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Total Synthesis of Murisolins and Evaluation of Tumor-Growth Inhibitory Activity

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Abstract: Convergent total syntheses of murisolin (**1**), natural 16,19-*cis*-murisolin **2**, and unnatural 16,19-*cis*-murisolin **3** were accomplished by asymmetric alkynylation of α-tetrahydrofuranic aldehyde with a diyne and Sonogashira coupling with a γ-lactone segment as the key steps. Stereoisomers of α-tetrahydrofuranic aldehyde were synthesized with high optical purity and the asymmetric alkynylation of these with 1,6-heptadiyne proceeded in good yield and with high diastereoselectivity. The cell-growth inhibition profile and COMPARE analysis of the synthetic compounds **1**–**3** were also investigated.

Keywords: acetogenins · antitumor agents · murisolin · natural products · total synthesis

Introduction

Acetogenins are polyketides featuring one to three tetrahydrofuran (THF) ring(s) with various stereoconfigurations connected with a butenolide moiety by a long hydrocarbon chain, which often contains oxygenated moieties. More than 400 annonaceous acetogenins have been isolated from nature so far. They have attracted worldwide attention due to a broad range of biological activities, such as cytotoxic, antitumor, immunosuppressive, pesticidal, antifeedant, and antimalarial effects. In particular, their potent and selective cytotoxicity against human cancer cell lines makes them attractive lead compounds for new types of antitumor drugs. Furthermore, it is known that some acetogenins inhibit multidrug-resistant cancer cells with an adenosine triphosphate (ATP) driven transporter system. The mode of action is assumed to be based on inhibitory activity against the NADH:ubiquinone oxidoreductase of mitochondrial complex I (NADH = reduced nicotinamide adenine dinucleotide).[1,2]

Murisolin (**1**)[3] is a mono-THF acetogenin isolated from the seed of *Annona muricata* by the Cortes group in 1990. After five years, the diastereoisomer 16,19-*cis*-murisolin **2**[4] was isolated, along with murisolin, from the seed of *Asimina triloba* by McLaughlin's group. Biological evaluation of these compounds revealed that murisolin is one million times more potent against human lung (A-549), kidney (A-498), and colon (HT-29) cancer cells than adriamycin and that 16,19-*cis*-murisolin shows activity greater than or equal to that of adriamycin against human breast (MCF-7) and lung (A-549) cancer cells. In spite of the comparatively simple structure and interesting biological activity, there was no total synthesis of these compounds for a long time. In 2004, Curran and co-workers[5] and our group[6] accomplished the first total syntheses of murisolin. At the same time, Curran and co-workers reported the first total synthesis of a 16,19-*cis*-murisolin in a communication.[5] However, the synthetic reports of these compounds are restricted to these examples.

We were interested in the relationship between the stereochemistry of the THF moiety and the cytotoxicity against various cancer cell lines. So we synthesized murisolin congeners **2** and **3**, in addition to murisolin (**1**), for evaluation of our methodology and the biological activity of these compounds. Herein, we describe in detail the total syntheses of **1**–**3** (Scheme 1). The comparison of growth inhibition against various cancer cells and the results of the COMPARE analysis are also described.

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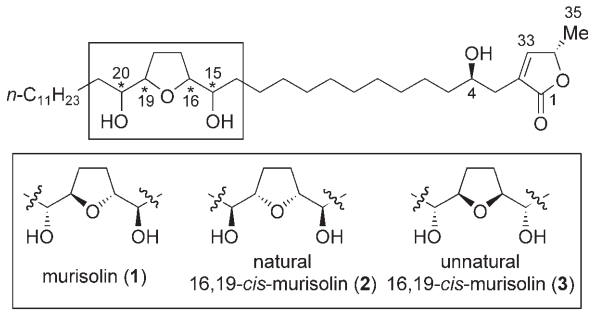
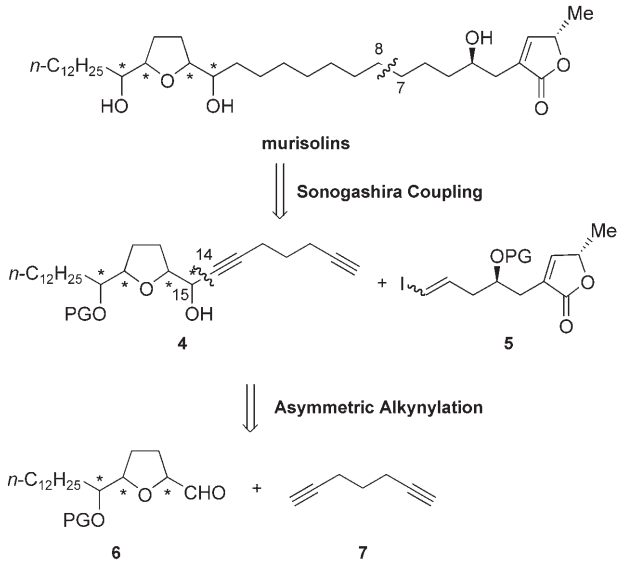


Scheme 1. Structure of the murisolins.

Results and Discussion

We have developed a methodology of systematic and stereoselective construction of the THF ring moiety for acetogenins. The library of mono- and bis-THF ring moieties was synthesized by applying this method.[7] Next, we focused on the synthesis of murisolin congeners and the evaluation of their biological activity.

Scheme 2 shows a retrosynthetic analysis for the murisolins. Murisolins are bisected at the C7 and C8 carbons into THF-ring segment **4** and γ-lactone segment **5**.[8,9] Segment **4**

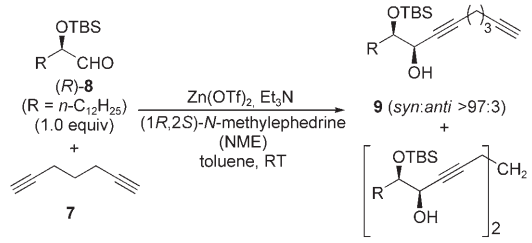


Scheme 2. Retrosynthetic analysis of murisolins. PG = protecting group.

is synthesized by an asymmetric alkynylation of THF-ring segment **6** with diyne **7**. The α-tetrahydrofuranic aldehyde **6** can be prepared stereoselectively from α-oxyaldehyde by the previously established method.[7] In this project, we planned an unprecedented asymmetric alkynylation of **6** with unprotected 1,6-heptadiyne (**7**) to eliminate the steps of protection and deprotection.

In order to establish suitable reaction conditions for the partial reaction of the diyne **7**, a model study was carried out with α-oxyaldehyde (*R*)-**8**[7b] as a substrate under the conditions of Carreira and co-workers.[10] The results are summarized in Table 1.

Table 1. Asymmetric alkynylation of α-oxyaldehyde with diyne **7**.

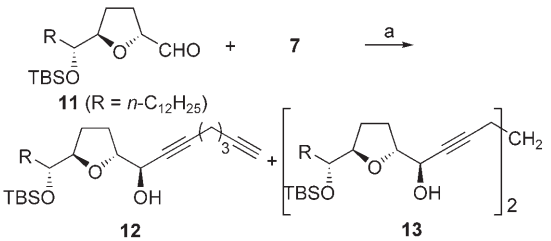


Conditions	**7**[a]	$Zn(OTf)_2$[a]	NME[a]	Et_3N[a]	Yield [%] **9**	**10**
A	1.2	1.3	1.4	1.4	58	27
B	2.0	2.2	2.4	2.4	71	24
C	2.0	1.3	1.4	1.4	72	20
D	4.0	1.3	1.4	1.4	84	12

[a] Values given are equivalents of reagents. TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, NME = (1*R*,2*S*)-*N*-methylephedrine.

According to the protocol of Carreira and co-workers, (*R*)-**8** was treated with the diyne **7** (1.2 equiv), $Zn(OTf)_2$ (1.3 equiv), (1*R*,2*S*)-NME (1.4 equiv), and Et_3N (1.4 equiv) in toluene. Although the desired *syn* adduct **9** was obtained in 58% yield, a considerable amount of byproduct **10** was produced (conditions A). When about twice the amount of diyne and reagents were used, the yield of **9** was improved to 71% (conditions B). However, this improved yield was not changed when the amounts of the reagents were reduced if the amount of diyne remained the same (conditions C). Finally, the yield of **9** was improved to 84% by using 4 equivalents of the diyne **7** (conditions D). The alkynylation proceeded with excellent diastereoselectivity to give adducts **9** and **10**, each as a single isomer.

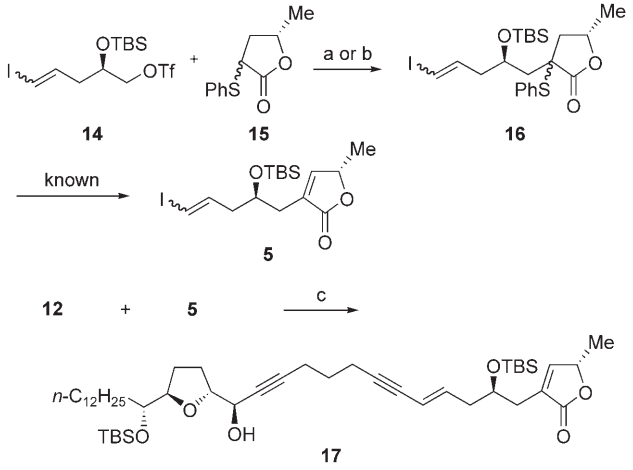
Next, we conducted an asymmetric alkynylation of the α-tetrahydrofuranic aldehyde **11** with diyne **7** under the optimized conditions (Scheme 3). The α-tetrahydrofuranic aldehyde **11** was synthesized from α-oxyaldehyde (*R*)-**8** by asymmetric alkynylation with (1*R*,2*S*)-NME followed by THF-ring formation.[7b] Upon treatment of the α-tetrahydrofuran-



Scheme 3. Asymmetric alkynylation of α-tetrahydrofuranic aldehyde **11** with diyne **7**: a) $Zn(OTf)_2$, Et_3N, (1*R*,2*S*)-NME, toluene, RT, 84% (α-OH:β-OH 3:>97) for **12** and 12% (β-OH/β-OH:other isomer >97:3) for **13**.

ic aldehyde **11** with the diyne **7** (4 equiv), alcohol **12** was obtained in 84% yield, along with 12% of diol **13**. Even in the functionalized aldehyde **11**, the alkynylation proceeded with very high diastereoselectivity (>97:3 d.r.). Thus, the THF moiety did not affect either the diastereoselectivity or the ratio of monool and diol. The absolute configuration of adduct **12** was confirmed to be the desired *R* configuration by the modified Mosher method.[11] Interestingly, the byproduct **13** was also a single isomer and is assumed to be a *syn*/*syn* adduct since the compound has C_2 symmetry.

