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Total Synthesis of an Antitumor Agent, Mucocin, Based on the "Chiron Approach"

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Received March 26, 2002

The total synthesis of a powerful antitumor acetogenin, mucocin (**1**), was achieved through a palladium-catalyzed cross-coupling reaction of the THP−THF fragment **2** and a terminal butenolide **3**. The key process for construction of the fragment **2** was chelation-controlled addition of ethynylmagnesium chloride to disilyl aldehyde **23a** and condensation of the alkyllithium prepared therefrom with THP aldehyde **4** in the presence of $CeCl_3$. Synthesis of the lactone **3** relied on a novel approach by taking advantage of a radical cyclization of acyclic selenocarbonate **6**. The three building blocks **4**, **5a**, and **6** were prepared stereoselectivly from D-galactose (**7**), 2,5-anhydro-D-mannitol (**8**), and L-rhamnose (**9**), respectively. A new and efficient method for desymmetrization of the C_2-symmetrical compound **8** is also described.

Introduction

Annonaceous acetogenins are a family of polyketide-derived fatty acid natural products isolated from the tropical and subtropical plant family, Annonaceae, and are characterized by a long alkyl chain with a terminal γ-lactone subunit, one to three tetrahydrofuran (THF) rings, and some carbinol chiral centers along it.[1] Many of these compounds exhibit a broad spectrum of biological activities such as cytotoxic, antitumor, insecticidal, fungicidal, anthelmintic, immunosuppressive, and antifeedant effects. As the mode of action, a blockage of the mitochondrial NADH-ubiquinone oxidoreductase in complex I, which is a membrane bound and essential enzyme for ATP production, is discussed.[2] Furthermore, these natural products were also shown to inhibit a ubiquinone-linked NADH oxidase found in the plasma membrane of specific tumor cell-lines, including some which show multidrug resistance.[3] Such consideration suggests that these natural products are expected to be new candidates for anticancer agents.

Recently, a new skeletal type of acetogenins bearing a hydroxylated or an unsubstituted tetrahydropyran (THP) ring has been discovered (Figure 1).[4−6] Mucocin (**1**), which was isolated from the leaves of *Rollinia mucosa* (Jacq.) Baill. (Annonaceae) by McLaughlin et al., is the first annonaceous acetogenin to be reported that bears a THP ring along with a THF ring.[7] This novel type of acetogenin was found to be quite active in the BST assay[8] (IC_{50} 1.3 μg/mL) and showed remarkable inhibitory activities against A-549 (lung cancer) and PACA-2 (pancreatic cancer) solid tumor lines with a potency of more than 10000 times that of adriamycin. The powerful antitumor activity and the unique structure of **1** have consequently made it an attractive target similar to other classical THF acetogenins[9] for synthetic chemists.[10] Here, we describe the stereocontrolled total synthesis of **1** utilizing the "chiron" approach[11] which involved a highly stereoselective addition of organometallic reagents to sugar-

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10.1021/jo020211h CCC: $22.00
Published on Web 07/09/2002

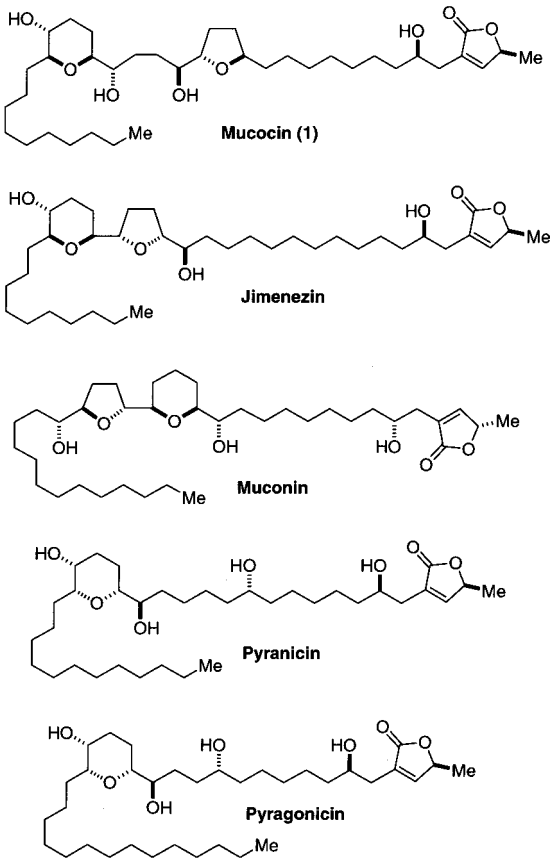


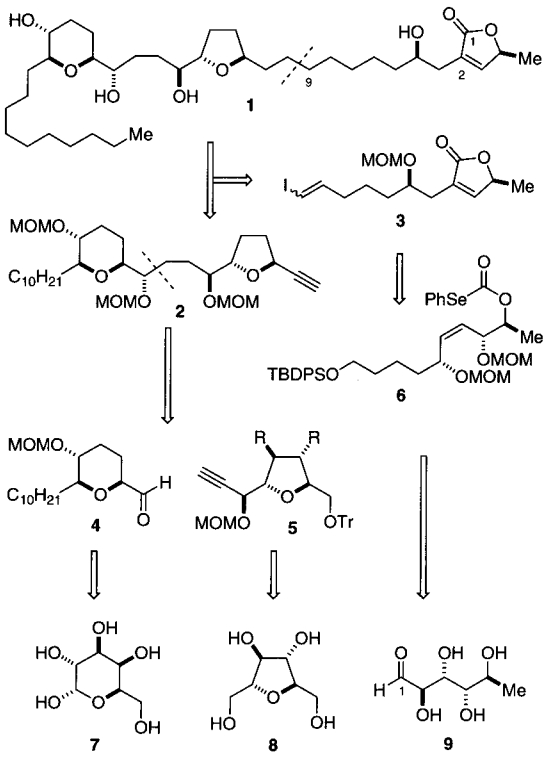
FIGURE 1.

derived carbonyl compounds.[12] In contrast to our substrate control approach, Keinan and Sinha et al.[13] and Koert et al.[14] disclosed total synthesis of **1** based on the reagent control.

Results and Discussion

Our synthetic strategy directed toward **1** was based on a convergent process which involves a Pd-catalyzed cross-coupling reaction of the THP−THF segment **2** and vinyl iodide **3** as illustrated in Scheme 1. The central core **2** can be further disconnected to THP aldehyde **4** and ethynyl THF **5**. Each compound would be synthesized from D-galactose (**7**) and 2,5-anhydro-D-mannitol (**8**), respectively. On the other hand, the C_1-C_2 bond cleavage of γ-lactone **3** leads to olefin **6**, which might be obtained via stereoselective alkylation at the C-1 position of L-rhamnose (**9**). The "chiron" approach starting from

SCHEME 1



three types of carbohydrates (**7**−**9**) was expected to be quite useful for synthesizing **1** in enantiometrically pure form.

Synthesis of the THP Fragment (4). A characteristic structural feature of **1** should be the presence of the 3-hydroxy-2,6-cis THP ring system with a long side chain at the C-2 position. For construction of such a ring system, we planned to utilize a *C*-glycosidation method[15] on a glycopyranolactone developed by Kishi et al. 2,3,4-Tri-*O*-benzyl-D-galactopyranose **10**[16] was silylated [1.0 equiv of chloro *tert*-butyldiphenylsilane (TBDPSCl), imidazole, DMF], and the resulting hemiacetal **11** was oxidized under Swern's conditions (DMSO, $(COCl)_2$, CH_2Cl_2, −70 °C then Et_3N, −70 to 0 °C) to give lactone **12a** in good yield (Scheme 2). Reaction of **12a** with decylmagnesium bromide in ether at −78 °C followed by reduction with triethylsilane in the presence of $BF_3 \cdot Et_2O$ proceeded stereoselectively, giving *C*-glycoside **13a** in 82% yield. In the ^1H NMR spectra of **13a**, the signal corresponding to the proton of H-2 was observed at 3.18 ppm as triplets of doublet ($J_{2,3}$ = 8.8 Hz). The large coupling constant value of this proton indicates the compound having 2,6-cis substituents on a six-membered ring. In this reaction the corresponding α-isomer could not be isolated. The high β-stereoselectivity would be explained by axial attack of hydride to the intermediary oxonium ion (Figure 2).[15] Debenzylation of **13a** with 10% Pd/C under a hydrogen atmosphere was accompanied by a little desilylation and provided the desired triol **15** in 52% yield along with tetraol **14** (36%). The latter was converted into the former by resilylation. As loss of the TBDPS group

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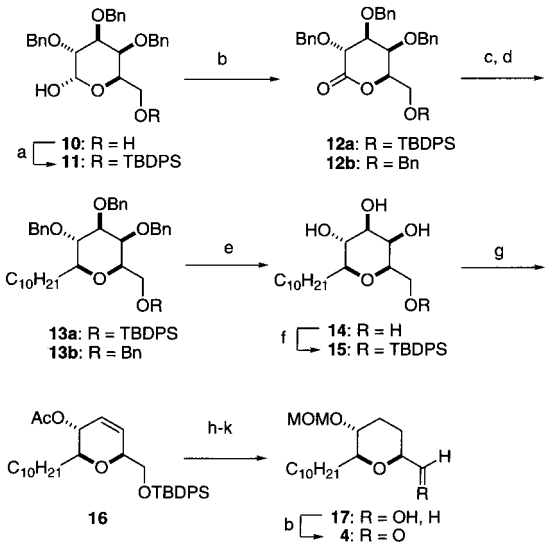
SCHEME 2[a]



[a] Reagents and conditions: (a) TBDPSCl (1.3 equiv), imidazole, DMF, rt, 89%; (b) $(COCl)_2$, DMSO, CH_2Cl_2, −70 °C and then Et_3N, −70 to 0 °C, quant.; (c) decylmagnesium bromide, Et_2O, −78 °C; (d) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −40 to −20 °C, 82% for **13a**, 80% for **13b**; (e) 10% Pd/C, H_2, EtOAc−MeOH, rt, 52% for **15** and 36% for **14** from **13a**; (f) TBDPSCl (1.0 equiv), imidazole, DMF, rt, 85% in two steps from **13b**; (g) $HC(OMe)_3$, CSA, CH_2Cl_2, rt, and then Ac_2O, 135 °C, 66%; (h) 10% Pd/C, H_2, EtOAc, rt; (i) NaOMe, MeOH, rt; (j) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to room temperature; (k) TBAF, THF, rt, 93% from **16** in four steps.

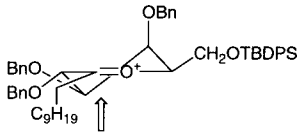
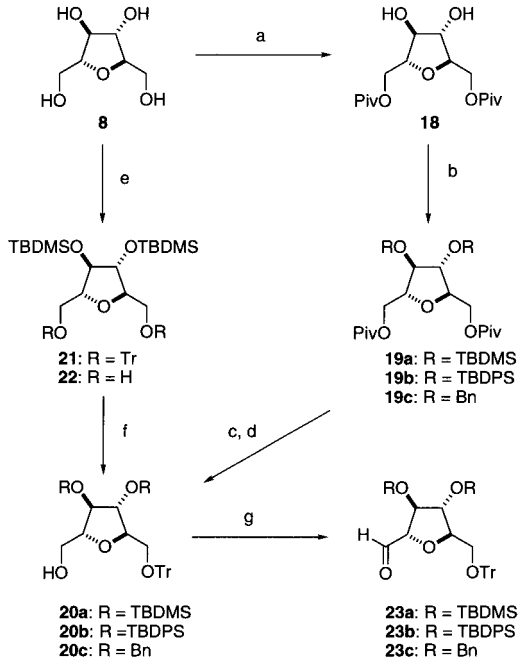


FIGURE 2.

was found to be not suitable for large-scale preparation of **15**, a more practical route starting from the benzyl analogue **12b**[17] was developed. As expected, *C*-glycosidation of **12b** under the same conditions also gave only the *β*-isomer **13b** in 80% yield. Hydrogenation and silylation of **13b** provided **15** in 85% yield. Regioselective deoxygenation of **15** was achieved by Ando's protocol.[18] Thus, **15** was treated with trimethyl orthoformate in the presence of *d*-camphorsulfonic acid, and the resulting ortho esters were, without purification, heated in acetic anhydride at 135 °C, giving allyl acetate **16** in 66% yield. This compound was converted into alcohol **17** in 93% overall yield by the following sequence: (1) hydrogenation of a double bond, (2) deacetylation with sodium methoxide, (3) methoxymethylation with methoxymethyl (MOM) chloride and *N*,*N*-diisopropylethylamine, (4) desilylation with tetrabutylammonium fluoride (TBAF). Swern oxidation of **17** gave the building block **4** in almost quantitative yield.

Synthesis of the THF Fragment (5a). The central core of **1** consists of a *threo-trans*-THF ring system. Our synthetic approach to the core system included stereo-

SCHEME 3[a]



[a] Reagents and conditions: (a) PivCl, pyridine, 0 °C to room temperature; (b) TBDMSCl, imidazole, DMF, rt, 69% from **8** for **19a**; TBDPSOTf, 2,6-lutidine, CH_2Cl_2, rt, 64% from **8** for **19b**; BnBr, NaH, *n*-Bu_4NI, DMF, 0 °C, 39% from **8** for **19c**; (c) LAH, Et_2O, 0 °C, 71% for **22**; (d) TrCl (1.1 equiv), 2,6-di-*tert*-butyl-4-methylpyridine or 2,6-lutidine, CH_2Cl_2, −20 °C to room temperature, 51−68% based on the SM consumed; (e) TrCl, pyridine, rt, and then TBDMSCl, imidazole, rt, 92%; (f) Et_2AlCl (2.3 equiv), hexane, −78 to 0 °C, 83%; (g) $(COCl)_2$, DMSO, CH_2Cl_2, −70 °C and then Et_3N, −70 to 0 °C, quant.

controlled elongation by a two-carbon unit at the side chain of the 2-formyl-5-(1-trityloxymethyl)THF derivative **23** as a key step.[19] The compound was prepared from a commercially available 2,5-anhydro-D-mannitol (**8**) through a unique desymmetrization as shown in Scheme 3. Compound **8** was treated with pivaloyl chloride (2.1 mol equiv) in pyridine, and the resulting diol **18** was subjected to silylation [chloro *tert*-butyldimethylsilane (TBDMSCl), imidazole, DMF] to afford fully protected compound **19a** in 69% yield. We expected the bulky silyl protecting groups introduced at the oxygen functions would prevent unfavorable chelation of C-3, -4 oxygen moieties with a metal in the stereocontrolled ethynylation.[21] Upon treatment with lithium aluminum hydride (LAH), **19a** gave diol **22** in 71% yield. Monotritylation of **22** was achieved with trityl chloride (1.1 mol equiv) in the presence of 2,6-

(17) This compound was prepared from a commercially available methyl α-D-galactopyranoside in three steps with 55% overall yield, see ref 15.

