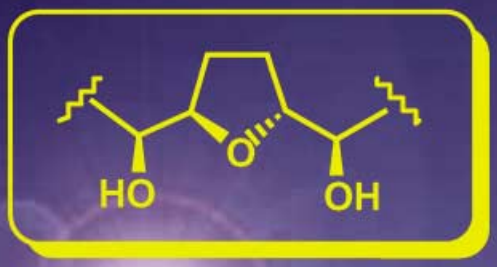
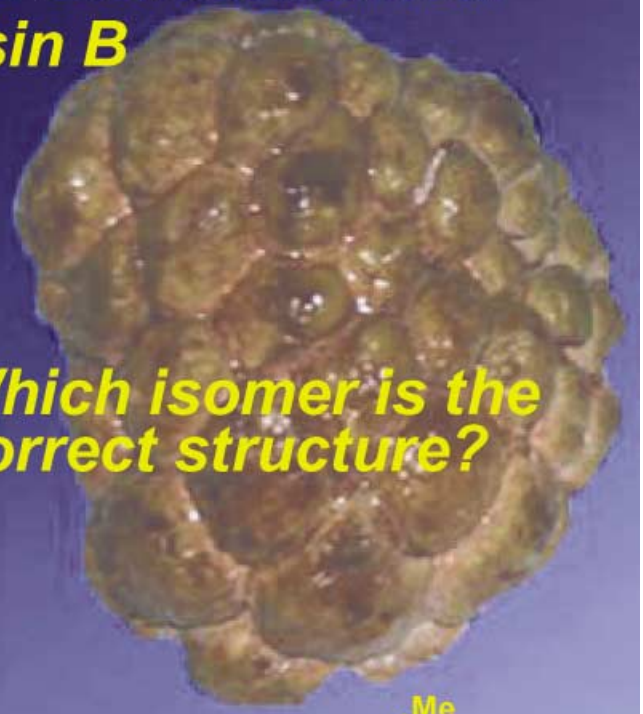
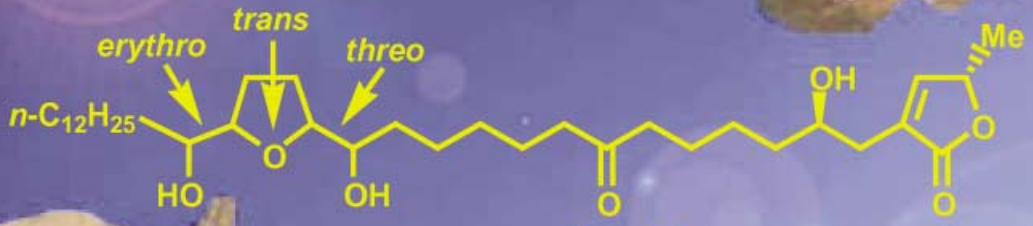
Total Synthesis and Stereochemical Assignment of Mosin B



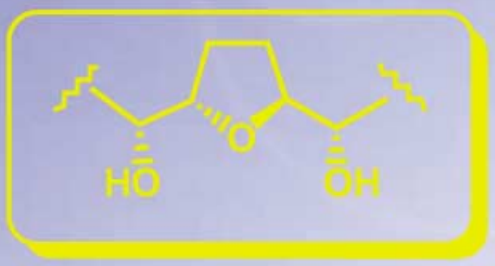


Which isomer is the correct structure?



mosin B

Their inhibition of tumor cell growth?



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Total Synthesis of the Antitumor Acetogenin Mosin B: Desymmetrization Approach to the Stereodivergent Synthesis of *threo*/*trans*/*erythro*-Type Acetogenins

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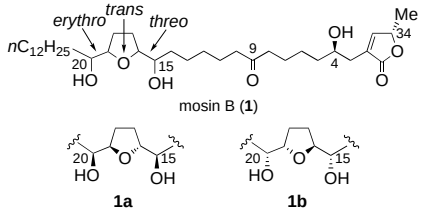
Abstract: A total synthesis of the *threo*/*trans*/*erythro*-type acetogenin mosin B and one of its diastereomers has been achieved. The carbon skeleton is assembled in a convergent fashion from two segments (a THF ring segment and a γ-lactone segment) through the Nozaki–Hiyama–Kishi reaction. The THF ring segment was stereoselectively constructed by a stereodivergent synthesis starting from a common intermediate (4-cyclohexene-1,2-diol) based on a desymmetrization strategy. The γ-lactone segment was synthesized by coupling a triflate and a chiral α-sulfenyl γ-lactone. By virtue of these synthetic results, we suggest that the absolute configuration of natural mosin B is **1a**. Antiproliferative effects of **1a** and **1b** were also investigated.

Keywords: *annonaceous* acetogenins · asymmetric desymmetrization · mosin B · structure elucidation · total synthesis

Introduction

Annonaceous acetogenins[1] are a new class of natural products which have attracted worldwide attention in recent years because of their potent biological activities such as cytotoxic, antitumor, immunosuppressive, pesticidal, antifeedant, and antimalarial effects. Inhibition of mitochondrial complex I (NADH–ubiquinone oxoreductase) is considered to be one mode of action for acetogenins, leading to a lack of ATP in the tumor cell and the subsequent apoptosis.[2] Some acetogenins inhibit multidrug-resistant cancer cells with an ATP-driven transporter system.[3] Furthermore, although more than 250 acetogenins have been isolated from various *Annonaceae* plants, the absolute configuration of many acetogenins have not been determined. In view of the scarcity of natural resources, more samples are required for further biological and clinical studies and for precise structural determination.

Mosin B (**1**) (Scheme 1) is a *threo*/*trans*/*erythro*-type mono-THF acetogenin isolated in 1997 from the bark of *Annona squamosa* by McLaughlin and co-workers.[4, 5] This natural product has selective and potent cytotoxic activity against the human pancreatic tumor cell line. The structure of **1** was



Scheme 1. Possible structures of mosin B.

assigned mainly on the basis of ^{1}H and ^{13}C NMR spectroscopy and MS data. Although the absolute configuration of the γ-lactone moiety was established as (4*R*,34*S*) and the relative stereochemistry of the THF part was determined as *threo*/*trans*/*erythro*,[1a] the absolute configuration remained unknown. Differentiation of the two possible structures **1a** and **1b** would be difficult by ^{1}H or ^{13}C NMR spectroscopic data, since two stereogenic regions, that is, the THF ring core part (C_{15}–C_{20}) and the γ-lactone segment (C_4 and C_{34}), are separated by a long carbon chain. Moreover, the absolute

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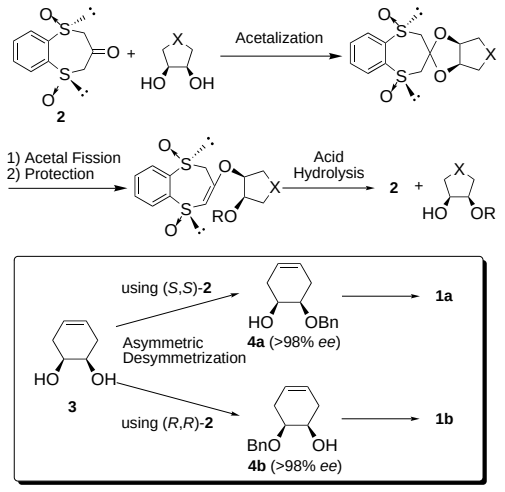
stereochemical assignment of the *threo*/*trans*/*erythro*-type acetogenin by the advanced Mosher ester methodology is generally difficult because the protons of the THF part are affected by the shielding from the two methoxy(trifluoromethyl)phenylacetate (MTPA) esters flanking both sides of the THF ring.[4, 6] X-ray analysis is also very difficult due to the waxy nature of this compound. To establish the absolute configuration of mosin B, we planned to synthesize the two candidate structures (**1a** and **1b**) by a stereodivergent synthesis based on a desymmetrization strategy starting from the common intermediate 4-cyclohexene-1,2-diol (**3**).[7]

In a preliminary communication,[8] we reported the first total synthesis of **1a** and **1b**, and suggested that compound **1a** is the correct structure of mosin B. In this paper, we describe full details of the synthesis of **1a** and **1b** including an investigation of an appropriate alkylating agent for an α-sulfenylated γ-lactone **9**. Furthermore, precise comparison of the ^{13}C NMR spectral data of the natural mosin B, **1a**, and **1b** afforded additional evidence that mosin B is identical with **1a** rather than **1b**. The antiproliferative effects of **1a** and **1b** against several anticancer cells are also reported.

Results and Discussion

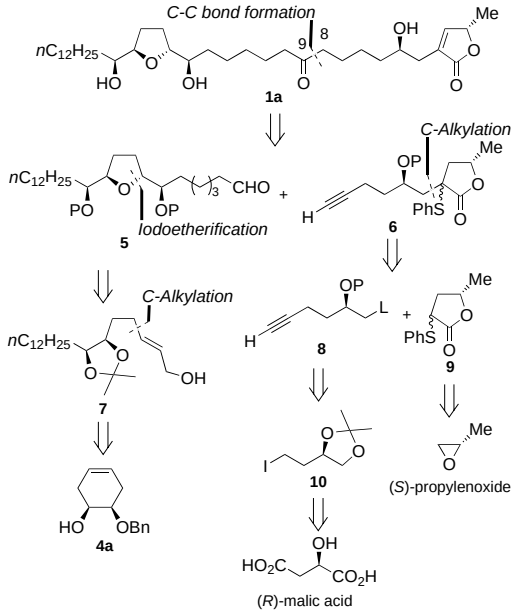
We have recently developed an efficient method for the asymmetric desymmetrization of cyclic *meso*-1,2-diols by using C_2-symmetric bis-sulfoxide **2** (Scheme 2).[7] After acetalization of the *meso*-1,2-diols with the chiral auxiliary **2**, the resulting acetals were subjected to base-promoted acetal



Scheme 2. Our asymmetric desymmetrization protocol for cyclic *meso*-1,2-diols.

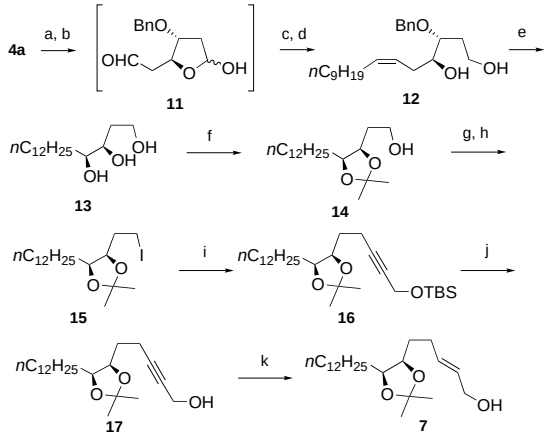
fission followed by benzylation to give the desymmetrized diol derivatives with high diastereoselectivity. The chiral auxiliary **2** was readily removed by acid hydrolysis and can be recovered without loss of enantiomeric excess. Based on this methodology, 4-cyclohexene-1,2-diol (**3**) can be converted to the desymmetrized alcohols **4a** and **4b** (>98% *ee*); the stereochemistry for both compounds was confirmed by a modified Mosher method. These are versatile chiral building blocks for the construction of stereogenic centers at the C_{19} and C_{20} positions in both **1a** and **1b**.

Scheme 3 shows a retrosynthetic analysis of the candidate **1a**. Compound **1a** is divided into the two key building blocks **5** and **6**. The THF core segment **5** is stereoselectively constructed by iodoetherification[9] of the *E* allylic alcohol **7**, which is prepared from the chiral alcohol **4a**.[7] The γ-lactone segment **6** is synthesized by α-alkylation of known α-sulfenyl γ-lactone **9**[10] with an alkyne **8** prepared from an iodide **10**.[11]



Scheme 3. Retrosynthetic analysis of mosin B.

The synthesis of the allylic alcohol **7** from the optically pure alcohol **4a** is summarized in Scheme 4. Alcohol **4a** was converted into a lactol **11** by dihydroxylation of the double bond followed by oxidative cleavage of the resulting 1,2-diol.