The α,β-unsaturated γ-lactone segment **5** (PG = TBS) was synthesized by Marshall and co-workers' from α-sulfenyl γ-lactone **16** through oxidation of the sulfide followed by thermolysis of the sulfoxide.[8] In their work, a coupling reaction of triflate **14** and γ-lactone **15** with lithium diisopropylamide (LDA) in the presence of hexamethyl phosphoramide (HMPA) proceeded in a moderate yield (54%). In the previous synthesis of mosin B, we reported that potassium 1,1,1,3,3,3-hexamethyldisilazanide (KHMDS) was a suitable base for the alkylation of the γ-lactone with the triflate. Therefore, we employed KHMDS in the alkylation of **15** with **14** (*E*:*Z* = 4.6:1) (Scheme 4); however, the adduct **16**

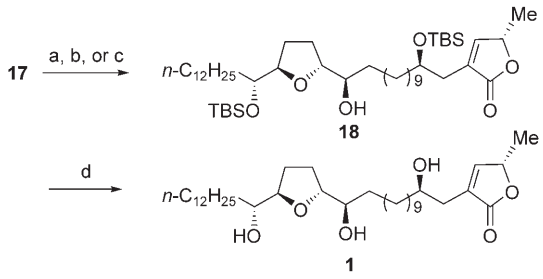


Scheme 4. Construction of the murisolin framework (**17**) through Sonogashira coupling: a) KHMDS, THF, 0°C→RT, 19%; b) KHMDS, HMPA, THF, 0°C→RT, 77%; c) $[(Ph_3P)_2PdCl_2]$, CuI, Et_3N, RT, 72%.

was produced in poor yield (19%). This problem was overcome by the addition of HMPA, to give **16** in 77% yield.

Assembly of the THF-ring segment **12** and the γ-lactone segment **5** was carried out by Sonogashira coupling (Scheme 4) to give the coupling product **17** in 72% yield.[12]

Next, we examined the selective reduction of enediyne **17** by using catalytic[13] or stoichiometric[14] amounts of Wilkinson catalyst, but compound **18** was obtained in moderate yields (Scheme 5). Marshall and Chen employed diimide instead of the Wilkinson catalyst for the selective reduction of an enyne.[15] They employed these conditions, instead of using the Wilkinson catalyst, to prevent overreduction of the α,β-unsaturated γ-lactone moiety, a problem that occur-

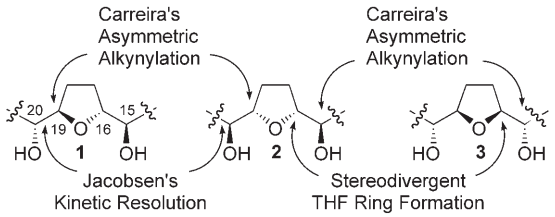


Scheme 5. Synthesis of murisolin (**1**): a) H_2, $[Rh(PPh_3)_3Cl]$ (0.4 equiv), benzene, RT, 41%; b) H_2, $[Rh(PPh_3)_3Cl]$ (1.0 equiv), benzene/MeOH (1:1), RT, 47%; c) $TsNHNH_2$, NaOAc, 1,2-dimethoxyethane/H_2O (1:1), reflux, 71%; d) 48% aq. HF, CH_3CN, THF, RT, 91%. Ts = toluene-4-sulfonyl.

red in the γ-lactone without a proximal C4 substituent. Fortunately, diimide reduction was also effective to retard the formation of the unidentified byproduct in the case of coupling product **17**, to give **18** in 71% yield. Finally, global deprotection with HF in MeCH/THF afforded murisolin (**1**) in excellent yield.

The spectroscopic and physical data (^{1}H NMR, ^{13}C NMR, IR, and MS spectra and m.p.) of synthetic **1** were in good agreement with those reported. On the other hand, the specific rotation of synthetic **1** ($[\alpha]_D^{23} = +20.7$ ($c = 0.39$, MeOH); $[\alpha]_D^{22} = +21.5$ ($c = 0.36$, $CHCl_3$)) was consistent with the highest values reported in the literature ($[\alpha]_D = +14.8$ ($c = 0.1$, MeOH); $[\alpha]_D = +16.0$ ($c = 0.1$, $CHCl_3$); $[\alpha]_D^{14.5} = +19.05$ ($c = 0.84$, $CHCl_3$); $[\alpha]_D^{18.5} = +20.44$ ($c = 5.92$, $CHCl_3$)).[3,4,16] Our synthetic sample was also compared with Professor Curran's sample by HPLC analysis in his laboratory.

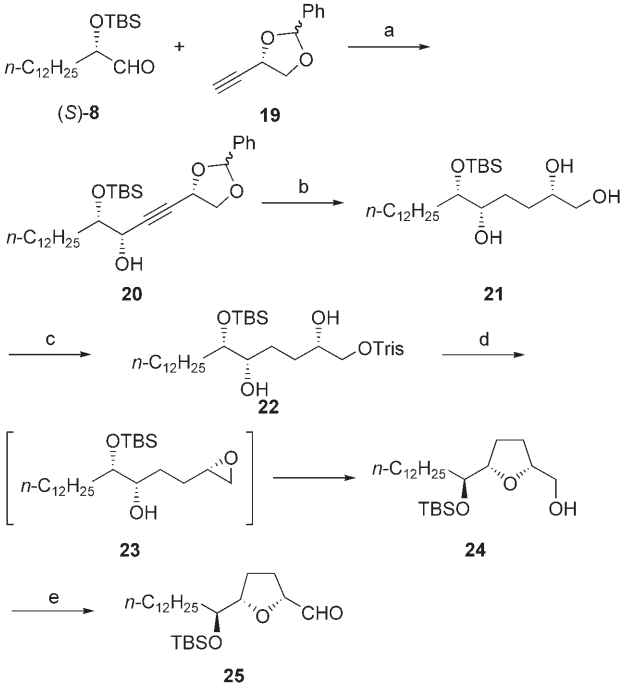
To demonstrate the stereodivergency of our methodology, we synthesized the two stereoisomers of 16,19-*cis*-murisolin, **2** and **3** (Scheme 6). The unnatural 16,19-*cis*-murisolin **3** has



Scheme 6. Stereodivergent syntheses of **1**–**3**.

a THF moiety that is a mirror image to that of **2**. We were also interested in the biological activity of these compounds. The stereocenters at the C15 and C19 positions can be constructed stereodivergently by changing the *N*-methylephedrine configuration in the asymmetric alkynylation. On the other hand, stereoselective construction of the C16 and C20 stereocenters can be accomplished by changing the mode of THF-ring formation and by choosing an appropriate enantiomer of Jacobsen's catalyst,[17] respectively (Scheme 6).

16,19-*cis*-Murisolin **2** was synthesized from α-oxyaldehyde (*S*)-**8**, which was prepared through kinetic resolution of (±)-tetradecene oxide with an antipode of Jacobsen's salen-cobalt catalyst (Scheme 7). Asymmetric alkynylation of (*S*)-



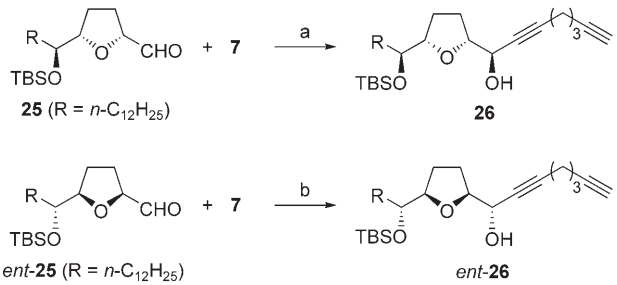
Scheme 7. Preparation of aldehyde **25**: a) $ZnO(Tf)_2$, (1*S*,2*R*)-NME, Et_3N, toluene, RT, 92% (α-OH:β-OH >97:3); b) H_2, Pd/C, EtOAc, RT, 84%; c) TrisCl, pyridine, CH_2Cl_2, 0°C→RT, 86%; d) K_2CO_3, MeOH, 0°C→RT, 70%; e) Dess–Martin periodinane, pyridine, CH_2Cl_2, 0°C→RT, 65%. Tris = 2,4,6-triisopropylbenzenesulfonyl.

8 with alkyne **19**[7b] by using (1*S*,2*R*)-NME afforded *syn*-propargyl alcohol **20** in 92% yield with excellent diastereoselectivity. Hydrogenation of **20** on Pd/C in EtOAc gave triol **21** in 84% yield. After conversion of the primary alcohol into the leaving group, one-pot THF-ring formation was carried out by treatment with K_2CO_3 in MeOH, through an epoxide intermediate, to provide α-tetrahydrofuranic alcohol **24**. Finally, Dess–Martin oxidation of the primary alcohol gave the aldehyde **25**[7b] in 65% yield.