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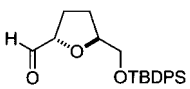
(19) Reaction of **5b**[20] with lithium trimethylsilylacetylide or ethynylmagnesium chloride in ethereal solvent resulted in a 1:1 to 1:3 mixture of the corresponding ethynyl alcohols. The selectivity was not improved even if in the presence of additives such as zinc, copper, and lithium salt. Recently, the paper has appeared dealing with the similar results.[9c] On the other hand, Koert et al. reported that reaction of **5b** with alkyl Grignard reagents in the presence of CuBr gave α-chelation-controlled products in high diastereoselectivity (∼90% de).[20]



5b

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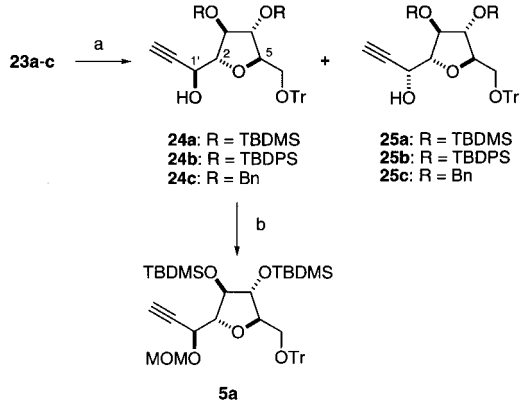
TABLE 1. Nucleophilic Addition to the Aldehydes 23a−c

entry	compd	conditions[a]	ratio (**24**/**25**)	yield (%)
1	**23a**	HC≡CMgCl, THF−Et_2O, 0 °C	78/22	72
2	**23a**	HC≡CMgCl, $ZnCl_2$, CH_2Cl_2−Et_2O−THF, −78 °C	93/7	70
3	**23a**	HC≡CMgCl, $ZnCl_2$, Et_2O−THF, −78 °C	89/11	63
4	**23a**	TMSC≡CLi, THF, 0 °C	66/34	47[b]
5	**23b**	HC≡CMgCl, THF−Et_2O, 0 °C	36/64	69
6	**23b**	HC≡CMgCl, $ZnCl_2$, Et_2O−THF, −78 °C	58/42	47
7	**23b**	TMSC≡CLi, THF, 0 °C	29/71	53[b]
8	**23c**	HC≡CMgCl, THF−Et_2O, 0 °C	25/75	83
9	**23c**	HC≡CMgCl, $ZnCl_2$, Et_2O−THF, −78 °C	66/34	40
10	**23c**	TMSC≡CLi, THF, 0 °C	42/58	70[b]

[a] 6.0−10 mol equiv of organometallic reagent and $ZnCl_2$ (3.0 mol equiv) were employed. [b] After workup, the crude product was treated with K_2CO_3 in methanol before purification.

lutidine or 2,6-di-*tert*-butyl-4-methylpyridine to furnish monotrityl alcohol **20a** (68%, based upon **22** consumed). In contrast to the monotritylation, selective detritylation gave a quite promising result as follows. Successive treatment of **8** with trityl chloride and TBDMSCl in one-pot manner gave fully protected THF **21** in 92% yield. Deprotection of **21** using diethylaluminum chloride[22] (2.3 mol equiv) in hexane at −78 to 0 °C proceeded cleanly, giving **20a** in 83% yield. Production of the corresponding diol **22** was revealed to be a trace amount by judging TLC analyses. It should be noted that this reaction is strongly solvent dependent. For example, deprotection reaction in CH_2Cl_2 resulted in a mixture of **20a** and **22**. Precipitation of the monoaluminum alkoxide complex derived from **21** may cause the selectivity. In this way, desymmetrization of **8** was efficiently established [75% yield from **8** via **21** (2 steps) vs 35% yield in four steps for the previous route]. The alcohol **20a** was transformed into aldehyde **23a** using the Swern oxidation in a quantitative yield. To examine the effect of hydroxy protecting groups in the ethynylation, the TBDPS and benzyl analogues **23b** and **23c** were also prepared through **19b**,**c** and **20b**,**c** from **8** in the same way.

SCHEME 4[a]



[a] Reagents and conditions: (a) See Table 1; (b) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to room temperature, 90%.

Having three types of aldehyde **23a**−**c**, we investigated stereoselective ethynylation (Scheme 4). As shown in Table 1, the ratio of produced Cram and anti-Cram compounds varied in a wide range depending on the kind of the protecting group and the reagent employed, whereas chemical yields were in a narrow range in all entries and moderately good. The best result was obtained by using **23a** and ethynylmagnesium chloride in the presence of $ZnCl_2$ in dichloromethane−ether−THF to give a 93:7 mixture of the desired *β*-alcohol **24a** and its epimer **25a** in 70% yield. These isomers could be easily separated by chromatography on silica gel, and their stereochemistry was determined by the modified Mosher's method[23] of the corresponding MTPA esters.[24] The stereoselective formation of compound **24a** (entry 2,3) would be explained by the formation of cyclic chelate involving the aldehyde carbonyl and the ring oxygen as shown in Figure 3A.[25] On the other hand, addition of $ZnCl_2$ did not improve the selectivity in the case of **23b**,**c** (entries 6 and 9). Therefore, we estimated that the addition to **23b** or **23c** (entry 5,7,8, and 10) proceeded in accordance with Cram's rule through a transition state corresponding to the Felkin−Anh model (Figure 3B)[26] rather than the chelate-controlled addition. However, the possibility of competing *β*-chelation also cannot be ruled out as several examples were reported in the literature.[27]

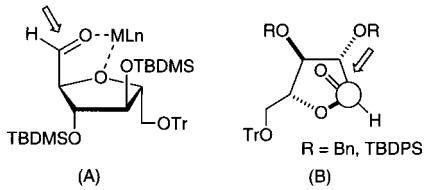


FIGURE 3.

The alcohol **24a** thus obtained was converted into the corresponding MOM ether **5a**[28] and employed to the next coupling reaction.

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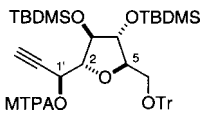
(24) Differences in the chemical shifts (Δ_{S-R} values in δ (500 MHz, $CDCl_3$)) between (*R*)- and (*S*)-MTPA esters of **24a** are as follows; H-2 (+0.06), H-3 (+0.01), H-4 (−0.01), H-5 (+0.02), H-1′ (−0.07), H-3′ (−0.07), H_2-1″ (+0.06, +0.02). In addition, the stereochemistry of **24b**,**c** and **25b**,**c** was determined by the correlation with **24a**,**25a** and **5a**.



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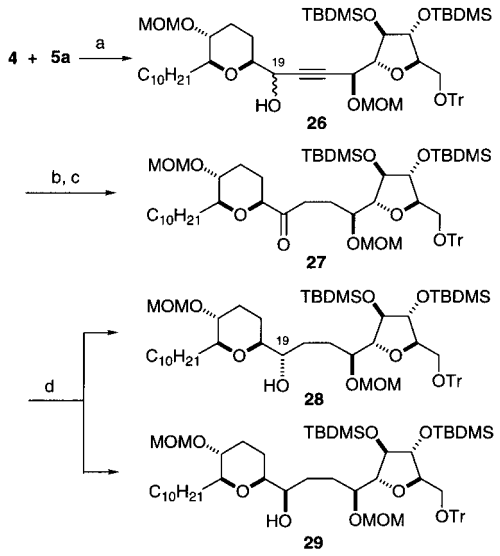
(27) For example, Izumi, M.; Tsuruta, O.; Hashimoto, H. *Carbohydr. Res.* **1996**, *280*, 287- 302. Giuliano, R. M.; Villani, F. J., Jr.; *J. Org. Chem.* **1995**, *60*, 202−211.

(28) When **24a** was employed to the coupling reaction with **4**, the silyl migration occurred.

Synthesis of the $C_{10}-C_{34}$ Segment (2). As we could secure two components (**4** and **5a**) needed for synthesis of **2**, the condensation reaction was examined (Scheme 5). Initial attempts to react **4** with a lithium or magnesium reagent derived from **5a** resulted in low-moderate yield of the coupled product **26** as an inseparable mixture (Table 2). In contrast, addition of anhydrous $CeCl_3$[29] to the solution of the lithium acetylide prior to addition of **4** gave **26** in good yield (78%). ^{1}H NMR analyses,[23] however, revealed that the major isomer was an undesired β-alcohol (86% de).[30] In these cases, it would be reasonable to assume a transition state as shown in Figure 4. After further experimentation, the corresponding saturated isomers (**28** and **29**) obtained after hydrogenation were found to be readily separated by column chromatography on silica gel. Furthermore, highly stereoselective production of compound **28** was realized by

SCHEME 5[a]



[a] Reagents and conditions: (a) See Table 2; (b) 5% PtO_2, H_2, EtOAc, rt; (c) TPAP, NMO, MS4A, CH_2Cl_2, rt, 97% from **26** in two steps; (d) L-Selectride, THF, −78 °C, 94% (**28**/**29** = 24/1).

TABLE 2. Coupling Reaction between 4 and 5a

entry	conditions[a]	ratio (α/β)[b]	yield (%)
1	*n*-BuLi, LiI, Et_2O, −78 °C	40/60	23
2	EtMgBr, Et_2O, −78 °C	25/75	66
3	*n*-BuLi, Et_2O, −12 to 0 °C	20/80	59
4	*n*-BuLi, $CeCl_3$, THF, −78 °C	7/93	78

[a] 1.6−2.0 mol equiv of organometallic reagent was employed. [b] The ratio was determined by ^{1}H NMR analyses (400 MHz).

using a simple two-step oxidation−reduction sequence of the mixture. Thus, the mixture of reduction products (**28**/**29** = ca. 7/93) was oxidized by *n*-tetrapropylammonium perruthenate in the presence of *N*-methylmorpholine *N*-oxide,[31] and then the corresponding ketone **27** was reduced with L-Selectride in THF at −78 °C to afford the desired α-alcohol **28** in high yield (88% from **26**) and its isomer **29** (3%).[32] This simple procedure made possible the efficient installation of the C-19 stereochemistry.

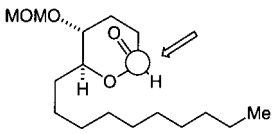
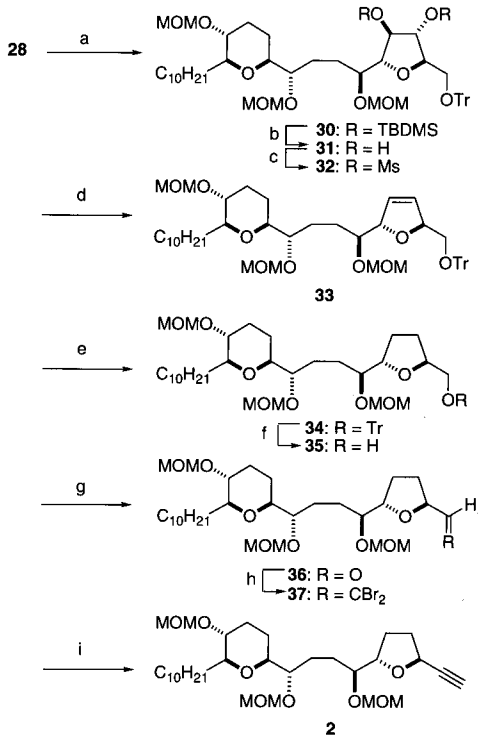


FIGURE 4.

Our attention was next turned to deoxygenation of the THF ring with two oxygen functionality, which could provide a clue for preparing novel analogues of **1**.[33] Prior to the deoxygenation, the 19-hydroxyl group in **28** was protected as MOM ether (Scheme 6). Cleavage of the silyl

SCHEME 6[a]

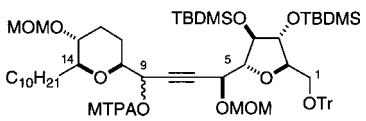


[a] Reagents and conditions: (a) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to room temperature; (b) TBAF, THF, rt, 92% from **28** in two steps; (c) MsCl, Et_3N, CH_2Cl_2, 0 °C to room temperature; (d) Zn, NaI, DMF, 140 °C; (e) 10% Pd/C, H_2, EtOAc, rt; (f) aq AcOH, 50 °C, 74% from **31** in four steps; (g) $(COCl)_2$, DMSO, CH_2Cl_2, −70 °C and then Et_3N, −70 to 0 °C, quant.; (h) Ph_3P, CBr_4, Et_3N, CH_2Cl_2, 0 °C, 78% from **35** in two steps; (i) EtMgBr (2.1 equiv), THF, −5 °C, 97%.

protecting groups in **30** with TBAF yielded diol **31** in 92% yield from **28**. Treatment of **31** with methanesulfonyl chloride−triethylamine afforded dimesylate **32**, which

(29) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233−4236. Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904−3912.

(30) Differences in the chemical shifts (Δ_{S-R} values of major isomer in δ (400 MHz, $CDCl_3$))between (*R*)- and (*S*)-MTPA esters of **26** are as follows; H_2-1 (+0.01, +0.02), H-2 (+0.00), H-3 (+0.02), H-4 (+0.02), H-5 (+0.03), H-6 (+0.01), H-9 (+0.01), H-10 (- 0.06), H_2-11 (−0.15, −0.06), H_2-12 (−0.02, −0.06), H-13 (−0.09), H-14 (−0.09), H_2-15 (−0.26, −0.05).



(31) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625−1627.

(32) Reduction of **27** with $Zn(BH_4)_2$ in ether at −10 °C gave **29** predominantly (**28**/**29** = 6/94, total 98% yield).

was subjected to a reductive elimination by using sodium iodide−zinc powder[34] in DMF at 130 °C to furnish olefin **33**. Hydrogenation followed by detritylation of **34** under acidic conditions produced alcohol **35** in 74% overall yield in four steps. After Swern oxidation of **35**, the resulting aldehyde **36** reacted with $(MeO)_2P(O)C(N_2)COCH_3$[35] in the presence of potassium carbonate to give terminal acetylene **2** in 63% yield. On the other hand, a two-step sequence[36] via dibromoolefin **37** afforded a somewhat higher overall yield (76% from **35**) than that in the foregoing procedure. Thus, **36** was treated with triphenylphosphine−carbon tetrabromide in the presence of triethtylamine to give **37** in 78% yield. The olefination in the absence of triethylamine resulted in a mixture of demethoxymethylated products. Upon treatment with 2.1 equiv of *n*-butyllithium, **37** led to **2** in 60% yield, while the use of ethylmagnesium bromide (2.1 equiv) as a base gave 97% yield of **2**.