Scheme 4. Synthesis of allylic alcohol **7**. a) cat. OsO_4, *N*-methylmorpholine *N*-oxide, acetone/THF, RT; b) $NaIO_4$, acetone/H_2O, RT; c) $Ph_3PC_{10}H_{21}Br$, KHMDS, THF, -78 to 0 °C; d) $NaBH_4$, MeOH, RT, 20% over four steps; e) H_2, Pd/C, 3 atm, MeOH, RT, quant.; f) *p*TsOH, acetone, RT, 93%; g) MsCl, Et_3N, CH_2Cl_2, RT; h) NaI, $NaHCO_3$, acetone, reflux, 88% over two steps; i) 1-*tert*-butyldimethylsilyloxy-2-propyne, *n*BuLi, THF/HMPA, 0 °C, 74%; j) TBAF, THF, RT, quant.; k) $LiAlH_4$, THF, reflux, 90%.

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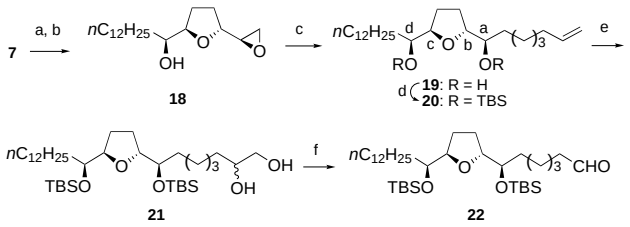
Wittig reaction proceeded selectively on the free aldehyde moiety of lactol **11**, and the lactol itself was then reduced with $NaBH_4$ in MeOH at room temperature to give diol **12** in overall 20% yield from **4a**. Hydrogenation of the double bond accompanied by debenzylation afforded a triol **13** in quantitative yield. The 1,2-diol was selectively protected as an acetonide to give **14** in 93% yield.[12] Mesylation of **14** followed by iodination gave an iodide **15** (88% in two steps). The iodide **15** was coupled with the acetylide generated from the *tert*-butyldimethylsilyl (TBS) ether of propargyl alcohol[13] on treatment with *n*BuLi to give alkyne **16** in 74% yield. Alkylation of **15** with the acetylide generated from an unprotected propargyl alcohol afforded no desired product, and instead, elimination of the iodide occurred due to the basicity of the alkoxide. The alkyne **16** was converted into the *E* allylic alcohol **7** by deprotection of the TBS ether to give alcohol **17** followed by an *E*-selective reduction of the triple bond with $LiAlH_4$. Attempted Birch reduction of **16** afforded an *E*-selective reduction product, but the TBS ether was lost.

Upon treatment of **7** with $I(collidine)_2ClO_4$,[9] iodoetherification proceeded highly stereoselectively to give epoxide **18** as a single isomer after subsequent base treatment (Scheme 5). The epoxide **18** was subjected to nucleophilic ring opening[9b, 14] with 5-hexenylmagnesium bromide in the



Scheme 5. Synthesis of THF core segment **22**. a) $I(collidine)_2ClO_4$, MeCN/H_2O, RT; b) K_2CO_3, MeOH, RT, 80% over two steps; c) 6-bromo-1-hexene, Mg, CuBr, THF, 0 °C, 89%; d) TBSOTf, 2,6-lutidine, CH_2Cl_2, RT, 83%; e) cat. OsO_4, *N*-methylmorpholine *N*-oxide, THF/acetone/H_2O, RT, 79%; f) $NaIO_4$, CH_2Cl_2/acetone/H_2O, RT, 75%.

presence of CuBr to give diol **19** regioselectively in 89% yield.[15] The stereochemistry around the THF ring was assigned as *threo*/*trans*/*erythro* by comparison of the ^{13}C NMR spectral data of **19** with those of Fujimoto's synthetic model compounds.[16] As shown in Figure 1, the ^{13}C NMR spectral data around the THF ring of **19** nicely matched those of the model compound with *threo*/*trans*/*erythro* stereochemistry. The THF core segment **22** was then synthesized by silylation of the diol **19** followed by oxidative cleavage of the terminal olefin via the intermediate diol **21**.

Preparation of the γ-lactone segment **28** is summarized in Scheme 6. The known iodide **10**[11] prepared from (*R*)-malic acid was converted into an alkyne **23** on treatment with lithium trimethylsilyl acetylide. Deacetonization of **23** with AcOH to give diol **24** was followed by desilylation to give acetylenic diol **25** in 90% yield. Selective tosylation of the primary alcohol in **25** and subsequent silylation of the secondary alcohol gave tosylate **26** in 69% yield in two steps. Iodination of **26** with NaI gave the iodide **27** in 88% yield. Unfortunately, alkylation of the known lactone **9**[10] with **27** in

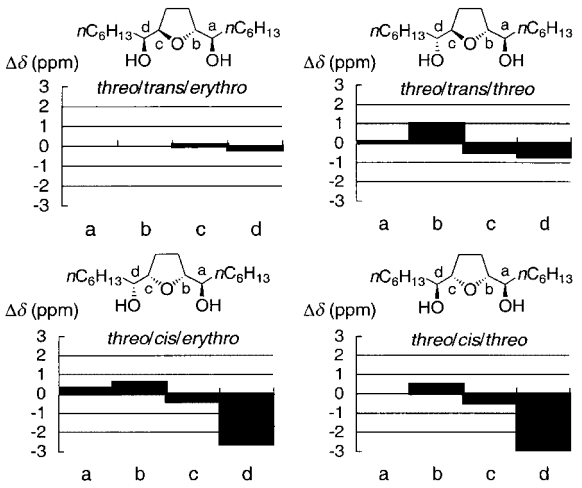
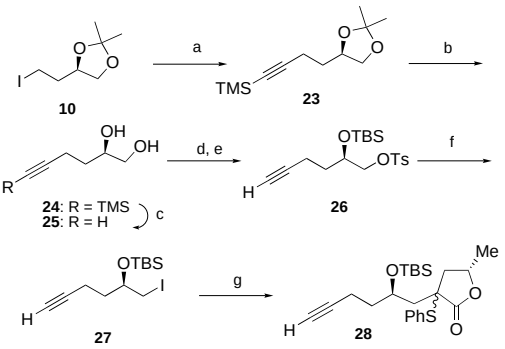


Figure 1. Differences between the characteristic chemical shifts of the carbon atoms of **19** and those of Fujimoto's model compounds. The *x* and *y* axes represent the carbon position and $\Delta\delta$ ($\delta_{\mathbf{19}} - \delta_{\text{model compound}}$), respectively.



Scheme 6. Synthesis of γ-lactone segment **28**. a) Trimethylsilylacetylene, *n*BuLi, THF/HMPA, −78 to 0 °C, 85%; b) AcOH, H_2O, RT, 92%; c) TBAF, THF, RT, 90%; d) *p*TsCl, pyridine, RT; e) TBSCl, imidazole, DMF, RT, 69% over two steps; f) NaI, $NaHCO_3$, acetone, reflux, 88%; g) **9**, KHMDS, THF/HMPA, 0 °C to reflux, 16%.

the presence of potassium hexamethyldisilazane (KHMDS) in THF/HMPA (hexamethylphosphoramide) gave the sulfide **28** in only 16% yield.[17, 18] We suggest that the bulky TBS ether adjacent to the iodo substituent prevents the alkylation, since alkylation of **9** with 1-iodohexane proceeded in good yield (74%) under the same conditions. Thus, we investigated an appropriate protecting and leaving group for the α-alkylation of **9**.

We selected a methoxymethyl (MOM) group as a less bulky protecting group, and triflate (OTf) and chloromethanesulfonate (OMc)[19] as more efficient leaving groups. The MOM-protected iodide **30** was synthesized from the diol **25** by the same procedure as that described for **27** (Scheme 7). The alkylating agents **36**–**39** with OTf or OMc as the leaving group were prepared as follows: selective esterification of the primary alcohol of **25** to a pivaloyl ester **31** followed by protection of the secondary alcohol as the TBS or MOM ether afforded **32** or **33**, respectively. Deprotection of the pivaloyl ester of **32** or **33** with diisobutylaluminum hydride (DIBALH) was carried out in 98% and 92% yield, respectively. Conversion of the primary alcohol in **34** or **35** into the leaving group gave four alkylating agents **36**–**39**. The alkylating agent

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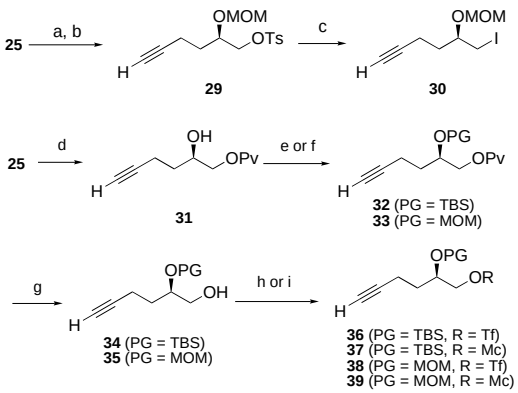
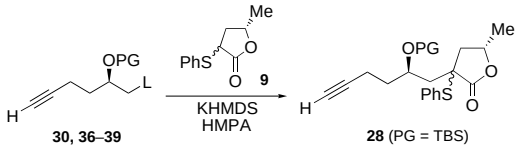


Scheme 7. Synthesis of alkylating agents **30** and **36**–**39**. a) *p*TsCl, pyridine, RT; b) MOMCl, *i*Pr_2NEt, CH_2Cl_2, RT, 67% over two steps; c) NaI, $NaHCO_3$, acetone, reflux, 79%; d) pivaloyl chloride, pyridine, CH_2Cl_2, 0°C to RT, 89%; e) TBSCl, imidazole, DMF, RT, quant.; f) MOMCl, *i*Pr_2NEt, CH_2Cl_2, 0°C to RT, 93%; g) DIBALH, CH_2Cl_2, −78°C, 98% for **34** and 92% for **35**; h) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0°C, 91% for **36**; i) McCl, 2,6-lutidine, CH_2Cl_2, 0°C, 90% for **37** and 84% for **39**.

38 was used immediately in the next reaction without further purification due to its instability.

The results of the coupling reaction of the alkylating agents **30** and **36**–**39** with the lactone **9** are summarized in Table 1. For substrates bearing a MOM ether, the reaction resulted in decomposition and gave the coupling product in poor yield (entries 1–3). For the substrates with a TBS ether, triflate was the best leaving group (entries 4–6). Thus, the product **28** was obtained in 26% yield.

Table 1. Coupling reaction of lactone and alkylating agents.

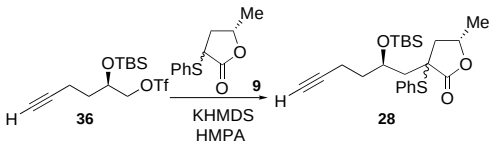


Entry	Compound	PG	L	Conditions	Yield [%]
1	**30**	MOM	I	0°C to RT	trace
2	**38**	MOM	OTf	0°C	decomp.
3	**39**	MOM	OMc	0°C to RT	trace
4	**27**	TBS	I	0°C to reflux	16
5	**36**	TBS	OTf	0°C	26
6	**37**	TBS	OMc	0°C to reflux	trace

Next, we examined the effect of HMPA on the yield of alkylation (Table 2). We found that the yield was optimized at 69% when five equivalents of HMPA were used. The correct combination of the protecting group (TBS) and the leaving group (OTf) in the alkylating agent, and the amount of HMPA were therefore important to achieve high yields. This procedure will be useful for the synthesis of other acetogenins with an hydroxy group at the C_4-position.[20]

We investigated the reaction of the acetylide derived from **28** with 1-pentanal (**40**) as a model study (Table 3). Although an adduct **41** was obtained, the yield was low. All efforts to improve the yield were unsuccessful and led to decomposition of **40** probably as a result of the high basicity of the acetylide.

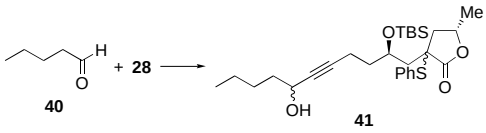
Table 2. Effect of HMPA in coupling reaction of lactone and triflate.



Entry	HMPA [equiv]	Conditions	Yield [%]
1	0	0°C to RT	10 (20)[a]
2	1	0°C	48
3	5	0°C	69
4	5	−20 to −10°C	65
5	14	0°C	26

[a] Yield in parentheses based on the consumed triflate.