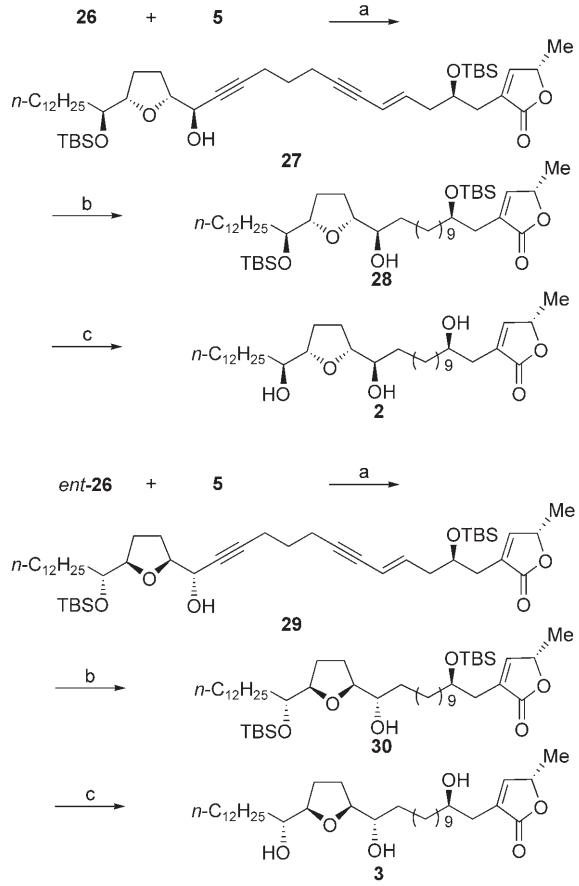
α-Tetrahydrofuranic aldehyde *ent*-**25** was synthesized from (*R*)-**8** according to the procedure described in reference [7b].

Asymmetric alkynylation with 1,6-heptadiyne (**7**) was conducted on the α-tetrahydrofuranic aldehydes **25** and *ent*-**25** in a similar manner to that performed in the murisolin synthesis. By using the appropriate NME, both (*R*)- and (*S*)-propargyl alcohols **26** and *ent*-**26** were synthesized with excellent diastereoselectivity and in 79% yield without being influenced by the three internal stereogenic centers in the aldehydes (Scheme 8).[18]

With both enantiomers **26** and *ent*-**26** in hand, the Sonogashira coupling with γ-lactone segment **5** was examined (Scheme 9). The coupling reaction proceeded smoothly to



Scheme 8. Asymmetric alkynylation of α-tetrahydrofuranic aldehyde **25** or *ent*-**25** with diyne **7**: a) $Zn(OTf)_2$, Et_3N, (1*R*,2*S*)-NME, toluene, RT, 79% (α-OH:β-OH 6:94); b) $Zn(OTf)_2$, Et_3N, (1*S*,2*R*)-NME, toluene, RT, 79% (α-OH:β-OH 94:6).



Scheme 9. Syntheses of 16,19-*cis*-murisolin **2** and unnatural 16,19-*cis*-murisolin **3**: a) $[(Ph_3P)_2PdCl_2]$, CuI, Et_3N, RT, 73% for **27** and 78% for **29**; b) $TsNHNH_2$, NaOAc, 1,2-dimethoxyethane, H_2O, reflux, 60% for **28** and 61% for **30**; c) 48% aq. HF, CH_3CN, THF, RT, 85% for **2** and 82% for **3**.

give enediynes **27** and **29** in 73 and 78% yield, respectively. Subsequent diimide reduction delivered **28** and **30** and removal of the protecting groups yielded 16,19-*cis*-murisolin **2** and the unnatural isomer **3**.

The spectroscopic data (^1H NMR, ^{13}C NMR, IR, and MS spectra and $[\alpha]_D$) of synthetic **2** were in good agreement with those reported. However, the melting point of the syn-

thetic **2** (76.5–77.5 °C) was higher than that of the natural product (67–68 °C).[4] The data (^{1}H NMR, ^{13}C NMR, IR, and MS spectra) of **3** were almost identical to those of **2**. Furthermore, the value of specific rotation of **3** ($[\alpha]_D^{29} = +9.1$ ($c = 0.50$ in CH_2Cl_2)) was relatively close to that of **2** ($[\alpha]_D^{27} = +11.3$ ($c = 0.62$ in CH_2Cl_2)). Interestingly, the value of the melting point of **3** (65.0–66.0 °C) was closer to the reported value of **2**. Since the natural product is not available at the present time, the difference in melting points cannot be explained clearly. However, we suggest that great care is necessary in identification of 16,19-*cis*-murisolins since both the specific rotation and spectral data for **2** and **3** are very close.[19]

Biological evaluation of 1–3: The growth inhibitory activity of **1**–**3** was evaluated against a panel of human cancer cell lines.[20,21] Figure 1 shows the mean graphs for murisolin (**1**), 16,19-*cis*-murisolin **2**, and unnatural 16,19-*cis*-murisolin **3**. The graphs were drawn based on a set of GI_{50} values for each compound against 39 cancer cell lines, where the GI_{50} value indicates the concentration that induces 50 % inhibition of cell growth. These compounds commonly showed significant effects against some lung and stomach cancer cell lines. In particular, these compounds inhibited the growth of DMS114 lung cancer cells very potently (log $GI_{50} = -7.53$ (3.0×10^{-8} M) to -8.00 (1.0×10^{-8} M)). Among **1**–**3**, the natural 16,19-*cis*-murisolin **2** exhibited the highest growth inhibition against MKN28 stomach cancer cells (log $GI_{50} = -8.00$). The activity was considerably influenced by the stereochemistry of the THF-ring moiety (order of activity (log GI_{50}): **2** (-8.00) > **3** (-5.89) > **1** (-5.56)). An effect of the stereochemistry on the growth inhibition was also found against NCI-H23 cells (order of activity (log GI_{50}): **3** (-6.76) > **1** (-6.67) > **2** (-4.97)) and MKN7 cells (order of activity (log GI_{50}): **1** (-6.15) > **2** (-5.83) > **3** (-4.72)). Moderate inhibition was observed against some breast cancer cells (BSY-1 and MCF-7), CNS cancer cells (SF-295), lung cancer cells (NCI-H522), melanoma cells (LOX-IMVI), and stomach cancer cells (MKN74).

COMPARE analysis[20,21] is a tool to examine a pair of compounds in terms of their mean graphs, and it was revealed here that compounds **1**–**3** were different from any of the present anticancer drugs ($r < 0.5$). This result suggests that they have unique modes of action. In addition, the

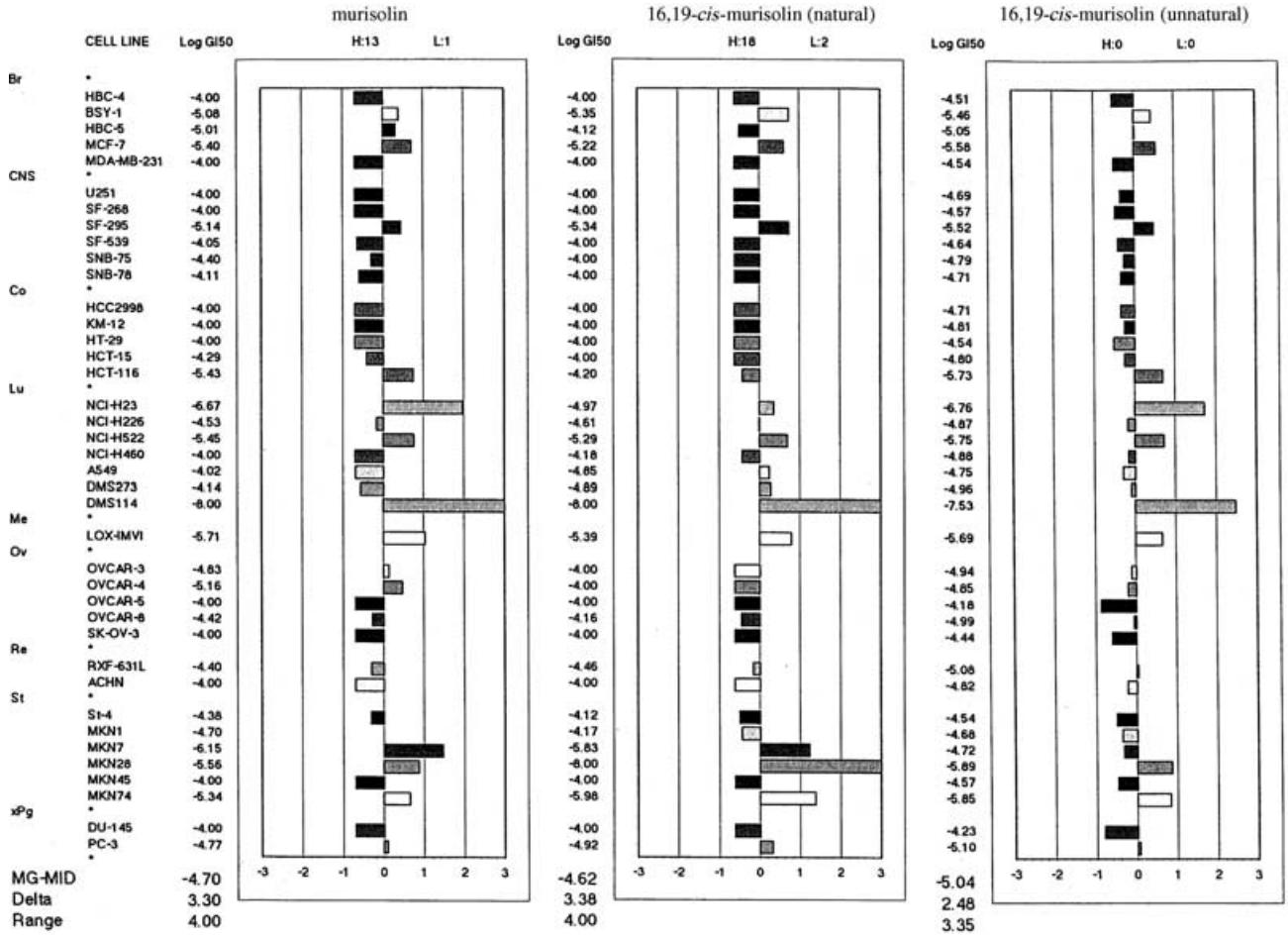


Figure 1. Growth inhibition of **1**–**3** against a panel of 39 human cancer cell lines. Columns extending to the right indicate the degree of the sensitivity of a cell line to the compound; columns extending to the left indicate the degree of resistance of a cell line to the compound. For details of the procedure for the assay, see reference [20]. GI_{50} = concentration that induces 50 % growth inhibition, Br = breast, CNS = central nervous system (brain), Co = colon, Lu = lung, Me = melanoma, Ov = ovarian, Re = renal, St = stomach, xPg = prostate. MG-MID = the mean of the log GI_{50} values.