Synthesis of the C_1−C_9 Segment (3). As a γ-hydroxy butenolide unit such as the right-half segment **3** is a key building block for synthesis of annonaceous acetogenins, several methods for the preparation of such subunit have been devised. However, the synthetic examples reported so far have mainly relied on aldol addition of γ-alkyloxy esters with a chiral aldehyde or alkylation with an optical active terminal epoxide or a chiral γ-lactone.[37] Our new synthetic approach to **3** was based on a radical cyclization[38] of acyclic selenocarbonate **6**.[39] Synthesis began with methanolysis of phenyl 5-*O*-acetyl-2,3-*O*-isopropylidene-1-thio-L-rhamnofuranoside **38**, which was synthesized from L-rhamnose (**9**) in three steps.[40] The 2,3-*O*-isopropylidene group was expected to function as not only a foothold for 1,2-asymmetric induction but also the equivalent of olefin needed in the later radical cyclization. After protection of the hydroxy group in **39** as a methoxyphenylmethyl (MPM) ether, the furanoside was treated with *N*-bromosuccinimide to afford **40** in 85% yield (Scheme 7). Stereoselective introduction of the C_4-side chain into **40** was examined under several conditions (Table 3). Reaction of **40** with the lithium reagent obtained from **41**[41] in ether gave the desired alcohol **43**[42] and its epimer **42** in 58 and 15% yield, respectively. Furthermore, the use of a mixed solvent system (hexane−ether = 3:1) was effective; 67% yield of **43** was attained along with **42** (11%). Addition of HMPA markedly improved the stereoselectivity (**42**/**43** = 6/94), but was not so practical due to the low yield (42%). On the other hand, reverse diastereofacial selectivity (**42**/**43** = 81/19) was observed when the corresponding magnesium derivative was employed. The minor alcohol **42** could be taken back to the desired isomer **43** in 72% overall yield by a two-step sequence (1. MnO_2 oxidation, 2. $NaBH_4$−$CeCl_3\cdot 7H_2O$). The difference in these stereoselectivities would be explained by two types of chelation as shown in Figure 5. According to this explanation, the use of more hindered alkyllithium was expected to increase the selectivity. However, reaction with the alkyllithium derived from **44**[43] gave a similar result (**45**/**46** = 18/82, 65% yield).[44]

TABLE 3. Nucleophilic Addition to the Hemiacetal 40

entry	conditions[a]	ratio {**42**(**45**)/**43**(**46**)}	yield (%)
1	**41**, *n*-BuLi, Et_2O, −78 °C to rt	20/80	73
2	**41**, *n*-BuLi, toluene, −78 °C to rt	33/67	66
3	**41**, *n*-BuLi, hexane−Et_2O (3:1), −78 °C to rt	14/86	78
4	**41**, *n*-BuLi, LiI, Et_2O, −78 °C to rt	29/71	79
5	**41**, *n*-BuLi, $MgBr_2$, Et_2O, −78 °C to rt	45/55	21
6	**41**, *n*-BuLi, $CeCl_3$, Et_2O−HMPA, −78 °C to rt	24/76	41
7	**41**, n-BuLi, Et_2O−HMPA, −78 °C to rt	6/94	42
8	**41**, EtMgBr, Et_2O, −78 °C to rt	81/19	79
9	**44**, hexane−Et_2O (5:4), −78 °C to rt	18/82	65

[a] 3.0−4.0 mol equiv of silyl ether and organometallic reagent (2.9−3.8 mol equiv) were employed.

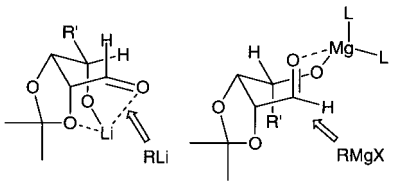


FIGURE 5.

For further transformation, the two hydroxy groups in **43** were protected as MOM ether (90%), and the resulting triple bond in **47** was hydrogenated over 5% Rh/Al_2O_3, giving **48** in 95% yield. Exposure of this to mild acidic conditions led to removal of the acetonide group, giving **49** in 73% yield along with triol **50** (23%). The latter was taken back to the former by monosilylation (89%). Deoxygenation of **49** via the corresponding ortho ester afforded *Z*-olefin **51** in 87% yield. After debenzylation of **51** with DDQ,[45] the resulting alcohol **52** was transformed into selenocarbonate **6** according to Corey's procedure[38] (1. $(CCl_3O)_2CO$,[46] pyridine; 2.PhSeH, Et_3N). Radical cycliza-

(33) Several THF acetogenins carrying a hydroxyl group on the THF ring have been recently isolated, see: (a) mucoxin;[4] (b) goniotriocin: Alali, F. Q.; Rogers, L.; Zhang, Y.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 31−34.

(34) Tipson, R. S.; Cohen, A.; *Carbohydr. Res.* **1965**, *1*, 338−340.

(35) Muller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521−522.

(36) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769−3772.

(37) For example, see: (a) Hoye, T. R.; Hanson, P. R. *Tetrahedron Lett.* **1993**, *34*, 5043−5046. (b) Yao, Z.-J.; Wu, Y.-L. *Tetrahedron Lett.* **1994**, *35*, 157−160. (c) Koert, U. *Tetrahedron Lett.* **1994**, *35*, 2517−2520. (d) Hoye, T. R.; Humpal, P. E.; Jimenez, J. I. Mayer, M. J.; Tan, L.; Ye, Z. *Tetrahedron Lett.* **1994**, *35*, 7517−7520. (e) Hanessian, S.; Grillo, T. A. *J. Org. Chem.* **1998**, *63*, 1049−1057. (f) Schaus, S. E.; Branalt, J.; Jacobsen, E. N.; *J. Org. Chem.* **1998**, *63*, 4876−4877, and references therein.

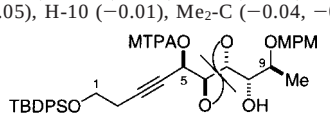
(38) Singh, A. K.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc.* **1987**, *109*, 6187−6189.

(39) A similar radical approach was also reported by Evans and Murthy; see ref 10c.

(40) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 2430−2434.

(41) Nicolaou, K. C.; Petasis, N. A.; Li, W. S.; Ladduwahetty, T.; Randall, J. L.; Webber, S. E.; Hernandez, P. E. *J. Org. Chem.* **1983**, *48*, 5400−5403.

(42) Differences in the chemical shifts (Δ_{S-R} values in δ (500 MHz, $CDCl_3$)) between (*R*)- and (*S*)-MTPA esters of **43** are as follows; H_2-1 (+0.05), H_2-2 (+0.04), H-5 (−0.03), H-6 (−0.10), H-7 (−0.14), H-8 (−0.17), H-9 (−0.05), H-10 (−0.01), Me_2-C (−0.04, −0.08).



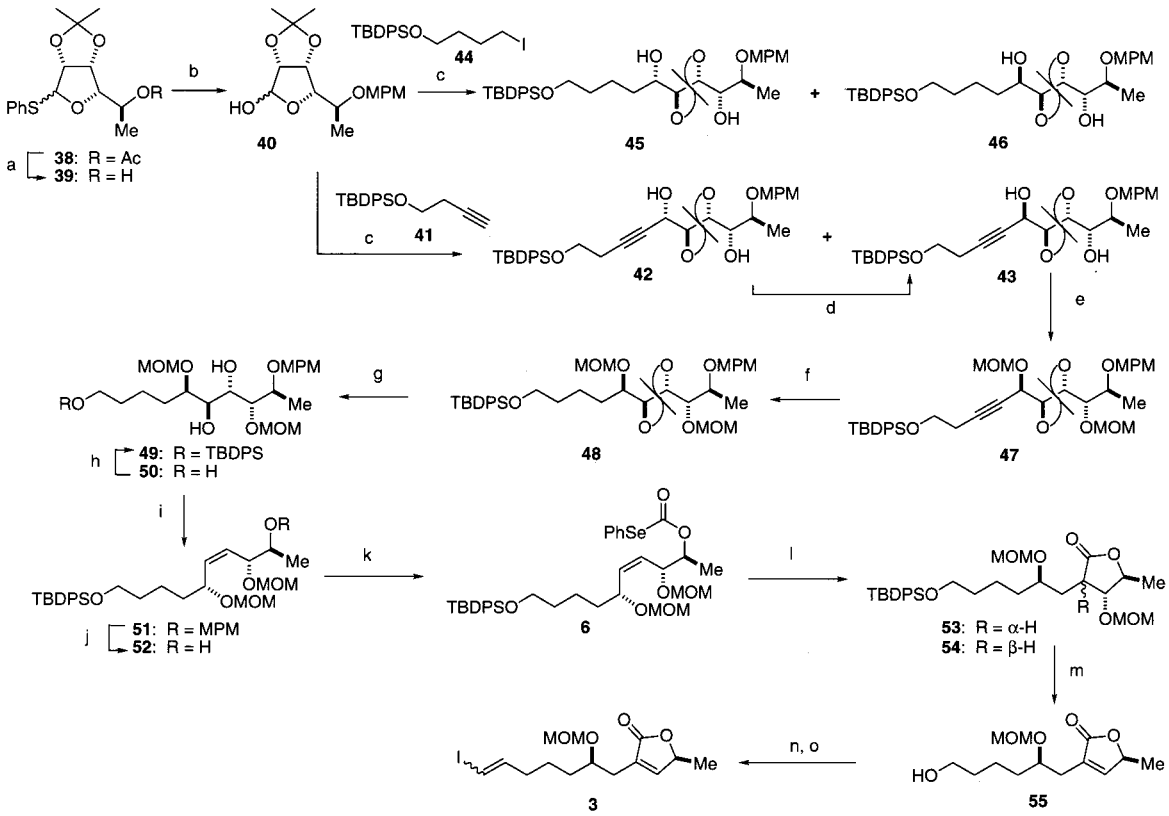
(43) McGarvey, G. J.; Stepanian, M. W. *Tetrahedron Lett.* **1996**, *37*, 5461−5464.

(44) The structure was determined by transformation of **46** into the corresponding MOM ether **48**.

(45) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885−888.

(46) Eckert, H.; Forster, B. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 894−895.

SCHEME 7[a]



[a] Reagents and conditions: (a) NaOMe, MeOH, rt, quant.; (b) MPMCl, NaH, *n*-Bu_4NI, DMF, 0 °C, and then *N*-bromosuccinimide, aq THF, 0 °C, 85% in two steps; (c) see Table 3; (d) MnO_2, CH_2Cl_2, rt, and then $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 72%; (e) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 90%; (f) 5% Rh/Al_2O_3, H_2, EtOAc, rt, 95%; (g) aq AcOH, rt, 73% for **49** and 23% for **50**; (h) TBDPSCl, imidazole, DMF, 0 °C, 89%; (i) $HC(OMe)_3$, CSA, CH_2Cl_2, rt, and then Ac_2O, 135 °C, 87% in two steps; (j) DDQ, aq CH_2Cl_2, 0 °C, 89%; (k) triphosgene, pyridine, CH_2Cl_2, 0 °C, and then PhSeH, Et_3N, 78% in two steps; (l) Bu_3SnH, AIBN, toluene, 100 °C, 86% for **53** and 4% for **54**; (m) TBAF, AcOH, THF, rt, and then DBU, CH_3CN, −10 °C, 60% in two steps; (n) $(COCl)_2$, DMSO, CH_2Cl_2, −70 °C and then Et_3N, −70 to 0 °C, 88%; (o) CHI_3, $CrCl_2$, THF, 0 °C to room temperature, 84%.

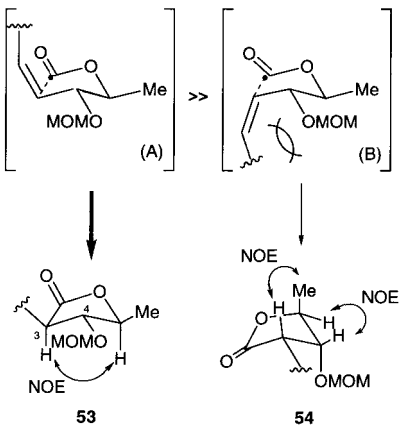


FIGURE 6.

tion of **6** with tributyltin hydride (Bu_3SnH) in toluene at 100 °C proceeded nicely to give 3,4-*trans*-γ-lactone **53** and 3,4-*cis*-isomer **54** in 86 and 3% yield, respectively. These relative stereochemistry were established by the NMR analyses together with the difference NOE experiments. The 3,4-*trans* stereoselection in the radical cyclization would result from reaction of the acyl radical through a transition state (A) rather than B because of an allylic strain[47] (Figure 6). Although both isomers could be a key intermediate for preparation of **3**, the major isomer **53** was employed to the next step. The TBDPS group in **53** was removed by TBAF in the presence of acetic acid, and then the resulting alcohol was treated briefly with DBU in acetonitrile at −10 °C, affording butenolide **55** in 60% yield from **53**. Partial epimerization at C-5 was observed when the elimination reaction was conducted in THF at room temperature. After Swern oxidation of **55**, the aldehyde was subjected to a vinyl iodide formation[48] with chromous chloride and iodoform, affording the right-half segment **3** as a 4.5:1 mixture of *E*/*Z* isomers in 74% yield.

Total Synthesis of Mucocin (1). The complete carbon skeleton of **1** was assembled by joining **2** and **3** in the presence of $(PPh_3)_2PdCl_2$ and CuI in triethylamine[49] to give a labile enyne **56** in 79% yield. This underwent regioselective reduction with Wilkinson's catalyst in benzene−ethanol to give fully protected mucocin **57** in 70% yield (Scheme 8). Finally, all of the MOM groups in **57** were cleaved by $BF_3 \cdot Et_2O$ in methyl sulfide[50] to give mucocin (**1**), whose spectral properties were indistinguishable from those of the natural product.

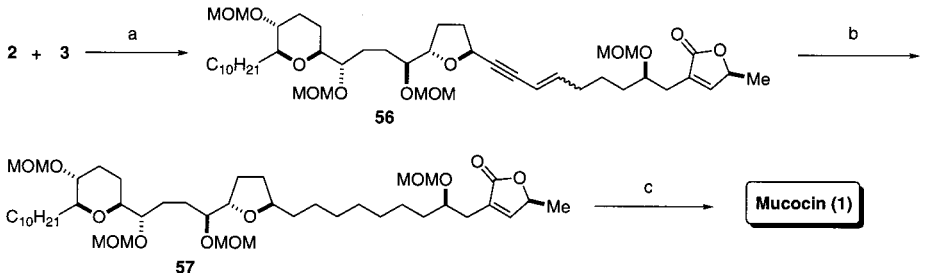
(47) Johnson, F.; Malhotra, S. K. *J. Am. Chem. Soc.* **1965**, *87*, 5492−5493. Malhotra, S. K.; Johnson, F. *J. Am. Chem. Soc.* **1965**, *87*, 5493−5495.

(48) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408−7410.

(49) Hoye, T. R.; Ye, Z. *J. Am. Chem. Soc.* **1996**, *118*, 1801−1802.

(50) Naito, H.; Kawahara, E.; Maruta, K.; Maeda, M.; Sasaki, S. *J. Org. Chem.* **1995**, *60*, 4419−4427.

SCHEME 8[a]



[a] Reagents and conditions: (a) $(Ph_3P)_2PdCl_2$, CuI, Et_3N, rt, 78%; (b) $(Ph_3P)_3RhCl$, H_2, benzene−EtOH (6:1), rt, 70%; (c) $BF_3{\cdot}Et_2O$, Me_2S, −10 to 0 °C, 77%.