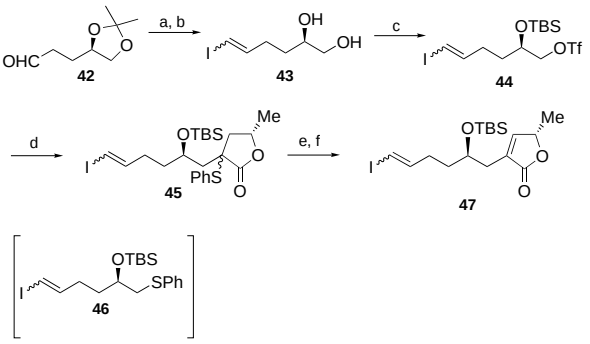
Table 3. Coupling reaction of aldehyde and acetylide.



Entry	Base	Additive	Yield [%]
1	*n*BuLi	–	20
2	*n*BuLi	HMPA	complex mixture
3	*t*BuLi	–	23
4	*t*BuLi	$BF_3 \cdot OEt_2$	20
5	*t*BuLi	$CeCl_3$	complex mixture
6	KHMDS	–	trace

The corresponding cerium acetylide has a low basicity; however, coupling with this also failed because of the decomposition of the sulfide **28** (entry 5). We therefore abandoned the coupling reaction of the aldehyde with the acetylide and planned an alternative route with the Nozaki–Hiyama–Kishi reaction.[21]

Synthesis of the γ-lactone segment **47** started from the known aldehyde **42**[22] prepared from D-glutamic acid, which was converted into a diol **43** by Takai's olefination[23] followed by deacetalization. Selective triflation of the primary alcohol in **43** with Tf_2O at −50°C and subsequent silylation of the secondary alcohol with TBSOTf at 0°C were carried out in a one-pot reaction.[24] In contrast to **36**, the coupling reaction of



Scheme 8. Synthesis of γ-lactone segment **47**. a) $CrCl_2$, CHI_3, THF, RT; b) Dowex 50W, MeOH, RT, 58% over two steps; c) Tf_2O, 2,6-lutidine, CH_2Cl_2, −50°C then TBSOTf, 0°C, 92%; d) **9**, KHMDS, THF, 0°C then **39**, RT, 79%; e) *m*CPBA, CH_2Cl_2, 0°C; f) toluene, reflux, 85% over two steps.

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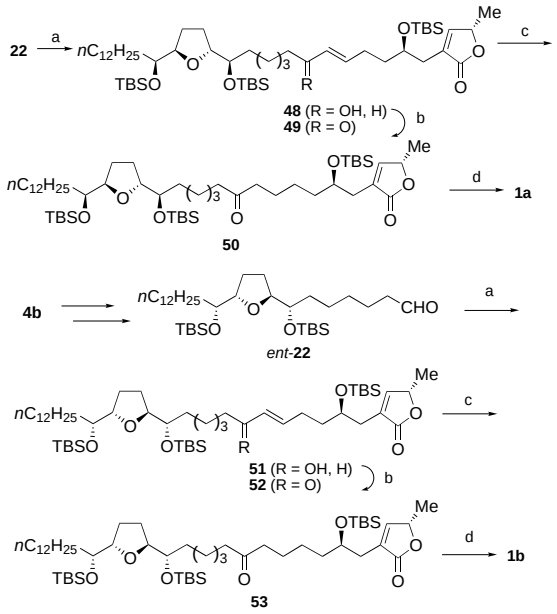
44 with lactone **9**[10] in the presence of HMPA (5 equiv) gave the desired product **45** in poor yield (13%) along with the by-product **46** in 12% yield. In this case, the yield was improved up to 79% when the reaction was carried out without HMPA. Oxidation of the sulfide **45** into sulfoxide followed by thermal elimination afforded the γ-lactone segment **47**.

Assembly of the two segments **22** and **47** was performed with the Nozaki–Hiyama–Kishi reaction (Scheme 9). Treatment of **47** with $CrCl_2$ (5 equiv) in the presence of catalytic



Scheme 9. Synthesis of mosin B **1a** and the diastereomer **1b**. a) **47**, $CrCl_2$, cat. $NiCl_2$, DMF/Me_2S, RT, 71% from **22**, 70% from *ent*-**22**; b) SO_3·pyridine, DMSO, Et_3N, CH_2Cl_2, 0 °C to RT, 72% from **48**, 83% from **51**; c) H_2, [$(Ph_3P)_3RhCl$], benzene, RT, 78% from **49**, 74% from **52**; d) aq. HF, MeCN/THF, RT, 72% from **50**, 78% from **53**.

$NiCl_2$ in DMF afforded **48** in low yield, although rapid consumption of aldehyde **22** was observed. With the DMF/Me_2S solvent system,[25] the yield was remarkably improved and gave **48**[26] in 59% yield and recovered aldehyde **22** in 35% yield. Moreover, the alcohol **48** was obtained in 71% yield when ten equivalents of $CrCl_2$ were used. Oxidation of **48** with SO_3·pyridine complex and DMSO followed by selective reduction of the resulting enone **49** with Wilkinson's catalyst afforded the tri-TBS ether **50**. Finally, deprotection of all the TBS ethers with HF afforded the candidate **1a**. The other candidate **1b** was synthesized from **4b** by using the same procedure as for **1a**.

The specific rotations of the two synthetic samples **1a** and **1b** were very different. While the specific rotation of synthetic **1a** ($[\alpha]_D^{25} = +18.7$, $c = 0.50$, CH_2Cl_2) is higher than the reported value of the naturally occurring mosin B[4] ($[\alpha]_D^{23} = +11.5$, $c = 0.005$, CH_2Cl_2), the specific rotation of **1b** ($[\alpha]_D^{26} = +2.2$, $c = 0.39$, CH_2Cl_2) was very small. Due to the unavailability of mosin B, a comparison of our synthetic samples with the authentic natural product was not possible. However, taking into account the fact that the reported optical rotations of acetogenins are sometimes smaller than their actual values when they are measured at low concentrations, presumably owing to experimental error or the presence of impurities,[5c, d, 27] the synthetic compound **1a** was assumed to be the natural mosin B.

Compounds **1a** and **1b** could not be differentiated by ^1H NMR spectral data. The ^{13}C NMR spectral data of **1a** and **1b** were also very close to those of natural mosin B. It would therefore be difficult to distinguish which compound was identical to the natural mosin B unless *both* **1a** and **1b** were available. We compared the ^{13}C NMR spectral data more precisely by plotting the difference between the chemical shifts of natural mosin B and those of each candidate **1a** and **1b** as shown in Figure 2. The chemical shifts of **1a** were almost identical to the reported values of mosin B, and the differences in the chemical shifts were within 0.04 ppm except for one carbon. In contrast, the differences in **1b** exceeded more than 0.04 ppm for many carbons. From this evidence, we concluded that natural mosin B is **1a** and not **1b**.

Biological evaluation of 1a and 1b: Comparison of the antiproliferative effects of mosin B (**1a**) and the unnatural diastereomer **1b** is of great interest. Thus, we evaluated their antiproliferative effects by using adriamycin as a positive control. The results are shown in Figure 3. Both compounds **1a** and **1b** inhibited proliferation of two pancreatic cancer cell lines (PaCa-2 and PSN-1) in a dose-dependent manner. In the growth-inhibitory assay (for 4 d), they had approximately sixfold greater ED_{50} values than adriamycin against PaCa-2 and PSN-1.[28] Unexpectedly, the growth-inhibitory effect of **1b** is almost the same as that of **1a** (the differences were not statistically significant, $p > 0.05$). The growth-inhibitory assays with **1a**, **1b**, and adriamycin were also performed on HT-29 (colon adenocarcinoma) and MCF-7 (breast adenocarcinoma) cell lines. Compounds **1a** and **1b** did not have superior

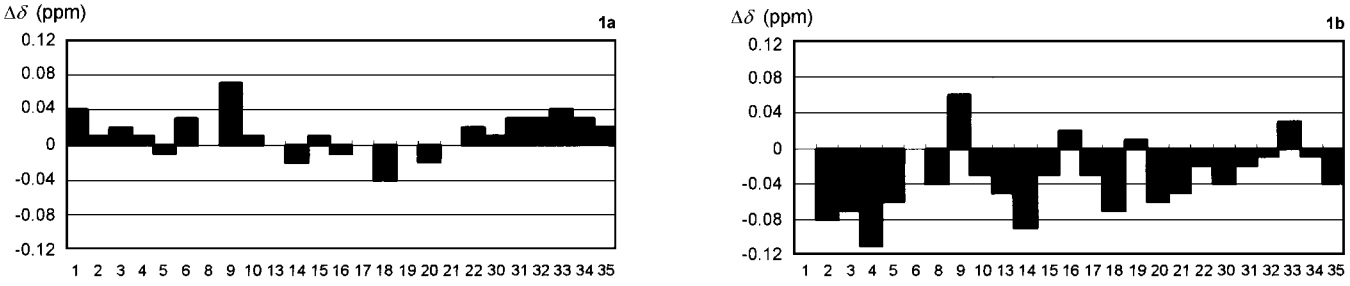


Figure 2. Differences between the characteristic chemical shifts of the carbon atoms of natural mosin B and those of each candidate **1a** (left) and **1b** (right) (75 MHz, $CDCl_3$). The x and y axes represent the carbon number and $\Delta\delta$ ($\delta_{\mathbf{1a,b}} - \delta_{\text{mosin B}}$), respectively.

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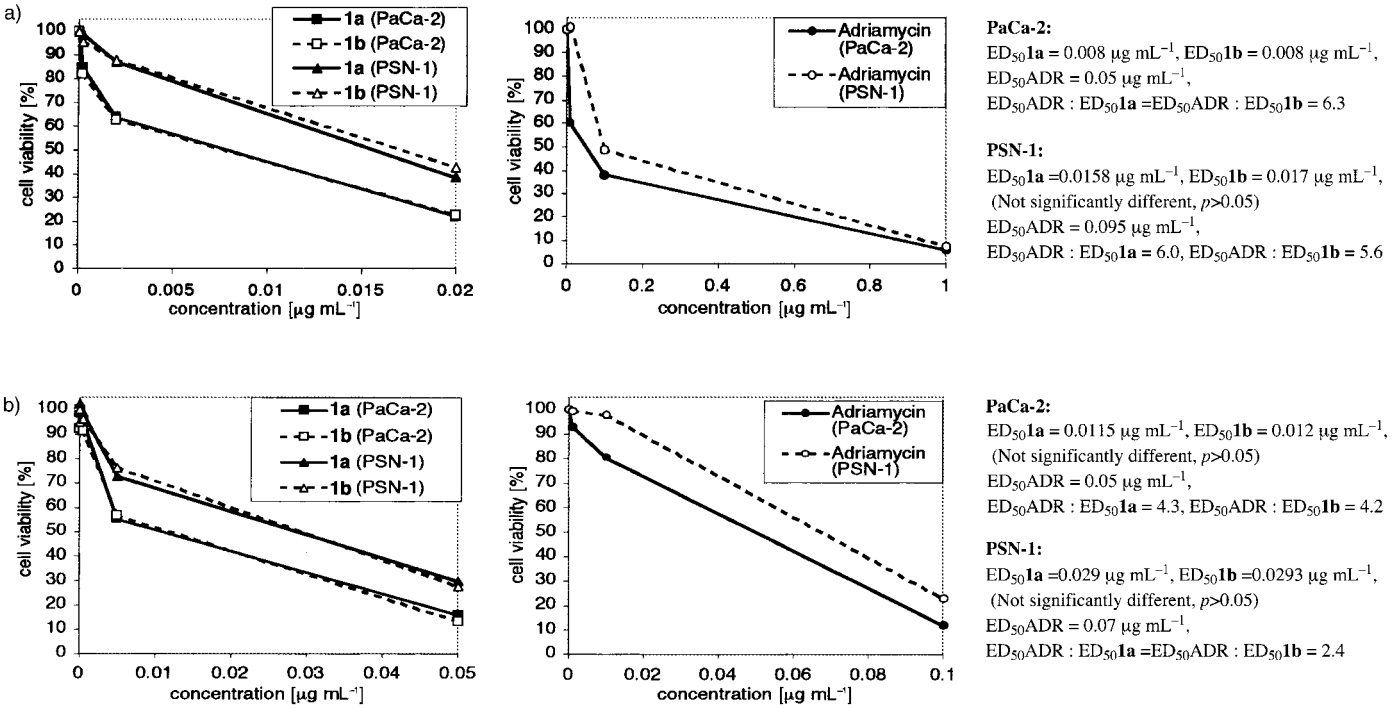

Figure 3. Antiproliferative effect of **1a**, **1b**, and adriamycin in PaCa-2 and PSN-1 cells: a) Growth-inhibitory assay for 4 d (average data from four independent experiments). b) Growth-inhibitory assay for 7 d (average data from four independent experiments).

growth-inhibition effects relative to adriamycin in those cells or in the KMP-5 (pancreatic adenocarcinoma) cell line (data not shown).