COMPARE analysis indicated that compounds **1**–**3** were very like each other (**1** versus **2**: $r=0.768$; **1** versus **3**: $r=0.889$; **2** versus **3**: $r=0.762$), as shown in Figure 1. This may indicate that these three compounds share the same mode of action, albeit one that is unknown at present.

Conclusion

We have accomplished the total syntheses of murisolin congeners **1**–**3** by employing our systematic synthesis of the THF-ring moiety, asymmetric alkynylation with the diyne, and Sonogashira coupling as the key steps. Evaluation of cell-growth inhibition of these compounds indicated that they commonly have strong inhibitory activity against lung cancer cells (DMS114). 16,19-*cis*-murisolin **2** exhibited potent activity against stomach cancer cells (MKN28) and the effect of the compounds was affected by the stereochemistry of the THF moiety. COMPARE analysis of **1**–**3** indicated that they may share a mode of action that is different from those of currently used anticancer drugs.

Experimental Section

Melting points are uncorrected. Optical rotations were measured by using a JASCO DIP-360 digital polarimeter. ^{1}H NMR spectra were recorded in $CDCl_3$ solution with a JEOL JNM-GX-500 spectrometer (500 MHz). ^{13}C NMR spectra were recorded in $CDCl_3$ solution with a JEOL JNM-AL300 spectrometer (75 MHz). All signals are expressed as δ values in ppm downfield from the tetramethylsilane internal standard. The following abbreviations are used: br = broad, s = singlet, d = doublet, tr = triplet, q = quartet, qn = quintet, sep = septet, and m = multiplet. IR absorption spectra (FT = diffuse reflectance spectroscopy) were recorded with KBr powder by using a Horiba FT-210 IR spectrophotometer, and only noteworthy absorptions (in cm^{-1}) are listed. Mass spectra were obtained with JEOL JMS-600H and JEOL JMS-700 mass spectrometers. Column chromatography was carried out by using Kanto Chemical silica gel 60N (spherical, neutral, 63–210 μm). All air- or moisture-sensitive reactions were carried out in flame-dried glassware under an atmosphere of Ar or N_2. All solvents were dried and distilled according to standard procedures. All organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure with rotary evaporator.

(8*R*,9*R*)-9-(*tert*-Butyldimethylsilyloxy)heneicosa-1,6-diyn-8-ol (9) and (13*R*,14*R*,22*R*,23*R*)-13,23-bis-(*tert*-butyldimethylsilyloxy)pentatriaconta-15,20-diyne-14,22-diol (10): A flask was charged with $Zn(OTf)_2$ (138 mg, 0.379 mmol). Vacuum (5 mmHg) was applied and the flask was heated to 125 °C overnight. The vacuum was released and the flask was cooled to room temperature. (1*R*,2*S*)-*N*-Methylephedrine (73.2 mg, 0.409 mmol), toluene (0.7 mL), and Et_3N (0.057 mL, 0.409 mmol) were added to the flask with stirring at room temperature for 2.75 h. A solution of 1,6-heptadiyne (**7**; 111 mg, 11.7 mmol) in toluene (0.3 mL) was added to the mixture. After the mixture had been stirred at room temperature for 0.25 h, a solution of (*R*)-**8** (100 mg, 0.292 mmol) in toluene (0.3 mL) was added with stirring at room temperature for 1.5 h. The reaction was quenched with saturated NH_4Cl and the mixture was extracted with EtOAc. The combined organic layers were washed with brine prior to drying and solvent evaporation. Purification by column chromatography on silica gel (hexane/EtOAc 20:1→10:1) yielded **9** (106 mg, 84%, *anti*:*syn* 3:>97) and **10** (13.1 mg, 12%), both as colorless oils. **9**: $[\alpha]_D^{25}=-3.56$ ($c=1.03$ in $CHCl_3$); ^{1}H NMR: $\delta=0.10$ (s, 3H), 0.13 (s, 3H), 0.88 (t, $J=7.0$ Hz, 3H), 0.92, (s, 9H), 1.26–1.34 (m, 20H), 1.49–1.56 (m, 1H), 1.59–1.66 (m, 1H), 1.73 (qn, $J=7.0$ Hz, 2H), 1.95 (t, $J=2.4$ Hz, 1H), 2.30 (td, $J=6.7$, 2.4 Hz, 2H), 2.34 (td, $J=7.3$, 1.8 Hz, 2H), 2.45 (br d, $J=6.1$ Hz, 1H), 3.68 (q, $J=5.5$ Hz, 1H), 4.19 ppm (br s, 1H); ^{13}C NMR $\delta=-4.5$, −4.4, 14.1, 17.6, 17.8, 18.1, 22.6, 24.9, 25.8 (3C), 27.4, 29.3, 29.48, 29.53, 29.59 (2C), 29.63, 29.7, 31.9, 33.7, 65.0, 68.8, 75.8, 80.4, 83.3, 84.4 ppm; IR (KBr): $\tilde{\nu}=3552$, 3464, 3313, 2119, 636 cm^{-1}; MS (FAB): *m*/*z*: 441 $[M+Li]^+$; HRMS (FAB): *m*/*z* calcd for $C_{27}H_{50}LiO_2Si$: 441.3740; found: 441.3752 $[M+Li]^+$. **10**: $[\alpha]_D^{26}=-1.59$ ($c=1.32$ in $CHCl_3$); ^{1}H NMR: $\delta=0.10$ (s, 6H), 0.12 (s, 6H), 0.88 (t, $J=7.0$ Hz, 6H), 0.91, (s, 18H), 1.26–1.34 (m, 40H), 1.48–1.55 (m, 2H), 1.58–1.65 (m, 2H), 1.71 (qn, $J=7.0$ Hz, 2H), 2.31 (td, $J=7.0$, 1.8 Hz, 4H), 2.45 (d, $J=6.7$ Hz, 2H), 3.68 (q, $J=5.5$ Hz, 2H), 4.17–4.20 ppm (m, 2H); ^{13}C NMR: $\delta=-4.5$ (2C), −4.4 (2C), 14.1 (2C), 18.07 (2C), 18.15 (2C), 22.7 (2C), 24.9 (2C), 25.9 (6C), 27.5, 29.3 (2C), 29.55 (2C), 29.58 (2C), 29.64 (4C), 29.7 (2C), 29.8 (2C), 31.9 (2C), 33.7 (2C), 65.0 (2C), 75.8 (2C), 80.4 (2C), 84.5 ppm (2C); IR (KBr): $\tilde{\nu}=3559$, 3463 cm^{-1}; MS (FAB): *m*/*z*: 800 $[M+Na]^+$; HRMS (FAB): *m*/*z* calcd for $C_{47}H_{92}NaO_4Si_2$: 799.6432; found: 799.6404 $[M+Na]^+$.

(8*R*,9*R*,12*R*,13*R*)-13-(*tert*-Butyldimethylsilyloxy)-9,12-epoxy-pentacosa-1,6-diyn-8-ol (12) and (13*R*,14*R*,17*R*,18*R*,26*R*,27*R*,30*R*,31*R*)-13,31-bis-(*tert*-butyldimethylsilyloxy)-14,17:27,30-diepoxytritetraconta-19,24-diyne-18,26-diol (13): The procedure was the same as that used for the preparation of **9** and **10**. Compounds **12** (129 mg, 84%, α-OH:β-OH 3:>97) and **13** (14.1 mg, 12%) were prepared as colorless oils from **11** (126 mg, 0.305 mmol). **12**: $[\alpha]_D^{24}=+11.2$ ($c=1.10$ in $CHCl_3$); ^{1}H NMR: $\delta=0.06$ (s, 3H), 0.08 (s, 3H), 0.88 (t, $J=7.0$ Hz, 3H), 0.89 (s, 9H), 1.23–1.49 (m, 22H), 1.65–1.79 (m, 2H), 1.73 (qn, $J=6.7$ Hz, 2H), 1.89–1.94 (m, 1H), 1.95 (t, $J=2.4$ Hz, 1H), 2.02–2.08 (m, 1H), 2.30 (td, $J=6.7$, 2.4 Hz, 2H), 2.35 (td, $J=6.7$, 1.8 Hz, 2H), 2.47 (d, $J=4.3$ Hz, 1H), 3.57 (td, $J=6.1$, 3.7 Hz, 1H), 3.91 (dt, $J=7.3$, 6.1 Hz, 1H), 4.01 (q, $J=6.7$ Hz, 1H), 4.14–4.18 ppm (m, 1H); ^{13}C NMR: $\delta=-4.7$, −4.2, 14.1, 17.5, 17.7, 18.2, 22.6, 25.5, 25.9 (3C), 27.3, 27.6, 28.3, 29.3, 29.55, 29.59 (3C), 29.63, 29.8, 31.9, 32.9, 65.5, 68.8, 74.9, 78.9, 82.3, 82.7, 83.3, 84.9 ppm; IR (KBr): $\tilde{\nu}=3450$, 3313, 2233, 2119 cm^{-1}; MS (FAB): *m*/*z*: 505 $[M+H]^+$; HRMS (FAB): *m*/*z* calcd for $C_{31}H_{57}O_3Si$: 505.4077; found: 505.4084 $[M+H]^+$. **13**: $[\alpha]_D^{24}=+12.4$ ($c=1.74$ in $CHCl_3$); ^{1}H NMR: $\delta=0.06$ (s, 6H), 0.08 (s, 6H), 0.88 (t, $J=7.0$ Hz, 6H), 0.89 (s, 18H), 1.23–1.47 (m, 44H), 1.64–1.78 (m, 6H), 1.89–1.94 (m, 2H), 2.02–2.08 (m, 2H), 2.31 (td, $J=7.0$, 1.8 Hz, 4H), 2.51 (br d, $J=3.1$ Hz, 2H), 3.57 (td, $J=6.7$, 3.1 Hz, 2H), 3.91 (dt, $J=7.9$, 6.1 Hz, 2H), 4.00 (q, $J=6.7$ Hz, 2H), 4.15 ppm (br d, $J=6.7$ Hz, 2H); ^{13}C NMR: $\delta=-4.6$ (2C), −4.2 (2C), 14.1 (2C), 17.9 (2C), 18.2 (2C), 22.7 (2C), 25.5 (2C), 25.9 (6C), 27.4, 27.6 (2C), 28.3 (2C), 29.3 (2C), 29.58 (2C), 29.62 (6C), 29.7 (2C), 29.8 (2C), 31.9 (2C), 32.9 (2C), 65.5 (2C), 74.8 (2C), 78.7 (2C), 82.3 (2C), 82.6 (2C), 85.0 ppm (2C); IR (KBr): $\tilde{\nu}=3429$, 2233 cm^{-1}; MS (FAB): *m*/*z*: 940 $[M+Na]^+$; HRMS (FAB): *m*/*z* calcd for $C_{55}H_{104}NaO_6Si_2$: 939.7269; found: 939.7256 $[M+Na]^+$.