In conclusion, total synthesis of mucocin (**1**) based on a substrate control was achieved in 30 steps with 3.4% overall yield from methyl α-D-galactopyranoside; the chiral centers C-20 (*S*) and C-23 (*R*) of **1** were derived from **7**, C-12 (*R*) and C-15 (*S*) from **8**, and C-36 (*S*) from **9**, respectively, while the stereochemistry at C-4 (*R*), C-16 (*S*), C-19 (*S*), and C-24 (*S*) were mainly constructed by a 1,2-asymmetric induction derived from the preexisting chirality in the substrate. The strategy described herein should be applicable to preparation of pharmacologicaliy important analogues of **1**.

Experimental Section

(2*R*,3*R*,4*S*,5*R*,6*S*)-3,4,5-Tribenzyloxy-2-(1-benzyloxymethyl)-6-decyltetrahydropyran (13b). To a stirred solution of **12b** (1.19 g, 2.21 mmol) in ether (21 mL) was added dropwise a solution of decylmagnesium bromide (1.0 M solution in ether, 2.65 mL) at −78 °C, and the mixture was stirred at the same temperature for 2.5 h. Saturated aqueous NH_4Cl was added at −78 °C with vigorously stirring, and then the resulting mixture was extracted with ether (20 mL × 2). The extracts were washed successively with water, brine, dried, and concentrated to give a syrup (1.60 g), which was dissolved in CH_2Cl_2 (27 mL). To the stirred solution was added dropwise $BF_3{\cdot}Et_2O$ (0.28 mL, 2.21 mmol) and triethylsilane (1.76 mL, 11.1 mL) at −40 °C, and then the mixture was stirred at −30 to −40 °C for 3.5 h. Saturated aqueous $NaHCO_3$ was added, and the resulting mixture was stirred at −30 °C → rt for 1 h, extracted with CH_2Cl_2 (30 mL × 2). The extracts were washed with water, brine, dried, and concentrated. Chromatography on silica gel with hexane−ether (8:1) as the eluent yielded **13b** (1.17 g, 80%): $[\alpha]^{27}_D$ −5.9° (*c* 0.36, $CHCl_3$); IR (neat) 3064, 3031, 2924, 1454, 1117, 1101, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* = 6.8 Hz), 1.22−1.38 (15H, m), 1.46−1.63 (2H, m), 1.87 (1H, m), 3.23 (1H, ddd, *J* = 8.8, 8.8, 2.4 Hz), 3.54 (1H, t, *J* = 6.4 Hz), 3.58−3.64 (3H, m), 3.70 (1H, t, *J* = 9.3 Hz), 4.01 (1H, brd, *J* = 2.4 Hz), 4.46, 4.52 (2H, each d, *J* = 11.7 Hz), 4.68, 4.98 (2H, each d, *J* = 11.7 Hz), 4.71, 4.79 (2H, each d, *J* = 11.7 Hz), 7.29−7.53 (20H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 25.7, 29.3, 29.6, 31.9, 69.1, 72.2, 73.5, 73.7, 74.4, 75.5, 77.3, 79.3, 79.8, 84.9, 127.5, 127.6, 127.7, 127.8, 128.1, 128.2, 128.3, 128.4, 138.0, 138.4, 138.5, 138.8. Anal. Found: C, 79.40; H, 8.77. Calcd for $C_{44}H_{56}O_5$: C, 79.48; H, 8.49.

(2*R*,3*R*,4*S*,5*R*,6*S*)-2-Hydroxymethyl-3,4,5-trihydroxy-6-decyltetrahydropyran (14). A mixture of **13b** (15.0 g, 22.6 mmol) and 10% Pd/C (1.25 g) in methanol-ethyl acetate (1:1, 70 mL) was vigorously stirred at room temperature for 4 d under hydrogen atmosphere, filtered through a pad of Celite. The Celite pad was washed thoroughly with methanol. The filtrate and washings were combined, concentrated, and then coevaporated with toluene−pyridine to give **14** (6.75 g), which was employed to the next step without further purification. Analytical sample was prepared by chromatography on silica gel with $CHCl_3$−MeOH (10:1) as the eluent.

14: $[\alpha]^{27}_D$ −0.72° (*c* 0.14, MeOH); IR (KBr) 3400, 3332, 2918, 2850, 1093, 1080, 1046, 989 cm^{-1}; ^1H NMR (400 MHz, MeOH-d_4) δ 0.89 (3H, t, *J* = 6.8 Hz), 1.03−1.45 (16H, m), 1.58 (1H, m), 1.83 (1H, m), 3.04 (1H, brt, *J* = 8.8 Hz), 3.32−3.43 (3H, m), 3.65 (1H, dd, *J* = 12, 5.9 Hz), 3.69(1H, dd, *J* = 12, 6.8 Hz), 3.85 (1H, brd, *J* = 2.0 Hz); ^{13}C NMR (100 MHz, MeOH-d_4) δ 14.4, 23.7, 26.6, 30.4, 30.7, 30.8, 32.8, 33.0, 62.7, 70.8, 72.8, 76.5, 80.1, 81.5. Anal. Found: C, 62.91; H, 10.44. Calcd for $C_{16}H_{32}O_5$: C, 63.13; H, 10.60.

(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(1-*tert*-Butyldiphenylsilyl)oxymethyl-3,4,5-trihydroxy-6-decyltetrahydropyran (15). To a stirred solution of **14** (6.75 g) and imidazole (4.53 g, 66.6 mmol) in DMF (100 mL) was added chloro *tert*-butyldiphenylsilane (5.77 mL, 22.2 mmol), and then the mixture was stirred at room temperature for 18 h. After addition of ice−water, the resulting mixture was directly concentrated, diluted with CH_2Cl_2 (100 mL), washed successively with water, cold dil HCl solution, sat. $NaHCO_3$ solution, water, and brine, dried, and concentrated. Chromatography on silica gel with toluene−ethyl acetate (1:1) and then $CHCl_3$−MeOH (20:1) as the eluent yielded **15** (10.4 g, 85% in 2 steps): $[\alpha]^{27}_D$ −0.58° (*c* 1.72, $CHCl_3$); IR (neat) 3400, 3080, 2930, 1430, 1118, 1080, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 6.8 Hz), 1.06 (9H, s), 1.21−1.40 (15H,m), 1.42−1.62 (2H, m), 1.81−1.91 (1H, m), 3.10 (1H, td, *J* = 8.8, 8.8, 2.0 Hz), 3.43 (1H, brt, *J* = 5.2 Hz), 3.47 (1H, dd, *J* = 9.3, 2.9 Hz), 3.52 (1H, dd, *J* = 9.3, 8.7 Hz), 3.40−3.75 (2H, brs), 3.85−3.95 (2H, m), 4.08 (1H, brd, *J* = 2.5 Hz), 4.16−4.38 (1H, brs), 7.36−7.43 (6H, m), 7.69−7.73 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.1, 22.7, 25.6, 26.8, 29.3, 29.6, 29.7, 29.8, 31.9, 64.1, 70.4, 72.0, 75.8, 77.5, 79.9, 127.7, 129.8, 132.9, 133.1, 135.5, 135.6; HRMS calcd for $C_{32}H_{51}O_5Si$ $[M + H]^+$ 543.3506, found 543.3512. Anal. Found: C, 70.76; H, 9.56. Calcd for $C_{32}H_{50}O_5Si$: C, 70.80; H, 9.28.

(2*S*,5*R*,6*S*)-2-(1-*tert*-Butyldiphenylsilyl)oxymethyl-5-acetoxy-6-decyl-3,4-dihydropyran (16). To a stirred mixture of **15** (129 mg, 0.24 mmol) and trimethyl orthoformate (0.26 mL, 2.38 mmol) in CH_2Cl_2 (1.0 mL) was added *d*-camphorsulfonic acid (3.1 mg, 0.01 mmol). The mixture was stirred at room temperature for 3 h, and then diluted with ether (10 mL), washed with sat. $NaHCO_3$ solution, water, brine, dried, and concentrated to give a 4:1 mixture of the corresponding ortho esters (151 mg): ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 6.8 Hz), 1.06 (9H, s), 1.21−1.43 (16H, m), 1.58 (1H, m), 1.77 (1H, m), 2.15 (0.8H, d, *J* = 3.9 Hz), 2.21 (0.2H, d, *J* = 3.9 Hz), 3.03 (0.2H, m), 3.05 (0.8H, ddd, *J* = 9.3, 8.8, 2.4 Hz), 3.30−3.35 (1H, m), 3.33 (2.4H, s), 3.38 (0.6H, s), 3.72 (0.2H, ddd, *J* = 6.9, 6.3, 2.0 Hz), 3.79 (0.8H, ddd, *J* = 7.4, 6.8, 2.0 Hz), 3.85−3.93 (2H, m), 4.01 (0.2H, dd, *J* = 7.4, 5.4 Hz), 4.19 (0.8H, dd, *J* = 7.4, 5.4 Hz), 4.22 (0.2H, dd, *J* = 5.8, 2.0 Hz), 4.38 (0.8H, dd, *J* = 5.3, 2.0 Hz), 5.73 (0.2H, s), 5.80 (0.8H, s), 5.94 (1H, dt, *J* = 10, 1.5, 1.5 Hz), 7.35−7.42 (6H, m), 7.67−7.70 (4H, m), which was heated in acetic anhydride (1.5 mL) at 130 °C with stirring for 7 h, concentered and coevaporated with xylene (× 5). Chromatography on silica gel

with hexane−ethyl acetate (10:1) as the eluent yielded **16** (86.1 mg, 66%): $[\alpha]^{26}_D$ −90.2° (*c* 0.26, $CHCl_3$); IR (neat) 3075, 2930, 1743, 1428, 1235, 1118, 1030, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 6.8 Hz), 1.06 (9H, s), 1.21−1.34 (16H, m), 1.43 (1H, m), 1.57 (1H, m), 2.08 (3H, s), 3.43 (1H, ddd, J = 8.7, 8.7, 2.2 Hz), 3.60 (1H, dd, J = 10, 6.3 Hz), 3.73 (1H, dd, J = 10, 5.9 Hz), 4.22 (1H, m), 5.09 (1H, m), 5.74 (1H, ddd, J = 10, 2.0, 2.0 Hz), 5.94 (1H, dt, J = 10, 1.5, 1.5 Hz), 7.35−7.42 (6H, m), 7.67−7.70 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.3, 21.2, 22.7, 25.2, 26.8, 29.3, 29.6, 31.9, 32.5, 66.3, 69.8, 75.6, 75.8, 119.4, 126.5, 127.6, 129.6, 130.6, 133.5, 133.6, 134.3, 135.6, 170.6. Anal. Found: C, 74.15; H, 9.23. Calcd for $C_{34}H_{50}O_4Si$: C, 74.13; H, 9.15.

(2*S*,5*R*,6*S*)-2-Hydroxymethyl-5-methoxymethyloxy-6-decyltetrahydropyran (17). A mixture of **16** (6.84 g, 12.4 mmol) and 10% Pd/C (0.67 g) in ethyl acetate−methanol (2:1, 30 mL) was vigorously stirred at room temperature for 8 h under hydrogen atmosphere and filtered through a pad of Celite. The Celite pad was washed thoroughly with ethyl acetate. The filtrate and washings were combined, concentrated, and coevaporated with toluene to give a syrup (7.30 g), which was dissolved in methanol−CH_2Cl_2 (1:1, 50 mL). Sodium methoxide (0.13 g, 2.4 mmol) was added to the solution, and the mixture was stirred at room temperature for 4 d, made neutral with Dowex 50W X-8 (H^+) resin. The mixture was filtered and the filtrate evaporated, coevaporated with toluene to give a syrup (7.02 g), which was dissolved in CH_2Cl_2 (85 mL). To this solution were added *N*,*N*-diisopropylethylamine (17.3 mL, 99.3 mmol) and chloromethyl methyl ether (4.72 mL, 62.1 mmol) at 0 °C, and then the mixture was stirred at 0 °C to rt for 2 d. After addition of ice−water, the resulting mixture was extracted with ether (30 mL × 2). The extracts were washed successively with water, cold dil HCl solution, sat. $NaHCO_3$ solution, water and brine, dried, and concentrated to give a syrup (7.03 g). To a stirred solution of the syrup (7.03 g) in THF (40 mL) was added dropwise 1.0 M solution of TBAF in THF (14 mL, 14 mmol) at room temperature, and the mixture was stirred at room temperature for 18 h, concentrated. The residue was diluted with CH_2Cl_2. The solution was washed with water, brine, dried, and concentrated. The residue was purified by chromatography on silica gel with hexane−ethyl acetate (10:1→4:1) as the eluent to yield **17** (3.64 g, 93% from **16**): $[\alpha]^{26}_D$ −42.3° (*c* 2.23, $CHCl_3$); IR (neat) 3450, 2930, 1430, 1110, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 6.8 Hz), 1.19−1.63 (23H, m), 1.82 (1H, m), 2.02 (1H, dd, J = 8.5, 3.9 Hz), 2.22 (1H, m), 3.17 (1H, ddd, J = 8.8, 8.8, 2.3 Hz), 3.22 (1H, ddd, J = 9.3, 9.3, 3.9 Hz), 3.37 (3H, s), 3.43 (1H, m), 3.49 (1H, m), 3.58 (1H, m), 4.60, 4.72 (2H, each d, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 25.4, 26.6, 29.3, 29.6, 29.7, 29.8, 31.9, 32.1, 55.6, 65.8, 75.8, 80.4, 95.4. Anal. Found: C, 67.99; H, 11.59. Calcd for $C_{18}H_{36}O_4$: C, 68.31; H, 11.47.

(2*S*,5*R*,6*S*)-2-Formyl-5-methoxymethyloxy-6-decyltetrahydropyran (4). To a stirred solution of oxalyl chloride (0.07 mL, 0.79 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise a solution of DMSO (0.12 mL, 1.58 mmol) in CH_2Cl_2 (0.5 mL) at −70 °C under Ar, and the mixture was stirred for 25 min at −70 °C. At −70 °C, a solution of **17** (50.0 mg, 0.16 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise, and the mixture was stirred at the same temperature for 30 min. Triethylamine (0.33 mL, 2.37 mmol) was added, and the resulting mixture was gradually warmed to 0 °C with stirring and poured into ice−water. The mixture was extracted with ether (15 mL × 2). The extracts were washed with cold HCl solution, sat. $NaHCO_3$ solution, water and brine, dried, and concentrated to give **4** (49.6 mg, quantitative), which was employed to the next step without further purification. $[\alpha]^{27}_D$ −79.8° (*c* 0.38, $CHCl_3$); IR (neat) 2940, 1742, 1470, 1110, 1043, 922 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 6.8 Hz), 1.22−1.40 (17H, m), 1.41−1.58 (2H, m), 1.82−1.96 (2H, m), 2.26−2.34 (1H, m), 3.22 (1H, ddd, J = 8.8, 8.8, 2.4 Hz), 3.24 (1H, ddd, J = 9.4, 9.4, 4.4 Hz), 3.37 (3H, s), 3.74 (1H, dd, J = 11.2, 2.4 Hz), 4.61, 4.72 (2H, each d, J = 6.8 Hz), 9.63 (1H, brs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 25.2, 25.7, 29.3, 29.5, 29.6, 29.7, 31.8, 31.9, 55.6, 75.0, 80.7, 81.0, 95.4, 201.7; HRMS calcd for $C_{18}H_{35}O_4$ $[M + H]^+$ 315.2535, found 315.2519.