Conclusion

The total synthesis of mosin B (**1a**) and the diastereomer **1b** was accomplished by using asymmetric desymmetrization of the σ-symmetric diol **3** and the Nozaki–Hiyama–Kishi reaction as key steps. The overall yield was 1.1% for 20 steps from the desymmetrized alcohol **4a**. Based on the spectral data, we suggest that mosin B is **1a** and not **1b**. Diastereomer **1b** exhibited a higher antiproliferative effect than adriamycin and had a similar profile of growth inhibition as **1a** against used cancer cells.

Experimental Section

General: Melting points are uncorrected. Optical rotations were measured with a JASCO DIP-360 digital polarimeter. IR spectra were measured with an Horiba FT-210 IR spectrometer. ^{1}H NMR spectra were measured with a JEOL JNM-GX500 spectrometer (500 MHz) or a JEOL JNM-AL300 spectrometer (300 MHz). ^{13}C NMR spectra were measured with a JEOL JNM-AL300 spectrometer (75 MHz) or a JEOL JNM-EX270 spectrometer (67.8 MHz). All signals are expressed as ppm downfield from tetramethylsilane used as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), quintet (qn), multiplet (m). Mass spectra were recorded on a Shimadzu QP-1000 mass spectrometer, a JEOL JMS-D300, or a JEOL JMS-600 mass spectrometer. High-resolution mass spectra were obtained with a JEOL JMS-D300 or a JEOL JMS-600 mass spectrometer. FAB mass spectra were measured with a JEOL-JMS-700 mass spectrometer. Unless otherwise stated, all solvents were dry and all extracts were dried over $MgSO_4$. Merck Kieselgel 60 was used as an adsorbent for column chromatography. Known compounds **4a**,[7] **4b**,[7] **9**,[10] **10**,[11] and **42**[22] were synthesized according to the literature methods. Experimental procedures and characterization data of **23**–**39** and **41** are included in the Supporting Information.

(6*Z*,3*R*,4*S*)-3-Benzyloxy-6-hexadecene-1,4-diol (12): *N*-Methylmorpholine *N*-oxide (2.15 g, 18.4 mmol) and OsO_4 (31.1 mg, 0.122 mmol) were added successively to a stirred solution of **4a** (1.25 g, 6.12 mmol) in acetone/water (1:1, 60 mL) at RT. After 3 h, the reaction was quenched with saturated $Na_2S_2O_3$. Celite was added to the mixture and stirring was continued for 1 h. The Celite was filtered off, and the filtrate was concentrated under reduced pressure. $NaIO_4$ (1.57 g, 7.24 mmol) was added to a stirred solution of the crude diol in acetone/water (3:1, 40 mL) at RT. The stirring was continued at the same temperature for 10 min. After filtration through Celite, the solvent was evaporated under reduced pressure. The residue was extracted with EtOAc prior to drying and solvent evaporation. KHMDS (0.5 M in toluene, 10.6 mL, 5.31 mmol) was added slowly to a stirred suspension of $Ph_3P(nC_{10}H_{21})Br$ (2.57 g, 5.31 mmol) in THF (10 mL) at 0 °C. A solution of the crude aldehyde in THF (10 mL) was added to the mixture at −78 °C, and this was stirred at 0 °C for 2 h. The reaction was quenched with water, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine prior to drying and solvent evaporation. $NaBH_4$ (183 mg, 4.83 mmol) was added to a stirred solution of the crude lactol in MeOH (48 mL) at RT. After 5 min, the reaction was quenched with water, and the solvent was concentrated under reduced pressure. The residue was extracted with EtOAc, and the extract was washed with water and brine prior to drying and solvent evaporation. The residue was purified by chromatography (hexane/EtOAc 3:1) to give **12** (435 mg, 20% in four steps) as a colorless oil. $[\alpha]_D^{27} = +3.1$ ($c = 0.92$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 7.0$ Hz, 3H), 1.26–1.35 (m, 14H), 1.78–1.84 (m, 1H), 1.88–1.95 (m, 1H), 2.05 (dt, $J = 7.3$, 6.7 Hz, 2H), 2.22–2.27 (m, 1H), 2.30–2.36 (m, 1H), 2.38 (m, 2H), 3.62 (dt, $J = 7.3$, 3.7 Hz, 1H), 3.72–3.76 (m, 1H), 3.82 (ddd, $J = 11.0$, 7.3, 3.7 Hz, 1H), 3.89 (dt, $J = 8.5$, 4.3 Hz, 1H), 4.58 (d, $J = 11.6$ Hz, 1H), 4.64 (d, $J = 11.6$ Hz, 1H), 5.37–5.43 (m, 1H), 5.56 (dt, $J = 10.4$, 7.3 Hz, 1H), 7.30–7.38 (m, 5H); ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta = 14.1$, 22.6, 27.5, 29.3 (2C), 29.5, 29.56, 29.60, 30.6, 31.2, 31.9, 59.5, 71.7, 71.8, 80.0, 124.7, 127.9 (3C), 128.5 (2C), 133.4, 138.0; IR (KBr): $\tilde{\nu} = 3358$ cm^{-1}; MS (EI): m/z (%): 362 (0.2) $[M]^+$, 253 (4.1), 177 (18.2), 91 (100); elemental analysis calcd (%) for $C_{23}H_{38}O_3$: C 76.20, H 10.56; found: C 76.01, H 10.50.

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(3*R*,4*S*)-1,3,4-Hexadecanetriol (13): Pd/C (4.0 mg) was added to a solution of **12** (37.8 mg, 0.104 mmol) in MeOH (1 mL). The mixture was stirred under 3 atm pressure of hydrogen at RT for 6.5 h. The Pd/C was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography (hexane/EtOAc 1:1) to give **13** (28.7 mg, 100 %) as a colorless powder. M.p. 109.5 – 110.0 °C (EtOAc/MeOH); $[\alpha]_D^{28} = +0.58$ ($c = 1.00$, MeOH); ^{1}H NMR (500 MHz, [D$_4$]MeOH): $\delta = 0.90$ (t, $J = 7.0$ Hz, 3H), 1.29 – 1.37 (m, 20H), 1.52 – 1.63 (m, 3H), 1.80 – 1.86 (m, 1H), 3.34 – 3.44 (m, 1H), 3.52 – 3.55 (m, 1H), 3.67 – 3.76 (m, 2H); ^{13}C NMR (67.8 MHz, [D$_4$]MeOH): $\delta = 14.4$, 23.7, 27.0, 30.5, 30.8 (5C), 30.9, 33.1, 33.7, 35.9, 60.4, 73.5, 76.0; IR (KBr): $\tilde{\nu} = 3263$ cm^{-1}; MS (FAB): *m*/*z*: 275 [*M*+H]$^+$; elemental analysis calcd (%) for $C_{16}H_{34}O_3$: C 70.02, H 12.49; found: C 69.64, H 12.21.

(3*R*,4*S*)-3,4-*O*-Isopropylidene-1,3,4-hexadecanetriol (14): A mixture of **13** (54.7 mg, 0.199 mmol) and *p*TsOH·H$_2$O (0.8 mg) in acetone (4 mL) was stirred at RT for 24 h. The reaction was quenched with NaHCO$_3$. After filtration, the solvent was concentrated under reduced pressure. The residue was purified by chromatography (hexane/EtOAc 1:1) to give **14** (58.0 mg, 93 %) as a colorless oil. $[\alpha]_D^{28} = +16.3$ ($c = 1.13$, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$): $\delta = 0.88$ (t, $J = 7.0$ Hz, 3H), 1.23 – 1.58 (m, 23H), 1.35 (s, 3H), 1.46 (s, 3H), 1.74 – 1.81 (m, 1H), 2.35 – 2.36 (m, 1H), 3.80 – 3.85 (m, 2H), 4.07 – 4.11 (m, 1H), 4.24 (ddd, $J = 11.0$, 5.8, 2.7 Hz, 1H); ^{13}C NMR (67.8 MHz, CDCl$_3$): $\delta = 14.1$, 22.7, 25.9, 26.3, 28.4, 29.3, 29.49, 29.54, 29.6 (5C), 31.9, 31.9, 61.3, 77.3, 78.0, 107.8; IR (KBr): $\tilde{\nu} = 3410$ cm^{-1}; MS (FAB): *m*/*z*: 315 [*M*+H]$^+$; elemental analysis calcd (%) for $C_{19}H_{38}O_3$: C 72.56, H 12.18; found: C 72.46, H 12.00.

(3*R*,4*S*)-1-Iodo-3,4-*O*-isopropylidene-3,4-hexadecanediol (15): Methanesulfonyl chloride (0.144 mL, 1.86 mmol) was added to a stirred mixture of **14** (488 mg, 1.55 mmol) and Et$_3$N (0.260 mL, 1.86 mmol) in CH$_2$Cl$_2$ (16 mL) at RT. After 5 min, the reaction was quenched with water. The mixture was extracted with EtOAc, and the extract was washed with brine prior to drying and solvent evaporation. NaHCO$_3$ (1.04 g, 12.4 mmol) and NaI (698 mg, 4.65 mmol) were added to the mixture of the residue in acetone (16 mL), and the mixture was heated at reflux for 11 h. Water was added and the mixture was extracted with EtOAc. The extract was washed with brine prior to drying and solvent evaporation. The residue was purified by chromatography (hexane/EtOAc 4:1) to give **15** (578 mg, 88 % in two steps) as a colorless oil. $[\alpha]_D^{29} = +31.6$ ($c = 1.02$, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$): $\delta = 0.88$ (t, $J = 7.0$ Hz, 3H), 1.23 – 1.54 (m, 22H), 1.35 (s, 3H), 1.42 (s, 3H), 1.81 – 1.87 (m, 1H), 1.92 – 1.99 (m, 1H), 3.24 (dt, $J =$ 9.2, 7.3 Hz, 1H), 3.37 (ddd, $J = 9.2$, 7.3, 4.3 Hz, 1H), 4.07 – 4.13 (m, 2H); ^{13}C NMR (67.8 MHz, CDCl$_3$): $\delta = 2.8$, 14.1, 22.7, 25.9, 26.3, 28.6, 29.3, 29.5 (2C), 29.56, 29.62 (2C), 29.7 (2C), 31.9, 34.2, 77.5, 77.6, 107.8; IR (KBr): $\tilde{\nu} =$ 1092 cm^{-1}; MS (FAB): *m*/*z*: 425 [*M*+H]$^+$; elemental analysis calcd (%) for $C_{19}H_{37}IO_2$: C 53.77, H 8.79, I 29.90; found: C 53.73, H 8.56, I 29.57.