(3*RS*,5*S*)-3-Phenylthio-3-[(*EZ*,2*R*)-2-(*tert*-butyldimethylsiloxy)-5-iodo-4-pentenyl]-5-methyl-2(5*H*)-2,3-dihydrofuranone (16): Method without HMPA: KHMDS (0.5 M in toluene, 0.422 mL, 0.211 mmol) was added to a solution of **15** (43.9 mg, 0.211 mmol) in THF (0.2 mL) with stirring at 0 °C. After 5 min, a solution of **14** (100 mg, 0.211 mmol) in THF (0.2 mL) was added to the mixture with stirring at 0 °C. After being stirred for 2 h at room temperature, the reaction was quenched with saturated NH_4Cl and the mixture was extracted with EtOAc. The combined organic layers were washed with brine prior to drying and solvent evaporation. Purification by column chromatography on silica gel (hexane/EtOAc 20:1→10:1) yielded **16** (20.8 mg, 19%).

Method with HMPA: HMPA (0.668 mL, 3.84 mmol) was added to a solution of **15** (159 mg, 0.767 mmol) in THF (1.1 mL) with stirring at room temperature and then KHMDS (0.5 M in toluene, 1.53 mL, 0.767 mmol) was added to the solution at 0 °C. After the mixture had been stirred for 5 min at the same temperature, a solution of **14** (364 mg, 0.767 mmol) in THF (1.1 mL) was added with stirring. After being stirred for 1 h at room temperature, the reaction was quenched with saturated NH_4Cl and the mixture was extracted with EtOAc. The combined organic layers were washed with saturated NH_4Cl, water, and brine prior to drying and solvent evaporation. Purification by column chromatography on silica gel (hexane/EtOAc 20:1→10:1) yielded **16** (315 mg, 77%). The spectral data (^{1}H NMR, ^{13}C NMR spectra) were identical to those reported previously.[8]

(5*S*)-3-[(*E*,2*R*,13*R*)-2-(*tert*-Butyldimethylsilyloxy)-13-hydroxy-13-[(2*R*,5*R*)-5-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)tridecyl]tetrahydrofuran-2-yl]tridec-4-ene-6,11-diynyl]-5-methyl-2,5-dihydrofuran-2-one (17): Pd(PPh_3)$_2Cl_2$ (6.4 mg, 0.0092 mmol) and CuI (7.0 mg, 0.037 mmol) were added to a solution of **5** (77.3 mg, 0.183 mmol) in Et_3N (1.0 mL) with stirring at room temperature. After 0.5 h, a solution of **12** (92.4 mg, 0.183 mmol) in Et_3N (0.5 mL) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 6.5 h and concentrated. Purification by column chromatography on silica gel (hexane/EtOAc 10:1→5:1) yielded **17** (112 mg, 72%) as a yellow oil. $[\alpha]_D^{24}=+0.50$ ($c=0.96$ in $CHCl_3$); ^{1}H NMR: $\delta=0.02$ (s, 3H), 0.06 (s, 6H), 0.08 (s, 3H), 0.86–0.90 (m, 3H), 0.88 (s, 9H), 0.89 (s, 9H), 1.23–1.35 (m, 21H), 1.36–1.46 (m, 1H), 1.42 (d, $J=6.7$ Hz, 3H), 1.66–1.79 (m, 4H), 1.89–1.95 (m, 1H), 2.02–2.08 (m, 1H), 2.24–2.29 (m, 2H), 2.33 (td, $J=7.3$, 1.8 Hz, 2H), 2.39 (td, $J=6.7$, 1.2 Hz, 2H), 2.42 (d, $J=6.1$ Hz, 2H), 2.47 (d, $J=4.3$ Hz, 1H), 3.56–3.59 (m, 1H), 3.91 (dt, $J=7.9$, 6.1 Hz, 1H), 4.00 (q, $J=6.7$ Hz, 1H), 4.05 (qn, $J=6.1$ Hz, 1H), 4.14–4.17 (m, 1H), 5.00 (qd, $J=6.7$, 1.2 Hz, 1H), 5.47 (dt, $J=15.9$, 1.8 Hz, 1H), 6.03 (dt, $J=15.9$, 7.3 Hz, 1H), 7.10 ppm (brs, 1H); ^{13}C NMR: $\delta=-4.6$ (2C), −4.5, −4.2, 14.0, 17.87, 17.95, 18.2, 18.5, 18.8, 22.6, 25.5, 25.8 (3C), 25.9 (3C), 27.6, 27.7, 28.3, 29.3, 29.5, 29.57 (3C), 29.60, 29.8, 31.9, 32.8, 32.9, 40.7, 65.6, 69.3, 74.9, 77.4, 78.8, 79.5, 82.4, 82.7, 85.1, 88.1, 112.7, 130.6, 138.4, 151.7, 173.7 ppm; IR (KBr): $\tilde{\nu}=3456$, 2219, 1759, 1653 cm^{-1}; MS (FAB): m/z: 800 $[M+H]^+$; HRMS (FAB): m/z calcd for $C_{47}H_{83}O_6Si_2$: 799.5728; found: 799.5720 $[M+H]^+$.

(5*S*)-3-[(2*R*,13*R*)-2-(*tert*-Butyldimethylsilyloxy)-13-hydroxy-13-[(2*R*,5*R*)-5-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)tridecyl]tetrahydrofuran-2-yl]tridecyl]-5-methyl-2,5-dihydrofuran-2-one (18): A solution of NaOAc (811 mg, 9.89 mmol) in water (13 mL) was added to a stirred solution of **17** (101 mg, 0.126 mmol) and *p*-toluenesulfonylhydrazine (1.62 g, 8.67 mmol) in dimethoxyethane (13 mL) at reflux over 5 h. The mixture was then cooled to room temperature, poured into water, and extracted with CH_2Cl_2. The combined organic layers were dried and concentrated. Purification by column chromatography on silica gel (hexane/EtOAc 6:1) yielded **18** (72.8 mg, 71%) as a colorless oil. $[\alpha]_D^{24}=+15.8$ ($c=1.49$ in $CHCl_3$); ^{1}H NMR: $\delta=0.02$ (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.08 (s, 3H), 0.85–0.90 (m, 3H), 0.87 (s, 9H), 0.89 (s, 9H), 1.25–1.46 (m, 42H), 1.42 (d, $J=6.7$ Hz, 3H), 1.56–1.68 (m, 2H), 1.90–1.96 (m, 2H), 2.424 (d, $J=4.3$ Hz, 1H), 2.425 (d, $J=5.5$ Hz, 2H), 3.35–3.40 (m, 1H), 3.55 (td, $J=6.1$, 3.7 Hz, 1H), 3.77 (dt, $J=7.9$, 6.1 Hz, 1H), 3.85 (dt, $J=7.9$, 6.1 Hz, 1H), 3.95 (qn, $J=5.5$ Hz, 1H), 5.01 (qd, $J=6.7$, 1.2 Hz, 1H), 7.13 ppm (d, $J=1.2$ Hz, 1H); ^{13}C NMR: $\delta=-4.6$, −4.49, −4.48, −4.1, 14.1, 18.0, 18.3, 18.9, 22.7, 25.1, 25.4, 25.6, 25.8 (3C), 25.9 (3C), 28.5, 28.6, 29.3, 29.57 (4C), 29.63 (3C), 29.67 (2C), 29.68, 29.71, 29.8, 31.9, 32.7, 33.1, 33.4, 36.9, 70.1, 74.1, 75.2, 77.5, 82.2, 82.4, 130.8, 151.6, 174.1 ppm; IR (KBr): $\tilde{\nu}=3597$, 1759, 1653 cm^{-1}; MS (FAB): m/z: 832 $[M+Na]^+$; HRMS (FAB): m/z calcd for $C_{47}H_{92}NaO_6Si_2$: 831.6330; found: 831.6331 $[M+Na]^+$.