(2*R*,3*R*,4*R*,5*R*)-3,4-Di-*tert*-butyldimethylsilyloxy-2,5-di-(1-trityloxymethyl)tetrahydrofuran (21). To a stirred solution of **8** (1.64 g, 10.0 mmol) in pyridine (12 mL) was added chloro triphenylmethane (5.85 g, 21 mmol) at room temperature, and then the mixture was stirred rt for 5 h. More chloro triphenylmethane (0.59 g, 2.1 mmol) was added, and stirring was continued for 3 h. The reaction mixture was diluted with pyridine (12 mL). To this solution was added chloro *tert*-butyldimethylsilane (6.78 g, 45 mmol) and imidazole (4.08 g, 60 mmol) at room temperature, and then the mixture was stirred at rt for 3 h. After addition of ice−water, the mixture was extracted with ether (30 mL × 3). The extracts were washed successively with water, cold dil HCl solution, sat. $NaHCO_3$ solution, water and brine, dried, and concentrated. Chromatography on silica gel with hexane−ethyl acetate (40:1) as the eluent yielded **21** (8.11 g, 92%); $[\alpha]^{23}_D$ +1.8° (*c* 0.56, $CHCl_3$); IR (neat) 3060, 3033, 3023, 2929, 1597, 1491, 1471, 1448, 1251, 1088, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.08 (3H, s), −0.04 (3H, s), 0.72 (9H, s), 3.15 (1H, dd, J = 9.3, 5.8 Hz), 3.33 (1H, dd, J = 9.3, 6.3 Hz), 4.01 (1H, brs), 4.13 (1H, brt, J = 6.0 Hz), 7.20−7.28 (8H, m), 7.46−7.48 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, 17.7, 25.7, 64.8, 80.6, 86.0, 86.7, 126.9, 127.7, 128.9, 144.1. Anal. Found: C, 76.50; H, 7.91. Calcd for $C_{56}H_{68}O_5Si_2$: C, 76.67; H, 7.81.

(2*R*,3*R*,4*R*,5*R*)-3,4-Di-*tert*-butyldimethylsilyloxy-5-(hydroxymethyl)-2-(1-trityloxymethyl) tetrahydrofuran (20a) from 21. To a stirred solution of **21** (268 mg, 0.31 mmol) in hexane (4 mL) was added dropwise a solution of diethylaluminum chloride (0.7 mL, 1.0 M solution in hexane) at −78 °C, and then the yellow color suspension was stirred at −78 °C for 1 h and −78 → 0 °C for 3 h. After addition of sat. $NaHCO_3$ solution at 0 °C, the resulting mixture was stirred vigorously at 0 °C for 1 h and then extracted with dichloromethane (10 mL × 2). The extracts were washed successively with water and brine, dried, and concentrated. Chromatography on silica gel with hexane−ethyl acetate (6:1 → 4:1) as the eluent yielded **20a** (160 mg, 83%): $[\alpha]^{26}_D$ +13.1° (*c* 1.10, $CHCl_3$); IR (neat) 3469, 3060, 2954, 2930, 1471, 1449, 1252, 1092, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ −0.02 (3H, s), −0.01 (3H, s), 0.06 (3H, s), 0.09 (3H, s), 0.73 (9H, s), 0.88 (9H, s), 1.53 (1H, t, J = 1.0 Hz), 2.49 (1H, dd, J = 5.9, 5.5 Hz), 3.11 (1H, dd, J = 9.7, 6.0 Hz), 3.37 (1H, dd, J = 9.7, 7.0 Hz), 3.71 (2H, m), 3.97 (2H, m), 4.06 (1H, brs), 4.19 (1H, t, J = 6.3 Hz), 7.20−7.29 (8H, m), 7.42−7.47 (7H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.8, −4.7, −4.6, 17.7, 17.8, 25.6, 25.7, 62.9, 64.0, 80.2, 80.5, 86.5, 86.8, 87.5, 126.9, 127.7, 128.7, 144.0. Anal. Found: C, 69.70; H, 8.62. Calcd for $C_{37}H_{54}O_5Si_2$: C, 69.99; H, 8.57.

(2*S*,3*R*,4*R*,5*R*)-3,4-Di-*tert*-butyldimethylsilyloxy-2-formyl-5-(1-trityloxymethyl)tetrahydrofuran (23a). To a stirred solution of oxalyl chloride (0.15 mL, 1.70 mmol) in CH_2Cl_2 (4 mL) was added dropwise a solution of DMSO (0.27 mL, 3.43 mmol) in CH_2Cl_2 (0.3 mL) at −70 °C under Ar, and the mixture was stirred for 30 min at −70 °C. At −70 °C a solution of **20a** (240 mg, 0.38 mmol) in CH_2Cl_2 (1 mL) was added dropwise, and the mixture was stirred at the same temperature for 1 h. Triethylamine (0.52 mL, 3.73 mmol) was added, and the resulting mixture was gradually warmed to 0 °C with stirring and poured into ice−water. The mixture was extracted with ether (10 mL × 3). The extracts were washed with cold HCl solution, sat. $NaHCO_3$ solution, water, and brine, dried, and concentrated to give **23a** (240 mg, quantitative), which was employed to the next step without further purification. $[\alpha]^{26}_D$ +2.6° (*c* 0.43, $CHCl_3$); IR (neat) 3060, 2954, 2930, 2885, 2858, 1733, 1598, 1471, 1449, 1253, 1109, 1089, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.02 (3H, s), 0.01 (3H, s), 0.07 (3H, s), 0.11 (3H, s), 0.72 (9H, s), 0.87 (9H, s), 3.16 (1H, dd, J = 9.3, 6.3 Hz), 3.47 (1H, dd, J = 9.3, 7.3 Hz), 4.02 (1H, d, J = 1.0 Hz), 4.03 (1H, brs), 4.10 (1H, brs), 4.35 (1H, t, J = 6.8 Hz),

7.20−7.29 (8H, m), 7.42−7.47 (7H, m), 9.63 (1H, d, J = 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.1, −4.8, 17.7, 17.8, 25.6, 64.5, 78.3, 82.1, 86.8, 88.5, 90.8, 126.9, 127.7, 128.7, 144.0, 203.2; HRMS calcd for $C_{37}H_{52}O_5Si_2Na$ $[M + Na]^+$ 655.3251, found 655.3240.

(2*R*,3*R*,4*R*,5*R*)-3,4-Di-*tert*-butyldimethylsilyloxy-2-[(1*S*)-(1-hydroxy)ethynyl]-5-(1-trityloxymethyl)tetrahydrofuran (24a) and (2*R*,3*R*,4*R*,5*R*)-3,4-Di-*tert*-butyldimethylsilyloxy-2-[(1*R*)-(1-hydroxy)ethynyl]-5-(1-trityloxymethyl)-tetrahydrofuran (25a). To a stirred solution of **23a** (320 mg, 0.51 mmol) in CH_2Cl_2 (8.3 mL) was added dropwise a 1.0 M etheral solution of $ZnCl_2$ (1.52 mL, 1.52 mmol) at −70 °C under Ar, and the mixture was stirred for 1 h at −70 °C. To this stirred solution was added dropwise a solution of ethynylmagnesium chloride (0.5 M solution in THF, 6.08 mL, 3.04 mmol) at −70 °C, and the mixture was stirred at the same temperature for 6 h and at −70∼20 °C for 12 h. Saturated aqueous NH_4Cl was added at 0 °C with vigorously stirring, and then the resulting mixture was extracted with ether (20 mL × 3). The extracts were washed successively with water and brine, dried, and concentrated. Chromatography on silica gel with hexane−ethyl acetate (30:1 → 4:1) as the eluent yielded **24a** (215 mg, 65%) and **25a** (17 mg, 5%).

24a: $[\alpha]^{24}_D$ +2.9° (*c* 1.34, $CHCl_3$); IR (neat) 3448, 3312, 3060, 2929, 1471, 1449, 1252, 1086, 836 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (3H, s), 0.01 (3H, s), 0.10 (3H, s), 0.11 (3H, s), 0.72 (9H, s), 0.89 (9H, s), 2.47 (1H, d, J = 2.0 Hz), 2.90 (1H, d, J = 3.4 Hz), 3.11 (1H, dd, J = 9.8, 7.3 Hz), 3.41 (1H, dd, J = 9.8, 6.8 Hz), 3.95 (1H, brd, J = 7.3 Hz), 4.07 (1H, brs), 4.10 (1H, brs), 4.22 (1H, t, J = 6.8 Hz), 4.54 (1H, ddd, J = 7.3, 3.4, 2.0 Hz), 7.20−7.29 (8H, m), 7.42−7.45 (7H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.9, −4.8, −4.7, −4.6, 17.7, 17.8, 25.6, 25.7, 62.6, 64.2, 73.8, 80.1, 80.3, 82.1, 86.8, 87.5, 90.4, 126.9, 127.8, 128.7, 143.9. Anal. Found: C, 71.05; H, 8.41. Calcd for $C_{39}H_{54}O_5Si_2$: C, 71.08; H, 8.26.

25a: $[\alpha]^{24}_D$ +9.0° (*c* 1.07, $CHCl_3$); IR (neat) 3414, 3310, 3060, 2930, 1471, 1449, 1254, 1114, 1069, 837 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (3H, s), 0.03 (3H, s), 0.15 (3H, s), 0.16 (3H, s), 0.71 (9H, s), 0.92 (9H, s), 2.47 (1H, d, J = 2.00 Hz), 3.11 (1H, dd, J = 9.8, 7.4 Hz), 3.43 (1H, dd, J = 9.8, 7.3 Hz), 3.88 (1H, brd, J = 6.4 Hz), 4.08 (1H, brd, J = 3.9 Hz), 4.09 (1H, brs), 4.30 (1H, dd, J = 7.4, 7.3 Hz), 4.33 (1H, brs), 4.53 (1H, ddd, J = 6.4, 3.9, 2.0 Hz),7.20−7.29 (8H, m), 7.42−7.44 (7H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.9, −4.7, −4.6, 17.6, 17.9, 25.6, 25.7, 62.9, 63.9, 74.2, 79.5, 80.0, 83.0, 86.9, 87.8, 90.1, 127.0, 127.8, 128.7, 143.9. Anal. Found: C, 71.10; H, 8.31. Calcd for $C_{39}H_{54}O_5Si_2$: C, 71.08; H, 8.26.

(2*R*,3*R*,4*R*,5*R*)-3,4-Di-*tert*-butyldimethylsilyloxy-2-[(1*S*)−(1-methoxymethyloxy)ethynyl]-5-(1-trityloxymethyl)tetrahydrofuran (5a). To a stirred mixture of **24a** (3.46 g, 5.25 mmol) and *N*,*N*-diisopropylethylamine (7.30 mL, 41.9 mmol) in CH_2Cl_2 (50 mL) was added dropwise chloromethyl methyl ether (2.00 mL, 26.2 mmol) at 0 °C, and then the mixture was stirred at 0 °C to room temperature for 1 d. After addition water, the mixture was extracted with ether (30 mL × 2). The extracts were washed successively with water, cold dil HCl solution, sat. $NaHCO_3$ solution, water, and brine, dried, and concentrated. Chromatography on silica gel with hexane−ethyl acetate (20:1 → 10:1 → 1:1) as the eluent yielded **5a** (3.32 g, 90%): mp 66−68 °C (hexane−ether), $[\alpha]^{28}_D$ +28.6° (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (3H, s), 0.02 (3H, s), 0.12 (3H, s), 0.13 (3H, s), 0.73 (9H, s), 0.91 (9H, s), 2.44 (1H, d, J = 2.0 Hz), 3.17 (1H, dd, J = 9.3, 8.3 Hz), 3.36 (1H, dd, J = 9.3, 5.9 Hz), 3.41 (3H, s), 3.99 (1H, d, J = 9.3 Hz), 4.12 (1H, brs), 4.14 (1H, dd, J = 7.8, 5.9 Hz), 4.24 (1H, brs), 4.58 (1H, dd, J = 9.3, 2.0 Hz), 4.69, 4.91 (2H, each d, J = 6.3 Hz), 7.20−7.28 (8H, m), 7.41−7.44 (7H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.9, −4.8, −4.7, −4.6, 17.7, 17.8, 25.6, 25.7, 55.4, 64.4, 66.0, 75.0, 80.1, 80.6, 80.7, 86.7, 87.5, 89.0, 94.4, 126.9, 127.7, 128.7, 144.0. Anal. Found: C, 70.04; H, 8.38. Calcd for $C_{41}H_{58}O_6Si_2$: C, 70.04; H, 8.32.

(2*R*,3*R*,4*R*,5*R*,6*S*,9*RS*,10*S*,13*R*,14*S*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-2,5:10,14-dioxido-6,13-bis(methoxymethoxy)-1-trityloxytetracos-7-yn-9-ol (26). To a stirred mixture of **5a** (6.03 g, 8.57 mmol) in THF (100 mL) was added dropwise a 1.58 M solution of *n*-BuLi (5.06 mL, 8.00 mmol) in hexane at −78 °C, and the mixture was stirred at −78 °C for 1 h. To the resulting solution was added anhydrous cerium chloride (1.97 g,. 8.00 mmol), and then stirring was continued for 1 h at −78 °C. A solution of **4** (1.58 g, 5.00 mmol) in THF (10 mL) was added dropwise at −78 °C, and the mixture was stirred at −78 °C for 2 h and then at −78∼ −23 °C for 3 h. After being quenched with sat. NH_4Cl solution at −23 °C, the resulting suspension was stirred at −23 °C to rt for 0.5 h. Ether (100 mL) was added, and then the organic layer was separated. The aqueous layer was treated with cold oxalic acid and extracted with ether (100 mL × 2). The organic layers were combined, washed with sat. $NaHCO_3$ solution, water, and brine, dried, and concentrated. The residue was subjected to chromatograpy on silica gel with hexane−ethyl acetate (7:1 → 5:1 → 4:1) as the eluent, giving **26** (3.95 g, 78%) as an unseparable mixture of alcohols. Starting acetylene compound **5a** (2.82 g, 47%) was also recovered.