(6*R*,7*S*)-1-(*tert*-Butyldimethylsilyloxy)-6,7-*O*-isopropylidene-2-nonadecyne-6,7-diol (16): *n*BuLi (1.54 M in *n*-hexane, 2.88 mL, 4.44 mmol) was added to a stirred solution of 1-(*tert*-butyldimethylsilyloxy)-2-propyne (756 mg, 4.44 mmol) in THF (19 mL) at 0 °C. After 5 min, a solution of **15** (942 mg, 2.22 mmol) in HMPA (3.2 mL) was added to the mixture at the same temperature, and the stirring was continued for 10 min. The reaction was quenched with saturated NH$_4$Cl, and the solvent was concentrated under reduced pressure. The residue was extracted with EtOAc, and the extract was washed with saturated NH$_4$Cl, water, and brine prior to drying and solvent evaporation. The residue was purified by chromatography (hexane/EtOAc 50:1) to give **16** (763 mg, 74 %) as a colorless oil. $[\alpha]_D^{29} =$ +17.1 ($c = 1.04$, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$): $\delta = 0.11$ (s, 6H), 0.88 (t, $J = 7.0$ Hz, 3H), 0.91 (s, 9H), 1.26 – 1.40 (m, 20H), 1.33 (s, 3H), 1.42 (s, 3H), 1.45 – 1.58 (m, 3H), 1.63 – 1.70 (m, 1H), 2.26 – 2.32 (m, 1H), 2.39 – 2.45 (m, 1H), 4.06 (dt, $J = 8.5$, 4.3 Hz, 1H), 4.12 (ddd, $J = 10.4$, 5.5, 3.1 Hz, 1H), 4.29 (t, $J = 2.1$ Hz, 2H); ^{13}C NMR (67.8 MHz, CDCl$_3$): $\delta = -5.1$ (2C), 14.1, 15.6, 18.3, 22.7, 25.9 (3C), 26.0, 26.3, 28.6, 29.1, 29.3, 29.5 (2C), 29.59 (2C), 29.65 (2C), 29.71, 31.9, 52.0, 76.6, 77.8, 79.1, 84.6, 107.5; IR (KBr): $\tilde{\nu} =$ 2233 cm^{-1}; MS (EI): *m*/*z* (%): 465 (3.6) [*M* – H]$^+$, 451 (31.5) [*M* – CH$_3$]$^+$, 351 (100) [*M* – TBS]$^+$; elemental analysis calcd (%) for $C_{28}H_{54}O_3Si$: C 72.04, H 11.66; found: C 72.24, H 11.36.

(6*R*,7*S*)-6,7-*O*-Isopropylidene-2-nonadecyne-1,6,7-triol (17): TBAF (1.0 M in THF, 0.163 mL, 0.163 mmol) was added to a stirred solution of **16** (38.0 mg, 0.081 mmol) in THF (0.8 mL) at RT. After 10 min, water was added and the mixture was extracted with EtOAc. The organic phase was washed with water and brine prior to drying and solvent evaporation. The residue was purified by chromatography (hexane/EtOAc 3:1) to give **17** (28.8 mg, 100 %) as a colorless oil. $[\alpha]_D^{30} = +23.1$ ($c = 1.05$, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$): $\delta = 0.88$ (t, $J = 7.0$ Hz, 3H), 1.26 – 1.40 (m, 20H), 1.34 (s, 3H), 1.42 (s, 3H), 1.50 – 1.60 (m, 3H), 1.67 (dddd, $J = 12.8$, 10.4, 8.2, 5.0 Hz, 1H), 2.32 (dtt, $J = 17.1$, 8.2, 2.1 Hz, 1H), 2.44 (dddt, $J = 17.1$, 7.8, 5.0, 2.4 Hz, 1H), 4.08 (dt, $J = 10.4$, 4.3 Hz, 1H), 4.12 (ddd, $J = 10.4$, 6.1, 3.1 Hz, 1H), 4.25 (br s, 2H); ^{13}C NMR (67.8 MHz, CDCl$_3$): $\delta = 14.1$, 15.5, 22.7, 25.9, 26.4, 28.6, 29.1, 29.3, 29.4, 29.5, 29.57, 29.61 (2C), 29.65, 29.68, 31.9, 51.3, 76.5, 77.8, 78.8, 85.6, 107.6; IR (KBr): $\tilde{\nu} = 3381$, 2224 cm^{-1}; MS (FAB): *m*/*z*: 353 [*M*+H]$^+$; elemental analysis calcd (%) for $C_{22}H_{40}O_3$: C 74.95, H 11.44; found: C 74.79, H 11.39.

(*E*,6*R*,7*S*)-6,7-*O*-Isopropylidene-2-nonadecene-1,6,7-triol (7): LiAlH$_4$ (22.0 mg, 0.579 mmol) was added to a stirred solution of **17** (102 mg, 0.289 mmol) in Et$_2$O (3 mL) at RT. The mixture was heated at reflux for 3 h. Saturated Rochelle salt was gradually added to the vigorously stirred mixture. After 10 min, the mixture was extracted with EtOAc, and the extract was washed with water and brine prior to drying and solvent evaporation. The residue was purified by chromatography (hexane/EtOAc 3:1) to give **7** (92.4 mg, 90 %) as a colorless oil. $[\alpha]_D^{28} = +4.3$ ($c = 1.02$, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$): $\delta = 0.88$ (t, $J = 6.7$ Hz, 3H), 1.26 – 1.63 (m, 24H), 1.34 (s, 3H), 1.43 (s, 3H), 2.06 – 2.13 (m, 1H), 2.45 – 2.32 (m, 1H), 4.01 – 4.06 (m, 2H), 4.09 – 4.11 (m, 2H), 5.66 – 5.76 (m, 2H); ^{13}C NMR (67.8 MHz, CDCl$_3$): $\delta = 14.1$, 22.6, 26.0, 26.2, 28.6, 28.7, 29.3 (2C), 29.5, 29.56, 29.60 (3C), 29.63, 29.7, 31.9, 63.5, 77.3, 78.0, 107.4, 129.5, 132.2; IR (KBr): $\tilde{\nu} = 3396$ cm^{-1}; MS (FAB): *m*/*z*: 355 [*M*+H]$^+$; elemental analysis calcd (%) for $C_{22}H_{42}O_3$: C 74.52, H 11.94; found: C 74.46, H 11.85.

(2*R*,3*R*,6*R*,7*S*)-1,2:3,6-Diepoxy-7-hydroxynonadecane (18): I(collidine)$_2$-ClO$_4$ (552 mg, 1.18 mmol) was added to a stirred solution of **7** (348 mg, 0.981 mmol) in MeCN/water (100:1, 9.8 mL) at RT. After 5 min, water was added and the mixture was extracted with EtOAc. The organic phase was washed with water and brine prior to drying and solvent evaporation. K$_2$CO$_3$ (814 mg, 5.89 mmol) was added to a stirred solution of the residue in MeOH (10 mL) at RT. After 30 min, water was added and the mixture was extracted with CHCl$_3$. The extract was washed with saturated NH$_4$Cl, water, and brine prior to drying and solvent evaporation. The residue was purified by chromatography (hexane/EtOAc 3:1) to give **18** (244 mg, 80 % in two steps) as a colorless powder. M.p. 52.0 – 52.5 °C (hexane); $[\alpha]_D^{28} =$ +1.5 ($c = 1.04$, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$): $\delta = 0.88$ (t, $J = 7.0$ Hz, 3H), 1.25 – 1.51 (m, 22H), 1.83 – 1.94 (m, 3H), 2.01 (br s, 1H), 2.05 – 2.16 (m, 1H), 2.70 (dd, $J = 5.2$, 2.7 Hz, 1H), 2.79 (t, $J = 4.5$ Hz, 1H), 2.98 (dt, $J = 4.5$, 2.7 Hz, 1H), 3.82 (dt, $J = 6.1$, 3.1 Hz, 1H), 3.87 (dd, $J = 12.2$, 6.7 Hz, 1H), 3.94 (ddd, $J = 8.9$, 5.8, 3.1 Hz, 1H); ^{13}C NMR (67.8 MHz, CDCl$_3$): $\delta = 14.1$, 22.6, 24.6, 25.9, 29.0, 29.3, 29.5, 29.56, 29.60 (2C), 29.62 (2C), 31.9, 32.5, 44.2, 54.2, 71.5, 79.2, 83.0; IR (KBr): $\tilde{\nu} = 3421$ cm^{-1}; MS (FAB): *m*/*z*: 319 [*M*+Li]$^+$; elemental analysis calcd (%) for $C_{19}H_{36}O_3$: C 73.03, H 11.61; found: C 72.86, H 11.22.

(8*R*,9*R*,12*R*,13*S*)-9,12-Epoxy-8,13-dihydroxy-1-pentacosene (19): 6-Bromo-1-hexene (0.090 mL, 0.672 mmol) was added to a stirred mixture of Mg (17.2 mg, 0.706 mmol) in THF (0.3 mL) at RT. After 1.5 h, THF (0.3 mL) was added to the mixture. The mixture was cooled at – 30 °C, and CuBr (9.6 mg, 0.067 mmol) was added. After 5 min, **18** (10.5 mg, 0.034 mmol) in THF (0.34 mL) was added, and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with saturated NH$_4$Cl, and the solvent was concentrated under reduced pressure. The residue was extracted with EtOAc, and the extract was washed with water and brine prior to drying and solvent evaporation. The residue was purified by chromatography (hexane/EtOAc 2:1) to give **19** (11.8 mg, 89 %) as a colorless powder. M.p. 55.0 – 56.0 °C (hexane); $[\alpha]_D^{28} = +14.0$ ($c = 1.03$, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$): $\delta = 0.88$ (t, $J = 6.7$ Hz, 3H), 1.26 – 1.43 (m, 28H), 1.50 – 1.53 (m, 2H), 1.62 – 1.67 (m, 1H), 1.82 – 1.94 (m, 2H), 1.97 – 2.01 (m, 1H), 2.03 – 2.07 (m, 3H), 2.37 (br s, 1H), 3.38 – 3.39 (m, 1H), 3.79 – 3.89 (m, 3H), 4.93 (dd, $J = 10.4$, 1.8 Hz, 1H), 4.99 (dq, $J = 17.1$, 1.8 Hz, 1H), 5.81 (ddt, $J = 17.1$, 10.4, 6.7 Hz, 1H); ^{13}C NMR (67.8 MHz, CDCl$_3$): $\delta = 14.1$, 22.6, 25.2, 25.4, 26.0, 28.6, 28.8, 29.1, 29.3, 29.5, 29.57, 29.60 (2C), 29.63, 29.7, 31.9, 32.5, 33.0, 33.7, 71.4, 74.3, 82.3, 83.3, 114.2, 139.0; IR (KBr): $\tilde{\nu} = 3425$ cm^{-1}; MS (FAB): *m*/*z*: 397 [*M*+H]$^+$; elemental analysis calcd (%) for $C_{25}H_{48}O_3$: C 75.70, H 12.20; found: C 75.62, H 11.95.

(8*R*,9*R*,12*R*,13*S*)-8,13-Bis(*tert*-butyldimethylsilyloxy)-9,12-epoxy-1-pentacosene (20): TBSOTf (17.9 μL, 0.078 mmol) was added to a stirred mixture of **19** (10.3 mg, 0.026 mmol) and 2,6-lutidine (12.1 μL, 0.104 mmol) in CH$_2$Cl$_2$ (0.3 mL) at RT. After 10 min, the reaction mixture was quenched

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with saturated NH_4Cl. The mixture was extracted with EtOAc, and the extract was washed with water and brine prior to drying and solvent evaporation. The residue was purified by chromatography (hexane) to give **20** (13.5 mg, 83%) as a colorless oil. $[\alpha]_D^{26} = +13.6$ ($c = 1.03$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.05$ (s, 9H), 0.06 (s, 3H), 0.88 (m, 21H), 1.26–1.51 (m, 30H), 1.59–1.66 (m, 1H), 1.78–1.89 (m, 3H), 2.02–2.06 (m, 2H), 3.52–3.55 (m, 1H), 3.69–3.72 (m, 1H), 3.81 (td, $J = 7.0$, 4.3 Hz, 1H), 3.88 (td, $J = 8.5$, 6.1 Hz, 1H), 4.91–4.94 (m, 1H), 4.99 (ddd, $J = 17.1$, 3.7, 1.8 Hz, 1H), 5.81 (tdd, $J = 17.1$, 10.4, 6.7 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta = -4.6$, -4.5, -4.24, -4.18, 14.1, 18.2, 18.3, 21.5, 22.7, 25.2, 25.5, 26.0 (6C), 26.7, 27.7, 28.9, 29.36, 29.42, 29.6 (2C), 29.7 (2C), 29.9, 31.9, 32.9, 33.8, 34.7, 73.8, 75.1, 81.9, 82.0, 114.1, 139.2; IR (KBr): $\tilde{\nu} = 1088\ cm^{-1}$; MS (FAB): m/z: 624 $[M+H]^+$; elemental analysis calcd (%) for $C_{37}H_{76}O_3Si_2$: C 71.08, H 12.25; found: C 71.04, H 12.04.