(5*S*)-3-[(2*R*,13*R*)-2,13-Dihydroxy-13-[(2*R*,5*R*)-5-[(1*R*)-1-hydroxytridecyl]tetrahydrofuran-2-yl]tridecyl]-5-methyl-2,5-dihydrofuran-2-one (murisolin, 1): Two drops of 48% aqueous HF was added to a stirred solution of **18** (27.5 mg, 0.034 mmol) in MeCN/THF (1.6:1, 0.55 mL) at room temperature. After being stirred at room temperature for 13.5 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. Purification by column chromatography on silica gel (hexane/EtOAc 1:1) yielded **1** (17.9 mg, 91%) as a colorless waxy solid. M.p. = 72.5–73.5 °C; $[\alpha]_D^{23}=+20.7$ ($c=0.39$ in MeOH), $[\alpha]_D^{22}=+21.5$ ($c=0.36$ in $CHCl_3$); ^{1}H NMR: $\delta=0.88$ (t, $J=7.0$ Hz, 3H), 1.25–1.57 (m, 42H), 1.44 (d, $J=6.7$ Hz, 3H), 1.63–1.71 (m, 2H), 1.94–2.02 (m, 2H), 2.40 (dd, $J=15.3$, 8.6 Hz, 1H), 2.47–2.58 (m, 3H), 2.51–2.55 (m, 1H), 3.41 (td, $J=6.7$, 4.9 Hz, 2H), 3.80 (q, $J=6.7$ Hz, 2H), 3.82–3.87 (m, 1H), 5.07 (qd, $J=6.7$, 1.2 Hz, 1H), 7.20 ppm (d, $J=1.2$ Hz, 1H); ^{13}C NMR: $\delta=14.1$, 19.1, 22.7, 25.5 (2C), 25.6, 28.7 (2C), 29.3, 29.4, 29.5 (4C), 29.57, 29.62 (4C), 29.65, 29.69, 31.9, 33.3, 33.4 (2C), 37.4, 70.0, 74.0 (2C), 78.0, 82.6 (2C), 131.2, 151.8, 174.6 ppm; IR (KBr): $\tilde{\nu}=3435$, 3419, 2916, 2848, 1751, 1470, 1319, 1201, 1119, 1074, 1028, 960, 847, 721 cm^{-1}; MS (FAB): m/z: 582 $[M+H]^+$; HRMS (FAB): m/z calcd for $C_{35}H_{65}O_6$: 581.4781; found: 581.4786 $[M+H]^+$.

(2*RS*,4*S*)-4-[(3′*S*,4′*S*)-4′-*tert*-Butyldimethylsilyloxy-3′-hydroxy-1′-hexadecynyl]-2-phenyl-1,3-dioxolane (20): A flask was charged with $Zn(OTf)_2$ (3.49 g, 9.60 mmol). Vacuum (15 mmHg) was applied and heated to 125 °C for 8 h. The vacuum was released and the flask was cooled to room temperature. (1*S*,2*R*)-*N*-Methylephedrine (1.84 g, 10.3 mmol), toluene (9.0 mL), and Et_3N (1.44 mL, 10.3 mmol) were added to the flask with stirring at room temperature. A solution of **19** (1.54 g, 8.86 mmol) in toluene (3.0 mL) was added to the mixture with stirring at room temperature. After 0.25 h, a solution of (*S*)-**8** (2.53 g, 7.38 mmol) in toluene (3.0 mL) was added to the mixture with stirring at room temperature. After being stirred for 18 h, the reaction was quenched with saturated NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine prior to drying and solvent evaporation. Purification by column chromatography on silica gel (hexane/EtOAc 30:1→20:1→10:1→4:1) yielded **20** (3.52 g, 92%, *anti*:*syn* 3:>97) as a yellow oil. $[\alpha]_D^{17}=+32.6$ ($c=1.09$ in $CHCl_3$); ^{1}H NMR: $\delta=0.10$ (s, 1.2H), 0.12 (s, 3H), 0.15 (s, 1.8H), 0.88 (t, $J=7.0$ Hz, 3H), 0.91 (s, 3.6H), 0.93 (s, 5.4H), 1.26–1.34 (m, 20H), 1.47–1.57 (m, 1H), 1.58–1.69 (m, 1H), 2.53 (d, $J=7.3$ Hz, 0.4H), 2.58 (d, $J=7.3$ Hz, 0.6H), 3.72 (td, $J=6.1$, 4.3 Hz, 0.4H), 3.76 (td, $J=5.5$, 4.9 Hz, 0.6H), 3.98 (dd, $J=7.9$, 6.1 Hz, 0.6H), 4.06 (dd, $J=7.9$, 6.1 Hz, 0.4H), 4.18 (dd, $J=7.9$, 6.1 Hz, 0.4H), 4.28 (ddd, $J=7.3$, 4.3, 1.2 Hz, 0.4H), 4.30 (ddd, $J=7.3$, 4.3, 1.8 Hz, 0.6H), 4.36 (dd, $J=7.9$, 6.1 Hz, 0.6H), 4.89 (td, $J=6.1$, 1.2 Hz, 0.4H), 4.94 (td, $J=6.1$, 1.8 Hz, 0.6H), 5.85 (s, 0.4H), 5.95 (s, 0.6H), 7.37–7.39 (m, 3H), 7.46–7.48 (m, 1.2H), 7.51–7.53 ppm (m, 0.8H); ^{13}C NMR: $\delta=-4.49$ (0.4C), −4.46 (0.6C), −4.44 (0.4C), −4.41 (0.6C), 14.1, 18.0 (0.4C), 18.1 (0.6C), 22.6, 24.9 (0.4C), 25.0 (0.6C), 25.8 (3C), 29.3, 29.46, 29.50, 29.57 (2C), 29.60, 29.7, 31.9, 33.57 (0.4C), 33.62 (0.6C), 64.68 (0.6C), 64.70 (0.4C), 65.8 (0.6C), 66.4 (0.4C), 70.5 (0.4C), 71.0 (0.6C), 75.17 (0.4C), 75.20 (0.6C), 81.5 (0.4C), 81.9 (0.6C), 86.1 (0.4C), 86.5 (0.6C), 103.6 (0.6C), 104.8 (0.4C), 126.5 (1.2C), 126.8 (0.8C), 128.2 (0.8C), 128.3 (1.2C), 129.3 (0.4C), 129.4 (0.6C), 136.6 (0.6C), 137.0 ppm (0.4C); IR (KBr): $\tilde{\nu}=3478$, 3037, 2360, 1068 cm^{-1}; MS (FAB): m/z: 539 $[M+Na]^+$; HRMS (FAB): m/z calcd for $C_{31}H_{52}NaO_4Si$: 539.3533; found: 539.3535 $[M+Na]^+$.

(2*S*,5*S*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)octadecane-1,2,5-triol (21): A solution of **20** (1.20 g, 2.13 mmol) in EtOAc (15 mL) was hydrogenated on 10% Pd/C (60.0 mg) with stirring at room temperature for 14.5 h. The Pd/C was filtered off and the filtrate was concentrated under reduced pressure. Purification by column chromatography on silica gel (hexane/EtOAc 10:1→1:1) yielded **21** (842 mg, 84%) as a colorless waxy oil. $[\alpha]_D^{19}=+3.0$ ($c=1.01$ in $CHCl_3$); ^{1}H NMR: $\delta=0.08$ (s, 3H), 0.09 (s, 3H), 0.88 (t, $J=7.0$ Hz, 3H), 0.90 (s, 9H), 1.26–1.33 (m, 20H), 1.39–1.44 (m, 1H), 1.49–1.70 (m, 5H), 2.12 (brs, 1H), 2.22 (brs, 1H), 2.68 (brs, 1H), 3.44–3.53 (m, 3H), 3.61–3.65 (m, 1H), 3.70–3.74 ppm (m, 1H); ^{13}C NMR: $\delta=-4.6$, −4.2, 14.1, 18.0, 22.6, 25.0, 25.8 (3C), 29.3, 29.56 (2C), 29.60 (2C), 29.64 (2C), 29.9, 30.3, 31.9, 33.4, 66.8, 72.4, 73.3, 75.4 ppm; IR (KBr): $\tilde{\nu}=3311$ cm^{-1}; MS (FAB): m/z: 433 $[M+H]^+$; HRMS (FAB): m/z calcd for $C_{24}H_{53}O_4Si$: 433.3713; found: 433.3726 $[M+H]^+$.

(2*S*,5*S*,6*S*)-6-*tert*-Butyldimethylsilyloxy-2,5-dihydroxyoctadecanyl 2′,4′,6′-triisopropylbenzenesulfonate (22): 2,4,6-Triisopropylbenzenesulfonyl chloride (1.77 g, 5.83 mmol) was added to a solution of **21** (842 mg, 1.94 mmol) in pyridine (6.3 mL) and CH_2Cl_2 (11 mL) at 0 °C with stirring for 0.25 h. After the mixture had been left for 34 h at room temperature, water (6.3 mL) was added. The mixture was then extracted with EtOAc. The combined organic layers were washed with brine prior to drying and solvent evaporation. Purification by column chromatography on silica gel (hexane/EtOAc 5:1→2:1) yielded **22** (1.17 g, 86%) as a colorless waxy oil. $[\alpha]_D^{24}=+1.2$ ($c=1.00$ in $CHCl_3$); ^{1}H NMR: $\delta=0.06$ (s, 3H), 0.08 (s, 3H), 0.87–0.90 (m, 3H), 0.89 (s, 9H), 1.23–1.31 (m, 38H), 1.37–1.44 (m, 1H), 1.49–1.66 (m, 4H), 1.74–1.79 (m, 1H), 2.54 (brs, 1H), 2.91 (sep, $J=6.7$ Hz, 1H), 3.44–3.51 (m, 3H), 3.87–3.92 (m, 1H), 3.97 (dd, $J=9.8$, 6.1 Hz, 1H), 4.00 (dd, $J=9.8$, 4.9 Hz, 1H), 4.14 (sep, $J=6.7$ Hz, 2H), 7.19 ppm (s, 2H); ^{13}C NMR: $\delta=-4.7$, −4.2, 14.1, 18.0, 22.6, 23.5 (2C), 24.69 (2C), 24.72 (2C), 24.8, 25.8 (3C), 29.3, 29.52, 29.54, 29.59 (3C), 29.63 (2C), 29.8, 30.2, 30.4, 31.9, 33.7, 34.2, 69.6, 72.76, 72.80, 75.4, 123.8 (2C), 129.1, 150.8 (2C), 153.8 ppm; IR (KBr): $\tilde{\nu}=3300$, 1463, 1178 cm^{-1}; MS (FAB): m/z: 699 $[M+H]^+$; HRMS (FAB): m/z calcd for $C_{39}H_{75}O_6SSi$: 699.5054; found: 699.5041 $[M+H]^+$.