26: IR (neat) 3450, 3060, 2930, 1473, 1449, 1254, 1100, 1035, 839 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10 (3H, s), 0.12 (3H, s), 0.20 (3H, s), 0.21 (3H, s), 0.81 (9H, s), 0.96 (3H, t, J = 6.4 Hz), 0.99 (9H, s), 1.33−1.99 (21H, m), 2.31 (1H, m), 2.51 (0.93H, d, J = 6.8 Hz), 2.72 (0.04H, d, J = 6.9 Hz), 3.22−3.43 (3H, m), 3.40−3.55 (2H, m), 3.43 (3H, s), 3.47 (3H, s), 4.07 (1H, brd, J = 9.3 Hz), 4.19 (1H, s), 4.22 (1H, brt, J = 7.8 Hz), 4.30 (1H, s), 4.49 (1H, brdd, J = 5.9, 2.4 Hz), 4.65−4.80 (4H, m), 4.97 (1H, d, J = 6.3 Hz), 7.20−7.28 (8H, m), 7.41−7.43 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.1, −4.9, −4.8, −4.7, −4.5, 14.1, 17.6, 17.7, 22.6, 24.9, 25.4, 25.6, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 32.0, 53.3, 55.3, 55.4, 64.5, 64.6, 66.0, 75.3, 78.6, 79.6, 80.1, 80.5, 80.6, 80.9, 82.6, 84.6, 84.8, 86.7, 87.3, 88.9, 94.2, 94.3, 95.2, 96.1, 126.8, 127.6, 128.7, 144.0. HRMS calcd for $C_{59}H_{92}O_{10}Si_2Na$ $[M + Na]^+$ 1039.6127, found 1039.6146. Anal. Found: C, 69.37; H, 9.16. Calcd for $C_{59}H_{92}O_{10}Si_2$: C, 69.64; H, 9.11.

(2*R*,3*R*,4*R*,5*R*,6*S*,10*S*,13*R*,14*S*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-2,5:10,14-dioxido-6,13-bis(methoxymethoxy)-1-trityloxytetracos-9-one (27). A suspension of PtO_2 (11 mg) in ethyl acetate (1.0 mL) was vigorously stirred at room temperature for 10 min under hydrogen atmosphere. Then, a solution of **26** (46.0 mg, 45 μmol) in ethyl acetate (0.2 mL) was added to a stirred above suspension, and the mixture was vigorously stirred at room temperature for 7 h under hydrogen atmosphere and filtered through a pad of Celite. The Celite pad was washed thoroughly with ethyl acetate. The filtrate and washings were combined and concentrated to give a syrupy oil (45.2 mg), which was dissolved in CH_2Cl_2 (0.5 mL). To a stirried solution were added TPAP (15.6 mg, 44 mmol), NMO (7.7 mg, 66 mmol), and 4 Å molecular sieves (30 mg) at room temperature, and the mixture was stirried at room temperature for 1.2 h. After being quenched with *i*-PrOH (0.1 mL), the reaction mixture was diluted with CH_2Cl_2 and then poured into a colomn of silica gel (hexane:ethyl acetate = 10:1). Elution with hexane−ethyl acetate (10:1) gave ketone **27** (44.5 mg, 97%): $[\alpha]^{25}_D$ −38.0° (*c* 0.75, $CHCl_3$); IR (neat) 3034, 2930, 1719, 1471, 1449, 1260, 1100, 1035, 839 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (3H, s), 0.08 (3H, s), 0.11 (6H, s), 0.78 (9H, s), 0.91 (9H, s), 1.11−2.03 (21H, m), 2.27 (1H, m), 2.81 (2H, brt, J = 7.0 Hz), 3.15−3.38 (4H, m), 3.41 (3H, s), 3.44 (3H, s), 3.76 (1H, m), 3.84 (1H, ddd, J = 7.3, 7.3, 1.8 Hz), 4.05 (1H, brs), 4.12 (1H, brs), 4.14 (1H, m), 4.63, 4.72, 4.75, 4.80 (4H, each d, J = 6.8 Hz), 7.24−7.32 (8H, m), 7.45−7.47 (7H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.8, −4.6, −0.03, 0.09, 14.1, 17.6, 17.8, 22.7, 24.8, 25.3, 25.6, 25.7, 27.4, 29.3, 29.6, 29.7, 29.8, 29.9, 31.9, 32.0, 34.2, 55.5, 55.8, 64.3, 75.2, 76.3, 80.6, 80.7, 80.9, 82.2, 85.9, 86.7, 89.4, 95.3, 97.0, 126.8, 127.6, 128.7, 144.0, 210.1; HRMS calcd for $C_{59}H_{94}O_{10}Si_2Na$ [M

+ Na]$^+$ 1041.6283, found 1041.6287. Anal. Found: C, 69.48; H, 9.21. Calcd for $C_{59}H_{94}O_{10}Si_2$: C, 69.50; H, 9.29.

(2*R*,3*R*,4*R*,5*R*,6*S*,9*S*,10*S*,13*R*,14*S*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-2,5:10,14-dioxido-6,13-bis(methoxymethoxy)-1-trityloxytetracos-9-ol (28) and (2*R*,3*R*,4*R*,5*R*,6*S*,9*R*,10*S*,13*R*,14*S*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-2,5:10,14-dioxido-6,13-bis(methoxymethoxy)-1-trityloxytetracos-9-ol (29). To a stirred solution of ketone **27** (63.8 mg, 62 μmol) in THF (2.0 mL) was added L-Selectride (1.0 M solution in THF; 0.13 mL, 0.13 mmol) at −78 °C, and then the mixture was stirred at the same temperature for 2 h. After addition of sat. NH_4Cl solution followed by $MgSO_4$, the resulting mixture was stirred at −78 °C to rt for 1.5 h and then filtered through a pad of Celite. The Celite pad was washed thoroughly with ethyl acetate. The filtrate and washings were combined and concentrated. The residue was subjected to chromatograpy on silica gel with hexane−ethyl acetate (10:1 → 4:1) as the eluent, giving a mixture of **28** and **29** (**28**/**29** = ca. 24/1 by ^{1}H NMR analyses), which were separated into each isomer {**28** (58.0 mg, 91%) and **29** (2.0 mg, 3%)} by chromatograpy on silica gel with hexane−ethyl acetate (8:1) as the eluent.

28: [α]$^{27}_D$ −31.5° (*c* 0.18, $CHCl_3$); IR (neat) 3580, 3060, 2930, 1477, 1450, 1254, 1100, 1038, 839 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (6H, s), 0.03 (3H, s), 0.07 (3H, s), 0.74 (9H, s), 0.86−0.88 (12H, brs), 1.20−1.43 (22H, m), 1.45−1.78 (3H, m), 1.81 (1H, brt), 2.18 (1H, m), 2.56 (1H, d, *J* = 3.0 Hz), 3.10−3.15 (3H, m), 3.18 (1H, ddd, *J* = 9.3, 9.3, 3.9 Hz), 3.31 (1H, dd, *J* = 9.3, 6.3 Hz), 3.37 (3H, s), 3.39 (3H, s), 3.40 (1H, m), 3.76 (1H, ddd, *J* = 7.4, 7.4, 3.9 Hz), 3.84 (1H, dd, *J* = 6.8, 2.0 Hz), 4.01 (1H, brs), 4.08−4.10 (2H, brs), 4.60 (1H, d, *J* = 6.8 Hz), 4.70−4.73 (2H, m), 4.78 (1H, d, *J* = 6.8 Hz), 7.20−7.28 (8H, m), 7.41−7.44 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.7, 14.0, 17.5, 17.7, 22.5, 25.2, 25.5, 25.6, 26.5, 27.4, 28.4, 29.2, 29.5, 29.6, 31.8, 31.9, 55.3, 55.6, 64.2, 73.2, 75.5, 76.6, 80.2, 80.5, 80.9, 85.7, 86.5, 89.0, 95.1, 96.9, 126.7, 126.9, 127.4, 127.5, 127.7, 128.4, 128.6, 128.9, 143.9. HRMS calcd for $C_{59}H_{96}O_{10}Si_2Na$ [M + Na]$^+$ 1043.6440, found 1043.6431. Anal. Found: C, 69.42; H, 9.49. Calcd for $C_{59}H_{96}O_{10}Si_2$: C, 69.37; H, 9.47.

29: [α]$^{27}_D$ −23.4° (*c* 1.13, $CHCl_3$); IR (neat) 3478, 3060, 2930, 1477, 1450, 1254, 1100, 1038, 839 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (6H, s), 0.03 (3H, s), 0.07 (3H, s), 0.75 (9H, s), 0.87−0.89 (12H, brs), 1.22−1.55 (22H, m), 1.62−1.93 (4H, m), 2.22 (1H, m), 2.32 (1H, d, *J* = 3.9 Hz), 3.12−3.24 (4H, m), 3.31 (1H, dd, *J* = 9.3, 6.3 Hz), 3.37 (3H, s), 3.41 (3H, s), 3.59 (1H, m), 3.79 (1H, m), 3.85 (1H, dd, *J* = 6.8, 2.0 Hz), 4.00 (1H, brs), 4.09 (1H, brs), 4.10 (1H, brt, *J* = 6.3 Hz), 4.60, 4.72 (2H, each d, *J* = 6.8 Hz), 4.73, 4.79 (2H, each d, *J* = 6.8 Hz), 7.20−7.29 (8H, m), 7.41−7.44 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.5, 14.1, 17.7, 17.8, 22.7, 24.5, 25.4, 25.6, 25.7, 28.4, 28.5, 29.3, 29.6, 29.7, 29.8, 31.9, 32.1, 55.5, 55.9, 64.2, 73.4, 75.8, 79.6, 80.6, 80.7, 80.9, 85.8, 86.7, 89.1, 95.3, 97.1, 126.9, 127.7, 128.7, 144.0. HRMS calcd for $C_{59}H_{96}O_{10}Si_2Na$ [M + Na]$^+$ 1043.6440, found 1043.6453. Anal. Found: C, 69.26; H, 9.53. Calcd for $C_{59}H_{96}O_{10}Si_2$: C, 69.37; H, 9.47.

(2R,3*R*,4*R*,5*R*,6*S*,9*S*,10*S*,13*R*,14*S*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-2,5:10,14-dioxido-6,9,13-tris(methoxymethoxy)-1-trityloxytetracosane (30). To a stirred mixture of **28** (63 mg, 62.3 μmol) and *N*,*N*-diisopropylethylamine (0.22 mL, 1.24 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise chloromethyl methyl ether (50 μL, 0.62 mmol) at 0 °C, and then the mixture was stirred at 0 °C for 2 h and room temperature for 16 h. After addition of water, the mixture was extracted with ether (3 mL ×3). The extracts were washed successively with water, cold dil HCl solution, sat. $NaHCO_3$ solution, water, and brine, dried, and concentrated to give **30** (64 mg, 97%), which was employed to the next step without further purification. Analytical sample was prepared by chromatography on silica gel with hexane−ethyl acetate (10:1) as the eluent.

30: [α]$_D$ −30.8° (*c* 0.21, $CHCl_3$). IR (neat) 2927, 1252, 1150, 1101, 1034, 919 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (3H,s), 0.02 (6H,s), 0.06 (3H,s), 0.75 (9H,s), 0.86 (9H, s), 0.87 (3H, t, *J* = 6.5 Hz), 1.20−1.84 (31H, m), 2.21 (1H, m), 3.09 (1H, ddd, *J* = 8.8, 8.3, 2.4 Hz), 3.15 (1H, dd, *J* = 9.7, 6.8 Hz), 3.19 (1H, m), 3.30 (1H, dd, *J* = 9.7, 6.4 Hz), 3.33 (1H, m), 3.36 (3H, s), 3.37 (3H, s), 3.40 (3H, s), 3.47 (1H, m), 3.75 (1H, m), 3.83 (1H, 1H, dd, *J* = 6.8, 2.4 Hz), 4.00 (1H, brs), 4.05−4.11 (2H, m), 4.59 (1H, d, *J* = 6.8 Hz), 4.64−4.78 (5H, m), 7.22−7.33 (9H, m), 7.44−7.46 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, −4.5, 14.1, 17.7, 17.8, 22.7, 25.5, 25.6, 25.7, 26.2, 26.8, 27.9, 29.4, 29.6, 29.7, 29.8, 30.0, 31.9, 32.2, 55.5, 55.7, 55.8, 64.4, 75.8, 77.2, 79.3, 79.6, 80.6, 80.9, 81.0, 85.7, 86.7, 89.1, 95.3, 96.9, 97.0, 126.9, 127.7, 128.8, 144.1; HRMS calcd for $C_{61}H_{100}O_{11}Si_2Na$ [M + Na]$^+$ 1087.6702, found 1087.6697. Anal. Found: C, 68.84; H, 9.58. Calcd for $C_{61}H_{100}O_{11}Si_2$: C, 68.75; H, 9.46.

(2*R*,3*S*,4*S*,5*S*,6*S*,9*S*,10*S*,13*R*,14*S*)-2,5:10,14-Dioxido-6,9,13-tris(methoxymethoxy)-1-trityloxytetracos-3,4-diol (31). To a stirred solution of **30** (64.0 mg, 60 μmol) in THF (1.0 mL) was added dropwise 1.0 M solution of TBAF in THF (0.15 mL, 0.15 mmol) at room temperature, and the mixture was stirred at room temperature for 5.5 h and diluted with ethyl acetate (5 mL). The solution was washed with sat. NH_4Cl solution, water, and brine, dried, and concentrated. The residue was purified by chromatography on silica gel with hexane−ethyl acetate (2:1→ 1:1→ 1:2) as the eluent to yield **31** (47.8 mg, 92% form **28**); [α]$^{26}_D$ −10.6° (*c* 0.11, $CHCl_3$); IR (neat) 3442, 2926, 1448, 1150, 1101, 1033, 918 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (3H, t, *J* = 6.5 Hz), 1.20−1.84 (31H, m), 2.21 (1H, m), 3.10 (1H, ddd, *J* = 8.1, 8.1, 1.5 Hz), 3.15−3.27 (3H, m), 3.35 (1H, m), 3.36 (3H, s), 3.38 (3H, s), 3.41 (3H, s), 3.50 (1H, m), 3.76 (1H, m), 3.99−4.15 (4H, m), 4.59 (1H, d, *J* = 6.8 Hz), 4.66−4.78 (5H, m), 7.22−7.33 (9H, m), 7.44−7.46 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 25.5, 26.3, 26.5, 29.3, 29.6, 29.7, 30.0, 31.9, 32.1, 55.5, 55.8, 56.1, 64.9, 75.7, 77.7, 78.9, 79.4, 79.6, 79.8, 80.9, 83.5, 86.1, 87.5, 95.3, 96.4, 97.3, 127.2, 127.9, 128.7, 143.2; HRMS calcd for $C_{49}H_{72}O_{11}Na$ [M + Na]$^+$ 859.4972, found 859.4995. Anal. Found: C, 70.09; H, 8.43. Calcd for $C_{49}H_{72}O_{11}$: C, 70.31; H, 8.67.

(2*R*,3*R*,4*R*,5*R*,6*S*,9*S*,10*S*,13*R*,14*S*)-2,5:10,14-Dioxido-3,4-bis(methanesulfonyloxy)-6,9,13-tris(methoxymethoxy)-1-trityloxytetracosane (32). To a stirred mixture of **31** (47.8 mg, 57.0 μmol) and triethylamine (0.06 mL, 0.40 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise methanesulfonyl chloride (13 μL, 0.17 mmol) at 0 °C, and then the mixture was stirred at 0 °C to room temperature for 12 h. After addition water, the mixture was extracted with CH_2Cl_2 (5 mL × 3). The extracts were washed successively with water, cold dil HCl solution, sat. $NaHCO_3$ solution, water, and brine, dried, and concentrated to give **32** (55.3 mg, 98%), which was employed to the next step without further purification. Analytical sample was prepared by chromatography on silica gel with hexane−ethyl acetate (2:1 → 1:1) as the eluent.