(2*RS*,8*R*,9*R*,12*R*,13*S*)-8,13-Bis(*tert*-butyldimethylsilyloxy)-9,12-epoxypentacosan-1,2-diol (21): A catalytic amount of OsO_4 was added to a stirred mixture of **20** (330 mg, 0.528 mmol) and *N*-methylmorpholine *N*-oxide (92.8 mg, 0.792 mmol) in THF/acetone/water (1:1:1, 8 mL) at RT. After stirring at RT for 17 h, saturated $Na_2S_2O_3$ was added and the mixture was stirred for a further 1 h. The mixture was extracted with EtOAc, and the extract was washed with brine prior to drying and solvent evaporation. The residue was purified by chromatography (hexane/EtOAc 1:1) to give **21** (274 mg, 79%) as a colorless oil. $[\alpha]_D^{25} = +10.2$ ($c = 1.06$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.04$ (s, 3H), 0.05 (s, 6H), 0.07 (s, 3H), 0.88 (br s, 21H), 1.26–1.43 (m, 32H), 1.63 (td, $J = 10.4$, 8.5 Hz, 1H), 1.78–1.89 (m, 3H), 2.40 (br s, 2H), 3.43 (dd, $J = 11.0$, 7.9 Hz, 1H), 3.51–3.54 (m, 1H), 3.64 (dd, $J = 11.0$, 3.1 Hz, 1H), 3.68–3.73 (m, 2H), 3.82 (td, $J = 7.0$, 4.3 Hz, 1H), 3.88 (td, $J = 7.9$, 6.1 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta = -4.6$, -4.5, -4.3, -4.2, 14.1, 18.16, 18.22, 22.7, 25.2, 25.5, 25.6, 26.0 (9C), 26.6, 27.7, 29.3, 29.58, 29.63 (2C), 29.9, 31.9, 32.8, 33.1, 34.7, 66.8, 72.3, 73.7, 75.0, 81.9, 82.0; IR (KBr): $\tilde{\nu} = 3356\ cm^{-1}$; MS (FAB) m/z: 660 $[M+H]^+$; HRMS (FAB): m/z: calcd for $C_{37}H_{79}O_5Si_2$: 659.5466; found: 659.5464 $[M+H]^+$.

(8*R*,9*R*,12*R*,13*S*)-8,13-Bis(*tert*-butyldimethylsilyloxy)-9,12-epoxytetaracosanal (22): $NaIO_4$ (187 mg, 0.876 mmol) was added to a stirred solution of **21** (274 mg, 0.416 mmol) in CH_2Cl_2/acetone/water (10:6:1, 9 mL) at 0°C. After stirring at RT for 12 h, Et_2O was added to the mixture. The organic layer was separated, dried, and evaporated. The residue was purified by chromatography (hexane/EtOAc 3:1) to give **22** (196 mg, 75%) as a colorless oil. The aldehyde was unstable and was therefore used immediately in the next step.

(*EZ*,*R*)-6-Iodo-5-hexene-1,2-diol (43): A solution of **42** (97.3 mg, 0.615 mmol) and iodoform (484 mg, 1.23 mmol) in THF (6 mL) was added to a slurry of flame-dried chromium chloride (567 mg, 4.61 mmol) in THF (4 mL) at RT. The resulting suspension was stirred at RT for 15 h. After water was added, the mixture was extracted with EtOAc. The organic phase was washed with saturated $Na_2S_2O_3$ and brine prior to drying and solvent evaporation. The residue was filtered through a short plug of silica gel, eluted with hexane/EtOAc (10:1), and the combined filtrates were concentrated under reduced pressure. The residue was dissolved in MeOH (4 mL), and Dowex 50W (100 mg) was added to the solution. The mixture was stirred at RT for 4.5 h, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography (EtOAc) to give **43** (9:1 *E*/*Z* mixture, 85.8 mg, 58% in two steps) as a colorless oil. $[\alpha]_D^{25} = +6.8$ ($c = 0.88$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.54$ (q, $J = 7.3$ Hz, 1H), 2.17 (qn, $J = 7.5$ Hz, 9/10H), 2.24 (qn, $J = 7.8$ Hz, 9/10H), 2.13–2.33 (m, 6/5H), 3.42–3.48 (m, 1H), 3.63–3.67 (m, 1H), 3.68–3.73 (m, 1H), 6.06 (d, $J = 14.6$ Hz, 9/10H), 6.18–6.26 (m, 1/5H), 6.52 (td, $J = 14.0$, 7.3 Hz, 9/10H); ^{13}C NMR (75 MHz, $CDCl_3$) (major): $\delta = 31.4$, 32.0, 66.5, 71.1, 75.4, 145.5; (minor): $\delta = 31.0$, 31.1, 66.5, 71.5, 83.3, 140.4; IR (KBr): $\tilde{\nu} = 3331\ cm^{-1}$; MS (EI): m/z (%): 242 (0.2) $[M]^+$, 224 (23.4) $[M - H_2O]^+$, 115 (9.6) $[M - I]^+$, 97 (27.2) $[M - H_2O - I]^+$, 55 (100); HRMS (EI): m/z: calcd for $C_6H_{11}IO_2$: 241.9804; found: 241.9796 $[M]^+$.

(*EZ*,*R*)-2-(*tert*-Butyldimethylsilyloxy)-6-iodo-5-hexenyl trifloromethanesulfonate (44): Tf_2O (0.106 mL, 0.647 mmol) was added to a mixture of **43** (131 mg, 0.539 mmol) and 2,6-lutidine (0.314 mL, 2.70 mmol) in CH_2Cl_2 (5 mL) at −50°C. After 15 min, TBSOTf (0.210 mL, 0.916 mmol) was added and the mixture was stirred for 5 min at 0°C. Saturated NH_4Cl was added, and the mixture was extracted with Et_2O. The extract was washed with saturated NH_4Cl, water, and brine prior to drying and solvent evaporation. The residue was purified by chromatography (hexane/EtOAc 20:1) to give **44** (243 mg, 92%) as a colorless oil. The triflate was unstable and was therefore used immediately in the next step.

(3*RS*,5*S*)-3-[(*EZ*,2*R*)-2-(*tert*-Butyldimethylsilyloxy)-6-iodo-5-hexenyl]-5-methyl-3-(phenylsulfenyl)tetrahydrofuran-2-one (45) and (5*R*)-5-(*tert*-Butyldimethylsilyloxy)-1-iodo-6-phenylsulfenyl-1-hexene (46): KHMDS (0.5 M in toluene, 6.42 mL, 3.21 mmol) was added to a stirred solution of **9** (669 mg, 3.21 mmol) in THF (3 mL) at 0°C. After 5 min, a solution of **44** (1.57 g, 3.21 mmol) in THF (3 mL) was added to the mixture at 0°C. After stirring at RT for 2 h, saturated NH_4Cl was added, and the mixture was extracted with EtOAc. The organic phase was washed with saturated NH_4Cl, water, and brine prior to drying and solvent evaporation. The residue was purified by chromatography (hexane/EtOAc 20:1) to give **45** (1.38 g, 79%) as a colorless oil along with **46**.

Compound **45**: $[\alpha]_D^{24} = -49.9$ ($c = 0.85$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) (major): $\delta = 0.12$ (s, 3H), 0.17 (s, 3H), 0.87 (s, 9H), 1.25 (d, 3H, $J = 6.1$ Hz), 1.48–1.65 (m, 2H), 1.86 (dd, 1H, $J = 14.0$, 6.7 Hz), 1.90 (dd, 2H, $J = 7.6$, 3.1 Hz), 1.95 (td, 2H, $J = 7.3$, 4.9 Hz), 3.00 (dd, 1H, $J = 14.0$, 7.3 Hz), 4.27–4.31 (m, 1H), 4.53 (qd, 1H, $J = 14.0$, 6.1 Hz), 5.98 (d, 1H, $J = 14.6$ Hz), 6.44 (td, 1H, $J = 14.6$, 7.3 Hz), 7.34–7.44 (m, 3H), 7.53–7.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) (major): $\delta = -4.0$ (2C), 17.9, 21.3, 25.9 (3C), 30.8, 36.7, 39.5, 41.0, 54.9, 68.3, 73.2, 75.1, 129.0 (2C), 129.7, 130.0, 136.6 (2C), 145.4, 177.2; IR (KBr): $\tilde{\nu} = 1767\ cm^{-1}$; MS (FAB): m/z: 547 $[M+H]^+$; HRMS (FAB): m/z: calcd for $C_{23}H_{36}IO_3SSi$: 547.1199; found: 547.1170 $[M+H]^+$.

Compound **46**: $[\alpha]_D^{22} = +38.0$ ($c = 0.53$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) (major): $\delta = 0.00$ (s, 3H), 0.03 (s, 3H), 0.87 (s, 9H), 1.58–1.71 (m, 1H), 1.75–1.88 (m, 1H), 2.01–2.21 (m, 2H), 2.91 (dd, $J = 13.1$, 7.3 Hz, 1H), 3.03 (dd, $J = 13.4$, 5.0 Hz, 1H), 3.76–3.88 (m, 1H), 5.98 (d, $J = 14.0$ Hz, 1H), 6.50 (td, $J = 14.3$, 7.0 Hz, 1H), 7.14–7.22 (m, 1H), 7.28–7.37 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) (major): $\delta = -4.7$, −4.4, 18.0, 25.8 (3C), 31.5, 34.5, 40.7, 70.5, 74.8, 126.2, 128.9 (2C), 129.6 (2C), 136.5, 146.0; IR (KBr): $\tilde{\nu} = 1585$, $1080\ cm^{-1}$; MS (FAB): m/z: 455 $[M+Li]^+$; HRMS (FAB): m/z: calcd for $C_{18}H_{29}INaOSSi$: 471.0651; found: 471.0633 $[M+Na]^+$.

(5*S*)-3-[(*EZ*,2*R*)-2-(*tert*-Butyldimethylsilyloxy)-6-iodo-5-hexenyl]-5-methyl-2,5-dihydrofuran-2-one (47): A solution of *m*CPBA (10.5 mg, 0.061 mmol) in CH_2Cl_2 (0.6 mL) was added to a stirred solution of **45** (27.7 mg, 0.051 mmol) in CH_2Cl_2 (0.6 mL) at 0°C. After 20 min, the mixture was partitioned between Et_2O and saturated $NaHCO_3$. The organic layer was separated, and washed with saturated $NaHCO_3$ and brine prior to drying and solvent evaporation. The residue was dissolved in toluene (2 mL), and the mixture was stirred at 130°C for 20 min. The solvent was concentrated under reduced pressure. The residue was purified by chromatography (hexane/EtOAc 20:1) to give **47** (9:1 *E*/*Z* mixture, 18.8 mg, 85% in two steps) as a colorless oil. $[\alpha]_D^{25} = +15.1$ ($c = 1.33$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.04$ (s, 27/10H), 0.05 (s, 3/10H), 0.06 (s, 27/10H), 0.09 (s, 3/10H), 0.88 (s, 8H), 0.89 (s, 1H), 1.42 (d, $J = 6.7$ Hz, 3H), 1.53 (td, $J = 7.9$, 6.1 Hz, 2H), 2.05–2.28 (m, 2H), 2.40 (dd, $J = 14.6$, 5.5 Hz, 9/10H), 2.41 (dd, $J = 14.6$, 5.5 Hz, 1/10H), 2.46 (dd, 9/10H, $J = 14.6$, 5.5 Hz), 2.50 (dd, $J = 14.6$, 6.1 Hz, 1/10H), 3.97 (qn, $J = 5.8$ Hz, 9/10H), 4.02 (qn, $J = 5.8$ Hz, 1/10H), 5.02 (qd, $J = 6.7$, 1.2 Hz, 1H), 6.02 (td, 9/10H, $J = 14.0$, 1.5 Hz), 6.16–6.21 (m, 3/5H), 6.49 (td, $J = 14.0$, 7.3 Hz, 9/10H), 7.12 (d, $J = 1.2$ Hz, 9/10H), 7.15 (d, $J = 1.2$ Hz, 1/10H); ^{13}C NMR (75 MHz, $CDCl_3$) (major): $\delta = -4.6$, −4.5, 17.9, 18.9, 25.8 (3C), 31.7, 32.6, 35.2, 69.2, 74.9, 77.5, 130.3, 145.8, 151.8, 173.8; (minor): $\delta = -4.6$, −4.5, 17.9, 18.9, 25.8 (3C), 30.5, 32.6, 34.7, 69.4, 77.5, 82.8, 130.4, 140.6, 151.8, 173.8; IR (KBr): $\tilde{\nu} = 1755\ cm^{-1}$; MS (EI): m/z (%): 436 (2.3) $[M]^+$, 379 (100); HRMS (EI): m/z: calcd for $C_{17}H_{29}IO_3Si$: 436.0931; found: 436.0928 $[M]^+$.