(2*R*,5*S*,6*S*)-6-(*tert*-Butyldimethylsiloxy)-2,5-epoxyoctadecan-1-ol (24): K_2CO_3 (730 mg, 5.28 mmol) was added to a mixture of **22** (739 mg, 1.06 mmol) with stirring at 0 °C. After 2 h at the same temperature, the whole mixture was stirred for 66.5 h at room temperature. Water was added to the reaction mixture. The mixture was extracted with EtOAc and the combined organic layers were washed with brine prior to drying and solvent evaporation. Purification by column chromatography on silica gel (hexane/EtOAc 10:1) yielded **24** (307 mg, 70 %) as a colorless oil. $[\alpha]_D^{23} = +3.2$ ($c = 0.95$, $CHCl_3$). The spectral data (^{1}H NMR, ^{13}C NMR, and MS spectra) were identical to those reported for the enantiomer of **24**.[7b]

(2*R*,5*S*,6*S*)-6-(*tert*-Butyldimethylsiloxy)-2,5-epoxyoctadecanal (25): Dess–Martin periodinane (1.16 g, 2.74 mmol) was added to a solution of **24** (284 mg, 0.685 mmol) in pyridine (0.62 mL) and CH_2Cl_2 (7.5 mL) with stirring at 0 °C. After 0.5 h at the same temperature, the whole mixture was stirred for 3 h at room temperature. The mixture was filtered through silica gel and the filtrate was concentrated under the reduced pressure. Purification by flash column chromatography (hexane/EtOAc 30:1) yielded **25** (183 mg, 65 %) as colorless oil. The aldehyde was unstable and was therefore used immediately in the next step.

(8*R*,9*R*,12*S*,13*S*)-13-(*tert*-Butyldimethylsilyloxy)-9,12-epoxy-pentacosa-1,6-diyn-8-ol (26): The procedure was the same as that used for the preparation of **9**. Compound **26** (160 mg, 79 %) was prepared from **25** (166 mg, 0.401 mmol) as a pale yellow oil. $[\alpha]_D^{25} = +6.8$ ($c = 1.02$ in $CHCl_3$); ^{1}H NMR: $\delta = 0.078$ (s, 3H), 0.081 (s, 3H), 0.88 (t, $J = 7.0$ Hz, 3H), 0.90 (s, 9H), 1.23–1.45 (m, 21H), 1.60–1.67 (m, 1H), 1.73 (qn, $J = 7.0$ Hz, 2H), 1.77–1.91 (m, 3H), 1.95 (t, $J = 2.4$ Hz, 1H), 1.99 (dq, $J = 12.8$, 7.9 Hz, 1H), 2.30 (td, $J = 7.0$, 2.4 Hz, 2H), 2.35 (td, $J = 7.0$, 1.8 Hz, 2H), 2.90 (d, $J = 4.3$ Hz, 1H), 3.58 (td, $J = 6.1$, 3.7 Hz, 1H), 3.98–4.02 (m, 2H), 4.16 ppm (brs, 1H); ^{13}C NMR: $\delta = -4.6$, -4.4, 14.1, 17.5, 17.8, 18.2, 22.6, 25.4, 25.9 (3C), 27.0, 27.4, 28.1, 29.3, 29.55, 29.59 (3C), 29.62, 29.8, 31.9, 33.9, 65.5, 68.7, 74.3, 79.6, 82.10, 82.12, 83.4, 84.3 ppm; IR (KBr): $\tilde{\nu} = 3450$, 3313, 2231, 2119 cm^{-1}; MS (FAB): m/z: 505 $[M+H]^+$; HRMS (FAB): m/z calcd for $C_{31}H_{57}O_3Si$: 505.4077; found: 505.4091 $[M+H]^+$.

(5*S*)-3-[(*E*,2*R*,13*R*)-2-(*tert*-Butyldimethylsilyloxy)-13-hydroxy-13-[(2*R*,5*S*)-5-[(1*S*)-1-(*tert*-butyldimethylsilyloxy)tridecyl]tetrahydrofuran-2-yl]tridec-4-ene-6,11-diynyl]-5-methyl-2,5-dihydrofuran-2-one (27): The procedure was the same as that used for the preparation of **17**. Compound **27** (98.7 mg, 73 %) was prepared from **26** (85.6 mg, 0.170 mmol) and **5** (71.6 mg, 0.170 mmol) as a yellow oil. $[\alpha]_D^{24} = -3.0$ ($c = 0.75$ in $CHCl_3$); ^{1}H NMR: $\delta = 0.01$ (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.08 (s, 3H), 0.86–0.90 (m, 3H), 0.87 (s, 9H), 0.90 (s, 9H), 1.23–1.47 (m, 21H), 1.42 (d, $J = 6.7$ Hz, 3H), 1.58–1.65 (m, 1H), 1.70–1.91(m, 5H), 1.94–2.03 (m, 1H), 2.23–2.31 (m, 2H), 2.33 (td, $J = 7.3$, 1.8 Hz, 2H), 2.38–2.43 (m, 2H), 2.42 (d, $J = 6.1$ Hz, 2H), 2.87 (d, $J = 4.9$ Hz, 1H), 3.58 (td, $J = 6.1$, 4.3 Hz, 1H), 3.97–4.01 (m, 2H), 4.05 (qn, $J = 6.1$ Hz, 1H), 4.15–4.17 (m, 1H), 5.01 (qd, $J = 6.7$, 1.2 Hz, 1H), 5.47 (d, $J = 15.9$ Hz, 1H), 6.03 (dt, $J = 15.9$, 7.9 Hz, 1H), 7.11 ppm (brs, 1H); ^{13}C NMR: $\delta = -4.7$, -4.6, -4.5, -4.3, 14.1, 17.92, 17.95, 18.2, 18.5,18.8, 22.6, 25.4, 25.8 (3C), 25.9 (3C), 27.0, 27.7, 28.1, 29.3, 29.5, 29.57 (3C), 29.61, 29.8, 31.9, 32.7, 33.9, 40.7, 65.5, 69.2, 74.3, 77.4, 79.4, 79.5, 82.1, 82.2, 84.6, 88.2, 112.7, 130.6, 138.4, 151.7, 173.7 ppm; IR (KBr): $\tilde{\nu} = 3484$, 2222, 1759, 1653 cm^{-1}; MS (FAB): m/z: 800 $[M+H]^+$; HRMS (FAB): m/z calcd for $C_{47}H_{83}O_6Si_2$: 799.5728; found: 799.5710 $[M+H]^+$.

(5*S*)-3-[(2*R*,13*R*)-2-(*tert*-Butyldimethylsilyloxy)-13-hydroxy-13-[(2*R*,5*S*)-5-[(1*S*)-1-(*tert*-butyldimethylsilyloxy)tridecyl]tetrahydrofuran-2-yl]tridecyl]-5-methyl-2,5-dihydrofuran-2-one (28): The procedure was the same as the diimide reduction used for the preparation of **18**. Compound **28** (45.5 mg, 60 %) was prepared from **27** (73.7 mg, 0.0922 mmol) as a yellow oil. $[\alpha]_D^{26} = +14.1$ ($c = 0.95$ in $CHCl_3$); ^{1}H NMR: $\delta = 0.01$ (s, 3H), 0.04 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.86–0.89 (m, 3H), 0.86 (s, 9H), 0.89 (s, 9H), 1.25–1.51 (m, 41H), 1.41 (d, $J = 6.7$ Hz, 3H), 1.56–1.63 (m, 1H), 1.70–1.93 (m, 4H), 2.41 (d, $J = 5.5$ Hz, 2H), 2.65 (brd, $J = 2.4$ Hz, 1H), 3.35–3.37 (m, 1H), 3.57 (td, $J = 5.5$, 4.3 Hz, 1H), 3.77 (dt, $J = 7.3$, 5.5 Hz, 1H), 3.91 (td, $J = 6.7$, 4.3 Hz, 1H), 3.94 (qn, $J = 5.5$ Hz, 1H), 5.00 (qd, $J = 6.7$, 1.2 Hz, 1H), 7.11 ppm (d, $J = 1.2$ Hz, 1H); ^{13}C NMR: $\delta = -4.53$, -4.49, -4.47, -4.3, 14.1, 18.0, 18.2, 19.0, 22.7, 25.1, 25.4, 25.8, 25.85 (3C), 25.93 (3C), 27.4, 28.2, 29.3, 29.57 (4C), 29.61 (3C), 29.65 (2C), 29.69, 29.74, 29.8, 31.9, 32.7, 34.0, 34.3, 36.9, 70.2, 74.2, 74.6, 77.4, 81.5, 82.1, 130.8, 151.4, 174.0 ppm; IR (KBr): $\nu = 3509$, 1761, 1657 cm^{-1}; MS (FAB): m/z: 810 $[M+H]^+$; HRMS (FAB): m/z calcd for $C_{47}H_{93}O_6Si_2$: 809.6511; found: 809.6546 $[M+H]^+$.

(5*S*)-3-[(2*R*,13*R*)-2,13-Dihydroxy-13-[(2*R*,5*S*)-5-[(1*S*)-1-hydroxytridecyl]-tetrahydrofuran-2-yl]tridecyl]-5-methyl-2,5-dihydrofuran-2-one (16,19-*cis*-murisolin, 2): The procedure was the same as that used for the preparation of **1**. Compound **2** (20.9 mg, 85 %) was prepared from **28** (34.3 mg, 0.0424 mmol) as a colorless waxy solid. M.p. = 76.5–77.5 °C; $[\alpha]_D^{27} = +11.3$ ($c = 0.62$ in CH_2Cl_2); ^{1}H NMR: $\delta = 0.88$ (t, $J = 7.0$ Hz, 3H), 1.23–1.53 (m, 42H), 1.43 (d, $J = 6.7$ Hz, 3H), 1.71–1.78 (m, 2H), 1.90–1.97 (m, 2H), 2.40 (dd, $J = 15.3$, 8.5 Hz, 1H), 2.48 (brs, 1H), 2.52 (ddd, $J = 15.3$, 1.8, 1.2 Hz, 1H), 2.66 (brs, 2H), 3.42 (dt, $J = 7.3$, 4.9 Hz, 2H), 3.80–3.86 (m, 3H), 5.06 (qd, $J = 6.7$, 1.2 Hz, 1H), 7.19 ppm (d, $J = 1.2$ Hz, 1H); ^{13}C NMR: $\delta = 14.1$, 19.1, 22.7, 25.5, 25.6, 25.7, 28.1 (2C), 29.3, 29.4, 29.5 (2C), 29.59 (3C), 29.60 (3C), 29.64 (2C), 29.7, 31.9, 33.3, 34.03, 34.04, 37.4, 69.9, 74.3 (2C), 78.0, 82.7 (2C), 131.1, 151.8, 174.7 ppm; IR (KBr): $\tilde{\nu} = 3438$, 3342, 2918, 2848, 1747, 1649, 1469, 1315, 1203, 1120, 1074, 1028, 968, 849, 721 cm^{-1}; MS (FAB): m/z: 581 $[M+H]^+$; HRMS (FAB): m/z calcd for $C_{35}H_{65}O_6$: 581.4781; found: 581.4763 $[M+H]^+$.