32: [α]$_D$ −4.1° (*c* 0.22, $CHCl_3$). IR (neat) 2926, 1366, 1179, 1151, 1101, 1033, 960, 918 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.7 Hz), 1.20−1.91 (29H, m), 2.18 (1H, m), 2.96 (3H, s), 3.05−3.52 (6H, m), 3.11 (3H, s), 3.35 (3H, s), 3.36 (3H, s), 3.42 (3H, s), 3.83 (1H, m), 4.32−4.38 (2H, m), 4.59 (1H, d, *J* = 6.8 Hz), 4.65 (1H, d, *J* = 6.8 Hz), 4.70−4.75 (3H, m), 4.78 (1H, d, *J* = 6.8 Hz), 5.33−5.38 (2H, m), 7.22−7.33 (9H, m), 7.44−7.46 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 25.5, 26.2, 26.4, 27.2, 29.3, 29.5, 29.6, 29.7, 30.0, 31.9, 32.1, 38.2, 38.3, 42.9, 55.5, 55.8, 56.1, 62.8, 75.8, 79.3, 80.9, 81.6, 83.5, 83.6, 83.7, 83.9, 87.2, 95.3, 97.1, 97.2, 127.2, 127.9, 128.7, 143.4; HRMS calcd for $C_{51}H_{76}O_{15}S_2Na$ [M + Na]$^+$ 1015.4523, found 1015.4525.

(2*S*,5*S*,6*S*,9*S*,10*S*,13*R*,14*S*)-2,5:10,14-Dioxido-6,9,13-tris(methoxymethoxy)-1-trityloxytetracos-3-ene (33). A mixture of **32** (55.3 mg, 56.0 μmol), NaI (66.7 mg, 0.445 mmol), and Zn powder (54.5 mg, 0.834 mmol) in DMF (1.0 mL) was heated at 140−145 °C with stirring for 13 h. Additional NaI (66.7 mg, 0.445 mmol) and Zn powder (54.5 mg, 0.834 mmol) were added, and stirring was continued for 5 h. More additional NaI (71.0 mg, mmol) and Zn powder (60.0 mg, mmol) were added, and stirring was further continued for 7 h. After

being cooled to room temperature, the reaction mixture was diluted with water (3 mL) and then extracted with CH_2Cl_2 (5 mL × 3). The extracts were washed with water and brine, dried, and concentrated to give **33** (45.0 mg, quantitative yield), which was employed to the next step without further purification. Analytical sample was prepared by chromatography on silica gel with hexane−ethyl acetate (10:1 → 6:1 → 4:1) as the eluent.

33: $[\alpha]_D$ −128.8° (*c* 0.16, $CHCl_3$). IR (neat) 3059, 2926, 1491, 1449, 1150, 1102, 1035, 918 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 6.7 Hz), 1.20−1.81 (27H, m), 2.22 (1H, m), 3.06−3.12 (2H, m), 3.16−3.23 (2H, m), 3.33 (1H, m), 3.36 (3H, s), 3.37 (3H, s), 3.39 (3H, s), 3.50 (1H, m), 3.61 (1H, m), 4.59 (1H, d, J = 6.4 Hz), 4.66−4.77 (5H, m), 4.96−5.00 (2H, m), 5.89, 5.95 (2H, each brd, J = 6.3 Hz), 7.19−7.30 (9H, m), 7.43−7.46 (6H, d, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 25.5, 26.3, 26.5, 26.9, 29.3, 29.6, 29.7, 30.1, 31.9, 32.1, 55.5, 55.7, 55.8, 66.5, 75.8, 79.2, 79.3, 79.9, 80.9, 85.4, 86.4, 88.1, 95.3, 96.9, 97.0, 126.6, 126.9, 127.7, 128.0, 128.7, 129.8, 144.1; HRMS calcd for $C_{49}H_{70}O_9Na$ $[M + Na]^+$ 825.4918, found 825.4929. Anal. Found: C, 73.10; H, 9.10. Calcd for $C_{49}H_{70}O_9$: C, 73.28; H, 8.79.

(2*S*,5*S*,6*S*,9*S*,10*S*,13*R*,14*S*)-2,5:10,14-Dioxido-6,9,13-tris(methoxymethoxy)-1-trityloxytetracosane (34). A mixture of **33** (45.0 mg, 56 μmol) and 10% Pd/C (22 mg) in ethanol (0.8 mL) was vigorously stirred at room temperature for 18 h under hydrogen atmosphere and filtered through a pad of Celite. The Celite pad was washed thoroughly with ethyl acetate. The filtrate and washings were combined and concentrated to give **34** (44.6 mg), which was employed to the next step without further purification. Analytical sample was prepared by chromatography on silica gel with hexane−ethyl acetate (4:1) as the eluent.

34: $[\alpha]^{23}_D$ −55.7° (*c* 0.30, $CHCl_3$). IR (neat) 2925, 1449, 1150, 1101, 1038, 919 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 6.7 Hz), 1.20−2.05 (29H, m), 2.22 (1H, m), 2.99 (1H, dd, J = 9.3, 4.8 Hz), 3.09 (1H, ddd, J = 9.7, 8.9, 2.4 Hz), 3.15 (1H, dd, J = 9.3, 5.3 Hz), 3.19 (1H, ddd, J = 9.8, 9.3, 3.8 Hz), 3.30−3.35 (1H, m), 3.36 (3H, s), 3.37 (3H, s), 3.41 (3H, s), 3.45−3.53 (2H, m), 4.01 (1H, m), 4.21 (1H, m), 4.59 (1H, d, J = 6.8 Hz), 4.65−4.78 (4H, m), 4.90 (1H, d, J = 6.8 Hz), 7.19−7.30 (9H, m), 7.45−7.47 (6H, d, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 25.6, 26.4, 26.7, 27.1, 28.4, 28.8, 29.4, 29.6, 29.7, 29.8, 30.1, 30.3, 31.9, 32.1, 55.5, 55.7, 55.8, 66.5, 75.8, 78.1, 79.3, 79.5, 79.7, 80.9, 81.7, 86.3, 95.3, 96.8, 97.0, 126.9, 127.7, 128.8, 144.2; HRMS calcd for $C_{49}H_{72}O_9Na$ $[M + Na]^+$ 827.5074, found 827.5064. Anal. Found: C, 73.01; H, 9.14. Calcd for $C_{49}H_{72}O_9$: C, 73.10; H, 9.01.

(2*S*,5*S*,6*S*,9*S*,10*S*,13*R*,14*S*)-2,5:10,14-Dioxido-6,9,13-tris(methoxymethoxy)tetracos-1-ol (35). A solution of **34** (44.6 mg) in 90% AcOH (1.1 mL) was heated at 50 °C with stirring for 3 h, concentrated, and coevaporated with toluene. The residue was purified by chromatography on silica gel with toluene−ethyl acetate (1:1 → 1:2 → 1:3) as the eluent to give alcohol **35** (23.5 mg, 74% from **31** in four steps): $[\alpha]^{27}_D$ −51.7° (*c* 0.33, $CHCl_3$); IR (neat) 3470, 2920, 1150, 1110, 1038, 918 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 6.7 Hz), 1.20−2.04 (29H, m), 2.22 (1H, m), 3.09 (1H, ddd, J = 9.1, 9.1, 2.1 Hz), 3.20 (1H, ddd, J = 9.8, 9.8, 4.3 Hz), 3.33 (1H, m), 3.37 (3H, s), 3.38 (3H, s), 3.40 (3H, s), 3.45−3.53 (3H, m), 3.65 (1H, m), 3.99 (1H, dd, J = 7.9, 6.4 Hz), 4.10 (1H, m), 4.59 (1H, d, J = 6.7 Hz), 4.66−4.75 (4H, m), 4.79 (1H, d, J = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 25.5, 26.3, 26.5, 27.0, 27.4, 28.9, 29.3, 29.6, 29.7, 30.1, 31.9, 32.1, 55.5, 55.7, 55.8, 64.7, 75.8, 79.1, 79.4, 79.8, 80.9, 81.5, 95.3, 96.8, 96.9; HRMS calcd for $C_{30}H_{58}O_9Na$ $[M + Na]^+$ 585.3979, found 585.3972. Anal. Found: C, 63.85; H, 10.51. Calcd for $C_{30}H_{58}O_9$: C, 64.03; H, 10.39.

(3*S*,6*S*,7*S*,10*S*,11*S*,14*R*,15*S*)-3,6:11,15-Dioxido-7,10,14-tris(methoxymethoxy)pentacos-1-yne (2). To a stirred solution of oxalyl chloride (54 μL, 0.62 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise a solution of DMSO (0.13 mL, 1.24 mmol) in CH_2Cl_2 (0.5 mL) at −70 °C under Ar, and the mixture was stirred for 30 min at −70 °C. At −70 °C a solution of **35** (70.0 mg, 0.12 mmol) in CH_2Cl_2 (0.6 mL) was added dropwise, and the mixture was stirred at the same temperature for 1 h. Triethylamine (0.26 mL, 1.86 mmol) was added, and the resulting mixture was gradually warmed to 0 °C with stirring and poured into ice−water. The mixture was extracted with ether (10 mL × 3). The extracts were washed with cold HCl solution, sat. $NaHCO_3$ solution, water, and brine, dried, and concentrated to give aldehyde **36** (69.0 mg): IR (neat) 2920, 1738, 1465, 1150, 1103, 1038, 918 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 6.8 Hz), 1.20−2.02 (29H, m), 2.22 (1H, m), 3.08 (1H, ddd, J = 9.2, 9.2, 2.4 Hz), 3.19 (1H, ddd, J = 9.3, 9.3, 3.9 Hz), 3.32 (1H, m), 3.35 (3H, s), 3.37 (3H, s), 3.39 (3H, s), 3.47 (1H, m), 3.52 (1H, m), 4.10 (1H, m), 4.31 (1H, ddd, J = 8.3, 7.8, 1.9 Hz), 4.59 (1H, d, J = 6.7 Hz), 4.66−4.75 (4H, m), 4.79 (1H, d, J = 6.7 Hz), 9.65 (1H, d, J = 1.9 Hz). This compound was employed to the next step without further purification. To a stirried solution of CBr_4 (82.2 mg, 0.25 mmol) in CH_2Cl_2 (1.0 mL) was added triphenylphosphine (130 mg, 0.50 mmol) in CH_2Cl_2 (0.3 mL) at 0 °C. After 5 min, triethylamine (0.14 mL, 0.99 mmol) was added. After 3 min, a solution of the aldehyde **36** (69.0 mg) in CH_2Cl_2 (0.6 mL) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 20 h, poured into sat. $NaHCO_3$ solution, and then extracted with CH_2Cl_2 (10 mL × 3). The extracts were washed with water and brine, dried, and concentrated. The residue was purified by chromatography on silica gel with hexane−ethyl acetate (10:1) as the eluent to give **37** (69.0 mg, 78% from **35** in two steps): ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 6.8 Hz), 1.21−1.84 (H, m), 1.95−2.05 (1H, m), 2.18−2.28 (2H, m), 3.10 (1H, ddd, J = 9.3, 8.8, 2.2 Hz), 3.20 (1H, ddd, J = 9.6, 8.8, 4.2 Hz), 3.30−3.51 (2H, m), 3.36 (3H, s), 3.38 (3H, s), 3.39 (3H, s), 4.04 (1H, m), 4.54−4.82 (7H, m), 6.50 (1H, d, J = 7.3 Hz). To a stirred solution of **37** (27.5 mg, 0.04 mmol) in THF (0.4 mL) was added a 1.0 M solution of ethylmagnesium bromide in THF (0.08 mL, 0.08 mmol) dropwise at −5 °C, and then the mixture was stirred at the same temperature for 0.5 h. After addition of sat. NH_4Cl solution, the resulting mixture was extracted with ether (5 mL × 3). The extracts were washed with water and brine, dried, and concentrated. The residue was purified by chromatography on silica gel with hexane−ethyl acetate (10:1 → 4:1) as the eluent to give **2** (20.7 mg, 97%): $[\alpha]^{24}_D$ −67.8° (*c* 0.46, $CHCl_3$); IR (neat) 3260, 2930, 1150, 1100, 1038, 918 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 6.6 Hz), 1.20−1.82 (26H, m), 1.94−2.27 (4H, m), 2.40 (1H, d, J = 2.0 Hz), 3.09 (1H, ddd, J = 9.3, 8.8, 2.4 Hz), 3.19 (1H, ddd, J = 9.8, 8.8, 3.9 Hz), 3.31−3.42 (2H, m), 3.36 (3H, s), 3.37 (3H, s), 3.38 (3H, s), 3.45−3.52 (2H, m), 4.16 (1H, brq, J = 7.0 Hz), 4.57−4.78 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 25.5, 26.3, 26.7, 27.0, 27.3, 29.3, 29.6, 29.7, 30.1, 31.9, 32.1, 33.3, 55.5, 55.8, 68.1, 72.6, 75.8, 79.1, 79.3, 79.4, 80.9, 81.0, 83.8, 95.3, 96.8, 97.0; HRMS calcd for $C_{31}H_{56}O_8Na$ $[M + Na]^+$ 579.3873, found 579.3846. Anal. Found: C, 66.84; H, 10.27. Calcd for $C_{31}H_{56}O_8$: C, 66.87; H, 10.14.

(5*S*,6*S*,7*R*,8*S*,9*S*)-6,7-Isopropylidenedioxy-9-*p*-methoxybenzyloxy-3-decyne-5,8-diol (42) and (5*R*,6*S*,7*R*,8*S*,9*S*)-6,7-Isopropylidenedioxy-9-*p*-methoxybenzyloxy-3-decyne-5,8-diol (43). To a stirred mixture of **41** (194 mg, 0.63 mmol) in hexane−ether (3:1, 0.8 mL) was added dropwise a 1.50 M solution of *n*-BuLi in hexane (0.41 mL, 0.62 mmol) at −78 °C, and the mixture was stirred at −78 °C for 1 h. A solution of **40** (68.0 mg, 0.21 mmol) in ether (0.2 mL) was added dropwise at −60 °C, and the mixture was gradually warmed to 5 °C for 17 h with stirring. After being quenched with sat. NH_4Cl solution at 0 °C, the resulting mixture was extracted with ether (10 mL × 2). The extracts were washed with water and brine, dried, and concentrated. The residue was subjected to chromatograpy on silica gel with hexane−ether (1:1 → 1:2) as the eluent, giving desired alcohol **43** (89.0 mg, 67%) and **42** (15.0 mg, 11%).