(5*S*)-3-[(*E*,2*R*,7*RS*,13*R*)-2,13-Bis(*tert*-butyldimethylsilyloxy)-13-[(2*R*,5*R*)-5-[(1*S*)-1-(*tert*-butyldimethylsilyloxy)tridesyl]tetrahydrofuran-2-yl]-7-hydroxytridec-5-enyl]-5-methyl-2,5-dihydrofuran-2-one (48): $CrCl_2$ (291 mg, 2.37 mmol) and $NiCl_2$ (1.5 mg, 0.012 mmol) were added to a stirred mixture of **22** (149 mg, 0.237 mmol) and **47** (207 mg, 0.447 mmol) in DMF/Me_2S (2:1, 4 mL) at RT. After 20 h, EtOAc and saturated NH_4Cl were added and the mixture was stirred for 10 min. The mixture was extracted with EtOAc, and the organic phase was washed with water and brine prior to drying and solvent evaporation. The residue was purified by chromatography (hexane/EtOAc 5:1) to give **48** (1:1 diastereomeric mixture, 158 mg, 71%) and **22** (27.6 mg, 19%) each as a colorless oil. $[\alpha]_D^{19} = +16.9$ ($c = 0.93$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.02$ (s, 3H), 0.03 (s, 3H), 0.035 (s, 3H), 0.039 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.88

(brs, 30H), 1.25–1.31 (m, 32H), 1.41 (d, J = 6.7 Hz, 3H), 1.49–1.58 (m, 2H), 1.62 (td, J = 11.6, 8.5 Hz, 1H), 1.77–1.84 (m, 2H), 1.86 (td, J = 6.7, 4.3 Hz, 1H), 2.02–2.17 (m, 2H), 2.43–2.45 (m, 2H), 3.50–3.53 (m, 1H), 3.70 (td, J = 6.1, 4.3 Hz, 1H), 3.81 (td, J = 7.3, 4.3 Hz, 1H), 3.87 (td, J = 8.5, 6.1 Hz, 1H), 3.98 (tdd, J = 11.6, 8.5, 3.1 Hz, 1H), 4.02 (q, J = 6.7 Hz, 1H), 5.01 (qd, J = 6.7, 1.2 Hz, 1H), 5.47 (dd, J = 15.3, 7.0 Hz, 1H), 5.60 (td, J = 15.9, 6.7 Hz, 1H), 7.12 (d, J = 1.2 Hz, ½H), 7.13 (d, J = 1.2 Hz, ½H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.6, −4.5, −4.4 (2C), −4.24, −4.19, 14.1, 18.0, 18.17, 18.24, 18.9 (0.5C), 19.0 (0.5C), 22.7, 25.2, 25.5, 25.6, 25.7, 25.8 (3C), 25.97 (3C), 25.99 (3C), 26.7, 27.7, 27.9, 29.3, 29.59, 29.64 (2C), 29.7 (2C), 29.9, 31.9, 32.6 (0.5C), 32.7 (0.5C), 32.9, 34.7, 36.2, 37.3, 69.5 (0.5C), 69.6 (0.5C), 73.0 (0.5C), 73.0 (0.5C), 73.7, 75.1, 77.5, 81.9, 82.0, 130.6 (0.5C), 130.7 (0.5C), 131.1 (0.5C), 131.2 (0.5C), 133.5 (0.5C), 133.6 (0.5C), 151.7, 174.0; IR (KBr): $\tilde{\nu}$ = 3502, 1759 cm^{-1}; MS (FAB): m/z: 960 $[M+Na]^+$; HRMS (FAB): m/z: calcd for $C_{53}H_{104}NaO_7Si_3$: 959.6987; found: 959.6962 $[M+Na]^+$.

(5*S*)-3-[(*E*,2*R*,13*R*)-2,13-Bis(*tert*-butyldimethylsilyloxy)-13-[(2*R*,5*R*)-5-[(1*S*)-1-(*tert*-butyldimethylsilyloxy)tridesyl]tetrahydrofuran-2-yl]-7-oxotridec-5-enyl]-5-methyl-2,5-dihydrofuran-2-one (49): SO_3·pyridine complex (58.6 mg, 0.368 mmol) was added to a mixture of **48** (86.3 mg, 0.092 mmol), DMSO (52.2 μL, 0.736 mmol), and Et_3N (0.154 mL, 1.10 mmol) in CH_2Cl_2 (0.3 mL) at 0 °C. After stirring at RT for 4 h, water was added to the reaction mixture. The mixture was extracted with EtOAc, and the organic phase was washed with water and brine prior to drying and solvent evaporation. The residue was purified by chromatography (hexane/EtOAc 5:1) to give **49** (61.7 mg, 72 %) as a colorless oil. $[\alpha]_D^{25}$ = +13.8 (c = 0.26, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.01 (s, 3H), 0.02 (s, 3H), 0.038 (s, 3H), 0.044 (s, 3H), 0.05 (s, 3H), 0.07 (s, 3H), 0.86–0.89 (m, 30H), 1.25–1.31 (m, 30H), 1.43 (d, J = 7.3 Hz, 3H), 1.57–1.63 (m, 3H), 1.78–1.87 (m, 3H), 2.22–2.36 (m, 2H), 2.44 (d, 1H, J = 6.1 Hz), 2.48 (d, 1H, J = 6.1 Hz), 2.52 (t, J = 7.3 Hz, 2H), 3.50–3.54 (m, 1H), 3.71 (td, J = 6.1, 4.3 Hz, 1H), 3.81 (td, J = 7.3, 4.3 Hz, 1H), 3.87 (td, J = 7.9, 5.5 Hz, 1H), 4.02 (qn, J = 5.5 Hz, 1H), 5.02 (qd, J = 6.7, 1.2 Hz, 1H), 6.09 (d, J = 15.9 Hz, 1H), 6.80 (td, J = 15.9, 6.7 Hz, 1H), 7.13 (d, J = 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.63, −4.57, −4.53, −4.47, −4.3, −4.2, 14.1, 17.9, 18.1, 18.2, 18.9, 22.6, 24.1, 25.1, 25.5, 25.8, 25.9 (4C), 26.0 (5C), 26.6, 27.6, 28.0, 29.3, 29.55 (2C), 29.59, 29.60, 29.63, 29.9, 31.9, 32.67, 32.71, 34.7, 35.0, 40.1, 69.4, 73.7, 75.0, 77.5, 81.8, 82.0, 130.3, 130.4, 146.3, 151.8, 173.8, 200.6; IR (KBr): $\tilde{\nu}$ = 1759, 1697 cm^{-1}; MS (FAB): m/z: 958 $[M+Na]^+$; HRMS (FAB): m/z: calcd for $C_{53}H_{102}NaO_7Si_3$: 957.6831; found: 957.6827 $[M+Na]^+$.

(5*S*)-3-[(2*R*,13*R*)-2,13-Bis(*tert*-butyldimethylsilyloxy)-13-[(2*R*,5*R*)-5-[(1*S*)-1-(*tert*-butyldimethylsilyloxy)tridesyl]tetrahydrofuran-2-yl]-7-oxotridecyl]-5-methyl-2,5-dihydrofuran-2-one (50): $[(Ph_3P)_3RhCl]$ (28.4 mg, 0.031 mmol) was added to a solution of **49** (57.2 mg, 0.061 mmol) in benzene (0.6 mL). The mixture was stirred under H_2 at RT for 27 h. The solution was purified by chromatography (hexane/EtOAc 5:1) to give **50** (44.5 mg, 78 %) as a colorless oil. $[\alpha]_D^{26}$ = +11.9 (c = 0.55, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.02 (s, 3H), 0.038 (s, 3H), 0.044 (s, 6H), 0.05 (s, 3H), 0.06 (s, 3H), 0.88 (brs, 30H), 1.26–1.40 (m, 32H), 1.42 (d, J = 6.7 Hz, 3H), 1.53–1.68 (m, 5H), 1.78–1.81 (m, 1H), 1.83 (td, J = 6.7, 4.3 Hz, 1H), 1.87 (td, J = 6.1, 4.3 Hz, 1H), 2.376 (t, J = 7.3 Hz, 2H), 2.382 (t, J = 7.3 Hz, 2H), 2.41 (dd, J = 2.4, 1.2 Hz, 1H), 2.42 (dd, J = 3.1, 1.2 Hz, 1H), 3.50–3.55 (m, 1H), 3.71 (td, J = 6.1, 4.0 Hz, 1H), 3.81 (td, J = 7.3, 4.3 Hz, 1H), 3.87 (td, J = 8.5, 6.1 Hz, 1H), 3.95 (qn, J = 5.5 Hz, 1H), 5.01 (qd, J = 6.7, 1.2 Hz, 1H), 7.12 (d, J = 1.2 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = −4.6 (2C), −4.5 (2C), −4.3, −4.2, 14.1, 18.0, 18.1, 18.2, 18.9, 22.6, 23.8, 23.9, 24.7, 25.1, 25.4, 25.8 (4C), 25.9 (5C), 26.6, 27.7, 29.3, 29.56 (3C), 29.60 (3C), 29.9, 31.9, 32.6, 32.7, 34.7, 36.7, 42.6, 42.8, 69.9, 73.7, 75.0, 77.5, 81.8, 82.0, 130.7, 151.5, 173.9, 211.1; IR (KBr): $\tilde{\nu}$ = 1759, 1716 cm^{-1}; MS (FAB): m/z: 960 $[M+Na]^+$; HRMS (FAB): m/z: calcd for $C_{53}H_{104}NaO_7Si_3$: 959.6988; found: 959.6993 $[M+Na]^+$.

(5*S*)-3-[(2*R*,13*R*)-2,13-Dihydroxy-13-[(2*R*,5*R*)-5-[(1*S*)-1-hydroxytridesyl]-tetrahydrofuran-2-yl]-7-oxotridecyl]-5-methyl-2,5-dihydrofuran-2-one (1a): Four drops of 48 % aqueous HF was added to a stirred solution of **50** (84.9 mg, 0.091 mmol) in MeCN/THF (1.5:1, 1.5 mL) at RT. After stirring at RT for 2.5 h, the reaction mixture was partitioned between CH_2Cl_2 and brine. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine prior to drying and solvent evaporation. The residue was purified by chromatography (EtOAc) to give **1a** (39.0 mg, 72 %) as a white waxy solid. $[\alpha]_D^{25}$ = +18.7 (c = 0.50, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.7 Hz, 3H), 1.26 (brs, 30H), 1.35–1.41 (m, 4H), 1.44 (d, J = 6.7 Hz, 3H), 1.46–1.51 (m, 2H), 1.56–1.65 (m, 1H), 1.82–1.94 (m, 2H), 1.97–2.02 (m, 1H), 2.38–2.43 (m, 1H), 2.40 (t, J = 7.3 Hz, 2H), 2.42 (t, J = 7.3 Hz, 2H), 2.52 (ddd, J = 15.3, 3.1, 1.8 Hz, 1H), 3.36–3.40 (m, 1H), 3.79–3.84 (m, 2H), 3.85–3.89 (m, 2H), 5.06 (qd, J = 6.7, 1.2 Hz, 1H), 7.19 (d, J = 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 19.1, 22.7, 23.4, 23.6, 25.1, 25.2, 25.3, 26.0, 28.6, 29.2, 29.3, 29.5, 29.59, 29.63 (2C), 29.7 (2C), 31.9, 32.5, 32.9, 33.4, 37.0, 42.5, 42.7, 69.6, 71.5, 74.2, 78.0, 82.1, 83.2, 131.0, 152.0, 174.7, 211.4; IR (KBr): $\tilde{\nu}$ = 3444, 1767, 1755, 1743, 1703 cm^{-1}; MS (EI): m/z (%): 325, 307, 289, 225, 207; MS (FAB): m/z: 595 $[M+H]^+$ 595; HRMS (FAB): m/z: calcd for $C_{35}H_{63}O_7$: 595.4574; found: 595.4556 $[M+H]^+$.