(8*S*,9*S*,12*R*,13*R*)-13-(*tert*-Butyldimethylsilyloxy)-9,12-epoxy-pentacosa-1,6-diyn-8-ol (*ent*-26): The procedure was the same as that used for the preparation of **12**. The compound *ent*-**26** (105 mg, 79 %) was prepared from *ent*-**25** (109 mg, 0.265 mmol) as a pale yellow oil. $[\alpha]_D^{27} = -8.0$ ($c = 1.06$ in $CHCl_3$). The spectral data (^{1}H NMR, ^{13}C NMR, and MS spectra) were identical to those of **26**.

(5*S*)-3-[(*E*,2*R*,13*S*)-2-(*tert*-Butyldimethylsilyloxy)-13-hydroxy-13-[(2*S*,5*R*)-5-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)tridecyl]tetrahydrofuran-2-yl]tridec-4-ene-6,11-diynyl]-5-methyl-2,5-dihydrofuran-2-one (29): The procedure was the same as that used for the preparation of **17**. Compound **29** (170 mg, 78 %) was prepared from *ent*-**26** (138 mg, 0.273 mmol) and **5** (115 mg, 0.273 mmol) as a yellow oil. $[\alpha]_D^{26} = -9.2$ ($c = 0.95$ in $CHCl_3$); ^{1}H NMR: $\delta = 0.01$ (s, 3H), 0.05 (s, 3H), 0.068 (s, 3H), 0.072 (s, 3H), 0.86–0.90 (m, 3H), 0.87 (s, 9H), 0.90 (s, 9H), 1.22–1.46 (m, 21H), 1.41 (d, $J = 6.7$ Hz, 3H), 1.59–1.65 (m, 1H), 1.69–1.90 (m, 5H), 1.95–2.02 (m, 1H), 2.20–2.30 (m, 2H), 2.33 (td, $J = 7.0$, 1.8 Hz, 2H), 2.37–2.42 (m, 4H), 2.89 (brd, $J = 3.7$ Hz, 1H), 3.58 (td, $J = 6.1$, 4.3 Hz, 1H), 3.97–4.01 (m, 2H), 4.04 (qn, $J = 5.5$ Hz, 1H), 4.15 (brs, 1H), 5.00 (qd, $J = 6.7$, 1.2 Hz, 1H), 5.46 (dt, $J = 15.9$, 1.8 Hz, 1H), 6.03 (dt, $J = 15.9$, 7.3 Hz, 1H), 7.11 ppm (d, $J = 1.2$ Hz, 1H); ^{13}C NMR: $\delta = -4.7$, -4.6, -4.5, -4.3, 14.1, 17.9, 18.0, 18.2, 18.5, 18.9, 22.6, 25.4, 25.8 (3C), 25.9 (3C), 27.0, 27.7, 28.1, 29.3, 29.55, 29.59 (3C), 29.62, 29.8, 31.9, 32.8, 33.9, 40.7, 65.5, 69.2, 74.3, 77.5, 79.4, 79.5, 82.1, 82.2, 84.6, 88.2, 112.7, 130.6, 138.4, 151.8, 173.7 ppm; IR (KBr): $\tilde{\nu} = 3480$, 2222, 1759, 1655 cm^{-1}; MS (FAB): m/z: 800 $[M+H]^+$; HRMS (FAB): m/z calcd for $C_{47}H_{83}O_6Si_2$: 799.5728; found: 799.5700 $[M+H]^+$.

(5*S*)-3-[(2*R*,13*S*)-2-(*tert*-Butyldimethylsilyloxy)-13-hydroxy-13-[(2*S*,5*R*)-5-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)tridecyl]tetrahydrofuran-2-yl]tridecyl]-5-methyl-2,5-dihydrofuran-2-one (30): The procedure was the same as the diimide reduction used for the preparation of **18**. Compound **30** (37.0 mg, 61 %) was prepared from **29** (60.0 mg, 0.0751 mmol) as a colorless oil. $[\alpha]_D^{28} = +2.1$ ($c = 1.09$ in $CHCl_3$); ^{1}H NMR: $\delta = 0.01$ (s, 3H), 0.04 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.86–0.89 (m, 3H), 0.86 (s, 9H), 0.89 (s, 9H), 1.22–1.48 (m, 41H), 1.41 (d, $J = 6.7$ Hz, 3H), 1.60 (dq, $J = 14.0$, 6.7 Hz, 1H), 1.71–1.92 (m, 4H), 2.41 (d, $J = 5.5$ Hz, 2H), 3.36 (ddd, $J = 7.9$, 5.5, 4.3 Hz, 1H), 3.57 (td, $J = 6.1$, 3.7 Hz, 1H), 3.77 (dt, $J = 6.7$, 5.5 Hz, 1H), 3.89–3.97 (m, 2H), 5.00 (qd, $J = 6.7$, 1.2 Hz, 1H), 7.12 ppm (s, 1H); ^{13}C NMR: $\delta = -4.53$, -4.49, -4.48, -4.3, 14.1, 18.0, 18.2, 18.9, 22.7, 25.1, 25.4, 25.8, 25.85 (3C), 25.93 (3C), 27.4, 28.2, 29.3, 29.58 (3C), 29.59 (3C), 29.62 (2C), 29.65, 29.69, 29.74, 29.8, 31.9, 32.7, 34.0, 34.3, 36.9, 70.2, 74.2, 74.6, 77.4, 81.5, 82.1, 130.8, 151.4, 174.0 ppm; IR (KBr): $\tilde{\nu} = 3510$, 1761, 1658 cm^{-1}; MS (FAB): m/z: 810 $[M+H]^+$; HRMS (FAB): m/z calcd for $C_{47}H_{93}O_6Si_2$: 809.6511; found: 809.6536 $[M+H]^+$.

(5*S*)-3-[(2*R*,13*S*)-2,13-Dihydroxy-13-[(2*S*,5*R*)-5-[(1*R*)-1-hydroxytridecyl]-tetrahydrofuran-2-yl]tridecyl]-5-methyl-2,5-dihydrofuran-2-one (unnatural 16,19-*cis*-murisolin, 3): The procedure was the same as that used for the preparation of **1**. Compound **3** (21.1 mg, 82 %) was prepared from **30** (36.1 mg, 0.0446 mmol) as a colorless waxy solid. M.p. = 65.0–66.0 °C;

$[\alpha]_D^{29} = +9.1$ ($c = 0.50$ in CH_2Cl_2); ^{1}H NMR: $\delta = 0.88$ (t, $J = 7.0$ Hz, 3H), 1.26–1.51 (m, 42H), 1.43 (d, $J = 6.7$ Hz, 3H), 1.72–1.79 (m, 2H), 1.88–1.97 (m, 2H), 2.33–2.64 (m, 3H), 2.40 (dd, $J = 15.3$, 8.5 Hz, 1H), 2.52 (ddd, $J = 15.3$, 1.8, 1.2 Hz, 1H), 3.42 (dt, $J = 7.3$, 5.5 Hz, 2H), 3.80–3.87 (m, 3H), 5.06 (qd, $J = 6.7$, 1.2 Hz, 1H), 7.19 ppm (d, $J = 1.2$ Hz, 1H); ^{13}C NMR: $\delta = 14.1$, 19.1, 22.7, 25.5, 25.6, 25.7, 28.1 (2C), 29.3, 29.40, 29.43, 29.5 (3C), 29.62 (3C), 29.64 (3C), 29.7, 31.9, 33.3, 34.0, 34.1, 37.4, 70.0, 74.3 (2C), 78.0, 82.7 (2C), 131.2, 151.8, 174.6 ppm; IR (KBr): $\tilde{\nu} = 3444$, 3340, 2918, 2850, 1747, 1716, 1651, 1464, 1321, 1205, 1120, 1093, 1030, 971, 850, 721 cm^{-1}; MS (FAB): m/z: 581 $[M+H]^+$; HRMS (FAB): m/z calcd for $C_{35}H_{65}O_6$: 581.4781; found: 581.4795 $[M+H]^+$.

Cell-growth inhibition analysis: This experiment was carried out at the Cancer Chemotherapy Center, Japanese Foundation for Cancer Research. The screening panel consisted of the following 39 human cancer cell lines: breast cancer HBC-4, BSY-1, HBC-5, MCF-7, and MDA-MB-231; brain cancer U251, SF-268, SF-295, SF-539, SNB-75, and SNB-78; colon cancer HCC2998, KM-12, HT-29, HCT-15, and HCT-116; lung cancer NCI-H23, NCIH-226, NCI-H522, NCI-H460, A549, DMS273, and DMS114; melanoma LOX-IMVI; ovarian cancer OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, and SK-OV-3; renal cancer RXF-631L and ACHN; stomach cancer St-4, MKN1, MKN7, MKN28, MKN45, and MKN74; and prostate cancer DU-145 and PC-3. The GI_{50} (50% growth inhibition) value for these cell lines was determined by using the sulforhodamine B colorimetric method. A detailed method is described elsewhere.[20]

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