1.5 H, m), 4.65 (1 H, s), 4.64 (1 H, s), 4.55 (0.5 H, d, *J* = 6.6 Hz), 4.00–3.81 (4 H, m), 3.80–3.71 (1 H, m), 3.62–3.60 (2 H, m), 3.55–3.45 (2 H, m), 3.40–3.27 (1 H, m), 3.40 (1.5 H, s), 3.39 (1.5 H, s), 3.38 (1.5 H, s), 3.37 (1.5 H, s), 3.36 (1.5 H, s), 3.33 (1.5 H, s), 2.05–1.12 (48 H, m), 0.89 (9 H, s), 0.88 (3 H, t, *J* = 6.9 Hz), 0.04 (6 H, s); FABMAS *m/z* 979 (M + Na), 957 (M + H), 863 (M − OMe); HRFABMS calcd for $C_{52}H_{96}O_{11}SiSNa$ 979.6340, found 979.6351.

To a solution of the dimethoxymethylate (26.3 mg, 0.027 mmol) in ethanol (2.0 mL) was added sodium amalgam (30 mg). The mixture was stirred for 24 h at rt. To the resultant mixture was added saturated aqueous NH_4Cl and diluted with ether. The mixture was washed with water and brine and dried over Na_2SO_4. Filtration and evaporation of the solvents *in vacuo* afforded the crude mixture which was fractionated by column chromatography on silica gel (hexane/AcOEt = 4/1) to give **23** (21.0 mg, 93%) as a colorless oil: $[\alpha]^{25}_D$ = +6.57° (*c* 0.73, $CHCl_3$); IR (neat) 1255, 1100, 1040 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.80 (2 H, dd, *J* = 8.5, 6.9 Hz), 4.65 (2 H, t, *J* = 6.3 Hz), 4.63 (2 H, s), 4.08–3.94 (2 H, m), 3.94–3.85 (2H, m), 3.75–3.45 (5 H, m), 3.39 (3 H, s), 3.38 (3 H, s), 3.37 (3 H, s), 2.05–1.20 (50 H, m), 0.90 (9 H, s), 0.88 (3 H, t, *J* = 6.6 Hz), 0.04 (6 H, s); FABMAS *m/z* 839 (M + Na), 814 (M − 2H), 785 (M − OMe), 723 (M − 3OMe), 709 (M − $C_4H_{11}O_3$), 499 (M − 3MOMO); HRFABMS calcd for $C_{46}H_{92}O_9SiNa$ 839.6408, found 839.6414.

(+)-(15,24)-*bisepi*-Bullatacin (2). The synthesis of (+)-(15,24)-*bisepi*-bullatacin (**2**) was performed as described for the synthesis of (+)-bullatacin (**1**). **2** was obtained from **23** in 41% overall yield in eight steps as white crystals. The retention time of HPLC (flow rate: 0.6 mL/min) for **2** was 13.5 min and different from those of squamocin G and H: mp 90–93 °C; $[\alpha]^{28}_D$ = +5.70° (*c* 0.07, $CHCl_3$); IR (neat) 3600–3200, 1750–1720, 1460, 1280, 1140, 1100, 1040, 920 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.18 (1 H, d, *J* = 1.1 Hz), 5.06 (1 H, dq, *J* = 6.9, 1.4 Hz), 3.97–3.90 (2 H, m), 3.90–3.80 (4 H, m), 3.43–3.38 (1 H, m), 2.55 (1 H, ddd, *J* = 15.1, 3.3, 1.7 Hz), 2.41 (1 H, dd, *J* = 15.0, 8.3 Hz), 2.04–1.94 (42 H, m), 1.44 (3 H, d, *J* = 6.7 Hz), 0.86 (3 H, t, *J* = 6.6 Hz); FABMAS *m/z* 645 (M + Na), 623 (M), 605 (M − H_2O), 523 (M − $C_5H_8O_2$); HRFABMS calcd for $C_{37}H_{67}O_7$ 623.4886, found 623.4882.

Bioassays. Cytotoxicities to P388 leukemia (Table 1) were determined at the the Exploratory Research Laboratories I, Daiichi Pharmaceutical CO., LTD., Japan, using modifications of standard protocols of the National Cancer Institute.[19]

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Supplementary Material Available: ^1H- and ^{13}C-NMR spectra of all new compounds and HPLC chromatograms of synthetic **1** and **2** and natural products squamocin G and H (28 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.

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