(5*S*)-3-[(*E*,2*R*,7*RS*,13*S*)-2,13-Bis(*tert*-butyldimethylsilyloxy)-13-[(2*S*,5*S*)-5-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)tridesyl]tetrahydrofuran-2-yl]-7-hydroxytridec-5-enyl]-5-methyl-2,5-dihydrofuran-2-one (51): The procedure was the same as that used for preparation of **48**. $[\alpha]_D^{28}$ = −0.16 (c = 1.01, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.01 (s, 3H), 0.02 (s, 3H), 0.025 (s, 3H), 0.030 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.86 (brs, 30H), 1.23–1.30 (m, 32H), 1.40 (d, 3H, J = 6.7 Hz), 1.49–1.56 (m, 2H), 1.61 (td, J = 11.0, 8.9 Hz, 1H), 1.76–1.87 (m, 3H), 2.01–2.16 (m, 2H), 2.42–2.44 (m, 2H), 3.49–3.51 (m, 1H), 3.68–3.71 (m, 1H), 3.80 (td, J = 7.0, 4.3 Hz, 1H), 3.86 (td, J = 7.9, 6.1 Hz, 1H), 3.94–3.99 (m, 1H), 4.02 (td, 1H, J = 6.7, 3.1 Hz), 5.00 (qd, J = 6.7, 1.2 Hz, 1H), 5.46 (dd, J = 15.3, 7.0 Hz, 1H), 5.59 (td, J = 14.6, 6.7 Hz, 1H), 7.11 (d, J = 1.2 Hz, ½H), 7.12 (d, J = 1.2 Hz, ½H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.6, −4.53 (2C), −4.47, −4.3, −4.2, 14.1, 18.0, 18.1, 18.2, 18.89 (0.5C), 18.92 (0.5C), 22.6, 25.1, 25.47, 25.48, 25.6, 25.8 (3C), 25.9 (3C), 26.0 (3C), 26.6, 27.7, 27.9, 29.3, 29.56 (2C), 29.61 (2C), 29.64, 29.9, 31.9, 32.6 (0.5C), 32.7 (0.5C), 32.8, 34.7, 36.2, 37.2, 69.4 (0.5C), 69.6 (0.5C), 72.9 (0.5C), 73.0 (0.5C), 73.7, 75.1, 77.5, 81.9, 82.0, 130.5 (0.5C), 130.6 (0.5C), 131.0 (0.5C), 131.1 (0.5C), 133.5 (0.5C), 133.6 (0.5C), 151.7, 174.0; IR (KBr): $\tilde{\nu}$ = 3437, 1759 cm^{-1}; MS (FAB): m/z: 960 $[M+Na]^+$; HRMS (FAB): m/z: calcd for $C_{53}H_{104}NaO_7Si_3$: 959.6987; found: 959.6963 $[M+Na]^+$.

(5*S*)-3-[(*E*,2*R*,13*S*)-2,13-Bis(*tert*-butyldimethylsilyloxy)-13-[(2*S*,5*S*)-5-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)tridesyl]tetrahydrofuran-2-yl]-7-oxotridec-5-enyl]-5-methyl-2,5-dihydrofuran-2-one (52): The procedure was the same as that used for preparation of **49**. $[\alpha]_D^{27}$ = −1.6 (c = 0.58, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.02 (s, 3H), 0.025 (s, 6H), 0.031 (s, 3H), 0.05 (s, 6H), 0.86 (brs, 30H), 1.24–1.31 (m, 30H), 1.40 (d, J = 6.7 Hz, 3H), 1.55–1.63 (m, 3H), 1.76–1.87 (m, 3H), 2.19–2.34 (m, 2H), 2.41 (dd, J = 14.0, 5.5 Hz, 1H), 2.46 (d, 1H, J = 5.5 Hz), 2.50 (t, 2H, J = 7.3 Hz), 3.49–3.52 (m, 1H), 3.69 (td, J = 6.1, 4.3 Hz, 1H), 3.79 (td, J = 7.3, 4.3 Hz, 1H), 3.85 (td, J = 7.9, 6.1 Hz, 1H), 4.00 (qn, J = 5.5 Hz, 1H), 5.00 (qd, J = 6.7, 1.2 Hz, 1H), 6.07 (d, J = 15.9 Hz, 1H), 6.78 (td, J = 15.3, 6.7 Hz, 1H), 7.12 (d, J = 1.2 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = −4.5, −4.40, −4.37, −4.3, −4.12, −4.06, 14.2, 18.1, 18.2, 18.3, 19.0, 22.7, 24.2, 25.2, 25.6, 25.8 (3C), 26.0 (3C), 26.1 (3C), 26.7, 27.7, 28.1, 29.4, 29.6 (2C), 29.68 (2C), 29.72 (2C), 29.9, 32.0, 32.79, 32.81, 34.8, 35.1, 40.2, 69.4, 73.7, 75.0, 77.5, 81.8, 82.0, 130.2, 130.3, 146.2, 151.6, 173.6, 200.4; IR (KBr): $\tilde{\nu}$ = 1759, 1697 cm^{-1}; MS (FAB): m/z: 958 $[M+Na]^+$; HRMS (FAB): m/z: calcd for $C_{53}H_{102}NaO_7Si_3$: 957.6831; found: 957.6830 $[M+Na]^+$.

(5*S*)-3-[(2*R*,13*S*)-2,13-Bis(*tert*-butyldimethylsilyloxy)-13-[(2*S*,5*S*)-5-[(1*R*)-1-(*tert*-butyl-dimethylsilyloxy)tridesyl]tetrahydrofuran-2-yl]-7-oxotridecyl]-5-methyl-2,5-dihydrofuran-2-one (53): The procedure was the same as that used for preparation of **50**. $[\alpha]_D^{25}$ = −1.9 (c = 0.57, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.01 (s, 3H), 0.026 (s, 6H), 0.032 (s, 6H), 0.05 (s, 3H), 0.87 (brs, 30H), 1.24–1.47 (m, 32H), 1.40 (d, J = 6.7 Hz, 3H), 1.51–1.63 (m, 5H), 1.77–1.87 (m, 3H), 2.365 (t, J = 7.3 Hz, 2H), 2.371 (t, J = 7.3 Hz, 2H), 2.40–2.41 (m, 2H), 3.49–3.53 (m, 1H), 3.68–3.71 (m, 1H), 3.80 (td, J = 7.0, 4.3 Hz, 1H), 3.85 (td, J = 8.5, 6.1 Hz, 1H), 3.94 (qn, J = 5.5 Hz, 1H), 5.00 (qd, J = 6.7, 1.2 Hz, 1H), 7.11 (d, 1H, J = 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.6, −4.5 (3C), −4.3, −4.2, 14.1, 18.0, 18.1, 18.2, 18.9, 22.7, 23.8, 23.9, 24.7, 25.1, 25.5, 25.8 (3C), 25.9 (3C), 26.0 (3C), 26.6, 27.6, 29.3, 29.5, 29.56 (2C), 29.62 (2C), 29.6, 29.9, 31.9, 32.6, 32.7, 34.7, 36.7, 42.7, 42.8, 69.9, 73.7, 75.0, 77.5, 81.8, 82.0, 130.7, 151.6, 174.0, 211.2; IR (KBr): $\tilde{\nu}$ = 1759, 1714 cm^{-1}; MS (FAB): m/z: 960 $[M+Na]^+$; HRMS (FAB): m/z: calcd for $C_{53}H_{104}NaO_7Si_3$: 959.6988; found: 959.6981 $[M+Na]^+$.

(5*S*)-3-[(2*R*,13*S*)-2,13-Dihydroxy-13-[(2*S*,5*S*)-5-[(1*R*)-1-hydroxytridesyl]-tetrahydrofuran-2-yl]-7-oxotridecyl]-5-methyl-2,5-dihydrofuran-2-one (1b): The procedure was the same as that used for preparation of **1a**. $[\alpha]_D^{26}$ = +2.2 (c = 0.39, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (t,

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$J = 7.0$ Hz, 3H), 1.23 (br s, 30H), 1.33–1.38 (m, 4H), 1.41 (d, $J = 6.7$ Hz, 3H), 1.45–1.49 (m, 2H), 1.51–1.64 (m, 1H), 1.79–1.92 (m, 2H), 1.94–2.00 (m, 1H), 2.29 (br, 1H), 2.38 (t, $J = 7.3$ Hz, 2H), 2.39 (t, $J = 7.3$ Hz, 2H), 2.36–2.41 (m, 1H), 2.47–2.51 (m, 1H), 2.56 (br, 1H), 2.72 (br, 1H), 3.34–3.38 (m, 1H), 3.76–3.83 (m, 2H), 3.84–3.87 (m, 2H), 5.04 (qd, $J = 6.7$, 1.2 Hz, 1H), 7.18 (d, $J = 1.2$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$, 19.0, 22.6, 23.4, 23.6, 25.1, 25.16, 25.23, 26.0, 28.5, 29.1, 29.3, 29.5, 29.55, 29.59 (2C), 29.61, 29.64, 31.9, 32.5, 32.9, 33.3, 37.0, 42.5, 42.6, 69.5, 71.5, 74.2, 78.0, 82.2, 83.2, 131.0, 152.0, 174.6, 211.4; IR (KBr): $\tilde{\nu} = 3439$, 1740, 1720, 1716, 1705 cm^{-1}; MS (EI): *m*/*z*: 325, 307, 289, 225, 207; MS (FAB): *m*/*z*: 595 $[M+H]^+$; HRMS (FAB): *m*/*z*: calcd for $C_{35}H_{63}O_7$: 595.4574; found: 595.4561 $[M+H]^+$.

Biological assay: The two human pancreatic cancer cell lines, PaCa-2 and PSN-1, were purchased from the Japanese Cancer Research Resources Bank (Tokyo, Japan). The KMP-5 cell line was a gift from Prof. M. Imamura (Kyoto University, Kyoto, Japan).[29] They were maintained in Dulbecco's Modified Eagle Medium supplemented with 10% fetal bovine serum, 100 units mL^{-1} penicillin and 100 μg mL^{-1} streptomycin at 37 °C in a humidified incubator with 5% CO_2 in air.

Growth inhibitory assays: Cells with a density of 3×10^3 per well were added in triplicate to a 96-well microplate. After 24 h, the medium was replaced by fresh medium (0.1 mL) containing various concentrations of mosin B (**1a**), its diastereomer **1b**, or adriamycin. The concentrations of **1a** and **1b** tested were 0.0002–0.05 μg mL^{-1}; those of adrimycin were 0.001–1 μg mL^{-1}. Tumor cells suspended in complete medium were used as a control for cell viability. The medium was changed every 72 h, and 3 or 6 d after the addition of drugs, the numbers of viable cells were assessed by MTT (Sigma Co, St.Louis, MO) assay. Briefly, 10 μL (50 μg) of MTT was added to each well. The plate was incubated for 4 h at 37 °C. Unreacted MTT was then removed, leaving the resultant formazan crystals at the bottom of the well. Then, 2-propanol (0.1 mL) was added to each well to dissolve the crystals. The absorbance of the plate was measured in a microplate reader at a wavelength of 570 nm. These assays were repeated four times, and similar results were obtained.

The inhibitory activities (ED_{50}, μg mL^{-1}) of mosin B, its diastereomer, and adriamycin against used cell growth were evaluated by using the growth-inhibitory curves and the results represent the averages from four independent experiments.

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[28] McLaughlin and co-workers reported that the ED_{50} value of mosin B against PaCa-2 cells was 72-fold higher than that of adriamycin (ref. [4]). The discrepancy from our results was probably caused by a difference in the passage of cancer cells or in the bioassay protocol. However, we cannot prove this at the present time, since the natural mosin B is not available.

[29] M. Kato, Y. Shimada, H. Tanaka, R. Hosotani, G. Ohshio, K. Ishizaki, M. Imamura, *Cancer* **1999**, *85*, 832–840.

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