42: $[\alpha]^{27}_D$ +8.0° (*c* 0.20, $CHCl_3$); IR (neat) 3400, 3070, 2940, 1615, 1515, 1250, 1113, 1038, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.27 (3H, d, J = 5.8 Hz), 1.34 (3H, s), 1.49 (3H, s), 2.47 (2H, dt, J = 7.3, 7.3, 2.0 Hz), 2.81 (1H, d, J = 7.8 Hz), 3.52 (1H, dq, J = 7.8, 5.8 Hz), 3.68 (1H, d, J = 7.3 Hz), 3.76 (2H, t, J = 7.3 Hz), 3.79 (3H, s), 4.02 (1H, brt, J = 7.8, 7.8, 1.5 Hz), 4.12 (1H, dd, J = 6.8, 5.4 Hz); 4.37, 4.55 (2H, each d, J = 11.7 Hz), 4.47 (1H, dd, J = 6.8, 2.0 Hz), 4.58 (1H, m), 6.86 (2H, m), 7.22 (2H, d, J = 8.8 Hz), 7.35−7.42 (6H, m), 7.66 (4H, dd, J = 7.3, 1.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 19.1, 22.9, 24.9, 26.7, 26.8, 55.2, 61.9, 62.2, 70.6, 70.9, 75.3, 75.4, 79.1, 79.8, 83.6, 108.0, 113.8, 127.7, 129.4, 129.6, 130.3, 133.5, 135.5, 135.7, 159.2. Anal. Found: C, 70.05; H, 7.69. Calcd for $C_{37}H_{48}O_7Si$: C, 70.22; H, 7.64.

43: $[\alpha]^{26}_D$ +12.9° (*c* 0.16, $CHCl_3$); IR (neat) 3440, 3075, 2940, 1615, 1515, 1477, 1250, 1113, 1038, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.27 (3H, d, J = 5.8 Hz), 1.35, 1.51 (6H, each s), 2.47 (2H, dt, J = 7.3, 7.3, 2.0 Hz), 2.65 (1H, d, J = 7.3 Hz), 2.75 (1H, d, J = 5.4 Hz), 3.49 (1H, dq, J = 7.8, 5.8 Hz), 3.72 (1H, dt, J = 8.3, 8.3, 1.4 Hz), 3.75 (2H, t, J = 7.3 Hz), 3.79 (3H, s), 4.15 (1H, dd, J = 7.3, 5.9 Hz), 4.35, 4.52 (2H, each d, J = 11.2 Hz), 4.47 (1H, dd, J = 7.3, 2.0 Hz), 4.62 (1H, brt), 6.85 (2H, m), 7.22 (2H, d, J = 8.8 Hz), 7.35−7.44 (6H, m), 7.66 (4H, dd, J = 7.8, 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 19.1, 22.9, 24.5, 26.6, 26.7, 55.2, 61.6, 62.2, 70.6, 71.4, 75.0, 75.6, 76.6, 79.3, 79.9, 83.5, 108.3, 113.7, 127.6, 129.3, 129.6, 130.3, 133.5, 135.5, 159.1. Anal. Found: C, 69.93; H, 7.70. Calcd for $C_{37}H_{48}O_7Si$: C, 70.22; H, 7.64.

(2′*R*,3*R*,4*R*,5*S*)-3-(6′-*tert*-Butyldiphenylsilyloxy-2′-(methoxymethoxy)hexyl)-5-methyl-tetrahydrofuran-2-one (53) and (2′*R*,3*S*,4*R*,5*S*)-3-(6′-*tert*-Butyldiphenylsilyloxy-2′-(methoxymethoxy)hexyl)-5-methyltetrahydrofuran-2-one (54). To a stirred solution of **6** (2.22 g, 3.11 mmol) in toluene (130 mL) was added dropwise a mixture of tributyltin hydride (1.67 mL, 6.22 mmol) and 2,2′-azobisisobutyronitrile in toluene (50 mL) over 30 min at 100−110 °C, and the mixture was stirred at the same temperature for 1.5 h and concentrated. Chromatography on silica gel with hexane−ethyl acetate (9:1 → 5:1 → 3:1) as the eluent yielded *trans*-lactone **53** (1.49 g, 86%) and *cis*-lactone **54** (63.0 mg, 4%).

53: $[\alpha]^{26}_D$ −28.3° (*c* 1.42, $CHCl_3$); IR (neat) 3070, 2930, 1778, 1430, 1150, 1110, 1045, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.46 (3H, d, J = 6.4 Hz), 1.43−1.60 (6H, m), 1.74 (1H, ddd, J = 13.1, 8.6, 4.6 Hz), 2.09 (1H, ddd, J = 13.1, 4.9, 3.4 Hz), 2.84 (1H, ddd, J = 6.4, 4.6, 3.4 Hz), 3.36 (3H, s), 3.37 (3H, s), 3.66 (2H, t, J = 6.4 Hz), 3.77 (1H, m), 3.82 (1H, dd, J = 7.3, 6.1 Hz), 4.34 (1H, dd, J = 6.4, 6.1 Hz), 4.64 (2H, s), 4.66, 4.70 (2H, each d, J = 7.0 Hz), 7.36−7.42 (6H, m), 7.65−7.67 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 21.0, 26.6, 32.4, 33.7, 34.0, 43.9, 55.4, 55.5, 63.5, 75.1, 79.4, 85.2, 95.6, 96.4, 127.4, 129.3, 133.7, 135.3, 175.8; HRMS calcd for $C_{31}H_{46}O_7SiNa$ [M + Na]$^+$ 581.2911, found 581.2912. Anal. Found: C, 66.57; H, 8.33. Calcd for $C_{31}H_{46}O_7Si$: C, 66.63; H, 8.30.

54: $[\alpha]^{26}_D$ −12.0° (*c* 0.44, $CHCl_3$); IR (neat) 3070, 2930, 1775, 1430, 1150, 1110, 1030, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (9H, s), 1.34 (3H, d, J = 6.8 Hz), 1.46−1.60 (6H, m), 1.79 (1H, ddd, J = 14.6, 8.3, 6.3 Hz), 1.94 (1H, ddd, J = 14.6, 6.8, 3.9 Hz), 2.91 (1H, ddd, J = 6.8, 6.3, 5.9 Hz), 3.35 (3H, s), 3.38 (3H, s), 3.66 (2H, t, J = 6.4 Hz), 3.82 (1H, m), 4.02 (1H, d, J = 5.9 Hz), 4.60 (1H, brq, J = 6.9 Hz), 4.64−4.71 (4H, m), 7.35−7.42 (6H, m), 7.65−7.67 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1, 19.2, 21.4, 26.8, 28.6, 32.6, 34.8, 39.1, 55.6, 55.9, 63.7, 76.2, 80.0, 80.2, 96.0, 96.2, 127.6, 129.5, 134.0, 135.5, 177.4; HRMS calcd for $C_{31}H_{46}O_7SiNa$ [M + Na]$^+$ 581.2911, found 581.2902. Anal. Found: C, 66.47; H, 8.16. Calcd for $C_{31}H_{46}O_7Si$: C, 66.63; H, 8.30.

{**8(*E*,*Z*)**}**-4,16,19,23-Tetra(methoxymethoxy)mucocin-8-ene-10-yne (56).** To a stirried solution of **2** (28.0 mg, 50 mmol) and **3** (32.0 mg, 84 mmol) in Et_3N (1 mL) were added $(Ph_3P)_2PdCl_2$ (3.5 mg, 5 mmol) and CuI (3.0 mg, 16 mmol) at room temperature, and the reaction mixture was stirred at room temperature for 1 h and poured into ice−water. The resulting mixture was extracted with ethyl acetate (3 mL × 3). The extracts were washed with cold HCl solution, water, sat. $NaHCO_3$ solution, water, and brine, dried, concentrated. Chromatography on silica gel with hexane−ethyl acetate (2:1 → 3:2) as the eluent yielded an unstable enyne **56** (32.1 mg, 79%) as a stereoisomeric mixture (E/Z = 27/1). Starting iodide **3** (11.3 mg) was also recovered. **56:** IR (neat) 2930, 1760, 1460, 1150, 1105, 1038, 920 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 8.7 Hz), 1.18−1.82 (30H, m), 1.40 (3H, d, J = 6.8 Hz), 1.85−2.25 (6H, m), 2.47 (2H, brd, J = 5.4 Hz), 3.07 (1H, ddd, J = 8.8, 8.8, 2.0 Hz), 3.18 (1H, ddd, J = 9.5, 9.5, 3.8 Hz), 3.28−3.40 (2H, m), 3.32, 3.35, 3.36, 3.37 (12H, each s), 3.47 (2H, m), 3.81 (1H, m), 4.13 (1H, dd, J = 7.4, 5.9 Hz), 4.57−4.78 (8H, m), 5.00 (1H, qd, J = 6.8, 1.5 Hz), 5.46 (0.97H, brdd, J = 16.1, 1.5 Hz), 5.80−5.88 (0.06H, m), 6.07 (0.97H, ddd, J = 16.1, 7.3, 6.9 Hz), 7.14−7.16 (1H, m), ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.0, 22.6, 24.3, 25.5, 26.3, 26.7, 26.9, 27.5, 29.3, 29.57, 29.62, 29.69, 30.0, 30.1, 31.9, 32.0, 32.8, 33.5, 33.6, 55.4, 55.6, 55.7, 55.8, 68.7, 68.8, 75.1, 75.3, 75.8, 77.5, 79.2, 79.4, 79.5, 80.8, 80.9, 83.1, 87.6, 95.3, 95.6, 96.8, 96.9, 109.2, 109.6, 130.4, 144.3, 151.5, 173.8; HRMS calcd for $C_{45}H_{76}O_{12}Na$ [M + Na]$^+$ 831.5234, found 831.5253.

4,16,19,23-Tetra(methoxymethoxy)mucocin (57). A mixture of **56** (22.4 mg, 28 μmol) and tris(triphenylphosphine)-rhodium chloride (8.1 mg, 8.7 μmol) in benzene−ethanol (6:1, 0.7 mL) was stirred at room temperature for 4.5 h under hydrogen atmosphere and concentrated. Again, the residue was diluted with benzene−ethanol (6:1, 0.7 mL), and more tris-(triphenylphosphine)rhodium chloride (8.1 mg, 8.7 μmol) was added. The resulting mixture was stirred at room temperature for 2 h under hydrogen atmosphere, concentrated, and then passed through a column of silica gel {hexane−ethyl acetate (2:1 → 1:1) } to give a syrup, which was purified by preparative TLC {hexane−ethyl acetate (1:1) } to give **57** (15.9 mg, 70%): $[\alpha]^{22}_D$ −34.6° (*c* 0.10, $CHCl_3$), IR (neat) 2927, 1759, 1457, 1318, 1212, 1150, 1101, 1035, 918 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 6.3 Hz), 1.20−1.81 (41H, m), 1.41 (3H, d, J = 6.8 Hz), 1.90−2.05 (2H, m), 2.22 (1H, m), 2.49 (2H, brd, J = 5.4 Hz), 3.08 (1H, ddd, J = 8.8, 8.8, 2.2 Hz), 3.19 (1H, ddd, J = 9.3, 9.3, 3.9 Hz), 3.32 (1H, m), 3.34, 3.37, 3.38, 3.39 (12H, each s), 3.47 (2H, m), 3.78−3.90 (2H, m), 3.97 (1H, qd, J = 8.3, 6.8 Hz), 4.46−4.76 (8H, m), 5.01 (1H, qd, J = 6.8, 1.5 Hz), 7.16 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.1, 22.7, 25.2, 25.5, 26.3, 26.4, 26.7, 26.9, 28.6, 29.3, 29.6, 29.7, 29.8, 30.0, 30.1, 31.9, 32.0, 32.2, 34.4, 35.8, 55.5, 55.6, 55.7, 75.6, 75.8, 77.5, 79.15, 79.2, 79.3, 79.5, 79.9, 80.9, 95.3, 95.6, 96.8, 96.9, 130.6, 151.3, 173.9; HRMS calcd for $C_{45}H_{82}O_{12}Na$ [M + Na]$^+$ 837.5704, found 837.5692. Anal. Found: C, 66.65; H, 10.27. Calcd for $C_{45}H_{82}O_{12}$: C, 66.31; H, 10.14.

Mucocin (1). To a stirred solution of **57** (6.6 mg, 8.1 μmol) in methyl sulfide (0.7 mL) was added $BF_3{\cdot}Et_2O$ (40 μL, 0.30 mmol) at −10 °C, and the mixture was stirred at −10 to 0 °C for 1 h. After addition of sat. $NaHCO_3$ solution, the resulting mixture was extracted with EtOAc (4 mL × 3). The extracts were washed with water, brine, dried, and concentrated. Chromatography on silica gel with ethyl acetate−hexane (1:1) → ethyl acetate as the eluent yielded **7** (4.0 mg, 77%): mp 59−60 °C (hexane−ether), $[\alpha]^{24}_D$ −13.9° (*c* 0.11, CH_2Cl_2); IR ($CHCl_3$) 3421, 2925, 1747, 1456, 1079 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 6.8 Hz), 1.20−1.78 (41H, m), 1.43 (3H, d, J = 6.8 Hz), 1.82 (1H, m), 1.95−2.05 (2H, m), 2.11 (1H, m), 2.27 (1H, brs), 2.40 (1H, brdd, J = 15.1, 8.3 Hz), 2.52 (1H, brd, J = 15.1 Hz), 2.72 (1H, brs), 2.85 (1H, brs), 3.05 (1H, ddd, J = 8.8, 8.8, 2.4 Hz), 3.15 (1H, brt, J = 6.3 Hz), 3.27 (1H, ddd, J = 9.3, 9.3, 4.9 Hz), 3.42 (1H, brt, J = 7.3 Hz), 3.46 (1H, m), 3.79 (1H, ddd, J = 7.3, 7.3, 7.3 Hz), 3.82−3.90 (2H, m), 5.05 (1H, qd, J = 6.8, 1.5 Hz), 7.18 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.1, 22.7, 25.5, 26.2, 26.9, 28.3, 28.7, 28.8, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 32.0, 32.4, 32.6, 33.3, 35.6, 37.4, 69.9, 70.6, 73.5, 73.8, 78.0, 79.3, 80.1, 81.9, 82.0,

131.2, 151.8, 174.6; HRMS calcd for $C_{37}H_{67}O_8$ $[M + H]^+$ 639.4836, found 639.4833.

Acknowledgment. This work was supported by Grant-in-Aid for Encouragement of Young Scientists from the Ministry of Education, Science and Culture in Japan and a Special Grant for Promotion of Research from the Institute of Physical and Chemical Research (RIKEN). We would like to thank Prof. J. L. McLaughlin (Purdue University) for providing spectra of mucocin and its related compounds. We also express our thanks to Dr. H. Koshino (RIKEN) for measurement of 2D-NMR spectra, Ms. K. Harata (RIKEN) for mass spectral measurements, and Dr. T. Chihara and his collaborators in RIKEN for the elemental analyses.

Supporting Information Available: ^1H and ^{13}C spectra for compounds **3**, **4**, **6**, **32**, and **56**, general procedures, and experimental details for compounds **3**, **6**, **11**−**15**, **18**-**20**, **22**, **23b**,**c**−**25b**,**c**, **39**, **40**, **45**−**52**, and **55**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO020211H